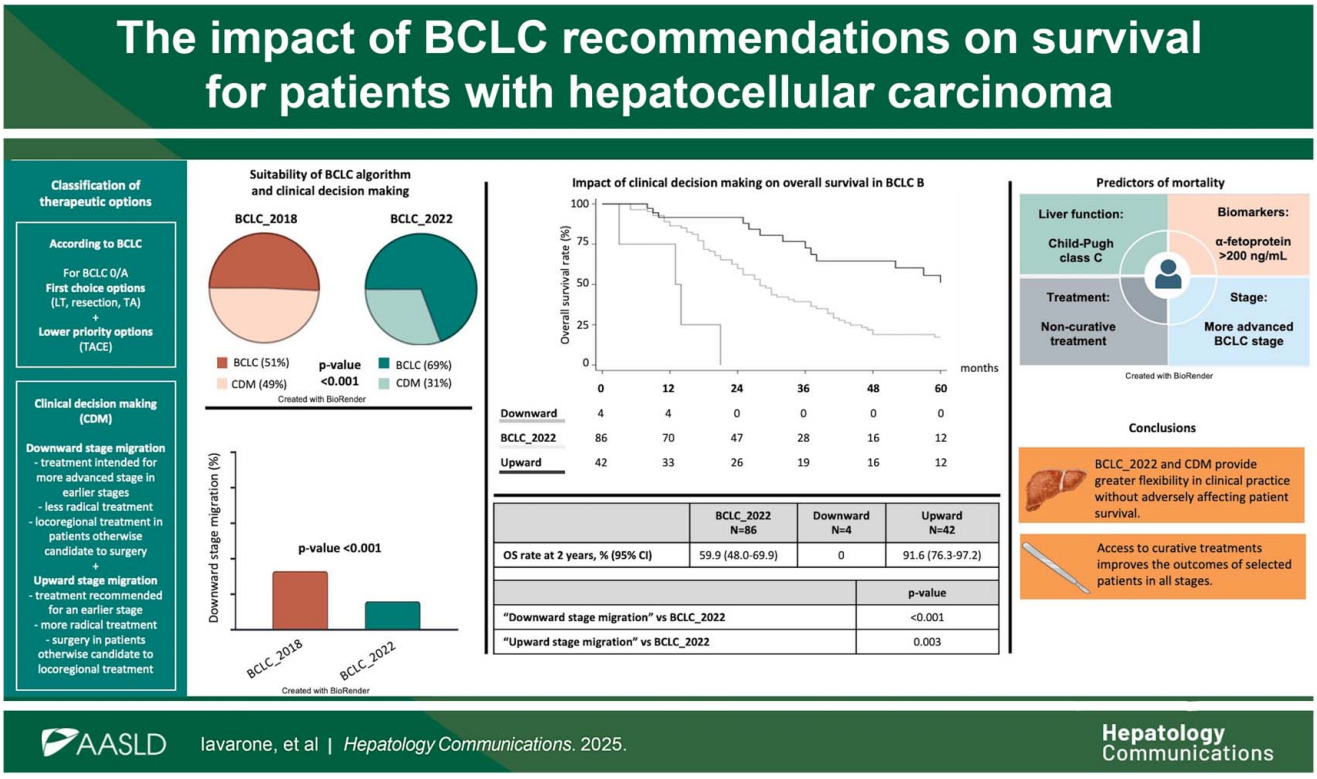
The impact of BCLC recommendations on survival for patients with hepatocellular carcinoma

VISUAL ABSTRACT



Received: 18 March 2025 | Accepted: 12 May 2025

DOI: 10.1097/HC9.0000000000000750

ORIGINAL ARTICLE

OPEN

The impact of BCLC recommendations on survival for patients with hepatocellular carcinoma

Massimo Iavarone[1,2] | **Eleonora Alimenti**[1] | **Lorenzo Canova**[1,3] | **Mariangela Bruccoleri**[1] | **Barbara Antonelli**[4] | **Anna Maria Ierardi**[5] | **Angelo Sangiovanni**[1] | **Giuseppe Cabibbo**[6] | **Annalisa De Silvestri**[7] | **Lucio Caccamo**[4] | **Gianpaolo Carrafiello**[5] | **Pietro Lampertico**[1,2]

[1]Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[2]Department of Pathophysiology and Transplantation, CRC "A. M. and A. Migliavacca" Center for Liver Disease, University of Milan, Milan, Italy

[3]Università degli Studi di Milano, Milan, Italy

[4]General and Liver Transplant Surgery Unit, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[5]Department of Radiology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

[6]Department of Health Promotion, Mother and Child Care, Internal Medicine and Medical Specialties PROMISE, Section of Gastroenterology and Hepatology, University of Palermo, Italy

[7]Clinical Epidemiology and Biometric Unit, Scientific Direction, IRCCS Policlinico S. Matteo Foundation, Pavia, Italy

Correspondence
Massimo Iavarone, CRC "A. M. and A. Migliavacca" Center for Liver Disease, Department of Pathophysiology and Transplantation, University of Milan, Division of Gastroenterology and Hepatology, Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via F Sforza 28, 20122 Milan, Italy.
Email: massimo.iavarone@policlinico.mi.it

Abstract

Background: The Barcelona Clinic Liver Cancer (BCLC) system for HCC was updated in 2022. The aim of the study was to assess the suitability and impact on overall survival (OS) of BCLC_2022, along with "clinical decision-making" (CDM), using BCLC_2018 as a benchmark.

Methods: We retrospectively evaluated 798 patients with de novo HCC followed prospectively from 2006 to 2022: 187 in BCLC 0, 371 in A, 132 in B, 87 in C, and 21 in D, all managed by a multidisciplinary team. Patients were followed until death or at the end of the follow-up period in December 2022.

Results: The suitability of the algorithm increased from 51% for BCLC_2018 to 69% for BCLC_2022 ($p < 0.001$). Among those treated with the newly introduced "lower priority options," 22% were in BCLC 0 and 37% in A, showing lower rates of complete response (CR) and shorter OS compared to first-line treatments. In BCLC 0 and A, CDM was associated with a significant decrease in "downward stage migration" with BCLC_2022 (from 33% to 16%, $p < 0.001$). Conversely, in BCLC B and C, "upward stage migration" correlated with higher CR rates and longer OS [63 (36–72) vs. 28 (18–44)

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin–bilirubin; BCLC, Barcelona Clinic Liver Cancer; CDM, clinical decision-making; CPT, Child–Pugh–Turcotte; CR, complete response; ECOG, Eastern Cooperative Oncology Group; LRT, locoregional treatment; LT, liver transplantation; MDT, multidisciplinary team; OS, overall survival; TA, thermal ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; UEG, upper gastrointestinal endoscopy.

Supplemental Digital Content is available for this article. Direct URL citations are provided in the HTML and PDF versions of this article on the journal's website, www.hepcommjournal.com.

months, $p = 0.003$ in BCLC B; 21 (15–44) vs. 11 (4–25) months, $p < 0.001$ in BCLC C]. Independent predictors of mortality included AFP > 200 ng/mL, Child–Pugh score C, advanced BCLC stage, and noncurative treatment.

Conclusions: BCLC_2022 and CDM provide greater flexibility in clinical practice without adversely affecting patient survival. Access to curative treatments improves the outcomes of selected patients in all stages.

Keywords: ablation, HCC, liver transplantation, surgery, systemic therapy

INTRODUCTION

The Barcelona Clinic Liver Cancer (BCLC) system for staging and treatment allocation has facilitated the categorization of HCC stages, enabling prognosis prediction and fostering a common language among HCC experts, while the continuous updating of recommendations has ensured its relevance.[1–4] Some known limitations of the system have been addressed in the latest version, which introduces the concepts of "clinical decision-making" (CDM) and "stage migration," taking into consideration variables such as age, comorbidities, and patient preferences, assessed by a multidisciplinary team (MDT), which cannot generally be included in a staging system.[4]

Upon diagnosis of HCC, patients and their families should be informed not only about the prognosis relative to the disease stage but also about the potential impact of the proposed therapy on survival. They should be made aware of alternative options, considering factors such as comorbidities, age, and frailty of the patient, as well as the suitability and potential complications associated with different treatments, which are eventually recommended for other stages.[4]

In our center, we have consistently utilized the BCLC system as a reference for treatment allocation, with each patient's case being discussed collegially by the MDT.[5,6] Our goal is to identify the most suitable treatment based on disease stage, comorbidities, patient preferences, as well as our evolving capabilities and resources, as has been recently proposed.[7] A study we published in 2018 demonstrated adherence to recommendations of 81% for BCLC A patients, 54% for BCLC B, and 53% for BCLC C.[5]

Significant changes in treatment allocations by the updated BCLC recommendations include the introduction of "lower priority options" for early stages when the first choices are not suitable (such as transarterial chemoembolization, TACE, and transarterial radioembolization, TARE). Another change is the inclusion of liver transplantation (LT) after effective downstaging and systemic therapy in selected cases for patients with intermediate-stage HCC, in addition to TACE, which was the sole recommended treatment in previous versions of BCLC.[3,4] Moreover, a major innovation is the introduction of the concept of "individualized clinical decision-making," which includes stage migration options, following the decision of the MDT on the basis of several factors.

This study aimed to assess the suitability of the 2022 BCLC updated recommendations compared to previous ones in a real-life setting, with a large cohort of patients diagnosed with HCC managed over an extended period in our center by an MDT. Additionally, we aimed to perform an exploratory analysis on how the introduction of "lower priority options" for earlier HCC stages and "clinical decision-making" approach for all stages, with "stage migration" according to MDT in the new BCLC, affects HCC management and overall survival (OS) compared to first-choice recommended treatments.

METHODS

This was a single-center retrospective study that included patients with a first diagnosis of HCC managed at the Center for Liver Disease of Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico (Milan) between June 1st, 2006, and April 15th, 2022. All patients were prospectively followed up, and clinical data were collected for analysis. The inclusion criteria were the first diagnosis of HCC according to updated international guidelines (either histologically proven or by radiological criteria) and availability of complete clinical baseline information (ie, at the first diagnosis of HCC).

All procedures followed the "Strengthening the Reporting of Observational Studies in Epidemiology" guidelines[8] and were approved by the Ethical Committee "Lombardia 3" (ID 4428_S_P); they complied with the ethical standards and with the Helsinki Declaration of 1975, as revised in 2008.

Study endpoints

The primary objective was to evaluate the proportion of patients for whom the initial treatment recommendations outlined in the BCLC_2022 algorithm were suitable, considering both direct allocation according

to the algorithm and "lower priority options" included in the updated version. The BCLC_2018 recommendations were employed as a benchmark based on the initial treatment decision made by the MDT.

Secondary endpoints were: (1) evolution of the suitability of BCLC_2022 recommendations over time (3 periods: 2006–2010, 2011–2015, 2016–2022); (2) impact of new recommendations of BCLC_2022 on treatment response; (3) exploratory analysis on the impact on survival of both adherence to BCLC_2022 recommendations (including "lower priority options") and "individualized decision-making" according to MDT ("stage migration" options); (4) predictors of mortality according to stage and treatment allocation; and (5) predictors of recurrence in patients with complete radiological response (CR) after upfront treatment.

HCC diagnosis, staging, treatment allocation, and response evaluation

HCC was diagnosed by radiology [either by contrast-enhanced computed tomography (CT) scan or magnetic resonance (MR)] or by histology according to updated international guidelines. HCC was staged according to the BCLC staging system, including the following features, recorded at the time of the assessment: Child–Pugh score (Child–Pugh–Turcotte, CPT),[9] performance status by the Eastern Cooperative Oncology Group (ECOG),[10] number and diameter of tumor, vascular invasion, and extrahepatic metastasis.[1–4] According to the BCLC system, HCCs at first diagnosis were staged as very early (BCLC 0), early (BCLC A), intermediate (BCLC B), advanced (BCLC C), and end-stage (BCLC D). At the time of the first diagnosis of HCC (baseline), all patients underwent a CT scan of the chest, bone scintigraphy, and upper gastrointestinal endoscopy (UEG) if not recently performed. These examinations were repeated whenever clinically relevant during follow-up.

First-line treatment allocation was based on the updated guidelines at the time of diagnosis:[1–4,11–15] each case was discussed by the MDT and allocated to treatment according to the up-to-date recommendations, recording the reason why the decision deviated from the expected indications by disease stage, such as the presence of comorbidities, availability of a certain type of treatment, or other factors determining the decision. Treatments considered curative were LT, surgical resection, radiofrequency/microwave thermal ablation (TA), and a combination of treatments (resection+TA or TA+TACE).

According to the BCLC_2022 updated version, the options were reported and grouped in: (1) According to "BCLC 2022," which for BCLC 0/A is classified as "first-choice" options (ie, LT, resection or TA, when indicated) and "lower priority options" (ie, TACE and TARE). (2) According to "clinical decision-making" by MDT in any BCLC stage, which includes 2 "stage migration options": the "downward stage migration" [ie, the application of a treatment intended for more advanced stage in earlier stages (ie, systemic treatment in BCLC A) or of a less radical treatment (ie, TA in patients candidate to resection or LT)], which is clearly stated in the BCLC_2022 system and the "upward stage migration" [ie, the application of a treatment recommended by the BCLC_2022 for an earlier stage in more advanced HCC stage (ie, surgery for BCLC C) or application of a more radical treatment (ie, resection in patients candidate to TA; LT in patients candidate to resection)]. The latter is not clearly stated in the BCLC_2022 recommendations. Furthermore, in BCLC 0/A, "downward stage migration" was classified as "downward stage migration with curative intent" (ie, liver resection in patients candidate to LT; TA in patients candidate to liver resection/LT) and as "downward stage migration without curative intent" (ie, in patients treated with TACE, TARE, or systemic treatment; in patients only in best supportive care) (Supplemental Figure S1, http://links.lww.com/HC9/C49).

If a patient had received locoregional treatment (LRT) during the transplant waiting list (bridging treatments), LT was considered the upfront allocated treatment. Radiological response to treatment was assessed by either contrast-enhanced CT scan or MR performed (1) 1 month apart after LT and then every 6 months; (2) 1 month apart for LRTs or surgery [if complete response (CR) was detected, then every 3–4 mo in the first 2 years or until recurrence]; (3) every other month for systemic treatment until progression, discontinuation of therapy for any reason, or transition to supportive therapy only.

Definition of etiology and staging of underlying chronic liver disease

Underlying liver disease etiology was classified as viral if patients had HCV infection and/or chronic HBV infection, with or without HDV infection. In our center, all patients with viral infections were offered antiviral therapy as soon as possible and according to national and international guidelines. Nonviral etiologies included alcohol-associated liver disease, metabolic-associated steatotic liver disease (MASLD, diagnosed in the presence of a steatotic liver associated with diabetes, overweight/obesity, or at least 2 metabolic risk abnormalities),[16] autoimmune hepatitis,[17] and primary biliary cholangitis.[18] If both viral and nonviral causes of liver disease coexisted, etiology was defined as mixed, while if all possible causes were ruled out, the liver disease was considered cryptogenic.

The diagnosis of cirrhosis was histological or non-invasive [ie, liver stiffness $>$ 12 kPa by elastography[19] or

indirect signs of advanced chronic liver disease (ie, platelet count $<100{,}000\ \times 10^9$/L, presence of esophageal or gastric varices at UEG, coarse liver texture, or hallmarks of portal hypertension on abdominal imaging)]. Grade of cirrhosis was defined according to CPT,[9] liver function was also evaluated through MELD score[20] and albumin–bilirubin grade for HCC (ALBI) score.[21] For the definition of clinically significant portal hypertension, reference was made to the updated criteria in accordance with the Baveno consensus.[22] Baseline characteristics at HCC diagnosis included patient demographics, comorbidities, presence of esophageal or gastric varices at the last available UEG, and laboratory variables.

Statistical analysis

Continuous variables were expressed as median and IQR and compared using Kruskal–Wallis one-way ANOVA. Categorical variables were reported as the number of cases and percentages and compared using the Fisher exact test or the chi-square test when appropriate. The response to treatment, HCC recurrence after first-line treatment, and death were reported as percentages. Follow-up time started from the first HCC diagnosis until death, last available access to hospital facilities, or data lock (December 31st, 2022), whichever occurred first. Kaplan–Meier analysis was used to estimate the OS and OS rates during the follow-up period. Moreover, the time to recurrence and HCC recurrence rate were calculated using the Kaplan–Meier estimator during the time from the first HCC treatment to HCC recurrence, death, last visit, or data lock. Comparisons of OS and HCC recurrence rates according to direct adherence to BCLC_2018 and BCLC_2022, and to the CDM approach ("upward stage migration" and "downward stage migration") were performed using the log-rank test. For patients with BCLC 0 and A, the comparison also included "downward stage migration" with and without curative intent and, in a further analysis, OS rates in patients treated with "first-choice options" and "lower priority options" were compared. Cox univariate proportional hazard models were applied to identify independent predictors of HCC recurrence and mortality, both in the whole cohort and in each BCLC stage. The baseline characteristics included in the analysis were: age, gender, underlying liver disease etiology, presence of cirrhosis, presence of ascites, esophageal/gastric varices and hepatic encephalopathy, albumin, bilirubin, international normalized ratio, creatinine, platelet count below 150×10^9/mL, alpha-fetoprotein (AFP, continuous and as dichotomic variable above/under 200 ng/mL), CPT, MELD, ALBI grade, HCC nodules number (single, 2–3 nodules and >3 nodules) and maximum diameter, presence of extrahepatic spread and/or vascular invasion, BCLC stage, presence of HCC exceeding the "Milan criteria," "according to BCLC 2022" (both "first-choice" option and "lower priority options"), or application of CDM (ie, "upward stage migration" and "downward stage migration"), and finally the different first-line HCC treatments applied. Variables that were significant in univariable analysis, selected to avoid collinearity, were included in multivariable models after excluding the presence of significant interaction between BCLC class and adherence to BCLC_2022 and between adherence to BCLC_2022 and first-line HCC treatment.

The impact of time-dependent variables, such as CR to treatment and HCC recurrence, on survival was also tested. Statistical significance was set at $p<0.05$. Results were reported as HRs and 95% CIs. Data management and analysis were performed using STATA SE 14.0 (Stata Corp).

RESULTS

Baseline characteristics of patients

Between 2006 and 2022, 875 patients were diagnosed with de novo HCC at our center, 77 (8.8%) patients were excluded from the analysis due to incomplete baseline data, and finally, 798 patients were included in

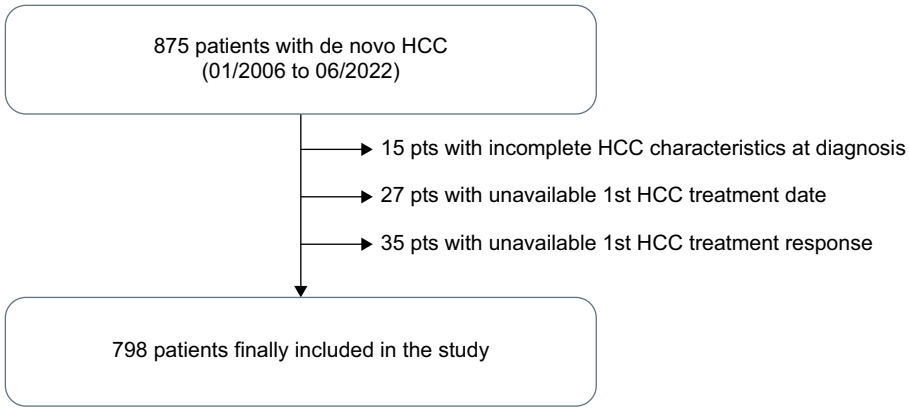


FIGURE 1 Patients' disposition.

the study, prospectively followed until death, last visit, or data lock (Figure 1). Baseline characteristics of the 798 patients included in the study are reported in Table 1: 74% males, median age 68 years (IQR 60–74), the most frequent etiology of liver disease was HCV infection (59%) and 738 (92%) patients had a previous diagnosis of cirrhosis mainly with preserved liver function (CPT A in 76%). In all, 187 (23%) patients were BCLC 0, 371 (47%) BCLC A, 132 (16%) B, 87 (11%) C, and 21 (3%) D. Among patients with BCLC C, 9 (10%) had both extrahepatic disease and vascular invasion, 42 (48%) extrahepatic disease only, and 18 (21%) vascular invasion only, 18 (21%) were staged C for ECOG PS 1 or above. Among patients with BCLC D, 2 (10%) were considered for LT due to the limited tumor burden beneath "Milan criteria" and thus were reclassified as BCLC A. Overall, HCC was a single nodule in 481 (60%) patients, outside "Milan criteria" in 262 (33%), and median diameter of the largest nodule was 2.5 cm (1.8–4.0).

First-line treatment allocation and adherence to the BCLC_2022 algorithm

Median time between HCC diagnosis and first-line treatment was 2 months (0.1–3); 479 (60%) patients were allocated to treatments with curative intent, whereas 212 (26.5%) were treated with TACE, 7 (1%) with TARE, 69 (8.5%) with systemic therapy, and 31 (4%) patients received supportive care only. Treatment allocation according to BCLC stage is reported in Table 2. Among the 96 patients BCLC 0/A with CPT B, 86 (91%) had a score B 7/8, which had no or minimal impact on treatment allocation. The combined treatments were considered the best option for further analysis.

Overall, the suitability of treatment algorithms increased from 51% for the BCLC_2018 to 69% for the BCLC_2022 ($p < 0.001$). No significant differences were observed in "upward stage migration" rates (from 16% to 15%, $p = 0.68$), while "downward stage migration" significantly decreased in BCLC_2022 (from 33% to 16%, $p < 0.001$).

The suitability of BCLC algorithm increased from 56% of BCLC_2018 to 73% of BCLC_2022 in stage 0 ($p = 0.001$): among patients treated according to BCLC_2022, 106 (78%) patients received a first-choice treatment (LT, resection, or TA), while 30 (22%) were allocated to TACE (ie, "lower priority option"). Among patients with a "downward stage migration," 35 (90%) received a treatment with curative intent. Similarly, in patients staged BCLC A, an increase in suitability from 45% to 72% was observed ($p < 0.001$): 169 (63%) patients received one of the first-choice treatments according to BCLC_2022 (LT, resection, or TA), while 100 (37%) were allocated to TACE (ie, "lower priority

TABLE 1 Clinical and demographic characteristics of 798 patients included in the study

Variables	Patients N = 798
Age, y[a]	68 (60–74)
Males, N (%)	594 (74)
Etiology, N (%)	
HCV	489 (61)
HBV	91 (11)
Nonviral	171 (22)
Mixed	47 (6)
Cirrhosis, N (%)	738 (92)
Ascites, N (%)	176 (22)
Encephalopathy, N (%)	68 (8)
Esophagogastric varices, N (%)	256 (35)[b]
Albumin, g/dL[a]	4.00 (3.6–4.4)
Total bilirubin, mg/dL[a]	0.94 (0.7–1.4)
INR[a]	1.12 (1.04–1.23)
Creatinine, mg/dL[a]	0.87 (0.74–1.03)
Platelets, 10^9/mL[a]	129 (85–179)
AFP, ng/mL[a]	12.20 (4.9–55.2)
AFP > 200 ng/mL, N (%)	102 (14)[b]
Child–Pugh class, N (%)	
A	552 (76)[c]
B	154 (22)[c]
C	16 (2)[c]
MELD[a]	9 (7–10)
ALBI grade, N (%)	
1	373 (49)[d]
2	365 (48)[d]
3	18 (3)[d]
BCLC stage, N (%)	
0	187 (23)
A	371 (47)
B	132 (16)
C	87 (11)
D	21 (3)[e]
Nodules, N (%)	
1	481 (60)
2–3	209 (26)
> 3	108 (14)
Largest nodule's diameter, cm[a]	2.5 (1.8–4.0)
Presence of MVI, EHS, or both, N (%)	
MVI	43 (5)
EHS	18 (2)
Both	11 (1)
"Milan criteria" out, N (%)	262 (33)
ECOG PS, N (%)	
0	767 (96)
≥ 1	29 (4)

Note: Data are expressed as numbers (percentages), unless otherwise specified.
[a]Median (IQR).
[b]Data is available for 720 patients.
[c]Data is available for 722 patients.
[d]Data is available for 756 patients.
[e]According to BCLC recommendations, 2/21 BCLC D patients undergoing LT were reclassified as BCLC A in the analysis.
Abbreviations: AFP, alpha-fetoprotein; ALBI score, albumin–bilirubin score; BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EHS, extrahepatic spread; INR, international normalized ratio; MVI, macrovascular invasion.

TABLE 2 First-line treatment allocation in 798 newly diagnosed HCC according to BCLC stage

First-line treatments, N (%)	Overall (N = 798)	BCLC 0 (N = 187)	BCLC A (N = 373)	BCLC B (N = 132)	BCLC C (N = 87)	BCLC D (N = 19)
Liver transplantation	41 (5)	11 (6)	20 (5.4)	7 (5.3)	3 (3.5)	0
Resection	139 (17.5)	23 (12)	96 (25.7)	17 (13)	3 (3.5)	0
Ablation	278 (35)	119 (64)	136 (36.5)	16 (12)	7 (8.1)	0
Resection+TA	9 (1)	0	3 (0.8)	3 (2.3)	3 (3.5)	0
TA+TACE	12 (1.5)	0	10 (2.7)	2 (1.5)	0	0
TACE	212 (26.5)	30 (16)	100 (26.8)	69 (52.3)	7 (8.1)	6 (29)
TARE	7 (1)	0	0	3 (2.3)	4 (5)	0
TKIs	63 (7.8)	0	3 (0.8)	9 (6.8)	50 (57)	1 (5)
Immunotherapy	6 (0.7)	0	2 (0.5)	2 (1.5)	2 (2)	0
Supportive care only	31 (4)	4 (2)	3 (0.8)	4 (3)	8 (9.3)	12 (57)
Treatments with curative intent[a]	479 (60)	153 (82)	265 (71.1)	45 (34.1)	16 (18.6)	0

[a]Liver transplantation, resection, TA, and combined treatment (resection+TA and TA + TACE).
Abbreviations: BCLC, Barcelona Clinic Liver Cancer; TA, thermal ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization; TKIs, tyrosine kinase inhibitors.

option"). Among the 71 patients with a "downward stage migration," 63 (89%) received a treatment with curative intent.

The suitability of the BCLC_2022 algorithm increased from 51% to 65% ($p = 0.02$) in BCLC B, mainly by a lower rate of "downward migration" (3% vs. 12%, $p = 0.005$). No significant differences were observed in the suitability of advanced stages of BCLC_2022 compared to the BCLC_2018 recommendations (Figure 2). Details on the suitability of the BCLC algorithm and treatment applied in patients with "upward stage migration" or "downward stage migration" are reported in Supplemental Table S1, http://links.lww.com/HC9/C50.

Evolution of the suitability of BCLC_2022 recommendations and "clinical decision-making" over time

According to the year of HCC diagnosis, patients were divided into cohort 1 (from 2006 to 2010, N = 330), cohort 2 (from 2011 to 2015, N = 269), and cohort 3 (from 2016 to 2022, N = 199). No significant differences in BCLC_2022 algorithm suitability were observed among the 3 cohorts, both in the whole population (72% vs. 70% vs. 65%, respectively; $p = 0.23$) and according to BCLC stage. In BCLC 0, throughout the 3 periods of time, the number of patients treated according to BCLC_2022 receiving one of the "first-choice option" was constantly high: 82% for cohort 1, 72% for cohort 2, and 81% for cohort 3; $p = 0.48$. As far as for BCLC A, a lower proportion of "first-choice treatment" was observed in cohort 2 only (69% for cohort 1, 45% in cohort 2, and 74% in cohort 3; $p < 0.001$), while an increase of "downward stage migrations" was observed along the years (14% in cohort 1, 21% in cohort 2, and 26% in cohort 3; $p = 0.04$), mainly with curative intent (91% in cohort 1, 92% in cohort 2, and 83% in cohort 3). In BCLC B, the "upward stage migration" progressively increased during the 3 periods of time (19%–38%–45%, $p = 0.02$), while no significant modifications were observed in BCLC C and D.

Response to first-line treatment and recurrence according to BCLC_2022 and "clinical decision-making"

After first-line treatment, 426 (53%) patients achieved a CR. Overall, CR was achieved in 276 (50%) patients who received a treatment according to the BCLC_2022 algorithm: 105 (77%) for BCLC 0, 155 (58%) for BCLC A, 15 (17%) for BCLC B, and 1 (2%) for BCLC C, respectively.

In BCLC 0, no differences were observed in achievement of CR, in patients treated with an "upward stage migration," while a "downward stage migration without curative intent" was associated to a lower proportion of CR as compared to patients treated according to BCLC_2022 (0% vs. 77%, $p = 0.003$) (Supplemental Table S2, http://links.lww.com/HC9/C50). In BCLC A, both "upward stage migration" and "downward stage migration with curative intent" were associated to a higher proportion of CR as compared to patients treated according to BCLC_2022 (76% vs. 58%, $p = 0.04$ and 79% vs. 58%, $p = 0.001$, respectively), while no patients undergoing a "downward stage migration without curative intent" achieved a CR (0% vs. 58%, $p = 0.001$). Moreover, both in BCLC 0 and A treated according to BCLC_2022, a CR was more

commonly achieved in those treated with first-choice treatments, compared to "lower priority options" (82% vs. 60%, $p = 0.01$, and 74% vs. 20%, $p < 0.001$, respectively) (Supplemental Table S2, http://links.lww.com/HC9/C50). In BCLC B and C patients, CR was more common in patients treated following an "upward stage migration" as compared to patients treated according to BCLC_2022 (52% vs. 17%, $p < 0.001$ and 41% vs. 2%, $p < 0.001$, respectively) (Supplemental Table S2, http://links.lww.com/HC9/C50).

Among the 426 patients who achieved CR to first-line treatment, 261 (61%) recurrence, corresponding to a recurrence rate at 1, 2, and 5 years of 22.4% (95% CI 18.5–26.9), 43.2% (95% CI 38.2–48.4), and 71.9% (95% CI 66.7–76.9), respectively. In the whole population, HCC recurrence was significantly higher in patients treated with an "upward stage migration" option, as compared to those treated according to the BCLC_2022 algorithm [at 1 year 32.8% (95% CI 22.3–46.5) vs. 21.3% (95% CI 16.8–26.9); at 2 years 58.2% (95% CI 45.4–71.5%) vs. 40.6% (95% CI 34.7–47.1); at 5 years 80.5% (95% CI 68.1–90.4) vs. 67.2% (60.7–73.6); $p = 0.02$] (Supplemental Figure S2, http://links.lww.com/HC9/C49). This subanalysis was repeated in each BCLC stage, except for BCLC C, due to the limited number of patients, and no differences between patients treated according to BCLC_2022 and those with an "upward stage migration" or "downward stage migration" were observed.

Survival according to BCLC_2022 and "clinical decision-making"

During a median follow-up of 32 (16–67) months, 499 (63%) patients died: 95 (51%) BCLC 0, 223 (60%) BCLC A, 91 (69%) BCLC B, 72 (83%) BCLC C, and 18 (95%) BCLC D. The corresponding OS was 48 months (IQR 24–104) for the whole cohort, with a cumulative survival rate at 1, 2, and 5 years of 88.3% (95% CI 85.9–90.4), 74.8% (71.4–77.8), and 43.2% (39.3–47.1), respectively. Survival rates at 1, 2, and 5 years according to the BCLC stage are presented in Figure 3.

In BCLC 0, no significant difference in terms of survival was observed between patients treated according to BCLC_2022 and patients with an "upward stage migration." Differently, patients with a "downward stage migration" receiving a treatment with curative intent had a longer OS as compared to patients treated according to BCLC_2022 [117 (80–NR) vs. 82 months (42–132), $p = 0.006$], while patients who did not receive a treatment with curative intent had a significantly shorter OS [6 mo (2–16), $p < 0.001$] (Figure 4A). Among patients treated according the BCLC_2022 recommendations, a shorter survival was observed in patients who received a "lower priority option" as compared to those being offered a first-choice one, even if the difference did not reach a statistical significance [61 (31–131) vs. 85 mo (44–132), $p = 0.35$].

In BCLC A, no significant difference in terms of survival was observed between patients treated according to BCLC_2022 and patients with an "upward stage

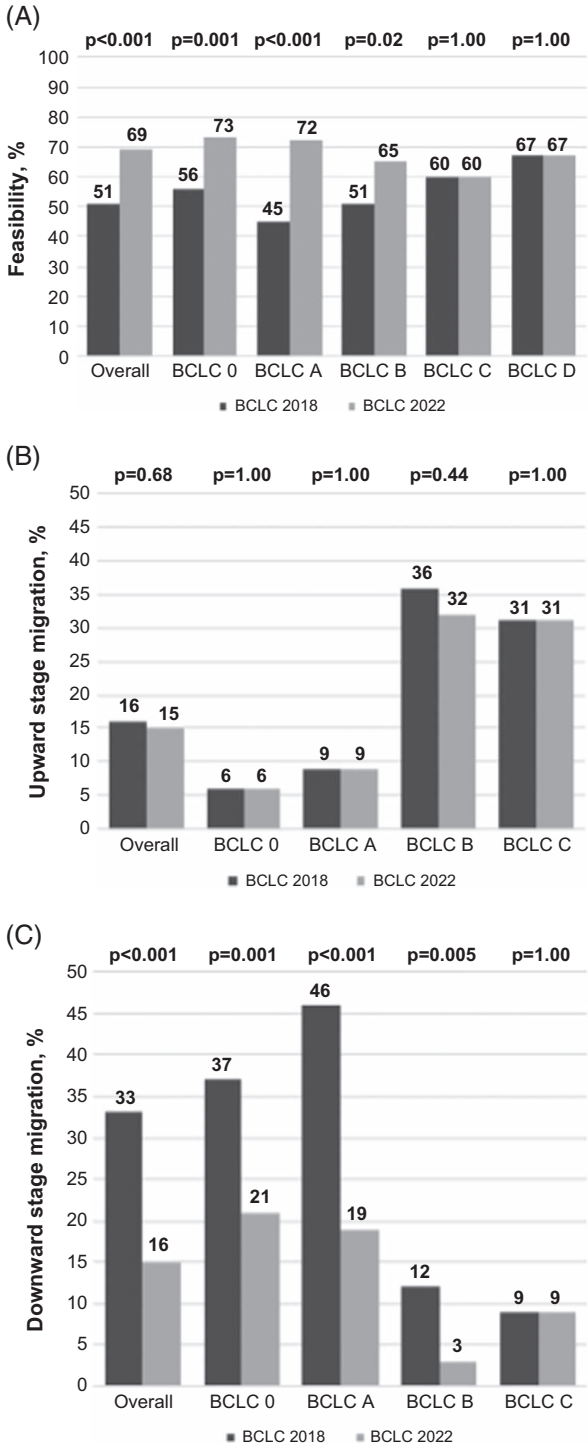


FIGURE 2 Suitability of BCLC_2022 recommendations for treatment allocation according to each stage, compared to BCLC_2018 recommendations. (A) Suitability; (B) "upward stage migration"; (C) "downward stage migration." Abbreviation: BCLC, Barcelona Clinic Liver Cancer.

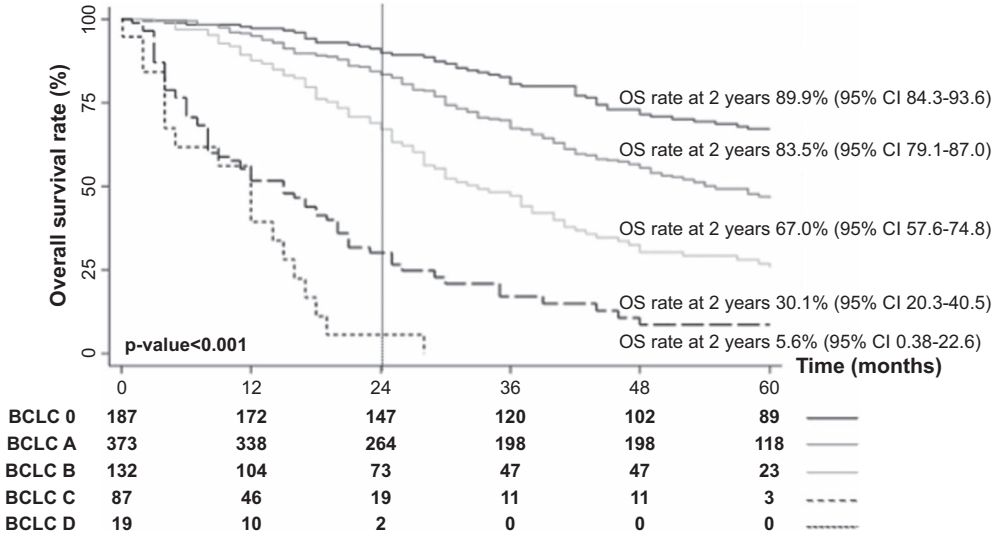


FIGURE 3 Overall survival rate stratified according to BCLC at HCC first diagnosis. Abbreviations: BCLC, Barcelona Clinic Liver Cancer; OS, overall survival.

migration" or a "downward stage migration" with or without curative intent (Figure 4B). Among patients treated according to the BCLC_2022 algorithm, those treated according to the "lower priority option" achieved a significantly shorter survival as compared to those being offered a first-choice one [33 (23–61) vs. 74 mo (42–137), $p < 0.001$] (Figure 4C).

In BCLC B patients, an "upward stage migration" was associated to a longer OS [63 mo (36–72) vs. 28 (18–44), $p = 0.003$], while a "downward stage migration" determined a shorter OS [13 (IQR 3–14) vs. 28 (18-44), $p < 0.001$] as compared to treatments adherent to BCLC_2022 (Figure 4D).

In BCLC C, an "upward stage migration" treatment was associated with a longer OS [21 mo (15–44) vs. 11 mo (4–25)] (Figure 4E).

Finally, in BCLC D patients, no difference in OS was observed between patients treated according to BCLC_2022 and those with an "upward stage migration."

Predictors of mortality

Variables significantly associated with mortality in univariate analysis are reported in Supplemental Table S3, http://links.lww.com/HC9/C50. The multivariable analysis is presented in Table 3. Independent baseline predictors of mortality included AFP values > 200 ng/mL, CPT C, a more advanced BCLC stage, and noncurative treatment for HCC. In a model including both baseline and time-dependent variables (Supplemental Table S4, http://links.lww.com/HC9/C50), radiological CR to first-line treatment was significantly associated with a lower mortality [HR 0.46 (95% CI 0.33–0.65), $p < 0.001$].

Independent predictors of mortality for each BCLC stage are presented in Table 3: in BCLC 0 age, higher AFP value, ALBI grade 3, and being treated either with a "lower priority option" or according to noncurative "downward stage migration"; in BCLC A age, CPT B, being treated either with a "lower priority option" or according to noncurative "downward stage migration"; in BCLC B higher creatinine values, AFP values > 200 ng/mL, treatment with TA; and finally in BCLC C AFP values > 200 ng/mL was the only independent predictor or mortality.

Predictors of HCC recurrence after achievement of CR to first-line treatment

Baseline variables significantly associated with HCC recurrence in univariate analysis are reported in Supplemental Table S5, http://links.lww.com/HC9/C50. In the multivariable model, the only predictor of recurrence was the first-line HCC treatment received, using LT as benchmark (resection HR 14.02, 95% CI 3.34–58.79, $p < 0.001$; TA HR 14.39, 95% CI 3.46–59.78, $p < 0.001$; TACE 21.93, 95% CI 5.18-–92.88, $p < 0.001$) (Table 4). In Table 4, the independent predictors of recurrence according to BCLC stage are also reported.

DISCUSSION

This study represents the first evaluation updated 2022 BCLC recommendation for the classification and treatment of HCC. We have shown an improvement flexibility in clinical practice of the new version of the BCLC algorithm (2022) and the positive impact of the clinical decision-making approach.

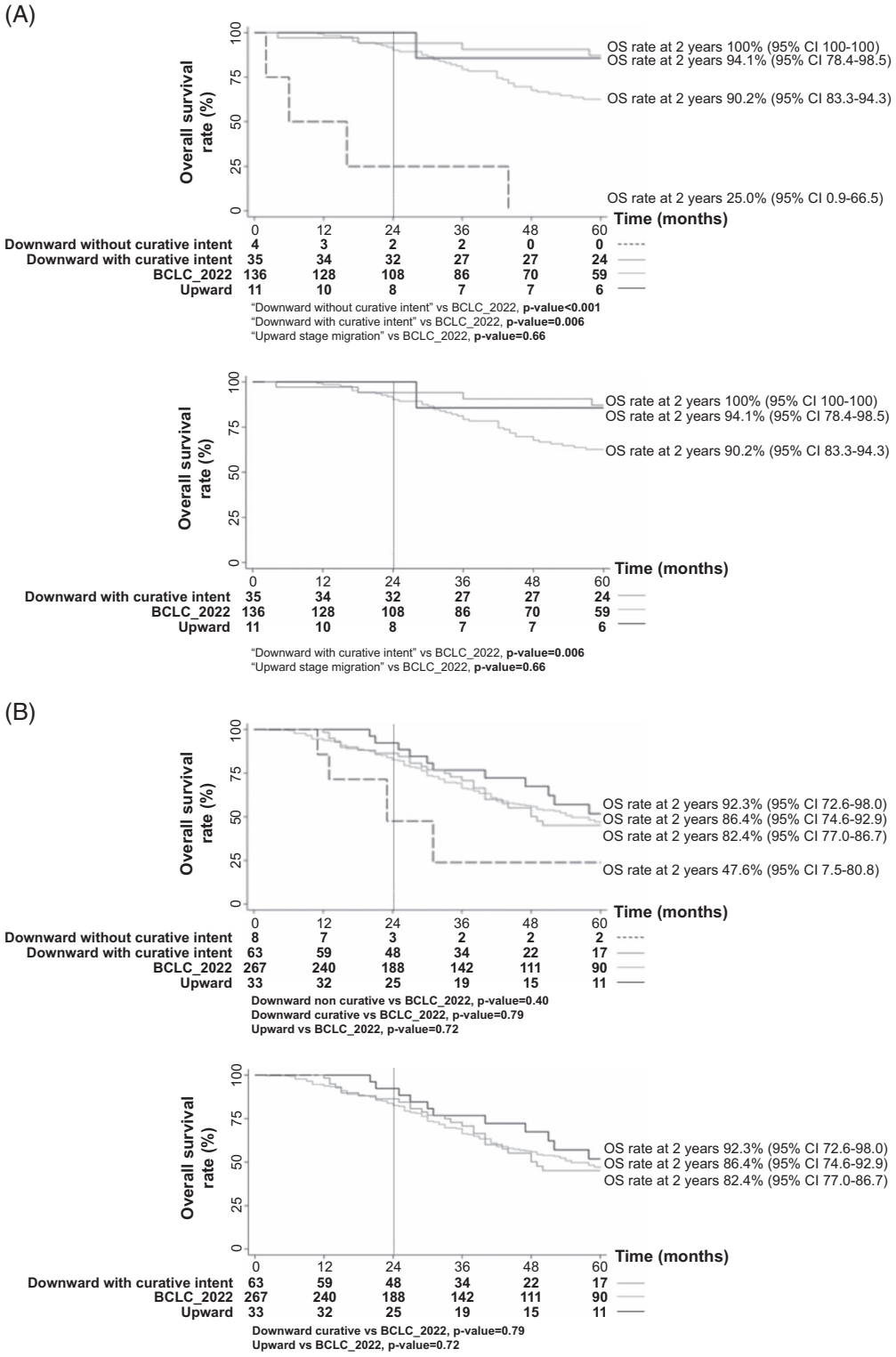


FIGURE 4 Overall survival rate stratified according to treatment allocation. (A) BCLC 0, BCLC_2022 recommendations versus "upward stage migration" versus "downward stage migration with curative intent" versus "downward stage migration without curative intent". (B) BCLC A, BCLC_2022 recommendations versus "upward stage migration" versus "downward stage migration with curative intent" versus "downward stage migration without curative intent". (C) BCLC A, BCLC_2022 recommendations first choice "lower priority options". (D) BCLC B, BCLC_2022 recommendations versus "upward stage migration" versus "downward stage migration". (E) BCLC C, BCLC_2022 recommendations versus "upward stage migration" versus "downward stage migration." Abbreviations: BCLC, Barcelona Clinic Liver Cancer; OS, overall survival.

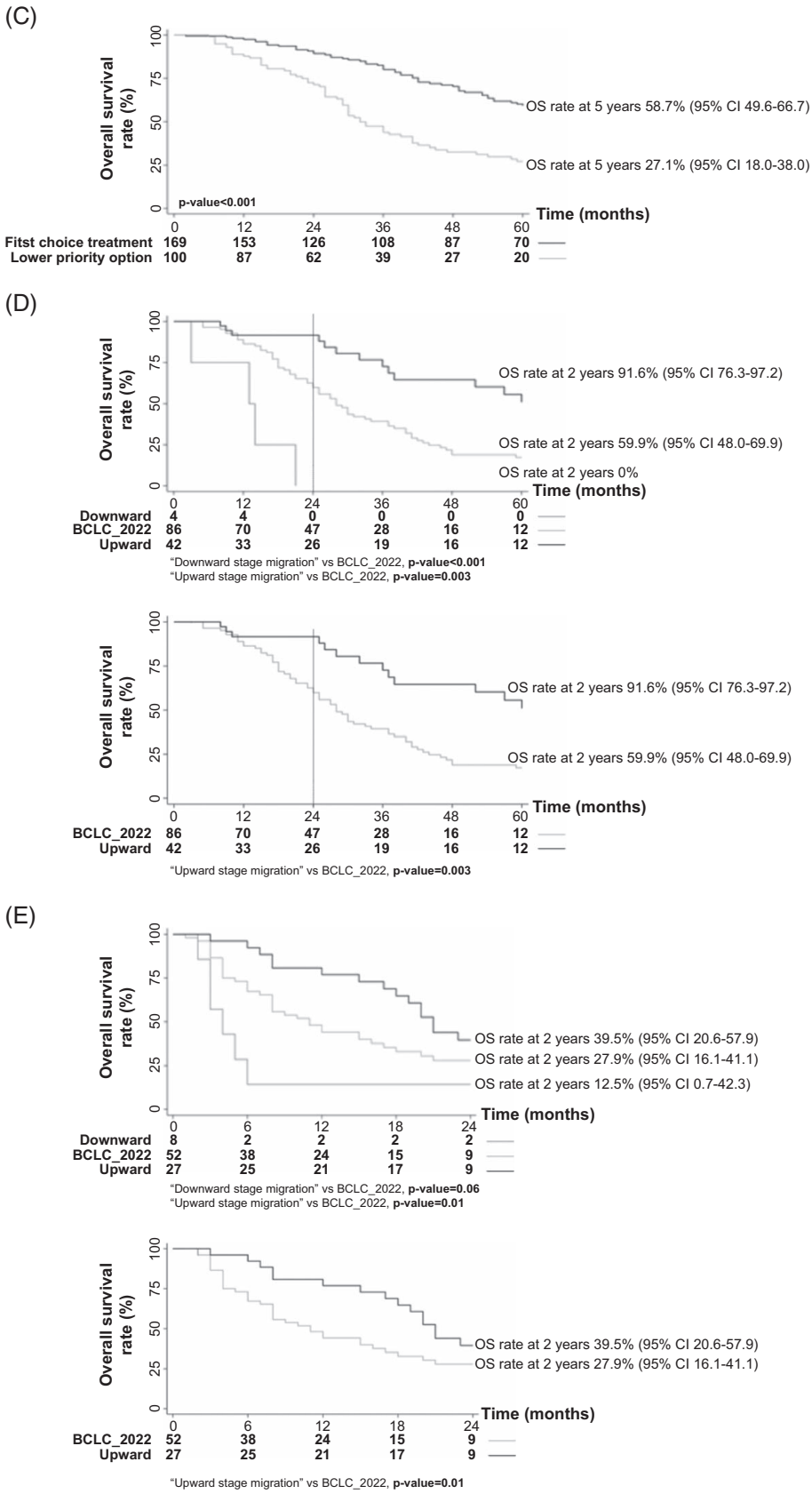


FIGURE 4B (Continued)

TABLE 3 Predictors of mortality at multivariable analysis, overall, and according to BCLC stage

	Total population (N = 798)		BCLC 0 (N = 186)		BCLC A (N = 373)		BCLC B (N = 132)		BCLC C (N = 87)	
Variable	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***
Age, y	1.03 (1.02–1.04)	< 0.001	1.07 (1.03–1.10)	< 0.001	1.03 (1.01–1.04)	< 0.001	1.01 (0.98–1.04)	0.50	0.98 (0.95–1.01)	0.15
Male gender							0.65 (0.37–1.14)	0.13		
Nonviral etiology	1.01 (0.78–1.31)	0.94								
Varices	1.39 (1.12–1.72)	0.002			1.35 (0.97–1.89)	0.07	1.52 (0.92–2.53)	0.10		
Creatinine, mg/dL	1.11 (1.05–1.18)	0.001					1.10 (1.02–1.19)	0.02		
Log AFP, ng/mL	Omitted for collinearity		1.24 (1.04–1.49)	0.02						
AFP > 200 ng/mL	1.82 (1.39–2.39)	< 0.001					2.30 (1.18–4.65)	0.01	2.09 (1.16–3.79)	0.01
CPT										
A	1 (base)				1 (base)				1 (base)	
B	1.19 (0.93–1.52)	0.17			1.59 (1.11–2.26)	0.01			0.76 (0.39–1.48)	0.41
C	3.04 (1.18–7.81)	0.02			4.73 (0.52–43.20)	0.17			-	-
ALBI grade	Omitted for collinearity									
1			1 (base)							
2			1.38 (0.82–2.31)	0.22						
3			9.27 (1.19–71.91)	0.03						
BCLC										
0	1 (base)									
A	1.49 (1.13–1.96)	0.004								
B	2.27 (1.57–3.29)	< 0.001	NA	NA	NA	NA	NA	NA		
C	5.39 (3.20–9.07)	< 0.001								
D	4.02 (1.44–11.16)	0.008								
Largest nodule's diameter, cm							1.01 (0.99–1.02)	0.21		

TABLE 3. (*continued*)

	Total population (N = 798)		BCLC 0 (N = 186)		BCLC A (N = 373)		BCLC B (N = 132)		BCLC C (N = 87)	
Variable	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***
BCLC_2022	1 (base)						1 (base)		1 (base)	
Downward stage migration	0.96 (0.68–1.35)	0.80	NA	NA	NA	NA	1.90 (0.16–22.72)	0.61	1.75 (0.69–4.44)	0.24
Upward stage migration	1.07 (0.73–1.56)	0.73					3.52^{-9} (4.05^{-10}–3.07^{-8})	< 0.001	1.83 (0.37–8.97)	0.46
BCLC_2022										
First choice			1 (base)		1 (base)					
Lower priority option			5.09 (1.24–20.85)	0.02	3.72 (1.30–10.66)	0.01				
Downward stage			43.73 (6.45–296.63)	< 0.001	14.08 (1.50–131.77)	0.02				
Migration noncurative	NA	NA					NA	NA		
Downward stage			0.80 (0.36–1.76)	0.57	1.48 (0.95–2.31)	0.08				
Migration curative										
Upward stage migration			2.80 (0.71–10.99)	0.14	1.02 (0.58–1.79)	0.95				
HCC treatment										
LT	1 (base)		1 (base)		1 (base)		1 (base)		1 (base)	
Resection	1.28 (0.61–2.71)	0.52	1.70 (0.38–7.55)	0.49	1.85 (0.63–5.43)	0.26	NA	NA	0.05	
TA	1.60 (0.79–3.23)	0.19	4.00 (0.98–16.38)	0.05	1.99 (0.71–5.60)	0.19	1.19^{8} (4.53^{7}–3.11^{8})	< 0.001	0.29 (0.01–0.50)	0.01
TACE	2.72 (1.34–5.53)	0.006	Omitt.[a]		Omitt.[a]		0.94 (0.12–7.24)	0.96	0.58 (0.05–1.83)	0.19
TARE	1.06 (0.13–8.93)	0.96	—		—		NA		0.23 (0.10–3.4)	0.55
Systemic treatment	2.74 (1.19–6.31)	0.02	—		NA		1.15 (0.13–10.12)	0.90	Omitt.[a](0.02–2.97)	0.26
BSC	6.18 (2.33–16.36)	< 0.001	Omitt.[a]		Omitt.[a]		Omitt.[a]		Omitt.[a]	

[a]Omitted for collinearity.

Abbreviations: AFP, alpha-fetoprotein; ALBI score, albumin–bilirubin score; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; CPT, Child–Pugh–Turcotte; LT, liver transplantation; TA, thermal ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

TABLE 4 Predictors of recurrence at multivariable analysis, overall, and according to BCLC stage

	Total population (N = 426)		BCLC 0 (N = 145)		BCLC A (N = 230)		BCLC B (N = 37)		BCLC C (N = 18)	
Variable	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***
Age, y	1.01 (0.99–1.03)	0.07	1.03 (0.99–1-06)	0.10	1.01 (0.99–1.03)	0.36				
Cirrhosis			0.41 (0.17–1.01)	0.05					NA	NA
Encephalopathy			1.54 (0.83–2.87)	0.17					NA	NA
Varices										
Albumin, g/dL	1.12 (0.86–1.46)	0.39								
Bilirubin, mg/dL							0.66 (0.35–1.27)	0.21		
Creatinine, mg/dL	1.53 (0.91–2.56)	0.11	2.32 (0.89–6.09)	0.08						
BCLC										
0	1 (base)									
A	1.09 (0.82–1.46)	0.54								
B	1.63 (0.94–2.82)	0.08	NA	NA	NA	NA	NA	NA	NA	NA
C	2.01 (0.72–5.58)	0.18								
D	4.58 (0.57–36.94)	0.15								
"Milan criteria" OUT	Omitted for collinearity		NA	NA	1.24 (0.75–2.05)	0.41	NA	NA	NA	NA
BCLC_2022	1 (base)									
Downward stage migration	1.13 (0.79–1.63)	0.49	NA	NA					NA	NA
Upward stage migration	1.37 (0.87–2.16)	0.17								
BCLC_2022										
First choice										
Lower priority option					1 (base) (3.18–62.82)	0.001				
Downward stage					14.12	—				
Migration noncurative										

TABLE 4. (*continued*)

	Total population (N = 426)		BCLC 0 (N = 145)		BCLC A (N = 230)		BCLC B (N = 37)		BCLC C (N = 18)	
Variable	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***	**HR 95% CI**	***p***
Downward stage					1.21 (0.78–1.89)	0.38				
Migration curative										
Upward stage migration					1.27 (0.73–2.21)	0.40				
HCC treatment										
LT	1 (base)		1 (base)		1 (base)		1 (base)		1 (base)	
Resection	14.02 (3.34–58.79)	< 0.001	11.90 (1.55–91.51)	< 0.001	7.18 (1.73–29.73)	0.007	1.19^{9} (3.34^{8}–4.26^{9})	< 0.001	820.83 (112.92–5966.89)	
TA	14.39 (3.46–59.87)	< 0.001	9.59 (1.26–72.69)	< 0.001	7.31 (1.74–30.55)	0.006	NA		NA	< 0.001
TACE	21.93 (5.18–92.88)	< 0.001	13.83 (1.74–109.63)	< 0.001	Omitted[a]	—	1.19^{9} (3.08^{8}–4.61^{9})	< 0.001	NA	
TARE	—	—	—		—				NA	
Systemic therapy	NA	NA	—		—				NA	
BSC	—	—	—		—				—	

[a]Omitted for collinearity.

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; LT, liver transplantation; TA, thermal ablation; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

For more than 20 years, the BCLC classification has been the standard for tumor classification and therapeutic management of patients with HCC, categorizing patients into 5 stages with different prognoses, and allocating treatment according to these stages based on the best available evidence.[3,4,23] In BCLC_2022, new features have been added compared to the previous version with the introduction of TARE in the algorithm, the extension of LT outside the Milan criteria (even in a subgroup of BCLC B patients if successful), the down-staging strategy, the use of laparoscopy for HCC resection, the division of stage B treatment options into 3 subgroups, and the introduction of new first-line systemic treatments for advanced HCC.[4,24] In addition, BCLC_2022 includes an expert clinical decision-making approach that allows personalized treatment based on patient and tumor characteristics as well as local expertise and technical availability. The latter includes the fundamental role of MDT, which has been formally established in our center since 2006, with weekly peer meetings to discuss all cases of HCC potentially amenable to treatment, including hepatologists, hepatobiliary and transplant surgeons, interventional radiologists, nuclear medicine physicians, and radiation oncologists for cases amenable to stereotactic body radiation. We recently implemented several key clinical quality performance indicators to promote the standardization of quality and efficiency of care in the routine management of our patients.[6] The role of MDT is evident from the proportion of patients whose first treatment was chosen outside the direct allocations of the BCLC (up or down in stage) or whenever the "lower priority option" was chosen according to BCLC_2022. This proportion, which ranges from 27% in BCLC 0 to 40% in BCLC C and represents 23% of the early stages in terms of "lower priority options," should not be considered as noncompliance, but rather as the proportion attributable to expert clinical decision-making, as we also have recently proposed in the multiparametric therapeutic hierarchy approach, provided that certain principles are made explicit.[4,7] When excluding first-line options for BCLC 0 and A patients, it is important to note that the expected survival rate will decrease with the "lower priority options." Our experience shows that OS decreased from 85 months (44–132) to 61 (31–131) in BCLC 0 and 74 months (42–137) to 33 (23–61) in BCLC A. Furthermore, for patients who were treated according to a "downward stage migration" in BCLC 0 and A and did not undergo treatment with curative intent, the median OS was 6 months (2–16) and 23 months (13–31), respectively. Based on this information, if "downward stage migration" to treatment without curative intent is inevitable for patients with HCC in BCLC 0/A, their survival may be reduced compared to what is expected for the corresponding stage. Similar considerations should be made for BCLC stages B and C. Since all these decisions translate into significant differences in survival, great efforts should be made to limit the number of patients receiving suboptimal treatments, and an effort must be made to identify and standardize the reasons why such a decision is taken, which, in our view, must be limited to the characteristics of the tumor (ie, location, relationship with vessels, or other organs) and the patient's condition with criteria that should be as standardized as possible.[7]

Another aspect that should be considered part of the clinical decision-making process of an expert MDT is the "upward stage migration," which might grant overall survival in selected patients. This is well-established in the literature, particularly in studies of intermediate stages, as we showed in our study, where more than 30% of patients benefited from an alternative, more curative treatment. The OS for these patients was 63 months compared with 28 months for patients treated according to BCLC_2022 recommendations for BCLC B stage.[4,5,7]

Furthermore, the proportion of patients with HCC in BCLC B treated in accordance to this "upward stage migration" concept has progressively increased over time, as demonstrated by dividing the population into 3 diagnosis periods (19%–38%–45%, $p = 0.02$), with a number of patients treated with resection, TA, and combination therapies. This progressive change in attitude by the MDT over time may have several explanations: on the one hand, the improvement of techniques and thus the extensibility of their application, but also the scientific evidence that has gradually matured with respect to this approach, such as the hierarchy of treatments proposed by Vitale et al.[25]

A CR was achieved in 77% of BCLC 0 and 58% of BCLC A patients treated in accordance with the 2022 recommendations. The success rate was affected by the MDT's clinical decision-making at the latter stage: both "upward stage migration" and "downward stage migration with curative intent" had a positive impact, while "downward stage migration without curative intent" and "lower priority options" had a negative impact. In BCLC B and C, CR treatment was more frequently obtained by the "upward stage migration" approach—whenever possible—in accordance with the clinical decision-making of the MDT.

Other secondary objectives of the study were to identify the predictors of OS and recurrence in our cohort. According to our findings, BCLC and AFP levels, severity of underlying cirrhosis (CPT and varices), and type of treatment received (noncurative) emerged as independent predictors of mortality. Going further into the details at the various stages, the type of treatment received ("lower priority option" and a noncurative "downward stage migration") was confirmed as an independent predictor of early-stage mortality, along with high AFP levels and more advanced underlying liver disease. In BCLC stage B, "upward stage

migration" emerges as an independent protective factor against mortality, similar to resection in BCLC C. These results highlight the relevance of stage in predicting prognosis, a crucial aspect that is pertinent not only for physicians but also for patients and their families. The established prognostic role of AFP is further reinforced by the finding that it emerges consistently throughout all stages of the disease, irrespective of treatment and treatment-related factors.

This study has limitations, as it is a single-center, retrospective study. Therefore, it reflects only the clinical experience of the local MDT. The composition of MDT has changed over the years, but its members have always tried to keep abreast of the available treatment options and related expertise. Several therapeutic options have been implemented in recent years, and this could be diluted by the enrolment time of our cohort, although the division into 3 study periods reassures us about the homogeneity of the data. The reproducibility of the information may be limited by the high number of patients in the early stages of the disease. This reflects the reality of a center where patients with advanced chronic liver disease undergo 6-monthly ultrasound surveillance. Finally, due to the retrospective nature of the study, we are not able to ascertain the role of patients' preferences in the decision-making process.

In conclusion, the results of our study demonstrated that the updated BCLC_2022 algorithm facilitated greater flexibility in clinical practice for first-line therapy of HCC, while also reinforcing the role of MDT in therapeutic decision-making. This highlights the potential benefits of "upward stage migration" as well as the limitations of "downward stage migration" or a "second-choice option" strategy. These findings reinforce the necessity of incorporating multiparametric evaluation in clinical practice to ensure the best treatment options for each patient.

DATA AVAILABILITY STATEMENT

Data are available by specific request to the corresponding author.

AUTHOR CONTRIBUTIONS

Massimo Iavarone conceived the study and wrote the article with Pietro Lampertico. Eleonora Alimenti made substantial contributions to the study design and analysis and contributed to the draft of the manuscript. Lorenzo Canova, Mariangela Bruccoleri, Barbara Antonelli, Anna Maria Ierardi, and Angelo Sangiovanni contributed to data collection and were actively involved in weekly discussions of cases in MDT. Giuseppe Cabibbo critically contributed to data analysis and interpretation. Annalisa De Silvestri performed the analysis. Lucio Caccamo, Gianpaolo Carrafiello, and Pietro Lampertico critically revised the manuscript. All the authors approved the final version of the manuscript.

FUNDING INFORMATION

This study was partly funded by "Ricerca Corrente" (RC2023/105_01).

CONFLICTS OF INTEREST

Massimo Iavarone participated in the advisory board and received speaker fees from Gilead Sciences, Bayer, AstraZeneca, Roche, Roche Diagnostics, EISAI, IPSEN, and MSD. Barbara Antonelli received speaker fees and travel grants from Chiesi SpA and Roche. Eleonora Alimenti received speaker fees from Roche and Gilead. Giuseppe Cabibbo participated in advisory boards and received speaker fees from Bayer, Eisai, Ipsen, AstraZeneca, MSD, Roche, and Gilead. Pietro Lampertico participated in the advisory board and received speaker fees for AbbVie, Aligos, Altona, Antios, Eiger, Gilead Sciences, GlaxoSmithKline, Grifols, Janssen, MYR, Roboscreen, Roche Pharma/Diagnostics, and Vir. The remaining authors have no conflicts to report.

ORCID

Massimo Iavarone https://orcid.org/0000–0003–3493–6504

REFERENCES

1. Llovet J, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis. 1999;19:329–38.
2. Forner A, Reig ME, Rodriguez de Lope C, Bruix J. Current strategy for staging and treatment: The BCLC update and future prospects. Semin Liver Dis. 2010;30:61–74.
3. Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet. 2018;391:1301–14.
4. Reig M, Forner A, Rimola J, Ferrer-Fàbrega J, Burrel M, Garcia-Criado Á, et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. J Hepatol. 2022;76:681–93.
5. Sangiovanni A, Triolo M, Iavarone M, Forzenigo LV, Nicolini A, Rossi G, et al. Multimodality treatment of hepatocellular carcinoma: How field practice complies with international recommendations. Liver Int. 2018;38:1624–34.
6. Iavarone M, Antonelli B, Ierardi AM, Topa M, Sangiovanni A, Gori A, et al. Reshape and secure HCC managing during COVID-19 pandemic: A single centre analysis of four periods in 2020 versus 2019. Liver Int. 2021;41:3028–32.
7. Vitale A, Cabibbo G, Iavarone M, Viganò L, Pinato DJ, Ponziani FR, et al. Personalised management of patients with hepatocellular carcinoma: A multiparametric therapeutic hierarchy concept. Lancet Oncol. 2023;24:e312–22.
8. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: Guidelines for reporting observational studies. Lancet. 2007;370:1453–7.
9. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646–9.
10. 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;5:649–55.

11. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepato-cellular carcinoma. Hepatology. 2005;42:1208–36.
12. Bruix J, Sherman M. Management of hepatocellular carcinoma, an update. Hepatology. 2011;53:1020–2.
13. European Association for the Study of the Liver; European Organization for Research and Treatment of Cancer. EASL–EORTC clinical practice guidelines: Management of hepato-cellular carcinoma. J Hepatol. 2012;56:908–43.
14. Heimbach JK, Kulik LM, Finn RS, Sirlin CB, Abecassis MM, Roberts LR, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology. 2018;67:358–80.
15. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018;69:182–236.
16. De A, Bhagat N, Mehta M, Taneja S, Duseja A. Metabolic dysfunction-associated steatotic liver disease (MASLD) definition is better than MAFLD criteria for lean patients with NAFLD. J Hepatol. 2024;80:e61–2.
17. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015;63: 971–1004.
18. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67:145–72.
19. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. Hepatology. 1996;24:289–93.
20. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33:464–70.
21. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL, et al. Assessment of liver function in patients with hepatocellular carcinoma: A new evidence-based approach—The ALBI grade. J Clin Oncol. 2015;33:550–8.
22. de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Abraldes JG, et al; Baveno VII Faculty. Baveno VII—Renewing consensus in portal hypertension. J Hepatol. 2022;76:959–74.
23. Sidali S, Trépo E, Sutter O, Nault JC. New concepts in the treatment of hepatocellular carcinoma. United European Gastro-enterol J. 2022;10:765–74.
24. Mazzaferro V, Citterio D, Bhoori S, Bongini M, Miceli R, De Carlis L, et al. Liver transplantation in hepatocellular carcinoma after tumour downstaging (XXL): A randomised, controlled, phase 2b/3 trial. Lancet Oncol. 2020;21:947–56.
25. Vitale A, Farinati F, Pawlik TM, Frigo AC, Giannini EG, Napoli L, et al. The concept of therapeutic hierarchy for patients with hepatocellular carcinoma: A multicenter cohort study. Liver Int. 2019;39:1478–89.

How to cite this article: Iavarone M, Alimenti E, Canova L, Bruccoleri M, Antonelli B, Ierardi AM, et al. The impact of BCLC recommendations on survival for patients with hepatocellular carcinoma. Hepatol Commun. 2025;9:e0750. https://doi.org/10.1097/HC9.0000000000000750