Predictive value of gadoxetic acid enhanced magnetic resonance imaging for posthepatectomy liver failure after a major hepatectomy.

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Abstract

Purpose: We assessed the usefulness of gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging for the prediction of posthepatectomy liver failure (PHLF) after a major hepatectomy.

Methods: We reviewed 140 cases involving a hepatectomy of two or more sections between 2010 and 2016 (study cohort). We used the standardized remnant hepatocellular uptake index (SrHUI) which was calculated by: SrHUI = future remnant liver volume × [(signal intensity of remnant liver on hepatobiliary phase images / signal intensity of spleen on hepatobiliary phase images) − 1] / body surface area. Validation of the SrHUI was performed in another cohort of 52 major hepatectomy cases between 2017 and 2018 (validation cohort).

Results: The SrHUI of patients with PHLF was significantly lower than that of non-PHLF cases. Receiver operating characteristic analysis and the Youden index revealed that the SrHUI cutoff value for the prediction of PHLF and PHLF grade $\geq$B were 0.313 L/m^2 and 0.257 L/m^2, respectively. In the validation cohort, the cutoff value of SrHUI for the prediction of PHLF or PHLF grade $\geq$B had a sensitivity of 75.0% or 88.8%, and specificity of 78.1% or 91.6%, respectively.

Conclusions: The SrHUI value is a predictor for PHLF after a major hepatectomy.

Introduction

Posthepatectomy liver failure (PHLF) is a feared complication of a hepatic resection and a major cause of perioperative mortality [1]. The incidence of PHLF has been reported to range from 1.2% to 32% in different series [2]. PHLF is closely related to the volume and function of the remnant liver, i.e. small remnant liver volumes with reduced function and compromised liver function increase the risk of this outcome [1]. Hepatocellular carcinoma (HCC) arises commonly in patients with chronic liver disease and cirrhosis and a major hepatectomy and small remnant liver volume are risk factors for PHLF [3]. Some cases of intrahepatic cholangiocarcinoma (ICC) have been reported to be related to hepatitis viral infection and liver cirrhosis [4]. Many patients with colorectal liver metastasis (CRLM) treated using preoperative chemotherapy also have impaired liver function [5]. Hence, precise preoperative evaluations of liver function are thus essential for reducing the incidence of this adverse event [6].

Gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (EOB-MRI) was introduced recently as a liver function evaluation method [7]. Because Gd-EOB-DTPA is characterized by its rapid and specific uptake by hepatocytes via the organic anion transporting polypeptides (OATPs) expressed in the sinusoidal membranes of these cells, Gd-EOB-DTPA uptake in the liver is considered to reflect hepatocyte function [8]. Nakagawa et al. have reported that the T1 relaxation time on a post-contrast of EOB-MRI has the potential to provide a robust measure of the liver functional reserve [9]. Several other parameters can reflect liver functional reserve such as the indocyanine green retention rate at 15 minutes (ICGR15), 99m diethylenetriaminepentaacetic acid galactosyl human serum albumin (99mTc-GSA) scintigraphy, Child-Pugh classification, or Albumin-Bilirubin (ALBI) grade [10]. However, these evaluations reflect the function of the whole liver and not just the remnant liver. Recently, Yamada et al. proposed a new evaluation method for liver function using EOB-MRI imaging, the so-called hepatocellular uptake index (HUI). This is a static signal intensity-based method and is derived from the signal intensities and volumes of the liver and spleen on EOB-MRI images at the hepatobiliary phase [11]. Since the HUI includes volume elements, the remnant HUI (rHUI) obtained by the future remnant liver volume (FRLV) can quantitatively evaluate partial liver function [11]. In addition, liver volume is known to have a close correlation with body surface area (BSA) [12]. Therefore, we introduced a formula that standardized rHUI by BSA.

In our present study, we reviewed a study cohort of patients who each underwent a major hepatectomy at our hospital and analyzed the PHLF frequency in this series. For this purpose, we used the standardized rHUI (SrHUI) value derived from the signal intensity (SI) of the liver and spleen on an EOB-MRI at the hepatobiliary phase and the FRLV calculated by computed tomography (CT) volumetry and standardized for BSA. We then evaluated the usefulness of SrHUI as a predictor of PHLF in a validation cohort.

Patients and Methods

Between 2010 and 2018, 478 HCC patients, 60 ICC patients, and 179 CRLM patients underwent several types of hepatectomy at the Department of Gastroenterological Surgery I at Hokkaido University Hospital. We excluded patients who did not undergo a preoperative MRI. We also excluded any cases who underwent a preoperative percutaneous transhepatic portal embolization (PTPE). A total of 192 cases including 132 HCC patients, 42 ICC patients, and 18 CRLM patients who underwent hepatectomy of two or more sections (right/left hemihepatectomy, central bisectionectomy, extended hemihepatectomy, or right/left trisectionectomy) was included in our final series. We divided this population into a study cohort and a validation cohort. Patients who underwent a hepatectomy between 2010 and 2016 were assigned to the study cohort (n = 140) and those who underwent this procedure between 2017 and 2018 were placed in the validation cohort (n = 52).

This study was approved by the institutional review board of Hokkaido University Hospital (approval number: 019-0372) and all analyses were performed in accordance with the ethical guidelines of Hokkaido University Hospital.

Preoperative management

Preoperative management was performed as described in our previous report [13]. We evaluated all patients by CT and EOB-MRI prior to surgery. We measured the liver parenchyma and tumor volumes using contrast-enhanced CT data and 3-dimensional workstations (Virtual Place Lexus; Medical Imaging Laboratory, AZE, Tokyo, Japan, and Synapse Vincent; Fujifilm Medical Co., Ltd., Tokyo, Japan), and thereby calculated the effective hepatic resection rate (%) and the future remnant liver volume (FRLV) (Fig. 1a). The indocyanine green retention rate at 15 minutes (ICGR15) was measured to evaluate the functional liver reserve. We then used our algorithm which incorporates the ICGR15 and FRLV to determine the optimal operative procedure, as previously described [13]. Briefly, if the ICGR15 is less than 15% and the resected liver volume is less than 60%, hepatectomy of two or more sections (right/left hemihepatectomy, central bisectionectomy, extended hemihepatectomy, or right/left trisectionectomy) can be performed. However, if the ICGR15 is less than 15% and the resected liver volume is greater than 60%, then PTPE is performed before surgery.

MR Imaging studies

MR imaging was performed with a 1.5-T system (Achieva A-series, Phillips Medical Systems, Best, The Netherlands). All scanning was performed using a 1.5 Tesla MR-unit (Achieva TX; Philips Healthcare, Best, Netherlands) with a 32-channel cardiac phased array coil. The MR images of a breath-hold axial three dimensional (3D) spoiled gradient echo sequence were scanned before and 20 min after an i.v. injection in all patients of gadoxetic acid (Primovist; Bayer Schering Pharma) at 0.1mL/kg at a rate of 2 mL/s. This bolus injection was followed by a 40 mL saline flush. The imaging parameters were as follows: a repetition time (TR) of 4.6 ms; echo time (TE) of 2.3 ms; flip angle of 15 degrees; slice thickness of 4 mm (2mm reconstruction); matrix size of 224×202 ; FOV of 350×262 mm; and a total scan time of 17.6 seconds. The sequence incorporated a spectral attenuated inversion recovery (SPAIR) RF pulse to provide fat suppression.

The SI was measured on a DICOM viewer with an MR scanning system (Phillips Medical Systems). The SI was measured in the future remnant liver parenchyma by using a circular (1–2 cm^2) region of interest (ROI). The SI of the spleen was also measured for standardization. Each ROI was placed in the future remnant liver and spleen, but vascular structures, artifacts, and focal liver lesions were avoided. In principle, one ROI was placed on each Couinaud's segment and a total of three ROIs were placed on the future remnant liver. All liver ROIs were not necessarily measured on the same axial plane of MR image since each ROI was measured on a plane where each segment is well depicted. A total of three ROIs of the spleen were measured on the plane with the largest surface of the spleen. The averages of three SI values of both the future remnant liver parenchyma and spleen were calculated (Fig. 1b). Based on these average values, the remnant liver function was calculated using the remnant hepatocellular uptake index (rHUI) which was derived from the SI of the liver and spleen on EOB-MRI images at the hepatobiliary phase and the FRLV calculated by CT volumetry. The rHUI, an index for the amount of gadoxetic acid uptake into the remnant liver hepatocytes, was calculated by: rHUI (in liters) = $rV_L \times [(rL_{20} / S_{20}) - 1]$, where rV_L is the FRLV, rL_{20} is the mean SI of the liver that would remain after hepatic resection on hepatobiliary phase images, and S_{20} is the mean SI of the spleen on the hepatobiliary phase images [11]. The SrHUI was calculated by standardizing rHUI by BSA: SrHUI (L/m^2) = rHUI (L) / BSA (m^2).

Surgical methods

The surgical methods used for liver resection have been previously described [13]. Briefly, transection of the liver parenchyma was performed using the hook spatula of an ultrasonic harmonic scalpel (Ethicon EndoSurgery, San Angelo, TX) and either a DS3.0 dissecting sealer (Medtronic, Minneapolis, MN) or bipolar cautery with a saline irrigation system. Inflow occlusion was applied in an intermittent manner, with 15 minutes of occlusion alternating with 5 minutes of reperfusion. We defined a major hepatectomy in our current study as hepatectomy of two or more sections (right/left hemihepatectomy, central bisectionectomy, extended hemihepatectomy, or right/left trisectionectomy).

Posthepatectomy liver failure

PHLF was diagnosed on the basis of the ISGLS definition [1]. In brief, PHLF is defined as an increased PT-INR and concomitant hyperbilirubinemia on or after postoperative day 5. The severity of PHLF was graded as follows: Grade A, abnormal laboratory parameters but no change in the clinical management of the patient; Grade B, deviation from the regular clinical management but manageable without invasive treatment; Grade C, deviation from the regular clinical management and requiring invasive treatment.

Statistical analysis

Categorical variables were compared between PHLF and non-PHLF cases using the Fisher exact test. Continuous variables were expressed as medians with ranges, and compared using the Mann-Whitney U test between the PHLF and non-PHLF group. Univariate and multivariate analyses to identify predictors of PHLF were performed by logistic regression analysis. The predictive value for PHLF was assessed using receiver operating characteristic (ROC) analysis. The cutoff value in the ROC analysis was calculated using the Youden index. The area under the receiver operating characteristic curve (AUROC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. The correlation coefficients were analyzed by Pearson correlation analysis. P values < 0.05 were considered significant. All statistical analyses were performed using JMP version 14 for

Windows (SAS Institute, Cary, NC).

Results

Patient characteristics in study cohort

The clinicopathological and operative features of the patients in study cohort analyzed in this study are presented in Table 1. The study cohort included 105 men and 35 women aged from 33 to 92 years with a median age of 65 years. The median body mass index (BMI), albumin value, total bilirubin value, and platelet count were 23.2 kg/m^2 (range, 12.5-41.2 kg/m^2), 4.0 g/dl (range, 2.6-5.2 g/dl), 0.7 mg/dl (range, 0.2-2.9 mg/dl), and 19.5$\times$10^4/μl (range, 7.2-43.1$\times$10^4/μl), respectively. Thirty eight patients were positive for hepatitis B surface antigen and 15 cases for hepatitis C virus antibody. The median ICGR15 was 10.9 % (range, 2.3-94.2 %), and the median tumor size was 8.0 cm (range, 0.7-22.0 cm). Ninety six patients had a single tumor and 44 patients had multiple tumors. Liver resections in the study population included 58 right hemihepatectomies, 34 left hemihepatectomies, 5 extended right hemihepatectomies, 18 extended left hemihepatectomies, 15 central bisectionectomies, 7 right trisectionectomies, and 3 left trisectionectomy. The study cohort included 98 HCC patients, 29 ICC patients, and 13 CRLM patients. The median FRLV and hepatic resection rate using volumetric CT were 655 ml (range, 322-1334 ml) and 43.2 % (range, 13.9-68.0 %). The median operation time and blood loss were 357 min (range, 188-637 min) and 460 ml (range, 0-6020 ml).

Comparison of clinical features in accordance with PHLF outcomes

In the study cohort, PHLF events based on the ISGLS definition occurred in 29 cases (20.7%), among which 16, 9, and 4 cases were grade A, B, and C, respectively. A comparison of the clinical and perioperative factors of the study cohort is provided in Table 2. There were no significant differences between the non-PHLF and PHLF groups in terms of age, gender, BMI, total bilirubin value, platelet count, HBs antigen, HCV antibody, Child-Pugh classification, ICGR15, ALBI-grade, or blood loss. In contrast, there were significant differences between these groups in terms of albumin level, hepatic uptake ratio to the liver plus heart at 15 min (LHL15) on 99mTc-GSA scintigraphy, FRLV, hepatic resection rate, operation time, and SrHUI. There were no significant differences between the non-PHLF group and PHLF grade $\geq$B cases in terms of age, gender, BMI, total bilirubin value, platelet count, HBs antigen, Child-Pugh classification, ICGR15, LHL15 on 99mTc-GSA scintigraphy, ALBI-grade, FRLV, hepatic resection rate, operation time, or blood loss. In contrast, there were significant differences between these two groups in terms of albumin value, HCV antibody, and SrHUI.

Univariate and multivariate analyses of preoperative predictive factors for PHLF

We screened for preoperative predictors of PHLF by univariate and multivariate analysis. Univariate analysis identified the albumin value, FRLV, and SrHUI as significant preoperative predictive factors for PHLF (Table 3). Multivariate analysis of these variables further revealed that FRLV and SrHUI were independent predictive factors for PHLF (Table 3). We also performed univariate and multivariate analysis of the impact of SrHUI on a PHLF grade ≥B which also indicated that the albumin value and this index were independent predictive factors for this outcome (Table 4).

Correlation of the SrHUI value with other functional and volumetric parameters

We assessed the correlation of the SrHUI value with other functional and volumetric parameters in our current cohort using Pearson correlation analysis. The correlation coefficient between the SrHUI and ICGR15 values was -0.2593, between the SrHUI and LHL15 was 0.1293, between the SrHUI and FRLV was 0.2771, between the SrHUI and the hepatic resection rate was 0.2196, between the SrHUI and LHL15 x FRLV was 0.2871, and between the SrHUI and ICGR15 x FRLV was -0.1879, all of which were weak correlations.

Receiver operating characteristic analysis of SrHUI and its cut-off value for the prediction of PHLF

ROC analysis revealed that the optimal SrHUI cutoff value for the prediction of PHLF and PHLF grade ≥B were 0.313 and 0.257, with an AUROC of 0.80 and 0.87, respectively (Fig. 2a and 2b).

Validation study of SrHUI

The characteristics of the validation cohort are presented in Table 1. There were significant differences between the study cohort and the validation cohort in terms of age, operation time, and blood loss, while there were no significant differences between these groups in terms of gender, BMI, albumin value, total bilirubin value, platelet count, HBs antigen, HCV antibody, Child-Pugh classification, ICGR15, LHL15 on 99mTc-GSA scintigraphy, ALBI-grade, tumor size, tumor number, type of liver resection, diagnosis, FRLV, or hepatic resection rate. In the validation cohort, PHLF occurred in 20 cases, among which 11, 9, and 0 cases were grade A, B, and C, respectively. We evaluated the predictive performance of the SrHUI for PHLF in this validation cohort. A SrHUI cutoff value of 0.313 for the prediction of PHLF had a sensitivity of 75.0%, specificity of 78.1%, PPV of 65.2%, and NPV of 83.3%. The cutoff value of 0.257 for the prediction of PHLF grade ≥B had a sensitivity of 88.8%, specificity of 91.6%, PPV of 53.3%, and NPV of 97.2% (Table 5).

Discussion

PHLF is the most serious complication of a hepatectomy because it is associated with increased postoperative mortality. A precise preoperative evaluation of the patient’s liver function prior to this surgery is therefore essential to reduce the risk of this adverse outcome.

The SrHUI, which is derived from the SI of the liver and spleen on EOB-MRI images at the hepatobiliary phase and from the FRLV calculated by CT volumetry and standardized by BSA, is an index marker of both the functional capacity and volume of the remnant liver. Our current analyses have revealed that the SrHUI is also a significant predictor of the PHLF after a major hepatectomy.

In terms of evaluation methods for liver function, a number of different parameters that reflect liver function can be measured, such as ICGR15, 99mTc-GSA scintigraphy, Child-Pugh classification, or ALBI grade. The ICGR15 value has been among the most widely used markers of liver function. According to Makuuchi’s criteria, an algorithm of liver resection includes ICGR15 [14]. The 99mTc-GSA estimates the extent of hepatocyte damage on the basis of a decline in the asialoglycoprotein receptors present on the hepatocyte membrane and permits a numerical evaluation of the hepatic functional reserve [15]. The Child–Pugh score has been the gold standard for assessing the hepatic functional reserve [16]. Recently however, Johnson et al. have reported an alternative measure of liver function in patients with HCC based solely on albumin and bilirubin, namely the ALBI grade [10]. The ALBI grade provides an objective hepatic reserve estimation and its clinical utility in HCC patients has been demonstrated [17].

These aforementioned assessment tools are reflective of whole liver function however and not the segmental liver. When there is a functional disparity between liver segments due to blood flow disturbances or biliary obstruction in the presence of a tumor, the functional assessment of the whole liver cannot predict the exact future remnant liver function. On the other hand, the SrHUI can evaluate segmental liver function quantitatively and is useful in the preoperative evaluation of remnant liver function prior to a hepatectomy.

PHLF onset is associated with the volume of the remnant liver and CT volumetry is essential during liver surgery for calculating the FRLV after a hepatectomy [5]. CT volumetry is effective for assessing the liver volume but cannot alone be used to determine liver function. Yamada et al. reported previously that an underestimation of the segmental liver reserve can occur if using volumetry data alone because the heterogeneity of liver function will not be taken into account by this measure [11]. For this reason, attempts have been made to combine volumetric and functional evaluations in liver surgery patients. A typical evaluation method is a combination of CT volumetry and 99mTc-GSA scintigraphy. The 99mTc-GSA scintigraphy single-photon emission computed tomography (SPECT)/ CT fusion system allows for the simultaneous evaluation of any part of the liver volume and the corresponding liver function [18-20]. Furthermore, EOB-MRI is a better evaluation method for the regional liver function reserve than GSA because its spatial resolution is superior [21]. EOB-MRI also has the potential for accurate noninvasive quantification of liver function because Gd-EOB-DTPA uptake in the liver is considered to closely reflect hepatocyte function [7, 8, 22, 23]. Itoh et al. have reported that functional liver assessments using the liver to major psoas muscle ratio obtained by EOB-MRI is useful for predicting liver-related morbidity after hepatic resection of a HCC [24]. Yamada et al. also reported that a standardized liver function assessment based on the SI from an EOB-MRI, the volume of each liver subsegment, and the body surface area are useful for calculating the resection limits for a hepatectomy [25]. Araki et al. reported that functional remnant liver volumetry using EOB-MRI could predict PHLF [26]. In a similar manner, our present results have indicated that the SrHUI calculated using a combination of CT volumetry and EOB-MRI, is a useful and viable predictor of PHLF. Furthermore, our present findings revealed weak correlations between the SrHUI and other existing functional and volumetric parameters such as the ICGR15, LHL15 from a 99mTc-GSA scintigraphy, FRLV, and hepatic resection rate. These results have indicated that the SrHUI does not reflect function alone or volume alone, but is a meaningful parameter that takes both into account.

HCC is the most common target of a hepatectomy, and affected patients often have an underlying impaired liver which is a risk factor for PHLF. Patients with ICC or CRLM treated by preoperative chemotherapy also often have impaired liver function. A major hepatectomy itself is also a risk factor for PHLF because of the small FRLV post-surgery. Further, patients with large tumors that require a major hepatectomy tend to have a segmental liver functional imbalance. We hypothesized that volumetric and functional data obtained using EOB-MRI may be useful for patients with a segmental liver functional imbalance that require a major hepatectomy. Our analyses have revealed that the SrHUI of PHLF cases is significantly lower than non-PHLF patients. Our results also indicated that the SrHUI is a significant predictive factor for both PHLF and PHLF grade $\geq$B, which supports our hypothesis regarding the utility of volumetric and functional assessments using EOB-MRI.

EOB-MRI as a preoperative liver functional test has the following advantages. First, it is the most routinely used method for the preoperative examination of HCC patients, and is more sensitive in detecting smaller (<2cm) lesions than CT [27]. Second, EOB-MRI can evaluate partial hepatic function as demonstrated through the use of the SrHUI in this present study. More accurate liver function assessments are needed when an interregional disparity in these functions are caused by a tumor [20]. Third, EOB-MRI has better spatial resolution than other modalities such as 99mTc-GSA scintigraphy, as mentioned above. EOB-MRI can also be used to evaluate liver function at the same time as preoperative diagnostic tests. Our current results have indicated in addition that EOB-MRI helps to determine the risk of PHLF in patients following resection.

Our present study had some limitations of note. This study was a retrospective analysis and selection bias could not be ruled out. Furthermore, the SrHUI PPV for the prediction of PHLF was relatively low, likely because the liver functions were very diverse, and only a small portion of the liver function is imaged by EOB-MRI. Therefore, even if the SrHUI is low, it does not necessarily mean to abandon to perform a major hepatectomy.

Surgical indication should be comprehensively judged with reference to existing liver functional test such as ICGR15 or 99mTc-GSA scintigraphy. The clinical significance of using SrHUI in daily practice could arise if, for example, there was a discrepancy between ICGR15 and 99mTc-GSA scintigraphy and the surgeon was hesitant regarding the indications for a hepatectomy. The SrHUI would assist with these surgical indications. Another limitation of this study is the static nature of the SrHUI. EOB-MRI can be used for dynamic imaging but this is more complicated [28]. Although there were weak correlations between SrHUI and the ICGR15 or LHL15 measures which indicate whole liver function, the SrHUI may indicate general liver function and not regional unless the acquisition is dynamic and voxel based. Hence, this method is not always superior to existing methods under current use such as ICGR15 [29]. In addition, we used CT volumetry when calculating the FRLV which was not fully consistent with the EOB-MRI data. The SrHUI uses CT volumetry for a determination of the liver volume and more accurate data would potentially be obtained by MRI volumetry. However, CT volumetry is an established method in liver surgery, and Kim et al. have reported in a smaller population than our current series that the MRI-related rHUI parameter is superior to ICG-related parameters for predicting PHLF [30], consistent with our current study results. We contend therefore that a SrHUI evaluation method combining liver function and the remnant liver volume is a viable and accurate prediction method for PHLF outcomes.

In conclusion, the SrHUI, calculated from the SI of the liver and spleen on EOB-MRI images at the hepatobiliary phase and from the FRLV calculated by CT volumetry, is an accurate and useful predictor of PHLF complications in patients who have undergone a major hepatectomy.

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Conflicts of interest: The authors declare no conflicts of interest in relation to this study.

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Figure Legends

Figure 1. (a) CT volumetry using contrast-enhanced CT data and a 3-dimensional workstation to calculate the effective hepatic resection rate (%) and the future remnant liver volume (FRLV). (b) Measurement of the signal intensity (SI) in the future remnant liver parenchyma using a circular region of interest (ROI) measurement. The SI of the spleen was also measured for standardization. The averages of the three SI values for the future remnant liver parenchyma and the spleen were calculated

Figure 2. Receiver operating characteristic analysis showing that the optimal SrHUI cutoff value for the prediction of PHLF and PHLF grade $\geq$B were 0.313 (a) and 0.257 (b), with an area under the receiver operating characteristic curve (AUROC) of 0.80 (a) and 0.87 (b), respectively.

Table 1 Baseline characteristics and clinical factors of study cohort and validation cohort

Variables		Study cohort (n = 140)	Validation cohort (n = 52)	p value
Age				0.0006
		65 (33-92)	71.5 (48-85)	
Gender				0.7043
	Female	35	11	
	Male	105	41	
BMI (kg/m^2)				0.5968
		23.2 (12.5-41.2)	22.6 (15.0-31.1)	
Alb (g/dl)				0.1503
		4.0 (2.6-5.2)	4.2 (3.0-4.8)	
T-Bil (mg/dl)				0.9390
		0.7 (0.2-2.9)	0.7 (0.4-1.9)	
Plt ($\times 10^4/\mu l$)				0.8345
		19.5 (7.2-43.1)	21.7 (7.2-55.6)	
HBs antigen				0.7116
	(-)	102	40	
	(+)	38	12	
HCV antibody				0.6141
	(-)	125	45	
	(+)	15	7	
Child Pugh classification				1.0000
	A	133	50	
	B	7	2	
ICG R15 (%)				0.3982
		10.9 (2.3-94.2)	10.2 (2.6-36.0)	
LHL15				0.9697
		0.929 (0.806-0.984)	0.930 (0.686-0.978)	
ALBI-grade				0.7767
	1	127	46	
	2	8	3	
	3	5	3	
Tumor size (cm)				0.3803
		8.0 (0.7-22.0)	7.0 (0.8-24.0)	
Tumor number				0.1249
	Single	96	34	
	Multiple	44	18	
Liver resection				0.1883
	Right hemihepatectomy	58	15	
	Left hemihepatectomy	34	11	
	Extended right hemihepatectomy	5	4	
	Extended left hemihepatectomy	18	5	
	Central bisectionectomy	15	8	
	Right trisectionectomy	7	7	
	Left trisectionectomy	3	2	
Diagnosis				0.7858
	HCC	98	34	
	ICC	29	13	
	CRLM	13	5	
FRLV (ml)				0.3520
		655 (322-1334)	658 (327-1266)	
Hepatic resection rate (%)				0.3765
		43.2 (13.9-68.0)	43.5 (18.9-62.3)	
Operation time (min)				0.0261
		357 (188-637)	321 (165-547)	
Blood loss (ml)				0.0064
		460 (0-6020)	332.5 (25-3310)	

Abbreviations: Alb, albumin; ALBI-grade, Albumin-Bilirubin grade; BMI, body mass index; CRLM, colorectal liver metastasis; FRLV, future remnant liver volume; HBs antigen, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCV antibody, hepatitis C virus antibody; ICC, intrahepatic cholangiocarcinoma; ICGR15, indocyanine green retention rate at 15 minutes; LHL15, The hepatic uptake ratio to the liver plus heart at 15 min of 99mTc-galactosyl human serum albumin; Plt, platelet; T-Bil, total bilirubin

Continuous variables are expressed as median (range)

Table 2 Comparison of clinical features according to PHLF of study cohort

Variables		non-PHLF (n = 111)	PHLF (n = 29)	p value*	PHLF grade ≥B (n = 13)	p value†
Age				0.1497		0.7104
		65 (33-92)	62 (42-83)		63 (46-83)	
Gender				0.4707		0.7307
	Female	26	9		2	
	Male	85	20		11	
BMI (kg/m2)				0.6714		0.6924
		23.1 (12.5-41.2)	23.3 (16.5-30.7)		22.6 (16.5-29.9)	
Alb (g/dl)				0.0299		0.0022
		4.0 (2.7-5.2)	3.8 (2.6-4.8)		3.5 (2.6-4.4)	
T-Bil (mg/dl)				0.2298		0.1820
		0.7 (0-2.7)	0.8 (0.2-2.9)		1.0 (0.2-1.9)	
Plt ($\times 10^4/\mu l$)				0.1414		0.9220
		19.5 (7.2-43.1)	19.7 (13.2-35.4)		18.5 (13.2-35.4)	
HBs antigen				0.6415		0.5147
	(-)	82	20		11	
	(+)	29	9		2	
HCV antibody				0.3079		0.0406
	(-)	101	24		9	
	(+)	10	5		4	
Child Pugh classification				0.6344		0.1578
	A	106	27		11	
	B	5	2		2	
ICG R15 (%)				0.4014		0.2411
		10.7 (2.6-94.2)	12.1 (2.3-87.8)		13.0 (4.0-87.8)	
LHL15				0.0241		0.4170
		0.926 (0.849-0.984)	0.940 (0.806-0.968)		0.931 (0.806-0.968)	
ALBI-grade				0.6319		0.7798
	1	101	26		11	
	2	7	1		1	
	3	3	2		1	
SrHUI (L/m^2)				<0.0001		<0.0001
		0.378 (0.024-1.199)	0.198 (0.013-1.770)		0.124 (0.013-0.311)	
FRLV (ml)				0.0082		0.9902
		682.0 (357-1334)	581.9 (322-1275)		736.0 (389-1275)	
Hepatic resection rate (%)				0.0007		0.2765
		40.9 (13.9-67.3)	49.6 (26.1-68.0)		43.4 (26.1-64.9)	
Operation time (min)				0.0183		0.2321
		348 (188-637)	390 (267-582)		359(267-582)	
Blood loss (ml)				0.4034		0.8320
		470 (0-6020)	430 (165-2050)		410 (165-2050)	

Abbreviations: Alb, albumin; ALBI-grade, Albumin-Bilirubin grade; BMI, body mass index; FRLV, future remnant liver volume; HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICGR15, indocyanine green retention rate at 15 minutes; LHL15, The hepatic uptake ratio to the liver plus heart at 15 min of 99mTc-galactosyl human serum albumin; PHLF, posthepatectomy liver failure; Plt, platelet; SrHUI, standardized remnant hepatocellular uptake index; T-Bil, total bilirubin

Continuous variables are expressed as median (range)
* non-PHLF vs PHLF
† non-PHLF vs PHLF grade ≥B

Table 3 Univariate and multivariate analyses of preoperative predicting factors for PHLF

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
BMI	1.003	0.989–1.017	0.0778	-		
Alb	0.376	0.161–0.876	0.0214	0.402	0.152–1.064	0.0665
T-Bil	1.856	0.749–4.597	0.1904	-		
Plt	1.001	0.996–1.001	0.5587	-		
Child Pugh classification	1.570	0.288–8.539	0.6124			
ICG R15	1.017	0.988–1.046	0.2521	-		
LHL15	11.021	0.560–216.903	0.0973	-		
ALBI-grade	2.564	0.407–16.152	0.6161			
FRLV	0.997	0.995–0.999	0.0175	0.997	0.994–0.999	0.0237
Hepatic resection rate	0.964	0.775–1.196	0.6825	-		
SrHUI	0.013	0.001–0.182	<0.0001	0.015	0.001–0.288	0.0053

Abbreviations: Alb, albumin; ALBI-grade, Albumin-Bilirubin grade; BMI, body mass index; CI, confidence interval; FRLV, future remnant liver volume; ICGR15, indocyanine green retention rate at 15 minutes; LHL15, The hepatic uptake ratio to the liver plus heart at 15 min of 99mTc-galactosyl human serum albumin; OR, odds ratio; PHLF, posthepatectomy liver failure; Plt, platelet; SrHUI, standardized remnant hepatocellular uptake index; T-Bil, total bilirubin

Table 4 Univariate and multivariate analyses of preoperative predicting factors for PHLF Grade >B

Variable	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	P value
BMI	0.988	0.863–1.131	0.6353	-		
Alb	0.149	0.044–0.508	0.0014	2.53E-01	0.064–0.993	0.0489
T-Bil	1.716	0.536–5.490	0.3892	-		
Plt	0.986	0.956–1.017	0.1458	-		
Child Pugh classification	4.436	0.769–25.582	0.1316			
ICG R15	1.023	0.991–1.055	0.1958	-		
LHL15	0.523	0.015–17.295	0.7204	-		
ALBI-grade	2.613	0.268–25.474	0.8350			
FRLV	1.001	0.998–1.003	0.5071	-		
Hepatic resection rate	0.937	0.550–1.559	0.7142	-		
SrHUI	2.06E-05	4.938e-8–0.00857	< 0.0001	6.13E-05	1.406e-7–0.0267	0.0018

Abbreviations: Alb, albumin; ALBI-grade, Albumin-Bilirubin grade; BMI, body mass index; CI, confidence interval; FRLV, future remnant liver volume; ICGR15, indocyanine green retention rate at 15 minutes; LHL15, The hepatic uptake ratio to the liver plus heart at 15 min of 99mTc-galactosyl human serum albumin; OR, odds ratio; PHLF, posthepatectomy liver failure; Plt, platelet; SrHUI, standardized remnant hepatocellular uptake index; T-Bil, total bilirubin

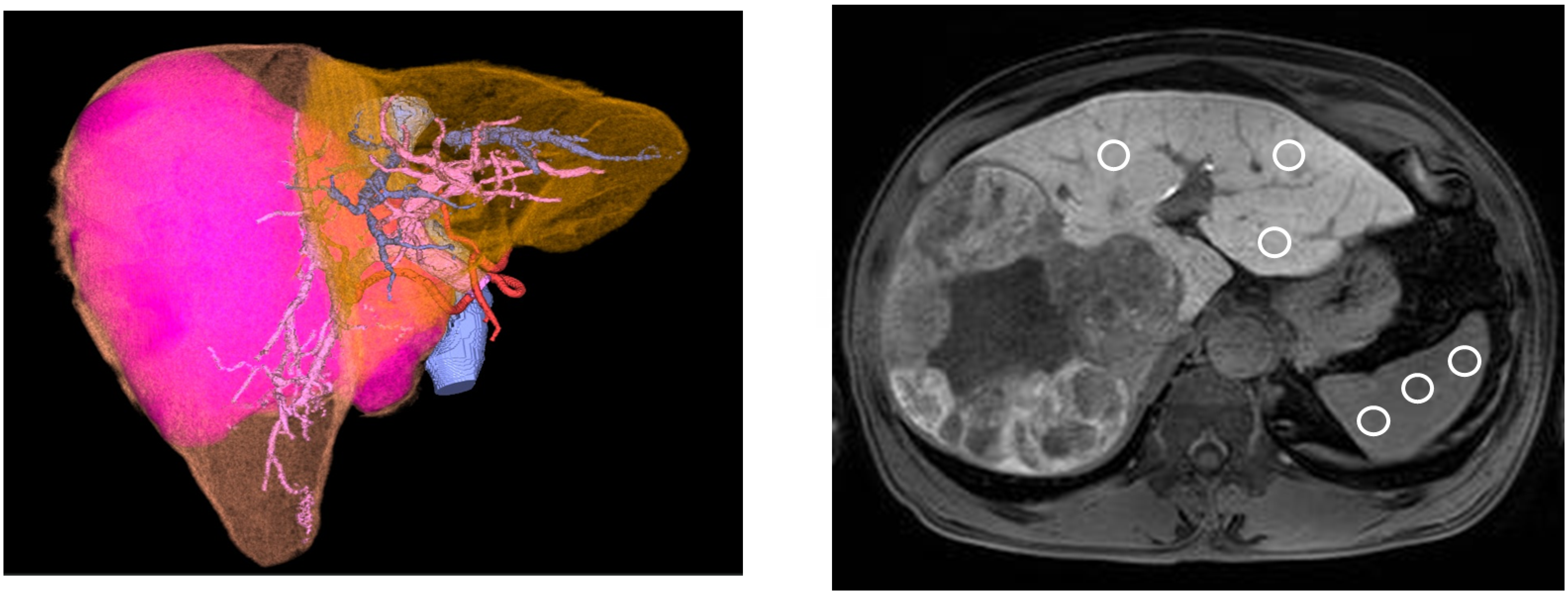
Table 5 Predictive performance of SrHUI for PHLF in the validation cohort

	Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV(%)
PHLF	0.313	75.00	78.12	65.21	83.33
PHLF grade ≥B	0.257	88.89	91.6	53.33	97.29

Abbreviations: NPV, negative predictive value; PHLF, posthepatectomy liver failure; PPV, positive predictive value; SrHUI, standardized remnant hepatocellular uptake index

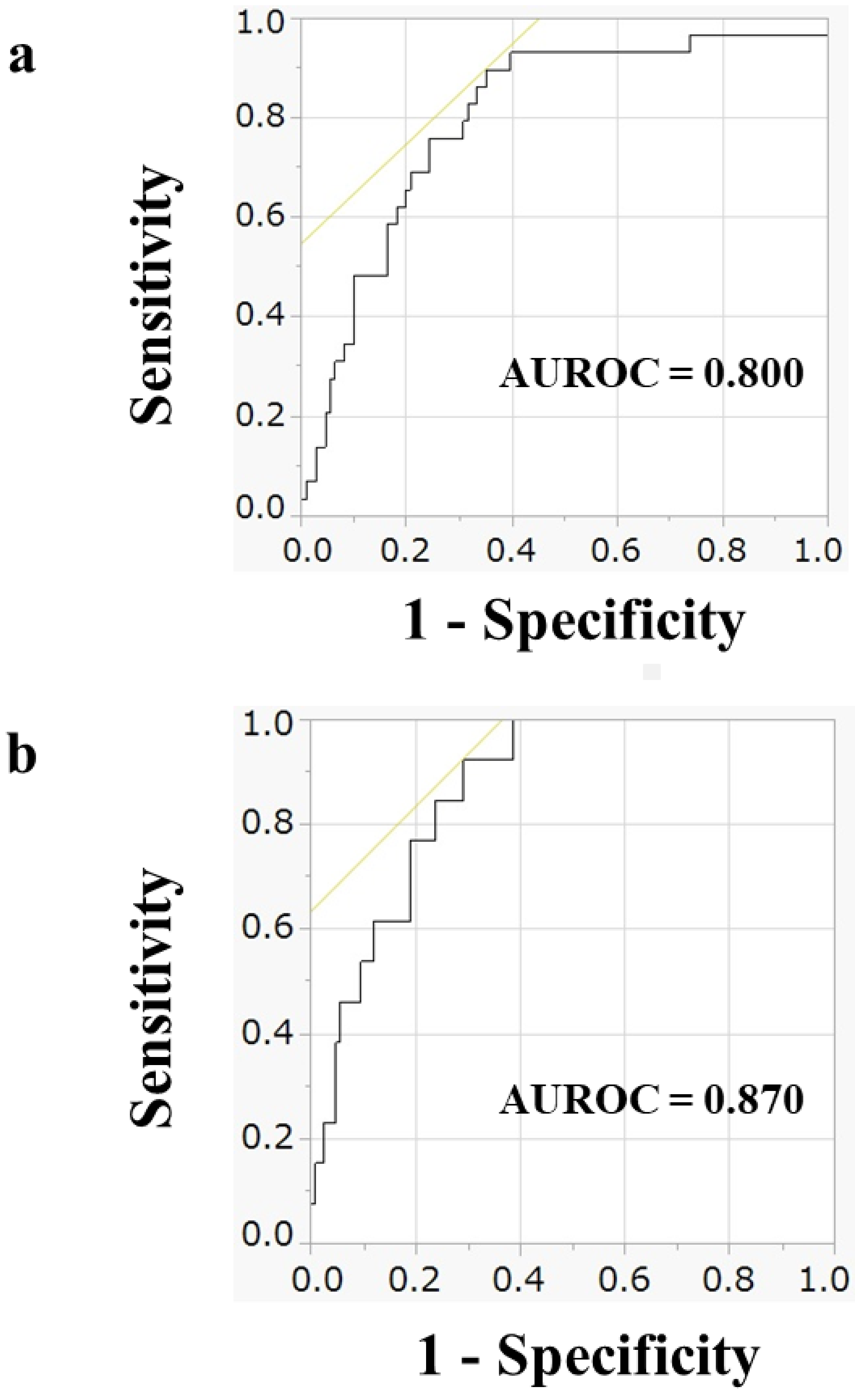
Figure 1

a **b**



CT volumetry **EOB-MRI**

Figure. 2


a
1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
AUROC = 0.800
0.0 0.2 0.4 0.6 0.8 1.0
1 - Specificity
b
1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
AUROC = 0.870
0.0 0.2 0.4 0.6 0.8 1.0
1 - Specificity