



ORIGINAL

Early postoperative mortality in liver transplant recipients involving indications other than hepatocellular carcinoma. A retrospective cohort study



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Received 5 September 2019; accepted 11 February 2020

KEYWORDS

Liver transplantation;
Hepatocellular carcinoma;
Postoperative complications;
Mortality;
Cox regression analysis

Abstract

Aims: To analyze the perioperative differences in a consecutive cohort of liver transplant recipients (LTRs) classified according to the indication of transplantation, and assess their impact upon early mortality 90 days after transplantation.

Design: A retrospective cohort study was carried out.

Scope: A single university hospital.

Patients: A total of 892 consecutive adult LTRs were included from January 1995 to December 2017. Recipients with acute liver failure, retransplantation or with grafts from non-brain death donors were excluded. Two cohorts were analyzed according to transplant indication: hepatocellular carcinoma (HCC-LTR) versus non-carcinoma (non-HCC-LTR).

Main variables of interest: Recipient early mortality was the primary endpoint. The pretransplant recipient and donor characteristics, surgical time data and postoperative complications were analyzed as independent predictors.

Results: The crude early postoperative mortality rate related to transplant indication was 13.3% in non-HCC-LTR and 6.6% in HCC-LTR (non-adjusted HR = 2.12, 95%CI = 1.25–3.60; $p = 0.005$). Comparison of the perioperative features between the cohorts revealed multiple differences. Multivariate analysis showed postoperative shock (HR = 2.02, 95%CI = 1.26–3.24; $p = 0.003$), early graft vascular complications (HR = 4.01, 95%CI = 2.45–6.56; $p < 0.001$) and multiorgan dysfunction syndrome (HR = 18.09, 95%CI = 10.70–30.58; $p < 0.001$) to be independent predictors of mortality. There were no differences in early mortality related to transplant indication (adjusted HR = 1.60, 95%CI = 0.93–2.76; $p = 0.086$).

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Conclusions: The crude early postoperative mortality rate in non-HCC-LTR was higher than in HCC-LTR, due to a greater incidence of postoperative complications with an impact upon mortality (shock at admission to intensive care and the development of multiorgan dysfunction syndrome).

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PALABRAS CLAVE

Trasplante de hígado;
Carcinoma
hepatocelular;
Complicaciones
postoperatorias;
Mortalidad;
Regresión de Cox

Mortalidad postoperatoria precoz en los receptores de trasplante hepático por indicaciones distintas al carcinoma hepatocelular (non-HCC). Estudio retrospectivo de cohortes

Resumen

Objetivos: Analizar las diferencias perioperatorias de una cohorte de trasplantados hepáticos (LTR) clasificados por la indicación de trasplante, y evaluar su impacto sobre la mortalidad precoz (90 días postrasplante).

Diseño: Estudio de cohorte retrospectivo.

Ámbito: Institución universitaria.

Pacientes: Desde 1995 hasta 2017 fueron incluidos 892 LTR. Se excluyeron los receptores con fallo hepático agudo, retrasplante o de donantes sin muerte cerebral. Se analizaron 2 cohortes según el motivo del trasplante: carcinoma hepatocelular (HCC-LTR) vs. causas diferente al carcinoma (non-HCC-LTR).

Principales variables de interés: La variable principal fue la mortalidad precoz. Las características pretrasplante de receptores, donantes, tiempo quirúrgico y complicaciones postoperatorias se estudiaron como predictores independientes.

Resultados: La mortalidad postoperatoria temprana bruta relacionada con la indicación de trasplante fue del 13,3% en non-HCC-LTR y del 6,6% en HCC-LTR (HR no ajustada: 2,12; IC 95%: 1,25-3,60; $p = 0,005$). La comparación de características perioperatorias entre las cohortes mostró múltiples diferencias. El *shock* postoperatorio (HR: 2,02; IC 95%: 1,26-3,24), complicaciones vasculares tempranas del injerto (HR: 4,01; IC 95%: 2,45-6,56) y síndrome de disfunción multiorgánica (HR: 18,09; IC 95%: 10,70-30,58) fueron predictores independientes de mortalidad. La indicación de trasplante no mostró significación en el análisis multivariante (HR ajustada: 1,60; IC 95%: 0,93-2,76; $p = 0,086$).

Conclusiones: La mortalidad postoperatoria temprana bruta en non-HCC-LTR fue mayor que en HCC-LTR debido a la mayor incidencia de complicaciones postoperatorias con impacto en la mortalidad (*shock* al ingreso en la UCI y aparición del síndrome de disfunción multiorgánica).

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Introduction

Liver transplantation is the only potentially curative therapy for patients with end-stage liver disease and early-stages hepatocellular carcinoma (HCC) but priority and equity to access to transplantation are a controversial issue.^{1,2}

Among liver transplant recipients (LTR), the highest incidence of mortality occurs within the early posttransplant period and it is close to 10% in elective recipients at 90 days.³ Although some baseline clinical features of donors or recipients may justify some cases of mortality,⁴⁻⁵ in most patients the postoperative complications directly derived from transplantation surgery are responsible for early death and usually unpredictable.⁶⁻⁹

Before the upcoming of Milan criteria¹⁰ there was a worldwide moratorium on access to transplant of patients with HCC. Currently, liver transplantation due to HCC accounts for 15–30% of all transplants performed in most

of the institutions.^{11,12} The indication for liver transplantation (HCC vs non-HCC) seems to have an impact on early postoperative mortality but literature around this issue is heterogeneous.^{13,14} Targeted studies examining the difference between mortality rates after whole-graft elective liver transplantation from brain-dead donors without inclusion of recipients with acute liver failure or retransplantation are lacking.

Liver transplant recipients due to HCC (HCC-LTR) could show lower perioperative mortality rates, mainly due to preserved pretransplant liver function, less portal hypertension¹⁵ and reduced comorbidities.¹⁶ In addition, while prioritization of LTR due to end-stage liver disease (non-HCC-LTR) depends on the MELD score in most centres in Europe and USA, prioritization of HCC-LTR is more arbitrary (ie. MELD exceptions) and may vary among different countries or even among institutions within the same country.¹⁷

Therefore, the aims of this study were to analyse the perioperative differences in a consecutive cohort of LTR classified according to indication to transplant and assess their impact on early mortality during 90 day after transplantation.

Patients and methods

The present study is a retrospective analysis of a prospectively collected database from a single centre. A consecutive cohort of adult (>16 aged) LTR with brain-dead donors from January 1995 to December 2017 was analysed.

All LTR after liver transplantation were admitted at Intensive Care Unit (ICU) and included in the study. Exclusion criteria were as follows: patients with acute liver failure enlisted for urgent transplantation, multiple organ transplantation, retransplantation, split or reduced donation, living donation and donation after cardiac death. Subsequently, the cohort was ordered according to transplant indication (HCC-LTR vs non-HCC-LTR).

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) recommendations¹⁸ were followed for the study design and the manuscript preparation.

The study fulfils all ethical requirements of the WHO code (Declaration of Helsinki) and was approved by the Regional Clinical Research and Ethics Committee (Code 0823-N-18, Act No. 278, ref 3948) without requirement of signed informed consent.

According to our regional prioritization system,¹⁹ patients with HCC (HCC-LTR cohort) empirically received 15 MELD points at inclusion in the waiting list. Extra-MELD points were granted only to a subgroup of patients with an increased risk of tumour progression (ie. a single tumour ≥ 3 cm, multinodular or with alpha fetoprotein > 200 ng/mL). In such patients one extra-MELD point was added every month within the waiting list up to 20 MELD points. The non-HCC-LTR cohort included LTR with end-stage liver disease and poor liver function irrespective of cirrhosis aetiology. They were prioritized according their actual MELD score which was updated at each patient visit. Patients enlisted for special indications such as refractory ascites or recurrent encephalopathy were also included in the non-HCC-LTR and prioritized as follows. In patients with refractory ascites, MELD-Na was considered after 3 months in the waiting list. In patients with encephalopathy, MELD 15 at inclusion, one extra MELD point every three months up to 18 points, and 1 extra MELD point every other month thereafter. Both indications were limited to MELD 20.

Throughout the study period, three different surgical techniques were performed in our institution. Until 1992, the *Standard technique* was the standard of care whenever the patient could tolerate the vascular clamping test. Subsequently, *Preservation of inferior cava vein technique* became the most commonly performed. In 2007, *Preservation of inferior cava vein with a temporary portacaval shunt* was adopted and since then it has been considered the technique of choice.

All patients included in the study had been admitted to ICU immediately after surgery. Initial postoperative treatment throughout the study period was fairly homogeneous,

with no significant clinical changes in terms of supportive treatment, antimicrobial prophylaxis or length of stay in ICU. Doppler ultrasound was routinely performed to rule out vascular complications within the first 24 h after transplant, at day 7th and whenever clinically indicated. Immunosuppressive regimens, however, have been changed according to the state of art of each period. Since 1997, tacrolimus was available in its oral formulation and after 2008 it is administered in a triple therapy regimen using initial low doses. Currently, induction therapy with anti-CD25 antibodies is restricted to patients with severe graft dysfunction or pretransplant renal impairment in order to avoid calcineurin inhibitors within the first 5–7 postoperative days.

Variables

The main dependent variable of the study was early postoperative mortality (ie. within the first 90 days after transplant). Other outcomes were urgent retransplantation in the first 7 days due to graft non-function (primary or vascular cause) and length of stay in ICU.

The following variables were explored as potential predictors of such outcomes. As for the recipients, demographic variables (age, gender, weight, height and body mass index), indication or reason for inclusion in waiting list for transplantation (HCC vs non-HCC), aetiology of liver disease, renal function tests (blood urea and creatinine levels) and pretransplant scores related to severity and prognosis of liver disease (Child–Pugh and MELD-Na) were recorded. The MELD-Na score was calculated with laboratory data obtained just before the transplant. Moreover, pretransplant comorbidities that could affect early postoperative mortality, such as diabetes mellitus, implantation of transjugular portosystemic shunt (TIPS) or supramesocolic surgery were studied. Criteria of hepatorenal syndrome, treatment with terlipressin, need for renal support (dialysis in any of its modalities) and hospital admissions in the course of the month prior to transplantation were also obtained from clinical records.

Explanatory variables of donors such as gender, age, weight, length of stay in ICU, graft cold ischemia time and graft or donor meaningful characteristics were recorded. Suboptimal graft or donor were considered when they met two or more of the following criteria: age over 80 years, obesity, prolonged or severe hypotension episodes requiring vasoactive drugs longer than 6 h, need for high doses of vasoactive agents (e.g., noradrenaline > 0.4 μ g/kg/min), length of stay in ICU > 7 days, graft injury during the harvesting process or steatosis greater than 30% found in the baseline graft biopsy.

Characteristics of surgical technique of transplantation, type of vascular clamping and need for biliary derivation as technique of biliary anastomosis, time of surgery, need for transfusions and severe intraoperative complications such as cardiac arrest or severe cardiac dysfunction were registered.

Several clinical features and analytical parameters of patients were obtained at admission and throughout their stay in ICU. Postoperative oxygenation status immediate upon ICU admission, serum lactate peak value within the first 48 h, aminotransferases (AST, ALT) peak value in the

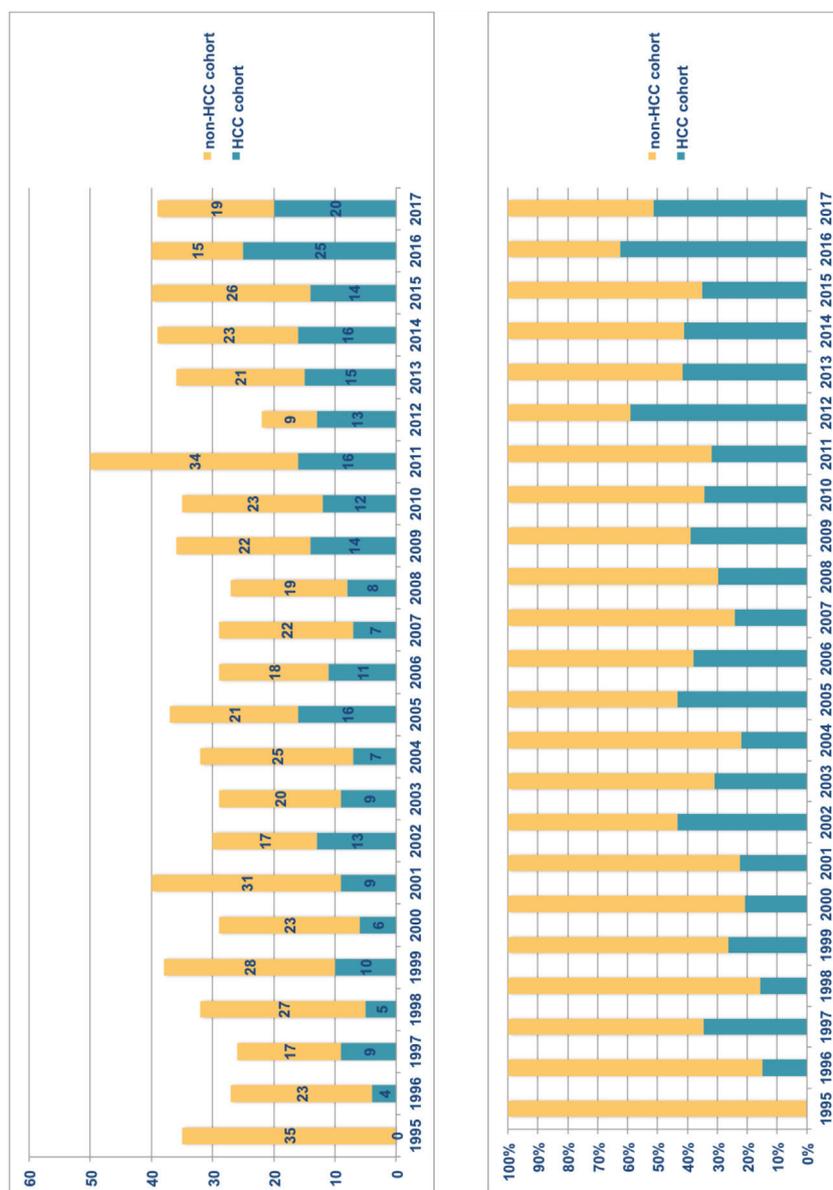


Figure 2 Annual numbers and proportions in both cohorts of liver transplant recipients.

MELD-Na score 12 [IQR 9-16] points in HCC-LTR vs 19 [IQR 16-23] points¹⁶⁻²³ in non-HCC-LTR, $p < 0.001$), as in parameters related to pretransplant renal function and need of previous hospital admission ($p < 0.001$).

Donors characteristics and surgical features during transplantation time are shown in Table 2. Significant differences between cohorts were found in age of donors and cold ischemia time of grafts. The proportion of sub-optimal donors was scarce in both cohorts. Non-HCC-LTR required more RBC and plasma transfusions ($p < 0.001$, in both).

Explanatory variables related to early postoperative period are shown in Table 3. Immediately after ICU admission, no differences were found between cohorts regarding to pulmonary oxygenation or serum lactate peak values. However, non-HCC-LTR showed an increase rate of shock at ICU admission, which was associated with lower hemoglobin

levels, a higher requirement of massive transfusions of RBC (>6 units) within the first 5 postoperative days, and an increased risk of early surgical reoperations (usually due to postoperative hemorrhage). Collinearity between shock upon ICU admission and intraoperative transfusion of RBC was demonstrated. Therefore, this latter was excluded from the final analysis.

A greater grade of ischemia/reperfusion injury, which was estimated by an increase in postransplant ALT peak value, was found in HCC-LTR. This cohort had shorter cold ischemia time but older donors. No meaningful differences were found in liver synthesis function tests assessed by INR at postoperative day 7 ($p = 0.277$) nor in urgent retransplantation rate (1.5% in HCC-LTR vs 1.7% in non-HCC-LTR, $p = 0.843$). However, cholestasis (serum bilirubin at 7th postoperative day) was more frequent in non-HCC-LTR ($p < 0.001$). No other meaningful differences were found in

Table 1 Baseline characteristics of liver transplant recipients. Comparison of risk between cohorts (non-HCC-LTR vs HCC-LTR) by binary logistic regression.

	N	LTR-cohort ^a N = 777	HCC – LTR n = 259	Non-HCC – LTR n = 518	OR	CI 95%	p
<i>Demographic data</i>							
Gender, Female (%)		185 (23.8)	33 (12.7)	152 (29.3)	2.844	1.885–4.291	<0.001
Age, years		54 (48–59)	56 (51–61)	53 (45–59)	0.933	0.914–0.952	<0.001
Weight, kg	761 ^b	75 (65–85)	79 (70–89)	72 (63–81)	0.972	0.962–0.982	<0.001
Height, cm	761	168 (162–173)	169 (164–173)	167 (161–173)	0.978	0.961–0.996	0.018
BMI, kg/m ²	761	26.4 (23.8–29.6)	27.7 (24.6–30.8)	25.9 (23.4–28.7)	0.922	0.891–0.953	<0.001
<i>Reason to transplant</i>							
HCC-LTR (%)			259 (100)				
Non-HCC-LTR (%)				518 (100)			
Hepatocellular insufficiency (%)				409 (79.0)			
Special indications and others (%)				62 (12.0)			
Biliary cirrhosis (%)				47 (9.1)			
<i>Liver disease stage</i>							
Child C stage (%)		292 (37.6)	37 (14.3)	255 (49.2)	5.783	3.920–8.531	<0.001
MELD-Na, points	772	17 (12–22)	12 (9–16)	19 (16–23)	1.229	1.186–1.273	<0.001
<i>Previous comorbidities</i>							
Diabetes mellitus (%)		225 (29.0)	83 (32.0)	142 (27.4)	0.801	0.579–1.108	0.181
TIPS previous (%)	776	41 (5.3)	10 (3.9)	31 (6.0)	1.588	0.766–3.292	0.237
Supramesocolic surgery (%)	776	105 (13.5)	42 (16.2)	63 (12.2)	0.717	0.470–1.094	0.148
Blood creatinine, mg/dL	773	0.9 (0.7–1.1)	0.8 (0.7–1.0)	0.9 (0.7–1.2)	1.744	1.178–2.544	0.006
Blood urea, mg/dL	772	33 (25–46)	30 (24–40)	35 (25–52)	1.013	1.006–1.019	<0.001
Hepatorenal syndrome (%) ^c	775	81 (10.5)	10 (3.9)	71 (13.8)	3.081	1.421–6.681	0.004
Dialysis (%)	776	6 (0.8)	2 (0.8)	4 (0.8)	1.002	0.182–5.506	1.000
Previous hospital admission (%)		85 (10.9)	6 (2.3)	79 (15.3)	7.047	2.757–18.012	<0.001

^a LTR-Cohort = Cohort of Liver Transplant Recipients. HCC-LTR = Patients transplanted due Hepatocellular Carcinoma. Non-HCC-LTR = Patients transplanted due to other causes than HCC.

^b Number of patients evaluated and followed when there were data missing or errors in the records or reports.

^c Hepatorenal syndrome. Dialysis and Previous hospital admission. All of them are referring to comorbidities within the prior month to transplantation.

Table 2 Donors characteristics and transplantation surgical time features. Comparison of risk between cohorts (non-HCC-LTR vs HCC-LTR) by binary logistic regression.

	N	LTR-cohort ^a N = 777	HCC – LTR n = 259	Non-HCC – LTR n = 518	OR	CI 95%	p
<i>Donor characteristics</i>							
Gender, Female (%)		294 (37.8)	95 (36.7)	199 (38.4)	1.077	0.791–1.466	0.638
Age, years	776 ^b	51 (34–64)	54 (34–66)	49 (34–62)	0.992	0.984–1.000	0.059
Weight, kg	769	75 (65–83)	75 (67–85)	75 (65–80)	0.991	0.979–1.003	0.138
ICU length of stay, days	765	2 (1–4)	2 (1–4)	2 (1–5)	1.005	0.966–1.045	0.819
Cold ischemia time, min	753	360 (300–540)	360 (300–480)	380 (300–558)	1.001	1.000–1.002	0.011
Suboptimal donors (%)	766	16 (2.1)	6 (2.3)	10 (1.9)	0.830	0.298–2.309	0.721
<i>Surgical features</i>							
<i>Vascular clamping methods</i>	776						
Standard technique (%)		86 (11.1)	31 (12.0)	55 (10.6)			
Caval flow preservation with and without porto-caval shunt (%)		690 (88.9)	227 (88.0)	463 (89.4)	1.150	0.720–1.836	0.559
<i>Hepatic-jejunostomy as biliary reconstruction (%)</i>	775	16 (2.1)	0	16 (3.1)			
<i>Intraoperative red blood cells transfusions, units</i>	634	5 (2–9)	3 (1–6)	6 (3–10)	1.109	1.070–1.149	<0.001
<i>Intraoperative plasma transfusions, units</i>	629	4 (0–9)	2 (0–5)	5 (2–10)	1.124	1.083–1.167	<0.001
<i>Transplantation surgical time, min</i>	764	270 (240–300)	270 (240–300)	270 (240–300)	1.001	0.999–1.003	0.394
<i>Severe intraoperative cardiac complications (%)^c</i>	775	56 (7.2)	12 (4.7)	44 (8.5)	1.911	0.991–3.684	0.056

^a LTR-cohort = Cohort of Liver Transplant Recipients. HCC-LTR = Patients transplanted due Hepatocellular Carcinoma. Non-HCC-LTR = Patients transplanted due to other causes than HCC.

^b Number of patients evaluated and followed when there were data missing or errors in the records or reports.

^c Intraoperative Severe Ventricular Dysfunction or Cardiac Arrest.

Table 3 Postoperative features in liver transplant recipients cohort.

	N	LTR cohort ^a N = 777	HCC - LTR n = 259	Non-HCC - LTR n = 518	OR	CI 95%	p
<i>At ICU admission</i>							
paO ₂ /FiO ₂	770 ^b	352 (262–453)	394 (291–477)	331 (252–429)	0.999	0.998–1.001	0.325
Lactate peak, mmol/L ^c	599	3.8 (2.3–6.3)	3.4 (2.0–6.0)	3.3 (2.0–5.5)	0.990	0.949–1.034	0.652
Shock (%)		98 (12.6)	18 (6.9)	80 (15.4)	2.445	1.432–4.175	0.001
<i>Perioperative complications</i>							
Lowest hemoglobin level in the first 5 days, g/L	761	84 (78–100)	90 (80–108)	80 (75–90)	0.971	0.962–0.980	<0.001
Massive RBC transfusion (%) ^d	776	83 (10.7)	14 (5.4)	69 (13.3)	2.695	1.486–4.888	0.001
Early surgical reoperations in the first 4 days (%)		98 (12.6)	19 (7.3)	79 (15.3)	2.273	1.345–3.842	0.002
Vascular thrombosis in the first 7 days (%)	776	51 (6.6)	16 (6.2)	35 (6.8)	1.103	0.598–2.032	0.754
Late or multiple surgical reoperations (%)	776	48 (6.2)	17 (6.6)	31 (6.0)	0.908	0.493–1.673	0.757
<i>Graft function test</i>							
AST peak value in the first 3 days, U/L	774	724 (379–1400)	740 (412–1534)	712 (369–1344)	1.000	1.000–1.000	0.058
ALT peak value in the first 3 days, U/L	774	526 (271–1040)	609 (316–1110)	499 (245–994)	1.000	1.000–1.000	0.011
INR on day 7	738	1.1 (1.0–1.2)	1.1 (1.0–1.1)	1.1 (1.0–1.2)	1.663	0.665–4.161	0.277
Total bilirubin on day 7, mg/dL	732	2.4 (1.1–5.7)	1.6 (0.9–3.5)	3.2 (1.4–6.7)	1.106	1.062–1.152	<0.001
<i>Renal function complications</i>							
Serum-creatinine peak value in the first 5 days, mg/dL	764	1.2 (0.9–1.8)	1.0 (0.8–1.6)	1.3 (0.9–1.9)	1.508	1.206–1.885	<0.001
Serum-urea peak value in the first 5 days, mg/dL	762	99 (68–144)	79 (59–109)	107 (73–155)	1.011	1.007–1.014	<0.001
Extra-renal deputation methods (%)	776	46 (5.9)	13 (5.0)	33 (6.4)	1.282	0.663–2.481	0.460

Table 3 (Continued)

	N	LTR cohort ^a N = 777	HCC – LTR n = 259	Non-HCC – LTR n = 518	OR	CI 95%	p
<i>Respiratory function complications</i>							
Post-transplant mechanical ventilation time, h	754	11 (7–19)	9 (6–15)	12 (7–21)	1.001	0.998–1.004	0.717
Mechanical ventilation time < 24 h (%)		655 (84.3)	231 (91.3)	424 (84.6)	0.524	0.318–0.865	0.011
Re-intubation and mechanical ventilation (%)		75 (9.7)	17 (6.6)	58 (11.2)	1.795	1.023–3.150	0.042
Tracheostomy (%)		19 (2.4)	3 (1.2)	16 (3.1)	2.720	0.785–9.420	0.101
<i>Infectious complications</i>							
Early infection (%)	776	144 (18.6)	33 (12.7)	111 (21.5)	1.872	1.229–2.853	0.004
Intra-abdominal infection (%)	776	67 (8.6)	17 (6.0)	50 (9.7)	1.555	0.879–2.750	0.127
<i>Multiorgan dysfunction</i>							
MODS criteria (%) ^e	777	94 (12.1)	20 (7.7)	74 (14.3)	1.992	1.186–3.345	0.009
<i>Other complications</i>							
Severe neurological complications (%) ^f	775	58 (7.5)	17 (6.6)	41 (7.9)	1.224	0.681–2.199	0.564
<i>Outcome variables</i>							
ICU length of stay, days	775	6 (4–8)	5 (4–6)	6 (5–8)	1.058	1.022–1.095	0.002
Retransplantation < 7th days (%)	777	13 (1.7)	4 (1.5)	9 (1.7)	1.127	0.344–3.695	0.843
Mortality (%) ^g	777	86 (11.1)	17 (6.6)	69 (13.3)	2.117	1.245–3.599	0.006

^a LTR-cohort = Overall Cohort of Liver Transplant Recipients. HCC-LTR = Patients transplanted due Hepatocellular Carcinoma. Non-HCC-LTR = Patients transplanted due to other causes than HCC.

^b Number of patients evaluated and followed when there were data missing or errors in the records or reports.

^c Automated analysis of serum lactate was not available in our institution until 1999, and therefore it is not recorded prior to that date. For the study, Lactate was determined in 599 patients, with a loss of 22.9% of the cases.

^d Masive Transfusion = Six or more transfusion of Red Blood Cells in the first 5 days.

^e MODS = Multiple Organ Dysfunction Syndrome.

^f Severe encephalopathy, seizures or cerebrovascular accidents.

^g Patients with urgent retransplantation were included.

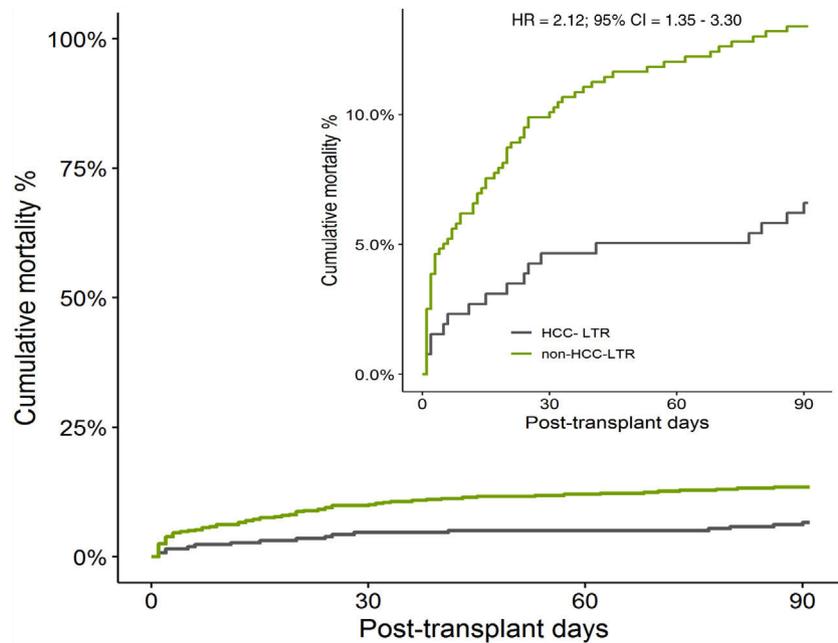


Figure 3 Comparison of liver transplant recipients cohorts. Un-adjusted Kaplan–Meier curve of mortality (patients with need of urgent retransplant were censored).

grafts function despite of different evolving characteristics between cohorts.

In relation to other organs function, on the one hand, the non-HCC-LTR reached higher levels of serum creatinine and urea within the first 5 postoperative days ($p < 0.001$ in both), although renal replacement therapy rate was similar (5.0% in HCC-LTR vs 6.4% in non-HCC-LTR, $p = 0.459$). Besides, the non-HCC-LTR had a lesser percentage of patients with mechanical ventilation shorter than 24 hours and had a greater rate of reintubations than the HCC-LTR ($p < 0.001$). However, there were no differences in the tracheostomy rate ($p = 0.101$) due to prolonged ventilation time.

On the other hand, MODS incidence was also higher in non-HCC-LTR (OR=1.99, 95% CI=1.19–3.35). An *ad hoc* multivariate analysis of patients with MODS showed a higher incidence of postoperative shock (OR=5.18, 95% CI=2.54–10.57), higher surgical reoperations rate (OR=4.63, 95% CI=2.36–9.10), higher incidence of renal dysfunction (OR=4.76, 95% CI=2.57–8.81), higher dialysis rate (OR=7.08, 95% CI=2.91–17.22), and infection rate (OR=7.02, 95% CI=3.66–13.48) in non-HCC-LTR.

Outcomes of cohorts

Length of stay in ICU showed no meaningful differences between cohorts in the central tendency values (Mann–Whitney U test) but it did it in variability or extreme values (Moses test, $p = 0.012$).

The overall cumulative mortality during 90 posttransplant days, when patients with urgent retransplant were censored, was 13.0% in non-HCC-LTR vs 5.9% in HCC-LTR (non-adjusted HR=2.12, 95% CI=1.25–3.61, $p = 0.005$) (Fig. 3). When this outcome was adjusted by their independent predictors, the mortality related to transplant indications (non-HCC-LTR vs HCC-LTR as reference)

reach no statistical significance (adjusted HR=1.60, 95% CI=0.93–2.76, $p = 0.086$) (Fig. 4).

Liver transplant recipients' survival time predictors

By a multivariate Cox proportional hazard model of differences between the transplant indication related cohorts were obtained three independent predictors of mortality in whole cohort (Table 4). These predictors were postoperative shock (HR=2.02, 95%CI=1.26–3.24, $p = 0.003$), early vascular complications of graft (HR=4.01, 95%CI=2.45–6.56, $p < 0.001$) and persistence of multi-organ dysfunction syndrome (HR=18.09, 95%CI=10.70–30.58, $p < 0.001$). Two of them (postoperative shock and appearance of MODS) had a higher risk in non-HCC cohort and explain the mortality difference between indication related cohorts. Therefore the indication related to transplant (non-HCC-LTR vs HCC-LTR as reference) no showed differences for itself in the early mortality and it had no meaningful impact on mortality (Fig. 4).

Mortality rates of overall and indication related cohorts are shown in Table 5 by time sequences during early postoperative period.

Discussion

In liver transplant recipients, early postoperative mortality is conditioned by complications emerged after transplant surgery and initial graft function, which could be associated with certain clinical pretransplant features and the way to access to transplant. In elective liver transplant candidates, waiting list prioritization is an eternally controversial issue since prioritization systems have to be periodically

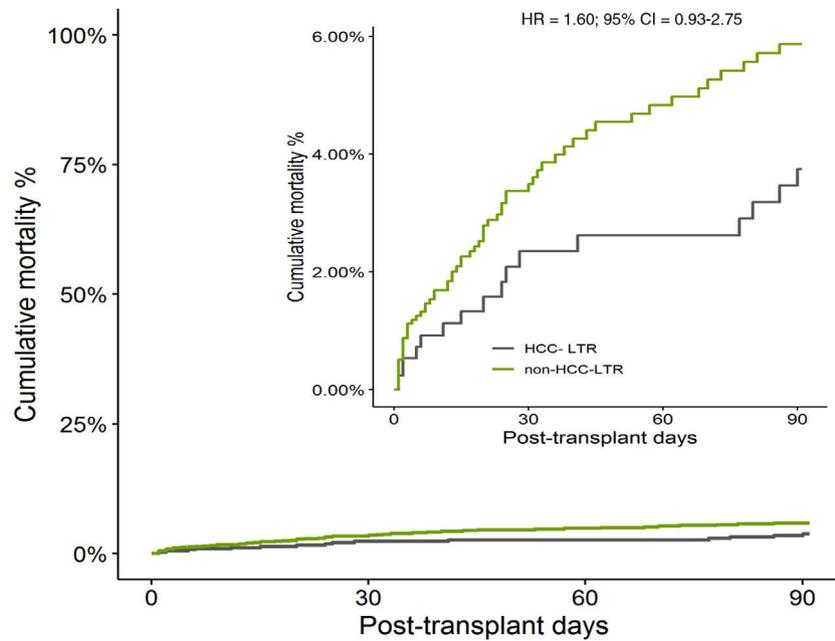


Figure 4 Comparison of liver transplant recipients cohorts. Adjusted Kaplan–Meier curve of mortality (patients with need of urgent retransplant were censored).

audited and further adapted to demographic changes and novel transplant indications.

The present study adds additional information to the actual body of research in this field. It does not try to demonstrate the homogeneity of the groups to obtain the validity of the results and predictors, but just the opposite, it tries to show that the cohorts HCC-LTR and non-HCC-LTR are not homogeneous and the mortality predictors have no the same risk in both cohorts.

First of all, in our population the non-HCC-LTR who received their first liver transplant from brain-dead donors showed a crude early mortality rates doubled compared to HCC-LTR (non-adjusted HR=2.12, 95% CI=1.25–3.60, $p=0.005$). The confirmation of a lower early perioperative mortality rate in HCC-LTR in other studies, it would be equivalent to a “possible advantage” in a short term in comparison to non-HCC-LTR. At present once the Milan criteria are universally applied, this early advantage for HCC patients could be balanced in the long term by mortality risk derived from tumour recurrence.^{14,20} However, taking into account the current guidelines for treatment of patients with HCC,²¹ these patients could have in future a lower mortality on the waiting list, a higher probability of transplantation, and a greater early posttransplantation survival.²²

Secondly, independent predictors of early postoperative mortality in LTR are almost exclusively related to postoperative complications: shock at ICU admission, graft vascular thrombosis and MODS occurrence. And the mortality related to transplant indication (non-HCC-LTR vs HCC-LTR as reference) reached no statistical significance when was adjusted by these independent predictors (adjusted HR=1.60, 95% CI=0.93–2.76, $p=0.086$). Therefore, the crude difference observed between HCC and non-HCC patients could be only justified by these predictors.

Two meaningful predictors of mortality (postoperative shock and MODS) had higher incidence in non-HCC-LTR. The first is related to a higher need for transfusions within surgery and early reinterventions.²³ The MODS is the confluence of higher incidence of postoperative shock, renal dysfunction, graft dysfunction, and a higher rate of postoperative infections. All of them cause a longer mechanical ventilation time and ICU length of stay.

Some of predictors analysed in our work have been previously reported but within heterogeneous populations that included patients with acute liver failure or retransplantation.^{24–31} Other risk factors that are not widely accepted could also be discussed. LTR stature is not universally accepted as a risk factor.⁵ However, a study demonstrated that coincidence of short stature recipients and donors with larger size and weight was an independent risk factor for early dysfunction and secondary graft lost.³² Pretransplant serum creatinine is a well-known predictor of posttransplant mortality^{33–34} but has collinearity with MELD-Na, which was expected since serum creatinine is contained in the MELD-Na. Also, blood lactic acid levels tested just after transplantation could also be considered a risk factor, although its clearance is more important than the postoperative peak.^{35–36}

There are several aspects for practical application of our results. On the one hand, a prospective study with separated cohorts according to reason for transplant (HCC vs non-HCC) should be taken into account in future studies to analyse the early mortality in liver transplant recipients. This could prove if overall cumulative mortality is due to other predictors as a higher risk of postoperative shock and MODS. On the other hand, there is a need to assess whether this “possible advantage” of short-term mortality in HCC-LTR (to which an exceptions to the MELD are applied) is in fact compensated.^{37–40} On the contrary, a re-design of

Table 4 Univariate and multivariate analysis of liver transplant recipients mortality endpoint using Cox's proportional hazards model.

	Univariate analysis		Cox regression	Multivariate analysis		Cox regression
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
<i>Baseline characteristics of recipients^a</i>						
Gender, female	1.246	0.778–1.996	0.359			
Age, per each year	1.018	0.993–1.043	0.141			
Body mass index, per each kg/m ²	1.022	0.977–1.069	0.329			
Non-HCC-LTR cohort (HCC-LTR as reference)	2.120	1.247–3.605	0.005	1.604	0.934–2.755	0.086
Child C	1.189	0.770–1.835	0.432			
MELD-Na, per each point	1.047	1.014–1.081	0.004			
Pre-transplant creatinine level, per each mg/dL	1.733	1.307–2.298	<0.001			
Pre-transplant urea level, per each mg/dL	1.007	1.003–1.011	<0.001			
Hepatorenal syndrome	2.087	1.211–3.595	0.008			
Previous supramesocolic surgery	1.672	0.983–2.844	0.057			
Previous hospital admission	2.483	1.492–4.134	<0.001			
<i>Features of donors and transplantation time</i>						
Cold ischemia time, per each min	1.001	0.999–1.002	0.067			
Intraoperative RBC transfusion, per each unit	1.045	1.029–1.061	<0.001			
Intraoperative plasma transfusion, per each unit	1.029	1.008–1.051	0.005			
<i>Features of postoperative period</i>						
Shock at ICU admission	8.923	5.840–13.632	<0.001	2.023	1.261–3.244	0.003
Massive transfusion	5.165	3.284–8.122	<0.001			
Early surgical reoperation	5.158	3.338–7.970	<0.001			
Mechanical ventilation < 24 h	0.209	0.134–0.326	<0.001			

Table 4 (Continued)

	Univariate analysis		Cox regression	Multivariate analysis		Cox regression
	HR	95% CI	<i>p</i>	HR	95% CI	<i>p</i>
Need of tracheal reintubation and mechanical ventilation	8.255	5.367–12.699	<0.001			
ALT peak value UI/L, log scale ^b	6.272	3.672–10.713	<0.001			
Graft vascular thrombosis in the first 7 days	12.101	7.692–19.036	<0.001	4.011	2.450–6.563	<0.001
S-creatinine peak value in the first 5 post-transplant days, per each mg/dL	1.837	1.532–2.202	<0.001			
S-urea peak value in the first 5 post-transplant days, per each mg/dL	1.005	1.001–1.008	0.008			
S-total bilirubin on day 7 per each mg/dL	1.042	1.015–1.069	0.002			
Infection in the post-operative first month	5.406	3.528–8.283	<0.001			
Severe neurological complications ^c	1.443	0.724–2.879	0.298			
Multi-organ dysfunction syndrome	31.722	19.801–50.818	<0.001	18.090	10.701–30.578	<0.001

^a Liver transplant patients with urgent retransplant were censored.

^b Serum Alanine aminotransferase postoperative peak transformed into a logarithmic scale (Log10).

^c Severe encephalopathy, Seizures or Cerebro-vascular accidents.

Table 5 Mortality rates of overall and indication related cohorts by time sequences during early postoperative period.

Postoperative day	1	2	7	30	60	90	Total
<i>Overall cohort</i>							
N patients at risk ^a	764	750	745	736	707	686	675
Mortality rate in time interval series ^b , <i>n</i>	14	5	9	29	11	11	79
Series aggregate mortality, <i>n</i>	14	19	28	57	68	79	
Mortality rate in time interval series, %	1.8	0.7	1.2	3.9	1.6	1.6	10.8
Series aggregate mortality, %	1.8	2.5	3.7	7.6	9.2	10.8	
Aggregate mortality, % overall cohort	17.7	24.1	35.4	72.2	86.1	100.0	
<i>HCC-cohort^c</i>							
N at risk ^a	255	254	253	251	245	244	240
Mortality rate in time interval series, <i>n</i>	1	1	2	6	1	4	15
Mortality rate in time interval series, %	0.4	0.4	0.8	2.4	0.4	1.6	6.0
Series aggregate mortality, %	0.4	0.8	1.6	4.0	4.4	6.0	
Aggregate mortality, % HCC-cohort	6.7	13.3	26.7	66.7	73.3	100	
<i>Non-HCC cohort^d</i>							
N at risk ^a	509	496	492	485	471	461	454
Mortality rate in time interval series, <i>n</i>	13	4	7	23	10	7	64
Mortality rate in time interval series, %	2.6	0.8	1.4	4.7	2.1	1.5	13.2
Series aggregate mortality, %	2.6	3.4	4.8	9.6	11.7	13.2	
Aggregate mortality, % non-HCC-cohort	20.3	26.6	37.5	73.4	89.1	100	

^a Liver transplant patients with urgent retransplantation were censored.

^b Time interval series between postoperative days.

^c HCC-cohort are liver transplant recipients due to Hepatocellular carcinoma.

^d Non-HCC-cohort are liver transplant recipients due to other indications than Hepatocellular carcinoma.

transplant access protocols of the “harmed cohort” should be considered.

Our study have several limitations. It is a single-centre involvement which could decrease external validity. It is a very old historic series which contain a certain grade of heterogeneity of the patients. It is a retrospective study, however there are several strengths including a large sample of patients with homogeneous characteristics and the prospective database of most of the explanatory variables.

Conclusion

In conclusion, our study report a higher crude postoperative mortality in non-HCC-LTR compared to HCC-LTR due to higher incidence of shock at ICU admission and occurrence of postoperative multiple organ dysfunction syndrome. The indication to transplant (non-HCC compared to HCC as reference) did not show a meaningful statistical difference in early mortality rate during 90 days after transplantation.

Authorship

Juan Carlos Pozo-Laderas: concept and design of study, data collected, statistical analysis, interpretation of results and writing of the manuscript. Ipek Guler: Statistical study. Manuel Rodríguez-Perálvarez: concept and design, interpretation of results, writing and critical revision of the manuscript. Juan Carlos Robles, Ana Mula, Pedro López-Cillero and Carmen de la Fuente: critical revision of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgment

To Carmen Pozo MD, Department of Urology, Vienna General Hospital, for her suggestions in the design, preparation and translation. To Elena Hernandez thanks for her help in translation.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.medint.2020.02.004](https://doi.org/10.1016/j.medint.2020.02.004).

References

- Samuel D, Coilly A. Management of patients with liver diseases on the waiting list for transplantation: a major impact to the success of liver transplantation. *BMC Med.* 2018;16:113–7.
- Sapisochin G, Bruix J. Liver transplantation for hepatocellular carcinoma: outcomes and novel surgical approaches. *Nat Rev Gastroenterol Hepatol.* 2017;14:203–17.
- Burroughs AK, Sabin CA, Rolles K, Delvart V, Karam V, Buckels J, et al. 3-Month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. *Lancet.* 2006;367:225–32.
- Lewsey JD, Dawwas M, Copley LP, Gimson A, Van der Meulen JH. Developing a prognostic model for 90-day mortality after

- liver transplantation based on pretransplant recipient factors. *Transplantation*. 2006;82:898–907.
5. Pozo-Laderas JC, Rodríguez-Perálvarez M, Muñoz-Villanueva MC, Rivera-Espinar F, Durban-García I, Muñoz-Trujillo, et al. Pretransplant predictors of early mortality in adult recipients of liver transplantation in the MELD-Na Era. *Med Intensiva*. 2019;43:261–9.
 6. Rana A, Petrowsky H, Hong JC, Agopian VG, Kaldas FM, Farmer D, et al. Blood transfusion requirement during liver transplantation is an important risk factor for mortality. *J Am Coll Surg*. 2013;216:902–7.
 7. Rana A, Kaplan B, Jie T, Porubsky M, Habib S, Rilo H, et al. A critical analysis of early death after adult liver transplants. *Clin Transplant*. 2013;27:E448–53.
 8. Fukazawa K, Pretto EA Jr, Nishida S, Reyes JD, Gologorsky E. Factors associated with mortality within 24h of liver transplantation: an updated analysis of 65,308 adult liver transplant recipients between 2002 and 2013. *J Clin Anesth*. 2018;44:35–40.
 9. Baganate F, Beal EW, Tumin D, Azoulay D, Mumtaz K, Black SM, et al. Early mortality after liver transplantation: defining the course and the cause. *Surgery*. 2018;164:694–704.
 10. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med*. 1996;334:693–9.
 11. Adam R, Karam V, Cailliez V, O'Grady JG, Mirza D, Cherqui D, et al. and the European Liver and Intestine Transplant Association (ELITA) 2018 annual report of the European Liver Transplant Registry (ELTR) – 50-year evolution of liver transplantation. *Transpl Int*. 2018;31:1293–317.
 12. Kim WR, Lake JR, Smith JM, Schladt DP, Skeans MA, Harper AM, et al. OPTN/SRTR 2016 annual data report: liver. *Am J Transplant*. 2018;18 Suppl. 1:172–253.
 13. Weismüller TJ, Negrn A, Becker T, Barg-Hock H, Klempnauer J, Manns MP, et al. The introduction of MELD-based organ allocation impacts 3-month survival after liver transplantation by influencing pretransplant patient characteristics. *Transpl Int*. 2009;22:970–8.
 14. Wallace D, Walker K, Charman S, Suddle A, Gimson A, Rowe I, et al. Assessing the impact of suboptimal donor characteristics on mortality after liver transplantation: a time-dependent analysis comparing HCC with non-HCC patients. *Transplantation*. 2019;109:e89–98.
 15. Faitot F, Allard MA, Pittau G, Ciaccio O, Adam R, Castaing D, et al. Impact of clinically evident portal hypertension on the course of hepatocellular carcinoma in patients listed for liver transplantation. *Hepatology*. 2015;62:179–87.
 16. Dolgin NH, Martins PN, Movahedi B, Lapane KL, Anderson FA, Bozorgzadeh A. Functional status predicts postoperative mortality after liver transplantation. *Clin Transplant*. 2016;30:1403–10.
 17. Fahrner R, Dondorf F, Ardelit M, Dittmar Y, Settmacher U, Rauchfuß F. Liver transplantation for hepatocellular carcinoma – factors influencing outcome and disease-free survival. *World J Gastroenterol*. 2015;21:12071–82.
 18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. STROBE Initiative. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med*. 2007;147:573–7.
 19. de la Mata M, Cuende N, Huet J, Bernardos A, Ferrón JA, Santoyo J, et al. Model for end-stage liver disease score-based allocation of donors for liver transplantation: a Spanish multicenter experience. *Transplantation*. 2006;82:1429–35.
 20. Mahmud N, Shaked A, Olthoff KM, Goldberg DS. Differences in posttransplant hepatocellular carcinoma recurrence by etiology of liver disease. *Liver Transpl*. 2019;25:388–98.
 21. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. *J Hepatol*. 2018;69:182–236.
 22. Jurado-García J, Muñoz García-Borruel M, Rodríguez-Perálvarez ML, Ruiz-Cuesta P, Poyato-González A, Barrera-Baena P, et al. Impact of MELD allocation system on waiting list and early post-liver transplant mortality. *PLOS ONE*. 2016;11:e0155822, <http://dx.doi.org/10.1371/journal.pone.0155822>.
 23. Ertel AE, Wima K, Chang AL, Hoehn RS, Hohmann SF, Edwards MJ, et al. Risk of reoperation within 90 days of liver transplantation: a necessary evil? *J Am Coll Surg*. 2016;222:419–28.
 24. Huang CT, Lin HC, Chang SC, Lee WC. Pre-operative risk factors predict post-operative respiratory failure after liver transplantation. *PLoS ONE*. 2011;6:e22689.
 25. Mourad MM, Liossis C, Gunson BK, Mergental H, Isaac J, Muiresan P, et al. Etiology and management of hepatic artery thrombosis after adult liver transplantation. *Liver Transpl*. 2014;20:713–23.
 26. Mueller AR, Platz KP, Krause P, Kahl A, Rayes N, Glanemann M, et al. Perioperative factors influencing patient outcome after liver transplantation. *Transpl Int*. 2000;13 Suppl. 1:S158–61.
 27. Wong CS, Lee WC, Jenq CC, Tian YC, Chang MY, Lin CY, et al. Scoring short-term mortality after liver transplantation. *Liver Transpl*. 2010;16:138–46.
 28. Parikh A, Washburn KW, Matsuoka L, Pandit U, Kim JE, Almeda J, et al. A multicenter study of 30 days complications after deceased donor liver transplantation in the model for end-stage liver disease score era. *Liver Transpl*. 2015;21:1160–8.
 29. Andrassy J, Wolf S, Hoffmann V, Rentsch M, Stangl M, Thomas M, et al. Rescue management of early complications after liver transplantation-key for the long-term success. *Langenbecks Arch Surg*. 2016;401:389–96.
 30. Jung B, Cisse M, Chanques G, Arsac E, Bismuth M, Panaro F, et al. Mortalité trois mois après transplantation hépatique: étude monocentrique sur une période de vingt ans. *Ann Fr Anesth Reanim*. 2011;30:899–904.
 31. Schoening W, Buescher N, Neidel N, Helbig M, Andreou A, Pascher A, et al. Cerebrovascular events in 20 years of follow-up after liver transplantation: an underestimated issue? *Clin Transplant*. 2016;30:1276–82.
 32. Salvalaggio P, Afonso RC, Felga G, Ferraz-Neto BH. A proposal to grade the severity of early allograft dysfunction after liver transplantation. *Einstein (Sao Paulo)*. 2013;11:23–31.
 33. Nair S, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology*. 2002;35:1179–85.
 34. Asrani SK, Saracino G, O'Leary JG, Gonzales S, Kim PT, McKenna GJ, et al. Recipient characteristics and morbidity and mortality after liver transplantation. *J Hepatol*. 2018;69:43–50.
 35. Basile-Filho A, Nicolini EA, Auxiliadora-Martins M, Silva Ode C Jr. The use of perioperative serial blood lactate levels, the APACHE II and the postoperative MELD as predictors of early mortality after liver transplantation. *Acta Cir Bras*. 2011;26:535–40.
 36. Wu JF, Wu RY, Chen J, Ou-Yang B, Chen MY, Guan XD. Early lactate clearance as a reliable predictor of initial poor graft function after orthotopic liver transplantation. *Hepatobiliary Pancreat Dis Int*. 2011;10:587–92.
 37. Bolondi G, Mocchegiani F, Montalti R, Nicolini D, Vivarelli M, De Pietri L. Predictive factors of short term outcome after liver transplantation: a review. *World J Gastroenterol*. 2016;22:5936–49.
 38. Knight M, Barber K, Gimson A, Collett D, Neuberger J. Liver Advisory Group of National Health Service Blood Transplant

- Implications of changing the minimal survival benefit in liver transplantation. *Liver Transpl.* 2012;18:549–57.
39. Cillo U, Vitale A, Polacco M, Fasolo E. Liver transplantation for hepatocellular carcinoma through the lens of transplant benefit. *Hepatology.* 2017;65:1741–8.
 40. Vutien P, Dodge J, Bambha KM, Nordstrom EM, Gralla J, Campbell K, et al. A simple measure of hepatocellular carcinoma burden predicts tumor recurrence after liver transplantation: the recurrent hepatocellular carcinoma-initial, maximum last classification. *Liver Transpl.* 2019;25:559–70.