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ORIGINAL RESEARCH

Indocyanine Green Retention Test as a Predictor of Postoperative Complications in Patients with Hepatitis B Virus-Related Hepatocellular Carcinoma

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Background: Accurate preoperative estimation of liver function reserve is the key to the safety of hepatectomy. Recently, indocyanine green retention test at 15 minutes (ICG-R15) has been widely used to estimate hepatic function reserve in different liver diseases. The purpose of this research was to investigate the clinical value of ICG-R15 in predicting postoperative major complications and severe posthepatectomy liver failure (PHLF) in patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) subjected to hepatectomy.

Methods: A total of 354 HBV-associated HCC patients who underwent hepatectomy were enrolled. The Child–Pugh, model for end-stage liver disease (MELD), albumin–bilirubin (ALBI) and ICG-R15 for assessing postoperative complications risk were compared using receiver operating characteristic (ROC) curve and decision curve analysis (DCA).

Results: Postoperative major complications developed in 32 patients (9.1%) and severe PHLF developed in 57 (16.1%) patients. Multivariate analyses revealed that ICG-R15 were independent factors for predicting postoperative major complications and severe PHLF. ROC curve analyses and DCA plots showed that the predictive abilities of ICG-R15 for postoperative major complications and severe PHLF risk was significantly greater than Child–Pugh, MELD, and ALBI scores. Similar results were obtained by stratifying different background subgroups. Then, patients were divided into three different risk cohorts, emphasizing the significantly discrepancy between the incidence of postoperative major complications and severe PHLF.

Conclusion: Compared with Child–Pugh, MELD and ALBI scores, ICG-R15 revealed significantly advantages in predicting postoperative major complications and severe PHLF in HBV-related HCC patients subjected to liver resection.

Keywords: hepatocellular carcinoma, hepatitis B virus, postoperative major complications, posthepatectomy liver failure, indocyanine green retention test

Introduction

Hepatitis B virus (HBV) infection is related to 70–90% of the patients with hepatocellular carcinoma (HCC) in the Asia-Pacific regions, especially China.[1] Partial hepatectomy is the preferred curative means in select HBV-related HCC patients.[2,3] Although advances in hepatectomy and perioperative care techniques have greatly improved the safety of surgery, postoperative major complications, especially severe posthepatectomy liver failure (PHLF) induced by residual hepatic functional insufficiency, remain the major cause of postoperative death.[4–8] Thus, it is of great significance to estimate liver function reserve prior to hepatectomy.

Currently, the Child–Pugh scoring system is the most commonly applied method to assess liver function reserve; however, its clinical applications is limited due to the use of two subjective and arbitrary indexes (hepatic encephalopathy and ascites) in its calculations.[9,10] The model for end-stage liver disease (MELD), originally established to estimate the outcomes of cirrhotic patients, has been gradually recognized as a standard for assessing liver function reserve and sequencing transplant candidates. Nevertheless, the level of serum creatinine is strongly influenced by individual reasons, such as gender and age, leading to its limited application.[11] The albumin–bilirubin (ALBI) score is the most recently

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recognized model for assessing hepatic functional reserve and is often used to predict the prognostic risk of different liver diseases, but it is still limited to accurately assess patients with obstructive jaundice.[12] Therefore, there is still a need to explore better tools to estimate liver reserve function.

Indocyanine green (ICG) is a water-soluble fluorescent dye that binds to lipoprotein and albumin and excretes bile as it is after intravenous injection.[13,14] As a quantitative excretory hepatic functional method to assess functional hepatocytes and liver blood flow, the ICG retention test at 15 minutes (ICG-R15) became a standard preoperative parameter to evaluate liver function reserve in patients with different hepatic diseases, mostly in Asian series.[15–18]

In this study, we compared the abilities of ICG-R15, Child–Pugh, MELD and ALBI scores for assessing postoperative major complications and severe PHLF risk.

Methods

Patient Population

In this study, 354 patients who were subjected to initial hepatectomy for HBV-related HCC between January 2017 and December 2018 in our hospital were included. HCC patients who received radiofrequency ablation, transarterial chemoembolization or other treatments for tumors prior to liver resection were excluded. This study was conducted with the written informed consent of each patient and approved by the Ethics Committee of Guangxi Medical University Cancer Hospital, as well as in accordance with the Helsinki Declaration.

Diagnosis and Definitions

Postoperative pathological examination was the basis for the diagnosis of HCC, and Barcelona Clinical Liver Cancer (BCLC) criterion was selected as the HCC stage. Splenomegaly or gastroesophageal varices with thrombocytopenia was defined as clinically significant portal hypertension (CSPH).[19] Patients with hyperbilirubinemia and abnormal coagulation on postoperative day 5 was defined as PHLF. Grade A PHLF not needed any specific therapy, grade B PHLF not needed invasive treatments, and grade C PHLF needed invasive therapies. Among them, grade B or above PHLF was defined as severe PHLF.[20] The severity of postoperative complications was classified based on the Dindo–Clavien grade, and grade III and above was defined as postoperative major complications.[21]

ICG Clearance

Generally, ICG clearance is performed using a continuous infusion technique during hepatic vein intubation. All enrolled patients in our study were received ICG clearance test prior to hepatectomy. After fasting overnight, an appropriate amount of ICG was quickly injected through a peripheral vein of forearm. Plasma ICG concentration was monitored by an optical probe connected to the patient, and the ICG-R15 value was measured by a pulsed dye density map analyzer (DDG3300K, Japan).

Hepatectomy and Follow-Up

Before hepatectomy, abdominal CT or MRI was carried out to estimate cancer situation and surgical safety. The Child–Pugh scoring system and residual hepatic volume were measured to assess hepatic function reserve. The surgical treatment of liver tumors were based on segmental anatomical resection. The extent of hepatectomy can be divided into major resection (removal of three or more Couinaud segments) or minor resection (removal of one or two segments or wedge resection) based on the number of liver segments resected.[22] More details and indications of liver resection procedures were described in previous research.[23]

All patients were routinely reviewed 1 month after discharge, every 2–3 months in the first postoperative year, and every 3–6 months in the second year. Routine re-examinations include serum biochemistry, α-fetoprotein, abdominal ultrasonography, CT or MRI, and so on.

Statistical Analyses

Categorical variables were shown as frequencies and proportions and were compared using χ^2 test. Continuous variables were shown as median (Q25-Q75) and were compared using Mann–Whitney *U*-tests.

Using univariate and multivariate logistic regression analyses, we confirmed independent risk parameters that predicted postoperative major complications and severe PHLF. Predictive abilities of Child–Pugh, MELD, ALBI and ICG-R15 to predict postoperative major complications and severe PHLF were tested via the areas under the receiver-operating characteristic (ROC) curves (AUCs) and decision curve analysis (DCA).[24] Additionally, three risk groups were generated by splitting its linear predictor at the 50th and 85th percentiles of ICG-R15. The low-risk group was less than 50%, the intermediate risk group was between the 50th and 85th percentiles, and the last 15% was high-risk.

SPSS software (version 25.0, IBM, USA) was used for statistical analyses. $P < 0.05$ was considered to be statistically significant.

Results

Patients' Characteristics

The clinical characteristics of 354 HBV-related HCC patients enrolled are shown in Table 1. The patients included 36 females and 318 males with a median age of 51 years. And, 9.4% of the patients suffered from CSPH, while most patients (60.2%) had cirrhosis. Moreover, most patients (86.2%) were categorized as Child–Pugh grade A, and the rest patients was grade B. The median MELD was 5 (4 to 7), the median ALBI was −2.38 (−2.59 to −2.16), and the median ICG-R15 was 4.6 (3.2 to 7.35).

Based on the BCLC grade system, 3.4% of the patients were grade 0, 57.9% were grade A, 20.3% were grade B, and 18.4% were grade C. The surgical resection included 235 major hepatectomy and 117 minor hepatectomy.

Postoperative Complications

Of the 354 patients, 199 patients (56.2%) had postoperative complications (Supplementary Table 1). The most post-operative complication was ascites or pleural effusion in 115 cases (32.5%), followed by PHLF in 109 cases (30.8%). Among them, 32 patients (9.1%) developed postoperative major complications, and 109 patients (30.8%) developed PHLF: (grade A: 14.7% [n = 52]; grade B: 15.0% [n = 53]; and grade C: 1.1% [n = 4]), of whom 57 patients (16.1%) developed severe PHLF.

Independent Predictors of Postoperative Major Complications

Factors related to postoperative major complications in univariate logistic regression analyses, included male, prealbumin, albumin, aspartate aminotransferase, creatinine, Child–Pugh, MELD, ALBI, ICG-R15, tumor size, blood loss and major resection (Table 2, $P < 0.05$ for all). For multivariate analysis, aspartate aminotransferase, ICG-R15 and major hepatectomy were confirmed as independent predictors of postoperative major complications in HBV-related HCC patients (Table 2, $P < 0.05$ for all).

Independent Predictors of Severe PHLF

Univariate logistic regression analyses indicated prothrombin time, prealbumin, albumin, CSPH, cirrhosis, Child–Pugh, MELD, ALBI, ICG-R15, tumor size, portal invasion or extrahepatic spread and major hepatectomy were related to severe PHLF (Table 3, $P < 0.05$ for all). Then, in a multivariate analysis, prothrombin time, cirrhosis, ICG-R15 and major hepatectomy were identified as independent predict variables of severe PHLF in HBV-related HCC patients (Table 3, $P < 0.05$ for all).

Discriminative Abilities of the Models for Major Complications

The AUC of the ICG-R15 (AUC 0.789, 95% confidence interval (c.i.) 0.707 to 0.872) for predicting postoperative major complications was higher than the Child–Pugh (AUC 0.619, 95% c.i. 0.515 to 0.723), MELD (AUC 0.617, 95% c.i. 0.516 to 0.721) and ALBI (AUC 0.666, 95% c.i. 0.561 to 0.771) scores (Figure 1A, $P < 0.05$ for all). Furthermore, the DCA plot

Table 1 Baseline Characteristics of the Included 354 Patients

Variables	Entire Patients (n=354)
Age (years)	51 (44, 58)
High (cm)	165 (161, 170)
Weight (kg)	60 (54, 67)
BMI (kg/m^2)	22 (20, 24)
Sex	
Male	318 (89.8)
Female	36 (10.2)
Positive HBeAg	91 (25.7)
Positive anti-HBe	114 (32.2)
Positive anti-HBC	157 (44.4)
HBV-DNA, IU/mL	
≥2000	192 (54.2)
<2000	162 (45.8)
PLT (× 10^9/l)	196.0 (151.3, 253.8)
PT (s)	12.5 (11.7, 13.3)
T-Bil (μmol/l)	16.2 (11.8, 20.4)
PA (mg/l)	163.5 (132.3, 201.8)
ALB (g/l)	37.4 (34.5, 39.7)
ALT (U/l)	42.0 (29.0, 60.0)
AST (U/l)	46.0 (34.0, 69.8)
ALP (U/l)	90.0 (73.3, 118.0)
CRE (μmol/l)	77.0 (69.0, 87.0)
BUN (mmol/l)	5.0 (4.1, 6.0)
AFP (ng/mL)	
≥400	150 (42.4)
<400	204 (57.6)
CSPH	34 (9.6)
Ascites	55 (15.5)
Cirrhosis	213 (60.2)
Child–Pugh score	5 (5, 6)
Child–Pugh grade	
A	305 (86.2)
B	49 (13.8)
MELD score	5 (4, 7)
ALBI score	−2.38 (−2.59, −2.16)
ICG-R15 (%)	4.6 (3.2, 7.35)
Tumour size (cm)	7 (4, 10)
Tumour number	
Multiple	143 (40.4)
Single	211 (59.6)
Portal invasion or extrahepatic spread	65 (18.4)
BCLC stage	
0	12 (3.4)
A	205 (57.9)
B	72 (20.3)
C	65 (18.4)
Operation time (min)	210 (180, 260)
Blood loss	250 (150, 500)

(*Continued*)

Table 1 (Continued).

Variables	Entire Patients (n=354)
Blood transfusion (mL)	98 (27.7)
Extent of hepatectomy	
Major resection	235 (66.4)
Minor resection	119 (33.6)

Notes: Data are median (IQR 25–75) unless otherwise indicated.
Abbreviations: BMI, body mass index; HBeAg, hepatitis Be antigen; anti-HBe, antibodies against hepatitis Be antigen; anti-HBC, antibody to hepatitis B core antigen; HBV-DNA, hepatitis B virus DNA load; PLT, platelet; PT, prothrombin time; T-Bil, total bilirubin; PA, prealbumin; ALB, albumin; ALT, alanine transaminase; AST, aspartic aminotransferase; GGT, γ-glutamyl transpeptadase; ALP, alkaline phosphatase; CRE, creatinine; BUN, blood urea nitrogen; AFP, α-fetoprotein; CSPH, clinically significant portal hypertension; MELD, model for end-stage liver disease; ALBI, albumin–bilirubin; ICG-R15, indocyanine green retention test at 15 minutes; BCLC, Barcelona Clinic Liver Cancer.

showed that ICG-R15 has a better net benefit and a wider threshold possibilities in assessing postoperative major complications (Figure 1B). Accordingly, the ICG-R15 was superior in estimating postoperative major complications risk.

Discriminative Abilities of the Models for Severe PHLF

The AUC of the ICG-R15 (AUC 0.823, 95% c.i. 0.775 to 0.871) to predict severe PHLF was remarkably higher than Child–Pugh (AUC 0.641, 95% c.i. 0.564 to 0.718), MELD (AUC 0.604, 95% c.i. 0.518 to 0.690) and ALBI (AUC 0.691, 95% c.i. 0.612 to 0.769) scores (Figure 2A, $P < 0.05$ for all). In addition, the DCA plot also indicated that ICG-R15 has a better net benefit and a wider threshold possibilities in predicting severe PHLF (Figure 2B). Thus, ICG-R15 also showed a significant advantage in predicting severe PHLF.

Subgroup Analyses

Subgroup analyses were performed according to the cirrhosis conditions, intraoperative status (hepatectomy, blood loss and blood transfusion), and tumor stage. In all subgroups, the AUCs values of ICG-R15 in predicting major postoperative complications (Figure 3 and Supplementary Table 2; $P < 0.05$ for all) and severe PHLF (Figure 4 and Supplementary Table 3; $P < 0.05$ for all) were greatly higher than the other scoring systems.

Application of the ICG-R15 in Patients Risk Stratification

The 50th percentile of ICG-R15 was 4.6%, and 85th percentile was 9.9%. Then, three risk groups were generated (low-risk ≤4.6%, intermediate-risk 4.6–9.9%, and high-risk >9.9%). The incidence of postoperative major complications and severe PHLF was significantly different among all enrolled patients in the ICG-R15 risk subgroups (Figure 5 and Supplementary Table 4; $P < 0.05$ for all). Moreover, similar findings were yielded for all the HCC patients' subgroup analyses that assessed postoperative major complications (Supplementary Figure 1 and Supplementary Table 4; $P < 0.05$ for all) and severe PHLF (Supplementary Figure 2 and Supplementary Table 4; $P < 0.05$ for all).

Discussion

In this research, we compared the differences of four methods (Child–Pugh, MELD, ALBI and ICG-R15) in assessing postoperative major complications and severe PHLF in HBV-related HCC patients after hepatectomy. We found that ICG-R15 was an independent predictor of postoperative major complications and severe PHLF, and the predictive abilities of ICG-R15 wwere greatly higher than other scoring systems. Furthermore, the ICG-R15 also has great advantages in predicting postoperative major complications and severe PHLF in subgroup analyses based on cirrhosis condition, intraoperative status (hepatectomy, blood loss and blood transfusion), and tumor stage. In addition, the incidence of postoperative major complications and severe PHLF risk also increased with ICG-R15-based risk stratification.

Table 2 Univariate and Multivariate Analyses to Identify Factors Predicting Postoperative Major Complications

Variables	Univariate Logistic Regression		Multivariate Logistic Regression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.041 (1.007, 1.075)	0.018	1.031 (0.988, 1.075)	0.161
High (cm)	1.012 (0.955, 1.072)	0.680		
Weight (kg)	0.993 (0.955, 1.032)	0.716		
BMI (kg/m^2)	0.951 (0.840, 1.076)	0.421		
Male sex	1.104 (0.319, 3.822)	0.876		
Positive HBeAg	1.352 (0.615, 2.976)	0.453		
Positive anti-HBe	1.114 (0.518, 2.396)	0.783		
Positive anti-HBC	1.473 (0.711, 3.052)	0.297		
HBV-DNA ≥2000 (IU/mL)	1.094 (0.526, 2.274)	0.811		
PLT counts (× 10^9/l)	0.999 (0.995, 1.004)	0.761		
PT (s)	1.180 (0.893, 1.559)	0.244		
T-Bil (μmol/l)	1.013 (0.998, 1.027)	0.093		
PA (mg/l)	0.989 (0.981, 0.996)	0.002	0.994 (0.985, 1.004)	0.267
ALB (g/l)	0.897 (0.821, 0.981)	0.018	1.385 (0.908, 2.111)	0.130
ALT (U/l)	1.002 (1.000, 1.005)	0.084		
AST (U/l)	1.004 (1.001, 1.008)	0.012	1.005 (1.000, 1.010)	0.033
ALP (U/l)	1.003 (0.999, 1.006)	0.114		
CRE (μmol/l)	1.010 (1.001, 1.019)	0.032	1.019 (0.998, 1.041)	0.079
BUN (mmol/l)	0.993 (0.980, 1.006)	0.311		
AFP (ng/mL)	1.000 (1.000, 1.000)	0.729		
CSPH	0.971 (0.280, 3.373)	0.963		
Ascites	1.007 (0.370, 2.740)	0.988		
Cirrhosis	1.509 (0.692, 3.291)	0.301		
Child–Pugh score	1.588 (1.069, 2.359)	0.022	0.522 (0.250, 1.091)	0.084
MELD score	1.182 (1.061, 1.318)	0.002	0.921 (0.682, 1.244)	0.592
ALBI score	4.404 (1.702, 11.400)	0.002	123.867 (0.816, 18799.190)	0.060
ICG-R15 (%)	1.139 (1.072, 1.211)	<0.001	1.108 (1.037, 1.184)	0.002
Tumor size (cm)	1.086 (1.014, 1.163)	0.018	1.002 (0.906, 1.109)	0.968
Multiple tumor number	1.164 (0.559, 2.422)	0.685		
Portal invasion or extrahepatic spread	1.550 (0.663, 3.625)	0.312		
BCLC stage	1.320 (0.868, 2.006)	0.194		
Operation time (min)	1.001 (0.996, 1.006)	0.712		
Blood loss (mL)	1.001 (1.000, 1.001)	0.003	1.001 (1.000, 1.001)	0.170
Blood transfusion	0.711 (0.297, 1.701)	0.443		
Major resection	3.889 (1.331, 11.362)	0.013	7.376 (1.553, 35.025)	0.012

Abbreviations: CI, confidence interval; BMI, body mass index; HBeAg, Hepatitis Be antigen; anti-HBe, antibodies against hepatitis Be antigen; anti-HBC, antibody to hepatitis B core antigen; HBV-DNA, hepatitis B virus DNA load; PLT, platelet; PT, prothrombin time; T-Bil, total bilirubin; PA, prealbumin; ALB, albumin; ALT, alanine transaminase; AST, aspartic aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; CRE, creatinine; BUN, Blood urea nitrogen; AFP, α-fetoprotein; CSPH, clinically significant portal hypertension; MELD, model for end-stage liver disease; ALBI, albumin–bilirubin; ICG-R15, indocyanine green retention test at 15 minutes; BCLC, Barcelona Clinic Liver Cancer.

PHLF is the most serious complication after hepatectomy and may lead to death of patients.[4–8] To reduce the risk of postoperative major complications and severe PHLF, it is of great significance to estimate hepatic functional reserve prior to surgery. Commonly, the Child–Pugh, MELD and ALBI scores are three applied tools for hepatic functional reserve assessment, but they all have obvious defects that limit their wide clinical application.[9–12] Recently, with the development of noninvasive pulse spectrophotometers, ICG-R15 test have became a standard preoperative parameter to assess liver function reserve is possible prior to hepatectomy in patients with sepsis in intensive care units, hepatosteatosis, acute hepatitis, or receiving chemotherapy.[13–18] However, it is not clear which of the four mentioned models is the optimal method to assess liver function reserve in HBV-related HCC patients prior

Table 3 Univariate and Multivariate Analyses to Identify Factors Predicting Severe PHLF

Variables	Univariate Logistic Regression		Multivariate Logistic Regression	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age (years)	1.005 (0.979, 1.030)	0.727		
High (cm)	0.967 (0.926, 1.011)	0.139		
Weight (kg)	0.971 (0.941, 1.002)	0.065		
BMI (kg/m^2)	0.931 (0.845, 1.026)	0.151		
Male sex	0.955 (0.378, 2.412)	0.922		
Positive HBeAg	1.562 (0.848, 2.879)	0.152		
Positive anti-HBe	0.966 (0.562, 1.777)	0.912		
Positive anti-HBC	1.487 (0.842, 2.626)	0.171		
HBV-DNA ≥ 2000 (IU/mL)	1.419 (0.794, 2.533)	0.237		
PLT (× 10^9/l)	0.997 (0.994, 1.001)	0.161		
PT (s)	1.808 (1.423, 2.297)	<0.001	1.458 (1.098, 1.936)	0.009
T-Bil (μmol/l)	1.012 (0.998, 1.027)	0.104		
PA (mg/l)	0.987 (0.981, 0.993)	0.000	0.997 (0.989, 1.005)	0.493
ALB (g/l)	0.918 (0.857, 0.984)	0.015	1.012 (0.775, 1.320)	0.933
ALT (U/l)	1.000 (0.998, 1.003)	0.755		
AST (U/l)	1.002 (0.998, 1.005)	0.294		
ALP (U/l)	1.002 (0.999, 1.005)	0.154		
CRE (μmol/l)	1.006 (0.998, 1.014)	0.163		
BUN (mmol/l)	0.999 (0.994, 1.003)	0.522		
AFP (ng/mL)	1.000 (1.000, 1.000)	0.823		
CSPH	2.420 (1.087, 5.386)	0.030	0.625 (0.198, 1.974)	0.423
Ascites	0.364 (0.126, 1.051)	0.062		
Cirrhosis	2.879 (1.463, 5.666)	0.002	2.583 (1.126, 5.924)	0.025
Child–Pugh score	1.579 (1.143, 2.182)	0.006	0.686 (0.390, 1.206)	0.190
MELD score	1.159 (1.057, 1.269)	0.002	1.093 (0.954, 1.253)	0.201
ALBI score	3.289 (1.538, 7.037)	0.002	1.417 (0.061, 32.896)	0.828
ICG-R15 (%)	1.265 (1.174, 1.363)	0.000	1.285 (1.168, 1.413)	0.000
Tumor size (cm)	1.072 (1.014, 1.134)	0.015	1.038 (0.967, 1.114)	0.305
Multiple tumor number	0.998 (0.560, 1.778)	0.994		
Portal invasion or etrahepatic spread	2.205 (1.155, 4.207)	0.016	1.601 (0.725, 3.538)	0.244
BCLC stage	1.281 (0.920, 1.783)	0.143		
Operation time (min)	1.003 (0.999, 1.007)	0.120		
Blood loss (mL)	1.000 (1.000, 1.001)	0.294		
Blood transfusion	1.252 (0.677, 2.315)	0.474		
Major resection	4.324 (1.895, 9.868)	0.001	4.449 (1.341, 14.758)	0.015

Abbreviations: CI., confidence interval; BMI, body mass index; HBeAg, hepatitis Be antigen; anti-HBe, antibodies against hepatitis Be antigen; anti-HBC, antibody to hepatitis B core antigen; HBV-DNA, hepatitis B virus DNA load; PLT, platelet; PT, prothrombin time; T-Bil, total bilirubin; PA, prealbumin; ALB, albumin; ALT, alanine transaminase; AST, aspartic aminotransferase; GGT, γ-glutamyl transpeptidase; ALP, alkaline phosphatase; CRE, creatinine; BUN, blood urea nitrogen; AFP, α-fetoprotein; CSPH, clinically significant portal hypertension; MELD, model for end-stage liver disease; ALBI, albumin–bilirubin; ICG-R15, indocyanine green retention test at 15 minutes; BCLC, Barcelona Clinic Liver Cancer; PHLF, posthepatectomy liver failure.

to hepatectomy. To solve this issue, we first carried out univariate logistic regression analyses to find indicators for predicting postoperative major complications and severe PHLF. As expected, all four mentioned methods showed significant differences in predicting major postoperative complications and severe PHLF alone. However, only ICG-R15 of the four methods can be used as an independent predictor of postoperative major complications and severe PHLF when the multivariate logistic analysis of other factors is taken into account. These findings preliminarily revealed that ICG-R15 is a better predictor of postoperative major complications and severe PHLF than other models. Furthermore, the ROC curve analyses showed that ICG-R15 had higher AUCs for predicting postoperative major complications and severe PHLF compared to the other three models, and DCA plots suggest that ICG-R15 had

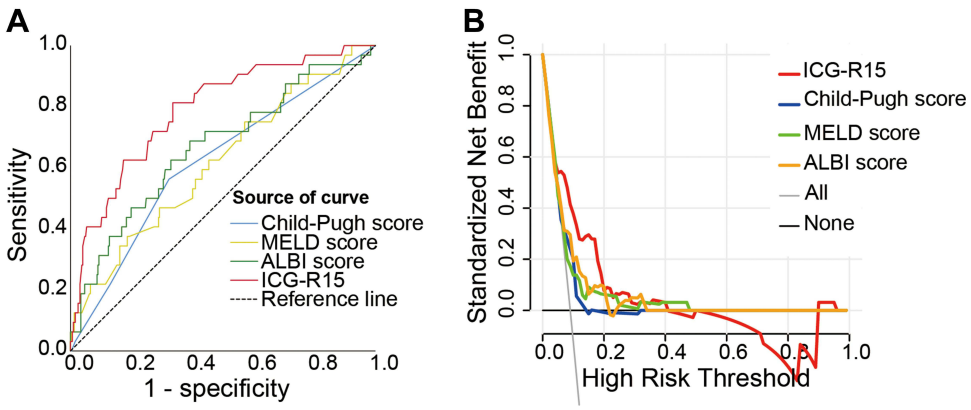

Figure 1 (**A**) ROC curves and (**B**) DCA plot analyses of ICG-R15, Child–Pugh, MELD and ALBI scores for assessing postoperative major complications.
Abbreviations: ICG-R15, indocyanine green retention test at 15 minutes; MELD, model for end-stage liver disease; ALBI, albumin–bilirubin; ROC, receiver operating characteristic; DCA, decision curve analysis.

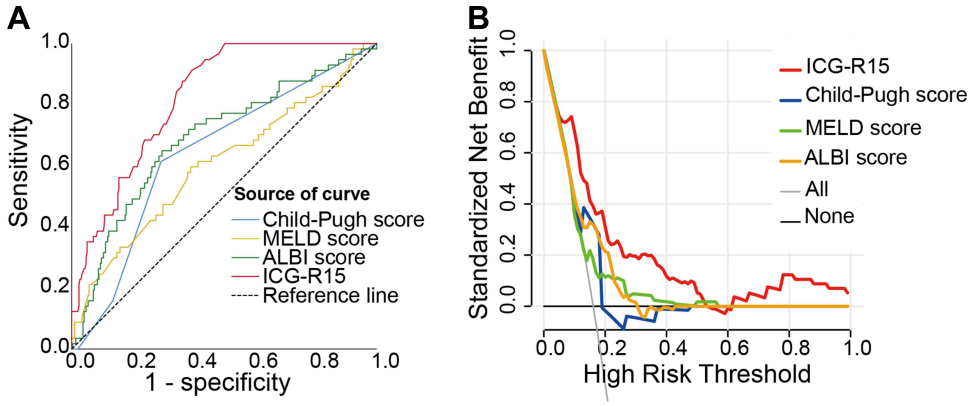

Figure 2 (**A**) ROC curves and (**B**) DCA plot analyses of ICG-R15, Child–Pugh, MELD and ALBI scores for assessing severe PHLF.
Abbreviations: ICG-R15, indocyanine green retention test at 15 minutes; MELD, model for end-stage liver disease; ALBI, albumin–bilirubin; ROC, receiver operating characteristic; DCA, decision curve analysis; PHLF, posthepatectomy liver failure.

a better net benefit and a wider range of threshold possibilities in predicting postoperative major complications and severe PHLF. These results further verified that ICG-R15 has significantly higher predictive power than the other three models in assessing postoperative major complications and severe PHLF.

In addition, many studies have shown that liver cirrhosis background, intraoperative status (hepatectomy, blood loss and blood transfusion) and tumor stage were also independent predictors for assessing postoperative complications.[6,19,25] In our research, only major hepatectomy has always been an independent risk parameter for predicting major complications and severe PHLF, while cirrhosis was only an independent predictor for severe PHLF. Then, according to these different subgroups, we continued to compare the predictive ability of those mentioned four methods to assess postoperative major complications and severe PHLF. Surprisingly, in all the subgroup analyses, the ICG-R15 showed stable and satisfactory predictive performance in assessing postoperative major complications and severe PHLF and was superior to the other three models.

On the basis of risk stratification, this study further analyzed the relationship between ICG-R15 and postoperative major complications and severe PHLF. Our study showed that the incidence of postoperative major complications and severe PHLF differed significantly among the three risk groups. Unsurprisingly, the incidence of major postoperative complications and severe PHLF was greatly higher in the high-risk cohort than in the other two groups. Therefore, from our results, it can be concluded that hepatectomy should be carefully selected for high-risk population.

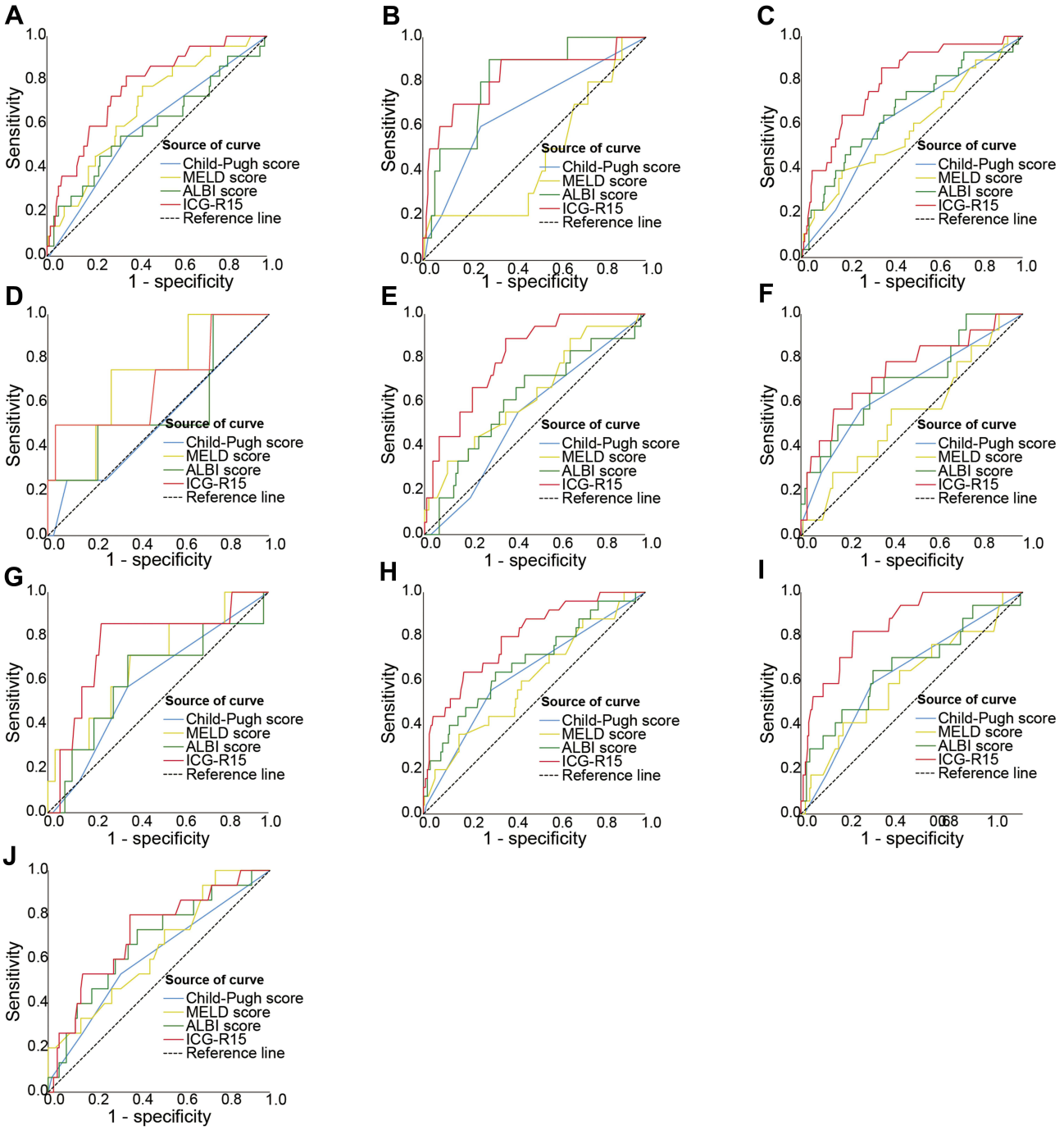

Figure 3 ROC curves of ICG-R15, Child–Pugh, MELD and ALBI scores for assessing postoperative major complications in the HBV-related HCC patients subgroups. Subgroups include (**A**) cirrhosis, (**B**) no cirrhosis, (**C**) major hepatectomy, (**D**) minor hepatectomy, (**E**) blood loss ≥400 mL, (**F**) blood loss <400 mL, (**G**) blood transfusion, (**H**) no blood transfusion, (**I**) BCLC-0 or -A stage, and (**J**) BCLC-B or -C stage.

Abbreviations: ICG-R15, indocyanine green retention test at 15 minutes; MELD, model for end-stage liver disease; ALBI, albumin–bilirubin; ROC, receiver operating characteristic; PHLF, posthepatectomy liver failure; BCLC, Barcelona Clinical Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

However, there are also some limitations in our research. Firstly, all included patients were HBV-related HCC patients, and other etiologies, such as hepatitis C virus or alcoholic liver disease, still need to be studied. Moreover, this is a retrospective and single-center project, and further larger and multicentric researches are required to verify our findings.

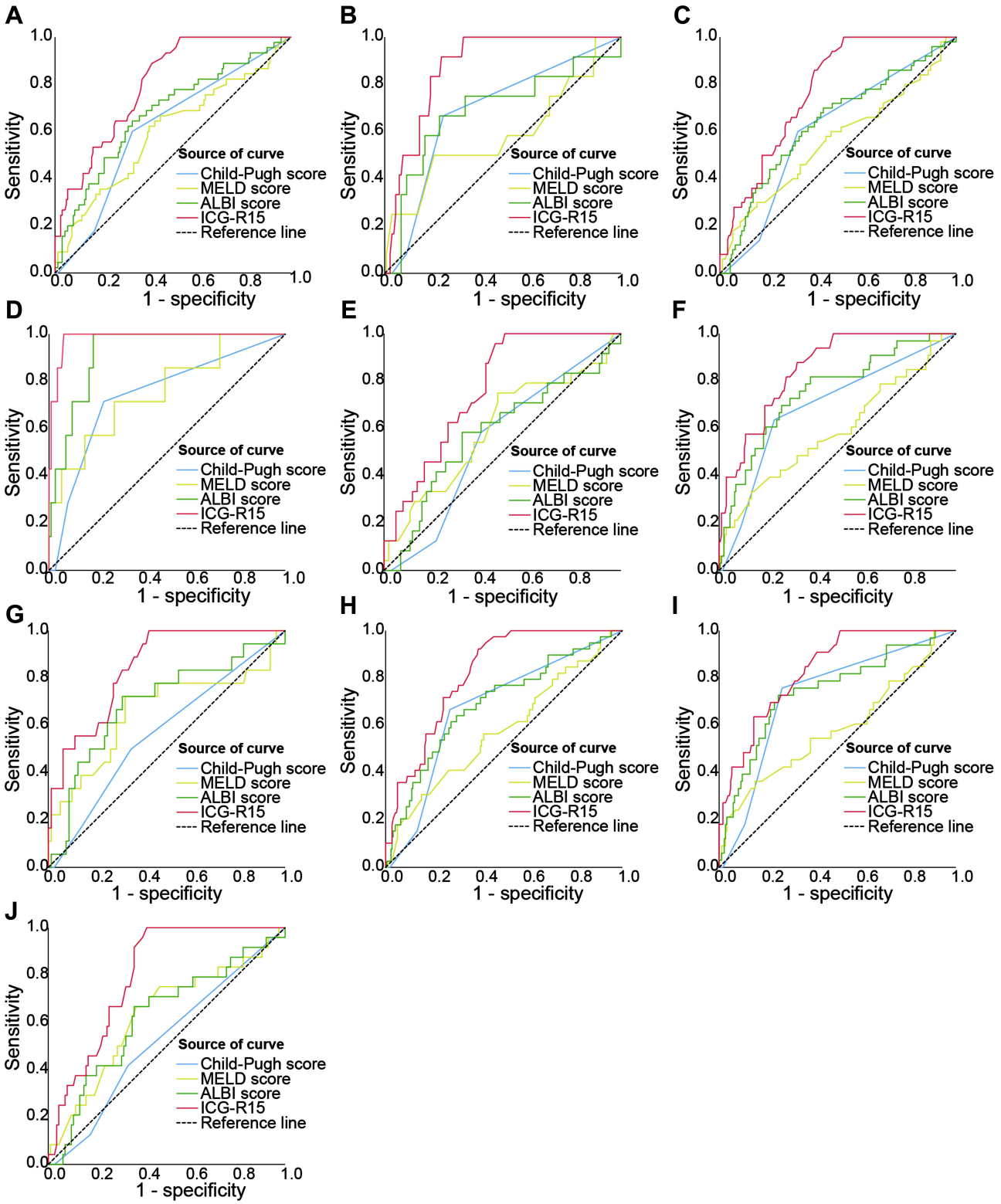

Figure 4 ROC curves of ICG-R15, Child–Pugh, MELD and ALBI scores for assessing severe PHLF in the HBV-related HCC patients. Subgroups include (**A**) cirrhosis, (**B**) no cirrhosis, (**C**) major hepatectomy, (**D**) minor hepatectomy, (**E**) blood loss ≥400 mL, (**F**) blood loss <400 mL, (**G**) blood transfusion, (**H**) no blood transfusion, (**I**) BCLC-0 or -A stage, and (**J**) BCLC-B or -C stage.

Abbreviations: ICG-R15, indocyanine green retention test at 15 minutes; MELD, model for end-stage liver disease; ALBI, albumin–bilirubin; ROC, receiver operating characteristic; PHLF, posthepatectomy liver failure; BCLC, Barcelona Clinical Liver Cancer; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

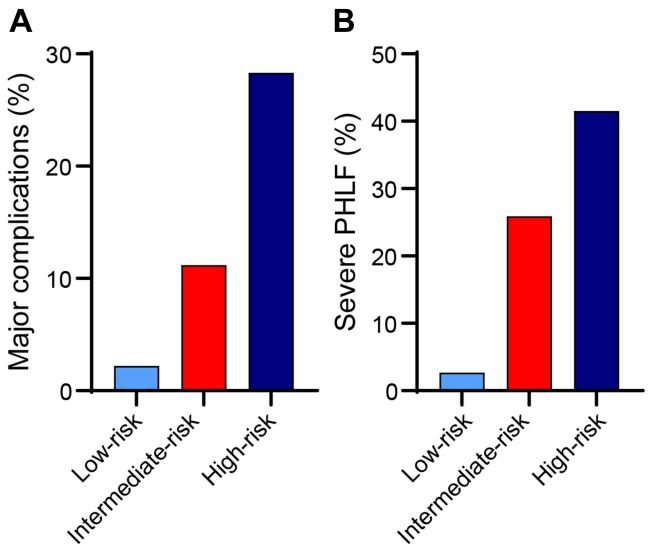

Figure 5 Relationship between the incidence of (**A**) postoperative major complications and (**B**) severe PHLF based upon risk group stratification assessed using the ICG-R15 in all included HBV-related HCC patients.
Abbreviations: PHLF, posthepatectomy liver failure; ICG-R15, indocyanine green retention test at 15 minutes; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

Conclusion

Compared with Child–Pugh, MELD and ALBI scores, preoperative ICG-R15 can more accurately predict the postoperative major complications and severe PHLF risk after hepatectomy in HBV-related HCC patients.

Abbreviations

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PHLF, posthepatectomy liver failure; MELD, model for end-stage liver disease; ALBI, albumin–bilirubin; ICG-R15, indocyanine green retention test at 15 min; AUC, area under the operating characteristic curve; DCA, decision curve analysis; BCLC, Barcelona Clinical Liver Cancer.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

The study was conducted in compliance with the Helsinki Declaration and approved by the institutional Ethics Committee of Guangxi Medical University Cancer Hospital, and all patients provided written informed consent.

Author Contributions

RYM and TB contributed equally to this work. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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