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ORIGINAL RESEARCH

ALBI Grade Enables Risk Stratification for Bleeding Events and Refines Prognostic Prediction in Advanced HCC Following Atezolizumab and Bevacizumab

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Background and Aims: Atezolizumab and bevacizumab (A+B) are recommended for treating unresectable hepatocellular carcinoma (HCC). Although highly effective, A+B can lead to potentially life-threatening adverse events including bleeding. We investigated whether albumin-bilirubin (ALBI) grade identifies patients with a higher risk of bleeding and its impact on prognosis than the Child-Pugh (CP) score.

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Methods: We performed a multicenter retrospective study of 15 tertiary referral centers that consecutively treated patients with A+B. We analyzed the association between the ALBI grade and gastrointestinal bleeding using the $\chi 2$ test. Overall survival (OS) stratified by ALBI was estimated using the Kaplan-Meier method and the predictive value for the 6-months OS landmark with ROC curves.

Results: Of the 368 patients included in the analysis, 163 (44.3%), 192 (52.2%) and 13 (3.5%) had ALBI 1, ALBI 2, and ALBI 3, respectively. ALBI grade was associated with a 3-fold increase in bleeding risk (3.1% in ALBI 1 vs 10.2% in ALBI 2/3, p=0.008). Among 192 patients with pre-treatment EGD, G2 and G3 varices were associated with an increased risk of bleeding, whereas G1 varices had a similar risk as no varices. Patients with ALBI 1 achieved a longer median OS (not reached; 95% CI, 24.9–33.7), than ALBI 2 (9.7 months; 95% CI, 7.0–12.3) or ALBI 3 (5.6 months; 95% CI, 0.1–12.0). ALBI outperformed the CP score for predicting 6-month OS with an AUC 0.79 of ALBI versus 0.71 for the CP score (p=0.01).

Conclusion: A Higher ALBI grade was associated with an increased risk of gastrointestinal bleeding after receiving A+B, and outperformed the CP score in predicting worse survival.

Keywords: hepatocellular carcinoma, ALBI, bleeding risk, systemic treatment

Introduction

Hepatocellular carcinoma (HCC) is one of the most common and deadliest cancers worldwide.[1] Despite current surveillance programs,[2] only a fraction of patients diagnosed with HCC are eligible for curative or locoregional therapies. Therefore, a significant number of patients receive systemic treatment either as front-line treatment or after relapse/progression following curative or local therapy.[3,4]

Over the last few years, the landscape of systemic treatments for HCC has changed rapidly and significantly. After the IMbrave150 trial and more recent randomized control trials (COSMIC-312, HIMALAYA, LEAP 002 and CARES-310)[5–8] patients with advanced HCC achieved an unprecedented median overall survival (OS) ranging between 16 and 22 months after the introduction of combination immunotherapy.[9,10] These results modified the natural history of patients with advanced HCC in terms of OS, quality of life, and side effects of systemic therapy.[11] As a consequence of this increase in OS, increasing attention has been paid to refining the assessment of liver function, given its central prognostic role in patients with HCC, and to stratify which patients should receive which systemic therapies.[12]

Historically, the Child-Pugh (CP) classification has been considered a paradigmatic tool to evaluate liver function, despite being developed 50 years ago as a tool to predict perioperative mortality in cirrhotic patients.[13] However, accumulating evidence has demonstrated that the ALBI score may refine the assessment of liver function across different therapeutic modalities, including in patients with early stages HCC,[14,15] patients undergoing non-curative locoregional treatments[16] and those receiving immunotherapy.[17,18]

The improved accuracy of ALBI, a score calculated from peripheral blood albumin and bilirubin, over CP is multifactorial and relates to the low interobserver reproducibility of the CP score related to the subjective assessment of some of its components (ascites and encephalopathy) and the limited number of classes available to categorize patients with different degrees of liver impairment in the CP classification.

Liver impairment has significant prognostic relevance, and it is also a major risk factor for bleeding events; patients with liver cirrhosis are more prone to develop episodes of bleeding than the general population,[19] mainly arising from the gastrointestinal tract. Furthermore, bleeding is a significant risk factor for VEGF-targeted drugs that are commonly used in patients with HCC in the context of cirrhosis. In the registrational IMbrave150 trial, despite enrollment of a selected population, patients still experienced a non-negligible number of gastrointestinal (GI) bleeding events, which are known to have significant implications for patients' prognosis.[20]

There is no consensus regarding an effective biomarker that can predict either the efficacy of the A+B combination or the development of significant toxicities (ie, severe bleeding events).

Herein, we report an investigation of the role of ALBI as a predictor of bleeding events in a group of patients with unresectable HCC who received A+B and compare it with the CP score.

Materials and Methods

Consecutive patients with unresectable or metastatic HCC treated with A+B as part of routine clinical care in 15 tertiary referral centers in Asia (n=236), Europe (n=111), and the US (n=86) from January 2019 to March 2022 (Figure 1) were enrolled in a prospectively collected database. All patients were at least 18 years old, had a histological or radiological diagnosis of HCC according to the American Association for the Study of Liver Diseases criteria,[21] and they were diagnosed with unresectable HCC disease, defined according to the Barcelona Clinic Liver Cancer (BCLC) criteria.[22]

Treatment Administration and Outcome Measures

A+B was administered and managed, including dose modification, according to the local standard of care. Treatment was continued until a loss of clinical benefit or unacceptable toxicity was observed. Data regarding patient demographics and clinical status were collected retrospectively and prospectively, and updated at each participating site. We included in the safety and efficacy analysis all patients receiving at least one dose of A+B in the first line, excluding patients with prior lines of systemic treatment.

Radiological response to treatment was evaluated according to RECIST criteria v1.1 on CT or MRI, and the interval between scans was in accordance with local practices. AEs, including bleeding events, were assessed at every contact with the patient and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. Bleeding events were classified as portal hypertensive related when the cause was directly correlated to an increase in the hepatic venous pressure gradient, therefore including acute variceal bleeding and bleeding from gastric varices, portal hypertensive gastropathy and gastric antral vascular ectasia. The attribution of causality to either drug was based on the published toxicity profile of A+B, the assessment of treating physicians at each center, and the judgment of the investigators. Principal investigators at each site had at least 5 years of expertise in administering systemic anticancer treatments.

Treatment duration was defined as the time from the date of the first dose of A+B to the date of treatment discontinuation. Progression free survival (PFS) was defined as the time from the date of the first dose of treatment to the date of radiological evidence of tumor progression or to the date of death. OS was defined as the time from the date of first treatment to the date of death. The objective response rate (ORR) was defined as the sum of the rates of complete response (CR) and partial response (PR), assessed using RECIST criteria v1.1, whereas the disease control rate (DCR) included the rates of CR, PR, and stable disease (SD). Radiological response and radiological diagnosis of progression were assessed locally by experienced radiologists at each center.

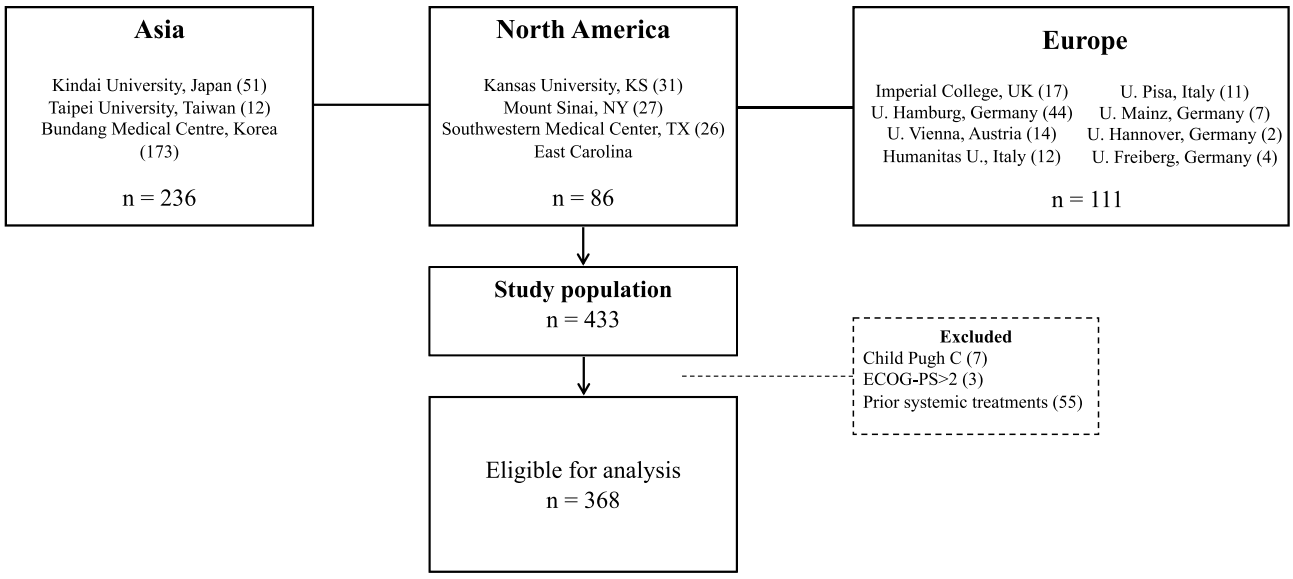

Figure 1 Flowchart of the study.

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Statistical Analysis

Fisher's exact test or $\chi 2$ test was used to compare nominal variables. The Student's *T*-test was used to compare parametric distributions of continuous variables across categories. OS and PFS were calculated using the Kaplan-Meier method. We further tested the independent prognostic value of each factor by multivariable analysis using Cox regression models with a log-likelihood ratio test. Receiver operating characteristic (ROC) curves were calculated for different prognostic factors, and the area under the curve (AUC) method was used to compare the prognostic ability of predicting OS at the 6-month landmark endpoint. All statistical analyses were performed using the IBM SPSS Statistics version 28.0, RStudio 2022.07.1, and GraphPad Prism version 9.0.

Ethical Considerations

This study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki. Ethical approval to conduct this study was granted following a review of the study protocol by the Imperial College Tissue Bank (Reference Number R16008) and locally by the ethics committee of each participating site. Considering the retrospective nature of the study and anonymization of the clinical data, the ethical committee waived the need for written consent.

Results

Patients Characteristics

At the time of the data cutoff, on the 1st of April 2022, 433 patients were included in the dataset. The entirety of the patients received treatment with atezolizumab 1200 mg and bevacizumab 15 mg/kg every 3 weeks intravenously until disease progression, loss of clinical benefit, or unacceptable toxicity from January 2019 to March 2022 as part of routine clinical practice. After excluding patients who did not meet the inclusion criteria (Figure 1), 368 patients were included in the primary analysis.

The baseline clinicopathological characteristics of patients are described in detail in Table 1.

The majority of patients were male (84.2%), with a median age of 66 years (interquartile range [IQR] 59–73) and an underlying viral etiology (HBV, 37.5%; HCV, 24.2%). The etiology of chronic liver disease in the remaining patients included alcohol-related liver disease (20.1%), metabolic liver disease (14.1%), and cryptogenic etiology (2.7%).

Table 1 Description of Baseline Characteristics

Variable	Tot= 368 Patients N (%)
Median Age (IQR)	66 (59–73)
Gender	
Male	310 (84.2)
Female	58 (15.8)
ECOG PS	
0	150 (40.8)
1	208 (56.5)
2	10 (2.7)
BCLC	
A	6 (1.6)
B	80 (21.7)
C	282 (76.6)
AFP	
≥400 ng/mL	128 (34.8)
<400 ng/mL	240 (65.2)

(*Continued*)

Table 1 (Continued).

Variable	Tot= 368 Patients N (%)
Child Pugh	
A	295 (80.2)
5	190
6	105
B	73 (19.8)
7	42
8	23
9	8
ALBI	
1	163 (44.3)
2	192 (52.2)
3	13 (3.5)
Cirrhosis	
Present	290 (78.8)
Absent	78 (21.2)
Etiology	
HBV	138 (37.5)
HCV	89 (24.2)
HBV-HCV coinfection	5 (1.4)
Alcohol	74 (20.1)
NASH/NAFLD	52 (14.1)
Other	10 (2.7)
PVT	
Present	154 (41.9)
Absent	214 (58.2)
EHS	
Present	175 (47.5)
Absent	193 (52.5)
Previous surgery	
Yes	91 (24.7)
No	277 (75.3)
Previous RFA	
Yes	54 (14.7)
No	314 (85.3)
Previous TACE	
Yes	145 (39.4)
No	223 (60.6)

Abbreviations: IQR, interquartile ratio; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BCLC, Barcelona Clinic Liver Cancer; EHS, extrahepatic spread; AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; HBV, hepatitis B virus; HCV, hepatitis C virus; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; PVT, portal vein thrombosis; RFA, radio-frequency ablation; TACE, transarterial chemoembolization.

Most of the patients had a clinical or radiological diagnosis of cirrhosis (78.8%), and median time from initial diagnosis of unresectable HCC to start of atezolizumab and bevacizumab was 4.5 months (IQR 0.9–25.2). At treatment commencement, 150 patients (40.8%) had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0, 208 (56.5%) had an ECOG PS of 1, and 10 (2.7%) had an ECOG PS of 2.

Most patients were staged as stage C according to the BCLC criteria (282 patients, 76.6%). Overall, 154 patients (41.9%) had evidence of neoplastic portal vein thrombosis (PVT) and 175 (47.5%) of extra-hepatic spread (EHS) at baseline. Evidence of both PVT and EHS was observed in 59 patients (16%) and the baseline AFP value was ≥ 400 ng/mL in 128 patients (34.5%). Baseline liver function was assessed according to the CP score and albumin-bilirubin grade: 295 patients (80.2%) were in the CP-A functional class and 73 (19.8%) were in CP-B, including 42 B7, 23 B8, and 8 B9. When categorized according to ALBI grade, 163 patients (44.3%) were graded as ALBI grade 1, 192 (52.2%) as ALBI grade 2, and 13 (3.5%) as ALBI grade 3. Among 290 patients (78.8%) diagnosed with cirrhosis, 109 (38.7%) had ascites and 9 (3.2%) had encephalopathy.

Safety Assessment and ALBI Grade Association with Bleeding Risk

All patients who received at least one dose of atezolizumab and bevacizumab were monitored for treatment-related AEs (trAEs). The median follow-up time was 9.7 months (95% CI, 9.2–10.3). A total of 248 patients (67.4%) experienced any-grade trAEs, of which 76 (20.7%) experienced grade 3–4 trAE. No Grade 5 trAEs were observed.

Any-grade atezolizumab-related AEs were reported in 162 patients (44.0%) and any-grade bevacizumab-related AEs were reported in 175 patients (47.6%). Thirty-two patients (8.7%) had grade 3–4 atezolizumab-related AEs, whereas 49 (13.3%) had grade 3–4 bevacizumab-related AEs (Table 2).

Bleeding events were reported in 10.1% (n=37) of patients, of whom 7.1% (n=26) had GI bleeding, including 20 bleeding events related to portal hypertension. Sixteen patients (4.3%) experienced grade 3–4 GI bleeding events (14 G3, 2 G4) GI bleeding events occurred at a median of 3.9 months after the start (IQR 1.2–6.5).

Table 2 Treatment-Related Adverse Events Occurring During the Treatment in the Safety Population

	***Atezolizumab and Bevacizumab* (n=*368*)**	
Any grade trAEs relating to either drug	248 (67.4%)	
Grade≥3 trAEs relating to either drug	76 (20.7%)	
Atezolizumab-related AE	32 (8.7%)	
Bevacizumab-related AE	49 (13.3%)	
trAEs leading to treatment discontinuation relating to either drug	29 (7.9%)	
trAEs atezolizumab-related	**Any Grade**	**Grade≥3**
Overall	162 (44.0%)	32 (8.7%)
Hepatotoxicity	89 (24.2%)	16 (4.3%)
Colitis	39 (10.6%)	9 (2.4%)
Skin toxicity	41 (11.1%)	2 (0.5%)
Thyroid toxicity	24 (6.5%)	1 (0.3%)
Arthritis	12 (3.3%)	2 (0.5%)
Pituitary toxicity	5 (1.4%)	0
Pneumonitis	4 (1.1%)	1 (0.3%)
Neuropathy	1 (0.3%)	1 (0.3%)
Nephritis	1 (0.3%)	0
Myositis	1 (0.3%)	1 (0.3%)
trAE bevacizumab-related	**Any Grade**	**Grade≥3**
Overall	175 (47.6%)	49 (13.3%)
Hypertension	95 (25.8%)	13 (3.5%)
Proteinuria	104 (28.3%)	15 (4.1%)
Bleeding	37 (10.1%)	18 (4.9%)
Thrombosis	9 (2.4%)	4 (1.1%)

Abbreviation: trAE, treatment-related adverse event.

When we considered bleeding events from any site, they were significantly associated with the presence of baseline PVT (p=0.003), a lower number of serum platelets (p= 0.003) and a higher baseline ALBI grade (1 vs 2/3, p=0.008), but not with BCLC stage (A/B vs C), ECOG PS (0 vs 1/2), ongoing antiplatelets treatment, or CP class (p>0.05).

Data on pre-treatment esophagogastroduodenoscopy (EGD) were available for 192 patients (52.1%), with a median of 0.7 months from EGD to treatment start (IQR 0.1–3.7). In total, 89 patients who underwent pre-treatment EGD had evidence of gastroesophageal varices (46.4%), graded as 1 (n=52), 2 (n=25), and 3 (n=12), respectively. Varices were managed according to local practices with either banding or medical treatment.

Among the patients who underwent baseline EGD, 44 (22.9%) received prophylactic treatment. In particular, 21 (10.9%) underwent band ligation, 13 (6.8%) were treated with beta-blockers, and 10 (5.3%) received both banding and pharmacological treatment. Of the remaining 148 patients (77.1%) without any prophylactic treatment, 103 (54%) did not have baseline varices and the remaining had grade 1 varices.

The presence of varices at pre-treatment EGD significantly correlated with the development of GI bleeding events of any grade, which were reported by 5 of 103 patients without varices at EGD (4.8%) and by 19 of 89 patients with varices of any grade (21.3%; p<0.001).

Notably, the risk of GI bleeding events was significantly higher in patients with G2 and G3 varices than in those with G1 varices (32.4% vs 13.5%, p=0.031), whereas the risk of developing GI bleeding events was comparable in patients with G1 varices and patients with no varices (13.5% vs 4.5%, p=0.11) (Figure 2A).

A subgroup analysis involving only portal hypertension related bleeding events was analyzed confirming the correlation between these events and ALBI grade together with PVT, a low platelet number and the presence of oesophageal varices, although neither of these variables confirmed their independent role at the multivariate analysis. (Table S1).

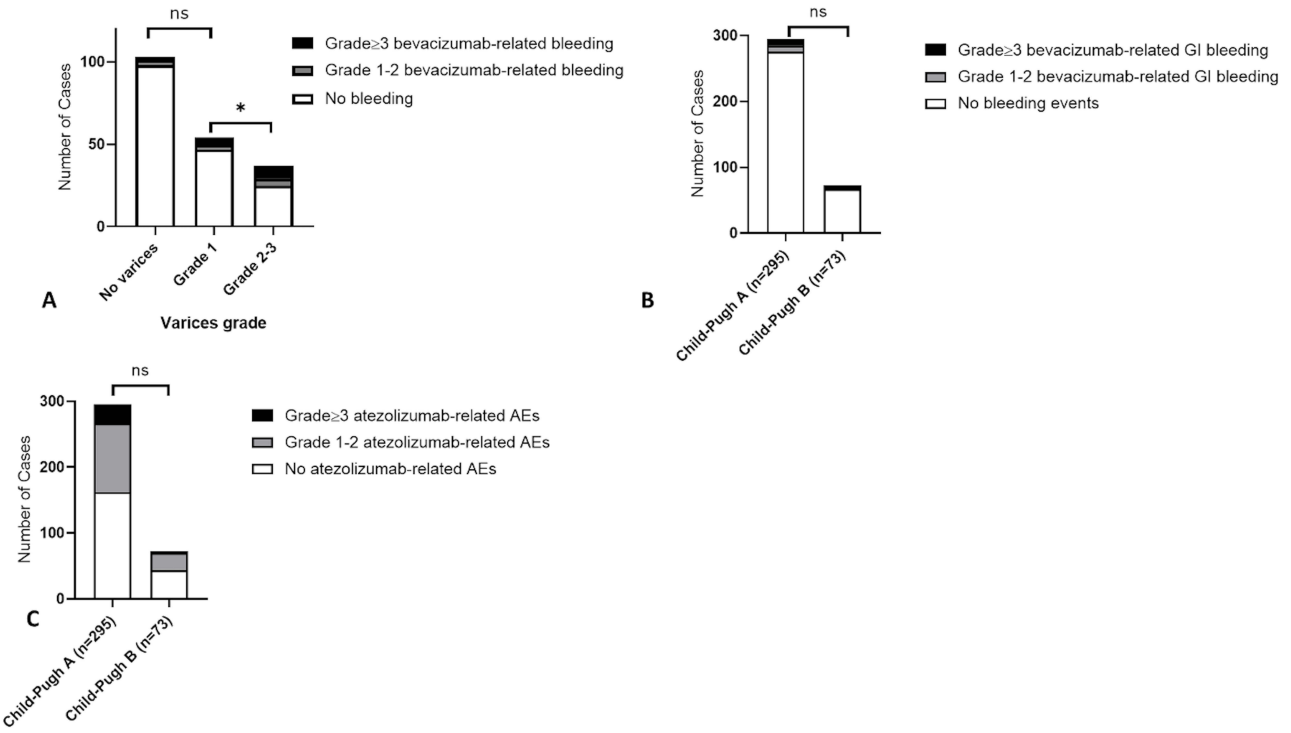

Figure 2 (**A**) Graphical representation of GI bleeding events in relationship with pre-treatment varices' grade. (**B**) Number of bevacizumab-related bleeding events across CP classes. (**C**) Number of Atezolizumab-related AE across CP classes.
Note: *p <0.05.
Abbreviation: ns, not significant.

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No differences were observed when comparing CP-A and CP-B patients in terms of toxicity (Figure 2B and C). In particular, GI bleeding events of any grade were reported by 20 CP-A patients (6.8%) and 6 CP-B patients (8.2%), whereas grade ≥3 GI bleeding events were reported by 24 CP-A (3.5%) and 6 CP-B (8.2%) patients (p>0.05).

Treatment Efficacy and Role of the ALBI Score as a Predictor of Overall Survival

In the overall population, the median OS (mOS) was 14.7 months (95% CI, 13.4–16.1) (Figure S1A). The 6-month survival rate were 78.6%, while the 12-month survival rate was 59.5%. CP-A patients achieved a mOS of 15.7 months (95% CI, 13.8–17.6), while it was 6.6 months (95% CI, 5.4–7.9) for CP-B patients (p<0.001) (Figure S2A). The median PFS (mPFS) of the overall sampled population was 5.9 months (95% CI, 4.8–7.1) (Figure S1B), while it was 6.8 months (95% CI, 5.4–8.2) for CP-A patients and 3.2 months (95% CI, 2.6–3.8) for CP-B patients (p<0.001) (Figure S2B).

In the univariable model, BCLC stage (A/B vs C), AFP (≥400 vs <400ng/mL), ALBI score (2/3 vs 1), CP class (B vs A), presence of PVT, and ECOG PS (1/2 vs 0) predicted OS and PFS, whereas in the multivariable models, AFP and ALBI were significantly associated with both OS and PFS, while PVT only predicted OS (Table 3).

Table 3 Univariate and Multivariate Analyses for Overall Survival (OS) and Progression Free Survival (PFS)

	Overall Survival HR;95% CI (P-value)		**Progression Free Survival HR;95% CI (P-value)**	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**
Age ***>65 vs ≤65***	1.56;1.07–0.76 (0.56)		0.91;0.70–1.18 (0.48)	
BCLC ***A/B vs C***	0.95;0.91–0.99 **(0.026)**	0.97;0.60–1.56 (0.88)	0.96;0.93–0.995 **(0.023)**	0.85;0.60–1.19 (0.33)
AFP ***≥400 vs <400***	1.78;1.26–2.51 **(0.001)**	1.51;1.06–2.14 **(0.021)**	1.54;1.19–1.99 **(0.001)**	1.44;1.10–1.88 **(0.007)**
ALBI ***2/3 vs 1***	4.10;2.72–6.19 **(<0.001)**	3.32;2.11–5.24 **(<0.001)**	1.03;1.01–1.04 **(<0.001)**	1.50;1.11–2.03 **(0.008)**
Child-Pugh ***B vs A***	2.70;1.85–3.97 **(<0.001)**	1.22;0.80–1.88 (0.35)	1.84;1.35–2.50 **(<0.001)**	1.28;0.90–1.83 (0.17)
Cirrhosis ***Y vs N***	1.54;0.95–2.51 (0.08)		1.16; 0.83–1.61 (0.39)	
PVT ***Y vs N***	2.57;1.81–3.65 **(<0.001)**	1.68;1.11–2.54 **(0.014)**	1.45;1.12–1.87 **(0.005)**	1.05;0.77–1.43 (0.75)
EHS ***Y vs N***	0.96;0.67–1.36 (0.79)		1.28;0.99–1.66 (0.059)	
ECOG PS ***1/2 vs 0***	1.49;1.04–2.12 **(0.029)**	1.40;0.95–2.09 (0.09)	1.37;1.06–1.78 **(0.017)**	1.24;0.93–1.65 (0.15)
Aetiology ***Viral vs Non Viral***	0.85;0.60–1.20 (0.85)		1.02;0.78–1.33 (0.89)	

Note: Bold p-values express significant differences.

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; BCLC, Barcelona Clinic Liver Cancer; AFP, alpha-fetoprotein; ALBI, Albumin Bilirubin grade; Y, yes; N, no; PVT, portal vein thrombosis; EHS, extra-hepatic spread; ECOG PS, Eastern Cooperative Oncology Group Performance Status.

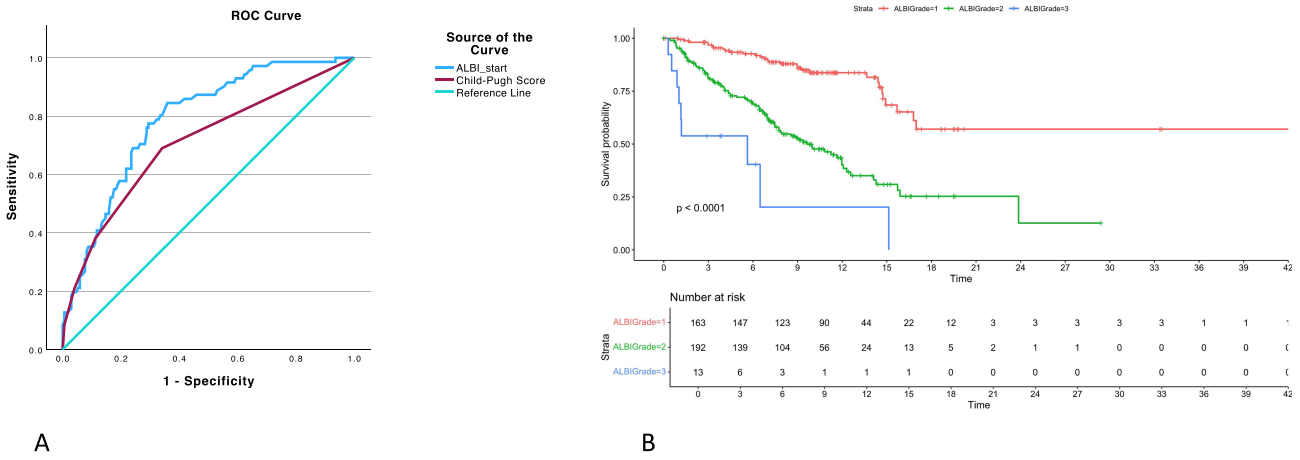

Figure 3 ROC curve analysis demonstrating the role of baseline ALBI and Child-Pugh score in predicting 6-month mortality from Atezolizumab and Bevacizumab commencement (**A**). Kaplan-Meier curves showing overall survival stratified per ALBI Grade at baseline (**B**).
Abbreviation: ROC, Receiving operating characteristic.

Baseline ALBI score, analysed as continuous variable, was a better predictor for 6-month survival than the CP Score, with an area under the curve of 0.79 (95% CI, 0.73–0.85) for ALBI score and 0.71 (95% CI, 0.63–0.78) for CP score (Figure 3A).

When stratifying OS for baseline ALBI grade, mOS for ALBI 1 patient was not reached (mean OS 29.3 months; 95% CI, 24.9–33.7), while it was 9.7 months (95% CI, 6.98–12.29) for ALBI 2, and 5.6 months (95% CI, 0.1–12.0) for ALBI 3 (p value for log-rank <0.001; Figure 3B). Coherently, mPFS stratified per ALBI grade was 8.1 months (95% CI, 6.0–10.2) for ALBI 1, 4.5 months (95% CI, 3.7–5.3) for ALBI 2, and 1.2 months (95% CI, 0.1–3.6) for ALBI 3 patients (p value for log-rank <0.001).

At the time of treatment discontinuation, all patients had ALBI scores of 2 or 3. ALBI score also predicted worse OS after discontinuing A+B, with ALBI 2 patients achieving a median post-ICI OS of 6.8 months (95% CI, 4.4–9.2), while ALBI 3 reached 1.6 months (95% CI, 0.6–2.7) (p value for log-rank <0.001).

The radiological response was assessed in 334 patients (90.5%) according to RECIST v1.1 criteria. Among these patients, eight (2.4%) achieved CR, 87 (26.0%) achieved PR, and 158 (47.3%) achieved SD, while PD was the best response in 81 (24.3%) patients. ORR was 28.4%, and the DCR was 75.7% (Table S2). The response was not significantly different across CP classes, with an ORR of 30.5% in CP-A and 18.6% in CP-B (p=0.12), and it was not influenced by age (>65 vs ≤65 years), presence of baseline PVT, aetiology (viral vs non-viral), ALBI grade (1 vs 2/3), and ECOG PS (0 vs 1/2) (p>0.05), while it was higher in patients with BCLC stage C vs A/B (32.2% vs 19.1%, p=0.017).

The median treatment duration was 3.6 months (IQR 1.4–8.3), and was longer in patients with CP-A liver function than in those with CP-B class (4.4 vs 2.1, p=0.002). At the data cutoff in April 2022, 252 patients (68.5%) discontinued treatment; 152 patients (41.3%) had radiologically proven disease progression, 30 (8.2%) because of clinical deterioration, 29 (7.9%) because of unacceptable toxicity, 20 (5.4%) due to death, and 21 (5.7%) due to other reasons.

When radiological progression was assessed, most patients (48%) had intrahepatic progression, 26% had extrahepatic progression, and 26% had combined intra-and extrahepatic progression. After treatment discontinuation, 127 patients (46%) received a further line of systemic treatment, of whom 90 received a tyrosine kinase inhibitor (TKI).

Discussion

Liver impairment plays a pivotal role in the prognosis of HCC patients. Solid evidence regarding its impact on patients with HCC has already been published[16,21,22] while data regarding the safety of systemic anticancer treatments in patients with limited liver function impairment are emerging.[23,24]

HCC is often associated with liver cirrhosis and affected patients are particularly prone to bleeding. The most frequent cause of bleeding is GI bleeding related to portal hypertension, provoking bleeding due to mechanical injury and/or hemostatic failure.[19]

In this multicenter study, we provided evidence regarding the use of ALBI grade as a potential predictor of GI bleeding events in patients with unresectable HCC receiving A+B as first-line treatment. In addition, and in keeping with evolving evidence across therapeutic modality,[17,25,26] we also showed that liver function assessed by ALBI rather than the CP score is a better predictor of OS in these patients.

The rate of GI bleeding events in our cohort was strikingly similar to that of the severe bleeding events reported in the IMbrave150 trial (7% in both studies). Pre-treatment EGD was available for only approximately half of the accrued patients; among them, 46% had gastroesophageal varices. Suboptimal adherence to pre-treatment EGD screening is probably related to the COVID-19 pandemic when access to EGD is deprioritized owing to the high risk of mortality in patients with cancer.[27]

Our data showed that baseline platelets, PVT and gastroesophageal varices were associated with an increased risk of GI bleeding events. Notably, in our cohort, only patients with high-risk (G2-G3) varices were at an increased risk of bleeding, while we did not observe such a difference between patients with G1 varices and those with no varices. These results coincides with known clinical evidence on varices in cirrhotic patients, albeit suggesting the applicability of this concept in the setting of advanced HCC in line with the results of Ha et al in a smaller cohort of patients.[28] Interestingly, only a worse ALBI grade, and not the CP class, was associated with an increased risk of bleeding, with 1 of 10 patients with ALBI grade 2 or 3 who experienced GI bleeding versus only 3 of 100 patients in the ALBI grade 1 subgroup. Such a result may seem counterintuitive because the CP score, in contrast to the ALBI grading system, includes the design of a coagulopathy test, namely, INR. However, INR primarily reflects liver synthetic function and it has been recently proved as largely ineffective in determining the risk of bleeding in cirrhotic patients, characterized by a labile rebalanced hemostatic state where pro-thrombotic and anti-hemostatic changes are present at the same time.[19] Our findings lead us to speculate that the association between a higher ALBI grade and bleeding events can be determined by different factors.

On the one hand, the ALBI grade is able to capture the impact of different degrees of liver impairment on patients' hemostatic balance by providing a more granular assessment of liver residual function. This aspect enables us to better estimate the risk of developing any kind of bleeding event in cirrhotic patients, including those non related to portal hypertension which are more related to liver dysfunction rather than portal hypertension.

In addition to this, the ALBI score demonstrated a better correlation than the CP score with the hepatic venous portal pressure gradient[29] which is directly associated with portal hypertensive bleeding events, thus representing another plausible explanation for the predictive role of ALBI in GI bleeding events related to portal hypertension.

The identification of an effective predictor of bleeding events is of utmost importance because it could potentially impact the choice of the first-line regimen. Given the recent approval by several regulatory agencies of the dual checkpoint inhibitor blockade durvalumab and tremelimumab for unresectable HCC, a first-line therapeutic option that does not include a vascular-modifying agent could gain popularity in patients with a baseline elevated risk of GI bleeding.

ALBI is progressively superseding the CP score as the most effective tool to assess liver function after demonstrating its superiority across different HCC treatment modalities,[25] however there is still limited real-world evidence regarding its prognostic impact in patients who received A+B as a first-line treatment, and no direct comparison with CP assessment is currently available.

In this cohort, both the CP score and ALBI grade were associated with OS in univariate analysis, along with other known prognostic factors (ie, ECOG-PS, extrahepatic spread, BCLC stage, AFP serum levels, and neoplastic portal vein thrombosis).

Notably, only ALBI confirmed its independent prognostic impact in multivariable analysis, where higher ALBI grade (2 and 3 versus 1) independently predicted a 3-fold risk of death, in line with previous reports from our group[24] and with other small-sized retrospective studies involving patients treated with A+B as the second or third line.[18,30]

Remarkably, the ALBI grade maintained its prognostic relevance even at treatment discontinuation, where an inferior ALBI grade was correlated with prolonged post-treatment OS, confirming similar results obtained in patients with HCC after receiving either TKI[31] or different therapeutic regimens with immune checkpoint inhibitors.[17]

Finally, to verify whether there were any differences between the CP and ALBI scores in predicting OS, we performed a 6-month landmark survival analysis comparing these two different methods of assessment of liver function, demonstrating that ALBI superiority, which was analyzed as a continuous variable, had an ROC of 0.79 vs 0.71 of the CP score. This result inclines us to further supports the idea that serum albumin and bilirubin levels alone are more accurate metrics of liver function impairment compared with the CP score, which in some of its composing items (ie, ascites and encephalopathy) is known to be more unreliable because of low interobserver agreement and less information regarding the residual liver function, particularly in cirrhotic patients with superimposed HCC, where ascites can even be secondary to other possible causes such as peritoneal metastasis.

Our study has several limitations. First, the retrospective nature of the dataset, although prospectively maintained, could not replace the evidence generated by prospective studies. Second, EGD was available for only approximately half of the population, and no data regarding previous episodes of bleeding was available, causing a possible selection bias.

Finally, the retrospective design of the study implies a lack of standardization in the management of AEs, eligibility assessments, and radiological follow-up, both in terms of timing and technique, thereby partially impairing the robustness of the findings. However, heterogeneity in the management of HCC should be partially reduced, because all patients were treated in tertiary centers with considerable experience in this field in the context of multidisciplinary meetings.

Conclusion

This retrospective study demonstrated that ALBI grade is an effective predictor of GI bleeding in patients receiving A+B as first-line systemic treatment for HCC. Additionally, we demonstrated that ALBI can independently identify a subgroup of patients receiving A+B with a higher probability of achieving improved OS. The ALBI score performed better as a prognostic tool than the CP score in predicting 6-month mortality and maintained its prognostic impact even after discontinuation of A+B. The role of the ALBI grade as a predictor of GI bleeding should be confirmed in prospective risk stratification studies.

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