

# Comparison of Two Methods of Future Liver Remnant Volume Measurement

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## Abstract

**Background** In liver transplantation, a minimum graft to patient body weight (BW) ratio is required for graft survival; in liver resection, total liver volume (TLV) calculated from body surface area (BSA) is used to determine the future liver remnant (FLR) volume needed for safe hepatic resection. These two methods of estimating liver volume have not previously been compared. The purpose of this study was to compare FLR volumes standardized to BW versus BSA and to assess their utility in predicting postoperative hepatic dysfunction after hepatic resection.

**Methods** Records were reviewed of 68 consecutive noncirrhotic patients who underwent major hepatectomy after portal vein embolization between 1998 and 2006. FLR (cubic centimeter) was measured preoperatively with three-dimensional helical computed tomography; TLV (cubic centimeter) was calculated from the patients' BSA. The relationship between FLR/TLV and FLR/BW (cubic centimeter per kilogram) was examined using linear regression analysis. Receiver operating characteristic (ROC) curve analysis was used to determine FLR/TLV and FLR/BW cutoff values for predicting postoperative hepatic dysfunction (defined as peak bilirubin level >3 mg/dl or prothrombin time >18 s).

**Results** Regression analysis revealed that the FLR/TLV and FLR/BW ratios were highly correlated (Pearson correlation coefficient, 0.98). The area under the ROC curve was 0.85 for FLR/TLV and 0.84 for FLR/BW (95% confidence interval, 0.71–0.97). Sixteen of the 68 patients developed postoperative hepatic dysfunction. The ROC curve analysis yielded a cutoff FLR/BW value of  $\leq 0.4$ , which had a positive predictive value (PPV) of 78% and a negative predictive value (NPV) of 85%. The corresponding FLR/TLV cutoff value of  $\leq 20\%$  had a PPV of 80% and a NPV of 86%.

**Conclusions** Based on the strong correlation between the FLR measurements standardized to BW and BSA and their similar ability to predict postoperative hepatic dysfunction, both methods are appropriate for assessing liver volume. In noncirrhotic patients, a FLR/BW ratio of  $\leq 0.4$  and FLR/TLV of  $\leq 20\%$  provide equivalent thresholds for performing safe hepatic resection.

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Hepatic insufficiency

## Introduction

Advances in surgical technique and perioperative care have allowed more patients to be eligible for living donor liver transplantation (LDLT) and major hepatectomy with low perioperative mortality.<sup>1,2</sup> The graft volume in LDLT and liver remnant volume in major hepatic resection are critical for predicting postoperative outcome. A small-for-size graft and inadequate future liver remnant (FLR) may not meet

the hepatic metabolic demands after LDLT or major hepatectomy.<sup>3,4</sup> Preoperative volumetric analysis is essential to ensure sufficient functional liver parenchyma remains. In hepatic resection, preoperative portal vein embolization (PVE) is performed to increase the FLR volume and enhance the safety of major hepatectomy.<sup>5</sup> A highly accurate means of measuring graft volume and FLR preoperatively is three-dimensional computed tomography (CT).<sup>6,7</sup> In LDLT, the CT-measured graft volume is equated with graft weight, as liver density is 1 g/dl.<sup>6,8</sup> The graft weight is standardized to recipient body weight and defined as the graft-to-recipient weight ratio (GRWR) to determine the minimum graft requirement.<sup>3,9</sup> Because the liver normally composes 2 to 2.5% of the body weight (BW), a GRWR of 1 corresponds to 50% of liver volume, and a GRWR of 0.8 corresponds to 40% of liver volume.<sup>10</sup> In hepatic resection, the FLR volume is standardized to the total liver volume (TLV), which is based on patient body surface area (BSA).<sup>11</sup> The FLR/TLV ratio based on BSA used for liver resection and the GRWR based on BW used for liver transplantation have not been previously compared. The purpose of this study was to compare FLR volumes standardized to BSA or BW and to assess their ability to predict postoperative hepatic dysfunction after hepatic resection. We examined volumetric measurements and postoperative outcome in patients without cirrhosis who underwent preoperative PVE followed by major hepatectomy for hepatobiliary malignancies. Because the TLV bears a constant relationship to BSA and BW, we hypothesized that both methods could provide standard means to estimate liver function before hepatic resection.<sup>12</sup>

## Materials and Methods

Between December 1998 and April 2006, 68 consecutive patients with hepatobiliary malignancies underwent PVE and measurement of the FLR volume using three-dimensional CT volumetry in preparation for major hepatectomy, as previously described.<sup>13</sup> The TLV was calculated from the patient's BSA using a mathematical formula ( $TLV[\text{cm}^3] = -794.41 + 1,267.28 \times BSA [\text{m}^2]$ ), which was developed in a multicenter study of three-dimensional CT volumetric reconstructions in 292 adult patients who underwent CT for conditions unrelated to the hepatobiliary system.<sup>11</sup> This formula was validated in a meta-analysis comparing 12 formulas to estimate TLV and found to be the most precise and least biased compared to other formulas.<sup>14</sup> BSA was calculated according to Mosteller's formula:  $[\text{height (cm)} \times \text{weight (kg)} \div 3,600]^{0.5}$ .<sup>15</sup> Clinicopathological factors were reviewed, including age, gender, race, risk factors for liver injury, tumor histology, pre- and post-PVE measurements of FLR, extent of surgery, and postoperative course.

Hepatic parenchyma remote from the resected tumor was examined for pathologic findings of hepatic injury, defined as more than 30% steatosis, steatohepatitis Kleiner score  $\geq 4$ , grades 2 to 3 sinusoidal dilation, and Ishak grades 4 to 5 fibrosis.<sup>16</sup> Obesity was defined as body mass index  $\geq 30 \text{ kg/m}^2$ .

Postoperative hepatic dysfunction was defined as peak bilirubin level  $> 3 \text{ mg/dl}$  or prothrombin time  $> 18 \text{ s}$ , based on prior studies showing a correlation between these parameters and postoperative complications.<sup>17–19</sup> Receiver operating characteristic (ROC) curve analysis was used to determine FLR/TLV and FLR/BW cutoff values for predicting postoperative hepatic dysfunction.<sup>20,21</sup> Cutoff values were determined by calculating the largest sum of the sensitivity and specificity values while maintaining the lowest probability of a negative test and the highest probability of a positive test.

Continuous data were expressed as means  $\pm$  standard deviations. Dichotomous variables were compared using the Chi-square test or the Fisher exact test where appropriate. Statistical significance was determined at  $P < 0.05$ .

## Results

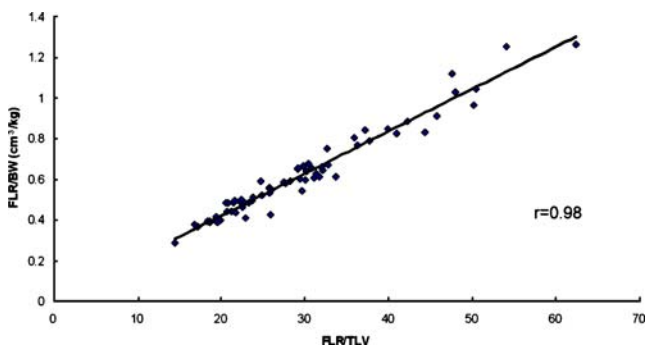
The clinical and pathological characteristics of the 68 patients in this study are presented in Table 1. Median age was 60 years for the entire cohort, and 79% of the patients were male. Preoperative PVE with subsequent right or extended right hepatectomy was performed in all patients. The most common tumor type was metastatic colorectal cancer ( $n=32$ , 47%), followed by hepatocellular carcinoma ( $n=16$ , 24%), then neuroendocrine metastases ( $n=8$ , 12%) and intrahepatic or hilar cholangiocarcinoma ( $n=7$ , 10%). The FLR/TLV and FLR/BW (cubic centimeters per kilogram) ratios were highly correlated by regression analysis (Pearson correlation coefficient, 0.98; Fig. 1). Even in patients with BW, height, and BSA values beyond one standard deviation of the mean, the correlation was excellent (Pearson correlation coefficient, 0.89). Sixteen of the 68 patients developed postoperative hepatic dysfunction. ROC curve analysis was performed to determine the utility of FLR/TLV and FLR/BW in predicting postoperative hepatic dysfunction (Fig. 2). The areas under the ROC curve were 0.85 for FLR/TLV and 0.84 for FLR/BW (95% confidence interval, 0.71–0.97), indicating good discrimination for predicting postoperative hepatic dysfunction. Cutoff values were determined to yield the highest probability of a positive test while maintaining a low probability of a negative test. A cutoff FLR/BW value of  $\leq 0.4$  had a positive predictive value (PPV) of 78% and a negative predictive value (NPV) of 85%. The corresponding FLR/TLV cutoff value of  $\leq 20\%$  had a PPV of

**Table 1** Clinicopathologic Factors of Patients Who Underwent Major Hepatectomy After Preoperative Portal Vein Embolization

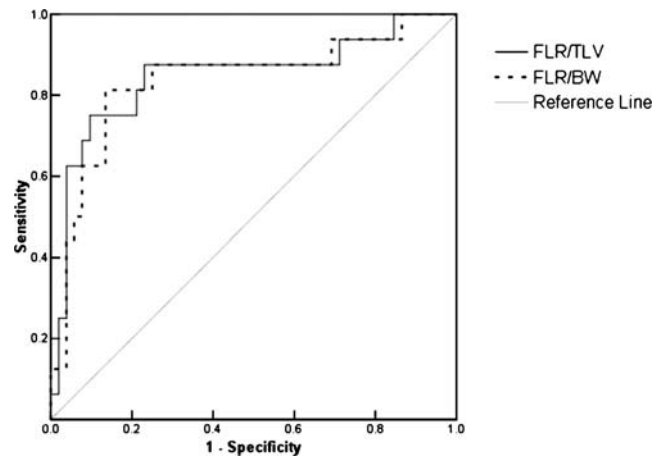
Clinicopathologic factor	
Mean age (year)	60±11 (36–78)
Gender ( <i>n</i> )	
Male	54
Female	14
Race ( <i>n</i> )	
Caucasian	55
Hispanic	6
African–American	4
Asian	3
Tumor type ( <i>n</i> )	
Colorectal metastases	32
Hepatocellular carcinoma	16
Neuroendocrine metastases	8
Intrahepatic or hilar cholangiocarcinoma	7
Gallbladder cancer	2
Thymoma metastases	1
Melanoma metastases	1
Endometrial metastases	1
Type of surgical resection ( <i>n</i> )	
Extended right hepatectomy	54
Right hepatectomy	14
Body height (cm)	173 (140–208) <sup>a</sup>
Body weight (BW, kg)	83 (49–157)
Body surface area (BSA, m <sup>2</sup> )	2.02 (1.45–2.67)
Body mass index	26.7 (19.8–48.4)
Future liver remnant volume (FLR, cm <sup>3</sup> )	459 (261–1,098)
Estimated total liver volume (TLV, cm <sup>3</sup> )	1,768 (1,037–2,593)
FLR/TLV (%)	27.7 (14.5–62.5)
FLR/BW (cm <sup>3</sup> /kg)	0.58 (0.29–1.26)

<sup>a</sup> Data expressed as median (range)

80% and a NPV of 86%. The incidence of postoperative hepatic dysfunction was stratified according to cutoff values, and FLR/TLV and FLR/BW values of ≤20% and ≤0.4 emerged as most significant (Table 2). Six of the 18 patients with FLR/TLV between 20 and 25% and FLR/BW between 0.4 and 0.5 had postoperative hepatic dysfunction. Two of the 40 patients with FLR/TLV >25% or FLR/BW >0.5 had postoperative hepatic dysfunction—one patient with



**Figure 1** Correlation between FLR/TLV and FLR/BW.



**Figure 2** ROC curve of FLR/TLV and FLR/BW measurements in predicting postoperative hepatic dysfunction.

FLR/TLV of 33% and the other with FLR/TLV of 42%. Both patients had transient rises in bilirubin that normalized rapidly after postoperative days 5 and 9, respectively. The effects of risk factors for liver injury on postoperative hepatic dysfunction were assessed (Table 3). Preoperative systemic chemotherapy (median of 4 cycles, range 2–12), diabetes, obesity, and pre-existing liver injury (moderate steatosis, steatohepatitis, and/or fibrosis) were not significant risk factors. FLR/TLV ≤20% and FLR/BW ≤0.4 were significantly associated with postoperative hepatic dysfunction.

**Discussion**

The volume of the remnant liver or graft, which is measured preoperatively with three-dimensional CT, is critical for successful hepatic resection and LDLT. In adults without chronic liver disease, liver volume correlates linearly with body size.<sup>11</sup> Thus, the volume of the remnant liver after resection or graft to be transplanted can be normalized to patient BSA or BW. In LDLT, the graft volume is normalized to patient BW, which yields the GRWR. In hepatic resection, the FLR volume is standardized to TLV, which is calculated with a formula based on BSA. These measurements are used to determine the necessary volume of graft or FLR to minimize the likelihood of postoperative hepatic dysfunction.<sup>4,9</sup>

In this report, we examined the relationship between FLR standardized to BW versus BSA and the ability of these measurements to predict postoperative hepatic dysfunction in noncirrhotic patients undergoing major hepatectomy after PVE. We focused on postoperative hepatic dysfunction instead of overall postoperative morbidity as an endpoint to avoid confounding variables such as patient comorbidities and intraoperative factors. We found excellent correlation between FLR measurements standardized to

**Table 2** Postoperative Hepatic Dysfunction Stratified by FLR/TLV and FLR/BW Values

	Number of patients	Postoperative hepatic dysfunction	PPV (%)	NPV (%)	P value
FLR/TLV $\leq 20\%$	10	8	80	86	<0.05
FLR/BW $\leq 0.4$	9	7	78	85	<0.05
FLR/TLV $\leq 25\%$ or FLR/BW $\leq 0.5$	28	14	50	92	<0.05
FLR/TLV $> 25\%$ or FLR/BW $> 0.5$	40	2	–	–	–

PPV Positive predictive value,  
NPV negative predictive value

BW and BSA. Even in patients at the extremes of body height and weight, we found good correlation between FLR/TLV and FLR/BW ratios. Using ROC curve analysis, the areas under the curve for FLR/TLV and FLR/BW exceeded 0.8, demonstrating that both methods have high discrimination for predicting postoperative hepatic dysfunction.

Our results support previous studies showing the importance of volumetric analysis as a tool to predict postoperative outcome.<sup>18,22</sup> Previously, we showed that in non-cirrhotic patients, the ratio of FLR to TLV increased 9.2–15.6% after PVE.<sup>19</sup> This increase in FLR/TLV is caused by hypertrophy of the remnant liver and not by a change in TLV, which is calculated in relation to BSA, both pre- and post-PVE. Increased FLR volume is associated with improved hepatic metabolic function, as shown by increased indocyanine green excretion, improved biliary drainage, and faster normalization of postoperative liver function tests.<sup>23–25</sup> In LDLT, a GRWR of  $\leq 0.8$  (40% of TLV) results in increased postoperative morbidity and impaired graft survival.<sup>3,9</sup> In adult patients without underlying liver disease, a FLR/TLV ratio of  $\leq 20\%$  is associated with increased complications after major hepatectomy.<sup>4,26</sup> In LDLT, a higher liver graft volume is required because of ischemia-reperfusion injury to the graft and episodes of organ rejection.

We determined cutoff values of FLR/TLV  $\leq 20\%$  and FLR/BW  $\leq 0.4$  to predict the likelihood of postoperative hepatic dysfunction. In a recently published study by Truant et al.,<sup>27</sup> increased 30-day mortality and morbidity were associated with FLR/BW  $\leq 0.5$ , which corresponds to FLR/TLV of 25%. They also found FLR/BW to be more specific than FLR/TLV in predicting postoperative outcome. However, their calculation of TLV was based on the traditional method, in which TLV, liver to be resected, and tumor

volume are measured separately with CT. This method is prone to multiplicative errors in patients with multiple tumors and cannot be used in patients with dilated bile ducts.<sup>24,28,29</sup>

In our study, we estimated TLV using a formula based on the BSA, which has been validated in a meta-analysis as a precise and unbiased approach to estimating TLV.<sup>14</sup>

When the incidence of postoperative hepatic dysfunction was stratified according to FLR volumes, FLR/TLV and FLR/BW values of  $\leq 20\%$  and  $\leq 0.4$  had the highest PPV of 80 and 78%, respectively. Patients with measurements near these cutoff values, specifically FLR/TLV between 20–25% or FLR/BW between 0.4–0.5, were also prone to developing postoperative hepatic dysfunction. These patients may have had other risk factors for impaired liver regeneration, such as diabetes mellitus, obesity, hepatic steatosis, and chemotherapy-induced hepatotoxicity. We did not, however, find a significant association between such risk factors and postoperative hepatic dysfunction, but the number of patients was small. Thirty-four patients received preoperative chemotherapy for a median of four cycles, and none received  $>12$  cycles, which has been associated with worse postoperative outcome.<sup>30</sup> In a previous report, we found that the presence of mild to moderate liver injury did not impair liver regeneration after PVE; similarly, response to PVE was comparable with or without neoadjuvant chemotherapy.<sup>19</sup> Until more data are available, patients with FLR/TLV between 20 and 30% and risk factors for liver injury, such as diabetes, obesity, and prolonged administration of chemotherapy, should be considered for preoperative PVE.<sup>31</sup>

A limitation of this study includes the restriction of the patient population to adults without underlying chronic liver disease. Although liver size bears a linear relationship to body size in patients with normal livers, this is not true with

**Table 3** Risk Factors for Liver Injury

Risk factor	Number of patients	Number with liver injury	Number with postoperative hepatic dysfunction	Univariate analysis
Preoperative chemotherapy	34	5/34 (15%)	9/34 (26%)	P=NS
Diabetes	13	2/13 (15%)	2/13 (15%)	P=NS
BMI $\geq 30$	18	1/18 (5%)	5/18 (28%)	P=NS
Pre-existing liver injury	6	–	1/6 (17%)	P=NS
FLR/TLV $\leq 20\%$	10	0	8/10 (80%)	P<0.05
FLR/BW $\leq 0.4$	9	0	7/9 (78%)	P<0.05

chronic liver disease, particularly in patients with shrunken, cirrhotic livers. Moreover, the estimation of TLV based on BW and BSA does not apply to children because the correlation between liver volume and body size is not constant during the growth period.<sup>8</sup>

In conclusion, we found excellent correlation between FLR standardized to BW versus BSA, with both methods similarly predictive of postoperative hepatic dysfunction. In noncirrhotic patients, a FLR/BW ratio of  $\leq 0.4$  and FLR/TLV of  $\leq 20\%$  provide equivalent thresholds for performing safe hepatic resection, confirming the importance of volumetric analysis in determining postoperative outcome after LDLT or major hepatectomy. Systematic measurement of the FLR and normalization to BW or BSA is an integral part of preoperative planning in patients with anticipated small remnant livers who will benefit from PVE.

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