World Journal of
Meta-Analysis

World Journal of Meta-Analysis

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Scoring criteria for determining the safety of liver resection for malignant liver tumors

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Abstract

BACKGROUND
Liver resection has become safer as it has become less invasive. However, the minimum residual liver volume (RLV) required to maintain homeostasis is unclear. Furthermore, the formulae used to calculate standard liver volume (SLV) are complex.

AIM
To review previously reported SLV formulae and the methods used to evaluate the minimum RLV, and explore the association between liver volume and mortality.

METHODS
A systematic review of Medline, PubMed, and grey literature was performed. References in the retrieved articles were cross-checked manually to obtain further studies. The last search was conducted on January 20, 2019. We developed an

SLV formula using data for 86 consecutive patients who underwent hepatectomy at our institution between July 2009 and August 2011.

RESULTS
Linear regression analysis revealed the following formula: SLV (mL) = 822.7 × body surface area (BSA) − 183.2 (R^2 = 0.419 and R = 0.644, P < 0.001). We retrieved 25 studies relating to SLV formulae and 12 studies about the RLV required for safe liver resection. Although the previously reported formulae included various coefficient and constant values, a simplified version of the SLV, the common SLV (cSLV), can be calculated as follows: cSLV (mL) = 710 or 770 × BSA. The minimum RLV for normal and damaged livers ranged from 20%-40% and 30%-50%, respectively. The Sapporo score indicated that the minimum RLV ranges from 35%-95% depending on liver function.

CONCLUSION
We reviewed SLV formulae and the minimum RLV required for safe liver resection. The Sapporo score is the only liver function-based method for determining the minimum RLV.

Key words: Standard liver volume; Residual liver volume; Hepatectomy; Mortality; Liver failure; Liver function

Core tip: We systematically reviewed standard liver volume (SLV) formulae, methods for assessing the minimum residual liver volume (RLV) required for safe liver resection, and the association between liver volume and mortality. Although the reported SLV formulae contained different coefficient/constant values, a simplified version of the SLV, the common SLV (cSLV), can be calculated as follows: cSLV (mL) = 710 or 770 × body surface area. The Sapporo score is the only liver function-based method for determining the minimum RLV.

INTRODUCTION

Liver resection is a potentially curative treatment for malignant liver tumors, such as hepatocellular carcinoma (HCC) and metastatic liver cancer, in cases in which no metastasis is present in other organs[1,2]. Although the mortality rate associated with liver resection has decreased, surgical complications still occur[3-7]. To ensure that liver resection is performed safely, it is important to preoperatively evaluate patients' liver function so that it is possible to estimate the maximum liver volume that can be safely removed[8,9]. The Child-Pugh classification and the liver damage classification established by the Liver Cancer Study Group of Japan are used to evaluate liver function[10-13]. The indications for liver resection are grade A or B liver function, according to either classification system. However, liver function varies greatly between grade A and B in patients with HCC. Therefore, in HCC patients it is difficult to accurately predict the maximum safe extent of liver resection.

Recent advances in radiological assessments of the liver have made it possible to precisely calculate liver volume prior to liver resection[8,9,14-16]. Multi-detector-row computed tomography (MDCT) can be used to evaluate not only liver volume, but also patients' individual anatomies prior to liver resection[17-19]. The aim of this systematic review was to summarize the methods used to assess liver volume in order to aid the establishment of a standard formula for calculating standard liver volume (SLV). In addition, we attempted to summarize the relationship between liver volume and liver failure in order to facilitate safe liver resection.

MATERIALS AND METHODS

This study was approved by the internal review board of Sapporo Medical University (approval ID: 302-195 and approval date: February 14, 2019). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines for conducting and reporting meta-analyses were followed[15]. To conduct this study, the study protocol was published on PROSPERO, which is the international prospective register of systematic reviews (reference: No. CRD42019123642).

Estimation of SLV

Between July 2009 and August 2011, 86 consecutive patients who underwent liver resection for malignant tumors were enrolled in this study. Clinical laboratory tests, including of the serum levels of aspartate aminotransferase, alanine aminotransferase, albumin, hyaluronic acid, hepatocyte growth factor, and antithrombin III (ATIII); the prothrombin time (PT); the indocyanine green retention rate at 15 min (ICGR15); and the platelet count were evaluated prior to liver resection. The uptake ratio of the heart at 15 min to that seen at 3 min (HH15) and the uptake ratio of the liver to the liver plus heart at 15 min (LHL15) were obtained from time activity curves of 99 m Tc-galactosyl human serum albumin scintigraphy.

Liver volume was evaluated using 64-row MDCT (LightSpeed VCT VISION; GE Healthcare, Milwaukee, WI, United States). The images were obtained in four phases, the early arterial phase, portal vein phase, hepatic vein phase, and late phase. A ZIO STATION 2 (Ziosoft Inc., Tokyo, Japan) was used to calculate liver volume. The images of the hepatic vein phase were used for volumetry, and image analysis was restricted to the first and second branches of the portal and hepatic veins, as described previously[20].

Definition of liver dysfunction

Liver failure was defined as a serum bilirubin concentration of > 10 mg/dL for > 2 d. Liver dysfunction was defined as a total bilirubin level of ≥ 3 mg/dL and a PT value of < 50% within 7 d after liver resection[21].

Database searches

A systematic review of Medline, PubMed, and grey literature was performed. References from the retrieved articles were also cross-checked manually to obtain further studies. When more than one study from the same institution was found, only the publication with the most complete data was included. The last search was conducted on January 20, 2019. The search strategy for the PubMed database was as follows: {["liver" (MeSH Terms) OR "liver" (All Fields)] AND volume (All Fields)} AND calculation (All Fields). The searches of other databases were conducted using the same medical subject headings (MeSH) and keywords in various combinations.

Statistical analyses

Patient demographics and perioperative laboratory tests were extracted from the database, and differences between the groups were compared using the chi-square test followed by a post-hoc 2 × 2 Fisher's exact test. The unpaired t-test was used for comparisons between the no liver dysfunction group (*n* = 78) and the liver dysfunction group (*n* = 8). The relationships among the various clinical parameters were evaluated using Spearman's rank correlation coefficient. The intraclass correlation coefficient (ICC) was used to assess inter-rater reliability. All calculations were performed using the SPSS 20.0 software program (SPSS Inc., Chicago, IL, United States). All results are expressed as the mean together with minimum and maximum levels. *P*-values of < 0.05 were considered to be statistically significant.

RESULTS

SLV at our institution

We investigated the cases of patients who underwent hepatectomy for various malignancies, including HCC, at our institution between July 2009 and August 2011. Table 1 shows the clinical demographics of the patients in three groups; *i.e.*, all patients (*n* = 86), the no liver dysfunction group (*n* = 78), and the liver dysfunction group (*n* = 8).

The ICGR15, serum ATIII level, operation time, the background of the malignancy, and the reduction in liver volume differed significantly between the no liver dysfunction group and liver dysfunction group (Table 1). The results of the linear regression analysis of the relationship between resectable liver volume and body surface area (BSA) are shown in Figure 1. The latter analysis resulted in the deve-

Table 1 Clinical demographics of the patients who underwent liver resection for malignant tumors in the no liver dysfunction group (*n* = 78) and liver dysfunction group (*n* = 8)

Clinical variables / characteristics	Total values (*n* = 86)	No liver dysfunction (*n* = 78)	Liver dysfunction (*n* = 8)	*P*-values
Age (yr)	67.0 ± 10.3	66.8 ± 10.5	68.7 ± 9.3	NS
BSA (cm^2)	1.61 ± 0.18	1.60 ± 0.18	1.65 ± 0.18	NS
Albumin (g/dL)	4.0 ± 0.4	4.0 ± 0.4	3.8 ± 0.4	NS
Bilirubin (mg/dL)	0.7 ± 0.3	0.6 ± 0.3	0.8 ± 0.4	NS
PT (%)	93.4 ± 11.9	93.9 ± 12.1	88.4 ± 9.7	NS
ICGR15 (%)	9.0 ± 4.6	8.4 ± 4.3	14.9 ± 2.5	< 0.001
HH15	0.578 ± 0.079	0.575 ± 0.078	0.617 ± 0.010	NS
LHL15	0.940 ± 0.027	0.940 ± 0.028	0.935 ± 0.024	NS
ATIII (%)	94.9 ± 17.2	96.0 ± 17.3	83.9 ± 13.4	0.036
Intraoperative bleeding (mL)	481.2 ± 468.5	455.8 ± 472.4	675.0 ± 430.0	NS
Operative time (min)	404.5 ± 135.2	390.8 ± 129.3	525.9 ± 140.9	0.014
Sex (male:female)	49:37	44:34	5:3	NS
Background (HCC: meta or CCC)	57:29	49:29	8:0	0.047
Hr (0/S:1:2/3)	53:17:16	49:16:13	4:1:3	NS
Sapporo score	13.2 ± 2.4	13.4 ± 2.5	11.0 ± 3.2	0.037
MELD score	7.6 ± 1.6	7.6 ± 1.7	7.8 ± 0.7	0.103
Child-Pugh score	3.2 ± 0.4	3.2 ± 0.4	3.4 ± 0.5	0.119
Total liver volume (cc)	1137.8 ± 222.9	1136.2 ± 228.5	1153.5 ± 221.4	NS
Reduction in liver volume (%)	19.0 ± 13.0	17.6 ± 12.1	32.8 ± 15.0	0.006
Residual liver volume (%)	85.1 ± 14.4	86.0 ± 13.7	75.4 ± 17.9	0.039

Continuous variables are expressed as the mean and standard deviation. BSA: Body surface area; PT-INR: Prothrombin time-international normalized ratio; ICG15: Indocyanine green retention rate at 15 min; ATIII: Serum anti-thrombin III level; HCC: Hepatocellular carcinoma; meta: Metastatic tumor; CCC: Cholangiocellular carcinoma; Hr: Hepatic resection; HH15: Uptake ratio of the heart at 15 min to that seen at 3 min on 99m Tc-galactosyl human serum albumin scintigraphy (GSA); LHL15: The uptake ratio of the liver to the liver plus heart at 15 min on GSA; MELD: Model For End-Stage Liver Disease; NS: Not significant.

lopment of the following formula for SLV: SLV (mL) = 822.7 × BSA - 183.2 (R^2 = 0.419 and R = 0.644, *P* < 0.001). On the other hand, MELD score and Child-Pugh score did not correlate with resectable liver volume at all (Supplement Figure 1 and 2).

Estimation of the minimum liver volume required for safe hepatectomy
The results of the linear regression analysis of the serum ATIII level and ICGR15 are shown in Figure 2. The sum of the values for the serum ATIII level and ICGR15 was almost 100%, which is consistent with the findings of previous studies[20]. We have also previously reported Sapporo scores for liver resection for malignant tumors (Table 2). The Sapporo score consists of four clinical variables, including the ICGR15, serum ATIII level, HH15, and LHL15. Each factor is awarded 1 to 4 points. Thus, the maximum total score is 16 points, and the minimum total score is 4 points.

The results of the linear regression analysis of the reduction in liver volume and the Sapporo score are shown in Figure 3. The closed circles indicate the patients who exhibited liver dysfunction after hepatectomy, and the open circles indicate the patients who did not display liver dysfunction after hepatectomy. Linear regression analysis revealed a formula for predicting the risk of liver dysfunction after hepatectomy. The linear coefficient was almost 5, which meant that each extra Sapporo score point indicated that a further 5% of the total liver volume could be removed safely *via* liver resection. Therefore, the maximum Sapporo score (16 points) indicates that 65% of the total liver volume can be removed safely. On the other hand, the minimum score (4 points) only allows 5% of the total liver volume to be safely removed. The relationships between the Sapporo score, the resectable liver volume, and residual liver volume (RLV) are shown in Figure 3B.

Systematic review of SLV and the minimum residual liver volume
A PRISMA flow diagram is shown in Figure 4. Among the 25 studies about SLV formulae, three types of calculations were reported. The first group used height and weight as independent factors (Table 3)[22-28]; the second group used BSA (Table 4)[24,25,29-36]; and the third group used other variables including age, gender, race, and radiological findings (Table 5)[37-43]. Although the SLV formulae in the first and second
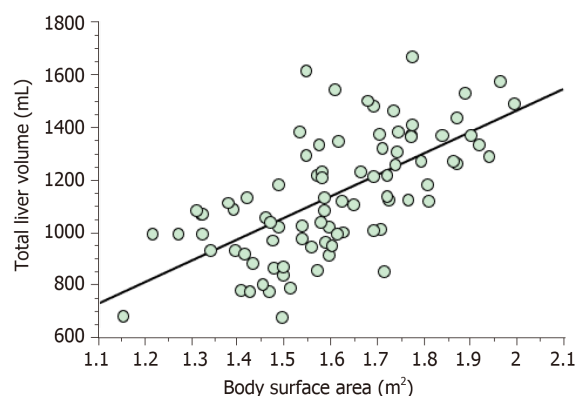
Figure 1 Linear regression analysis of total liver volume and body surface area. Standard liver volume (mL) = 822.7 × BSA - 183.2; R^2 = 0.419, R = 0.644; *P* < 0.001.

groups included a variety of coefficient and constant values, they exhibited very similar ICC of between 0.70 and 0.78. On the other hand, in the third group the ICC of the SLV values obtained using age alone were very low (0.39 and -0.39, respectively). A combination of age and other variables gave ICC of between 0.66 and 0.79. If BSA were fixed at the mean value for the second group, the SLV formulae for the second group could be simplified as shown in Table 6. Although the previously reported SLV formulae included different coefficients and constant values, they could be grouped into two clusters (Figure 5). In cluster A, a simplified version of the SLV, the common SLV (cSLV), could be calculated as follows: cSLV (mL) = 710 × BSA, whereas in cluster B the cSLV could be calculated as follows: cSLV (mL) = 770 × BSA.

The minimum RLV required for safe liver resection has been debated for several decades. Most studies that examined this issue involved the use of normal livers containing metastatic liver tumors or transplanted livers for volume estimation[44-48]. All of the studies except ours calculated minimum cut-off values based on pathological findings (Table 7)[16,17,49-57]. According to previous reports, the minimum RLV for normal livers ranged from 20%-40%[54-56], whereas that for damaged livers ranged from 30%-50%[16,52]. In contrast, the cut-off values obtained in the present study depended on liver function. According to the Sapporo score, the RLV cut-off values ranged from 35%-95%[20]. In addition, mortality rate ranged from 0.8% to 11% (Table 7).

DISCUSSION

We reviewed the previously described formulae for calculating SLV and the minimum RLV required for safe liver resection. Although various SLV formulae have been reported, some of them were similar[24,30,32-35]. Therefore, we simplified the formula for estimating SLV to produce the cSLV. Furthermore, we found that the minimum RLV required for a safe hepatectomy ranged from 25%-50% depending on the pathological background. The Sapporo score is the only liver function-based method for determining the minimum RLV.

Relationships between physical parameters and liver volume

Liver volume is obviously correlated with physical parameters[24,32-35]. However, the physiques of children and adults are markedly different[24]. In addition, the coefficients for the relationships among liver volume and physical parameters change during growth[24]. Yu *et al*[24] attempted to develop a non-linear or stepwise model for estimating liver volume, whereas the other reported models were linear models. Unfortunately, this elaborate model did not become popular. One possible explanation for this is that it might be too elaborate for estimating SLV, and the use of other simpler models does not result in favorable outcomes.

BSA-based models for calculating SLV are very simple and are widely used in the clinical setting. However, 25 different formulae for calculating BSA have been proposed[58]. The first formula for calculating BSA was reported in 1879 by Meeh *et al*[59]. Subsequently, the DuBios brothers developed a formula that included height and weight as variables[59,60]. This has remained the standard formula over the past century and we also used it for this study. However, these formulae do not produce precise estimates of BSA and provide no information regarding interindividual variability[58].

Table 2 Sapporo scores for liver resection of malignant tumors

Factors	Scores			
	4	3	2	1
ICGR15 (%)	≤ 10	10-19	20-29	≥ 30
ATIII (%)	≥ 90	80-89	70-79	≤ 69
HH15	≤ 0.55	0.56-0.59	0.60-0.64	≥ 0.65
LHL15	≥ 0.95	0.90-0.94	0.85-0.89	≤ 0.84

The total number of points was calculated as the sum of the scores for the ICGR15, serum ATIII level, HH15, and LHL15. Hr 2 or Hr 3: 16 points, Hr: 1 ≥ 12 points, Hr S: ≥ 8 points, Hr 0: ≤ 7 points. ICG15: Indocyanine green retention rate at 15 min; ATIII: Serum anti-thrombin III level; HH15: Uptake ratio of the heart at 15 min to that seen at 3 min on 99m Tc-galactosyl human serum albumin scintigraphy (GSA); LHL15: The uptake ratio of the liver to the liver plus heart at 15 min on GSA.

Therefore, SLV varies markedly depending on which BSA formula is used.

Since the variation in SLV is not as large as that in BSA, similar coefficient and constant values were used to calculate SLV in previous studies. We identified two clusters of SLV formulae, as shown in Figure 5, and created a simplified cSLV formula for each cluster. The cluster analysis actually identified three clusters, but two of the clusters were very similar and not significantly different (data not shown). Therefore, we combined them together as cluster B. The differences among the clusters related to age or BSA. The age and BSA of cluster A tended to be younger and smaller, respectively, than those of cluster B. Therefore, differences in the patients' background data might have affected the coefficients used and the resultant ICC. Cluster B displayed ICC greater values than cluster A, although the exact reason for this was unclear. One possible explanation is that cSLV stabilized in elderly patients, and so the error range became smaller than that found in younger patients.

Aging and SLV
SLV is affected by aging; *i.e.*, it was reported to be 4% of body weight at birth, but only 2%-2.7% of body weight in adults[30,61]. Therefore, age is an important factor when comparing the formulae used to calculate SLV. A study by Urata *et al*[30] involved young patients, whereas other studies involved adults[24,30,32-35]. Our study population was older than those employed in previous studies. However, the formulae produced in each study were very similar. Although the SLV is affected by aging, it might remain relatively constant in all patients.

Takahashi *et al*[37] and Kanamori *et al*[38] proposed that SLV can be assessed using age alone. However, their approach would not have been appropriate for our patient population, in which most patients were elderly. On the other hand, a combination of age and other variables provided ICC of between 0.66 and 0.79. Thus, it is likely that SLV is partially affected by aging. Although elaborate formulae were created in the third group, this did not result in better ICC compared with those seen in the other groups. Therefore, simple SLV formulas could be applied to patients who are > 10 years old.

Minimum RLV required for maintaining homeostasis after surgery
The issue of the minimum RLV does not only involve the reduction in liver volume, but also several other factors. For example, bile duct reconstruction could be one of the predictors of short-term clinical outcomes[62,63]. The frequency of bile leakage is higher in cases involving biliary reconstruction after hepatectomy than in cases in which biliary reconstruction is not performed[64]. In addition, biliary reconstruction can cause intra-abdominal leakage followed by intra-abdominal infection[64,65]. Therefore, the minimum RLV might differ between cases that do and do not involve biliary reconstruction. Second, the background of the liver also plays an important role in determining clinical outcomes. The general question is how we could evaluate liver damage before surgery. Several liver function evaluation methods have been proposed, including methods based on serum protein levels, serum enzyme levels, the ICGR15, and radiological assessments[66-68]. However, none of them represent liver function perfectly. For example, ICGR15 has been used for several decades; however, it does not reflect liver function in patients that exhibit ICG intolerance or possess an arteriovenous shunt. Radiological evaluations are also affected by the systemic circulation, *e.g.*, by dehydration and heart failure. Serum protein and enzyme levels are too stable to allow them to be used to evaluate liver function in the initial stages of liver damage, and they might not be valuable until the terminal stages of disease
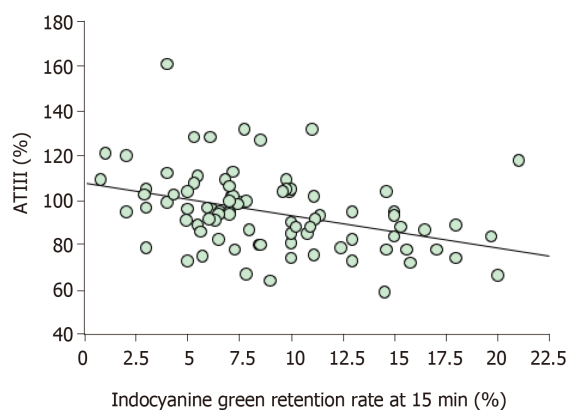
Figure 2 Linear regression analysis of serum antithrombin III levels and the indocyanine green retention rate at 15 min. ATIII + 1.461 × ICGR15 = 108.068; R^2 = 0.151, R = 0389: *P* < 0.001. ATIII: Antithrombin III; ICGR15: Indocyanine green retention rate at 15 min.

progression. Therefore, the Sapporo score is still the only method for evaluating liver function, regardless of the degree of disease progression.

The other factors that might affect postoperative liver function include the concordance rate of the removed segments and the blood supply[69]. The patency of veins is also considered to affect back-flow control[70,71]. Therefore, evaluations of liver function should take both biochemical and anatomical findings into account. Although the Sapporo score is a useful method for evaluating liver function, some technical issues need to be solved before it is used to assess liver function in the clinical setting.

In conclusion, we reviewed SLV formulae and the minimum RLV required for safe liver resection. Although several SLV formulae have been presented, we created two simple SLV formulae that could be applied to the clinical setting. The Sapporo score is the only liver function-based method for estimating the minimum RLV.

Table 3 Formulae for the calculation of standard liver volume based on height and weight

	Authors	Journals	Formulae	ICC
Height and weight	Ogiu *et al*[22]	*Health Phys*, 1997	LV = 576.9 × H + 8.9 × BW – 159.7 (males); LV = 674.3 × H + 6.5 × BW – 214.5 (females)	0.73
	Lin *et al*[23]	*Hepatogastroenterology*, 1998	LV = 133 × H + 12 × BW – 1530	0.78
	Yu *et al*[24]	*Liver Transpl*, 2004	LV = 21.585 × $BW^{0.7322}$ × $H^{0.225}$	0.77
	Chandramohan *et al*[25]	*Indian J Gastroenterol*, 2007	LV = 18.51 × BW + 191.80	0.77
	Fu-Gui *et al*[26]	*Transplant Proc*, 2009	LV = 11.508 × BW + 334.024	0.71
	Poovathumkadavil *et al*[27]	*Transplant Proc*, 2010	LV = 12.26 × BW + 555.65	0.72
	Herden *et al*[28]	*Transpl Int*, 2013	LV = −143.062973 + 4.274603051 × H + 14.78817631 × BW (Age: 0-1); LV = −20.2472281 + 3.339056437 × H + 13.11312561 × BW (Age: 1-16)	0.76

ICC: Intraclass correlation coefficient; LV: Liver volume; BW: Body weight; H: Height.

Table 4 Formulae for the calculation of standard liver volume based on body surface area

	Authors	Journals	Formulae	ICC
BSA	DeLand *et al*[29]	*Radiology*, 1968	LV = 1020 × BSA – 220	0.77
	Urata *et al*[30]	*Hepatology*, 1995	LV = 706.2 × BSA + 2.4	0.71
	Murry *et al*[31]	*Drug Metab Dispos*, 1995	LV = 710 × BSA	0.71
	Heinemann *et al*[32]	*Liver Transpl Surg*, 1999	LV = 1072.8 × BSA – 345.7	0.78
	Vauthey *et al*[33]	*Liver Transpl*, 2002	LV = 1267.28 × BSA – 794.41	0.78
	Yoshizumi *et al*[34]	*Transplant Proc*, 2003	LV = 772 × BSA	0.74
	Yu *et al*[24]	*Liver Transpl*, 2004	LV = 1145.4 × BSA − 506.1 (adults)	0.78
	Hashimoto *et al*[35]	*J Gastroenterol Hepatol*, 2006	LV = 961.3 × BSA – 404.8	0.77
	Chandramohan *et al*[25]	*Indian J Gastroenterol*, 2007	LV = 1267.28 × BSA – 794.41	0.78
	Saeki *et al*[36]	*Pediatr Transplant*, 2012	LV = 689.9 × BSA − 24.7	0.70
	Our study		LV = 822.7 × BSA – 183.2	0.74

ICC: Intraclass correlation coefficient; LV: Liver volume; BSA: Body surface area.

Table 5 Formulae for the calculation of standard liver volume based on age, gender, or radiological findings

	Authors	Journals	Formulae	ICC
Others	Takahashi *et al*[37]	*Clin Pharmacol Ther*, 2000	LV = 15 × (4.6 × Age + 19.8), Age: 1-18; LV = 15 × (0.31 × Age + 97.8), Age: 30-40; LV = 15 × (−0.91 × Age + 149), Age: ≥ 41	0.39
	Kanamori *et al*[38]	*Int J Clin Pharmacol Ther*, 2002	LV = 67.3 × Age + 229.8	−0.39
	Choukèr *et al*[39]	*Liver Transpl*, 2004	LV=452 + 16.34 × BW + 11.85 × Age – 166 × Gender (Age: 16–50, M: 0, F: 1); LV=1390 + 15.94 × BW – 12.86 × Age (Age: 51–70)	0.79
	Chan *et al*[40]	*World J Gastroenterol*, 2006	LV = 218 + BW × 12.3 + Gender × 51 (F: 0, M: 1)	0.74
	Yuan *et al*[41]	*Transplant Proc*, 2008	LV = 949.7 × BSA – 48.3 × Age − 247.4 (Age: 1: < 40, 2: 41–60, 3: > 60)	0.77
	Kokudo *et al*[42]	*J Hepatol*, 2015	LV = 203.3 − 3.61 × Age + 58.7 × Thoracic width − 463.7 × Race (Asian: 1, Caucasian: 0)	0.66
	Ma *et al*[43]	*Liver Transpl*, 2017	LV = (2 × Depth) + (10 × BW) + 190	0.75

ICC: Intraclass correlation coefficient; LV: Liver volume; BSA: Body surface area; BW: Body weight; F: Female; M: Male.

Table 6 Characteristics of the patients and simple standard liver volume formulae based on a mean body surface area of 1.61

Authors	Mean age ± SD (range)	BSA	Simple formulae (tentative mean BSA = 1.61)	ICC	Clusters
DeLand *et al*[29]	ND	ND	LV = 883 × BSA	0.75	B
Urata *et al*[30]	11.1 ± 8.8	1.078 ± 0.528 (0.248–1.935)	LV = 707 × BSA	0.71	A
Murry *et al*[31]	9.7 (3.3–18.8)	Median: 1.37 (0.57–2.0)	LV = 710 × BSA	0.71	A
Heinemann *et al*[32]	50.6±18.9	ND	LV = 858 × BSA	0.75	B
Vauthey *et al*[33]	Mean: 54, Median: 56 (14-90)	Median: 1.82 (1.32–2.90)	LV = 770 × BSA	0.74	B
Yoshizumi *et al*[34]	38.6 ± 20.6 (0–87) for males; 47.0 ± 19.7 (0–85) for females	1.86 ± 0.36 (0.24-2.88); 1.68 ± 0.28 (0.28-2.38)	LV = 772 × BSA	0.74	B
Yu *et al*[24]	42.4 ± 16.5	1.65 ± 0.26	LV = 831 × BSA	0.74	B
Hashimoto *et al*[35]	(17-66)	1.67 ± 0.18 (1.25-2.56)	LV = 710 × BSA	0.71	A
Chandramohan *et al*[25]	46.5 (10-70)	Median: 1.60 (0.88-2.25)	LV = 774 × BSA	0.73	B
Saeki *et al*[36]	5.8 (0 d-15)	ND	LV = 675 × BSA	0.70	A
Our study	67.0 ± 10.3	1.61 ± 0.18	LV = 709 × BSA	0.71	A

ICC: Intraclass correlation coefficient; BSA: Body surface area; ND: Not describe; LV: Liver volume.

Table 7 Minimum residual liver volume based on various functional assessments

Authors	Publications	Functional assessments	Minimum residual LV			Mortality
			NL	CH, liver injury	LC	
Shirabe *et al*[49]	*J Am Coll Surg*, 1999	Pathology (HCC, HB, or HC)	250 mL/m² (40%)			8.8% (180 d)
Shoup *et al*[50]	*J Gastrointest Surg*, 2003	Pathology (NL, CRC metastasis alone)	25%	-	-	ND
Schindl *et al*[51]	*Gut*, 2005	Pathology (NL, 99% metastasis)	26.6%	-	-	ND
Ferrero *et al*[17]	*World J Surg*, 2007	Pathology (NL, liver injury)	26.5%	31%	-	0.8% (60 d)
van den Esschert *et al*[52]	*J Gastrointest Surg*, 2009	Pathology (CH, LC)	-	40%	50%	ND
Kishi *et al*[53]	*Ann Surg*, 2009	Pathology (NL)	20%	-	-	2.0% (30 d) 4.7% (60 d) 6.0% (90 d)
Suda *et al*[54]	*Am J Surg*, 2009	Pathology (NL, HCCa, GBCa, ICCa)	40%	-	-	8.1% (ND)
Vauthey *et al*[55]	*HPB*, 2010	Pathology (NL, liver injury, LC)	20%	30%	40%	ND
Gulielmi *et al*[56]	*Dig Surg*, 2012	Pathology (NL, steatosis, LC)	20%	30%	40%	ND
Hwang *et al*[16]	*J Gastrointest Surg*, 2015	Pathology (CH, LC)	-	35%	30%	0.8% (90 d)
Ribero *et al*[57]	*J Am Coll Surg*, 2016	Pathology (NL, HCCa alone)	30%	-	-	11% (90 d)
Our series	*Hepatogastroenterology* (in press)	ATIII, ICG15, GSA	35%-95%			2.3% (90 d)

LV: Liver volume; NL: Normal liver; CH: Chronic hepatitis; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma; GBCa: Gallbladder cancer; ICCa: Intrahepatic cholangiocellular carcinoma; HCCa: Hilar cholangiocellular carcinoma; ATIII: Anti-thrombin III; ICG15: Indocyanine green retention rate at 15 min; GSA: 99m Tc-galactosyl human serum albumin scintigraphy; ND: Not describe.

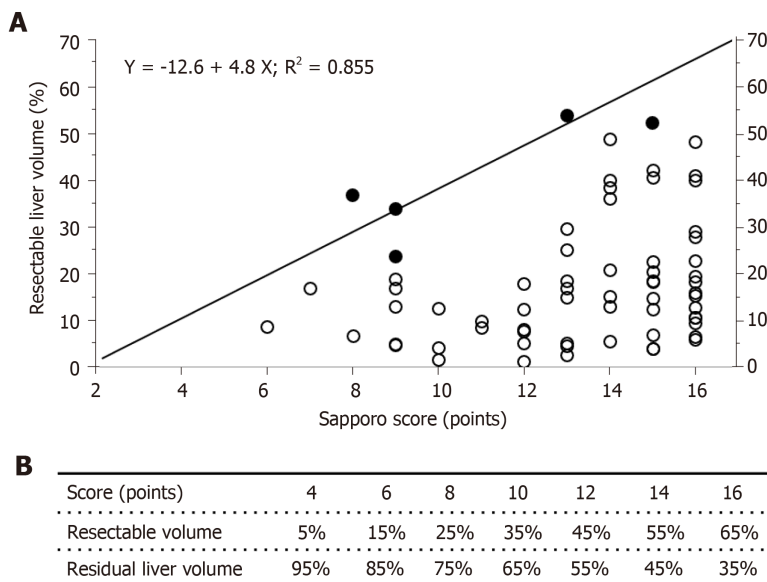**Figure 3 The results of the linear regression analysis of the reduction in liver volume and the Sapporo score.** A: Linear regression analysis of the reduction in liver volume and the Sapporo score; Closed circles: Grade IV and V postoperative liver failure/dysfunction Open circles: Complication-free cases; B: Relationships between the Sapporo score, resectable liver volume, and residual liver volume.
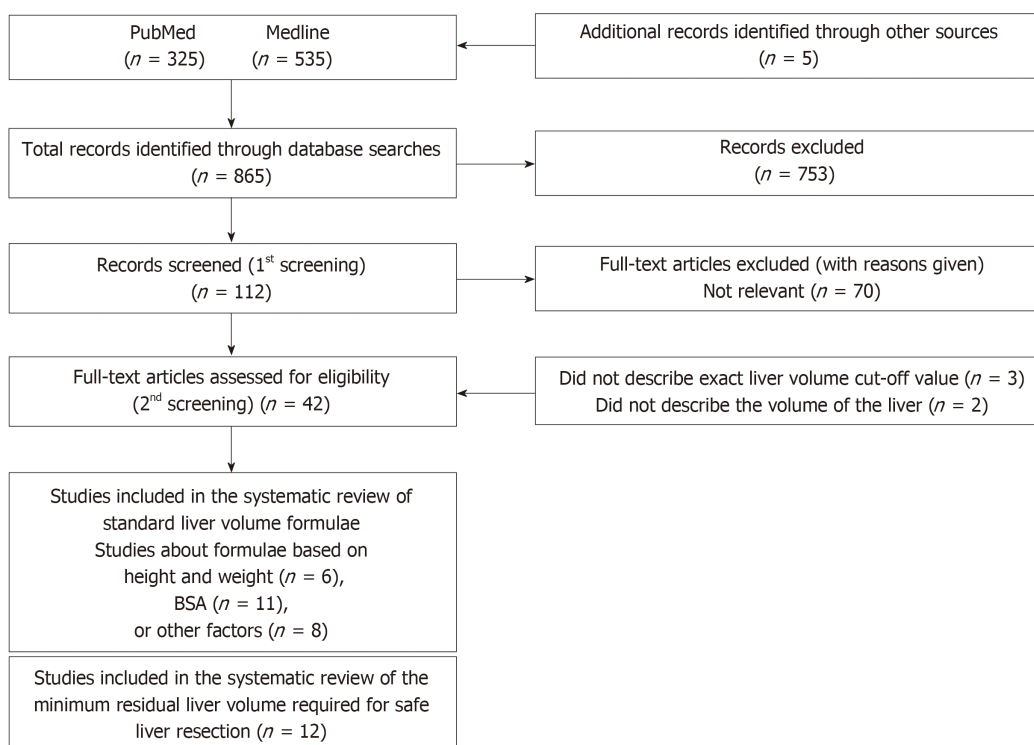
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┌─────────────────────────────────────────┐          ┌─────────────────────────────────────────────────┐
│        PubMed          Medline           │          │  Additional records identified through other       │
│       (n = 325)       (n = 535)          │ ◄─────── │  sources                                           │
│                                          │          │  (n = 5)                                           │
└─────────────────────────────────────────┘          └─────────────────────────────────────────────────┘
                     │
                     ▼
┌─────────────────────────────────────────┐          ┌─────────────────────────────────────────────────┐
│  Total records identified through        │          │          Records excluded                          │
│  database searches                       │ ───────► │            (n = 753)                               │
│  (n = 865)                               │          │                                                    │
└─────────────────────────────────────────┘          └─────────────────────────────────────────────────┘
                     │
                     ▼
┌─────────────────────────────────────────┐          ┌─────────────────────────────────────────────────┐
│  Records screened (1st screening)        │          │  Full-text articles excluded (with reasons given)  │
│  (n = 112)                               │ ───────► │  Not relevant (n = 70)                             │
└─────────────────────────────────────────┘          └─────────────────────────────────────────────────┘
                     │
                     ▼
┌─────────────────────────────────────────┐          ┌─────────────────────────────────────────────────┐
│  Full-text articles assessed for         │          │  Did not describe exact liver volume cut-off       │
│  eligibility                             │ ◄─────── │  value (n = 3)                                     │
│  (2nd screening) (n = 42)                │          │  Did not describe the volume of the liver (n = 2)  │
└─────────────────────────────────────────┘          └─────────────────────────────────────────────────┘
                     │
                     ▼
┌─────────────────────────────────────────┐
│  Studies included in the systematic      │
│  review of standard liver volume         │
│  formulae                                │
│  Studies about formulae based on         │
│  height and weight (n = 6),              │
│  BSA (n = 11),                           │
│  or other factors (n = 8)                │
└─────────────────────────────────────────┘
┌─────────────────────────────────────────┐
│  Studies included in the systematic      │
│  review of the minimum residual liver    │
│  volume required for safe liver          │
│  resection (n = 12)                      │
└─────────────────────────────────────────┘
```
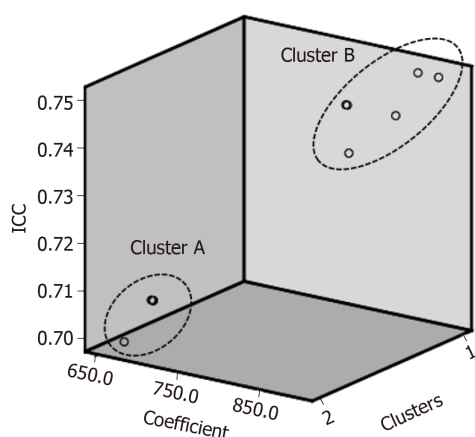
Figure 4 A PRISMA flow diagram.

Figure 5 Three-dimensional scatterplot of simple standard liver volume formulae and their intraclass correlation coefficients. ICC: Intraclass correlation coefficients.

ARTICLE HIGHLIGHTS

Research background
Various minimum residual liver volume (RLV) has been presented. In addition, many formulas of standard liver volume (SLV) were also established.

Research motivation
When we planned hepatectomy for malignant tumors, we had not proven which methods were the best reliable assessment to estimate minimum RLV and SLV.

Research objectives
Aim of this study was to review previous SLV formulae and the methods used to evaluate the minimum RLV, and explore the association between liver volume and mortality.

Research methods
A systematic review was performed (No. CRD42019123642). We developed an SLV formula using data for 86 consecutive patients who underwent hepatectomy at our institution between

July 2009 and August 2011.

Research results
Our formula: SLV (mL) = 822.7 × BSA − 183.2 (R^2 = 0.419 and R = 0.644, *P* < 0.001). We retrieved 25 studies relating to SLV formulae and 12 studies about the RLV required for safe liver resection. The minimum RLV for normal and damaged livers ranged from 20%-40% and 30%-50%, respectively. The Sapporo score indicated that the minimum RLV ranges from 35%-95% depending on liver function.

Research conclusions
We reviewed SLV formulae and the minimum RLV required for safe liver resection. Although several SLV formulae have been presented, we created two simple SLV formulae that could be applied to the clinical setting. The Sapporo score is the only liver function-based method for estimating the minimum RLV.

Research perspectives
The Sapporo score should be validated by large study with prospective registration. The common SLV, which is cSLV (mL) = 710 or 770 × body surface area, needs to verify in the specific population.

ACKNOWLEDGEMENTS

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