https://doi.org/10.1016/j.hpb.2020.05.008 HPB

ORIGINAL ARTICLE

A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma

Naruhiko Honmyo[1], Tsuyoshi Kobayashi[1], Shintaro Kuroda[1], Akihiko Oshita[2], Takashi Onoe[3], Toshihiko Kohashi[4], Saburo Fukuda[5], Ichiro Ohmori[6], Tomoyuki Abe[7], Yasuhiro Imaoka[8], Tomoyuki Akita[9], Junko Tanaka[9] & Hideki Ohdan[1]

[1]Department of Gastroenterological and Transplant Surgery, Hiroshima University, 1-2-3 Kasumi, Minami-ku, [2]Department of Gastroenterological, Breast, and Transplant Surgery, Hiroshima Prefectural Hospital, 1-5-54 Ujinakanda, Minami-ku, Hiroshima, [3]Department of Surgery, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, 3-1 Aoyamacho, Kure, [4]Department of Surgery, Hiroshima City Asa Citizens Hospital, 2-1-1 Kabeminami, Asakita-ku, Hiroshima, [5]Department of Surgery, Chugoku Rosai Hospital, 1-5-1 Hirotagaya, Kure, [6]Department of Surgery, National Hospital Organization Higashihiroshima Medical Center, 513 Saijochojike, Higashihiroshima, [7]Department of Surgery, Onomichi General Hospital, 1-10-23 Hirahara, Onomichi, [8]Department of Surgery, National Hospital Organization Hiroshima-nishi Medical Center, 4-4-1 Kuba, Otake, and [9]Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, Japan

Abstract

Background: The permissible liver resection rate for preventing posthepatectomy liver failure (PHLF) remains unclear. We aimed to develop a novel PHLF-predicting model and to strategize hepatectomy for hepatocellular carcinoma (HCC).

Methods: This retrospective study included 335 HCC patients who underwent anatomical hepatectomy at eight institutions between 2013 and 2017. Risk factors, including volume-associated liver-estimating parameters, for PHLF grade B–C were analyzed in a training set (n = 122) via multivariate analysis, and a PHLF prediction model was developed. The utility of the model was evaluated in a validation set (n = 213).

Results: Our model was based on the three independent risk factors for PHLF identified in the training set: volume-associated indocyanine green retention rate at 15 min, platelet count, and prothrombin time index (the VIPP score). The areas under the receiver operating characteristic curve of the VIPP scores for severe PHLF in the training and validation sets were 0.864 and 0.794, respectively. In both sets, the VIPP score stratified patients at risk for severe PHLF, with a score of 3 (specificity, 0.92) indicating higher risk.

Conclusion: Our model facilitates the selection of the appropriate hepatectomy procedure by providing permissible liver resection rates based on VIPP scores.

Received 19 December 2019; accepted 13 May 2020

Correspondence

Department of Gastroenterological and Transplant Surgery, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, 734-8551, Japan. E-mail: tsukoba@hiroshima-u.ac.jp

Introduction

Hepatectomy is one of the most effective treatments for hepatocellular carcinoma (HCC). Short-term outcomes after hepatectomy have improved owing to advances in imaging systems, surgical techniques, perioperative management, and understanding of liver anatomy. Although indications for hepatectomy have continuously increased, posthepatectomy liver failure (PHLF) occurs in 0.7%–34% of patients following liver resection and remains a potentially life-threatening complication directly associated with the procedure.[1–4]

Several risk factors for PHLF have been reported, including advanced age,[5,6] male sex,[2,3] pre-existing liver disease,[7–10] greater intraoperative blood loss and perioperative transfusion,[11,12] postoperative complications,[4] and small remnant-liver

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

volume.[13] Generally, the procedure for hepatectomy is selected based on the preoperative liver function of the patient; therefore, it is natural to conclude that the relationship between liver function and the degree of liver resection is closely related to the development of PHLF. Several articles have described the following acceptable future liver remnant rates: >20% in patients with normal livers, >30% in patients with steatosis or chemotherapeutically treated livers, and >40%–50% in patients with fibrotic or cirrhotic livers.[14–16] Because of the pathogenesis of HCC, most HCC patients have damaged livers owing to viral and/or alcoholic hepatitis, steatosis, and cirrhosis, the severity of which varies from patient to patient. For such patients, these criteria for hepatectomy seem to be vague. Therefore, a more detailed and flexible criterion is required.

The primary aim of this study was to construct a novel PHLF prediction model based on volume-associated liver-estimating parameters that considers liver function and liver resection degree simultaneously. The secondary aim was to test the validity of the model via multi-institutional surveillance.

Methods

This retrospective study included patients who underwent anatomical hepatectomy for HCC at eight institutions affiliated with the Hiroshima Surgical study group of Clinical Oncology (HiSCO), including Hiroshima University Hospital, between December 2013 and December 2017. Since the main objective of this study was to clarify the relationship between liver resection/remnant degree, as expressed using quantitative indicators, and the development of PHLF, patients who had undergone peripheral wedge resection and concurrent extrahepatic bile duct resection with hepatectomy, a likely risk for postoperative complications such as bile leakage, were excluded. Patients who had received preoperative portal vein embolization were also excluded owing to functional heterogeneity of the atrophied liver.

This study involved two key stages: first, a cohort was selected and used as a training set for the construction of the PHLF prediction model and, second, the validity of the model was tested using an additional cohort. The training set included consecutive patients who underwent hepatectomy at Hiroshima University Hospital between December 2013 and December 2015. Patients' clinical, laboratory, liver volumetric, surgical, pathological, and postoperative data were collected from the HCC database of the Department of Gastroenterological and Transplant Surgery at Hiroshima University Hospital. The validation set included patients who underwent hepatectomy at multiple institutions from January 2016 to December 2017. Patients' demographic data were collected from the integrated HCC database of the HiSCO.

This study conforms to the provisions of the Declaration of Helsinki and was approved by the ethics committee of our institution (E-1253). The collection and registration of data in the multi-institutional database of the HiSCO were executed with the approval of the ethics committees of all participating institutions. Informed consent was obtained from all patients.

Computed tomography (CT) volumetry

Total-, resection-, and remnant-liver volumes were evaluated using a CT volumetry system. Dynamically enhanced CT images were examined preoperatively in all patients (Revolution CT; General Electric Company, Boston, Massachusetts, USA, or Aquilion ONE/ViSION Edition; Toshiba Corp., Tokyo, Japan). After three-dimensional reconstruction of the liver, the volumes of the liver parenchyma, hepatic artery, portal vein, hepatic vein, and tumor(s) were separately calculated using volume-analyzing software for three-dimensional images (SYNAPSE VINCENT; Fujifilm Corp., Tokyo, Japan). Anatomical hepatectomy was defined as resection of the dominant liver parenchyma based on the structure of the portal vein, hepatic vein, and hepatic scissura. Liver specialists evaluated the area of liver resection manually using software and planned the optimal procedure for each patient. The liver resection rate (Res) was calculated by dividing the liver parenchyma volume to be removed, excluding the tumor volume, by the total volume of the liver parenchyma. The liver remnant rate (Rem) was calculated by dividing the liver parenchyma volume to be remnant by the total volume of the liver parenchyma. Res and Rem values ranged from 0.00 to 1.00.

Risk factors for severe PHLF

In general, liver-estimating parameters, which are obtained from blood examinations, are classified into two categories, namely, liver disability and liver function.[17] Liver disability is defined as the degree of liver damage and was evaluated using three parameters: total bilirubin level, alanine aminotransferase level, and indocyanine green (ICG) retention rate after 15 min (ICG R15); the higher the values of these parameters, the greater the risk of PHLF. Liver function is defined as functional ability or durability of the liver against stress and was evaluated using four parameters: albumin level, cholinesterase level, platelet (PLT) count, and prothrombin time index (PT); the lower the values of these parameters, the higher the risk of PHLF. A higher Res and lower Rem are also risk factors for PHLF. Therefore, in this study, volume-associated liver-estimating parameters were defined as the liver disability parameters multiplied by the Res and the liver function parameters multiplied by the Rem. The volume-associated liver-estimating parameters were analyzed as risk factors for severe PHLF in the training set.

Definition of PHLF

PHLF was defined by the International Study Group of Liver Surgery (ISGLS) as postoperative liver dysfunction in terms of excretion and detoxification, in particular, as an increased international normalized ratio (INR) and concomitant hyperbilirubinemia on or after postoperative day 5.[1] The severity of PHLF was graded as follows: grade A, requires no clinical management regardless of abnormal laboratory parameters;

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

grade B, manageable with non-invasive care (i.e., provision of fresh-frozen plasma, albumin, and daily diuretics) despite deviation from the standard clinical course; and grade C, requires invasive treatment at the intensive care unit. In this study, we focused only on severe PHLF (grades B and C) as the outcome because of its clinical importance.

Calculation of score values

The Child-Pugh score was calculated based on the total bilirubin level, albumin level, PT, degree of hepatic encephalopathy and ascites.[18] The albumin-bilirubin (ALBI) score was calculated as $0.66 \times \log_{10}$ (total bilirubin [μmol/L]) − $0.085 \times$ (albumin [g/L]).[19] The model for end-stage liver disease (MELD) score was calculated as follows: $9.6 \times \log_e$ (creatinine [mg/dL]) + $3.8 \times \log_e$ (bilirubin [mg/dL]) + $11.2 \times \log_e$ (INR) + 6.49.[20] In the MELD score, any values less than 1.0 were set to 1.0, and the maximum creatinine value was set to 4.0 mg/dL for patients on hemodialysis or with a creatinine level greater than 4.0 mg/dL. The preoperative risk score, reported by Dasari et al.,[21] was calculated based on the type of surgery, i.e., minor, major, or extra major hepatectomy; preoperative creatinine level; bilirubin level; and INR.

Statistical analysis

Continuous data were expressed as median (interquartile range). Cut-off values for continuous variables were derived using

Table 1 Patients characteristics

	All patients (n = 335)	Training set (n = 122)	Validation set (n = 213)
Age, years	71 (66–77)	71 (65–75)	72 (67–78)
Sex, male/female, *n*	268/67	92/30	176/37
Etiology, HBV/HCV/NBNC, *n*	62/144/129	25/58/39	37/86/90
Repeat hepatectomy, *n* (%)	71 (21.2%)	27 (22.1%)	44 (20.7%)
Liver-estimating parameter			
ICG R15, %	12.0 (8.0–17.8)	11.6 (7.4–16.3)	12.1 (8.0–18.4)
Total bilirubin, mg/dL	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.6–1.0)
Alanine aminotransferase, IU/L	26 (17–39)	26 (19–39)	26 (15–40)
Albumin, g/dL	4.1 (3.8–4.4)	4.1 (3.7–4.4)	4.1 (3.8–4.4)
Cholinesterase, IU/L	238 (198–291)	242 (197–299)	238 (199–288)
Platelet count, × 10^3/μL	156 (120–203)	150 (118–196)	160 (121–205)
Prothrombin time index, %	87 (79–95)	84 (79–92)	88 (78–96)
Child-Pugh grade, A/B, *n*	317/18	117/5	200/13
ALBI score	−2.70 (−2.99 to −2.45)	−2.74 (−2.99 to −2.43)	−2.70 (−2.97 to −2.48)
MELD score	8 (7–9)	8 (7–9)	8 (7–9)
Total liver volume, ml	1113 (957–1282)	1127 (999–1267)	1089 (934–1289)
Procedure of hepatectomy, *n* (%)			
Hemihepatectomy	67 (20.0%)	28 (23.0%)	39 (18.3%)
Sectionectomy	76 (22.7%)	22 (18.0%)	54 (25.4%)
Segmentectomy	132 (39.4%)	48 (39.3%)	84 (39.4%)
Atypical liver resection	60 (17.9%)	24 (19.7%)	36 (16.9%)
Liver resection rate, %	17.7 (10.9–27.1)	19.0 (12.7–28.6)	16.7 (10.0–25.8)
Operation time, min	336 (265–430)	370 (301–437)	316 (250–426)
Blood loss, ml	430 (215–834)	498 (254–862)	402 (200–731)
PHLF, *n* (%)			
Grade A	36 (10.7%)	17 (13.9%)	19 (8.9%)
Grade B	48 (14.3%)	19 (15.6%)	29 (13.6%)
Grade C	6 (1.8%)	1 (0.8%)	5 (2.3%)
Clavien-Dindo grade ≥ III, *n* (%)	50 (14.9%)	22 (18.0%)	28 (13.1%)
90-day mortality, *n* (%)	5 (1.4%)	1 (0.8%)	4 (1.9%)

Continuous data displayed as median (interquartile range). HBV, hepatitis B surface antigen; HCV, hepatitis C virus antibody; NBNC, non-B and non-C; ICG R15, indocyanine green retention rate after 15 min; ALBI, albumin-bilirubin; MELD, model for end-stage liver disease; PHLF, posthepatectomy liver failure.

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

receiver operating characteristic (ROC) curve analysis for severe PHLF. In the univariate analysis, categorical data were compared using the chi-square test and Fisher's exact test as appropriate. Multiple logistic regression analysis with a stepwise procedure using the Bayesian information criterion was performed to estimate the linear predictor for severe PHLF. Subsequently, we constructed a novel PHLF prediction score, named the VIPP score (for volume-associated ICG-PLT-PT score), to regulate all coefficients in the linear predictor for simplification. The accuracy of the scoring model (i.e., the linear predictor, VIPP score, ICG R15, Child-Pugh score, ALBI score, MELD score, and preoperative risk score) in predicting severe PHLF was evaluated using ROC analysis and calculation of the area under the ROC curve (AUROC). AUROCs between two models were compared using Delong's method. A *P*-value <0.050 was considered statistically significant. All statistical analyses were performed using JMP Genomics statistical software version 14 (SAS Institute Inc., Cary, NC, USA).

Results

Background characteristics

A total of 335 patients (122 in the training set and 213 in the validation set) were included in this study (Fig. S1, supporting information). The background characteristics of the patients are summarized in Table 1. The median age was 71 years and 268 patients (80.0%) were men. Among the patients, 71 (21.2%) had undergone repeat hepatectomy for recurrence. Hepatic sectionectomy was performed in 76 patients and segmentectomy in 132. Atypical liver resection, such as non-consecutive bi- or trisegmentectomy, accounted for 17.9% (n = 60) of patients (Table 1 and Table S1, supporting information). In the subgroup of 264 patients without past hepatectomy, hepatic sectionectomy and segmentectomy were performed in 57 and 98 patients, respectively. Although all types of sectionectomy (lateral, medial, anterior, and posterior) were equally considered in the conventional criteria,[22,23] the Res was different among them and dispersed within each identical section. Similar results were observed for hepatic segmentectomy (Fig. S2, supporting information).

PHLF occurred in 90 patients (26.9%) overall, and the proportions of PHLF grade A, grade B, and grade C were 10.7%, 14.3%, and 1.8%, respectively. The occurrence of severe PHLF was 16.4% (n = 20) in the training set and 16.0% (n = 34) in the validation set (Table 1). There was no significant difference in the occurrence of severe PHLF among the procedure types, namely, hemihepatectomy, sectionectomy, segmentectomy, and atypical resection (Table S2, supporting information).

Risk factors for severe PHLF in the training set

In the training set, the values for the three liver disability parameters (total bilirubin, aminotransferase, and ICG R15) were multiplied by the Res, and those for the four liver function parameters (albumin, cholinesterase, PLT count, and PT) were multiplied by the Rem. After adding four other factors (age, sex, viral hepatitis, and repeat hepatectomy), a total of 11 parameters were analyzed as risk factors for severe PHLF. Each continuous variable was converted into categorical data according to the cut-off value derived from the ROC curve (Table S3, supporting information).

In the univariate analysis, age ≥70 years, ICG R15 (%) × Res ≥3.0, PLT (× 10^3/μL) × Rem ≤130, and PT (%) × Rem ≤70 were significantly associated with the development of severe PHLF. After applying a stepwise procedure to

Table 2 Univariate and multivariate analyses for grade B and C posthepatectomy liver failure

			Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Age, years		≥70	3.12 (1.06–9.22)	0.040	–	–
Male sex			1.37 (0.42–4.47)	0.603	–	–
Viral hepatitis			3.09 (0.85–11.26)	0.087	–	–
Repeat hepatectomy			1.21 (0.40–3.70)	0.736	–	–
ICG R15, %	× Res	≥3.0	10.91 (3.57–33.32)	<0.001	8.68 (2.61–28.79)	<0.001
T-bil, mg/dL	× Res	≥0.2	2.40 (0.91–6.36)	0.078	–	–
ALT, IU/L	× Res	≥6.0	2.42 (0.91–6.45)	0.077	–	–
Alb, g/dL	× Rem	≤3.6	3.58 (0.78–16.39)	0.101	–	–
ChE, IU/L	× Rem	≤220	3.36 (0.92–12.24)	0.066	–	–
PLT, × 10^3/μL	× Rem	≤130	6.83 (1.50–30.98)	0.013	6.56 (1.28–33.54)	0.024
PT, %	× Rem	≤70	9.00 (1.99–40.80)	0.004	7.35 (1.47–36.85)	0.015

Res and Rem values range from 0.00 to 1.00. For the multivariate analysis, logistic regression using a stepwise procedure and the Bayesian criterion was performed.
OR, odds ratio; CI, confidence interval; ICG R15, indocyanine green retention rate after 15 min; T-bil, total bilirubin; ALT, alanine aminotransferase; Alb, albumin; ChE, cholinesterase; PLT, platelet; PT, prothrombin time index; Res, liver resection rate; Rem, liver remnant rate.

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

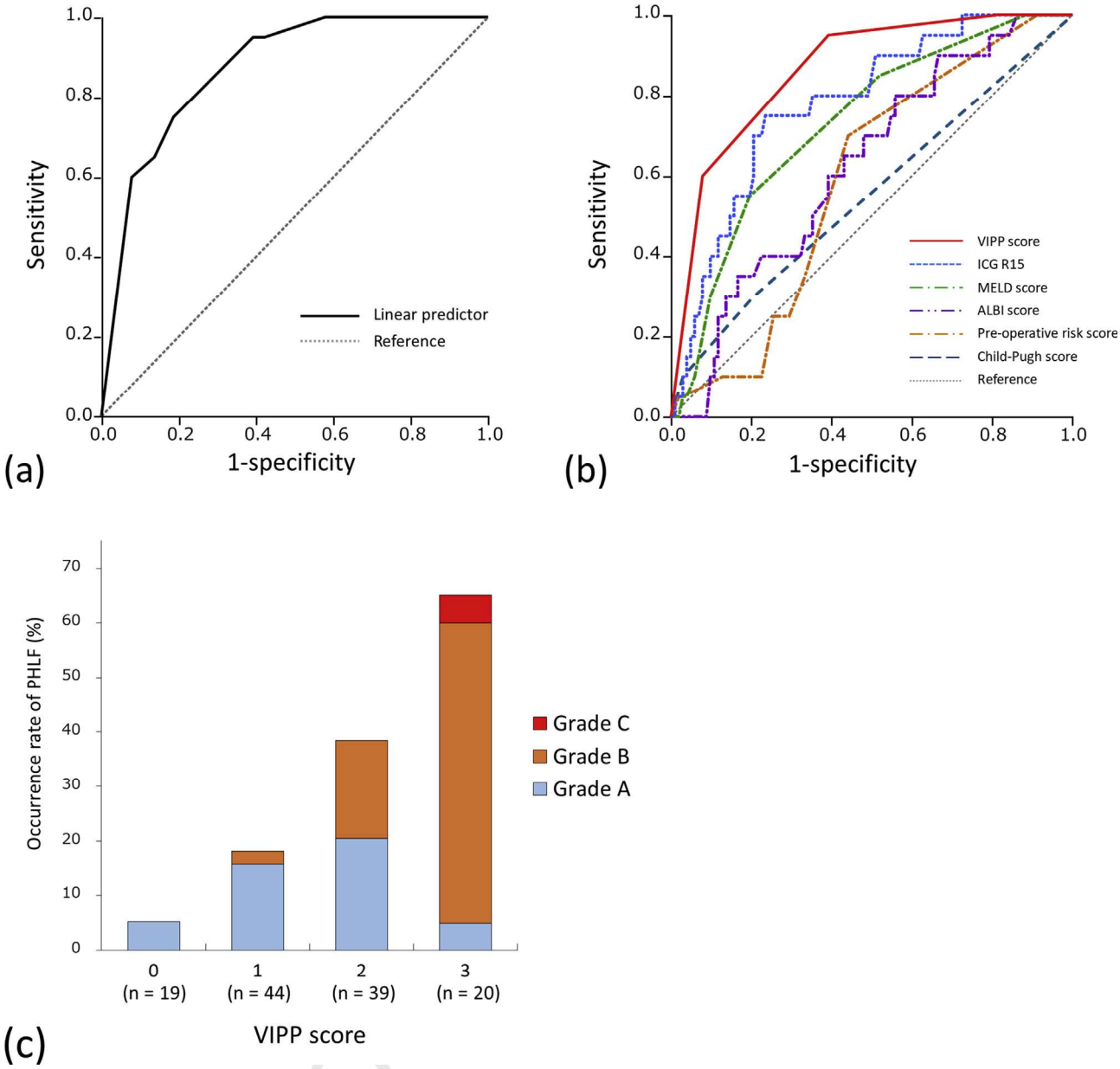

Figure 1 Prediction of posthepatectomy liver failure (PHLF) grade B or C in the training set. (a) The receiver operating characteristic curve of the linear predictor is shown; the area under the curve (AUROC) was 0.872. (b) The AUROC for the volume-associated indocyanine green retention rate at 15 min, platelet, and prothrombin time index (VIPP) score, indocyanine green retention rate at 15 min (ICG R15) alone, model for end-stage liver disease (MELD) score, albumin-bilirubin (ALBI) score, pre-operative risk score, and Child-Pugh score in predicting severe PHLF was 0.864, 0.780, 0.731, 0.626, 0.590, and 0.553, respectively. (c) The occurrence rate of PHLF grade B or C in patients with VIPP score of 0–3 was 0.0%, 2.3%, 18.0%, and 60.0%, respectively

all 11 parameters, three factors were selected: ICG R15 (%) × Res ≥3.0, PLT (× 10^3/μL) × Rem ≤130, and PT (%) × Rem ≤70. The multivariate analysis revealed that all three were independent risk factors for severe PHLF (Table 2). Although both PLT and PT were categorized as liver–functional parameters, there was no correlation between them (Fig. S3, supporting information).

Novel PHLF prediction score

A linear predictor equation was constructed from the logistic regression model using the aforementioned three categorical variables as follows: linear predictor = 1.08 × [ICG R15 (%) × Res ≥3.0: 1, <3.0: 0] + 0.94 × [PLT (× 10^3/μL) × Rem ≤130: 1, >130: 0] + 1.00 × [PT (%) × Rem ≤70: 1, >70: 0]. The AUROC of the linear predictor was 0.872 (95% confidence

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

interval [CI], 0.784–0.928; Fig. 1a). Subsequently, all coefficients in the linear predictor were unified to 1.00 to simplify the model since the coefficients of the three categorical variables were similar (1.08, 0.94, and 1.00, respectively). The novel PHLF prediction score, the VIPP score, was constructed as follows:

VIPP score = [ICG R15 (%) × Res ≥3.0: 1, <3.0: 0] + [PLT (× 10^3/μL) × Rem ≤130: 1, >130: 0] + [PT (%) × Rem ≤70: 1, >70: 0]

The VIPP score could be calculated as an integral number between 0 and 3 for each patient. The AUROC of the VIPP score was 0.864 (95% CI, 0.773–0.922), which was comparable to that of the linear predictor (ΔAUROC = 0.008, $P = 0.515$; Fig. 1a/b). Moreover, the AUROC of the VIPP score was greater than that of other scoring models: ICG R15 alone (0.780, 95% CI 0.659–0.867, $P = 0.213$), MELD score (0.731, 95% CI 0.608–0.827, $P = 0.066$), ALBI score (0.626, 95% CI 0.497–0.740, $P < 0.001$), the pre-operative risk score (0.590, 95% CI 0.475–0.696, $P < 0.001$), and the Child-Pugh score (0.553, 95% CI 0.438–0.662, $P < 0.001$) (Fig. 1b). The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) with their 95% CI of the VIPP score for predicting severe PHLF were 0.60 (0.39–0.78), 0.92 (0.85–0.96), 0.60 (0.39–0.78), and 0.92 (0.85–0.96) (cut-off, 3), respectively (Table S4, supporting information). The values of other scoring models, ICG R15 (cut-off, 15.5), Child-Pugh score (cut-off, 6), ALBI score (cut-off, −2.83), MELD score (cut-off, 9), and the pre-operative risk score (cut-off, 6) are summarized in Table S5, supporting information.

The relationship between the VIPP score and PHLF in the training set is shown in Fig. 1c and Fig. S4a, supporting information. The occurrence rates of PHLF in patients with a VIPP score of 0, 1, 2, and 3 were 5.3% (n = 1), 18.2% (n = 8), 38.5% (n = 15), and 65.0% (n = 13), respectively. With regard to the severity of the cases with PHLF, 1 of 9 patients (11.1%) with a VIPP score of 0–1 and 7 of 15 patients (46.7%) with a VIPP score of 2 were classified as grade B. Furthermore, the majority of the patients (92.3%; 11/13 grade B and 1/13 grade C) with a VIPP score of 3 were classified as having severe PHLF. The odds ratios (ORs) for predicting severe PHLF between VIPP scores 1 and 2 and between scores 2 and 3 were 9.41 (95% CI, 1.10–80.32, $P = 0.041$) and 6.86 (95% CI, 2.04–23.04, $P = 0.002$), respectively. That is, as the VIPP score increased, the incidence of severe PHLF markedly increased, especially between scores 2 and 3.

Assessment of the VIPP score in the validation set

The demographics of the 213 patients in the validation set are also presented in Table 1. After the procedures, 34 patients experienced severe PHLF (29, grade B; 5, grade C). The occurrence rate of severe PHLF in patients with VIPP scores of 0, 1, 2, and 3 was 1.6% (n = 1), 10.3% (n = 6), 18.9% (n = 10), and 51.6% (n = 16), respectively. The relationship between VIPP score and PHLF in the validation set was similar to that in the training set. All validation patients with PHLF and a VIPP score

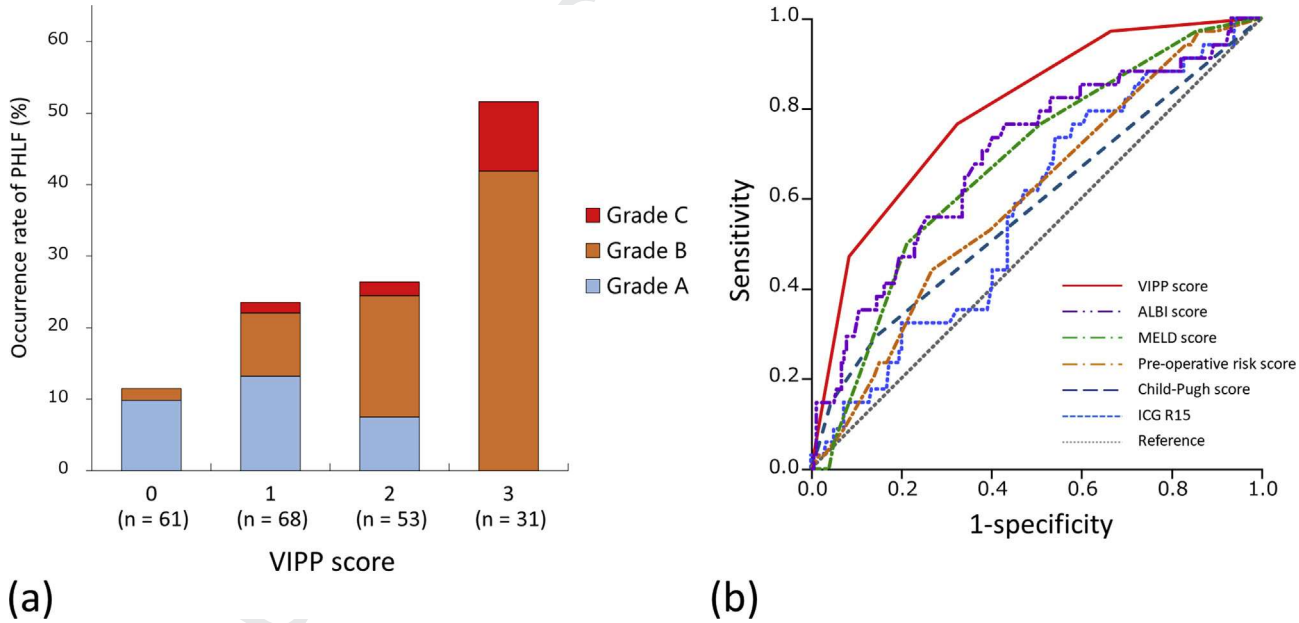

Figure 2 Relationship between the volume-associated indocyanine green retention rate at 15 min, platelet, and prothrombin time index (VIPP) score and the development of posthepatectomy liver failure (PHLF) in the validation set. (a) The occurrence rate of PHLF grade B or C in patients with VIPP score of 0–3 was 1.6%, 10.3%, 18.9%, and 51.6%, respectively. (b) The area under the receiver operating characteristic curve for the VIPP score, albumin-bilirubin (ALBI) score, model for end-stage liver disease (MELD) score, pre-operative risk score, Child-Pugh score, and indocyanine green retention rate at 15 min (ICG R15) was 0.794, 0.693, 0.676, 0.600, 0.578, and 0.574 respectively

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

of 3 had severe PHLF (13, grade B; 3, grade C) (Fig. 2a and Fig. S4b, supporting information). The difference in severe PHLF occurrence between groups with VIPP scores 2 and 3 was statistically significant (OR, 4.59; 95% CI, 1.71–12.28; $P = 0.002$), while that between groups with VIPP scores 1 and 2 was comparable (OR, 2.03; 95% CI, 0.72–5.74; $P = 0.184$).

The AUROC of the VIPP score for predicting severe PHLF was 0.794 (95% CI, 0.707–0.860), which was superior to that of the other scoring models: ALBI score, 0.693 (95% CI, 0.583–0.784, $P = 0.052$); MELD score, 0.676 (95% CI, 0.578–0.761, $P = 0.015$); the pre-operative risk score, 0.600 (95% CI, 0.501–0.691, $P = 0.001$); Child-Pugh score, 0.578 (95% CI, 0.493–0.659, $P < 0.001$); and ICG R15 alone, 0.574 (95% CI, 0.472–0.670, $P < 0.001$) (Fig. 2b). The VIPP score in the validation set had high specificity, similar to that in the training set, in predicting severe PHLF [cut-off, 3; sensitivity, 0.47 (0.31–0.63); specificity, 0.92 (0.87–0.95); PPV, 0.52 (0.35–0.68); NPV, 0.90 (0.85–0.94)] (Table S4, supporting information). The values of ICG R15 (cut-off, 11.0), Child-Pugh score (cut-off, 6), ALBI score (cut-off, −2.69), MELD score (cut-off, 9), and the pre-operative risk score (cut-off, 6.5) are summarized in Table S5, supporting information.

Discussion

This retrospective study conceptualized a novel PHLF prediction model incorporating three independent risk factors, which were all volume-associated liver-estimating parameters modified for simplicity. Furthermore, we confirmed that this simple and quantitative model can predict the development of severe PHLF.

In the present study, volume-associated liver-estimating parameters were adopted as risk factors for PHLF. This method appears original but is similar to the concept of "future liver remnant plasma clearance rate of ICG (KICG)," which is calculated as KICG × future Rem.[24–26] Because of the close relationship between preoperative liver condition and remnant or resected liver degree, this method is reasonable. Multivariate analysis revealed three independent risk factors for PHLF: volume-associated ICG R15, PLT count, and PT. Although each was assessed after multiplying by liver volume, all are universally considered important indices when planning hepatectomy. ICG R15 is one of the most useful indicators of preoperative liver condition, and is included in the Makuuchi criteria, which are widely used in Japan for hepatectomy planning.[22,23] Moreover, some authors posit a relationship between ICG R15 and PHLF and incorporate this into their criteria for hepatectomy.[27,28] PLT increases in response to thrombopoietin, which is produced predominantly in the liver, and the consequent proliferation of bone marrow megakaryocytes.[29–31] Animal studies suggest that PLT count is related to liver regeneration through the Ark and signal transducer and activator of transcription 3 pathways[32,33] and PLT-derived serotonin.[34,35] In clinical studies, PLT count better predicted PHLF than did ICG R15[36] and, when low, was a risk factor for morbidity and mortality after hepatectomy.[37] PT rapidly reflects the protein productivity of the liver and is included in the well-known Child-Pugh liver-estimating system. It is also included in the definition of PHLF by the ISGLS in the form of the PT-INR.[1] Based on the above, it appears that pre-operative ICG R15, PLT count, and PT are strongly associated with PHLF. Furthermore, the 3.0, 130, and 70 cut-off values for ICG R15 (%) × Res, PLT count (× 10^3/μl) × Rem and PT (%) × Rem are clinically acceptable.

The most important advantage of the VIPP score is its simplicity. We used categorical variables for calculating the PHLF

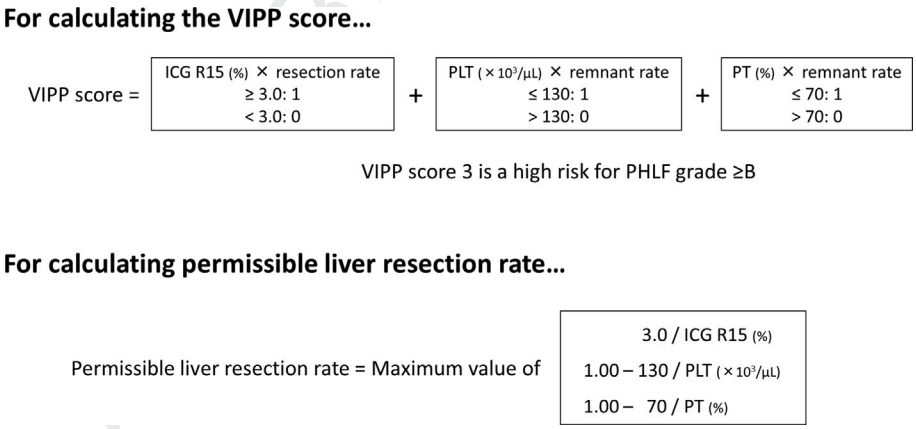

Figure 3 The VIPP score-based model for determining the procedure for anatomical hepatectomy. For example, when the values for the indocyanine green retention rate after 15 min (ICG R15), platelet (PLT) count, and prothrombin time index (PT) are 10.0%, 160 × 10^3/μL, and 90%, respectively, the permissible liver resection rate is calculated as 30%. If the planned resection rate is 35%, the risk of severe PHLF is high (the VIPP score is 3). On the other hand, a resection rate of 25% is considered to be safe (the VIPP score is 2). The calculations are available at https://home.hiroshima-u.ac.jp/home2ge/digestive/lgp/vipp-score.php. VIPP score, volume-associated indocyanine green retention rate at 15 min, platelet, and prothrombin time index score

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

prediction score. Consequently, a permissible resection rate can be obtained easily and quantitatively by calculating the point at which the VIPP score changes from 2 to 3 (Fig. 3). Moreover, the optimal procedure for hepatectomy can be determined by comparing the results of the image simulation systems. If continuous variables are used, the PHLF prediction formula can be constructed as a linear expression; however, deducing the permissible resection rate may be more complicated. Converting each indicator into an integral number also contributed to the simplification of the model, with an insignificant effect on the statistical results (Fig. 1a/b).

Discontinuous plural anatomical liver resection (e.g., left lateral sectionectomy plus segment-5 hepatectomy) or other atypical hepatectomy procedure is sometimes selected owing to advances in imaging technology and progress in surgical techniques. In such cases, the VIPP score can provide quantitative indications for safe hepatectomy, whereas conventional criteria, which classify the hepatectomy procedure using a single anatomical index, cannot. The same applies to the cases of repeat hepatectomy. Advances in image simulation technology using three-dimensional reconstruction models allow precise quantitative evaluation of the liver and have made the present study possible.

This study was based on the hypothesis that liver function is homogenous; hence, only laboratory and CT volumetric data were evaluated. Recently, several studies have reported the effectiveness of hepatic scintigraphy using single photon emission CT for estimating heterogeneous remnant-liver function.[38–41] Although the theory of liver functional heterogeneity is undeniable, its tendency and degree remain unclear. Liver scintigraphy has institutional restrictions owing to the use of nuclides and therefore is not widely performed. Furthermore, our approach using only preoperative blood samples and CT volumetric assessment has a cost advantage compared to liver scintigraphy; therefore, this model will be useful for many hepatopancreatic and biliary surgeons.

There are inherent limitations to this study. Given the characteristics of retrospective studies, certain biases may have been introduced during the selection of patients and procedures. This study did not include patients who had undergone limited resection or enucleation; in other words, most study patients were determined to be able to tolerate each anatomical hepatectomy procedure. Therefore, our VIPP score-based model cannot necessarily determine the contraindications for hepatectomy. Lastly, the VIPP score may not be suitable for patients receiving oral anticoagulants such as warfarin or with severe cardiac disease, which increases the ICG R15.

In conclusion, this study presented novel criteria (collectively termed the VIPP score) for anatomical hepatectomy in patients with HCC. The VIPP score had sufficient power to predict the development of severe PHLF in a patient cohort and was validated in a separate cohort. Although the VIPP score may not determine the maximum percentage of liver resection representing absolute contraindication, the quantitative percentage of permissible liver resection calculated using this simple and evidence-based scoring model can be useful for planning procedures.

Acknowledgments

The authors would like to thank HiSCO (Hiroshima, Japan) for its cooperation and support. We also thank Editage [http://www.editage.com] for editing and reviewing our manuscript for English language.

Financial support

This research was supported by the Japan Agency for Medical Research and Development (AMED, grant number JP19fk0210051) and the Japanese Society for the Promotion of Science (JSPS KAKENHI, grant number JP18K08706).

Conflicts of interest

None.

References

1. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R *et al.* (2011) Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). *Surgery* 149:713–724. https://doi.org/10.1016/j.surg.2010.10.001.
2. Schreckenbach T, Liese J, Bechstein WO, Moench C. (2012) Posthepatectomy liver failure. *Dig Surg* 29:79–85. https://doi.org/10.1159/000335741.
3. Lafaro K, Buettner S, Maqsood H, Wagner D, Bagante F, Spolverato G *et al.* (2015) Defining post hepatectomy liver insufficiency: where do we stand? *J Gastrointest Surg* 19:2079–2092. https://doi.org/10.1007/s11605-015-2872-6.
4. Rahnemai-Azar AA, Cloyd JM, Weber SM, Dillhoff M, Schmidt C, Winslow ER *et al.* (2018) Update on liver failure following hepatic resection: strategies for prediction and avoidance of post-operative liver insufficiency. *J Clin Transl Hepatol* 6:97–104. https://doi.org/10.14218/JCTH.2017.00060.
5. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D *et al.* (2005) The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* 242:824–828.
6. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S *et al.* (2007) Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. *J Am Coll Surg* 204:854–862. https://doi.org/10.1016/j.jamcollsurg.2006.12.032.
7. Bismuth H, Houssin D, Ornowski J, Meriggi F. (1986) Liver resections in cirrhotic patients: a Western experience. *World J Surg* 10:311–317.
8. Poon RT, Fan ST. (2004) Hepatectomy for hepatocellular carcinoma: patient selection and postoperative outcome. *Liver Transplant* 10:S39–S45. https://doi.org/10.1002/lt.20040.
9. de Meijer VE, Kalish BT, Puder M, Ijzermans JN. (2010) Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. *Br J Surg* 97:1331–1339. https://doi.org/10.1002/bjs.7194.
10. Reddy SK, Marsh JW, Varley PR, Mock BK, Chopra KB, Geller DA *et al.* (2012) Underlying steatohepatitis, but not simple hepatic steatosis, increases morbidity after liver resection: a case-control study. *Hepatology* 56:2221–2230. https://doi.org/10.1002/hep.25935.
11. Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S *et al.* (2002) Improvement in perioperative outcome after hepatic

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg* 236:397–406. https://doi.org/10.1097/01.SLA.0000029003.66466.B3.

12. Kooby DA, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, Dematteo RP *et al*. (2003) Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg* 237:860–869. https://doi.org/10.1097/01.SLA.0000072371.95588.DA.
13. Shirabe K, Shimada M, Gion T, Hasegawa H, Takenaka K, Utsunomiya T *et al*. (1999) Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *J Am Coll Surg* 188:304–309.
14. Abdalla EK, Adam R, Bilchik AJ, Jaeck D, Vauthey JN, Mahvi D. (2006) Improving resectability of hepatic colorectal metastases: expert consensus statement. *Ann Surg Oncol* 13:1271–1280. https://doi.org/10.1245/s10434-006-9045-5.
15. Vauthey JN, Chaoui A, Do KA, Bilimoria MM, Fenstermacher MJ, Charnsangavej C *et al*. (2000) Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery* 127:512–519. https://doi.org/10.1067/msy.2000.105294.
16. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ *et al*. (2009) Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. *Ann Surg* 250:540–548. https://doi.org/10.1097/SLA.0b013e3181b674df.
17. Field KM, Dow C, Michael M. (2008) Part I: liver function in oncology: biochemistry and beyond. *Lancet Oncol* 9:1092–1101. https://doi.org/10.1016/S1470-2045(08)70279-1.
18. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. (1973) Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 60:646–649. https://doi.org/10.1002/bjs.1800600817.
19. Johnson PJ, Berhane S, Kagebayashi C, Satomura S, Teng M, Reeves HL *et al*. (2015) Assessment of liver function in patients with hepatocellular carcinoma: a new evidence-based approach-the ALBI grade. *J Clin Oncol* 33:550–558. https://doi.org/10.1200/JCO.2014.57.9151.
20. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL *et al*. (2001) A model to predict survival in patients with end-stage liver disease. *Hepatology* 33:464–470. https://doi.org/10.1053/jhep.2001.22172.
21. Dasari BVM, Hodson J, Roberts KJ, Sutcliffe RP, Marudanayagam R, Mirza DF *et al*. (2019) Developing and validating a pre-operative risk score to predict post-hepatectomy liver failure. *HPB* 21:539–546. https://doi.org/10.1016/j.hpb.2018.09.011.
22. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S *et al*. (1993) Surgery for small liver cancers. *Semin Surg Oncol* 9:298–304.
23. Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K *et al*. (2003) One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg* 138:1198–1206. https://doi.org/10.1001/archsurg.138.11.1198.
24. Nagino M, Kamiya J, Nishio H, Ebata T, Arai T, Nimura Y. (2006) Two hundred forty consecutive portal vein embolizations before extended hepatectomy for biliary cancer: surgical outcome and long-term follow-up. *Ann Surg* 243:364–372. https://doi.org/10.1097/01.sla.0000201482.11876.14.
25. Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. (2010) Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. *Br J Surg* 97:1260–1268. https://doi.org/10.1002/bjs.7084.
26. Hwang S, Ha TY, Song GW, Jung DH, Ahn CS, Moon DB *et al*. (2015) Quantified risk assessment for major hepatectomy via the indocyanine green clearance rate and liver volumetry combined with standard liver volume. *J Gastrointest Surg* 19:1305–1314. https://doi.org/10.1007/s11605-015-2846-8.
27. Yamanaka N, Okamoto E, Oriyama T, Fujimoto J, Furukawa K, Kawamura E *et al*. (1994) A prediction scoring system to select the surgical treatment of liver cancer. Further refinement based on 10 years of use. *Ann Surg* 219:342–346.
28. Ariizumi S, Yamamoto M, Takasaki K. (2009) Right hepatectomy for hepatocellular carcinoma in patients with an indocyanine green retention rate at 15 minutes of 10% or higher. *Dig Surg* 26:135–142. https://doi.org/10.1159/000206151.
29. Sungaran R, Markovic B, Chong BH. (1997) Localization and regulation of thrombopoietin mRNa expression in human kidney, liver, bone marrow, and spleen using in situ hybridization. *Blood* 89:101–107.
30. Nagata Y, Nagahisa H, Aida Y, Okutomi K, Nagasawa T, Todokoro K. (1995) Thrombopoietin induces megakaryocyte differentiation in hematopoietic progenitor FDC-P2 cells. *J Biol Chem* 270:19673–19675.
31. de Sauvage FJ, Hass PE, Spencer SD, Malloy BE, Gurney AL, Spencer SA *et al*. (1994) Stimulation of megakaryocytopoiesis and thrombopoiesis by the c-Mpl ligand. *Nature* 369:533–538. https://doi.org/10.1038/369533a0.
32. Myronovych A, Murata S, Chiba M, Matsuo R, Ikeda O, Watanabe M *et al*. (2008) Role of platelets on liver regeneration after 90% hepatectomy in mice. *J Hepatol* 49:363–372. https://doi.org/10.1016/j.jhep.2008.04.019.
33. Matsuo R, Nakano Y, Ohkohchi N. (2011) Platelet administration via the portal vein promotes liver regeneration in rats after 70% hepatectomy. *Ann Surg* 253:759–763. https://doi.org/10.1097/SLA.0b013e318211caf8.
34. Lesurtel M, Graf R, Aleil B, Walther DJ, Tian Y, Jochum W *et al*. (2006) Platelet-derived serotonin mediates liver regeneration. *Science* 312:104–107. https://doi.org/10.1126/science.1123842.
35. Lesurtel M, Clavien PA. (2014) Platelet-derived serotonin: translational implications for liver regeneration. *Hepatology* 60:30–33. https://doi.org/10.1002/hep.27067.
36. Tomimaru Y, Eguchi H, Gotoh K, Kawamoto K, Wada H, Asaoka T *et al*. (2016) Platelet count is more useful for predicting posthepatectomy liver failure at surgery for hepatocellular carcinoma than indocyanine green clearance test. *J Surg Oncol* 113:565–569. https://doi.org/10.1002/jso.24166.
37. Maithel SK, Kneuertz PJ, Kooby DA, Scoggins CR, Weber SM, Martin RC, 2nd *et al*. (2011) Importance of low preoperative platelet count in selecting patients for resection of hepatocellular carcinoma: a multi-institutional analysis. *J Am Coll Surg* 212:638–648. https://doi.org/10.1016/j.jamcollsurg.2011.01.004.
38. Hayashi H, Beppu T, Okabe H, Kuroki H, Nakagawa S, Imai K *et al*. (2015) Functional assessment versus conventional volumetric assessment in the prediction of operative outcomes after major hepatectomy. *Surgery* 157:20–26. https://doi.org/10.1016/j.surg.2014.06.013.
39. Chapelle T, Op De Beeck B, Huyghe I, Francque S, Driessen A, Roeyen G *et al*. (2016) Future remnant liver function estimated by

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008

combining liver volumetry on magnetic resonance imaging with total liver function on (99m)Tc-mebrofenin hepatobiliary scintigraphy: can this tool predict post-hepatectomy liver failure? *HPB* 18:494–503. https://doi.org/10.1016/j.hpb.2015.08.002.

40. Sumiyoshi T, Shima Y, Okabayashi T, Kozuki A, Hata Y, Noda Y *et al*. (2016) Liver function assessment using 99mTc-GSA single-photon emission computed tomography (SPECT)/CT fusion imaging in hilar bile duct cancer: a retrospective study. *Surgery* 160:118–126. https://doi.org/10.1016/j.surg.2016.02.009.

41. Chapelle T, Op de Beeck B, Roeyen G, Bracke B, Hartman V, De Greef K *et al*. (2017) Measuring future liver remnant function prior to hepatectomy may guide the indication for portal vein occlusion and avoid posthepatectomy liver failure: a prospective interventional study. *HPB* 19:108–117. https://doi.org/10.1016/j.hpb.2016.11.005.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.05.008.

Please cite this article as: Honmyo N et al., A novel model for predicting posthepatectomy liver failure based on liver function and degree of liver resection in patients with hepatocellular carcinoma, HPB, https://doi.org/10.1016/j.hpb.2020.05.008