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Abstract

Small-for-size graft syndrome is an inevitable complication in living donor liver transplantation (LDLT). We hypothesized that graft weight measured after graft procurement is one of the variables predicting postoperative graft function.

Patients and methods: A total of 138 consecutive recipients of adult-to-adult LDLT between 1999 and Oct 2014 were included in this study. we investigated the factors associated with small-for-size associated early graft loss (SAGL) to determine the graft weight required for each patient. Both pre-operatively assessed and post-operatively obtained risk factors for SAGL were analyzed in univariate and multivariate logistic regression analysis.

Results: Twelve of the transplant recipients (8.8%) had SAGL. In multivariate logistic regression analyses using pre-operatively assessed variables, the pre-operative MELD score (P<0.001) and actual graft weight/recipient standard liver volume (SLV) ratio (P=0.008) were independent predictors of SAGL. The recommended graft volume by pre-operative CT volumetry was calculated as SLV x (1.616 x MELD+0.344)/100/0.85 (ml) [MELD $\geq$ 18.2], or SLV x 0.35 (ml) [MELD < 18.2].

Conclusion: The required allograft volume in LDLT can be determined by the

pre-operative MELD score of the recipient, and patients with higher MELD scores

require larger grafts or deceased donor whole liver transplant to avoid SAGL.

Introduction

Living donor liver transplantation (LDLT) has been established as a life saving treatment for end-stage liver disease (ESLD) and acute liver failure, though it is not considered to be as ideal a treatment as deceased donor liver transplantation due to substantial risk of mortality for live donors (1-6). Morbidities among live donors are reported to be more frequent in right lobectomy than left lobectomy or left lateral sectionectomy (7). Many transplant programs use a left lobe graft in LDLT to minimize morbidities in live donors (8, 9).

However, despite excellent postoperative results using the left lobe, it is not applicable to a certain group of LDLT candidates. We previously reported that a high preoperative MELD score (10, 11) was associated with postoperative graft failure (12, 13). A Kyushu group also pointed out that ESLD patients with high MELD scores are not suitable candidates for LDLT using a left lobe graft because of poor postoperative prognosis (9, 14). A study in Hong Kong reported that acute or chronic HBV-infected ESLD patients can be rescued by right lobe with middle hepatic vein (MHV) graft in their LDLT series (15). Graft volume and recipient prognosis are

thought to be correlated, and the minimal graft volume required for partial liver

transplantation is thought to be 40% of the standard liver volume (16, 17) or 0.6-0.8%

of the graft weight to patient weight ratio (18, 19). Otherwise, the recipients with small

grafts would develop small-for-size syndrome (SFSS) with poor graft survival (20-22).

Reviewing these reports, we considered that the minimal graft volume

necessary for each patient could be determined by a certain combination of more

essential parameters, such as pre-operative MELD score and graft volume or weight. An

accurate estimation of the suitable graft for each recipient could enable the selection of

an appropriate graft and donor, or even change LDLT to deceased donor whole liver

transplantation, in which the substantial risk to live donors and the waste of valuable

partial liver grafts from live donors can be avoided.

In this study, we hypothesized that graft weight measured after graft

procurement is one of the variables predicting postoperative graft function and

investigated the factors associated with small-for-size associated early graft loss to

determine the minimal graft weight required for each patient prior to LDLT.

Patients and methods

A total of 138 consecutive recipients of adult-to-adult LDLT between 1999

and Oct 2014 were included in this study. Data were collected prospectively in a

database. The study was performed in accordance with the principles of the Declaration

of Helsinki and was approved by the institutional review board of Osaka University

Hospital (No. 15150).

Donors

Pre-operative evaluations for live liver donors included a full workup with a

complete history and physical examination by expert hepatologists, psychiatrists,

hepatobiliary/transplant surgeons, and other specialized work-up team members with

laboratory tests as described previously (23). All live donors were adults between 20

and 65 years of age, and the donor selection criteria were approved by the ethics review

committee of Osaka University. Each specific case was approved by the donor and

recipient selection committee of Osaka University Graduate Hospital.

The criteria for donor selection were described previously (23). Briefly, the

graft type (left lobe with/without caudate, right lobe, or right posterior section) was

determined by the results of a volumetric study with Multidetector(MD)-CT. We did not

use right lobe graft with middle hepatic vein due to the risks to living donors reported in

Japan (2).

Our volumetric requirements for living donation were an estimated remnant

liver volume of more than 35% of the whole liver volume of the donor, and an

estimated donor graft liver volume of at least 35%, but preferably more than 40%, of the

recipient's standard liver volume (SLV).

Recipients

Recipient evaluation, surgery, and postoperative management were described

previously (24). No portal inflow modulation was performed to treat high portal venous

pressure. The immunosuppressive protocol consisted of corticosteroid and tacrolimus or

cyclosporine, or was corticosteroid-free with anti-CD25 monoclonal antibody.

Mycophenolate mofetil was added to increase the immunosuppression in rejection or as

a renal sparing protocol. Prophylactic administration of DHPG (5 mg/kg/day) was

routine for 10 days after transplantation. Dynamic abdominal CT scans and laboratory

data were obtained routinely at 7 and 14 days and 1, 3, 6, and 12 months and then yearly

thereafter.

<u>Small-for-size associated graft loss (SAGL)</u>

In this study, early graft loss (EGL) was defined as graft loss within 6 months

of liver transplantation in association with graft dysfunction. Patient mortality without

graft dysfunction, such as pneumonia or cardiovascular events, was excluded from

EGL.

We defined SAGL as graft loss with SFSS in the EGL group, where the

definition of SFSS by Dahm, et al. [22] was adopted, as liver dysfunction with the

presence of two of the following on three consecutive days: bilirubin $> 100\,\mu$ mol/l,

INR > 2, encephalopathy grade 3 or 4 during the first postoperative week. The apparent

cause of graft loss; technical (e.g. arterial or portal occlusion, outflow congestion, bile

leak), immunological (e.g. rejection), or infectious (e.g. cholangitis, sepsis) event,

which was not associated with SFSS, was excluded from the events of SAGL and

censored at the time of graft loss.

Statistical analysis

Pre-operative variables (i.e., age, gender, pre-operative MELD score,

etiology), donor variables (i.e., donor age, graft type, graft weight, ABO blood type

incompatibility), operative variables (i.e., blood loss, operative time, warm ischemic

time, cold ischemic time, splenectomy), and postoperative variables (i.e., highest serum

bilirubin level, morbidities, postoperative complications) were evaluated. Univariate

analysis was performed to determine the risk factors for SAGL using a logistic

regression model. The associated factors with P<0.10 and without correlation to each

other based on the Pearson product-moment correlation coefficient (P<0.9) were

brought into the multivariate logistic regression analysis.

Pre-operative variables that can be obtained prior to the surgery are useful in

determining the graft type of the donor liver and were investigated for their association

with SAGL. Actual graft weight (GW) was considered to be pre-operatively assessable

in a volumetric study using MD-CT scans of the donors.

A regression score was calculated using the significantly associated variables

in the logistic multivariate analysis. ROC curves were evaluated to decide the

appropriate cut-off point of the regression score. The minimal requirement for graft

liver volume was then calculated among the variables associated with SAGL.

Results

One of the 138 LDLT cases was excluded due to an unusual type of liver

transplantation (auxiliary partial orthotopic liver transplantation, APOLT), leaving 137

liver transplant recipients to be analyzed in this study. Primary diseases consisted of

HCV liver cirrhosis (n=50), HBV liver cirrhosis (n=29), fulminant liver failure (n=10),

autoimmune-associated disease (e.g., primary biliary cirrhosis, primary sclerosing

cholangitis, autoimmune hepatitis) (n=18), and others (n=19). Fifteen cases (10.9%) lost

their graft due to the graft failure within 6 months, including 3 in the EGL group that

were censored at the time of patient mortality considered not to be directly related to

SFSS: fibrosing cholestatic hepatitis (n=1), massive HCC recurrence (n=1), acute

antibody-mediated rejection (n=1). As a result, 12 cases (8.8%) were considered to have

SAGL.

Demography and pre/postoperative factors were compared in univariate logistic regression between the SAGL group (n=12) and control group (n=125) (Table 1). The pre-operative MELD score (P<0.001), actual GW/recipient estimated SLV ratio (P=0.021), operative time (P=0.030), and highest serum bilirubin level 4-28 days after transplant (P<0.001) were significantly different between the two groups. These significantly different factors and those with P<0.1 (donor age, P=0.054; operative blood loss, P=0.057) were brought into the multivariate logistic regression analysis. Multivariate analysis revealed that pre-operative MELD score (P=0.021), actual GW/recipient estimated SLV ratio (P=0.032), and highest serum bilirubin level 4-28 days after transplant (P=0.006) were independent predictors of SAGL (Table 2). When analysis was restricted only to pre-operatively assessable predictors, multivariate logistic analysis revealed that pre-operative MELD score (P<0.001) and actual GW/recipient estimated SLV ratio (P=0.008) were independent predictors of SAGL (Figure 1).

Using the regression equation from the logistic regression analysis, risk score

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was calculated in each case with pre-operative MELD score and the GW/SLV ratio: risk

score = -0.203 x MELD + 0.136 x GW/SLV (%) + 1.509. The ROC curve of SAGL and

calculated score revealed a cut-off value of 2.187 (AUC=0.914) for the risk score.

Recipient-donor matches were categorized into three groups according to the

risk score: Group A (n=107), risk score > 2.187; Group B (n=25), risk score > 0 and ≤

2.187; and Group C (n=5), risk score ≤ 0. The graft survival curve of the recipients

showed excellent stratification of these three groups (P=0.003, log rank test, Figure 2).

The graft survival rate at 6 months after LDLT was 90.6% in Group A, 67.8% in Group

B, and 40.0% in Group C.

Graft selection for recipient-donor pair

Two variables, namely pre-operative MELD score and GV/SLV ratio,

determined the risk score in each recipient-donor pair. We defined risk score > 0 as the

criteria for minimal graft weight and risk score > 2.187 as the recommended graft

weight. The baseline requirement for the GV/SLV ratio was 35% in both minimal and

recommended graft weight.

These formulas can be described as follows:

Minimal graft weight (g)

= SLV x (1.616 x MELD-14.139) /100 (g) [MELD $\geqq$ 27.2]

=SLV x 0.35 x 0.85 (g) [MELD < 27.2]

Recommended graft weight (g)

= SLV x (1.616 x MELD+0.344)/100 (g) [MELD $\geqq$ 18.2]

=SLV x 0.35 x 0.85 (g) [MELD < 18.2]

Where SLV is the recipient's SLV (25) and MELD is the pre-operative MELD score (10,

11).

According to the reported coefficient factor of 0.85 for graft weight

estimation from pre-operative CT volumetry in LDLT (26, 27):

Minimal graft volume by pre-operative CT volumetry (ml)

= SLV x (1.616 x MELD-14.139) /100/0.85 (ml) [MELD $\geqq$ 27.2]

= SLV x 0.35 (ml) [MELD < 27.2]

Recommended graft volume by pre-operative CT volumetry (ml)

= SLV x (1.616 x MELD+0.344)/100/0.85 (ml) [MELD $\geqq$ 18.2]

= SLV x 0.35 (ml) [MELD < 18.2]

2D map with MELD and the graft volume/SLV ratio is shown in Figure 3.

Zone A (with low risk of SAGL) is defined the area over "Recommended graft volume"

by pre-operative CT volumetry. Zone B (with acceptable risk of SAGL); the area over

"Minimal graft volume." Zone C (with high risk of SAGL); the area below "Minimal

graft volume." Once you calculate the preoperative MELD score, the risk of SAGL is

well determined by the graft volume/SLV ratio. For example, if MELD score is 30, the

graft volume/SLV ratio should be over 57.4% for Zone A.

Discussion

We found that two variables, namely actual GW/SLV ratio and pre-operative

MELD score, are independent determinants of SAGL after LDLT. Thus, the minimum

graft size for each recipient could be calculated using the pre-operative MELD score. In

LDLT, the type of liver graft should be selected according to volumetric analysis of

anatomical donor liver section(s): the right lobe, left lobe with or without caudate, or

right posterior section. Our process for determining the type of graft starts with the

baseline that the residual liver volume for the live donor should be >35%, and the

estimated graft volume/recipient's SLV should be >35%, preferably >40%. The graft

liver volume should then meet the criteria of the "recommended graft weight" formula.

Graft liver volume less than the "recommended graft weight" should be considered a

relative contraindication. In addition, there was a subgroup of less than "minimal graft

weight" with quite a poor prognosis. Liver transplantation with a donor graft weighing

less than the minimal graft weight should be considered an absolute contraindication for

partial liver transplantation, and the live donor should be changed to another appropriate

donor or deceased whole liver donor.

Previous reports from our group (12, 13) and other groups (28-32) have

shown that the risk factors for EGL include MELD score, graft volume, donor age, and

others. We developed the previous results (12, 13) with more data in this study,

focusing on the pre-operatively assessable variables. Our results indicate no significant

correlation between SAGL and donor age, though it was correlated with high MELD

score and small graft weight. One of the reasons for these differences may be due to the

difference between SAGL and EGF. EGF and SAGL overlap but are based on different

concepts of graft failure.

Although portal inflow modulation has been reported to prevent SFSS (33-36),

the role of modulation remains controversial (37, 38). We previously reported that small

graft size is associated with high portal venous pressure (PVP) and high PVP ($\geq$25

mmHg) is correlated with post-transplant thrombocytopenia (39), but we have not

performed any portal inflow modulation because there has not been a recipient with

high PVP since that study.

Actual GW as used in this study is the measured weight of the procured graft

after portal infusion of UW solution. We used this definition because it was considered

to be more accurate than the pre-operatively estimated graft volume. Pre-operative

estimation of the graft liver is achieved in various software programs using CT images.

The correlation is excellent using the coefficient of 0.85 in right or left lobe living donor

liver grafts (26, 40), with only slight errors between the true and estimated graft volume

or weight, which was calculated using pre-operative CT scans (26, 27, 41). Even if there

is an error between the true graft weight and estimated graft volume, the error would be

minimized in well-trained methods (26, 27, 41), suggesting that selection of a graft

using the estimated graft volume would be valid. We used the results of these studies

and calculated the estimated actual GW from the pre-operative donor graft volumetric

analysis.

In cases with high MELD scores, the graft weight of the donor liver should be

sufficient when planning LDLT. If the estimated graft volume is less than the

recommended graft weight, the graft may develop SAGL with substantial probability

and require re-transplantation. Under the current graft allocation system in Japan, graft

failure within 3 months of LDLT would be top priority for deceased donor liver

transplant, which could lead to the loss of one liver transplant for another patient

waiting at the top of the list. We should be careful to avoid such SAGL recipients and

plan liver transplantation in accordance with this graft volumetric analysis, selecting

live donors or rejecting live donors and using deceased donor whole liver

transplantation for the recipients with high MELD scores.

Sufficient graft volume of the donor graft discussing here is only a minimal

requirement for successful liver transplant, which is related to a variety of conditions

including graft condition (such as fatty liver, preservation method and time, background

liver dysfunction) and technical (e.g. arterial or portal occlusion, outflow congestion,

bile leak), immunological (e.g. rejection), and infectious (e.g. cholangitis, sepsis) events

as well as "graft volume". This explains the reason why liver transplant using a whole

liver graft with an adequate volume cannot be always successful. In addition, it is also

reasonable that 100% SLV graft liver, for example, mostly equivalent to whole liver

graft, is soundly located in Zone A even if the preoperative MELD score is as high as

over 40 in Figure 3.

One of the limitations of this study is the small number of cases investigated.

A large cohort analysis would be useful to validate the results of this study, as well as

the evaluation of donor age and other candidate factors associated with SAGL. Another

limitation is that the study was based on the hypothesis that graft weight is associated

with SAGL. Determination of postoperative graft function would include not only graft

volume or donor age, which were included in this study, but also graft type (right lobe,

left lobe, etc), steatosis, and prolonged ischemic time, among other factors. We did not

analyze data separately using graft type, but it may be more appropriate to include graft

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type in a large cohort study.

In conclusion, donor and graft type in LDLT could be determined by pre-operative volumetric analysis of the donor liver and the MELD score of the recipient. Patients with higher MELD scores require larger grafts or deceased donor whole liver transplantation in order to avoid SAGL.

Figure legends

Figure 1. Scatter plots of the actual graft weight/SLV ratios and pre-operative MELD

scores in LDLT recipients (n=137).

SAGL, small-for-size associated graft loss (n=12); EGL, early graft loss

(n=8); Control, the rest of the recipients (n=117).

Figure 2. Patient survival after LDLT in Groups A, B, and C.

Recipient-donor matches were categorized into three groups according to risk

score: Group A (n= 107), risk score > 2.187; Group B (n=25), risk score > 0 and ≤

2.187; Group C (n= 5), risk score ≤ 0. The risk score was calculated based on the

logistic regression model. The graft survival curve for the recipients showed excellent

stratification of these three groups (P=0.003, log rank test). The graft survival rate 6

months after LDLT was 90.6% in Group A, 67.8% in Group B, and 40.0% in Group C.

Figure 3. Zones A, B, and C according to graft volume and MELD score matches.

Zone A includes cases with low risk of SAGL, Zone B with acceptable risk of