Breaking the Child-Pugh Dogma in Hepatocellular Carcinoma

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The Child or Child-Turcotte score (1964) was proposed to assess prognosis in patients with cirrhosis and portal hypertension as a predictor of postoperative (portocaval shunt surgery) mortality.[1] The scoring system included five components, three subjective categorized variables: ascites, encephalopathy, and nutritional status and two objective continuous variables: serum albumin and bilirubin levels. The Child-Turcotte score was modified by Pugh in 1973, the nutritional status component being replaced by prothrombin time.[2] This modification has, henceforth, been referred to as the Child-Pugh score (C-P score) and has subsequently been applied as a prognostic tool for patients with chronic liver disease in other circumstances, including patients with hepatocellular carcinoma (HCC). The components of the C-P score were identified empirically as the principal factors perceived to reflect the severity and hence prognosis of cirrhosis. Each of the components was scored individually (0, 1, 2 or 3 points—3 being the most severe) on the basis of empirically assigned cutoff ranges and descriptive terms, contributing to a total score from 5 to 15 points. The total scores were then divided into three grades of increasing severity and poorer prognosis (A, B, and C, with C having the worst prognosis).

The outcome of patients with HCC is determined by two parameters: the tumor-related aspects (size, metastases, and vascular invasion, etc) and the degree of liver dysfunction.[3,4] In the most widely used staging classification, the Barcelona Clinic Liver Cancer stage system, which offers both a guide to the most appropriate treatment and the expected prognosis, liver dysfunction is accounted for by the C-P score.[5] In general clinical/hepatological practice, the C-P score informs many aspects of treatment allocation. The confinement of patients with the lowest risk category of C-P grade (CP-A) in clinical trials (thereby isolating the effect of the anticancer treatment from the adverse impact of liver dysfunction), has been one of the reasons suggested for the successful identification of sorafenib as an effective systemic agent for advanced HCC.[6,7]

Recently, the ALBI (albumin-bilirubin) score has been developed as an HCC-specific refinement of the C-P score.[8] It is a simple, statistical model derived from a large HCC data set that has been extensively validated. ALBI takes just two of the Child-Pugh variables, albumin and bilirubin, and to this extent implies that the clinical features are redundant in the prognostic impact of the C-P score. Again, it is presented as grades 1-3, with 3 having the worst prognosis. It is important to recognize that ALBI is not proposed as a prognostic system in its own right, but rather a better approach to assessing that portion of HCC prognosis that is affected by underlying liver function. Herein, we summarize the limitations of the C-P score as applied to patients with HCC and propose that the ALBI score may offer practical and practice-changing advantages.

Limitations of the C-P Score—Subjectivity and Inconsistency of Versions

The limitations of the C-P scoring system include the subjectivity of assessment of ascites and encephalopathy, the interdependence of the five parameters, the absence of some important prognostic parameters such as renal function, and the lack of specificity for different disease etiologies.[9,10] A review of the literature (This statement is based on a search for Child-Pugh score on the online Google search engine, Google Scholar, and PubMed. Values relating to the various C-P scoring systems were collated focusing on the application of these systems to prognosis of liver cirrhosis in general, rather than cirrhosis that is attributable to specific disease etiologies. References cited by the sources were also manually searched. Each source was required to meet the following criteria: [1] source must be complete, ie, [i] fully published in the literature [research papers, review articles, and textbooks] and [ii] complete website or database, and [2] source must provide a value for every component of the C-P score.) reveals that there are more than 30 different versions of the C-P score. There are no formal descriptors or values for ascites or encephalopathy status, and this results in profound inconsistencies in assessing each component of the score, with fundamental implications for the prognostic ability of this model. For example, if an investigator/clinician grades ascites as moderate, this scores 2 points according to some sources and 3 points according to others. Even with an ascites score of 1 (ascites absent), there can

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be controversy when, for example, ascites is clearly detected on imaging but not on clinical examination. This situation is further complicated by the fluctuant nature of encephalopathy. The issue of subjectivity of encephalopathy scoring in randomized clinical trials has been formally criticized and tackled by the amended West Haven Score, which scores lower grades of encephalopathy more specifically.[11,12] Moreover, the varying terminology is very rarely supported by subsequent explanations. For example, certain literature deems *chronicity* a valid factor when grading encephalopathy while other sources reference the subjective comatose state as a factor. The version of the C-P score used is seldom, if ever, reported in research publications.

Limitations of the C-P Score—Lack of Sensitivity in Patients With Mild Liver Dysfunction

Over the recent years, there has been a marked improvement in the liver function among those patients presenting with HCC. This may reflect recommended lifestyle changes (alcohol and obesity control), effective antiviral therapies, and likely improved HCC outcomes. The lowest grade is A, and the lowest score is 5. At the latter point, patients are, effectively, classified as having no liver dysfunction since this is the status at which the healthy population would be classified/graded. There is increasing evidence that the percentage of patients with CP-A and CP-A5 has risen recently.[13] In Japan, the percentage of HCC cases in the C-P score A grade has risen from 30% (1981-1982) to 70% (2006-2008).[14] Figure 1 shows the experience of one institution over a 30-year observation period where the percentage of CP-A5 cases has risen from < 25% to 67%.[15]

The initial ALBI analysis showed that most of the impact of serum bilirubin levels on prognosis was contained within the conventional normal/reference range, whereas within all C-P systems adverse points are only scored when values exceed twice the reference range. Hence, at least in the situation of HCC, the C-P score does not use the range of serum bilirubin levels that have prognostic impact. Thus, for the purposes of clinical practice and clinical trials when we classify a patient as Child-Pugh CP-A5, we are saying that, in effect, we do not recognize any degree of liver dysfunction when arriving at clinical decisions.

Advantages of the ALBI Score

A key advantage of the ALBI score is that it is entirely objective, obviating any need for subjective assessment of clinical signs, that it is derived from an entirely HCC population[16] and is a continuous score that readily lends itself for assessment of changes in liver reserve over time. By comparison, the C-P score, strictly speaking, should only be applied to patients with cirrhosis. It is well-recognized that the clinical diagnosis of cirrhosis is open to substantial interobserver and intraobserver variations, especially for cirrhosis at an early stage, and where, as is the case in most primary care situations, objective measurements such as the liver stiffness measurement are not readily accessible.[17] Indeed, current European Association for the Study of the Liver guidelines note that discrimination between severe fibrosis and compensated cirrhosis is often unclear.[18] ALBI was developed in an HCC population without any regard to the presence or absence of cirrhosis. Certainly 10%-20% of patients with HCC do not have cirrhosis.[19,20] Being a continuous and much more granular score the option remains to vary the cutoff point and add additional factors for further discrimination at different disease stages as several groups have done.[21]

ALBI offers prognostic discrimination in patients with early compensated liver disease in whom the C-P score often does not distinguish from the heathy population (ie, CP-A5 score). Thus, in a study involving more than 3,000 patients, the median survival for ALBI 1, 2, and 3 were 100, 65, and 20 months, respectively, compared with 68 months for CP-A5.[22] Similarly, in a cohort of more than 1,000 patients receiving sorafenib within clinical trials, who were classified (per protocol) as CP-A, ALBI still offered clear prognostic discrimination.[16]

Furthermore, since initial publication in 2015, the ALBI score has been validated in all clinical HCC stages and treatments. The initial large international validation study concluded "… the ALBI grade satisfied the criteria for accuracy and reproducibility…in Eastern and Western HCC patients…consideration should be given to the ALBI grade as a stratifying biomarker of liver reserve in routine clinical practice."[23(p338)] More recently (2020), a systematic review of the entire literature on HCC and ALBI concluded that "ALBI showed better discriminative ability than Child-Pugh for predicting the prognosis in HCC patients."[24(p383)] The performance of the Barcelona Clinic Liver Cancer classification is not decreased when ALBI is substituted for the C-P score,[25] and the addition of platelet count (P) to ALBI (PALBI) seems to further enhance its performance but has not yet been as excessively studied as ALBI.[22]

We anticipate that ALBI will find an important role within clinical trials involving novel therapeutics.[26] There is increasing evidence that not only can ALBI predict survival after therapy[16,27,28] but it may also be associated with improved outcomes in modern systemic therapies for advanced HCC, including lenvatinib,[29,30] immunotherapy,[31] and selective internal radiation therapy/transarterial chemoembolization where it may aid identification of toxicity posttreatment.[32,33] Indeed, classification of hepatotoxicity in patients with HCC is unsatisfactory, and criteria such as ALT/AST elevation seem to be poor measures of safety in HCC.[34] CP-A versus B classification is prognostic but does not identify patients who suffer from increased toxicity to sorafenib.[35,36] In the light of these perceived advantages,

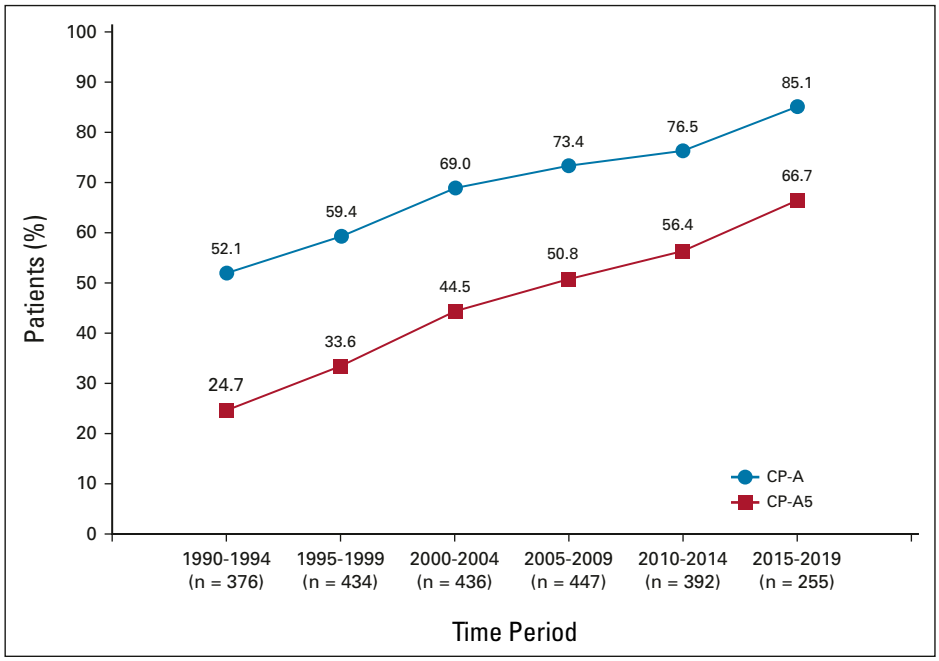

FIG 1. Changes in CP-A and CP-A5 over a 30-year period. Data collected prospectively from all patients with HCC seen at Ogaki Municipal Hospital, Japan (Data redrawn from Kumada et al[15]). CP-A, Child-Pugh Class A; CP-A5, Child-Pugh Class A5; HCC, hepatocellular carcinoma.

the ALBI score is already used in routine clinical practice in Japan and endorsed by the Japanese National Liver Cancer Study Group.[37]

Finally, ALBI is finding a significant role in prognostic models where it is important to consider liver function. Examples are the age–male–ALBI–platelets score[17] for prediction of HCC development in patients with chronic liver disease (where it is combined with sex and platelet count) and several other, extensively validated, prognostic models.[38]

Limitations of ALBI

Since ALBI is simply a statistically based refinement of the C-P score, it inevitably suffers from some of the inherent limitations of the C-P score. The investigation for both has been on their discriminatory performance rather than calibration. The variables used in the C-P score were chosen intuitively on the basis of clinical features that were known to associate with liver dysfunction and biochemical parameters that were plausible and linked to liver function because they become abnormal as the liver fails.[39] To this extent, the development of ALBI offers no mechanistic insights that throw light on its performance unlike ICG-15 (indocyanine green retention 15 minutes after administration) clearance, which is the standard measurement of hepatic excretion used extensively in Japan, as part of the Makuuchi criteria for safe hepatic resection.[40] Nonetheless, the correlation between ICG-15 and ALBI is good,[16,21] and ALBI is a much simpler parameter to assess and other methods of assessing liver function have not been widely adopted. Interestingly, experience in HIV-associated HCC revealed the ALBI score to reflect the quality of the underlying immune function, a parameter linked to faster progression of fibrosis in people living with HIV and hepatitis.[31]

The model for end-stage liver disease score, which like the C-P score was originally applied in the management of portal hypertension (transjugular intrahepatic portosystemic shunt) and again like the C-P score, has had its role extrapolated this time to liver transplantation, and hepatic resection[41] is an alternative approach to liver function assessment in HCC. However, it is by design aimed at *end-stage liver disease* where it plays an important role in informing graft allocation priority policy for liver transplantation and to the selection of patients for hepatic resection.[18,42] Nonetheless, in the setting of cirrhosis and HCC, head-to-head comparisons suggest that in most HCC cases ALBI offers better prognostic discrimination,[22,43] although focusing on ALBI for early cirrhosis and considering model for end-stage liver disease score in end-stage liver disease remains an option.

The fact that the original C-P score that was based on a total of 38 patients, unrelated to HCC, with no statistical analysis, has held the stage for nearly 50 years is surely a testament to clinical acumen. Although the C-P score will undoubtedly continue to guide treatment decisions in patients with cirrhosis, clinical care of patients with HCC, now counting on a number of local and systemic treatment options, demands solid and evidence-based instruments to deliver the promise of individualized patient management.

In an increasingly complex clinical landscape seeing patients with advanced HCC achieving previously unthinkable landmark survival end points at 2 years from diagnosis,[44]

the ALBI grade offers consistent prognostic discrimination within that increasing percentage of patients with HCC with very early liver disease, whereas the C-P score does not. The accumulating body of evidence in support of the ALBI grade as an optimal predictor of outcome in patients who are diagnosed with HCC today calls for its broader use in clinical practice and drug development. This is particularly so in a field where high attrition rates and incomplete disease phenotyping continue to delay the delivery of precision medicine.

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REFERENCES

1. Child CG, Turcotte JG: Surgery and portal hypertension. Major Probl Clin Surg 1:1-85, 1964
2. Pugh RN, Murray-Lyon IM, Dawson JL, et al: Transection of the oesophagus for bleeding oesophageal varices. Br J Surg 60:646-649, 1973
3. European Association for Study of Liver; European Organisation for Research and Treatment of Cancer: EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. Eur J Cancer 48:599-641, 2012
4. Heimbach JK, Kulik LM, Finn RS, et al: AASLD guidelines for the treatment of hepatocellular carcinoma. Hepatology 67:358-380, 2018
5. Llovet JM, Bru C, Bruix J: Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 19:329-338, 1999
6. Llovet JM, Hernandez-Gea V: Hepatocellular carcinoma: Reasons for phase III failure and novel perspectives on trial design. Clin Cancer Res 20:2072-2079, 2014
7. Llovet JM, Ricci S, Mazzaferro V, et al: Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 359:378-390, 2008
8. Bruix J, Sala M, Llovet JM: Chemoembolization for hepatocellular carcinoma. Gastroenterology 127:S179-S188, 2004 (5 suppl 1)
9. Durand F, Valla D: Assessment of prognosis of cirrhosis. Semin Liver Dis 28:110-122, 2008
10. Elmeliegy M, Yang DZ, Salama E, et al: Discordance between Child-Pugh and National Cancer Institute classifications for hepatic dysfunction: Implications on dosing recommendations for oncology compounds. J Clin Pharmacol 61:105-115, 2021
11. Weissenborn K: Hepatic encephalopathy: Definition, clinical grading and diagnostic principles. Drugs 79:5-9, 2019 (suppl 1)
12. Vilstrup H, Amodio P, Bajaj J, et al: Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 60:715-735, 2014
13. Hassan I, Gane E: Improving survival in patients with hepatocellular carcinoma related to chronic hepatitis C and B but not in those related to non-alcoholic steatohepatitis or alcoholic liver disease: A 20-year experience from a national programme. Intern Med J 49:1405-1411, 2019
14. Toyoda H, Kumada T, Tada T, et al: Characteristics and prognosis of patients with hepatocellular carcinoma after the year 2000 in Japan. J Gastroenterol Hepatol 26:1765-1771, 2011
15. Kumada T, Toyoda H, Tada T, et al: Changes in background liver function in patients with hepatocellular carcinoma over 30 years: Comparison of Child-Pugh classification and albumin bilirubin grade. Liver Cancer 9:518-528, 2020
16. Johnson PJ, Berhane S, Kagebayashi C, et al: Assessment of liver function in patients with hepatocellular carcinoma: A new evidence-based approach-the ALBI grade. J Clin Oncol 33:550-558, 2015
17. Fan R, Papatheodoridis G, Sun J, et al: aMAP risk score predicts hepatocellular carcinoma development in patients with chronic hepatitis. J Hepatol 73:1368-1378, 2020
18. European Association for the Study of the Liver: EASL clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 69:182-236, 2018
19. Italian Association for the Study of the Liver (AISF); AISF Expert Panel; AISF Coordinating Committee: Position paper of the Italian Association for the Study of the Liver (AISF): The multidisciplinary clinical approach to hepatocellular carcinoma. Dig Liver Dis 45:712-723, 2013
20. European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer: EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. J Hepatol 56:908-943, 2012

21. Sonohara F, Yamada S, Tanaka N, et al: Perioperative and prognostic implication of albumin-bilirubin-TNM score in Child-Pugh class A hepatocellular carcinoma. Ann Gastroenterol Surg 3:65-74, 2019
22. Liu PH, Hsu CY, Hsia CY, et al: ALBI and PALBI grade predict survival for HCC across treatment modalities and BCLC stages in the MELD Era. J Gastroenterol Hepatol 32:879-886, 2017
23. Pinato DJ, Sharma R, Allara E, et al: The ALBI grade provides objective hepatic reserve estimation across each BCLC stage of hepatocellular carcinoma. J Hepatol 66:338-346, 2017
24. Peng Y, Wei Q, He Y, et al: ALBI versus Child-Pugh in predicting outcome of patients with HCC: A systematic review. Expert Rev Gastroenterol Hepatol 14: 383-400, 2020
25. Chan AW, Kumada T, Toyoda H, et al: Integration of albumin-bilirubin (ALBI) score into Barcelona Clinic Liver Cancer (BCLC) system for hepatocellular carcinoma. J Gastroenterol Hepatol 31:1300-1306, 2016
26. Pinato DJ, Kaneko T, Saeed A, et al: Immunotherapy in hepatocellular cancer patients with mild to severe liver dysfunction: Adjunctive role of the ALBI grade. Cancers (Basel) 12:1862, 2020
27. Waked I, Berhane S, Toyoda H, et al: Transarterial chemo-embolisation of hepatocellular carcinoma: Impact of liver function and vascular invasion. Br J Cancer 116:448-454, 2017
28. Han G, Berhane S, Toyoda H, et al: Prediction of survival among patients receiving transarterial chemoembolization for hepatocellular carcinoma: A response-based approach. Hepatology 72:198-212, 2020
29. Ueshima K, Nishida N, Hagiwara S, et al: Impact of baseline ALBI grade on the outcomes of hepatocellular carcinoma patients treated with lenvatinib: A multicenter study. Cancers (Basel) 11:952, 2019
30. Tada T, Kumada T, Hiraoka A, et al: Impact of modified albumin-bilirubin grade on survival in patients with HCC who received lenvatinib. Sci Rep 11:14474, 2021
31. Pinato DJ, Sharma R, Citti C, et al: The albumin-bilirubin grade uncovers the prognostic relationship between hepatic reserve and immune dysfunction in HIV-associated hepatocellular carcinoma. Aliment Pharmacol Ther 47:95-103, 2018
32. Lescure C, Estrade F, Pedrono M, et al: ALBI score is a strong predictor of toxicity following SIRT for hepatocellular carcinoma. Cancers (Basel) 13:3794, 2021
33. Murray LJ, Sykes J, Brierley J, et al: Baseline albumin-bilirubin (ALBI) score in western patients with hepatocellular carcinoma treated with stereotactic body radiation therapy (SBRT). Int J Radiat Oncol Biol Phys 101:900-909, 2018
34. Puzanov I, Diab A, Abdallah K, et al: Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the society for immunotherapy of cancer (SITC) toxicity management working group. J Immunother Cancer 5:95, 2017
35. Fessas P, Kaseb A, Wang Y, et al: Post-registration experience of nivolumab in advanced hepatocellular carcinoma: An international study. J Immunother Cancer 8:e001033, 2020
36. Mansfield AS, Rudek MA, Vulih D, et al: The effect of hepatic Impairment on outcomes in phase I clinical trials in cancer subjects. Clin Cancer Res 22: 5472-5479, 2016
37. Hiraoka A, Kumada T, Kudo M, et al: Albumin-bilirubin (ALBI) grade as part of the evidence-based clinical practice guideline for HCC of the Japan society of hepatology: A comparison with the liver damage and Child-Pugh classifications. Liver Cancer 6:204-215, 2017
38. Liverpool Liver Disease Modelling Group: https://prediction-models.liverpool.ac.uk/
39. van Gulik TM: Assessment of liver function: What are we measuring? HPB (Oxford) 15:325-326, 2013
40. Makuuchi M, Sano K: The surgical approach to HCC: Our progress and results in Japan. Liver Transpl 10:S46-S52, 2004 (2 suppl 1)
41. Singal AK, Kamath PS, Francisco Ziller N, et al: Nutritional status of patients with alcoholic cirrhosis undergoing liver transplantation: Time trends and impact on survival. Transpl Int 26:788-794, 2013
42. Cucchetti A, Ercolani G, Vivarelli M, et al: Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. Liver Transpl 12:966-971, 2006
43. Ho SY, Liu PH, Hsu CY, et al: Comparison of twelve liver functional reserve models for outcome prediction in patients with hepatocellular carcinoma undergoing surgical resection. Sci Rep 8:4773, 2018
44. Weissenborn K: Minimal/covert hepatic encephalopathy—Impact of comorbid conditions. J Clin Exp Hepatol 9:109-111, 2019

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