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Organ survival after primary dysfunction of liver grafts in clinical orthotopic liver transplantation

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Abstract In a retrospective analysis of 632 orthototopic liver transplant procedures performed between 1982 and 1997, the incidence of primary dysfunction (PDF) of the liver and its influence on organ survival were studied. Graft function during the first 3 postoperative days was categorized into four groups: (1) good (GOT max < 1000 U/l, spontaneous PT > 50%, bile production > 100 ml/day); (2) fair (GOT 1000–2500 U/l, clotting factor support < 2 days, bile < 100 ml/day); (3) poor (GOT > 2500 U/l, clotting factor support > 2 days, bile < 20 ml/day); (4) primary non-function (PNF; retransplantation required within 7 days). The aim of this study was to evaluate graft survival comparing organs with PDF (poor function) and PNF vs organs with initial good or fair function. After a median follow- up of 45 months, initially good and fair function of liver grafts resulted in a significantly better long-term graft survival compared with grafts with initially poor function or primary non-function (if retransplanted) ($P < 0.01$). The Cox model revealed primary function as a highly significant factor in the prediction of long-term graft survival ($P < 0.0001$). We conclude that these results confirm the hypothesis that primary graft function is of major importance for the long-term survival of liver transplants. Patients with a poor primary function have the worst survival prognosis, which leads to the interpretation that these patients may be candidates for early retransplantation.

Key words Liver transplantation · Primary dysfunction · Organ survival

Introduction

One of the major postoperative complications after liver transplantation is primary dysfunction (PDF) of the transplanted graft, leading to significant morbidity and mortality. The initial function of the transplanted liver is a major determinant of the postoperative and long-term course. Primary non-function (PNF) following orthotopic liver transplantation is manifested by hepatic cytolysis and rapidly rising transaminases, absence of bile production, severe liver-related coagulation deficit, high lactate levels, aggressive ventilation support, need for circulatory assistance by catecholamines because of hepatic haemodynamic instability, hypoglycaemia and acute renal failure. It is a life-threatening event, making survival impossible without retransplantation. Initially poor function is a borderline syndrome with either complete recovery or retransplantation at a later date.

In order to reduce the incidence of PDF [1] and improve patient and graft survival, it becomes important to identify those risk factors associated with its occurrence [2, 3, 4]. In a retrospective univariate and multivariate analysis, we evaluated several donor, preservation and recipient parameters and their correlation with PDF.

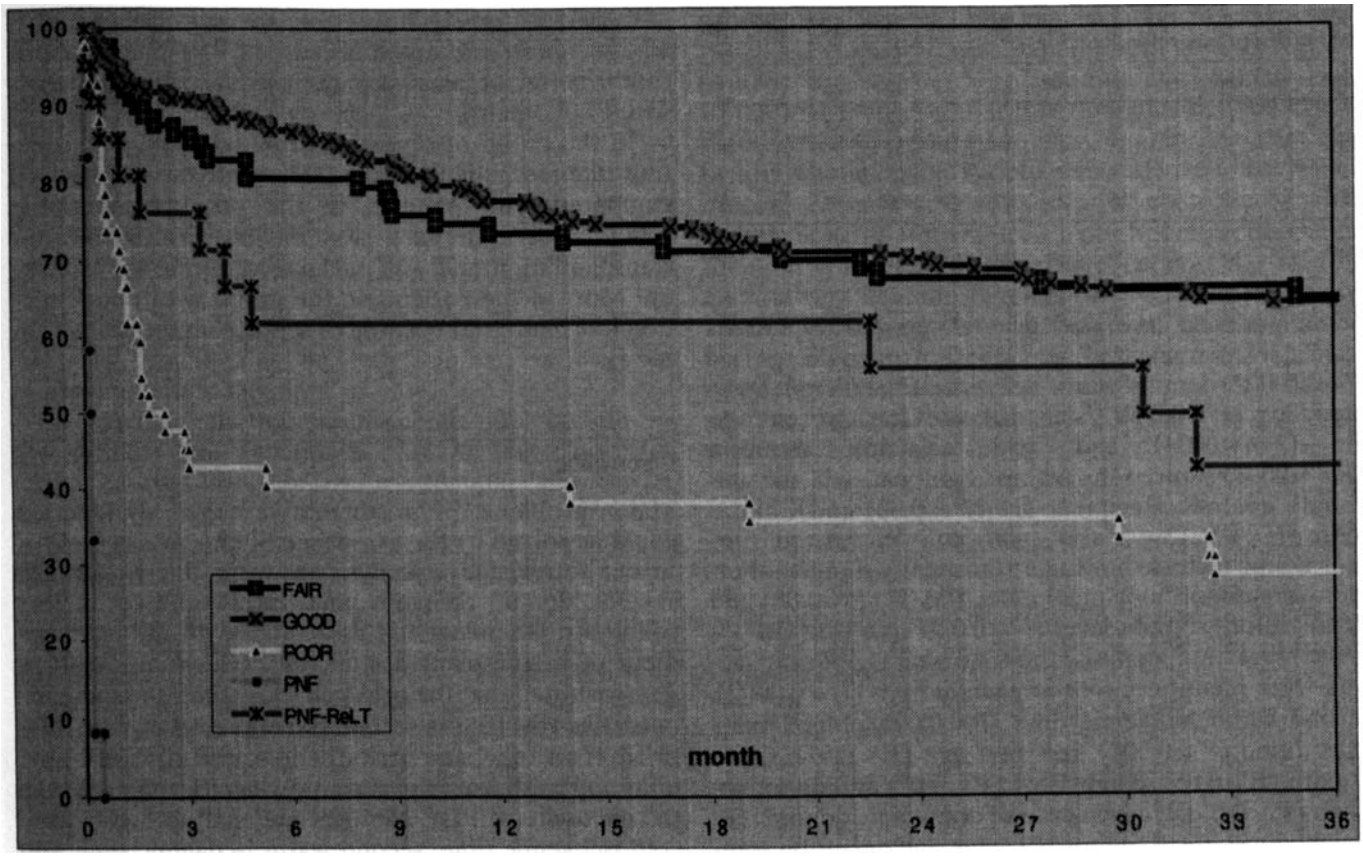

Fig. 1 Influence of postoperative liver function on long-term graft survival

Patients and methods

From 1982 to December 1997, 632 orthotopic liver transplantations were performed at the Department of Transplant Surgery, University of Vienna. Organs with postoperatively poor function or primary non-function were placed in the group of initial dysfunction and compared with the group of initially good or fair function.

For those eligible for transplantation, we examined the effect of the following donor criteria: age, size body weight index (Broca), duration of intensive care, liver function tests (bilirubin, aspartate aminotransferase, GOT, glutamic-pyrurate transaminase, GPT, lactate dehydrogenase, LDH, alkaline phosphatase, ALP, gamma glutamyl transferase, GGT, prothrombin time, PT); kidney function (creatinine, sodium). The effects of the following intraoperative factors were also studied: type of protective solution, cold ischaemic time, anhepatic period; blood loss (more or less than 10 blood units), anastomosis time, use of thrombocyte units, clotting factor support (fresh frozen plasma), and recipient age and child score of the recipient. For statistical analysis we first entered all factors in a univariate model. All factors that achieved significance in this model were then applied in a stepwise polychotomous logistic regression anlaysis to identify the independence and relative importance of each of these variables. Estimates of graft survival according to the four groups of postoperative function were obtained by the Kaplan – Meier method.

Results

Grafts suffering from postoperative thrombosis of graft vessels, patients who died prior to the 3rd postoperative day other than from PNF, and recipients of grafts with missing donor criteria were excluded from analysis. Of the 632 liver transplants, postoperative function was available in 549 first or second grafts. We analysed data from 489 (89%) first and 60 (11%) second transplants. The indication for liver transplantation was alcoholic cirrhosis in 140 patients (25.6%), malignant liver tumours in 162 patients (29.6%), other types of cirrhosis in 245 patients (44.8%) primary biliary cirrhosis in 46, posthepatitic cirrhosis in 57 and autoimmune cirrhosis in 15 patients.

Initial analysis showed that 65.6% (360 patients) had good function, 19.1% (105 patients) had fair function, 8.7% (48 patients) had poor function, and 6.6% (36 patients) had PNF (Table 1). After a median follow-up of 45 months, liver grafts with an initially good and fair function showed highly significantly better long-term graft survival compared with grafts with initially poor function or PNF (if retransplanted) ($P < 0.0001$). The influence of the postoperative liver function on the long-term graft survival is shown in Fig. 1.

Analysis of donor criteria, intraoperative data, and recipient factors and their influence on postoperative

Table 1 Liver transplant function within the first 3 postoperative days (*PNF* primary non-function)

	n	Percentage
Good	360	65.6
Fair	105	19.1
Poor	48	8.7
PNF	36	6.6

organ function revealed several prognostic factors which are summarized in Table 2. Anhepatic period ($P = 0.0002$), second warm ischaemic time ($P = 0.0001$), blood loss ($P = 0.0001$), substitution of fresh frozen plasma ($P = 0.0004$) and cold ischaemic duration ($P = 0.0001$) showed the highest significance in the univariate analysis. Recipient age ($P = 0.02$) and Child – score ($P = 0.02$) were also significantly correlated. Further donor factors showing a statistically significant effect were donor body mass index (BMI) ($P = 0.03$) and donor serum sodium level ($P = 0.02$). In a stepwise logistic regression analysis, the following significant factors were identified: cold ischaemic time ($P = 0.0002$), second warm ischaemic time ($P = 0.005$), blood units substituted ($P = 0.002$), recipient age ($P = 0.01$), Child – score ($P = 0,05$), donor BMI ($P = 0.02$) and donor sodium ($P = 0.05$). No influence of donor age, donor creatinine, donor GGT, donor ICU stay and perfusion solution used was seen.

It was especially interesting to note, that patients who were retransplanted because of PNF had a significantly better organ and patient survival than patients with PDF organs.

In the group of organs with initial dysfunction, retransplanted patients had a 20% graft survival benefit compared with patients in the poorly functioning group. This difference was obvious 3 months after transplantation and was unchanged during the follow-up. Most of the patients in the group with poor function lost their graft because of septic complications (Table 3).

Discussion

Major problems of postoperative organ dysfunction could be solved by the avoidance of known risk factors. In our retrospective analysis we were able to identify several donor, recipient and intraoperative factors which are independently associated with the development of a transplant dysfunction. Univariate analysis demonstrated that the cold ischaemic time and the perioperative risk factors second warm ischaemic time (defined as an anhepatic period) and substitution of blood units and fresh frozen plasma most significantly affected the incidence of PDF. Multivariate analysis highlighted cold ischaemic time, second warm ischaemic time and intraoperative blood loss as risk factors associated with

Table 2 Influence of donor and recipient factors and intraoperative data on postoperative graft function (*GGT* gamma glutamyl transferase, *ICU* intensive care unit)

	Range	Median	Univalent	Multivalent
Recipient age	6 months–69 years	50 years	0.02	0.01
Child – score	A–C	A: 20%, B: 35%, C: 45%	0.02	0.05
Operation time (h)	2.75–13	5.5	0.04	NS
Anhepatic time (min)	30–300	80	0.0002	NS
Second warm ischaemic time (min)	22–206	72	0.0001	0.005
Blood units	0–74	9	0.0001	0.002
FFP, octaplas	0–80	12	0.0004	NS
Thrombocyte units	0–13	1	0.05	NS
Cold ischaemic time (h)	2–24.5	8.5	0.0001	0.0002
Donor body mass index (BMI)	12–65	20–25: 68.6%, < 20 + > 25: 32%	0.03	0.02
Donor age (years)	1–71	30	NS	
Donor sodium (mmol/l)	118–176	145	0.02	0.05
Donor creatinine (mg/dl)	0.1–1.3	0.9	NS	
Donor GGT (U/l)	1–280	13	NS	
Donor ICU stay (days)	1–31	2	NS	
Perfusion solution	EC: 8%, UW: 81%, HTK: 11%		NS	

Table 3 Postoperative poor function and reasons for graft failure

	Patients	Percentage
Septic complication – MOF	19	54
Bacterial infection	3	9
Viral infection	6	9
Haemorrhage	2	6
Malignant recurrence	4	11
Cerebral oedema – brain death	3	9
Cardiac complication	1	3

the worst prognosis in our model, similar to the results of previous studies [5, 6].

We conclude that our results confirm the hypothesis that primary graft function is of major importance for the long-term survival of liver transplants. Patients with primary poor organ function have the worst survival prognosis compared with patients with good or fair organ function and retransplanted patients, which leads to the interpretation that these patients may be candidates for early retransplantation. Combinations of risk factors when possible should be avoided, and ischaemic time, as the only variable that can be controlled, should be kept as short as possible. If a postoperative poor liver function is diagnosed, our results support the idea of early retransplantation even in these patients to achieve an acceptable long-term graft survival. Retransplanted patients obtained a significantly better survival if primary dysfunction occurred. The unsolved problem of an indication for retransplanting 15% of all liver grafts remains the shortage of organs.

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