Donor Influence on Outcome in Patients Undergoing Liver Transplant for Primary Biliary Cirrhosis

Dietmar A. Jacob, Elena Haase, Fritz Klein, Johann Pratschke, Ulf P. Neumann, Peter Neuhaus, Marcus Bahra

Abstract

Objectives: **Risk factors for survival after liver transplant owing to primary biliary cirrhosis have been extensively investigated, whereas the donor-specific influence and particularly, the histologic data, has not been sufficiently analyzed.**

Patients and Methods: **Donor data of 121 patients who underwent liver transplant for primary biliary cirrhosis and histologic findings of 69 donor liver grafts were assessed according to preoperative status and histologic criteria. Findings were correlated with the histologic and clinical course up to 20 years after orthotopic liver transplant.**

Results: **Risk factors for death were a longer stay in intensive care units (> 7 days) (*P* < .02), a hypotensive period > 60 minutes (*P* < .03), and the administration of red blood cells (*P* < .04). Grafts from donors with liver fibrosis (*P* < .03), fatty degeneration (*P* < .04), and liver cell hydrops (*P* < .04) resulted in a significantly higher risk of primary biliary cirrhosis recurrence. Log rank analysis revealed a significant decreased survival for patients if donors had a prolonged hypotensive period (*P* < .02) and administration of epinephrine (*P* < .03) and red blood cells (*P* < .05).**

Conclusions: **Our results show that donor histology can affect disease recurrence, especially the grade of inflammation, fibrosis, and fatty degeneration. In addition, prolonged intensive care hospitalization for donors should be avoided.**

From the Department of General, Visceral and Transplantation Surgery, Humboldt University of Berlin, Germany

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Address reprint requests to: *Dietmar A Jacob, MD, PhD, Department of General, Visceral and Transplantation Surgery, Humboldt University of Berlin, Charité Virchow Clinic, Augustenburger Platz 1, 13353 Berlin, Germany*

Phone: *+49-30-130225450* ***Fax:*** *+49-30-450552900* ***E-mail:*** *dr.djacob@web.de*

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Liver transplant significantly improves the prognosis of patients with primary biliary cirrhosis (PBC) compared with survival in mathematical models without transplant (1). Recurrence of PBC does occur, however. In 1982, Neuberger and associates described PBC recurrence after orthotopic liver transplant for the first time (2), and since then, several studies have reported a PBC recurrence rate after liver transplant in 8% to 32% of the grafts (3-7). Currently, the most-important risk factors for PBC recurrence are recipient age and cold ischemia. In addition, some studies also reported a correlation between early PBC recurrence and tacrolimus-based immunosuppression (8-11). However, donor-specific influence on disease recurrence, graft, and patient survival have not been sufficiently analyzed in the PBC population (10, 12, 13). Particularly, for patients with PBC, the histologic data of donor organs does not exist. Because of the deceased-donor organ shortage and the increased use of older or marginal donor livers, these data and their impact on long-term survival may be important in the future.

Therefore, we retrospectively analyzed our prospectively collected data from 121 consecutive patients who underwent liver transplant owing to PBC. Especially, demographic and histologic donor data were analyzed to identify risk factors for survival, disease recurrence, retransplant, and rejection episodes.

Patients and Methods

Between April 1989 and April 2007, a total of 121 patients underwent orthotopic liver transplant for PBC-related chronic liver disease at the Charité Virchow Clinic, Berlin, Germany. Pretransplant donor histology was available for 69 patients. All

patients were routinely examined 1, 3, 5, 7, 10, 13, and 15 years after liver transplant. Tests included abdominal ultrasound, chest radiograph, blood samples, bone density measurement, and protocol liver biopsies. Prior to the study, the study protocol, which conforms with the ethical guidelines of the 1975 Helsinki Declaration, was approved by our local institutional ethics committee. Written informed consent was obtained from all of the subjects.

Liver transplant

Surgery was performed using standard surgical techniques as previously described (14). Standard biliary reconstruction was performed as side-to-side choledochocholedochostomy in 119 patients. Two patients had a benign stricture of the bile duct and received a choledocho-jejunostomy. One hundred twelve patients (93%) received a t-tube to stent the anastomotic site, which was then closed after control cholangiography and removed 6 weeks later in patients with normal graft function (14-16).

The median cold ischemic time in our patient population was 567 minutes (range, 40-1064 minutes), and the median operation time 295 minutes (range, 144-620 minutes). Furthermore, a median number of 5 red blood cells (range, 0-27 red blood cells) and 6 fresh frozen plasma (range, 0-33 fresh frozen plasma) were intraoperatively administered.

Immunosuppressive therapy

Primary immunosuppression was started with 2 mg of oral tacrolimus 6 hours after orthotopic liver transplant, and continued with 0.05 mg/kg body weight on postoperative day 1 and 2, or 4 mg/kg body weight of oral cyclosporine 2 hours before orthotopic liver transplant, and continued with 2 to 4 mg/kg body weight on postoperative days 1 and 2. In both regimens, the immunosuppressive dosage was adjusted according to clinical requirements and controlled by whole blood trough levels. After 3 months, tacrolimus-serum through levels were adapted to 5 ng/mL and cyclosporine levels to 100-120 ng/mL. Methylprednisolone was given as a bolus injection of 500 mg at the time of reperfusion, and 250 mg was administered 6 hours postoperatively. Prednisolone was started at 100 mg orally on postoperative day 1, and then decreased to 40 mg daily on postoperative day 7, 20 mg after 2 weeks, 15 mg after 2 months, and then tapered down.

Donor-specific data and histologic assessment of donor grafts

One hundred and six grafts were preserved using the University of Wisconsin solution (UW) (88%), and 15 grafts with the histidine-tryptophan-ketoglutarate (12%) solution. Liver biopsies were taken from 69 donor grafts before reperfusion. Biopsies were formalin-fixed and paraffin-embedded and stained with hematoxylin and eosin. Two experienced pathologist assessed each liver specimen to determine the degree of macrovesicular steatosis in a semiquantitative fashion as a percentage of the involved hepatocytes by using a 40× magnification light microscope. The grade of portal inflammation, fibrosis, fatty degeneration, hepatocellular necrosis, cell hydrops, and preservative damage of the donor grafts was assessed using the following semiquantitative histologic scores: 0, no signs; 1, mild signs; 2, severe signs. For fatty degeneration, mild signs were under 40%, and severe were about 40% fatty degeneration.

Primary biliary cirrhosis recurrence and fibrosis course after orthotopic liver transplant

Recurrence of PBC was diagnosed by protocol liver biopsies after 1, 3, 5, 7, 10, 13, 15, and 18 years. According to the criteria determined by Hubscher and associates (17), PBC recurrence was diagnosed in case of florid duct lesions, bile duct injury, epithelioid granulomas, formation of lymphoid aggregates, and mononuclear inflammatory infiltrates. Histologic fibrosis progression was defined as stage 0 (no fibrosis), 1 (fibrous portal expansion), 2 (periportal fibrosis), 3 (septal fibrosis), and 4 (cirrhosis). All examined specimens had more than 3 portal fields for accuracy of diagnosis and were reviewed by 2 pathologists blinded to the clinical information.

Statistics

Data were collected in a database (Microsoft Access 2.3, Microsoft Corporation, USA) and retrospectively analyzed. Data are described as median and range, or mean and standard deviation. Statistical analyses were performed with SPSS software for Windows (Statistical Product and Service Solutions, version 16.0, SSPS Inc, Chicago, IL, USA). Survival analysis was performed using the Kaplan-Meier method (log-rank test). The nonparametric Wilcoxon rank sum test was used to compare median values. The Cox proportional hazard model was performed to

evaluate risk factors for death, disease recurrence, retransplant, and rejection episodes. All tests were 2-sided, and *P* values less than .05 were considered statistically significant.

Results

Recipients

Median age of 104 women (86%) and 17 men (14%) was 54 years (range, 25-69 years), and median follow-up after orthotopic liver transplant was 129 months (range, 0.4-225 months). Actuarial survival of all 121 patients after 5, 10, and 15 years was 90%, 87%, and 80%, and graft survival was 95%, 93%, and 88%, respectively.

Median hospital stay was 32 days (range, 10-230 days). Nineteen patients died (16%) after a median survival of 42 months (range, 1-186 months). The initial immunosuppression consisted of tacrolimus for 65 patients (54%) and cyclosporine for 56 patients (46%). In 13 patients, a retransplant was performed (11%) and a histologically proven PBC recurrence was diagnosed in 18 patients of 121 patients (15%).

Demographic and histologic data of donors

The median age of 71 males (59%) and 50 females (41%) was 36 years (range, 7-78 years). In most patients (47%), cerebral hemorrhage was the cause of death. Median stay in the intensive care unit (ICU) was 3 days (tacrolimus 1-27 days), and 40 patients (33%) developed a hypotensive episode. Eighty-seven patients (72%) received catecholamines, and 39 patients received red blood cells (32%) (Table 1)

The assessment of 6 different histologic graft criteria before reperfusion showed the following patterns: 17 liver grafts had an intrahepatic inflammation with a mean score of 0.25 ± 0.43 (25% of 69 grafts). Ten donor livers (15%) had fibrosis with a mean score of 0.14 ± 0.35. Hepatic fatty degeneration was detected in 18 liver grafts (26%) with a mean score of 0.29 ± 0.51. Necrotic hepatocytes were seen in 36 livers (52%) with a mean score of 0.58 ± 0.60. In addition, 29 patients (42%) showed liver cell hydrops (mean, 0.48 ± 0.60) and 15 grafts (22%) showed preservative damage (Table 2a). Protocol biopsies after orthotopic liver transplant in recipients with histologically proven PBC recurrence showed a progressive mean fibrosis score of 0.75 ± 0.86 after 1 year, up to 1.42 ± 1.16 after 3 years, and 2.71 ± 0.76 after 13 years (Table 2b). None of the 12 recipients

Table 1. Demographic data of 121 donors in the intensive care unit before recovery of organs.

Variable	Median (range) / number (%)	Mean ± SD
Sex		
Men	71 (59%)	—
Women	50 (41%)	—
Age	36 (7-78)	37.15 ± 17.48
Cause of death		
Cerebral hemorrhage	57 (47%)	—
Traumatic brain injury	44 (36%)	—
Ischemic brain insult	8 (7%)	—
Brain tumor	3 (2.5%)	—
Living-related liver transplant	3 (2.5%)	—
Other*	6 (5%)	—
Body-mass-index (BMI)	23 (15-62)	23.77 ± 4.97
Intensive care unit (ICU)		
Duration (days)	3 (1-27)	4.40 ± 4.94
Diuresis of last 24 hours (mL)	3400 (1000-13.000)	3842.81 ± 1895.75
Hypotensive episode	40 (33%)	
None	81 (68%)	—
< 30 minutes	15 (12%)	—
30-60 minutes	15 (12%)	—
> 60 minutes	10 (8%)	—
Asystole	17 (14%)	—
Catecholamines	87 (72%)	—
Red blood cells	39 (32%)	—
Amount	0.5 (0-30)	1.99 ± 4.70
AST (U/L)	35 (6-496)	57.83 ± 69.56
GGT (U/L)	22.5 (3-765)	61.36 ± 108.83
Bilirubin (μmol/L)	15.4 (1.7-393.3)	34.7 ± 3.36
Hemoglobin (g/L)	111.35 (55.5-160)	110.11 ± 2.45
Preservative solution		
University of Wisconsin	106 (88%)	—
Histidine-Tryptophan Ketoglutarate	15 (12%)	—
Organs shipped	61 (50%)	—

Abbreviations: AST, aspartate aminotransferase; GGT, glutamate dehydrogenase.
*other (heart attack, 2; aspiration, 1; pulmonary embolism, 1; brain edema, 1; asthmatic attack, 1)

Table 2a. Histologic data of 69 donor liver biopsies before reperfusion.

Variable	Grade	Patients	Mean ± SD
Inflammation			0.25 ± 0.43
Absent	0	52	
Mild	1	17	
Severe	2	0	
Fibrosis			0.14 ± 0.35
Absent	0	59	
Mild	1	10	
Severe	2	0	
Fatty degeneration			0.29 ± 0.51
Absent	0	51	
Mild	1	16	
Severe	2	2	
Necrosis			0.58 ± 0.60
Absent	0	33	
Mild	1	32	
Severe	2	4	
Cell hydrops			0.48 ± 0.60
Absent	0	40	
Mild	1	25	
Severe	2	4	
Preservative damage			0.26 ± 0.53
Absent	0	54	
Mild	1	12	
Severe	2	3	

Table 2b. Histologic donor data and fibrosis course of 12 patients (out of 69 patients with available data) with primary biliary cirrhosis recurrence after orthotopic liver transplant.

Sex	Time to recurrence (months)	Inflammation	Fibrosis	Fatty deg.	Necrosis	Cell hydrops	Preserv. damage	Fibrosis (grade) after recurrence (years) 1	3	5	7	10	13	16
f	36	1	0	0	0	1	0	2	3	3	3	3	—	—
f	36	0	0	1	1	0	0	2	2	2	2	2	2	—
f	36	0	0	1	0	1	1	1	1	2	2	3	—	—
f	37	0	0	0	0	1	0	0	3	*	—	—	—	—
f	61	0	0	0	1	0	0	1	1	1	1	1	—	—
f	61	0	0	1	0	0	0	1	1	2	2	2	2	—
f	61	1	1	0	0	0	0	2	3	3	3	3	4	—
f	85	1	0	0	1	0	0	0	1	3	3	3	3	4
f	109	0	0	0	0	1	0	0	0	2	2	4	—	—
f	122	0	0	0	0	0	0	0	2	2	2	3	3	—
m	122	0	0	1	0	0	0	0	0	2	2	3	3	—
f	158	1	1	0	1	1	1	0	0	0	0	0	2	2
mean	77.03	0.33	0.17	0.33	0.33	0.42	0.17	0.75	1.42	2.00	2.00	2.45	2.71	3.00
(± SD)	41.68	0.49	0.39	0.49	0.49	0.51	0.39	0.86	1.16	0.89	0.88	1.12	0.76	1.41

Abbreviation: deg, degeneration; f, female; m, male; preserv, preservative; *patient died.

had severe histologic criteria in the donor liver, or developed fibrosis stage 3/4 within the first year after orthotopic liver transplant. Eight patients showed signs of stage 3/4 fibrosis beginning 3 years after the transplant. From these patients, there was evidence for inflammation in 3 grafts, fatty degeneration in 2 grafts, and fibrosis in 1 liver. One patient died owing to progressive PBC recurrence with only a mild cell hydrops.

Univariate analysis of donor data for risk factors for death, recurrence of primary biliary cirrhosis, retransplant, and rejection episodes

Univariate analysis of donor data identified the following as significant increased risk factors for death: A prolonged stay in the ICU of about 7 days ($P = .02$), a hypotensive period in the ICU of about 60 minutes ($P = .03$), and administration of red blood cells in the ICU ($P = .04$), whereas histologic donor data had no affect as risk factors for death. In contrast, fibrosis ($P = .03$), fatty degeneration ($P = .04$), and cell hydrops ($P = .04$) were potentially risk factors for disease recurrence. Furthermore, a hypotensive period on ICU of about 60 minutes ($P = .03$) and a fatty degeneration ($P < .001$) were identified as significant risk factors for retransplant. Also, donor organs showing fatty degeneration had a significant increased risk for rejection episodes ($P = .01$) (Table 3).

Multivariate analysis of recipient and donor risk factors for death

Multivariate analysis showed a significant increased risk for death in a prolonged recipient hospital stay of about 60 days ($P < .001$) and a recipient stay in the ICU of about 21 days ($P < .02$). Analysis of donor data showed that a prolonged duration of about 7 days in an ICU and administration of red blood cells in an ICU ($P < .04$) are significant increased risk factors for death. In contrast, analysis for PBC-recurrence, retransplant, and rejection episodes revealed no significant risk factor for recipients and donor data (Table 4).

Table 3. Univariate analysis of donor risk factors for death, primary biliary cirrhosis recurrence, retransplantation, and rejection episodes. Analysis of demographic and histologic data.

Variable	Death	Recurrence	Retransplant	Rejection
	P value			
Duration ICU (days)				
> 7	**.02**	NS	NS	NS
Hypotensive period on ICU				
> 60 minutes	**.03**	NS	**.03**	NS
Red blood cells on ICU	**.04**	NS	NS	NS
Fibrosis	NS	**.03**	NS	NS
Fatty degeneration	NS	**.04**	**< .001**	**.01**
Cell hydrops	NS	**.04**	NS	NS

Abbreviations: ICU, intensive care unit; NS, not significant.

Table 4. Multivariate analysis of recipient and donor risk factors for death.

	95% CI	*P* value
Duration of hospital stay (recipient)		
> 60 days	0.693 - 1.023	**.001**
Duration of ICU stay (recipient)		
> 21 days	1.268 - 15.013	**.01**
Duration of ICU stay (donor)		
> 7 days	0.29 - 1.809	**.03**
Red blood cells on ICU (donor)	1.031 - 7.588	**.03**

Log-rank analysis of donor data for patient survival, primary biliary cirrhosis recurrence, and retransplant

Log-rank analysis of 121 patients for demographic data and 69 patients for histologic criteria of the graft before reperfusion showed a significantly reduced patient survival for donors with a longer

hypotensive period in the ICU. Survival of patients who received a graft with a hypotensive period between 30 and 60 minutes were significantly reduced versus periods below 30 minutes (P = .02). In donors, a hypotensive period of about 60 minutes was significant versus a period between 30 and 60 minutes (P = .01). In addition, administration of epinephrine (P = .02) and red blood cells (P = .04) also resulted in significantly reduced survival (Table 5). However, histologic criteria of donor organs had no significant impact on long-term patient survival. Furthermore, log rank analysis for PBC recurrence and retransplant did not show a significant difference.

Table 5. Log-rank analysis of donor data for patient survival.

Variable	Death *P* value
Hypotensive period on ICU	
< 30 minutes vs 30-60 minutes	.02
30-60 minutes vs > 60 minutes	.01
Catecholamines on ICU	
Epinephrine (n=25)	.02
Red blood cells on ICU	.04

Abbreviation: ICU, intensive care unit.

Discussion

We could demonstrate an influence of donor factors on recipient survival after liver transplant for end-stage PBC. Our survival analysis of 121 patients demonstrated excellent patient and graft survival after liver transplant for PBC. These findings conform with previously published data in 2006 from our group and are similar to results of other authors (10, 12, 18-20).

Several risk factors for patient and graft survival and disease recurrence after orthotopic liver transplant for PBC have been found in the last 20 years. However, risk factor analyses about donor influence on patient and graft survival was poor in the literature. We could demonstrate in a log rank analysis that a hypotensive period of about 30 minutes in the ICU, and administration of epinephrine and red blood cells, leads to a significant lower survival. Additional univariate analysis could identify a prolonged donor stay in the ICU of about 7 days, a hypotensive period about 60 minutes, and administration of red blood cells, as potential donor risk factors for recipient death.

In contrast with our results, Garcia and associates could not find a relation between a prolonged ICU stay and hypotensive periods and administrated catecholamines as risk factors for patient and graft survival (12). One reason might be an increased ICU stay in our donors of 3 days (range, 1-27 days) compared with 2 days (range, 1-29 days) in Garcia's group. Detailed data about the days of hypotension are lacking. Furthermore, Rull and associates reported about 228 patients with special focus on donor criteria. They found no significant effect on early graft function between inotropic support and prolonged hypotension in the ICU before harvesting organs (21).

A retrospective study of 365 liver donors by Mor and associates could show that a systolic blood pressure less than 90 mm Hg, despite the use of high-dose dopamine, was also associated with a significantly increase rate of hepatocellular damage (22). Although, hypotension is a well-described cause of shock liver, and prolonged hypotension in the donor may add to the risk for graft dysfunction, the duration of hypotension and the special treatment is not well-described in most studies. That might be one reason for different findings. However, it seems that in these days, the transplant indication for malignoma is increasing, and therefore, marginal donor organs with prolonged hypotension periods are being accepted more often for these patients.

Another risk factor for recipient and graft survival described Garcia and associates in association with older donor age and a high body mass index (BMI) (12). We could not observe this effect, and the reason for the difference regarding donor age between ours and Garcia's study is unclear. The mean age of donors is almost equal in both studies (38 vs 36 years), and details about the physical condition of donors are not given. An increased BMI causes many problems in the body. Hepatic steatosis is only 1 of them and is a limiting factor for organ acceptance. However, we could not identify an increased BMI as risk factor for patient and organ survival such as Garcia and associates. Donor BMI is almost similar in both studies with a median BMI of 23 (range, 15-62) in our population versus 23 (range, 14-40) in the study by Garcia (12). A focus on our retransplanted patients showed a median BMI of 24.5 (range, 18-31). Only 2 patients had a BMI of about 30, and were retransplanted because of acute liver failure owing to hepatitis B infection and chronic rejection.

One specific topic of our study was to evaluate histologic donor criteria as risk factors for death.

However, analysis of biopsies before reperfusion showed no significant affect on patient and graft survival in multivariate analysis. But histologic data of only 69 patients were available and therefore, statistical validity is poor. Causes for 13 retransplants were initial nonfunction, ischemic-type biliary lesions, chronic rejection, de novo hepatitis B infection, vanishing bile duct syndrome, and PBC recurrence. We could identify a hypotensive period in the ICU about 60 minutes and a fatty degeneration of the donor liver as significant risk factors for reduced graft survival. Both factors could play an important part in the development of initial nonfunction. Forty-two percent of all retransplants in our patient collective were performed due to initial nonfunction, and these patients had all the histologic signs of fatty degeneration. However, the number of patients is not representative for a statistical analysis. So far, the pathogenesis of PBC and recurrence remains unclear. There is no explanation for mechanisms of recurrence; defining more risk factors may give further insight into pathogenesis.

One of the largest series of liver transplants for PBC was published by Liermann Garcia and associates in 2001. One major part of the study focused on PBC recurrence, and the authors identified younger recipients and organs from younger donors as significant risk factors for PBC recurrence (10). A reason for this correlation was not given, and the authors described their results as very small difference and unlikely to be of clinical importance. Three years later the same study group reported about 485 patients, but they could not identify a risk factor for disease recurrence (23).

Charatcharoenwitthaya and associates compared 52 patients with PBC recurrence versus 102 patients without recurrence, and reported a significantly increased PBC recurrence in older donors. This observation is in contrast to Garcia and associates who identified younger donors as risk factors for disease recurrence. Both authors do not describe the cause of their finding. Our histologic analysis of 69 donor livers showed that organs with fibrosis, fatty degeneration, and cell hydrops had a significantly increased risk for developing PBC recurrence. Until now, this report describes, for the first time, a correlation between histologic analyses before transplant and survival for PBC patients after orthotopic liver transplant. Even if we attained significant results, the clinical impact of these findings is questionable.

Most recipients who get a disease recurrence and received positive organs for fibrosis, fatty degeneration, or cell hydrops had only mild signs of fibrosis on long-term follow-up. The risk of fibrosis progression and graft loss is not as important in PBC patients as it is in patients with hepatitis C (24). One patient out of 18 died owing to a progressive PBC recurrence, and the graft showed before transplant only a mild cell hydrops. Previously, Hytiroglou and associates reported severe fibrosis and cirrhosis in patients with PBC recurrence when features of autoimmunhepatitis are present (25). We could not confirm this effect. Our department of pathology could not identify an overlap syndrome in 18 patients with PBC recurrence. Because of the slowly progressive fibrosis in patients with recurrence, it may show an effect only in patients who were transplanted for 15 years or longer. These data are not available in the literature.

As we could demonstrate with histologic data in our 69 patients, organ quality in the last 2 decades was excellent in most cases. Currently, organs with a higher grade of fatty degeneration, mild fibrosis, and from older donors are more accepted, and the histologic criteria of these organs can affect patient and graft survival. Further investigations are necessary to confirm this observation, but these studies must be performed in transplant centers with protocol biopsies before and after orthotopic liver transplant in large numbers of PBC patients. Because patient numbers of PBC are decreasing, most questions can be answered only in a prospective multicenter study.

In conclusion, we demonstrated, for the first time, a correlation between donor histology before reperfusion and risk factors in PBC recurrence, retransplant, acute rejection episodes, and survival in a long-term follow-up. It seems that a prolonged or complicated course of organ donors in the ICU before organ recovery leads to decreased survival. Especially in older donors, prolonged intensive care hospitalization, and administration of epinephrine, should be avoided.

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