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99mTc-GSA scintigraphy and modified albumin–bilirubin score can be complementary to ICG for predicting posthepatectomy liver failure

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Abstract

Background Posthepatectomy liver failure (PHLF) remains a severe complication after liver resection. This retrospective study investigated the correlation of three hepatic functional tests and whether 99mTc-galactosyl human serum albumin (99mTc-GSA) scintigraphy and modified albumin–bilirubin (ALBI) score are useful for predicting PHLF.

Methods This retrospective cohort study included 413 consecutive patients undergoing hepatectomies between January 2017 and December 2020. To evaluate preoperative hepatic functional reserve, modified ALBI grade, indocyanine green clearance (ICG-R15), and 99mTc-GSA scintigraphy (LHL15) were examined before scheduled hepatectomy. Based on a retrospective chart review, multivariable logistic regression analysis adjusted for confounding factors was performed to confirm that mALBI, ICG-R15, and LHL15 are independent risk factors for PHLF.

Results ICG-R15 and LHL15 were moderately correlated ($r = -0.61$) but this correlation weakened when ICG-R15 was about ≥ 20. Weak correlations were observed between LHL15 and ALBI score ($r = -0.269$) and ALBI score and ICG-R15 ($r = 0.339$). Of 413 patients, 66 (19%) developed PHLF (20 grade A, 44 grade B, 2 grade C). Multivariable logistic regression analyses, major hepatectomy ($P < 0.001$), mALBI grade ($P = 0.01$), ICG-R15 ($P < 0.001$), and Esophagogastric varices ($P = 0.007$) were significant independent risk factors for PHLF. Subgroup analysis showed that ICG-R15 < 19, major hepatectomy, and mALBI grade and ICG-R15 ≥ 19, major hepatectomy, LHL15, and Esophagogastric varices were significant independent risk factors for PHLF ($P = 0.033$, 0.017, 0.02, 0.02, and 0.001, respectively).

Conclusion LHL15, the assessment of Esophagogastric varices, and mALBI grade are complementary to ICG-R15 for predicting PHLF risk.

Keywords 99mTc-GSA scintigraphy, LHL15, Modified ALBI grade, Hepatic functional reserve

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Introduction

For hepatic malignancies, surgical resection plays an essential role as a curative treatment option [1–4]. Although surgical outcomes of hepatectomy have improved recently due to the development of surgical devices and perioperative management, posthepatectomy liver failure (PHLF) remains a crucial complication after hepatectomy [5–10]. To prevent severe PHLF from potentially leading to lethal outcomes, it is important to accurately assess preoperative hepatic functional reserve. Several reports have demonstrated that the indocyanine green (ICG) clearance test, technetium-99 m-diethylenetriaminepentaacetic acid-galactosyl human serum albumin (99mTc-GSA) scintigraphy, albumin–bilirubin (ALBI) score, and ALBI grade are useful hepatic function tests for predicting PHLF [10–13]. Although the ICG retention rate at 15 min (ICG-R15) has been widely used, especially in Eastern countries, to assess preoperative hepatic functional reserve [14–16], there is sometimes a discrepancy between its value and the actual hepatic function in patients with hyperbilirubinemia and intrahepatic shunts [14, 17, 18]. In addition, the ICG test cannot be performed for patients allergic to this fluorescent cyanine dye [19–22]. As an alternative to the ICG test, the ALBI score, a parameter calculated from albumin and total bilirubin in the blood; the ALBI grade [13]; and the modified ALBI (mALBI) grade [23] are also available as preoperative hepatic function tests. In contrast, liver activity at 15 min as assessed by 99mTc-GSA scintigraphy (LHL15) has not been used as commonly as ICG-R15 or ALBI due to its high cost and requirement for radioactive agents [11, 24].

We have routinely measured both LHL15 and ICG-R15 and used the mALBI grade, ICG-R15, and LHL15 to evaluate preoperative hepatic functional reserve and determine the extent of hepatectomy. Although ICG-R15 and LHL15 are well correlated in most patients, a discrepancy is sometimes observed, especially in patients with deteriorated ICG-R15 values. It is difficult to interpret the hepatic functional reserve in such patients and thus to determine the appropriate procedure. However, a few reports have been published on the usefulness of measuring LHL15 in combination with ICG-R15 for predicting PHLF. In this study, we investigated the correlation of three hepatic functional tests (mALBI grade, ICG-R15, and LHL15) and evaluate whether LHL15 and ALBI are useful for predicting PHLF.

Methods

Patients

This was a single-center, retrospective cohort study. We included patients who underwent liver resection between January 2017 and December 2020. We excluded donors and recipients of living donor liver transplantation, patients with bile duct resection, and patients with early-stage gallbladder cancer who underwent liver bed resection only.

Preoperative physical assessment

We obtained study data through a review of our prospectively maintained database. The American Society of Anesthesiologists physical status (ASA-PS) was used to assess the general status of surgical tolerance [25].

Preoperative hepatic functional reserve

For patients at our institute who were scheduled to undergo hepatic resection, preoperative hepatic functional reserve was evaluated using the ALBI score, modified ALBI grade, ICG-R15, and LHL15, except for those with an ICG allergy or who had little time before surgery. The ALBI score was calculated as $-0.085 \times$ (albumin [g/L]) $+ 0.66 \times \log10(-$total bilirubin [μmol/L]), and was further categorized into three different grades as the modified ALBI grade: grade 1 (< -2.60), grade 2a (> -2.60 to < -2.27), grade 2b (≥ -2.27 to ≤ -1.39), and grade 3 (> -1.39) [23]. The ICG-R15 was the serum ICG level measured 5 min after injection of 0.5 mg/kg of ICG. The LHL15 was calculated by [(L15; the radioactivity of the liver at 15 min after 99mTc-GSA injection)] / [L15 + (H15; the radioactivity of the heart at 15 min after injection)]. We also calculated the count ratio of the liver to the sum of the counts and the blood disappearance rate (HH15) = [H15]/[H3; the counts of the heart at 3 min after injection] [12]. We evaluated the presence or absence of esophagogastric varices on preoperative upper gastrointestinal endoscopy to assess the presence of portal hypertension and liver cirrhosis. The Child–Pugh classification and the Model for End-stage Liver Disease (MELD) score [26] were used to evaluate liver cirrhosis and liver condition.

Surgical procedure

We conducted hepatectomy using Makuuchi's criteria [27]. The extent of hepatectomy was classified according to the Japanese general rules for the clinical pathological study of primary liver cancer [28]. Hr1, 2, and 3 were classified as major hepatectomy. Laparoscopic surgery has been the first choice at our institution. Open surgery is selected for cases requiring vascular reconstruction, cases in which a high degree of adhesion is expected after multiple liver resections, or when the patient's general condition is not good. In addition, in cases of laparoscopic surgery, robot-assisted surgery was performed if the patient strongly desired it and certain conditions were met, as previously described [29–31]. Details of the surgical procedures, including anatomical or nonanatomical liver resection, and open, laparoscopic, or robotic surgery were performed according to the previous reports [29–31].

PHLF and postoperative complications

Using the criteria of the International Study Group of Liver Surgery, we defined PHLF as an increase in the international normalized ratio of prothrombin time and concomitant hyperbilirubinemia (according to the normal limits of the local laboratory) on or after postoperative day 5 [32]. PHLF severity was classified as grade A, grade B, or grade C based on its impact on clinical management [24, 32]. We dichotomized liver failure into no failure and grade A/B/C failure. Complications after surgery during the same hospital stay were categorized according to Dindo and colleagues [33].

Statistical analysis

We present continuous data as the median and interquartile range. Categorical data are presented as count and proportion. We calculated Pearson's correlation coefficients to determine the correlations between ALBI score, ICG-R15, and LHL15. Multivariable logistic regression analysis was performed to confirm whether ALBI score, ICG-R15, and LHL15 are independent risk factors for PHLF. Age and major hepatectomy, which are considered to be associated with PHLF [34–36], and each factor (ALBI score, ICG-R15, and LHL15) were included in the model as adjusted factors. The explanatory variables of the model—ALBI score, ICG-R15, LHL15, and age—were treated as continuous variables, whereas major hepatectomy was treated as a binary categorical variable. We checked for multicollinearity using the variance inflation factor (VIF). A value of <2 for each variable was considered to indicate no multicollinearity. We also performed univariable logistic regression analysis to confirm the association between each factor and PHLF. The odds ratios are reported with 95% confidence intervals. A two-sided p value of <0.05 was considered statistically significant. We identified 29 cases with missing values in ICG-R15 and 12 cases with missing values in LHL15. The exclusion of such patients might have biased our results, and missing values were complemented by multiple imputations. We performed the multiple imputation method based on the variables entered into a multivariable logistic regression model, and the results obtained through five interactions were integrated according to Rubin's rule. To evaluate the predictive ability of PHLF by ICG-R15, we calculated the area under the curve (AUC) by the receiver-operating characteristic (ROC). The predictive ability of LHL15 was also evaluated by ROC and AUC in subgroups based on the cutoff point obtained by the Youden index. For the subgroup analysis, we performed multivariable logistic regression for the groups with ICG-R15 <19 and ≥ 19. We did not add the ICG-R15 to the covariates because it was used to separate the groups. The criteria for grouping using ICG-R15 were determined by the cutoff point obtained from the ROC curve. Statistical analyses were performed with R version 4.3.1 (The R Project for Statistical Computing, www.r-project.org) and EZR version 1.52 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). EZR is a graphical user interface for R version 4.02 (The R Foundation for Statistical Computing, Vienna, Austria) and is a modified version of R commander designed to add statistical functions frequently used in biostatistics [37].

Ethics

All procedures were conducted according to the ethical standards of the responsible committee on human experimentation (institutional and national) and the Helsinki Declaration of 1964 and later version. This study protocol was approved by the institutional review board of Fujita Health University (approval No. HM19-064).

Results

Patients

Between January 2017 and December 2020, 501 consecutive patients underwent hepatectomy in our department. After excluding 17 patients who were living liver transplant donors with normal hepatic function, 16 with end-stage liver failure during surgery, 4 who underwent only liver bed resection for early-stage gallbladder cancer with negligible extent of liver resection, 10 with neither preoperative ICG test nor 99mTc-GSAS, and 41 who underwent hepatectomy combined with bile duct resections, a total of 413 patients were selected (Fig. 1).

Corelationship of the three hepatic functional tests

Figure 2 shows the corelationship between the three hepatic functional tests. ICG-R15 and LHL15 were moderately correlated (correlation coefficients, $r = -0.61$). However, the correlation with LHL15 weakened when the ICG-R15 was about 20 or higher. The correlations between LHL15 and ALBI score ($r = -0.269$) and between ALBI score and ICG-R15 ($r = 0.339$) were weak.

Clinical outcome and the relationship between perioperative factors and PHLF

Table 1 shows the patients' characteristics and perioperative outcomes. Of the 413 patients, 42 patients (10.2%) experienced complications of the Clavien–Dindo classification of IIIA or higher, 28 patients (6.8%) IIIA, 6 patients (1.5%) IIIB, 6 patients (1.5%) IV, and 2 patients (0.5%) V. PHLF occurred in 66 patients (16.0%): 20

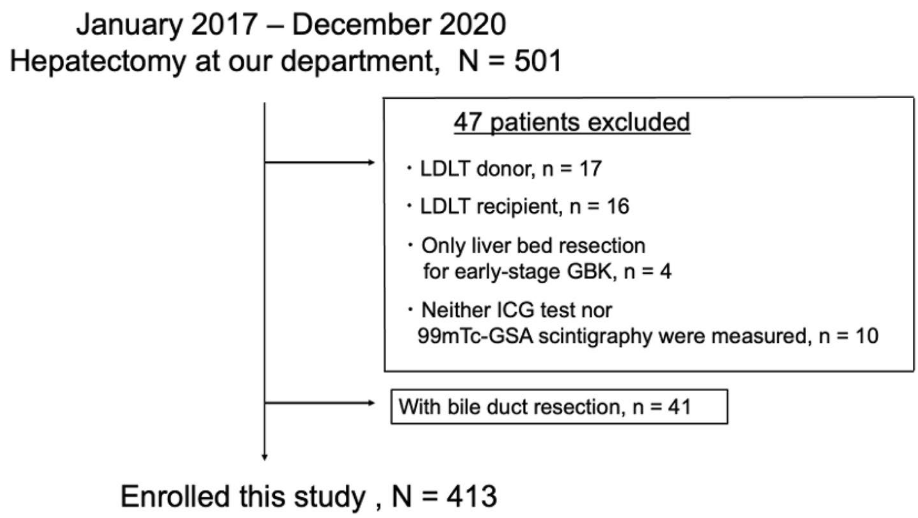

Fig. 1 Patient selection

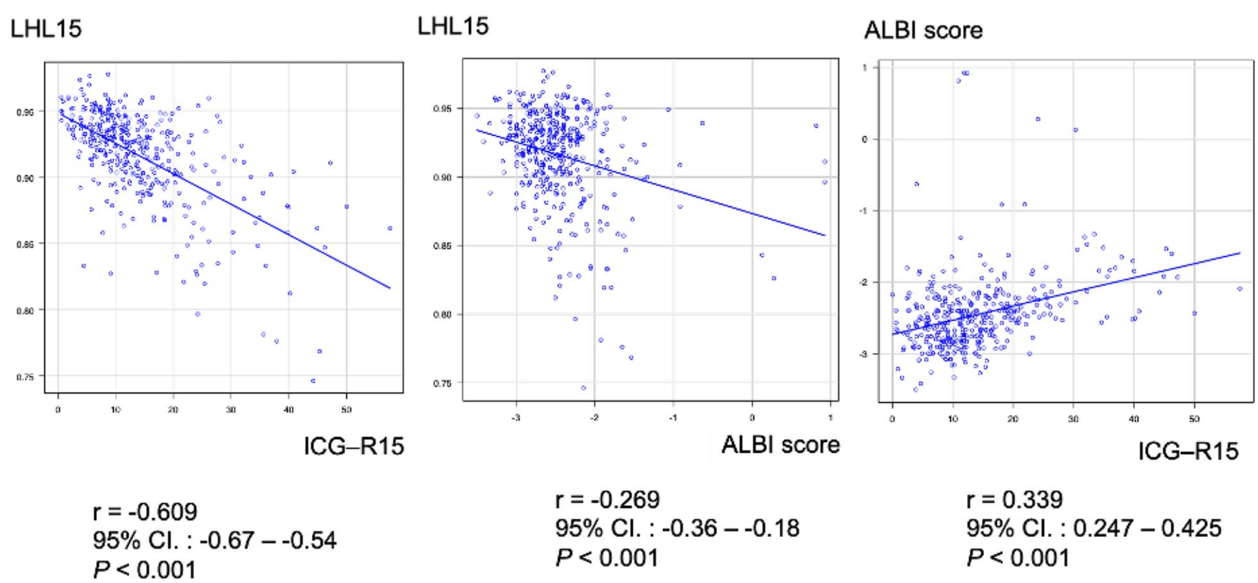

Fig. 2 Correlation of the three hepatic functional tests

patients (4.84%) in grade A, 44 patients (10.7%) in grade B, and 2 patients (0.48%) in grade C. Table 2 shows the summary results of the perioperative factors for each PHLF/non-PHLF. On univariable logistic regression analysis, several factors were noted to have a significant association with PHLF, including gender, age, ALBI score, mALBI grade, MELD score, ICG-R15, LHL15, Esophagogastric varices, major hepatectomy, operation time, and intraoperative blood loss. Multivariable regression analysis was performed using preoperative risk factors for PHLF. Table 3 shows the results of the univariable and multivariable logistic regression analysis evaluating the mALBI grade, ICG-R15, LHL15, and adjusted factor and PHLF. Multivariable logistic regression analysis identified mALBI grade (odds ratio [OR]: 1.72, 95% confidence interval [CI]: 1.17–2.52, $P=0.01$), ICG-R15 (OR: 1.08, 95% CI: 1.04–1.12, $P<0.001$), major hepatectomy (OR: 2.52, 95% CI: 1.35–4.71, $P=0.004$), and Esophagogastric varices (OR: 2.95, 95% CI: 1.34–6.47, $P=0.007$) as independent preoperative predictors of PHLF. VIF was 1.80 for ICG-R15, 1.68 for LHL15, 1.12 for mALBI grade, 1.15 for major hepatectomy, 1.18 for Esophagogastric varices, and 1.10 for age, all of which were less than 2 and therefore not considered multicollinear. The area under the

Table 1 Patient characteristics and perioperative outcomes

N	413
Preoperative factors	
Age, years[a]	69.0 [59.0, 75.0]
Male, gender[b]	262 (63.4%)
ASA-PS, n (1/2/3/4)	48/339/26/0
Child–Pugh classification[b]	
A	392 (94.9)
B	18 (4.4)
C	3 (0.7)
MELD score[a]	6.76 [6.20, 7.70]
ALBI score[a]	− 2.52 [− 2.78, − 2.25]
mALBI grade, n (1/2a/2b/3)	171/135/95/12
ICG-R15, %[a]	11.9 [7.8, 17.5]
LHL15[a]	0.92 [0.90, 0.94]
Esophagogastric varices[b]	
(−)	352 (85.2)
(+)	61 (14.8)
Intraoperative factors	
Approach[b]	
Open	125 (30.3)
Laparoscopic	237 (57.4)
Robotic	51 (12.3)
Extent of hepatectomy[b]	
Hr0	188 (45.5)
HrS	83 (20.1)
Hr1	69 (16.7)
Hr2	64 (15.5)
Hr3	9 (2.2)
Major hepatectomy[b]	
No	271 (65.6)
Yes	142 (34.4)
Operation time, min[a]	534.0 [360.0, 692.0]
Blood loss, mL[a]	220.0 [75.0, 640.0]
LOS, day[a]	15.0 [11.0, 20.0]
Pathological diagnosis[b]	
HCC	208 (50.4)
CCC	21 (5.1)
Metastatic	150 (36.3)
Gallbladder cancer	2 (0.5)
FNH	4 (1.0)
Others[c]	28 (6.8)
Postoperative factors	
Morbidity[b]	
IIIA >	371 (89.8)
IIIA ≤	42 (10.2)
PHLF[b]	
(+)	66 (16.0)
A	20 (4.8)
B	44 (10.7)
C	2 (0.5)

Table 1 (continued)

Continuous variables showed a nonnormal distribution and are presented as median and interquartile range. Hr1, 2, and 3 were classified as major hepatectomy

Morbidities after surgery during the same hospital stay were categorized according to Dindo and colleagues

ASA-PS American Society of Anesthesiologists physical status, *MELD score* Model for End Liver Disease, *ICG-R15* indocyanine green retention rate at 15 min, *LHL15* radioactivity of the heart and liver after intravenous injection of 99mTc-GSA, *Hr0* partial resection, *HrS* subsegmentectomy, *Hr1* segmentectomy, *Hr2* lobectomy and central bisegmentectomy, *Hr3* trisectomy and caudate lobectomy, *LOS* length of hospital stay after surgery, *HCC* hepatocellular carcinoma, *CCC* cholangiocellular carcinoma, *FNH* focal nodular hyperplasia, *PHLF* posthepatectomy liver failure

[a] Values are presented as median (interquartile range)

[b] Values are presented as number (%)

[c] Details of 28 other cases: hemorrhagic cyst, inflammatory pseudotumor, mucinous cystic tumor, pseudo lymphoma, epithelioid granuloma with necrosis, angiomyolipoma, cholangiocellular adenoma, cholangiectasis, hepatocellular adenoma malignant transformation, undifferentiated sarcoma, undifferentiated hepatocellular carcinoma, two cases of intraductal papillary neoplasia of the bile duct, two cases of hepatoblastoma, two cases of cholangiocyst, two cases of hepatocellular adenoma, and nine cases of hemangioma

receiver-operating characteristic curve (AUROC) of the ICG-R15 for PHLF was 0.716, and the optimal cutoff value was 19.2% (Fig. 3).

We divided the patients into subgroups with an ICG-R15 cutoff value of 19 and further examined the effect of LHL15 and ALBI on PHLF.

Patients with ICG-R15 < 19

Major hepatectomy (OR: 2.58, 95% CI: 1.08–6.15, $P = 0.033$) and mALBI grade (OR: 1.75, 95% CI: 1.10–2.77, $P = 0.017$) were independent risk factors for PHLF (Table 3). Twenty-eight patients developed PHLF, 10 patients (35.7%) in grade A and 18 patients (64.3%) in grade B.

Patients with ICG-R15 ≥ 19

Major hepatectomy (OR: 4.55, 95% CI: 1.28–10.6, $P = 0.02$), LHL15 (OR: 0.86, 95% CI: 0.76–0.97, $P = 0.02$), and Esophagogastric varices (OR: 4.12, 95% CI: 1.43–12.1, $P = 0.001$) were independent risk factors for PHLF (Table 3). Thirty-three patients developed PHLF, 6 patients (18.2%) in grade A, 25 patients (75.8%) in grade B, and 2 patients (6.1%) in grade C. Five patients with PHLF (four patients in grade A, one patient in grade B) had missing ICG-R15 data. The AUROC of the LHL15 for patients with ICG-R15 ≥ 19 for PHLF was 0.612, and the optimal cutoff value was 0.878 (Fig. 3).

Table 2 Relationship between perioperative factors and PHLF

	PHLF (−)	PHLF (+)	*P* value
n (%)	347(84)	66 (16)	
Age, years[a]	69.0 [58.0, 75.0]	72.0 [63.3, 75.8]	0.031
Gender[b]			0.026
Male	212 (61.1)	50 (75.8)	
Female	135 (38.9)	16 (24.2)	
ASA-PS[b]			0.306
1	43 (12.4)	5 (7.6)	
2	280 (80.7)	59 (89.7)	
3	24 (6.9)	2 (3.0)	
Approach[b]			0.667
Open	102 (29.4)	23 (34.8)	
Laparoscopic	201 (57.9)	36 (54.5)	
Robotic	44 (12.7)	7 (10.6)	
Child–Pugh classification			0.349
A	331 (95.4)	61 (92.4)	
B	14 (4.0)	4 (6.1)	
C	2 (0.6)	1 (1.5)	
MELD score	6.76 [6.09, 7.50]	7.40 [6.65, 8.42]	< 0.001
ALBI score[a]	− 2.57 [− 2.82, − 2.32]	− 2.28 [− 2.52, − 1.99]	< 0.001
mALBI grade[b]			< 0.001
1	161 (46.4)	10 (15.2)	
2a	112 (32.3)	23 (34.8)	
2b	65 (18.7)	30 (45.5)	
3	9 (2.6)	3 (4.5)	
ICG-R15,%[a]	11.4 [7.6, 16.0]	19.2 [10.4, 30.6]	< 0.001
LHL15[a]	0.93 [0.90, 0.94]	0.91 [0.87, 0.93]	0.002
Esophagogastric varices[b]			< 0.001
(−)	311 (89.6)	41 (62.1)	
(+)	36 (10.4)	25 (37.9)	
Major hepatectomy			0.048
No	235 (67.7)	36 (54.5)	
Yes	112 (32.3)	30 (45.5)	
Operation time, min[b]	510.0 [345.5, 641.5]	713.0 [491.3, 898.5]	< 0.001
Blood loss, mL[b]	185.0 [61.0, 546.5]	639.0 [216.3, 1279.3]	< 0.001

Continuous variables showed a nonnormal distribution and are presented as median and interquartile range. Hr1, 2, and 3 hepatectomy were classified as major hepatectomy

ASA-PS American Society of Anesthesiologists physical status, *MELD score* Model for End Liver Disease, *ICG-R15* indocyanine green retention rate at 15 min, *LHL15* radioactivity of the heart and liver after intravenous injection of 99mTc-GSA scintigraphy, *Hr0* partial resection, *HrS* subsegmentectomy, *Hr1* segmentectomy, *Hr2* lobectomy and central bisegmentectomy, *Hr3* trisectomy and caudate lobectomy, *PHLF* Posthepatectomy liver failure

[a] Values are presented as median (interquartile range)

[b] Values are presented as number (%)

Comparison of PHLF by LHL15 in patients with ICG-R15 ≥ 19

We compared the incidence of PHLF in patients with ICG-R15 ≥ 19 who underwent major hepatectomy with LHL15 ≥ 0.87 (LHL15 normal group) and in those with LHL15 < 0.87 (LHL15 worse group) who underwent major hepatectomy. In the LHL15 normal group, the incidence of PHLF was 42.1% in 8 of 19 patients, compared with 80.0% in 4 of 5 patients in the LHL15 worse group. There was a trend toward a higher incidence of PHLF in the LHL15 worse group.

Discussion

The current study showed that although LHL15 and ICG-R15 correlated well overall, the correlation weakened as hepatic function worsened. In patients with

Table 3 Logistic regression analysis for PHLF

Logistic regression analysis for PHLF						
	Univariable			**Multivariable**		
Variables	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age	1.03	1.00–1.05	0.024	1.00	0.97–1.03	0.94
Major hepatectomy	1.75	1.02–2.98	0.04	3.22	1.63–6.39	< 0.001
Child–Pugh classification	1.59	0.67–3.71	0.28			
MELD score	1.02	0.96–1.09	0.52			
mALBI grade	2.25	1.64–3.07	< 0.001	1.72	1.17–2.52	0.006
LHL15	0.86	0.81–0.93	< 0.001	1.01	0.97–1.06	0.58
ICG-R15	1.10	1.07–1.13	< 0.001	1.08	1.04–1.12	< 0.001
Esophagogastric varices	5.27	2.88–9.65	< 0.001	2.95	1.34–6.47	0.007
	Multivariable logistic regression analysis by subgroup on ICG-R15					
	ICG-R15 < 19 (*N* = 302)			ICG-R15 ≥ 19 (*N* = 82)		
Variable	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.03	0.99–1.07	0.14	0.98	0.92–1.03	0.40
Major hepatectomy	2.58	1.08–6.15	0.033	4.55	1.28–10.6	0.02
mALBI grade	1.75	1.10–2.77	0.017	1.85	0.89–3.86	0.10
LHL15	1.15	0.95–1.39	0.142	0.86	0.76–0.97	0.02
Esophagogastric varices	2.86	0.8–10.3	0.11	4.12	1.43–12.1	0.001

Multivariable logistic regression analysis was conducted to reveal preoperative risk factors for PHLF

MELD score Model for End Liver Disease, *LHL15* radioactivity of the heart and liver after intravenous injection of 99mTc-GSA, *ICG-R15* indocyanine green retention rate at 15 min, *OR* Odds ratio, *95% CI* 95% confidential interval, *PHLF* Posthepatectomy liver failure

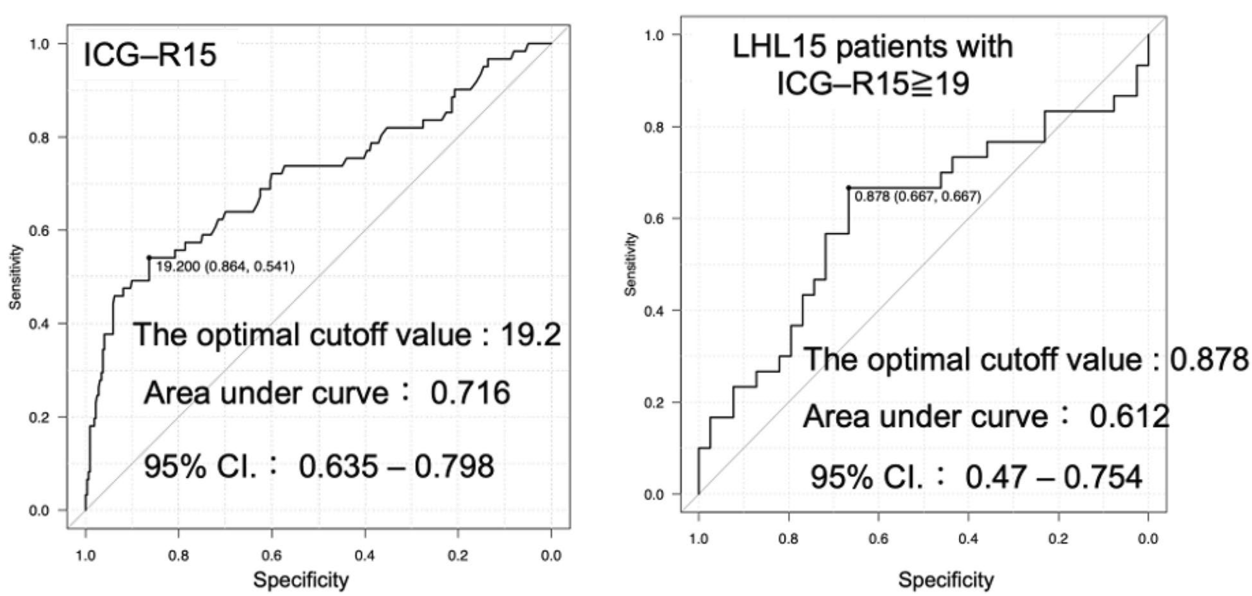

Fig. 3 Area under curve the receiver-operating characteristic curve (AUROC) for PHLF

good hepatic function with low ICG-R15, the contribution of LHL15 to predicting PHLF is small, but as ICG-R15 increased, the impact of LHL15 on PHLF became larger. To our knowledge, this is the first study to identify patients for whom LHL15 should be measured in addition to ICG-R15 to increase the predictive accuracy for PHLF.

Our study showed that LHL15 and ICG-R15 correlated well overall, but the correlation weakened as hepatic function worsened. As shown in Fig. 2, LHL15 and ICG-R15 correlated well in all patients ($r = -0.61$, 95% CI: -0.67 to -0.54, $P < 0.001$), but the correlation weakened as ICG-R15 increased. Patients with poor hepatic function generally have elevated ICG-R15 (high ICG-R15), whereas patients with obstructive jaundice or intrahepatic shunts may have worse ICG-R15 than their actual hepatic function. In patients with high ICG-R15, additional hepatic function tests are needed to determine whether the hepatic function is truly worse or worse due to intrahepatic shunts or other factors. The usefulness of 99mTc-GSA scintigraphy as an alternative test to the ICG test has been reported in recent years [24, 38]. Sumiyoshi et al. reported that there is a large discrepancy between ICG-R15 and actual hepatic function in patients with ICG-R15 > 40 and highly deteriorated ICG-R15 and that 99mTc-GSA scintigraphy assesses hepatic function more accurately than the ICG test does [22]. In patients with good hepatic function who have low ICG-R15, the contribution of LHL15 to the prediction of PHLF is small, but as ICG-R15 increases, the impact of LHL15 on PHLF becomes larger. Recently, researchers have reported the usefulness of the ALBI score and ALBI grade, calculated from serum albumin and bilirubin, in assessing hepatic function [23, 39, 40]. The greatest advantage of ALBI is that it can be obtained easily from routine blood test results. ALBI is worse in patients with hyperbilirubinemia, so as with ICG, it is useful for evaluating hepatic functional reserve in patients with low ICG-R15. However, its usefulness in patients with high bilirubin is unknown.

We divided the patients into subgroups with an ICG-R15 cutoff value of 19 and further examined the effect of LHL15 and ALBI on PHLF. Table 3 shows the multivariable analysis of the preoperative risk factors of PHLF. For patients with ICG-R15 < 19, mALBI and major hepatectomy were independent risk factors for PHLF ($P = 0.033$, $P = 0.017$). Our results indicate that in the group of patients with low ICG-R15, the mALBI grade was useful for assessing the risk of PHLF. The mALBI grade provides a detailed classification of hepatic function in patients whose albumin and bilirubin values are close to the reference values because it sensitively reflects albumin and bilirubin values. Because the mALBI grade may be useful for a detailed classification of liver function in patients with albumin and bilirubin near baseline values, it was useful for patients in the ICG-R15 < 19 subgroup.

Overall, the impact of LHL15 on the prediction of PHLF was not statistically significant. Concerning patients with ICG-R15 ≥ 19, LHL15 and Esophagogastric varices were independent risk factors for PHLF ($P = 0.02$ and 0.001). Esophagogastric varices are a major complication of portal hypertension, occurring in approximately 50% of patients with cirrhosis [41]. A high ICG-R15 and the presence of esophagogastric varices indicate a cirrhotic patient with portal hypertension and an increased risk of PHLF. The indication for hepatectomy should be determined carefully. When ICGR-15 is high, considering whether it is due to impaired bilirubin metabolism, portocaval shunt, or truly poor liver function is necessary. If the liver function is truly poor, hepatocyte function is impaired and uptake and excretion of ICG are delayed, resulting in high ICG-R15 values. Meanwhile, 99mTc-GSA scintigraphy to examine the processing capacity of asialoglycoprotein (ASGP) on the hepatocyte surface—which is specifically recognized by the ASGP receptor—is used to evaluate liver function. The number of ASGP receptors is recognized to be decreased in liver disease but is unaffected by hyperbilirubinemia or portocaval shunt. Therefore, situations in which ICG-R15 is high and hyperbilirubinemia or portocaval shunt is suspected, LHL15 may more accurately assess of liver function than ICG-R15 does, and a high ICG-R15 and poor LHL15 value may indicate truly poor liver function. This is probably why LHL15 was useful in predicting PHLF in cases in which ICG-R15 ≥ 19.

These results indicate that ALBI and ICG are useful for patients who have good hepatic function; on the contrary, for patients with poor hepatic function, the use of ICG only is not sufficient to predict the risk of PHLF, and LHL15 should also be measured. For patients for whom LHL15 should be measured, the cutoff value of ICG-R15 was 19.

Table 4 shows the main factors for PHLF, which were classified into the following four categories: intraoperative, postoperative morbidity, hepatic functional, and combined factors. There were some cases in which PHLF resulted but from a combination of factors rather than one. Among the cases that underwent surgeries exceeding the Makuuchi criteria, those with either intraoperative blood loss or operative time greater than the median were classified as PHLF because of combined factors. As shown in Table 4, among both subgroups, major hepatectomy was a risk factor for PHLF. Table 4 shows that in patients with ICG-R15 < 19, 17 of 28 patients with PHLF underwent major hepatectomy. In this group, intraoperative factors were the most common factor for PHLF. This might be due to the increased intraoperative bleeding and longer operative time associated major hepatectomy. Among patients with ICG-R15 ≥ 19, 12 of 33 patients with PHLF underwent major hepatectomy. In this group, combined factors were the most common for PHLF. Patients with poor liver function are at risk of coagulopathy, resulting in increased blood loss, and the repeated hemostatic maneuvers required can prolong the operative time. PHLF was more prevalent in the subgroup with ICG-R15 ≥ 19 because of combined

Table 4 Main factors of PHLF by subgroup

	ICG-R15 < 19	ICG-R15 ≥ 19
PHLF, n (%)	28	33
Grade A	10 (35.7)	6 (18.2)
Grade B	18 (64.3)	25 (75.8)
Grade C	0	2 (6.0)
Major hepatectomy, n (%)	17 (60.7)	12 (36.4)
Cause of PHLF, n (%)		
Intraoperative	18 (64.3)	7 (21.2)
Morbidity	5 (17.9)	1 (3.0)
Hepatic function	4 (14.3)	5 (15.2)
Combined factors	1 (3.6)	20 (60.6)

The extent of hepatectomy was classified according to the Japanese general rules for the clinical pathological study of primary liver cancer [28]. Hr1, 2, and 3 were classified as major hepatectomy. factors of PHLF; intraoperative factors mean PHLF caused by a prolonged operation time (≥ 713 min) or intraoperative massive bleeding (≥ 639 mL). Morbidity factors mean PHLF caused by postoperative complex. Hepatic functional factors mean PHLF caused by impaired hepatic function (PHLF except for intraoperative factors and morbidity factors). Cases that underwent surgeries exceeding the Makuuchi criteria or those with either intraoperative blood loss or operative time above the median were classified as PHLF due to combined factors

ICG-R15 Indocyanine green retention rate at 15 min, *PHLF* Posthepatectomy liver failure

factors of poor preoperative liver function and surgical factors. The AUROC of the LHL15 for PHLF was 0.612, and the optimal cutoff value was 0.878 (Fig. 3, right). At our institution, the extent of hepatectomy was essentially determined using Makuuchi's criteria. However, in some cases, surgeries deviating from Makuuchi's criteria were performed for some patients who were deemed to be tolerable. In such cases, we thought that evaluating hepatic function using LHL15 might be useful. Comparing the incidence of PHLF in patients with ICG-R15 ≥ 19 revealed notable differences based on LHL15 values. In groups with normal and impaired LHL15, the incidences of PHLF were 42.1% and 80.0%, respectively. There was a trend toward a higher incidence of PHLF in the LHL15 worse group. Our result indicates that LHL15 may be a useful test for assessing hepatic functional reserve when ICG-R15 does not accurately reflect hepatic function. Our result also indicates the reliability of LHL15 in the selection of hepatectomy candidates among the patient group with high ICG-R15.

There are several limitations to this study. First, 99mTc-GSA scintigraphy is relatively widespread in Eastern countries, but is not yet widely used in European countries; thus, it might be difficult to extrapolate this result to European countries. Second, we did not consider resection volume because more than half of the patients were considered candidates for hepatic resection with a small resection volume. Therefore, predicting the accurate resection volume was difficult, and the effect of resection volume on perioperative results was considered small in patients with small resection volumes. Third, this study included only patients who had received hepatectomy; patients who did not have received hepatectomy due to impaired hepatic function. As mentioned in previous reports [42], this might imply that we excluded from this analysis patients with low LHL15 values for whom hepatectomy would not be safely performed due to impaired hepatic function.

Conclusions

Although LHL15 and ICG-R15 correlated well overall, the correlation weakened as hepatic function worsened. In patients with good hepatic function, the contribution of LHL15 to the prediction of PHLF is small, but as ICG-R15 increased, the impact of LHL15 on PHLF became larger. In patients with low ICG-R15, assessing hepatic function by mALBI grade would be useful. In patients with high ICG-R15, evaluating hepatic function using LHL15 and assessment of esophagogasteric varices would be useful for predicting the risk of PHLF. For predicting PHLF, 99mTc-GSA scintigraphy, an assessment of esophagogasteric varices and modified ALBI score can complement ICG.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used *DeepL* in order to translate the text into English (www.Deep.com/Translator (free version)). After using this tool, the authors reviewed and edited the contents as required and take full responsibility for content of this publication.

Abbreviations

AUC	Area under the curve
AUROC	Area under the receiver-operating characteristic curve
ISGLS	International study group of liver surgery
ROC	Receiver-operating characteristic

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Authors' contributions

All authors have fully satisfied the ICMJE authorship criteria as follows: study design: S. M, T. T, S. S, and K. S; data collection: S. M and Y. K; statistical analysis and interpretation of results: S. M, T. I, T. T, S. S, and K. S; drafting of the manuscript: S. M, T. I, T. T, S. S, and K. S; and critical revision of the manuscript for important intellectual content: T. T, S. S, Y. K, and K. S. All authors have read and approved the final manuscript and are accountable for all aspects of the work, particularly in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the institutional review board of Fujita Health University (HM19-064) and other participating hospitals. This study was also performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent for this study was obtained through an opt-out method.

Consent for publication
Not applicable. Individual identifying data were not included in this manuscript.

Competing interests
The authors declare no competing interests.

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References

1. Zhong JH, Ke Y, Gong WF, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Ann Surg. 2014;260:329–40. https://doi.org/10.1097/SLA.0000000000000236.
2. Pinna AD, Yang T, Mazzaferro V, et al. Liver transplantation and hepatic resection can achieve cure for hepatocellular carcinoma. Ann Surg. 2018;268:868–75. https://doi.org/10.1097/SLA.0000000000002889.
3. Margonis GA, Buettner S, Andreatos N, et al. Anatomical resections improve disease-free survival in patients with KRAS-mutated colorectal liver metastases. Ann Surg. 2017;266:641–9. https://doi.org/10.1097/SLA.0000000000002367.
4. Abdalla EK, Vauthey J-N, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239:818–25. https://doi.org/10.1097/01.sla.0000128305.90650.71. discussion 825–817.
5. Poon RT, Fan ST, Lo CM, et al. Improving perioperative outcome expands the role of hepatectomy in management of benign and malignant hepatobiliary diseases: analysis of 1222 consecutive patients from a prospective database. Ann Surg. 2004;240:698–708. https://doi.org/10.1097/01.sla.0000141195.66155.0c. discussion 708–610.
6. Schroeder RA, Marroquin CE, Bute BP, Khuri S, Henderson WG, Kuo PC. Predictive indices of morbidity and mortality after liver resection. Ann Surg. 2006;243:373–9. https://doi.org/10.1097/01.sla.0000201483.95911.08.
7. Sadot E, Koerkamp BG, Leal JN, et al. Resection margin and survival in 2368 patients undergoing hepatic resection for metastatic colorectal cancer: surgical technique or biologic surrogate? Ann Surg. 2015;262:476–85. https://doi.org/10.1097/SLA.0000000000001427. discussion 483.
8. Utsunomiya T, Shimada M, Kudo M, et al. A comparison of the surgical outcomes among patients with HBV-positive, HCV-positive, and non-B non-C hepatocellular carcinoma: a nationwide study of 11,950 patients. Ann Surg. 2015;261:513–20. https://doi.org/10.1097/SLA.0000000000000821.
9. Wang C, Zheng G, Zhang W, et al. Enhanced recovery after surgery programs for liver resection: a meta-analysis. J Gastrointest Surg. 2017;21:472–86. https://doi.org/10.1007/s11605-017-3360-y.
10. Okabayashi T, Shima Y, Morita S, et al. Liver function assessment using technetium 99m-galactosyl single-photon emission computed tomography/CT fusion imaging: a prospective trial. J Am Coll Surg. 2017;225:789–97. https://doi.org/10.1016/j.jamcollsurg.2017.08.021.
11. Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. Br J Surg. 2010;97:1260–8. https://doi.org/10.1002/bjs.7084.
12. Kato A, Nakamoto Y, Ishimori T, Seo S, Uemoto S, Togashi K. Predictability of 99mTc-galactosyl human serum albumin scintigraphy for posthepatectomy liver failure. AJR Am J Roentgenol. 2018;210:158–65. https://doi.org/10.2214/AJR.17.18411.
13. Zhang Z-Q, Xiong L, Zhou J-J, et al. Ability of the ALBI grade to predict posthepatectomy liver failure and long-term survival after liver resection for different BCLC stages of HCC. World J Surg Oncol. 2018;16:208. https://doi.org/10.1186/s12957-018-1500-9.
14. Imamura H, Sano K, Sugawara Y, Kokudo N, Makuuchi M. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg. 2005;12:16–22. https://doi.org/10.1007/s00534-004-0965-9.
15. Lisotti A, Azzaroli F, Buonfiglioli F, et al. Indocyanine green retention test as a noninvasive marker of portal hypertension and esophageal varices in compensated liver cirrhosis. Hepatology. 2014;59:643–50. https://doi.org/10.1002/hep.26700.
16. Ohwada S, Kawate S, Hamada K, et al. Perioperative real-time monitoring of indocyanine green clearance by pulse spectrophotometry predicts remnant liver functional reserve in resection of hepatocellular carcinoma. Br J Surg. 2006;93:339–46. https://doi.org/10.1002/bjs.5258.
17. de Graaf W, Häusler S, Heger M, et al. Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. J Hepatol. 2011;54:738–45. https://doi.org/10.1016/j.jhep.2010.07.047.
18. Cui Y, Ko'nig J, Leier I, Buchholz U, Keppler D. Hepatic uptake of bilirubin and its conjugates by the human organic anion-transporting polypeptide SLC21A6. J Biol Chem. 2000;276:9626–30. https://doi.org/10.1074/jbc.M004968200.
19. Kwon AH, Ha-Kawa SK, Uetsuji S, Inoue T, Matsui Y, Kamiyama Y. Preoperative determination of the surgical procedure for hepatectomy using technetium-99m-galactosyl human serum albumin (99mTc-GSA) liver scintigraphy. Hepatology. 1997;25:426–9. https://doi.org/10.1002/hep.510250228.
20. Maeda H, Okabayashi T, Kobayashi M, et al. Hepatectomy for hepatocellular carcinoma with indocyanine green excretory defect: a case report. Hepatogastroenterology. 2007;54:1810–2.
21. Sumiyoshi T, Shima Y, Okabayashi T, et al. Liver function assessment using 99mTc-GSA single-photon emission computed tomography (SPECT)/CT fusion imaging in hilar bile duct cancer: a retrospective study. Surgery. 2016;160:118–26. https://doi.org/10.1016/j.surg.2016.02.009.
22. Sumiyoshi T, Okabayashi T, Negoro Y, et al. 99mTc-GSA SPECT/CT fusion imaging for hepatectomy candidates with extremely deteriorated ICG value. Jpn J Radiol. 2018;36:537–43. https://doi.org/10.1007/s11604-018-0753-0.
23. Hiraoka A, Kumada T. Clinical role of newly developed ALBI and mALBI grades for treatment of hepatocellular carcinoma. Appl Sci. 2020;10:7178. https://doi.org/10.3390/app10207178.
24. Nakamura I, Iimuro Y, Hai S, Kondo Y, Hatano E, Fujimoto J. Impaired value of 99m Tc-GSA scintigraphy as an independent risk factor for posthepatectomy liver failure in patients with hepatocellular carcinoma. Eur Surg Res. 2018;59:12–22. https://doi.org/10.1159/000484044.
25. Hackett NJ, De Oliveira GS, Jain UK, Kim JYS. ASA class is a reliable independent predictor of medical complications and mortality following surgery. Int J Surg. 2015;18:184–90. https://doi.org/10.1016/j.ijsu.2015.04.079.
26. Kamath PS, Kim WR. Advanced liver disease study group. The model for end-stage liver disease (MELD). Hepatology. 2007;45:797–805. https://doi.org/10.1002/hep.21563.
27. Imamura H, Seyama Y, Kokudo N, et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg. 2003;138:1198–206. https://doi.org/10.1001/archsurg.138.11.1198. discussion 1206.
28. Kudo M, Kitano M, Sakurai T, Nishida N. General rules for the clinical and pathological study of primary liver cancer, nationwide follow-up survey and clinical practice guidelines: the outstanding achievements of the Liver Cancer Study Group of Japan. Dig Dis. 2015;33:765–70. https://doi.org/10.1159/000439101.
29. Kato Y, Sugioka A, Kojima M, et al. Initial experience with robotic liver resection: audit of 120 consecutive cases at a single center and comparison with open and laparoscopic approaches. J Hepatobiliary Pancreat Sci. 2023;30:72–90. https://doi.org/10.1002/jhbp.1206.

30. Kato Y, Sugioka A, Kojima M, et al. Minimally invasive anatomic liver resection for hepatocellular carcinoma using the extrahepatic Glissonian approach: surgical techniques and comparison of outcomes with the open approach and between the laparoscopic and robotic approaches. Cancers. 2023;15:2219. https://doi.org/10.3390/cancers15082219.
31. Kato Y, Sugioka A, Uyama I. Robotic liver resection for hepatocellular carcinoma: A focus on anatomic resection. Hepatoma Res. 2021:10. https://doi.org/10.20517/2394-5079.2020.129.
32. Rahbari NN, Garden OJ, Padbury R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149:713–24. https://doi.org/10.1016/j.surg.2010.10.001.
33. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
34. Lei Z, Cheng N, Si A, et al. A novel nomogram for predicting postoperative liver failure after major hepatectomy for hepatocellular carcinoma. Front Oncol. 2022;12: 817895. https://doi.org/10.3389/fonc.2022.817895.
35. Søreide JA, Deshpande R. Post hepatectomy liver failure (PHLF) – Recent advances in prevention and clinical management. Eur J Surg Oncol. 2021;47:216–24. https://doi.org/10.1016/j.ejso.2020.09.001.
36. Guglielmi A, Ruzzenente A, Conci S, Valdegamberi A, Iacono C. How much remnant is enough in liver resection? Dig Surg. 2012;29:6–17. https://doi.org/10.1159/000335713.
37. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013;48:452–8. https://doi.org/10.1038/bmt.2012.244.
38. Hayashi H, Beppu T, Okabe H, et al. Functional assessment versus conventional volumetric assessment in the prediction of operative outcomes after major hepatectomy. Surgery. 2015;157:20–6. https://doi.org/10.1016/j.surg.2014.06.013.
39. Hiraoka A, Michitaka K, Kumada T, et al. Validation and potential of albumin-bilirubin grade and prognostication in a nationwide survey of 46,681 hepatocellular carcinoma patients in Japan: the need for a more detailed evaluation of hepatic function. Liver Cancer. 2017;6:325–36. https://doi.org/10.1159/000479984.
40. Aida T, Haruki K, Akaoka M, et al. A novel combined C-reactive protein-albumin ratio and modified albumin-bilirubin score can predict long-term outcomes in patients with hepatocellular carcinoma after hepatic resection. Ann Gastroenterol Surg. 2024;8:143–50. https://doi.org/10.1002/ags3.12727.
41. Maruyama H, Yokosuka O. Pathophysiology of portal hypertension and esophageal varices. Int J Hepatol. 2012;2012: 895787. https://doi.org/10.1155/2012/895787.
42. Tomimaru Y, Eguchi H, Gotoh K, et al. Platelet count is more useful for predicting posthepatectomy liver failure at surgery for hepatocellular carcinoma than indocyanine green clearance test. J Surg Oncol. 2016;113:565–9. https://doi.org/10.1002/jso.24166.

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