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## Retrospective Study

# Role of intelligent/interactive qualitative and quantitative analysis-three-dimensional estimated model in donor-recipient size mismatch following deceased donor liver transplantation

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## Abstract

### BACKGROUND

Donor-recipient size mismatch (DRSM) is considered a crucial factor for poor outcomes in liver transplantation (LT) because of complications, such as massive intraoperative blood loss (IBL) and early allograft dysfunction (EAD). Liver volumetry is performed routinely in living donor LT, but rarely in deceased donor LT (DDLTL), which amplifies the adverse effects of DRSM in DDLTL. Due to the various shortcomings of traditional manual liver volumetry and formula methods, a feasible model based on intelligent/interactive qualitative and quantitative analysis-three-dimensional (IQQA-3D) for estimating the degree of DRSM is needed.

**AIM**

To identify benefits of IQQA-3D liver volumetry in DDLT and establish an estimation model to guide perioperative management.

**METHODS**

We retrospectively determined the accuracy of IQQA-3D liver volumetry for standard total liver volume (TLV) (sTLV) and established an estimation TLV (eTLV) index (eTLVi) model. Receiver operating characteristic (ROC) curves were drawn to detect the optimal cut-off values for predicting massive IBL and EAD in DDLT using donor sTLV to recipient sTLV (called sTLVi). The factors influencing the occurrence of massive IBL and EAD were explored through logistic regression analysis. Finally, the eTLVi model was compared with the sTLVi model through the ROC curve for verification.

**RESULTS**

A total of 133 patients were included in the analysis. The Changzheng formula was accurate for calculating donor sTLV ( $P = 0.083$ ) but not for recipient sTLV ( $P = 0.036$ ). Recipient eTLV calculated using IQQA-3D highly matched with recipient sTLV ( $P = 0.221$ ). Alcoholic liver disease, gastrointestinal bleeding, and sTLVi  $> 1.24$  were independent risk factors for massive IBL, and drug-induced liver failure was an independent protective factor for massive IBL. Male donor-female recipient combination, model for end-stage liver disease score, sTLVi  $\leq 0.85$ , and sTLVi  $\geq 1.32$  were independent risk factors for EAD, and viral hepatitis was an independent protective factor for EAD. The overall survival of patients in the  $0.85 < \text{sTLVi} < 1.32$  group was better compared to the sTLVi  $\leq 0.85$  group and sTLVi  $\geq 1.32$  group ( $P < 0.001$ ). There was no statistically significant difference in the area under the curve of the sTLVi model and IQQA-3D eTLVi model in the detection of massive IBL and EAD (all  $P > 0.05$ ).

**CONCLUSION**

IQQA-3D eTLVi model has high accuracy in predicting massive IBL and EAD in DDLT. We should follow the guidance of the IQQA-3D eTLVi model in perioperative management.

**Key Words:** Intelligent/interactive qualitative and quantitative analysis-three-dimensional; Donor-recipient size mismatch; Intraoperative blood loss; Early allograft dysfunction

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**Core Tip:** This is a retrospective study to identify benefits of intelligent/interactive qualitative and quantitative analysis-three-dimensional (IQQA-3D) liver volumetry in deceased donor liver transplantation and establish an estimation model to guide perioperative management. Patients with estimation total liver volume index (eTLVi)  $\geq 1.24$  have an increased risk of massive intraoperative blood loss and patients with eTLVi  $\leq 0.85$  or eTLVi  $\geq 1.32$  have an increased risk of early allograft dysfunction. To improve the overall survival of patients, we should follow the guidance of the IQQA-3D eTLVi model either for organ allocation or perioperative management.

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**INTRODUCTION**

An understanding of the interaction between donors and recipients is crucial to ensure optimum outcomes in liver transplantation (LT)[1]. Studies have investigated the effects of mismatch in age, gender[2,3] and ethnicity[4] on the outcomes of LT, with donor-recipient size mismatch (DRSM) being the most important factor[5,6]. Nowadays, with most organ allocation systems worldwide relying on the 'sickest first' policy. However, they do not consider the mismatch of the mismatch of the morphological parameters in the abdominal cavity between donors and recipients[7]. Liver volumetry is rarely undertaken in deceased donor LT (DDLT), which amplifies the adverse effects of DRSM. Massive intraoperative blood loss (IBL), early allograft dysfunction (EAD)[8-10], and other complications caused by small-for-size syndrome (SFSS) or large-for-size syndrome (LFSS) have been found to lead to lower allograft survival and higher patient mortality[11,12]. Therefore, experienced centers have focused more on liver volumetry for total liver volume (TLV) and are committed to establishing a model to estimate the degree of DRSM.

The use of the Archimedes drainage method, the gold standard for liver volumetry, is restricted due to the disadvantage of measuring only for liver *in vitro*[13]. Whether TLV is calculated by height/weight or by body surface

area (BSA), the results are subject to differences in race, gender, and various clinical factors[14]. Estimations by simple empirical formulas are handy and suitable for donor TLV but not for recipient TLV (mostly accompanied by ascites, hepatic carcinomas, cirrhosis, or post-hepatectomy status). Over the years, imaging equipment and visualization techniques have improved significantly and become increasingly refined. Consequently, liver volumetry, based on Doppler ultrasound (DUS), contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI) scans, has shown a close correlation with TLV when highly trained operators spend considerable time in postprocessing analysis[15-17]. However, the expensive and time-consuming post process may impede the widespread application of non-automatic liver volumetry, particularly in some emerging transplantation centers.

With advanced technology, the trend towards automated interactive volumetry-assist software replacing manual liver volumetry in the future is anecdotally known. Intelligent/interactive qualitative and quantitative analysis-three-dimensional (IQQA-3D), one of the automated computerized liver volumetry calculators, is characterized by real accuracy, high intelligence, and robust applicability. Scattered reports[18] indicated that the advantages of high repeatability, stability, and reliability of IQQA-3D in measuring standard liver volume can reduce IBL, operative duration, and postoperative complications in precise hepatectomy and living donor LT (LDLT). However, few results have been reported on the role of IQQA-3D in liver volumetry in DDLT. Thus, we conducted this study to identify the benefits of IQQA-3D-based liver volumetry in DDLT and establish a convenient, feasible, and accurate estimation model to guide perioperative management, especially for DRSM-induced massive IBL and EAD.

## MATERIALS AND METHODS

### Patient selection

We retrospectively analyzed patients who underwent DDLT by a single experienced surgeon between November 2017 and February 2022 in our center and ensured that all surviving patients had been followed up for more than 1 year. All liver allografts were allocated by China Organ Transplant Response System which follows the sickest first policy. Recipients with extreme marginal allografts were excluded according to the following criteria: (1) Donors over 70 years old; (2) Severe allografts steatosis with more than 60% macrosteatosis confirmed by wedge biopsy 1 h after reperfusion; (3) The warm ischemia time of allografts of > 20 min or cold ischemia time of allografts of > 12 h; (4) Prolonged hypotension of the donors (diastolic blood pressure < 60 mmHg, maintenance time > 2 h); (5) Continuous serum total bilirubin and transaminase higher than normal by more than 3 times (maintenance time > 7 d); and (6) ABO-incompatible LT. The recipients of multiorgan transplants or liver re-transplants and recipients with missing demographic characteristics or LT-related information were also excluded.

The study was conducted in accordance with the Helsinki Declaration, and the protocol was approved by the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (No. XHEC-D-2023-076).

### Procedures

IQQA-3D was applied to calculate estimated TLV (eTLV) for all recipients by analyzing the imported contrast-enhanced CT/MRI scan and automatically outlining the liver parenchyma contour in each layer according to the liver anatomy and density. To improve the accuracy of eTLV, further amendments were carried out by experienced surgeons if necessary.

Donors included in this study were free of liver disease and hence the donor eTLV was similar to that of the normal population. Therefore, due to the extensive practicability for the Chinese population among existing studies, we chose the formula[19] derived by the Shanghai Changzheng Hospital to calculate donor eTLV:  $TLV (cm^3) = 758.259 \times BSA (m^2) - 124.272$ . Standard TLV (sTLV) was preferably determined using the Archimedes method and secondly deduced from liver weight and density[20] ( $1.00 \pm 0.06$  kg/L). To estimate the degree of DRSM, the sTLV index (sTLVi), which was calculated as the ratio of donor TLV to recipient TLV, became a crucial parameter and a gold standard model in this study.

All enrolled patients underwent classic orthotopic LT without the piggyback technique, portocaval shunt, or venovenous bypass. Anesthesiologists ensured that hypotension and hypothermia did not occur during the operation. An autotransfusion machine was used for all patients to not only maintain the concentration of blood hemoglobin but also to determine IBL. Liver allografts were weighed or volume was measured using the Archimedes method immediately after back-table procedures. Native diseased livers were subjected to the same measurement after removing the gallbladder and accessory ligaments. The donor risk index (DRI) for liver allografts was calculated using the formula described formula[21].

### Outcomes

The primary outcomes were massive IBL and EAD caused by DRSM during the perioperative period. Massive IBL was defined as 2000 mL as the baseline. EAD was determined based on the presence of 1 or more of the following most widely accepted criteria[22]: (1) Bilirubin  $\geq 10$  mg/dL on post operative day 7; (2) International normalized ratio  $\geq 1.6$  on post operative day 7; and (3) Alanine or aspartate aminotransferase  $\geq 2000$  IU/L within the first 7 d.

Secondary outcomes included: (1) Procedure-related outcomes including tracheal extubation time, intensive care unit (ICU) stay, postoperative hospital stay, and complications, such as infection and incision nonunion; and (2) perioperative mortality and overall survival (OS) at the end of follow-up.

## Statistical analysis

Continuous variables were expressed as mean  $\pm$  SD or median (interquartile range) and categorical variables as numbers and percentages. Statistical methods used in this study included the Student's *t*-test (or Mann-Whitney U test), Fisher's exact test (or Pearson's chi-square test), Kaplan-Meier method for survival analysis, and Cox regression analyses. All tests were two-sided and differences were considered statistically significant when the *P*-value was  $< 0.05$ . Receiver operating characteristic (ROC) curves were drawn to not only detect the optimal cut-off values for the index but also confirm the equivalence of the sTLVi model and the eTLV index (eTLVi) model in predicting massive IBL and EAD. Univariate and multivariable logistic regression analyses were performed successively to predict how sTLVi affected the development of massive IBL and EAD.

## RESULTS

### Demographics of recipients and donors

A total of 133 patients were enrolled in this study. Patients with chronic hepatitis B virus/hepatitis C virus (HBV/HCV) infection accounted for the majority (63.9%) of the patients, followed by those with chronic alcoholic liver disease (ALD) (18.0%) and drug-induced liver failure (DILF) (9.0%; [Table 1](#)). Gastrointestinal bleeding (64.7%), ascites (51.9%), and hepatic encephalopathy (23.3%) were the most common clinical symptoms in the included patients. Pathologically confirmed hepatic carcinomas were found in 42 removed livers (31.6%). Twenty-eight patients (21.1%) used to undergo open upper abdominal surgery and 29 patients (21.8%) had a history of one or more artificial liver support system (ALSS) use.

Donors were younger (mean age,  $48.1 \pm 13.1$  years *vs*  $49.4 \pm 12.8$  years,  $P = 0.388$ ) than recipients and had a higher proportion of males (83.5% *vs* 76.7%,  $P = 0.002$ ). Although the body shape of recipients was generally smaller than that of donors, which was reflected in mean height ( $168.1 \pm 10.2$  cm *vs*  $170.6 \pm 11.2$  cm,  $P = 0.032$ ) and mean weight ( $67.5 \pm 18.0$  kg *vs*  $73.7 \pm 17.5$  kg,  $P = 0.003$ ), there was no statistical difference in sTLV of recipients and donors ( $1299 \pm 482$  mL *vs*  $1311 \pm 267$  mL,  $P = 0.799$ ). Notably, considering the shortage of donor pool in China, 23 liver allografts with HBV or HCV infection (17.3%) and 43 allografts with mild or moderate steatosis (32.3%) were transplanted after exclusion of extreme marginal allografts through a rapid biopsy. The mean DRI of liver allografts was  $2.28 \pm 0.42$ . Male donor-female recipient (MD-FR) combination and female donor-male recipient (FD-MR) combination were observed in 26 cases (19.5%) and 17 cases (12.8%), respectively, which were also considered for our analyses.

### Operational parameters and outcomes

The mean cold ischemia time was  $5.9 \pm 1.8$  h, and the mean anhepatic phase time was  $50.7 \pm 9.0$  min. Massive IBL developed in 71.4% of recipients with a mean IBL of  $3117 \pm 1725$  mL and a mean intraoperative blood transfusion (IBT) of  $1949 \pm 1749$  mL. The median tracheal extubation time, ICU stay, and postoperative hospital stay were 1 (1-3) d, 2 (1-6) d, and 15 (11-23) d, respectively. EAD developed in 42.1% of recipients, of which SFSS was the cause in 36 recipients (27.1%) and LFSS was the cause in 20 recipients (15.0%). Infection occurred in 36.8% of recipients, and incision nonunion occurred in 21.8%. In terms of perioperative adverse events, there were 29 perioperative deaths (21.8%), including 7 blood loss-specific deaths (5.3%), and 17 EAD-specific deaths (12.8%).

### Accuracy of IQQA-3D and the formula method for calculating donor and recipient eTLV

Compared with donor sTLV, there was no statistical difference in donor eTLV calculated using the Changzheng formula ( $1287 \pm 207$  mL *vs*  $1311 \pm 267$  mL,  $P = 0.083$ ). However, compared with recipient sTLV, the Changzheng formula for calculating recipient eTLV was not accurate ( $1213 \pm 212$  mL *vs*  $1299 \pm 482$  mL,  $P = 0.036$ ), while recipient eTLV calculated using IQQA-3D was highly matched up with recipient sTLV ( $1311 \pm 522$  mL *vs*  $1299 \pm 482$  mL,  $P = 0.221$ ). Therefore, the IQQA-3D eTLVi model was defined as the ratio of donor eTLV to IQQA-3D recipient eTLV and selected as an estimation model in the study.

### Association between sTLVi and massive IBL

Univariate logistic regression revealed that sTLVi was a risk factor for massive IBL [odds ratio (OR) = 2.968,  $P = 0.037$ ]. The optimal cut-off value of sTLVi in predicting massive IBL calculated using the ROC curve was 1.24, with a sensitivity of 46.3% and a specificity of 94.7% ([Figure 1A](#)). Except for a higher proportion of males (82.8% *vs* 65.2%,  $P = 0.023$ ) in the sTLVi  $< 1.24$  group, there was no significant statistical difference in other recipient characteristics (all  $P > 0.05$ ). The distribution of donor characteristics was similar, except for the MD-FR combination (11.5% *vs* 34.8%,  $P = 0.001$ ) and allograft steatosis (25.3% *vs* 45.7%,  $P = 0.017$ ). In addition, the sTLVi  $< 1.24$  group showed advantages in terms of the anhepatic phase time ( $49.3 \pm 7.2$  min *vs*  $53.6 \pm 11.4$  min,  $P = 0.024$ ), IBL ( $2430 \pm 1203$  mL *vs*  $4417 \pm 1821$  mL,  $P < 0.001$ ), and IBT ( $1366 \pm 1235$  mL *vs*  $3052 \pm 2039$  mL,  $P < 0.001$ ). In terms of recovery course, the sTLVi  $< 1.24$  group had a longer survival time ( $45.6 \pm 2.8$  mo *vs*  $37.0 \pm 4.1$  mo,  $P = 0.132$ ), and shorter tracheal extubation time (median, 1 d *vs* 2 d,  $P = 0.089$ ), ICU stay (median, 2 d *vs* 3 d,  $P = 0.082$ ) and postoperative hospital stay (median, 15 d *vs* 16 d,  $P = 0.239$ ) than the sTLVi  $\geq 1.24$  group. These data were not statistically significant except for blood loss-specific mortality (1.1% *vs* 13.0%,  $P = 0.007$ ).

The results of multivariate logistic regression analysis revealed that sTLVi  $\geq 1.24$  (OR = 18.43,  $P < 0.001$ ), ALD (OR = 9.371,  $P = 0.040$ ) and gastrointestinal bleeding (OR = 3.954,  $P = 0.005$ ) were associated with massive IBL, while DILF (OR = 0.226,  $P = 0.047$ ) was protective against massive IBL ([Table 2](#)).

**Table 1** Demographics, operational parameters and outcomes of recipients and donors

	Recipient	Donor
<b>Demographics</b>		
Age (yr)	49.4 ± 12.8	48.1 ± 13.1
Male	102 (76.7)	111 (83.5)
Height (cm)	168.1 ± 10.2	170.6 ± 11.2
Weight (kg)	67.5 ± 18.0	73.7 ± 17.5
sTLV (mL)	1299 ± 482	1311 ± 267
eTLV by formula (mL)	1213 ± 212	1287 ± 207
eTLV by IQQA-3D (mL)	1311 ± 522	-
DRI	-	2.28 ± 0.42
Cold ischemia time (h)	-	5.9 ± 1.8
<b>Liver disease</b>		
HBV/HCV	85 (63.9)	23 (17.3)
ALD	24 (18.0)	0
DILF	12 (9.0)	0
Steatosis	8 (6.0)	43 (32.3)
Hepatic carcinoma	42 (31.6)	0
<b>Signs and symptoms</b>		
Moderate or severe ascites	69 (51.9)	-
Gastrointestinal bleeding	86 (64.7)	-
Hepatic encephalopathy	31 (23.3)	-
<b>Operational parameters</b>		
Anhepatic phase time (min)	50.7 ± 9.0	-
IBL (mL)	3117 ± 1725	-
IBT (mL)	1949 ± 1749	-
<b>Hospitalization Information</b>		
Tracheal extubation time (d)	1 (1-3)	-
ICU stay (d)	2 (1-6)	-
Postoperative hospital stay (d)	15 (11-23)	-
<b>Complications</b>		
Massive intraoperative blood loss	95 (71.4)	-
EAD caused by SFSS	36 (27.1)	-
EAD caused by LFSS	20 (15.0)	-
Infection	49 (36.8)	-
Incision nonunion	29 (21.8)	-
<b>Outcomes and follow-up</b>		
Perioperative mortality	29 (21.8)	-
Blood loss-specific mortality	7 (5.3)	-
EAD-specific mortality	17 (12.8)	-
All-cause mortality	46 (34.6)	-
Follow-up time (mo)	27 (9-44)	-

Values are mean  $\pm$  SD, *n* (%), or median (interquartile range). sTLV: Standard total liver volume; eTLV: estimated total liver volume; DRI: Donor risk index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALD: Alcoholic liver disease; DILF: Drug-induced liver failure; IBL: Intraoperative blood loss; IBT: Intraoperative blood transfusion; ICU: Intensive care unit; EAD: Early allograft dysfunction; SFSS: Small-for-size syndrome; LFSS: Large-for-size syndrome; IQQA-3D: Intelligent/interactive qualitative and quantitative analysis-three-dimensional.

**Table 2 Univariate and multivariate logistic regression to predict massive intraoperative blood loss**

	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Recipient age	1.038	1.007-1.070	0.017			0.106
Male	0.835	0.336-2.074	0.697			0.815
sTLVi $\geq$ 1.24	22.00	4.804-100.8	< 0.001	18.43	3.809-89.15	< 0.001
Donor age	1.014	0.986-1.042	0.340			
MD-FR combination	1.873	0.650-5.396	0.245			
FD-MR combination	0.698	0.238-2.046	0.513			
Graft steatosis (< 60%)	2.187	0.903-5.297	0.083			
Cold ischemia time	1.005	0.815-1.239	0.963			
DRI	1.074	0.437-2.644	0.876			
HBV/HCV	1.225	0.564-2.661	0.608			
ALD	11.82	1.535-90.99	0.018	9.371	1.112-78.98	0.040
DILF	0.165	0.406-0.586	0.005	0.226	0.052-0.983	0.047
Hepatic carcinoma	1.422	0.615-3.288	0.410			
Gastrointestinal bleeding	2.393	1.104-5.188	0.027	3.954	1.502-10.41	0.005
Moderate or severe ascites	1.065	0.502-2.261	0.869			
History of open upper abdominal surgery	2.108	0.737-6.032	0.164			
Platelet count	1.000	0.955-1.005	0.914			
PT	1.011	0.976-1.045	0.577			
Child-Pugh grade C	2.347	0.961-5.731	0.061			
MELD score	1.012	0.975-1.052	0.526			
Anhepatic phase time	1.020	0.975-1.067	0.396			

OR: Odds ratio; 95%CI: 95% confidence interval; sTLVi: Standard total liver volume index; MD-FR: Male donor-female recipient; FD-MR: Female donor-male recipient; DRI: Donor risk index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALD: Alcoholic liver disease; DILF: Drug-induced liver failure; PT: Prothrombin time; MELD: Model for end-stage liver disease.

### Association between sTLVi with EAD

Unconventional sTLVi was found to be related to an increased risk of EAD ( $P < 0.001$ ). The optimal cut-off values of sTLVi calculated using the ROC curve for predicting EAD caused by SFSS and LFSS were 0.85 (sensitivity 96.0%, specificity 88.0%) and 1.32 (sensitivity 95.0%, specificity 85.0%), respectively (Figure 1B and C). In the sTLVi  $\geq$  1.32 group, there were significant differences in the proportion of males (61.1% vs 83.8% and 81.7%,  $P = 0.034$ ), MD-FR combination (41.7% vs 8.1% and 13.3%,  $P < 0.001$ ), and allograft steatosis (50.0% vs 13.5% and 33.3%,  $P = 0.004$ ) compared to the 0.85 < sTLVi < 1.32 group and the sTLVi  $\leq$  0.85 group. The mean Child-Pugh score for patients in the 0.85 < sTLVi < 1.32 group was the lowest among the 3 groups ( $8.2 \pm 2.8$  vs  $9.6 \pm 2.8$  and  $9.4 \pm 2.7$ ,  $P = 0.033$ ). The distribution of other characteristics was similar between the 3 groups, except for the prolonged anhepatic phase time with the increase of sTLVi ( $P = 0.002$ ).

An sTLVi of  $\leq$  0.85 (OR = 21234,  $P < 0.001$ ) and model for end-stage liver disease (MELD) score (OR = 1.333,  $P = 0.002$ ) were associated with EAD caused by SFSS, whereas HBV/HCV (OR = 0.095,  $P = 0.042$ ) infection was protective against EAD on multivariate logistic regression (Table 3). An sTLVi of  $\geq$  1.32 (OR = 78.56,  $P < 0.001$ ) and MD-FR combination (OR = 6.540,  $P = 0.008$ ) were associated with EAD caused by LFSS on multivariate logistic regression.

In general, patients with sTLVi between 0.85 and 1.32 had a longer survival time ( $52.5 \pm 2.6$  mo vs  $37.3 \pm 4.4$  mo and  $25.0 \pm 4.3$  mo,  $P < 0.001$ ), shorter tracheal extubation time (median, 1 d vs 1 d and 2 d,  $P = 0.002$ ), lower EAD-associated

**Table 3 Univariate and multivariate logistic regression to predict early allograft dysfunction**

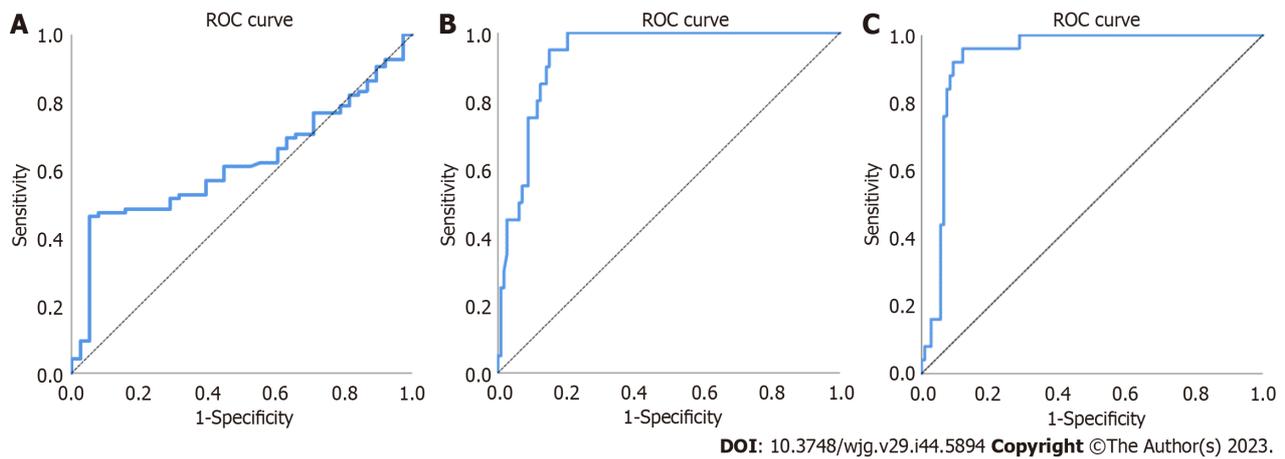
	EAD caused by SFSS						EAD caused by LFSS					
	Univariate			Multivariate			Univariate			Multivariate		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Recipient age	0.980	0.948-1.013	0.235			0.992	1.062	1.014-1.113	0.012			0.069
Male	1.268	0.433-3.715	0.665			0.357	0.295	0.109-0.800	0.016			0.134
sTLVi ≤ 0.85/≥ 1.32	175.4	21.85-1407	< 0.001	21234	126-3585713	< 0.001	100.3	16.06-970.4	< 0.001	78.56	9.529-648.0	< 0.001
Donor age	0.992	0.961-1.025	0.645				1.003	0.967-1.040	0.887			
MD-FR combination	0.504	0.139-1.833	0.298				10.61	3.693-30.47	< 0.001	6.540	1.617-26.45	0.008
FD-MR combination	0.916	0.242-3.464	0.897				1.923	0.557-6.637	0.301			
Graft steatosis (< 60%)	0.065	0.009-0.502	0.009			0.444	2.424	0.923-6.368	0.072			
Cold ischemia time	0.923	0.725-1.174	0.512				1.006	0.772-1.312	0.962			
DRI	2.376	0.859-6.573	0.095			0.086	1.069	0.346-3.305	0.908			
HBV/HCV positive graft	0.163	0.021-1.271	0.083				2.420	0.817-7.174	0.111			
HBV/HCV	0.361	0.149-0.877	0.025	0.095	0.010-0.919	0.042	1.058	0.391-2.862	0.912			
ALD	0.838	0.259-2.712	0.768				1.649	0.535-5.084	0.384			
DILF	3.607	1.040-12.51	0.043			0.979	0.488	0.059-4.005	0.504			
Hepatic carcinoma	0.480	0.167-1.381	0.173				0.493	0.154-1.579	0.234			
Hepatic encephalopathy	1.739	0.667-4.534	0.258				3.384	1.249-9.167	0.016			0.186
History of ALSS	2.475	0.957-6.400	0.062				1.677	0.581-4.842	0.339			
Child-Pugh grade C	18.85	2.408-147.5	0.005			0.319	2.200	0.563-8.598	0.257			
MELD score	1.082	1.035-1.133	0.001	1.333	1.109-1.602	0.002	1.024	0.978-1.073	0.305			
Anhepatic phase time	0.949	0.893-1.009	0.097				1.049	1.000-1.100	0.050			0.808

OR: Odds ratio; 95%CI: 95% confidence interval; sTLVi: Standard total liver volume index; MD-FR: Male donor-female recipient; FD-MR: Female donor-male recipient; DRI: Donor risk index; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ALD: Alcoholic liver disease; DILF: Drug-induced liver failure; PT: Prothrombin time; MELD: Model for end-stage liver disease.

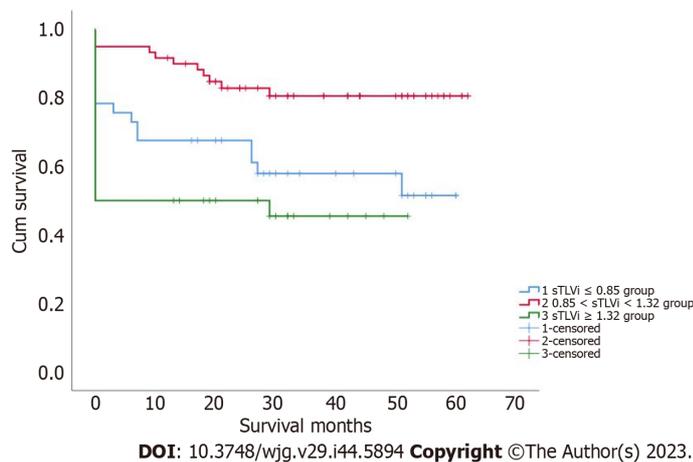
morbidity (3.4% vs 64.9% and 52.8%,  $P < 0.001$ ) and lower EAD-specific mortality (1.7% vs 13.5% and 30.6%,  $P < 0.001$ ) compared to the sTLVi ≥ 1.32 group and the sTLVi ≤ 0.85 group. However, the sTLVi did not influence ICU stay ( $P = 0.383$ ) and postoperative hospital stay ( $P = 0.101$ ). There were significant differences in terms of median survival time between the 3 groups (median, 57 mo vs 60 mo vs 24 mo,  $P < 0.001$ ). Figure 2 shows that the OS of patients with sTLVi between 0.85 and 1.32 was significantly superior to those with sTLVi ≤ 0.85 ( $P = 0.006$ ) and sTLVi ≥ 1.32 ( $P < 0.001$ ).

**Equivalence between the sTLVi model and IQQA-3D eTLVi model**

The area under the curve (AUC) of the sTLVi and IQQA-3D eTLVi models for the detection of massive IBL were 0.618 and 0.598 ( $Z = 0.889$ ,  $P = 0.374$ ; Figure 3A), respectively. The AUC of the sTLVi model and IQQA-3D eTLVi model for predicting EAD caused by SFSS and LFSS were 0.932 and 0.889 ( $Z = 1.501$ ,  $P = 0.133$ ), 0.933 and 0.922 ( $Z = 0.710$ ,  $P =$



**Figure 1** Optimal cut-off values of the index in predicting massive intraoperative blood loss and early allograft dysfunction. A: The standard total liver volume index (sTLVi) value of 1.24 was the optimal cutoff value for predicting massive intraoperative blood loss, with a sensitivity of 46.3% and a specificity of 94.7%; B: The sTLVi value of 0.85 was the optimal cutoff value for predicting early allograft dysfunction (EAD) caused by small-for-size syndrome, with a sensitivity of 96.0% and a specificity of 88.0%; C: The sTLVi value of 1.32 was the optimal cutoff value for predicting EAD caused by large-for-size syndrome, with a sensitivity of 95.0% and a specificity of 85.0%. ROC: Receiver operating characteristic.



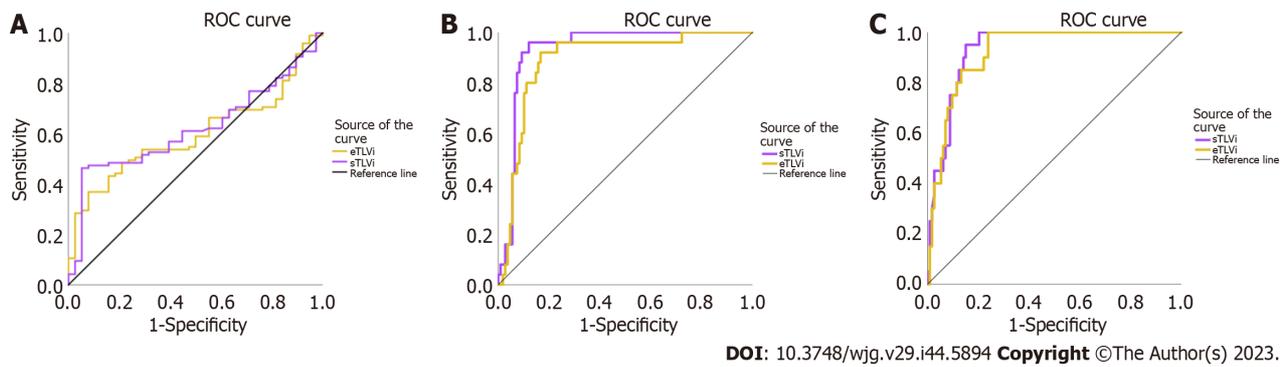
**Figure 2** Overall survival of patients in  $0.85 < \text{standard total liver volume index} < 1.32$  group was significantly superior to those in  $\text{standard total liver volume index} \leq 0.85$  group ( $P = 0.006$ ) and  $\text{sTLVi} \geq 1.32$  group ( $P < 0.001$ ). sTLVi: Standard total liver volume index.

0.478), respectively (Figure 3B and C). There were no statistically significant differences in the AUC of the sTLVi model and IQQA-3D eTLVi model for predicting massive IBL and EAD. Finally, we found that the IQQA-3D eTLVi model was also applicable to all optimal cut-off values and was equivalent to the sTLVi model in predicting massive IBL and EAD after verification.

## DISCUSSION

Postoperative complications associated with DRSM have been reported in an increasing number of DDLT studies[8-12, 23]. Conclusions drawn from LDLT-related studies are that  $\text{sTLVi} < 0.5$  is associated with poor outcomes[24] and cannot be used for DRSM in DDLT because additional risk factors, such as brain death and longer preservation injury, result in the need for a larger allograft in DDLT. Therefore, this study aimed to establish an easy, feasible, and accurate estimation model using IQQA-3D to predict massive IBL and EAD associated with DRSM and guide perioperative management in DDLT.

Massive IBT has been reported to possibly increase the risk of acute renal failure, surgical site infections, and recurrence of hepatic carcinomas in patients[25-27]. McCluskey *et al*[28] and Cywinski *et al*[29] attempt to create a model to predict the demand for IBT based on preoperative variables was not successful. The influence of preoperative risk factors and surgical factors on massive IBL have been widely studied[30], but donor factors were rarely mentioned. We have concluded that  $\text{sTLVi} \geq 1.24$  is an independent risk factor for massive IBL, which has not been reported in existing literatures. This may be attributed to the greater surgical difficulty and longer anhepatic phase time. In addition, the



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**Figure 3** The equivalence of the standard total liver volume index model and the estimation total liver volume index model in predicting massive intraoperative blood loss and early allograft dysfunction.

A: The area under the curve (AUC) of standard total liver volume index (sTLVi) model and intelligent/interactive qualitative and quantitative analysis-three-dimensional (IQQA-3D) estimation total liver volume index (eTLVi) model in detection of massive IBL were 0.618 and 0.598 ( $Z = 0.889$ ,  $P = 0.374$ ), demonstrating equivalence; B: The AUC of sTLVi model and IQQA-3D eTLVi model in detection of early allograft dysfunction (EAD) caused by small-for-size syndrome were 0.932 and 0.889 ( $Z = 1.501$ ,  $P = 0.133$ ), demonstrating equivalence; C: The AUC of sTLVi model and IQQA-3D eTLVi model in detection of EAD caused by large-for-size syndrome were 0.933 and 0.922 ( $Z = 0.710$ ,  $P = 0.478$ ), demonstrating equivalence. eTLVi: estimation total liver volume index; sTLVi: Standard total liver volume index; ROC: Receiver operating characteristic.

probability of large allografts accompanied by steatosis is higher than that of small allografts, which was seen in our analysis. Theoretically, a large allograft can fill the abdominal space to tamponade of bleeding, but allograft steatosis can have a greater effect on massive IBL due to the delayed recovery of coagulation function after reperfusion.

Besides DRSM, we observed that ALD and gastrointestinal bleeding were independent risk factors for massive IBL. Patients with ALD always experience a long course of liver disease and usually experience portal hypertension, plentiful collateral circulation, and cavernous transformation of the portal vein. Gastrointestinal bleeding can serve as a significant marker of portal hypertension, indicating a greater likelihood of multiple thin and varicose blood vessels being transected during surgical dissection. Animal experiments have shown that replacing the exact IBL volume results in an increase in portal pressure by 20% [31], higher rates of massive IBL, and worse outcome [32] in portal hypertensive rats subjected to a period of gastrointestinal bleeding. This has subsequently been demonstrated in our study, as adequate IBT was usually given to recipients with gastrointestinal bleeding before transplantation to correct hypovolemia. Surprisingly, we observed that DILF, a severe liver disease characterized by rapid onset and progression, has become an independent protective factor for massive IBL. Since patients with DILF rarely show anatomic changes in the native liver, the incidence of massive IBL can be reduced with a shorter hepatectomy duration, which is consistent with other reports [33].

Studies have reported factors related to EAD, with the most important being ischemia-reperfusion injury (IRI), which is difficult to regulate. We found that improper sTLVi is associated with an increased risk of EAD and this effect is 'U' shaped. Due to the unavailability of an index to quantify the magnitude of the DRSM effect and of a statistical methodology to formulate the model for describing its nonlinear effect, scattered studies [5,10] only reported the impact of SFSS or LFSS on EAD separately. To overcome the statistical difficulty, we divided recipients into 3 groups and found that the effect on EAD becomes stronger toward both ends of sTLVi values.

MELD score and  $sTLVi \leq 0.85$  were independent risk factors for EAD caused by SFSS. SFSS occurs when the functional liver volume is too small to provide enough activated hepatocytes for hepatic metabolism. Moreover, the small allograft will withstand the entire blood flow of the original liver, leading to severe congestion of the hepatic sinuses and portal hypertension after reperfusion. MELD score has been reported by various authors as an independent risk factor for the occurrence of EAD in DDLT recipients [34,35], which is consistent with our conclusion.

The MD-FR combination and  $sTLVi \geq 1.32$  were independent risk factors for EAD caused by LFSS. Patients with  $sTLVi \geq 1.32$  underwent a higher number of challenging surgeries, had longer anhepatic phase time, and had a higher probability of allograft steatosis, which aggravated IRI. Other anatomical causes of LFSS-related EAD included external compression affecting allograft perfusion and outflow tract obstruction, which were also potential factors with the lowest median survival time in the  $sTLVi \geq 1.32$  group. In terms of secondary outcomes, the tracheal extubation time in the  $sTLVi \geq 1.32$  group was longer than that in the other 2 groups, indicating the potential impact of large volume allograft on respiratory complications, consistent with Levesque *et al* report [6]. Gender mismatch, especially the FD-MR combination, has been reported in most studies as an independent risk factor for EAD [2,36,37]. Hormonal factors and differences in IRI and SFSS are the main hypotheses currently [38]. It is speculated that female allografts face a greater risk of IRI due to the sudden loss of protection from estrogen during implantation [2]. However, in our study, the MD-FR combination rather than the FD-MR combination played a significant role in EAD, size which could be related to the differences among males and females.

Because of time constraints with organ allocation and limited services at the donor hospital, donor eTLV measured using cross-sectional imaging is usually not feasible. We confirmed the accuracy of the Changzheng formula method in calculating donor eTLV rather than recipient eTLV. Therefore, we focused on IQQA-3D because of its high accuracy, shorter time, and not having to rely on experienced operators [39,40]. Foreign studies [41] have reported the application of IQQA-3D in precise hepatectomy and LDLT, which not only shortens the operation time but also reduces IBL and other complications. The application of IQQA-3D was rarely reported in DDLT. However, our study has innovatively used

IQQA-3D into the eTLVi model after demonstrating its accuracy in measuring recipient eTLV and confirmed its equivalence with the sTLVi model in predicting massive IBL and EAD. For patients with stable liver diseases, the IQQA-3D eTLVi model can be used to exclude extremely sized mismatched allografts. For patients with critical diseases having minimal choice but to receive unsuitable allografts, timely and sufficient perioperative management can suppress adverse outcomes. For patients with eTLVi  $\geq 1.24$ , sufficient blood products, antifibrinolytics, terlipressin, autotransfusion machine, and liver resection time should be prepared for and reserved before DDLT to reduce IBL. For patients with eTLVi  $\leq 0.85$ , the intraoperative ligation of the splenic artery or resection of the spleen should be considered to control the velocity of the portal vein. Also, if necessary, ALSS therapy should be performed promptly to reduce the burden of the allografts. For patients with eTLVi  $\geq 1.32$ , in addition to sufficient preoperative treatments to reduce the Child-Pugh score and MELD score, strict respiratory management and frequent DUS monitoring to prevent vascular complications, reduced-size LT should be considered.

To improve the accuracy of the results of this impact, we first used sTLVi calculated using the Archimedes method as the gold standard instead of the formula method based on BSA[9,42,43] or graft-to-recipient weight ratio[6,44]. If a simpler or more accurate liver volumetry tool other than IQQA-3D is developed in the future, researchers can still create a new eTLVi model to compare with the sTLVi model in our study. However, like the shortcomings of other studies on DRSM, we only compared TLV between donors and recipients, but failed to compare the abdominal parameters in detail. Due to the limitations of a single-center retrospective study without numerous patients and sufficient follow-up time, future prospective studies are warranted to be carried out.

## CONCLUSION

We established the IQQA-3D eTLVi model to estimate the degree of DRSM and predict massive IBL and EAD in DDLT. Patients with eTLVi  $\geq 1.24$  have an increased risk of massive IBL and patients with eTLVi  $\leq 0.85$  or eTLVi  $\geq 1.32$  have an increased risk of EAD. To improve the OS of patients, we should follow the guidance of the IQQA-3D eTLVi model either for organ allocation or perioperative management.

## ARTICLE HIGHLIGHTS

### Research background

Donor-recipient size mismatch (DRSM) is considered a crucial factor for poor outcomes in deceased donor liver transplantation (DDLTL).

### Research motivation

A feasible model for estimating the degree of DRSM is needed.

### Research objectives

To identify benefits of intelligent/interactive qualitative and quantitative analysis-three-dimensional (IQQA-3D) liver volumetry in DDLTL and establish an estimation model to guide perioperative management.

### Research methods

A retrospective study was conducted to determine the accuracy of IQQA-3D liver volumetry and to establish an estimation total liver volume (TLV) index (eTLVi) model. Receiver operating characteristic curves and logistic regression analysis were used to detect the influencing factors for the occurrence of massive intraoperative blood loss (IBL) and early allograft dysfunction (EAD) in DDLTL.

### Research results

Recipient estimation TLV calculated using IQQA-3D highly matched with recipient standard TLV ( $P = 0.221$ ). Alcoholic liver disease, gastrointestinal bleeding, and standard TLV index (sTLVi)  $> 1.24$  were independent risk factors for massive IBL, and drug-induced liver failure was an independent protective factor for massive IBL. Male donor-female recipient combination, model for end-stage liver disease score, sTLVi  $\leq 0.85$ , and sTLVi  $\geq 1.32$  were independent risk factors for EAD, and viral hepatitis was an independent protective factor for EAD. The overall survival of patients in the  $0.85 < \text{sTLVi} < 1.32$  group was better compared to the sTLVi  $\leq 0.85$  group and sTLVi  $\geq 1.32$  group ( $P < 0.001$ ). There was no statistically significant difference in the area under the curve of the sTLVi model and IQQA-3D eTLVi model in the detection of massive IBL and EAD (all  $P > 0.05$ ).

### Research conclusions

IQQA-3D eTLVi model has high accuracy in predicting massive IBL and EAD in DDLTL. We should follow the guidance of the IQQA-3D eTLVi model in perioperative management.

### Research perspectives

By establishing the eTLVi model, the degree of DRSM was estimated and IQQA-3D proved to be of guiding value in

perioperative management in DDLT.

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## FOOTNOTES

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**Co-first authors:** Zhi-Guo Ding and Wen-Jing Xiao.

**Co-corresponding authors:** Hao Cai and Yi-Chi Zhang.

**Author contributions:** Gong W, Cai H and Zhang YC contributed to the study conception and design; Material preparation and data collection were performed by Ding H, Ding ZG and Wang Q; Data analysis was performed by Xiao WJ and Mao XN; The first draft of the manuscript was written by Ding H and all authors commented on previous versions of the manuscript; All authors read and approved the final manuscript. Ding ZG and Xiao WJ contributed equally to this work as co-first authors. The follow-up and data collection of 133 patients included in this study were all completed by Ding ZG, which is a time-consuming and difficult task. Therefore, it is reasonable to list him as a co-first author. The data analysis and figure drawing involved in this article were mostly completed by Xiao WJ. She maintained the rigorous principle and ensured data authenticity in the process of data analysis, which justifies her as a qualified co-first author. Cai H and Zhang YC contributed equally to this work as co-corresponding authors. Cai H consulted a large amount of relevant literature and designed this study together with Gong Wei and Zhang YC. The details of the study (such as primary outcomes, secondary outcomes, influencing factors, *etc.*) were determined by Cai H, which makes it reasonable for him to become a co-corresponding author. Zhang YC also participated in the design of the study, and as an experienced surgeon, he was mainly responsible for calculating eTLV using IQQA-3D and carrying out further amendments if necessary. In addition, he was mainly committed to revising the manuscript, which makes it reasonable for him to become a co-corresponding author.

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