Retrospective Cohort Study

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The adverse impact of perioperative body composition abnormalities on outcomes after split liver transplantation: a multicenter retrospective cohort study

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Background: Split liver transplantation (SLT) increases graft availability, but it's safe and effective utilization is insufficiently documented. This study aimed to investigate the association between perioperative body composition abnormalities and outcomes in adult SLT.

Materials and methods: Two hundred forty recipients who underwent SLT in three centers were enrolled in this retrospective cohort study. Body composition abnormalities including sarcopenia, myosteatosis, visceral obesity, and sarcopenic obesity were evaluated at baseline and 1 month after surgery using computed tomography. Their impact on outcomes including early allograft dysfunction, early complications, ICU stay, graft regeneration rate, and survival was analyzed.

Results: Recipients with sarcopenia or myosteatosis had a higher risk of early allograft dysfunction, higher early complication rate, and longer length of ICU stay (all $P < 0.05$), while there was no difference in graft regeneration rate. Recipient and graft survival were significantly worse for recipients with body composition abnormalities (all $P < 0.05$). In multivariable Cox-regression analysis, sarcopenia [hazard ratio (HR) = 1.765, $P = 0.015$], myosteatosis (HR = 2.066, $P = 0.002$), and visceral obesity (HR = 1.863, $P = 0.008$) were independently associated with shorter overall survival. Piling up of the three factors increased the mortality risk stepwise ($P < 0.001$). Recipients experienced skeletal muscle loss and muscle fat infiltration 1 month after surgery. Postoperative worsening sarcopenia (HR = 2.359, $P = 0.009$) and myosteatosis (HR = 1.878, $P = 0.026$) were also identified as independent risk factors for mortality.

Conclusion: Sarcopenia, myosteatosis, and their progression negatively affect outcomes including early allograft dysfunction, early complications, ICU stay and survival after SLT. Systemic evaluation and dynamic monitoring of body composition are valuable.

Keywords: muscle fat infiltration, obesity, perioperative, prognosis, skeletal muscle mass, split liver transplantation

Introduction

Liver transplantation (LT) is the most effective therapy for end-stage liver diseases (ESLD). However, the shortage of donor livers limits its clinical application[1]. In this context, split liver transplantation (SLT) has become an attractive means of increasing the number of available grafts and reducing waitlist time and

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mortality[2,3]. Nonetheless, SLT remains technically demanding and may cause increased perioperative complications and impaired survival[4,5]. The safe and effective application of SLT warrants further exploration.

Accumulating evidence suggests the prognostic significance of body composition in chronic and neoplastic diseases[6–9]. The incidence of pathological alterations in body composition (e.g. sarcopenia, myosteatosis, or sarcopenic obesity) among LT recipients and candidates with chronic liver disease has been reported to vary from 30 to 70%[10]. Body composition abnormalities are significantly associated with post-LT adverse outcomes, including decreased quality of life, impaired graft regeneration, and mortality[10,11]. Recent clinical practice guidelines from North America and Europe recommend incorporating body composition into the preoperative evaluation of transplant candidates[12,13]. However, the exact effect of abnormal body composition on SLT recipients remains unknown, and perioperative changes in body composition and their potential clinical implications remain unexplored. Therefore, we conducted this multicenter study, which enrolled the largest number of SLT recipients to date in Asia to fill this gap.

HIGHLIGHTS

- Preoperative sarcopenia and myosteatosis were associated with adverse outcomes after split liver transplantation (SLT).
- SLT recipients experienced skeletal muscle loss and muscle fat infiltration 1 month after the surgery.
- Worsening sarcopenia and myosteatosis were risk factors for mortality after SLT.
- Graft regeneration after SLT was independent of perioperative body composition.

Material and methods

Study population and ethics

Between 1 January 2015, and 31 December 2022, all recipients underwent SLT in three transplant centers in China were considered for inclusion. Of these, pediatric cases, multiorgan transplantations, liver cancer patients with macrovascular invasion or distant metastasis, and recipients without computed tomography (CT) scan within 3 months before SLT were excluded from the analysis.

This multicenter retrospective cohort study has been reported in line with the strengthening the reporting of cohort, cross-sectional, and case–control studies in surgery (STROCSS) (Supplemental Digital Content 1, http://links.lww.com/JS9/C73) criteria[14]. The procedures of organ donation and transplantation were strictly implemented under the regulation of the China Organ Donation Committee (CODC), Organ Transplant Committee (OTC), and the Declaration of Helsinki (as revised in 2013). All donor livers came from donations after citizens' death, and there was no procurement from prisoners. The study was approved by the Chinese Liver Transplant Registry (CLTR) and retrospectively registered in ClinicalTrials.gov. Informed consent was waived as previously collected data that did not include personally identifiable information were used.

SLT procedures and imaging follow-up

Liver split was performed using two surgical forms. According to the classical split procedure, the donor liver was divided into a left lateral lobe graft (segments II and III) for a pediatric recipient and an extended right lobe graft for an adult recipient. In the full-left-full-right split procedure, full hemi-liver grafts consisting of segments I–IV (left lobe) and segments V–VIII (right lobe) enabled transplantation of two adult recipients[15]. In situ splitting of the liver was the preferred technique and intraoperative cholangiography was performed routinely to confirm biliary anatomy before splitting. Split liver grafts were submerged in cold preservation solution and kept on melting ice until transplantation. Vascular and biliary reconstruction were performed according to standard procedures[16]. After surgery, all recipients were closely followed by regular clinical evaluation and imaging examinations including CT scans. However, owing to the differences in imaging follow-up schemes among transplant centers, the time points of CT scans are not fixed. To reduce the effect of postoperative CT interval differences, only CT scans performed between 20 and 40 days after SLT were included in the perioperative body composition and graft regeneration analyses.

Body composition analyses

CT images at the level of the third lumbar vertebra (L3) were extracted by a researcher trained in radiologic anatomy for the assessment of body composition. The SliceOmatic 5.0 software (Tomovision) was used to measure the total cross-sectional area of the skeletal muscle (SM, – 29 to 150 HU), subcutaneous adipose tissue (SAT, – 190 to – 30 HU), and visceral adipose tissue (VAT, – 150 to – 50 HU) using predefined HU ranges. The tissue area (cm^2) was normalized for height squared (m^2) to obtain the L3-index (cm^2/m^2), including the SM index (SMI), SAT index (SATI), and VAT index (VATI), which corresponded well with whole-body muscle and adipose tissue mass[17]. The skeletal muscle mass-to-visceral fat area ratio (SVR) was defined as the ratio of SMI to VATI. Tissue radiation attenuation (RA) is the average HU value of the total tissue area, which is negatively correlated with fat content[18,19]. For graft-recipient matching and avoidance of small-for-size syndrome (SFSS), SLT recipients tend to have a lower weight and are inevitably accompanied by a relatively worse nutritional status. If conventional criteria were adopted, the proportion of recipients with sarcopenia or myosteatosis in our study would be too high (both over 75%)[10]. Besides, body composition varies greatly among different regions and ethnicities. Therefore, the cut-off values for our cohort were determined based on tertiles, as performed in other studies[20–22]. Sex-specific cut-off values were determined considering the great impact of sex on body composition. Sarcopenia, myosteatosis, and sarcopenic obesity were defined as L3 SMI, SM-RA, and SVR less than the sex-specific lowest tertiles[10]. Visceral obesity was defined as L3 VATI more than the sex-specific highest tertile. The rate of SMI change after SLT was calculated using the following formula:

$$\Delta\mathrm{SMI}\% = \left(\mathrm{SMI}_{1\ \mathrm{month\ post-SLT}} - \mathrm{SMI}_{\mathrm{pre-SLT}}\right) \times 100/\mathrm{SMI}_{\mathrm{pre-SLT}}\%$$

Changes in other body composition parameters were defined in the same way. Worsening sarcopenia, myosteatosis, sarcopenic obesity, and reduced visceral obesity were defined as declines in SMI, SM-RA, SVR, and VATI more than 25% at 1 month after transplantation.

Graft regeneration assessment

In clinical practice, it is difficult to measure the actual graft volume (GV) before LT. As the donor liver has a density close to water, the actual GV in milliliters was assumed to correspond to the graft weight in grams routinely measured after procuring and perfusing[23]. A MacBook Pro (16-inch, M1 pro, 2021) with OsiriX Lite software version 13.0.1 (https://www.osirix-viewer.com) was used for GV measurement post-SLT. The liver contour was manually outlined on transverse slices of the venous phase of postoperative contrast-enhanced CT scans. The intrahepatic vascular and biliary spaces were depicted and excluded from the regions of interest (ROIs). After measuring the area of all ROIs within one series, slice volumes were calculated by multiplying area and slice thickness and then summed up to obtain the final GV[24]. Graft regeneration rate (GRR) was calculated using the following formula[11]:

$$\mathrm{GRR} = \left(\mathrm{GV}_{1\ \mathrm{month\ post-SLT}} - \mathrm{GV}_{\mathrm{pre-SLT}}\right) \times 100/\mathrm{GV}_{\mathrm{pre-SLT}}$$

Data sources and study endpoints

The data used in this study were extracted from the CLTR database and three centers enrolled. The following donor data were recorded for analysis: age, BMI, donation type, split method, graft type, graft weight-to-recipient ratio (GRWR), and ABO compatibility. Characteristics of the recipients included age, sex, BMI, Child-Pugh scores, model for end-stage liver disease (MELD) scores, and indication for transplantation. Operative data included split methods, cold ischemic time (CIT), operative time, and blood loss. Graft survival was defined as the time from LT to recipient death or retransplantation. The length of ICU stay was defined as the initial stay after SLT in ICU until the transfer of the recipients to the general ward. Early postoperative complications were defined as those occurring within the first month after SLT, including intra-abdominal bleeding, thromboembolism, biliary complications, primary non-function (PNF), delayed graft function (DGF), and infection. Early allograft dysfunction (EAD) was defined according to Olthoff *et al*.[25] SFSS was defined according to Hernandez-Alejandro *et al*.[26] The primary endpoint was recipient overall survival (OS), and secondary endpoints included EAD, early complications, length of ICU stay, GRR, and graft survival.

Statistical analysis

The Kolmogorov–Smirnov test was used to evaluate the normality of the variable distributions. Numerical data were expressed as mean ± SD if the distribution was normal, or median with interquartile range (IQR) if not. Depending on the distribution normality, they were compared using the Student's *t*-test or Mann–Whitney *U* test. Categorical data were expressed as numbers with frequencies. Differences in categorical variables between groups were tested using the χ^2 or Fisher's exact test. The preoperative and postoperative body composition were compared using the paired *t*-test, Wilcoxon matched pairs test, or McNemar's test. The associations between recipient survival and body composition abnormalities were assessed using univariate and multivariate Cox proportional hazards regression models. Variables significant at the 0.05 level were included in the multivariate analysis using the forward likelihood ratio (LR) method. Survival curves were generated using the Kaplan–Meier method, compared by the log-rank test, and then plotted with Xiantao website tool (http://www.xiantao.love). Spearman correlation coefficients were used to explore the correlation between graft regeneration and continuous variables. Multivariate linear regression analysis was performed, including all variables significant at $P < 0.05$ in the aforementioned analysis. The variance inflation factors and tolerance values were computed to determine the presence of statistically significant multicollinearity; no significant collinearity was found. All *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using GraphPad Prism 9.0 (GraphPad Software Inc.) and SPSS 26.0 (IBM, SPSS).

Results

Baseline characteristics

Out of all 458 consecutive SLT performed, 240 recipients met the inclusion criteria. Pediatric cases ($n = 176$), liver cancer patients with macrovascular invasion or distant metastasis ($n = 10$), and recipients without a CT scan within 3 months before SLT ($n = 32$) were excluded (Fig. 1). A total of 134 recipients had available postoperative abdominal CT images around 1 month. The median interval between the included CT images and transplant was 14.0 days (IQR: 5.0–32.3 days) before SLT and 30.5 days (IQR: 27.0–34.0 days) after SLT. The median follow-up time was 24.7 months. Donor and recipient characteristics are summarized in Table 1 and Table S1 (Supplemental Digital Content 2, http://links.lww.com/JS9/C74). Hepatitis B (30.0%), alcoholic liver disease (7.1%), autoimmune liver disease (15.0%), and tumor (34.2%) were the main indications for transplantation. Of the 82 tumor recipients, 73 had hepatocellular carcinoma (HCC) and the rest had cholangiocellular carcinoma. A total of 148 (61.7%) deceased donor livers were derived from donation after brain death (DBD) and 92 (38.3%) from donation after cardiac

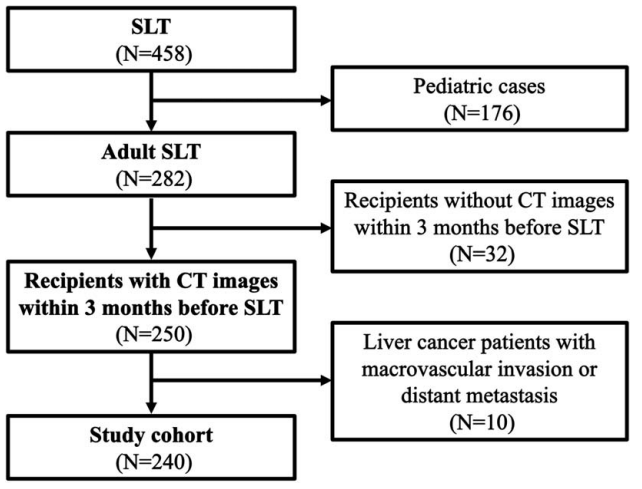

Figure 1. Flow chart for patient enrollment. CT, computed tomography; SLT, split liver transplantation.

Table 1

Donor and recipient characteristics classified according to sarcopenia and myosteatosis.

		Sarcopenia			Myosteatosis		
Characteristics	**All (*N* = 240)**	**No (*N* = 160)**	**Yes (*N* = 80)**	***P***	**No (*N* = 160)**	**Yes (*N* = 80)**	***P***
Recipient age (year)	53.0 (46.0–59.0)	51.5 (45.0–59.0)	56.0 (48.8–61.3)	**0.048**	51 (44.8–58.0)	56.5 (49.0–63.0)	**< 0.001**
Recipient sex				0.926			0.926
Male	143 (59.6%)	95 (59.4%)	48 (60.0%)		95 (59.4%)	48 (60.0%)	
Female	97 (40.2%)	65 (40.6%)	32 (40.0%)		65 (40.6%)	32 (40.0%)	
Recipient BMI (kg/m^2)	21.8 (19.6–23.4)	22.7 (20.6–24.2)	20.1 (18.1–22.3)	**< 0.001**	22.0 (19.5–23.4)	21.5 (19.7–23.6)	0.877
Child-Pugh score	10.0 (8.0–11.0)	10.0 (8.0–11.0)	10.0 (8.8–11.0)	0.168	10.0 (8.0–11.0)	10.0 (9.0–11.0)	**0.019**
MELD score	25.0 (14.0–40.0)	24.0 (13.0–40.0)	25.0 (16.8–40.0)	0.657	22.5 (12.0–40.0)	31.0 (18.0–40.0)	**0.024**
Transplant indication				**0.019**			0.964
Hepatitis B	72 (30.0%)	51 (31.9%)	21 (26.3%)		48 (30.0%)	24 (30.0%)	
Alcohol liver disease	17 (7.1%)	10 (6.3%)	7 (8.8%)		11 (6.9%)	6 (7.5%)	
Autoimmune disease	36 (15.0%)	20 (12.5%)	16 (20.0%)		23 (14.4%)	13 (16.3%)	
Tumor	82 (34.2%)	63 (39.4%)	19 (23.8%)		57 (35.6%)	25 (31.3%)	
Others	33 (13.8%)	16 (10.0%)	17 (21.3%)		21 (13.1%)	12 (15.0%)	
Donation type				0.222			0.302
DBD	148 (61.7%)	103 (64.4%)	45 (56.3%)		95 (59.4%)	53 (66.3%)	
DCD	92 (38.3%)	57 (35.6%)	35 (43.8%)		65 (40.6%)	27 (33.8%)	
Split method				0.365			0.821
In situ	191 (79.6%)	130 (81.3%)	61 (76.3%)		128 (80.0%)	63 (78.8%)	
Ex vivo	49 (20.4%)	30 (18.8%)	19 (23.8%)		32 (20.0%)	17 (21.3%)	
Graft type				0.157			0.819
Left lobe	49 (20.4%)	27 (16.9%)	22 (27.5%)		31 (19.4%)	18 (22.5%)	
Right lobe	59 (24.6%)	41 (25.6%)	18 (22.5%)		39 (24.4%)	20 (25.0%)	
Extended right lobe	132 (55.0%)	92 (57.5%)	40 (50.0%)		90 (56.3%)	42 (52.5%)	
GRWR (%)	1.6 (1.3–1.9)	1.5 (1.2–1.9)	1.7 (1.3–2.1)	**0.032**	1.6 (1.3–1.9)	1.6 (1.2–2.0)	0.896
Donor age (year)	40.0 (32.0–49.0)	39.0 (32.0–49.0)	42.5 (32.8–51.0)	0.138	40.0 (32.0–49.0)	41.0 (32.0–50.0)	0.481
Donor BMI (kg/m^2)	23.4 (21.7–25.7)	23.2 (21.7–25.0)	24.2 (21.9–26.1)	**0.032**	23.4 (21.5–25.4)	23.9 (22.3–26.0)	0.102
CIT (min)	360.0 (283.5–492.0)	359.0 (283.5–480.3)	369.5 (278.0–502.3)	0.625	359.0 (254.8–474.3)	394.0 (301.5–521.8)	**0.030**
ABO incompatibility	5 (2.1%)	3 (1.9%)	2 (2.5%)	1.000	2 (1.3%)	3 (3.8%)	0.424
Operation time (min)	393.0 (334.8–501.3)	394.0 (342.0–489.8)	385.0 (333.5–509.8)	0.923	391.0 (331.5–524.3)	397.0 (349.0–489.3)	0.894
Blood loss (ml)	1500 (1000–2500)	1500 (1000–2500)	1750 (1200–2500)	0.119	1500 (1000–2000)	2000 (1000–3000)	**0.013**
EAD	96 (40.0%)	56 (35.0%)	40 (50.0%)	**0.025**	52 (32.5%)	44 (55.0%)	**< 0.001**
ICU stay (hour)	206.5 (134.0–331.5)	200.2 (116.8–304.3)	236.5 (157.5–500.8)	**0.014**	186.5 (121.8–278.3)	274.5 (163.4–512.0)	**< 0.001**
Early complications	72 (30.0%)	38 (23.8%)	34 (42.5%)	**0.003**	41 (25.6%)	31 (38.8%)	**0.036**
90-day-mortalilty	47 (19.6%)	24 (15.0%)	23 (28.8%)	**0.011**	20 (12.5%)	27 (33.8%)	**< 0.001**

Numerical data were compared using the Mann–Whitney *U* test. Differences in categorical data were tested using the χ^2 or Fisher's exact test.

P-values in bold indicate statistical significance.

CIT, cold ischemia time; DBD, donation after brain death; DCD, donation after cardiac death; EAD, early allograft dysfunction; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease.

death (DCD). The major graft type was extended right lobes (55.0%), while left lobes and right lobes accounted for 20.4 and 24.6%, respectively. The median GRWR was 1.6% (IQR: 1.3–1.9%), and no recipient developed SFSS in our study. To evaluate the potential selection bias introduced by reimaging, we compared the characteristics between recipients who had available CT scans around 1 month post-SLT and those who did not; no significant differences were observed in terms of body composition, disease features, and particularly early complications (Table S2, Supplemental Digital Content 2, http://links.lww.com/JS9/C74).

Preoperative body composition analysis

Sex differences existed in the body composition parameters (Table S3, Supplemental Digital Content 2, http://links.lww.com/JS9/C74). Female recipients had lower SMI (34.6 vs. 42.4 cm^2/m^2, $P < 0.001$), SM-RA (31.7 vs. 36.2 HU, $P < 0.001$) and SAT-RA (−86.6 vs. −81.1 HU, $P = 0.011$) but higher SATI (38.4 vs. 21.1 cm^2/m^2, $P < 0.001$) compared with male recipients. Therefore, we defined body composition abnormalities based on sex-specific tertiles (sarcopenia: SMI, male < 38.8 cm^2/m^2, female < 31.6 cm^2/m^2; myosteatosis: SM-RA, male < 33.6 HU, female < 27.6 HU; visceral obesity, VATI, male > 32.3 cm^2/m^2, female > 27.6 cm^2/m^2; sarcopenic obesity: SVR, male < 1.4, female < 1.3). Correlations between body composition abnormalities and other parameters are shown in Table 1 and Table S1 Supplemental Digital Content 2, http://links.lww.com/JS9/C74). Sarcopenic recipients had an older age ($P = 0.048$), lower recipient BMI ($P < 0.001$), and higher GRWR ($P = 0.032$), while myosteatotic recipients had an older age ($P < 0.001$), and higher MELD scores ($P = 0.024$) and Child-Pugh scores ($P = 0.019$). As expected, recipients with visceral obesity or sarcopenic obesity had a higher BMI (both $P < 0.001$).

Relationship between preoperative body composition and post-transplant outcomes

The incidence of EAD, early complication rate, length of ICU stay, and 90-day mortality were higher in the sarcopenia and

myosteatosis groups (all $P < 0.05$) (Table 1), while no significant difference was observed in the visceral obesity or sarcopenic obesity groups (all $P > 0.05$) (Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/C74). A total of 78 (32.5%) recipients died during the follow-up. Multiple organ failure (33.3%), sepsis (16.7%), tumor recurrence (15.4%), graft failure (7.7%), and massive bleeding (7.7%) were major causes of mortality. The OS rate was significantly lower for each group of recipients with sarcopenia ($P = 0.006$), myosteatosis ($P < 0.001$), visceral obesity ($P = 0.013$), or sarcopenic obesity ($P = 0.012$) compared with the respective normal groups (Fig. 2, A–C). Similar to the recipient survival, graft survival was also significantly worse in recipients with these body composition abnormalities (all $P < 0.05$) (Figure S1, Supplemental Digital Content 2, http://links.lww.com/JS9/C74).

Risk factors for poor survival after SLT

Univariate and multivariate Cox-regression analyses were performed to identify independent risk factors for overall mortality (Table 2). Univariate Cox-regression analysis identified that sarcopenia ($P = 0.007$), myosteatosis ($P < 0.001$), visceral obesity ($P = 0.014$), sarcopenic obesity ($P = 0.014$), high MELD scores ($P < 0.001$), Child-Pugh class B ($P = 0.038$) and C ($P = 0.016$), massive blood loss ($P = 0.021$), left lobe graft ($P < 0.001$), and right lobe graft ($P = 0.017$) were all significant risk factors for post-SLT mortality. Multivariate analysis identified sarcopenia [hazard ratio (HR) 1.765, 95% CI: 1.116–2.793, $P = 0.015$], myosteatosis (HR 2.066, 95% CI: 1.307–3.264, $P = 0.002$), visceral obesity (HR 1.863, 95% CI: 1.176–2.952, $P = 0.008$), high MELD scores (HR 1.959, 95% CI: 1.150–3.336, $P = 0.013$), and left lobe graft (HR 2.582, 95% CI: 1.492–4.469, $P < 0.001$) as independent risk factors for overall mortality. In addition, these three body composition abnormalities contributed to an increased risk of death in an additive manner ($P < 0.001$; Fig. 2D), suggesting that they were complementary predictors of poor prognosis in SLT recipients.

Changes in body composition after SLT

The changes in body composition after SLT are shown in Table 3. In 134 recipients with abdominal CT at 1 month after SLT, the mean SMI decreased from 38.2 cm^2/m^2 to 35.3 cm^2/m^2 ($P < 0.001$), and the mean SM-RA decreased from 34.6 HU to 28.4 HU ($P < 0.001$). According to the diagnostic criteria defined based on preoperative body composition, the proportion of recipients with sarcopenia and myosteatosis increased from 38.1 to 56.7% ($P < 0.001$) and 35.1 to 57.5%

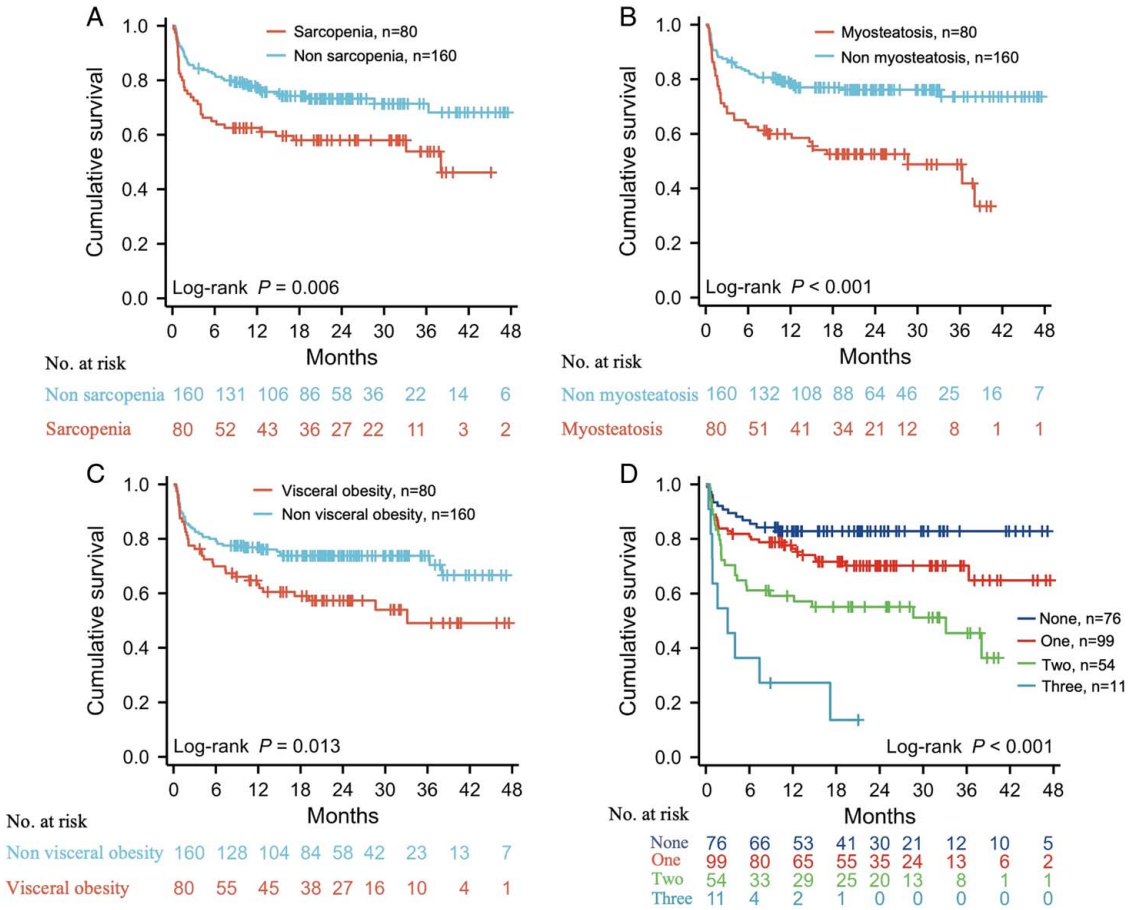

Figure 2. Survival of SLT recipients with preoperative body composition abnormalities ($N = 240$). Survival curves were plotted with the Kaplan–Meier method and compared using the log-rank test. Shorter survival was noticed in recipients with preoperative sarcopenia (A, $P = 0.006$), myosteatosis (B, $P < 0.001$), and visceral obesity (C, $P = 0.013$). Piling up of the three factors increased the mortality risk stepwise (D, $P < 0.001$).

Table 2

Cox regression evaluation of factors associated with mortality following split liver transplantation.

	Univariable		Multivariable	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Recipient age > 60 years	0.734 (0.412–1.308)	0.294		
Female sex	1.092 (0.697–1.712)	0.700		
Recipient BMI > 24 kg/m^2	0.882 (0.681–1.142)	0.340		
MELD score > 20	2.581 (1.549–4.300)	**< 0.001**	1.959 (1.150–3.336)	**0.013**
Child-Pugh class				
A	Reference			
B	8.327 (1.126–61.560)	**0.038**	—	—
C	11.379 (1.537–82.345)	**0.016**	—	—
Transplant indication				
Hepatitis B	Reference			
Alcohol	1.777 (0.695–4.543)	0.230		
Autoimmune cirrhosis	1.754 (0.843–3.647)	0.133		
Tumor	1.610 (0.877–2.954)	0.124		
Others	1.895 (0.911–3.942)	0.087		
DCD	0.683 (0.423–1.104)	0.119		
Split in situ	0.958 (0.553–1.661)	0.880		
Donor type				
Extended right graft	Reference			
Left lobe	2.651 (1.540–4.563)	**< 0.001**	2.582 (1.492–4.469)	**< 0.001**
Right lobe	1.940 (1.128–3.337)	**0.017**	1.688 (0.965–2.952)	0.067
GRWR < 1.0%	1.129 (0.563–2.261)	0.733		
Donor age > 50 years	0.921 (0.507–1.671)	0.786		
Donor BMI > 24 kg/m^2	1.044 (0.668–1.631)	0.851		
CIT > 420 min	0.876 (0.549–1.396)	0.577		
ABO incompatibility	2.736 (0.998–7.505)	0.051		
Blood loss > 2000 ml	1.716 (1.087–2.709)	**0.021**	—	—
Available CT at 1month post-SLT	1.492 (0.932–2.390)	0.096		
Sarcopenia	1.844 (1.180–2.883)	**0.007**	1.765 (1.116–2.793)	**0.015**
Myosteatosis	2.496 (1.599–3.896)	**< 0.001**	2.066 (1.307–3.264)	**0.002**
Visceral obesity	1.750 (1.120–2.735)	**0.014**	1.863 (1.176–2.952)	**0.008**
Sarcopenic obesity	1.753 (1.122–2.740)	**0.014**	—	—
High SATI	1.218 (0.769–1.930)	0.400		
High SAT-RA	0.928 (0.577–1.492)	0.757		
High VAT-RA	1.080 (0.677–1.722)	0.747		

The associations of recipient survival with body composition abnormalities were assessed by univariate and multivariable Cox proportional hazards regression models.

P-values in bold indicate statistical significance

CIT, cold ischemia time; CT, computed tomography; DCD, donation after cardiac death; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease; SATI, subcutaneous adipose tissue index; SAT-RA, subcutaneous adipose tissue radiation; VAT-RA, visceral adipose tissue radiation.

($P < 0.001$), respectively. Eighteen (13.4%) and 47 (35.1%) recipients suffered worsening sarcopenia and worsening myosteatosis (more than 25% decline in SMI and SM-RA) 1 month after SLT.

Association between perioperative changes of body composition and outcomes

The OS rate was significantly lower for each group of recipients with worsening sarcopenia ($P < 0.001$) and worsening myosteatosis ($P = 0.003$) compared with the respective normal groups (Fig. 3). Besides, worsening sarcopenia (HR 2.359, 95% CI: 1.243–4.474, $P = 0.009$) and worsening myosteatosis (HR 1.878, 95% CI: 1.080–3.267, $P = 0.026$) were also identified as independent risk factors for mortality after SLT (Table 4).

As for perioperative outcomes, recipients with worsening sarcopenia had longer ICU stay (403.0 vs. 227.5 h, $P = 0.001$) and higher 90-day mortality (44.4 vs. 14.7%, $P = 0.007$), while recipients with worsening myosteatosis had higher EAD incidence (55.3 vs. 32.2%, $P = 0.009$), early complication rate (48.9 vs. 17.2%, $P < 0.001$), and 90-day mortality (38.3 vs. 8.0%, $P < 0.001$) (Table S4, Supplemental Digital Content 2, http://links.lww.com/JS9/C74).

Correlation between perioperative body composition and graft regeneration

The median GRR at 1 month post-SLT was 45.9% (IQR: 25.3–76.4%). Recipient age ($P = 0.033$), GRWR ($P < 0.001$), and donor BMI ($P = 0.002$) showed a significant negative correlation with GRR by performing a Spearman correlation analysis. Further multiple linear regression analysis identified GRWR as the only determinant of GRR ($P < 0.001$). None of the preoperative parameters and perioperative body composition changes showed a significant correlation with GRR (Table 5).

Table 3

Perioperative changes of body compositions.

Variable	Pretransplant	Post-transplant	*P*
SMI (cm^2/m^2)	38.2 (33.9–45.7)	35.3 (29.9–40.1)	**< 0.001**
SM-RA (HU)	34.6 ± 8.8	28.4 ± 8.9	**< 0.001**
VATI (cm^2/m^2)	21.1 (12.0–33.0)	20.8 (11.7–32.4)	0.510
SATI (cm^2/m^2)	25.6 (14.9–46.6)	22.1 (11.8–39.7)	**< 0.001**
SVR	1.8 (1.1–3.5)	1.8 (1.1–3.0)	**0.004**
Sarcopenia	51 (38.1%)	76 (56.7%)	**< 0.001**
Myosteatosis	47 (35.1%)	77 (57.5%)	**< 0.001**
Visceral obesity	45 (33.6%)	39 (29.1%)	0.286
Sarcopenic obesity	45 (33.6%)	53 (39.6%)	0.134

The preoperative and postoperative body composition were compared using paired *t*-test, Wilcoxon matched pairs test or McNemar's test.

P-values in bold indicate statistical significance.

SATI, subcutaneous adipose tissue index; SMI, skeletal muscle index; SM-RA, skeletal muscle radiation attenuation; SVR, skeletal muscle mass-to-visceral fat area ratio; VATI, visceral adipose tissue index.

Discussion

To our knowledge, this is the first and largest study to describe the relationship between perioperative body composition and outcomes following SLT. In this study, sarcopenia, myosteatosis, and visceral obesity were identified as independent risk factors for recipient survival and contributed to an increased risk of death. Moreover, recipients with sarcopenia or myosteatosis had higher rates of early complications, EAD, and longer ICU stay.

Recently, a meta-analysis revealed that graft and patient survival following SLT are predominantly compromised during the early postoperative period, likely attributed to an elevated incidence of postoperative complications[5]. Similar to some other studies, our cohort also had a relatively high but comparable early mortality rate and complication rate[4,27–29]. This illustrates the importance of selecting suitable recipients to achieve a safer and more effective application of SLT. In other words, our study suggests that preoperative abnormal body composition may be a potential contraindication for SLT. A comprehensive prognostic evaluation system based on body composition will help to guide recipient selection and risk stratification.

Perioperative changes in body composition are another matter of concern. It is reported that sarcopenia progresses up to 1 year following LT[30]. This may be related to persistent catabolic state, immunosuppressive treatment, and prolonged hospitalizations[31]. Several studies have revealed the impact of dynamic SM changes on recipient outcomes after WLT and living donor liver transplantation (LDLT). Newly developed sarcopenia and massive SM loss post-LT are risk factors for recipient mortality[32–34]. However, alterations in body composition and their significance in clinical outcomes following SLT remain unclear. This study found that the mean SMI and SM-RA clearly decreased 1 month after SLT, leading to an increased incidence of sarcopenia and myosteatosis. Besides, worsening sarcopenia and myosteatosis were also independent risk factors for mortality after SLT. They were associated with worse perioperative outcomes, including prolonged ICU stay, higher early complication rate, and higher 90-day mortality. These findings indicate that body composition is a dynamic feature that varies perioperatively. Therefore, continuous monitoring is thus of great significance. A randomized controlled trial demonstrated that the administration of a leucine metabolite-enriched formula post LDLT significantly increases SMI, shortens postoperative hospital stays, and decreases the occurrence of bacteremia[35]. Furthermore, it was shown that sufficient perioperative nutritional therapy improves the survival of sarcopenic recipients after LDLT[36]. These findings suggest that perioperative strategies to reverse abnormal body composition may also improve the prognosis of SLT recipients. Such management requires a multipronged approach, including nutritional counseling, physiotherapy, and pharmacological therapy[37]. Further prospective, multicenter, randomized clinical trials are needed.

EAD is a life-threatening complication of LT and is thought to be mediated in large part by ischemia/reperfusion injury (IRI)[38]. Typically, grafts split ex vivo experience longer CIT and suffer more severe IRI[39]. Compared with whole grafts, split grafts have a higher incidence of EAD[40]. In this study, 40% of the recipients developed EAD. The incidence reached 50.0 and 55.0% in recipients with sarcopenia and myosteatosis, respectively. Our study confirmed for the first time the correlation between recipient body composition and EAD. This means that marginal donor livers

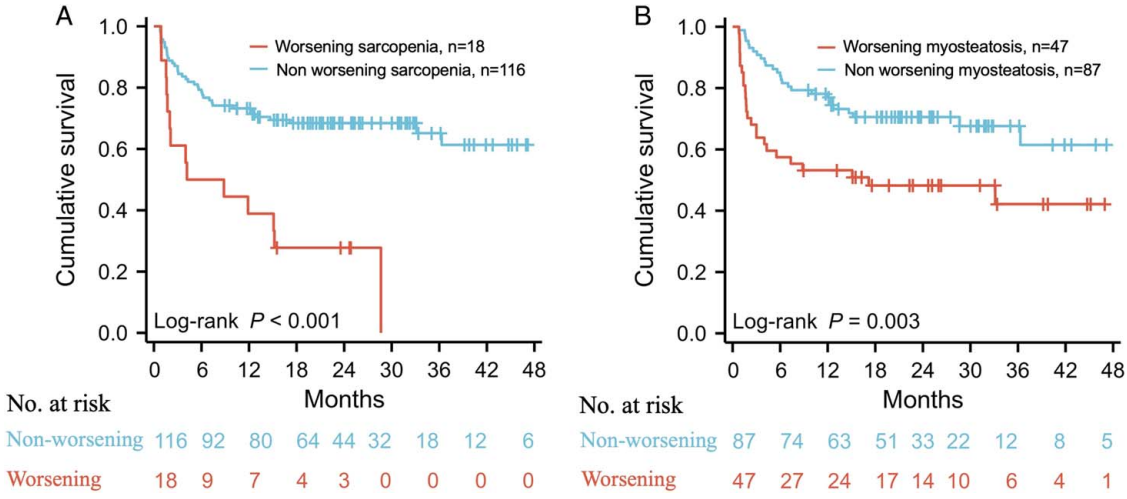

Figure 3. Survival of SLT recipients with postoperative worsening sarcopenia and myosteatosis ($N = 134$). Kaplan–Meier survival curves were compared using the log-rank test. Recipients with worsening sarcopenia (A, $P < 0.001$) and worsening myosteatosis (B, $P = 0.003$) had significantly worse survival.

Table 4

Univariate and multivariate analyses of perioperative factors affecting overall survival in patients with postoperative computed tomography.

	Univariable		Multivariable	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Recipient age > 60 years	0.838 (0.431–1.631)	0.604		
Female sex	1.029 (0.593–1.784)	0.919		
Recipient BMI > 24 kg/m^2	1.020 (0.739–1.409)	0.904		
MELD score > 20	3.261 (1.733–6.138)	< **0.001**	2.341 (1.208–4.536)	**0.012**
Child-Pugh class				
A	Reference			
B	4.418 (0.581–33.605)	0.151		
C	7.686 (1.053–56.111)	**0.044**	—	—
Transplant indication				
Hepatitis B	Reference			
Alcohol	0.968 (0.270–3.470)	0.960		
Autoimmune cirrhosis	1.299 (0.503–3.355)	0.589		
Tumor	1.375 (0.663–2.851)	0.393		
Others	2.005 (0.851–4.723)	0.112		
DCD	0.699 (0.387–1.263)	0.236		
Split in situ	1.198 (0.600–2.390)	0.609		
Donor type				
Extended right graft	Reference			
Left lobe	1.521 (0.773–2.994)	0.224		
Right lobe	1.399 (0.730–2.680)	0.312		
GRWR < 1.0%	0.845 (0.336–2.126)	0.720		
Donor age > 50 years	1.276 (0.638–2.551)	0.491		
Donor BMI > 24 kg/m^2	0.872 (0.503–1.512)	0.626		
CIT > 420 minutes	1.276 (0.725–2.246)	0.398		
ABO incompatibility	2.425 (0.871–6.753)	0.090		
Blood loss > 2000 ml	2.410 (1.392–4.171)	**0.002**	—	—
Sarcopenia	1.669 (0.967–2.881)	0.066		
Myosteatosis	3.014 (1.741–5.218)	< **0.001**	2.118 (1.192–3.763)	**0.010**
Visceral obesity	1.546 (0.892–2.681)	0.121		
Sarcopenic obesity	1.705 (0.986–2.947)	0.056		
High SATI	1.074 (0.601–1.919)	0.810		
High SAT-RA	0.942 (0.528–1.681)	0.839		
High VAT-RA	0.886 (0.496–1.582)	0.682		
Worsening sarcopenia	3.439 (1.848–6.399)	< **0.001**	2.359 (1.243–4.474)	**0.009**
Reduced visceral obesity	1.275 (0.699–2.325)	0.429		
Worsening myosteatosis	2.062 (1.194–3.560)	**0.009**	1.878 (1.080–3.267)	**0.026**
Worsening sarcopenic obesity	0.946 (0.534–1.676)	0.848		

The associations of recipient survival with perioperative body composition abnormalities were assessed by univariate and multivariable Cox proportional hazards regression models. Multivariate analysis was conducted by forward: LR method.

P-values in bold indicate statistical significance.

CIT, cold ischemia time; DCD, donation after cardiac death; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease; SATI, subcutaneous adipose tissue index; SAT-RA, subcutaneous adipose tissue radiation; VAT-RA, visceral adipose tissue radiation.

should be used cautiously for SLT, especially in sarcopenic or myosteatotic patients. There could be multiple potential reasons for this, such as elevated levels of proinflammatory cytokines and higher MELD scores among recipients with abnormal body composition[41,42].

Sufficient GV and regeneration are essential for the success of partial liver transplantation[43]. In our study, recipients who received left lobes (the smallest GV compared with other graft types) had significantly worse OS rates, suggesting the importance of adequate GV. Riccardo *et al.*[11] reported that pre-LDLT low SMI was associated with impaired GRR, and this negative impact was more pronounced in male recipients. Another study found that sarcopenic obesity predicts impaired graft regeneration after LDLT[44]. However, none of the preoperative and perioperative changes in body composition parameters, including SMI and SVR, showed a significant correlation with GRR in this study. This difference may be due to several possibilities. Firstly, the GRWR in our SLT cohort was higher, and the GRR was lower than that in their population. Therefore, the influence of body composition on graft regeneration may not be so significant in this setting. Secondly, differences in surgical procedures and hemodynamic factors of portal circulation may also lead to inconsistent conclusions[45]. Thirdly, preoperative and postoperative GVs were calculated using two different methods and this inevitably led to measurement bias of GRR. Fourthly, differences in intervals between volume measurement and methods of body composition assessment might also account for the disparity in conclusions. Further studies are needed to confirm these associations.

Table 5

Correlations between graft regeneration rate and recipient, or donor characteristics, preoperative or perioperative changes of body composition parameters.

	Univariable correalation		Multivariate linear regression	
Variable	Spearman correlation coefficient	*P*	Regression coefficient (95% CI)	*P*
Recipient age	– 0.185	**0.033**	– 0.609 (– 1.267–0.049)	0.069
Recipient BMI	– 0.022	0.802		
Child-Pugh score	– 0.029	0.744		
MELD score	– 0.026	0.762		
GRWR	– 0.548	< **0.001**	– 35.062 (– 46.128, – 23.996)	< **0.001**
Donor age	0.005	0.951		
Donor BMI	– 0.267	**0.002**	– 1.398 (– 3.769–0.973)	0.246
CIT	0.056	0.518		
Operation time	0.038	0.662		
Blood loss	0.098	0.260		
ICU stay	0.042	0.631		
SMI	0.131	0.130		
SATI	– 0.070	0.420		
VATI	– 0.028	0.749		
SVR	0.076	0.385		
SM-RA	0.059	0.500		
SAT-RA	0.106	0.223		
VAT-RA	0.075	0.391		
ΔSMI%	– 0.042	0.628		
ΔSATI%	0.087	0.316		
ΔVATI%	0.031	0.722		
ΔSVR%	– 0.056	0.522		
ΔSM-RA%	– 0.088	0.315		
ΔSAT-RA%	– 0.024	0.784		
ΔVAT-RA%	– 0.075	0.389		

Spearman correlation and multivariate linear regression analyses were applied to analyze these associations.

P-values in bold indicate statistical significance.

-CIT, cold ischemia time; GRWR, graft-to-recipient weight ratio-; MELD, model for end-stage liver disease; SATI, subcutaneous adipose tissue index; SAT-RA, subcutaneous adipose tissue radiation attenuation; SMI, skeletal muscle index; SM-RA, skeletal muscle radiation attenuation; SVR, skeletal muscle mass-to-visceral fat area ratio; VATI, visceral adipose tissue index; VAT-RA, visceral adipose tissue radiation attenuation.

There are several limitations to our study. Firstly, this study was designed retrospectively and was subject to the inherent limitations associated with retrospective analyses. Secondly, recipients were excluded from perioperative body composition and graft regeneration analyses if a CT scan around one month post-SLT was unavailable. This could potentially introduce selection bias, as recipients who were sicker or developed more complications may have been getting more imaging. However, no significant differences in clinical features or early complications were observed between the dynamic cohort and excluded recipients. Given the large similarity between the two groups, the dynamic cohort was likely representative of the whole population. Prospective studies are still needed to examine our results. Thirdly, as the number of SLT in China has increased significantly only in recent years, the study had a limited sample size and follow-up time. Meanwhile, most deaths occurred early after SLT; therefore, the analysis was focused on short-term postoperative outcomes. Finally, our study established new criteria for the diagnosis of abnormal body composition in SLT recipients due to the heterogeneity of the study population. Further studies are required to validate the applicability of these findings.

Conclusion

In summary, sarcopenia, myosteatosis and visceral obesity are independent risk factors for mortality after SLT. One month after the surgery, SLT recipients experienced exacerbated SM loss and muscle fat infiltration. Postoperative worsening sarcopenia and myosteatosis were also associated with adverse outcomes. Early identification and timely intervention are expected to improve the prognosis of this particular recipient population.

Ethical approval

Ethical approval for this study (Reference number: NO. 20220021) was provided by the Institutional Review Board of the China Liver Transplantation Registration Scientific Committee, Hangzhou, China on 22 June 2022.

Consent

Informed consent was waived as previously collected data that did not include personally identifiable information were used.

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Author contribution

H.C., Q.X., and Z.H.: conceptualization, investigation, data curation, and writing – original draft; C.H., X.Y., and W.S.: investigation; Z.L., H.L., and L.Z.: data curation; J.C., S.Z., and J.L.: writing – reviewing and editing; D.L.: writing – reviewing and editing and funding acquisition; X.X.: writing – reviewing and editing and funding acquisition.

Conflicts of interest disclosure

The authors have declared no conflicts of interest.

Research registration unique identifying number (UIN)

1. Name of the registry: Clinical Trials.
2. Unique identifying number or registration ID: NCT06209775.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.clinicaltrials.gov/study/NCT06209775.

Guarantor

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Data availability statements

All relevant data were reported within the article. Further supporting data will be provided upon written request addressed to the corresponding authors.

Provenance and peer review

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