
ORIGINAL ARTICLE

Albumin-bilirubin versus Child-Pugh Grade as a Predictor of Survival after Individualised Hypofractionated Radiotherapy for Hepatocellular Carcinoma

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ABSTRACT

Purpose: To evaluate the ability of Child-Pugh (CP) versus albumin-bilirubin (ALBI) grade to predict overall survival (OS) in patients with hepatocellular carcinoma (HCC) undergoing individualised hypofractionated radiotherapy (IHRT) using stereotactic body radiotherapy (SBRT).

Methods: We retrospectively reviewed data on our patients with HCC treated with IHRT using SBRT per our institutional protocol from May 2006 to February 2015. We collected CP and ALBI grades prior to treatment and analysed their prognostic value for OS.

Results: A total of 174 consecutive patients were included in this study. Among them, 63% were CP grade A5 and 37% were A6. The median ALBI score was -2.39 (range, -3.61 to -1.41) with 35% grade A1 and 65% grade A2. OS was significantly associated with ALBI grade ($p = 0.015$), but not with CP grade ($p = 0.47$). On multivariable regression analysis, the ALBI score, tumour size, number of lesions, total biologically effective dose, presence of portal vein thrombosis, and the presence of metastasis were shown to be independent factors for OS.

Conclusion: ALBI grade is a better predictor of survival than the CP grade in patients with HCC receiving IHRT.

Key Words: Albumins; Carcinoma, hepatocellular

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中文摘要

比較白蛋白—膽紅素與Child-Pugh分級作為個體化肝細胞癌大分割放療後存活率的預測指標

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目的：評估Child-Pugh和白蛋白—膽紅素（ALBI）分級預測使用立體定向放療（SBRT）接受個體化肝細胞癌大分割放療（IHRT）的肝細胞癌患者的總體存活率的表現。

方法：回顧分析2006年5月至2015年2月期間，根據協議使用SBRT接受IHRT治療的肝細胞癌患者數據，並於患者接受治療前收集Child-Pugh和ALBI分級和分析它們對總體存活率的預後價值。

結果：納入174例連續患者，其中Child-Pugh分級為A5佔63%，Child-Pugh分級為A6佔37%。ALBI的中位數評分為-2.39（介乎-3.61至-1.41），其中A1級佔35%，A2級佔65%。總體存活率與ALBI分級顯著相關（ $p = 0.015$ ），但與Child-Pugh分級無顯著差異（ $p = 0.47$ ）。多變量迴歸分析顯示ALBI評分、腫瘤大小、病灶變數量、總生物學有效劑量、門靜脈血栓形成和轉移是預測總體存活率的獨立因素。

結論：在接受IHRT的肝細胞癌患者中，ALBI分級比Child-Pugh分級更能預測存活率。

INTRODUCTION

Most patients with hepatocellular carcinoma (HCC) have compromised liver function due to pre-existing liver diseases. Treatment decisions depend very much on hepatic function as estimated by Child-Pugh (CP) grade.¹ However, its calculation involves subjective variables. Albumin-bilirubin (ALBI) grade is an objective test.² ALBI grade has recently been shown to be better than CP grade as a predictor of overall survival (OS) in patients with HCC undergoing surgical resection,^{3,4} transarterial chemoembolisation (TACE),⁵ yttrium-90 radioembolisation,⁵ sorafenib,^{6,7} or stereotactic ablative radiation therapy (SBAR).⁸

In our centre, we offer patients with HCC individualised hypofractionated radiotherapy (IHRT) with stereotactic body radiotherapy. IHRT is administered to patients with HCC who are not eligible for, or have failed, standard locoregional therapy. In contrast to SBAR, which delivers a high dose to a relatively small tumour in three to five fractions, IHRT delivers doses to HCC that are individualised to each patient according to the normal tissue constraints, rather than relative to size, in five to 10 fractions. This permits more patients with HCC to benefit from high-precision radiotherapy.

In a previous study, we investigated the predictive value of platelet-albumin-bilirubin, ALBI, and CP scores for

patients with advanced HCC receiving radiotherapy.⁹ However, to the best of our knowledge there are no studies that have investigated the prognostic value of ALBI grade in routine daily practice for patients with HCC treated with IHRT. The purpose of the present study was to compare the ability of CP versus ALBI grade to predict OS in patients with HCC with CP grade A5 or A6 treated with IHRT.

METHODS

Patients

Data from consecutive patients who were treated between 2006 and 2015 with our institutional IHRT protocol were retrospectively extracted from medical records in Tuen Mun Hospital, Hong Kong. Those patients who fulfilled the inclusion criteria for this study were included for analysis. The diagnosis of HCC was established either by biopsy or by the American Association for the Study of Liver Diseases criteria. The eligibility criteria for this study were: unsuitable for, failed or refused standard local treatments (including resection, liver transplantation, local ablation therapies); a minimum of 700 mL of uninvolved liver; an Eastern Cooperative Oncology Group performance score ≤ 2 ; CP grade A5 or A6; and adequate liver function and complete blood counts. Patients with small-volume distant metastases were included. Patients were excluded if they had infiltrative disease or more than five tumour

nodules. There was no limit on tumour size.

Treatment and Follow-up

Different techniques of stereotactic body radiotherapy have been used in our institution over the years. Patients were immobilised with a customised device (Vac-Lok™; MEDTEC, Orange City [IA], United States). Computed tomography (CT) with multiphasic intravenous contrast was used to define gross tumour volume (GTV). Breath-hold CT or four-dimensional CT (average phase or respiratory phase sorted) was used to determine internal target volume and/or planning target volume. Motion management was done with maximum intensity projection, respiratory gating, active breathing control, or abdominal compression. IHRT was delivered using dynamic conformal arc, intensity-modulated radiotherapy, or volumetric arc therapy. Image guidance was done with an infrared body positioning system (ExacTrac™; BrainLab AG, Feldkirchen, Germany) or cone beam CT.

Our IHRT protocol divides patients into 'favourable' and 'unfavourable' groups depending on dose and fractionation. Individuals who meet all the following criteria are classified into the favourable group: tumour size ≤ 10 cm, Eastern Cooperative Oncology Group score 0-1, and liver volume minus GTV ≥ 700 mL. For 47 patients classified into the favourable group, 5-9 Gy for six fractions was prescribed; for the other 127 patients classified into the unfavourable group, 4 Gy for five to 10 fractions was prescribed. The dose was individualised by normal tissue constraints, as described previously.⁹ The normal liver was allowed to receive a biological effective dose with $\alpha/\beta = 3$ of 30 Gy_3 $< 40\%$ and mean dose $< 28 \text{ Gy}_3$. Minor dose constraint violation was allowed in patients who were not carriers of hepatitis B or C and were without evidence of cirrhosis.

Baseline liver function data were obtained within 1 week prior to IHRT. The ALBI score was calculated using the formula: $\text{ALBI score} = (\log_{10} \text{bilirubin } [\mu\text{mol/L}] \times 0.66) + (-0.085 \times \text{albumin } [\text{g/L}])$. The ALBI scores are stratified into: ALBI grade A1 (≤ -2.60); ALBI grade A2 (> -2.60 to ≤ -1.39); and ALBI grade A3 (> -1.39).

We assessed the patients weekly during IHRT, every 6 weeks after treatment, every 3 months for the first 2 years, and every 4 months thereafter. Physical examinations and blood tests were done at every follow-up. Triphasic liver CT was performed every 3 months in the first and second year, and then every 6 months.

Statistical Analyses

OS was calculated by the Kaplan-Meier curve. Log rank test was used to compare outcomes among survival curves for potential prognostic factors. Significant factors in the univariate analyses ($p < 0.1$) were included in the multivariable regression analyses using the Cox proportional hazards regression model. Factors with $p < 0.05$ were considered to be significant in the Cox model.

RESULTS

Baseline Demographics and Clinic Characteristics

A total of 174 patients undergoing IHRT for HCC were included in this study. Patients with ALBI grade A3 were excluded as there were only three of them. The majority (86%) of the patients were male, and a majority (79%) of them were hepatitis B carriers. Most (74%) patients had Barcelona clinic liver cancer stage C disease. The median size of the tumour was 9.8 cm (range, 2.3-25.7 cm) and median GTV was approximately 440 mL (range, 9.2-4009 mL).

All patients in this study had CP grade A liver reserve; 63% had CP grade A5 and 37% had CP grade A6. The median ALBI score was -2.39 (range, -3.61 to -1.41). According to the ALBI grading system, 34.5% were classified as grade A1, 65.5% were grade A2.

Correlation between Child-Pugh and Albumin-bilirubin Grades

Table 1 shows the correlations between CP and ALBI grades. Of patients with ALBI grade A1, 95% had CP grade A5. Of patients with ALBI grade A2, 46% had CP grade A5 and 54% had CP grade A6. Among patients with CP grade A5, 53% were stratified into ALBI grade A1 and 47% into ALBI grade A2. For patients with CP grade A6, 95% had ALBI grade A2.

Prognostic Factors of Overall Survival

With a median follow-up of 23.5 months (range, 2.8-136.3 months), the median OS of the entire cohort was 24.1 months (95% confidence interval [CI]=19.7-28.4 months). The 1-year and 2-year

Table 1. Correlations between Child-Pugh and albumin-bilirubin grade.

Albumin-bilirubin grades	Child-Pugh A5	Child-Pugh A6
A1	58	3
A2	52	61

OS were 74.6% (95% CI=71.3-77.9%) and 50.2% (95% CI=46.4%-54.0%), respectively.

in terms of ALBI and CP grades, respectively. Pretreatment ALBI grade stratified patients into distinct survival cohorts with a median OS of 34.7 months (95% CI=25.6-43.7 months) for grade A1

Figures 1 and 2 show the OS of our patients

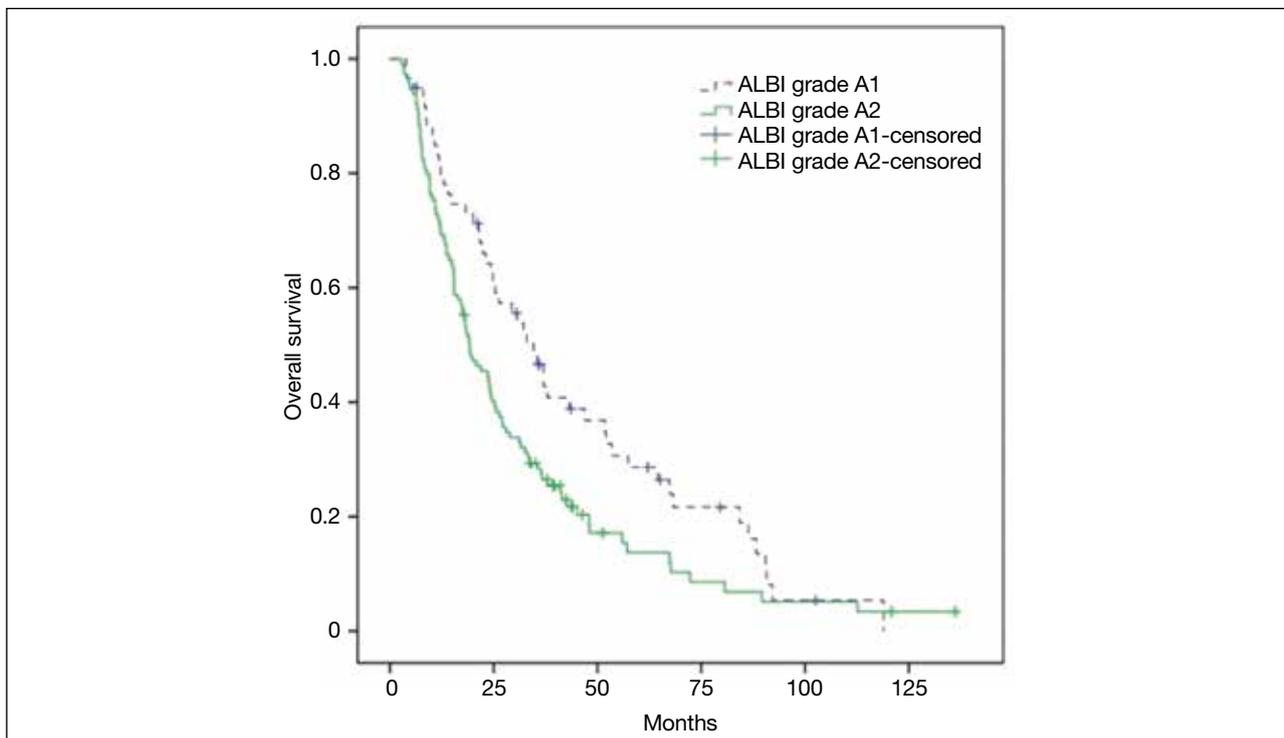


Figure 1. Overall survival for albumin-bilirubin (ALBI) grade A1 versus A2 patients.

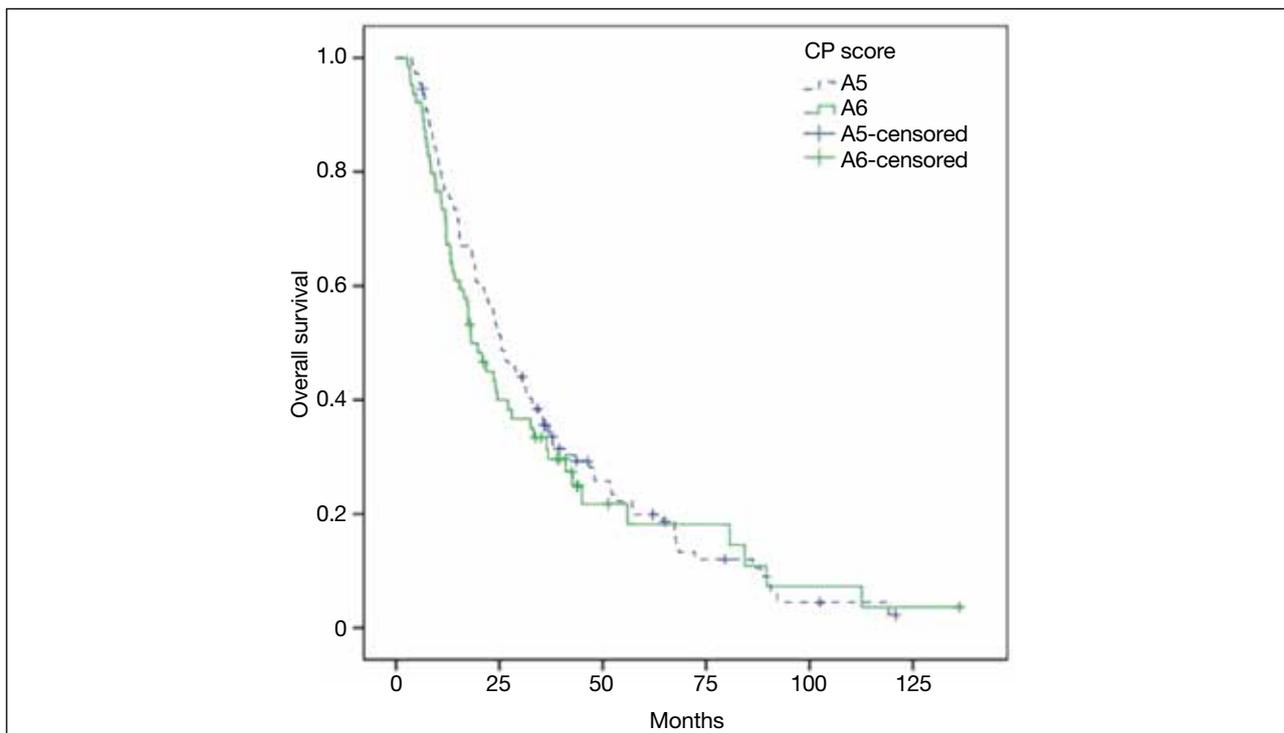


Figure 2. Overall survival for Child-Pugh (CP) grade A5 versus A6 patients.

versus 19.2 months (95% CI=13.9-24.3 months) for grade A2 ($p = 0.015$). For CP classified patients, the median OS for CP grade A5 was 25.4 months (95% CI=20.4-30.4 months) and for CP grade A6 was 18.2 months (95% CI=14.0-24.2 months). The difference was not significantly different ($p = 0.467$).

In the univariate analysis for the OS, the ALBI grade, tumour size, number of lesions, presence of portal vein thrombosis, presence of metastases, and the total biological effective dose with $\alpha/\beta = 10$ were significantly associated with OS (Table 2). CP score was not a significant factor.

In the multivariable analysis for OS, pretreatment ALBI score ($p = 0.007$) remained a significant independent factor in predicting OS. Other significant factors included: size of lesion ($p = 0.014$), number of lesions ($p = 0.005$), presence of portal vein thrombosis ($p = 0.023$), presence of metastasis ($p = 0.002$), and total dose of radiotherapy (BED with $\alpha/\beta = 10$, $p = 0.014$; Table 3).

DISCUSSION

In this study, we investigated the CP versus ALBI grade in patients with HCC treated with IHRT. Our data showed that patients with CP grade A5 were stratified almost equally by ALBI into grades A1 and A2. For patients with CP grade A6, the majority were classified as ALBI grade A2. In contrast, nearly all patients with ALBI grade A1 had CP grade A5. Patients with ALBI grade A2 were roughly distributed equally between CP grades A5 and A6.

In the OS analysis, this study demonstrated that the median OS of patients with ALBI grade A1 (35 months) almost doubled that of patients with ALBI grade A2 (19 months). Conversely, the median OS difference between CP grade A5 (25 months) and CP grade A6 (18 months) was not significant. In multivariable regression analysis, ALBI was shown to be an independent predictor of OS, whereas CP was not. This indicates that ALBI grade is a significantly better predictor of OS than CP.

Our findings that ALBI is superior to CP in predicting survival are consistent with the current evidence of ALBI grade as a predictor of survival for other HCC treatments, including surgical resection,^{3,4} TACE, yttrium-90 radioembolisation,⁵ sorafenib,^{6,7} and SBAR.⁸ In the study by Wang et al⁴ that evaluated the prognostic

Table 2. Univariate analysis of the factors for predicting overall survival.

Variables	p Value
Age (<65 years vs. ≥ 65 years)	0.120
Sex (male vs. female)	0.280
ECOG (ECOG 0 vs. 1)	0.317
Size of lesion (<5 cm vs. ≥ 5 cm)	<0.001
No. of lesions (solitary vs. uninodular vs. multinodular)	0.023
Portal vein thrombosis (yes vs. no)	0.011
Presence of metastasis	0.002
BCLC stage (A vs. B vs. C)	0.269
ALBI grade (1 vs. 2 vs. 3)	0.015
CP grade (A5 vs. A6)	0.467
Total BED10 dose	<0.001
Post-RT resection (yes vs. no)	0.208
Post-RT transarterial chemoembolisation (yes vs. no)	0.077
Post-RT sorafenib (yes vs. no)	0.408

Abbreviations: ALBI = albumin-bilirubin; BCLC = Barcelona clinic liver cancer; BED10 = biologically effective dose with $\alpha/\beta = 10$; CP = Child-Pugh; ECOG = Eastern Cooperative Oncology Group; RT = radiotherapy.

Table 3. Variables for multivariable analysis.

Variables	p Value
Size of lesion (<5 cm vs. ≥ 5 cm)	0.014
No. of lesions (solitary vs. uninodular vs. multinodular)	0.005
Portal vein thrombosis (yes vs. no)	0.023
Presence of metastasis	0.002
ALBI grade (1 vs. 2 vs. 3)	0.007
Total BED10 dose	0.014

Abbreviations: ALBI = albumin-bilirubin; BED10 = biologically effective dose with $\alpha/\beta = 10$.

performance of ALBI versus CP after liver resection and the study by Lo et al⁸ on SBAR, both demonstrated no significant differences in OS between CP grades A5 and A6. Their findings were consistent with our data, although the patient and tumour characteristics, as well as treatments, were different. The result of this study may help to stratify patients with CP grade A5 into two distinct prognostic groups using ALBI. A prospective study will likely give a more definitive result for ALBI to be used in daily practice.

The present study had some limitations. The retrospective design of this study is prone to selection bias. Also, the different doses may have an effect on OS. We have strived to make this study a valuable one by including all consecutive eligible patients, which resulted in a relatively large sample size, a long follow-up period, and a long recruitment period of nearly a decade. Toxicities were not included in the analysis owing to the fact that grade ≥ 3 toxicities (prospectively collected) were very rare, and no radiation-induced liver disease occurred.

In conclusion, our findings suggest that ALBI grade is a better predictor of OS than the CP grade in patients with HCC who receive IHRT. A prospective study is recommended in order to validate the use of ALBI grade in daily practice.

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