Observational Study

Albumin-bilirubin and platelet-albumin-bilirubin grades for hepatitis B-associated hepatocellular carcinoma in Child–Pugh A patients treated with radical surgery

A retrospective observational study

Binquan Wu, MD, Xiaosi Hu, MD, Hao Jin, MD, Lei Zhou, MD, Dengyong Zhang, MD, Zhongran Man, MD, Yong Wang, MD, Song Yang, MD, Qing Pang, MD, PhD*, Huichun Liu, MD*, Peiyuan Cui, MD*

Abstract
Child–Pugh (CP) grade A patients with early stage hepatocellular carcinoma (HCC) are candidates for curative surgery, while some patients still have a poor outcome. The aim of this study was to investigate the prognostic values of 2 new evaluation models for liver function, namely albumin-bilirubin (ALBI) and platelet-albumin-bilirubin (PALBI) grades, in CP grade A patients with HCC.

In this retrospective cohort study, we reviewed 134 cases of CP grade A patients with hepatitis B-associated HCC who underwent radical surgery. ALBI and PALBI grades were calculated based on preoperative serologic examinations. Overall survival (OS) and recurrence-free survival (RFS) were estimated by Kaplan–Meier curve and Cox regression. The prognostic performances of the models were estimated by using the concordance index (C-index).

During a median follow-up time of 27 months, 27.6% (37/134) of patients died and 26.1% (35/134) experienced recurrence. Kaplan–Meier analyses showed that ALBI and PALBI grades were significantly associated with OS and RFS. Multivariate analyses further revealed that both ALBI and PALBI grades were independent predictors for survival. Furthermore, the prognostic values of the combination of tumor size with ALBI (C-index = 0.754, 95% confidence interval [CI]: 0.675–0.849) or with PALBI (C-index = 0.762, 95% CI: 0.664–0.844) may be comparable with both Barcelona Clinic Liver Cancer and Cancer of Liver Italian Program staging systems.

The ALBI and PALBI grades, in particular the combination with tumor size, are effective models for discriminating survival in CP grade A patients with HCC.

Abbreviations: AFP = alpha-fetoprotein, ALB = albumin, ALBI = albumin-bilirubin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CLIP = Cancer of Liver Italian Program, CP = Child–Pugh, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, MELD = model for end-stage liver disease, OS = overall survival, PALBI = platelet-albumin-bilirubin, PLT = platelet count, PT-INR = prothrombin time-international normalized ratio, RFS = recurrence-free survival, TBIL = total bilirubin.

Keywords: albumin-bilirubin, Child–Pugh, hepatocellular carcinoma, platelet-albumin-bilirubin, survival

1. Introduction
Worldwide, hepatocellular carcinoma (HCC) is the 4th leading cause of cancer death, with approximately 841,000 new cases and 782,000 deaths annually. Chronic infections with hepatitis B virus (HBV) and/or hepatitis C virus (HCV), chronic alcohol abuse, and nonalcoholic steatohepatitis are the major risk factors for HCC. In high risk areas for HCC, such as China and Sub-Saharan Africa, HBV is the main pathogenic factor. Surgical resection is the crucial curative treatment option for patients with early stage HCC, with 5-year survival rate up to 70%. As HCC mainly develops in the background of chronic liver diseases and cirrhosis, hepatic dysfunction is relatively
common at the time of diagnosis. Previous studies have suggested that in addition to tumor burden, liver function determines treatment options and prognosis of HCC.\(^5\) For decades, the Child–Pugh (CP) grade is widely used as the standard method for assessing liver function. In the HCC guidelines of American and European, CP grade has been adopted in tumor stage and treatment selection.\(^4,6\) According to the guidelines, radical surgery is recommended in CP grade A patients with early stage HCC; however, some of the patients may still have a poor prognosis.\(^7\) Therefore, the prognostic assessment according to CP grade remains unsatisfactory in HCC.

The classic model for end-stage liver disease (MELD) score has also been recognized as a good mortality predictor in HCC.\(^8\) Recently, a novel and simple evaluation model for liver function, called albumin-bilirubin (ALBI) grade, has been established by Johnson et al.\(^9\) The new grade model has been demonstrated to be superior to conventional CP grade in evaluating liver function, posthepatectomy liver failure, and survival of patients with HCC.\(^10,11\) Another new model for liver function, named platelet-albumin-bilirubin (PALBI), has also been validated as a better method of assessing liver function and prognosis than CP grade.\(^12,13\) However, to our knowledge, the prognostic values of ALBI and PALBI grades have rarely been investigated in CP grade A patients with HCC. In this study, we firstly compared the prognostic performance of the 2 grades with MELD and classic prognostic models for HCC, including the Barcelona Clinic Liver Cancer (BCLC) and Cancer of the Liver Italian Program (CLIP) staging systems.

2. Methods

2.1. Study population

The medical records of patients with HCC who underwent radical resection in our department between January 2014 and June 2018 were retrospectively analyzed. The inclusion criteria were: HCC with histologic confirmation; positive hepatitis B surface antigen; received radical hepatectomy (complete resection of the tumor with negative margin) for the 1st time; and CP grade A. Exclusion criteria were: surgery-related mortality; rehepatectomy; coinfection with HCV; mixed hepatocellular cholangiocarcinoma; extrahepatic metastasis; incomplete information on the calculation of ALBI and PALBI; and coexistent hematologic disorders, malnutrition, or other serious diseases that significantly influence scores of ALBI and PALBI. The present report was in compliance with the guideline of Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD).\(^14\) Our study was in accordance with the Declaration of Helsinki\(^15\) and was approved by the Ethics Committee of the First Affiliated Hospital of Bengbu Medical College. Written informed consent was given by patients.

2.2. Data collection

We extracted the following baseline information by using the electronic medical records: age, gender, tumor characteristics (number, diameter of the largest lesion, and vascular invasion), presence of ascites, presence of liver cirrhosis, pathologic results, and preoperative serologic tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total serum bilirubin (TBIL), albumin (ALB), platelet count (PLT), prothrombin time-international normalized ratio (PT-INR), creatinine (Cr), and alpha-fetoprotein (AFP). TBIL and ALB were detected by automatic biochemistry analyser (Cobas C8000; Roche Inc, Basel, Switzerland) and PLT was detected by automatic hematology analyzer (XE-5000; Sysmex Inc, Kobe, Japan). Preoperative clinical data were used to calculate ALBI, PALBI, and MELD scores according to the following formula:

1. ALBI score: \(0.66 \times \log_{10} \text{TBIL (\(\mu\text{mol/L}) – 0.085 \times \text{ALB (g/L)}\).} \)
2. PALBI score: \(2.02 \times \log_{10} \text{TBIL (\(\mu\text{mol/L}) – 0.37 \times (\log_{10} \text{T-BIL})^2 – 0.04 \times \text{ALB (g/L)} – 3.48 \times \log_{10} \text{PLT (10^9/L)} + 1.01 \times (\log_{10} \text{PT-INR})^2\).} \)
3. MELD score: \(9.57 \times \log_{10} \text{Cr (mg/dL)} + 3.78 \times \log_{10} \text{TBIL (mg/dL)} + 11.2 \times \log_{10} \text{INR} + 6.43\).

2.3. Follow-up

After discharge from the hospital, patients were regularly followed-up (every 2 months for the 1st year, every 3 months for the 2nd year, and every 6 months thereafter) until December 2018 or until death. The follow-up contents mainly included CT/MRI, abdominal ultrasound, and serologic tests. Postoperative recurrence and death were recorded. Recurrent patients received salvage treatments, including re-resection, ablation, or transcatheter arterial chemoembolization, as appropriate.

2.4. Statistical analysis

We used SPSS version 18.0 for data collection and analysis. Continuous variables with normal distribution (Kolmogorov–Smirnov test, \(P > 0.05\)) were expressed as mean value ± standard deviation (SD). Or else, median (interquartile range) was used. Comparisons between groups were performed by using the \(t\) Wilcoxon, or \(\chi^2\) test, as appropriate.

The primary outcomes were overall survival (OS) and recurrence-free survival (RFS), which were estimated by Kaplan–Meier curve and log-rank test. All variables that were found to be statistically or nearly significant (\(P < 0.10\)) entered into the multivariate Cox regression model. The prognostic values were compared between different models by using concordance index (C-index), a value reflects the prognostic discrimination ability: the higher the C-index, the more accurate the prognostic prediction is (C-index, low accuracy: 0.50–0.70; medium accuracy: 0.70–0.90; high accuracy: > 0.90).\(^17\) A \(P\)-value < 0.05 was considered statistically significant.

3. Results

3.1. Patients’ characteristics

A total of 134 CP grade A patients with HCC were included in this study. It consisted of 102 men and 32 women, with a mean age of 51.8 ± 11.1 years. Based on ALBI grade, patients could be divided into 2 groups: ALBI grade 1 (n = 86, 64.2%) and grade 2 (n = 48, 35.8%). According to the PALBI grade, there were 83 (61.9%) patients with grade 1, 44 (32.8%) patients with grade 2, and 7 (5.2%) patients with grade 3. During a median follow-up time of 27 months, 35 (26.1%) experienced postoperative recurrence, and 37 (27.6%) patients died (29 died from recurrence and tumor progression, 3 from distant metastasis, 3 from hepatic failure, and 2 from gastrointestinal hemorrhage).
3.2. Associations between the ALBI, PALBI grades, and clinicopathologic feature

Table 1 shows the demographic data, serologic tests, tumor characteristics, and stages of patients stratified according to preoperative ALBI and PALBI grades. Clinical characteristics were comparable between ALBI grade 1 and grade 2 except for ALT, TBIL, ALB, tumor size, and PALBI grade. In contrast, patients with elevated grades (2 and 3) of PALBI had significantly higher levels of AST, TBIL, PLT, larger tumor size, lower ALB, and higher ALBI grade. The scatter plot further revealed the strong correlation between ALBI score and PALBI score (Fig. 1, Pearson $r = 0.6804$, $P < .0001$).

![Figure 1](image1.png)

3.3. Prognosis of the entire cohort

Figure 2A, B showed the Kaplan–Meier cumulative OS and RFS curves of the entire cohort. The 1-, 2-, and 3-year OS rates were 83.5%, 72.9%, and 66.4%, respectively, and the 1-, 2-, and 3-year RFS rates were 78.4%, 65.4%, and 62.1%, respectively.
Moreover, Figure 2C–F showed the Kaplan–Meier curves of patients stratified according to BCLC stage and CLIP stage. The log-rank tests demonstrated that OS and RFS varied significantly with different BCLC stage (Fig. 2C, D, both $P < .05$) and CLIP stage (Fig. 2E, F, both $P < .05$).

3.4. Predictors of OS and RFS
Kaplan–Meier analyses with log-rank tests showed that ALBI (Fig. 3A, B, both $P < .05$) and PALBI (Fig. 3C, D, both $P < .05$) were both significantly associated with OS and RFS. Univariate analyses revealed that AST, AFP, tumor size, tumor number,
BCLC, CLIP, ALBI, and PALBI were significantly associated with OS. In addition to the above factors, TBIL and status of cirrhosis were also found to be significantly associated with RFS (Table 2). Surprisingly, vascular invasion was not a significant prognostic factor in our study, which was consistent with several previous reports.\(^{18,19}\)

Furthermore, multivariate analyses were performed and the results were presented in the forest plots (Fig. 4). AFP, tumor size, tumor number, CLIP, ALBI, and PALBI grades were independent predictors for OS and RFS. However, BCLC stage was not independently associated RFS.

3.5. Comparison of predictive accuracy for survival between the ALBI, PALBI grades, and BCLC, CLIP staging systems

Based on C-index, the order of the models in discriminating survival was as follows: CLIP, PALBI, ALBI, BCLC, and MELD. As all patients in our study were ALBI grades 1 and 2 and no patients belonged to BCLC stage 0, the integration of ALBI grade into original BCLC stage (BCLC-ALBI) had the same value of C-index as BCLC stage. In addition, the integration of ALBI grade into original CLIP stage (CLIP-ALBI) provided higher
better OS and RFS (Fig. 5C, D, tumor size and tumor size patients as stage I (PALBI grade 1 and tumor size ≤ 5 cm). The 1-, 2-, and 3-year OS rates were 100.0%, 92.9%, and 68.2%, 57.9% vs 55.6%, 47.3%, and 4.702) .007 2.194 (1.220–3.945) .009 0.684 (0.709–9.140) .281

Statistically significant values are given in bold. Allometric index (AI), ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, C-index = concordance index of patients according to the combination of tumor size with ALBI or with PALBI, showed higher performance for survival prediction than MELD, BCLC, and CLIP staging systems.

### 3.6. Stratification of patients according to the combination of tumor size with ALBI or with PALBI

The simple combination of tumor size with ALBI or with PALBI presented medium accuracy (the value of C-index more than 0.70) in predicting survival. Based on ALBI and tumor size, we stratified patients as stage I (ALBI grade 1 and tumor size ≤ 5 cm), stage II (ALBI grade 1 and tumor size > 5 cm, or ALBI grade 2 and tumor size ≤ 5 cm), and stage III (ALBI grade 2 and tumor size > 5 cm). The 1-, 2-, and 3-year OS rates were 100.0%, 92.9%, and 92.9% vs 82.7%, 68.2%, and 57.9% vs 55.6%, 47.3%, and 35.5% for patients with stages I, II, and III, respectively (Fig. 5A, P < .001). In addition, compared with stages II and III, patients in stage I had significantly better RFS (Fig. 5B, P < .001).

In the present study, patients with CP grade A were divided into 2 groups with clearly different prognoses. In the present study, patients with CP grade A were divided into 2 groups with clearly different prognoses. In the present study, patients with CP grade A were divided into 2 groups with clearly different prognoses.

### 4. Discussion

As most cases originate from damaged liver tissue, prognosis of HCC depends on not only tumor burden but also liver functional reserve. Worldwide, classic CP grade is used as a standard for assessing the degree of liver function injury, selecting treatment, and evaluating prognosis in HCC. CONCLUSIONS: Moreover, several HCC staging systems that consider CP grade, such as CLIP and BCLC, have been widely proposed as effective tools for predicting survival in HCC. However, flaws of the CP grade have recently been proposed.

According to HCC clinical guidelines, CP grade A is the requirement for hepatectomy, while some patients still have a poor prognosis. Therefore, derived from a cohort of 1313 patients with HCC, Johnson et al recently established the new ALBI grade system. The ALBI grade only contains serum TBIL and ALB, and has been demonstrated to have superior prognostic value than the CP grade. ALBI grade has also been recommended as a substitute for CP grade in BCLC stage, CLIP stage and as the addition of tumor-lymph node-metastasis stage for HCC. In addition, the PALBI grade offers better performance of evaluating hepatic functional reserve and prognosis than the CP grade.

According to the ALBI grade, CP grade A patients with HCC could be divided into 2 groups with clearly different prognoses. In the present study, patients with CP grade A were divided into ALBI grade 1 (64.2%) and 2 (35.8%) groups, and PALBI grade 1 (61.9%) and PALBI grades 2 and 3 (38.1%) groups. In line with previous reports, we found that patients with ALBI grade 2 had significantly worse survival than patients with ALBI grade 1. Our findings also indicated that PALBI grade could be used as a predictor of survival in CP grade A patients with HCC.

The comparisons of prognostic ability between ALBI, PALBI, MELD, and classic HCC stages have rarely been performed. In the present study, the combination of tumor size with ALBI, particularly with PALBI, showed higher performance for survival prediction than MELD, BCLC, and CLIP staging systems. Patients with lower grade of ALBI (or PALBI) and smaller tumor size had significantly better outcomes. Chan et al recently
| Variables                        | HR (95% CI)      | P     |
|---------------------------------|------------------|-------|
| AST (>45/≤45U/L)                | 1.93(0.98-3.79)  | 0.058 |
| AFP (≥400/<400ng/ml)            | 2.01(1.00-4.01)  | 0.049 |
| Tumor size (>5/≤5cm)            | 4.89(2.07-11.54) | <0.001|
| Tumor number (multiple/single)  | 2.78(1.20-6.47)  | 0.017 |
| Cirrhosis (yes/no)              | 1.68(0.80-3.56)  | 0.172 |
| BCLC stage (B-C/A)              | 2.35(1.16-4.77)  | 0.018 |
| CLIP (1-4/0)                    | 3.08(1.45-6.52)  | 0.003 |
| ALBI grade (2/1)                | 2.33(1.17-4.63)  | 0.016 |
| PALBI grade (2-3/≤1)            | 2.34(1.19-4.62)  | 0.014 |

**Figure 4.** Forest plots based the results of multivariate analysis for overall survival (A) and recurrence-free survival (B).
### Table 3
Ranking of discriminatory ability of the prognostic systems on the basis of the C-index.

| Rank | System                              | C-index | 95% CI       |
|------|-------------------------------------|---------|--------------|
| 1    | PALBI + tumor size                  | 0.762   | 0.675–0.849  |
| 2    | ALBI + tumor size                   | 0.744   | 0.664–0.844  |
| 3    | CLIP-ALBI                           | 0.727   | 0.629–0.828  |
| 4    | PALBI                              | 0.699   | 0.594–0.804  |
| 5    | BCLC-ALBI                           | 0.670   | 0.565–0.776  |
| 6    | ALBI + tumor size                   | 0.660   | 0.542–0.758  |
| 7    | MELD                                | 0.650   | 0.542–0.758  |
| 8    | MELD                                | 0.670   | 0.565–0.775  |
| 9    | ALBI + tumor size                   | 0.477   | 0.366–0.588  |

ALBI = albumin-bilirubin, BCLC = Barcelona Clinic Liver Cancer, CI = confidence interval, CLIP = Cancer of the Liver Italian Program, MELD = model for end-stage liver disease, PALBI = platelet-albumin-bilirubin.

---

**Figure 5.** Cumulative overall survival and recurrence-free survival curves of patients stratified according to the albumin-bilirubin (ALBI) and tumor size (A, B, stage I: ALBI grade 1 and tumor size ≤5 cm; stage II: ALBI grade 1 and tumor size >5 cm, or ALBI grade 2 and tumor size ≤5 cm; stage III: ALBI grade 2 and tumor size >5 cm), platelet-albumin-bilirubin (PALBI), and tumor size (C, D: stage I: PALBI grade 1 and tumor size ≤5 cm; stage II: PALBI grade 1 and tumor size >5 cm, or PALBI grades 2 and 3 and tumor size ≤5 cm; stage III: PALBI grades 2 and 3 and tumor size >5 cm).
recruited 1973 patients with HCC regardless of CP grade and showed that the integrations of ALBI grade into original BCLC and CLIP staging systems provided high accuracy in predicting survival, with the C-indices 0.760 and 0.789, respectively. Other studies have also suggested that the modification of BCLC and CLIP systems with ALBI grade can improve prognosis prediction for HCC. However, substituting CP grade by ALBI grade in the 2 staging systems has never been investigated in CP grade A patients. In our study, the simple combinations of tumor size with ALBI and with PALBI showed comparable C-indices when compared to BCLC-ALBI and CLIP-ALBI, indicating that both of them can be recommended to assess the prognosis of CP grade A patients with HCC.

The underlying mechanisms enable higher grades of ALBI and PALBI to indicate worse OS and RFS in HCC are not well established. All the components in the 2 grades, including ALB, TBIL, and platelets, may contribute to the development and prognosis of HCC. In vitro study showed that direct addition of exogenous ALB could inhibit tumor growth in HCC cell lines via the modulation of α-fetoprotein and growth-controlling kinases. Hypoalbuminemia has widely been demonstrated to be associated with the progress, survival, and recurrence of several types of tumors, including HCC. Elevated serum TBIL is a sensitive reflection of liver injury due to an injurious effect on hepatocytes. A systematic review summarized the prognostic indicators of liver function and identified serum ALB and TBIL as the 2 most prominent prognostic factors. Platelets are known to stimulate HCC tumor growth via producing several stimulants, including vascular endothelial growth factor, platelet-derived growth factor, serotonin, and so forth. Platelets can also accelerate angiogenesis and metastasis of HCC via releasing platelet-derived mediators, used for PALBI, might affect survival by the presence of portal hypertension. Numerous studies have shown that PLT is significantly associated with OS and RFS of HCC. In addition, PLT is positively correlated with tumor size in patients with HCC and platelets promote tumor growth while ALB inhabits tumor growth in vitro.

Therefore, PALBI and ALBI may be significant factors related to tumor size.

There are several limitations in the present study. Firstly, this is a single-center retrospective study with relatively small sample size, thus external validation from larger multicenter prospective studies is still needed. Secondly, the results are based on patients with HCC who underwent radical resection and who were CP grade A. Less than 20% of patients with HCC were BCLC stages B and C. Therefore, further study is needed to validate the prognostic accuracy of ALBI and PALBI grades in patients with HCC with different treatment modalities and to compare with BCLC and CLIP in patients regardless of CP grade. Thirdly, it has been recently reported that postoperative grade of ALBI may be more valuable than preoperative grade in predicting outcome of HCC. However, as the retrospective design, the majority of patients in the cohort had missing data of dynamic measures. Lastly, the ALB replacement therapy, methods for measuring serum ALB, and the presence of constitutional jaundice may affect the role of ALBI and PALBI.

In conclusion, ALBI and PALBI grades, in particular the combination with tumor size, are effective models for discriminating survival in HBV-associated patients with HCC with CP grade A. Future studies should explore whether the survival of HCC can be prolonged by improving ALBI and PALBI grades.

Author contributions
Conceptualization: Yong Wang, Qing Pang.
Data curation: Binquan Wu, Xiaosi Hu, Song Yang.
Formal analysis: Hao Jin, Yong Wang.
Funding acquisition: Dengyong Zhang, Qing Pang.
Methodology: Xiaosi Hu, Dengyong Zhang.
Project administration: Lei Zhou, Huichun Liu, Peiyuan Cui.
Resources: Zhongran Man.
Software: Lei Zhou.
Supervision: Hao Jin.
Validation: Zhongran Man, Peiyuan Cui.
Writing – original draft: Binquan Wu, Xiaosi Hu.
Writing – review & editing: Qing Pang, Huichun Liu, Peiyuan Cui.

References
[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[2] El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011;365:1118–27.
[3] Forner A, Reig M, Bruix J. Hepatocellular carcinoma. Lancet 2018;391:1301–14.
[4] European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.
[5] Kulik L, El-Serag HB. Epidemiology and management of hepatocellular carcinoma. Gastroenterology 2019;156:477–91.
[6] Bruix J, Sherman M. American Association for the Study of Liver Disease. Management of hepatocellular carcinoma: an update. Hepatology 2018;63:1020–2.
[7] Rahbari NN, Mehrabi A, Mollberg NM, et al. Hepatocellular carcinoma: current management and perspectives for the future. Ann Surg 2011;253:453–69.
[8] Jaruvongvanch V, Sempokuya T, Wong L. Is there an optimal staging system or liver reserve model that can predict outcome in hepatocellular carcinoma? J Gastrointest Oncol 2018;9:750–61.
[9] 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 2015;33:550–8.
[10] Chan AW, Chong CC, Mo FK, et al. Applicability of albumin-bilirubin-based Japan integrated staging score in hepatitis B-associated hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31:1766–72.
[11] Zou H, Yang X, Li QL, et al. A comparative study of albumin-bilirubin score with Child-Pugh score, model for end-stage liver disease score and indocyanine green R15 in predicting posthepatectomy liver failure for hepatocellular carcinoma patients.Dig Dis 2018;36:236–43.
[12] 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 2017;32:879–86.
[13] Luo HM, Zhao SZ, Li C, et al. Preoperative platelet-albumin-bilirubin grades predict the prognosis of patients with hepatitis B virus-related hepatocellular carcinoma after liver resection: a retrospective study. Medicine (Baltimore) 2018;97:e1226.
[14] Collins GS, Reitsma JB, Altman DG, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. Ann Intern Med 2018;169:65–68.
[15] World Medical A. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191–4.
[16] Hsu TL, Huang YH, Lin HC, et al. Proposal of a modified Cancer of the Liver Italian Program staging system based on the model for end-stage liver disease for patients with hepatocellular carcinoma undergoing loco-regional therapy. Am J Gastroenterol 2006;101:975–82.
[17] Harrell FE Jr, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.
Llovet JM, Bruix J. Prospective validation of the Cancer of the Liver Italian Program (CLIP) score: a new prognostic system for patients with cirrhosis and hepatocellular carcinoma. Hepatology 2000;32:679-80.

Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329-38.

Kaplan DE, Dai F, Aytaman A, et al. Development and performance of an algorithm to estimate the Child-Turcotte-Pugh score from a National Electronic Healthcare Database. Clin Gastroenterol Hepatol 2015;13:2333-41.e1-6.

Xavier SA, Vilas-Boas R, Boal Carvalho P, et al. Assessment of prognostic performance of albumin-bilirubin, Child-Pugh, and model for end-stage liver disease scores in patients with liver cirrhosis complicated with acute upper gastrointestinal bleeding. Eur J Gastroenterol Hepatol 2018;30:652-8.

Wang YY, Zhong JH, Su ZY, et al. Albumin-bilirubin versus Child-Pugh score as a predictor of outcome after liver resection for hepatocellular carcinoma. Br J Surg 2016;103:725-34.

Chan AWH, Zhong J, Berhane S, et al. Development of pre and postoperative models to predict early recurrence of hepatocellular carcinoma after surgical resection. J Hepatol 2018;69:1284-93.

Toyoda H, Lai PB, O’Searie J, et al. Long-term impact of liver function on curative therapy for hepatocellular carcinoma: application of the ALBI grade. Br J Cancer 2016;114:744-50.

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 2016;31:1300-6.

Hirooka A, Kumada T, Michitaka K, et al. Usefulness of albumin-bilirubin grade for evaluation of prognosis of 2584 Japanese patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31:1031-6.

Chan AW, Chong CC, Mo FK, et al. Incorporating albumin-bilirubin grade into the cancer of the liver program system for hepatocellular carcinoma. J Gastroenterol Hepatol 2017;32:221-8.

Ho CHM, Chang CL, Lee FAS, et al. Comparison of platelet-albumin-bilirubin (PALBI), albumin-bilirubin (ALBI), and child-pugh (CP) score for predicting of survival in advanced HCC patients receiving radiotherapy (RT). Oncotarget 2018;9:28818-29.

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 2017;66:338-46.

Shao YY, Liu TH, Lee YH, et al. Modified CLIP with objective liver reserve assessment retains prognosis prediction for patients with advanced hepatocellular carcinoma. J Gastroenterol Hepatol 2016;31:1336-41.

Bagirsakci E, Sahin E, Atabey N, et al. Role of albumin in growth inhibition in hepatocellular carcinoma. Oncology 2017;93:136-42.

Gupta D, Lu CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. Nutr J 2010;9:69.

Shim JH, Jun MJ, Han S, et al. Prognostic nomograms for prediction of recurrence and survival after curative liver resection for hepatocellular carcinoma. Ann Surg 2015;261:939-46.

Du ZG, Wei YG, Chen KF, et al. Risk factors associated with early and late recurrence after curative resection of hepatocellular carcinoma: a single institution’s experience with 398 consecutive patients. Hepatobiliary Pancreat Dis Int 2014;13:153-61.

D’Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol 2006;44:217-31.

Fatima S, Shi X, Lin Z, et al. 5-Hydroxytryptamine promotes hepatocellular carcinoma proliferation by influencing beta-catenin. Mol Oncol 2016;10:215-212.

Carr BI, Guerra V. Thrombocytosis and hepatocellular carcinoma. Dig Dis Sci 2013;58:1790-6.

Nalesnik MA, Michalopoulos GK. Growth factor pathways in development and progression of hepatocellular carcinoma. Front Biosci (Schol Ed) 2012;4:1487-515.

Carr BI, Cavallini A, D’Alessandro R, et al. Platelet extracts induce growth, migration and invasion in human hepatocellular carcinoma in vitro. BMC Cancer 2014;14:63.

Gay LJ, Felding-Habermann B. Contribution of platelets to tumour metastasis. Nat Rev Cancer 2011;11:123-34.

Au KP, Chan SC, Chok KS, et al. Child-Pugh parameters and platelet count as an alternative to ICG test for assessing liver function for major hepatectomy. HPB Surg 2017;2017: 2948030.

Bihari C, Rastogi A, Shashtri SM, et al. Platelets contribute to growth and metastasis in hepatocellular carcinoma. APMIS 2016;124:776-86.

Pang Q, Qu K, Zhang JY, et al. The prognostic value of platelet count in patients with hepatocellular carcinoma: a systematic review and meta-analysis. Medicine (Baltimore) 2015;94:e1431.

Amisaki M, Uchinaka E, Morimoto M, et al. Post-operative albumin-bilirubin grade predicts long-term outcomes among Child-Pugh grade A patients with hepatocellular carcinoma after curative resection. Hepatobiliary Pancreat Dis Int 2018;17:502-9.