Application of the Intermediate-Stage Subclassification to Patients With Untreated Hepatocellular Carcinoma

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OBJECTIVES: **The Barcelona Clinic Liver Cancer (BCLC) intermediate stage (BCLC B) includes a heterogeneous population of patients with hepatocellular carcinoma (HCC). Recently, in order to facilitate treatment decisions, a panel of experts proposed to subclassify BCLC B patients. In this study, we aimed to assess the prognostic capability of the BCLC B stage reclassification in a large cohort of patients with untreated HCC managed by the Italian Liver Cancer Group.**

METHODS: **We assessed the prognosis of 269 untreated HCC patients observed in the period 1987–2012 who were reclassified according to the proposed subclassification of the BCLC B stage from stage B1 to stage B4. We evaluated and compared the survival of the various substages.**

RESULTS: **Median survival progressively decreased from stage B1 (n=65, 24.2%: 25 months) through stages B2 (n=105, 39.0%: 16 months) and B3 (n=22, 8.2%: 9 months), to stage B4 (n=77, 28.6%: 5 months; P<0.0001). Moreover, we observed a significantly different survival between contiguous stages (B1 vs. B2, P=0.0002; B2 vs. B3, P<0.0001; B3 vs. B4, P=0.0219). In multivariate analysis, the BCLC B subclassification (P<0.0001), MELD score (P=0.0013), and platelet count (P=0.0252) were independent predictors of survival.**

CONCLUSIONS: **The subclassification of the intermediate-stage HCC predicts the prognosis of patients with untreated HCC. The prognostic figures identified in this study may be used as a benchmark to assess the efficacy of therapeutic intervention in the various BCLC B substages, whereas it remains to be established whether incorporation of the MELD score might improve the prognosis of treated patients.**

SUPPLEMENTARY MATERIAL is linked to the online version of the paper at http://www.nature.com/ajg

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INTRODUCTION

Despite implementation of surveillance programs for the early diagnosis of hepatocellular carcinoma (HCC), a significant proportion of patients are currently diagnosed with large tumor burden; moreover, even if HCC is diagnosed in a nonadvanced stage, some patients may have mildly decompensated liver disease (1–3). Patients with these characteristics are considered by the Barcelona Clinic Liver Cancer (BCLC) classification as patients with intermediate-stage HCC (BCLC B), and their primary therapeutic indication is trans-catheter arterial chemoembolization (4–6). Nevertheless, some studies have emphasized the fact that the BCLC B stage includes a heterogeneous population of HCC patients, who have varying degrees of both liver function impairment and tumor burden (7–9). In clinical practice, this finding often translates into the application of different therapeutic approaches—thus providing evidence that a single therapeutic option may not fit all intermediate-stage patients—and different survival expectancy (7–11). Moreover, BCLC B patients represent ~30% of patients with HCC, and therefore a rigorous prognostic stratification linked to the most appropriate treatment option is eagerly awaited for this population (12).

Recently, taking into account the marked heterogeneity of this population, a panel of experts has proposed to subclassify patients with intermediate-stage HCC, suggesting possible treatment options for each substage in order to facilitate treatment decisions in clinical practice (8). According to these suggestions, BCLC B patient were reclassified into four subgroups on the basis of impairment in liver function assessed by the Child-Pugh score, tumor burden staged according to the Milan and 'up-to-seven' *criteria*, and patients' performance status (PS), also including patients with tumor-related PS 1, included in the advanced HCC stage (BCLC C) (7). This subclassification was mainly based on experts' opinions derived from the results of studies carried out in BCLC B patients, and its prognostic capability has never been tested. Indeed, few studies assessing the prognostic power of the BCLC B subclassification have been recently published, but they report contrasting results likely because of the presence of the confounding effect caused by a nonstandardized therapeutic management (13–16). A reliable assessment of the prognostic ability of the BCLC-B subclassification can be obtained by analyzing the 'natural history' of untreated BCLC-B patients, and definitively confirmed with a prospective study in which the treatment choice should follow the indications of the algorithm.

In this study, our aim was to assess the prognosis of a large population of untreated patients with HCC who were reclassified according to the proposed subclassification of the intermediate (BCLC B) stage. The evaluation of the outcome of untreated BCLC B patients allows us to test the prognostic capability of the proposed subclassification without incurring in the potential bias of treatment allocation, thus providing a solid point of reference for comparison of survival once a determined treatment is applied to a definite subpopulation.

METHODS

Patients

The Italian Liver Cancer database currently contains data of 5,136 HCC patients consecutively diagnosed with HCC from 1987 to 2012 at 21 Italian medical institutions in Italy. These data were collected prospectively and updated every 2 years with information on the follow-up of the patients. After data entry by any single center, the consistency of the data set was checked by the group coordinator (F.T.) and, when clarification or additional information was needed, it was resubmitted to each center before statistical evaluation. For the purpose of this study, we included all intermediate-stage patients (BCLC B) who received no anticancer treatment but best supportive care alone or tamoxifen and whose data were available to assess BCLC stage and calculate Model for End-stage Liver Disease (MELD) score (74 patients were excluded because of the lack of data for the calculation of the MELD score) (4,17). Patients who received tamoxifen (n=101, 37.5%) were included into this study because of the demonstrated lack of any effect of this drug on survival of HCC patients (18). Moreover, we performed a sensitivity analysis assessing the survival of patients who received best supportive care alone and tamoxifen and found no statistically significant difference in median survival (tamoxifen, 12 months vs. best supportive care alone, 13 months; P=0.148; **Supplementary Figure 1** online). The reasons for treatment withdrawal were various and related to the presence of comorbidities preventing any therapeutic approach, advanced age, advanced tumor stage, poor residual liver function in patients who are not candidates for liver transplantation, and refusal of treatment by the patient.

Methods

Common biochemical liver tests and tests used to calculate the MELD score were carried out by conventional methods using commercially available assays. Similarly, tests used to identify the etiology of liver disease were those available at each center at the time of patients' inclusion. The MELD score was calculated in all patients according to the original formula proposed by the Mayo Clinic group: $3.78\times\log_e$ (bilirubin [mg/dl])$+11.2\times\log_e$ (I.N.R.)$+9.57\times\log_e$ (creatinine (mg/dl)) (17,19). The presence of cirrhosis was assessed by the physician in charge of the patient according to histological or unequivocal clinical and instrumental evidence, and liver function was evaluated using the Child–Pugh classification (20). The diagnosis of HCC was made by ultrasound-guided biopsy or by characteristic, contrast-enhanced, radiological imaging results according to the guidelines published at the time of patients inclusion. Cancer size and stage were evaluated by radiological imaging, and PS was assessed according to the Eastern Cooperative Oncology Group (21). Briefly, an Eastern Cooperative Oncology Group PS score of 0 is assigned to asymptomatic patients (fully active, able to carry on all predisease activities without restriction), a PS score of 1 to symptomatic but completely ambulatory patients (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature), a PS of 2 to symptomatic patients who spend <50% in bed

Table 1. Proposed sub-classification of the intermediate (BCLC B) stage hepatocellular carcinoma patients

BCLC sub-stage	B1	B2	B3	B4
Child-Pugh score	5–6–7	5–6	7	8–9
Beyond Milan and within up-to-seven	In	Out	Out	Any
ECOG performance status (tumor-related)	0	0	0	0-1
Portal vein thrombosis	No	No	No	No

BCLC, Barcelona Cancer Liver Clinic; ECOG, Eastern Cooperative Oncology Group.

during the day (ambulatory and capable of all self-care but unable to carry out any work activities), a PS of 3 to symptomatic patients who spend >50% of the day-time in bed but are not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours), and a PS of 4 to bed-bound patients (completely disabled, cannot carry on any self-care, totally confined to bed or chair).

Cancer stage was assessed using both the Milan criteria and the up-to-seven criterion. The Milan criteria encompass a single tumor ≤5 cm or a maximum of 3 total tumors with none >3 cm, whereas the up-to-7 criterion combines the number of nodules and the size of the largest tumor, with the sum being no >7 (e.g., 3 nodes up to 4 cm in size (3+4=7)) (22,23).

Intermediate-stage patients were further subdivided according to the subclassification of the BCLC B stage proposed by Bolondi *et al.* in 4 substages from B1 to B4 (**Table 1**) (7). Patient survival was defined as the time—expressed in months—elapsed from the date of HCC diagnosis and the date of death or the last follow-up information.

Statistical analysis

Continuous data are shown as median value and range, and discrete variables as absolute and relative frequencies. Comparison of continuous data were carried out using the Mann–Whitney *U*-test, and comparison of discrete variable was carried out using the Fisher's exact test or the χ^2 test with Yates correction, as appropriate. Cumulative overall survival was estimated by the Kaplan–Meier method, and statistical comparison of survival distribution was analyzed by the log-rank test. Associations with a *P*-value ≤0.1 at univariate analysis were entered into a Cox's stepwise multivariate regression analysis where the cutoffs for platelet count and MELD score was the median value of the series, for the year of diagnosis we used two groups (1987–2000 vs. 2001–2012), while for age we used the commonly accepted definition of elderly (>65 years), and for alpha-fetoprotein we used both the upper limit of normal (i.e., 10 ng/ml) and an arbitrary cutoff of 400 ng/ml. A *P*-value <0.05 in a two-tailed test was considered statistically significant. Statistical analysis was performed using MedCalc statistical package (MedCalc Software, Mariakerke, Belgium).

Ethics

The Italian Liver Cancer database management conforms to the past and current Italian legislation on privacy, and the present study conforms to the ethical guidelines of the Declaration of Helsinki. Approval for the study was obtained by the Institutional Review Board of the participating centers.

RESULTS

Baseline cohort characteristics

A total of 269 patients with untreated HCC were included into this study. Patients were prevalently male (*n*=204, 75.8%), their median age was 69 years (24–95 years), and 171 patients (63.6%) were older than 65 years. The main etiology of liver disease was infection with hepatitis virus alone (*n*=154, 57.2%: *n*=116 hepatitis C virus, *n*=27 hepatitis B virus, *n*=11 hepatitis B and C viruses) or with alcohol abuse (*n*=37, 13.8%). Ascites and hepatic encephalopathy were present in 76 (28.3%) and 12 patients (4.5%), respectively, whereas 191 patients (66.1%) had esophageal varices. Median albumin, bilirubin, and creatinine levels were 35 g/dl (21–50 g/dl), 1.4 (0.6–14.0 mg/dl), and 1.0 mg/dl (0.5–6.1 mg/dl), respectively, and median international normalized ratio value was 1.30 (0.91–2.56). Median MELD score was 11 (6–32), and median serum alpha-fetoprotein was 108 mg/ml (6–72,918 ng/ml). In the whole cohort, overall median survival was 13 months. Causes of death were HCC progression in 90 patients (51.1%), liver failure in 38 patients (21.6%), gastrointestinal bleeding in 10 patients (5.7%), infection in 4 patients (2.3%), various causes in 12 patients (6.8%), while in 22 patients the causes of death were not known (12.5%).

Characteristics and survival of patients according to the proposed subclassification of the intermediate (BCLC B) stage

Patients were subdivided into 4 stages according to the BCLC B subclassification, from stage B1 to stage B4 (**Table 1**). According to this subclassification, 65 patients were classified as B1 (24.2%), 105 patients as B2 (39.0%), 22 patients as B3 (8.2%), and 77 patients as B4 (28.6%). The main characteristics of patients subdivided according the intermediate-stage HCC subclassification are shown in **Table 2**. Among the demographic, biochemical, and clinical parameters, the presence of esophageal varices (*P*<0.0001), platelet counts (*P*=0.0225), serum albumin (*P*<0001) and bilirubin levels (*P*<0.0001), international normalized ratio values (*P*<0.0001), and MELD scores (*P*<0.0001) were significantly different among the various substages.

Median survival progressively decreased from stage B1 (25 months) through stages B2 (16 months), B3 (9 months), and B4 (5 months, *P*<0.0001, **Figure 1**). Moreover, we observed a significantly different survival between contiguous stages (**Figure 2a**: B1 vs. B2, *P*=0.0002; **Figure 2b**: B2 vs. B3, *P*<0.0001; **Figure 2c**: B3 vs. B4, *P*=0.0219).

Table 3 shows the results of the univariate analysis for survival in the whole cohort. A MELD score <11 (*P*<0.0001), the absence of esophageal varices (*P*=0.0003), and being diagnosed after the year

Table 2. Main demographic, biochemical, and clinical characteristics of the study population subdivided according to the proposed subclassification of the intermediate stage hepatocellular carcinoma

		BCLC B sub-stages			
		B1 (*n*=65)	**B2 (*n*=105)**	**B3 (*n*=22)**	**B4 (*n*=77)**
Gender	Male	47 (85.5)	83 (79.0)	19 (86.4)	55 (71.4)
Age	Years	67 (44–92)	69 (43–89)	67 (24–82)	69 (40–95)
Etiology	Virus	49 (75.4)	70 (66.7)	15 (68.2)	57 (74.0)
	Alcohol	12 (18.5)	20 (19.0)	5 (22.7)	17 (22.1)
	Others	4 (6.1)	15 (14.3)	2 (9.1)	3 (3.9)
Albumin	g/dl	3.6 (2.7–4.9)	3.6 (2.8–5.0)	3.4 (2.6–4.5)	3.0 (2.1–4.2)
Bilirubin	mg/dl	1.1 (0.6–2.2)	1.2 (0.3–2.9)	2.1 (0.4–14.0)	2.5 (0.3–12.2)
Creatinine	mg/dl	1.0 (0.6–6.1)	1.0 (0.6–2.6)	1.0 (0.7–2.3)	1.0 (0.5–1.8)
INR		1.28 (0.93–2.28)	1.21 (0.91–2.0)	1.33 (1.11–2.22)	1.43 (1.0–2.56)
Platelet count	$\times 10^9$/l	126 (45–270)	130 (26–557)	121 (36–345)	103 (37–400)
Esophageal varices	Present	37 (56.9)	47 (44.8)	14 (63.6)	66 (85.7)
Child-Pugh score	5	33 (50.8)	62 (59.0)		
	6	24 (36.9)	43 (41.0)		
	7	8 (12.3)		22 (100)	
	8				46 (59.7)
	9				31 (40.3)
MELD	score	11 (6–32)	10 (6–16)	14 (8–19)	15 (8–22)
Alpha-fetoprotein	ng/ml	52 (6–45,000)	68 (6–36,000)	54 (6–18,141)	318 (6–72,918)
Up-to-7 criteria	out		105 (100)	22 (100)	59 (76.6)
ECOG PS	1				65 (84.4)

BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; INR, international normalized ratio; MELD, Model for End-stage Liver Disease; PS, performance status.

Data are shown as median and range or absolute value and percentage. Virus category includes patients with viral hepatitis alone and patients with viral hepatitis and alcohol.

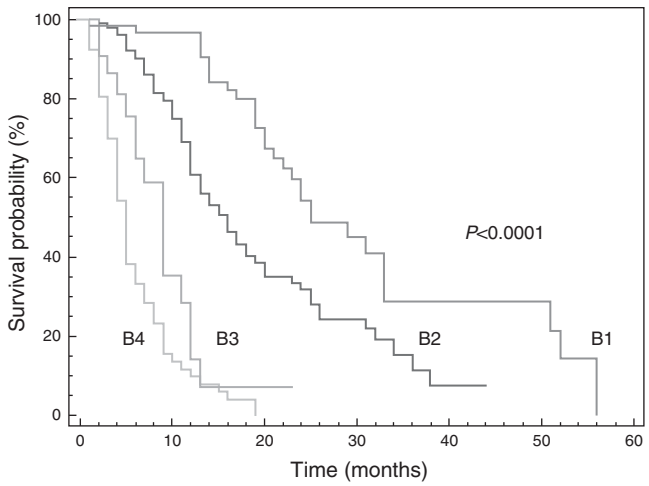

Figure 1. Kaplan–Meier survival curves of untreated patients with hepatocellular carcinoma subdivided according to the subclassification of the intermediate stage hepatocellular carcinoma (blue line, BCLC B1; red line, BCLC B2; green line, BCLC B3; yellow line, BCLC B4). BCLC, Barcelona Clinic Liver Cancer. A full color version of this figure is available at the *American College of Gastroenterology* journal online.

2000 (P=0.0009) were associated with a better survival, whereas low platelet counts (P=0.065) and very high alpha-fetoprotein levels (P=0.073) were marginally associated with worse survival. In Cox's regression multivariate analysis, the BCLC B subclassification (Hazard Ratio=2.194 (95% confidence interval, 1.846–2.604), P<0.0001), MELD score (Hazard Ratio=1.899, (95% confidence interval, 1.287–2.800), P=0.0013), and platelet count (Hazard Ratio=1.499, (95% confidence interval, 1.053–2.132), P=0.0252) were independent predictors of survival.

Last, we evaluated the prognosis of the various BCLC substages further subdivided according to the overall median MELD score. **Table 4** shows that the only substage in which further breakdown of patients according to the MELD score was statistically significant and clinically meaningful was stage B1, with an observed median survival in B1 patients with a MELD score ≤11 of 33 months and in those with a MELD score >11 of 20 months (P=0.003). Less impressive, but statistically significant, was the different survivals observed in B2 patients (P=0.047). Instead, MELD score did not provide additional prognostic information in B3 and B4 patients.

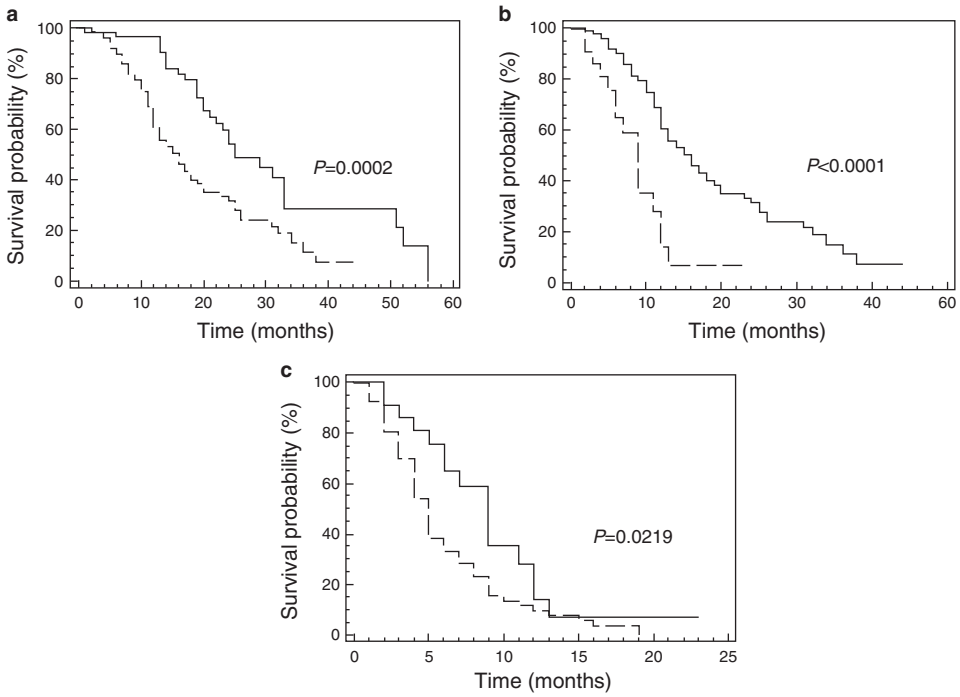

Figure 2. Kaplan–Meier survival curves in contiguous stages of the BCLC B subclassification of patients with intermediate stage hepatocellular carcinoma (**a**: thick line=BCLC B1, dotted line=BCLC B2; **b**: thick line=BCLC B2, dotted line=BCLC B3; **c**: thick line=BCLC B3, dotted line=BCLC B4). BCLC, Barcelona Clinic Liver Cancer.

Table 3. Results of the univariate analysis for survival in the study cohort

Parameter	Unit	*n*	Survival (months)	Hazard ratio (95% CI)	*P* value
Gender	Male vs. Female	204/65	13 vs. 13	0.924 (0.645–1.308)	0.636
Age	<65 vs. ≥65 years	98/171	12 vs. 13	0.917 (0.662–1.253)	0.567
Etiology	Non-viral vs. viral	78/191	13 vs. 13	1.166 (0.842–1.668)	0.330
Year of HCC diagnosis	'87-'00 vs. '01-'12	145/124	11 vs. 17	1.657 (1.239–2.296)	0.0009
Platelet count	<127 vs. ≥127×10^9/l	143/126	12 vs. 15	1.312 (0.982–1.807)	0.065
MELD score	≤11 vs. >11	137/132	19 vs. 8	0.395 (0.215–0.426)	<0.0001
Alpha-fetoprotein	≤10 vs. >10	64/205	13 vs. 13	0.850 (0.598–1.190)	0.332
Alpha-fetoprotein	≤400 vs. >400	160/109	14 vs. 12	0.769 (0.532–1.028)	0.073
Esophageal varices	Absent vs. present	105/164	16 vs. 11	0.584 (0.417–0.774)	0.0003

HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease.

DISCUSSION

Intermediate-stage patients represent ~30% of patients with HCC, and their prognosis is quite variable because of the inclusion in the same stage of a population with various degrees of liver dysfunction and different tumor burden (8,12). Because of these findings, despite clinical guidelines suggesting a unique first-line treatment for this stage, in clinical practice patients are often treated with various therapeutic approaches (9–11). With the aim to rationalize patient stratification and to therefore improve the staging–treatment association, a panel of experts recently suggested to substage patients with intermediate HCC, basing their suggestions on the breakdown of patients according to liver function, tumor burden, and tumor-induced impairment of everyday activities (7). However, this subclassification has never been fully validated, and the few recent studies that tried to assess its prognostic capability were carried out mainly in patients treated with trans-catheter arterial chemoembolization, reporting contrasting results (13–16).

In this study, the median survival of untreated patients with intermediate-stage HCC slightly exceeded one year, a finding

Table 4. Survival in the various intermediate stage hepatocellular carcinoma sub-stages subdivided according to model for end-stage liver disease score

	MELD score ≤11		MELD score >11		
Sub-stage	*n*	Survival (months)	*n*	Survival (months)	*P* value
BCLC B1	41	33	20	20	0.003
BCLC B2	80	17	25	12	0.047
BCLC B3	5	6	17	9	0.848
BCLC B4	11	5	66	5	0.250

BCLC, Barcelona Clinic Liver Cancer; MELD, Model for End-stage Liver Disease.

consistent—yet with a minimal improvement—both with the results of our previous study carried out in a limited number of untreated, intermediate patients (i.e., 10 months) and the placebo arm of the patients with intermediate stage (BCLC B) included in the SHARP trial (i.e., 11.4 months) (24,25). The re-staging according to the proposed subclassification of the BCLC B stage provided an important prognostic indication, as the median survival progressively, and significantly, decreased across all the substages. Thus, discriminatory ability and gradient monotonicity, two essential performance characteristics of a prognostic system, were fulfilled (26). As a matter of fact, while untreated stage B1 patients showed a median survival overlapping the one we observed in untreated BCLC stage A patients (i.e., 25 months), the prognosis of stage B4 patients was dismal, with a median survival of 5 months, which was even worse than the one previously observed in untreated stage D patients (24). All in all, these findings once again emphasize the marked heterogeneity of BCLC B stage, and provide baseline survival figures that may be used to counsel patients and their families, to assess the efficacy of treatments in each substage, and to discourage anticancer treatment when prognosis is unlikely to be improved by therapy.

As far as patients' distribution among the intermediate substages is concerned, it is worth noting that although we selected patients who were not treated our results are in keeping with those of the studies that assessed the prognosis of subclassified BCLC B patients treated with trans-catheter arterial chemoembolization (13,14,16). As a fact, stage B1 and B2 patients represented more than half of the population, with stage B2 being the most numerous stage in our cohort, as well as in the previous series. However, despite a similar patients' distribution among the various substages, the comparison of other figures—in particular survival—was difficult to perform among studies. In fact, the series presented by Ha *et al.* and Wang *et al.* included patients who were fit enough to undergo trans-catheter arterial chemoembolization and were carried out in Eastern patients, and in one study B3 and B4 stages were merged because of a similar prognosis (13,14). Moreover, the study by Wang *et al.* included >70% of patients with chronic HBV infection and with an unknown proportion of patients with cirrhosis (14). The only study including a Western population somehow similar to ours was performed by Weinmann *et al.*, who obtained a general behavior of survival similar to the one seen in our study, especially in B1 and B4 stages, after patients who underwent liver transplantation were excluded from the analysis (15). Indeed, they too observed a wide survival range, spanning from 28.5 to 5.9 months, thus confirming the marked heterogeneity of intermediate-stage HCC patients. However, the lack of survival difference between contiguous substages did not allow this study to support the prognostic quality of the BCLC B subclassification. Nevertheless, as the authors themselves observed, the lack of discriminatory ability could have been caused by the small number of patients in some substages, as, despite a median survival of B3 patients more than double the one of B4 patients (12.3 vs. 5.9 months), this difference did not reach statistical significance (15).

Another interesting finding of our study is that MELD score and platelet count were independent predictors of survival in untreated patients with intermediate HCC. We did not use platelet count to further subclassify the various BCLC B substages because of its marginal statistical significance. Instead, a sensitive analysis indicated that MELD score was able to provide a finer tuning of prognosis in the BCLC B subclassification, and in particular in stages B1 and B2. The additional prognostic information was particularly striking in stage B1 patients, where a MELD score cutoff of 11 identified two groups of patients with a survival difference of >1 year (33 vs. 20 months), whereas the discriminatory ability of MELD score was less evident (17 vs. 12 months) and only marginally significant in B2 substage patients. The lack of further prognostic stratification provided by the MELD score in B4 patients, on the contrary, was probably because of the presence in this substage of a large proportion of patients with an HCC beyond the 'up-to-seven' *criterion* and with a PS 1, and thus with a short-term outcome unlikely to be profoundly influenced by the residual liver function.

This study has some undoubted limitations. First, patients were accrued over a long period of time, as this was required in order to reach an adequate sample size for this specific clinical question. In this regard, the period of HCC diagnosis turned out to be a predictor of survival, and this may be related to the improvement in clinical care of patients with cirrhosis in more recent years (27–29). However, when the period of HCC diagnosis was included into multivariate analysis, its prognostic relevance was not significant, thus suggesting that other clinical variables weighed more on prognostic assessment. Second, another study limitation may

be related to the absence of further subcategorization of patients with viral etiology of disease, as cirrhotic patients infected with hepatitis B virus may have a better prognosis as compared with patients infected with hepatitis C virus. Nevertheless, among the 154 patients with viral etiology of cirrhosis alone, only 16 patients had hepatitis B virus infection as a single etiological factor, and therefore this subanalysis was not clinically meaningful and statistically sound. Third, a subgroup of patients included in this study received tamoxifen. Although some authors may still hypothesize a potential effect of tamoxifen—even a negative one—on the prognosis of patients with HCC, we decided to include taxoxifen-treated patients among the untreated patients in this study on the basis of the results of several studies and of a systematic review showing no effect of tamoxifen on prognosis of HCC patients (18). Moreover, we have previously shown no effect of tamoxifen on survival in a larger series of untreated HCC patients distributed across all BCLC stages, and also in this study we performed a sensitivity subanalysis of our cohort showing no survival effect of tamoxifen (**Supplementary Figure 1**) (24). Fourth, it may be objected that the absence of treatment because of comorbidities or advanced age may represent a bias of the study and therefore flaw its results; however, the fact that the main cause of death (i.e., 78.4%) was represented either by tumor progression or liver-related events (e.g., liver failure, gastrointestinal bleeding) seems to be against this objection. Last, we acknowledge that it remains to be established whether the results of this study may be generalizable to treated intermediate-stage HCC patients, as this was not the aim of our study, although we feel that our results provide a first, substantial step in this direction and provide solid data to compare survival in treated patients in the various intermediate-stage substages. In this regard, preliminary results of the Italian Liver Cancer group seem to show that the subclassification of the intermediate-stage HCC may have prognostic relevance also in treated patients, although we do acknowledge that our results need to be confirmed in prospectively enrolled, independent, larger cohorts of untreated intermediate-stage HCC patients (30).

To conclude, in untreated patients with intermediate-stage HCC, further subclassification on the basis of tumor burden, liver function, and PS have prognostic meaning. Subclassification of BCLC B patients based on these features identifies subgroups with statistically significant and clinically relevant different prognosis. The survival figures that we identified in these untreated patients may be used to compare the potential survival advantage provided by various treatments. Further studies are warranted to assess whether inclusion of the MELD score may provide a finer prognostic tuning and more appropriate treatment allocation.

CONFLICT OF INTEREST

Guarantor of the article: Edoardo G. Giannini.

Specific author contributions: Design of the work, acquisition, analysis and interpretation of data, and drafting the work: Edoardo G. Giannini; acquisition of data and revising the work critically for important intellectual content: Alessandro Moscatelli, Gaia Pellegatta; analysis and interpretation of data, and revising the work critically for important intellectual content: Alessandro Vitale; acquisition and interpretation of data, and revising the work critically for important intellectual content: Fabio Farinati, Francesca Ciccarese, Fabio Piscaglia, Gian Lodovico Rapaccini, Maria Di Marco, Eugenio Caturelli, Marco Zoli, Franco Borzio, Giuseppe Cabibbo, Martina Felder, Rodolfo Sacco, Filomena Morisco, Gabriele Missale, Francesco Giuseppe Foschi, Antonio Gasbarrini, Gianluca Svegliati Baroni, Roberto Virdone, and Alberto Masotto; design of the work, acquisition and interpretation of data, and revising the work critically for important intellectual content: Franco Trevisani; approved the final version of the submitted work: all the authors.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Patients with intermediate-stage hepatocellular carcinoma have a wide survival range, mainly because of the fact that this stage includes a heterogeneous group of patients.
- ✓ A panel of experts recently proposed to subclassify the hepatocellular carcinoma intermediate stage into various substages on the basis of tumor burden, liver function, and performance status.
- ✓ As of today, this proposed subclassification has not been fully validated, and its prognostic accuracy in patients with untreated hepatocellular carcinoma is unknown.

WHAT IS NEW HERE

- ✓ Subclassification of the intermediate-stage, untreated hepatocellular carcinoma has prognostic relevance, being able to identify substages with different survival.
- ✓ Use of the Model for End-stage Liver Disease may provide additional prognostic information in the early substages of the intermediate stage.
- ✓ The survival figures that have been observed in the various substages may be used to counsel patients and to provide a benchmark against which potential therapies can be tested.

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