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Liver Transplantation for Hepatocellular Carcinoma Within Milan Criteria in Patients With Model For End-Stage Liver Disease Score Below 15: The Impact of the Etiology of Cirrhosis on Long-Term Survival

F. Tandoi, E. Ponte, M.C. Saffioti, D. Patrono, S. Mirabella, F. Lupo, R. Romagnoli, and M. Salizzoni

ABSTRACT

Background. Liver transplantation (OLT) is the gold standard therapy for patients with cirrhosis complicated by hepatocellular carcinoma (HCC) within Milan Criteria (MC). We evaluated the impact of the etiology of the underlying liver disease on long-term outcomes of patients undergoing OLT for HCC within MC having a Model for End-stage Liver Disease (MELD) score < 15.

Methods. From November 2002 to December 2009, we performed 203 primary OLTs from brain-dead donors in recipients with HCC and cirrhosis with biochemical MELD scores below 15. We excluded 31 patients outside MC on the explant pathology of the native liver. The remaining 172 were divided into 3 groups according to the etiology of the underlying cirrhosis: hepatitis C virus-positive (HCV+; $n = 78$; 45%), hepatitis B virus-positive (HBV+; $n = 65$; 38%) and other indications ($n = 29$; 17%). The groups were compared for donor and recipient features, donor-recipient match, and transplant variables. The study endpoint was long-term patient survival.

Results. The groups were similar, except for a greater prevalence of hepatitis B core antibody-positive grafts in the HBV+ group and less frequent HCC bridging procedures in the other indications group. After a median follow-up of 72 months, HCC recurrence was observed in 8 (4.7%) patients (6 HCV+, 2 other indications), 5 of whom died. Overall 5-year patient survival of 82%, revealed significant differences among groups: 98.3% in HBV+, 67.1% in HCV+, and 85.8% in other indications (HBV+ vs other indications: $P = .01$; HBV+ vs HCV+: $P = .0001$; HCV+ vs other indications: $P =$ NS). In the HCV+ group, recurrent HCV hepatitis was the most frequent cause of death. Upon multivariate analysis, HBV positivity in the recipient was an independent predictor of better patient survival (hazard ratio = 0.10, 95% confidence interval 0.02–0.64, $P = .013$).

Conclusions. Etiology of the underlying cirrhosis significantly influenced the long-term survival after OLT of patients with HCC within MC and MELD < 15. It should be taken into account in estimation of survival benefit.

HEPATOCELLULAR CARCINOMA (HCC) is a major cause of morbidity and mortality worldwide. Long-term follow-up studies have demonstrated that approximately 1% to 8% of patients with cirrhosis per year develop HCC. The Barcelona-Clinic Liver Cancer classification suggests different therapeutic approaches to HCC depending on the tumor stage, liver function, patient performance status, and treatment characteristics. In

From the Liver Transplant Center, General Surgery Unit, A.O.–Città della Salute e della Scienza, S. Giovanni Battista Hospital, University of Turin, Italy.

Address correspondence to Francesco Tandoi, Liver Transplant Center, General Surgery Unit, A.O.–Città della Salute e della Scienza, S. Giovanni Battista Hospital, University of Turin, Italy. E-mail: Francesco.tandoi@unito.it

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Table 1. Characteristics of the Primary Transplants Performed in Adult Cirrhotic Patients with HCC Within Milan Criteria and MELD Score < 15

	HCV+ recipients ($n = 78$)	HBV+ recipients ($n = 65$)	Other indications recipients ($n = 29$)	P value
Donor				
Age (y)	60.0 (17.7–82.4)	64.1 (16.8–86.7)	60.8 (25.5–86.3)	.32
Sex (M:F)	48:30	43:22	19:10	.83
BMI	24 (18–48)	25 (18–33)	26 (21–33)	.15
BSA (m^2)	1.87 (1.40–2.29)	1.84 (1.56–2.33)	1.90 (1.47–2.26)	.47
Cause of brain death				
Cerebrovascular	56 (72%)	46 (71%)	20 (69%)	.99
Trauma	15 (19%)	13 (20%)	6 (21%)	
Others	7 (9%)	6 (9%)	3 (10%)	
Donor Risk Index	1.76 (0.94–2.39)	1.91 (1.14–2.39)	1.87 (1.12–2.28)	.24
Macrovesicular steatosis (%)	0 (0–50)	1 (0–50)	0 (0–75)	.63
HBcAb positivity	9 (12%)	20 (31%)	2 (7%)	.0027
Suboptimal graft	43 (55%)	41 (63%)	14 (48%)	.37
Recipient				
Age (y)	56.9 (36.6–67.8)	56.5 (41.4–64.8)	57.0 (25.4–65.2)	.6
Sex (M:F)	65:13	59:6	26:3	.38
BMI	25 (17–33)	26 (18–33)	25 (19–31)	.14
BSA (m^2)	1.85 (1.44–2.15)	1.86 (1.46–2.10)	1.82 (1.49–2.37)	.9
Biochemical MELD at listing	11 (6–16)	10 (6–22)	11 (6–18)	.46
Biochemical MELD at OLT	11 (7–14)	9 (6–14)	11 (6–14)	.06
Waiting list time (d)	81 (1–395)	82 (2–869)	74 (2–249)	.86
HCC pre-OLT bridging procedure				
Null	10 (13%)	18 (28%)	14 (48%)	
PEI	11 (14%)	3 (5%)	0 (0%)	
RFA	23 (290%)	19 (29%)	3 (10%)	.0063
TACE	20 (26%)	16 (25%)	7 (24%)	
Surgical resection	0 (0%)	1 (1%)	1 (4%)	
Combined	14 (18%)	8 (12%)	4 (14%)	
HCC G3-G4 prevalence	15 (19%)	11 (17%)	5 (17%)	.9
HCC recurrence	6 (8%)	0 (0%)	2 (7%)	.07
Donor-recipient match				
D-MELD	646 (150–1178)	601 (118–1037)	636 (236–1094)	.94
Transplant procedure				
Total ischemia (min)	495 (210–689)	528 (213–741)	520 (312–625)	.72
Cold ischemia (min)	470 (189–661)	507 (194–709)	494 (284–621)	.72
Warm ischemia (min)	23 (14–55)	24 (14–44)	22 (14–36)	.51
Retransplantation	7 (9%)	4 (6%)	1 (3%)	.6

Quantitative variables are expressed as median (range). Categorical variables are expressed as number (prevalence, %). HCC, hepatocellular corcinoma; HCV, hepatitis C virus; HBV, hepatitis B virus; BMI, body mass index; BSA, body surface area; MELD, Model for End-stage Liver Disease; HBcAb, hepatitis B core antibody; OLT, liver transplantation; PEI, percutaneous ethanol injection; RFA, radio-frequency ablation; TACE, trans-arterial chemo-embolization; D-MELD, donor age × MELD.

1996, Mazzaferro et al[1] proposed the so-called Milan Criteria (MC) for transplantation, focusing on the size and number of lesions and the presence of vascular invasion. Nowadays, liver transplantation (OLT) is considered to be the gold standard treatment for patients with HCC within MC even if many studies have suggested that extensions of the MC could be acceptable. In recent years, the "survival benefit" concept has strongly emerged as a guide to evaluate OLT results. For a cirrhotic patient on the waiting list, the mortality risk at 1 year was higher with OLT than without OLT for patients with a Model for End-stage Liver Disease (MELD) scores below 15.[2] On that basis, the United States United Network for Organ Sharing "Share 15" rule was instituted (and recently revisited in September 2012)[3] for liver graft allocation. It provides priority to patients with MELD scores $\geq$ 15. Also in Italy,[4] from January 2011, a cirrhotic patient without HCC can be transplanted only with a MELD scores $\geq$ 15, unless there is a well-motivated exception. Among HCC patients with MELD score $\geq$ 15, the indication for OLT is obviously based on hepatic decompensation; whereas in patients with HCC and MELD score $<$ 15, the issue of survival benefit is relevant. Indeed, in those cases the presence of hepatic functional reserve allows alternative curative treatments for HCC (resection and/or radiofrequency ablation). In this perspective, it is crucial to have up-to-date results of OLT in that subset of patients. Therefore, the aim of this study was to evaluate whether the etiology of the underlying cirrhosis impacted the long-term outcome of HCC patients within MC who undergo OLT having a MELD score $<$ 15.

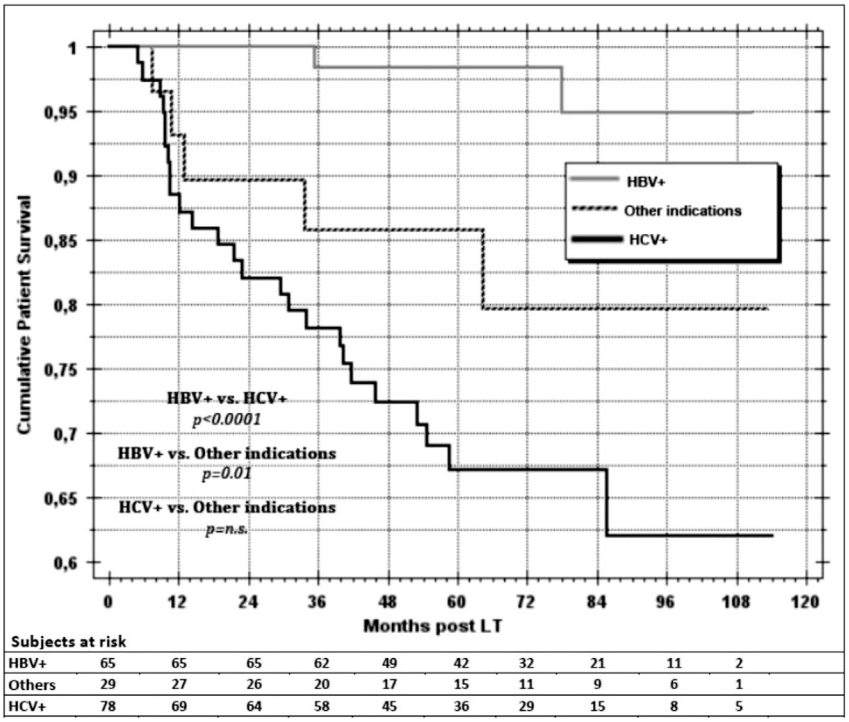

Fig 1. Patient Survival in the 3 study groups. HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplantation.

METHODS

From November 2002 to December 2009, we performed 1000 OLTs from deceased heart-beating donors, including, 217 grafts in 203 adult cirrhotic patients with HCC and biochemical MELD scores at OLT < 15. Thirty-one patients were excluded from the analysis because histopathologic examination of the native liver showed progression of the tumor beyond the MC. The remaining 172 patients were divided into 3 groups on the basis of their etiology of the liver disease: hepatitis C virus (HCV+, $n = 78$); hepatitis B virus (HBV+, $n = 65$, including 20 patients with hepatitis delta coinfection), and other causes (other indications, $n = 29$), including alcohol ($n = 16$), cryptogenic ($n = 10$), hemochromatosis ($n = 1$), nonalcoholic steatohepatitis ($n = 1$), and type III glycogen storage disease ($n = 1$). Five patients with HCV-HBV coinfection were classified in the HCV+ group. The following variables were collected for analysis: donor features included age, sex, body mass index (BMI), body surface area (BSA), cause of brain death, Donor Risk Index (DRI), macrovesicular steatosis, hepatitis B core antibody (HBcAb) positivity, suboptimal graft (defined as graft from donor ≥ 65 years and/or with macrovesicular steatosis ≥ 15%).[5] The recipient factors were: age, sex, BMI, BSA, biochemical MELD score at listing and at OLT, waiting list time, pre-OLT bridging procedure, HCC grade; HCV+ features, (HCV-RNA level pre-OLT, HCV genotype, and HCV histologic recurrence), donor-recipient match (D-MELD [donor age × biochemical MELD at OLT]), transplant procedure (total, cold and warm ischemia times and retransplantations). Standard immunosuppression was based on a calcineurin inhibitor (cyclosporine for HCV+ vs tacrolimus for HBV+ and other indications), mycophenolate, and steroids (tapered and withdrawn within 6 months). Anti-HBV prophylaxis included anti-HBs immunoglobulins, starting from the anhepatic phase and subsequently adjusted to protective serum levels plus nucleoside analogues. We recorded HCC recurrences and causes of graft loss. Categorical variables were analyzed with the χ^2 test, continuous ones with the nonparametric Kruskal-Wallis test. Patient survival was evaluated using Kaplan-Meier analysis with comparisons by the log-rank test. The Cox model was used for multivariate analysis for predictors of survival. The level of significance was set at $P < .05$.

RESULTS

Table 1 summarizes the characteristics of donor, recipient, donor-recipient match, and transplant procedures in the 3 groups. No significant differences were observed, except for the prevalence of HBcAb-positive donor (HBcAb-positive liver grafts were allocated preferentially to HBV+ patients), and the pre-OLT HCC bridging procedures (less frequent among the other indications group). In the HCV+ group, the median pre-OLT HCV-RNA level was 459,425 copies/mL, with 68% genotype 1 virus. During follow-ups ranging from 29 to 114 (median, 72) months for surviving patients, 8 (4.7%) HCC recurrences were observed: 6 in HCV+, 2 in other indications and none in HBV+. There were 5 patient deaths due to HCC recurrence. The HCC grade of differentiation in the explanted liver of patients with post-OLT HCC recurrence was G1 to G2 in 3 (37.5%) and G3 to G4 in 5 (63.5%), 2 of whom showed microvascular invasion by anti-CD34 immunohistochemstry.[6] Overall 5-year patient survival was 82%. There were significant differences among the 3 groups (Fig 1): 98.3% in HBV+, 85.8% in other indications and 67.1% in HCV+ (HBV+ vs

other indications: $P = .01$; HBV+ vs HCV+: $P = .0001$; HCV+ vs other indications: P = NS).

In the HBV+ group, no case of recurrent HBV hepatitis was recorded and only 2 patients died during the follow-up. In the HCV+ group, 25 patients died, only one of whom succumbed due to HCC recurrence; histologic HCV-recurrence was observed in 64 (82%) patients. A dismal course of recurrent HCV hepatitis was the most frequent cause of death (20/25 = 80%). In the HCV+ group, 5-year patient survival was lower when donor age was >65 years (77.0% vs 55.3% for donor ≤65 vs >65 years, respectively; $P < .05$). Multivariate analysis with the Cox model showed independent predictors of worse patient survival to be: donor age >65 years [hazard ratio (HR) = 2.22, 95% confidence interval (CI) 1.07–4.61, $P = .032$] and recurrence HCC post-OLT (HR = 4.06, 95% CI 1.48–11.14, $P = .006$). A significant protective effect on survival was exerted by recipient HBV positivity (HR = 0.10, 95% CI 0.02–0.64, $P = .013$).

DISCUSSION

This study confirmed that HCC recurrence after OLT within MC is rare (<5% at 5 years). It is often associated with G3 to G4 tumors and microvascular invasion. Although outcomes of OLT in patients with MELD score < 15, was globally good, it was influenced significantly by the underlying etiology of the cirrhosis.

Today, HBV infection is the best indication for OLT in this setting, because of the excellent results even in the presence of older or higher DRI donors. This is mainly due to the fact that HBV+ recipients can be treated with effective prophylactic strategies capable of preventing recurrent hepatitis in almost every case. HBV+ patients with HCC within MC and with a MELD score < 15, OLT appears to be the most powerful therapy that we currently have at our disposal. In contrast, HCV-infected patient survivals after OLT were reduced by recurrent HCV hepatitis, which can rapidly progress to liver failure in the background of immunosuppression. HCV+ patients with HCC within MC and MELD score < 15 have emerged as a population with potentially worse outcomes after OLT, especially in geographical areas (like ours) where a major portion of the transplant activity relies on elderly donors. So, in the Italian reality, HCC treatment alternatives to OLT should always be considered for HCV patients who still maintain some hepatic functional reserve.[7]

In conclusion, any estimate of the survival benefit of OLT in HCC patients within MC and MELD score < 15 should take the etiology of the underlying cirrhosis into consideration.

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