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Adherence to Barcelona Clinic Liver Cancer therapeutic algorithm for hepatocellular carcinoma in the daily practice: a multicenter cohort study from Argentina

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Background and aim Adherence to the Barcelona Clinic Liver Cancer (BCLC) staging algorithm for the treatment of hepatocellular carcinoma is challenging in the daily practice. We aimed to analyze adherence to BCLC along with its effect on patient survival.

Patients and methods A cohort study was conducted in 14 hospitals from Argentina including patients with newly diagnosed hepatocellular carcinoma (2009–2016). Adherence was considered when the first treatment was the one recommended by the BCLC.

Results Overall, 708 patients were included. At diagnosis, BCLC stages were as follows: stage 0 4%, A 43%, B 22%, C 9% and D 22%. Overall, 53% of the patients were treated according to BCLC, 24% were undertreated, and 23% overtreated. Adherence to BCLC increased to 63% in subsequent treatments. Independent factors associated with adherence to BCLC were the presence of portal hypertension [odds ratio: 1.63; 95% confidence interval (CI): 1.11–2.39] and BCLC stage C (odds ratio: 0.32; 95% CI: 0.12–0.72). In a multivariable model adjusting for portal hypertension and BCLC stages, adherence to BCLC showed improved survival (hazard ratio: 0.67; 95% CI: 0.52–0.87).

Conclusion Adherence to BCLC represents a challenge in the daily practice, with almost half of the patients being treated accordingly, showing that the decision-making process should be tailored to each individual patient. Eur J Gastroenterol Hepatol 30:376–383

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Introduction

Liver cancer or hepatocellular carcinoma (HCC) is currently the fifth most common cancer and the second most common cause of death owing to cancer worldwide [1]. Staging of HCC is multifactorial as it includes tumor burden, cancer-associated symptoms, portal hypertension, and the degree of liver function impairment [2]. The Barcelona Clinic Liver Cancer (BCLC) staging system meets these objectives and was consequently adopted as the standard clinical algorithm in international guidelines [3–5].

The BCLC system distinguishes five stages of disease, that is, very early, early, intermediate, advanced, and end stage, and each stage bears its own recommended treatment strategy. Various other staging systems have been proposed, but none of which have been accepted worldwide [6–11]. Recent data from Europe and Asia showed that adherence to BCLC still represents a challenge in the daily practice, with adherence rates between 40 and 60% [12,13]. Discrepancy between each recommendation and the treatments performed is heterogeneous [12,13], owing to individual patient factors such as advanced age, severe comorbidities, and tumor location [14].

Measuring applicability of the BCLC system in other populations, which have not been studied so far, will help to understand the regional daily-faced barriers that might arise when selecting the appropriate treatment for individual patients. It is in these different country-specific scenarios where the BCLC needs to be evaluated further. To the best of our knowledge, few data have been reported

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Keywords: candidate selection, guidelines, liver cancer, treatment

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to date evaluating the BCLC system in Latin America [15]. Our objective, therefore, was to describe the treatments in the daily practice, adherence to BCLC recommendation, and its effect on survival in a multicenter cohort from Argentina.

Patients and methods

Study design, setting, and participating centers

This observational cohort study was conducted between 1 January 2009 and 1 January 2016, in 14 different regional hospitals from Argentina. Liver transplant (LT) and non-LT centers from different regions of the country were invited to participate in this registry. Feasibility of each HCC treatment modality in each center was recorded at the time of each patient's HCC diagnosis. Non-LT centers had the possibility to refer to transplant centers when appropriate. Sites were instructed to enroll all eligible patients on a sequential basis, and individual data were obtained from medical charts. Study data were registered into a web-based electronic system. Conflicting or missing data were settled by central revision and requested resubmission.

Cohort characteristics and study variables

Consecutive adult patients (>17 years of age) with newly diagnosed HCC from 1 January 2009 through 1 January 2016 were included and followed until death or last patient visit. Between 1 January 2009 and 1 September 2014, a retrospective cohort was followed up to 1 January 2016 (cohort 1), and starting on 2 September 2014 through 1 January 2016, a second prospective cohort was included (cohort 2).

Criteria for inclusion required patients to be adults with newly diagnosed HCC by either pathological criteria or imaging evaluation as recommended by international guidelines [4,5]. Patients were excluded if complete clinical baseline data were missing.

Baseline characteristics at HCC diagnosis included patients' demographics, performance status [Eastern Cooperative Oncology Group (ECOG) grade 0–4] [16], liver fibrosis grade (I–IV), and laboratory variables. Specific major comorbidities for each subject were also registered including the following: diabetes mellitus, severe pulmonary chronic disease, coronary or congestive heart disease, previous ischemic or hemorrhagic stroke, periphery vascular disease, chronic kidney failure (glomerular filtration rate <30 ml/min), and any other non-HCC malignancies.

Screening for HCC was considered as recommended by international guidelines (excluding noncirrhotic patients, non-hepatitis B virus, non-hepatitis C virus stage 3 fibrosis) [4,5]. Computed tomography or MRI was evaluated considering tumor number and diameter, macrovascular invasion (either portal or hepatic veins), and extrahepatic or lymph node metastasis. In addition, Milan criteria were assessed [17]. Serum α-fetoprotein (AFP) level recorded at HCC diagnosis was categorized in three cutoff values: up to 100, 101–1000, and more than 1000 ng/ml [18,19].

Tumor staging was classified according to BCLC criteria including the following: Child–Pugh score, performance status by ECOG or cancer-related symptoms, number and tumor diameter, vascular invasion, and lymph node or extrahepatic metastasis [3–5]. The BCLC staging was stratified into very early-stage (BCLC 0), early-stage (BCLC-A), intermediate-stage (BCLC B), advanced-stage (BCLC C), and end-stage HCC (BCLC-D). All the study centers followed the international guidelines for the treatment of HCC [3–5].

Every treatment performed and corresponding dates were recorded. These included radiofrequency ablation (RFA), percutaneous ethanol injection (PEI), liver resection (LR), LT, transarterial chemoembolization (TACE) [20], sorafenib [21], or best supportive care (BSC) [3–5]. It is noteworthy of mention an important footnote in the BCLC algorithm regarding BCLC-D stage in which LT is recommended in patients with heavily impaired liver function and with no contraindication for LT regarding HCC burden [22]. This point was also considered in our study as recommended.

Study end points

Primary end point analyzed the proportion of cases adhering to BCLC clinical algorithm comparing the first treatment decision to the BCLC recommendation. Adherence was considered when the first therapy implemented was the one recommended by the BCLC [3–5,22]. If the treatment done was that from a higher BCLC stage (e.g. a patient being BCLC-A received sorafenib), this subject was considered as being 'subtreated' whereas 'overtreated' in the opposite situation. Patients receiving any locoregional treatment during the waitlist (e.g. TACE) as a bridge to LT were considered in adherence to BCLC [23]. Two independent and blinded investigators evaluated and agreed each corresponding BCLC stage and therapeutic recommendation for each individual subject. Investigators were asked if each treatment decision was done in a multidisciplinary tumor board or not. In addition, the secondary objective was to evaluate the effect on survival according to adherence to BCLC adjusted with other confounding variables.

All procedures followed the Strengthening the Reporting of Observational Studies in Epidemiology guideline [24] and were approved by each center; they complied with the ethical standards and with Helsinki Declaration of 1975, as revised in 2008.

Statistical analysis

Categorical data were compared using Fisher's exact test (two-tailed) or χ^2-test. Continuous variables were compared employing Student's *t*-test or Mann–Whitney *U*-test according to their respective distributions. Unadjusted and adjusted odds ratios (OR) and its corresponding 95% confidence intervals (CIs) evaluating potential confounding effect were evaluated from a multivariate logistic regression analysis to identify variables related to adherence. Variables with a *P* value of less than 0.1 after the univariate analysis were included in the multivariate model, generated by stepwise forward selection. Final model's calibration and discrimination power was performed using Hosmer–Lemeshow test and receiving operator curve, respectively. Interaction term analysis was performed for each BCLC staging and adherence. For survival analysis, Kaplan–Meier survival curves were compared using the log-rank test, and a multivariate Cox

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regression analysis with hazard ratios (HR) and 95% CI was performed. Proportional hazard assumption was evaluated through graphic (log – log curves, cumulative hazard Cox regression curves, and smoothed hazard estimates) and statistical method (Schoenfeld residuals test). Calibration was assessed by comparison of observed and predicted curves and evaluation of the goodness of fit of the model by Harrell's *c*-statistic index. Collected data were analyzed using Stata 10.0 (StataCorp LLC, College Station, Texas, USA).

Results

Participating centers and baseline patient characteristics

A total of 708 consecutive adult patients with newly diagnosed HCC were included in this study (Fig. 1). Six of 14 hospitals were LT centers, and 68.4% ($n=484$) of the patients were followed up in these hospitals. In six centers, all the treatment modalities including RFA/PEI, LR, LT, and TACE were available, of which two centers had in addition transarterial radioembolization (TARE); four centers had all the treatment modalities except for LT and TARE, two centers had only TACE, and two centers did not had any treatment modality and were referral centers.

Table 1 describes the main baseline patient characteristics. Overall, 58.1% of the cohort was under screening ($n=375$ of 645 in which screening was recommended). At diagnosis, 4.2% ($n=30$), 43.1% ($n=305$), 21.3% ($n=151$), 9.5% ($n=67$), and 21.9% ($n=155$) of the patients were within BCLC 0, A, B, C, and D stages, respectively. Overall, 47% of the cohort fell within Milan criteria ($n=333$). Serum AFP more tan 1000 ng/ml presented less frequently in very early and early stages when compared with BCLC-B-D stages (7.6 vs. 22.6%; $P<0.0001$).

Overall analysis of treatments according to Barcelona Clinic Liver Cancer

A multidisciplinary tumor board accomplished each treatment decision in 60% of the cohort ($n=425$). Median time from diagnosis to the first treatment was 1 month [interquartile range (IQR): 0–4.0 months]. Adherence to BCLC recommendation for the overall cohort showed that 53% of the patients were first treated according to BCLC ($n=378$), 24% were undertreated ($n=167$), and 23% overtreated ($n=163$).

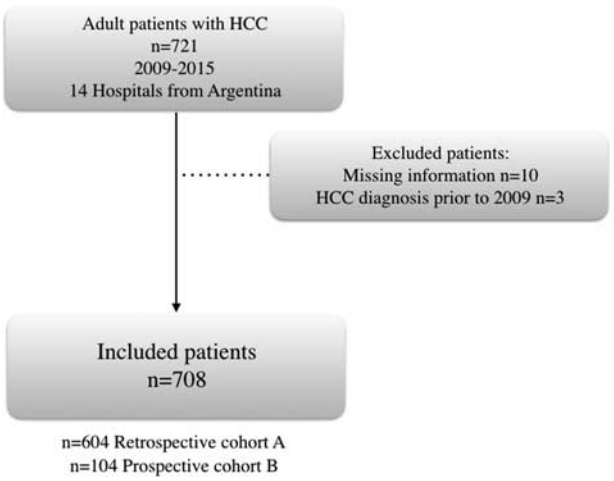

Fig. 1. Inclusion and exclusion criteria flow chart. HCC, hepatocellular carcinoma.

Table 1. Patients' baseline characteristics

Variables	Values
Age (mean ± SD) (years)	62 ± 10
Sex (male) [*n* (%)]	537 (75.9)
Noncirrhotic liver [*n* (%)]	89 (12.6)
Child–Pugh A/B/C [*n* (%)]	352 (49.7)/238 (33.6)/118 (16.7)
Etiology of liver disease [*n* (%)]	
Hepatitis C virus	262 (37.0)
Alcohol	147 (20.8)
NASH	81 (11.4)
Cryptogenic	68 (9.6)
Hepatitis B virus	38 (5.4)
Cholestatic[a]	13 (1.8)
Autoimmune	3 (0.4)
Hemochromatosis	23 (3.2)
Miscellaneous	47 (6.6)
Comorbidities [*n* (%)]	299 (42.2)
Diabetes mellitus [*n* (%)]	196 (27.7)
Ascites [*n* (%)]	253 (35.7)
Mild	144 (20.3)
Moderate-severe	109 (15.4)
Encephalopathy [*n* (%)]	147 (20.8)
Grade I–II	137 (19.3)
Grade III–IV	10 (1.4)
Esophageal varices [*n* (%)]	394 (56.7)
ECOG 0–2/3–4 [*n* (%)]	637 (89.9)/71 (10.1)

ECOG, Eastern Cooperative Oncology Group; NASH, nonalcoholic steatohepatitis.
[a]Cholestatic: primary biliary cholangitis, primary and secondary sclerosing cholangitis.

Treatment adherence to different BCLC stages was as follows:

Stage 0: HCC eligible for RFA/PEI or LT ($n=30$). Adherence to BCLC in this stage was 53.3% ($n=16$). The most frequent first treatments performed in this stage were RFA/PEI in 11 patients, LT or evaluation for LT in eight patients, and TACE in seven patients.

Stage A: HCC eligible for RFA/PEI or LR or LT ($n=305$). Adherence to BCLC was 57.4% ($n=175$), of which 36 were treated with RFA/PEI, 34 with LR, and 105 were transplanted. TACE was performed as a first treatment in 142 patients, of which in 49.1% was done as a bridge for LT.

Stage B: HCC eligible for TACE ($n=151$). Adherence reached 51% in this stage, with TACE being the most frequent first treatment performed ($n=76$), followed by LR ($n=26$), sorafenib ($n=13$), RFA/PEI ($n=10$), LT ($n=7$), and BSC ($n=16$). Three patients were included in a study protocol.

Stage C: HCC eligible for sorafenib ($n=67$). Sorafenib was the first treatment performed in this stage in 29.8% of the cases ($n=20$). Other first treatments included: RFA ($n=1$), LR ($n=4$), LT ($n=2$), TACE ($n=19$), TARE ($n=1$). and BSC ($n=16$). One patient was included in a study protocol. The two patients who were transplanted were exceeding Milan criteria.

Stage D: HCC eligible for BSC ($n=155$). Adherence to BCLC was 58.1% in this stage ($n=76$). Other first treatments performed in this stage included RFA ($n=1$), LR ($n=1$), LT ($n=32$), TACE ($n=36$), and sorafenib ($n=7$). Twenty-eight patients were transplanted within Milan criteria without any treatment while on the waitlist.

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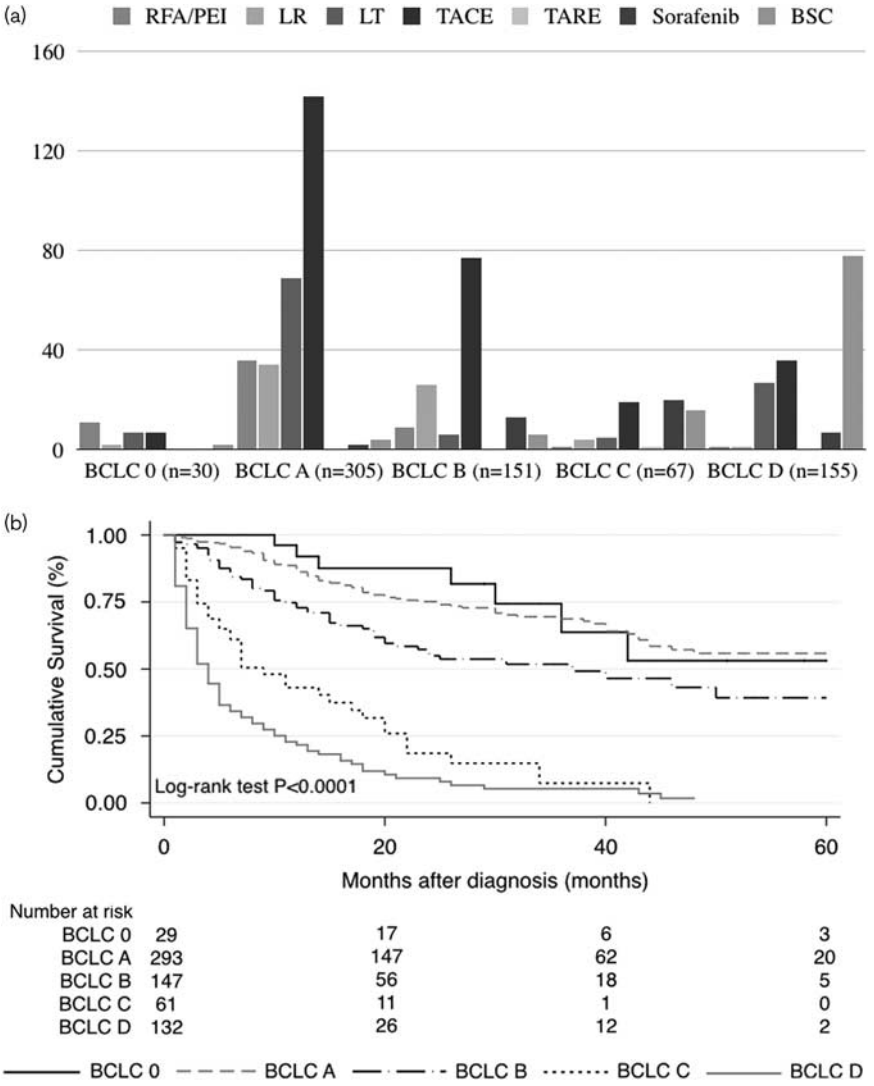

Fig. 2. First treatments performed according to BCLC stages (a). Survival according to BCLC stages (dummies categories, reference BCLC stage 0) (b). Note: Corresponding median survival for BCLC stages were as follows: stage 0 58 months (95% CI: 38–65 months), stage A 62 months (95% CI: 40–73 months) HR: 1.23 (95% CI: 0.57–2.67; $P=0.48$), stage B 36 months (95% CI: 20–56 months) HR: 2.22 (95% CI: 1.01–4.87; $P=0.036$), stage C 7 months (95% CI: 2–13 months) HR: 7.05 (3.16–15.69; $P=0.0001$), and stage D 3 months (95% CI: 1–13 months) HR: 12.29 (95% CI: 5.69–26.54; $P=0.0001$). BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; LR, transarterial chemoembolization; LT, liver transplant; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

After the first treatment, 208 patients underwent a second treatment, of which 137 were not treated according to BCLC at the first treatment. Among these patients, 69 received a second treatment in accordance to BCLC recommendation, representing an increasing BCLC adherence to 63% for subsequent treatments. Median time from the first to the second treatment was 5 months (IQR: 2.0–11.0 months). Figure 2a shows the first treatments performed in each BCLC stage.

Variables associated with adherence to Barcelona Clinic Liver Cancer clinical algorithm

Univariate and multivariate logistic regression analyses considering related variables to BCLC adherence are shown in Table 2 (Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/EJGH/A257*). Independent factors associated with BCLC adherence were presence of portal hypertension (OR: 1.63; 95% CI: 1.11–2.39) and BCLC stage C (OR: 0.29; 95% CI: 0.12–0.72) compared with BCLC 0–A (reference). No significant difference was observed between expected and observed events (Hosmer–Lemeshow test $P=0.70$).

Stratified analysis of adherence comparing transplant and nontransplant centers

Univariate analysis considering adherence between LT versus non-LT centers showed that although adherence was numerically higher in LT centers, it was not statistically significant (55.8 vs. 48.2%; $P=0.061$) (Table 2). In LT centers, most patients belonged to BCLC 0–A 53.1% ($n=257$), whereas in non-LT centers, most patients were diagnosed in BCLC stages C–D 43.3% ($n=97$).

Comparison of adherence at each BCLC stage stratified between LT centers and non-LT centers showed that LT

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Table 2. Baseline pretreatment variables associated with adherence to Barcelona Clinic Liver Cancer

Variables	Adherence to BCLC (%)	Unadjusted odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
Age (years)		0.98 (0.97–0.99)	0.033	0.98 (0.97–1.02)	0.10
Sex					
Male ($n=537$)	54.7	1.26 (0.89–1.79)	0.18		
Female ($n=171$)	48.8				
Liver transplant center					
Yes ($n=484$)	55.8	1.35 (0.98–1.86)	0.06	1.32 (0.94–1.85)	0.11
No ($n=224$)	48.2				
Comorbidity					
Yes ($n=299$)	51.2	0.86 (0.63–1.16)	0.31		
No ($n=409$)	55.0				
Cirrhosis or F3 fibrosis					
Yes ($n=639$)	54.6				
No ($n=69$)	42.0	0.60 (0.36–0.99)	0.048	0.85 (0.47–1.52)	0.58
Child–Pugh					
A ($n=352$)	51.1				
B ($n=238$)	55.5	1.19 (0.85–1.65)	0.30		
C ($n=118$)	55.9	1.21 (0.79–1.84)	0.36		
Portal hypertension					
Yes ($n=484$)	58.1	1.81 (1.31–2.49)	<0.0001	1.63 (1.11–2.39)	0.012
No ($n=224$)	43.3				
BCLC stage[a]					
0–A ($n=335$)	57.0	–	–	–	–
B ($n=151$)	50.9	0.78 (0.53–1.15)	0.22	0.97 (0.65–1.45)	0.89
C ($n=67$)	29.8	0.32 (0.18–0.56)	<0.0001	0.29 (0.12–0.72)	0.007
D ($n=155$)	58.1	1.04 (0.71–1.53)	0.82	0.98 (0.64–1.52)	0.95
AFP (>1000 ng/ml)					
Yes ($n=106$)	51.9	0.94 (0.62–1.43)	0.78		
No ($n=602$)	53.3				
Vascular invasion					
Yes ($n=74$)	40.5	0.56 (0.34–0.91)	0.02	0.98 (0.49–1.94)	0.96
No ($n=634$)	54.9				
Extrahepatic tumor disease					
Yes ($n=48$)	41.7	0.60 (0.33–1.09)	0.09	1.41 (0.63–3.12)	0.39
No ($n=660$)	54.2				

Univariate and multivariate logistic regression analyses.
Normal values: α-fetoprotein 0.6–4.4 ng/ml.
AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; HCC, hepatocellular carcinoma; LT, liver transplantation; OR, odds ratio.
[a]Dummy or categorical variable, reference BCLC 0–A.

centers had the greatest proportional adherence at BCLC 0–A (62.6%, $n=160$) and lower at BCLC stage C (24.4%, $n=24.4\%$; $P<0.0001$). In non-LT centers, the highest proportion of adherence was observed in BCLC-D stage (66.2%, $n=47$) whereas the lowest adherence was observed in the BCLC C stage 38.5% ($P=0.003$).

Survival analysis according to Barcelona Clinic Liver Cancer stages and adherence to Barcelona Clinic Liver Cancer algorithm

Outcomes were assessed in all patients during follow-up with a median follow-up of 12.0 months (IQR: 4.0–27.0 months). Main causes of death were advanced HCC ($n=135$), portal hypertension-related complications ($n=51$), and sepsis ($n=21$). Corresponding survival curves for BCLC stages are shown in Fig. 2b.

Unadjusted and adjusted HR from a Cox regression analysis of pretreatment baseline patient and tumor characteristics since HCC diagnosis showed that variables independently associated with 5-year mortality were age (HR: 1.04; 95% CI: 1.02–1.05), ECOG performance status 0–2 h (0.43; 95% CI: 0.29–0.62), Child–Pugh score B (HR: 1.55; 95% CI: 1.16–2.06), Child–Pugh score C (HR: 2.89; 95% CI: 2.04–4.08), serum AFP more than 1000 ng/ml (HR: 2.02; 95% CI: 1.46–2.82), and tumor macrovascular invasion (HR: 2.51; 95% CI: 1.74–3.62) (Table 3).

Survival since the first treatment decision was higher in patients with adherence to BCLC when compared with patients without adherence (HR: 0.57; 95% CI: 0.44–0.73) (Fig. 3a). This effect on survival was independent from the presence of portal hypertension and BCLC stage with adjusted HR for adherence to BCLC of 0.67 (95% CI: 0.52–0.87) (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/EJGH/A257*). Harrells's C concordance statistic of this final adjusted survival model was 0.74; calibration of the model showed no significant differences between expected and observed events, and proportional hazard assumption was kept in time (Supplementary Fig. S1, Supplemental digital content 2, *http://links.lww.com/EJGH/A256*). Survival was lower in patients who were undertreated or overtreated according to BCLC with a HR: 1.73 (95% CI: 1.29–2.32) and HR: 1.50 (95% CI: 1.14–1.99), respectively, when compared with those patients with adherence to BCLC (Fig. 3b).

Sensitivity analysis

A sensitivity analysis was done after excluding patients without cirrhosis. Adherence was lower among patients without cirrhosis when compared with patients with cirrhosis (42 vs. 55%; $P=0.04$). The effect of adherence upon survival was not significant among patients without cirrhosis, with an HR: 0.78 (95% CI: 0.36–1.72), whereas in patients with cirrhosis, the presence of adherence

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Table 3. Baseline variables associated with 5-year mortality

Variables	5-Year mortality rate (%)	Unadjusted hazard ratio (95% CI)	*P*	Adjusted hazard ratio (95% CI)	*P*
Age (years)		1.03 (1.01–1.04)	<0.0001	1.04 (1.02–1.05)	<0.0001
Sex					
Male (*n* = 537)	42.3	1.08 (0.82–1.42)	0.55		
Female (*n* = 171)	42.7				
Comorbidity					
Yes (*n* = 299)	45.1	1.08 (0.86–1.37)	0.49		
No (*n* = 409)	40.7				
Diabetes mellitus					
Yes (*n* = 196)	38.8	0.83 (0.63–1.08)	0.17		
No (*n* = 512)	44.0				
ECOG 0–2					
Yes (*n* = 637)	37.9	0.19 (0.14–0.26)	0.0001	0.43 (0.29–0.62)	<0.0001
No (*n* = 71)	84.5				
Cirrhosis or F3 fibrosis					
Yes (*n* = 639)	42.9	0.86 (0.58–1.28)	0.45		
No (*n* = 69)	39.1				
Child–Pugh					
A (*n* = 352)	34.5	–	0.019	–	0.003
B (*n* = 238)	41.6	1.38 (1.06–1.83)	0.0001	1.55 (1.16–2.06)	<0.0001
C (*n* = 118)	68.6	3.23 (2.41–4.34)		2.89 (2.04–4.08)	
Portal hypertension					
Yes (*n* = 484)	40.2	1.22 (0.94–1.57)	0.13		
No (*n* = 224)	43.7				
AFP (>1000 ng/ml)					
Yes (*n* = 106)	64.1	3.09 (2.31–4.15)	0.0001	2.02 (1.46–2.82)	<0.0001
No (*n* = 602)	39.5				
Vascular invasion					
Yes (*n* = 74)	77.0	4.74 (3.48–6.44)	0.0001	2.51 (1.74–3.62)	<0.0001
No (*n* = 634)	38.5				
Extrahepatic disease					
Yes (*n* = 48)	70.8	3.29 (2.25–4.81)	0.0001	1.36 (0.88–2.09)	0.16
No (*n* = 660)	40.5				

Cox regression analysis.
Normal values: α-fetoprotein 0.6–4.4 ng/ml.
AFP, α-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; LT, liver transplantation.

remained significantly related with 5-year survival with a HR: 0.60 (95% CI: 0.47–0.77). Finally, evaluating only the effect upon survival among patients who received only one treatment ($n = 338$) to exclude any subsequent treatment bias, adherence to BCLC remained related with survival with an HR: 0.66 (95% CI: 0.48–0.91).

Discussion

This is the first cohort study to assess adherence or applicability of BCLC treatment recommendation in a non-European, non-Asian population. We found that overall first treatment adherence to BCLC was barely beyond 50% and increased in subsequent treatments. Adherence to BCLC at the first treatment had an effect on patient survival independently from the presence of portal hypertension and from BCLC stage.

The BCLC clinical algorithm is based on effective treatments that have shown a survival benefit in clinical trials and in observational studies [4,5]. Although the BCLC has been proposed in western countries, it has been assessed in Asian populations with a good prognostic performance [25].

In the BRIDGE retrospective cohort study, in which global patterns of HCC management were evaluated, patients from Latin America were not included [26]. This study showed that in western countries, the most frequent BCLC stage was C, whereas in Asian populations, stage A was the most frequent one. In our cohort, the most frequent BCLC stages at diagnosis were stage 0–A, as seen in almost 50% of the cases. In Asian populations, the most frequent first treatment performed was RFA/PEI or LT, whereas TACE was the first treatment performed for most patients in our study. LT was the second most frequent treatment in our cohort, similar to what was observed in the USA [26]. However, in our study, the most parts of TACEs were performed as a 'treatment stage migration' considering it as a bridge to LT [23]. In this sense, those patients treated with this modality were adherent to BCLC as previously mentioned.

We observed that in LT centers, most of the patients were diagnosed at early stages whereas in non-LT centers, most of the patients presented with advanced HCC. This might probably respond to the fact that patients who are transferred to non-LT centers were not candidates for LT any longer (referral bias). In LT centers, although adherence to BCLC was numerically higher than that of non-LT centers, it did not reach statistical significance. In both LT and non-LT centers, adherence was low in BCLC-C patients, candidates for sorafenib treatment. This finding suggests that the access of sorafenib should be reviewed in the coming years in our population considering that this drug was available in our country during the whole period of time included in this study.

Some series have reported different rate of adherence to BCLC [12,13,27–29]. In a Korean single-center study, in which the most frequent BCLC stage was A, adherence to BCLC reached 40%. In this study, the most frequent discrepancies were refusal to living donor LT and financial limitations [13]. In that study, the greatest deviation from

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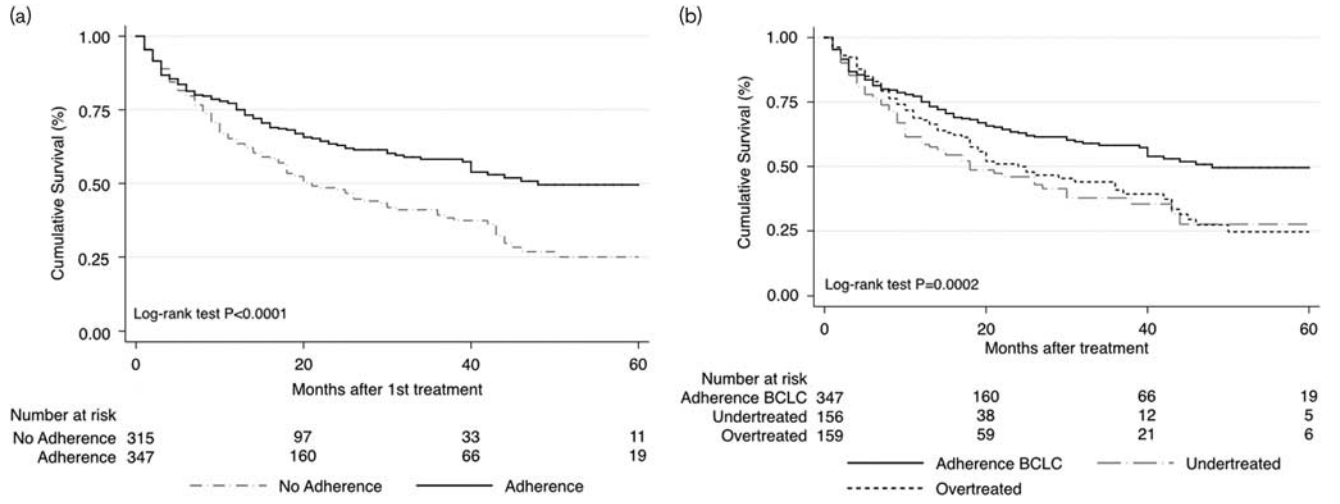

Fig. 3. Survival according to adherence to BCLC recommendation (a) and comparing 'overtreated' and 'undertreated' subgroups (b). Note: Adherence to BCLC in the first treatment decision affected survival; independently from the presence of portal hypertension and from each BCLC stage. BCLC, Barcelona Clinic Liver Cancer.

the BCLC recommendation accounted for stages A and C, similar to what we have observed in our study. Another European single-center study showed a low rate of adherence in BCLC stage B [27]. However, an important selection bias of candidates for TACE was observed in that study. Other researchers from Europe have reported adherence rates ranging from 48 to 60% [12,28,29]. A multicenter study from Italy compared treatments performed applying the 2005 version of the BCLC, in which sorafenib was not yet included [28]. In Italy, the highest adherence rate was observed in BCLC stage A [12], whereas in Switzerland this figure corresponded to BCLC stage D [29].

Although in our study adherence was more than 50% for the first HCC treatment, when we considera the subsequent treatment, the overall adherence was 63%. Independent variables related with adherence to BCLC from a multivariate logistic regression model showed that presence of portal hypertension almost increased two-fold the probability of adherence to BCLC. Adherence showed an effect on patient survival not only in the univariate analysis but also when its effect was adjusted by the presence of portal hypertension and each BCLC stage. When compared in a stratified analysis, adherence showed improved survival when compared with either 'overtreated' or 'undertreated' subgroup of patients. Finally, it might be argued that evaluation of adherence to BCLC should not include noncirrhotic population. In this sense, a sensitivity analysis excluding patients without cirrhosis showed that adherence was higher in those with cirrhosis and the effect on survival still remained in these patients.

We faced limitations in this study, which we tried to overcome. First, given the fact that in cohort studies with no control group prognostic factors are likely to be biased, a strict revision of the data was centrally requested and a complete follow-up and outcome assessment was available for all included patients. Second, when considering subsequent treatment, re-assessment of BCLC status was not recorded, although the time elapsed from the first to the second treatment was short. Third, it may be argued that subsequent treatments after the first therapeutic decision might be influenced by the clinical outcomes (subsequent treatment bias); however, when we performed a sensitivity analysis excluding subsequent treatments, the effect of adherence on survival still remained. Finally, we did not include any intermediate BCLC subclassification [7,30], as this has not been validated yet [31].

In summary, in our cohort, adherence to BCLC was more than 50% and increased in subsequent treatments with an effect on patient survival. Although the BCLC approach appears to be rigid, it is flexible and should be cautiously implemented and tailored to each individual patient. It is important to consider the most adequate option for every individual patient, including the tumor burden, Child–Pugh and ECOG status, but also age, comorbidities, and tumor localization, and for most, regional or local hospital treatment feasibility are determinant factors [14]. Consequently, the best treatment option depends not only on the BCLC as a fixed recommendation but rather based on an individualized clinical decision-making process.

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Conflicts of interest

There are no conflicts of interest.

References

1 Sherman M. Hepatocellular carcinoma: epidemiology, surveillance, and diagnosis. *Semin Liver Dis* 2010; 30:003–016.
2 Bruix J, Han KH, Gores G, Llovet JM, Mazzaferro V. Liver cancer: approaching a personalized care. *J Hepatol* 2015; 62:S144–S156.
3 Llovet JM, Fuster J, Bruix J. Barcelona-Clinic Liver Cancer Group. The Barcelona approach: Diagnosis, staging, and treatment of hepatocellular carcinoma. *Liver Transpl* 2004; 10:S115–S120.
4 European Association For The Study Of The Liver; European Organisation For Research And Treatment Of Cancer. EASL-EORTC

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clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; 56:908–943.
5 Bruix J, Sherman M. American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. *Hepatology* 2011; 53:1020–1022.
6 Yau T, Tang VYF, Yao TJ, Fan ST, Lo CM, Poon RTP. Development of Hong Kong liver cancer staging system with treatment stratification for patients with hepatocellular carcinoma. *Gastroenterology* 2014; 146: 1691–1700.e3.
7 Bolondi L, Burroughs A, Dufour JF, Galle P, 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* 2013; 32:348–359.
8 Tateishi R. Proposal of a new prognostic model for hepatocellular carcinoma: an analysis of 403 patients. *Gut* 2005; 54:419–425.
9 Kudo M, Chung H, Haji S, Osaki Y, Oka H, Seki T, *et al*. Validation of a new prognostic staging system for hepatocellular carcinoma: the JIS score compared with the CLIP score. *Hepatology* 2004; 40:1396–1405.
10 Leung TWT, Tang AMY, Zee B, Lau WY, Lai PBS, Leung KL, *et al*. Construction of the Chinese University Prognostic Index for hepatocellular carcinoma and comparison with the TNM staging system, the Okuda staging system, and the Cancer of the Liver Italian Program staging system. *Cancer* 2002; 94:1760–1769.
11 Chevret S, Trinchet JC, Mathieu D, Rached AA, Beaugrand M, Chastang C. A new prognostic classification for predicting survival in patients with hepatocellular carcinoma. Groupe d'Etude et de Traitement du Carcinome Hépatocellulaire. *J Hepatol* 1999; 31:133–141.
12 Leoni S, Piscaglia F, Serio I, Terzi E, Pettinari I, Croci L, *et al*. Adherence to AASLD guidelines for the treatment of hepatocellular carcinoma in clinical practice: Experience of the Bologna Liver Oncology Group. *Dig Liver Dis* 2014; 46:549–555.
13 Kim SE, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, *et al*. Applicability of the BCLC staging system to patients with hepatocellular carcinoma in Korea: analysis at a single center with a liver transplant center. *Korean J Hepatol* 2011; 17:113.
14 Colombo M, Sangiovanni A. Treatment of hepatocellular carcinoma: beyond international guidelines. *Liver Int* 2014; 35:129–138.
15 Lencioni R, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, *et al*. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. *Int J Clin Pract* 2013; 68:609–617.
16 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.
17 Mazzaferro VV, Regalia EE, Doci RR, Andreola SS, Pulvirenti AA, Bozzetti FF, *et al*. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; 334:693–699.
18 Duvoux C, Thoraval FR, Decaens T, Pessione F, Badran H, Piardi T, *et al*. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012; 143:986–994.e3.
19 Piñero F, Tisi Baña M, de Ataide EC, Hoyos Duque S, Marciano S, Varón A, *et al*. Liver transplantation for hepatocellular carcinoma: evaluation of the AFP model in a multicenter cohort from Latin America. *Liver Int* 2016; 36:1657–1667.
20 Llovet JMJ, Real MIM, Montaña XX, Planas RR, Coll SS, Aponte JJ, *et al*. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet* 2002; 359:6–6.
21 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, *et al*. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; 359:378–390.
22 Bruix J, Reig M, Sherman M. Evidence-based diagnosis, staging, and treatment of patients with hepatocellular carcinoma. *Gastroenterology* 2016; 150:835–853.
23 Reig M, Darnell A, Forner A, Rimola J, Ayuso C, Bruix J. Systemic therapy for hepatocellular carcinoma: the issue of treatment stage migration and registration of progression using the BCLC-Refined RECIST. *Semin Liver Dis* 2014; 34:444–455.
24 Elm von E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007; 370:1453–1457.
25 Hsu CY, Liu PH, Hsia CY, Lee YH, Juboori Al A, Lee RC, *et al*. Nomogram of the Barcelona Clinic Liver Cancer system for individual prognostic prediction in hepatocellular carcinoma. *Liver Int* 2016; 36:1498–1506.
26 Park JW, Chen M, Colombo M, Roberts LR, Schwartz M, Chen PJ, *et al*. Global patterns of hepatocellular carcinoma management from diagnosis to death: the BRIDGE Study. *Liver Int* 2015; 35:2155–2166.
27 Radu P, Groza I, Iancu C, Hajjar Al N, Andreica V. Treatment of hepatocellular carcinoma in a tertiary Romanian center. Deviations from BCLC recommendations and influence on survival rate. *J Gastrointestin Liver Dis* 2013; 22:291–297.
28 Borzio M, Fornari F, De Sio I, Andriulli A, Terracciano F, Parisi G, *et al*. Adherence to American Association for the Study of Liver Diseases guidelines for the management of hepatocellular carcinoma: results of an Italian field practice multicenter study. *Future Oncol* 2013; 9:283–294.
29 Richani M, Kolly P, Knoepfli M, Herrmann E, Zweifel M, Tengg-Kobligk von H, *et al*. Treatment allocation in hepatocellular carcinoma: assessment of the BCLC algorithm. *Ann Hepatol* 2015; 15:82–90.
30 Hiraoka A, Kumada T, Nouso K, Tsuji K, Itobayashi E, Hirooka M, *et al*. Proposed new sub-grouping for intermediate-stage hepatocellular carcinoma using albumin-bilirubin grade. *Oncology* 2016; 91:153–161.
31 Weinmann A, Koch S, Sprinzl M, Kloeckner R, Schulze-Bergkamen H, Düber C, *et al*. Survival analysis of proposed BCLC-B subgroups in hepatocellular carcinoma patients. *Liver Int* 2014; 35:591–600.

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