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Relation	



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

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

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 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

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4 required.

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

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25 This retrospective study included patients who underwent anatomical hepatectomy
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28 for HCC at eight institutions affiliated with the Hiroshima Surgical study group of Clinical
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31 Oncology (HiSCO), including Hiroshima University Hospital, between December 2013 and
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34 December 2017. Since the main objective of this study was to clarify the relationship
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37 between liver resection/remnant degree, as expressed using quantitative indicators, and the
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40 development of PHLF, patients who had undergone peripheral wedge resection and
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43 concurrent extrahepatic bile duct resection with hepatectomy, a likely risk for postoperative
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46 complications such as bile leakage, were excluded. Patients who had received preoperative
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49 portal vein embolization were also excluded owing to functional heterogeneity of the
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52 atrophied liver.
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55 This study involved two key stages: first, a cohort was selected and used as a
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58 training set for the construction of the PHLF prediction model and, second, the validity of the
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4 model was tested using an additional cohort. The training set included consecutive patients
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7 who underwent hepatectomy at Hiroshima University Hospital between December 2013 and
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10 December 2015. Patients' clinical, laboratory, liver volumetric, surgical, pathological, and
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13 postoperative data were collected from the HCC database of the Department of
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16 Gastroenterological and Transplant Surgery at Hiroshima University Hospital. The validation
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19 set included patients who underwent hepatectomy at multiple institutions from January 2016
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22 to December 2017. Patients' demographic data were collected from the integrated HCC
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25 database of the HiSCO.
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28 This study conforms to the provisions of the Declaration of Helsinki and was
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31 approved by the ethics committee of our institution (E-1253). The collection and registration
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34 of data in the multi-institutional database of the HiSCO were executed with the approval of
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37 the ethics committees of all participating institutions. Informed consent was obtained from all
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40 patients.
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46 *Computed tomography (CT) volumetry*

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

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

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28 PHLF was defined by the International Study Group of Liver Surgery (ISGLS) as
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31 postoperative liver dysfunction in terms of excretion and detoxification, in particular, as an
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34 increased international normalized ratio (INR) and concomitant hyperbilirubinemia on or
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37 after postoperative day 5.¹ The severity of PHLF was graded as follows: grade A, requires no
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40 clinical management regardless of abnormal laboratory parameters; grade B, manageable
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43 with non-invasive care (i.e., provision of fresh-frozen plasma, albumin, and daily diuretics)
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46 despite deviation from the standard clinical course; and grade C, requires invasive treatment
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49 at the intensive care unit. In this study, we focused only on severe PHLF (grades B and C) as
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52 the outcome because of its clinical importance.
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58 *Calculation of score values*

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4 The Child-Pugh score was calculated based on the total bilirubin level, albumin
5 level, PT, degree of hepatic encephalopathy and ascites.¹⁸ The albumin-bilirubin (ALBI)
6 score was calculated as $0.66 \times \log_{10}(\text{total bilirubin } [\mu\text{mol/L}]) - 0.085 \times (\text{albumin } [\text{g/L}])$.¹⁹
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12 The model for end-stage liver disease (MELD) score was calculated as follows: $9.6 \times \log_e$
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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.

Statistical analysis

Continuous data were expressed as median (interquartile range). Cut-off values for
continuous variables were derived using 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, Child-Pugh score, ALBI score, and MELD

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. 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 tri- segmentectomy, 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,^{21, 22} the Res was different among them and dispersed within each identical section. Similar results were observed for

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4 hepatic segmentectomy (Fig. S1, supporting information).
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7 PHLF occurred in 90 patients (26.9%) overall, and the proportions of PHLF grade A,
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10 grade B, and grade C were 10.7%, 14.3%, and 1.8%, respectively. The occurrence of severe
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13 PHLF was 16.4% (n = 20) in the training set and 16.0% (n = 34) in the validation set (Table
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16 1). There was no significant difference in the occurrence of severe PHLF among the
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19 procedure types, namely, hemihepatectomy, sectionectomy, segmentectomy, and atypical
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22 resection (Table S2, supporting information).
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28 *Risk factors for severe PHLF in the training set*

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31 In the training set, the values for the three liver disability parameters (total bilirubin,
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34 aminotransferase, and ICG R15) were multiplied by the Res, and those for the four liver
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37 function parameters (albumin, cholinesterase, PLT count, and PT) were multiplied by the
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40 Rem. After adding four other factors (age, sex, viral hepatitis, and repeat hepatectomy), a
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43 total of 11 parameters were analyzed as risk factors for severe PHLF. Each continuous
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46 variable was converted into categorical data according to the cut-off value derived from the
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49 ROC curve (Table S3, supporting information).
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52 In the univariate analysis, age ≥ 70 years, ICG R15 (%) \times Res ≥ 3.0 , PLT ($\times 10^3/\mu\text{L}$) \times
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55 Rem ≤ 130 , and PT (%) \times Rem ≤ 70 were significantly associated with the development of
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58 severe PHLF. After applying a stepwise procedure to all 11 parameters, three factors were
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selected: ICG R15 (%) \times Res \geq 3.0, PLT ($\times 10^3/\mu\text{L}$) \times Rem \leq 130, and PT (%) \times Rem \leq 70. The multivariate analysis revealed that all three were independent risk factors for severe PHLF (Table 2).

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 = $1.08 \times [\text{ICG R15} (\%) \times \text{Res} \geq 3.0: 1, <3.0: 0] + 0.94 \times [\text{PLT} (\times 10^3/\mu\text{L}) \times \text{Rem} \leq 130: 1, >130: 0] + 1.00 \times [\text{PT} (\%) \times \text{Rem} \leq 70: 1, >70: 0]$. The AUROC of the linear predictor was 0.872 (95% confidence 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:

$$\begin{aligned} \text{VIPP score} = & [\text{ICG R15} (\%) \times \text{Res} \geq 3.0: 1, <3.0: 0] \\ & + [\text{PLT} (\times 10^3/\mu\text{L}) \times \text{Rem} \leq 130: 1, >130: 0] \\ & + [\text{PT} (\%) \times \text{Rem} \leq 70: 1, >70: 0] \end{aligned}$$

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 ($\Delta\text{AUROC} = 0.008$, $P = 0.515$; Fig. 1a/b).

Moreover, the AUROC of the VIPP score was greater than that of the Child-Pugh score (0.553, 95% CI 0.438–0.662, $P < 0.001$), ALBI score (0.626, 95% CI 0.497–0.740, $P < 0.001$), and MELD score (0.731, 95% CI 0.608–0.827, $P = 0.066$) (Fig. 1b). The sensitivity and specificity of the VIPP score, Child-Pugh score, ALBI score, and MELD score were 0.60 and 0.92 (cut-off, 3), 0.30 and 0.79 (cut-off, 6), 0.80 and 0.44 (cut-off, -2.83), and 0.55 and 0.80 (cut-off, 9), respectively.

The relationship between the VIPP score and PHLF in the training set is shown in Fig. 1c. 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 of 3 had severe PHLF (13, grade B; 3, grade C) (Fig. 2a). 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: Child-Pugh score, 0.578 (95% CI, 0.493–0.659, $P < 0.001$); ALBI score, 0.693 (95% CI, 0.583–0.784, $P = 0.052$); and MELD score, 0.676 (95% CI, 0.578–0.761, $P = 0.015$) (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; specificity, 0.92).

Discussion

This retrospective study conceptualized a novel PHLF prediction model

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4 incorporating three independent risk factors, which were all volume-associated liver-
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7 estimating parameters modified for simplicity. Furthermore, we confirmed that this simple
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10 and quantitative model can predict the development of severe PHLF.
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13 In the present study, volume-associated liver-estimating parameters were adopted as
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16 risk factors for PHLF. This method appears original but is similar to the concept of “future
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19 liver remnant plasma clearance rate of ICG (KICG),” which is calculated as $KICG \times \text{future}$
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22 Rem.^{23-25} Because of the close relationship between preoperative liver condition and remnant
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25 or resected liver degree, this method is reasonable. Multivariate analysis revealed three
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28 independent risk factors for PHLF: volume-associated ICG R15, PLT count, and PT.
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31 Although each was assessed after multiplying by liver volume, all are universally considered
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34 important indices when planning hepatectomy. ICG R15 is one of the most useful indicators
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37 of preoperative liver condition, and is included in the Makuuchi criteria, which are widely
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40 used in Japan for hepatectomy planning.^{21, 22} Moreover, some authors posit a relationship
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43 between ICG R15 and PHLF and incorporate this into their criteria for hepatectomy.^{26, 27} PLT
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46 increases in response to thrombopoietin, which is produced predominantly in the liver, and
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49 the consequent proliferation of bone marrow megakaryocytes.²⁸⁻³⁰ Animal studies suggest
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52 that PLT count is related to liver regeneration through the Ark and signal transducer and
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55 activator of transcription 3 pathways^{31, 32} and PLT-derived serotonin.^{33, 34} In clinical studies,
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58 PLT count better predicted PHLF than did ICG R15³⁵ and, when low, was a risk factor for
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4 morbidity and mortality after hepatectomy.³⁶ PT rapidly reflects the protein productivity of
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7 the liver and is included in the well-known Child-Pugh liver-estimating system. It is also
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10 included in the definition of PHLF by the ISGLS in the form of the PT-INR.¹ Based on the
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13 above, it appears that preoperative ICG R15, PLT count, and PT are strongly associated with
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16 PHLF. Furthermore, the 3.0, 130, and 70 cut-off values for ICG R15 (%) × Res, PLT count
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19 ($\times 10^3/\mu\text{l}$) × Rem and PT (%) × Rem are clinically acceptable.
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22 The most important advantage of the VIPP score is its simplicity. We used
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25 categorical variables for calculating the PHLF prediction score. Consequently, a permissible
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28 resection rate can be obtained easily and quantitatively by calculating the point at which the
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31 VIPP score changes from 2 to 3 (Fig. 3). Moreover, the optimal procedure for hepatectomy
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34 can be determined by comparing the results of the image simulation systems. If continuous
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37 variables are used, the PHLF prediction formula can be constructed as a linear expression;
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40 however, deducing the permissible resection rate may be more complicated. Converting each
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43 indicator into an integral number also contributed to the simplification of the model, with an
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46 insignificant effect on the statistical results (Fig. 1a/b).
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49 Discontinuous plural anatomical liver resection (e.g., left lateral sectionectomy plus
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52 segment-5 hepatectomy) or other atypical hepatectomy procedure is sometimes selected
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55 owing to advances in imaging technology and progress in surgical techniques. In such cases,
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58 the VIPP score can provide quantitative indications for safe hepatectomy, whereas
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4 conventional criteria, which classify the hepatectomy procedure using a single anatomical
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7 index, cannot. The same applies to the cases of repeat hepatectomy. Advances in image
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10 simulation technology using three-dimensional reconstruction models allow precise
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13 quantitative evaluation of the liver and have made the present study possible.
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16 This study was based on the hypothesis that liver function is homogenous; hence,
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18 only laboratory and CT volumetric data were evaluated. Recently, several studies have
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20 reported the effectiveness of hepatic scintigraphy using single photon emission CT for
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22 estimating heterogeneous remnant-liver function.³⁷⁻⁴⁰ Although the theory of liver functional
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24 heterogeneity is undeniable, its tendency and degree remain unclear. Liver scintigraphy has
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26 institutional restrictions owing to the use of nuclides and therefore is not widely performed.
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34 There are inherent limitations to this study. Given the characteristics of retrospective
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36 studies, certain biases may have been introduced during the selection of patients and
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38 procedures. This study did not include patients who had undergone limited resection or
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40 enucleation; in other words, most study patients were determined to be able to tolerate each
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42 anatomical hepatectomy procedure. Therefore, our VIPP score-based model cannot
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44 necessarily determine the contraindications for hepatectomy. Lastly, the VIPP score may not
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46 be suitable for patients receiving oral anticoagulants such as warfarin or with severe cardiac
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48 disease, which increases the ICG R15.
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58 In conclusion, this study presented novel criteria (collectively termed the VIPP
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4 score) for anatomical hepatectomy in patients with HCC. The VIPP score had sufficient
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7 power to predict the development of severe PHLF in a patient cohort and was validated in a
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10 separate cohort. Although the VIPP score may not determine the maximum percentage of
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13 liver resection representing absolute contraindication, the quantitative percentage of
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16 permissible liver resection calculated using this simple and evidence-based scoring model can
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19 be useful for planning procedures.
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Figure Legends

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, model for end-stage liver disease (MELD) score, albumin-bilirubin (ALBI) score, and Child-Pugh score in predicting severe PHLF was 0.864, 0.731, 0.626, 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.

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, model for end-stage liver disease (MELD) score, albumin-bilirubin (ALBI) score, and

Child-Pugh score was 0.794, 0.676, 0.693, and 0.578, respectively.

Figure 3. The VIPP score-based model for determining the procedure for anatomical

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4 hepatectomy. For example, when the values for the indocyanine green retention rate after 15
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7 min (ICG R15), platelet (PLT) count, and prothrombin time index (PT) are 10.0%, 160
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10 $\times 10^3/\mu\text{L}$, and 90%, respectively, the permissible liver resection rate is calculated as 30%. If
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13 the planned resection rate is 35%, the risk of severe PHLF is high (the VIPP score is 3). On
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16 the other hand, a resection rate of 25% is considered to be safe (the VIPP score is 2). The
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19 calculations are available at [https://home.hiroshima-u.ac.jp/home2ge/digestive/lgp/vipp-](https://home.hiroshima-u.ac.jp/home2ge/digestive/lgp/vipp-score.php)
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22 [score.php](https://home.hiroshima-u.ac.jp/home2ge/digestive/lgp/vipp-score.php). VIPP score, volume-associated indocyanine green retention rate at 15 min,
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25 platelet, and prothrombin time index score.
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31 Figure S1, supporting information: Liver resection rates of hepatectomy-naïve patients who
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34 underwent (a) sectionectomy (n = 57) and (b) segmentectomy (n = 98). The resection rate
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37 varies widely within each procedure. (a) Resection rates differed significantly between
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40 medial sectionectomy and other sectionectomy types and between lateral and posterior
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43 sectionectomy. (b) The resection rate was significantly lower for segment 5 hepatectomy than
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46 for segment 6, 7, and 8 hepatectomies. Mann-Whitney *U* test. **P* < 0.050, ** *P* < 0.010.
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Table 1. Patients characteristics

	All patients (<i>n</i> = 335)	Training set (<i>n</i> = 122)	Validation set (<i>n</i> = 213)
Age, years	71 (66–77)	71 (65–75)	72 (67–78)
Sex, male/female, <i>n</i>	268/67	92/30	176/37
Etiology, HBV/HCV/NBNC, <i>n</i>	62/144/129	25/58/39	37/86/90
Repeat hepatectomy, <i>n</i> (%)	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, <i>n</i>	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, <i>n</i> (%)			
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, <i>n</i> (%)			
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, <i>n</i> (%)	50 (14.9%)	22 (18.0%)	28 (13.1%)
90-day mortality, <i>n</i> (%)	5 (1.4%)	1 (0.8%)	4 (1.9%)

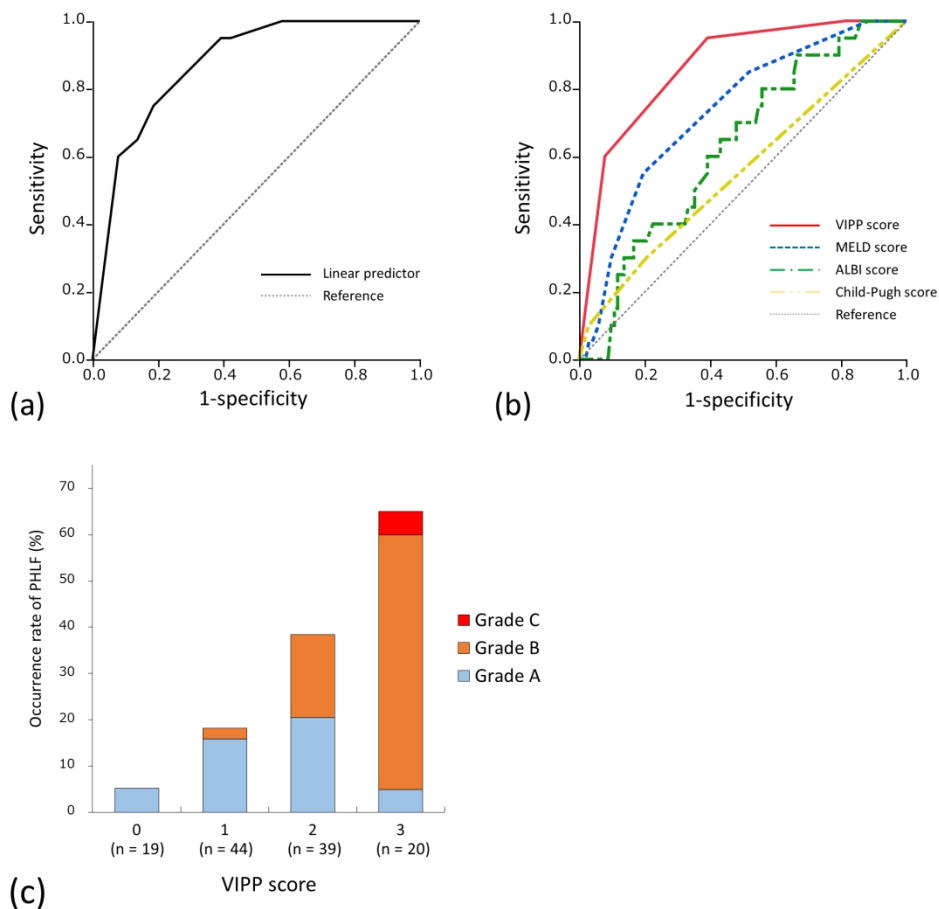
Continuous data displayed as median (interquartile range). HBV, hepatitis B surface antigen; HCV, hepatitis C virus antibody; NBNC, non-B and non-C; ICG R15, indocyanine green retention rate after 15 minutes; ALBI, albumin-bilirubin; MELD, model for end-stage liver disease; PHLF, posthepatectomy liver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

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

			Univariate analysis		Multivariate analysis	
			OR (95% CI)	<i>P</i>	OR (95% CI)	<i>P</i>
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

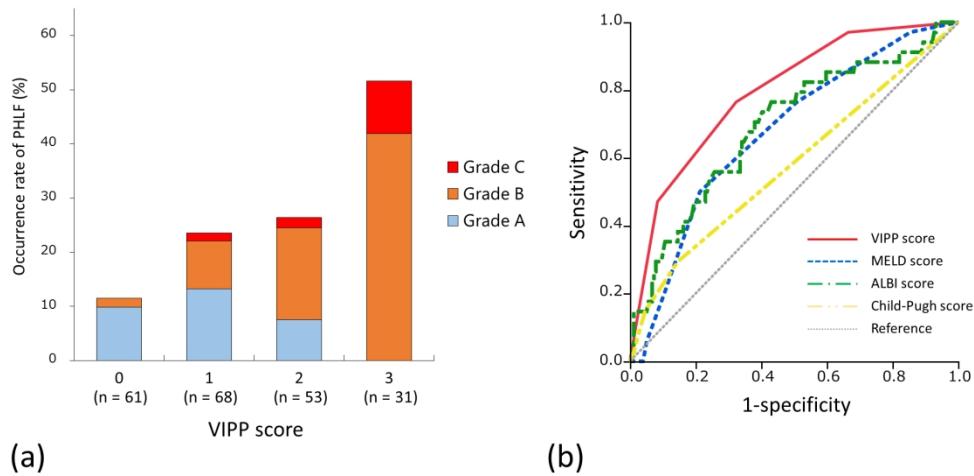
Res and Rem values range from 0.00 to 1.00. For the multivariate analysis, logistic regression using a stepwise procedure and the Bayesian criterion was performed.

OR, odds ratio; CI, confidence interval; ICG R15, indocyanine green retention rate after 15 minutes; 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.



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 (VIIP) score, model for end-stage liver disease (MELD) score, albumin-bilirubin (ALBI) score, and Child-Pugh score in predicting severe PHLF was 0.864, 0.731, 0.626, and 0.553, respectively. (c) The occurrence rate of PHLF grade B or C in patients with VIIP score of 0–3 was 0.0%, 2.3%, 18.0%, and 60.0%, respectively.

181x181mm (300 x 300 DPI)



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, model for end-stage liver disease (MELD) score, albumin-bilirubin (ALBI) score, and Child-Pugh score was 0.794, 0.676, 0.693, and 0.578, respectively.

180x102mm (300 x 300 DPI)

For calculating the VIPP score...

$$\text{VIPP score} = \left[\begin{array}{l} \text{ICG R15 (\%)} \times \text{resection rate} \\ \geq 3.0: 1 \\ < 3.0: 0 \end{array} \right] + \left[\begin{array}{l} \text{PLT } (\times 10^3/\mu\text{L}) \times \text{remnant rate} \\ \leq 130: 1 \\ > 130: 0 \end{array} \right] + \left[\begin{array}{l} \text{PT (\%)} \times \text{remnant rate} \\ \leq 70: 1 \\ > 70: 0 \end{array} \right]$$

VIPP score 3 is a high risk for PHLF grade \geq B

For calculating permissible liver resection rate...

$$\text{Permissible liver resection rate} = \text{Maximum value of } \left[\begin{array}{l} 3.0 / \text{ICG R15 (\%)} \\ 1.00 - 130 / \text{PLT } (\times 10^3/\mu\text{L}) \\ 1.00 - 70 / \text{PT (\%)} \end{array} \right]$$

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%, $160 \times 10^3/\mu\text{L}$, 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.

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Table S1, supporting information. Detail of performed hepatectomy

	All patients (<i>n</i> = 335)	Training set (<i>n</i> = 122)	Validation set (<i>n</i> = 213)
Hemihepatectomy			
Right	22 (6.6%)	7 (5.7%)	15 (7.0%)
Left	40 (11.9%)	19 (15.6%)	21 (9.9%)
Central hepatectomy	5 (1.5%)	2 (1.6%)	3 (1.4%)
Sectionectomy			
Lateral	12 (3.6%)	2 (1.6%)	10 (4.7%)
Medial	22 (6.6%)	4 (3.3%)	18 (8.5%)
Anterior	25 (7.5%)	10 (8.2%)	15 (7.0%)
Posterior	17 (5.1%)	6 (4.9%)	11 (5.2%)
Segmentectomy			
S1	3 (0.9%)	1 (0.8%)	2 (0.9%)
S2	8 (2.4%)	3 (2.5%)	5 (2.3%)
S3	14 (4.2%)	6 (4.9%)	8 (3.8%)
S5	20 (6.0%)	6 (4.9%)	14 (6.6%)
S6	20 (6.0%)	9 (7.4%)	11 (5.2%)
S7	26 (7.8%)	8 (6.6%)	18 (8.5%)
S8	41 (12.2%)	15 (12.3%)	26 (12.2%)
Atypical liver resection	60 (17.9%)	24 (19.7%)	36 (16.9%)

Table S2, supporting information. Occurrence of PHLF by types of procedure in the first hepatectomy patients
(*n* = 264)

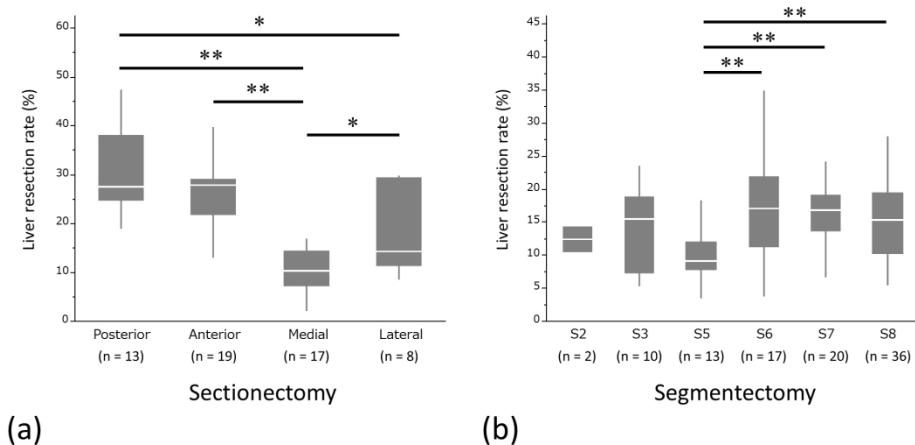
	Hemihepatectomy (<i>n</i> = 61)	Sectionectomy (<i>n</i> = 57)	Segmentectomy (<i>n</i> = 98)	Atypical resection (<i>n</i> = 48)	<i>P</i>
PHLF, <i>n</i> (%)					0.406
Grade A	8 (13.1%)	3 (5.3%)	15 (15.3%)	3 (6.3%)	
Grade B	6 (9.8%)	7 (12.3%)	14 (14.3%)	8 (16.7%)	
Grade C	1 (1.6%)	0 (0.0%)	3 (3.1%)	2 (4.2%)	
PHLF, posthepatectomy liver failure.					

Table S3, supporting information. Receiver operating characteristic analysis for prediction of severe PHLF

		Prediction of PHLF \geq grade B		
		AUROC (95% CI)	Calculated cut-off value*	Cut-off value**
Age (years)		0.647 (0.523–0.753)	72.0	70
ICG R15, %	× Res	0.753 (0.597–0.862)	3.36	3.0
T-bil, mg/dL	× Res	0.597 (0.443–0.733)	0.23	0.2
ALT, IU/L	× Res	0.599 (0.453–0.728)	5.72	6.0
Alb, g/dL	× Rem	0.548 (0.431–0.660)	3.63	3.6
ChE, IU/L	× Rem	0.565 (0.431–0.690)	219	220
PLT, $\times 10^3/\mu\text{L}$	× Rem	0.668 (0.546–0.771)	130	130
PT, %	× Rem	0.647 (0.537–0.742)	70.6	70

*Calculated cut-off value using the Youden's Index, **Cut-off value determined in this study reference to the calculated cut-off value*.

PHLF, posthepatectomy liver failure; AUROC, area under receiver operating characteristic curve; CI, confidence interval; ICG R15, indocyanine green retention rate after 15 minutes; T-bil, total bilirubin; ALT, alanine aminotransferase; Alb, albumin; ChE, cholinesterase; PLT, platelet count; PT, prothrombin time index; Res, liver resection rate; Rem, liver remnant rate.



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