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Patients With Advanced Hepatocellular Carcinoma Need a Personalized Management: A Lesson From Clinical Practice

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The Barcelona Clinic Liver Cancer (BCLC) advanced stage (BCLC C) of hepatocellular carcinoma (HCC) includes a heterogeneous population, where sorafenib alone is the recommended treatment. In this study, our aim was to assess treatment and overall survival (OS) of BCLC C patients subclassified according to clinical features (performance status [PS], macrovascular invasion [MVI], extrahepatic spread [EHS] or MVI + EHS) determining their allocation to this stage. From the Italian Liver Cancer database, we analyzed 835 consecutive BCLC C patients diagnosed between 2008 and 2014. Patients were subclassified as: PS1 alone (n = 385; 46.1%), PS2 alone (n = 146; 17.5%), MVI (n = 224; 26.8%), EHS (n = 51; 6.1%), and MVI + EHS (n = 29; 3.5%). MVI, EHS, and MVI + EHS patients had larger and multifocal/massive HCCs and higher alpha-fetoprotein (AFP) levels than PS1 and PS2 patients. Median OS significantly declined from PS1 (38.6 months) to PS2 (22.3 months), EHS (11.2 months), MVI (8.2 months), and MVI + EHS (3.1 months; $P < 0.001$). Among MVI patients, OS was longer in those with peripheral than with central (portal trunk) MVI (11.2 vs. 7.1 months; $P = 0.005$). The most frequent treatments were: curative approaches in PS1 (39.7%), supportive therapy in PS2 (41.8%), sorafenib in MVI (39.3%) and EHS (37.3%), and best supportive care in MVI + EHS patients (51.7%). Independent prognostic factors were: Model for End-stage Liver Disease score, Child-Pugh class, ascites, platelet count, albumin, tumor size, MVI, EHS, AFP levels, and treatment type. *Conclusion:* BCLC C stage does not identify patients homogeneous enough to be allocated to a single stage. PS1 alone is not sufficient to include a patient into this stage. The remaining patients should be subclassified according to PS and tumor features, and new patient-tailored therapeutic indications are needed. (HEPATOLOGY 2018;00:000-000).

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Hepatocellular carcinoma (HCC) represents a leading cause of mortality in patients with liver cirrhosis (LC).[1] Although all the hepatology and oncology scientific societies recommend surveillance for HCC with ultrasound—with or without alpha-fetoprotein (AFP) determination—in patients at risk,[2-4] only a minority of HCCs are detected during surveillance in the Western world, and

Abbreviations: AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CEUS, contrast enhanced ultrasound; CI, confidence interval; c-MVI, central MVI; CT, dynamic computed tomography; ECOG, Eastern Cooperative Oncology Group; EHS, extrahepatic spread; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; INR, international normalized ratio; ITA.LI.CA, Italian Liver Cancer; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; MVI, macrovascular invasion; OLT, orthotopic liver transplant; OS, overall survival; p-MVI, peripheral MVI; PS, performance status; TACE/TAE, transcatheter arterial chemoembolization/embolization; ^{90}Y, Yttrium^{90}.

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therefore most tumors are not eligible for curative treatments.[5-8] In fact, in countries without nationwide HCC surveillance programs, up to 30%-35% of patients present with macrovascular invasion (MVI) and/or extrahepatic spread (EHS) or with a poor performance status (PS) caused by the development of the tumor.[9-11] According to the Barcelona Clinic Liver Cancer (BCLC) system, these patients are classified as having "advanced" HCC (BCLC C), and the only recommended antitumoral treatment is systemic therapy with the multikinase inhibitor, sorafenib.[3,12,13] In fact, sorafenib proved to be able to significantly prolong the survival of BCLC C patients compared to placebo in two randomized phase 3 trials, and its efficacy has been confirmed in postmarketing studies.[13-16] Post-hoc analyses of registration trials have confirmed the efficacy of this treatment in various patient subclasses, including those with MVI and/or EHS, or poor PS, although these features adversely affect survival.[15,17] Moreover, the occurrence of MVI or EHS on treatment entails the poorest prognostic meaning, indicating that the modality of cancer progression cannot be disregarded when planning trials aimed at evaluating the efficacy of postsorafenib therapies.[18,19]

In order to evaluate whether, and how much, the clinical and oncological features characterizing BCLC C stage can influence the prognosis and treatment choice in clinical practice, we assessed the management and survival of these patients according to a subclassification based on PS and presence of MVI and/or EHS. Our results provide propedeutic information to a patient-tailored management of advanced-stage HCC, likewise already suggested for the intermediate (BCLC B) stage.[20,21]

Patients and Methods

PATIENTS

Data were extracted from the last version of the Italian Liver Cancer (ITA.LI.CA) database, including

*These authors contributed equally to the design and conduction of the study.

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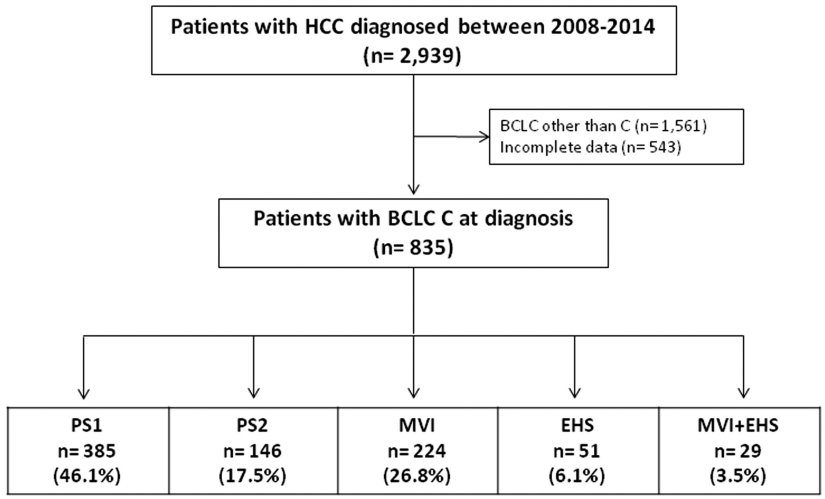

FIG. 1. Flow chart of the patient enrollment from the ITA.LI.CA database.

Abbreviations: HCC: hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; PS: Performance Status; MVI: macrovascular invasion; EHS: extrahepatic spread.

6,477 HCC patients consecutively evaluated and managed from January 1987 to December 2014 at 24 Italian medical centers. Data were prospectively collected and updated every 2 years. Before statistical evaluation, the consistency and accuracy of the data set were checked by the group coordinator (F.T.), and, whenever clarification or additional information were needed, resubmitted to the generating center.

For the purpose of this study, we selected 835 patients diagnosed with a *naïve* advanced-stage HCC (BCLC C), recruited by ITA.LI.CA centers from January 1, 2008 (first year of sorafenib reimbursement by the Italian National Health Service) to December 31, 2014 (date of the last database update; Fig. 1). Patients were subclassified in five groups according to the characteristics that allocate a subject to the BCLC advanced stage, that is, either PS1 or 2, or MVI, or EHS, or both of these pathological characteristics. Therefore, patients with PS0 were included into the MVI, EHS, or MVI + EHS subgroups. The five subgroups thus identified are reported on in Table 1. PS was assessed according to the Eastern Cooperative Oncology Group (ECOG).[22]

DIAGNOSIS

HCC diagnosis was histological in 111 (13.3%) cases whereas in the remaining cases it was based on typical features in one or more imaging techniques (dynamic computed tomography [CT], magnetic resonance imaging [MRI], or contrast enhanced ultrasound [CEUS]), according to the international or Italian guideline editions available at the time of patient recruitment.[3,23,24]

TREATMENT

Patients who underwent more than one treatment were categorized according to the following hierarchy: orthotopic liver transplant (OLT), hepatic resection, ablation, radioembolization with Yttrium^{90} (^{90}Y), transcatheter arterial chemoembolization/embolization (TACE/TAE), sorafenib, other treatments, and best supportive care (BSC).

STATISTICAL ANALYSIS

Continuous data are shown as median and 95% confidence interval (CI) and discrete variables as absolute and relative frequencies. Child-Pugh score[25] was categorized as A, B 7 (threshold for eligibility to TACE), and B 8-9, and the size of HCC (largest lesion of multinodular tumours) was categorized as ≤2, 2.1-5.0, and

TABLE 1. BCLC C Subgroups Classified According to the Characteristics That Allocate Patients to the Advanced Stage

Patients Subgroups	Characteristics
PS1	Patients with PS1 alone (without MVI or EHS)
PS2	Patients with PS2 alone (without MVI or EHS)
MVI	Patients with MVI and without EHS, regardless of PS
EHS	Patients with EHS and without MVI, regardless of PS
MVI + EHS	Patients with both MVI and EHS, regardless of PS

>5 cm. In Cox regression models, continuous variables were categorized according to the median values or the biochemical limit of normal range. Selected cutoffs were: age 70 years, creatinine 1.2 mg/dL, albumin 3.5 g/dL, bilirubin 1.1 mg/dL, and international normalized ratio (INR) 1.25. Platelet count was categorized as $<100 \times 10^9$/L (cutoff for clinically significant portal hypertension), 100-149 $\times 10^9$/L, and $\geq 150 \times 10^9$/L (lower normal value) and AFP as ≤20, 21-200, and >200 ng/mL. Comparison of continuous data was carried out using the Kruskal-Wallis test, and comparison between discrete variables was carried out using the Fisher's exact test or the χ^2 test with Yates' correction, as appropriate.

Patient survival was calculated from the date of HCC diagnosis to that of death or the last contact. Overall survival (OS) was estimated by the Kaplan-Meier method, and differences were tested with the log-rank test. Variables associated ($P < 0.10$) with survival at univariate analysis were entered into a Cox's multivariate regression analysis. A P value <0.05 in a two-tailed test was considered statistically significant. Statistical analysis was performed using SPSS software (v23.0; Apache Software Foundation, Chicago, IL).

ETHICS

The ITA.LI.CA database management conforms to the current Italian legislation on patient confidentiality, and this study conforms to the ethics guidelines of the Declaration of Helsinki. All patients provided informed consent to having their data recorded in an anonymous way in the ITA.LI.CA database. The creation of the ITA.LI.CA database and its use for cooperative studies were approved by the ethic committees/institutional boards of participating centers.

Results

PATIENT CHARACTERISTICS

Table 2 reports demographic and clinical features of BCLC C patient subclassified according to PS, and presence of MVI and/or EHS. PS1 patients accounted for 46.1% of the entire cohort (n = 385), MVI patients for 26.8% (n = 224), PS2 patients for 17.5% (n = 146), EHS patients for 6.1% (n = 51), and MVI+EHS patients for 3.5% (n = 29). Male sex was more represented in all subclasses, but it was significantly ($P = 0.001$) more prevalent among MVI+EHS patients (89.7%) as compared to other subclasses (PS1, 69.9%; PS2, 68.7%; MVI, 81.3%; EHS, 84.3%). Child-Pugh class A was more frequent in EHS patients (72.5%), followed by PS1 (61%), MVI (53.1%), MVI + EHS (48.3%), and PS2 (41.8%) patients ($P = 0.001$). Ascites was more prevalent in MVI + EHS patients (44.8%), followed by PS2 (40.4%), MVI (40.1%), PS1 (22.7%), and EHS (22.9%) patients ($P < 0.001$). Moreover, HCC characteristics and AFP levels were significantly different among the various subclasses ($P < 0.001$). In particular, PS1 and PS2 patients presented more frequently with smaller, single HCCs, and low AFP values, whereas MVI + EHS patients had more frequently an infiltrative/massive tumor and the highest AFP levels ($P < 0.001$). Interestingly, median platelet count progressively increased from PS1 and PS2 patients to MVI and EHS patients, with the highest values observed in MVI + EHS patients ($P < 0.001$).

TREATMENT

Treatment distribution significantly differed among BCLC C subclasses (Table 3). In PS1 patients, curative therapies (OLT 2.6%, resection 7.5%, and percutaneous ablation 29.6%) were more frequently applied (39.7%), followed by transarterial treatments (35.3%) and BSC (18.4%), whereas sorafenib was administered only in 3.6% of patients. In PS2 patients, BSC was the most frequent therapeutic approach (41.8%), followed by curative (29.5%; mainly percutaneous ablation 24%) and transarterial (17.1%) therapies, whereas sorafenib was administered in 8.2% of these patients. Expectedly, in both MVI and EHS patients, sorafenib was the most frequent treatment option (39.3% and 37.3%, respectively), whereas the majority (51.7%) of patients with MVI + EHS were managed with BSC.

In a further subanalysis that included Child-Pugh class A patients only (Supporting Fig. S1), sorafenib was the most common treatment not only in patients with either MVI (47.1%) or EHS (45.9%), but also in those with MVI + EHS (57.1%).

SURVIVAL ANALYSES

During a median follow-up of 13.1 months (95% CI, 1.0-58.0), 462 (55.3%) patients died. The death rate progressively increased across subclasses, as follows: 177 (46.0%) in the PS1 group, 78 (53.4%) in the PS2 group, 149 (66.5%) in the MVI group, 37 (72.5%) in the EHS group, and 21 (72.4%) in the MVI + EHS group. Causes of death were: cancer

TABLE 2. Demographic and Clinical Characteristics of the 835 Patients With Advanced (BCLC C) HCC

		PS1 (n = 385, 46.1)	PS2 (n = 146, 17.5)	MVI (n = 224, 26.8)	EHS (n = 51, 6.1)	MVI + EHS (n = 29, 3.5)	*P* Value
Age	Years	72.0 (49.0-84.7)	73 (51.0-85.6)	67 (46.0-82.8)	69 (50.0-83.0)	68 (62-73)	<0.001
Sex	Male	269 (69.9)	100 (68.5)	182 (81.2)	43 (84.3)	26 (89.7)	0.001
Etiology	HCV	190 (49.4)	70 (47.9)	94 (42.0)	17 (33.3)	10 (34.5)	0.112
	HBV (± HDV)	20 (5.2)	12 (8.2)	28 (12.5)	5 (9.8)	2 (6.9)	
	Alcohol	66 (17.1)	20 (13.7)	33 (14.7)	10 (19.6)	5 (17.2)	
	NAFLD/ cryptogenic	38 (9.9)	10 (6.8)	22 (9.8)	4 (7.8)	5 (17.2)	
	Multietiology	51 (13.2)	22 (15.1)	41 (18.3)	12 (23.5)	7 (24.1)	
	Other	11 (2.9)	5 (3.4)	3 (1.3)	1 (2.0)	0 (0.0)	
	Unknown	9 (2.3)	7 (4.8)	3 (1.3)	2 (3.9)	0 (0.0)	
ECOG-PS	0	—	—	98 (43.8)	22 (43.1)	10 (34.5)	<0.001
	1	385 (100)	—	83 (37.1)	21 (41.2)	15 (51.7)	
	2	—	146 (100)	43 (19.2)	8 (15.7)	4 (13.8)	
Albumin	g/dL	3.5 (2.7-4.3)	3.3 (2.5-4.2)	3.4 (2.4-4.4)	3.5 (2.5-4.4)	3.5 (2.9-4.2)	0.014
Bilirubin	mg/dL	1.2 (0.5-3.6)	1.2 (0.4-3.7)	1.2 (0.5-4.8)	1 (0.4-6.7)	1.5 (0.7-11.8)	0.149
Creatinine	mg/dL	0.9 (0.5-1.5)	1 (0.5-2.3)	0.8 (0.5-1.5)	0.8 (0.5-3.0)	0.9 (0.5-5.5)	0.004
INR		1.2 (0.9-1.7)	1.2 (1.0-1.7)	1.2 (1.0-1.6)	1.1 (0.9-1.5)	1.2 (1.0-1.6)	0.101
Platelet count	10^9/L	105 (44-261)	102 (44-305)	136 (50-358)	165 (63-444)	173 (52-404)	<0.001
Child-Pugh score	5-6	235 (61.0)	61 (41.8)	119 (53.1)	37 (72.5)	14 (48.3)	0.001
	7	73 (19.0)	35 (24.0)	46 (20.5)	5 (9.8)	8 (27.6)	
	8-9	77 (20.0)	50 (34.2)	59 (26.3)	9 (17.6)	7 (24.1)	
MELD	Score	10 (6-18)	10 (6-20)	10 (6-16)	9 (6-18)	10 (6-20)	0.111
Esophageal varices	Present	206 (60.4)	79 (65.8)	107 (59.1)	18 (43.9)	17 (65.4)	0.163
HCC gross pathology	Single	202 (53.6)	72 (51.1)	48 (22.1)	7 (14.3)	2 (6.9)	<0.001
	Multifocal	159 (42.2)	55 (39.0)	87 (40.1)	30 (61.2)	10 (34.5)	
	Infiltrating/ massive	16 (4.2)	14 (9.9)	82 (37.8)	12 (24.5)	17 (58.6)	
HCC main nodule size	≤2 cm	101 (28.4)	29 (21.6)	13 (7.1)	2 (4.5)	1 (4.0)	<0.001
	>2 ≤ 5 cm	188 (52.8)	71 (53.0)	69 (37.7)	13 (29.5)	7 (28.0)	
	≥5 cm	67 (18.8)	34 (25.4)	101 (55.2)	29 (65.9)	17 (68.0)	
AFP	ng/mL	12.7 (2.0-2,309.0)	15.0 (2.0-635)	264 (3.4-57,140)	108.5 (2.5-24,997)	661 (2.4-61,400)	<0.001

Data are shown as median and 95% CI or absolute value and (percentage).
Abbreviations: CLC, Barcelona Clinic Liver Cancer; HDV, hepatitis D virus; NAFLD, nonalcoholic fatty liver disease.

progression in 242 patients (52.4%), hepatic failure in 105 (22.7%), gastrointestinal hemorrhage in 14 (3.0%), renal failure in 6 (1.3%), infection in 6 (1.3%), embolism in 3 (0.6%), other causes (cardiovascular diseases, cerebral hemorrhage, and other cancers) in 42 (9.1%), and unknown causes in 44 patients (9.5%).

In the whole population, median OS was 22.3 months (95% CI, 19.6-25.0). Survival remarkably differed across BCLC C subclasses ($P < 0.001$; Fig. 2A). In particular, it was 38.6 months (95% CI, 32.5-44.6) in PS1 patients, 22.3 months (95% CI, 14.4-30.3) in PS2 patients, 11.2 months (95% CI, 9.8-12.5) in EHS patients, 8.1 months (95% CI, 6.9-9.3) in MVI

TABLE 3. Treatment Distribution in the Various BCLC C Subclasses

	PS1 n = 385 (46.1)	PS2 n = 146 (17.5)	MVI n = 224 (26.8)	EHS n = 51 (6.1)	MVI + EHS n = 29 (3.5)
Liver transplant	10 (2.6)	1 (0.7)	—	—	—
Resection	29 (7.5)	7 (4.8)	23 (10.3)	2 (3.9)	1 (3.4)
Ablation	114 (29.6)	35 (24.0)	4 (1.8)	1 (2.0)	—
TA(C)E	133 (34.5)	25 (17.1)	11 (4.9)	7 (13.7)	—
TARE	3 (0.8)	—	10 (4.5)	2 (3.9)	—
Sorafenib	14 (3.6)	12 (8.2)	88 (39.3)	19 (37.3)	12 (41.4)
Other	11 (2.8)	5 (3.5)	16 (7.1)	5 (9.8)	1 (3.4)
BSC	71 (18.4)	61 (41.8)	72 (32.1)	15 (29.4)	15 (51.7)

Data are shown as absolute value and (percentage).
Abbreviation: TARE, ^{90}Y transarterial radioembolization.

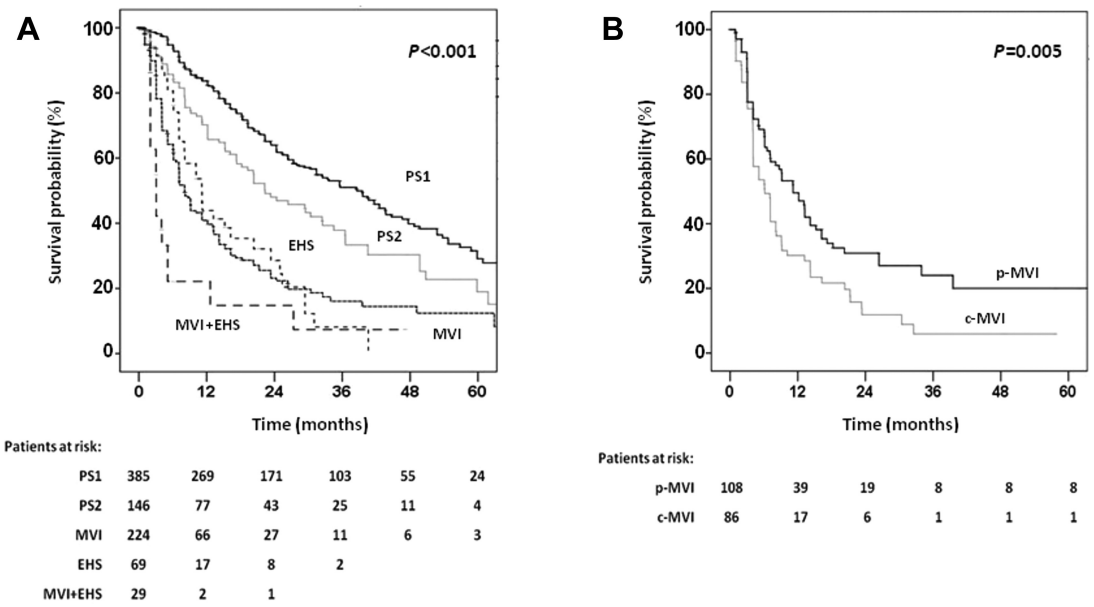

FIG. 2. Survival of patients according to BCLC C subclasses (A) and according to the type of MVI extension (black line, p-MVI; gray line, c-MVI (main portal trunk); B).

patients, and 3.1 months (95% CI, 2.1-4.0) in MVI + EHS patients. PS1 patients had a longer survival compared to PS2 patients ($P = 0.001$). MVI and EHS patients had similar OS ($P = 0.663$), which was significantly shorter as compared to that of PS2 patients ($P < 0.001$, for both MVI and EHS). Last, MVI + EHS patients had the shortest survival, which was significantly different from that of both MVI ($P < 0.001$) and EHS ($P = 0.001$) patients.

In order to assess whether the degree of vascular invasion had a prognostic impact, MVI patients were further subdivided according to the location/extension of vascular invasion, as follows: central MVI (c-MVI) if it involved the main portal trunk (n = 86; 38.4%) and peripheral MVI (p-MVI) if only first-order or segmental portal vein branches were involved (n = 108; 48.2%). This substratification was possible in 86.6% of MVI patients, because the location/extension of vascular invasion was missing in 30. Median OS was longer in patients with p-MVI (11.2 months; 95% CI, 7.4-15.0) as compared to those with c-MVI (6.1 months; 95% CI, 4.1-8.2; $P = 0.005$; Fig. 2B).

Last, we performed a sensitive analysis to assess the impact of Child-Pugh classes on the survival of the BCLC C subgroups. Class A patients' survival was significantly longer in the subgroups of patients with a PS1 alone and in those with a p-MVI, and a trend toward significance was observed in the PS2 group (Supporting Fig. S2).

PROGNOSTIC INDICATORS

The prognostic relevance of demographic, clinical, biochemical, and tumoral parameters, as well as HCC treatment, were tested in univariate analysis (Table 4). This analysis showed that mortality was associated with: male sex, hepatitis B virus (HBV) etiology, multietiology, PS2, presence of esophageal varices, ascites, Child-Pugh class B, Model for End-stage Liver Disease (MELD) score >10, creatinine >1.2 mg/dL, albumin <3.5 g/dL, INR >1.25, bilirubin >1.1 mg/dL, platelet count $\geq 150 \times 10^9$/L, HCC gross pathology, tumor size >5 cm, MVI, EHS, AFP >200 ng/mL, and treatment. These variables were entered into a multivariate analysis. In order to avoid collinearities, three models were created (Table 5). All models included the oncological features significantly associated with mortality whereas they differed in terms of variables exploring liver function: Model 1 included the Child-Pugh score; model 2 the MELD score; and model 3 the variables forming these scores.

In all models, platelet count (cutoff 150×10^9/L), MVI (both peripheral and central), EHS, AFP (cutoff 200 ng/mL), and type of treatment were

TABLE 4. Risk Factors for Mortality in Patients With Advanced HCC (BCLC C Stage)

	Univariate HR (95% CI)	*P* Value
Age, years		
≤70	1	
>70	0.90 (0.75-1.08)	0.270
Sex		
Female	1	
Male	1.24 (1.00-1.53)	0.050
Etiology		
HCV	1	
HBV (± HDV)	1.61 (1.15-2.23)	0.005
Alcohol	1.14 (0.87-1.49)	0.344
NAFLD/c ryptogenic	1.31 (0.95-1.82)	0.102
Multietiology	1.25 (0.96-1.82)	0.091
Other	1.39 (0.81-2.38)	0.238
Unknown	0.93 (0.50-1.70)	0.805
ECOG-PS		
0-1	1	
2	1.47 (1.20-1.80)	<0.001
Child-Pugh class		
A	1	
B7	1.67 (1.32-2.12)	<0.001
B8-9	2.18 (1.75-2.71)	<0.001
MELD score		
≤10	1	
>10	1.48 (1.23-1.78)	<0.001
Esophageal varices		
No	1	
Yes	1.21 (0.98-1.48)	0.076
Ascites		
No	1	
Yes	2.12 (1.74-2.58)	<0.001
HCC gross pathology		
Single	1	
Multifocal	1.65 (1.34-2.04)	<0.001
Infiltrating/massive	3.57 (2.77-4.61)	<0.001
Macrovascular invasion		
No	1	
Peripheral	2.25 (1.73-2.93)	<0.001
Central	4.31 (3.31-5.60)	<0.001
HCC main nodule size, cm		
≤2	1	
2-5	1.19 (0.90-1.55)	0.216
>5	2.27 (1.71-3.00)	<0.001
EHS		
No	1	
Yes	2.72 (2.05-3.59)	<0.001
AFP, ng/mL		
≤20	1	
21-200	1.21 (0.94-1.55)	0.134
>200	2.16 (1.71-2.72)	<0.001
Albumin, g/dL		
≥3.5	1	
<3.5	1.56 (1.29-1.88)	<0.001
Bilirubin, mg/dL		
≤1.1	1	
>1.1	1.27 (1.06-1.53)	0.011
INR		
<1.25	1	
≥1.25	1.31 (1.08-1.59)	0.006
Creatinine, mg/dL		
≤1.2	1	
>1.2	1.28 (1.00-1.64)	0.054
Platelets, $\times 10^9$/L		
<100	1	
100-149	1.06 (0.83-1.34)	0.661
≥150	1.27 (1.01-1.58)	0.037
Treatment		
Curative	1	
TACE/TAE/TARE	1.89 (1.41-2.52)	<0.001
Sorafenib	4.75 (3.52-6.39)	<0.001
BSC	7.34 (5.55-9.70)	<0.001
Other/unknown	2.21 (1.27-3.83)	0.005

Abbreviations: HDV, hepatitis D virus; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; TARE, ^{90}Y transarterial radioembolization.

independently associated with survival. Further independent predictors of survival were:

- in model 1: Child-Pugh class
- in model 2: MELD score (10), nodule size (5 cm), ascites and albumin (3.5 g/dL)
- in model 3: ascites and albumin (3.5 g/dL).

OUTCOME OF PATIENTS UNDERGOING BSC

In order to describe the "natural" history of these patients, we also assessed the outcome of those who received BSC alone. Even in this analysis, median OS was significantly different among some subclasses ($P < 0.001$): PS1 and PS2 patients had similar survival (13.2 [95% CI, 7.9-18.5] vs. 11.2 months [95% CI, 8.0-14.3]; $P = 0.235$) and significantly longer ($P \leq 0.024$) than that of MVI and EHS patients (4.0 [95% CI, 2.2-5.9] and 5.1 months [95% CI 1.7-8.4], respectively). OS reached the lowest figure in MVI + EHS patients (2.0 months [95% CI 1.9-2.1]; $P \leq 0.045$, compared to MVI and EHS patients; Fig. 3).

Discussion

European and American guidelines for HCC management have endorsed the BCLC staging system in order to stratify patients and recommend the first-line therapy for each stage.[3,23] However, in this system, the advanced stage—like the intermediate stage—encompasses a very heterogeneous patient population given that the allocation to this stage may be driven by the presence of any of the following features: PS1 or 2,

TABLE 5. Independent Risk Factors for Mortality in Patients With Advanced HCC (Multivariate Regression Analysis)

	Multivariate (Model 1) HR (95% CI)	*P* Value	Multivariate (Model 2) HR (95% CI)	*P* Value	Multivariate (Model 3) HR (95% CI)	*P* Value
Sex						
Female	1		1		1	
Male	0.99 (0.73-1.36)	1.000	1.01 (0.74-1.38)	0.953	1.01 (0.73-1.39)	0.957
Etiology						
HCV/alcohol/NAFLD/ cryptogenic/other/unknown	1		1		1	
Multietiology	1.05 (0.74-1.47)	0.800	1.03 (0.73-1.46)	0.871	1.01 (0.71-1.43)	0.976
HBV (± HDV)	1.40 (0.88-2.22)	0.152	1.15 (0.72-1.83)	0.563	1.18 (0.73-1.88)	0.501
ECOG-PS						
0-1	1		1		1	
2	1.18 (0.87-1.60)	0.290	1.21 (0.89-1.64)	0.218	1.22 (0.90-1.66)	0.203
Esophageal varices						
No	1		1		1	
Yes	1.19 (0.91-1.57)	0.210	0.97 (0.73-1.29)	0.824	0.97 (0.73-1.29)	0.850
Ascites						
No			1		1	
Yes			1.78 (1.32-2.41)	<**0.001**	1.80 (1.33-2.43)	<**0.001**
Child-Pugh class						
A	1					
B7	2.08 (1.51-2.86)	<**0.001**				
B8-9	2.90 (2.08-4.04)	<**0.001**				
MELD score						
≤10			1			
>10			1.50 (1.13-2.00)	**0.005**		
Creatinine (mg/dL)						
≤1.2	1				1	
>1.2	1.00 (0.70-1.43)	0.986			1.03 (0.71-1.49)	0.874
Albumin (g/dL)						
≥3.5			1		1	
<3.5			1.37 (1.03-1.82)	**0.029**	1.40 (1.05-1.85)	**0.021**
Bilirubin (mg/dL)						
≤1.1					1	
>1.1					1.21 (0.90-1.62)	0.209
INR						
≤1.25					1	
>1.25					1.23 (0.92-1.64)	0.157
Platelets ($\times 10^9$/L)						
<150	1		1		1	
≥150	1.44 (1.08-1.91)	**0.012**	1.45 (1.10-1.92)	**0.009**	1.50 (1.12-2.00)	**0.007**
HCC gross pathology						
Single	1		1		1	
Multifocal	1.19 (0.88-1.61)	0.269	1.21 (0.89-1.64)	0.223	1.19 (0.87-1.61)	0.273
Infiltrating/massive	1.03 (0.64-1.64)	0.917	1.00 (0.62-1.60)	0.996	1.00 (0.63-1.61)	0.993
Main nodule size (cm)						
≤5	1		1		1	
>5	1.24 (0.91-1.67)	0.168	1.39 (1.02-1.90)	**0.037**	1.37 (1.00-1.87)	0.051
MVI						
No	1		1		1	
Peripheral	2.95 (1.84-4.72)	<**0.001**	2.34 (1.43-3.83)	**0.001**	2.30 (1.40-3.77)	**0.001**
Central	2.59 (1.66-4.05)	<**0.001**	2.80 (1.79-4.36)	<**0.001**	2.75 (1.76-4.31)	<**0.001**
EHS						
No	1		1		1	
Yes	2..46 (1.61-3.77)	<**0.001**	2.22 (1.45-3.40)	<**0.001**	2.23 (1.45-3.44)	<**0.001**
AFP (ng/mL)						
≤200	1		1		1	
>200	1.44 (1.06-1.96)	**0.020**	1.52 (1.11-2.08)	**0.010**	1.49 (1.09-2.04)	**0.013**
Treatment						
Curative	1		1		1	
TACE/TAE/TARE	2.34 (1.59-3.44)	<**0.001**	2.59 (1.73-3.86)	<**0.001**	2.56 (1.72-3.81)	<**0.001**
Sorafenib	1.59 (0.94-2.69)	0.083	2.43 (1.42-4.17)	**0.001**	2.42 (1.41-4.16)	**0.001**

TABLE 5. *Continued*

	Multivariate (Model 1) HR (95% CI)	*P* Value	Multivariate (Model 2) HR (95% CI)	*P* Value	Multivariate (Model 3) HR (95% CI)	*P* Value
BSC	6.09 (3.98-9.31)	<**0.001**	7.06 (4.53-10.99)	<**0.001**	7.32 (4.69-11.43)	<**0.001**
Other/unknown	0.82 (0.31-2.21)	0.700	0.90 (0.33-2.42)	0.828	0.97 (0.36-2.63)	0.958

Bolded values are statistical significant values.
Abbreviations: HDV, hepatitis D virus; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; TARE, ^{90}Y transarterial radioembolization.

MVI, and EHS.[20,21] Moreover, liver function can range from Child-Pugh A5 to B9 score. Nevertheless, the suggested treatment for all these patients is sorafenib, which has a suboptimal tolerability and a modest efficacy, being able to prolong the median survival by about 3 months compared to placebo.[13,14]

SURVIVAL DIFFERENCES

In a *real-world* setting, such as the one described in our study, BCLC C patients showed a markedly different prognosis according to the characteristics that determined the assignment to this stage. In particular, when a mild impairment of general health status (PS1) was the only reason for the allocation, approximately 75% of cases were treated with curative or transarterial treatments, and sorafenib was seldom (3.6% of cases) considered the best therapeutic option. In fact, the presence of a PS1 (i.e., patients restricted in physically strenuous activity, but ambulatory and able to carry out a light/sedentary work[22]) does not preclude the access to all available HCC treatments. We do not have data on posttreatment morbidity in these patients, in particular in those who underwent treatment with curative intent—and this represents a limitation of this analysis—although approximately 1 of 5 PS1 patients were fit enough to undergo a second-line treatment, and this subclass had a median survival long enough (38.6 months) to compete with that of patients with an intermediate stage tumor.[21] Furthermore, the attribution of a *tumour-dependent*—as recommended by the BCLC system—mild deterioration of PS is very subjective in the setting of HCC given that several confounding factors, such as advanced age (median age in our series ranged from 67 to 73 years), presence of cirrhosis (Child-Pugh class B in 45% of our patients), and the frequent presence of extrahepatic comorbidities may play a major role. Further evidence of this finding is provided by the distribution of the main variables related to liver function (Child-Pugh class, MELD score) and of indirect markers of portal hypertension (platelet count) in patients with various PS (Supporting Table S1), showing that a decrease in liver function and signs of portal hypertension are associated with worsening PS, although more than half of patients with PS1 had fully compensated liver disease. Last, this finding is also further emphasized by the evaluation of HCC lines of treatment in the various study subgroups (Supporting Table S2): This analysis showed that patients with PS1 more frequently went through more than one line of HCC treatment as compared to the other groups, underscoring the fact that these patients are able to tolerate more than one treatment, and that this occurrence does not seem to have a negative effect on survival. For these reasons, the Italian community of hepatologists recommended

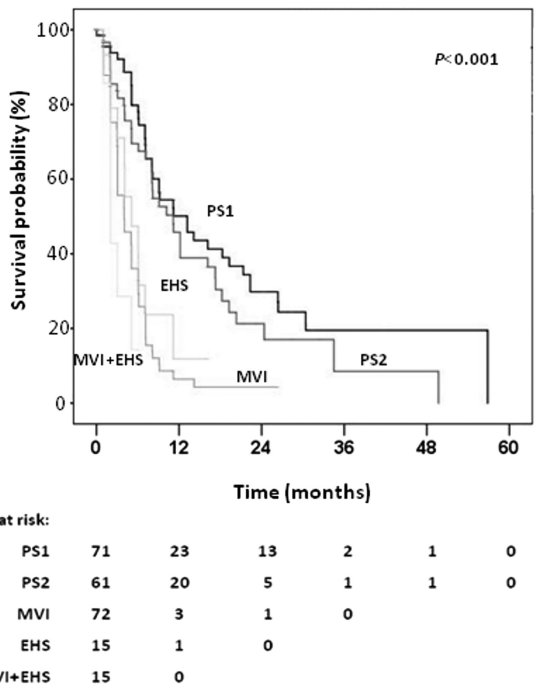

FIG. 3. Survival of patients treated with BSC in the BCLC C subclasses.

that PS1 *per se* should no longer be accepted as a characteristic sufficient to assign patients to the advanced stage.[24] Noteworthy, following this suggestion, 46% of our BCLC C patients would be reclassified into earlier HCC stages. Last, as far as this issue is concerned, Hsu et al. showed that reassigning PS1 patients to BCLC B improved the prognostic ability and gradient monotonicity of BCLC classification.[26]

Interestingly, in PS2 patients, the most common treatment was BSC (41.8%) likely because of a high prevalence of ascites and of a Child-Pugh B 8-9 score, given that both of these characteristics generally preclude all active HCC treatments but OLT. Nonetheless, these patients also showed a rather long survival (median, 22.3 months), which exceeded by far that of patients with MVI and/or EHS. Such a result, confirmed in patients managed with BSC alone (Fig. 3), would indicate that unfavorable oncological features purport a worse prognosis as compared to a mild/moderate deterioration of general conditions attributed to cirrhosis and/or to extrahepatic comorbidities.

When either MVI or EHS were present, sorafenib was the most frequently administered treatment (approximately 40% of cases in both subclasses), particularly in Child-Pugh A patients (46% and 57%, respectively) for whom, in Italy, the expense for this therapy is charged to the National Health System. However, it is worth noting that 10% of patients with MVI underwent surgical resection. This treatment option was likely suggested by studies showing that hepatectomy provides a better outcome as compared to nonsurgical treatments when portal invasion is limited to peripheral branches.[27] Moreover, 4.5% of MVI patients underwent ^{90}Y radioembolization, which has been reported to provide median survivals of 17-19 months in patients with peripheral MVI.[28,29]

Our study also showed that survival of EHS and p-MVI patients was similar, but significantly ($P = 0.014$) longer than in the c-MVI subgroup, suggesting that the invasion of portal trunk represents the worst oncological feature of the advanced HCC stage. This finding seems at variance with the one reported in an Eastern series, in which patients with EHS had a survival similar to that of subjects with a "*significant*" (lobar, main trunk, or bilateral) MVI.[30] However, in that study, a distinction between c-MVI and p-MVI was not performed. Therefore, we feel that the extent of MVI represents a key prognostic indicator for HCC patients, and that the distinction between central and peripheral portal invasion is clinically meaningful. Our assumption is supported by a recent study reporting that a segmental/sectorial invasion of portal branches is associated with a more favorable outcome as compared to left/right branches or main trunk invasion.[31]

Our study indicates that, even in the sorafenib era, we should expect a very short survival (median, 3.1 months) in patients with both MVI and EHS attributed to the most advanced tumor burden and the fact that more than 50% of them belong to Child-Pugh class B (Table 1), limiting the applicability and efficacy of sorafenib.

TREATMENT DIFFERENCES

The heterogeneity of BCLC C patients was also primarily responsible for the frequent deviation from the "*one size fits all*" approach recommended by the European and American guidelines for these cases.[3,23] In fact, we found a frequent shift toward curative or transarterial therapies in patients allocated to the advanced stage attributed to PS1 or 2, suggesting that, in clinical practice, oncological characteristics—rather than PS—guide treatment selection. A certain shift toward locoregional treatments was also observed in MVI patients, and, unexpectedly, this deviation was also observed in patients with EHS. The individual scrutiny of these cases (data not reported) showed that it generally occurred in patients with metastatic lymphnodes at the hepatic hylum or with tiny (<1 cm) pulmonary nodules, likely misclassified as benign at the time of treatment. This shift and, above all, a compromised liver function (Child-Pugh B class) restrained the use of sorafenib in MVI and/or EHS patients.

Our results are not isolated, given that another European study carried out in the sorafenib era reported a poor adherence to Western guidelines in the advanced HCC stage.[32] In that study, two thirds of cases were treated at variance with the BCLC algorithm. Besides the possible presence of a severely compromised liver function, a reason behind this frequent deviation relies on the fact that the BCLC algorithm does not propose any therapy, potentially more effective than sorafenib, in well-selected cases, particularly in Child-Pugh class A and PS1 patients.[32,33] This limitation cannot be (and is not) any longer accepted for an updated management of HCC patients. As a matter of fact, using a patient-tailored management established by a multidisciplinary expert team, we achieved a median survival of 22.3 months in BCLC C patients, which is remarkably longer than the one achieved with sorafenib in both randomized and post-marketing Western studies.[14,15] To reconcile our

results with those of the cited series, we can suppose that the presence of a PS1 or 2 was not sufficient to enroll patients in those studies. In fact, the reported median survivals are closer to those of our MVI or EHS patients, rather than to those of our PS1 or PS2 patients.

Last, we identified a number of independent predictors of mortality for BCLC C patients—most of them expected or well known—such as liver function tests (Child-Pugh and MELD score), tumor features (AFP, MVI, and EHS), and treatment. Considering Child-Pugh classes, we found that a poor liver function significantly affected prognosis only in patients with a limited tumor burden (Supporting Fig. S2). Interestingly, in the setting of advanced HCC, we confirmed the dismal prognostic meaning of increasing platelet count, which has been already described in unselected HCC patients. This finding would support the hypothesized participation of platelets in the HCC microenvironment, with the ability to promote tumor growth and drug resistance.[34]

LIMITATIONS

The retrospective nature of our study does not allow us to exclude unintended biases and precluded a regimented follow-up of patients and an estimation of the effect of unrecorded confounding factors, such as severity of comorbidities, local facility to access to certain treatments, and patient's and physician's preferences. However, these shortcomings should be weighed in light of a multicenter large registry collecting *real-world* observational data generated by the clinical practice and partnership of academic and nonacademic centers. Moreover, our data pertain to an European population of patients mainly infected with hepatitis C virus (HCV), and a validation in other populations with different clinical and ethnic background, and where inherent variations may exist in the provision of locoregional and systemic therapies are needed and eagerly awaited.

Our results indicate that: (1) PS1 *per se* should not be considered sufficient to allocate a patient to the advanced BCLC stage, given that PS1 patients with limited tumor burden are generally eligible to surgical or locoregional therapies and display a long survival; (2) in Italy, management of HCC escapes from a rigid application of the BCLC algorithm-inspired guidelines, having embraced the principles of Precision Medicine.[35] This method postulates a management established by a *multidisciplinary expert team* and principally based on an *individualized* (rather than *stage-based*) approach in order to offer the best treatment to each patient, according to his or her own characteristics.[24]

Our study emphasises the urgent need of an articulate reclassification of HCC patients with MVI and/or EHS, capable to refine our prognostic ability, and generate new therapeutic paradigms aimed at improving outcomes for these patients.

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REFERENCES

1) Fattovich G, Stroffolini T, Zagni I, Donato F. Hepatocellular carcinoma in cirrhosis: incidence and risk factors. Gastroenterology 2004;127(5 Suppl 1):S35-S50.
2) Poon D, Anderson BO, Chen LT, Tanaka K, Lau WY, Van Cutsem E, et al. Asian Oncology Summit. Management of hepatocellular carcinoma in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol 2009;10:1111-1118.
3) European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer. EASL-EORTC Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2012;56:908-943.
4) Verslype C, Rosmorduc O, Rougier P. ESMO Guidelines Working Group. Hepatocellular carcinoma: ESMO-ESDO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23(Suppl 7):vii41-vii48.
5) Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. HEPATOLOGY 2010;52:132-141.
6) Singal AG, Nehra M, Adams-Huet B, Yopp AC, Tiro JA, Marrero JA, et al. Detection of hepatocellular carcinoma at advanced stages among patients in the HALT-C trial: where did surveillance fail? Am J Gastroenterol 2013;108:425-432.
7) Giannini EG, Cucchetti A, Erroi V, Garuti F, Odaldi F, Trevisani F. Surveillance for early diagnosis of hepatocellular carcinoma: how best to do it? World J Gastroenterol 2013;19:8808-8821.
8) Dam Fialla A, Schaffalitzky de Muckadell OB, Touborg Lassen A. Incidence, etiology and mortality of cirrhosis: a population-based cohort study. Scand J Gastroenterol 2012;47:702-709.
9) Villanueva A, Hernandez-Gea V, Llovet JM. Medical therapies for hepatocellular carcinoma: a critical view of the evidence. Nature Rev Gastroenterol Hepatol 2013;10:34-42.
10) **Bucci L**, **Garuti F**, Lenzi B, Pecorelli A, Farinati F, Giannini EG, et al. The evolutionary scenario of hepatocellular carcinoma in Italy: an update. Liver Int 2017;37:259-270.
11) Mittal S, Kanwal F, Ying J, Chung R, Sada YH, Temple S, et al. Effectiveness of surveillance for hepatocellular carcinoma in clinical practice: a United States cohort. J Hepatol 2016;65:1148-1154.
12) Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. HEPATOLOGY 2011;53:1020-1022.
13) Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 2009;10:25-34.
14) Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-390.
15) Iavarone M, Cabibbo G, Piscaglia F, Zavaglia C, Grieco A, Villa E, et al. Field-practice study of sorafenib therapy for hepatocellular carcinoma: a prospective multicenter study in Italy. HEPATOLOGY 2011;54:2055-2063.
16) Daniele B, Croitoru A, Papandreou C, Bronowicki JP, Mathurin P, Serejo F, et al. Impact of sorafenib dosing on outcome from the European patient subset of the GIDEON study. Future Oncol 2015;11:2553-2562.
17) Bruix J, Raoul JC, Sherman M, Mazzaferro V, Bolondi L, Craxi A, et al. Efficacy and safety of sorafenib in patients with advanced hepatocellular carcinoma: subanalyses of a phase III trial. J Hepatol 2012;57:821-829.
18) Reig M, Rimola J, Torres F, Darnell A, Rodriguez-Lope C, Forner A, et al. Postprogression survival of patients with advanced hepatocellular carcinoma: rationale for second-line trial design. HEPATOLOGY 2013;58:2023-2031.
19) Iavarone M, Cabibbo G, Biolato M, Della Corte C, Maida M, Barbara M, et al. Predictors of survival in patients with advanced hepatocellular carcinoma who permanently discontinued sorafenib. HEPATOLOGY 2015;62:784-791.
20) Bolondi L, Burroughs A, Dufour JF, Galle PR, Mazzaferro V, Piscaglia F, et al. Heterogeneity of patients with intermediate (BCLC B) hepatocellular carcinoma: proposal for a subclassification to facilitate treatment decisions. Semin Liver Dis 2012;32:348-359.
21) Pecorelli A, Lenzi B, Gramenzi A, Garuti F, Farinati F, Giannini EG, et al.; Italian Liver Cancer (ITA.LI.CA) group. Curative therapies are superior to standard of care (transarterial chemoembolization) for intermediate stage hepatocellular carcinoma. Liver Int 2017;37:423-433.
22) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.
23) Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. HEPATOLOGY 2005;42:1208-1236.

24) Italian Association for the Study of the Liver (AISF); AISF Expert Panel; AISF Coordinating Committee. Position paper of the Italian Association for the Study of the Liver (AISF): the multidisciplinary clinical approach to hepatocellular carcinoma. Dig Liver Dis 2013;45:712-723.
25) Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding esophageal varices. Br J Surg 1973;60:646-649.
26) Hsu CY, Lee YH, Hsia CY, Huang YH, Su CW, Lin HC, et al. Performance status in patients with hepatocellular carcinoma: determinants, prognostic impact, and ability to improve the Barcelona Clinic Liver Cancer system. HEPATOLOGY 2013; 57:112-119.
27) Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al.; Liver Cancer Study Group of Japan. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol 2016;65:938-943.
28) Golfieri R, Mosconi C, Cappelli A, Giampalma E, Galaverni MC, Pettinato C, et al. Efficacy of radioembolization according to tumor morphology and portal vein thrombosis in intermediate advanced hepatocellular carcinoma. Future Oncol 2015;11:3133-3142.
29) Woo HY, Kim DY, Heo J, Kim CW, Kim S, Yoon KT, et al. Effect of yttrium-90 radioembolization on outcomes in Asian patients with early to advanced stage hepatocellular carcinoma. Hepatol Res 2017;47:387-397.
30) Lee S, Kim BK, Song K, Park JY, Ahn SH, Kim SU, et al. Korea Central Cancer Registry. Subclassification of Barcelona Clinic Liver Cancer B and C hepatocellular carcinoma: a cohort study of the multicenter registry database. J Gastroenterol Hepatol 2016;31:842-847.
31) Sinn DH, Cho JY, Gwak GY, Paik YH, Choi MS, Lee JH, et al. Different survival of Barcelona clinic liver cancer stage C hepatocellular carcinoma patients by the extent of portal vein invasion and the type of extrahepatic spread. PLoS One 2015;10: e0124434.
32) Richani M, Kolly P, Knoepfli M, Herrmann E, Zweifel M, von Tengg-Kobligk H, et al. Treatment allocation in hepatocellular carcinoma: assessment of the BCLC algorithm. Ann Hepatol 2016;15:82-90.
33) Graf D, Vallböhmer D, Knoefel WT, Kröpil P, Antoch G, Sagir A, et al. Multimodal treatment of hepatocellular carcinoma. Eur J Intern Med 2014;25:430-437.
34) Carr BI, Guerra V, Giannini EG, Farinati F, Ciccarese F, Rapaccini GL, et al. A liver index and its relationship to indices of HCC aggressiveness. J Integr Oncol 2016;5:178-184.
35) Maizes V, Rakel D, Niemiec C. Integrative medicine and patient-centered care. Explore (NY) 2009;5:277-289.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29668/suppinfo.