2094

Hepatic Retransplantation in Cholestatic Liver Disease: Impact of the Interval to Retransplantation on Survival and Resource Utilization

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The aim of our study was to quantitatively assess the impact of hepatic retransplantation on patient and graft survival and resource utilization. We studied patients undergoing hepatic retransplantation among 447 transplant recipients with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) at 3 transplantation centers. Cox proportional hazards regression analysis was used for survival analysis. Measures of resource utilization included the duration of hospitalization, length of stay in the intensive care unit, and the duration of transplantation surgery. Forty-six (10.3%) patients received 2 or more grafts during the follow-up period (median, 2.8 years). Patients who underwent retransplantation had a 3.8-fold increase in the risk of death compared with those without retransplantation ($P < .01$). Retransplantation after an interval of greater than 30 days from the primary graft was associated with a 6.7-fold increase in the risk of death ($P < .01$). The survival following retransplantations performed 30 days or earlier was similar to primary transplantations. Resource utilization was higher in patients who underwent multiple consecutive transplantations, even after adjustment for the number of grafts during the hospitalization. Among cholestatic liver disease patients, poor survival following hepatic retransplantation is attributed to late retransplantations, namely those performed more than 30 days after the initial transplantation. While efforts must be made to improve the outcome following retransplantation, a more critical evaluation may be warranted for late retransplantation candidates. (HEPATOLOGY 1999;30:395-400.)

Despite recent progress in liver transplantation, a gap remains between the patient and graft survival rates, underscoring a continued need for retransplantation.[1] For many patients with initial graft failure, retransplantation constitutes the only alternative to death.[2] At this time, over 10% of all donor organs are being used for retransplantation.[3]

Retransplantation is a difficult clinical dilemma. First, retransplantation is associated with a lower survival. Patients who receive retransplantation have a survival that is consistently 20 percentage points or more below that of primary transplant recipients, a difference apparent as early as 3 months' posttransplantation.[3] Second, given the severe shortage of organs available for transplantation, there is an ethical question of equity in the distribution of these scarce resources.[4,5] During 1996, 923 patients died while awaiting a liver, while 422 patients received retransplants.[3] Finally, retransplantation is known to be more expensive. The charges incurred for evaluation, transplantation, and 6 months of postoperative care of patients who had retransplantation were found to be more than twice that of patients with a single graft.[6]

To derive a rational strategy for organ distribution, as well as optimal patient management, the transplantation community must better understand the pathophysiology, risk factors, and determinants of outcome of hepatic retransplantation. Therefore, this analysis was undertaken with 3 objectives in mind: 1) to quantitatively assess the impact of retransplantation on survival in patients with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC); 2) to identify risk factors or patient subgroups that may be particularly responsible for the poor prognosis associated with retransplantation; and 3) to compare resource utilization between primary and retransplantation.

PATIENTS AND METHODS

Patient Selection and Management. We prospectively collected data in 448 patients with PBC and PSC undergoing liver transplantation at 3 transplantation centers (Baylor University Medical Center, Mayo Clinic, and University of Pittsburgh). The overall goal of the study was to systematically analyze the outcome of liver transplantation in patients with cholestatic liver disease. The study was approved by the Institutional Review Board of each of the contributing centers. A complete pretransplantation evaluation had been conducted to verify the diagnosis in each patient. Following transplantation, patients were followed regularly, with clinical examination and laboratory tests, including liver biochemistry, drug levels, and graft biopsies. Individual patient management, including the immunosuppressive regimen and decisions for retransplantation, was conducted by transplantation physicians at each institution. Our patient population has been described in detail previously.[7]

Abbreviations: PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; ICU, intensive care unit.

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Data Collection and Statistical Analysis. Information, including pretransplantation patient characteristics, intra- and postoperative events, and posttransplantation follow-up, was prospectively collected for each patient. The National Institute of Diabetes, Digestive and Kidney Diseases–Liver Transplant Database (NIDDK-LTD) forms were used for data collection. These data were entered at each center and transmitted electronically to the Mayo Clinic data coordinating center. All data management and analysis was undertaken using the SAS package (SAS Institute, Cary, NC).

Comparison of survival between groups was performed by Cox proportional hazards regression analysis. Graft survival was defined as the time that elapsed from each transplantation until graft failure, patient death, or last follow-up. In the analysis of graft survival, survival of each graft, including retransplants, was individually assessed. Patient survival was assessed by the interval between the first transplantation and patient's death or last follow-up. Proportional hazards analysis for patient survival was conducted treating retransplantation as a time-dependent covariate. This method is considered most appropriate in assessing the impact on patient survival of variables that occur after a given treatment. In this case, the treatment at time zero was the first transplantation and the variable being evaluated was retransplantation.[8] Thus, on the one hand, our analysis of graft survival addresses the following question: what is the likelihood for graft failure when a given organ is used for a retransplant as compared with a primary transplant? On the other hand, our analysis of patient survival compares the survival of individuals who later required retransplantation with those who did not, as assessed from the time of first transplantation.

Resource utilization was measured in terms of the duration of the transplantation procedure, the number of days in the intensive care units (ICU), and the total length of hospitalization, all of which have been shown to highly correlate with overall resource utilization.[9] The length-of-stay parameters were counted from the day of transplantation. In light of the skewed distribution of these variables, the rank sum test was employed for group comparisons. Two-tailed P values are reported with the traditional cut-off of 0.05.

RESULTS

Description of Patient Population. Pretransplantation patient characteristics are summarized in Table 1. Of the 448 patients, 1 had missing data on retransplantation and was therefore excluded from the analysis. Patients were almost equally divided between PBC and PSC. Approximately two thirds were female. When the Mayo risk scores were used as a measure of disease severity, patients at all 3 centers were comparable in both diagnoses.[10,11] Although the data collection spanned over a decade, most of the transplantations were performed since 1990, leading to a median length of follow-up of 2.8 years (range, 0.1-10.0 years).

Overall, 500 grafts were used for the 447 patients, 46 of whom (10.3%) received 2 or more grafts. Forty patients had 2 grafts, 5 received 3, and 1 patient required 4 grafts, while 401 patients did not require a retransplant. The retransplantation rate between 1985 and 1989 was 19.8%. Since 1990, however, the retransplantation rate has decreased to 8.2%, which was similar at all 3 centers (7.3%, 8.1%, and 9.4%; $P = .55$).

TABLE 1. Pretransplant Patient Characteristics and Survival

Center	Center 1 (n = 205)	Center 2 (n = 106)	Center 3 (n = 136)	Total (n = 447)
PBC/PSC	115/90	42/64	77/59	234/213
Age*	49.3 ± 10.4	50.2 ± 10.2	52.9 ± 12.3	50.6 ± 11.1
Sex (% female)	71.6	64.2	65.9	68.1
Mayo Risk score*				
PBC	7.33 ± 1.48	7.76 ± 1.31	7.38 ± 1.42	7.43 ± 1.44
PSC	5.20 ± 0.77	5.31 ± 0.93	4.94 ± 0.92	5.16 ± 0.88
Dates of OLT	4/85-5/95	4/90-4/94	8/90-1/95	4/85-1/95
Deaths	36	6	12	54

Abbreviation: OLT, orthotopic liver transplantation.
*Mean ± SD.

Survival Following Retransplantation. Figure 1A compares the graft survival rates for primary transplants and retransplants. Liver grafts used for retransplantation had clearly shorter survival than those used for primary transplants. Figure 1B demonstrates that the survival of patients who received retransplantation was shorter despite the usage of multiple grafts. The Cox model indicates that the relative risk of death is 3.8 times greater (95% confidence interval: 2.0-8.0; $P < .01$) in patients who had retransplants than those who had only primary graft. This difference was independent of the era of transplantation: when patients since 1990 only were considered, the relative risk decreased slightly to 2.7 (95% confidence interval: 1.1-7.2; $P = .04$).

Interval to Retransplantation. We next examined the influence of the interval to retransplantation on the survival outcome. The interval had a skewed distribution (median, 84 days; range, 1-1,441 days). We chose 30 days as a cut-off criterion and compared graft and patient survival between the early (≤30 days) and late (>30 days) retransplants. In the 6 patients who had more than 1 retransplant, the classification was based on the interval to the first retransplant. The interval from the primary graft to early retransplants (median [range]) was 4 (1-29) days, and to late retransplants, it was 150.5 (36-1,441) days.

In Fig. 2A, graft survival between the early and late retransplant groups is compared. The late retransplants were 3.0 times more likely to fail than primary transplants (95% confidence interval: 1.7-5.3; $P < .01$). Survival of early retransplants was not statistically different from that of the primary transplants (relative risk = 0.8; 95% confidence interval: 0.3-2.3).

Figure 2B clearly shows the difference in patient survival between the early and late retransplant groups. The late retransplant group had a significantly lower survival with a relative risk of death of 6.7 ($P < .01$) compared with the primary transplant group (95% confidence interval: 3.3-13.6). Survival in patients in the early retransplant group was not different from the primary transplant group (relative risk = 1.2 [$P = .82$]; 95% confidence interval: 0.3-4.9). The survival difference between the late retransplant and primary transplant groups persisted when patients transplanted since 1990 only were considered (relative risk = 4.6 [$P < .01$]; 95% confidence interval: 1.6-13.6).

Early Versus Late Retransplants. Table 2 describes the reasons for retransplantation (first retransplantation in patients with more than 2 transplants) in the early and late retransplant groups. More than half of the early retransplants were the result of primary nonfunction, whereas late retransplantation was mostly performed for rejection and biliary complications. Thus, the reason for graft failure may underlie the difference in the outcome of early and late retransplants. Unfortunately, the small number of patients in each of these categories precluded a meaningful analysis to separate out such effects. Nine of the 10 primary nonfunctions were since 1990, suggesting that with the recent donor shortage, transplant centers may be willing to accept more marginal organs.

We also considered the severity of hepatic dysfunction before retransplantation as a possible explanation for the

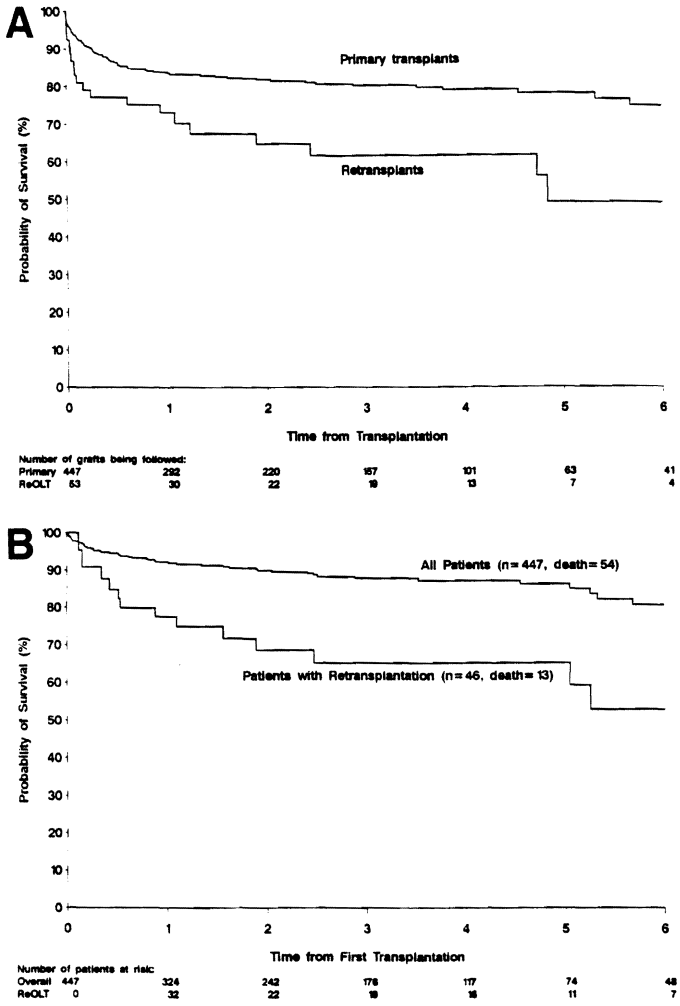

FIG. 1. Survival (Kaplan-Meier estimates) following hepatic retransplantation. (A) Comparison of graft survival evaluating each graft individually. (B) Comparison of patient survival as assessed from the time of initial transplantation. Patients and grafts in the retransplantation group had a significantly shorter survival than those who did not have retransplants ($P < .01$).

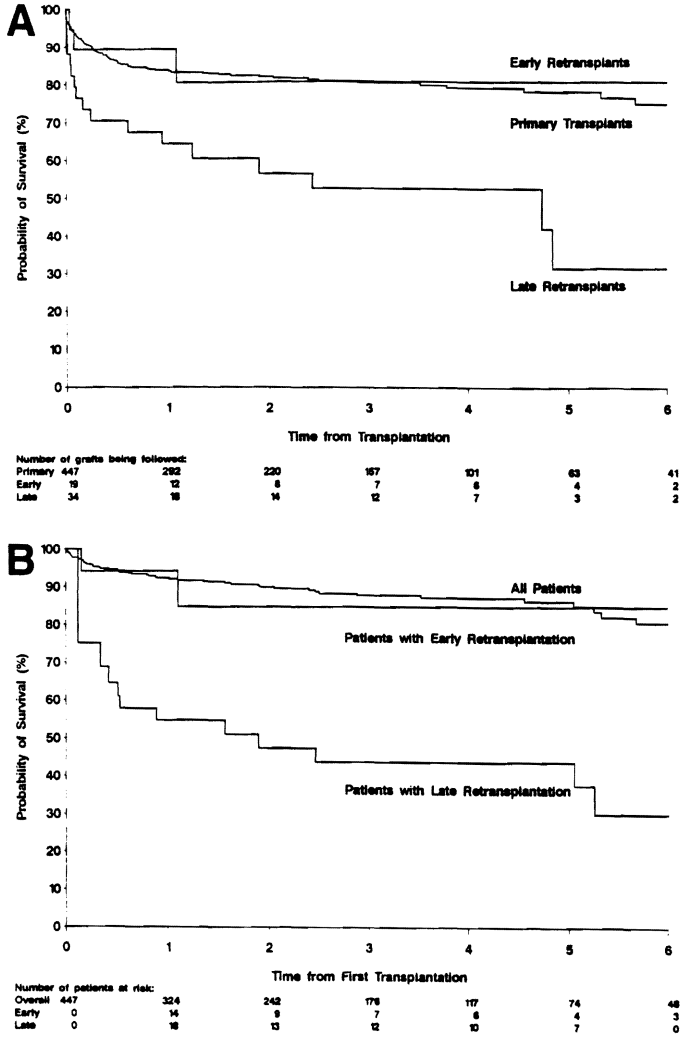

FIG. 2. Graft (A) and patient (B) survival following early (<30 days) and late (≥30 days) hepatic retransplantation. Late retransplants had a significantly shorter survival than primary grafts or early retransplants ($P < .01$).

difference of outcome between early and late retransplants (Table 3). The early retransplant group had more severe liver dysfunction at the time of retransplantation as indicated by biochemical parameters and functional status. Thus, the worse outcome in the late retransplant group could not be attributed to their preoperative condition.

Table 4 lists the primary cause of death as reported by the centers for each group of patients. The proportion of deaths from hepatic failure and intraoperative deaths appeared higher in the late retransplant group than the other 2 groups, although this difference may or may not be significant, given the subjective influence in assigning causes of death in a population in which simultaneous multiorgan failure is frequent. Of the 6 patients who had more than 1 retransplant, 4 died within 1 year of the last retransplantation.

Resource Utilization Associated With Retransplantation. As noted previously, we used 3 indicators of resource utilization including the duration of the transplantation procedure, the number of days in the ICU, and total length of hospitalization. The duration of the transplantation procedure was compared between the early and late retransplantations. On average, late retransplantation performed more than 30 days after initial transplantation took 2.4 hours longer than early retransplantation, after adjusting for the institution ($P < .01$).The length-of-stay data are summarized in Table 5. The 500 transplantations occurred during 478 hospitalizations. Of these, 428 hospitalizations were for a single primary transplant, and 29 were for a single retransplant. In the remaining 21 hospitalizations, 2 or more transplantations occurred during 1 stay. Of these 21 hospitalizations with multiple transplants, 14 (67%) included early retransplants within 30 days of the primary transplantation. In contrast, 25

TABLE 2. Reasons for First Retransplantation

Reason	Early Retransplants (≤30 d)	Late Retransplants (>30 d)	Total
Primary nonfunction	10	—	10 (22%)
Rejection	5	12	17 (37%)
Hepatic artery thrombosis	1	3	4 (9%)
Biliary stricture/cholangitis	2	7	9 (19%)
Other (unknown)	—	6 (5)	6 (13%)
Total	18	28	46 (100%)

TABLE 3. Indicators of the Severity of Hepatic Dysfunction Before Primary Transplantation and Retransplantation

	Primary Transplants (N = 447)	Early Retransplants (N = 19)	Late Retransplants (N = 34)	P*
Age	50.6 ± 11.1	52.0 ± 10.0	45.3 ± 9.2	.04
Bilirubin	9.2 ± 9.7	14.8 ± 14.6	14.8 ± 11.9	.9
Albumin	3.2 ± 0.7	2.7 ± 0.7	4.3 ± 4.8	<.01
Prothrombin time	13.7 ± 2.1	20.9 ± 8.9	13.9 ± 4.2	<.01
Aspartate transaminase	193 ± 323	2403 ± 3542	406 ± 852	<.01
Alkaline phosphatase	782 ± 690	349 ± 270	1202 ± 1255	<.01
Creatinine	1.1 ± 0.8	1.4 ± 0.9	1.4 ± 0.7	.8
Karnofsky score†	56.6 ± 21.6	22.1 ± 21.0	50.7 ± 27.1	<.01

*Comparison between the early and late groups (Wilcoxon).

†Definition of the Karnofsky score: 100: normal; 90: minor signs or symptoms of disease, but able to carry on normal activity; 80: some signs or symptoms of disease. Normal activity with effort; 70: cares for self but unable to carry on normal activity; 60: requires occasional assistance but is able to care for most of own needs; 50: requires considerable assistance and frequent medical care; 40: disabled. Requires special care and assistance; 30: severely disabled. Hospitalization is indicated, although death is not imminent; 20: active supportive treatment is necessary to sustain life; 10: moribund, fatal processes progressing rapidly.

(86%) of the 29 hospitalizations for single retransplants were late retransplants.

In Table 5, the length of stay for a single retransplant was similar to those for a single primary transplant. In contrast, the length of hospitalization was significantly longer in patients who received multiple transplants during 1 hospitalization as compared with those who underwent a single primary or retransplant. Of note, data in patients who received multiple transplants during a continuous hospitalization are presented on a per-graft basis. For example, the length of stay in hospital was divided by the number of transplants, because these patients were essentially recovering from 2 or more consecutive transplants. Similarly, the duration of ICU stay was longer in the multiple-transplant group, although the difference did not reach statistical significance. We also considered the number of in-hospital deaths for each group, because the duration of hospitalization, particularly for the retransplant groups, could have been spuriously shortened by early deaths. Although the proportion of in-hospital deaths was, indeed, higher in the retransplant groups, these few deaths did not have a significant effect on the overall length of stay.

TABLE 4. Causes of Death

Causes*	Primary Transplantation (n = 41)	Early Retransplantation (n = 2)	Late Retransplantation (n = 11)
Hepatic failure	9	1	5
Infection/multiorgan failure without hepatic failure	14	1	2
Intraabdominal complications	7	—	—
Malignancies	5	—	1
Intraoperative	2	—	2
Other (unknown)	4 (1)	—	1 (1)

*n = number of deaths.

TABLE 5. Length of Stay in Hospital and ICU

	Single Primary Transplant (n = 428)	Single Retransplant* (n = 29)	Multiple Transplants† (n = 21)	P
Length of stay in hospital (d)‡	17 (13-28)	17 (13-25)	28§ (12-47)	.05
Length of stay in ICU (d)‡	3 (2-6)	3 (2-6)	5.75§ (2.75-16)	.12
In-hospital death (%)	14 (3.3%)	3 (10.3%)	2 (9.5%)	.05

*Retransplantation followed by a successful dismissal from the hospital.

†More than one transplant given during one hospitalization.

‡Median (interquartile range) in days.

§Total duration (in days)/number of grafts.

DISCUSSION

Lower survival in patients undergoing retransplantation has been well documented. According to a report from the UNOS, the 3-year survival rate in patients who had retransplants was 53.7%, as compared with 77.4% in primary transplant recipients.[3] In our series, we observed that the difference in survival still exists in patients who otherwise have the most favorable outcome after liver transplantation, namely those with PBC and PSC. Retransplantation was associated with almost a 4-fold increase in the risk of death. Fortunately, with the advent of more potent immunosuppressants, improved donor organ selection, and better organ preservation in the last decade, the retransplantation rate has been substantially reduced, as has been confirmed in this report.[12-14]

The pathophysiological mechanism underlying the lower survival rate associated with retransplantation remains to be defined, although multiorgan dysfunction associated with failing grafts is likely to contribute to a high perioperative mortality.[15,16] Our data suggest that at least in patients with cholestatic liver disease, the poor outcome of retransplantation may be attributed to late retransplantation performed more than 30 days after the first transplantation. We believe there are several explanations for the differences in outcome between early and late retransplantation.

First, primary nonfunction, which accounted for more than one half of the early retransplants, is most likely to be related to donor factors, rather than recipient characteristics.[17] Therefore, replacing the defective graft should result in outcomes similar to patients who had a functional graft in the first place, provided that retransplantation is performed in a timely fashion.[18] Second, early retransplantation performed shortly after the primary transplantation is likely to be easier technically than late retransplants, where fibrosis surrounding the graft and blood vessels renders surgery more difficult.[19] In our patients, the operative time for late retransplants was significantly longer than early retransplants. Late retransplants have also been reported to require more blood transfusion than early retransplants.[2] Third, factors specific to recipient disease may play a role. Cholestatic liver disease patients tend to be relatively stable at initial transplantation, which may enable them to retain more physical reserve to withstand the stress associated with early retransplants. Alternatively, the immunologic basis of the diseases may predispose certain recipients to experience graft loss repeatedly, resulting in poor outcome after late retransplants.[20]

Finally, patients with late retransplantation have been subject to immunosuppression longer than early retransplant recipients. Long-term immunosuppression is likely to have an adverse impact on the outcome of retransplantation, in terms of infectious, renal, and metabolic complications.

So far, few studies have examined the interval between the first and subsequent grafts. Powelson reported that patients who received retransplantation 4 to 30 days after the initial transplantation had the worst outcome as compared with those with shorter or longer intervals.[5] The authors attributed the poor outcome in early retransplant recipients to infectious complications and multiple-organ failure following the initial transplantation. Another report indicated that the risk of graft failure increased linearly to reach a peak between 30 and 50 days from the previous transplant.[21] It was suggested that procrastinating retransplantation in the setting of failing graft accounts for the progressive inerease in the risk of death.

We would like to remind the reader that our results must be interpreted within the context that this was an observational study. In particular, an implicit selection of patients for retransplantation is embedded in our data, because the decision to perform retransplantation in patients with failing first graft was made by individual transplant physicians and surgeons. Obviously, not all patients with failing graft received retransplantation (Table 4). Thus, for example, early retransplantation does not guarantee uniformly good outcomes in all patients with failing graft within 30 days of initial transplantation. In this regard, the timing for the first transplantation may also be important in the outcome of retransplantation. Because the need for early retransplants is mostly determined by factors extraneous to the recipient, it would be better to have a margin of error in the recipient's physical reserve, should a need for retransplantation arise. Fortunately, in our patient population of PBC and PSC, the natural history of disease progression has been well characterized, making it possible to predict patient survival.[10,11] Such consideration is particularly relevant at a time when the median waiting time for transplantation exceeds well over 1 year.

Our analysis was also limited by the extent of information recorded in the database, although our data were prospectively collected on a relatively large number of patients (n = 447). Some variables had missing data, while there was not sufficiently detailed information to study specific subgroups of patients. For example, we were not able to elucidate the underlying physiological process that determines the outcome of retransplantation. We did exclude the preoperative morbidity level as the reason for the difference in outcome between the early and late retransplant groups.

Although we speculate that the length of the waiting period for retransplantation is an important factor in determining the outcome of retransplantation, particularly early in the posttransplantation period, our database did not include the waiting time for retransplantation to address the question. Nonetheless, we believe the ability to predict the failure of the graft early in the course is critically important.[22,23] A timely clinical assessment of the long-term viability of the existing graft and a prompt decision for retransplantation may prevent potentially life-threatening complications and improve the eventual outcome. Unfortunately, our ability to perform retransplantation in the most timely manner is limited by the severe donor organ shortage and long waiting time. Moreover, the current definitions of the UNOS statuses is based on the Child-Pugh score for patients awaiting retransplantation as well as primary transplanatation, which may put retransplant candidates at a disadvantage. The degree of graft dysfunction may not be accurately measured by the Child-Pugh score, because ascites or severe hepatic synthetic dysfunction may not appear until a very late stage.

From an economic standpoint, retransplantation has been regarded as an inappropriate use of scarce resources.[4,24] In this analysis, we discovered that the length of hospitalization and ICU stay for a single retransplantation was not different from that of primary transplants. In contrast, patients who underwent multiple transplants consecutively had a significantly longer stay even after adjustment for the number of transplants performed during the hospitalization. Many of these patients were early retransplant recipients. In light of the favorable long-term outcome, however, we believe that early retransplantation may be justified, despite higher resource utilization. Perhaps early retransplants should be viewed as an extension of the first transplant similar to other postsurgical morbidities. Then, the additional resource requirement including the donor organs for early retransplants may be supported in the same context. Moreover, the length of stay following early retransplantation may be shortened by timing the retransplant in such a way that multisystem dysfunction can be minimized before and after the second transplantation.

In summary, although retransplantation has decreased by more than 50% since 1990, patients who receive retransplantation still have significantly lower survival. In our sample of liver transplant recipients with PBC and PSC, those who undergo late retransplantation are largely responsible for the poor outcome of retransplantation. Resource utilization is particularly high in patients undergoing multiple transplants consecutively. We conclude that given the good long-term results, early retransplants should not be discouraged, whereas a more careful selection is required for late retransplant candidates. In-depth investigation is needed to understand factors leading to poor outcome following late retransplants and, more importantly, how to avoid them.

REFERENCES

1. Belle SH, Beringer KC, Detre KM. Trends in liver transplantation in the United States. In: Terasaki PI, ed. Clinical Transplants. 1993:19-35.
2. D'Alessandro AM, Ploef RJ, Knechtle SJ, Pirsch JD, Stegall MD, Hoffmann R, Sollinger HW, et al. Retransplantation of the liver—a seven year experience. Transplantation 1993;55:1083-1087.
3. 1997 Annual report of the U.S. Scientific Registry for Transplant Recipients and the Organ Procurement and Transplantation Network–Transplant Data: 1988-1996. UNOS, Richmond, VA, and the Division of Organ Transplantation, Bureau of Health Resources Development, Health Resources and Services Administration, U.S. Department of Health and Human Services, Rockville, MD.
4. Ubel PA, Arnold RM, Caplan AL. Rationing failure. The ethical lessons of the retransplantation of scarce vital organs. JAMA 1993;270:2469-2474.
5. Powelson JA, Cosimi AB, Lewis WD, Rohrer RJ, Freeman RB, Vacanti JP, Jonas M, et al. Hepatic retransplantation in New England—a regional experience and survival model. Transplantation 1993;55:802-806.
6. Evans RW. A cost-outcome analysis of retransplantation: the need for accountability. Transplant Rev 1993;7:163-175.
7. Ricci P, Therneau TM, Malinchoc M, Benson JT, Petz J, Klintmalm GB, Crippin JS, et al. A prognostic model for the outcome of liver transplantation in patients with cholestatic liver disease. HEPATOLOGY 1997;25:672-677.
8. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response. J Clin Oncol 1983;11:710-719.
9. Evans RW, Manninnen DL, Dong FB. An economic analysis of liver transplantation. Costs, insurance coverage, and reimbursement. Gastroenterol Clin North Am 1993;22:451-473.

10. Dickson ER, Grambsch PM, Fleming TR, Fisher LD, Langworthy A. Prognosis in primary biliary cirrhosis: Model for decision making. HEPATOLOGY 1989;10:1-7.
11. Dickson ER, Murtaugh PA, Wiesner RH, Grambsch PM, Fleming TR, Ludwig J, LaRusso NF, et al. Primary sclerosing cholangitis: Refinement and validation of survival models. Gastroenterology 1992;103:1893-1901.
12. Starzl TE, Demetris AJ, Van Thiel D. Liver transplantation. N Engl J Med 1989;321:1092-1099.
13. Belzer FO, D'Alessandro AM, Hoffmann RM, et al. The use of UW solution in clinical transplantation: a four-year experience. Ann Surg 1992;215:579-583.
14. Shaw BW, Gordon RD, Iwatsuki S, Starzl TE. Hepatic retransplantation. Transplant Proc 1985;17:264-271..
15. Anthuber M, Pratschke E, Jauch KW, Zuelke C, Groh J, Welte M, Forst H. Liver retransplanatation-indications, frequencies, results. Transplant Proc 1992;24:1965-1996.
16. Lemmens HP, Tsiblakis N, Langrehr JM, Blumhardt G, Lohmann R, Keck H, Neuhaus P. Comparison of perioperative morbidity following primary liver transplantation and liver retransplantation. Transplant Proc 1993; 25:1923-1924.
17. Ploeg RJ, D'Alessandro AM, Knechtle SJ, Stegall MD, Pirsch JD, Hoffmann RM, Sasaki T, et al. Risk factors for primary dysfunction after liver transplantation—a multivariate analysis. Transplanatation 1993;55: 807-813.
18. Fangmann J, Ringe B, Hauss J, Pichlmayr R. Hepatic retransplantation: the Hannover experience of two decades. Transplant Proc 1993;25:1077-1078.
19. Mora NP, Klintmalm GB, Cofer JB, Poplawski SS, Goldstein RM, Gonwa TA, Husberg BS. Results after liver transplantation: a comparative study between "elective" vs "nonelective" retransplantation. Transplant Proc 1990;22:1509-1511.
20. Pappo O, Ramos H, Starzl TE, Fung JJ, Demetris AJ. Structural integrity and identification of causes of liver allograft dysfunction occurring more than 5 years after transplantation. Am J Surg Path 1995;19:192-206.
21. Doyle HR, Morelli F, McMichael J, Doria C, Aldrighetti L, Starzl TE, Marino IR. Hepatic retransplantation—an analysis of risk factors associated with outcome. Transplantation 1996;61:1499-1505.
22. Kamath GS, Plevak DJ, Wiesner RH, et al. Primary nonfunction of the liver graft: when should we retransplant? Transplant Proc 1991;23:1954.
23. Doyle HR, Marino IR, Jabbour N, Zetti G, McMichael J, Mitchell S, Fung J, et al. Early death or retransplantation in adults after orthotopic liver transplantation. Can outcome be predicted? Transplantation 1994;57: 1028-1036.
24. Evans RW, Manninen DL, Dong FB, McLynne DA. Is retransplantation cost effective? Transplant Proc 1993;25:1694-1696.