



ORIGINAL ARTICLE

Comparative liver function models for ruptured hepatocellular carcinoma: A 10-year single center experience



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KEYWORDS

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Model

Summary *Background/Objective:* Previous studies have proposed several objective means for liver function assessment in hepatocellular carcinoma (HCC) patients; however, their efficiency in predicting survival of HCC rupture is unknown. Our study aims to confirm which is a better liver function model for ruptured HCC.

Methods: A total of 230 patients with HCC ruptures at our center were included. Kaplan–Meier and Cox regression analyses were performed to compare long-term survival and short-term mortality. The 90-day mortality was compared with the area under the receiver characteristic curve. Logistic regression was used to determine the risk factors for 90-day deaths, and the discriminant ability of the model was measured.

Results: There were significant differences in predicting OS of the Child-Pugh (CP) score in all patients, the non-surgical subgroup, and the surgical subgroup (all $P < 0.0001$). But no statistical significance was shown of the ALBI score in the surgical ($P = 0.8985$) or non-surgical subgroup ($P = 0.0634$). The CP score yielded a better performance among all patients (AUC = 0.746 vs. 0.712), the surgical subgroup (AUC = 0.558 vs. 0.530), and the non-

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surgical subgroup (AUC = 0.715 vs. 0.634) compared to ALBI score in predicting ninety-day mortality. A similar result can be found in the subgroup of surgical and non-surgical treatment group. Moreover, the logistic model that included CP or MELD had a better discriminatory ability than ALBI in predicting ninety-day mortality.

Conclusion: The CP or MELD rather than ALBI score should be used as a liver function classification criterion for HCC rupture.

Clinical trial number: NCT03534843 (retrospectively).

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1. Introduction

As a standard malignancy, Hepatocellular Carcinoma (HCC) is one of the major causes of cancer-related death globally, particularly in Asia.^{1–3} Between regions or nations, spontaneous rupture of the tumor is considered to be one of the most dangerous complications that occur in approximately 3%–15% of all patients with HCC.^{4,5} Mortality rates of spontaneous HCC rupture remain high in the acute stage (25%–75%).^{4,6} Although a ruptured HCC is classified as T4 grade, which indicates an advanced stage according to the AJCC/UICC classification,⁷ appropriate treatment can still improve outcomes.^{4,6} Furthermore, a liver function scoring system is necessary for effective treatment selection. A patient with severely poor liver function is considered intolerant to the operation or interventional therapy. The Child-Pugh (CP) grade is currently the recognized scoring system for evaluating the limit of potential liver dysfunction in patients with HCC.^{8–10} However, the CP grade has some limitations, such as the empirical characteristics of the model and the subjectivity of some parameters (such as ascites and encephalopathy notation). Recently, a new

model named the albumin-bilirubin (ALBI) score was developed as a substitute for the CP grade in HCC patients.¹¹ The albumin–bilirubin (ALBI) grade was calculated using the following formula: $\text{ALBI score} = (\log_{10} \text{bilirubin} \times 0.66) + (\text{albumin} \times -0.085)$, and the continuous ALBI score was attributed as follows: grade 1 (score ≤ -2.60); grade 2 (score > -2.60 but ≤ -1.39); grade 3 (score > -1.39). Only two objective variables (albumin and bilirubin) were included in the model. Its performance is superior to the CP grade in predicting outcomes of HCC patients,^{11,12} but in some HCC populations, ALBI was reported to not be as effective as the CP grade.¹³

All these models were initially developed for HCC without consideration of rupture. Whether the ALBI grade can accurately reflect the liver function of patients with HCC rupture remains unknown. Therefore, we carried out a retrospective (10 years) cohort study that included ruptured HCC patients at our center, aiming at comparing the abilities of the ALBI and CP or MELD in prognosis prediction.

2. Materials and methods

2.1. Study population

The data were obtained from the Department of Hepatic Surgery, Tongji Hospital, Tongji Medical College of Huazhong University of Science and Technology University from January 2005 to August 2015. The choice of study subjects is shown in Fig. 1. People who had the first diagnosis of ruptured HCC but had repeated transcatheter arterial chemoembolization (TACE) or a long history (more than 1 year) of cancer treatment were excluded. Three patients who were pathologically diagnosed not as HCC were excluded. We also excluded 21 cases due to loss of follow up or because there was incomplete data. Ultimately, 230 patients, including 144 patients who received surgical treatment and 86 patients who received non-surgical treatment, were included.

2.2. Diagnosis, treatment, and follow-up

The diagnosis of HCC was through a noninvasive method or histopathologic examination in accordance to the European Association guidelines for the Study of the Liver, the American Association for the Study of the Liver, and the

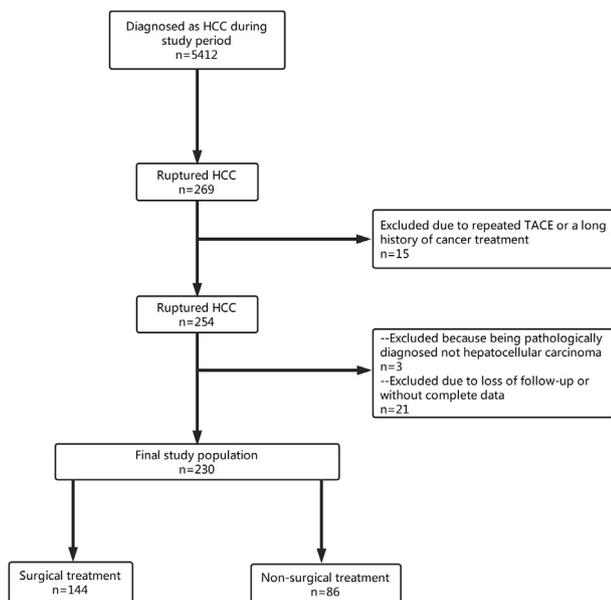


Figure 1 Study flow chart. HCC, hepatocellular carcinoma; TACE, transcatheter arterial chemoembolization.

guidelines on the diagnosis and treatment of primary liver cancer developed by Primary Liver Cancer Diagnosis and Treatment Expert Panel of the Chinese Ministry of Health.^{9,14,15} Normally, the main diagnosis of a tumor rupture is based on the clinical signs and symptoms upon admission to the hospital, such as acute abdominal pain and shock, and confirmed by at least 2 types of imaging examinations. Diagnostic abdominal paracentesis was performed if there were no contraindications. Bleeding resulting from a tumor can also be confirmed by surgical exploration in surgically treated patients, or by digital subtraction angiography (DSA) in transcatheter arterial embolization (TAE) treated patients. Routine preoperative tests included peripheral blood tests, routine urine tests, liver and kidney function assessment, coagulation function detection, serum electrolytes analysis, hepatitis B and C virus marker tests, serologic alpha-fetoprotein (AFP) tests, electrocardiography, and a chest X-ray.

The main objective of acute management was maintaining stable hemodynamics using active vein fluid resuscitation and blood products if indicated. All hospitalized patients were closely monitored for unstable hemodynamics in the intensive care unit or emergency ward. In most cases, hemorrhage was controlled spontaneously following initial immediate treatment. TAE was considered to have hemostatic effects without severe poor liver function or other contraindications. TAE would be performed in patients with unstable hemodynamics or with active bleeding. An appropriate amount of iodized oil, combined with gelatin sponge particles, was used. A small percentage of cases that showed good liver conditions received TACE based on the interventional physician's experience. When hemostasis was not able to be achieved via non-surgical treatments, emergency laparotomy and surgical hemostasis were performed after evaluation. Depending on the circumstances, partial hepatectomy was preferred, and other operative procedures (palliative surgery) such as ligation of the hepatic artery, suturing of bleeding tumor, and perihepatic packing was performed. After the hemodynamic parameters were improved, a detailed preoperative assessment was carried out to determine the further treatments. The evaluation included Eastern Cooperative Oncology Group score, cardiopulmonary function, serological test, Child-Pugh score, the tumor status, indocyanine green retention rate at 15 min, imaging scans and liver volume measurement. Definitive treatment was based on the general condition of patients, the extent of the tumor, the status of liver function, and the treatment requested by the patients and their family members.

CP C grade was recognized as absolute contraindications for liver surgery. Other contraindications include main portal vein tumor thrombosis, intractable hepatic encephalopathy, severe coagulopathy, poor performance status, distant metastasis, heart, renal or lung function that was unable to tolerate the operation. In stable patients, the definitive treatment plan was developed by multidisciplinary liver tumor conference. Partial hepatectomy (whether emergency or staged) was performed on single or multiple liver resections to eliminate all macroscopic lesions. Both anatomical resections and parenchymal-preserving resections were preferred based on the extent of hepatic cirrhosis. All operative procedures were

performed by experienced surgeons; the abdominal cavity was extensively explored during surgery. Pringle's maneuver was applied, when necessary, to occlude hepatic blood inflow bleeding during parenchymal transection. The ideal tumor margin during resection was greater than 1 cm. Liver cirrhosis was confirmed by histopathology or conventional imaging examination.

Follow-up data were acquired via telephone interviews, outpatient examinations, or during the re-admission period of the study. All patients were monitored regularly with surveillance for recurrence, metastasis, and survival, following the proper timetable. For the first six months after discharge, all patients were followed-up once a month, then every three months if there was no recurrence or metastasis. The follow-up period ended on January 1, 2018, or at death, or when patient contact was lost. Moreover, overall survival (OS) was recorded. The treatment recommendations for tumor recurrence or metastasis were conducted by multidisciplinary liver tumor conference, and a decision was usually made after consultation with the patient and his or her family members. Treatment recommendations included reoperation, percutaneous ethanol injection, percutaneous ablative therapy, TACE, intravenous chemotherapy, radiotherapy, or sorafenib (since 2008) oral tablets. The treatments and research were in accordance with the ethical standards set by the Declaration of Helsinki and approved by the Ethics Committee of Tongji Hospital. The research was registered on ClinicalTrials.gov (NCT03534843).

2.3. Statistical analysis

All of the statistical analyses were conducted with MedCalc software 18.2.1 (bvba, Ostend, Belgium), SPSS 24.0 (IBM Corp., Armonk, NY, USA), and R software 3.4.4 for Windows (R Foundation for Statistical Computing, Vienna, Austria) (<http://www.r-project.org>), combining with some packages (Harrell Miscellaneous [Hmisc], survival, survminer, ggsvplot, ggpar, DescTools). A two-sided $P < 0.05$ was considered statistically significant. Categorical data were presented as number (n) or proportion (%). Continuous variables were summarized as mean \pm standard deviation (SD) or median (quartiles). Comparison of continuous variables between groups was analyzed using Student's *t*-test when meeting application condition; otherwise, the Mann-Whitney U test was applied. Categorical variables were compared by the χ^2 test with (or without) the Yates' correction or using Fisher's exact test. Survival analysis of the OS was performed using the Kaplan-Meier method compared by the log-rank test or using the Cox regression. Receiver operating characteristic (ROC) analysis was performed to evaluate the performance of the 2 hepatic function scoring systems in predicting 90-day mortality. To determine the diagnostic efficiency of the given scoring systems we measured the areas under the ROC curve (AUCs) from ROC analyses. Binary logistic regression of factors relating to 90-day mortality was performed as well as the odds ratio (OR) and its 95% confidence interval (CI) was estimated.

Discriminatory ability was observed to measure the performance of a classification system.^{16,17} Harrell's C

statistics (C-index) was calculated to determine the discriminatory ability of the ALBI classification system and the CP scoring system. The C-index varies from 0.5 to 1.0. A higher C-index implies superior discriminative ability in each prognostic system. In addition, the Akaike Information Criteria (AIC) was also implemented to assess the discriminatory ability of a given model. A lower AIC implies less information loss of a model and better goodness of fit. The relative likelihood of models represents the probability that CP minimizes information loss as effectively as ALBI and can be interpreted succinctly as a *P* value for the comparison of AIC differences. The relative likelihood of CP vs. ALBI model was calculated using the following formula: $\exp((AIC_{Child}/AIC_{ALBI})/2)$. In addition, the Hosmer–Lemeshow (H-L) test was performed to measure the goodness of fit of a given model. The work has been reported in line with the STROCSS criteria.¹⁸

3. Results

3.1. Clinical characteristics

The overall patient demographics and clinicopathologic features are shown in Table 1. All patients (208 males and 22 females) had a mean age of 47.6 ± 12.4 years. Among them, 201 patients (87.4%) were HBsAg positive. A total of 131 patients (57.0%) received liver resection. Unfortunately, a minority of patients with unresectable lesions ($n = 13$, 5.7%) received only palliative surgery, such as microwave coagulation therapy, hepatic artery ligation, or suturing ligation. Other patients were treated with TAE or TACE ($n = 50$, 21.7%) and conservative treatment ($n = 36$, 15.7%). In this cohort, more than half of the patients had CP A grade ($n = 143$, 62.2%), whereas most patients were in ALBI 2 grade ($n = 169$, 73.5%). Further details can be found in Table 1 and S1 Table.

3.2. Long-term survival

The median survival time (MST) was 7.4 (IQR 2.7–20.3) months in all patients with HCC rupture. More specifically, MST was 10.8, 5.0, and 0.2 months vs. 15.0, 7.5, and 0.5 months respectively in CP-A, -B, and -C grade vs. ALBI 1, 2, and 3, respectively. Significant survival differences could be found among both CP ($P < 0.0001$) (Fig. 2A) and ALBI grades ($P = 0.0034$) (Fig. 2B) of all patients. In the surgical treatment subgroup, there were significant survival differences ($P < 0.0001$) among different CP grades (Fig. 2C), but there were no significances among different ALBI grades ($P = 0.8985$) (Fig. 2D). Likewise, in the non-surgical treatment subgroup, there were significances among CP ($P < 0.0001$) (Fig. 2E) but no significances were observed among ALBI grades ($P = 0.0634$) (Fig. 2F).

Furthermore, homogeneity and discriminatory ability were evaluated by Harrell's C statistics, AIC, and the relative likelihood ratio. The CP classification system showed higher Harrell's C statistics than the ALBI classification system (0.623 vs. 0.568 of all cohort, 0.533 vs. 0.514 of the surgical cohort, and 0.653 vs. 0.582 of non-surgical cohort). Likewise, the CP classification correlated with less

Table 1 Patient demographics and baseline characteristics.

Variables	All patients (n = 230)
Age, years; mean \pm SD	47.6 \pm 12.4
Male/Female	208 (90.4)/22(9.6)
HBs-Ag (+)	201 (87.4)
HCV-Ab (+)	17 (7.4)
Tumor size, cm; median (IQR)	8.6 (6.0–11.6)
Tumor number	
1	141 (61.3)
2–3	27 (11.7)
≥ 4	62 (27.0)
MVI	55 (23.9)
Cirrhosis	167 (72.6)
Haemorrhagic shock	62 (27.0)
Hemoglobin, g/L; mean \pm SD	109.0 \pm 27.0
RBC transfusion	143 (62.2)
AFP, ng/mL	
0–20	50 (21.7)
20–400	39 (17.0)
> 400	141 (61.3)
ALT, U/L; median (IQR)	35.0 (23.0–70.0)
AST, U/L; median (IQR)	50.0 (29.0–97.5)
Albumin, g/L; mean \pm SD	33.2 \pm 6.8
T-Bil, μ mol/L; median (IQR)	15.1 (10.8–21.8)
Creatinine, μ mol/L; mean \pm SD	81.07 \pm 36.08
Treatment	
Liver resection	131 (57.0)
Palliative surgery	13 (5.7)
TAE	50 (21.7)
Conservative treatment	36 (15.7)
Child-Pugh grade	
A	143 (62.2)
B	73 (31.7)
C	14 (6.1)
ALBI score	
1	35 (15.2)
2	169 (73.5)
3	26 (11.3)
MELD score	
6–8	97 (42.2)
9–12	80 (34.8)
≥ 13	53 (23.0)
BCLC stage	
A	107 (46.5)
B	51 (22.2)
C	58 (25.2)
D	14 (6.1)
Sorafenib	6 (2.6)
Survival time, months; median (IQR)	7.4 (2.7–20.3)

Data are presented as number (%), if not specified. SD, standard deviation; IQR, interquartile range; MVI, Macroscopic vascular invasion; AFP, α -fetoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; T-Bil, total bilirubin; ALBI, albumin-bilirubin; MELD, model for end-stage liver disease; BCLC, Barcelona Clinic Liver Cancer.

information loss than the ALBI grade in predicting survival (all relative likelihood < 0.001) (Table 2).

In subgroup compare, The CP classification system showed better performance in both liver resection group,

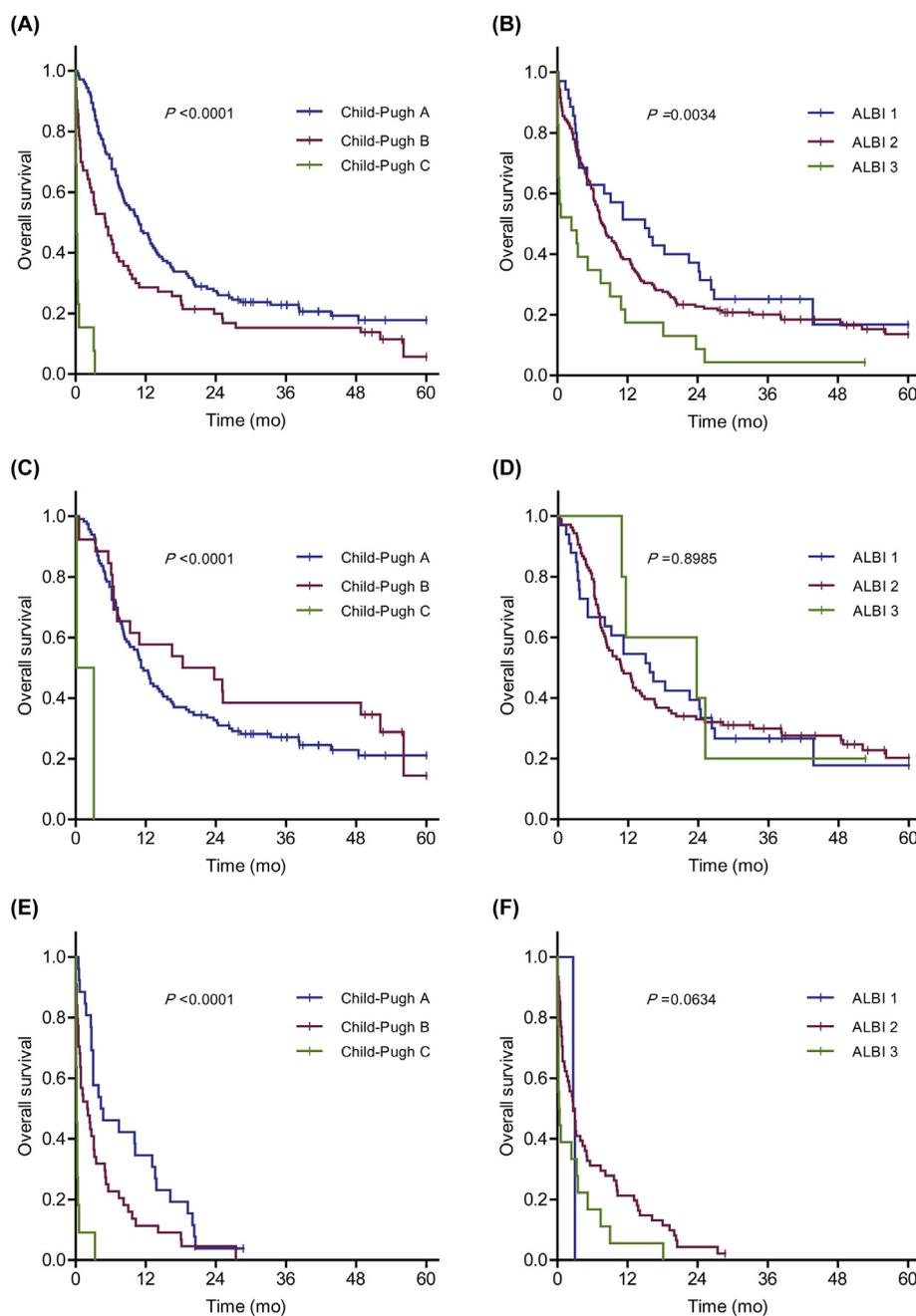


Figure 2 Overall survival of Child-Pugh scoring systems and ALBI scoring systems. There is a significant difference between both Child-Pugh (A) and ALBI (B) score in all patients. There is a significant difference in Child-Pugh (C) but not in the ALBI score (D) in surgically treated patients. There is a significant difference in Child-Pugh (E) but not in the ALBI score (F) in non-surgically treated patients.

and TAE treatment group, but there is no difference in the conservative treatment group (S2 Table).

Thus, the traditional CP score is superior to ALBI grade for HCC rupture in predicting long-term survival.

3.3. Short-term survival

In the cohort, there are seven, four and fifty-two patients died within 90-days in liver resection group, palliative surgery group, and non-surgical treatment group. Among them, only 1 patient died of myocardial infarction after

emergency partial hepatectomy, and other 6 patients (6/7) died from other tumor-related or liver-related causes (such as hepatic encephalopathy, liver failure, renal failure, gastroesophageal variceal hemorrhage) in the surgical treatment group. In the palliative surgery group, 2 (2/4) died of bleeding caused by tumor rupture or re-rupture, and the other two cases died from tumor-related or liver-related causes. In the non-surgical treatment group, similarly, more than half patients ($n = 32$, 61.5%) died of bleeding caused by tumor rupture or re-rupture, and 20 cases died from other tumor-related or liver-related

Table 2 Discriminative abilities of Child-Pugh scores and ALBI grades in predicting overall survival (OS).

Predictor	All patients (n = 230)		Surgical group (n = 144)		Non-surgical group (n = 86)	
	Child-Pugh	ALBI	Child-Pugh	ALBI	Child-Pugh	ALBI
Harrell's C statistic	0.623	0.568	0.533	0.514	0.653	0.582
AIC	1800.74	1837.42	957.51	967.34	580.04	594.47
Relative likelihood of AIC (ALBI vs Child-Pugh)	<0.001		<0.001		<0.001	

AIC, Akaike information criterion; ALBI, albumin-bilirubin.

causes. The 90-day mortalities were 14.0%, 42.5%, and 92.9% vs. 17.1%, 24.9%, and 57.7% in CP-A, B, C and ALBI 1, 2, 3 grade, respectively. There were significances among both the CP score ($P < 0.001$) and ALBI classification ($P = 0.001$), but the differences between each of the CP grades seemed clear (14.0%-A, 42.5%-B, 92.9%-C vs. 17.1%-ALBI1, 24.9%-ALBI2, 57.7%-ALBI3). In the surgical treatment subgroup, 90-day mortality was 6.9%, 7.7%, and 50.0% for the CP A, B, C grade, but 12.1%, 6.6%, and 0.0% for the ALBI 1, 2, 3 grades. Strangely, higher ALBI grades revealed a lower mortality rate. Similarly, in the non-surgical treatment subgroup, 90-day mortality was 44.4%, 61.7%, and 91.7% for the CP-A, B, C grade but was 100.0%, 55.6%, and 71.4% for the ALBI 1, 2, 3 grades (S3 Table).

The ROC curve analysis was performed to determine the performance of the 2 liver function classification models at discriminating ruptured HCC patients with or without 90-day mortality (Fig. 3). CP score indicated a higher discrimination accuracy than the ALBI grade, quantified by the AUC of ROC (0.746 vs. 0.712). Also, similar results were found in the surgical treatment (0.558 vs. 0.530) and, especially, in the non-surgical treatment subgroup (0.715 vs. 0.634) (S1 Fig).

In subgroup analysis, the AUC of CP was 0.521, 0.589, and 0.795 vs. ALBI 0.516, 0.532, and 0.696 in the liver resection group, TAE treatment group, and conservative treatment group respectively.

To further identify if the 2 liver function classification systems could be a risk factor for 90-day mortality, logistic regression analysis was performed. After selecting risk factors (with $P < 0.10$) by univariate analysis (S4 Table), a multivariate regression model was applied. When CP, rather than ALBI grade, was included in the model (model 1), the CP grade could be an independent risk factor of mortality ($P < 0.001$). More importantly, when the CP A grade was used as the reference, both CP B grade (OR = 4.747, $P < 0.001$) and CP C grade (OR = 67.943, $P < 0.001$) exhibited a significantly higher risk in predicting 90-day mortality. However, when the ALBI grade was included in model 2, although the CP grade could have been an independent risk factor of mortality as a whole ($P < 0.001$), ALBI 2, which comprised of the majority of the patients, could not have been a risk factor in model 2 (OR = 1.546, $P = 0.399$) when the ALBI 1 grade was used as the reference (Table 3). In addition, the model for end-stage liver disease (MELD) score was also observed to be a risk factor of 90-day mortality independently ($P < 0.001$). Using the MELD score 6–8 as the reference, score 9–11 seemed to have no significance (OR = 2.457, $P = 0.052$) (S5 Table). In the non-surgical treatment subgroup, both CP and MELD scores were

an independent risk factor of 90-day mortality, which was confirmed by multivariate regression analysis; however, ALBI had no predicting role in univariate analysis (S6 and S7 Table). For the relatively low 90-day mortality in surgical patients, surgical sub-group was inappropriate for further logistic regression analysis.

Moreover, we compared the homogeneity and discriminatory ability of the logistic regression models. Model 1 had a higher Harrell's C statistics (0.856) than model 2 (0.801). Likewise, model 1 had a lower AIC (204.23) than model 2 (229.26). Hosmer–Lemeshow test for goodness of fit was better in model 1 (0.906) compared to model 2 (0.868). Parameters of model 3 were close to those of model 1.

Hence, the ALBI grade was less informative than both CP and MELD scores in the short-term survival.

4. Discussion

Spontaneous tumor rupture, as a life-threatening complication, represents an approximate rate of 6–10% mortality in HCC patients.^{4,19} In western countries, the incidence of spontaneous HCC rupture is less than 3% but up to 15% in the East.^{4–6,20} The current classification (arbitrarily classified into T4) for ruptured HCC remains controversial due to its limitation of reflecting prognosis inaccurately. The worldwide population-based analysis of HCC rupture was performed in Asia, a Japanese national survey, and it is revealed that tumor rupture had an additional negative impact on the baseline tumor status, which corresponded to an additional 0.5 to 2.0 TNM stage.²¹ Thus, the prognosis becomes poor once ruptured. Hemorrhage and shock can influence the clinical prognosis of these patients, so the initial treatment aiming at resuscitation and hemodynamic stabilization is the most important step in all different strategies. The one-stage emergency operation was effective in achieving both hemostasis and tumor removal^{22–24} but was reported to have high in-hospital mortality rates.^{4,25,26} In addition, TAE was considered an effective method to achieve hemostasis. Other palliative treatments, such as hepatic artery ligation, suturing of bleeding tumor, packing and microwave (or radiofrequency) ablation, have been proposed to stop bleeding for those patients with unresectable lesions.^{4,19,22,27,28} All the treatments above should be based on an accurate liver function classification. CP A-B liver function was preferable for surgical treatment or interventional therapy, and patients with CP C grade could receive only the best supportive care. However, the CP score had some limitations. First, it was proposed the empirically rather than in an evidence-based manner and

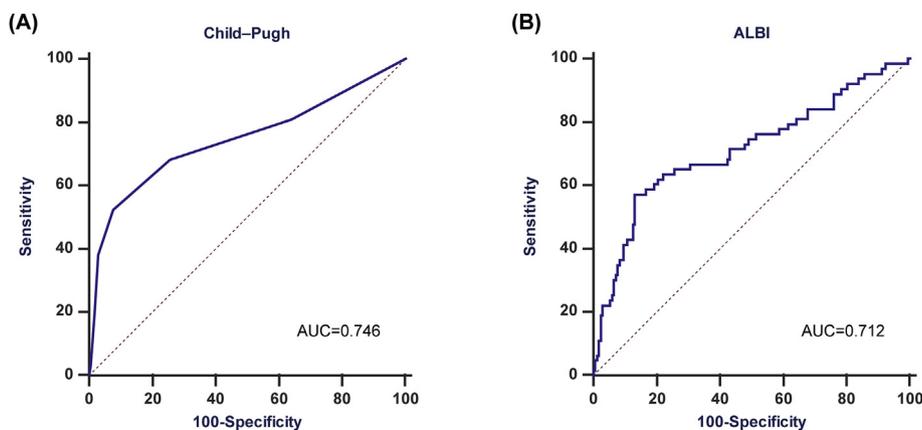


Figure 3 Receiver operating characteristic (ROC) curve in predicting 90-day mortality among all patients. (A) The area under the ROC curve for Child-Pugh score in predicting mortality was 0.746. (B) The area under the ROC curve for ALBI score in predicting mortality was 0.712.

Table 3 Multivariate logistic regression analysis of 90-day mortality in all patients (n = 230).

Variables	Model 1			Model 2		
	OR	95% CI	P value	OR	95% CI	P value
Tumor size, cm			0.025			0.023
5–10/<5	38.724	2.751–545.171	0.007	20.078	2.364–170.497	0.006
≥10/<5	37.915	2.540–565.905	0.008	18.123	2.032–161.613	0.009
Tumor number			0.030			0.005
2–3/1	0.552	0.132–2.307	0.416	0.702	0.191–2.579	0.594
≥4/1	2.469	1.112–5.482	0.026	3.083	1.466–6.487	0.003
MVI (yes/no)	1.419	0.621–3.244	0.407	1.537	0.720–3.281	0.267
Distant metastasis (yes/no)	2.868	0.743–11.065	0.126	2.357	0.650–8.546	0.192
Hemorrhagic shock (yes/no)	1.218	0.508–2.922	0.658	2.070	0.971–4.414	0.060
AFP, ng/ml (≥400/<400)	1.712	0.734–3.995	0.214	1.376	0.652–2.903	0.403
Child-Pugh grade			<0.001			–
B/A	4.747	2.107–10.696	<0.001	–	–	–
C/A	67.943	6.978–661.495	<0.001	–	–	–
ALBI score			–			0.032
2/1	–	–	–	1.546	0.562–4.249	0.399
3/1	–	–	–	5.456	1.392–21.392	0.015

MVI, Macroscopic vascular invasion; AFP, α -fetoprotein; ALBI, albumin-bilirubin.

was initially generated for evaluating the surgical risk in patients with cirrhosis, especially those with esophageal varices. Second, the scoring system assigns the same weights to parameters that might not have a similar prognostic importance. Finally, among the CP scores, 2 factors, including encephalopathy and ascites was estimated subjectively and may be prone to error, to some extent. The ALBI score, an evidence-based classification system, had been developed as a substitute for the CP scoring of liver function assessment in HCC patients. However, in the current study, we discovered that the CP or MELD score is superior to ALBI score for patients with spontaneous HCC rupture in predicting prognosis for the first time.

The median serum albumin level was 33.2 ± 6.8 g/L in all patients with tumor rupture, 30.3 ± 6.5 g/L in the TAE treatment group, and 29.5 ± 7.3 g/L in the conservative treatment group, respectively. What is more, we observed that a patient had an albumin level as low as 13.4 g/L with a

normal serum total bilirubin before operation (who was classified into a CP B grade but an ALBI 3 grade) was still alive 52 months and free from the tumor to this day. This suggests that we rethink and explore the efficiency of ALBI in predicting outcomes of patients with tumor rupture. A worse status of liver function was also observed in ruptured HCC patients than those without rupture according to reports from published literature.²⁹ However, the ALBI scoring system was developed for HCC without consideration for tumor rupture. Hence, not surprisingly, most patients (73.5%) were at ALBI 2 grade, and only 35 patients (15.2%) were classified into the ALBI 1 grade in the current study. The difference in baseline data of liver function among patients with non-ruptured and ruptured HCC may explain the lower efficiency of ALBI to some extent in our study.

In the current study, hemorrhage caused by tumor rupture or re-rupture is a major cause of death for patients with the tumor. In addition, bleeding complications were

reported as the leading cause of death for ruptured HCC in the short-term.³⁰ Most coagulation factors involved in bleeding and hemostasis progress, including anticoagulant and procoagulant factors, are synthesized in the liver. Thus, coagulation function plays a non-negligible role in judging the synthetic function of the liver, especially in patients with cirrhosis,³¹ and has been included in the model for end-stage liver disease.³² But, coagulation function (international normalized ratio [INR] or prothrombin time [PT]) was included in the CP classification rather than the ALBI grade. The CP scoring system contains 3 objective parameters such as albumin, total bilirubin, and coagulation function (INR is preferred over PT). The MELD score 4 parameters—albumin, creatinine, INR, and etiology of liver disease. Coagulation function should not be neglected, and this may be partly responsible for a better performance of CP or MELD than that of the ALBI score in predicting survival of patients with tumor rupture, especially in the non-surgical group, which had a high short-term mortality. In the surgical subgroup, generally patients had a good liver function (mainly CP-A) (S1 Table), and a low discriminatory ability of both CP (Harrell's C statistic of 0.558) and ALBI scores (Harrell's C statistic of 0.530) in predicting survival, which may be attributed to low discrimination among the subgroups (S1 Table). Even so, the CP (especially grade C) score had a better performance than the ALBI score in predicting both long-term and short-term survival in all groups. In general, patients died from hemorrhagic shock within a few days, but those with worse poor liver function can live for more than a month. So we used 90-day, not 30-day mortality when comparing short-term mortality.

This study was conducted in one of the largest high-volume centers in China. All surgeons had a wealth of practical experience in the resection of liver tumors. When a patient was primarily diagnosed with HCC rupture, partial liver resection was considered at first after admission. Partial hepatectomy (either emergent or staged) was performed if the liver functional reserve was suitable, the tumor was resectable, and the general condition was good. Therefore, the rate of liver resection for patients with HCC rupture was 57.0% (131 of 230), which was higher than in the previous studies.^{4,6,19,33} The postoperative OS rates for patients with HCC rupture were comparable to previous reports.^{20,25,33–35}

To our knowledge, this study is the first to investigate the efficiency of ALBI score for patients with HCC rupture. As an effective liver function scoring system for ruptured HCC, CP grading, containing 3 objective parameters—albumin, total bilirubin, coagulation function, and other 2 parameters, or MELD score, which contains 4 objective parameters, have a better performance in outcomes compared to ALBI grading. In conclusion, this research supports the continued application of CP grading as a liver function classification criterion for patients with HCC rupture. Other score systems of liver function, such as ALBI will be no longer useful in liver function test for ruptured HCC.

There were also some limitations of this research. First, due to the retrospective nature of this research, its inherent shortcomings were unavoidable. Because of the ethical issues and rare incidence of this disease, it is not easy to conduct a prospective study. Based on the findings of the current study, we can expect that in the future a

possible prospective study might be conducted. Second, because of the background, hepatic disease is related to hepatitis B in the current study, which is different from Western countries, hence, the results should be confirmed cautiously when applied to other regions.

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Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.asjsur.2018.12.015>.

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