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ORIGINAL ARTICLE

New prediction factors of small-for-size syndrome in living donor adult liver transplantation for chronic liver disease

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graft-to-recipient native liver volume ratio, living donor liver transplantation, prediction model, recipient native liver volume, small-for-size syndrome.

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Summary

Small-for-size syndrome (SFSS), which is characterized by synthetic dysfunction and prolonged cholestasis, is a major cause of worse short-term prognoses after living donor adult liver transplantation (LDALT). However, the risks of SFSS remain unclear. The aim of this study was to clarify the risks of SFSS, which were analysed in 172 patients who underwent LDALT for chronic liver disease. Graft types included left lobe with caudate lobe graft (n = 110) and right lobe graft (n = 62). Thirty-four cases (24 with left lobe grafts and 10 with right lobe grafts) were determined as SFSS. SFSS developed even if the actual graft-to-recipient standard liver volume ratio was >40%. Logistic regression analysis revealed three independent factors associated with SFSS development in left and right lobe grafts: donor age, actual graft-to-recipient native liver volume ratio, and Child's score. Donor age and actual graft-to-recipient native liver volume ratio may become predictive factors for SFSS development in left and right lobe grafts in patients undergoing LDALT.

Introduction

Small-for-size syndrome (SFSS), which is characterized by synthetic dysfunction and prolonged cholestasis [1,2], is a major cause of worse short-term prognoses after living donor adult liver transplantation (LDALT) [2]. Understanding the technical factors related to transplant surgery and innovations, including reconstruction of venous outflow, has solved some of the problems associated with this procedure [3]. It is true that a number of donor and recipient factors other than graft volume (GV), such as donor age, status of parenchymal quality (fibrosis or steatosis), and preoperative status of the recipient [model for end-stage liver disease (MELD) or Child's score], influence the graft functionality. However, SFSS seems to be primarily linked to relative overperfusion of the graft [4]. Development of SFSS depends on many factors related to both donors and recipients; therefore, prediction of this complication prior to LDALT remains limited.

Several concepts have been reported for SFSS management. A simple method is to increase GV by application of right lobe or auxiliary LDALT [1,5]. Another method is by decompression of excessive portal pressure and flow into a graft. This includes forming a portocaval shunt or performing splenectomy or splenic artery ligation [6]. However, SFSS cannot be completely avoided, even if an appropriate ratio of graft size to portal pressure is obtained [7]. Thus, we believe that other factors might affect the development of SFSS. In this study, we analysed the outcome of LDALT and tried to clarify the risks of SFSS.

Patients and methods

Patients

During the period between July 1998 and January 2007, 174 LDALTs were performed for chronic liver disease at Kyushu University Hospital. This study analysed 172

LDALTs, excluding one case of LDALT using dual graft [8] and one of auxiliary partial orthotopic liver transplantation [9]. The indications for LDALT were liver cirrhosis resulting from hepatitis C ($n = 87$), primary biliary cirrhosis ($n = 37$), liver cirrhosis resulting from hepatitis B ($n = 16$), cryptogenic cirrhosis ($n = 7$), biliary atresia treated with the Kasai operation ($n = 6$), primary sclerosing cholangitis ($n = 5$), liver cirrhosis resulting from alcohol abuse ($n = 5$), autoimmune hepatitis ($n = 2$), and others ($n = 7$). Graft types included left lobe with caudate lobe graft that included the middle hepatic vein ($n = 110$) and right lobe graft without the middle hepatic vein ($n = 62$). This investigation was performed only after written informed consent was obtained prior to the operation, and the protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Donor selection

Donors were selected from among the candidates offering to be living donors [1,10]. Donors were limited within a third degree of consanguinity with recipients or spouses. They were aged between 20 and 65 years. For a donor without a third degree of consanguinity with the recipient, individual approval was obtained from the ethics committee of Kyushu University Hospital. Good Samaritans were not used as living donors. Potential donors were evaluated for blood group compatibility, liver function test, human leukocyte antigen crossmatch, and serologic test for hepatitis B, hepatitis C, human immunodeficiency viruses, human T-cell lymphotropic virus type 1, and other transmissible viruses. Electrocardiography and pulmonary function test were also performed.

Abdominal ultrasound was routinely performed on all donors, and a percutaneous liver biopsy was performed in candidates with fatty liver suspected to be of more than moderate degree by ultrasound [11]. For evaluating donor candidates aged above 50 years, ultrasound echocardiography and exercise stress electrocardiography were routinely performed to rule out any asymptomatic heart disease. Donors with abnormal tumor marker levels underwent chest computed tomography (CT), gastrointestinal fiberscopy, and colon fiberscopy to exclude malignant disease. Candidates with fatty liver or with cardiac or malignant diseases were excluded and did not undergo further evaluation.

Eligible donors underwent imaging studies, including chest and abdominal X-rays and a 3-mm slice CT scan, to exclude any unrecognized intra-abdominal pathologic states. CT scan was also used for volumetric analysis of graft-size matching, delineation of vascular anatomy, and evaluation of fat content.

After confirming that the donors were suitable, informed consent was obtained from each donor by the surgical team and members of the ethical committee independently. The donor was informed that he/she could withdraw at any time. As a precaution, 400–1200 ml of autologous blood was collected and stored before surgery.

Graft selection

At the start of our LDALT program in 1997, a left lobe graft was the only option available for all patients. Our general selection criterion for LDALT grafts was an actual graft-to-recipient standard liver volume (GV/SLV) ratio >30%. However, occasionally, grafts with GV/SLV <30% were accepted and used. In October 1998, we performed the first LDALT using a right lobe graft in patients with glycogen storage disease. Since then, right lobe grafts have been used sporadically. From December 2000, we decided to use right lobe grafts more often, especially for patients with a GV/SLV ratio <35% if left lobe grafts were selected or for those with a high MELD score (≥20). Currently, our selection criteria for left lobe grafts include predicted GV/SLV >35%, whereas those for right lobe grafts include an estimated remnant liver volume ≥35% in the donor [1,12]. A three-dimensional CT was introduced for volumetric analysis in October 2000 [12,13]. SLVs of recipients were calculated according to the formula of Urata *et al.* [14]. GV was predicted by CT volumetric analysis. Actual GV was measured at the back table after flushing the graft with University of Wisconsin solution. Our criterion to decide the graft type for recipients was based on preoperatively predicted GC/SLV. A left lobe graft was used when preoperatively predicted GV/SLV was >35%, whereas a right lobe graft was used when the estimated remnant liver volume was >35% in the donor [1].

Surgical procedure and modulation of portal venous flow

The surgical procedures were described elsewhere [15–17]. Briefly, donor hepatectomy was performed using CUSA (Valleylab Inc, Boulder, CO, USA) and electrocautery using the hanging maneuver for both left and right lobe grafts [17]. In the recipient, total hepatectomy was usually performed while preserving the vena cava. After venous and portal anastomoses, arterial reconstruction was performed under a microscope. Bile duct reconstruction was performed using either a Roux-en-Y or duct-to-duct technique. When the portal pressure was >20 mmHg after reperfusion or a patient had chronic liver disease resulting from hepatitis C, splenectomy was performed to decrease the portal pressure or improve platelet counts for early induction of interferon therapy [18].

A temporary portocaval shunt was constructed if the portal venous pressure after splenectomy was >20 mmHg [19]. All shunts used were closed as much as possible if the portal venous pressure was <20 mmHg after closure.

Definition of small-for-size syndrome

Small-for-size syndrome is hard to define because its symptoms overlap with those of other causes of graft dysfunction. However, to determine the risk of SFSS, we defined SFSS as the existence of both prolonged functional cholestasis and intractable ascites. Prolonged functional cholestasis was defined as a total bilirubin concentration >86.2 μmol/l (5 mg/dl) on postoperative day 14 in the absence of any other definitive causes of cholestasis, such as technical problems or immunological and infectious conditions. Intractable ascites was defined as a daily production of ascites of >1000 ml on postoperative day 14 or >500 ml on postoperative day 28. Ascites production was defined as the daily amount of ascites through indwelling drains (plus leakage through the drain orifice) [20]. Liver biopsy during the early period after LDALT because of related complications has been reported [21]. To exclude acute rejection, with the exception of impaired coagulation status, liver biopsies were performed only when acute rejections were suspected.

Statistical analysis

Univariate survival analysis was performed using the Kaplan–Meier method, and the results were compared statistically using the univariate log-rank and Wilcoxon tests. Continuous variables were compared with independent samples using the nonparametric Wilcoxon test or with dependent samples using the parametric paired *t* test. Categorical data were compared using Fisher's test and the chi-squared test, and these data were compared with multivariate data using multivariate logistic regression analysis. *P* values <0.05 were considered significant. All statistical analyses were performed using JMP 6.0 software for Macintosh (SAS Institute Inc, Cary, NC, USA).

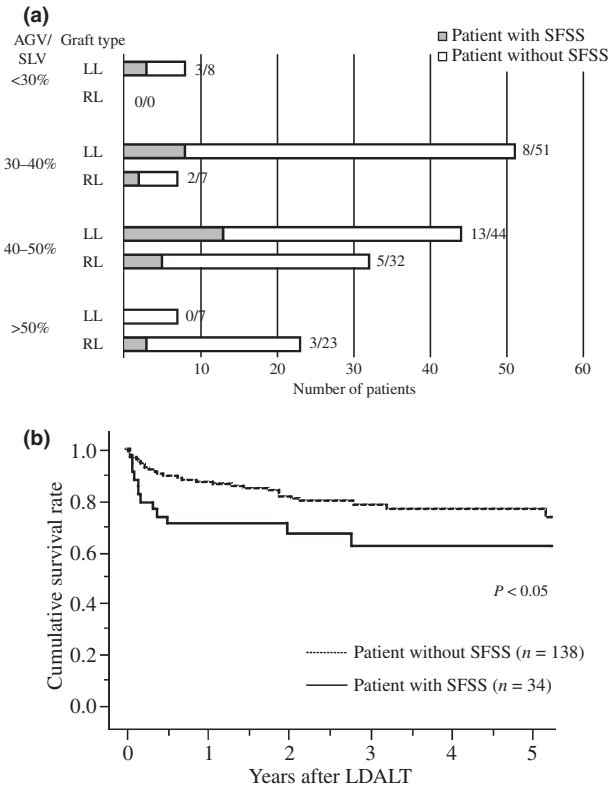

Figure 1 Panel (a): Graft size and small-for-size syndrome (SFSS) distribution according to actual graft-to-standard liver volume ratio (AGV/SLV). Panel (b): Comparison of cumulative survival rates between patients with or without SFSS. LL, left lobe graft; RL, right lobe graft.

Results

Graft size and SFSS distribution

The mean actual GV of left lobe grafts was 445 g (range: 250–630 g), which was significantly smaller than that of right lobe grafts (580 g; range: 400–760 g; $P < 0.0001$). The mean actual GV/SLV of left lobe grafts was 39.5% (range: 23.7–56.9%), which was significantly smaller than that of right lobe grafts (49.0%; range: 36.5–74.8%; $P < 0.0001$). Figure 1a depicts the distribution with or without SFSS of the left and right lobe grafts according to the actual GV/SLV. Thirty-four cases (24 with left lobe grafts and 10 with right lobe grafts) of LDALT were determined as SFSS. SFSS developed even when the actual GV/SLV was >40%. Surprisingly, the mean actual GV, graft-recipient body weight ratio, and actual GV/SLV were comparable between patients with and without SFSS, as shown in Table 1. These results indicated that post-transplantation cholestasis does not necessarily correlate with graft size.

Overall patient survival rates with or without SFSS

The mean duration of follow-up after transplantation was 917 days (range: 22–2635 days) in patients with SFSS and 976 days (range: 9–2964 days) in patients without SFSS. The cumulative overall 1-, 3-, and 5-year patient survival rates were 87.3%, 77.9%, and 76.1% respectively, of patients without SFSS, which were significantly different from those of patients with SFSS (70.6%, 62.4%, and 62.4% respectively; $P < 0.05$; Fig. 1b). SFSS was one of the risks that worsened short-term prognosis after

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Table 1. Clinical features of patients with or without SFSS.

Factors	Patient without SFSS, *n* = 138	Patient with SFSS, *n* = 34	*P* value
Cholestatic liver disease (yes)	23.2%	47.1%	<0.01
Acute rejection (yes)	16.7%	29.4%	N.S.
Surgical bleeding (g)*	7523 ± 8257	6790 ± 5584	N.S.
Surgical time (min)*	822 ± 177	753 ± 123	N.S.
Pre-LDALT PVP (mmHg)*	24.73 ± 5.98	23.11 ± 5.50	N.S.
Post-LDALT PVP (mmHg)*	18.29 ± 4.54	17.96 ± 5.03	N.S.
PVF/AGV (ml/min/g)*	3.25 ± 1.31	3.36 ± 1.54	N.S.
PVF (ml/min)*	1592 ± 645	1555 ± 710	N.S.
Major shunt (yes)	53.6%	50.0%	N.S.
Graft inflow modulation (yes)	62.3%	55.9%	N.S.
Shunt closure (yes)	39.5%	38.2%	N.S.
Splenectomy (yes)	32.6%	23.5%	N.S.
Portocaval shunt (yes)	5.07%	2.94%	N.S.
Donor age (years)*	34.4 ± 11.2	43.1 ± 10.6	<0.0001
Donor gender (male)	65.9%	67.7%	N.S.
Donor BMI (kg/m^2)*	22.8 ± 3.0	22.2 ± 3.2	N.S.
Graft type (left lobe)	62.3%	70.6%	N.S.
AGV (g)*	497.8 ± 101.2	477.2 ± 104.1	N.S.
GRWR (%)*	0.833 ± 0.203	0.827 ± 0.174	N.S.
AGV/SLV (%)*	43.2 ± 8.7	41.8 ± 8.0	N.S.
Recipient age (years)*	52.4 ± 11.3	48.2 ± 11.3	<0.05
Recipient gender (male)	54.4%	41.2%	N.S.
Child's score*	9.4 ± 2.3	9.9 ± 2.2	N.S.
MELD score*	14.5 ± 6.9	16.0 ± 6.5	N.S.
SLV (ml)*	1155.7 ± 116.3	1140.6 ± 120.4	N.S.
NLV (g)*	997.3 ± 402.2	1363.3 ± 890.7	<0.05

*Mean ± standard deviation. LDALT, living donor adult liver transplantation; PVP, portal venous pressure; PVF, portal venous flow; AGV, actual graft volume; BMI, body mass index; GRWR, graft-recipient body weight ratio; SLV, standard liver volume; MELD, model for end-stage liver disease; NLV, native liver volume; SFSS, small-for-size syndrome.

LDALT. SFSS had no apparent adverse effect on long-term prognosis after LDALT.

Comparison of clinical characteristics

The clinical features of patients with and without SFSS are listed in Table 1. Portal venous pressure, portal venous flow, and portal venous flow-to-actual GV ratio were not significantly different between patients with and without SFSS. The mean donor age of patients with SFSS (43.1 years; range: 20–60 years) was significantly greater ($P < 0.0001$) than that of patients without SFSS (34.4 years; range: 19–65 years). The mean recipient age of patients with SFSS (48.2 years; range: 21–69 years) was significantly lower ($P < 0.05$) than that of patients without SFSS (52.4 years; range: 18–70 years). Older recipients undergoing LDALT tend to receive grafts from younger donors such as children. In contrast, younger recipients undergoing LDALT tend to receive grafts from older donors such as parents. However, there was no significant correlation between donor and recipient age. Although SLV was not significantly different between patients with and without SFSS, the mean recipient native liver volume of patients with SFSS was 1382.1 g (range: 520–4800 g), which was significantly larger ($P < 0.05$) than that of patients without SFSS (997.3 g; range: 480–2850 g). The rate of cholestatic liver diseases (primary biliary cirrhosis, primary sclerosing cholangitis, and biliary atresia) in patients with SFSS was significantly greater than that in patients without SFSS ($P < 0.01$). Hence, SFSS could not have been completely avoided even if an appropriate ratio of graft size to portal pressure had been ensured. In contrast, recipient native liver volume and cholestatic liver may become suitable indicators of SFSS risk.

Implication of recipient native liver volume and cholestatic liver

Hepatomegaly is a known complication of cholestatic liver disease. The mean preoperative serous bilirubin level with or without cholestatic liver disease was 222.4 (range: 10.3–820.7) μmol/l or 86.2 (range: 3.4–724.1) μmol/l

Table 2. Risk of SFSS (n = 172).

Factors	Odds	95% CI	P value
Donor age (years)	1.070	1.033–1.112	0.0002
AGV/NLV (%)	0.969	0.969–0.947	0.0046
Child's score	1.230	1.230–1.018	0.037

AGV, actual graft volume; NLV, native liver volume; SFSS, small-for-size syndrome.

respectively. In addition, the mean serum bilirubin level at postoperative day 14, with or without cholestatic liver disease, was196.6 (range: 15.5–819.0) μmol/l or 136.2 (range: 6.9–356.9) μmol/l respectively. Serum bilirubin with cholestatic liver disease decreased significantly as compared with that without cholestatic liver disease. Bilirubin is metabolized in the liver, and the value is thought to be an indicator of pure liver function. Even in patients with cholestatic liver disease, the serum bilirubin concentration decreased after the operation. The standardized mean recipient native liver-to-SLV ratio of patients with cholestatic liver disease was 1.28 (range: 0.50–3.22), which was significantly higher ($P < 0.001$) than that of patients without cholestatic liver disease (0.81; range: 0.38–4.04). The two largest recipient native liver-to-SLV ratios in patients without cholestatic liver disease were in patients with giant hemangioma.

Risks of SFSS

To clarify the risk of SFSS, multivariate data (recipient age, recipient gender, with or without cholestatic liver disease, Child's score, MELD score, absence or presence of a major shunt, absence or presence of portal venous modulation, portal venous flow, donor age, donor gender, donor BMI, graft type, actual GV/SLV, and actual graft-to-recipient native liver volume ratio) were analysed by stepwise multivariate logistic regression analysis (step-down). Donor age, Child's score, and actual graft-to-recipient native liver volume ratio were significantly correlated in patients with SFSS, as shown in Table 2. As a result, recipient native liver volume, and not cholestatic liver, is the new indicator of SFSS risk. Although previous studies have reported that donor age, graft size, and Child's score are predictive factors for prognosis after LDALT, there have been no reports about recipient native liver volume.

Implication of actual graft-to-recipient native liver volume ratio as a new indicator of SFSS risk

We also examined actual graft-to-recipient native liver volume ratio as a univariate indicator to determine whether it is a suitable indicator of SFSS risk. The G^2

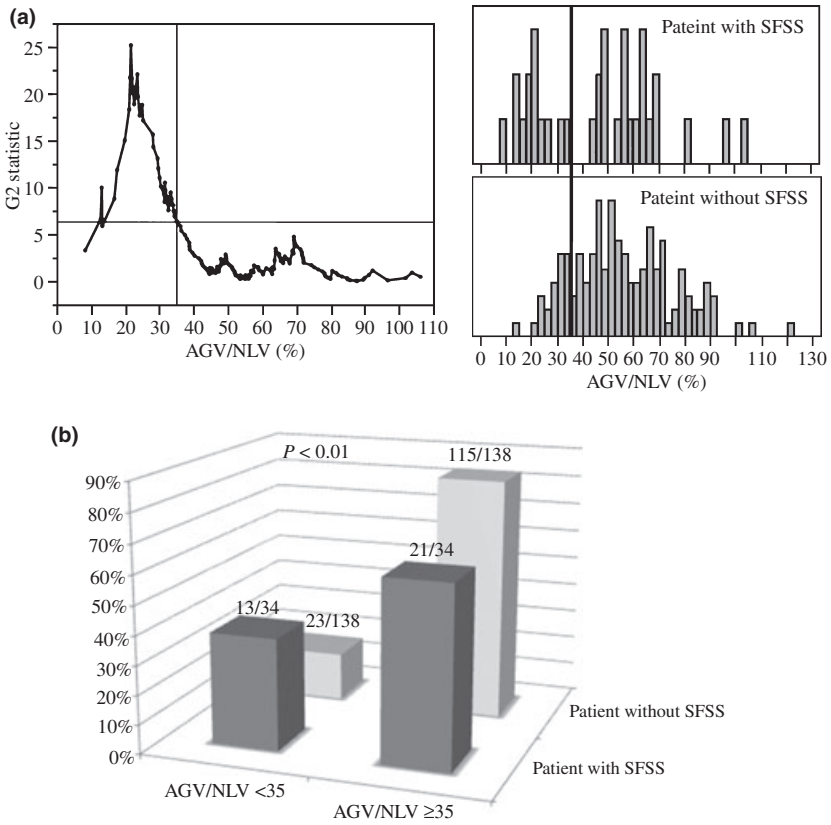

Figure 2 Panel (a): Implication of actual graft-to-recipient native liver volume ratio. Panel (b): small-for-size syndrome (SFSS) distribution according to the actual graft-to-recipient native liver volume ratio (AGV/NLV).

Table 3. Risk of SFSS only in left lobe graft (n = 110).

Factors	Odds	95% CI	P value
Donor age (years)	1.066	1.024–1.115	0.0028
AGV/NLV (%)	0.969	0.941–0.996	0.0318

AGV, actual graft volume; NLV, native liver volume; SFSS, small-for-size syndrome.

statistic, which indicates statistical significance, and distribution of actual graft-to-recipient native liver volume ratio with or without SFSS are shown in Fig. 2a. The distribution of actual graft-to-recipient native liver volume ratio with SFSS shows bimodality. According to the results, the optimal cutoff value was 35; lower values indicate a risk of SFSS. The population of patients with SFSS and an actual graft-to-recipient native liver volume ratio <35 was 38%, which was significantly higher than that in patients without SFSS (17%; $P < 0.01$; Fig. 2b). Therefore, the actual graft-to-recipient native liver volume ratio might be a useful univariate indicator for SFSS risk after LDALT.

Risks of SFSS analysed in the left lobe graft

In right lobe grafts, the development of SFSS was strongly influenced by the recently developed techniques that are used to decompress congestion in the middle hepatic vein. To exclude technical factors, the risks of SFSS were analysed only in left lobe grafts. Multivariate data (recipient age, recipient gender, absence or presence of cholestatic liver disease, Child's score, MELD score, absence or presence of a major shunt, absence or presence of portal venous modulation, portal venous flow, donor age, donor gender, donor BMI, graft type, actual GV/SLV, and actual graft-to-recipient native liver volume ratio) were analysed by stepwise multivariate logistic regression analysis (step-down). Donor age and actual graft-to-recipient native liver volume ratio were significantly correlated in patients with SFSS (Table 3). As a result, the actual graft-to-recipient native liver volume ratio has become the new, as also a remarkable indicator for development of SFSS.

Discussion

Small-for-size syndrome is characterized by synthetic dysfunction and prolonged cholestasis, whereas there is no consensus about the definition and pathogenesis of SFSS. Characteristics such as synthetic dysfunction and prolonged cholestasis are clinical phenotypes associated with liver dysfunction. Although small graft size might be a risk factor for SFSS, SFSS is not necessarily correlated with graft size. Not all the cases of SFSS correlated with a small graft size, and SFSS developed even when the actual GV/SLV was >40%. Thus, we investigated the risk of SFSS without the restriction of graft size. Recently, actual graft size has been considered less important because the graft selection criteria had been established with considerable accuracy Previous reports suggest that post-transplantation cholestasis is not necessarily correlated with graft size, but it is affected by a number of recipient and donor factors, consistent with our result [7,22,23].

Marginal graft size was determined based on SLV calculated from the formula used in liver volumetric analysis of normal healthy subjects [14]. However, it is not possible to adjust to all recipients because the individual preoperative condition is different. Moreover, different etiologies may affect short-term prognosis after LDALT because the load on hepatic metabolism is thought to be different. It is thought that the size of the graft size that is needed increases with the load on hepatic metabolism. In this study, recipient native liver volume was found to be an important factor affecting prognosis after LDALT. There have been no reports on the relationship between the recipient native liver volume and prognosis after LDALT. Thus, we analysed recipient native liver volume in detail, and concluded that it is a statistically significant independent indicator of SFSS. In contrast, cholestatic liver is not a significantly independent indicator. Despite the statistical results, immune components of cholestatic liver disease, such as primary biliary cirrhosis and primary sclerosing cholangitis, may play an important role in graft dysfunction. Additional investigations are needed to determine whether this is true. The distribution of the actual graft-to-recipient native liver volume ratio with SFSS was bimodal. Therefore, two possible groups may exist. In other words, one group of the recipients had a small native liver volume, while the other had a large native liver volume. In addition, the number of SFSS patients with a small native liver volume was less than the number of patients without SFSS. Therefore, a univariate recipient native liver-to-SLV ratio was found to be a suitable indicator of SFSS risk after LDALT. Recipient native liver volume is thought to represent the marginal graft size at the point of LDALT.

End-stage liver disease is a cause of portal hypertension. It is possible that Child's score correlates with the portal hyperperfusion state and that the association influences the cause of SFSS. Although the preoperative portal venous pressure increased significantly with Child's score ($P = 0.0002$), post-transplant portal venous pressure and flow did not correlate with Child's score by graft inflow modulation. It is well known that the MELD score reflects prognosis after LDALT and renal function. On the other hand, Child's score reflects liver function.

Therefore, it is reasonable to consider Child's score a predictive factor because liver function after LDALT is emphasized in this study.

Many reports have suggested that donor age affects patient survival after liver transplantation, especially in patients with hepatitis C [24]. However, it remains controversial whether donor age affects short-term outcome after LDLT [22,23]. Previous reports have shown a trend toward increased risk with older donors. Our previous study suggests that early graft function is better in young donors than in older donors [25]. Furthermore, national data have reported an increase in the rate of graft failure as donor age increases [26]. Graft size increases gradually as a result of liver regeneration, and thus, long-term survival is not adversely affected by SFSS. SFSS is one factor that worsens short-term prognosis after LDALT. There is concern that livers from older donors will have diminished regenerative capacity; therefore, donor age is a risk factor for SFSS in LDALT [27,28]. For cadaveric liver transplantation, whole liver grafts do not need to regenerate. Thus, there may be other risks that affect early graft function. Furthermore, livers from older donors have diminished function because of reduction in blood flow as a result of aging [29]. Therefore, donor age is considered to be an important factor in early graft function after LDALT. The cutoff value for donor age was determined in a statistical analysis using the same method employed to determine the cutoff value for actual GV/native liver volume. The optimal cutoff donor age was determined to be 40 years.

Two of the three independent factors associated with SFSS development, donor age and Child's score, were obtained prior to the LDALT procedure. Another factor, actual graft-to-recipient native liver volume ratio, can be predicted by CT volumetric analysis prior to LDALT [30]. Consequently, this new model might allow prediction of SFSS prior to the LDALT procedure. Thus, graft selection criteria may be established with more accuracy by considering these factors to avoid SFSS development. However, this new model is not versatile because it was obtained under limited conditions that include preoperative donor or graft selection and surgical methods such as modulation of portal venous flow and pressure. Further examination is necessary to assess whether the new model is useful prior to LDALT.

Small-for-size syndrome, depicted as the result of small graft size in initial reports, includes enhanced hepatocyte injury, delayed synthetic function, prolonged cholestasis, and reduced graft survival [31]. Furthermore, SFSS was histologically characterized as hepatocellular cholestasis, ischemic findings, and changes associated with regeneration, such as mitosis, small cell changes, pseudogland formation, double-cell plates, and the presence of multinucleated cells. In our series, these histological or clinical findings were observed even if the graft was large enough (50% of actual GV/SLV or more). The grafts after LDALT were small in size as compared with those after cadaveric whole-liver transplantation. Thus, all recipients who underwent LDALT were thought to potentially have small graft sizes. Thus, the term 'small-for-size graft syndrome' might not reflect its condition precisely. The cause of this condition may be the imbalance between the load on hepatic metabolism and the metabolic capacity of the graft.

In conclusion, the new SFSS risk model considers donor age, actual graft-to-recipient native liver volume ratio, and Child's score. This model can be a valuable tool for effectively predicting SFSS risk in patients undergoing LDALT.

Authorship

KS: wrote the paper, analysed data, and performed research. TI: collected data. SU, SN, KS, TI and TG: collected data. YS: collected data and designed research. AT: designed research, adviser. YM: designed research, adviser

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