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Volumetric analysis and indocyanine green retention rate at 15 min as predictors of post-hepatectomy liver failure

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Abstract

Objectives: The actual future liver remnant (aFLR) is calculated as the ratio of remnant liver volume (RLV) to total functional liver volume (TFLV). The standardized future liver remnant (sFLR) is calculated as the ratio of RLV to standard liver volume (SLV). The aims of this study were to compare the aFLR with the sFLR and to determine criteria for safe hepatectomy using computed tomography volumetry and indocyanine green retention rate at 15 min (ICG R15).

Methods: Medical records and volumetric measurements were obtained retrospectively for 81 patients who underwent right hemi-hepatectomy for malignant hepatic tumours from January 2010 to November 2013. The sFLR was compared with the aFLR, and a ratio of sFLR to ICG R15 as a predictor of postoperative hepatic function was established.

Results: In patients without cirrhosis, the sFLR showed a stronger correlation with the total serum bilirubin level than the aFLR ($R^2 = 0.499$ versus $R^2 = 0.239$). Post-hepatectomy liver failure developed only in the group with an sFLR of <25%, regardless of ICG R15. In patients with cirrhosis, the aFLR and sFLR had no correlation with postoperative total serum bilirubin. An sFLR : ICG R15 ratio of >1.9 showed 66.7% sensitivity and 100% specificity.

Conclusions: Regardless of ICG R15, an sFLR of 25% in patients without cirrhosis, and an sFLR of 25% with an sFLR : ICG R15 ratio of >1.9 in patients with cirrhosis indicate acceptable levels of safety in major hepatectomy.

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Introduction

Post-hepatectomy liver failure (PHLF) is one of the most serious complications to arise after liver resection. Its occurrence is closely related to the volume and functional capacity of the remnant liver. Patients with a small future liver remnant (FLR) are at higher risk for developing PHLF. There are two methods of calculating FLR. Actual FLR (aFLR) is expressed as the ratio of remnant liver volume (RLV) to total functional liver volume (TFLV). The TFLV is calculated by subtracting the tumour volume (TV) from the total liver volume (TLV). However, some patients have a smaller TLV than expected. In these patients, a sufficient ratio would not result in enough volume to meet metabolic demand. Therefore, aFLR does not seem to be an appropriate metric for such patients.

The other method uses the standardized FLR (sFLR), which is expressed as the ratio of RLV to standard liver volume (SLV). The standardization of FLR is usually performed according to body weight (BW) or body surface area (BSA).[1–6] In the case of liver transplantation, it is generally accepted that the ratio of graft volume to SLV should be at least 30–40% to fulfil the hepatic metabolic demand of the recipient.[7–9] This concept is similar to that of the sFLR. In a previous study by this group, the sFLR was found to be more closely correlated with postoperative morbidity and PHLF.[10] An sFLR of about 20 30% has been reported as representing the limits of safety in hepatectomy by some authors.[1–3,5,6,11,12] However, these studies were performed mainly in patients without cirrhosis and thus their data are not suitable for application in patients with cirrhosis. In previous studies, the

critical minimum FLR was estimated to be approximately 40% in patients with cirrhosis.[11,13] However, because patients with cirrhosis have impaired liver function, the risk associated with hepatectomy cannot be determined accurately with volumetry alone. Indocyanine green retention rate at 15 min (ICG R15) is the most common preoperative test for evaluating hepatic functional reserve.[14,15] Some authors have proposed different surgical approaches depending on ICG R15. Lee *et al.* reported a formula for predicting a safe FLR ratio using ICG R15.[16] Yamanaka *et al.* proposed a predictive score for postoperative mortality calculated from resection rate, ICG R15, and the patient's age.[17] In patients with cirrhosis, these methods were more accurate, but were complex to calculate. The aims of the present study were to evaluate the significance of the sFLR (RLV : SLV) as a factor predictive of liver function and liver failure after hepatic resection, in comparison with the aFLR (RLV : TFLV), and to determine accurate, but easy-to-use and simple criteria for predicting PHLF using computed tomography (CT) volumetry and ICG R15.

Materials and methods

From January 2010 to November 2013, 82 Korean patients underwent right hemi-hepatectomy without biliary reconstruction for malignant hepatic tumours at the Department of Surgery, Chonnam National University Hwasun (CNUH) Hospital. The medical records for the 82 patients were reviewed retrospectively. One patient, who died of aspiration pneumonia following multiorgan failure on postoperative day (PoD) 5, was excluded from the study. Before the event, there were no abnormal clinical or laboratory findings. Thus, a total of 81 patients were selected. In order to allow for a comparison of postoperative total serum bilirubin level as an indicator of post-hepatectomy liver function, patients with perihilar cholangiocarcinomas and gallbladder cancers were excluded because all such patients submitted to right hemi-hepatectomy had a biliary drainage catheter inserted at the time of surgery. The biliary drainage catheter is the most important cause of cholangitis and biliary infection can affect hepatic function. In addition, routine lymphatic dissection in operations for hilar cholangiocarcinomas and gallbladder cancers may affect the amount of postoperative ascites.

Operative procedures

The liver was exposed via a right subcostal abdominal incision with midline extension to the xiphoid process. Intraoperative ultrasonography was used to confirm tumour resectability and determine the appropriate line of resection. The liver was mobilized completely from the posterior abdominal wall and rotated anteromedially to expose the retrohepatic inferior vena cava (IVC). Small tributaries draining into the IVC from the liver were ligated individually and divided. The hepatocaval ligament was separated and the right hepatic vein was looped. Hilar dissection was undertaken to isolate and divide the right hepatic artery and portal vein. The Pringle manoeuvre was not used in any patient.

Hepatic parenchymal transection was performed using an ultrasonic aspirator. After parenchymal dissection, the right hepatic vein was divided and sutured.

Postoperative care

All patients received the same postoperative care delivered by the same team of surgeons in the intensive care unit during the early postoperative period. Parenteral nutritional support was provided for patients with liver cirrhosis. Early enteric nutrition was encouraged once bowel activity returned. All intraoperative and postoperative complications were recorded prospectively. Liver function tests, including serum total bilirubin level and prothrombin time (PT), were sampled routinely on PoD 1, 3, 5 and 7. Serum total bilirubin at PoD 1, 3, 5 and 7, and peak serum total bilirubin were assessed to evaluate the relationship between postoperative hepatic function and FLR. In addition, PT at PoD 1, 3, 5 and 7, and the lowest rate of PT were assessed. At PoD 7, postoperative CT was carried out to recheck the anatomic resection and the similarity between the CT and virtual resection line (Fig. 1). Post-hepatectomy liver failure was defined according to three different methods. Firstly, clinical PHLF (PHLF$_{clinic}$) was defined as mortality with postoperative hepatic dysfunction or the development of clinical symptoms such as bleeding tendency, intractable ascites or hepatic encephalopathy.[18] Secondly, PHLF according to the '50–50 criterion' (PHLF$_{50-50}$) was defined as both a PT of <50% and total serum bilirubin of >2.9 mg/dl after PoD 5.[19] Thirdly, PHLF according to total serum bilirubin (PHLF$_{peakBil7}$) was defined as a peak total serum bilirubin ($_{peak}$Bil) of >7 mg/dl.[20] Postoperative mortality was defined as death occurring during the postoperative hospital stay or within 90 days of surgery.[20]

Standard liver volume calculation

Standard liver volume was calculated using the formula reported by Yu *et al.*[21] as:

$$SLV \text{ (ml)} = 21.585 \times BW \text{ (kg)}^{0.732} \times height \text{ (cm)}^{0.225}.$$

Volumetric liver analysis using Dr Liver

All patients underwent contrast-enhanced CT as part of routine preoperative assessment. Arterial, portal and venous phase series of images from preoperative CT scans were used for CT volumetry. Volumetric analysis using Dr Liver (Humanopia Co. Ltd, Pohang, Gyungbuk, South Korea) was performed by two surgeons (HJK and CYK). The liver was semi-automatically extracted once multiple seed points had been selected on five or six slices. The portal vein, hepatic vein, IVC and tumour were extracted in the same manner. The TLV and TV were calculated automatically with Dr Liver. The gallbladder and IVC were excluded and the intrahepatic vascular and biliary structures were
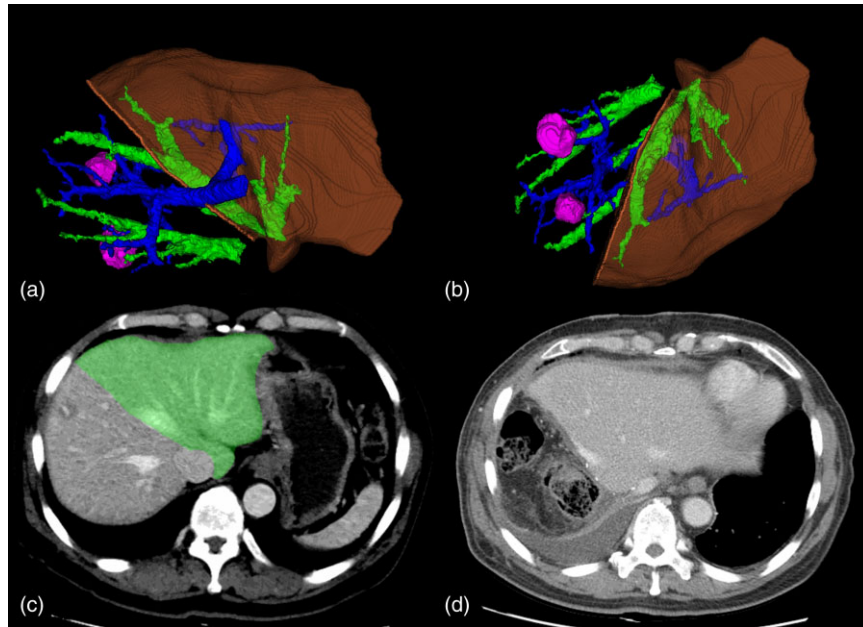
Figure 1 (a–c) Virtual resection of liver using Dr Liver. The transection line of the virtual liver resection followed the middle hepatic vein. The middle hepatic vein was excluded from the virtual resection area. (d) Follow-up computed tomography at postoperative day 7, used to recheck the ⊠anatomical⊠right hemi-hepatectomy following the middle hepatic vein. The real resection line was similar to the virtual resection line

included in the liver volume calculation. The TFLV was calculated using the formula:

$$TLV \quad TV = TFLV.$$

The transection line of the virtual liver resection followed the middle hepatic vein (Fig. 1). The middle hepatic vein was excluded from the virtual resection area.

Indocyanine green test

All patients underwent preoperative ICG R15 tests. Indocyanine green tests consisted of an injection 0.5 mg/kg of ICG into a peripheral vein and the drawing of a blood sample from another site 15 min later. Results were expressed as the percentage of ICG retained at 15 min after the injection.

Statistics

Continuous variables were expressed as the median (range) and compared using the Mann–Whitney U-test. Discrete variables were compared using the chi-squared test or Fisher's exact test. Correlations between continuous variables were assessed using regression analysis. The resulting regression line was described as a linear equation, and the correlation coefficients (R and R^2) were calculated. Cut-off values for the occurrence of PHLF were determined using receiver operating characteristic (ROC) curve analysis. A P-value of <0.05 was considered to indicate statistical

significance. Statistical analysis was performed using PASW Statistics for Windows Version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Clinicopathologic characteristics and operative outcomes

A total of 81 patients were evaluated in the present study. Their median age was 59 years (range: 34–81 years). A total of 68 (84.0%) patients were male. Overall, 54 (66.7%) patients underwent right hemi-hepatectomy for hepatocellular carcinoma, 16 (19.8%) for metastatic tumours, 10 (12.3%) for intrahepatic cholangiocarcinoma, and one (1.3%) for carcinosarcoma. A total of 38 (46.9%) patients had histologic evidence of liver cirrhosis. All patients with a cirrhotic liver were of Child–Pugh class A status. No patients had biliary obstruction, preoperative hyperbilirubinaemia or preoperative PT prolongation. The clinicopathologic characteristics of patients are shown in Table 1. Of the 81 patients who underwent right hemi-hepatectomy, clinical PHLF occurred in eight (9.9%) patients, including four (4.9%) who died. One patient with PHLF$_{clinic}$ underwent a liver transplantation; four patients recovered with conservative treatment. Of the four patients who died from liver failure in the postoperative period, three had liver cirrhosis and one had chronic hepatitis B without histologic evidence of liver cirrhosis. Of the 81 patients, nine (11.1%) were classified in the PHLF$_{50–50}$ group. All patients with PHLF$_{clinic}$ were included in the PHLF$_{50–50}$ group. One patient

Table 1 Clinicopathologic and preoperative laboratory characteristics in 81 patients submitted to hemi-hepatectomy

	All patients (n = 81)	Without cirrhosis (n = 43)	With cirrhosis (n = 38)	*P*-value
Age, years, median (range)	59 (34–81)	61 (42–81)	58 (34–73)	NS
Gender, male/female, n	68/13	35/8	33/5	NS
Type of tumour, n (%)				
Hepatocellular carcinoma	54 (66.7%)	18 (41.9%)	36 (94.7%)	<0.001
Metastases	16 (19.8%)	16 (37.2%)	0	
IHCCA	10 (12.3%)	8 (18.6%)	2 (5.3%)	
Others	1 (1.2%)	1 (2.3%)	0	
Preoperative liver function, median (range)				
Serum total bilirubin, mg/dl	0.60 (0.20–1.20)	0.50 (0.30–1.20)	0.60 (0.20–1.10)	NS
Prothrombin time, %	101.00 (68.00–134.00)	105.00 (68.00–126.00)	95.50 (75.00–134.00)	NS
ICG R15, %	11.40 (0.10–22.40)	10.30 (0.10–22.40)	12.20 (0.40–22.20)	NS
Volumetric assessment, median (range)				
TFLV, ml	1214 (773–2297)	1217 (773–1745)	1172 (793–2297)	NS
SLV, ml	1407 (1032–2338)	1360 (1163–1730)	1434 (1032–2338)	NS
TFLV : SLV, %	87.55 (47.82–116.75)	88.91 (47.82–116.75)	84.09 (59.72–113.53)	NS
RLV, ml	514.00 (276–1040)	514.00 (276–1035)	514.50 (316–1040)	NS
aFLR, %	41.58 (28.15–68.26)	41.34 (28.15–60.39)	43.05 (30.07–68.26)	NS
sFLR, %	37.02 (18.00–70.50)	37.02 (18.00–70.50)	37.25 (25.20–58.58)	NS

IHCCA, intrahepatic cholangiocarcinoma; ICG R15, indocyanine green retention rate at 15 min; TFLV, total functional liver volume; SLV, standard liver volume; aFLR, actual future liver remnant; sFLR, standardized future liver remnant; NS, not significant.

showed a serum total bilirubin level of 5.7 mg/dl and PT of 44% at PoD 5, but displayed no symptoms of hepatic dysfunction such as ascites, encephalopathy or bleeding tendency. The 50–50 criterion showed sensitivity of 100% and specificity of 98.6% for the prediction of clinical PHLF; however, sensitivity and specificity for the prediction of mortality from PHLF declined to 44.4% and 93.5%, respectively. Four patients were classified in the PHLF$_{peakBil7}$ group, including three of the four patients who died and one patient who underwent liver transplantation. The other patient who died showed a peak serum bilirubin level of 6.8 mg/dl, which was close to the 7 mg/dl level. Thus, all patients with grade C PHLF (graded according to severity in line with the International Study Group of Liver Surgery[18]) were classified as within the PHLF$_{peakBil7}$ group. The criterion defined as a peak bilirubin level of >7 mg/dl (except for the patient with peak bilirubin of 6.8 mg/dl) showed sensitivity of 75.0% and specificity of 98.7% for the prediction of mortality, but showed lower sensitivity (50.0%) and specificity (94.8%) for the prediction of clinical PHLF.

Correlations between aFLR, sFLR, sFLR : ICG R15 and postoperative liver function

In patients without cirrhosis, aFLR, sFLR and the sFLR : ICG R15 ratio showed significant correlations with postoperative total serum bilirubin and PT at every postoperative measurement and with peak values. Among postoperative total serum bilirubin measurements, the level at PoD 5 showed a stronger correlation with sFLR (correlation between bilirubin level and 1/sFLR: $P <$

0.001, $R = 0.763$, $R^2 = 0.582$) than with aFLR (correlation between bilirubin level and 1/aFLR: $P < 0.001$, $R = 0.309$, $R^2 = 0.556$) and the sFLR : ICG R15 ratio (correlation between bilirubin level and sFLR : ICG R15: $P < 0.001$, $R = 0.574$, $R^2 = 0.329$) (Fig. 2). In patients with cirrhosis, aFLR, sFLR and sFLR : ICG R15 showed no significant correlation with postoperative serum total bilirubin and PT at any PoD in regression analysis (Fig. 2).

Determination of cut-off value of sFLR : ICG R15 in patients with cirrhosis

When the ratio of sFLR to ICG R15 was assessed with ROC analysis for the occurrence of PHLF in patients with cirrhosis, the same cut-off value, 1.87, was obtained (area under the curve [AUC]: 0.755). An additional assessment was performed to obtain the cut-off value of the sFLR : ICG R15 ratio in patients with cirrhosis. Lee *et al.* have reported a formula for predicting the safe limit of hepatectomy,[16] expressed as:

$$\text{safe FLR limit (Lee's FLR)} = 1.98 \times \text{ICG R15} + 0.3672.$$

In this equation, FLR is expressed as the sFLR and SLV is calculated from the equation:

$$\text{SLV (ml)} = 706.2 \times \text{BSA (m}^2) + 2.4.^{[16,22]}$$

Given the differences in the methods of calculating SLV, a ratio of sFLR to Lee's FLR was calculated to compare sFLR and Lee's
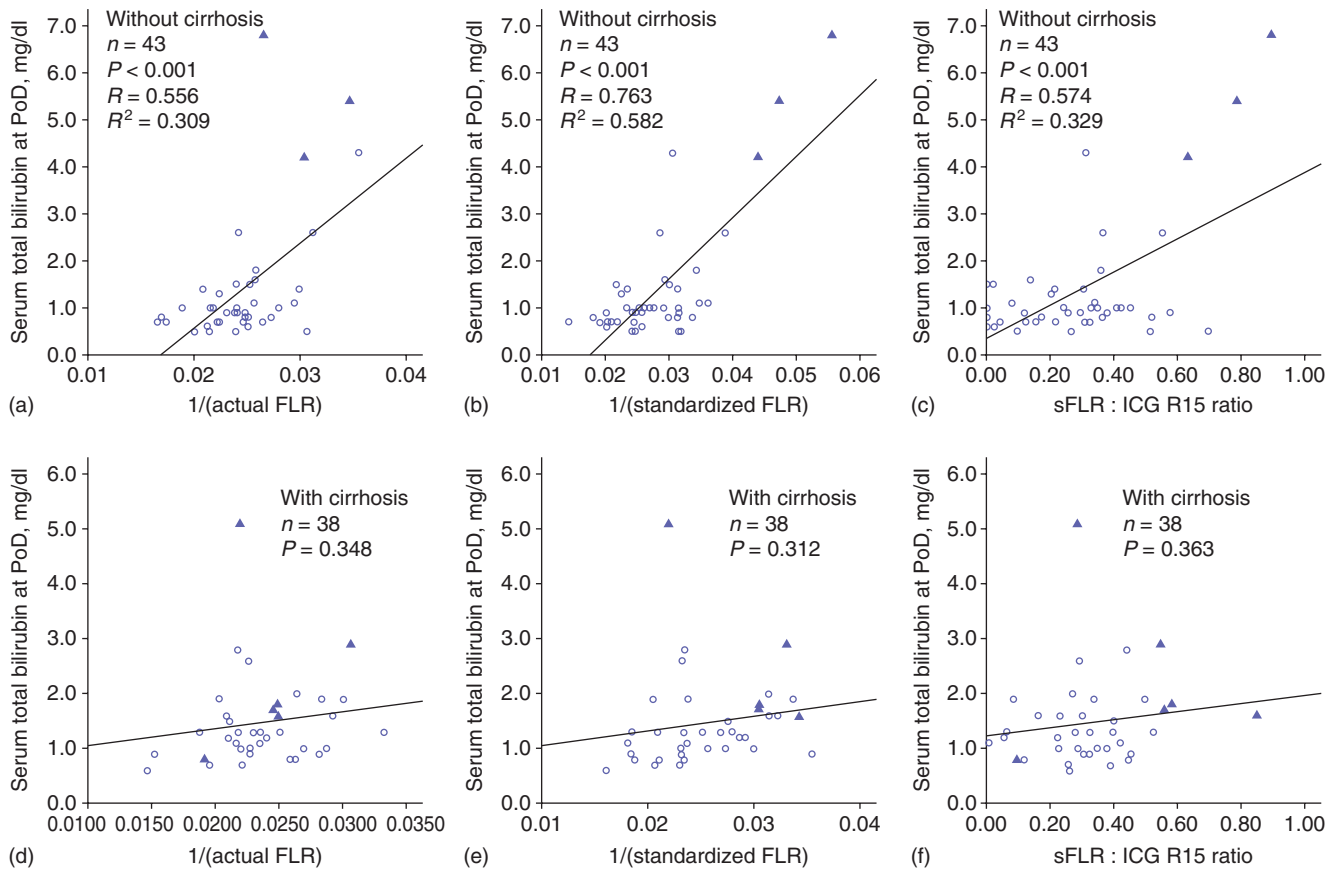
Figure 2 Correlations between actual future liver remnant (aFLR), standardized future liver remnant (sFLR), the sFLR : indocyanine green retention at 15 min (ICG R15) ratio and postoperative serum total bilirubin on postoperative day (PoD) 5. Open circles indicate patients without post-hepatectomy liver failure (PHLF); closed triangles indicate patients with PHLF. (a–c) Significant correlations emerged between aFLR, sFLR, sFLR : ICG R15 and serum total bilirubin in patients without cirrhosis: sFLR showed the strongest correlation with postoperative serum total bilirubin compared with aFLR and sFLR : ICG R15. (d–f) However, aFLR, sFLR and sFLR : ICG R15 did not show significant correlations with serum total bilirubin at PoD 5 in patients with cirrhosis

FLR. Receiver operating curve analysis was used to identify a cut-off value of the sFLR : Lee's FLR ratio in predicting PHLF; the identified cut-off value was 0.9595. Accordingly, this resulted in the formula:

$$\text{safe limit of sFLR} = 0.9595 \times \text{Lee's FLR}$$
$$= 1.8998 \times \text{ICG R15} + 0.3523.$$

Because 0.3523% of sFLR is a very small value, the equation can be simplified and expressed as:

$$\text{safe limit of sFLR} \approx 1.9 \times \text{ICG R15}.$$

Two methods to determine the cut-off value of sFLR : ICG R15 showed similar results. Therefore, a safe limit for hepatectomy in patients with cirrhosis can be expressed as the following simple equation:

$$\frac{\text{sFLR}}{\text{ICGR15}} > 1.9$$

Comparison of aFLR, sFLR and sFLR : ICGR15 as predictor of PHLF

In patients without cirrhosis, aFLR, sFLR and sFLR : ICG R15 were significantly lower in the PHLF group than in the non-PHLF group ($P = 0.021$, $P < 0.001$ and $P = 0.001$, respectively). However, in patients with cirrhosis, there were no significant differences in aFLR and sFLR between the PHLF and non-PHLF groups. Only the sFLR : ICG R15 ratio differed significantly between the PHLF and non-PHLF groups (Table 2). In patients without cirrhosis, the cut-off values for aFLR, sFLR and sFLR : ICG R15 determined using ROC analysis were 33%, 25% and 1.7, respectively (AUC: 0.908, 1.000 and 0.992, respectively). Among these, sFLR was the most useful predictor of PHLF in patients without cirrhosis. In

Table 2 Comparison of actual future liver remnant (FLR), standardized FLR, indocyanine green retention rate at 15 min (ICG R15), and the standardized FLR : ICG R15 ratio between patients with and without post-hepatectomy liver failure (PHLF)

	PHLF$_{50\%50}$		*P*-value
	Yes	**No**	
Without cirrhosis	*n* = 3	*n* = 40	
aFLR, %, median (range)	32.94 (28.84–37.65)	41.55 (28.15–60.39)	0.013
sFLR, %, median (range)	21.12 (18.00–22.73)	38.54 (25.74–70.50)	<0.001
ICG R15, %, median (range)	16.10 (14.40–16.60)	9.95 (0.10–22.40)	0.074
sFLR : ICG R15 median (range)	1.27 (1.11–1.57)	3.59 (1.43–460.6)	<0.001
With cirrhosis	*n* = 6	*n* = 32	
aFLR, %, median (range)	40.50 (32.63–52.19)	43.77 (30.07–68.26)	0.740
sFLR, %, median (range)	29.48 (26.13–49.54)	38.43 (25.20–58.58)	0.297
ICG R15, %, median (range)	15.65 (4.80–22.20)	11.80 (0.40–19.90)	0.199
sFLR : ICG R15 median (range)	1.80 (1.17–10.32)	3.29 (1.90–128.80)	0.050

Statistical significance was tested using the Mann–Whitney *U*-test.
aFLR, actual future liver remnant; sFLR, standardized future liver remnant.

Table 3 Actual future liver remnant (FLR), standardized FLR, and the ratio of standardized FLR to indocyanine green retention rate at 15 min (ICG R15) as predictors of post-hepatectomy liver failure (PHLF) after major hepatectomy

		PHLF$_{50\%50}$		AUC	Sensitivity	Specificity	PPV	NPV	*P*-value
		Yes	**No**						
Without cirrhosis									
aFLR	<33%	2	3	0.908	66.7%	92.5%	40.0%	97.4%	0.032
	33%	1	37						
sFLR	<25%	3	0	1.000	100%	100%	100%	100%	<0.001
	25%	0	40						
sFLR : ICG R15	<1.7	3	1	0.992	100%	97.5%	75.0%	100%	<0.001
	1.7	0	39						
With cirrhosis									
aFLR	<41%	4	12	0.547	66.7%	62.5%	25.0%	90.9%	0.190
	41%	2	20						
sFLR	<30%	4	6	0.641	66.7%	81.3%	40.0%	92.9%	0.031
	30%	2	26						
sFLR : ICG R15	<1.9	4	0	0.755	66.7%	100%	100%	94.1%	<0.001
	1.9	2	32						

AUC, area under the curve; PPV, positive predictive value; NPV, negative predictive value; aFLR, actual future liver remnant; sFLR, standardized future liver remnant.

patients without cirrhosis, PHLF developed only in patients with an sFLR of <25%, among whom an sFLR of <25% demonstrated 100% sensitivity and 100% specificity in predicting PHLF. In patients with cirrhosis, the cut-off values of aFLR, sFLR and sFLR : ICG R15 determined using ROC analysis were 41%, 30% and 1.9, respectively (AUC: 0.547, 0.641 and 0.755, respectively). An sFLR : ICG R15 ratio of <1.9 was the most useful predictor of PHLF in patients with cirrhosis, demonstrating 66.7% sensitivity and 100% specificity. Predictive values of the aFLR, sFLR and sFLR : ICG R15 ratio are displayed in Table 3. Because patients with cirrhosis have impaired hepatic function compared with patients without cirrhosis, in patients with cirrhosis the sFLR should exceed 25%. Therefore, a simple set of criteria for safe hepatic resection, named the CNUH criteria, are proposed: (i) in patients without cirrhosis, if the sFLR is >25%, hepatectomy can be performed safely, and (ii) in patients with cirrhosis, if the sFLR is >25% and the sFLR : ICG R15 ratio is >1.9, hepatectomy can be performed safely.

Discussion

Remnant liver volume after resection is a critical factor for predicting postoperative outcomes. Generally, the accepted limit for the ratio of the FLR for safe resection in normal liver ranges from

20% to 30%, according to different authors.[3,6,11,23,24] Several authors have proposed that direct CT measurement of the TFLV may be inaccurate for the following reasons: (i) measurement of TFLV is subject to cumulative error associated with the presence of multiple tumours or intrahepatic bile duct dilatation;[3,25,26] (ii) tumours compressing or invading the portal vein or bile ducts induce atrophy of the involved liver and in such cases measured TFLV may not reflect accurate liver function, and (iii) measured TFLV does not provide a fixed estimation of TFLV before and after portal vein embolization (PVE) because in cases of atrophy without contralateral hypertrophy from PVE, the use of a smaller post-PVE TFLV as a denominator for calculating the FLR may falsely indicate a change in volume (hypertrophy).[3] To overcome the errors associated with traditional liver volumetry, Urata et al. introduced the concept of SLV based on the observation that in adults without chronic liver disease, liver volume has a linear correlation with body size and weight.[22] Vauthey et al. described a minimum safe sFLR of 25% in patients without cirrhosis undergoing extended right hepatectomy and described the occurrence of major postoperative complications in three of five patients with sFLR volumes of 25%, compared with no major complications in the remaining 10 of the resected group with sFLR volumes of >25% ($P = 0.002$).[6] Abdalla et al. reported the occurrence of postoperative complications in 50% of patients submitted to extended right hepatectomy with sFLR volumes of 20% but in only 13% of patients with sFLR volumes of >20%.[2] Kishi et al. identified significant increases in the frequencies of liver insufficiency and death from liver failure in patients with sFLR volumes of 20% (34% and 11%, respectively), compared with patients with sFLR volumes of 20 30% (10% and 3%, respectively; $P < 0.001$ and $P = 0.038$).[3] More recently, Narita et al. reported that aFLR and sFLR were independent predictors of the occurrence of postoperative liver failure.[5] However, no direct comparison of the two ratios was performed. All of these studies were performed in patients without cirrhosis. In the present study, sFLR showed a stronger correlation with postoperative total serum bilirubin and a more accurate predictive value compared with sFLR and sFLR : ICG R15 values in patients without cirrhosis (Fig. 2, Table 2). Further, an sFLR volume of >25% was found to be an acceptable indicator for safe hepatectomy in patients without cirrhosis. This is consistent with values reported in previous studies.

Truant et al. reported that an FLR measurement standardized to BW was more specific than an aFLR in predicting the postoperative course after extended hepatectomy.[4] More recently, a comparison of FLR measurements standardized to BW and BSA showed the two methods to be highly correlated and to yield similar results in predicting postoperative hepatic dysfunction.[1] The authors reported that in patients without cirrhosis, an FLR : BW of 0.4 and an FLR : SLV ratio of 20% provide equivalent thresholds for safe hepatic resection.[1] Although the method of standardizing the FLR differed from that used in the present study, the finding that sFLR is more accurate than aFLR is similar to the present results.

The determination of the safe limits for liver resection in patients with cirrhosis is more complex because the degree of hepatic dysfunction that is not describable by Child–Pugh class is widely variable. Therefore, some authors have proposed a different surgical approach depending on the ICG R15. Lee et al. demonstrated the relationship between the ratio of RLV and preoperative ICG R15 in patients with postoperative liver dysfunction.[16] The authors calculated the FLR ratio with the SLV. The SLV was calculated using the formula:

$$SLV\ (ml) = 706.2 \times BSA\ (m^2) + 2.4.^{22}$$

The authors expressed the limit of safe hepatic resection using the formula:

$$ratio\ of\ RLV\ (RR) = 1.98 \times ICG\ R15 + 0.3672.$$

The safe limit for hepatic resection for all patients enrolled in the present study was calculated using the equation and methods described by Lee et al.[16] When the criteria selected in the present study and Lee et al.'s formula[16] were compared as predictors of PHLF, the latter showed good predictive value; however, the specificity of the criteria outlined in the present study was slightly higher in patients without cirrhosis, and their sensitivity in patients with cirrhosis was slightly higher (Table 4). The most remarkable difference between the present criteria and Lee et al.'s formula[16] refers to the need to secure the minimal volume required to meet the patient's metabolic demand, regardless of the ICG R15. The minimal volume identified in the present study was 25% of sFLR.

In 1984, Yamanaka et al. reported a formula for predicting mortality.[27] Later, in 1994, the same authors reported further outcomes of using this method.[17] Yamanaka et al. used the parenchymal hepatic resection rate (PHRR) calculated using CT. This represented the concept of 'actual FLR'. In this system, patients were classified within the following categories of safe, borderline and risky according to prediction score. The authors reported that all of the three patients with metastatic cancers in the risky zone died, but none of the six patients in the borderline zone and the 49 patients in the safe zone with metastatic cancers died. The prediction scores for the 81 patients in the present series were calculated according to the formula of Yamanaka et al.[27] The PHRR was calculated with the formula:

$$PHRR\ (\%) = 100\ \ aFLR.$$

When this prediction scoring system was applied in the present patient series, it showed a favourable negative predictive value, but its positive predictive value was not satisfactory, especially in patients with cirrhosis (Table 4). There were some remarkable differences between this method and the criteria developed in the present study. Firstly, the method described by Yamanaka et al. uses aFLR expressed as the PHRR.[27,28] Secondly, the authors

Table 4 Comparison of predictive value among the Chonnam National University Hwasun Hospital (CNUH) criteria and other methods

| | | PHLF$_{50\times50}$ | | Sensitivity | Specificity | PPV | NPV | *P*-value |
		Yes	No					
Without cirrhosis								
CNUH	Risky	3	0	100%	100%	100%	100%	<0.001
	Safe	0	40					
Lee *et al.*[16]	Risky	3	1	100%	97.5%	75%	100%	<0.001
	Safe	0	39					
Yamanaka *et al.*[27]	Risky	3	4	100%[a]	90.0%[a]	42.9%[a]	100%[a]	0.001[c]
	Borderline	0	11	100%[b]	62.5%[b]	16.7%[b]	100%[b]	
	Safe	0	25					
With cirrhosis								
CNUH	Risky	4	0	66.7%	100%	100%	94.1%	<0.001
	Safe	2	32					
Lee *et al.*[16]	Risky	3	0	50.0%	100%	100%	91.4%	0.002
	Safe	3	32					
Yamanaka *et al.*[27]	Risky	2	3	33.3%[a]	90.6%[a]	40.0%[a]	87.9%[a]	0.011[c]
	Borderline	3	5	83.3%[b]	75.0%[b]	38.5%[b]	96.0%[b]	
	Safe	1	24					

[a]Values were calculated as risky versus others.
[b]Values were calculated as others versus safe.
[c]Statistical significance was tested using linear-by-linear association.
PHLF, post-hepatectomy liver failure; PPV, positive predictive value; NPV, negative predictive value.

assessed the scoring system for mortality, not for PHLF, and thus deaths from other causes were included. Thirdly, age was used as a predictor. However, the present authors were unable to find any significant correlation between age and PHLF. Previously, Nanashima *et al.* showed the incidence of PHLF to be unaffected by age despite the fact that systemic complications increase in elderly patients.[29]

In the present study, sFLR was more suitable for the prediction of PHLF in patients without cirrhosis than the sFLR : ICG R15 ratio; however, the sFLR : ICG R15 ratio was more suitable in patients with cirrhosis than the sFLR. This result is generally attributed to the difference in regenerative function between patients with and without cirrhosis. Tiberio *et al.* reported that cirrhotic livers demonstrate lower levels of hepatocyte growth factor and other transcription factors, leading to a reduction in DNA synthesis and lower volumes of regenerated liver.[30] Moreover, Corpechot *et al.* reported that cirrhotic livers show an increased risk for ischaemia–reperfusion injury and fibrosis, leading to regional ischaemia and contributing to impaired growth and regeneration.[31] This claim needs to be investigated further.

The present study is subject to some notable limitations. Firstly, because the incidence of PHLF was very low, it is difficult to confirm whether an sFLR volume of 25% and an sFLR : ICG R15 ratio of 1.9 are truly acceptable or not. In addition, the small size of the retrospective cohort highlights the need for more highly powered prospective studies. Nonetheless, the present study has

delivered a set of 'simple' criteria for determining the safety of hepatic resection in patients with and without cirrhosis.

Conclusions

In conclusion, the sFLR volume was more relevant than that of the aFLR in predicting postoperative hepatic function and PHLF after right hemi-hepatectomy. The present simple criteria, expressed as an sFLR volume of >25%, regardless of ICG R15 level, in patients without cirrhosis, and an sFLR of >25% and an sFLR : ICG R15 ratio of >1.9 in patients with cirrhosis, are acceptable for predicting the safety of hepatic resection. These results require to be confirmed in a larger-scale, multicentre and prospective study.

Conflicts of interest

None declared.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1. Correlations between future liver remnant (FLR) volumes and the ratio of FLR to indocyanine green retention at 15 min (ICG R15) and postoperative laboratory findings.