ORIGINAL ARTICLE

A New Priority Policy for Patients with Hepatocellular Carcinoma Awaiting Liver Transplantation Within the Model for End-Stage Liver Disease System

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The best prioritization of patients with hepatocellular carcinoma (HCC) waiting for liver transplantation under the model for end-stage liver disease (MELD) allocation system is still being debated. We analyzed the impact of a MELD adjustment for HCC, which consisted of the addition of an extra score (based on the HCC stage and waiting time) to the native MELD score. The outcome was analyzed for 301 patients with chronic liver disease listed for liver transplantation between March 1, 2001 and February 28, 2003 [United Network for Organ Sharing (UNOS)-Child-Turcotte-Pugh (CTP) era, 163 patients, 28.8% with HCC] and between March 1, 2003 and February 28, 2004 (HCC-MELD era, 138 patients, 29.7% with HCC). In the HCC-MELD era, the cumulative dropout risk at 6 months was 17.6% for patients with HCC versus 22.3% for those patients without HCC (P = NS), similar to that in the UNOS-CTP era. The cumulative probability of transplantation at 6 months was 70.3% versus 39.0% ($P = 0.005$), being higher than that in the UNOS-CTP era for patients with HCC ($P = 0.02$). At the end of the HCC-MELD era, 12 patients with HCC (29.3%) versus 57 without HCC (58.8%) were still on the list ($P = 0.001$). Both native and adjusted MELD scores were higher ($P < 0.05$) and progressed more in patients with HCC who dropped out than in those who underwent transplantation or remained on the list (the initial-final native MELD scores were 17.3-23.1, 15.5-15.6, and 12.8-14.1, respectively). The patients without HCC remaining on the list showed stable MELD scores (initial-final: 15.1-15.4). In conclusion, the present data support the strategy of including the native MELD scores in the allocation system for HCC. This model allows the timely transplantation of patients with HCC without severely affecting the outcome of patients without HCC.
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Excellent long-term survival rates are achieved after liver transplantation (LT) in patients with early stage hepatocellular carcinoma (HCC).[1-5] However, the results of LT are limited by the mismatch between the growing demand and the shortage of donor livers because prolonged time on the waiting list increases the dropout rate on account of tumor progression beyond the accepted transplantation criteria.[4,6] To warrant an equitable graft allocation based on medical urgency,[7,8] on February 27, 2002, the model for end-stage liver disease (MELD) score, based on 3 ready available and objective parameters (international normalized ratio for the prothrombine time, bilirubin, and creatinine), replaced the status of the United Network for Organ Sharing (UNOS) in the stratification of patients waiting for LT in the United States.[9] The MELD score has been validated to predict 3-month mortality in patients with cirrhosis,[10] but it lacks any predictive power in LT candidates with HCC, as their risk of death and exclusion from the list results not only from liver function (which

Abbreviations: AFP, alpha-fetoprotein; CI, confidence interval; CTP, Child-Turcotte-Pugh; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing.

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is often preserved) but mainly from tumor growth. HCC candidates, therefore, need prioritization beyond the degree of their hepatic decompensation.

Under the UNOS status allocation policy, patients with HCC were listed in status 2B independently of their Child-Turcotte-Pugh (CTP) score.[11] At the implementation of the new allocation system in the United States, a fixed MELD score was attributed to patients with HCC, based on an estimation of the risk of progression and exclusion from the waiting list. Candidates with stage T1 HCC (1 lesion, <2 cm) and with stage T2 HCC (single lesion, 2-5 cm, or up to 3 lesions, ≤3 cm each) received 24 and 29 points, respectively. A few months after the new policy was introduced, a marked increase in LT for HCC was recorded,[12,13] leading to 87% of the patients with HCC undergoing transplantation within 3 months. These findings raised the concern that the priority given to patients with HCC was excessive, clearly pointing out how complex it is to predict the risk of exclusion from the waiting list in any given patient with HCC.[14] As a result, in January 2003 and again in January 2004, the score assigned to patients with HCC was reduced. Currently, in 2006, UNOS policy states that only patients with stage T2 HCC may receive extra priority on the waiting list, which consists of registration at a MELD score equivalent to a 15% probability of death within 3 months (24 points). Additional MELD points equivalent to a 10% increase in mortality risk are assigned every 3 months.

At the beginning of 2003, the Bologna Transplantation Center adopted a MELD-based allocation policy but applied its own prioritization criteria for HCC. The aim of this study was to analyze at 1 year the results of the new allocation policy: How did it influence the dropout and transplantation rate in patients with and without HCC? Is the native MELD score associated with dropout in patients with HCC? What is the short-term and mid-term impact of the new allocation system on the rate of grafts assigned to patients with HCC?

PATIENTS AND METHODS

Patient Population and Study Period

An analysis was made of all consecutive patients enlisted for, or submitted to, cadaveric LT for chronic liver disease (with or without HCC) at the Bologna Transplantation Center from March 1, 2001 to February 28, 2004. Patients listed or undergoing transplantation because of acute liver failure and patients who underwent retransplantation for urgent conditions were excluded from the analysis. A living donor LT program had not yet been implemented at the center in that period.

Information was collected concerning the age, sex, and indication to LT, including the etiology of the liver disease, date of listing, date of LT, date and cause of dropout, number of HCCs (single or multiple), size of the largest HCC, and serum alpha-fetoprotein (AFP). After the introduction of the new allocation policy, the MELD score (native and adjusted for HCC) was recorded at the time of enlisting (initial MELD score) and at the last visit available within 3 months from LT, dropout, or the end of the study period (final MELD score).

Patients were grouped according to time periods as UNOS-CTP and HCC-MELD with respect to the date of implementation of the new allocation policy (March 1, 2003).

Patients with HCC: Diagnosis and Listing Criteria

We designated all patients with a known diagnosis of HCC at the time of enlisting or found to have HCC while on the waiting list as patients with HCC. Patients not diagnosed with HCC before LT, including those with incidental HCC diagnosed after LT on the explanted liver, were called patients without HCC.

The HCC diagnosis was based on the concordant findings of at least 2 imaging techniques showing the characteristic arterial hypervascularization or on biopsy findings.[15] The imaging techniques used for diagnosis and staging were ultrasonography (including Doppler and real-time contrast-enhanced ultrasonography),[16] computed tomography, magnetic resonance imaging, and angiography.

Patients with HCC should fulfill the Milan criteria (single tumor, ≤5 cm in diameter, or up to 3 tumors, each ≤3 cm in diameter, without vascular invasion or extrahepatic spread)[1] upon enlistment and until LT. Patients with HCC who had undergone percutaneous ablation or transarterial chemoembolization, either before or after enlistment, still retained HCC priority, even if imaging techniques suggested complete necrosis of the treated lesion(s). The treated lesions, including those apparently necrotic, were kept in the count when the fulfillment of the transplantation criteria were assessed.

Up to shortly before the beginning of the HCC-MELD era (January 15, 2003), patients were definitively removed from the list if the Milan criteria were exceeded. Thereafter, a downstaging protocol was implemented, open to patients with HCC beyond the T2 stage but within the following inclusion criteria: single nodule, ≤8 cm; bifocal/trifocal HCC, each ≤5.0 cm; or up to 5 nodules, each ≤4.0 cm (in any case with a total tumor diameter below 12 cm). These patients underwent surgery or locoregional treatments. If the size of the still active tumor(s) was reduced to within the Milan criteria, the patients could be enlisted for LT, provided that AFP was less than 400 ng/ml. Subsequently, the Milan criteria had to be met until LT, but in this specific case, only those nodules with signs of activity according to the imaging techniques were considered. Also, in these instances, AFP should not exceed 400 ng/ml at the time during which the patients were active on the list.

Bologna Transplantation Center Allocation Policy

During the UNOS-CTP era (March 1, 2001 to February 28, 2003), patients were placed on the list in the order of the UNOS status and, in each status, in the order of the CTP score. This allocation strategy differed from the

TABLE 1. New Allocation Policy of the Bologna Transplantation Center

Patients without HCC	Native MELD score = $9.6 \times \log_e$(creatinine, mg/dl) + $3.8 \times \log_e$(total bilirubin, mg/dl) + $11.2 \times \log_e$(INR) + 6.4
Patients with HCC	Adjusted MELD score = native MELD score + stage score + waiting time score
	Stage score:
	Single nodule ≤3 cm = 5
	Single nodule >3 cm or multifocal tumor (within the Milan criteria) = 8
	Downstaging protocol = 12
	Waiting time score: 1.0 × (waiting time, months)

Abbreviation: INR, international normalized ratio.

U.S. pre-MELD policy, as the CTP score was the tiebreaker within each UNOS status in Bologna. The waiting time discriminated patients with the same CTP score. Patients with HCC were listed as UNOS status 2B.

In the HCC-MELD era (March 1, 2003 to February 28, 2004), patients were listed in order of the MELD score. Patients with HCC received an extra score based on the HCC stage (stage score), plus 1 additional point for every month on the list (waiting time score), to be added to their native MELD score, as reported in Table 1.

Upon the implementation of the new allocation policy, patients with HCC already on the list received all the additional points due, because they were active on the list with a diagnosis of HCC.

Statistical Analysis

We first investigated the outcome of the patients enlisted in the 2 eras (enlisted patients' analysis). The follow-up was censored at the end of the study period to which the patient belonged to avoid the confounding factor that all the patients on the list on March 1, 2003 abruptly changed their priority after that date. Moreover, after February 28, 2004, the allocation policy was slightly modified.

We considered death and removal from the list (due to tumor growth or clinical deterioration, making transplantation no longer feasible) as 1 single combined endpoint (called dropout in the study) because both represent a failure of the allocation policy.

The probability of the various outcomes for patients enlisted in each respective era was analyzed by Kaplan-Meier survival analysis and by competing risk analysis. The latter analysis better takes into account the probability of reaching 1 of different mutually exclusive outcomes when these are more than 2 (*e.g.*, undergoing transplantation, dropping out, or remaining on the list, because the reduction of an endpoint could make another event relatively more frequent; the competing risk analysis better considers the relative balance among more than 2 events than other individual analyses).

The initial and final MELD scores of patients enlisted in the HCC-MELD era were analyzed according to outcome to establish whether the new priority policy for HCC was associated with a significant clinical deterioration of the patients without HCC who remained on the list and whether the native MELD score was associated with different outcomes in patients with HCC. A multivariate regression logistic analysis was performed to identify possible predictors of MELD progression (initial to final) during the waiting time. The analysis was carried out also to search for independent predictors of dropout.

We then considered LTs performed in the 2 study periods, independently of the recipient's date of enlistment, to assess the rate of grafts assigned to patients with HCC in comparison to patients without HCC before and after the introduction of the MELD score (graft allocation analysis).

An analysis of variance for quantitative variable distribution and a chi-square test for qualitative variables were used in the comparison of the groups. Probability curves for LT and dropout were calculated according to the Kaplan-Meier method. The study protocol was approved by the local institutional review board. SPSS version 10.0 for PC (SPSS Inc., Chicago, IL) and STATA/SE 9.0 (Stata Corp., College Station, TX) were used for the calculations.

RESULTS

Enlisted Patients' Analysis

Three hundred one patients were enlisted during the 3-year study period. A total of 163 patients (on average 6.8 patients per month) were enlisted during the UNOS-CTP era; 138 (11.5 patients per month) were enlisted in the HCC-MELD era. There were 47 patients with HCC (28.8% of the total) in the UNOS-CTP era and 41 (29.7%) in the HCC-MELD era (P = NS). The general characteristics of the patients with and without HCC are reported in Table 2. The overall mean CTP score ± SD in all enlisted patients was 9.6 ± 1.9 (the median and range were 10 and 5-14, respectively). The HCC stage is shown in Table 3.

During the HCC-MELD era, the mean native MELD score at enlistment was similar in the patients with and without HCC, but the adjusted MELD score for the patients with HCC exceeded the native score of patients without HCC (Table 2). The average liver function in patients with HCC, assessed by the CTP score, was

TABLE 2. Baseline Characteristics of the Enlisted Patients

	Patients with HCC	Patients without HCC	*P*
Enlisted patients	88 (29.2%)	213 (70.8%)	NS
UNOS-CTP era	47 (28.8%)	116 (71.2%)	
HCC-MELD era	41 (29.7%)	97 (70.3%)	
Age (mean ± SD)	55.6 ± 7.0	51.7 ± 9.4	0.001
Sex			0.001
Male	76 (86.2%)	144 (67.6%)	
Female	12 (13.8%)	69 (32.4%)	
Liver disease etiology			0.005
Viral hepatitis	74 (84.1%)	137 (64.3%)	
Alcohol	8 (9.1%)	37 (17.4%)	
Cholestatic diseases	0 (0.0%)	8 (3.6%)	
Other	6 (6.8%)	31 (14.6%)	
Blood group			NS
O	39 (44.3%)	92 (43.2%)	
A	34 (38.6%)	79 (37.1%)	
AB	3 (3.4%)	6 (2.8%)	
B	12 (13.6)	36 (16.9%)	
CTP class at enlistment			
A (score 5-6)	5 (5.7%)	—	<0.05
B (score 7-9)	47 (53.4%)	96 (45.1%)	
C (score 10-15)	36 (40.9%)	117 (54.9%)	
Mean CTP score ± SD	9.1 ± 1.9	9.8 ± 1.9	<0.001
Median (range)	9 (5-13)	10 (7-14)	<0.001
Native MELD score at enlistment (mean ± SD, only HCC-MELD era)	15.3 ± 4.5	16.7 ± 5.4	NS
Adjusted MELD score at enlistment (mean ± SD, only HCC-MELD era)	22.3 ± 4.7	16.7 ± 5.4	<0.001

The HCC patients were patients for whom a diagnosis of hepatocellular carcinoma was made before transplantation; patients without HCC were patients enlisted for chronic liver disease not complicated by HCC.

significantly impaired already at the time of listing, justifying LT per se in many instances.

The treatment of HCC with any modality (transarterial chemoembolization, percutaneous alcohol injection, thermal ablation, or a combined treatment) was attempted in 27 patients (57.5%) in the UNOS-CTP era and in 29 patients (70.7%) in the HCC-MELD era (*P* = NS). Individual allocation to treatment was decided as follows: the aim of radicality and the technical feasibility of the various techniques were taken into account, but concurrently, the need of avoiding significant risks of dropping out from the list, either for progression of liver failure or tumoral needle-track seeding, in the case of percutaneous ablation, was also taken into account. Most cases, particularly all complex situations, were discussed together by the surgical and medical liver teams of the hospital during the weekly meeting to provide the best treatment to any patient.

Outcome of Patients Enlisted Under the 2 Allocation Policies.

In the UNOS-CTP era, 7 patients with HCC and 19 patients without HCC dropped out (14.9% and 16.4%, respectively, *P* = NS). Six patients with HCC were excluded because of tumor progression (12.8%), and 1 was excluded because of clinical deterioration in the absence of tumor progression (2.1%). The Kaplan-Meier analysis showed cumulative dropout risks at 3 and 6 months of 10.8% and 20.4%, respectively, for the HCC group versus 9.5% and 13.6%, respectively, for the non-HCC group (*P* = NS, Fig. 1).

During the HCC-MELD era, 7 patients with HCC and 14 patients without HCC dropped out (17.1% and 14.1%, respectively, *P* = NS). Only 1 patient with HCC dropped out because of HCC progression (2.4%); the others dropped out because of clinical deterioration (1 patient, 2.4%) or death related to liver failure (5 patients, 12.2%) without HCC progression beyond the Milan criteria (in 1 case, progression from the T1 stage to the T2 stage was observed before dropout). The cumulative dropout risks at 3 and 6 months were 17.6% and 17.6% for the HCC group versus 15.7% and 22.3% for the non-HCC group (*P* = NS, Fig. 1). The cumulative dropout risk recorded in the HCC-MELD era was not significantly different from that of the UNOS-CTP era for both the HCC group and the non-HCC group (*P* = NS in both groups).

In the UNOS-CTP era, 22 patients with HCC (46.8%) and 66 patients without HCC (56.9%, *P* = NS) received LT before the end of the study period. The cumulative probability of LT at 3 and 6 months was 24.8% and 44.6%, respectively, versus 23.5% and 45.6%, respec-

TABLE 3. HCC Staging at Enlistment and at the End of the Follow-Up

Stage	UNOS-CTP era	HCC-MELD era
Single nodule, ≤3 cm	26 patients (55.3%)	15 patients (36.6%)
Stable disease at the end of follow-up	21	13
Progression (within the Milan criteria)	3	0
Progression beyond the Milan criteria (enrolled in the downstaging protocol)	0	0
Progression beyond the Milan criteria (removed from the list)	2	0
Single nodule, 3-5 cm, or 2-3 nodules, ≤3 cm	21 patients (44.7%)	22 patients (53.7%)
Stable disease at the end of follow-up	16	19
Progression beyond the Milan criteria (enrolled in the downstaging protocol)	1	2
Progression beyond the Milan criteria (removed from the list)	4	1
Downstaging protocol	0 patients (0.0%)	4 patients (9.8%)
Stable disease at the end of follow-up	—	4
Progression (removed from the list)	—	0

Only removal from the list due to neoplastic progression is considered in this table. Until the implementation of the downstaging protocol, shortly before the end of the UNOS-CTP era, patients progressing beyond the Milan criteria were definitively removed from the list. After the introduction of the protocol, patients progressing beyond the Milan criteria, but within the downstaging criteria, were maintained on the list if a reduction of the active tumor within the Milan criteria was achieved by the treatment. Progression beyond the downstaged Milan criteria led to definitive removal from the list.

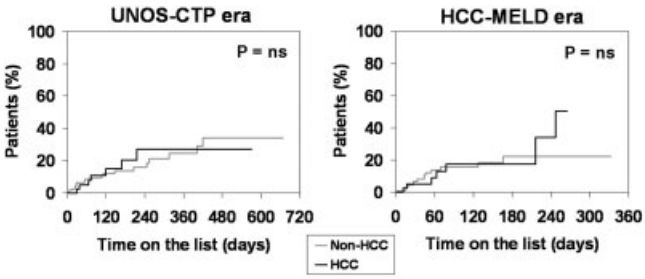

Figure 1. Kaplan-Meier curves comparing the cumulative dropout risk of patients with and without HCC under the 2 allocation policies. No differences were observed in the 2 study periods. The dropout for all causes (either tumor progression or liver failure) is considered for patients with HCC.

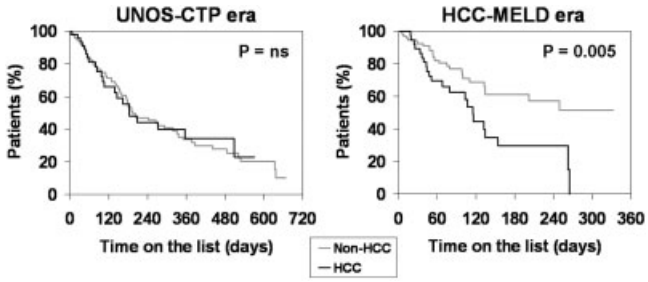

Figure 2. Kaplan-Meier curves comparing the cumulative transplantation probability of patients with and without HCC under the 2 allocation policies. After the introduction of the new allocation policy, the probability of transplantation was significantly higher for patients with HCC than for those without HCC.

tively (the median estimated time to LT was 194 versus 184 days, P = NS, Fig. 2).

During the HCC-MELD era, 22 patients with HCC (53.7%) and 26 patients without HCC (26.8%, P = 0.003) received LT before the end of the study period. The cumulative probability of LT at 3 and 6 months was 37.7% and 70.3%, respectively, in patients with HCC versus 23.2% and 39.0%, respectively, in patients without HCC patients (the median estimated time to LT was 115 versus 249 days, P = 0.005, Fig. 2). The HCC patients' cumulative probability of LT was higher in the HCC-MELD era than in the UNOS-CTP era (P = 0.02), whereas patients without HCC cumulative probability of LT was not significantly different in the 2 eras (P = NS).

Also, the competing risk analysis, which better takes into account that a progressively reduced number of patients is to be considered when patients reach an endpoint and are censored, did not show significant differences in the rates of dropout between the 2 eras, considering either all patients or only those with an HCC (Fig. 3). An increased rate of transplantation was instead documented in the MELD-HCC era in comparison with the UNOS-CTP era ($P < 0.027$) in patients with HCC, but not in patients without HCC (P = NS)

At the end of the UNOS-CTP era, 18 patients with HCC (38.3%) and 31 patients without HCC (26.7%) were still waiting for LT (P = NS). At the end of the HCC-MELD era, there were 12 patients still waiting for LT in the HCC group (29.3%) and 57 in the non-HCC group (58.8%, P = 0.001). Similar results were found by the competing risk analysis.

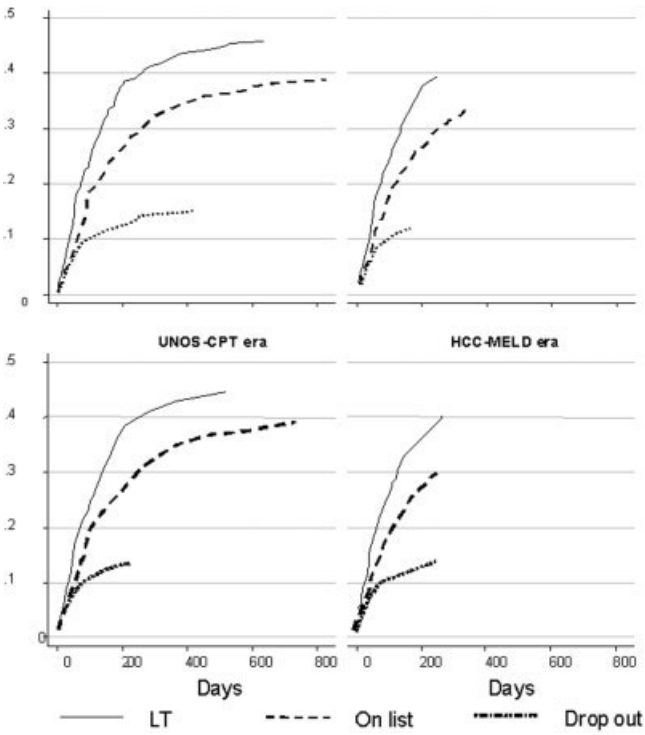

Figure 3. Competing risk analysis curves comparing the cumulative probability of LT, dropout, and remaining on the list for nonmalignant patients (upper graph) and patients with HCC (lower graph) in the 2 study eras (the UNOS-CTP era, from March 2001 to February 2003, and the HCC-MELD era, from March 2003 to February 2004). No significant difference is shown in the rates of LT and dropout, whereas an increase in the rate of patients remaining on the list is apparent in the HCC-MELD era for nonmalignant patients.

MELD Scores for Patients Who Underwent Transplantation, Were Excluded, or Were Still Waiting

In the non-HCC group, both the initial and final native MELD scores were significantly higher for patients who subsequently dropped out or underwent transplantation than in those who remained on the list (the mean initial scores were 19.6, 18.7, and 15.1, respectively, $P = 0.001$; the mean final scores were 22.1, 19.9, and 15.4, respectively, $P < 0.001$). In particular, patients who remained on the list did not present a significant increase in their final MELD score (the mean score was 15.1) in comparison with the initial value (the mean score was 15.4, P = NS).

In the HCC group, the initial native MELD score was marginally higher (without reaching significance) for patients who were subsequently excluded (17.3 ± 5.9) or underwent transplantation (15.5 ± 3.9) than for those remaining on the list (12.8 ± 4.0, P = NS). When considering the initial HCC-adjusted MELD score, we observed statistically higher values for patients who later dropped out (25.3 ± 5.9) than for those who underwent transplantation (22.8 ± 3.7) or remained on the list (19.6 ± 4.4, $P = 0.02$); this agreed with the higher dropout risk assigned to these patients.

A higher final MELD scores was observed for patients with HCC who dropped out in comparison with patients who underwent transplantation or remained on the list. The difference was significant when both the adjusted MELD score (the means ± SD were 34.0 ± 10.9, 25.3 ± 4.5, and 25.6 ± 7.3, respectively, $P = 0.02$) and especially the native MELD score (23.1 ± 10.1, 15.6 ±4.9, and 14.1 ± 5.2, respectively, $P = 0.009$) were analyzed. The change from the initial MELD score to the final native MELD score was statistically significant ($P < 0.01$) only for patients who dropped out. This is consistent with the fact that most of the dropouts were related to liver failure.

An assessment was carried out to identify predictors of a MELD increase, which is defined as a rise in the MELD score over the median value of the increase recorded in the study population (minor increase, corresponding to +0.6, rounded to +1.0) and over the third interquartile (major increase, corresponding to +3.06 MELD points, rounded to +3.00). Among the tested variables (shown in Table 4), nonalcoholic etiology and male sex were significantly associated with minor MELD increases in univariate analysis. Only nonalcoholic etiology was associated with a major MELD increase in univariate analysis. In logistic regression analysis, both sex and etiology were confirmed to be independent predictors of progressing ≥1.0 MELD point during the waiting time. Male sex had a relative risk of 2.06 [95% confidence interval (CI) = 1.20-3.55, $P = 0.01$], and an etiology different from alcoholic had a relative risk of 2.87 (95% CI = 1.29-6.37, $P = 0.01$).

The same analysis was carried out to identify variables associated with the risk of dropout. The analysis was performed for the whole series of patients and separately for patients with HCC. The analyzed variables are shown in Table 5. When all patients were considered, a significantly higher risk of dropout was present for patients of blood group B and with a high initial MELD score (categorized according to common clinical management as below or ≥20 points). In multivariate analysis, both variables remained significant independent predictors of dropout (relative risk of dropout for blood group B = 2.80, 95% CI = 1.34-5.82, $P = 0.006$; relative risk for MELD ≥ 20 at enlistment = 2.35, 95% CI = 1.19-4.66, $P = 0.014$). In the HCC group, no variable was significantly associated with a higher risk of dropout in univariate analysis, although some trends were apparent for HCC nodules ≥2 (in logistic regression, relative risk of dropping out = 3.18, 95% CI = 0.96-10.51, $P = 0.057$) and for the same variables significant for the overall study population. Statistical significance probably was not reached because of the lower number of HCC patients.

Graft Allocation Analysis

During the 3-year study period, 173 viable grafts became available at the Bologna Transplantation Center, excluding the grafts allocated to patients with acute hepatic failure or who needed retransplantation. A total of 54

TABLE 4. Rate of Patients for Each Variable Undergoing Increases in the Native MELD Score ≥1 and ≥3 (from Enlistment to Censorization)

	≥1-point increase in the MELD score	*P*	≥3-point increase in the MELD score	*P*
Total patients	42.9%		26.2%	
Sex total		0.02		NS
Male	47.0%		27.4%	
Female	31.7%		23.2%	
Age		NS		NS
>60	43.7%		26.2%	
≤60	40.3%		26.4%	
Blood group		NS		NS
O	49.6.%		28.2%	
A	38.9%		23.0%	
AB	33.3%		33.3%	
B	35.4%		27.1%	
Indication to LT				
HCC	46.6%		25.0%	
Viral hepatitis	48.3%		33.6%	
Alcohol	24.3%	NS	5.4%	0.03
Cholestatic diseases	37.5%		37.5%	
Other	32.3%		19.4%	
Grouped indications to LT		0.02		0.001
Alcoholic cirrhosis	24.3%		5.4%	
Other	45.5%		29.2%	

The 2 cutoffs are rounded to integer values corresponding to approximately median and interquartile values (75%).

grafts were allocated to patients with HCC (31.2%), and 119 were allocated to patients without HCC (68.8%).

During the UNOS-CTP era, 23 of the 110 available grafts (20.9%) were assigned to patients with HCC, and 87 were assigned to patients without HCC (79.1%). In contrast, during the HCC-MELD era, patients with and without HCC received 31 (49.2%) and 32 (50.8%) of the 63 grafts, respectively, with a significant difference in the graft distribution ($P < 0.001$).

To better understand the dynamics of the increased graft allocation to patients with HCC, we further split the HCC-MELD era into 2 semesters (first semester from March 1, 2003 to August 31, 2003 and second semester from September 1, 2003 to February 28, 2004). In the first semester, 36 grafts became available, 23 of which were assigned to patients with HCC (63.9%); 9 of the patients with HCC who underwent transplantation were enlisted in the UNOS-CTP period (39.1% of the patients with HCC underwent transplantation in the first HCC-MELD semester). In the second semester, only 8 grafts of 27 (29.6%) were assigned to patients with HCC, with a significant reduction in comparison with the first semester ($P = 0.007$).

DISCUSSION

The definition of allocation rules for patients with HCC, under the MELD-based allocation policy, is still a difficult issue in continuous evolution.[8,17-20] The UNOS priority policy for patients with HCC is based on the replacement of the native MELD score, assessing the risk of death due to liver failure by an estimation of the risk of tumoral progression.

In developing its new priority policy, the Bologna Transplantation Committee assumed that such a fixed score would not take sufficiently into account the role of the underlying liver disease in patients with HCC. Indeed, patients with cirrhosis who have HCC are both at risk of tumor progression beyond transplantation criteria and at risk of dying due to liver failure. Moreover, it should first be considered that effective HCC treatments (*e.g.*, percutaneous ablation or transarterial chemoembolization) during the waiting time are thought to decrease the risk of tumor progression,[18,21-24] but they are rarely feasible in patients with impaired liver function. On the other hand, transarterial chemoembolization, the most common treatment in these patients, may lead to liver decompensation, increasing the risk of liver-related death. Second, in patients with cirrhosis undergoing surveillance programs, the risk of developing HCC is higher in patients with more advanced CTP scores.[25,26] A similar finding has not been reported in patients already with a diagnosis of HCC, but it might be hypothesized that patients with HCC with a more advanced chronic liver disease are more predisposed to develop further nodules. Third, the tumor stage being equal, patients with a higher native MELD score are at higher risk of death, independently of HCC.

Consequently, the Bologna Transplantation Committee decided to add an HCC-specific adjunctive score to the native MELD instead of replacing it, with the aim of

TABLE 5. Rate of Patients for Each Variable Dropping Out from the List During the Waiting Time (for Tumor Progression or Death or Too Sick)

	Overall (n = 301)	*P*	HCC Patients Only (n = 88)	*P*
Sex total		NS		0.09
Male	14.6%		18.7%	
Female	18.3%		0.0%	
Age		NS		NS
>60	16.7%		14.3%	
≤60	15.3%		16.7%	
Blood group		0.05		NS
O	12.2.%		15.4%	
A	14.2%		14.7%	
AB	11.1%		0.0%	
B	29.2%		25.0%	
Blood group		0.01		NS
B	29.2%		25.0%	
Other	13.0%		14.5%	
Native MELD at enlistment		0.02		NS
MELD < 20	12.8%		15.4%	
MELD ≥ 20	25.5%		25.0%	
Number of tumors				0.074
Single			9.9%	
≥2			25.7%	
Maximum size of HCC				NS
<3 cm			13.0%	
≥3 cm			29.4%	
AFP (available n = 77)				NS
<30 ng/ml (n = 47)			13.3%	
≥30 ng/ml (n = 30)			17.0%	
AFP (available n = 77)				NS
<100 ng/ml (n = 65)			13.8%	
≥100 ng/ml (n = 12)			25.0%	

considering both the HCC-related and cirrhosis-related risks of death (Table 1). The actual additional priority was based on a purely arbitrary measure because no previous experience with similar systems was available at the time of implementation of the policy. As in the United States, the extra priority was defined in accordance with the HCC stage, reflecting the higher risk of dropout with stage progression.[6] A further adjunctive score, increasing with the waiting time, was assigned to patients with HCC. In fact, when all candidates are considered, the waiting time is reported not to affect waiting list mortality,[27] but when we consider selectively patients with HCC, the waiting time correlates with the dropout rate due to tumor progression.[4,6,18]

More recently, an attempt to quantify the individual risk of removal from the waiting list for patients with HCC in the UNOS system was carried out.[28] Contributors to the risk of removal for patients with HCC were the MELD score at listing, AFP level, and maximum tumor size. Our results are in line with those of the U.S. study:[28] in our system, a native MELD score ≥20 was confirmed to be independently associated with dropout. Multiple HCCs, the tumor size, and the AFP serum level showed a trend to higher dropout risk but did not reach statistical significance, possibly because of the small size of the HCC group.

One of the most interesting data emerging from our study regards the role of hepatic dysfunction in determining the outcome of patients with HCC awaiting orthotopic liver transplantation. Patients with HCC who dropped out had both native and adjusted MELD scores higher than those of patients who underwent transplantation or were still on the list, and they experimented a significant increase in their native MELD score during the waiting time. Such a finding could also derive from the fact that many patients showed a relevant liver failure (CTP class C) at the time of listing. Indeed, these patients are at a higher risk of dropping out from the list because they are exposed, while waiting, both to the risk of undergoing an increase in tumor size beyond transplantation limits and to the risk of a progressive liver failure, especially in cases submitted to local HCC treatment, given the critical and frail liver function.

These data support our initial assumption that hepatic dysfunction affects the outcome of patients with HCC and therefore should be considered in assessing their risk of exclusion from the waiting list. Under our new allocation policy, patients with both HCC and relevant hepatic failure underwent transplantation, mainly because of their high native MELD score. Whether the fair results obtained with the present allo-

cation system would remain valid also in series of transplant candidates in which HCCs had arisen most commonly in well-functioning livers (CTP class A) remains to be demonstrated.

The quantification of the priority remains a critical issue. In our system, the amount of additional priority assigned to patients with HCC was, as said, arbitrarily chosen. Indeed, an allocation policy would be more acceptable if evidence-based, as proposed in the recent study by Freeman et al.[28] Nevertheless, in our opinion, the priority points for patients with HCC should be tailored for each transplantation center, taking into account the length of the waiting list and the severity of the listed patients (and thus may even change over the years). The aim of prioritizing HCC is to offer timely LT to these high-risk patients: if the average MELD score at transplantation becomes higher, the actual adjunctive score would not be enough to warrant LT before tumor progression. On the contrary, in a hypothetical center in which the patients undergo transplantation with a lower MELD score, a lower priority score would be adequate.

The issue may be even more complex in the case of a very long waiting list due to a persistent shortage of grafts: it may happen that, in the long term, only patients with HCC would reach the top of the list because of the progressive monthly accumulation of MELD points. In this case, patients without HCC would have a chance of undergoing transplantation only if they were very sick (MELD $>$ 30).

Bearing in mind these problems, we analyzed the dynamic changes in our waiting list after the new allocation system implementation. In particular, we compared the outcome of patients without HCC with the outcome of patients with HCC to assess if a MELD adjustment so favorable to the latter ones would be detrimental to patients without HCC.

No significant decrease in the dropout rate was observed in the HCC-MELD era in either patients with or without HCC. However, it should be considered that, even in the pre-MELD era, the Bologna Transplantation Center ranked LT candidates according to an index of disease severity, namely the CTP score, and used it to match marginal donors and recipients without severe liver dysfunction (mainly patients with HCC), thus obtaining a relatively low HCC waiting time.[29]

The major effect of the new policy was a marked increase in the transplantation rate of HCC patients. The probability of LT at 6 months for patients with HCC rose from 44.6% to 70.3%, being significantly higher than that of patients without HCC in that same period (39.0%). Of the available grafts, 49.2% were allocated to patients with HCC. This situation might appear unacceptable at first glance, although similar to what happened in some U.S. centers, where 48% of liver grafts were allocated to patients with HCC after implementation of the MELD system.[30] However, some considerations have to be made.

First, patients with HCC enlisted during the UNOS-CTP era and still waiting for LT when the MELD score was implemented promptly gained the top of the list in the HCC-MELD era because of their long waiting time. Once nearly all these patients with HCC had undergone transplantation, a significant reduction in graft assignment to HCC patients was recorded, as became apparent in the second HCC-MELD semester (from 63.9% to 29.6%). It is noteworthy that the rate of graft assignment to patients with HCC in the second MELD semester was almost equal to the rate of patients with HCC enlisted under the MELD-based allocation policy (29.7% of all enlisted patients), suggesting that a steady state had been reached.

Furthermore, the increase in the HCC transplantation rate was not associated with a significant worsening in the outcome of patients without HCC. Their dropout risk was comparable to that of patients with HCC in both study periods. The accelerated access to LT of patients with HCC produced instead an increased proportion of patients without HCC still waiting for LT at the end of the study period (58.8% versus 26.7% in the UNOS-CTP era). However, the still-on-list patients without HCC did not present a significant increase in their final MELD score in comparison with the enlistment value. As the increase in the MELD score during follow-up is reported to be an independent risk factor for death,[31] it would appear that patients without HCC that remained on the list were the most stable ones, those who did not present such a clinical deterioration as to drive them to the top of the list or to exclude them from LT. Predictors of not increasing the MELD score were found to be female sex and alcoholic etiology. Although no definite interpretation for sex is available, the effect of alcoholic etiology could be explained by the possibility of removing the liver injury with abstinence.

On the basis of these results, in March 2004, the Bologna Transplantation Committee confirmed the validity of summing an adjunctive score for HCC to the native MELD score but considered excessive the increased rate of still-on-list patients without HCC and the higher probability of overall and short-term transplantation for patients with HCC. Consequently, the committee reduced the adjunctive score to 3 points for a single tumor $\leq$3 cm (plus 0.5 point every month on the list) and 6 points (plus 1 point per month) for patients with larger or multiple tumors or in the downstaging protocol. As in the United States, no adjunctive score has been provided to patients with stage T1 HCC since 2005.

In conclusion, the new Bologna allocation system appears feasible and valid, as it prioritizes patients with HCC without severely affecting the outcome of other patients. Because it takes into account the severity of the underlying liver dysfunction in patients with HCC, this priority policy offers the advantage of discriminating among patients with HCC with different risk profiles (preponderance of liver-related or tumor-related risk).

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