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ORIGINAL RESEARCH

Prognostic Value of Changes in Combined Child–Pugh Class and ALBI Grade in Hepatocellular Carcinoma Treated with Transcatheter Intra-Arterial Therapy Plus Targeted Therapy and PD-(L)1 Inhibitors

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Purpose: This study aims to investigate liver function changes in hepatocellular carcinoma (HCC) patients treated with transcatheter intra-arterial therapy plus molecular targeted agents and programmed cell death-1 (ligand-1) inhibitors, and evaluate the prognostic significance of the combination of Child–Pugh (CP) class and albumin-bilirubin (ALBI) grade (CP/ALBI).

Methods: This is a retrospective study. A total of 149 patients from 2019 to 2023 in China were included. Changes in CP score, ALBI grade, and CP/ALBI grade at 4–8 weeks, 12–16 weeks, and 20–28 weeks post-treatment was evaluated. Cox regression models identified prognostic factors for overall survival (OS) and progression-free survival (PFS). The discrimination of the scoring systems was determined by concordance index (C-index) and time-dependent area under the receiver operating characteristic curve (AUC).

Results: Among CP-A patients (n = 137), 11.68% (n = 16) progressed to CP-B by 20–28 weeks ($p < 0.001$). Multivariate analysis identified CP/ALBI grade at 20–28 weeks as an independent prognostic factor for OS (grade 2 vs grade 1, hazard ratio [HR] 3.12, $p < 0.001$; grade 3 vs grade 1, HR 4.95, $p < 0.001$) and at 4–8 weeks for PFS (grade 3 vs grade 1, HR 3.26, $p = 0.002$). The combination of CP/ALBI grade and baseline clinical prognostic factors (Eastern Cooperative Oncology Group Performance Status, Barcelona Clinic Liver Cancer stage, tumor size) demonstrated superior discrimination for OS (C-index: 0.74–0.77; time-dependent AUC: 0.74–0.92). Baseline factors associated with maintaining CP/ALBI grade 1 in CP-A patients included ALBI grade 1 (odds ratio [OR] 3.09, $p = 0.030$) and aspartate aminotransferase < 40 U/L (OR 3.35, $p = 0.017$).

Conclusion: A small but notable proportion of HCC patients experienced liver function deterioration within 28-week of combined treatment. Dynamic monitoring of CP/ALBI grade provides valuable prognostic insights for patient stratification.

Keywords: transarterial chemoembolization, hepatic arterial infusion chemotherapy, tyrosine kinase inhibitors, immunotherapy, child–Pugh score, albumin-bilirubin grade

Introduction

Hepatocellular carcinoma (HCC) is the most common type of primary liver cancer and a leading cause of cancer-related mortality globally.[1,2] The majority of patients are diagnosed at an advanced stage, resulting in a poor prognosis.[2]

Transcatheter intra-arterial therapy, including transarterial chemoembolization (TACE) and hepatic artery infusion chemotherapy (HAIC), is commonly used to manage intermediate to advanced stages of HCC.[3] TACE is the first-line treatment for intermediate-stage HCC,[4] while HAIC has shown promising efficacy for large tumors[5] and is recommended

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by several Asian guidelines as an alternative for advanced HCC.[6–8] Currently, the combination of atezolizumab and bevacizumab is the standard first-line treatment for eligible patients with advanced HCC.[4,9] Additionally, several large real-world studies[10,11] have reported promising outcomes from combining transcatheter intra-arterial therapy with molecular targeted agents (MTAs) and programmed cell death-1 (ligand-1) (PD-(L)1) inhibitors. More recently, the ongoing randomized controlled trial[12] suggest that TACE combined with durvalumab plus bevacizumab prolongs progression-free survival (PFS) compared to TACE alone.

Maintaining hepatic reserve is crucial in the management of HCC. Studies have reported that deteriorated liver function during treatment is typically related to poor prognosis in HCC patients treated with locoregional therapies[13,14] and MTAs.[15,16] The Child–Pugh (CP) score is the most commonly used tool to assess liver function.[17] However, its reliance on subjective measures including ascites and hepatic encephalopathy poses limitations.[18] In recent years, the albumin to bilirubin (ALBI) score,[19] comprise only two serum parameters, has been introduced as a predictor of HCC prognosis and is useful for stratifying patients with CP class A (CP-A).[20] Additionally, the model for end-stage liver disease (MELD),[21] a quantitative and objective measure primarily used for liver transplant allocation, has shown certain advantages over the CP score.[22] Despite these, the relative changes in these scores for predicting outcomes in HCC patients receiving TACE or HAIC combined with MTAs and PD-(L)1 inhibitors have not been fully elucidated.

Therefore, this study aims to assess the dynamic changes in liver function during the combined regimen for HCC and explore the prognostic value of these scores in this patient cohort.

Materials and Methods

Study Design

The medical records of 307 consecutive patients diagnosed with HCC and treated with TACE or HAIC combined with MTAs and PD-(L)1 inhibitors between January 2019 and July 2023 at our center were reviewed. This retrospective single-center study was approved by the institutional review board of the National Cancer Center in China, and the requirement for written informed consent was waived.

Inclusion criteria were as follows: age between 18 and 80 years; histologically or clinically confirmed diagnosis of HCC according to the American Association for the Study of Liver Diseases (AASLD) criteria;[23] Barcelona Clinic Liver Cancer (BCLC) stage B or C; Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1; CP-A or CP-B; received combined treatment of TACE or HAIC with MTA and PD-(L)1 inhibitor during the same timeframe (refers to the period during which systemic agents were administered within 4 weeks before or after the transcatheter intra-arterial therapy); at least one measurable target lesion that can be assessed by the modified Response Evaluation Criteria in Solid Tumors (mRECIST),[24] baseline laboratory tests within 2 weeks before therapy; overall survival (OS) longer than 6 months; prior locoregional therapies, including surgery, ablation, and TACE, were also included. Exclusion criteria were: prior systemic therapy; concurrent anticancer therapy; diagnosis of other primary malignancies; missing follow-up data.

Liver Function Assessment and Definitions

The CP score was calculated based on five parameters: serum albumin, total bilirubin (TBIL), international normalized ratio (INR), ascites, and hepatic encephalopathy.[17] The ALBI score was determined using the formula: ($\log_{10}$ TBIL [μmol/L] × 0.66) + (albumin [g/L] × −0.085) and was classified as follows: grade 1 for a score ≤ −2.60; grade 2 for a score > −2.60 but ≤ −1.39; and grade 3 for a score > −1.39.[19] The MELD score was calculated using the formula: 3.78 × ln [TBIL (μmol/L) ÷ 17.1] + 11.2 × ln [INR] + 9.57 × ln [Cr (μmol/L) ÷ 88.4] + 6.43.[21] Additionally, we categorized the CP/ALBI grade according to the combination of CP class and ALBI grade: grade 1 for patients with both CP-A and ALBI grade 1; grade 3 for patients with both CP-B and ALBI grade ≥ 2; and grade 2 for all remaining combinations. These scores were recorded at baseline, as well as at 4–8 weeks, 12–16 weeks, and 20–28 weeks after therapy. Delta measures for each score were defined as the post-treatment score at each time point minus the baseline score.

Tumor responses were evaluated according to the mRECIST. The objective response rate (ORR) was defined as the proportion of patients achieving a complete response (CR) or partial response (PR). The Disease Control Rate (DCR)

was defined as the proportion of patients with CR, PR, or stable disease (SD). PFS was measured from the start of combined therapy until tumor progression, death, or the last follow-up. OS was defined as the time from the initiation of combined therapy to death from any cause or the last follow-up. The follow-up period concluded in June 2024.

Transcatheter Intra-Arterial Therapy

Interventional radiologists with at least 10 years of clinical experience performed the transcatheter intra-arterial therapies under local anesthesia. Access was obtained through the right femoral artery using the Seldinger technique with a 5-French vessel access kit (Radiofocus; Terumo). Angiography of the celiac trunk, common hepatic arteries, and superior mesenteric artery was performed using a 0.035-inch hydrophilic wire and a 5-French catheter.

During TACE, the primary tumor-feeding arteries were super-selectively catheterized with a 2.4-French microcatheter, through which an emulsion of lipiodol (2–20 mL) and chemotherapeutic agents (anthracycline or platinum, 10–50 mg/m^2) was delivered. Absorbable gelatin sponge particles were used to embolize the proximal tumor-feeding arteries until arterial flow stasis was achieved. TACE procedures were repeated on-demand based on follow-up imaging results showing tumor variability.

During HAIC, a 2.7-French microcatheter was selectively placed into the tumor-feeding artery. In cases with a short access pathway from the intrahepatic arteries to the gastroduodenal artery, potentially causing chemotherapy reflux into the stomach and duodenum, coils were used to embolize this pathway. The external portion of the catheter was covered with sterile gauze and securely fastened to the thigh with rubberized fabric and a bandage. The FOLFOX regimen, consisting of fluorouracil, leucovorin, and oxaliplatin, was administered within two days after catheter insertion. Specifically, oxaliplatin (85 mg/m^2) was infused over 2–4 hours, followed by leucovorin (400 mg/m^2) over 2 hours, fluorouracil (400 mg/m^2) over 1 hour, and an additional dose of fluorouracil (2400 mg/m^2) over more than 46 hours using an arterial pump. HAIC procedures were repeated every 4–6 weeks.

Systemic Therapy

Various MTAs and PD-(L)1 inhibitors were administered according to standard doses and frequencies as recommended in the guidelines (Table S1). The MTAs included lenvatinib, bevacizumab, sorafenib, and apatinib, while the PD-(L)1 inhibitors included sintilimab, atezolizumab, toripalimab, camrelizumab, tislelizumab, and pembrolizumab. These agents were administered within 4 weeks before or after the transcatheter intra-arterial therapies. Bevacizumab was given concurrently with the PD-(L)1 inhibitors. Systemic therapy continued until disease progression or the onset of unacceptable toxicities.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) and compared using Student's *t*-test or Mann-Whitney U-test, as appropriate. Categorical variables were presented as frequencies (percentages) and compared using Pearson's χ^2 test or Fisher's exact test according to distribution. Changes in liver function scores were assessed using paired Wilcoxon signed-rank tests or paired Student's t-tests. The optimal cutoff values for baseline MELD score, delta MELD, and delta ALBI were determined with X-tile software version 3.6.1.[25] PFS and OS curves were generated using the Kaplan–Meier method and compared with the log-rank test. Multivariate analyses employing the Cox proportional hazards model with stepwise selection were conducted to identify prognostic factors for PFS and OS, with hazard ratios (HRs) and 95% confidence intervals (CIs) calculated. Additionally, the models' performance in predicting OS was evaluated through discrimination and calibration. Discrimination was assessed using Harrell's concordance index (C-index) and time-dependent area under the receiver operating characteristic curve (AUC) at 12, 24, and 36 months. Calibration was evaluated with calibration plots and the corresponding calibration slope at these time points. Multivariate logistic regression with stepwise selection were used to identify factors associated with ORR. Additionally, significant predictors for maintaining CP/ALBI grade 1 at three follow-up time points were identified through univariate and multivariate logistic regression analysis. Variables with $p < 0.05$ in univariate analyses were included in the multivariate analyses. All statistical analyses were performed using R software version 4.2.3 (http://www.R- project.org) and Prism 9.0 (GraphPad software, San Diego, USA), with $p < 0.05$ considered statistically significant. All tests were two-sided.

Results

Patient Characteristics

A total of 149 patients were included in the study (Figure S1). Among these, 137 patients had well-compensated liver function classified as CP-A, while 12 patients had CP-B. The baseline characteristics are detailed in Table 1. In CP-A patients, 70 were assigned a CP/ALBI grade of 1 and 67 a grade of 2. All CP-B patients were assigned a CP/ALBI grade

Table 1 Baseline Characteristics

Characteristics	Total (n = 149)	CP-A (n = 137)	CP-B (n = 12)	*p*
Sex, n (%)				1.000
Female	19 (12.75)	17 (12.41)	2 (16.67)	
Male	130 (87.25)	120 (87.59)	10 (83.33)	
Age, n (%)				0.286
< 60 years	97 (65.10)	87 (63.50)	9 (75.00)	
≥ 60 years	52 (34.90)	50 (36.50)	3 (25.00)	
ECOG PS, n (%)				1.000
0	108 (72.48)	99 (72.26)	9 (75.00)	
1	41 (27.52)	38 (27.74)	3 (25.00)	
BCLC stage, n (%)				0.483
B	64 (42.95)	60 (43.80)	4 (33.33)	
C	85 (57.05)	77 (56.20)	8 (66.67)	
Etiology, n (%)				1.000
None	21 (14.09)	20 (14.60)	1 (8.33)	
HBV	126 (84.56)	115 (83.94)	11 (91.67)	
HCV	2 (1.34)	2 (1.46)	0 (0.00)	
Tumor size, n (%)				1.000
< 5 cm	38 (25.50)	35 (25.55)	3 (25.00)	
≥ 5 cm	111 (74.50)	102 (74.45)	9 (75.00)	
Tumor number, n (%)				0.800
< 3	61 (40.94)	57 (41.61)	4 (33.33)	
≥ 3	88 (59.06)	80 (58.39)	8 (66.67)	
Macrovascular invasion, n (%)				0.240
No	86 (57.72)	81 (59.12)	5 (41.67)	
Yes	63 (42.28)	56 (40.88)	7 (58.33)	
Extrahepatic metastases, n (%)				0.352
No	110 (73.83)	103 (75.18)	7 (58.33)	
Yes	39 (26.17)	34 (24.82)	5 (41.67)	

(*Continued*)

Table 1 (Continued).

Characteristics	Total (n = 149)	CP-A (n = 137)	CP-B (n = 12)	*p*
Cirrhosis, n (%)				0.101
No	71 (47.65)	68 (49.64)	3 (25.00)	
Yes	78 (52.35)	69 (50.36)	9 (75.00)	
AFP, n (%)				0.206
< 400 ng/ml	86 (57.72)	77 (56.20)	9 (75.00)	
≥ 400 ng/ml	63 (42.28)	60 (43.80)	3 (25.00)	
AST, n (%)				0.061
< 40 U/L	56 (37.58)	55 (40.15)	1 (8.33)	
≥ 40 U/L	93 (62.42)	82 (59.85)	11 (91.67)	
ALT, n (%)				0.093
< 40 U/L	84 (56.38)	80 (58.39)	4 (33.33)	
≥ 40 U/L	65 (43.62)	57 (41.61)	8 (66.67)	
PLT, n (%)				0.095
< 100×10^9/L	20 (13.42)	16 (11.68)	4 (33.33)	
≥ 100×10^9/L	129 (86.58)	121 (88.32)	8 (66.67)	
CP score, n (%)				<0.001
5	92 (61.74)	92 (67.15)	0 (0.00)	
6	45 (30.20)	45 (32.85)	0 (0.00)	
7	6 (4.03)	0 (0.00)	6 (50.00)	
8	5 (3.36)	0 (0.00)	5 (41.67)	
9	1 (0.67)	0 (0.00)	1 (8.33)	
ALBI grade, n (%)				<0.001
1	70 (46.98)	70 (51.09)	0 (0.00)	
2	77 (51.68)	67 (48.91)	10 (83.33)	
3	2 (1.34)	0 (0.00)	2 (16.67)	
CP/ALBI grade, n (%)				<0.001
1	70 (46.98)	70 (51.09)	0 (0.00)	
2	67 (44.97)	67 (48.91)	0 (0.00)	
3	12 (8.05)	0 (0.00)	12 (100.00)	
MELD, Mean ± SD	4.61 ± 2.67	4.26 ± 2.33	8.55 ± 3.19	<0.001
Prior Therapy, n (%)				1.000
No	108 (72.48)	99 (72.26)	9 (75.00)	
Yes	41 (27.52)	38 (27.74)	3 (25.00)	

Abbreviations: CP-A, Child–Pugh class A; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count; ALBI, albumin to bilirubin; CP/ALBI, combination of CP class and ALBI grade.

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of 3. TACE was performed in 90 patients (65.69%) with CP-A and 6 patients (50.00%) with CP-B, while HAIC was performed in 47 patients (34.31%) with CP-A and 6 patients (50.00%) with CP-B. The median number of TACE and HAIC sessions was 3.00 (IQR 2.00–4.00) and 3.00 (IQR 2.00–5.00), respectively. The median number of PD-(L)1 inhibitor cycles was 7.00 (IQR 4.00–11.00) for TACE and 8.00 (IQR 4.00–11.50) for HAIC.

Impact of Combined Therapy on Liver Function

The median times for laboratory test measurements were −0.07 months (IQR, −0.20 to −0.03) at baseline, 1.27 months (IQR, 1.00 to 1.63) at 4–8 weeks, 3.50 months (IQR, 3.10 to 3.78) at 12–16 weeks, and 6.00 months (IQR, 5.60 to 6.37) post-treatment. Among the 137 patients with CP-A, 8.76% (n = 12), 7.30% (n = 10), and 11.68% (n = 16) were reclassified as CP-B at 4–8 weeks, 12–16 weeks, and 20–28 weeks post-treatment, respectively, with significant differences compared to baseline ($p < 0.0001$, $p = 0.0007$, $p < 0.0001$; Figure 1A). An increase in CP scores was observed in 17.52% (n = 24), 16.06% (n = 22), and 27.01% (n = 37) of patients at 4–8 weeks, 12–16 weeks, and 20–28 weeks, respectively. The mean ALBI scores were −2.60 ± 0.34 at baseline, −2.50 ± 0.40 at 4–8 weeks, −2.50 ± 0.39 at 12–16 weeks, and −2.45 ± 0.40 at 20–28 weeks. ALBI grade 3 was observed in 1.46% (n = 2) of patients at 4–8 weeks, showing a significant difference from baseline ($p < 0.001$; Figure 1B). CP/ALBI grade 3 was observed in 8.03% (n = 11), 6.57% (n = 9), and 10.22% (n = 14) of patients at 4–8 weeks, 12–16 weeks, and 20–28 weeks, respectively, with significant differences from baseline at these time points ($p = 0.0002$, $p = 0.0107$, p = 0.0002; Figure 1C). The median delta ALBI scores at 4–8 weeks, 12–16 weeks, and 20–28 weeks were 0.09 (IQR, −0.05 to 0.28), 0.07 (IQR, −0.15 to 0.32), and 0.17 (IQR, −0.08 to 0.42), respectively. The median delta MELD scores at these time points were −0.46 (IQR, −1.86 to 1.14), −0.75 (IQR, −2.13 to 1.24), and −0.32 (IQR, −1.80 to 1.17), respectively.

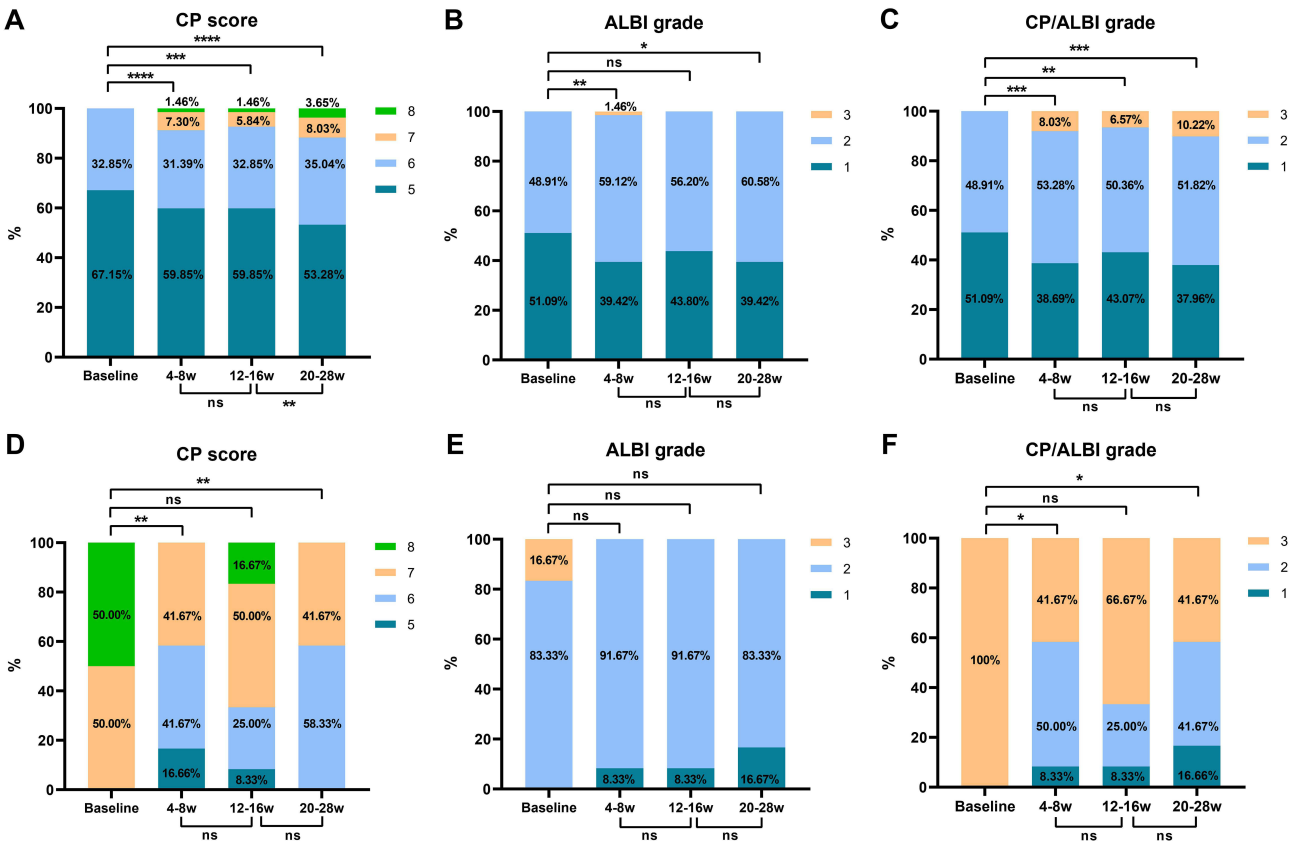

Figure 1 Changes in Child–Pugh (CP) Score, albumin to bilirubin (ALBI) grade, and combination of CP class and ALBI grade (CP/ALBI) grade at baseline and at 4–8, 12–16, and 20–28 weeks post-treatment in hepatocellular carcinoma patients with baseline CP-A (**A**–**C**) and CP-B (**D**–**F**).
Notes: *p-value < 0.05; **p-value < 0.01; ***p-value < 0.001; ****p-value < 0.0001.

For patients with CP-B (n = 12), 58.33% (n = 7) were reclassified as CP-A at both 4–8 weeks and 20–28 weeks post-treatment, with significant differences compared to baseline ($p = 0.031$ and $p = 0.027$; Figure 1D). In terms of ALBI grade, 8.33% (n = 1), 8.33% (n = 1), and 16.67% (n = 2) of patients were classified as ALBI grade 1 at three follow-up time points (Figure 1E). Moreover, 58.33% (n = 7) of patients were categorized as CP/ALBI grade 1 or 2 at both 4–8 weeks and 20–28 weeks, with significant differences compared to baseline ($p = 0.016$ and $p = 0.016$; Figure 1F).

Changes in ALBI score between CP-B and CP-A patients during follow-up are shown in Figure S2A, with a statistically significant difference observed at 20–28 weeks post-treatment (−2.15 vs −2.45, $p = 0.013$). Stratified by the type of transcatheter intra-arterial therapy, patients who underwent HAIC had a higher baseline ALBI score than those who underwent TACE, with a significant difference observed at 20–28 weeks post-treatment (−2.50 vs −2.35, $p = 0.050$; Figure S2B). There was no significant difference in ALBI scores between the combination of atezolizumab plus bevacizumab and lenvatinib plus PD-1 inhibitors at 20–28 weeks post-treatment (−2.47 vs −2.42, $p = 0.532$; Figure S2C).

OS and Prognostic Factors in CP-A Patients

The median follow-up time for all patients was 31.43 months. Among CP-A patients (n = 137), median OS did not differ significantly when stratified by baseline CP/ALBI grades, CP scores, ALBI grades, and MELD scores ($p = 0.891$, $p = 0.301$, $p = 0.891$, and 0.151). During follow-up, CP/ALBI grades demonstrated statistical significance at all three time points: grade 1 vs grade 2 ($p = 0.267$, $p = 0.048$, $p = 0.010$), grade 1 vs grade 3 ($p = 0.006$, $p = 0.001$, $p < 0.001$), grade 2 vs grade 3 ($p = 0.074$, $p = 0.081$, $p = 0.039$) (Figure 2A–C). However, for CP and ALBI, statistically significant differences between groups were observed only at 12–16 weeks ($p = 0.043$ and $p = 0.021$) and 20–28 weeks post-treatment ($p = 0.001$ and $p = 0.002$) (Figures 2D–F and S3A–S3C). Significant differences in delta ALBI and delta CP were noted only at 20–28 weeks post-treatment ($p = 0.006$ and $p < 0.001$; Figures 2G–I and S3D–S3F). Delta MELD did not show significant differences between groups at any time point (Figure S3G–S3I).

In univariate analyses, OS was significantly associated with ECOG PS ($p = 0.020$), BCLC stage ($p = 0.005$), tumor size ($p = 0.001$), tumor numbers ($p = 0.010$), macrovascular invasion ($p = 0.006$), CP-B at 4–8 weeks ($p = 0.023$), CP/ALBI grade 3 at 4–8 ($p = 0.012$) and 12–16 weeks ($p = 0.004$), and CP/ALBI grades at 20–28 weeks (grade 2, $p = 0.012$; grade 3, $p < 0.001$) (Table 2). Multivariate analysis identified independent prognostic factors for poor OS as follows: ECOG PS of 1 (HR, 2.45; 95% CI, 1.43–4.20; $p = 0.001$), BCLC stage C (HR, 1.92; 95% CI, 1.08–3.41; $p = 0.027$), tumor size ≥ 5 cm (HR, 3.31; 95% CI, 1.59–6.89; $p = 0.001$), and CP/ALBI grades at 20–28 weeks (grade 2, HR, 3.12; 95% CI, 1.66–5.85; $p < 0.001$; grade 3, HR, 4.95; 95% CI, 2.21–11.10; $p < 0.001$) (Table 2).

Performance of CP/ALBI Grade for OS in CP-A Patients

The CP/ALBI grade demonstrated higher discrimination compared to other liver function scores, with C-index values ranging from 0.60 to 0.65 and time-dependent AUC values between 0.61 and 0.69 (Table S2). When combined with baseline clinical prognostic factors (ECOG PS, BCLC stage, and tumor size) for OS prediction, the combined model achieved the highest C-index of 0.74 (95% CI, 0.61–0.88) at 4–8 weeks, 0.74 (95% CI, 0.61–0.87) at 12–16 weeks, and 0.77 (95% CI, 0.65–0.88) at 20–28 weeks (Table S2). Time-dependent AUC values are shown in Figure 3. Notably, the combined model exhibited robust time-dependent AUC values at 20–28 weeks: 0.89 (95% CI, 0.81–0.97), 0.78 (95% CI, 0.69–0.87), and 0.81 (95% CI, 0.71–0.91) for predicting 12-, 24-, and 36-month OS, respectively (Table S2). Calibration plots of the combined model indicated good agreement between predicted and observed probabilities for 24- and 36-month OS at all three follow-up time points (Figure S4), with calibration slopes ranging from 0.74 to 1.21 (Table S3).

PFS and Prognostic Factors in CP-A Patients

In CP-A patients (n = 137), the median PFS was significantly shorter in those with a baseline CP score of 6 compared to those with a score of 5 ($p = 0.039$; Figure 4C). No significant differences were observed for baseline CP/ALBI grade ($p = 0.618$; Figure 4A). At 4–8 weeks post-treatment, both CP/ALBI grade and CP score demonstrated significant differences for PFS ($p = 0.010$ and $p = 0.005$; Figure 4B and D). However, delta ALBI, delta CP, and delta MELD did not show significant differences for PFS ($p = 0.103$, $p = 0.204$, $p = 0.273$; Figures S5A–S5C).

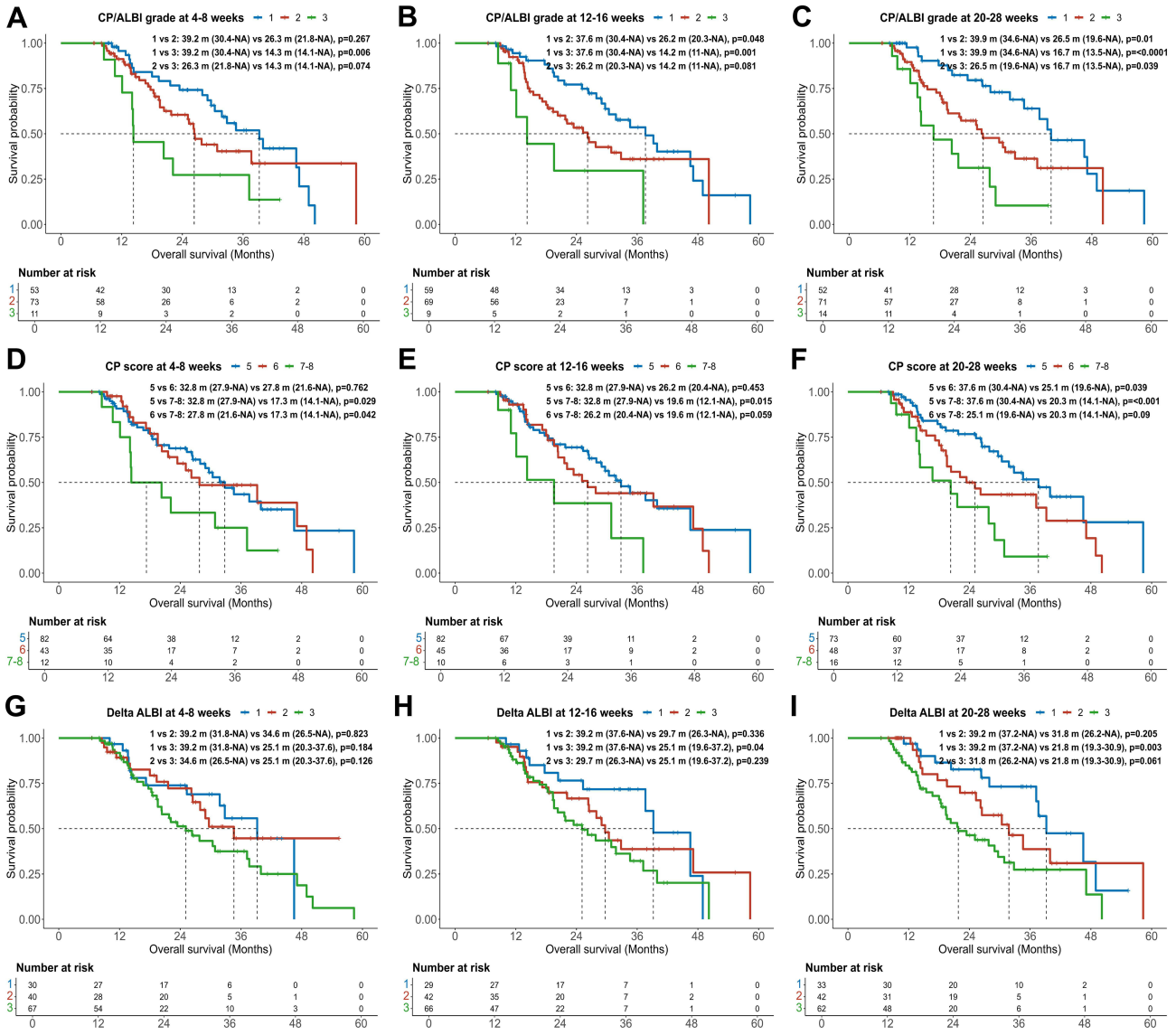

Figure 2 Kaplan–Meier curves of overall survival according to combination of Child–Pugh (CP) class and albumin to bilirubin (ALBI) grade (CP/ALBI) (**A–C**), CP Score (**D–F**), and delta ALBI (**G–I**) at 4–8, 12–16, and 20–28 weeks post-treatment in hepatocellular carcinoma patients with CP-A.

In univariate analysis, several factors were associated with PFS in CP-A patients: ECOG PS ($p = 0.012$), BCLC stage ($p = 0.012$), presence of cirrhosis ($p = 0.041$), baseline CP score ($p = 0.041$), CP-B at 4–8 weeks ($p = 0.002$), and CP/ALBI grade 3 at 4–8 weeks ($p = 0.004$) (Table 2). Multivariate analysis identified ECOG PS of 1 (HR, 1.77; 95% CI,

Table 2 Prognostic Factors for Progression-Free Survival and Overall Survival in HCC Patients With CP-A

Variables	Progression-Free Survival				Overall Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Sex, Male vs Female	1.15 (0.58–2.29)	0.694			0.79 (0.38–1.67)	0.539		
Age (years), ≥ 60 vs < 60	0.96 (0.62–1.50)	0.866			0.65 (0.37–1.12)	0.119		
ECOG PS, 1 vs 0	1.74 (1.13–2.67)	0.012	1.77 (1.13–2.76)	0.012	1.81 (1.10–3.00)	0.020	2.45 (1.43–4.20)	0.001

(*Continued*)

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Table 2 (Continued).

Variables	Progression-Free Survival				Overall Survival			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
BCLC stage, C vs B	1.75 (1.13–2.72)	0.012	1.70 (1.07–2.68)	0.023	2.22 (1.28–3.88)	0.005	1.92 (1.08–3.41)	0.027
Etiology, HBV vs Other	1.85 (0.93–3.71)	0.081			1.20 (0.58–2.47)	0.629		
Tumor size (cm), ≥ 5 vs <5	0.79 (0.50–1.25)	0.307			3.17 (1.56–6.43)	0.001	3.31 (1.59–6.89)	0.001
Tumor number, ≥ 3 vs < 3	0.97 (0.64–1.47)	0.879			1.98 (1.18–3.34)	0.010		
Macrovascular invasion, Yes vs No	1.50 (1.00–2.27)	0.052			1.99 (1.21–3.27)	0.006		
Extrahepatic metastases, Yes vs No	1.56 (0.98–2.49)	0.060			1.62 (0.97–2.73)	0.067		
Cirrhosis, Yes vs No	1.55 (1.02–2.37)	0.041			1.03 (0.63–1.68)	0.909		
AFP (ng/ml), ≥ 400 vs < 400	0.93 (0.62–1.42)	0.750			1.25 (0.76–2.06)	0.380		
AST (U/L), ≥ 40 vs < 40	1.13 (0.74–1.73)	0.567			1.64 (0.96–2.81)	0.071		
ALT (U/L), ≥ 40 vs < 40	1.28 (0.85–1.94)	0.244			1.36 (0.83–2.23)	0.227		
PLT (10^9/L), ≥ 100 vs < 100	0.69 (0.36–1.30)	0.250			1.64 (0.70–3.82)	0.251		
Baseline CP score, 6 vs 5	1.56 (1.02–2.40)	0.041			1.30 (0.79–2.15)	0.303		
Baseline ALBI grade, 2 vs 1	0.90 (0.59–1.37)	0.619			0.97 (0.59–1.59)	0.892		
CP score at 4–8 weeks								
5	1.00 (Reference)				1.00 (Reference)			
6	1.08 (0.68–1.72)	0.738			1.09 (0.63–1.90)	0.762		
7/8	2.97 (1.48–5.95)	0.002			2.27 (1.12–4.61)	0.023		
CP/ALBI grade at 4–8 weeks								
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)			
2	1.24 (0.80–1.93)	0.340	1.55 (0.98–2.46)	0.063	1.33 (0.77–2.29)	0.301		
3	3.05 (1.44–6.47)	0.004	3.26 (1.53–6.99)	0.002	2.68 (1.24–5.80)	0.012		
CP/ALBI grade at 12–16 weeks								
1	–	–	–	–	1.00 (Reference)			
2	–	–	–	–	1.69 (1.00–2.88)	0.051		
3	–	–	–	–	3.83 (1.54–9.49)	0.004		
CP/ALBI grade at 20–28 weeks								
1	–	–	–	–	1.00 (Reference)		1.00 (Reference)	
2	–	–	–	–	2.10 (1.17–3.75)	0.012	3.12 (1.66–5.85)	<0.001
3	–	–	–	–	4.40 (2.03–9.53)	<0.001	4.95 (2.21–11.10)	<0.001
HAIC vs TACE	1.11 (0.72–1.69)	0.642			1.37 (0.82–2.30)	0.225		
Prior Therapy, Yes vs No	1.34 (0.86–2.11)	0.197			0.76 (0.43–1.34)	0.341		

Abbreviations: HCC, hepatocellular carcinoma; CP-A, Child–Pugh class A; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; HBV, Hepatitis B Virus; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count; ALBI, albumin to bilirubin; CP/ALBI, combination of CP class and ALBI grade; TACE, transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy; HR, hazard ratio; CI, confidence interval.

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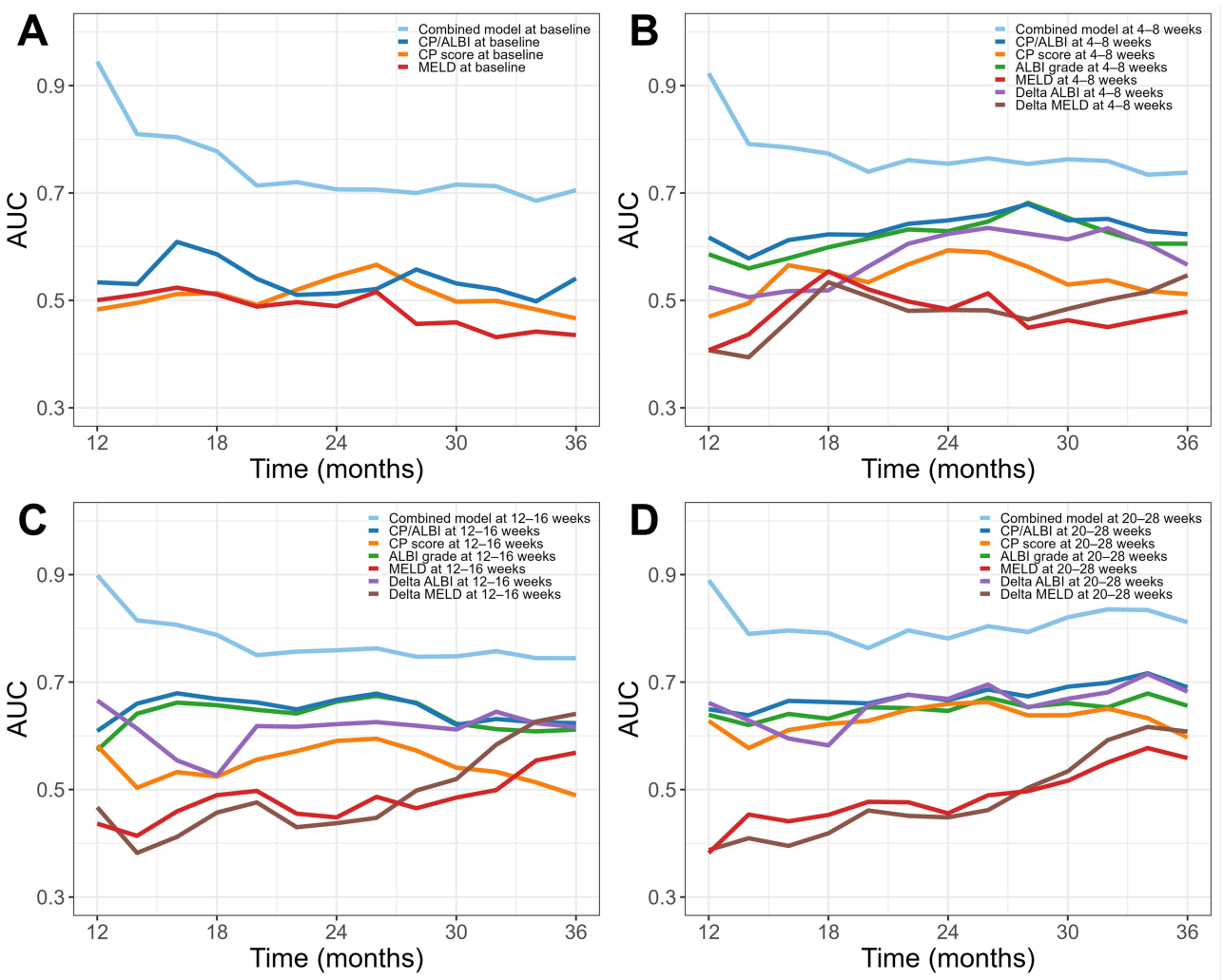

Figure 3 Time-dependent area under the receiver operating characteristics curve (AUC) for the prediction of overall survival using liver function scores at baseline (**A**), and at 4–8 (**B**), 12–16 (**C**), and 20–28 (**D**) weeks post-treatment in hepatocellular carcinoma patients with Child–Pugh (CP) class A.

Notes: Combined model integrates CP/ALBI grade with baseline clinical prognostic factors, including Eastern Cooperative Oncology Group Performance Status, Barcelona Clinic Liver Cancer stage, and tumor size.

Abbreviations: ALBI, albumin to bilirubin; CP/ALBI, combination of CP class and ALBI grade; MELD, model for end-stage liver disease.

1.13–2.76; $p = 0.012$), BCLC stage C (HR, 1.70; 95% CI, 1.07–2.68; $p = 0.023$), and CP/ALBI grade 3 at 4–8 weeks (HR, 3.26; 95% CI, 1.53–6.99; $p = 0.002$) as independent prognostic factors for poorer PFS (Table 2).

Baseline Factors for Maintaining CP/ALBI Grade 1 in CP-A Patients

In univariate analysis, factors associated with maintaining CP/ALBI grade 1 in patients with CP-A included ECOG PS ($p = 0.015$), tumor size ($p = 0.023$), AST levels ($p = 0.003$), and ALBI grade ($p = 0.025$) (Table 3). Multivariate analysis revealed that AST levels below 40 U/L (OR, 3.35; 95% CI, 1.25–9.01; $p = 0.017$) and ALBI grade 1 (OR, 3.09; 95% CI, 1.12–8.56; $p = 0.030$) were significant factors for maintaining CP/ALBI grade 1 during follow-up (Table 3).

Tumor Response

Among all patients, the response rates were 8.05% for CR, 61.07% for PR, 26.84% for SD, and 4.03% for PD. The ORR was 69.13%, and the DCR was 95.97%. Multivariate analysis revealed that an ECOG PS of 1 (OR,

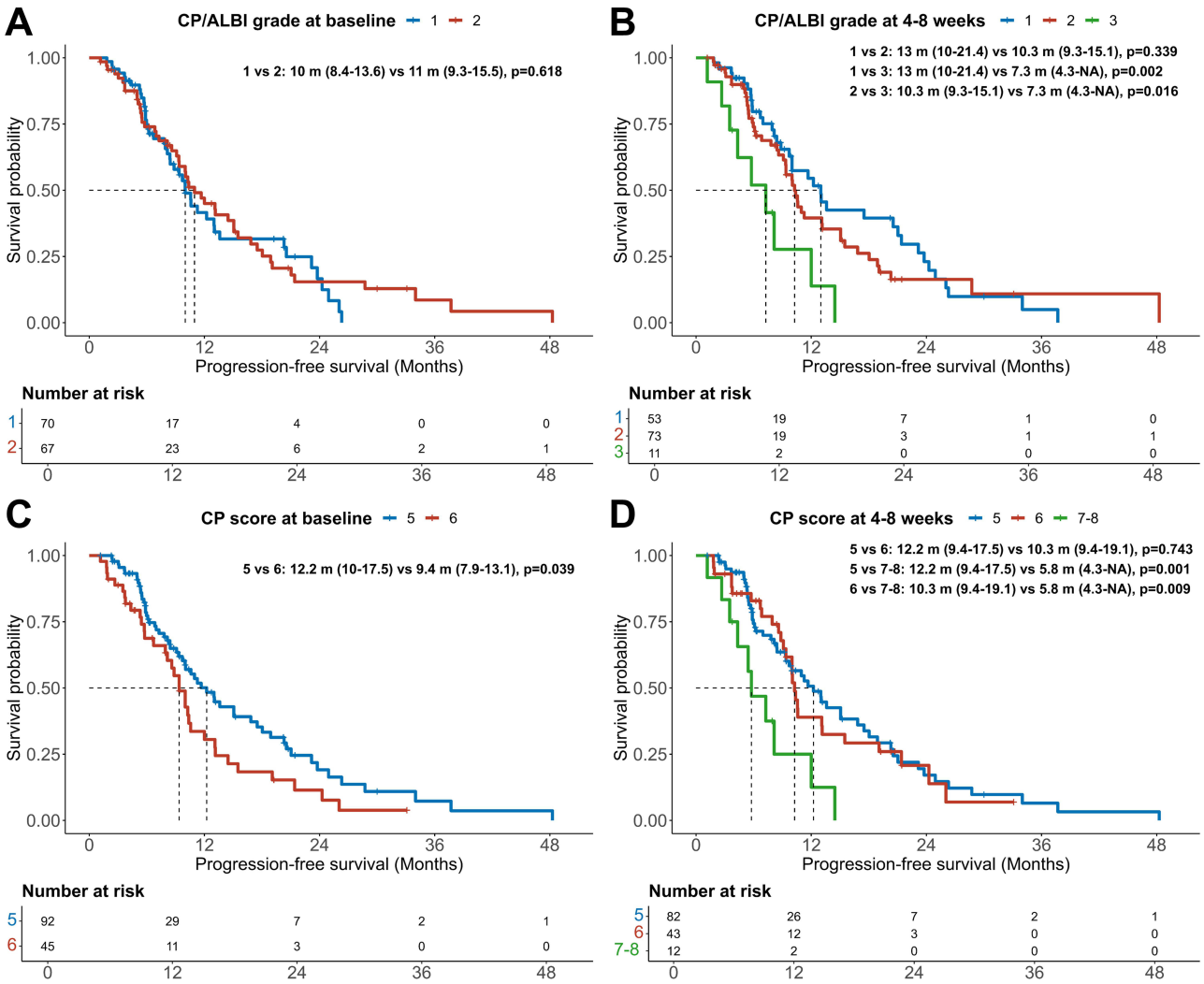

Figure 4 Kaplan–Meier curves of progression-free survival according to combination of Child–Pugh (CP) class and albumin to bilirubin (ALBI) grade (CP/ALBI) (**A** and **B**) and CP score (**C** and **D**) at baseline and at 4–8 weeks post-treatment in hepatocellular carcinoma patients with CP-A.

0.35; 95% CI, 0.16–0.80; $p = 0.013$) and a CP score of 6 at 4–8 weeks (OR, 0.41; 95% CI, 0.18–0.93; $p = 0.033$) or scores of 7 and 8 (OR, 0.22; 95% CI, 0.06–0.79; $p = 0.021$) were significantly negatively associated with ORR (Table S4).

Table 3 Baseline Factors Contributing to the Maintenance of CP/ALBI Grade 1 at Three Follow-up Time Points in HCC Patients With CP-A

Variables	Maintaining CP/ALBI Grade 1			
	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Sex, Male vs Female	4.00 (0.51–31.67)	0.189		
Age (years), ≥ 60 vs < 60	0.78 (0.31–1.97)	0.606		
ECOG PS, 0 vs 1	3.05 (1.24–7.50)	0.015	2.45 (0.91–6.59)	0.077
BCLC stage, C vs B	0.99 (0.41–2.37)	0.982		

(*Continued*)

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Table 3 (Continued).

Variables	Maintaining CP/ALBI Grade 1			
	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Etiology, HBV vs Other	0.72 (0.24–2.17)	0.554		
Tumor size (cm), < 5 vs ≥ 5	2.88 (1.16–7.15)	0.023	2.15 (0.76–6.10)	0.149
Tumor number, < 3 vs ≥ 3	1.13 (0.47–2.70)	0.788		
Macrovascular invasion, No vs Yes	1.29 (0.52–3.16)	0.584		
Extrahepatic metastases, No vs Yes	0.82 (0.31–2.16)	0.684		
Cirrhosis, Yes vs No	0.73 (0.31–1.75)	0.482		
AFP (ng/ml), ≥ 400 vs < 400	0.54 (0.22–1.36)	0.193		
AST (U/L), < 40 vs ≥ 40	4.14 (1.64–10.46)	0.003	3.35 (1.25–9.01)	0.017
ALT (U/L), ≥ 40 vs < 40	0.92 (0.38–2.23)	0.857		
PLT (10^9/L), ≥ 100 vs < 100	0.96 (0.25–3.67)	0.956		
Baseline CP score, 6 vs 5	0.59 (0.22–1.60)	0.301		
Baseline ALBI grade, 1 vs 2	2.97 (1.15–7.66)	0.025	3.09 (1.12–8.56)	0.030
HAIC vs TACE	0.42 (0.15–1.19)	0.103		
Prior Therapy, Yes vs No	2.00 (0.81–4.96)	0.134		

Abbreviations: CP/ALBI, combination of CP class and ALBI grade; HCC, hepatocellular carcinoma; CP-A, Child–Pugh class A; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; HBV, Hepatitis B Virus; AFP, alpha-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PLT, platelet count; ALBI, albumin to bilirubin; TACE, transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy; OR, odds ratio; CI, confidence interval.

Discussion

Transcatheter intra-arterial therapy combined with MTAs and PD-(L)1 inhibitors has shown promising outcomes in treating HCC. Changes in hepatic reserve are known to affect HCC prognosis. However, their specific impact on patients receiving this combined therapy have not been clearly elucidated. Our study observed that the proportion of CP-A patients progressing to CP-B was 8.63%, 7.91%, and 11.68% at 4–8 weeks, 12–16 weeks, and 20–28 weeks post-treatment, respectively. Interestingly, baseline liver function scores did not stratify OS in these patients. However, deterioration in these scores at 20–28 weeks was significantly correlated with poor OS. Notably, the CP/ALBI grade showed better discrimination for OS compared to other scores. When combined with baseline clinical prognostic factors, the combined model exhibited superior discrimination, with C-index values ranging from 0.74 to 0.77 and time-dependent AUC values between 0.74 and 0.92.

Several studies have reported changes in liver function during systemic therapies and transcatheter intra-arterial therapies for HCC. Explicitly, 12.7%–27.4% of CP-A HCC patients treated with sorafenib or lenvatinib advanced to CP-B within 6–8 weeks.[15,16,26] Uchikawa et al[27] found the median ALBI score changing from −2.53 at baseline to −2.36 after 6 months of MTA treatment. Hiraoka et al[13] demonstrated that 13.5%–15.9% of baseline CP-A patients experienced an increase in CP scores to 7 or higher after three TACE sessions. Moreover, Terashima et al[14] reported better hepatic functional reserve with HAIC than with sorafenib, evidenced by a lower percentage of patients with worsening CP scores at 12 weeks (28.8% vs 52.3%). In contrast, studies on ramucirumab,[28] nivolumab,[29] and atezolizumab plus bevacizumab[30] showed maintained hepatic reserve. Specifically, Hiraoka et al[30] reported that 9.0%–12.9% of CP-A patients progressed to CP-B after 3–6 weeks of atezolizumab plus bevacizumab treatment, and Maesaka et al[31] found this

combination superior to lenvatinib in maintaining liver function. Our study showed that HCC patients treated with TACE or HAIC combined with MTAs and PD-(L)1 inhibitors experienced a relatively lower incidence of liver function deterioration compared to those receiving MTAs alone, and similar to those treated with TACE, HAIC, or atezolizumab plus bevacizumab (7.91%–11.68% progressing to CP-B; mean ALBI score changing from −2.60 to −2.44; 27.01% of patients had increased CP scores after 28 weeks). These differences may be attributed to the favorable baseline liver function of our cohort and the promising efficacy of the combined therapy in reducing tumor burden, as indicated by an ORR of 69.13%. When stratified by different MTAs and PD-(L)1 inhibitors combinations, we found that during atezolizumab plus bevacizumab, ALBI scores initially increased until 16 weeks before declining, similar to the findings of Maesaka et al.[31] However, ALBI scores showed a trend of increase over time during administration of lenvatinib plus PD-1 therapy. These results suggest the need for further exploration of liver function changes with different MTA and PD-(L)1 inhibitor combinations.

Previous studies have indicated that even mild deterioration in liver function during treatment can adversely affect the prognosis of HCC, even in patients with well-preserved baseline liver function. Similarly, we found that deterioration in CP score and ALBI grade during this combined regimen is associated with shorter OS and PFS. Regarding the prognostic value of CP scores and ALBI grade for HCC, previous study has favored ALBI grade for stratifying CP-A patients.[20] Likewise, our findings revealed no significant difference in median OS between patients with CP scores of 5 and 6 at baseline, as well as at 4–8 weeks and 12–16 weeks post-treatment. Conversely, a statistically significant difference in median OS between ALBI grades 1 and 2 over time. Furthermore, we observed that only 1.46% of patients were graded as ALBI grade 3 after 4–8 weeks of treatment. Thus, ALBI grade alone is insufficient to categorize HCC patients receiving this combined therapy into three risk groups. Notably, when CP class and ALBI grade are combined, the OS curves of patients in each group diverge more sharply. Specifically, a small proportion of patients with a CP score of 5 were classified as CP/ALBI class 2, leading to a differentiation between CP/ALBI classes 1 and 2. In univariate analysis, CP/ALBI grade 3 was associated with poor OS at all follow-up points. Multivariate analysis further identified CP/ALBI grade 3 at 20–28 weeks as an independent prognostic factor for poor OS (HR, 4.95; $p < 0.001$). Additionally, previous studies[14,32] have indicated that changes in ALBI score, CP score, and MELD score are associated with HCC prognosis. In our study, only patients with substantial changes in delta ALBI, delta CP, and delta MELD at 20–28 weeks post-treatment experienced significantly shorter OS compared to those with minimal changes. Interestingly, this pattern was not observed at earlier follow-up time points. These results indicate that liver function scores offer robust stratification ability compared to delta scores in these patients. Consistent with these findings, CP/ALBI grade demonstrated superior discrimination compared to other scores, achieving the highest C-index (0.74–0.77) and time-dependent AUC (0.74–0.92) when combined with baseline clinical prognostic factors. However, the calibration of the combined model for predicting 12-month OS was suboptimal (calibration slope: 1.85–2.12), likely due to only 20.4% of patients having an OS shorter than 12 months, with only half of them experiencing an event. These findings suggest that the combination of CP/ALBI grade and baseline clinical prognostic factors offers superior discriminatory ability, particularly for predicting 24- and 36-month OS.

For PFS, baseline CP scores, as well as CP scores and CP/ALBI grades at 4–8 weeks post-treatment, showed statistical significances. Furthermore, multivariate analysis confirmed that CP/ALBI grade 3 was significantly associated with shorter PFS (HR, 3.26; $p = 0.004$). These findings suggest that both CP scores and CP/ALBI grades can effectively stratify PFS in these patients. For tumor response, the CP scores at baseline and 4 weeks after treatment were significant predictors of ORR in univariate analysis. Multivariate analysis further revealed that a higher CP score after 4 weeks was significantly associated with a lower ORR. These findings emphasize the importance of monitoring liver function during TACE or HAIC combined with MTAs and PD-(L)1 inhibitors for HCC patients with initially preserved liver function. Furthermore, the CP/ALBI grades may provide timely prognostic value and enable early stratification of patient outcomes.

Despite the generally poor prognosis for HCC patients with impaired liver function, studies[33,34] indicate that immunotherapy and MTAs can be both safe and effective for those with CP-B liver function. In our study, we evaluated liver function changes in 12 CP-B patients receiving this combined therapy and found that this treatment seems not to worsen liver function over the 28-week period. Specifically, 58.3% of these patients improved to CP-A after 4 weeks of treatment. This improvement aligns with findings from another study where 28.6% of CP-B patients improved to CP-A after 4 weeks of sorafenib.[26] One possible speculation is that this regimen might effectively reduce tumor burden,

potentially leading to improved liver function. Therefore, patients with CP-B may benefit from the first-line treatment of this regimen. Nevertheless, these findings should be interpreted with caution due to the small number of CP-B patients in this study, and the long-term changes in these scores require further investigation.

Previous studies[26,35,36] have demonstrated that liver function is commonly compromised by baseline factors such as CP score, ECOG PS, ALBI grade, AST level, and vessel invasion. In our study, ECOG PS of 0, tumor size less than 5 cm, AST levels below 40 U/L, and ALBI grade 1 were identified as favorable factors for maintaining a CP/ALBI grade of 1 during follow-up. Multivariate analysis confirmed that ALBI grade 1 (OR, 3.09; $p = 0.030$) and AST < 40 U/L (OR, 3.35; $p = 0.017$) were significant contributing factors. ALBI grade 1, rather than a CP score of 5, was the contributing factor for maintaining CP/ALBI grade 1 during follow-up. This could be explained by the fact that ALBI grade 1 can differentiate between patients with better preserved liver function among patients with a CP score of 5, as evidenced by the 22 patients with a CP score of 5 who were classified as ALBI grade 2 in our cohort. Additionally, the identification of AST < 40 U/L as another significant factor for maintaining liver function may be associated with the potential contribution of antiviral therapy in managing chronic liver disease caused by hepatitis B. Given that approximately 85% of our cohort have hepatitis B, it is possible that many have received antiviral therapy. Effective antiviral therapy has been shown to maintain serum albumin levels and support liver function in patients with hepatitis-related HCC.[37] Therefore, antiviral therapy may be associated with the preservation of hepatic function during treatment for hepatitis B virus-associated HCC.

This study has several limitations. Firstly, this is a single-center, retrospective analysis with a relatively small sample size, it may be influenced by various confounding factors. Thus, larger, prospective, randomized controlled trials are necessary for further validation. Secondly, the observation period was limited to the first 6 months post-treatment initiation; a longer follow-up is needed to more comprehensively assess the dynamic changes in hepatic reserve. Thirdly, the lack of an external validation cohort from another center may limit the generalization of our study findings. Additionally, the small number of patients with CP-B restricts our understanding of hepatic reserve changes in this subgroup, indicating a need for further investigation in these patients.

Conclusion

Overall, a small but notable proportion of HCC patients experienced liver function deterioration within the 28-week period of TACE or HAIC combined with MTAs and PD-(L)1 inhibitors. The CP/ALBI grade has demonstrated valuable prognostic potential for predicting outcomes during follow-up, which could assist in guiding individualized treatment strategies. This study contributes additional evidence supporting the use of the combined treatment in the first-line setting for HCC, highlighting its potential to inform prognosis and optimize patient management.

Abbreviations

HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization; HAIC, hepatic artery infusion chemotherapy; MTAs, molecular targeted agents; PD-(L)1, programmed cell death-1 (ligand-1); BCLC, Barcelona Clinic Liver Cancer; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PFS, progression-free survival; OS, overall survival; CP, Child–Pugh; ALBI, the albumin to bilirubin; MELD, model for end-stage liver disease; AFP, alpha-feto-protein; TBIL, total bilirubin, INR, international normalized ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; mRECIST, Modified Response Evaluation Criteria in Solid Tumors; CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; ORR, objective response rate; DCR, disease control rate; IQR, interquartile range; SD, standard deviation; HR, hazard ratio; CI, confidence interval.

Data Sharing Statement

Patient data were fully anonymized to remove any identifying details. All data were securely stored with restricted access and utilized exclusively for research purposes in compliance with ethical standards and confidentiality requirements.

Statement of Ethics

This retrospective study was conducted in compliance with the ethical guidelines of the 1975 Declaration of Helsinki and received approval from the Independent Ethics Committee of the Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (IRB Approval No. 24/175–4455). Written informed consent for treatment was obtained from all patients. The requirement for additional written informed consent for this study was waived due to its retrospective nature.

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Disclosure

The authors declare no conflicts of interest related to this study.

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