One-month mortality rate after liver transplantation for parenchymal cirrhosis : analysis of risk factors in a ten year period

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Abstract

Accurate prediction of short-term survival rate after liver transplantation is one way of selecting recipients and should improve organ allocation. We observed, during the first ten years of our program a striking decline in postoperative mortality with time, a well known observation in Europe as well as in the United States. In 65 adults with parenchymal cirrhosis having received a liver transplant between 1984 and 1994, we examined the possible influence of various preoperative risk factors on one-month mortality rate which was 13.8% in this series. Univariate analysis led to the identification of five significant risk factors : date of transplantation, low serum sodium, previous history of jaundice, ascites and encephalopathy. In the final multivariate analysis however, the date of transplantation emerged as the sole predictive factor of early mortality rate. Therefore, factors such as pretransplantation state of the patient and poor hepatic reserve are counterbalanced by the improvement of surgical skill and other technical aspects, as well as by better perioperative management which have all contributed to the improved results of liver transplantation with time. (Acta gastroenterol. belg., **1999**, 62, **381-385**).

Key words : parenchymal cirrhosis, liver transplantation.

Introduction

The determination of the optimal timing for orthotopic liver transplantation (OLTX) remains a challenging clinical problem, particularly now, in a period of organ shortage and a 15 to 30% death rate on the waiting list (1).

Prioritary allocation of donor organs in cirrhotic patients can be based on two sets of prognostic estimates : i) analysis of the patient's course over the one or two pretransplant years (2,3,4,5,6) ; ii) identification of those patients with the greatest chance of survival after OLTX.

Some reports (7,8,9,10) stress the lack of correlation between OLTX mortality and the pretransplant status of the recipient.

For others (11,12,13), post-OLTX death is believed to be mainly related to pretransplant risk factors. Confounding variables might however be present such as the team's experience, the surgical technique, the anesthesiological monitoring, the perioperative care, and the preservation methods which all can contribute to improved patient and graft survival. These factors can probably partly explain declined postoperative mortality with time in Europe (14) as well in the USA (15).

In our OLTX program, we also observed an improvement of the two years survival with time ranging from less than 50% during the years 1984 to 1989 to more than 80% from 1990 to 1994.

The aim of our study was to analyse the potential contribution of recipient characteristics on the early prognosis which changed mostly during the first ten years of our program.

Material and methods

Patients

Among the 119 OLT recipients treated in our institution between 1984 and 1994, the 65 adult patients with parenchymal cirrhosis constitute the basis of the present study.

Triple based immunosuppressive therapy (cyclosporine azathioprine prednisolone) was administered following OLT in all patients.

Etiology of cirrhosis

Viral hepatitis B or C was the primary cause of cirrhosis in 36 patients, alcohol in 22, autoimmune hepatitis in 1, α1 antitrypsin deficiency in 1 and hemochromatosis in 1. The etiology of cirrhosis was undetermined in 7 patients. Alcoholism (ALC) was defined as a daily intake of 60 g alcohol or more for over 5 years.

In 11 patients, a small (less than 3 cm diameter) hepatocellular carcinoma was discovered in the course of preoperative work-up.

Risk factors

The numerous risk factors that were submitted to statistical analysis were tabulated under two distinct headings : 1) qualitative and 2) quantitative, according to their susceptibility to measurements.

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Qualitative risk factors

Alcoholism (ALC).

Date of LTX: before (10 patients) or after (55 patients) the 1st of January 1989. The median death date was chosen as the cut-off.

History of the patients included the following data: jaundice (HICT); ascites (HASC); encephalopathy (HENC); variceal haemorrhage (HVH); variceal sclerotherapy (HSCL); infected ascites (HINF); upper abdominal surgery or/and shunt (HAS); recent intake of diuretics (HDIUR); UNOS scoring scale (UNOS): 1 = patient at home and working; 2 = at home and disabled; 3 = hospitalized; 4 = critically ill and on life support.

Physical examination on admission yielded further data: jaundice (ICT); grade of encephalopathy (ENC) (16), of ascites (ASC) (6) and of malnutrition (MAL) (17); hepatomegaly (HM); upper gastrointestinal endoscopy (18) was used for grading esophageal varices (VAR) in 61 of the 65 patients.

Quantitative risk factors

Age at liver transplantation.

Liver volume (LV): was determined on CT scan by summing up the liver volumes represented on contiguous images.

Child-Pugh score (PUGH) (19)

Hepatic venous pressure gradient (HVPG) measured through the transvenous route.

Laboratory data: aminopyrine breath test (ABT) (20); prothrombin time (PT); platelets (PLAT); serum concentrations of albumin (ALB), bilirubin (BILI), aspartate aminotransferase (ASAT), alanine arninotransferase (ALAT), creatinine (GREAT) and sodium (Na); 24-hours creatinine clearance (CREATCL).

Statistical analysis

The end-point of the study was set at one-month post-transplantation, the patient being recorded as alive or dead at this time.

Data were analyzed with the Kruskal-Wallis and Fisher exact test for univariate analysis, and with logistic regression for multivariate analysis (21). P values lower than 0.05 were considered as statistically significant in both univariate and multivariate analyses.

Results

The overall one-month mortality rate was 9/65 (13.8%). Causes of death were sepsis in 4 patients, peroperative in 2, haemorrhage in 2, and thrombosis of the hepatic artery leading to liver failure in 1.

Each of the 31 risk factors under consideration were correlated with the outcome of each patient at 30 days post-transplantation (alive or dead).

Table 1 shows that only 4/17 qualitative risk factors significantly influenced early mortality rate in those 65 patients: history of jaundice, history of ascites, history of encephalopathy and date of liver transplantation. It should be noted however that jaundice, ascites or encephalopathy observed on admission did not significantly affect early mortality rate.

Among the 14 quantitative factors listed in Table 2, only the serum sodium level affected early mortality rate since it was signifcantly lower in the 9 patients who died within 30 days than in the 56 patients surviving at the end of this period.

The five significant risk factors of the univariate analysis (Tables 1 and 2) were introduced into a multivariate analysis, and the date of liver transplantation emerged as the sole significant factor predicting one-month survival rate (regression coefficient ± standard error = 2.5455 ± 0.5192; $P < 0.001$).

Table 1. — **Qualitative risk factors**

	N° patients Alive at 30 days (N = 56)	N° patients Dead at 30 days (N = 9)	P Significance
ALC. (yes/no)	18/38	2/7	0.7
UNOS (1/2/3/4)	13/25/10/8	0/3/2/4	0.1
VAR (1/2/3)	15/25/12	2/3/4	0.47
LTX (before/after 01/01/89)	5/51	5/4	0.007
HM (yes / no)	10/46	1/8	1
HAS (yes / no)	6/50	3/6	0.10
HICT (yes / no)	11/45	6/3	0.007
HASC(yes / no)	11/45	5/4	0.03
HENC (yes / no)	11/45	5/4	0.03
HVH (yes / no)	20/36	2/7	0.7
HINF (yes / no)	3/53	0/9	1
HSCL (yes / no)	16/40	2/7	1.0
MAL (abs / mod / sev)	39/12/5	7/1/1	0.15
ICT (yes / no)	26/30	7/2	0.08
ASC (abs / mod / sev)	22/18/16	2/4/3	0.6
ENC (abs / mod / sev)	38/15/3	7/1/1	0.5
HDIUR (yes / no)	29/27	2/7	0.09

abs: absent; mod: moderate; sev: severe; other abbreviations are defined in material and methods.

Table 2. — **Quantitative risk factors**

	Patients Alive at 30 days (N = 56) Mean ± SD	Patients Dead at 30 days (N = 9) Mean ± SD	P Significance
Age (years)	49 ± 9	51 ± 7	0.20
LV (ml)	952 ± 616	691 + 452	0.27
ABT(%)	1.66i 1.6	1.46i 1.2	0.7
PUGH score	9.1 ± 2.0	10 + 1.9	0.3
HVPG (mmHg)	18.2 ± 7.2	18.8 ± 8.9	0.8
PT (%)	51 ± 12	50 ± 8	0.5
ALB (g/dl)	3.5 ± 0.6	3.7 ± 1.0	0.35
CREAT (mg/dl)	1.14 ± 1.0	0.92 ± 0.2	0.55
CREAT CL (ml/min)	91 ± 30	84 ± 24	0.71
Na (mEq/l)	136 ± 5	132 + 5	0.05
PLAT (× 10^3/mm^3)	85 ± 47	95 ± 42	0.58
BILI(mg/dl)	3.5 ± 3.9	2.7 ± 1.2	0.79
ASAT (IU/l)	64.9 ± 43	80 ± 54	0.69
ALAT (IU/l)	47.4 ± 37.6	54 ± 35	0.56

Abbreviations are defined in material and methods.

Table 3. — **Patients outcome at 30 days after LTX according to date of transplantation**

		Issue		Total
		N° patients alive at 30 days	N° patients dead at 30 days	
Date of LTX	before 1 January 1989	5 (50%)	5	10
	after 1 January 1989	51(93%)	4	55
Total		56 (86%)	9	65

Since this variable was both unique and categorized, it could be entered into a two-way table (Table 3). The probability of surviving at 30 days for a patient transplanted prior to 1 January 1989 was 5/10 (50%), but is was 51/55 (93%) for a patient transplanted after 1 January 1989 (Fisher exact test = 0.003).

Discussion

Accurate prediction of survival rate following OLTX should improve patients selection. This is a critical issue in the present era of organs shortage, requiring an improved utilisation. It should be stressed here that the lack of suitable organs for OLTX is responsible for a 15 to 30% mortality rate on the waiting-list (1).

Table 4 summarises the main data collected from the literature concerning the preoperative risk factors in OLTX recipients, and it deserves some comments. Several groups apparently identified predictive factors, albeit with controversial conclusions, whereas others strongly emphasized the significant role of the transplant team experience that improves with time. According to Stock *et al.* (7), recipient's age, prothrombin time, serum albumin and bilirubin levels at time of surgery did not predict the outcome of transplantation, and this group stressed the importance of the date of transplantation, which was closely related to surgical skill and perioperative care improvements. Brems *et al.* (8) showed that preoperative factors (recipient's age, liver disease, previous surgery, encephalopathy, laboratory values) were devoid of any significant effect on 3 month survival rate. Busutil *et al.* (9) compared the outcome of their first 100 cases with those of their subsequent 200 OLXT. Although more high risk patients (UNOS 4) were included in the more recent series, the 1-year survival rate rose from 73% to 88%. The improvement was ascribed to increased skill of the transplant team and to standardization of the procedure, leading to a more stable hemodynamic and metabolic course. Finally, a recent study from Canada (30) nicely demonstrated that the surgical technique was a major determinant of outcome in contrast to markers of disease severity which predicted only 10% of the early mortality observed.

In the present study, multivariate analysis showed that among the 31 preoperative risk factors considered, only one — the date of OLTX — would predict mortality rate at one month.

In comparison with previous studies (table 4), the present one is characterized by the homogeneity of the group at risk, by the large number of factors analyzed, and by the use of a multivariate analysis for selecting highly correlated variables.

It is well known (25,27) that OLTX survival rate is strongly influenced by the nature of the liver disease requiring the procedure : cholestatic liver disease invariably bearing a better prognosis than post-hepatitis or alcoholic cirrhosis. Our series included only adult

Table 4. — **Preoperative risk factors from the literature**

Reference	End-point	Population	Statistical analysis	Pre-OLT prognostic factors
13	hosp. mort.	A, P, CH, F, CHR	multiv. (logistic regression)	creatinin level UNOS status
22	hosp. mort.	A	multiv. (logistic regression)	malnutrition
23	hosp. mort.	A, P, CH, F, CHR	univ. and multiv. (Cox model)	creatinin level
24	hosp. mort.	A, P, CH, F, CHR	univ. and multiv. (discriminant)	creatinin level
25	hosp. mort.	A, P, CHR	univ. and multiv. (logistic regression)	BUN level
12	1 mo. mort.	A, C, P, CH, F, CHR	NR	UNOS status
26	1 mo. mort.	A, C, P, CH, F, CHR	NR	UNOS status
27	1 mo. mort.	NR	NR	encephalopathy
28	1 mo. mort.	A, C, P, CH, F, CHR	multiv. (Cox model)	date of OLT
29	1 mo. mort.	A, P, CH	univ.	no pronostic factor
2	3 mo. mort.	NR	NR	diuretic resistant ascites
8	3 mo. mort.	A, C, P, CH, F, CHR	univ.	no prognostic factor
11	6 mo. mort.	A, C, P, CH, F, CHR	risk factor scoring equation	encephalopathy, ascites, malnutrition, age, bilirubin, transfusions, coagulopathy
30	6 mo. mort.	A, C, P, CH, F, CHR	univ. multiv. (logistic regression)	ascites, bilirubin
31	6 mo. mort.	A, P, CH, CHR	univ.	creatinin level
7	6 mo. mort.	A, C, P, CH, F, CHR	univ.	date of OLT
32	6 mo. mort.	A, C, P, CH, F, CHR	univ. and multiv. (Cox model)	creatinin level
10	3 mo. OLTX failure	A, P, CHR	univ. and multiv. (logistic regression)	creatinin level
Present study	1 mo. mort.	A, P, CHR	univ. and multiv. (logistic regression)	date of OLT

A = adults ; C = children ; P = parenchymal liver disease ; CH = cholestatic liver disease ; F = fulminant liver disease ; CHR = chronic liver disease ; NR = not reported ; mort. = mortality ; hosp. = hospital ; mot = month ; multiv. = multivariate ; univ. = univariate.

patients with parenchymal cirrhosis, which was secondary to viral hepatitis or alcohol abuse in 58 of the 65 patients. This strongly contrasts with the high heterogeneity of previous series (Table 4) where biliary liver disease was mixed with parenchymal cirrhosis, fulminant with chronic conditions, and even adult patients with children (11,13,7,8,24). A recent study from Spain (25) included also only non biliary adult cirrhotic patients.

Univariate analysis shows that only 5 of the 31 risk factors under consideration are significantly related to short-term survival. Four of the factors are related to cinhosis and liver failure : history of jaundice, of ascites and of encephalopathy are markers of decompensated cirrhosis, and hyponatremia is probably due to impairment of water excretion as demonstrated by the fact that, in our series, the use of diuretics is not more frequent in the patients who will die after OLTX. However, when included in a multivariate analysis, only one of those 5 factors — the date of transplantation — emerges as the sole prognostic marker in our study. This is in agreement with other reports (7,28,9,30) and emphasizes the crucial role of increased skill of the transplant team. Therefore, our data strongly suggest that preoperative risk factors are devoid of prognostic value. In particular, indicators of the severity of liver disease, such as Child-Pugh class, arninopyrine breath test, liver volume, prothombin time, albumin, degree of encephalopathy and ascites and/or of portal hypertension (such as hepatic venous portosystemic gradient, stage of oesophageal varices) are not related to the posttransplant outcome.

Current results of liver transplantation for cirrhosis are excellent. One-year survival rates are presently 83% in the United States (33,15) and 76% in Europe (14). At the present time, this rate is 89% for our last 53 patients transplanted.

Although the preoperative status of the patients does not appear to significantly influence the results, this conclusion must be somewhat tempered since it concerns cirrhotic patients who were selected for a pretransplant work-up and possessed sufficient hepatic reserve to survive long enough on the waiting-list. Besides, if severe illness does not affect surgical mortality rate, it does however influence costs (34) and postoperative morbidity, particularly in the intensive care unit (35).

In the future, perioperative risk factors should be identified : peroperative factors, such as improved surgical and anesthetic experience, use of veno-venous bypass, optimal control of hemostasis, as well as early postoperative factors, such as reduced immunosuppression, improved infections prophylaxis, and accurate diagnosis and therapy of both rejection and infection.

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