Analysis of Marginal Donor Parameters in Liver Transplantation for Primary Biliary Cirrhosis

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The shortage in cadaveric donor livers is pushing the transplant centers to expand the pool by using "marginal" donors. Primary biliary cirrhosis (PBC) remains an important indication for transplantation. We conducted a retrospective analysis of prospectively collected data in a well-defined group of patients with PBC where 301 consecutive donor-PBC recipient pairs transplanted were analyzed to identify donor and operative factors influencing recipient outcome. Mean follow-up was 56 months.

The 1-, 3- and 5-year actuarial patient and graft survival was 93.97%, 90.64%, and 81.75%, and 85.49%, 82.57%, and 75.21%, respectively. Factors showing influence in decreased total patient survival were recipient old age (*P* = 0.003) and low recipient albumin (*P* = 0.01). However, the only variables showing an association with decreased patient survival within 90 days are old donor age (*P* = 0.002) and high donor body weight (*P* = 0.03) or high body mass index (BMI) (*P* = 0.055). Cold ischaemic time (CIT) of 18 hours showed statistical significance in patient survival (*P* = 0.025). Obesity did have a significant adverse impact on survival compared with normal or overweight donors (BMI < 30), decreasing survival by 50% at 5 years.

In conclusion, this study of several factors considered "marginal" for transplantation in a recipient population with predictable liver disease (PBC), donor BMI and age were shown to be associated with decreased graft and patient survival.

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The growth in cadaveric donor liver transplantation has been limited by the shortage of available donor organs resulting in a significant imbalance between organ availability and demand. This shortage results in transplant centers expanding the donor pool by using donor livers previously not considered suitable for transplantation, referred to as "marginal" or "expanded pool" donors.

Although the definition of a marginal donor liver is not clearly defined, several features of the donor and the liver have been used to characterize a marginal liver: these include extremes of age, adverse past medical history, preexisting liver damage or disease (intoxication, deranged liver biochemistry, steatosis, positive hepatitis serology), obesity, haemodynamic instability (hypotension, non–heart-beating donors, high inotrope use), risk of sepsis and malignancy, hypernatraemia, and prolonged intensive therapy unit (ITU) stay [1] have been used over the years to define a marginal donor.

To identify the outcome using marginal livers, earlier studies arbitrarily grouped together biochemical criteria, and several of these demonstrated that primary nonfunction (PNF) rate and overall outcome was satisfactory [2]. However, there remains the need for a validated objective test or group of tests to reliably assess graft function. Several indices of liver function from liver biochemistry to the use of functional tests such as the lignocaine-MEGX excretion test, indocyanine green excretion, arterial ketone body ratio, magnetic resonance spectroscopy, bile acid clearance, though helpful, have not provided conclusive information to justify their routine use in selection of donors.

Primary biliary cirrhosis (PBC) remains an important indication for transplantation. Although

the pathogenesis remains uncertain and the medical therapy, at best, only slows progression of the disease, the natural history is well understood. Timing for orthotopic liver transplantation (OLT) in PBC is probably easier than any other indication, and there are several prognostic models, which have been developed to predict not only survival in the absence of transplantation but also after transplantation [3]. We therefore used a well-defined group of patients with PBC in a retrospective analysis of prospectively collected data of 301 consecutive donor-PBC recipient pairs transplanted in our center to identify donor and operative factors influencing recipient outcome.

Materials and Methods

Between 1982 and 1999, 400 consecutive patients were transplanted for PBC at Queen Elizabeth Hospital, Birmingham. Data were collected from the liver unit database, medical records as well from donor alert sheets. From 400 patients transplanted, data from 301 donor-alert sheets were available, 99 donors were excluded for missing data, and the same number of recipients was excluded to maintain homogeneity of the analysis. Median follow-up was 56 months.

The following donor variables were analyzed:

- **-Demographic:** age, weight (kilogram), height (meters), and body mass index (BMI).
- **-Biochemistry:** serum sodium (mmol/L), creatinine (μmol/L), urea (mmol/L), bilirubin (μmol/L), alkaline phosphatase (U/L), aspartate aminotransferase-AST (U/L), alanine aminotransferase -ALT (U/L), gamma-glutamyl transferase -γ-GT (U/L), prothrombin time -PT (seconds), INR, viral markers (HBsAg, anti-HBc, HCV)
- **-Clinical:** days of hospital admission, days on ventilator (ITU), significant hypotension (2) (systolic pressure less than 80 mm Hg for more than 60 minutes), cardiac or respiratory arrest, inotropes (dopamine, dobutamine, noradrenaline, or adrenaline), urinary output (24 h or last hour). Presence or absence of metabolic acidosis, chest infection, history alcohol excess, drug abuse, bacterial meningitis, acetaminophen overdose, history of untreated hypertension, Von Willebrand's disease.

Body mass index (BMI), defined by weight/(height)^2, where weight is in kilograms and height is in meters. A normal BMI is defined as 18.5 to 24.9 kg/m^2, overweight is from 25.0 to 29.9 kg/m^2, obesity is a BMI of 30.0 to 39.9 kg/m^2, and morbid obesity is a BMI > 40 kg/m^2.

Recipient variables analyzed were:

- -Age, weight (kilograms), height (meters)
- -Bilirubin (μmol/L), albumin (g/L) pre-OLT.
- -Presence or absence of ascites, variceal hemorrhage.
- -ITU and hospital stay (days).
- -Retransplantation

Postoperative immunosuppressive therapy is in detail described elsewhere [3]: initially included cyclosporin A (Sandimmune), which was administered intravenously until the patient was able to take the drug by mouth. The dose of cyclosporin was adjusted to maintain trough whole blood levels, (between 150 and 200 ng/mL in the first three months and 100-150 ng/mL, thereafter). In addition, all patients received prednisolone (20 mg/day, reducing to zero at three months) and azathioprine (1-2 mg/kg/day, according to white cell count). After 1995, the microemulsion formulation of cyclosporin was used (Neoral). Tacrolimus (Prograf) was instituted since the early 1990s for patients unable to tolerate cyclosporin or with late acute allograft rejection. Episodes of acute graft rejection were confirmed histologically and treated with 3 days of high dose steroids (prednisolone 200 mg/day).

Prognostic index (PI) by European Model, published by Christensen [4] for PBC patients were calculated, identifying severely ill patients, and correlated with ITU and hospital stay. Note this model correlates well with the Mayo Clinic Prognostic model for PBC [5]. The former model was chosen as this was based on European patients.

Survival analysis was performed using Kaplan-Meier method (log-rank test). The nonparametric Wilcoxon rank sum test was used to compare median values.

Statistical analysis: Chi-square *t* tests, and Mann-Whitney *U* tests were used to analyze differences in proportions, means and nonparametric distributions, respectively. Survival curves, according with time, in relation with donor/recipient variables were performed by multiple Cox regression analysis. Statistical significance was at $P = 0.05$.

Table 1. Donor factors and risk of death

Features**	Total No.	Median	Range	B	S.E.	Wald	Sig	R	*Exp(B)
Hospital admission	241	2	1-29	- 0.806	0.0562	2.0530	0.1519	-0.0094	0.9226
Ventilation time	296	2	1-18	- 0.0408	0.0619	0.4349	0.5096	0.0	0.9600
Hypotension	252			- 0.1718	0.2639	0.4237	0.5151	0.0	0.8422
Cardiac arrest	223			- 0.1315	0.3269	0.1619	0.6874	0.0	0.8768
Adrenalin/noradrenalin	250			- 0.1944	0.3164	0.3775	0.5390	0.0	0.8233
Chest infection	247			0.1395	0.3080	0.2051	0.6506	0.0	1.1497
Bacterial meningitis	182			3.0406	4.5240	0.4517	0.5015	0.0	20.9175
Alcohol intake	150			- 0.4157	0.3839	1.1729	0.2788	0.0	0.6599
Drug abuse	52			3.1843	3.9920	0.6363	0.4251	0.0	24.15
Nontreatment of hypertension	249			0.0941	0.7200	0.0171	0.8960	0.0	1.0987
Age	297	38	9-70	0.0160	0.0082	3.8149	0.0508	0.050	1.0161
ALT	122	26	4-344	8.155	0.0027	0.0896	0.7647	0.0	1.0008
ALP	250	75	4-352	-3.990	0.0020	0.0413	0.8390	0.0	0.9996
AST	200	33	3-963	- 0.0013	0.0023	0.3123	0.5763	0.0	0.9987
Bilirubin	261	12	3-188	0.0073	0.0059	1.5458	0.2138	0.0	1.0074
Creatinine	272	91	1-705	0.0010	0.0018	0.3447	0.5572	0.0	1.0010
GGT	97	22	4-318	- 0.0013	0.0054	0.0611	0.8048	0.0	0.9987
Hyponatremia (Na)	285	147	126-175	0.2039	0.7190	0.0804	0.7767	0.0	1.2262
Hypernatremia (Na)	286			0.0707	0.2654	0.0710	0.7899	0.0	1.0733
INR	23	1.2	0.9-2.4	-1.8083	1.7456	1.0732	0.3002	0.0	0.1639
PT	18	15	10-29	- 0.0033	0.1205	0.0008	0.9780	0.0	0.9967
Urea	292	5	0.6-38.8	- 0.0212	0.0360	0.3467	0.5560	0.0	0.9790
Urinary volume/hour	268	143.75	5.17-400	- 6.8300	0.0016	0.0018	0.9662	0.0	0.9999
BMI	240	23.629	14-40.15	0.0055	0.0386	0.0203	0.8867	0.0	1.0055

***Exp(B):** e (2.718) raised to the value of the regression coefficient **R:** R squared-coefficient of determination **Sig:** observed significance level **S.E.:** standard error
** Normal range: creatinin (50-120μmol/L), urea (3.0-8.0 μmol/L), sodium (134-146 mEq/L), bilirubin (3-17 mmol/L), ALT (5-35 U/L), AST (5-40 U/L), GGT (9-40), PT (16/16 secs), AP (35-130 U/L), INR (1.0), PO_2 (12-14 KPa), urinary volume (3-5 mL/kg/h)

Results

The median recipient age was 54 years (range 33 to 73); 41% aged between 50 and 60 years, male:female ratio was 1:9.4. The mean donor age was 38 years (range 9 to 70), with 52% of female and 48% of males.

Donor variables are shown in Table 1. The median cold ischemic time (CIT) was 743 minutes (range from 112–1387 min) and warm ischemic time was 48 minutes (range from 24-85 min). Donors' factors and the risk of death are in Table 1.

There were 61 deaths in 301 recipients with 62% (n = 38) within 6 months (early deaths) and 38% (n = 23) late deaths (more than 6 months). Twenty-seven (9%) patients received a second graft and 3 (1%) a third graft.

Primary nonfunction: Two patients had primary nonfunction of the first graft, one of them whose donor liver showed no abnormal features died 7 days after the first OLT; the other one had a liver from a donor whose BMI was greater than 30; the patient was re-grafted at 4 days and died 16 months later.

Normal BMI was found in 67.5% of donors,

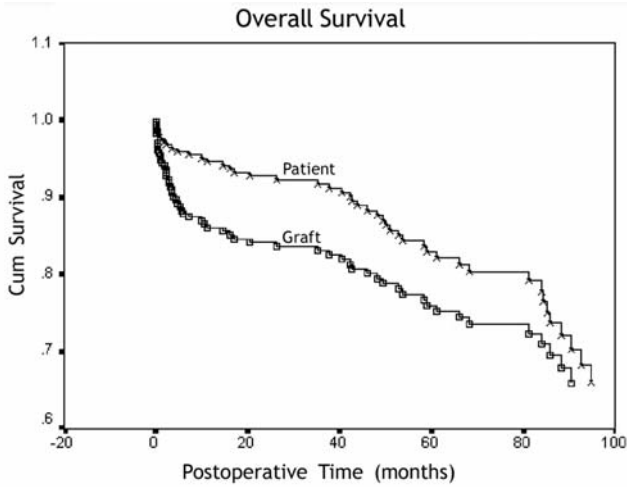

Figure 1. Overall patient and graft survival in patients undergoing OLTx for PBC

29.7% overweight, 2.4% obese, and 0.4% with morbid obesity.

Donor's Factors Influencing Graft Survival: The Kaplan-Meier curves demonstrate that 1-, 3- and 5-year graft survival was 85.49%, 82.57%, and 75.21%, respectively (Figure 1). Factors showing influence in decreased total graft survival were high donor age (P = 0.1343), recipient old age (P = 0.1641), and low

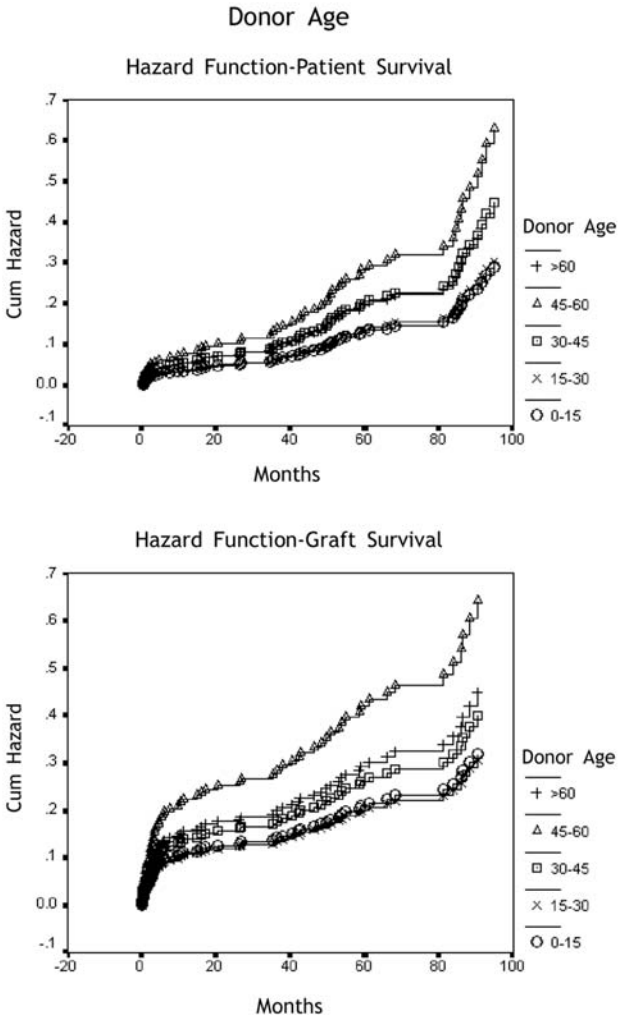

Figure 2. Impact of donor age on graft and patient survival

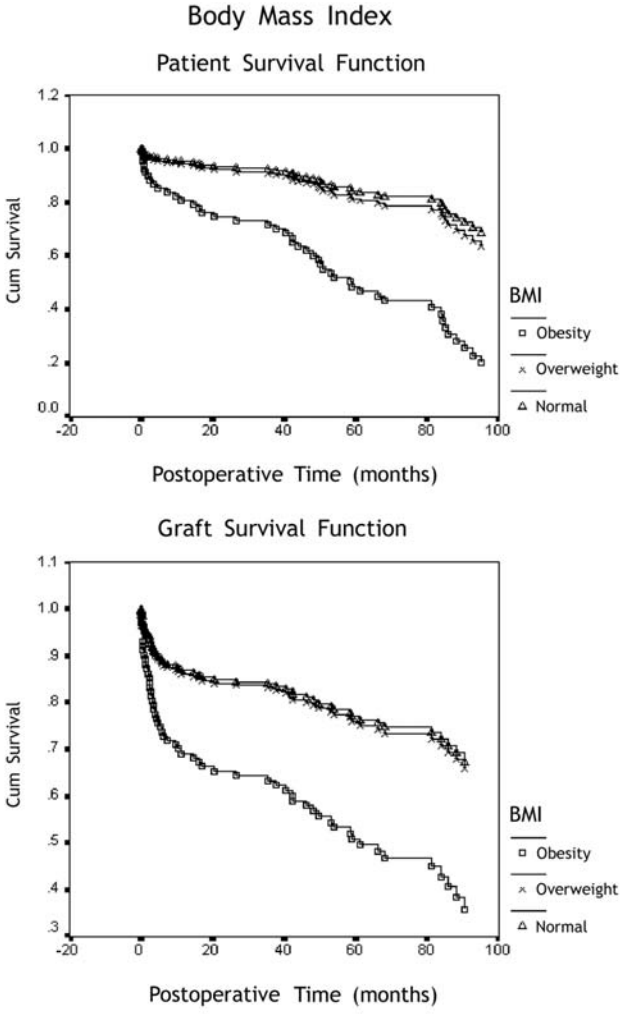

Figure 3. Impact of donor BMI on patient and graft survival

recipient albumin ($P = 0.05147$). However, the only variables showing an association with an increased risk (or decreased graft survival within 90 days) are old donor age ($P = 0.003$) (Figure 2), high donor body weight ($P = 0.029$), and high donor BMI ($P = 0.0661$) (Figure 3)

Donor's Factors Influencing Patient Survival: The 1-, 3-, and 5-year patient survival was 93.97%, 90.64% and 81.75%, respectively (Figure 1). Factors showing influence in decreased total patient survival were recipient old age ($P = 0.00346$) and low recipient albumin ($P = 0.01079$). However the only variables showing an association with an increased risk (or decreased patient survival within 90 days) are old donor age ($P = 0.0027$) (Figure 2) and high donor body weight ($P = 0.0307$) or high BMI ($P = 0.055$) (Figure 3).

Severely ill patients (higher PI values) are correlated with longer ITU stay ($r = 0.196$, $P = 0.001$). The risk of death associated with CIT, comparing less and more than 12 hours and 18 hours, and warm ischemic time (WIT), comparing less and more than 45 minutes and 60 minutes are shown in Table 2. Only a CIT of 18 hours (less than 18h–N = 290, more than 18h–N = 11) showed statistical significance ($P = 0.025$).

Discussion

The shortage of suitable liver donors has contributed to long waiting times and deaths on waiting lists. This has led to modification in liver donor acceptance criteria in an attempt to bridge this gap. With the total number of available cadaveric organs decreasing (as in the UK) or remaining constant (as in the US), and demand exceeding

Table 2. Procedure related factors and risk of death

Features	Total No.	Exposure[a]	RR	95% Confidence Interval	X2	P value
Cold ischemic time (12 h)	301	164	1.478	0.967-2.258	3.37	0.066
Cold ischemic time (18 h)	301	11	2.397	1.342-4.279	-	0.025[b]
Warm ischemic time (45 min)	301	191	0.681	0.456-1.015	3.521	0.061
Warm ischemic time (60 min)	301	27	0.923	0.442-1.927	0.47	0.828

[a]Exposure was considered abnormal value, [b]Fisher's test, RR: Relative risk

supply, a better understanding of what defines a "marginal" liver is needed.

In primary biliary cirrhosis several prognostic variables have been identified, the most important being: high bilirubin, old age, low albumin, ascites or oedema, cirrhosis, gastrointestinal (GI) bleeding or oesophageal varices, which all indicate a poor prognosis [3]. These variables can be quantified and expressed as a number. The prognosis for a group of patients may be very well described by the average and distribution of their prognostic indices [6,7].

From our data the only variables showing an association with an increased risk in both graft and patient survival were: old donor age and high donor body weight or BMI. Unlike kidneys, the liver does not become diseased with age and atherosclerosis is seldom a contraindication to transplantation. Age-related changes in the liver include a reduction in liver mass and blood flow, with fibrous thickening of the capsule. However, livers from older donors demonstrate good functional reserve and maintain regenerative capacity [8]. Primary nonfunction is not correlated with donor age [9], although older livers may be more susceptible to prolonged ischaemia, and a shortening of cold ischemic may minimize the degree of preservation-reperfusion injury. However, Gayowski et al, looking at factors determining outcome in high-risk patients, found donor age (one of only two donor factors studied) to be a significant independent predictor of mortality [10]. In North America, there was an increase in accepted livers; however, donors aged 50 and older increased from 12.9% in 1991 to 29.8% in 1999, while donors in the 18-34 age group decreased from 38.7% to 26.1% in 1999 [11].

The presence of hepatic steatosis has been reported to be a limiting factor in accepting a graft from an older donor [12]. Because we do not perform routine liver biopsies in all donors, steatosis was not considered as an individual variable. There is a close correlation between BMI and hepatic steatosis [13]. Although only 6 donors were obese (BMI between 30 and 39.9 kg/m^2), obesity did have a significant adverse impact on survival compared with normal or overweight donors (BMI < 30), decreasing survival by 50% at 5 years. Severe macrovesicular steatosis is associated with graft dysfunction and high rates of primary non-function (PNF) [14], although Canelo et al report satisfactory though inferior (60% survival) outcome with severely steatotic donor livers, concluding that the use of a fatty liver from a young donor without associated diseases or prolonged cold ischemia, and short intensive care stay, should be considered in selected cases for OLT [15]. Morbid obesity has been identified as a potential risk factor for graft dysfunction, owing to its association with hepatic steatosis [15,16]. In contrast, mild steatosis does not have an adverse impact on graft outcome [17,18]. Histologic examination is the only way to quantify degree of steatosis, and biopsies should be taken when steatosis is suspected. However, the time taken to process the liver will add to the ischaemic time and so could add to the morbidity of the outcome.

Conclusions

In a well-known recipient population with predictable disease (PBC), donor BMI and age have been shown to be factors associated with decreased graft and patient survival. Effort must be made to keep ischaemia time short and evaluate with histology steatotic livers and/or donors with high BMI especially in older donors.

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