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Epidemiological study of survival after liver transplant from a living donor

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Summary

The safety and success of solid organ transplants from living donors are critical issues in the overall decisional process; we are reporting here mortality outcome data collected from a single center. A cohort of 154 subjects who received a liver transplant from a living donor between 2001 and 2006 was retrospectively assembled at the University of Pittsburgh Transplant Center. The average follow up after transplant was 22.9 ± 18.5 months. During this time, 25 subjects died, contributing to an overall survival rate of 84%, similar to that reported by other studies on liver transplant from living donors. A multivariate analysis of the factors affecting survival did not identify any significant predictor of death. The study supports the safety of living liver transplants; larger collaborative studies that include detailed information on both recipients and donors, as well as the study of biological predictors of outcome are needed in order to continue monitoring the success of this approach.

Introduction

The utilization of living liver donors has become an accepted procedure in recent years in order to avoid long waiting-list times for urgent cases; however, this approach is not a very common choice in US and Western Europe, where it comprises roughly only 10% of the overall transplants [1].

Several studies have shown how living liver transplant may decrease the overall recipient mortality by shortening the time on the waiting list and by increasing the pool of potential donors [2]. However, concerns still remain on the overall safety for the donors and the possible negative outcome for the recipients [3]. Studies conducted in centers performing living liver transplants on a routine basis have evaluated both the graft- and the patients' survival, with contrasting results. Overall, the patient survival is reported by some authors [1,4,5], but not others [6–8] to be similar to what is observed in liver transplants performed with organs from deceased donors. Reasons for these discrepancies could lie in the selection of the recipients and/or of the donors, the indication for transplant, the length of the follow up, or differences in clinical/surgical management of the case. Often, the small sample size and the lack of appropriate statistical analysis hamper the possibility to draw firm conclusions on the safety of a transplant from a living donor.

The safety of the procedure and the recipient outcome are critical issues in the overall decisional process; the risks and benefits of waiting for an appropriate cadaveric donor versus undergoing a living transplant, thus exposing a living person to the donation process, have to be carefully considered before a strategy is put forward to the patient and his/her family. We are reporting here the data collected from a single center, in order to contribute further data on mortality after liver transplant from a living donor.

Material and methods

A cohort of subjects who received a liver transplant from a living donor between 2001 and 2006 was retrospectively assembled at the University of Pittsburgh Transplant Center, where a clinical electronic data base is in place with

all the demographic characteristics of the donors and the recipients, as well as follow-up information.

Anonymous information on demographics of the liver recipients from living donors (gender, ethnicity, age at transplant, smoking status) the pathology underlying the need for a transplant and the cause of death for patients who were deceased were extracted from the data set for this study.

Information on patients' follow up included the date of their last clinical visit, or the date of death or the date of loss at follow up, whichever came first. All patients have signed an informed consent to be included in a research registry at the time of transplant.

Demographics of the living donors, as well as on their post-surgery short- and long-term complications, were also available from the same data set.

Statistical analysis

Categorical data are presented as frequencies, continuous variables as means and standard deviations. The statistical endpoint for survival analysis was death, while the time frame for this analysis was from the date of liver transplant to the date of death or date of current status. Cross tabulations were created to identify relationships between variables via 2×2 tables.

Pearson Chi-squared test was used to test for the significance of the relationship between variables associated with death. The product-limit method based on actual survival times (Kaplan–Meier plots) was used to study the determinants of survival. Univariate and multivariate hazard ratios with confidence intervals were calculated using maximum-likelihood proportional hazard models. This analysis allows the independent contribution of several factors (age of the donor, age of the recipient, gender match, diagnosis at transplant etc) to the risk of death. Continuous variables were categorized according to the median value of the population when the multivariate model was run. All statistical analyses were done using Intercooled Stata (Version 8.2; Stata Corp LP, College Station, TX, USA).

Results

The cohort consisted of 154 liver transplants from living donors; half of the recipients were male subjects, mostly Caucasians; mean age at transplant was 51.2 ± 13.9 years. Subjects underwent a liver transplant for several underlying pathologies that are summarized in Table 1. The most common cause for the transplant was autoimmune cirrhosis, followed by cirrhosis of viral origin. Five percent of the subjects underwent a living liver transplant for liver cancer. Gender match between donor and recipient was observed in 52% of the transplants.

Table 1. General characteristics of the transplanted patients under study.

Variable	*n*	%
Gender		
Female	84	54.6
Male	70	45.4
Ethnicity		
Caucasian	146	94.8
African–American	5	3.3
Latin	2	1.3
Pacific Islander	1	0.6
Diagnosis at transplant		
Autoimmune	44	28.6
Viral	41	26.6
ETOH	16	10.4
NASH	15	9.7
Congenital	10	6.5
Neoplasia (benign and malignant)	9	5.8
Cryptogenic	8	5.2
Other*	11	7.1
Gender match		
Donor and recipient female	46	29.9
Donor and recipient male	34	22.1
Donor female/recipient male	36	23.4
Donor male/recipient female	38	24.6
	Mean	SD
Age (years)	51.2	13.9
Weight (kg)	76.5	17.0
Height (cm)	168.8	10.2
Length of follow up (months)	22.9	18.5
MELD score	13.6	5.6

*Includes α-1 antitrypsin deficiency (five cases), oxalosis (three cases), hemochromatosis (one case), hepatic arterial thrombosis (one case), unknown (one case).

The average follow up after transplant was 22.9 ± 18.5 months. During this time, 25 subjects died (16.2%), while 83.8% of the population was still alive at the end of the follow up; the causes of death are reported in Table 2. The most frequent cause of death was major cardiovascular problems, followed by graft failure/rejection. In three cases (12% of the deceased) cancer recurrence was the cause of death. The average time from the transplant to death for each cause of death is also reported in Table 2. Earlier deaths were attributable to Adult respiratory distress syndrome (ARDS), hepatic artery problems and sepsis. The main circumstances that led to multiple organ failure were severe infections (three cases) and failure to thrive (one case), to cardiovascular death were intraoperatory cardiac arrest (two cases), massive myocardial infarction (two cases) and a cardiac arrest while waiting for re-transplant (one case).

Table 2. Cause of death in living liver transplanted.

Cause of death	*n* (25)	% of deaths	Average time from transplant (months)
ARDS	1	4	0.33
Cardiovascular, IMA, cardiac arrest*	5	20	15.89
Cerebral anoxia	1	4	3.77
Graft failure, rejection	4	16	17.66
Malignancy, recurrent, and hepatocarcinoma	3	12	28.33
Multiple organ failure	4	16	14.18
Sepsis	3	12	1.98
Withdrawal from dialysis	1	4	36.6
Hepatic artery problem	2	8	1.0
Respiratory failure	1	4	2.17

*Two events were intra operative and were excluded from the calculation of time from transplant to event.

The biliary complication rate in the recipients after transplant was 35%.

Donors

The donors' characteristics are reported in Table 3. Donors were significantly younger than their organ recipients, but similar in gender and ethnicity; anthropometric measurements were also overlapping between donors and recipients. Roughly one-third (29.8%) of the donors were not biologically related to the recipient.

In 16 subjects (10.4%) a complication requiring medical assistance was recorded: one donor experienced deep venous thrombosis with pulmonary embolism, six subjects had pleural effusion/pulmonary insufficiency, eight had infections requiring antibiotic treatment, one had a transient diabetes episode requiring insulin treatment.

Table 3. General characteristics of the living donors.

Variable	*n*	%
Gender		
Males	72	46.7
Females	82	53.3
Ethnicity		
Caucasian	149	97.7
African–American	4	2.7
Latino	1	0.6
Relation with recipient		
Son/daughter	62	40.3
Sister/brother	34	22.1
Mother/father	8	5.2
Other relative – non 1st degree	7	4.5
Husband	4	2.6
Friend	39	25.3
	Mean	SD
Age (years)	37.7	11.2
Weight (kg)	78.5	15.8
Height (cm)	171.4	10.5

Table 4. Association between main outcome (patient death) and characteristics of the donors and the recipients.

Variable	Patients alive at the end of follow-up (*n* = 129)	Patients who died during the follow-up (*n* = 25)	*P*-value
Follow up months	24.99 ± 18.47	12.37 ± 15.21	0.0007
Age of donor (years)	37.41 ± 11.16	39.52 ± 11.69	n.s.
Age of patient (years)	50.62 ± 14.12	54.32 ± 12.45	n.s.
Donor weight (kg)	79.27 ± 16.49	74.81 ± 11.21	n.s.
Donor height (cm)	171.68 ± 10.45	169.96 ± 10.73	n.s.
Patient weight (kg)	75.98 ± 17.47	79.15 ± 14.6	n.s.
Patient height (cm)	168.27 ± 10.37	171.56 ± 9.02	n.s.
MELD score	13.67 ± 5.31	12.92 ± 6.7	n.s.
Patient/donor match	%	%	χ^2
F/F	31.0	24.0	
M/M	22.5	20.0	
F/M	20.1	40.0	
M/F	26.4	16.0	n.s.
Consanguinity	67.4	68.0	n.s

Survival analysis

Table 4 reports the association between the main outcome (death) and some of the characteristics of both the donors and the recipients. There were no significant differences in such characteristics between the subjects who were alive at the end of the follow up, and subjects who died, other than, as expected, the average length of the follow up.

The 2-year patient survival rate was 85%, the 3-year survival rate was 80%. Very few subjects ($n = 54$) had a follow up that was longer than 3 years. Univariate analyses according to gender (Fig. 1), donor/recipient gender match (Fig. 2) or consanguinity (Fig 3) did not show any association between these variables and patients survival. A multivariate analysis of the factors affecting survival (Table 5) did not identify any predictor of survival among the variables simultaneously considered: age of the recipient and of the donor, gender matching, ethnicity, Body Mass Index, consanguinity of the donor.

Discussion

This study reports overall mortality in a large cohort of liver transplants from living donors collected in a single US institution. The results indicate that living liver transplants achieve similar survival rates to transplants performed with

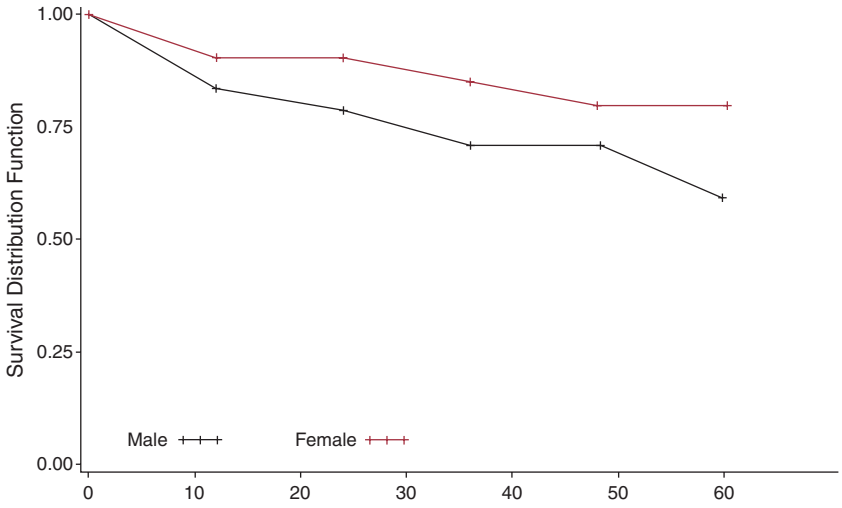

Figure 1 Five year patient survival according to gender – liver transplants from a living donor.

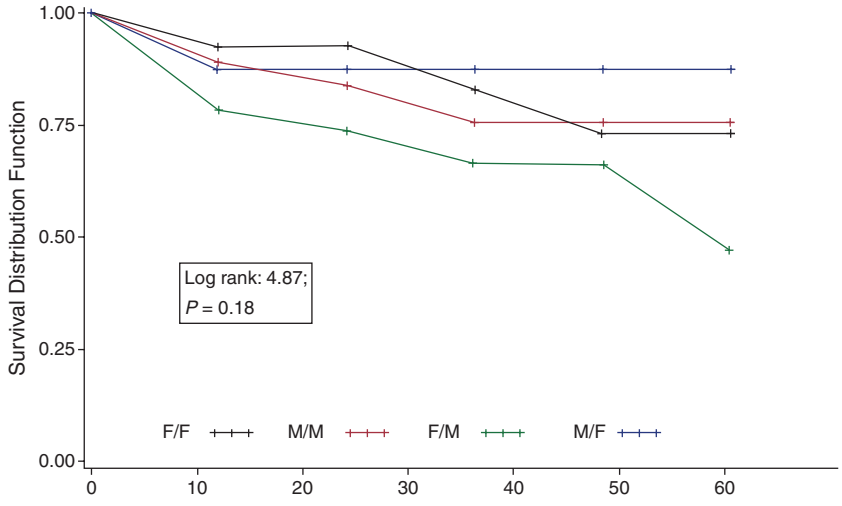

Figure 2 Five year patient survival according to donor/recipient match – liver transplants from a living donor.

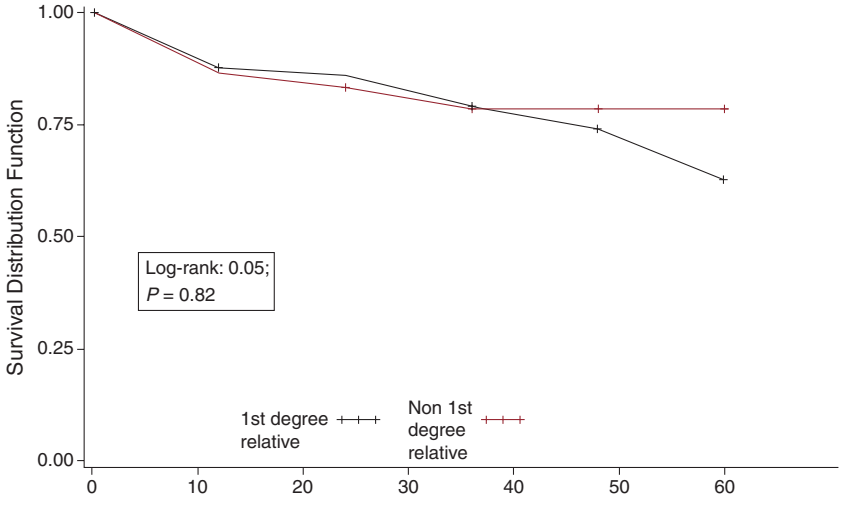

Figure 3 Five year patient survival according to donors' relation to the recipient – liver transplants from a living donor.

Table 5. Multivariate survival analysis – association between main outcome (patient death) and characteristics of the donors and the recipients.

Variable	χ^2	*P*-value	HR (95% CI)
Patient/donor match	0.0102	0.92	0.98 (0.70–1.39)
Consanguinity (no/yes)	0.0061	0.94	0.97 (0.41–2.28)
Diagnosis	0.4186	0.52	1.06 (0.89–1.26)
Donor age (>37.5/≤37.5 year)	0.3907	0.53	1.31 (0.56–3.03)
Patient age (>53/≤53 years)	1.8297	0.18	1.75 (0.78–3.93)
Patient BMI (>26/≤26 kg/m^2)	0.1879	0.66	1.20 (0.53–2.72)
Donor BMI (>26/≤26 kg/m^2)	0.2662	0.61	0.81 (0.36–1.82)
MELD score (>12/≤12)	1.3550	0.24	0.62 (0.27–1.39)

livers from cadaveric donors. The observed mortality rates are also similar to that reported by other studies on liver transplant from living donors [1,4,5]. The UNOS website indicates a 3-year survival rate of 82% in patients receiving a liver from a living donor (http://www.unos.org). In our study, a small proportion of subjects had a follow up that was longer than 3 years. Therefore survival rates after that time should be evaluated with caution.

We observed causes of death similar to those reported by large multicentric studies on liver transplant from cadaveric donors. For example, the report of the European Liver Transplant Registry reported cardiovascular causes of death as 25% of the total mortality, and multiple organ failure to account for 22% of the deaths, similar to what we are indicating in this study in liver transplant from living donors [9].

The average MELD score reported in our population is similar to the one reported by a recent review [2]; MELD score did not reveal any correlation to survival in our study as also in the published report [2].

Biliary complications are amongst the main causes of graft loss. Their etiology is multifactorial, and includes the age and gender of the recipient, the severity of the original disease, some of the techniques used for reconstruction, and ABO blood-type incompatibility. In this study, such complications were significantly higher than what was observed in liver transplants from cadaveric donors [10]. In a recent review [11], a summary of biliary complication recorded by other centers performing living liver transplant is included. We computed a weighted average of the individual data, and found that overall the rate of biliary complications is 30.4% on 298 transplants, a value very similar to what we have found in our study and to that was reported in a recent review [1].

The completeness of the database allowed the study of the independent contribution of several donors' and recipients' characteristics to the long-term transplant outcome, such as their age, weight and height, gender matching, and degree of consanguinity, ethnicity. However, none of these variables resulted to be significantly independent predictors of survival.

Strengths of our study are the large sample size gathered from a single institution, the detailed epidemiological information available for both the donor and the recipient, the availability of the follow up and its completeness, the standardization of data collection within the institution, the availability of clinical information on the whole cohort. This allowed us to conduct a sophisticated multivariate analysis to disentangle the independent prognostic factors contributing to the overall mortality after transplant in this population.

One possible limitation is the lack of a longer follow up for these patients, because of the fact that transplants from living donors became an integral part of surgical practice only recently; however, the active follow up and records of all the outcomes are now in place and will be the basis for continuing the assessment of the overall safety of the procedure in the subsequent years.

In conclusion, our study supports the safety of living liver transplants; despite the important psychological burden imposed on the living donor, the risk associated with this approach seems to be partially justified by the high risk of dying while waiting for a cadaveric donor [2]. Larger collaborative studies that include detailed information on both recipients and donors, as well as the study of biological predictors of outcome are needed in order to continue monitoring the success of this approach.

Authorship

ET: analyzed data and wrote the manuscript. WM: recruited the patients, completed the follow-up and contributed to manuscript writing.

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