American Journal of Transplantation 2004; 4: 1792–1797
Blackwell Munksgaard



doi: 10.1111/j.1600-6143.2004.00594.x

# Predicted Lifetimes for Adult and Pediatric Split Liver Versus Adult Whole Liver Transplant Recipients

**Robert M. Merion[a,b,*], Sarah H. Rush[b,c], Dawn M. Dykstra[b,c], Nathan Goodrich[b,c], Richard B. Freeman, Jr.[d] and Robert A. Wolfe[b,e]**

[a] *Department of Surgery, University of Michigan, Ann Arbor, Michigan, USA*
[b] *Scientific Registry of Transplant Recipients, Ann Arbor, Michigan, USA*
[c] *University Renal Research and Education Association, Ann Arbor, Michigan, USA*
[d] *Tufts-New England Medical Center, Boston, Massachusetts, USA*
[e] *Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA*
**Corresponding author: Robert M. Merion, merionb@umich.edu*

**Split liver transplantation allows 2 recipients to receive transplants from one organ. Comparisons of predicted lifetimes for two alternatives (split liver for an adult and pediatric recipient vs. whole liver for an adult recipient) can help guide the use of donor livers. We analyzed mortality risk for 48 888 waitlisted candidates, 907 split and 21 913 whole deceased donor liver transplant recipients between January 1, 1995 and February 26, 2002. Cox regression models for pediatric and adult patients assessed average relative wait list and post-transplant death risks, for split liver recipients. Life years gained compared with remaining on the waiting list over a 2-year period were calculated. Seventy-six splits (152 recipients) and 24 re-transplants resulted from every 100 livers (13.1% [adult] and 18.0% [pediatric] 2-year re-transplant rates, respectively). Whole livers used for 93 adults also utilized 100 livers (re-transplant rate 7.0%). Eleven extra life years and 59 incremental recipients accrued from each 100 livers used for split compared with whole organ transplants. Split liver transplantation could provide enough organs to satisfy the entire current demand for pediatric donor livers in the United States, provide more aggregate years of life than whole organ transplants and result in larger numbers of recipients.**

**Received 9 March 2004, revised and accepted for publication 21 June 2004**

## Introduction

The first successful liver transplant procedures were performed in the 1960s in small children with biliary atresia (1,2). Since that time, liver transplantation has matured into an accepted, and in many cases preferred, therapy for a wide range of irreversible and previously fatal acute and chronic hepatic diseases. By the 1980s, the shortage of donor organs, particularly for small children, led to unacceptably high waiting list mortality for children and spurred the development of surgical techniques to transplant a portion of an adult deceased donor liver into a child (3,4). In this procedure, termed partial or reduced size liver transplantation, the left lateral segment or left lobe of the donor liver is used, and the remaining hepatic parenchyma is discarded. By 1993, several reports appeared describing techniques of split liver transplantation (5–8). The application of split liver transplantation increases the donor pool for all patients on the liver transplant waiting list by giving a partial graft to 2 patients instead of a whole organ to 1 adult or a partial graft to 1 child. However, consensus exists that livers can be split only from donors who are relatively young, hemodynamically stable and functionally normal. As a result SRTR data show that split livers account for only 3% of all liver transplants done in the United States.

Although concerns about outcomes for split liver grafts were raised (9,10), favorable reports from single centers have been published (11–16). Most studies demonstrated good results for pediatric recipients of the left-sided split grafts, but partial or split liver grafts transplanted into adults had a higher rate of failure, leading to increased need for re-transplantation and potentially higher death rate for recipients (17–19). Since the transplant system must allocate scarce organs to both adults and children, it is critical not only to know the outcomes of whole organ and split transplants for adults but also to understand how split liver transplants affect the outcomes for pediatric candidates on the waiting list. Thus, the aim of this study was to compare predicted lifetimes for the two most common alternatives for the use of a deceased donor liver (split liver for an adult and pediatric recipient vs. whole liver for an adult) to help determine the best use of the limited supply of available organs.

## Methods

### *Data sources*

This study used data from the Scientific Registry of Transplant Recipients (SRTR) regarding access to transplantation, waiting list mortality and post-transplant graft and patient survival among all listed candidates and

transplant recipients in the United States, as submitted by the members of the Organ Procurement and Transplantation Network and supplemented by mortality information from the Social Security Death Master File (20).

***Study population***

The study cohort included 48 888 patients with an initial waiting list registration for deceased donor liver transplantation between January 1, 1995 and February 26, 2002. The accrual end date was chosen to correspond with the initiation of MELD-based deceased donor liver allocation. Patients were followed to the earliest of death, loss to follow-up or the end of the observation period on December 1, 2002. Patient follow-up was also censored in the event of living donor liver transplant, since the underlying objective of the analysis related to determining the benefit of alternative forms of deceased donor liver transplantation. Patients' with missing data on age, sex or race were excluded from all analyses (n = 86; 0.1%).

***Analytic approach***

To determine the donor characteristics significantly associated with the use of deceased donor organs for split liver transplantation, a logistic regression model was fitted using available donor demographic, biologic, hemodynamic and pathologic data.

To assess the relative transplant benefit between recipients of deceased donor split livers and recipients of whole livers, the risk of mortality for each group was compared with the mortality risk while on the liver transplant waiting list. The risk of mortality was analyzed using Cox regression models adjusted for recipient age, sex, race and medical urgency status. Separate models of time to death were developed for 907 split (471 pediatric and 436 adult) and 21 913 adult whole cadaveric liver recipients, as well as for 48 888 candidates placed on the waiting list during the study timeframe. Candidates on the waiting list and transplant recipients were restricted to 73 centers that performed at least one split liver transplant during the study period. Follow-up observations in the wait list survival models were censored at either the end of study on December 1, 2002 or at removal from the waiting list, whichever occurred earlier. For the post-transplant mortality models, patients were censored at either the end of study on December 1, 2002 or at the end of their expected date of last follow-up, whichever occurred earlier. Pediatric and adult patients were modeled separately using all patients, and these models were used to predict all wait list and post-transplant survival estimates for the split liver recipients (adult or pedialic) according to their age, sex, race and medical urgency status.

The predicted lifetime gained from transplantation compared with remaining on the waiting list, defined as the difference in the area under the survival curves over a 2-year period, for pediatric split, adult split and adult whole liver recipients was estimated using results from the Cox regression models described above. In addition, rates of re-transplantation during the 2-year post-transplant period were also calculated for pediatric split, adult split and adult whole liver recipients using Cox regression models of time to graft failure. The survival benefit of using donor livers for pediatric and adult split transplant recipients was compared with that of adult whole liver transplants by estimating the life years gained for each type of transplant and averaging the results. For splits, it was assumed that a pediatric and an adult candidate received a liver transplant from each split organ. For whole organ transplants, it was assumed that an adult received a whole organ allograft. In both cases, observed re-transplant rates were used to adjust the number of recipients projected to receive transplants, using whole organs for re-transplants.

In order to assess the potential aggregate effect of split liver transplantation on projected lifetimes across the entire transplant system, we estimated the number of donor livers suitable for use as a split transplant in the United States from whole liver transplants that occurred between January 1, 1995 and December 31, 2002. The following donor characteristics, developed by a subcommittee of the Organ Procurement and Transplantation Network Pediatric Committee, were used to exclude liver donors from the suitable for split category: donor age <10 or >40 years, history of cancer or insulin-dependent diabetes mellitus, presence of infection with human immunodeficiency virus, hepatitis C virus, hepatitis B virus, use of both dopamine and dobutamine, serum bilirubin >3 mg/dL, SGOT/AST, and SGPT/ALT > 150 IU/L, cardiac arrest after neurologic event leading to brain death and serum sodium >170 mEq/L (21). Livers were considered suitable for splitting even if there were missing values for some variables. This resulted in a maximum estimate for the number of livers that could be split. The average number of livers/year that met the split criteria was multiplied by the estimated number of net life years gained by splitting donor livers to obtain an estimate for the maximum potential net gain in life years that could result from splitting all suitable livers.

## Results

Characteristics of the study population are shown in Table 1. The proportion of females was higher among adult split liver recipients than among adult whole organ recipients and liver transplant candidates. This may reflect decisions made about the required mass of hepatic parenchyma and is supported by findings regarding recipient body mass index (BMI, Table 1). As expected, medical urgency status was higher at transplant than at listing. The distribution of categories of underlying hepatic diagnosis did not differ markedly between candidates and recipients or between split and whole organ recipients.

Among 23 996 donor livers used for transplantation between 1995 and 2002, 533 were split (Figure 1). Donors aged 10–39 years comprised 81.6% of split livers and 48.5% of livers used for whole organ transplants. Only 11.8% of livers that were split were from donors who were 40 years and older, compared with 42.1% of livers used for whole organ transplant. Obese (BMI >30 kg/m$^2$) donors accounted for 8.1% of split livers and 16.9% of whole livers. A number of factors were significantly associated with use or non-use of a donor liver for a split transplant in the logistic regression model. When compared with donors aged 10–39 years, livers from younger (<10 years) and older (≥40 years) donors were significantly less likely to be split (Table 2). Donors who were underweight (BMI <20 kg/m$^2$) and overweight or obese (BMI >25 kg/m$^2$) had a 46–76% lower likelihood of being split compared with donors with normal BMI ($p < 0.02$ for comparison with overweight; $p < 0.01$ for comparisons with underweight and obese). Donor livers from males were nearly 30% more likely to be split than those from females ($p < 0.02$), even after adjustment for BMI. Livers from Hispanic donors were also significantly more likely to be split than those from non-Hispanics ($p < 0.001$).

Survival curves from the Cox models for pediatric liver transplant candidates and split recipients are shown in Figure 2; survival curves for adult candidates, whole organ recipients and split recipients are shown in Figure 3. These curves for the average patient graphically display

**Table 1:** Characteristics of the study population

| Patient characteristic | Split liver recipients | | Whole liver recipients | Liver transplant candidates | |
|---|---|---|---|---|---|
| | Adult (n = 436) | Pediatric (n = 471) | Adult (n = 21 913) | Adult (n = 43 749) | Pediatric (n = 5139) |
| Age (years) | 50.5 | 3.8 | 50.4 | 50.1 | 4.7 |
| Sex | | | | | |
| Male (%) | 49.8 | 45.4 | 61.6 | 60.1 | 48.9 |
| Female (%) | 50.2 | 54.6 | 38.4 | 39.9 | 51.1 |
| Race | | | | | |
| Caucasian (%) | 83.7 | 74.1 | 86.7 | 86.0 | 74.8 |
| African American (%) | 7.3 | 17.6 | 7.5 | 7.5 | 18.1 |
| Asian (%) | 6.4 | 3.4 | 3.5 | 4.2 | 4.1 |
| Others (%) | 2.5 | 4.5 | 2.3 | 2.3 | 2.8 |
| Hispanic (%) | 22.2 | 26.3 | 11.2 | 12.7 | 17.4 |
| BMI | | | | | |
| 0–19 (%) | 10.3 | 60.3 | 5.5 | 4.6 | 55.8 |
| 20–24 (%) | 32.6 | 11.3 | 26.4 | 25.1 | 11.0 |
| 25–29 (%) | 27.3 | 2.5 | 29.8 | 30.0 | 3.5 |
| 30+ (%) | 14.4 | 2.8 | 24.3 | 26.8 | 4.5 |
| Missing (%) | 15.4 | 23.1 | 14.0 | 13.6 | 25.2 |
| Urgency status (transplant or listing) | | | | | |
| Status 1 (%) | 13.3 | 48.4 | 12.8 | 4.9 | 19.4 |
| Status 2a (%) | 16.7 | 0.0 | 15.6 | 2.5 | 0.0 |
| Status 2b (%) | 43.8 | 27.8 | 36.0 | 16.6 | 21.0 |
| Status 3 (%) | 22.0 | 17.0 | 25.1 | 63.5 | 46.7 |
| Old status 2 (%) | 3.9 | 5.5 | 9.9 | 4.8 | 7.3 |
| Old status 4 (%) | 0.2 | 0.0 | 0.2 | 6.3 | 3.5 |
| Inactive status (%) | 0.0 | 0.6 | 0.1 | 1.6 | 2.1 |
| Missing status (%) | 0.0 | 0.6 | 0.2 | 0.0 | 0.0 |
| Diagnosis | | | | | |
| Cholestatic (%) | 16.7 | 4.7 | 13.5 | 11.3 | 4.7 |
| Fulminant (%) | 8.7 | 13.8 | 7.3 | 6.5 | 13.8 |
| Non-cholestatic (%) | 62.4 | 5.9 | 68.0 | 72.2 | 9.5 |
| Biliary atresia (%) | 0.2 | 47.1 | 0.2 | 0.2 | 33.1 |
| Metabolic diseases (%) | 3.4 | 10.4 | 3.3 | 2.1 | 8.9 |
| Malignancy (%) | 5.1 | 3.0 | 3.3 | 1.7 | 3.2 |
| Others (%) | 3.4 | 15.1 | 4.4 | 6.1 | 26.9 |

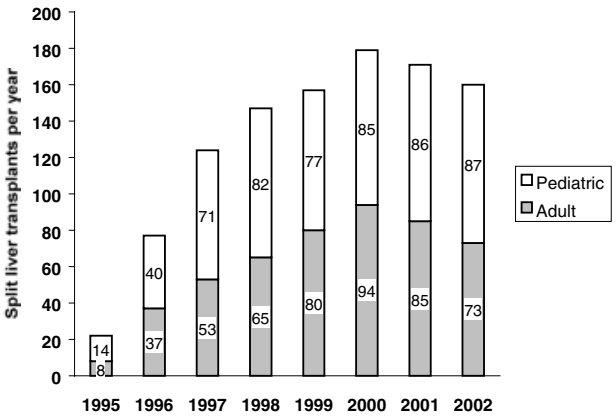


**Figure 1: Adult and pediatric split liver transplant recipients by year 1995–2002.**

how the actual results were obtained for each individual patient. Compared with candidates on the waiting list, adult whole organ transplant recipients gained an average of 5.8 months of extra life during the first 2 post-transplant years (Table 3). The alternative, where the liver was split, resulted in 8.9 months of extra life—5.2 months of extra life for the adult recipient and 3.7 months for the pediatric recipient. The re-transplant rate for split recipients was about twice as high as that for whole organ recipients.

For every 100 donor livers suitable to use for split transplants, 76 could be split for 152 recipients and 24 would be required for re-transplants. Whole organ grafts could be provided to 93 adult recipients, 7 of whom would require re-transplant. Applying the extra life years gained by each recipient type to the number of transplanted recipients yields a predicted aggregate total of 56 extra life years for split recipients and 45 for whole organ recipients. Thus, split liver transplantation results in 11 extra life years and 59 additional patients transplanted per 100 donor livers.

The average number of donor livers/year that met the split criteria during the time period of the analysis was 1532. This number represents the average incremental number of livers available to be split in addition to those already used for split liver transplants. The predicted maximum number of life years gained during the first 2 years

**Table 2:** Adjusted odds ratio (AOR) split transplant use from 23 996 liver donors (from January 1, 1995 to December 31, 2002)*

| Donor factor | Frequency (%) or mean | AOR | 95% lower confidence limit | 95% upper confidence limit | p-value |
|---|---|---|---|---|---|
| Age | | | | | |
| <10 years | 2243 (9.4) | 0.48 | 0.33 | 0.71 | 0.0002 |
| 10–39 years (Reference) | 11806 (49.2) | 1.00 | | | Ref. |
| 40–49 years | 3866 (16.1) | 0.38 | 0.27 | 0.53 | <0.0001 |
| 50–59 years | 3275 (13.7) | 0.16 | 0.09 | 0.27 | <0.0001 |
| 60+ years | 2806 (11.7) | 0.02 | 0.01 | 0.09 | <0.0001 |
| Male (vs. female) | 14205 (59.2) | 1.29 | 1.055 | 1.58 | 0.0131 |
| Hispanic (vs. non-Hispanic) | 2625 (10.9) | 1.51 | 1.20 | 1.91 | 0.0005 |
| BMI | | | | | |
| 0–19 | 4557 (19.0) | 0.69 | 0.533 | 0.89 | 0.0048 |
| 20–24 (Reference) | 9241 (38.5) | 1.00 | | | Ref. |
| 25–29 | 6205 (25.9) | 0.76 | 0.61 | 0.94 | 0.0132 |
| 30+ | 3993 (16.6) | 0.46 | 0.33 | 0.64 | <0.0001 |
| Biopsy result | | | | | |
| No biopsy (Reference) | 21561 (89.9) | 1.00 | | | Ref. |
| Steatosis 0–19% | 2044 (8.5) | 0.72 | 0.45 | 1.15 | 0.1690 |
| Steatosis 20%+ | 391 (1.6) | 0.17 | 0.02 | 1.24 | 0.0809 |
| Serum creatinine > 1.5 mg/dL | 3660 (15.3) | 0.81 | 0.61 | 1.08 | 0.1452 |

*Donors from 73 centers that performed split liver transplants were used in the analysis. Analysis was adjusted for donor race, cause of death, history of hypertension, alcohol dependency, blood infection, insulin-dependent diabetes mellitus, hepatitis B core antibody status, hepatitis C antibody status, occurrence of cardiac arrest after neurologic injury leading to brain death, use of multiple pressors, bilirubin >3 mg/dL, transaminases >150 IU/L and serum sodium >170 mEq/L. (Ref. = reference group).

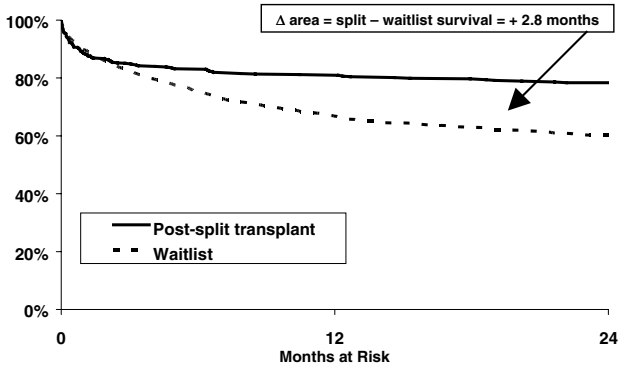


**Figure 2: Patient survival for pediatric split liver recipients versus candidates on the waiting list.** Both sets of survival estimates are adjusted to the average split recipient.

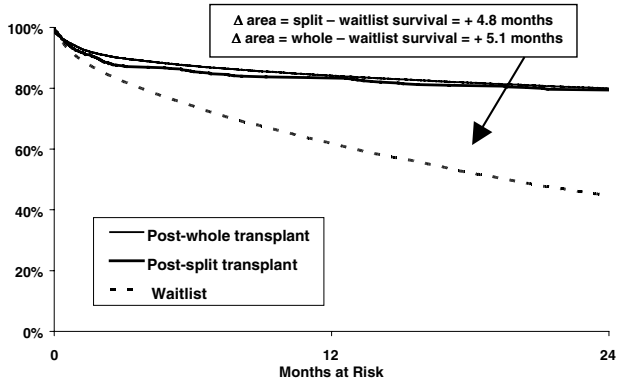


**Figure 3: Patient survival for adult split and whole recipients versus candidates on the waiting list.** All sets of survival estimates are adjusted to the average split recipient.

of follow-up by splitting these livers was 168.5 years (1532 × 11 years per 100 donor livers). However, this estimate assumes that there is a suitable adult and pediatric candidate available for each split liver transplant. In actuality, there are not enough new pediatric listings to equal the number of livers eligible for splitting. For example, during the year ending March 31, 2002, there were 857 children under 18 years added to the liver transplant waiting list. If all these children received a split liver transplant, 94.3 years of extra life would be gained during the first 2 post-transplant years. Using a more realistic age of 11 years for pediatric recipients of a split transplant, such transplants for these 661 candidates added to the waiting list would result in a net gain of 72.7 years of extra life.

## Discussion

The advent of split liver transplantation represents an important technical advance, developed in response to the severe shortage of donor organs for pediatric liver transplant candidates. Most of the surgical issues in split liver transplantation relating to anomalies of the venous and arterial systems of the liver have been solved (19). Despite this, the number of split liver transplants done in the United States has remained stable at around 160/year since 1999 (SRTR data as on July 1, 2003). A variety of issues have contributed to the reluctance about practicing this procedure more widely. Until they are resolved, this technique is unlikely to expand beyond its current use in 3% of deceased donor liver transplants.

**Table 3:** Lifetime gained in first 2 years: split and whole transplant versus waiting list

| | Recipient type | | |
|---|---|---|---|
| | Adult split | Pediatric split | Adult whole organ |
| Lifetime gained versus waiting list per recipient (months) | 5.2 | 3.7 | 5.8 |
| 2-year re-transplant rate(%) | 13.1 | 18.0 | 7.0 |
| Organ usage per 100 donor livers | | | |
| Primary transplant | 76 split | 76 split | 93 whole |
| Re-transplant | 10 whole | 14 whole | 7 whole |
| Aggregate lifetime gained versus waiting list per 100 donor livers (years) | | Split | Whole |
| Adult | | 33 | 45 |
| Pediatric | | 23 | 0 |
| Total | | 56 | 45 |

Our results indicate that split liver transplantation results in a net gain in life years and a larger number of successfully transplanted recipients using the existing supply of donor livers, even after accounting for the higher rate of re-transplantation and death associated with these procedures. The potential annual net gain in life years could be as high as 169 patient-years in the first 2 post-transplant years, if all livers meeting suitability criteria were used for split liver transplants. Put another way, for every 100 donor livers, 11 extra years of life are predicted over the first 2 years of follow-up if the organs are split rather than transplanted whole.

Thus, with 100 livers, 152 patients can be transplanted (76 each for pediatric and adult recipients, plus required re-transplants) compared with 93 adult whole organ recipients (plus required re-transplants). However, the number of available pediatric candidates limits the number of split liver transplants that could be performed. The analysis also assumes that the transplant survival benefit at the individual patient level would be the same for each incremental patient transplanted with a split liver. This assumption may not be completely valid, because a higher transplant rate due to more available split grafts might result in transplantation of candidates at lower risk of death on the waiting list. Alternatively, use of split livers for higher-risk candidates could result in more post-transplant deaths. In addition, the overall benefit of split liver transplantation might be somewhat diminished if waiting list mortality were to decrease, as has been suggested to occur with the implementation of organ allocation policies based on more accurate assessment of waiting list mortality under the MELD/PELD system. Finally, failure to successfully utilize both portions of each potentially suitable donor liver would result in a slight reduction of the overall predicted number of transplanted patients and the corresponding calculated survival benefit.

Since adult split liver recipients have a reduced post-transplant lifetime with a functioning graft compared with whole organ recipients, the split transplant option is understandably unattractive to patients. However, the increased lifetime compared with the waiting list for children who receive a split liver graft more than makes up for this deficit, resulting in an overall net benefit and leading to a divergence between societal and individual goals (22). Resolution of this ethical issue remains an important objective.

Current national allocation policy does not specify the initial fate of a donated liver that may be suitable for use as a split transplant. The use of an organ for whole or split liver transplantation into the designated candidate is left to the discretion of the transplant team and transplant candidate. Depending on the practice of the transplant center and the local organ procurement organization, in some cases a candidate may elect to receive the split transplant or decline that particular offer, but not insist on the use of the donated liver as a whole organ. In other cases, the candidate might be given the option to choose to have the whole liver transplanted and decline the request to allow a segment or lobe to be used for a pediatric candidate. In contrast, orderly allocation of the remaining segment or lobe, if available, to a pediatric candidate is governed by national policy (23). These policies suggest that the process of informed consent for potential liver transplant candidates should include discussion of the possibility of split liver transplant.

Certain adult candidates may not be well suited to receive a split liver transplant. We found that adult recipients of split liver transplants who were male, African American or listed as status 1 had significantly higher adjusted risks of graft failure or death compared with females, non-African Americans and less urgent patients, respectively (data not shown). This is consistent with previous observations of poor outcomes when split transplants were done in patients at high risk or under urgent circumstances (24,25). With better recipient selection criteria, the deficit in outcome for adult recipients of split transplants may be ameliorated, making the procedure more palatable to patients and caregivers.

Similar issues hold for pediatric candidates. Our data suggest a significant survival benefit for pediatric recipients of split transplants compared with children on the waiting list. The potential alternative of living donor liver transplantation exists for children, and Roberts et al. have recently reported that children <2 years of age had significantly lower mortality risk with a living donor graft compared with split or whole grafts from deceased donors (26). In contrast, children 2–10 years old had worse survival after living donor grafts. Adolescents had significantly worse graft survival with living donor grafts than either type of deceased donor graft, but mortality risk was similar among the three groups. Decisions about the best graft type for a young child must therefore take age and availability of a living donor into consideration.

Finally, the criteria by which to judge whether a given donor liver is suitable for use as a split organ are open to interpretation. Livers were considered to be feasible for use as a split transplant by Toso et al. (27) when the following donor criteria were met: age between 14 and 50 years; body weight >45 kg and BMI <27 kg/m$^2$; maximum intensive care unit length of stay of 3 days; mean arterial pressure at least 60 mmHg; serum sodium no higher than 160 mEq/L; SGPT no higher than 60 IU/L; gamma-glutamyl transpeptidase no higher than 50 IU/L and no steatosis on pre-procurement ultrasound. We used similar criteria (21) for the current study and found that these criteria were usually but not always adhered to in the selection of split donors. Additional, studies defining donor characteristics that are favorable for use as a split graft are clearly needed.

## Acknowledgments

Presented in part at the American Transplant Congress, May 2003, Washington, DC. Supported by contract number 231-00-0116 from the Health Resources and Services Administration, U.S. Department of Health and Human Services.

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