Comparison of remnant to total functional liver volume ratio and remnant to standard liver volume ratio as a predictor of postoperative liver function after liver resection

Hee Joon Kim, Choong Young Kim, Young Hoe Hur, Yang Seok Koh, Jung Chul Kim, Chol Kyoon Cho, and Hyun Jong Kim

Department of Surgery, Chonnam National University College of Medicine, Gwangju, Korea

Backgrounds/Aims: The future liver remnant (FLR) is usually calculated as a ratio of the remnant liver volume (RLV) to the total functional liver volume (RLV/TFLV). In liver transplantation, it is generally accepted that the ratio of the graft volume to standard liver volume (SLV) needs to be at least 30% to 40% to fit the hepatic metabolic demands of the recipient. The aim of this study was to compare RLV/TFLV versus RLV/SLV as a predictor of postoperative liver function and liver failure.

Methods: CT volumetric measurements of RLV were obtained retrospectively in 74 patients who underwent right hemihepatectomy for a malignant tumor from January 2010 to May 2013. RLV and TFLV were obtained using CT volumetry, and SLV was calculated using Yu’s formula: SLV (ml)=21.585×body weight (kg)0.732×height (cm)0.225. The RLV/SLV ratio was compared with the RLV/TFLV as a predictor of postoperative hepatic function.

Results: Posthepectomy liver failure (PHLF), morbidity, and serum total bilirubin level at postoperative day 5 (POD 5) were increased significantly in the group with the RLV/SLV ≤ 30% compared with the group with the RLV/SLV > 30% (p=0.002, p=0.004, and p<0.001, respectively). But RLV/TFLV was not correlated with PHLF and morbidity (p=1.000 and 0.798, respectively). RLV/SLV showed a stronger correlation with serum total bilirubin level than RLV/TFLV (RLV/SLV vs. RLV/TFLV, R=0.706 vs. 0.499, R²=0.499 vs. 0.239). Conclusions: RLV/SLV was more specific than RLV/TFLV in predicting the postoperative course after right hemihepatectomy. To determine the safe limit of hepatic resection, a larger-scaled prospective study is needed.

Key Words: Liver volumetry; Future liver remnant; Liver resection; Liver failure

INTRODUCTION

Over the recent decade, liver resection has become increasingly safe as a result of improvements in surgical technique. But, posthepatectomy liver failure (PHLF) remains one of the most serious complications after liver resection. The occurrence of PHLF after major liver resection has been reported in up to 8% of liver resection patients, depending on the patient’s condition and the functional reserve of the liver before resection.1-3 PHLF is closely related to the volume and function of the remnant liver. Patients with a small future liver remnant (FLR) are at a higher risk for developing PHLF. FLR is usually expressed as the ratio of the remnant liver volume (RLV) and the total functioning liver volume (TFLV).4,5 The TFLV is calculated using the following formula: total liver volume (TLV)-tumor volume (TV)=TFLV. The critical minimum FLR has been estimated to be approximately 20% in normal livers, and 40% in cirrhotic livers.6 However, it is still unclear why some patients with a smaller FLR do not develop PHLF, whereas some with a greater FLR do. In liver transplantation, a major concern is determining the minimum graft volume required for a recipient to meet his or her metabolic demands.7,8 It is generally accepted that the ratio of the graft volume to the standard liver volume (SLV) needs to be at least 30% to 40% to fit the hepatic metabolic demands of the recipient.7,10,11 The Indocyanine green retention rate at 15 minutes (ICG R15) is the most common preoperative test for evaluating hepatic functional reserve.12,13
total bilirubin level and prothrombin time (PT) at post-operative day 5 are known as markers of liver function and are predictive markers of hepatic failure after hepatic resection.\textsuperscript{14,15}

Based on the above theories, the aim of the present study was to evaluate the significance of the standardized FLR (RLV/SLV) as a predictive factor of liver function and liver failure after hepatic resection, compared to the actual FLR (RLV/TFLV).

**METHODS**

From January 2010 to May 2013, 74 patients underwent right hemihepatectomy for malignant hepatic tumor at the Department of Surgery, Chonnam National University Hwasun Hospital. The records for 74 patients were reviewed retrospectively. Patients with perihilar cholangiocarcinomas and gallbladder cancers were excluded because of the frequency of preoperative hyperbilirubinemia. No patient underwent preoperative portal vein embolization (PVE).

**Operative procedures**

The liver was exposed via a right subcostal abdominal incision with a midline extension to the xiphoid process. Intraoperative ultrasonography was used to confirm tumor 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. After separating the hepatocaval ligament, the right hepatic vein was looped. Hilar dissection was undertaken to isolate and divide the right hepatic artery and portal vein. Pringle's maneuver was not used in any of the patients. Hepatic parenchymal transection was performed using an ultrasonic aspirator. After parenchymal dissection, the right hepatic vein was subsequently divided and sutured.

**Postoperative care**

All patients received the same postoperative care by the same team of surgeons in the intensive care unit during the early postoperative course. Parenteral nutritional support was provided for patients with liver cirrhosis. Early enteral nutrition was encouraged once bowel activity returned. All intraoperative and postoperative complications were recorded prospectively. Liver function tests including the serum total bilirubin level and PT were sampled routinely on postoperative days (POD) 1, 3, 5, and 7. Serum total bilirubin level and PT at POD 5 were chosen to evaluate the hepatic function after liver resection.\textsuperscript{14} The PHLF was defined as both a PT of <50% and a total serum bilirubin level >2.9 mg/dl after postoperative day 5 according to the “50-50 criteria”, and the development of intractable ascites or hepatic encephalopathy.\textsuperscript{14,15}

Postoperative mortality was defined as death occurring during the postoperative period during the hospital stay or within 30 days of surgery.

**Standard liver volume calculation**

The SLV was calculated using the following formula reported by Yu et al.\textsuperscript{16}: 

\[ \text{SLV} (\text{ml}) = 21.585 \times \text{body weight (kg)}^{0.732} \times \text{height (cm)}^{0.225} \]

**Volumetric liver analysis using Dr. Liver**

All patient underwent contrast-enhanced computed tomography (CT) as part of the routine preoperative assessment. Arterial, portal, and venous phase series of images from the preoperative CT scans were used for the CT volumetry. Volumetric analysis using Dr. Liver (Humanopia co., Ltd, Pohang, Gyeongbuk, Korea) was performed by two surgeons (HJ Kim and CY Kim). The liver was semi-automatically extracted once multiple seed points had been selected on 5 to 6 slices. The portal vein, hepatic vein, IVC, and tumor were extracted in the same manner. The total liver volume (TLV) and tumor volume (TV) were automatically calculated with Dr. Liver. The gall bladder and IVC were excluded in the liver volume, and the intrahepatic vascular and biliary structures were included. The total functional liver volume (TFLV) was calculated using the following formula: 

\[ \text{TLV-TV} = \text{TFLV} \]

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

**Statistics**

Continuous variables were expressed as the median (range) or the mean±standard deviation and compared using the Mann-Whitney U test. The impact of the
RLV/SLV and RLV/TFLV was evaluated both as categorical and continuous variables. Discrete variables were compared using the chi-square test or Fisher's exact test. Correlations between continuous variables were assessed using regression analysis. The resulting regression line was described as a logarithmic equation, and the correlation coefficients (R and R^2) were calculated. The RLV/SLV with cut-off values of 30% and 40% and the RLV/TFLV with a cut-off value of 40% were calculated to look for the occurrence of PHLF and elevation of the liver function test using receiver operating characteristic (ROC) curve analysis. A p-value of < 0.05 was considered to indicate statistical significance. Statistical analysis was performed using SPSS for windows version 18.0 (SPSS, Inc., Chicago, IL, USA).

RESULT

Patients
A total of 74 patients were evaluated in the present study. Their median age was 58 years (range: 34-81 years). 52 (70.3%) patients underwent right hemi-hepatectomy because of hepatocellular carcinoma, 13 (17.6%) patients because of metastatic tumor, 8 (10.8%) patients because of intrahepatic cholangiocarcinoma, and 1 (1.4%) patient because of carcinosarcoma. A total of 37 (50%) patients had histologic evidence of liver cirrhosis. All patients with cirrhotic liver were in the Child A class. None of the patients had biliary obstruction, preoperative hyperbilirubinemia, or preoperative PT prolongation. Clinicopathologic characteristics of the patients are shown in Table 1. For each ratio, the groups were comparable in terms of the preoperative data.

Liver volume assessment
There were no significant differences in TFLV, SLV, RLV/TFLV, and RLV/SLV between the liver cirrhosis (LC) positive group and negative group. The mean TFLV was smaller than SLV in each group, but it was not significant, statistically (Table 2). In 8 patients (10.8%), TFLV was significantly smaller than SLV (TFLV/SLV <70%). There was a good correlation between RLV/TFLV and RLV/SLV (ρ < 0.001, R=0.718) (Fig. 2). However, some discordant results were observed. Of the 46 patients in the RLV/TFLV
Table 1. Clinicopathologic and preoperative laboratory characteristics of 74 patients

|                  | FRL ratio   | RS ratio   |       |       |       |       |       |       |       |       |       |       |       |
|------------------|-------------|------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|                  | ≤40% | >40% | p | ≤40% | >40% | p | ≤30% | >30% | p |
| Age, median (range) | 28  | 46 | NS | 59 (36-81) | 57 (34-74) | NS | 61 (42-76) | 58 (34-81) | NS |
| Gender (M/F)      | 58/20 | NS | 45/20 | NS | 15/0 | NS | 50/9 | NS |
| DM, n (%)         | 3 (10.7%) | 9 (19.6%) | NS | 9 (18.4%) | 3 (12.0%) | NS | 1 (6.7%) | 11 (18.6%) | NS |
| Type of tumor, n (%) |       |       |       |       |       |       |       |       |       |
| HCC              | 22 (78.6%) | 30 (65.2%) | NS | 38 (77.6%) | 14 (56.0%) | NS | 13 (86.7%) | 39 (66.1%) | NS |
| Metastases       | 4 (14.3%) | 9 (19.6%) | NS | 6 (12.2%) | 7 (28.0%) | NS | 1 (6.7%) | 12 (20.3%) | NS |
| IHCCA            | 2 (7.1%) | 6 (13.0%) | NS | 4 (8.2%) | 4 (16.0%) | NS | 1 (6.7%) | 7 (11.9%) | NS |
| Others           | 0 (0%) | 1 (2.2%) | NS | 1 (2.0%) | 0 (0%) | NS | 0 (0%) | 1 (1.7%) | NS |
| Liver cirrhosis, n (%) |       |       |       |       |       |       |       |       |       |
| Yes              | 13 (46.4%) | 24 (52.2%) | NS | 27 (55.1%) | 10 (40.0%) | NS | 9 (60.0%) | 28 (47.5%) | NS |
| No               | 15 (53.6%) | 22 (47.8%) | NS | 22 (44.9%) | 15 (60.0%) | NS | 6 (40.0%) | 31 (52.5%) | NS |
| Preoperative liver function test, mean±SD |       |       |       |       |       |       |       |       |       |
| Serum total bilirubin (mg/dl) | 0.61±0.21 | 0.59±0.22 | NS | 0.61±0.21 | 0.56±0.22 | NS | 0.70±0.23 | 0.57±0.20 | NS |
| PT (%)           | 99.41±13.25 | 102.00±12.03 | NS | 100.10±12.07 | 100.96±14.32 | NS | 95.20±12.58 | 101.71±12.60 | NS |
| ICG R15          | 10.04±6.13 | 10.87±6.25 | NS | 11.15±6.23 | 9.37±6.03 | NS | 10.90±6.17 | 10.46±6.23 | NS |

HCC, hepatocellular carcinoma; IHCCA, intrahepatic cholangiocarcinoma; PT, prothrombin time; ICG R15, indocyanine green retention rate at 15 minutes; NS, not significant

Table 2. Comparison of the total functional liver volume (TFLV), standard liver volume (SLV), remnant-to-total functional liver volume (RLV/TFLV), and remnant-to-standard liver volume (RLV/SLV) between cirrhotic patients (LC (+)) and non-cirrhotic patients (LC(-)) group

|                  | Total (mean±SD) | LC (+) (mean±SD) | LC (-) (mean±SD) | p-value* |
|------------------|----------------|------------------|------------------|---------|
| TFLV (ml)        | 1,263±262      | 1,247±295        | 1,279±227        | 0.247   |
| SLV (ml)         | 1,421±176      | 1,464±214        | 1,396±127        | 0.250   |
| RLV/TFLV (%)     | 42.22±7.63     | 43.20±8.10       | 41.24±7.10       | 0.289   |
| RLV/SLV (%)      | 37.54±9.10     | 37.00±8.27       | 38.08±9.95       | 0.520   |

LC, Liver cirrhosis
*Statistical significance test was done by the Mann-Whitney U-test

>40% group, 23 patients (50.0%) were classified in the RLV/SLV ≤40% group, including 4 patients (8.7%) of the RLV/SLV less than 30% group (Table 3). Differences between RLV/TFLV and RLV/SLV were over 10% in 13 patients (17.6%). Only 2 patients had a RLV/TFLV less than 30%; therefore, the RLV/TFLV with a cut-off value of 30% could not be analyzed.

Operative outcomes

Of the 74 patients who underwent right hemihepatectomy, 15 patients developed a complication, with a perioperative morbidity rate of 20.2%. Complications included ascites of over 1,000 ml/day at POD5 (n=8), wound infection (n=3), biliary requiring drainage (n=1), pleural effusion requiring drainage (n=1), pneumonia (n=1), and urinary complications (n=1). PHIL occurred in 9 patients (10.8%) including 4 patients who died (5.4%). 1 patient with PHIL underwent a liver transplantation and 4 patients recovered without a liver transplantation.
shown in Table 4, the increase of PHLF and morbidity was statistically significant only when the RLV/SLV with a cut-off value of 30% was used. Four patients (5.4%) died in the postoperative period from liver failure. Of the 4 patients, 3 had liver cirrhosis and 1 patient had chronic hepatitis B without histologic evidence of liver cirrhosis.

Correlation between RLV/TFLV, RLV/SLV and postoperative liver function test
Total serum bilirubin and PT did not correlate with the RLV/TFLV in the liver cirrhosis-positive group. However, there were significant correlations in non-cirrhotic patients. RLV/SLV had a significant correlation with total serum bilirubin and PT, especially, in the non-cirrhotic patients group (Table 5). When the correlations were analyzed in continuous variables, serum total bilirubin was significantly correlated to RLV/TFLV and RLV/SLV. Especially, a very good correlation was observed for the group with RLV/SLV 30% in both the LC (+) and LC (-) groups. However, PT was correlated only with the RLV/SLV 30% group (Table 6). In regression analysis, serum total bilirubin level had a better correlation with the RLV/SLV \( (p<0.001, R=0.442, R^2=0.195) \) than with the RLV/TFLV \( (p=0.022, R=0.265, R^2=0.061) \) (Fig. 3). When the patients were classified into LC-positive and LC-negative groups, significant correlations were found between the RLV/SLV and serum total bilirubin level in the LC-negative patients; however, no correlation was observed in LC-positive patients (Fig. 3). RLV/SLV showed a closer correlation with the postoperative serum total bilirubin level than the RLV/TFLV (\( R^2 \), RLV/SLV vs. RLV/TFLV, 0.499 vs. 0.239). ICG R15 was not correlated with PHLF and the postoperative liver function test in any of the groups.

**DISCUSSION**

Advances in surgical techniques and perioperative care,
and improvements in patent selection criteria were able to increase the number of patients who could undergo major and extended hepatectomy. With such extensive resections of the hepatic parenchyma, the risk of PHLF is increased, and it is associated with a high frequency of postoperative complications, mortality and an increased length of hospital stay.17

The remnant liver volume after resection is a critical factor for predicting the postoperative outcome. The generally accepted FLR ratio limit for safe resection in the
normal liver ranges from 20 to 30% according to different authors.17-21 Several methods for liver volume determination have been reported. The traditional method of measuring liver volumes focused on the liver to be resected, with the CT measurement of the TFLV and volume of the liver to be left as a remnant.4,5 Shoup et al.17 re-

Fig. 3. Correlation between RLV/SLV and serum total bilirubin level at POD 5 in all patients (A). No correlation was observed in LC-positive patients (B), however, Significant correlations were found between RLV/SLV and serum total bilirubin level in LC-negative patients (C). RLV/SLV showed a more close correlation with postoperative serum total bilirubin level than RLV/TFLV.
ported that patients without liver disease undergoing right trisectionectomy, with less than 25% of the actual FLR, demonstrated a 90% incidence of hepatic dysfunction.

However, several authors proposed that direct CT measurement of the TFLV may be inaccurate for the following reasons: (1) measurement of the TFLV is associated with a cumulative error associated with multiple tumors or intrahepatic bile duct dilatation\textsuperscript{21-23}, (2) tumors compressing or invading the portal vein or bile ducts induce atrophy of the involved liver and in such cases, the measured TFLV may not reflect accurate liver function; and (3) TFLV does not provide a fixed estimation for total functional liver volume before and after portal vein embolization (PVE); in cases of atrophy without contralateral hypertrophy from the PVE, the use of a smaller post-PVE TFLV as a denominator for the calculation of the FLR will falsely indicate volume change (hypertrophy).\textsuperscript{21} To overcome the errors associated with traditional liver volumetry, Urata et al.\textsuperscript{24} introduced the concept of the total estimated liver volume (TELV), based on the observation that in adults without chronic liver disease, the liver volume correlates linearly with body size and weight. Vauthey et al. described a minimum safe standardized FLR of 25% in patients who underwent extended right hepatectomy. The authors described the occurrence of major postoperative complications in 3 of 5 patients with standardized FLR volumes of $\leq 25\%$ compared with no major complications in the remaining 10 of the resected group with a standardized FLR of $> 25\%$ ($p=0.002$)\textsuperscript{19}. Abdalla et al.\textsuperscript{25} reported that postoperative complications occurred in 50% of patients who underwent extended right hepatectomy with a standardized FLR of $\leq 20\%$ versus only 13% for patients with a standardized FLR volume of over 20%, and Kishi et al.\textsuperscript{21} identified a significant increase in the frequency of liver insufficiency and death from liver failure in patients with a standardized FLR volume of $\leq 20\%$ (34 and 11%, respectively), compared with patients with a standardized FLR of 20-30% (10 and 3%, respectively, $p < 0.001$ and $p=0.038$). More recently, Narita et al. have reported that the actual FLR and standardized FLR were independent predictive factors of the occurrence of postoperative liver failure.\textsuperscript{26} But, a direct comparison of the two ratios was not performed. In the present study, half of the 46 patients in the RLV/TFLV $> 40\%$ group were classified in the RLV/SLV $\leq 40\%$ group, including 4 patients (8.7%) of the RLV/SLV less than 30% group (Table 3). And, the standardized FLR (RLV/SLV) showed a stronger correlation with the postoperative total serum bilirubin level compared to the actual FLR (RLV/TFLV) (Fig. 3). In our series, among 4 patients who died of liver failure, a patient with chronic hepatitis had an RLV/TFLV of 37.65%, but the RLV/SLV was 18.00%.

Truant et al.\textsuperscript{27} have reported that the FLR measurement standardized to body weight was more specific than the actual FLR (RLV/TFLV) in predicting the postoperative course after extended hepatectomy. More recently, a comparison of the FLR measurements standardized to the body weight and BSA showed that the two methods were highly correlated and yielded similar results in predicting postoperative hepatic dysfunction.\textsuperscript{28} The authors reported that in noncirrhotic patients, a FLR/BW ratio of $\leq 0.4$ and FLR/SLV of $\leq 20\%$ provide equivalent thresholds for performing safe hepatic resection.

The safe limit for liver resection in chronic liver disease and cirrhosis is not well-established. Determination of the safe limit of liver resection in these patients is more complex because the degree of hepatic dysfunction which is not describable with the Child-Pugh classification is widely variable. Therefore, some authors proposed a different surgical approach that depended on the ICG R15, with surgical procedures ranging from simple enucleation to major hepatectomy. Imamura et al. proposed a decision tree for the selection of the operative procedure in patients with impaired liver function.\textsuperscript{29} With this approach, the authors reported on every single death in over 1,400 liver resections during a 10-year period.

In conclusion, in the present study, the standardized FLR ratio (RLV/SLV) was more relevant than the actual FLR ratio (RLV/TFLV) in predicting postoperative hepatic function after right hemihepatectomy. Cirrhotic patients with a RLV/SLV of $\leq 30\%$ were at considerable risk for PHLF. These results need to be confirmed in a larger-scaled prospective study.

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