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Variables Associated With the Risk of Early Death After Liver Transplantation at a Liver Transplant Unit in a University Hospital

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ABSTRACT

Background. Graft dysfunction after liver transplantation is a serious complication that can lead to graft loss and patient death. This was a study to identify risk factors for early death (up to 30 days after transplantation).

Methods. It was an observational and retrospective analysis at the Liver Transplantation Unit, Hospital de Clinicas, State University of Campinas, Brazil. From July 1994 to December 2012, 302 patients were included (>18 years old, piggyback technique). Of these cases, 26% died within 30 days. For analysis, Student *t* tests and chi-square were used to analyze receptor-related (age, body mass index, serum sodium, graft dysfunction, Model for End-Stage Liver Disease score, renal function, and early graft dysfunction [EGD type 1, 2, or 3]), surgery (hot and cold ischemia, surgical time, and units of packed erythrocytes [pRBC]), and donor (age, hypotension, and brain death cause) factors. Risk factors were identified by means of logistic regression model adjusted by the Hosmer-Lemeshow test with significance set at $P < .05$.

Results. We found that hyponatremic recipients had a 6.26-fold higher risk for early death. There was a 9% reduced chance of death when the recipient serum sodium increased 1 unit. The chance of EGD3 to have early death was 18-fold higher than for EGD1 and there was a 13% increased risk for death for each unit of pRBC transfused.

Conclusions. Donor total bilirubin, hyponatremia, massive transfusion, and EGD3 in the allocation graft should be observed for better results in the postoperative period.

ACCORDING to data from the Brazilian Organ Transplant Association (ABTO) [1], 16,186 liver transplants were performed in Brazil from 2003 to 2012, and there were ~7,005 patients on the liver transplant waiting list [2]. Because, invariably, major surgeries are performed on patients under difficult clinical conditions owing to advanced chronic liver disease, the risk of complications can lead to graft rejection requiring retransplantation and receptor death [2–4].

The vast majority of deaths occurred in the first 30 days after surgery, and although much effort has been made to find an early diagnosis and treatment of complications, it is still insufficient to minimize the suffering while waiting on the transplant list. Primary nonfunction (PNF) is the main cause for early graft loss, with an incidence ranging from 2% to 23%, as shown by some studies [5,6]. Its etiology remains unknown, although some factors related to the donor at the time of reperfusion, among others, are closely related to the occurrence of PNF [7,8].

Vascular complications after liver transplantation (LT) are another important reason for graft loss, with an incidence ranging from 2.6% to 20%, the most severe being hepatic artery thrombosis [8–12].

A previous analysis carried out by our service showed that the major causes of graft loss and death of the patient within 30 days are early graft dysfunction and coagulopathy, respectively [13,14].

The present study aimed to analyze and identify the risk factors for early death defined as occurring in the first 30 days after LT.

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Table 1. Descriptive Demographic and Clinical Data from Qualitative Recipients' and Liver Donors' Variables According to Status of Early Death or Alive

	Early Death	Alive	*P* Value
Recipients' variables			
Sex			
Female	23 (28.0%)	59 (72.0%)	.38
Male	51 (23.2%)	169 (76.8%)	
Aging			
No	60 (23.7%)	193 (76.3%)	.46
Yes	14 (28.6%)	35 (71.4%)	
Obesity			
No	58 (22.7%)	197 (77.3%)	.09
Yes	16 (34.0%)	31 (66.0%)	
Diabetes			
No	56 (23.4%)	183 (76.6%)	.26
Yes	16 (30,8%)	36 (69.2%)	
Hyponatremia			
A	57 (22.8%)	193 (77.2%)	.13
B	17 (32.7%)	35 (67.3%)	
EGD			
EGD1	4 (3.4%)	113 (96.6%)	.001
EGD2	7 (8.8%)	73 (91.2%)	
EGD3	13 (28.3%)	33 (71.1%)	
CTP			
A	5 (19.2%)	21 (80.8%)	.03
B	17 (17.7%)	79 (82.3%)	
C	52 (28.9%)	128 (71.1%)	
Sepsis			
Yes	9 (27.3%)	24 (72.7%)	.06
No	65 (24.2%)	204 (75.8%)	
HAT			
Yes	6 (50.0%)	6 (50.0%)	.03
No	68 (23.4%)	222 (76.6%)	
Donors' variables			
Age			
<50 y	62 (24.4%)	192 (75.6%)	.88
Brain death cause			
Anoxia	14 (29.8%)	33 (70.2%)	.34
Trauma	7 (22.6%)	24 (77.4%)	
Other	52 (23.4%)	170 (76.6%)	
Arterial hypotension			
Yes	12 (17.6%)	56 (82.4%)	.13
No	62 (26.6%)	171 (73.4%)	

Abbreviations: EGD, early graft dysfunction; CTP, Child-Turcotte-Pugh classification; HAT, hepatic arterial thrombosis.

METHODS

This was an observational, cross-sectional and retrospective study through medical records and the prospective electronic database from the Unit of Liver Transplantation, Hospital de Clínicas, State University of Campinas, and the São Paulo Health Transplant System.

A total of 302 liver transplantations in adult patients from July 1994 to December 2012 with the use of the piggyback technique were included in this analysis. We excluded patients submitted to retransplantation, liver-kidney transplantation, and acute liver failure as cause for transplantation. All patients received liver grafts from deceased donors. We considered early death when the event occurred up to the 30th postoperative day and the patients were distributed according to this event: dead versus alive. For diagnosis of primary graft failure and early graft dysfunction the following classification [2] was used:

- Primary nonfunction (PNF): patients who died within the 1st 7 days with aspartate aminotransferase (AST) >5,000 UI/L, international normalized ratio (INR) ≥2.5 or acidosis, arterial pH <7.30 or venous pH <7.25, or lactate ≥4 mmol/L according to the United Network of Organ Sharing (UNOS).
- Early graft dysfunction (EGD): according to the following definitions, the classification used by Boin et al in 2008 [4], adapted from Heise and other criteria in 2003 [5]: a) EGD1: patients who died within 30 days with maximum alanine aminotransferase (ALT) >1,000 IU/L; b) EGD2: ALT 1,001–2,499 IU/L; c) EGD3: ALT >2,500 IU/L [2].

Other complications defined were:

- Hepatic artery thrombosis (HAT): thrombosis diagnosed with the use of a Doppler ultrasonography or computerized tomography with contrast or during surgical procedure.
- Glomerular filtration rate (GFR): as estimated with the use of the Cockcroft-Gault formula: [140 − age (y)] × weight (kg)/creatinine (mg/dL) × 72 (× 0.85 if female) [15].
- Sepsis: defined by the criteria of critical care medicine [2,13].
- Cardiac arrest (CA): the patient died during surgery owing to cardiac arrest in the preoperative period.

The preservation solution used in the period 1991–2009 was the Belzer solution (WS), and in 2010 we started to use the HTK solution. All patients underwent standard immunosuppressive therapy based on calcineurin inhibitors: cyclosporine (CsA; 4–8 mg/kg) or FK506 (0.1 mg/kg) and steroids until the 180th day after transplantation with tapering and withdrawal. The CsA blood level was 200–400 ng/mL in the 1st 3 months and 150–250 ng/mL for another month. The FK506 blood level was 8–12 ng/mL in the 1st 3 months and 5–10 for another month [7].

The recipients' quantitative variables studied were: age (y), body mass index (BMI; kg/m^2), serum sodium (mEq/L), Model for End-Stage Liver Disease (MELD) score [16], warm ischemia time (min), cold ischemia time (min), surgical time (min), and packed red blood

Table 2. Descriptive Demographic and Clinical Data from Quantitative Recipients' and Liver Donors' Variables According to Status of Early Death or Alive

	Early Death	Alive	*P* Value
Recipients' variables			
Age (y)	50.0 ± 9.8	47.8 ± 10.9	.099
Body mass index (kg/m^2)	26.6 ± 5.1	25.7 ± 4.1	.193
Serum sodium (mEq/L)	134.3 ± 7.3	135.3 ± 5.2	.269
ALT max (UI/L)	5132 ± 4378	1635 ± 2203	<.001
MELD score	21.0 ± 7.3	18.4 ± 5.6	.004
GFR (mL/min)	98.5 ± 52.9	101.5 ± 40.7	.656
Warm ischemia (min)	74.7 ± 43.6	58.1 ± 16.9	.003
Cold ischemia (min)	675.1 ± 205.1	646.5 ± 194.6	.697
Surgical time (min)	536 ± 168.3	502.3 ± 134.2	.122
pRBC (units)	13.0 ± 10.2	5.0 ± 4.5	<.001
Donors' variables			
Age (y)	33.6 ± 13.4	34.2 ± 13.6	.743
Total bilirubin (mg/dL)	0.92 ± 0.7	0.78 ± 0.62	.137
Serum sodium (mEq/L)	155.4 ± 16.3	151.8 ± 14.8	.093

Abbreviations: ALT max, maximum alanine aminotransferase up to 30th postoperative day; MELD, Model for End-Stage Liver Disease; GFR, glomerular filtration rate; pRBC, packed red blood cells.

Table 3. Logistic Regression Model Applied to Recipients' Variables Stratifying to Hyponatremic Patients According to Early Death

Variables	Beta	OR	95% CI	*P* Value
Sodium	−0.098	0.91	0.84–0.98	.01
EGD3	2.880	17.76	4.24–74.32	.001
pRBC	0.125	1.13	1.04–1.24	.005

Abbreviations: OR, odds ratio; CI, confidence interval; other abbreviations as in Tables 1 and 2.

cells (pRBC) transfused (units). The categorical variables were: dead/alive (after 30th postoperative day), sex (male/female), aging (yes/no), obesity (yes/no, BMI >30 kg/m^2), diabetes (yes/no, glycemia >125 mg/dL), hyponatremia (yes/no, serum sodium <130 mEq/L), Child-Turcotte-Pugh classification (CTP score A, B, or C) [17], and etiology of recipient's hepatic disease.

The donors' quantitative variables were: age (y), total bilirubin (mg/dL), and serum sodium (Na, mEq/L). The qualitative variables were: aging (yes/no, >50 years), arterial hypertension (yes/no), and cause of brain death (anoxia, trauma, or other).

The quantitative variables were analyzed with the use of descriptive statistics and Student *t* test, and categoric variables with the use of chi-square test, applying Fisher exact test when necessary. When the variables had *P* values <.25 in those tests, we applied Hosmer-Lemeshow test to adjust selection criteria after we applied a logistic regression model to identify risk factors. The significant *P* value was <.05.

RESULTS

Seventy-four patients (24.5%) died by the 30th postoperative day and 228 (75.5%) were alive. Hepatitis C associated or not with alcohol was present in 32/74 (43.2%) and 106/228 (46.5%) of the cases.

The major cause of recipient early death was PNF (24/74, 32.4%) followed by CA (8/74, 10.8%). The qualitative recipients' and liver donors' descriptive statistics are presented in Table 1.

When the quantitative variables were compared according to early-death versus alive patients we can observe that early-death patients had higher MELD score (21 ± 7.3; range, 7–46; $P = .004$); max ALT (5,132 ± 4,378 IU/L; range, 274–22,700; $P < .001$); pRBC (13.0 ± 10.2 units; range, 0–62; $P < .001$), and warm ischemia time (74.2 ± 46.6 min; range 30–155). These and the other variables are presented in Table 2. As a result we found that hyponatremic recipients had 6.26 times higher risk for early death.

According to Table 3, we can observe that there is a 9% reduced chance of death when the recipient serum sodium increases 1 unit. The chance of patients with EGD3 having early death is 18 times greater than for patients with EGD1, and there is a 13% increased risk of death for each unit of pRBC transfused.

DISCUSSION

Although many studies describe the relationship between the occurrence of PNF and EGD [5–7], we observed in our study that 24.5% patients died in the early period after LT and the great majority owing to PNF. EGD3 was a major risk factor for such death (an almost 18-fold increase). Similar results are described in the literature [2,6,7].

We observed that high MELD score, CTP C, or severe patients with major complications and mortality were associated with HAT as a risk factor for early death, as reported in the literature [2,17,18].

Long warm ischemia time was associated with either early or long-term death, as reported in the literature [2,5,13,19–21]. Vrochides et al also reported that parameters that were identified with early postoperative mortality were CTP score, MELD score, bilirubin, creatinine, INR, and warm ischemia time [21].

In the present study, hyponatremic patients showed a 6-fold higher risk for early death. Leise et al [22] reported that there was no difference in in-hospital mortality or 90-day survival between patients with hyponatremia and patients with normonatremia. After adjustments for important clinical variables, the association of pre-LT hypernatremia with post-transplantation mortality remained significant with a hazard ratio of 1.13 for each unit increase in the Na level >145 mEq/L ($P < .001$). The duration of hospitalization after LT was significantly longer for hypernatremic patients ($P < .001$), and the authors concluded that pre-LT hypernatremia is a highly significant risk factor for post-LT mortality, as we observed in our study.

Many studies have reported allogeneic blood transfusions to be associated with adverse effects in recipients [19]. Although some data show the relationship between the amount of transfused pRBC and poor outcome after LT, the mechanism is unknown. Blood transfusion can interfere with the immune system of the recipient [20]; residual amounts of donor leukocytes present in red blood as well as preservation-related changes in erythrocytes and a duration of storage of transfused blood are important risk factors for poor outcome after LT [23].

In conclusion, hyponatremia, massive transfusion, and severe EGD should be observed in the allocation graft for better results in the postoperative period.

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