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ORIGINAL ARTICLE

Comparison of Clinical Outcomes in Chronic Hepatitis B Liver Transplant Candidates With and Without Hepatocellular Carcinoma

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Patients with hepatocellular carcinoma (HCC) receive a higher MELD score and may undergo liver transplantation (OLT) earlier compared to patients with cirrhosis, potentially decreasing waiting list mortality. However, post-OLT survival may be reduced by recurrence of HCC. We compared clinical outcomes between patients with HBV-cirrhosis and no HCC and patients with HBV-HCC. A total of 279 patients (HBV-cirrhosis = 183; HBV-HCC = 96) in the US HBV-OLT study were followed for a median of 30.2 months from listing. Patients with HCC were older, more likely to be Asian, and had less severe liver impairment than patients with HBV-cirrhosis. Despite a higher rate of OLT in patients with HCC (78.1% vs. 51.4%; $P < 0.001$), intention-to-treat (ITT) survival (73% vs. 78%) and survival without OLT (82% vs. 79%) at 5 years were similar for patients with and without HCC. Cox regression analysis identified higher albumin, lower MELD, no HCC at listing, and being transplanted to be associated with better ITT survival. Ninety-four patients with HCC (including 19 new HCC) and 75 with HBV-cirrhosis underwent OLT. Post-OLT survival (83% vs. 90%) and HBV recurrence (11% vs. 10%) at 3 years were similar, while disease (HBV and/or HCC) recurrence (19% vs. 10%; $P = 0.043$) was higher in patients with HBV-HCC vs. HBV-cirrhosis. Disease recurrence was the only independent predictor of post-OLT survival. In conclusion, despite more advanced liver disease and a lower rate of transplantation, ITT survival of patients listed for HBV-cirrhosis was comparable to those with HBV-HCC, possibly related to beneficial effects of antiviral therapy. ***Liver Transpl 13:334-342, 2007.*** © **2007 AASLD.**

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Recent studies report that patients undergoing liver transplantation (OLT) for hepatocellular carcinoma (HCC) based on the Milan criteria[1] have similar post-OLT survival as those undergoing OLT for non-malignant liver disease.[2,3] However, as many as 23% of patients with HCC die or are precluded from OLT because of tumor progression while waiting for liver transplantation.[4] Thus, the potential impact of OLT on survival of patients with HCC should take into consideration all patients who are listed for liver transplantation, and adverse outcomes while on the waiting list such as death and removal from the waiting list due to tumor progression or worsening of the underlying liver disease should be reported. The concept of intention-to-treat (ITT) survival analysis for HCC patients was first introduced by Llovet and colleagues[5] in their study comparing the outcome of HCC patients undergoing OLT or

Abbreviations: OLT, liver transplant; HCC, hepatocellular carcinoma; ITT, intention-to-treat; HBV, hepatitis B virus; HBV-cirrhosis, hepatitis B virus-related cirrhosis; MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing.

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resection. Since then, there have been very few studies in which the analysis of survival was performed based on this principle.[4,6,7] Furthermore, previous studies included patients with various etiologies of liver disease. The outcomes of patients with hepatitis B virus (HBV)-related liver disease may be different from that of patients with liver disease due to other etiologies in that HCC may occur in a non-cirrhotic liver,[8] and patients with decompensated HBV-related cirrhosis (HBV-cirrhosis) may be stabilized, and complications and mortality reduced by antiviral treatment.[9-12]

The introduction of the Model for End-stage Liver Disease (MELD) to prioritize liver allocation and the assignment of a higher MELD score to patients with HCC increases the probability of OLT and shortens the waiting period for patients with HCC.[13-15] On the other hand, putting HCC patients on a fast-track to OLT may allow patients with aggressive tumor biology to be transplanted and result in an increase in the rate of HCC recurrence.[16-18]

We aimed to compare the rates and independent predictors of survival without OLT, and ITT and post-OLT survival between HBV patients listed for cirrhosis with no HCC and HBV patients listed for HCC. We also aimed to compare the rates of drop-out from the transplant waiting list, and HBV and disease (HBV and/or HCC) recurrence between the 2 groups.

METHODS

Study population and follow-up

All hepatitis B surface antigen (HBsAg)-positive patients >13 years old in the multicenter (15 U.S. centers) National Institutes of Health-sponsored HBV-OLT study were included. From November 2001 to June 2005, consecutive HBV patients listed for primary OLT with cirrhosis and/or HCC and patients up to 12 months post-OLT were enrolled and prospectively followed. The study was approved by the Institutional Review Board of each of the participating centers, and written consent was obtained from all patients. Data were collected prospectively from listing for patients not yet transplanted. For patients enrolled after OLT, data from listing up to enrollment were collected retrospectively. Data were censored in October 2005. Patients listed for fulminant hepatitis, chronic hepatitis B with co-existing non-viral liver disease, and for retransplantation were excluded.

Demographic (age, gender and ethnicity) and laboratory (complete blood count, international normalized ratio for prothrombin time, creatinine, alpha-fetoprotein, hepatic function panel, and HBV markers) data at listing and at the time of OLT were reviewed. MELD score was computed from laboratory data for all patients including those with HCC. Antiviral therapy and tumor staging according to the Milan[1] and the University of California in San Francisco (UCSF) criteria[19] were recorded. Patients who were still on the waiting list for OLT were followed every 6 months while post-OLT patients were followed every 3 months for the first year and every 6 months thereafter. Recurrence of HBV infection was defined as the reappearance of serum HBsAg and/or detection of HBV DNA > 5 $\log_{10}$ copies/ml (PCR assays for HBV DNA were not available at all centers at the beginning of the study) more than 1 month post-OLT while disease recurrence was defined as recurrence of HBV and/or HCC post-OLT. Drop-outs from the transplant list were defined as patients who died without OLT and patients who were taken off the transplant waiting list. The diagnoses of HCC pre-OLT and of HCC recurrence were based on the United Network of Organ Sharing (UNOS) criteria.[20]

All laboratory tests except for HBV DNA and genotype were performed using commercially available assays at the participating centers.

The primary endpoint of this study was death. Secondary endpoints were OLT, drop-out from the transplant list, and HBV and disease recurrence.

Tests for HBV markers

Serum HBV DNA levels were quantified by the Cobas Amplicor HBV Monitor assay (Roche Molecular Systems, Inc., Branchburg, NJ) at the central laboratory in the University of Michigan. For patients with missing samples, HBV DNA results determined at the participating centers were used and the results converted into log copies/ml using a standard conversion table based on the manufacturer's instructions. HBV genotype was determined using INNO-LiPA genotyping assay (Innogenetics NV, Ghent, Belgium).

Statistical analysis

Categorical data were presented as number (percent) and compared using Fisher's exact test or χ^2 test, whichever was applicable. Continuous variables were expressed as mean ± standard deviation unless specified otherwise, and analyzed using Mann-Whitney *U* test. HBV DNA values were logarithmically transformed. Cumulative probability of OLT, survival (ITT, survival without OLT and post-OLT survival, and HBV and disease recurrence-free survival), and HBV and disease recurrence were estimated using Kaplan-Meier (KM) curves and differences between patients with and without HCC were determined by log rank test. Patients were grouped according to the presence (group 2b) or absence of HCC (group 1b) at OLT when analyzing post-OLT events (survival and HBV and disease recurrence) while the rest of the analyses was done according to the presence (group 2a) or absence of HCC diagnosis (group 1a) at listing (Fig. 1).

Univariate analyses of factors associated with survival without OLT, and ITT and post-OLT survival were performed using KM analysis with log rank test. Demographic (age, gender and ethnicity) and laboratory data (blood counts, liver panel, MELD score, ALPHA-FETOPROTEIN, and HBV markers [HBeAg and HBV DNA]) at the time of listing, and at the time of OLT (for post-OLT survival only) were included in the univariate analysis. Continuous variables were dichotomized by taking the

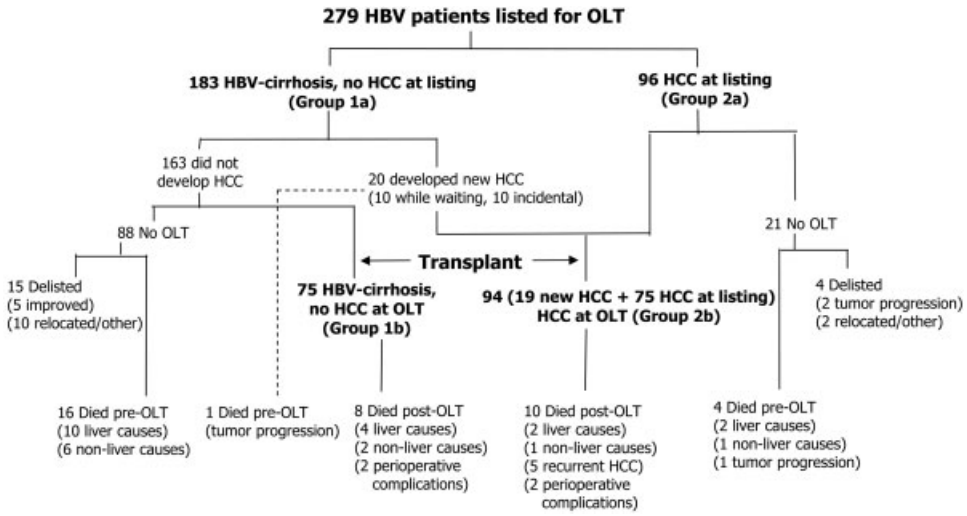

Figure 1. Flow diagram of patients and frequencies of OLT, delisting and death.

median as the cut-off point except for creatinine (> or < 1.5) and HBV DNA (> or < 5 log copies/ml). Age, patient grouping (with and without HCC), and variables that had a *P*-value of <0.1 on univariate analysis were entered into a Cox regression hazards model by forward logistic regression to determine independent predictors of survival. In order to account for possible differences in rates of transplant and survival brought about by changes in organ allocation practices during the course of the study, analyses were repeated after dividing patients into pre- (Era 1 [listed before Feb. 27, 2002]) and post- MELD eras (Era 2 [listed after Feb 27, 2002]). *P*-values <0.05 were considered significant. All statistical analyses were performed using SPSS v. 12.0.2 statistical software. (SPSS Inc. Chicago, IL).

RESULTS

Characteristics of Patients at Listing

A total of 279 HBV patients (183 with cirrhosis and no HCC at listing and 96 with HCC at listing) were included. Patients with HCC were older, more likely to be Asian, and to have genotype C infection, while patients listed for cirrhosis had more advanced liver disease (higher international normalized ratio, total bilirubin levels and MELD score, and lower platelet counts and albumin levels) and higher HBV DNA levels. Most of the patients were receiving antiviral therapy that was started before or soon after listing, and continued up to the last day of follow-up (Table 1). Among the patients with HCC, 69 (72%) had tumors within and 25 (26%) had tumors that exceeded the Milan criteria at listing while two patients had insufficient data to determine tumor staging. Two patients whose tumor did not meet Milan criteria met UCSF criteria. The majority (23 of 25) of patients with tumors exceeding Milan criteria had some form of HCC treatment (10 had transarterial chemoembolization, 13 had combination of TRANSARTERIAL CHEMOEMBOLIZATION, local ablation or resection) while waiting for OLT.

Most patients were enrolled prior to OLT: 155 (84.7%) patients with cirrhosis and no HCC, and 81 (84.4%) patients with HCC diagnosis at listing. There was no difference in demographics, laboratory values, or tumor characteristics at listing between patients who were enrolled prior to or after OLT.

Intention-to-Treat Survival

After a median follow-up of 30.2 months (interquartile range 13.9-47.1 months) from listing, the ITT survival of patients with and without HCC diagnosis at listing was comparable. Cumulative probabilities of ITT survival at 1, 3 and 5 years were 92%, 86% and 78% for patients with no HCC and 90%, 86% and 73% for patients with HCC ($P = 0.792$) (Fig. 2A). However, there was a trend towards decreased survival among the patients with HCC with longer duration of follow-up.

Liver Transplantation

A significantly higher proportion of patients with HCC at listing were transplanted (group 2a vs. group 1a: 78.1% vs. 51.4%, $P < 0.001$) compared to those with cirrhosis and no HCC, and the interval from listing to transplant was shorter (6.1 ± 8 months vs. 14.2 ± 18.5 months; $P = 0.067$). Cumulative probabilities of OLT at 1, 3 and 5 years were 60%, 83% and 86% for patients with HCC vs. 34%, 50% and 63% for patients without HCC ($P < 0.001$) (Fig. 3A). The vast majority of patients received deceased donor liver transplant. Only 4 (4%) and 3 (4%) patients in groups 1a and 2a, respectively, underwent living donor liver transplantation. As expected, the higher rate of OLT among patients with HCC was evident only in the post-MELD era (Fig. 3B and 3C).

Outcomes on the Waiting List

The outcomes of the patients are summarized in Figure 1. Among the patients with cirrhosis, 5 were taken off the transplant waiting list due to improvement in liver

TABLE 1. Characteristics at Listing

	All patients n=279	No HCC at listing (Group 1a; n=183)	HCC at listing (Group 2a; n=96)	*P*-value
Age	53.4 ± 9.2	52.3 ± 8.7	55.6 ± 9.9	0.001
Male	226 (81)	150 (82)	76 (79.2)	0.57
Ethnicity:				
Asian	127 (45.5)	63 (34.4)	64 (66.7)	<0.001
Non-Asian	152 (54.5)	120 (65.6)	32 (33.3)	
Genotype: n=101				
C	37 (36.6)	18 (27.3)	19 (54.3)	0.007
Non-C	64 (63.4)	48 (72.7)	16 (45.7)	
On antiviral therapy*	243 (87.1)	160 (87.4)	83 (86.5)	0.82
Platelet ($\times 10^3$ cells/ml) n=264	94 ± 54.2	83.7 ± 49.1	112.6 ± 58.1	<0.001
Creatinine (mg/dl) n=266	1.3 ± 1.3	1.4 ± 1.6	0.98 ± 0.5	0.059
Alk phos (IU/ml) n=260	148.9 ± 83.5	160.7 ± 82.9	127.4 ± 80.6	<0.001
Bilirubin (mg/dl) n=261	4.1 ± 8.1	5.2 ± 9.4	1.9 ± 3.6	<0.001
Albumin (G/dl) n=259	3.2 ± 0.8	3 ± 0.7	3.5 ± 0.8	<0.001
INR n=259	1.5 ± 0.5	1.6 ± 0.6	1.3 ± 0.3	<0.001
AST (IU/L) n=260	148.4 ± 379.8	153.9 ± 427.5	138.3 ± 274.2	0.015
ALT (IU/L) n=257	121.9 ± 299.6	125.7 ± 341.3	114.6 ± 198	0.43
MELD† n=243	13 ± 8.3	15 ± 9	9.5 ± 5.3	<0.001
AFP (ng/ml) n=168	129.6 ± 788.3	16.4 ± 29	328.3 ± 1290.4	<0.001
HBeAg positive	64/183 (35.0)	44/128 (34.4)	20/55 (36.4)	0.80
Log HBV DNA (copies/ml) n=195	4.6 ± 2.6	5 ± 2.7	4 ± 2.3	0.002

*Defined as any anti-HBV treatment started before or within 6 months after listing, and continuing up to the date of last follow-up.
†MELD computed from laboratory data for all patients.

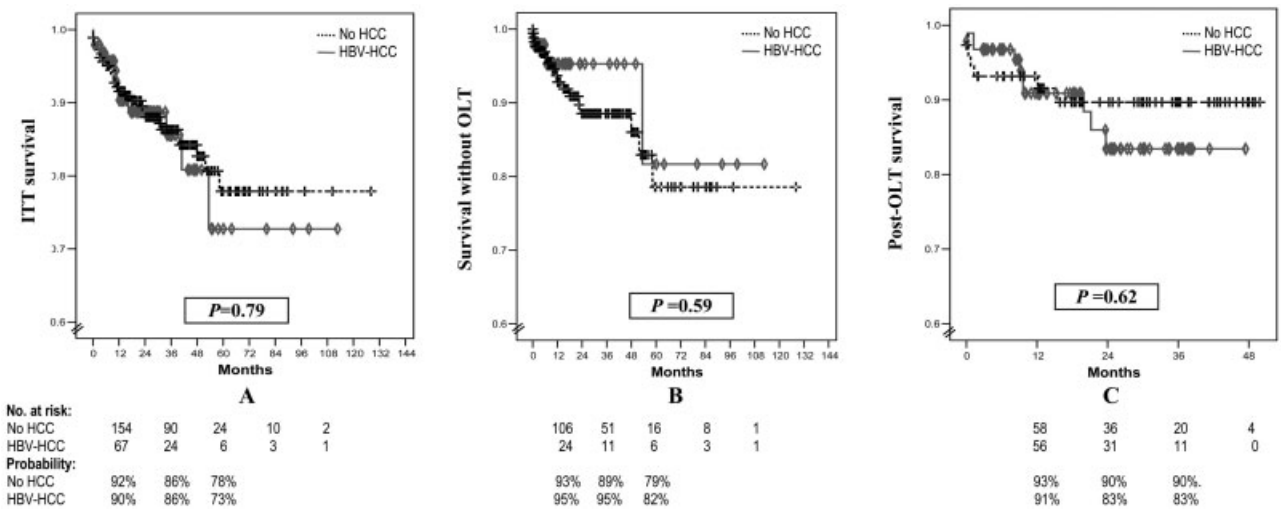

Figure 2. Cumulative probability of ITT survival (A), survival without OLT (B) and post-OLT survival (C) between patients with and without HCC.

disease while none was delisted due to worsening of liver disease. In contrast, two patients with HCC were delisted due to progression of HCC and none was taken off the list because of tumor regression. Seventeen (9.3%) patients with no HCC and 4 (4.2%) patients with HCC died while waiting for OLT (p=0.123). Most deaths were related to liver failure. One patient with HCC died due to tumor progression 6 months after listing while another patient who had no HCC at listing was diagnosed to have HCC 52 months after listing and died shortly thereafter due to rapid tumor progression (Figure 1). There was no difference in the drop out rates between the two groups, the cumulative probabilities 1, 3 and 5 years after listing were 7.9%, 21.2% and 37% for patients with no HCC vs. 9.1%, 16.7% and 36.5% for those with HCC, respectively p=0.76). Cumulative

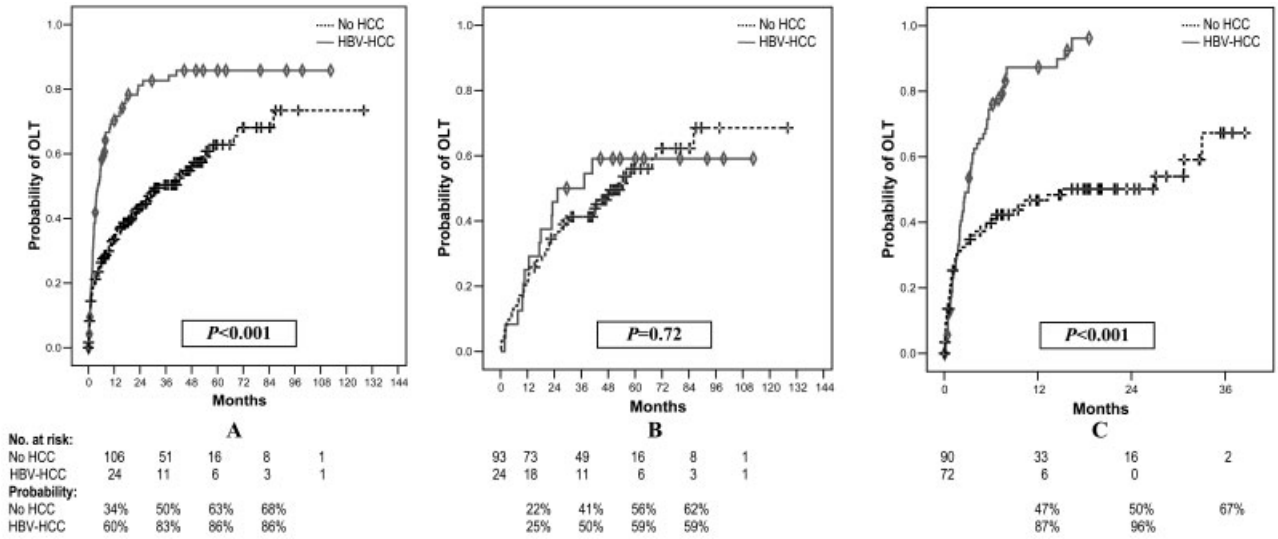

Figure 3. Cumulative probability of OLT for all patients (A), patients listed in Era 1 (B) and patients listed in Era 2 (C). Era 1 and 2: pre- and post- MELD.

probabilities of survival without OLT were likewise similar in the two groups, with 1, 3, and 5 year probabilities being 93%, 89% and 79% for patients with no HCC, and 95%, 95% and 82% for patients with HCC at listing (p=0.590) (Figure 2b). However, only 13 (13.5%) HCC patients were still on the transplant waiting list after year 1 compared to 71 (38.8%) patients with no HCC, ($P < 0.001$). Among the 21 HCC patients who had not been transplanted 15 (71.4%) had received some form of treatment for HCC, including 6 who had surgical resection. Of the 88 patients with no HCC that had not been transplanted 70 (79.5%) were receiving antiviral therapy, of which 15 (21.4%) had improved (decrease in MELD scores of > 25% from listing), 34 (48.6%) had stable (< 25% change in MELD scores from listing), and 13 (18.6%) had worsened MELD scores (increase in MELD scores of > 25% from listing) at the time of data analyses. In comparison, 44.4% (8/18) of patients without HCC who were not on antiviral therapy had worsening, 33.3% (6/18) had stable, and none had improvement in their MELD scores.

Characteristics of Transplanted Patients

Twenty (11%) patients who did not have HCC at listing (group 1a) had new diagnosis of HCC while waiting for transplantation (n= 10) or on the explanted liver (n = 10). Nineteen of these 20 patients (1 patient died without OLT) and 75 patients with HCC at listing who had been transplanted were combined as group 2b while the remaining 75 group 1a patients who had been transplanted and had no evidence of HCC up to the time of transplant were included in group 1b(Fig. 1). Characteristics of the patients in groups 1b and 2b are listed in Table 2.

Post-OLT Survival

After a median post-OLT follow-up of 18.3 months (interquartile range 8.9-32.7 months), 10 (10.6%) patients with HCC and 8 (10.6%) without HCC at transplant had died ($P = 0.779$). A summary of the causes of death are presented in Figure 1. One patient without HCC had HBV recurrence and died of sepsis shortly after retransplantation while 5 patients with HCC died due to tumor recurrence. Post-OLT survival was similar between the two groups, with probabilities at 1, 2, and 3 years being 93%, 90% and 90% for patients without HCC and 91%, 83% and 83% for patients with HCC at transplant. (Fig. 2C).

Impact of Co-Infection With Other Viruses

Eleven (6%) patients without HCC and 5 (5%) patients with HCC were co-infected with hepatitis C virus, and one patient without HCC was co-infected with human immunodeficiency virus. Ten (3.8%) patients were co-infected with hepatitis D virus. However, hepatitis D virus antibody data was available in only 34% of patients. Hepatitis C virus co-infection did not influence survival, and HBV or disease recurrence rates (data not shown).

HBV and HCC Recurrence

Five (6.7%) patients without HCC and 7 (7.4%) patients with HCC at transplant had HBV recurrence; cumulative probability of HBV recurrence in the two groups was similar (Table 3). Two of these 12 patients died, one from sepsis after retransplantation, and another from primary adenocarcinoma of lungs.

Seven (7.4%) patients with HCC at transplant had HCC recurrence a median of 5.9 months (range 1.2-22.9 months) after OLT, two of whom had tumors that exceeded Milan criteria at listing. Five (71.4%) patients with HCC recurrence died, all within 1-8 months after diagnosis of HCC recurrence. The 2 remaining patients were alive at the time of analysis, 2 and 32 months after the diagnosis of HCC recurrence.

TABLE 2. Characteristics of Transplanted Patients With and Without HCC

	No HCC at OLT (Group 1b; n=75)	HCC at OLT (Group 2b; n=94)	*P*-value
Age	50.9±8.5	55.6±9.7	<0.001
Male	60 (80)	73 (77.7)	0.71
Ethnicity:			
Asian	26 (34.7)	51 (54.3)	0.011
Non-Asian	49 (65.3)	43 (45.7)	
Genotype: n=52			
C	7 (28.0)	10 (37.0)	0.49
Non-C	18 (72.0)	17 (63.0)	
HCC treatment before OLT*	na	66 (70.2)	na
Milan criteria (Yes/No/indeterminate)†	na	59/23/12	na
UCSF criteria (Yes/No/indeterminate)†	na	62/20/12	na
Labs at Listing:			
Platelet ($\times 10^3$ cells/ml) n=162	83.7 ± 55.1	99 ± 52.5	0.011
Creatinine (mg/dl) n=162	1.5 ± 1.7	1.1 ± 0.9	0.019
Alk phos (IU/ml) n=157	158.8 ± 80.5	143.2 ± 88.4	0.053
Bilirubin (mg/dl) n=157	7.9 ± 12.6	2.7 ± 5.4	<0.001
Albumin (G/dl) n=154	2.8 ± 0.8	3.3 ± 0.8	<0.001
INR n=157	1.8 ± 0.7	1.3 ± 0.4	<0.001
AST (IU/L) n=157	229.6 ± 656.9	146.1 ± 277.7	0.11
ALT (IU/L) n=157	181.8 ± 519.1	110.5 ± 195.8	0.44
AFP (ng/ml) n=97	16.6 ± 24	283.3 ± 1305.1	0.005
MELD‡ n=146	18.3 ± 9.7	10.9 ± 7.1	<0.001
HBeAg positive	16/58 (27.6)	18/54 (33.3)	0.51
Log HBV DNA (copies/ml) n=124	4.7 ± 2.5	4.1 ± 2.7	0.028
Labs at OLT:			
Platelet (x 10^3 cells/ml) n=163	73.8 ± 47.1	94.4 ± 48.7	0.001
Creatinine (mg/dl) n=163	1.9 ± 1.9	1.2 ± 1.2	<0.001
Alk phos (IU/ml) n=153	154.5 ± 84.5	149.9 ± 104.9	0.16
Bilirubin (mg/dl) n=154	10.2 ± 12.6	3.1 ± 5.8	<0.001
Albumin (G/dl) n=145	2.8 ± 0.6	3.3 ± 0.7	<0.001
INR n=158	2 ± 0.9	1.2 ± 0.5	<0.001
AST (IU/L) n=153	330.9 ± 907.2	152.1 ± 316	0.002
ALT (IU/L) n=154	239.1 ± 662.4	104.1 ± 199.3	0.11
MELD‡ n=147	22.7 ± 10.3	12.3 ± 8.2	<0.001
HBeAg positive	15/58 (25.9)	17/56 (30.4)	0.59
Log HBV DNA (copies/ml) n=120	4.3 ± 2.4	4.2 ± 2.3	0.66

Abbrevation: na = not applicable.
*Thirty one had TACE, 14 had ablation, 2 had resection, and 19 had combination treatment.
†Patients meeting Milan & UCSF criteria on pre-OLT imaging. Indeterminate includes 10 patients with incidental tumors and 2 patients with missing data.
‡MELD computed from laboratory data for all patients.

Five (6.7%) patients without HCC and 13 (13.8%) patients with HCC at transplant had disease (HBV and/or HCC) recurrence. Cumulative probability of disease recurrence was higher in patients with HCC, being 13% and 19% at 1 and 3 years compared to 2% and 10% in patients without HCC (P =0.043) (Table 3).

Independent Factors Predictive of Outcome

Cox regression analysis showed that the strongest predictor of ITT survival was OLT, followed by lower MELD, higher albumin, and no HCC at listing. Higher albumin and lower MELD at listing were independent predictors of survival without OLT while the absence of disease recurrence was the only factor associated with post-OLT survival (Table 4). Factors that were associated with survival on univariate analysis but did not reach statistical significance on Cox regression analysis were antiviral therapy (P = 0.19) for ITT survival, and alkaline phosphatase at listing (P = 0.36) and antiviral therapy (p=0.062) for survival without OLT.

Analysis of Patients Enrolled Prior to OLT

In order to minimize bias on adverse outcomes during the waiting period, analyses were repeated after exclu-

TABLE 3. Cumulative Probabilities of HBV, HCC, and Disease Recurrence, and Recurrence-Free Survival

Probability (%)	No HCC at OLT Group 1b (1, 2 & 3 years)	HCC at OLT Group 2b (1, 2 & 3 years)	*P*-value
HBV recurrence	2, 7, 10	6, 11, 11	0.43
Disease recurrence	2, 7, 10	13, 19, 19	0.043
HCC recurrence	na	6, 11, 11	na
HBV recurrence-free survival	92, 85, 82	85, 78, 78	0.43
HCC recurrence-free survival	na	90, 86, 81	na
Disease recurrence-free survival	93, 84, 82	84, 78, 78	0.34

Abbreviations: na, not applicable.

TABLE 4. Independent Predictors of Survival

	Hazard ratio	95% CI	*P*-value
ITT survival			
Albumin at listing	2.0	1.1–3.3	0.016
MELD at listing	0.9	0.9–1.0	0.001
OLT	4.9	2.2–11	<0.001
HCC at listing	0.4	0.2–0.9	0.023
Survival without OLT			
MELD at listing	0.9	0.8–1.0	0.02
Albumin at listing	5.0	1.4–10	0.014
Post-OLT survival			
Disease (HBV and/or HCC) recurrence	0.1	0.05–0.4	<0.001

sion of patients enrolled after OLT (n = 43). The results were unchanged, with 1 and 3 year ITT survival in patients with and without HCC diagnosis at listing being 88.4% and 82.3%, and 90% and 84.6% ($P = 0.61$); and survival without OLT at 1 and 3 years being 94.3% and 94.3%, and 92% and 87.6% ($P = 0.61$), respectively. The 1- and 3-year post-OLT survival in patients with and without HCC at transplantation were 85% and 80.5%, and 92.2% and 88% ($P = 0.4$), respectively. As expected, the probability of OLT was lower when patients who were enrolled after OLT were excluded, but the difference between patients with and without HCC remained significant, with 1 and 3 year probabilities of OLT for patients with and without HCC diagnosis at listing being 65.2% and 78.5%, and 26.4% and 39.8%, respectively ($P < 0.001$).

DISCUSSION

The adoption of the MELD system in donor liver allocation by UNOS has resulted in an increase in the number of patients transplanted for HCC and a concomitant decrease in waiting time.[13-15] Analysis of the UNOS database showed that the proportion of patients transplanted for HCC increased from 8% to 22% in the first 6 months after the implementation of MELD.[13] The realization that earlier policies unduly favored patients with HCC has led to a number of amendments in the past 4 years such that currently, only TNM stage 2 (American Liver Tumor Study Group) tumors are exempted and the assigned MELD score has decreased from 29 to 22.[20] Our study confirmed that the adoption of the MELD system (era 2) tipped the scales in favor of patients with HCC, with 78.1% of patients with HCC transplanted within 1 year of listing compared to 48.1% for patients with no HCC. However, there was no difference in survival without OLT, and ITT and post-OLT survival between patients with or without HCC whether they were enrolled before or after the MELD era ($P > 0.05$).

Given the high assigned MELD score for patients with HCC plus additional points awarded the longer that they are on the waiting list, patients with cirrhosis and no HCC need to have severe decompensation to compete for transplantation. It was reassuring to find that there was no difference in ITT survival between our patients with HBV-cirrhosis and no HCC and those with HBV-HCC although the patients with no HCC had more advanced liver disease and a lower rate of transplantation (Fig. 2B). The favorable outcome among the patients with cirrhosis and no HCC may be unique to HBV patients where antiviral therapy that is safe and effective in stabilizing liver disease and reversing complications of cirrhosis are available.[9-12] In our study, of the 88 patients with HBV-cirrhosis who had not been transplanted 49 of 70 (70%) patients receiving antiviral therapy had stable or improved MELD scores. In addition, five patients with no HCC were taken off the transplant list because of significant improvement in liver function after initiation of antiviral therapy.

Our results show that the post-OLT survival of patients with chronic HBV infection with or without HCC was similar (Fig. 2C). Recent studies comparing the post-OLT survival of patients with HCC and nonmalignant liver disease have yielded conflicting results with 5-year survival rates ranging from 50-75% and 68-90% for patients with and without HCC, respectively.[2,3,7,16,21,22] While tumor staging is the single most important determinant of post-OLT survival in HCC patients,[23] this cannot explain the discrepant results since most of the HCC patients in these studies (>80%) met the Milan criteria. Two factors may account for the differences in survival: pre-OLT treatment of HCC and length of post-OLT follow-up. Some studies found that adjunctive treatment before OLT was an independent predictor of post-OLT survival and recurrence-free survival in patients with HCC.[21,24] This may explain why post-OLT survival in HCC patients was lower in studies where a lower proportion of patients underwent pre-OLT treatment of HCC.[2,21,22] A recent study showed that 70% of tumors that do not initially meet Milan criteria can be successfully downstaged with ablation, TRANSARTERIAL CHEMOEMBOLIZATION, or resection before OLT, with no HCC recurrence at 16 months and an 82% post-OLT survival rate.[25] In our study, 23/94 (24.5%) patients transplanted for HCC did not meet Milan criteria. Twenty (87%) of these 23 patients and a total of 46/71 (65%) patients with tumors within the Milan criteria received HCC treatment prior to transplant (Table 2). This may account for the encouraging post-OLT survival rate in our study. Length of post-OLT follow-up is another factor that may account for differences between the findings of our study and some prior reports. Studies that had a longer duration of post-OLT follow-up all showed poorer survival in HCC patients,[16,21] while studies with a shorter duration of follow-up showed equivalent survival in patients with and without HCC.[3,22] Our study demonstrated similar survival in patients with and without HCC during the first 2 years post-OLT. There was a trend towards more deaths in the HCC group after year 2, but the number of patients in each group was small. Additional follow-up will be needed to determine if there is a difference in long-term post-OLT survival between HBV patients with and without HCC.

Not surprisingly, in this cohort of patients waiting for liver transplant, the most important predictor of ITT survival was the performance of OLT. Indeed, while multivariate analysis identified having HCC at listing as a predictor of poorer ITT survival, Kaplan-Meier analysis showed that the ITT survival of patients with HCC was similar to those with cirrhosis and no HCC. This discrepancy may be related to the fact that patients with HCC had less advanced liver disease and yet a higher probability of undergoing OLT. That HCC remained a predictor of ITT survival may be related to a trend for a higher probability of post-OLT deaths due to recurrent HCC. While HCC recurrence was diagnosed in only 7 patients, it was associated with a high mortality (71.4%). Our study included a large number of HBV patients with and without HCC. However, we acknowledge that this is not a true ITT analysis of survival because outcomes after delisting were not recorded. To address this limitation, further analysis where patients who were delisted because of disease worsening and patients delisted due to reasons other than disease improvement were assumed to have died were performed. The results showed that ITT survival and survival without OLT between patients with and without HCC remained comparable ($P > 0.05$) (data not shown).

Our study found that the rate of HBV recurrence was similar in the patients with and without HCC. This may be related to the fact that a similar proportion of patients with and without HCC had detectable HBV DNA by PCR at OLT and had received antiviral therapy prior to OLT. The HBV prophylactic regimen post-OLT was also similar in the two groups of patients. Moreover, only one patient with HCC received systemic chemotherapy.

In conclusion, in this large cohort of HBV patients listed for liver transplantation, we showed that the adoption of the MELD system by UNOS had a significant impact by shifting donor liver allocation in favor of patients with HCC. Performance of OLT was the most important determinant of survival regardless of the presence or absence of HCC. HCC patients had a higher probability of undergoing OLT despite having less advanced liver disease, but the higher rate of post-OLT disease recurrence may have negated this advantage in HCC patients accounting for the comparable ITT survival in HBV patients with and without HCC diagnosis at listing. On the other hand, the availability of safe and effective antiviral therapies that can improve or stabilize liver disease may explain why HBV patients with cirrhosis and no HCC had similar ITT survival despite having more advanced liver disease and a lower probability of undergoing OLT. Studies comparing ITT survival of patients with other etiologies of liver disease with and without HCC should be performed to determine if patients with cirrhosis and no HCC are disadvantaged by MELD.

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