ALBI grade: Evidence for an improved model for liver functional estimation in patients with hepatocellular carcinoma

Coskun O. Demirtas,[1,†] Antonio D'Alessio,[2,3,†] Lorenza Rimassa,[3,4] Rohini Sharma,[2] David J. Pinato[2,5,*]

Summary

Hepatocellular carcinoma (HCC) usually arises in the context of a chronically damaged liver. Liver functional estimation is of paramount importance in clinical decision making. The Child-Pugh score (CPS) can be used to categorise patients into 3 classes (A to C) based on the severity of liver functional impairment according to 5 parameters (albumin, bilirubin, prothrombin time, presence of ascites and hepatic encephalopathy). The albumin-bilirubin (ALBI) grade has emerged as an alternative, reproducible and objective measure of liver functional reserve in patients with HCC, defining worsening liver impairment across 3 grades (I to III). The ALBI score can identify different subgroups of patients with different prognoses across the diverse Barcelona Clinic Liver Cancer stages and CP classes, making it an appealing clinical predictor. In patients treated with potentially curative approaches (resection, transplantation, radiofrequency ablation, microwave ablation), ALBI grade has been shown to correlate with survival, tumour relapse, and post-hepatectomy liver failure. ALBI grade also predicts survival, toxicity and post-procedural liver failure in patients treated with transarterial chemoembolisation, radioembolisation, external beam radiotherapy as well as multi-kinase inhibitors (sorafenib, lenvatinib, cabozantinib, regorafenib) and immune checkpoint inhibitor therapy. In this review, we summarise the body of evidence surrounding the role of ALBI grade as a biomarker capable of optimising patient selection and therapeutic sequencing in HCC.

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer-related deaths worldwide and, unlike other cancer types, its incidence and mortality rates continue to rise.[1] Most HCC-related deaths occur on a background of chronic liver disease (CLD)[2] secondary to hepatitis B or C virus infection and alcohol-related liver disease and increasingly non-alcoholic fatty liver disease.[2,3] As such, patients with HCC usually have 2 distinct pathologies that compete in terms of prognostic impact. Whilst there are therapies directed against the cancer itself, CLD and its sequelae, once established, cannot be reversed.

With the progression of CLD, the liver becomes fibrotic and cirrhotic resulting in portal hypertension, synthetic dysfunction, encephalopathy, hepatorenal or hepatopulmonary syndrome. It is well established that the severity of CLD is an independent prognostic factor in patients with HCC, and that the degree of liver function also impacts on the metabolism of cancer therapeutics influencing both efficacy and toxicity.[4] The prognostic importance of CLD severity is reflected in the myriad of staging systems for HCC that incorporate a measure of liver function or features of portal hypertension, including measures of synthetic function such as albumin and prothrombin time, serum bilirubin, ascites and encephalopathy.[5] However, the most widely used score to assess the mortality risk associated with CLD is the Child-Pugh score (CPS). CPS is made up of 5 parameters: albumin, bilirubin, prothrombin/international normalised ratio, extent of ascites, and degree of hepatic encephalopathy, each parameter of which is weighted to derive a cumulative score and associated prognosis: CP-A is associated with a 2-year survival of 85%, CP-B 60% and CP-C 35%. Whilst CPS was originally introduced in 1964 for the preoperative assessment of mortality from bleeding varices as a result of portal hypertension,[6] its use has been extended to all areas of CLD and it has been included in many HCC staging systems, including the Cancer of the Liver Italian Program score,[7] the Japan Integrated Staging score[8] and the widely used Barcelona Clinic Liver Cancer (BCLC) score.[9] However, despite its widespread acceptance, it is unclear if CPS is the most suitable score for assessing liver dysfunction in patients with HCC.

Real-world studies have illustrated that patients with CP-B have worse survival outcomes than patients with CP-A when treated with sorafenib.[10] However, with the introduction of antiviral therapies, and the steady increase in cases of NAFLD-associated HCC,[11] there has been an improvement

[1]Marmara University, School of Medicine, Department of Gastroenterology, Istanbul, Turkey; [2]Department of Surgery & Cancer, Imperial College London, Hammersmith Hospital, London, UK; [3]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; [4]Medical Oncology and Hematology Unit, Humanitas Cancer Center, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; [5]Division of Oncology, Department of Translational Medicine, University of Piemonte Orientale, Novara, Italy
[†]Equal contribution.

* Corresponding author. Address: Department of Surgery & Cancer, Imperial College London Hammersmith Campus, Du Cane Road, W12 0HS, London UK; Tel.: +44 020 83833720 E-mail address: david.pinato@imperial.ac.uk (D.J. Pinato).

in hepatic reserve in patients with HCC allowing more patients to receive systemic therapy. Most patients with HCC will have CP-A at presentation[12] and there is a need for better prognostic delineation in this group.

CPS has a number of key limitations which further limit its applicability to HCC.[13] Firstly, the assessment of 2 key components of the score, hepatic encephalopathy and ascites, are subjective and the severity may vary with the use of lactulose and diuretics. Secondly, the cut-off points for the laboratory variables albumin, bilirubin and prothrombin time were arbitrarily defined to predict operative mortality and their applicability to non-cirrhotic patients with HCC has not been determined.[6] Moreover, patients at the extremes of the distribution for each blood parameter are classified equally as patients with marginally deranged laboratory parameters, producing "floor" and "ceiling effects", which limit accurate prognostication.[14] Apart from grade of ascites, the score does not include platelet counts or other biomarkers of portal hypertension which have been illustrated to impact on outcome, as demonstrated by the BCLC score which incorporates measures of portal pressure to determine post-surgical outcomes. Finally, liver dysfunction in patients with HCC will reflect tumour burden rather than CLD, which again is not addressed by the CPS.

In order to address these limitations of CPS when applied to HCC, the albumin-bilirubin (ALBI) score was proposed by Johnson and colleagues in 2014 as an evidence-based scoring system designed specifically to assess liver function in patients with HCC.[15] The score only uses albumin and bilirubin, which are independently associated with overall survival (OS),[16] in a complex nomogram ([log10 bilirubin (in μmol/L) × 0.66] + [albumin (in g/L) × –0.085]), such that grades 1, 2, 3 = ≤–2.60, <–2.60 to ≤–1.39, > –1.39, respectively. The formula allows for the analysis of albumin and bilirubin as continuous variables rather than categorical variables using international units, further strengthening its appeal for HCC prognostication. The ALBI grade was initially applied in a Japanese training set where grade 1 was classified based on the 25% of patients with the lowest risk of death, grade 3 was based on the 10% with highest risk of death and grade 2 was defined as those in between. The model was then validated in independent international cohorts from Europe, China and the United States in patients with different background aetiologies of liver disease who had received different treatment modalities.

ALBI grade as a predictor in early-stage HCC

Patients who present with small, liver-confined HCC and have preserved performance status and liver function are categorised within the BCLC 0-A stage. For these patients, liver resection and ablation either using radiofrequency (RFA) or microwave (MWA) approaches are potentially curative, however the relapse rates can be as high as 70%. Whilst liver resection and ablation are thought to be equivalent in terms of efficacy in obtaining local disease control,[17] liver function and co-morbid burden are factors of paramount importance in determining suitability to either approach.

Several retrospective studies have reported that ALBI grade is superior to CPS (both at baseline and postoperatively) for OS prediction in patients who undergo surgical resection.[18-21] Normally, surgical HCC candidates are pre-selected from patients with CP class A. However, survival outcomes can still

be quite heterogeneous within patients undergoing surgery. Preoperative ALBI grade was able to stratify patients according to different survival outcomes within CP class A in 2 retrospective studies from China.[22,23] From this perspective, ALBI grade has the potential to be used as an additional tool for selecting surgical candidates, and guiding physician and patient decisions.

Both preoperative and postoperative ALBI grades were found to be independently associated with recurrence after surgery.[24-27] Two retrospective studies from Taiwan have demonstrated a more effective role of postoperative than preoperative ALBI grade in predicting late-recurrences and long-term prognosis, even years after surgery.[28,29] Moreover, changes in ALBI grade after hepatectomy were found to be independently associated with inferior OS and recurrence-free survival (RFS).[30] Additionally, ALBI grade was able to predict postoperative outcomes and major complications, including post-hepatectomy liver failure (PHLF), better than the CP classification in several retrospective studies.[18,31-34] Similarly, ALBI grade predicted OS and RFS better than model for end-stage liver disease (MELD) score in patients with HCC who underwent liver transplantation (LT). ALBI grade was also associated with fatal complications of post-transplant graft dysfunction and infection, suggesting that it could be useful in selecting LT candidates with low oncological risk.[35,36] The superior prognostic value of ALBI compared to CPS has been reported for RFA and MWA as well,[37-40] where patients in the most favourable groups (ALBI grade I) had a higher 5-year OS rate ranging from 77.9% to 88.5% compared to others (ALBI grade II/III) with a 5-year OS rate ranging from 38.6% to 73.8%.

A number of studies have proposed prognostic nomograms based on ALBI grade to predict recurrence,[25-27] PHLF,[31] or OS[38,40] after surgical resection or ablative therapies.[25-27,31,38,40] In addition to ALBI grade, the nomograms to predict recurrence were constructed with other well-established prognostic co-variates including alpha-fetoprotein (AFP) level, macrovascular invasion, cirrhosis, tumour size and number of tumoral lesions or total tumour volume instead. To predict PHLF after surgery, Shi et al. analysed 767 patients with HCC who underwent surgery in 6 Chinese centres, and derived 2 prognostic nomograms using the combination of preoperative or postoperative ALBI grade with aspartate aminotransferase to platelet count index (APRI).[31] These 2 online calculators combining ALBI and APRI were proposed as useful preoperative and postoperative tools for individually predicting the occurrence of PHLF among patients with

Table 1. Summary of studies investigating the role of ALBI grade in early-stage HCC therapy options.

Reference	Study design	Patients	Treatment modality	Key findings
Wang et al.[18]	Retrospective	1,242	Resection	ALBI grade predicted PHLF and OS more accurately than the CP class.
Li et al.[19]	Retrospective	491	Resection	ALBI grade was shown to be an independent prognostic factor for OS, and it showed superior predictive value for postoperative outcomes over CP score.
Ho et al.[20]	Retrospective	645	Resection	ALBI revealed the highest homogeneity and lowest value among 12 models in survival prediction, indicating a better prognostic performance.
Zhao et al.[21]	Retrospective	196	Resection	ALBI grade had better prognostic performance than CP score following hepatectomy.
Ma et al.[22]	Retrospective	318	Resection	ALBI grade was the most significant independent predictor of OS and was able to stratify CP class A according to different survival outcomes.
Dong et al.[23]	Retrospective	654	Resection	Preoperative ALBI grade was an independent predictor of OS and DFS in solitary HCC cases within the Milan criteria and CP class A cirrhosis.
Lee et al.[24]	Retrospective	465	Resection	Preoperative ALBI grade, but not postoperative ALBI, was an independent risk factor for early recurrence (<1 year). ALBI grade was not found to be associated with late recurrence (>1 year).
Ho et al.[25]	Retrospective	1,038	Resection	ALBI grade was independently associated with tumour recurrence, and it was integrated into a nomogram to predict recurrence.
Xu et al.[26]	Retrospective	318	Resection	ALBI is associated with early-relapse after curative hepatectomy and integrated into a nomogram to predict early-relapse after surgery.
Wu et al.[27]	Retrospective	485	Resection	Preoperative and postoperative high ALBI grade were independent risk factors for recurrence. ALBI grade was integrated into 2 nomograms (preoperative and postoperative) to predict recurrence.
Lin et al.[28]	Retrospective	383	Resection	Postoperative 5th year higher ALBI grade (2 and 3), not preoperative ALBI, was an independent predictor of HCC recurrence, poorer OS and RFS.
Cho et al.[29]	Retrospective	525	Resection	Postoperative first year ALBI grade was an independent predictor of RFS and liver-related survival. The postoperative ALBI grade showed better performance for predicting outcomes after curative hepatectomy than the preoperative ALBI grade.
Ye et al.[30]	Retrospective	300	Resection	Higher postoperative ALBI grade and ALBI changes after hepatectomy were independent predictors of an inferior OS and RFS.
Shi et al.[31]	Retrospective	767	Resection	Preoperative and postoperative high ALBI grade were independent risk factors associated with PHLF. ALBI grade was integrated into preoperative and postoperative nomograms.
Amisaki et al.[32]	Retrospective	136	Resection	Postoperative ALBI grade was associated with patients' surgical factors of repeated hepatic resection, intra-operative bleeding and surgery duration. Postoperative ALBI grade, but not preoperative ALBI grade, was an independent predictive factor for OS and RFS.
Zou et al.[33]	Retrospective	229	Resection	ALBI score showed superior predictive value for postoperative outcomes (major complications, including PHLF) over CP score in patients with HBV-related HCC.
Fagenson et al.[34]	Retrospective	13,783	Resection	ALBI grade II or III was a stronger predictor than MELD ≥10 with respect to severe PHLF and OS. ALBI had better discrimination compared with MELD for severe PHLF (AUC: 0.67 vs. 0.60) and mortality (AUC: 0.70 vs. 0.58).
Kornberg et al.[35]	Retrospective	123	LT	Preoperative ALBI grade I or II were identified as independent predictors of RFS. ALBI grade III proved to be the strongest indicator of microvascular invasion. ALBI was integrated into an oncological risk score to select liver recipients with a low oncological risk profile.
Tai et al.[36]	Retrospective	81	LT	Higher ALBI grade (grade III or ≥ -1.28) was an independent predictor of post-transplant survival, but not the MELD score. ALBI score was also associated with fatal complications of post-transplant graft dysfunction and infection.
Oh et al.[37]	Retrospective	368	RFA	Among patients with very early-stage HCC treated with RFA, ALBI grade showed a better performance in assessing liver function than CP score.
An et al.[38]	Retrospective	183	MWA	ALBI grade was independently associated with OS and was integrated into a nomogram for patients with HCV-related HCC.
Chen et al.[39]	Retrospective	271	RFA	In patients with very early-stage HCC treated with RFA, ALBI grade was an independent risk factor for predicting inferior OS and RFS.
Kao et al.[40]	Retrospective	622	RFA	ALBI grade is independently associated with OS and was used to generate a prognostic nomogram.

ALBI, albumin-bilirubin; AUC, area under the curve; CP, Child-Pugh; DFS, disease-free survival; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; MWA, microwave ablation; OS, overall survival; PHLF, post-hepatectomy liver failure; RFA, radiofrequency ablation; RFS, recurrence-free survival.

HCC. Two nomograms were constructed from retrospective Chinese cohorts to predict OS for patients undergoing locoregional therapies including RFA and MWA.[38,40] The newly constructed nomogram for patients undergoing RFA used ALBI grade, age, international normalised ratio, AFP and number of tumoral lesions. The prognostic nomogram proposed for those undergoing MWA used ALBI grade, age, AFP, tumour number, platelet count, location of tumour, and CPS. The evidence in support of the clinical utility of ALBI grade in early-stage HCC is summarised in Table 1.

ALBI grade and the prognostic heterogeneity of intermediate-stage HCC

According to the BCLC staging system, intermediate-stage HCC is defined as patients with CP class A or B, with a single tumour larger than 5 cm, or 2 to 3 tumours larger than 3 cm, or more than 3 tumours regardless of size, and without macrovascular invasion or extrahepatic spread.[41] In general, transarterial chemoembolisation (TACE) is the recommended treatment modality for patients with intermediate-stage HCC by the European Association for the Study of Liver Disease and American Association

for the Study of Liver Disease guidelines.[42,43] However, the definition of BCLC B staging is still widely heterogenous due to either tumour extension (from unifocal HCC or small bifocal HCC to nearly total tumour replacement of liver parenchyma with multiple lesions) or liver synthetic function (from CPS A5 to B9). Therefore, recommending a single treatment option for this highly heterogeneous group may be too restrictive and irrational in clinical practice.[44] In this regard, treatment migration is recommended across BCLC stages based on a multidisciplinary appraisal. For instance, transarterial radioembolisation (TARE) is considered a more suitable therapeutic option for intermediate-stage HCC with multiple lesions and preserved liver function. However, for patients with higher CPS scores (7 to 9) within intermediate-stage HCC, TARE carries a higher risk of decompensation because of radiation-induced liver disease. To facilitate these treatment migration decisions in this highly heterogeneous patient population, Bolondi criteria were proposed in 2012 as a subclassification method for intermediate-stage HCCs based on CPS and up-to-7 criteria, with treatment recommendations for each substage.[45] Modified Bolondi criteria were then proposed in 2015 by migrating CPS and fulfilment of up-to-7 criteria across substages. Modified Bolondi criteria recommended more diverse treatment options beyond TACE and suggested a more aggressive approach using curative options for patients in the B1 substage.[46] Still, the majority of patients with intermediate-stage HCC are treated with local interventional therapies in clinical practice.

ALBI grade successfully predicted OS and RFS and outperformed the CPS in terms of prognostic ability in patients with unresectable HCC undergoing non-curative locoregional therapy, including TACE[47-54] and TARE.[55-57] Mohammed et al. demonstrated that higher pre-treatment ALBI grade (III vs. I-II) was associated with severe adverse events and independently predicted acute-on-chronic liver failure at 90 days after TACE.[58] In retrospective evaluation studies of patients with HCC treated with stereotactic radiation therapy, ALBI grade could predict OS, as well as acute and late radiation toxicities.[59-63] Several prognostic nomograms were constructed based on ALBI grade to predict prognostic outcomes of patients treated with TACE[49,51,52,54] (Table 2).

ALBI grade as a prognostic biomarker in the expanding landscape of systemic therapy for HCC

Traditionally, patients with intermediate-stage (BCLC B) HCC are initially considered for standard TACE therapy, while advanced stage (BCLC C) patients or BCLC B patients not deemed amenable to further locoregional approaches are generally offered systemic treatment options. The mainstay of systemic treatment for HCC has been the multikinase inhibitor sorafenib for a decade[64,65]; recently, another multikinase inhibitor, lenvatinib, was shown to be non-inferior to sorafenib as first-line treatment.[66] Only recently, the combination of atezolizumab, an anti-programmed cell death ligand-1 (PD-L1) monoclonal antibody (mAb), and bevacizumab, an anti-vascular endothelial growth factor (VEGF) mAb, has been defined as standard of care for first-line treatment, having performed better than sorafenib in terms of survival in the IMbrave150 study.[67]

Optimising the switch from locoregional to systemic treatment is crucial, since repeated TACE could lead to liver function deterioration,[68] while abandoning locoregional approaches too early in the continuum of care could have a detrimental effect on survival.[69] The preservation of liver function is a non-negotiable criterion in the management of patients with HCC, since all currently available therapies have been approved for CP-A patients, and no robust prospective safety data are available for patients with more impaired liver function. Also, liver function impairment is a decisive confounding factor in clinical trials evaluating survival, since it acts as a competitive cause of death and can impair drug metabolism, potentially worsening tolerability. For these reasons, liver function has to be carefully monitored, as it could be the underlying cause of failure of clinical trials evaluating survival.[70] CPS has been the main system used to screen patients for entry into HCC clinical trials, however, the same CP class can include patients with different outcomes. This is why ALBI grade plays an important role in patient stratification, since it highlights the presence of subgroups within the same CP classes with different prognoses. ALBI grade was also shown to correlate with liver function across the different BCLC stages in a wide multicentre retrospective study.[71] In particular, for patients with advanced disease treated with sorafenib, the ALBI grade was found to be an independent predictor of OS, which ranged from 16 months in ALBI I to 7.6 in ALBI II to 4.8 in ALBI III patients (hazard ratio 1.6; 95% CI 1.3–2.0; p <0.001).[71] In a retrospective analysis of 1,019 sorafenib-treated patients with HCC, regarding patients with CP-A liver function, both CPS and ALBI grades were similarly effective at predicting survival.[12] Anyway, within CP-A patients, survival greatly varied between ALBI I and II patients, indicating a possible role for ALBI in clinical trial stratification. Several other retrospective studies corroborated the prognostic role of ALBI grade for advanced disease, showing that patients with lower ALBI grades had a better OS, progression-free survival, objective response rate (ORR), and tolerability when treated with sorafenib.[10,72-76] Other than baseline ALBI grade, a change in ALBI grade during treatment was also able to predict OS and reflect the hepatic reserve of these patients,[77] and thereby contribute to patient selection for second-line treatment after sorafenib.[78]

The predictive role of ALBI grade has also been explored in patients treated with lenvatinib. A post hoc analysis conducted on patients treated within the phase III REFLECT study[66] showed a possible prognostic role of ALBI grade, since patients with ALBI I vs. ALBI II had a better median OS, a higher ORR and less frequent grade ≥3 treatment-related adverse events, in both the sorafenib and lenvatinib arms.[79] A number of other retrospective analyses confirmed the role of the ALBI grade as a predictor of survival, ORR, toxicity, and eligibility to further systemic lines of treatment.[80-84] Also, in a retrospective study investigating 375 patients with HCC treated with lenvatinib, the ALBI grade was found to have a good correlation with nutritional status.[85]

The predictive role of ALBI grade was also confirmed for further lines of treatment. In particular, in 2 post hoc analyses conducted on patients treated with cabozantinib and ramucirumab in the CELESTIAL and REACH-2 trials, respectively, a more favourable ALBI grade correlated with improved OS and progression-free survival following treatment.[86,87] Besides, treatment-related adverse events were observed less frequently in patients with lower ALBI grade (I vs. II-III). For CP-B patients treated with regorafenib, a higher ALBI grade (III vs. I-II) predicted significantly poorer survival.[88] Moreover, patients with ALBI III liver function reported a significantly higher rate of grade 3-4 AEs, with a particular concern regarding bilirubin increase, and a higher rate of treatment discontinuation due to AEs. Also, no response to regorafenib was reported in CP-B ALBI III patients,

Table 2. Summary of studies investigating the role of ALBI grade in local therapy options in unresectable HCC.

Reference	Study design	Patients	Treatment modality	Key findings
Ho et al.[47]	Retrospective	881	TACE	ALBI grade served as an objective and feasible surrogate to predict the prognosis of patients undergoing TACE.
Waked et al.[48]	Retrospective	202	TACE	ALBI grade categorised patients receiving TACE into 3 clear prognostic groups, thereby emphasising the importance of underlying liver function in the outcome of TACE.
Lee et al.[49]	Retrospective	570	TACE	ALBI grade is an independent predictor of OS, and it was integrated into a prognostic nomogram.
Zhong et al.[50]	Retrospective	838	TACE	ALBI grade was an independent predictor of OS. ALBI grade performs at least no worse than CP score regarding survival prediction.
Ni et al.[51]	Retrospective	546	TACE + MWA	ALBI grade was an independent predictor of OS and RFS. ALBI was integrated into a nomogram to predict OS.
Nam et al.[52]	Retrospective	597	TACE	ALBI is an independent risk factor of OS and was integrated in an OS prediction model.
Zhao et al.[53]	Retrospective	221	TACE	Both ALBI and CP score are associated with OS, but ALBI grade had a better discriminatory ability than CP score in predicting survival.
Ho et al.[54]	Retrospective	1,051	TACE	Having ALBI grade II or III was independently associated with decreased OS. ALBI grade was integrated into a prognostic model to predict individual 3–5-year survival probability.
Mohammed et al.[58]	Retrospective	123	TACE	ALBI score before TACE is an independent predictor of ACLF at 90 days.
Mohammadi et al.[55]	Retrospective	124	TARE	ALBI showed a better performance and is a more sensitive marker of liver function to predict survival outcomes than CP score in the setting of mild dysfunction.
Gui et al.[56]	Retrospective	117	TARE	ALBI grade demonstrated clear survival discrimination that is superior to CP class among patients treated with TARE, particularly within the subgroup of CP class A patients.
Antkowiak et al.[57]	Retrospective	1,000	TARE	ALBI grade outperformed CP score in survival prognosis. ALBI was able to stratify prognostic outcomes across various BCLC stages. On sub-analyses, serum albumin, not bilirubin, appears to be the main driver of survival prediction.
Lo et al.[59]	Retrospective	152	SART	ALBI was an independent predictor of both OS and liver toxicity.
Murray et al.[60]	Retrospective	102	SBRT	The baseline ALBI grade was an independent predictor of post-SBRT toxicity (defined as an increase in CP score ≥2 within 3 months) and OS. ALBI was more discriminating than the CP score in predicting OS and toxicity in patients with CP class A.
Gkika et al.[61]	Retrospective	182	SBRT	A higher ALBI grade, as well as CP score, at baseline correlated with a higher incidence of acute and late radiation toxicities.
Su et al.[62]	Retrospective	594	SBRT	ALBI grade was able to stratify OS outcomes within CP class A (5 or 6), but has no predictive power for CP scores ≥7. The performance of ALBI and CP score for OS prediction was similar among CP class A patients.
Moczetuma-Velazquez et al.[63]	Retrospective	132	SIRT	ALBI grade III is an independent predictor of inferior OS and severe adverse events.

ACLF, acute-on-chronic liver disease; ALBI, albumin-bilirubin; CP, Child-Pugh; HCC, hepatocellular carcinoma; OS, overall survival; RFS, recurrence-free survival; SART, stereotactic ablative radiation therapy; SBRT, stereotactic body radiation therapy; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TARE, transarterial radioembolisation.

suggesting that the use of regorafenib in this subset of patients may be ineffective and, for this reason, should be discouraged.

Over the last years, the treatment algorithm for advanced HCC has been enriched by the introduction of immune checkpoint inhibitors (ICIs), which are mAbs that target immunomodulatory cellular pathways, thus counteracting tumour-mediated immunosuppression. Currently, the FDA-approved agents for sorafenib-pretreated patients are nivolumab and pembrolizumab, 2 anti-programmed cell death 1 (PD-1) mAbs, and the combination of nivolumab plus ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) mAb. These mAbs, by acting on 2 key immunosuppressor checkpoints, enhance the T cell-mediated immune response against tumour cells. The use of ICIs in the context of underlying chronic hepatic inflammation makes the development of an immune-related hepatotoxicity an issue of particular concern. Around 9–20% of patients report immune-related hepatitis, especially when treated with a combination of anti-PD-1 and anti-CTLA-4 mAbs.[89] For this reason, accurate patient selection and dedicated monitoring are crucial for the safe use of ICIs in HCC. However, no biomarker is currently available to predict the development of immune-related hepatitis, and even if the use of ICIs has only been approved for CP-A patients, preliminary data are promising in terms of safety even in patients with CP-B liver function.[90]

While ICIs have ushered in a new era of HCC management, only a few studies have investigated the potential role of ALBI grade in guiding the use of this novel treatment option. Although these studies were conducted in low numbers of patients, ALBI grade was still able to independently predict OS achieved by ICIs both in first and second line.[91-93] In 1 relatively large multicentre study investigating 341 ICI-treated patients with HCC, pretreatment ALBI grade independently predicted OS and was superior to CPS in predicting 90-day mortality. Moreover, ALBI grade at ICI cessation independently predicted post-immunotherapy OS as well.[94] The use of ALBI grade in patients undergoing systemic therapy is summarised in Table 3.

Future directions

The landscape of HCC treatment is becoming increasingly intricate. The availability of many new options poses the challenge of therapeutic sequencing and increases the complexity of personalising therapy across the continuum of care. However, less than 50% of patients with advanced HCC are eligible for second-line treatment, mainly because of liver impairment.[95] For this reason, the implementation of valid tools to adequately monitor liver function is crucial, in order to optimise treatment for each patient. In this regard, ALBI grade can play a key role in patient selection (Fig. 1). First, for BCLC B patients the baseline ALBI

Table 3. Studies investigating the role of ALBI grade in systemic agents in unresectable HCC.

Reference	Study design	Patients	Treatment modality	Key findings
Pinato et al.[72]	Retrospective	447	Sorafenib	ALBI grade at sorafenib discontinuation identified a subset of patients with prolonged stability of hepatic reserve and superior OS.
King et al.[10]	Retrospective	448	Sorafenib	Higher ALBI (II vs. I) grade showed lower median OS.
Lee et al.[73]	Retrospective	404	Sorafenib	ALBI grade III at progressive disease independently predicted poor PPS, suggesting that ALBI can stratify patients for second-line trials or salvage therapy.
Abdel-Rahman et al.[74]	RCT, phase III (NCT00699374)	544	Sorafenib	Low ALBI Grade (I vs. II) is associated with higher OS and PFS, and lower high-grade toxicity.
Tada et al.[75]	Retrospective	567	Sorafenib	ALBI grade was an independent predictor of OS and had a higher AUC value than CP score for predicting OS.
Rovesti et al.[76]	Retrospective	398	Sorafenib	Higher ALBI grade (II vs. I) independently predicted poorer OS.
Kuo et al.[77]	Retrospective	260	Sorafenib	Baseline ALBI grade and ALBI grade change during treatment independently predicts OS.
Takada et al.[78]	Retrospective	190	Sorafenib	Baseline ALBI grade and ALBI grade change at 4 weeks could guide second-line treatment after sorafenib.
Edeline et al.[12]	Retrospective	1,019	Sorafenib	Discriminatory abilities of CP score and ALBI were similar in CP class A patients, but better for CP score in the overall population.
Vogel et al.[79]	RCT, Phase III (REFLECT)	926	Lenvatinib/sorafenib (n = 452/474)	Median OS and ORR were higher, while TEAEs grade ≥3 were lower in lower ALBI grade (I vs. II).
Ueshima et al.[80]	Retrospective	82	Lenvatinib	ALBI grade (I vs. II-III) independently predicted a higher ORR and lower probability of treatment discontinuation due to adverse events
Shimose et al.[81]	Retrospective	177	Lenvatinib	Higher ALBI grade (II vs. I) independently predicts DLSAE.
Shimose et al.[82]	Retrospective	164	Lenvatinib	Low ALBI grade (I vs. II) independently predicted improved OS.
Hatanaka et al.[83]	Retrospective	93	Lenvatinib	The incidence of decreased appetite and fatigue was significantly less in patients with low ALBI grade (I vs. II+III)
Hatanaka et al.[84]	Retrospective	139	Lenvatinib	Baseline low ALBI grade (I vs. II) independently predicted the preserving of liver functions under lenvatinib therapy and eligibility for post-progression treatment.
Hiraoka et al.[85]	Retrospective	375	Lenvatinib	A good nutritional status or ALBI grade 1 was the best indication for lenvatinib use. ALBI had a good correlation with nutritional status.
Chan et al.[86]	RCT, phase III (CELESTIAL)	707	Cabozantinib/ placebo (n = 468/315)	Patients treated with cabozantinib had longer PFS and OS vs. those receiving placebo, regardless of ALBI grade. Outcomes were generally better in patients with ALBI grade I vs. II.
Kudo et al.[87]	RCT, phase III (REACH and REACH-II)	857	Ramucirumab/ placebo (n = 480/377)	Low baseline ALBI grade (I vs. II-III) independently predicted favourable OS. Baseline ALBI grades II and III were associated with increased incidence of liver-specific AEs and discontinuation rates in both treatments. Ramucirumab did not alter ALBI grade in the follow-up and improved OS irrespective of baseline ALBI grade.
Kim et al.[88]	Retrospective	59	Regorafenib	Among CP class B patients, higher ALBI grade (III vs. I-II) had a significantly poorer OS, suggesting regorafenib should not be used in CP class B patients with ALBI grade III.
Lee et al.[91]	Retrospective	95	Nivolumab/ pembrolizumab (monotherapy: 82/ combination: 13)	Low ALBI grade (I vs. II) independently predicted improved OS in a multivariate model.
Sung et al.[92]	Retrospective	33	Nivolumab	Low ALBI grade (I vs. II) independently predicted improved OS
Wong et al.[93]	Retrospective	25	Ipilimumab+ nivolumab/ Ipilimumab+ pembrolizumab (n=12 / 13)	Baseline ALBI grade, as well as CP score, was significantly associated with OS after a second-line ICI.
Pinato et al.[94]	Retrospective evaluation of prospectively maintained data	341	Anti-PD(L)-1 Monotherapy/ Anti-PD(L)1 + CTLA4 Anti-PD(L)1 + TKI Anti-CTLA-4 (n=290 / 25 / 24 / 1)	Pre-treatment ALBI independently predicted OS. ALBI was superior to CP score in predicting 90-day mortality, with a higher AUC. ALBI grade at ICI cessation independently predicted PIOS. Following adjustment for ICI regimen, neither ALBI nor CP score predicted ORR or TEAE.

AE, adverse event; ALBI, albumin-bilirubin; AUC, area under the curve; CP, Child-Pugh; DLSAE, discontinuation of lenvatinib due to severe adverse events; HCC, hepatocellular carcinoma; ICI, immune checkpoint inhibitor; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PIOS, post-immunotherapy overall survival; PPS, post-progression survival; TEAE, treatment-emerging adverse events; TKI, tyrosine kinase inhibitor.

grade and its change after TACE can help to disentangle the complex puzzle of switching from locoregional to systemic therapy. Also, for patients failing first-line systemic treatment, a close monitoring of changes in ALBI can help to select the ideal candidates for further lines of treatment. The use of ALBI score should be prospectively validated in large randomised clinical trials, since the knowledge derived from retrospective and observational studies is of limited value. Moreover, another possible application of the ALBI grade could be in the immunotherapy domain. Nivolumab is the only ICI with an acceptable safety profile in CP-B patients.[90] However, its use as monotherapy has failed to demonstrate any survival advantage when compared to sorafenib in first line in the phase III CheckMate-459 trial.[96] Anyway, it has demonstrated improved tolerability compared to sorafenib, in terms of toxicity and quality of life.[97] Maybe the integration of CP-B and ALBI could select patients
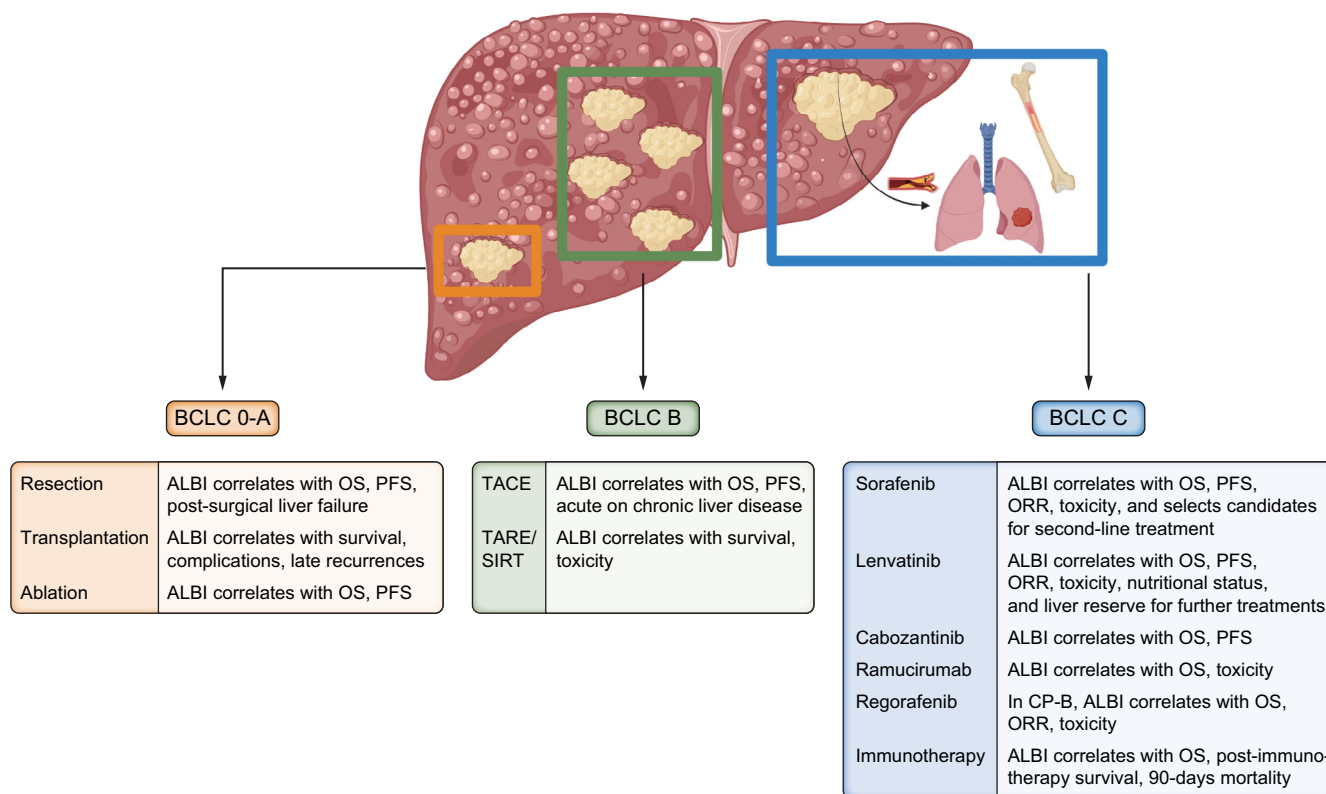
Fig. 1. Utility of the ALBI grade across BCLC stages and therapeutic modalities for HCC. ALBI, albumin-bilirubin; BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; SIRT, selective internal radiation therapy; TACE, transarterial chemoembolisation; TARE, transarterial radioembolization.

with impaired liver function who could still receive a safe and effective ICI-based regimen. Using ICIs in the context of a chronically inflamed liver, especially in patients with viral hepatitis, raises concerns regarding the development of immune-related hepatitis: in this regard, on-treatment ALBI grade variations could be used as an additional tool to monitor and eventually prevent the onset of hepatotoxicity. Also, ALBI could guide the possible future use of ICIs in earlier phases, as a neo-/adjuvant approach, in order to identify the patients who are least likely to develop hepatitis.

A major issue regarding the use of ICIs for HCC is the absence of predictive biomarkers of response and liver toxicity. ALBI grade could be the key to addressing this unmet need. However, its use must be prospectively validated in new immunotherapy trials, where it could be used to refine patient selection and improve clinical outcomes.

discussed in the manuscript apart from those disclosed. No writing assistance was utilised in the production of this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions
All the authors contributed to writing and revising the original draft. COD and AD contributed to conceptualization and visualization, DJP contributed to supervision and project administration.

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