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Original article

Real-world BCLC adherence and survival in hepatocellular carcinoma: first prospective study from Central America

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ABSTRACT

Introduction and Objectives: Hepatocellular carcinoma (HCC) is a major global health concern. The Barcelona Clinic Liver Cancer (BCLC) staging system provides evidence-based therapeutic guidance, yet real-world adherence remains suboptimal, particularly in underrepresented regions. This study aimed to evaluate adherence to 2022 BCLC first-line treatment recommendations and associated survival outcomes in a prospective cohort from Costa Rica, the first such study in Central America.

Patients and Methods: A total of 260 patients diagnosed with HCC between September 2018, and June 2024 were prospectively enrolled at a national liver transplant center. Clinical, tumor, and treatment characteristics were recorded. Adherence was defined as concordance with BCLC stage-specific first-line recommendations. Survival and predictors of adherence were analyzed using Kaplan–Meier curves and multivariate logistic regression.

Results: Overall adherence to BCLC first-line recommendations was 47.8 %, varying by stage: 44.9 % (BCLC 0/A), 53.7 % (B), 23.1 % (C), and 93.5 % (D) ($p < 0.001$). Adherent patients had significantly longer median survival (722 vs. 535 days; $p = 0.001$). Adherence conferred survival benefit in BCLC 0/A (1404 vs. 807 days; $p = 0.005$) and C (492 vs. 168 days; $p = 0.029$). Child-Pugh B/C (aOR: 3.82; $p < 0.001$) and ECOG > 0 (aOR: 5.04; $p = 0.022$) were associated with adherence, while stages B, C, and D were inversely associated.

Conclusions: Adherence to BCLC guidelines significantly improves survival in HCC, especially in early and advanced stages. Functional status and liver disease severity were key adherence predictors. Targeted strategies are needed to improve guideline implementation in Central America and other resource-limited settings.

1. Introduction

Liver cancer is the sixth most common malignancy and the third leading cause of cancer-related death worldwide, with hepatocellular carcinoma (HCC) accounting for nearly 90 % of all primary liver cancers [1]. The burden of HCC is particularly significant in low- and middle-income countries, where surveillance programs and access to early treatment remain limited.

Accurate staging of HCC is essential to guide therapeutic decision-making, estimate prognosis, and facilitate standardized comparisons across populations. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely endorsed algorithm by Western hepatology societies, including the AASLD and EASL, and integrates liver function, tumor burden, and patient performance status to assign treatment recommendations across five stages (0, A, B, C, D) [2,3].

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALD, alcohol-related liver disease; aOR, adjusted odds ratio; BCLC, Barcelona Clinic Liver Cancer; BSC, best supportive care; cTACE, conventional transarterial chemoembolization; CT, computed tomography; DDLT, deceased donor liver transplantation; EASL, European Association for the Study of the Liver; ECOG, Eastern Cooperative Oncology Group; FIB-4, Fibrosis-4 index; HCC, hepatocellular carcinoma; LT, liver transplantation; MASLD, metabolic dysfunction-associated steatotic liver disease; MDT, multidisciplinary tumor board; MELD, Model for End-stage Liver Disease; MetALD, metabolic and alcohol-related liver disease; MRI, magnetic resonance imaging; MS, metabolic syndrome; OR, odds ratio; OS, overall survival; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; SD, standard deviation; SPSS, Statistical Package for the Social Sciences; TAE, bland transarterial embolization; TSM, treatment stage migration; UCSF, University of California San Francisco

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Recent updates to the BCLC framework in 2022 introduced refinements such as subclassification of BCLC-B, incorporation of treatment stage migration (TSM), and emphasis on a personalized, multidisciplinary approach to care [2–4]. Despite its broad acceptance, real-world adherence to BCLC recommendations remains variable, with rates ranging from 25 % to 60 % in heterogeneous populations [5–7]. Factors influencing adherence may include institutional capacity, regional treatment availability, and the complexity of patient presentation.

To date, data from Central America are scarce, and no study has evaluated adherence to the 2022 BCLC system in this region. Understanding how the algorithm performs in underrepresented populations is critical for identifying barriers to care and designing context-specific strategies for improvement.

This study aims to describe treatment adherence according to the updated BCLC algorithm and its impact on survival outcomes in a cohort of HCC patients treated at a liver transplant center in Costa Rica—the first such analysis from Central America.

2. Patients and Methods

2.1. Study design

This prospective observational cohort study included all adult patients diagnosed with hepatocellular carcinoma (HCC), or referred for its management, between September 2018 and June 2024 at a national liver transplant (LT) center in San José, Costa Rica. Eligible patients were consecutively enrolled and followed prospectively. Clinical and imaging data were extracted from electronic medical records and reviewed by trained researchers. All data were anonymized prior to analysis. Cases with incomplete or inconsistent information were independently reassessed, and those with missing critical variables were excluded.

2.2. Cohort characteristics and study variables

Inclusion criteria comprised patients aged ≥18 years with a new diagnosis of HCC, established according to international guidelines using either radiological hallmarks (contrast-enhanced CT or MRI) or histopathological confirmation where necessary [2,3]. Baseline data collected included demographics, Eastern Cooperative Oncology Group performance status (ECOG-PS), etiology of liver disease, cancer-related symptoms, and comprehensive hepatic function evaluation: history of decompensation, portal hypertension (esophageal varices, ascites, collaterals), Child–Pugh classification, MELD and MELD 3.0 scores, Albumin-Bilirubin (ALBI) grade, and Fibrosis-4 (FIB-4) index. Documented comorbidities included obesity, diabetes mellitus, metabolic sindrome (MS), cardiovascular disease, chronic pulmonary or renal disease, and non-hepatic malignancies. Alpha-fetoprotein (AFP) levels and tumor burden variables (number, size, vascular invasion, and extrahepatic spread) were also recorded.

Patients were staged according to the 2022 version of the Barcelona Clinic Liver Cancer (BCLC) classification [4]. A multidisciplinary tumor board (MDT)—consisting of hepatologists, liver transplant surgeons, oncologists, interventional and diagnostic radiologists, pathologists, and primary care physicians—reviewed each case at diagnosis and during relevant clinical inflection points. All therapeutic decisions were MDT-guided, and written informed consent was obtained prior to initiating any treatment, in accordance with institutional policies.

2.3. Therapeutic strategies and definitions

Treatment modalities included local ablation (radiofrequency or microwave ablation), percutaneous ethanol injection (PEI), surgical resection, liver transplantation (LT), bland transarterial embolization (TAE), conventional transarterial chemoembolization (cTACE), systemic therapy (sorafenib or atezolizumab–bevacizumab—the latter available from August 2022 onward), and best supportive care (BSC). According to national regulations, LT eligibility criteria included age under 65 years, absence of contraindications, and tumor burden within the Milan criteria. Patients meeting the University of California San Francisco (UCSF) criteria (i.e., ≤1 lesion ≤6.5 cm, or ≤3 lesions with none >4.5 cm and total tumor diameter ≤8 cm) were also considered for LT if successfully downstaged to Milan criteria. Select patients in BCLC-B or BCLC-D stages were considered for LT as first-line therapy when criteria were met, based on multidisciplinary team (MDT) discretion.

2.4. Study outcomes

The primary outcome was overall survival (OS), stratified by adherence to first-line BCLC treatment recommendations. Secondary outcomes included adherence rates, characterization of the cohort's epidemiological and tumor-related features, analysis of MDT-based treatment decisions, and description of diagnostic and screening practices. OS was calculated from the date of diagnosis until death or last follow-up. Follow-up was censored on June 30, 2024.

2.5. Statistical analysis

Descriptive statistics were used to summarize baseline characteristics. Categorical variables were expressed as frequencies and percentages, and continuous variables were reported as means with standard deviations or medians with interquartile ranges, depending on distribution.

To evaluate predictors of adherence to BCLC recommendations, binary logistic regression was employed using adherence as the dependent variable (1 = adherent, 0 = non-adherent). Variables with $p < 0.20$ in univariate analysis and those of clinical relevance were entered into a multivariate model. Odds ratios (ORs) with 95 % confidence intervals (CIs) were calculated, with statistical significance defined as $p < 0.05$.

For survival analysis, Kaplan–Meier estimates were used to evaluate differences in OS between adherent and non-adherent groups. Differences were assessed using the log-rank test. Survival curves were additionally stratified by BCLC stage (0/A, B, C, D). Statistical analyses were performed using SPSS version 28.0 (IBM Corp., Armonk, NY, USA).

2.6. Ethical considerations

Although patients were prospectively enrolled and followed, data analysis was performed retrospectively using anonymized records, which justified the waiver of formal informed consent under national regulations. This study was conducted in accordance with institutional policies for the secondary use of anonymized clinical data. Given the retrospective nature of the analysis and the absence of any direct intervention or patient contact, formal ethics committee approval and informed consent were waived in line with national regulations. The study complies with the principles of the Declaration of Helsinki and relevant data protection legislation, including Costa Rica's Law 8968 on Protection of Individuals Regarding the Processing of their Personal Data.

3. Results

3.1. Baseline patient characteristics

A total of 260 patients were included in the study. Baseline characteristics are presented in Table 1. The mean age was 67 years, and 38.5 % (n = 100) were female. Most patients (95 %, n = 246) met at least one criterion for MS, and 54.6 % (n = 142) met full diagnostic

Table 1
Baseline clinical and demographic characteristics of the study cohort.

Variable	Value
Age (mean ± SD) (years)	67 ± 10
Sex (female) [n (%)]	100 (38.5)
Comorbidities [n (%)]	
Overweight	111 (42.7)
Obesity G1	65 (25)
Obesity G2	18 (6.9)
Morbid Obesity	4 (1.5)
High blood pressure	178 (68.5)
Glucose intolerance or Diabetes Mellitus	158 (60.8)
Dyslipidemia	103 (39.7)
Metabolic syndrome	142 (54.6)
Harmful drinking	87 (33.5)
Non-hepatic cancer	22 (8.5)
Noncirrhotic liver [n (%)]	19 (7.3)
FIB4 F3 >2.67 [n (%)]	205 (78.8)
Etiology of liver disease [n (%)]	
MASLD	138 (53.1)
Alcohol	55 (21.2)
MetALD	28 (10.8)
Hepatitis B virus	12 (4.6)
Hepatitis C virus	7 (2.7)
Autoimmune	4 (1.5)
Wilson's Disease	3 (1.2)
Cholestatic	2 (0.8)
Hereditary haemochromatosis	2 (0.8)
Cryptogenic	9 (3.5)
Child−Pugh A/B/C [n (%)]	146 (60.6)/ 80 (33.2)/ 15 (6.2)
Esophageal varices or collaterals [n (%)]	175 (67.3)
Decompensated [n (%)]	88 (33.8)
Ascites or medication	75 (28.8)
Encephalopathy	24 (9.2)
Elevated bilirubin ≥2/≥5 mg/dL	69 (24.5)/ 11 (4.2)
MELD Score 3.0 < 15/ ≥15 [n (%)]	174 (66.9)/ 86 (33.1)
ALBI score 1/2/3 [n (%)]	47 (18.1)/ 172 (66.2)/ 41 (15.8)
Detection under screening (US, CT/MRI) [n (%)]	113 (43.5)
ECOG 0/1/2/>2 [n (%)]	193 (74.2)/ 50 (19.2)/ 9 (3.5)/ 7 (2.7)
Number of nodules 1/2/3/>3 [n (%)]	165 (63.8)/ 50 (19.2)/ 15 (5.8)/ 29 (11.2)
Vascular invasion [n (%)]	19 (7.3)
Extrahepatic spread [n (%)]	31 (11.9)
BCLC Stage 0/ A/ B (B1, B2, B3)/ C/ D [n (%)]	5 (1.9)/127 (48.8)/ 44 (18 (6.9)/6 (2.3)/ 20 (7.7))/ 53 (20.4)/ 31 (11.9)
Within Milan criteria [n (%)]	121 (46.5)
Within UCSF criteria [n (%)]	148 (56.9)
Serum AFP ≥20/ ≥400/≥1000 ng/mL [n (%)]	110 (42.3)/ 55 (21.2)/ 41 (15.8)
First-line treatment according to BCLC [n (%)]	120/251 (47.8)
Stage 0 [n (%)]	4/5 (80)
Stage A [n (%)]	53/122 (43.4)
Stage B: B1, B2, B3 [n (%)]	22/41 (53.7): 15/18 (83.3), 3/6 (50), 4/17 (23.5)
Stage C [n (%)]	12/52 (23.1)
Stage D [n (%)]	29/31 (93.5)
Missing patients [n (%)]	9 (3.5)
Within LT criteria at diagnosis [n (%)]	52 (20)

Abbreviations: SD, standard deviation; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic-associated and alcohol-related liver disease; FIB4, fibrosis-4 score; MELD, Model for End-stage Liver Disease; ALBI, albumin-bilirubin grade; US, ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group performance status; BCLC, Barcelona Clinic Liver Cancer staging system; AFP, alpha-fetoprotein; LT, liver transplantation; UCSF, University of California, San Francisco.

criteria, being most prevalent in early stages (65 % in BCLC 0/A) and less frequent in advanced disease (48 % in BCLC D) (Table 2).

Cirrhosis was present in 92.7 % of the cohort. The most frequent etiologies of liver disease were metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic and alcohol related/associated liver disease (MetALD) and alcohol-related liver disease (ALD), comprising 85 % (n = 221) of all cases. Notably, 7.3 % (n = 19) were diagnosed with HCC in the absence of cirrhosis, with MASLD accounting for 74 % of these.

3.2. Tumor detection and staging

A 90.5 % increase in annual HCC diagnoses was observed over the study period, rising from 21 new cases in 2017−2018 to 40 in 2023−2024. Screening programs led to diagnosis in 43.5 % of patients (n = 113).

Ultrasound detected hepatic lesions in 90.4 % of cases (n = 236), with 40.7 % performed during surveillance. In 8.5 % (n = 22), CT or MRI was the initial study, of which 63 % were screening-driven. The mean interval between initial ultrasound and confirmatory imaging was 70 days (SD: 117). CT was used in 83.1 % (n = 217), MRI in 12.3 % (n = 32), and liver biopsy was required in 4.6 % (n = 12). Serum AFP was ≥20 IU/mL in 42.1 % (n = 110) and ≥400 IU/mL in 21.2 % (n = 55).

At diagnosis, 63.8 % (n = 165) had a single nodule. Liver function indicators worsened with stage: Child-Pugh A was present in 74 % of BCLC 0/A patients but only 19 % in stage D ($p < 0.001$). Similarly, MELD <15 decreased significantly across stages (from 78 % to 29 %, $p < 0.001$). ALBI grade 1 was observed in only 18.1 % overall, and

Table 2
Selected Baseline Clinical, Demographic, and Tumor Characteristics of HCC Patients by BCLC Stage (n = 260).

Category / Variable	N = 251	BCLC 0/A (n = 127)	BCLC B (n = 41)	BCLC C (n = 52)	BCLC D (n = 31)	p-value*
Age, mean (SD)	67.1	67 (9.8)	66.8 (7.3)	67.7 (12.8)	67 (11.5)	0.209
Female sex, n (%)	99	53 (42 %)	15 (37 %)	16 (31 %)	15 (48 %)	0.377
Metabolic syndrome, n (%)	138	82 (65 %)	21 (51 %)	20 (38 %)	15 (48 %)	0.011
Cirrhosis, n (%)	233	117 (92 %)	39 (95 %)	47 (90 %)	30 (97 %)	0.657
MASLD, n (%)	160	89 (70 %)	26 (63 %)	30 (58 %)	15 (48 %)	0.103
ALD, n (%)	85	39 (31 %)	16 (39 %)	17 (33 %)	13 (42 %)	0.575
Diagnosis via surveillance, n (%)	109	65 (51 %)	19 (46 %)	11 (21 %)	14 (45 %)	0.003
Child-Pugh A, n (%)	160	94 (74 %)	29 (71 %)	31 (60 %)	6 (19 %)	<0.001
Esophageal varices, n (%)	169	80 (63 %)	28 (68 %)	36 (69 %)	25 (81 %)	0.297
MELD 3.0 < 15, n (%)	167	99 (78 %)	27 (66 %)	32 (62 %)	9 (29 %)	<0.001
ECOG 0, n (%)	185	127 (100 %)	36 (88 %)	11 (21 %)	11 (35 %)	<0.001
ALBI grade 1, n (%)	44	33 (26 %)	5 (12 %)	5 (10 %)	1 (3 %)	0.003
Single lesion, n (%)	162	116 (91 %)	0 (0 %)	27 (52 %)	19 (61 %)	<0.001
Vascular invasion, n (%)	19	0 (0 %)	0 (0 %)	19 (37 %)	0 (0 %)	<0.001
Extrahepatic spread, n (%)	31	0 (0 %)	0 (0 %)	28 (54 %)	3 (10 %)	<0.001
AFP ≥20 IU/mL, n (%)	108	45 (35 %)	10 (24 %)	37 (71 %)	16 (52 %)	<0.001
Within Milan criteria, n (%)	117	91 (72 %)	9 (22 %)	4 (8 %)	13 (42 %)	<0.001
Eligible for LT, n (%)	52	42 (33 %)	6 (15 %)	0 (0 %)	4 (13 %)	<0.001
BCLC guideline adherence, n (%)	120	57 (45 %)	22 (54 %)	12 (23 %)	29 (94 %)	<0.001

* P-values calculated using one-way ANOVA for continuous variables and chi-square test for categorical variables. Abbreviations: SD, standard deviation; MASLD, metabolic dysfunction-associated steatotic liver disease; ALD, alcohol-related liver disease; MELD, Model for End-Stage Liver Disease; ECOG, Eastern Cooperative Oncology Group; ALBI, Albumin-Bilirubin; AFP, alpha-fetoprotein; LT, liver transplantation.

decreased with disease progression (p = 0.003). Baseline ECOG performance status was available for all patients: ECOG 0 (74.2 %), ECOG 1 (19.2 %), ECOG 2 (3.5 %), and ECOG >2 (2.7 %). The proportion of patients with ECOG ≥ 1 increased significantly with advancing BCLC stage (p < 0.001), indicating declining performance status. Esophageal varices were present in 67.3 % (n = 175).

BCLC staging was as follows: 0 in 5 (1.9 %), A in 127 (48.8 %), B in 44 (16.9 %), C in 53 (20.4 %), and D in 31 (11.9 %). Among BCLC-B cases, 18 were B1 (6.9 %), 6 B2 (2.3 %), and 20 B3 (7.7 %). Milan criteria were met in 46.5 % (n = 121), UCSF in 56.9 % (n = 148), and 20 % (n = 52) were transplant-eligible at diagnosis.

3.3. Adherence to treatment by BCLC stage

After excluding nine patients lost before treatment decision, 47.8 % (n = 120) received BCLC-consistent first-line therapy. The median time from imaging to treatment initiation was 47 days (SD: 27). Overall, 26.3 % received curative treatment: surgical resection (n = 21, 8.4 %), RFA (n = 40, 16 %), or LT (n = 5, 2 %). TAE/TACE was most common (n = 99, 39.4 %), followed by systemic therapy (n = 18, 7.0 %); 25 % (n = 62) received no HCC-specific therapy (Fig. 1).

Adherence rates by stage: 0/A: 44.9 %, B: 53.7 %, C: 23.1 %, D: 93.5 %. A chi-square test showed significant association between

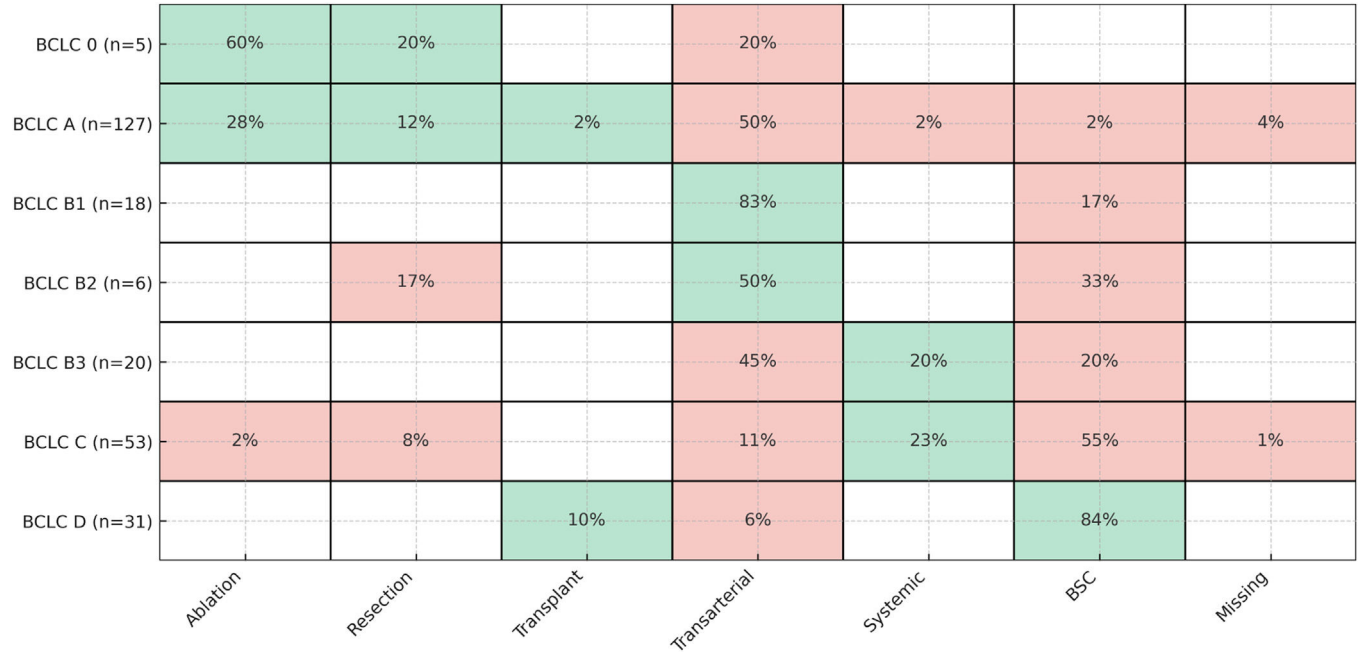


Fig. 1. Distribution of first-line treatments according to BCLC stage. Green boxes represent treatments consistent with BCLC recommendations, while orange boxes indicate non-adherent treatments. Values indicate the percentage of patients within each BCLC stage receiving each treatment. Abbreviations: BSC = Best Supportive Care; BCLC = Barcelona Clinic Liver Cancer.

stage and adherence (χ^2 = 39.74, df = 3, $p < 0.001$). The main reasons for non-adherence were systematically reviewed by the multidisciplinary tumor board and varied according to BCLC stage. In early stages (0/A), deviations were mainly due to lesions not suitable for ablative therapy based on interventional radiology assessment, leading to treatment migration toward transarterial approaches. Additionally, some patients fulfilled tumor burden criteria for liver transplantation but were excluded due to regulatory restrictions, such as age >65 years or social contraindications. In BCLC-B, non-adherence was observed in patients deemed unsuitable for TAE/TACE because of extensive tumor burden (e.g., bilobar involvement with multiple LI-RADS 3 accessory nodules) or insufficient hepatic reserve (e.g., bilirubin >2 mg/dL, ALBI grade ≥2). In BCLC—C, the predominant barrier was restricted access to systemic therapy: atezolizumab −bevacizumab became available only after August 2022 under a simplified medical indication, whereas sorafenib previously required central pharmacotherapy committee approval, typically causing delays of 2−3 months. Importantly, although adherence in this study was defined strictly as receipt of stage-specific first-line therapy, most non-adherent patients still received alternative treatments. Among 112 patients who underwent a second-line approach, 54.5 % (n = 61) ultimately received therapies consistent with guideline intent, underscoring the importance of flexible decision-making within the 2022 BCLC framework. Among 112 patients who received second-line therapy, 54.5 % (n = 61) remained adherent. The median interval between treatments was 217 days (SD: 305).

3.4. Liver transplant candidates and bridging therapy

According to Costa Rican legislation (age < 65 years, UCSF eligibility, and absence of contraindications), 20 % (n = 52) of patients qualified for LT. Of these, 86.5 % (n = 45) received bridging therapy—transarterial embolization (TAE/TACE, n = 27), percutaneous ablation (n = 18), or surgical resection (n = 2). Additionally, one patient was downstaged to become eligible for LT.

Among the 53 transplant candidates identified, 30.2 % (n = 16) progressed or died before being listed, 11.3 % (n = 6) remained stable under alternative treatments, 3.8 % (n = 2) were still awaiting LT at the time of analysis, 45 % (n = 24) successfully underwent transplantation, and 9.4 % (n = 5) either dropped out or died while on the waiting list. The mean wait time was 148.1 ± 93.5 days (Fig. 2).

Notably, expanding the age eligibility criterion to < 70 years would add 27 additional candidates, representing a 49 % increase over the current < 65 years threshold.

3.5. Predictors of adherence to BCLC

Univariate and multivariate logistic regression analyses are summarized in Table 3. In the multivariate logistic regression analysis evaluating factors associated with adherence to BCLC-recommended treatment, several variables showed significant associations.

Child-Pugh class B or C and ECOG performance status > 0 were more frequently observed among patients who received guideline-concordant therapy. In the adjusted model, both factors were significantly associated with being in the adherent group, although their odds ratios were <1 due to the coding of the dependent variable (1 = non-adherent, 0 = adherent).

Specifically, Child-Pugh B/C had an adjusted OR of 0.21 (95 % CI: 0.09−0.49; $p < 0.001$), and ECOG >0 had an adjusted OR of 0.22 (95 % CI: 0.06−0.89; p = 0.037), indicating that patients with worse liver function or performance status were more likely to be managed in alignment with guideline recommendations.

A strong inverse association was observed between BCLC stage and adherence. Compared to patients with BCLC stage 0/A, those with BCLC stage B had a markedly lower likelihood of adherence (adjusted OR: 0.008; 95 % CI: 0.001−0.06; $p < 0.001$), as did patients with BCLC stage C (adjusted OR: 0.012; 95 % CI: 0.001−0.05; $p < 0.001$) and stage D (adjusted OR: 0.006; 95 % CI: 0.001−0.05; $p < 0.001$).

While other variables such as AFP ≥1000 ng/mL (adjusted OR: 0.75; 95 % CI: 0.55−1.02; p = 0.076) and MASLD (adjusted OR: 0.70; 95 % CI: 0.35−1.40; p = 0.305) showed trends toward reduced adherence, these associations did not reach statistical significance. Similarly, vascular invasion and extrahepatic spread were not significantly associated with adherence after adjustment. No significant associations were observed for age, sex, metabolic syndrome, MELD ≥15, or detection through screening in the adjusted analysis.

A multivariate logistic regression model was constructed, including only those variables that showed a univariate association with a p-value < 0.20. To improve interpretability, the final multivariate logistic regression model was restructured so that the dependent variable was coded as 1 = adherent and 0 = non-adherent. This change

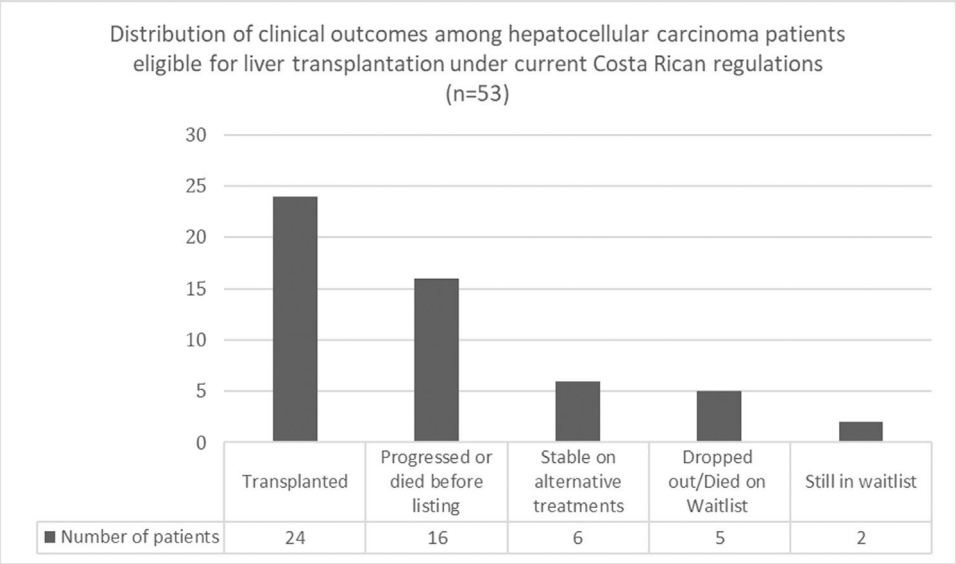


Fig. 2. Outcomes of Liver Transplant Candidates (n = 53). Distribution of clinical outcomes among hepatocellular carcinoma patients eligible for liver transplantation under current Costa Rican regulations (age <65, UCSF criteria).

Table 3
Multivariate Logistic Regression Analysis.

Variable	Unadjusted OR (95 % CI)	p (unadjusted)	Adjusted OR (95 % CI)	p (adjusted)
Age ≥70 years	1.04 (0.70–1.56)	.844	1.11 (0.59–2.09)	.753
Female	1.13 (0.62–2.03)	.731	0.79 (0.42–1.50)	.471
Metabolic syndrome	0.76 (0.44–1.32)	.450	0.80 (0.42–1.53)	.495
Cirrhosis	0.75 (0.22–2.50)	.495	0.78 (0.24–2.54)	.681
MASLD	0.57 (0.29–1.13)	.088	0.70 (0.35–1.40)	.305
Child-Pugh B or C	0.22 (0.09–0.53)	.000	0.21 (0.09–0.49)	.000
Esophageal varices	1.47 (0.76–2.83)	.257	1.26 (0.66–2.41)	.496
MELD ≥15	1.59 (0.78–3.24)	.447	1.67 (0.75–3.72)	.209
Vascular invasion	2.57 (1.20–5.50)	.015	1.36 (0.17–10.5)	.774
Extrahepatic spread	2.03 (0.79–5.17)	.142	2.10 (0.30–14.8)	.454
AFP ≥1000	0.53 (0.31–0.91)	.018	0.75 (0.55–1.02)	.076
ECOG > 0	0.45 (0.20–1.01)	.111	0.22 (0.06–0.89)	.037
BCLC B	0.49 (0.24–1.02)	.347	0.008 (0.001–0.06)	.000
BCLC C	0.03 (0.01–0.10)	.000	0.012 (0.001–0.05)	.000
BCLC D	0.07 (0.02–0.22)	.000	0.006 (0.001–0.05)	.000
Detected by screening	0.89 (0.51–1.54)	.630	0.98 (0.51–1.89)	.946

Multivariate logistic regression evaluating factors associated with adherence to BCLC treatment recommendations. Odds ratios (OR) are presented with 95 % confidence intervals (CI). Adjusted models account for all listed covariates. Statistically significant values ($p < 0.05$) are highlighted in the manuscript.

results in odds ratios greater than 1 reflecting factors positively associated with BCLC guideline adherence. All previously significant variables retained their directionality and significance under this specification.

In the final model, Child-Pugh B/C (aOR: 3.82; 95 % CI: 1.89–7.71; $p < 0.001$) and ECOG >0 (aOR: 5.04; 95 % CI: 1.27–19.99; $p = 0.022$) were associated with adherence. In contrast, BCLC stages B, C, and D were inversely associated compared to 0/A (stage B: aOR: 0.006; stage C: aOR: 0.012; stage D: aOR: 0.007; all $p < 0.001$). The final multivariate model ($\chi^2 = 78.41$, df = 16, $p < 0.001$; −2LL = 271.672) had moderate explanatory power (Cox & Snell $R^2 = 0.261$; Nagelkerke $R^2 = 0.348$) and good calibration (Hosmer-Lemeshow $\chi^2 = 3.217$; $p = 0.920$). Variables such as MASLD, AFP, and vascular invasion were not retained in the final model (Table 4).

3.6. Global survival analysis according to adherence

Among 251 patients with survival data, 174 deaths occurred. Median OS was longer in adherent patients (722 days) than in non-adherent ones (535 days), with a log-rank $p = 0.001$ (Fig. 3).

Stratified Survival Analysis by BCLC Stage (Fig. 4)

- BCLC 0/A ($n = 127$): Adherent ($n = 57$): 1404 days vs. non-adherent ($n = 70$): 807 days ($p = 0.005$).
- BCLC B ($n = 41$): Adherent ($n = 22$): 681 days vs. non-adherent ($n = 19$): 424 days ($p = 0.173$).
- BCLC C ($n = 52$): Adherent ($n = 12$): 492 days vs. non-adherent ($n = 40$): 168 days ($p = 0.029$).
- BCLC D ($n = 31$): Adherent ($n = 29$): 330 days. Non-adherent group ($n = 2$) was too small for comparison ($p = 0.766$).

4. Discussion

Our findings reinforce the growing body of evidence supporting the clinical utility of the BCLC algorithm, confirming that adherence to its treatment recommendations significantly improves overall survival in patients with HCC. With an adherence rate of 48 %, our results align with previous studies from Brazil and Argentina, yet they underscore ongoing barriers to standardized, guideline-based care throughout Latin America [5,6].

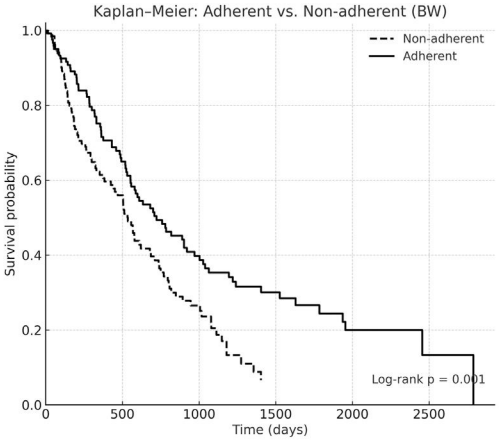
The predominance of MASLD as the leading etiology in our cohort (53 %) reflects a global epidemiological shift driven by increasing rates of metabolic syndrome and obesity [1,3]. This prevalence surpasses earlier data from Argentina and other regional studies, where MASLD accounted for 11.4 % to 37 % of HCC cases [8]. These findings highlight the urgent need to implement surveillance strategies tailored to metabolic risk profiles in Latin American populations.

Despite the well-established benefits of surveillance, only 43.5 % of patients in our study were diagnosed under active screening, a figure comparable to recent South American data but lower than historical rates from Argentina [6,8]. This gap in surveillance remains a

Table 4
Factors Associated with Adherence to BCLC-Recommended Treatment.

Variable	Unadjusted OR (95 % CI)	p	Adjusted OR (95 % CI)	p
MASLD	0.70 (0.39–1.26)	0.234	0.61 (0.32–1.14)	0.119
Child B/C	2.92 (1.68–5.06)	<0.001	3.82 (1.89–7.71)	<0.001
Vascular invasion	0.45 (0.23–0.89)	0.021	2.07 (0.41–10.55)	0.380
AFP 20–399	1.90 (1.01–3.56)	0.045	2.30 (0.86–6.15)	0.098
AFP 400–999	1.96 (0.79–4.86)	0.146	2.46 (0.85–7.15)	0.098
AFP ≥1000	0.83 (0.31–2.22)	0.709	0.78 (0.14–4.45)	0.780
ECOG > 0	0.43 (0.19–0.97)	0.041	5.04 (1.27–19.99)	0.022
BCLC B	0.15 (0.05–0.44)	<0.001	0.006 (0.001–0.047)	<0.001
BCLC C	0.19 (0.07–0.52)	0.001	0.011 (0.001–0.080)	<0.001
BCLC D	0.13 (0.05–0.38)	<0.001	0.007 (0.001–0.049)	<0.001

Multivariate logistic regression including variables with $p < 0.20$ in the univariate analysis. Adjusted odds ratios (OR) with 95 % confidence intervals (CI) are shown. The model demonstrated moderate explanatory power (Nagelkerke $R^2 = 0.348$) and good calibration (Hosmer-Lemeshow $p = 0.920$). Statistically significant results are in bold in the full text.



	0	365	730	1095	1460
Adherent	120	79	47	31	19
Non-adherent	131	70	36	12	2

Fig. 3. Overall survival according to BCLC adherence. Kaplan–Meier survival curves comparing patients who received BCLC-recommended treatment (solid line) versus those who did not (dashed line). Adherent patients had significantly longer median survival (log-rank $p = 0.001$).

modifiable factor with direct implications for earlier-stage detection and access to potentially curative therapy.

Stage-specific adherence varied across the cohort. High adherence in early (BCLC 0/A) and terminal (BCLC D) stages likely reflects clearer treatment pathways, whereas lower adherence in intermediate (BCLC B) and advanced (BCLC C) stages was mainly explained by stage-specific barriers identified by the MDT board. All treatment decisions in our cohort were reviewed by a MDT board comprising hepatologists, oncologists, interventional radiologists, transplant surgeons, and pathologists. Non-adherence to BCLC first-line recommendations therefore reflected collective clinical judgment rather than individual physician preference. The most frequent MDT-driven deviations involved anatomical or functional contraindications to ablation or TAE/TACE, exclusion from transplantation due to regulatory restrictions, and delayed or limited access to systemic agents prior to 2022.

Costa Rica delivers hepatology and oncology care predominantly through its universal public healthcare system under the Costa Rican Social Security Fund (CCSS). Advanced therapies are concentrated in three tertiary hospitals: two maintain MDT boards and selected BCLC-recommended treatments, whereas the study hospital is the only center with access to the full spectrum of 2022 BCLC-endorsed modalities, including LT, interventional procedures, and systemic therapies. These structural factors likely contributed to the stage-specific barriers and adherence gaps described above.

Notably, our cohort showed a low prevalence of viral hepatitis compared with the populations in which the BCLC system was originally developed [4], a shift driven by the predominance of MASLD that may partly explain the lower adherence, as most evidence supporting BCLC algorithms derives from viral hepatitis cohorts. During the study, a 90.5 % increase in annual HCC diagnoses was also observed, likely reflecting improved clinical awareness, wider imaging availability, strengthened national surveillance, and a growing burden of metabolic risk factors.

Collectively, these findings emphasize that structural, regulatory, and epidemiologic factors, rather than lack of guideline awareness, shaped real-world adherence patterns. The recent subclassification of BCLC-B into B1–B3 subgroups may provide additional clarity, although its impact on treatment decisions remains to be determined [4].

Only 26.3 % of the cohort received potentially curative treatment, reflecting the persistent limitations in access to surgical resection, local ablation, and transplantation. Among LT candidates, 45 % received BCLC-concordant therapy, echoing data from Brazil and Argentina [5,6]. However, transplantation in Costa Rica is significantly limited by donor availability and wait times; the national average donation rate was 5.72 donors per million population per year (pmp/y) from 2018 to 2022, with an average waiting time of 236 days. In contrast, Brazil demonstrates higher LT listing and completion rates, indicating disparities in infrastructure and donation rate.

In Costa Rica, current legislation restricts access to patients under 65 years old, limiting the applicability of this intervention for a substantial proportion of those affected. In our cohort, only 20 % met the criteria for LT under current regulations (age <65, UCSF criteria, no contraindications), and among them, 86.5 % received bridging therapy, mainly TAE/TACE or local ablation. Despite this approach, 30.2 % progressed or died before being listed, and 9.4 % died or dropped out while waiting for transplantation.

A proposed legal reform to extend the age limit to <70 years would increase the pool of eligible candidates by 49 %, adding 27 more patients. While this change could enhance access for older adults with HCC, it also raises concerns about its impact on prioritization within the transplant waitlist. Patients with HCC benefit from MELD exception points granted after three months of evaluation, potentially gaining priority over those with advanced liver failure and high functional MELD scores. In a setting where the national donation rate remains low, increasing the number of candidates without expanding the organ supply could result in the displacement of non-oncologic patients with critical liver disease. This scenario presents ethical and operational challenges that underscore the need for a comprehensive review of allocation policies, stronger organ procurement programs, and coordinated strategies to promote fair and effective access to LT across Latin America.

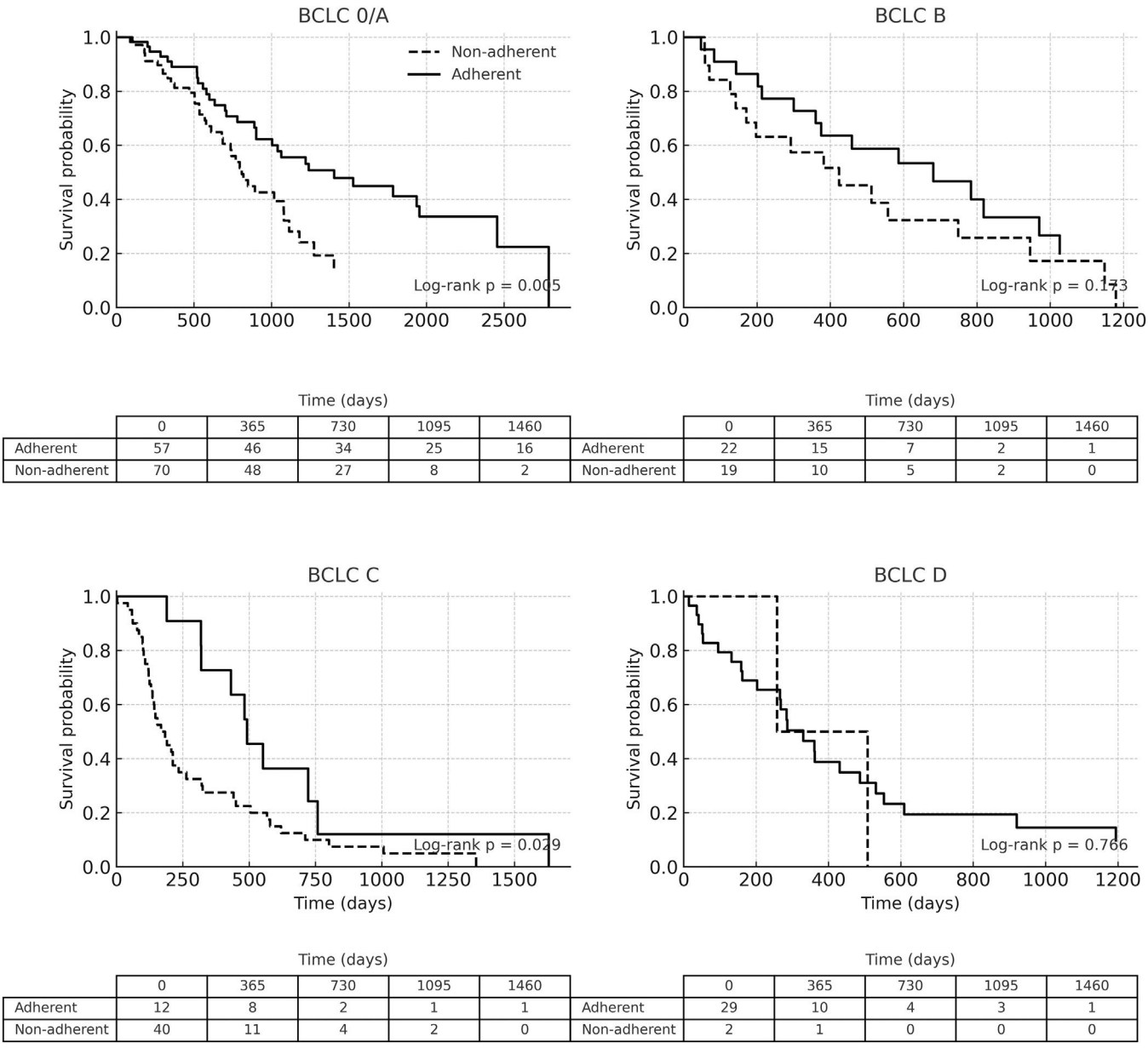
Multivariate analysis identified Child-Pugh class B or C and ECOG performance status >0 as strong positive predictors of adherence. This may suggest that more functionally impaired patients are managed more conservatively and in closer alignment with guidelines. Tumor biology variables such as AFP levels and vascular invasion were not predictive of adherence, reinforcing the predominant influence of liver function and clinical performance in guiding real-world decisions.

Survival outcomes further underscore the importance of guideline adherence. Patients receiving BCLC-concordant therapy had significantly improved median overall survival, particularly in BCLC 0/A and C stages. While the BCLC B group showed a favorable trend toward improved survival with adherence, this did not reach statistical significance—possibly due to limited sample size and treatment heterogeneity within this stage.

To improve adherence, innovative strategies such as virtual MTD boards, regionally harmonized protocols, and mobile decision-support tools, are gaining traction [9,10]. Future efforts should prioritize system-level enhancements, including physician education, patient engagement, and the use of digital decision-support platforms, along with multicenter registries and policy-level interventions to ensure equitable and consistent implementation of evidence-based care, particularly in low-resource settings.

4.1. Limitations

This study has several limitations. First, although prospectively assembled, it was conducted at a single tertiary liver transplant center, which may limit generalizability to broader healthcare settings in Central America. Second, despite efforts to capture a comprehensive cohort, referral bias may have influenced the representation of disease stages and available treatment options. Third, the definition of adherence was restricted to stage-specific first-line BCLC recommendations. Consequently, some patients categorized as non-adherent



	0	365	730	1095	1460
Adherent	57	46	34	25	16
Non-adherent	70	48	27	8	2

	0	365	730	1095	1460
Adherent	22	15	7	2	1
Non-adherent	19	10	5	2	0

	0	365	730	1095	1460
Adherent	12	8	2	1	1
Non-adherent	40	11	4	2	0

	0	365	730	1095	1460
Adherent	29	10	4	3	1
Non-adherent	2	1	0	0	0

Fig. 4. Overall and stage-specific survival by BCLC adherence. Kaplan–Meier survival curves comparing adherent and non-adherent patients overall and stratified by BCLC stage. Log-rank p-values are displayed within each panel. Significant differences were observed in stages 0/A and C.

ultimately received alternative therapies consistent with the algorithm's decision-making flexibility, which may have led to an underestimation of guideline-concordant care. Fourth, a potential survivor bias must be acknowledged, as patients who survived long enough to receive stage-specific therapy were inherently more likely to be classified as adherent, which may have partially inflated the observed survival benefit. Fifth, although the study included a robust sample size and subgroup analyses (particularly by BCLC subclassification or bridging strategies), may have been underpowered to detect small but clinically meaningful differences. Sixth, socioeconomic, psychosocial, and institutional factors that may influence adherence and access to care were not assessed, limiting interpretation of system-level barriers to BCLC implementation. Finally, the forthcoming 2025 BCLC update may refine therapeutic recommendations and adherence definitions; however, our findings remain relevant as they reflect the real-world application of the 2022 algorithm during the study period.

5. Conclusions

This is the first real-world prospective study to evaluate adherence to the updated 2022 BCLC algorithm and its impact on survival in a Central American population with hepatocellular carcinoma. Our findings confirm that BCLC-concordant treatment is significantly associated with improved overall survival, particularly in early and advanced stages. Adherence remains suboptimal, especially in intermediate stages, underscoring the need for improved access, clearer treatment pathways, and targeted implementation strategies. The high prevalence of MASLD and low surveillance rates emphasize a shifting regional epidemiology and the need for adapted screening policies. These results support the clinical utility of the BCLC staging system and highlight the urgent need for scalable, context-sensitive interventions to bridge adherence gaps and improve equity in HCC care across Latin America.

Author contributions

Conceptualization, methodology, data curation, formal analysis, visualization, writing (original draft), writing (review and editing), and supervision were carried out collaboratively by all authors.

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Declaration of interests

None.

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