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A proposed modification for the Barcelona Clinic Liver Cancer staging system: Adding bile duct tumor thrombus status in patients with hepatocellular carcinoma

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ABSTRACT

Background: The Barcelona Clinic Liver Cancer (BCLC) staging system is widely applied to stage hepatocellular carcinoma (HCC). However, it may be inaccurate when applied to East Asian HCC patients. In this study, a large Chinese HCC cohort was analyzed to evaluate possible modifications for the BCLC staging system.

Methods: Between January 1995 and December 2009, 622 HCC patients who underwent hepatectomy were enrolled. Prognostic risk factors were analyzed using univariate and multivariate analyses. The ability of the modified system to predict survival was evaluated by determining the area under the receiver operating characteristic curve.

Results: Patients without bile duct tumor thrombus (BDTT; 1-, 3- and 5-year overall survival, 80%, 60% and 48%, respectively) showed a substantial survival advantage over those with BDTT (1-, 3- and 5-year overall survival, 77%, 42% and 23%, respectively; $\chi^2 = 6.280$, $P = 0.012$). In BCLC stage 0-A patients, significant differences were identified between the BDTT group and the non-BDTT group, while no such differences were found in BCLC stage B patients. Based on this finding, BCLC stage 0-A BDTT patients were recategorized into stage B. The modified BCLC classification featured better performance in the prediction of overall survival than the original system (modified BCLC $\chi^2 = 53.596$, $P < 0.001$; original BCLC $\chi^2 = 46.335$, $P < 0.001$). The ability to predict mortality was also slightly higher using the modified BCLC system.

Conclusions: Modification of the BCLC system to include BDTT status might further enhance its prognostic ability.

Introduction

Hepatocellular carcinoma (HCC) is one of the most frequently diagnosed cancers and one of the leading causes of cancer-related deaths worldwide.[1–3] East Asia, particularly China, carries a disproportionately large share of the world's HCC cases, mainly due to the growing prevalence of hepatitis B and C virus infections.[4,5] Treatment for HCC is complicated due to the need for it to be radical from an oncological perspective but simultaneously conservative.[6] Furthermore, unlike other malignancies, prognostic assessment of HCC depends on not only the stage of the tumor but also multiple confounding factors.[7] Given the complexity and importance of prognostic assessment, multiple staging systems have been developed.[8] Among them, the Barcelona Clinic Liver Cancer (BCLC) staging system incorporates variables related to tumor stage, liver function, physical status and cancer-related symptoms and links staging with treatment modalities, as well as estimating life expectancy; the system is widely applied worldwide and serves as a treatment algorithm in HCC clinical practice.[9,10] However, there are still some uncertainties with regard to the best application of the BCLC staging system in East Asian HCC patients. Accumulating studies have suggested that possible modifications or improvements might be made to better suit Asian HCC

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populations,[11–14] as the BCLC system was mainly initiated in and based on data from Western HCC populations.[15]

According to the BCLC staging system, hepatectomy is indicated only for single-tumor patients with normal bilirubin levels without clinically relevant portal hypertension (PHT) (3). Liver transplantation is recommended for single-tumor patients with PHT/increased bilirubin or for multiple-tumor patients (up to three nodules and each smaller than three cm).[16] In HCC patients, bilirubin levels increase mostly as a result of liver decompensation. In HCC, increased bilirubin levels can be associated with bile duct tumor thrombosis (BDTT) due to tumor cell invasion into the bile duct. Therefore, it is of crucial importance to determine the cause of increased bilirubin in these patients before performing liver transplantation, as the possibility of posttransplantation recurrence in HCC patients with BDTT is inevitably increased.[17] The bilirubin level is elevated in HCC patients as a result of bile duct obstruction by tumor thrombus, which is observed in 0.53%–12% of HCC patients and is more commonly seen in Asian populations than in Western ones.[18–20] The biological features of BDTT might be fairly similar to those of portal vein tumor thrombus.[18,21] Therefore, it is of intrinsic value to incorporate BDTT into the HCC staging system. However, bile duct invasion is not included in the definition of advanced stage disease in the BCLC system.

As it is reasonably necessary to update and modify the current systems and recommendations according to new scientific evidence,[22] we retrospectively analyzed a well-followed cohort of 622 Chinese HCC patients to identify whether there was potential improvement in the performance of the BCLC system when it was applied in East Asian HCC populations; furthermore, special attention was placed on the prognostic influence of clinically significant BDTT.

Methods

Patients

The current study included a 15-year duration (from January 1995 to December 2009) and a cohort of patients with pathologically confirmed HCC who underwent hepatectomy as initial treatment at the Department of Hepatobiliary Surgery, Chinese PLA General Hospital (Beijing, China). The study protocol was approved by the Medical Ethics Committee of the Chinese PLA General Hospital. Written informed consent for treatment and use of patient data for clinical research was obtained from each patient before surgery. For all the patients enrolled in the study, demographic data and clinicopathological parameters were collected and analyzed by reviewing the medical computerized database of the cohort.

Diagnosis and definitions

For all patients enrolled, either enhanced computed tomography (CT) or magnetic resonance imaging (MRI) were performed prior to surgery. Preoperative imaging examinations were used to accurately assess the tumor nodule number, tumor size, portal vein thrombus status and BDTT status, which were reconfirmed by postoperative pathological examination. The presence of preoperative PHT was evaluated retrospectively, direct measurement of venous pressure was not performed routinely in our series, and PHT was indirectly defined as (1) esophageal varices detectable by endoscopy or (2) platelet count <100,000/μL in association with splenomegaly (major diameter, >12 cm), according to the BCLC criteria.[15,23] Ninety-day mortality included all deaths within 90 days of surgery in or out of hospital.[24] The duration of follow-up was defined as the period between the surgical procedure and death or final observation of patients.

Indications for hepatic resection

According to the criteria described above, the clinical indications for hepatic resection were 1) Child A or B liver function status, 2) absence of severe pulmonary or cardiovascular diseases, and 3) over 30% and 50% of the liver volume remnant in patients with normal liver parenchyma and cirrhosis, respectively.[2,25]

Surgical procedure

Surgery was performed via a right subcostal incision with a "J" extension. The liver was mobilized using standard procedures. Intraoperative ultrasonography was performed to determine the plane for parenchymal transection. For multiple HCCs, anatomical resection that was defined as complete removal of all the tumor-bearing segments was utilized. An intermittent Pringle maneuver was used in cycles of 15/5 min of clamping/unclamping. Transection of the liver parenchyma was performed using an ultrasonic aspirator (CUSA; Valleylab Inc., Boulder, CO) or by the clamp-crushing method. Hemostasis on the raw surface of the liver was maintained using an argon beam coagulator (Valleylab Inc.). Routine closed-suction abdominal drainage was used.

Statistical analysis

Statistical analysis was performed using SPSS v22.0 (IBM Corporation, Chicago, IL, USA). A P value less than 0.05 was considered statistically significant. Continuous data are presented as the mean with the standard deviation or the median with the range. Categorical data were compared using the chi-squared (χ^2) test (two-tailed). Survival rates were calculated using the Kaplan-Meier method and analyzed using the log-rank test. Univariate logistic regression analysis of the risk factors was performed to calculate the odds ratios (ORs), and variables with a P value less than 0.05 were consecutively subjected to multivariate logistic regression analysis to identify the independent risk factors for postoperative mortality. The original BCLC system was modified by incorporating BDTT status. The ability of the modified BCLC system to distinguish between patient categories with significantly different survival (homogeneity) was assessed by the Kaplan-Meier method with the log-rank test. Moreover, the power of the modified system (monotonicity) for predicting overall survival was evaluated by the linear trend χ^2 test. The ability of the modified system to prediction survival was evaluated by calculating the area under the receiver operating characteristic (ROC) curve for each score (c-index) with the censored patients eliminated before 1, 3, and 5 years.[26]

Results

Patient characteristics

During the study period, a total of 622 HCC patients who underwent hepatectomy at the Department of Hepatobiliary Surgery, Chinese PLA General Hospital, were enrolled. The baseline demographics of the enrolled patients are shown in Table 1. The majority of the patients were male (88%), and the mean age was 50 years old. The most frequent causes of the underlying liver disease were hepatitis B (77%) and hepatitis C (2%) infection. All patients were assigned a status of 0–1 according to the Eastern Cooperative Oncology Group performance status criteria. Of the total patients, 2%, 81%, 10%, 7%, and 0% belonged to BCLC stages 0, A, B, C, and D, respectively. Moreover, 78% (483/622) suffered from liver cirrhosis, 14% (89/622) had multiple tumors, 33% (205/622) had PHT, 27% (170/622) had increased total bilirubin, and 4% (22/622) had BDTT. Moreover, 4% (26/622) of the patients were in the 90-day mortality group.

Table 1
Baseline characteristics and operative variables of patients enrolled in the study.

Total, N = 622	Number (Percentage)
Male/Female (%)	545/77(88/12)
Age (years, mean ± SD)	50 ± 11
HBV (%)	481(77)
HCV (%)	12(2)
α-fetoprotein (ng/mL, mean ± SD)	127 ± 3187
Serum biochemistry (mean ± SD)	
Albumin (g/L)	44 ± 11
Bilirubin(μmol/L)	28 ± 62
Creatinine(μmol/L)	80 ± 18
Alanine aminotransferase (U/L)	62 ± 94
Aspartate aminotransferase (U/L)	67 ± 96
Liver cirrhosis	483(78)
Portal hypertension	205(33)
Child-Pugh classification	
A	588(95)
B	34(5)
Number and size of tumor (%)	
Single	533(86)
Multiple	89(14)
Major diameter ≤ 3 cm	110(18)
Major diameter > 3 cm	512(82)
Portal invasion (%)	417(67)
Bile duct invasion (%)	22(4)
Lymph node invasion (%)	14(2)
BCLC stage 0/A/B/C/D (%)	
0	10(2)
A	503(81)
B	61(10)
C	48(7)
D	0(0)
90-day Mortality (%)	26(4)

Risk factors associated with 90-day postoperative mortality

As illustrated in Table 2, the univariate analysis showed that the predictive factors associated with increased risk of 90-day postoperative mortality included higher serum levels of total bilirubin, alanine aminotransferase, and aspartate aminotransferase and PHT ($P < 0.05$ for all); further multivariate analysis confirmed that increased serum total bilirubin (OR: 3.941; 95% confidence interval (CI): 1.672–9.315; $P < 0.001$) and PHT (OR: 16.813; 95% CI: 4.937–57.260; $P < 0.001$) were independent risk factors for 90-day mortality in HCC patients after hepatectomy.

Long-term outcome of patients with PHT or increased serum total bilirubin

Long-term overall survival in the PHT group was substantially poorer than that in the non-PHT group (median survival values for the PHT group and non-PHT group were 32.4 and 62.9 months, respectively, $\chi^2 = 21.15$, $P < 0.001$). Likewise, the prognosis of the increased serum total bilirubin group was considerably worse than that of the normal serum bilirubin group (median survival values for the increased group and normal group were 29.2 and 66.0 months, respectively, $\chi^2 = 26.77$, $P < 0.001$).

Long-term outcome of patients with BDTT

The median survival of HCC patients with BDTT was 17.9 months (95% CI: 6.1–29.8 months), and the overall survival rates at 1, 3 and 5 years were 77%, 42% and 23%, respectively. In patients without BDTT, the median survival was 55.6 months (95% CI: 43.9–67.3 months), and the survival rates at 1, 3 and 5 years were 80%, 60% and 48%, respectively. Long-term overall survival in the BDTT group was poorer than that in the non-BDTT group ($\chi^2 = 6.280$, $P = 0.012$) (Fig. 1 A).

Comparison of the long-term outcomes between BCLC stage 0-A patients with BDTT and BCLC stage 0-D patients without BDTT

The comparison of long-term survival according to performance status in HCC patients is demonstrated in Fig. 1 B. With the exception of three patients (one patient with positive lymph nodes and two patients with large/multifocal HCC), 19 patients with BDTT were categorized in the early stage according to the BCLC system. Apart from the 19 patients with BDTT, 2%, 81%, 10%, 7%, and 0% of the 603 patients belonged to the original BCLC stages 0, A, B, C, and D, respectively. On the basis of log-rank results, differences in overall survival were found between patients with BDTT in the early stage and those without BDTT in stage 0 ($\chi^2 = 4.344$, $P = 0.037$), stage A ($\chi^2 = 6.761$, $P = 0.009$), stage B ($\chi^2 = 0.0.399$, $P = 0.528$) and stage C ($\chi^2 = 2.463$, $P = 0.117$). According to the Breslow test, differences in overall survival were found between patients with BDTT in the early stage and those without BDTT in stage 0 ($\chi^2 = 4.513$, $P = 0.034$), stage A ($\chi^2 = 4.872$, $P = 0.027$), stage B ($\chi^2 = 0.139$, $P = 0.710$) and stage C ($\chi^2 = 6.442$, $P = 0.011$). Overall survival differences were detected by the Tarone-Ware test between patients with BDTT in the early stage and those without

Table 2
Univariate and multivariate analysis of risk factors for 90-day mortality in 622 patients.

Item	N = 622	90-day Mortality	Univariate Analysis		Multivariate Analysis		
			Odds Ratio	*P* Value	Odds Ratio	95% Confidence interval	*P* Value
Gender (male/female)	545/77	26/0	_	0.997			
Age (<65/≥65)	566/56	24/2	0.693	0.623			
HBV (negative/positive)	141/481	4/22	1.642	0.369			
HCV (negative/positive)	610/12	26/0	0	0.999			
Albumin (<35/≥35 g/L)	551/71	25/1	0.301	0.242			
Total bilirubin (<21/21≥ μmol)	452/170	9/17	5.469	<0.001	**3.941**	**1.672–9.315**	< **0.001**
Creatinine (<110/≥110 μmol/L)	610/12	26/0	0.000	0.999			
Alanine aminotransferase (<40/≥40 U/L)	361/261	8/18	3.269	0.006	1.377	0.464–4.088	0.565
Aspartate aminotransferase (<40/≥40 U/L)	315/307	6/20	3.589	0.007	1.156	0.349–3.827	0.812
Liver cirrhosis (negative/positive)	139/483	5/21	1.218	0.697			
Portal hypertension (negative/positive)	417/205	3/23	20.195	<0.001	**16.813**	**4.937–57.260**	< **0.001**
Preoperative ascites (negative/positive)	586/36	24/2	1.377	0.672			
Child-Pugh classification (A/B)	588/34	23/3	2.377	0.177			
Bile duct invasion (negative/positive)	600/22	25/1	1.095	0.931			

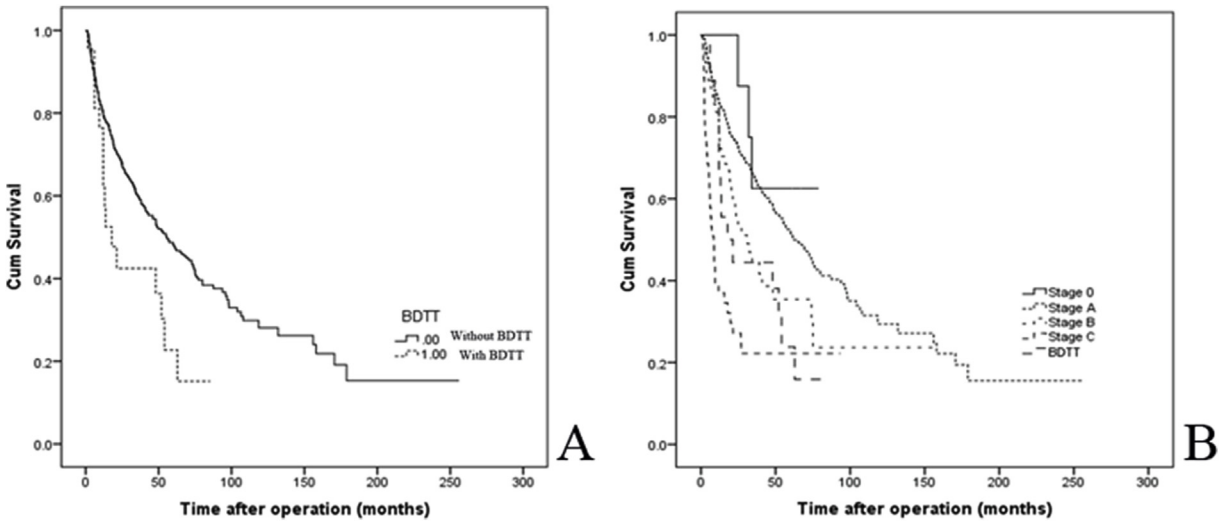

Fig. 1. A. Comparison of the overall survival rates in HCC patients with BDTT and those without BDTT. Long-term overall survival in the BDTT group (dashed line) was poorer than that in the non-BDTT group (solid line) ($\chi^2 = 6.280$, P = 0.012). **1 B**. Comparison of the long-term outcome between 19 patients with BDTT in BCLC stage 0–A and 603 HCC patients in other disease stages according to the BCLC system.

BDTT in stage 0 ($\chi^2 = 4.444$, P = 0.035), stage A ($\chi^2 = 5.804$, P = 0.016), stage B ($\chi^2 = 0.235$, P = 0.628) and stage C ($\chi^2 = 4.792$, P = 0.029). Noticeable differences were discovered between patients with BDTT in the early stage and patients in all the other stages, except for stage B. Therefore, patients with BDTT in the early stage should be reclassified into stage B (intermediate stage) (Fig. 1 B).

Modification of the BCLC staging system for survival prediction

During the follow-up period (mean, 38.3 months), 49.8% (310/622) of the patients died. The median overall survival was 54.1 months (95% CI: 44.4–63.7 months), and the survival rates at 1, 3 and 5 years were 80%, 59% and 47%, respectively. Table 3 presents the results of retrospective staging of the 622 patients using the original BCLC and modified BCLC systems, covering the components of distributions, median survival lengths and death rates. In accordance with the original and modified BCLC systems, the disease stages were found to range from 0 to C. None of the patients who received hepatectomy were grouped into advanced stage disease (stage D). The percentage of patients with original BCLC stage 0-A disease was 82% (513/622), which is higher than that of the patients with modified BCLC stage 0-A disease (79%, 494/622). In addition, 10% (1/10) of the patients with stage 0 disease and 4% (18/485) of the patients with stage A disease according to the original BCLC system were reclassified into stage B by the modified BCLC system. Of the patients with BDTT, 86% (19/22) of the intermediate-stage patients were misclassified into early stage (BCLC stage 0 and A) according to the original BCLC system, while one of the 22 BDTT patients (5%) with positive lymph nodes and two patients (9%) with large/multifocal HCC in BCLC stages C and B, respectively, were not reclassified based on the modified system.

There was a significant correlation between survival and tumor stage in the two systems (P < 0.005 for both). The original BCLC and modified BCLC systems showed no marked differences in survival between patients with stage 0 and stage A disease (P > 0.05 for both), while there were distinct differences in the survival rates of patients with stage 0-A, B, and C disease (P < 0.05 for all). On the basis of the original BCLC stages, the overall survival rates at 1, 3, and 5 years were 84%, 64%, and 51%, respectively, for BCLC stage 0-A; 78%, 44%, and 35%, respectively, for BCLC stage B; and 38%, 23%, and 23%, respectively, for BCLC stage C (P < 0.05 for all). According to the modified BCLC system, the overall survival rates at 1, 3, and 5 years were 84%, 65%, and 52%, respectively, for BCLC stage 0-A; 79%, 45%, and 41%, respectively, for BCLC stage B; and 38%, 23%, and 23%, respectively, for BCLC stage C (P < 0.05 for all).

Performance evaluation of the BCLC and modified BCLC systems

When entered into a Cox regression model, the modified BCLC system showed better performance with regard to prediction of overall survival than the original BCLC system (modified BCLC: likelihood = 3519.760, $\chi^2 = 53.596$, P < 0.001; original BCLC: likelihood = 3525.964, $\chi^2 = 46.335$, P < 0.001). In the same group of patients, higher χ^2 values and lower log likelihood values were associated with better performance of the score). The discriminatory ability for death at 1, 3, and 5 years, as evaluated by ROC area analysis, was slightly higher in the modified BCLC system than in the original BCLC system. However, no significant differences were found between the original BCLC and modified BCLC systems at 1, 3, and 5 years (P > 0.05).

Discussion

This study confirmed the validity of the BCLC staging system in a Chinese HCC cohort. Meanwhile, it revealed that possible modification of the BCLC staging system might be required for HCC patients with BDTT. Tumor invasion into the biliary system and subsequent formation of bile duct tumor thrombus (BDTT) is an uncommon but well-known feature of HCC. In our research, 22 of 622 HCC patients were identified with BDTT, showing a percentage of 3.5%. Due to the rarity of BDTT, limited studies have reported the incidence or approaches to systematically analyze clinical outcomes. HCC accompanied by BDTT is more commonly seen in Asian populations than in Western populations. Navadgi, S. reported a meta-analysis of 11 studies including 6051 patients. Most of the 11 studies were conducted in Asia (especially in China, Japan, and Korea), showing a BDTT incidence of 4.6%.[27] Kim, D. S. from Seoul, Korea, underwent an international collaboration project covering 25,938 HCC cases and concluded that the proportion of BDTT was 0.99%.[21] However, other researchers have reported higher percentages; Xiangji, L. described a percentage of 1.8%,[28] and Lau, W.

Table 3
Distribution of patients' retrospective staging of the 622 HCC cases using BCLC and modified BCLC systems.

Staging system	N	Median Survival (95% Confidence interval)	Deaths (%)	*P* Value
BCLC				<0.001
0	10	–	4(40)	
A	503	61.0(50.4–71.6)	236(47)	
B	61	31.0(18.6–43.4)	35(57)	
C	48	8.4(5.6–43.4)	35(73)	
Modified BCLC				<0.001
0	9	–	3(46)	
A	485	62.2(50.8–73.6)	223(46)	
B	80	27.2(12.9–41.6)	49(61)	
C	48	8.4(5.6–11.3)	35(73)	

For each score, survival curves calculated by the Kaplan-Maier method were compared using the log rank test.

revealed an incidence of 2.3%.[29] These findings are basically in accordance with our results.

Currently, the diagnosis and evaluation of BDTT primarily rely on clinical symptoms, physical examinations, imaging modalities, intraoperative surgical exploration and postoperative pathology. Of note, the preoperative diagnosis of HCC with BDTT has progressed greatly in the past few decades due to advances in imaging modalities. It is widely described and recognized that BDTT has three typical features on CT or MRI: 1) presence of intraluminal soft-tissue masses at the bile duct, with biliary dilation above the obstruction; 2) enhancement of the intraluminal soft-tissue masses in the arterial phase; and 3) lack of a thickened bile duct wall.[30,31] The intraductal masses are not necessarily or directly adhered to the primary HCC nodules.[32] However, these characteristic cholangiographic features should be differentiated from hilar cholangiocarcinoma. Symptoms of jaundice, increased levels of carbohydrate antigen 199 and carcinoembryonic antigen, intrahepatic bile duct calculus, and a thickened bile duct wall on CT or MRI images favor the diagnosis of hilar cholangiocarcinoma over BDTT.[31]

Regarding prognosis, the 5-year overall survival ranged from only 6.7%–50% after liver resection or liver transplantation in patients with BDTT.[17,20,21,33–37] Therefore, this specific category of HCC patients should not be categorized into the early stage by the original BCLC staging system. In the present study, the postoperative overall survival rates of patients with BDTT were significantly worse than those of patients without BDTT (5-year survival rate: 23% versus 48%). Moreover, the overall survival rates differed significantly between patients with BDTT in the early stage and those with other disease stages (according to the original BCLC system), except for BCLC stage B patients. Hence, such patients with BDTT should be reassigned from the early stage to the intermediate stage (stage B). Based on these findings, it is proposed that the BCLC staging system should be modified and updated to consider BDTT status. In the present study, 19 of the 22 patients with BDTT suffered intermediate-stage disease but were misclassified into early-stage disease (BCLC stage 0 and A) according to the original BCLC system, while one patient with positive lymph nodes and two patients with large/multifocal HCC were not reassigned from BCLC stage C and B, respectively.

The modified BCLC system proved to be superior to the original BCLC system with regard to distinguishing various subgroups in each disease stage. The comparison of the two systems revealed that the modified BCLC system featured higher accuracy in survival prediction and better discriminatory power at 1, 3 and 5 years, although the differences were not significant. Of note, the differences in the ROC curve area between the two systems might lack reliability, as the number of patients with BDTT was so limited that there was little change in the results from the modified BCLC system compared to those from the original one. Moreover, in the present patient group, modified BCLC staging offered better differentiation ability for early-stage HCCs.

On the other hand, PHT and bilirubin levels are endorsed as substantial competent and comprehensive parameters to assess liver function. Data from Japan and Italy have validated the role of portal pressure measurement in outcome prediction and in defining optimal candidates for hepatectomy.[15,38–42] The high-risk factors associated with postoperative mortality serve as valid contraindications for hepatectomy. However, few studies have focused on risk factors for postoperative mortality, as they merely focus on long-term survival.[15,38–44] In this study, the multivariate analysis identified PHT and bilirubin levels as two independent predictors of 90-day mortality. Although hepatectomy can be performed in certain patients with advanced liver disease, the 90-day mortality rate is relatively high. Thus, poor liver function (indicated by PHT and increased bilirubin levels) was the main obstacle to liver resection. Indeed, post-hepatectomy survival was dismal in patients with PHT and/or increased bilirubin levels. For our group of 622 patients who underwent hepatic resection, survival was significantly correlated with PHT and bilirubin levels. The median survival length of HCC patients with PHT was significantly shorter than that in the non-PHT group. Similarly, the median survival of HCC patients with increased serum total bilirubin was significantly poorer than that in patients with normal serum total bilirubin. Thus, patients with PHT or/and increased bilirubin levels are not appropriate candidates for liver resection, and there is therapeutic value of treatment algorithms based on BCLC staging in Chinese patients.

In summary, portal hypertension and/or increased bilirubin levels should be considered a contraindication for hepatic resection in patients with cirrhosis. Moreover, the BCLC staging system was validated in a large Chinese HCC population, the result of which suggested the value of the BCLC system in treatment selection and prognosis prediction for HCC patients. However, possible modification incorporating BDTT status could be added to achieve reliable application and improved performance in East Asian populations. Patients with BDTT in the early stage (BCLC stage 0-A) may need to be reclassified into the intermediate stage (BCLC stage B). Moreover, further studies will be required to determine the recommended treatment options for patients with BDTT, thus determining the appropriate treatment strategy for BCLC stage B disease in the modified BCLC system.

Author contributions

Conception: Wen-ping Lu; Study design: Yong-liang Chen, Wen-ping Lu, and Hao-wen Tang; Administrative support: Shi-chun Lu; Data collection and acquisition: Zhan-yu Yang and Kai Jiang; Data analysis: Wen-ping Lu and Hao-wen Tang; Manuscript preparation: Wen-ping Lu and Hao-wen Tang; Critical revision: Wen-ping Lu

and Hao-wen Tang; Final approval of manuscript: All authors.

Declaration of competing interest

We certify that Authors declare no conflict of interest.

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