TRANSPLANT INTERNATIONAL

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Determination of the safe range of graft size mismatch using body surface area index in deceased liver transplantation

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Keywords
complication, graft survival, hazard risk, liver transplant, postreperfusion syndrome.

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Conflicts of interest
No conflict of interest of any nature is declared.

Received: 11 December 2012
Revision requested: 11 February 2013
Accepted: 7 April 2013
Published online: 6 May 2013

doi:10.1111/tri.12111

Abstract

In live donor liver transplantation, rigorous standardized criteria for matching of liver volume between donor and recipient have prevented graft loss because of size mismatch. In deceased whole liver transplantation, the safe donor–recipient size mismatch range remains unknown. We developed a multivariate survival model (generalized additive model) to estimate hazard risk of body surface area index (BSAi) for 3-year graft survival using data derived from the national registry database between 2005 and 2010. BSAi was calculated by BSA of donor divided by BSA of recipient. 24 509 patients were included in the analysis. Small-for-size (SFS) grafts with BSAi less than 0.78 had a significant impact on graft dysfunction with progressive increase of hazard risk toward the lowest end and a higher incidence of primary graft nonfunction and vascular thrombosis. Large-for-size (LFS) grafts with BSAi greater than 1.24 had a significant impact on graft dysfunction with progressive increase of hazard risk toward the largest end. Our findings suggest that donor grafts with BSAi < 0.78 could be considered 'SFS' and donor grafts with BSAi > 1.24 could be considered 'LFS', with both extremes resulting in decreased graft survival. Therefore, BSAi > 0.78 and <1.24 appears to be a safe range to avoid adverse outcome associated with size mismatch.

Introduction

Advances in methods for matching liver volumes have greatly reduced the potential for graft loss from size mismatch in live donor liver transplant. However, this has not been the case in deceased whole liver transplantation, where there are no standard methods used to predict size mismatch. More importantly, the consequences of size mismatch are rarely studied in this population of liver graft recipients. In general terms, donor-to-recipient size mismatch can result in two adverse clinical scenarios: (i) a 'small for size (SFS) donor', in which the transplanted liver is unable to meet the functional demands of the recipient, with cholestatic liver injury, reduced graft survival and death of the recipient [1,2] or (ii) a 'large-for-size (LFS) donor' resulting in graft damage from vascular thrombosis or necrosis because of insufficient blood supply to the graft [1,3].

In live donor liver transplant, indices such as the standardized liver volume (SLV), which is based on recipient

body surface area (BSA) [4–7] and graft-weight-to-recipient-body-weight ratio (GWRBW) [1,8,9], which requires to estimate (or measure) graft weight, have been developed to better estimate liver volume, significantly improving post-transplant graft survival in these procedures. However, these approaches were not employed in deceased liver transplant because the prognostic impact of size mismatch has been underestimated.

Body surface area has been demonstrated to be a better indicator of metabolic mass than body weight alone, as it is less affected by abnormal adipose mass, making it a more reliable estimate of liver volume [10]. We have previously reported on the use of the ratio of donor to recipient BSA index (BSAi) to predict size mismatch [11]. In this study, we intended to explore the association between the lower and upper ranges of size mismatch and graft survival in a larger cohort of patients, to determine what could be considered as the optimum range of BSAi to prevent clinically significant size mismatch.

Methods

Study subjects in national transplant registry

Data from all adult patients who underwent liver transplantation in the United States between 2005 and 2010 were obtained from the Organ Procurement and Transplantation Network (OPTN). These data were available from the Standard Transplant Analysis and Research (STAR) database as of May 1, 2011. We were interested in knowing the safe range of size mismatch between donor and recipient, as determined by BSAi, in this patient population. We excluded pediatric recipients (recipient age below 18), patients who underwent split or partial liver transplants as well as those who underwent simultaneous other organ transplants, such as liver-kidney, liver-heart, liver-intestine and multivisceral transplants, or live donor liver transplants. The primary study end point of the study was failure of the liver graft from all causes. The cause of liver failure was determined based on the United Network for Organ Sharing (UNOS) diagnosis codes. In our study, donor risk index (DRI) was calculated without height [12]. The BSAi was calculated by the following equation:

$$\text{BSA} = \text{Weight (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 0.007184$$

$$\text{BSAi} = \text{Donor BSA}/\text{Recipient BSA}$$

Statistical analysis

Determination of risk factors for 3-year graft survival

As a first step, multivariable Cox proportional hazards regression model was used to determine the donor and recipient variables, which have a significant impact on the 3-year graft survival. Three-year graft survival was used to assess the short- and mid-term effects of donor–recipient size mismatch. The model included size group as the independent variable of interest, covariates of all donor (donor age, ethnicity, anoxia as a cause of death, cerebrovascular disease as a cause of death, donor after cardiac death, cold and warm ischemia time, national/regional donor, and micro- and macro-steatosis), and recipient variables [recipient age, ethnicity, cause of end-stage liver disease, pre-transplant laboratories (albumin, creatinine, total bilirubin, sodium, PT-INR)] to control for their confounding effects except for model for end-stage liver disease (MELD) score and DRI. Existence of highly correlated variables in the same regression model may erratically give coefficient (hazard risk) estimates, so-called 'multicollinearity' phenomenon. Because all variables to calculate MELD and DRI were included in the model, DRI and MELD were excluded from the regression model.

Hazard risk calculations for graft failure at each BSAi value

As a second step, all variables, which have significant impact on the 3-year graft survival, were included in the generalized additive models with smoothing splines to determine the nonlinear effect of size mismatch (BSAi) on the risk for graft failure [13]. Hazard risks for graft failure were calculated at each BSAi value ranging from 0.46 to 1.52. The smoothing spline curves permit depiction of the nonlinear relationship between the BSAi and graft failure.

Defining 'SFS' and 'LFS'

Based on the final result of generalized additive modeling, our cohort of patients was stratified into three categories based on the statistical significance to predict graft failure within three years. 'SFS', 'normal-for-size (NFS)', and 'LFS' were defined as BSAi < 0.78, BSAi 0.78–1.24, and BSAi > 1.24, respectively.

Background characteristics of each group

To investigate the group-specific characteristics in background demographics, mean and standard error of donor and recipient variables were analyzed in each group and group comparisons were performed by *post hoc* Tukey analysis.

Outcome measures

Graft survivals of those three groups were analyzed by Kaplan–Meier survival analysis with Generalized Wilcoxon analysis. Also, incidence of post-transplant primary nonfunction (PNF), graft dysfunction, vascular thrombosis, biliary complications, acute rejection, and infection as well as retransplantation of those three groups were analyzed by Pearson chi-square (χ^2) test with *post hoc* Tukey test.

UNOS diagnostic codes were used to determine those outcomes. Primary graft nonfunction was defined as irreversible graft dysfunction requiring liver replacement within 7 days postliver transplant. UNOS categorizes the contributing cause of graft failure as 'primary graft dysfunction' (a failure of graft function as a primary cause of graft loss), 'vascular thrombosis', 'biliary complications', 'acute rejection', 'infection', and 'other'. We used this UNOS classification in this study.

GraphPad Prism version 5 (GraphPad Software Inc., San Diego, CA, USA), SPSS statistics version 19.0 (SPSS Inc., Chicago, IL, USA), and SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) were used for statistical analysis. All reported *P* values are two-sided, and a p value of less than 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics of national registry data

Our study cohort consisted of 32 072 liver transplant cases. Pediatric liver transplants (age <18, 3009 cases), split or reduced-size liver transplants (2343 cases), simultaneous other organ transplants (4521 cases), and live donor liver transplants (1301 cases) were all excluded from our study. Cases that were missing data (1122 cases) necessary to calculate BSA, such as donor or recipient height or weight, were all excluded from this study, resulting in a total of 24 509 patients included in the analyses. The baseline characteristics of the recipients and donors for all liver transplants are summarized in Table 1. The overall mean and standard error of BSAi in our cohort was 0.989 ± 0.001. Also baseline characteristics of donors and recipients among three size mismatch groups were summarized in table 3.

Size mismatch and hazards ratio for graft survival

Hazard risk related to BSAi was assessed by multivariable Cox regression model, and then a generalized additive model with smoothing spline was used to identify nonlinear effect of BSAi on graft failure. The results are shown in Table 2. Size mismatch related changes in hazard risk for graft failure were depicted in Fig. 1. BSAi had a nonlinear-effect (bidirectional) on graft failure insofar as a decrease or an increased BSAi was associated with an increase in the risk of graft failure. The most meaningful differential effect of size mismatch on graft failure appears to occur at BSAi below 0.78 and above 1.24. Based on these clinically significant ranges of donor–recipient size mismatch, we redefined 'SFS' as BSAi less than 0.78 and 'LFS' as a BSAi greater than 1.24. We stratified our cohort of patients into three groups: 'SFS' (BSAi < 0.78), 'NFS' (BSAi 0.78–1.24), and 'LFS' (BSAi > 1.24). Graft survival was analyzed by the Kaplan–Meier Survival Model with Generalized Wilcoxon analysis (Fig. 2a) We identified 1713 patients in the SFS, 21 399 patients in the NFS, and 1393 patients in the LFS groups. Three-year graft survival was significantly lower in the SFS and LFS groups compared with the NFS group (71.2% in SFS, 74.2% in NFS, and 71.1% in LFS, SFS vs. NFS $P < 0.001$ and LFS versus NFS $P < 0.001$). There was no difference between the SFS and LFS group in terms of graft survival.

Group-specific characteristics of donor and recipient demographics

In the SFS group, pretransplant creatinine as well as MELD score were higher when compared with the NFS group. On the other hand, donor age, percentage of expanded criteria donor, and percentages of mild macro steatosis were lower compared with that in the NFS group. In the LFS group, percentages of mild steatosis, pretransplant bilirubin, and MELD score were higher compared with that in the LFS group. In contrast, recipient age and percentages of expanded criteria donors were lower when compared with that in the NFS group.

Size mismatch and post-transplant complications

The incidence of post-transplant PNF, graft dysfunction, vascular thrombosis, biliary complications, acute rejection, and infection as well as retransplantation of those three groups were analyzed by Pearson chi-square (χ^2) test with *post hoc* Tukey test (Fig. 2b). The incidence of PNF was significantly higher in the SFS group compared with that in the NFS group (SFS 1.3% vs. NFS 0.8%, $P = 0.036$). Of all categories of complications, primary graft dysfunction (median 30 days) and vascular thrombosis (median 26 days) were occurred within 30 days from transplant. The incidence of primary graft dysfunction was significantly higher in the SFS group compared with that in the NFS group (SFS 4.3% vs. NFS 3.0%, $P = 0.007$). The incidence of vascular thrombosis was significantly higher in the SFS group when compared with the NFS and the LFS group (SFS 2.7% vs. NFS 1.4% vs. LFS 1.2%, SFS vs. NFS: $P < 0.001$, SFS vs. LFS: $P = 0.002$). Other complications, such as biliary complications (median 180 days), acute rejection (median 203 days), and infection (median 195 days) were occurred after 180 days from transplant. Biliary complications and infection were slightly higher in the SFS group, but there were no significant difference among groups (Biliary complications: SFS 1.3% vs. NFS 0.9% vs. LFS 0.9%, Infection SFS 0.8% vs. NFS 0.6% vs. LFS 0.7%). There was no difference in the incidence of biliary complication and infection among three size mismatch groups. The incidence of acute rejection was higher in the SFS and LFS group when compared with the NFS group,

Table 1. Baseline characteristics of donors and recipients from STAR database (2005–2010).

Variables	Variable type	*N**	Mean ± SEM
Recipient	–	–	–
Demographic	–	–	–
Age (years)	Continuous	24 505	53.7 ± 0.1
Body surface area	Continuous	24 505	1.97 ± 0.00
Ethnicity	–	24 505	–
White-nonhispanic	Yes/no		72.1%
White-hispanic	Yes/no		13.0%
African American	Yes/no	–	9.3%
Liver diagnosis	–	24 505	–
Hepatitis C	Yes/no		30.0%
Hepatitis B	Yes/no		2.9%
Alcoholic	Yes/no		16.9
Biliary cirrhosis	Yes/no		7.5%
Laboratory values at transplant	–	–	–
Albumin (mg/dl)	Continuous	24 500	3.0 ± 0.0
Creatinine (mg/dl)	Continuous	24 451	1.4 ± 0.0
Prothrombin time international normalized ratio	Continuous	24 503	1.9 ± 0.0
Sodium (mEq/dl)	Continuous	24 503	136.0 ± 0.0
Total bilirubin (mg/dl)	Continuous	23 424	8.4 ± 0.1
MELD score	Continuous	24 451	21.4 ± 0.1
Donor	–	–	–
Demographic	–	–	–
Donor age (years)	Continuous	24 505	41.9 ± 0.1
Body surface area	Continuous	24 505	1.92 ± 0.00
Ethnicity	–	24 505	–
White-nonhispanic	Yes/no		66.7%
White-hispanic	Yes/no		13.1%
African American	Yes/No		17.1%
Donor quality	–	–	–
Donor Risk Index†	Continuous	24 505	1.70 ± 0.00
Donor cause of death (DCD)	–		
Anoxia	Yes/No	24 505	19.0%
Cerebrovascular accident	Yes/No	24 505	42.3%
Warm ischemia time (min)	Continuous Yes/no	24 505	48.0 ± 0.1
Donor after cardiac death	–	24 505	5.2%
Expanded donor including brain dead and DCD (after 4/1/1994)	Yes/no	24 505	27.0%
Donor steatosis: macro fat (%)	–	–	–
Moderate (30–60%)	Yes/no	24 505	0.91%
Severe (>60%)	Yes/no	24 505	0.14%
Donor steatosis: micro fat (%)	–		
Moderate (30–60%)	Yes/no	24 505	1.32%
Severe (>60%)	Yes/no	24 505	0.56%
Cold ischemia time (h)	Continuous	23 314	7.1 ± 0.0
Donor–recipient size mismatch	–		
Body surface area index	Continuous	24 505	0.99 ± 0.00

Data are means ± SEM.
*Number of patients with data available.
†Donor risk index without height [12].

but there was no difference among the groups (SFS 1.3% vs. NFS 0.9% vs. LFS 1.3%).

Rate of retransplantation were significantly higher in the SFS and LFS groups (SFS 10.5% vs. NFS 8.3% vs. LFS 10.0%, SFS vs. NFS: $P < 0.001$, SFS vs. LFS: $P = 0.046$).

Discussion

This is the first study to determine 'SFS' and 'LFS' in deceased liver transplant based on clinical graft outcomes associated with new size mismatch index 'BSAi'. The study

Table 2. Hazards ratio of graft failure related to donor–recipient size mismatch transplantation.

BSAi	Hazards ratio	95% CI	BSAi	Hazards ratio	95% CI	BSAi	Hazards ratio	95% CI
0.46	1.919	(1.262–2.918)	0.82	1.009	(0.972–1.047)	1.18	1.019	(0.973–1.067)
0.48	1.838	(1.258–2.685)	0.84	0.991	(0.956–1.027)	1.20	1.033	(0.983–1.085)
0.50	1.761	(1.252–2.476)	0.86	0.976	(0.942–1.011)	1.22	1.048	(0.994–1.106)
0.52	1.687	(1.244–2.288)	0.88	0.963	(0.929–0.998)	1.24	1.066	(1.006–1.130)
0.54	1.617	(1.234–2.119)	0.90	0.953	(0.919–0.988)	1.26	1.086	(1.019–1.158)
0.56	1.550	(1.221–1.968)	0.92	0.946	(0.912–0.981)	1.28	1.108	(1.032–1.189)
0.58	1.488	(1.207–1.833)	0.94	0.943	(0.909–0.978)	1.30	1.130	(1.045–1.223)
0.60	1.428	(1.191–1.713)	0.96	0.943	(0.909–0.979)	1.32	1.153	(1.056–1.259)
0.62	1.373	(1.174–1.605)	0.98	0.946	(0.911–0.982)	1.34	1.176	(1.066–1.296)
0.64	1.321	(1.155–1.510)	1.00	0.951	(0.915–0.987)	1.36	1.197	(1.074–1.334)
0.66	1.272	(1.136–1.425)	1.02	0.956	(0.920–0.993)	1.38	1.217	(1.079–1.373)
0.68	1.227	(1.115–1.350)	1.04	0.962	(0.926–1.000)	1.40	1.236	(1.083–1.412)
0.70	1.185	(1.094–1.285)	1.06	0.968	(0.931–1.006)	1.42	1.254	(1.083–1.452)
0.72	1.147	(1.072–1.227)	1.08	0.974	(0.937–1.013)	1.44	1.272	(1.082–1.494)
0.74	1.112	(1.050–1.178)	1.10	0.981	(0.943–1.021)	1.46	1.288	(1.079–1.537)
0.76	1.081	(1.029–1.136)	1.12	0.989	(0.949–1.029)	1.48	1.303	(1.073–1.582)
0.78	1.054	(1.009–1.101)	1.14	0.997	(0.956–1.040)	1.50	1.317	(1.066–1.628)
0.80	1.030	(0.990–1.071)	1.16	1.007	(0.964–1.052)	1.52	1.331	(1.057–1.676)

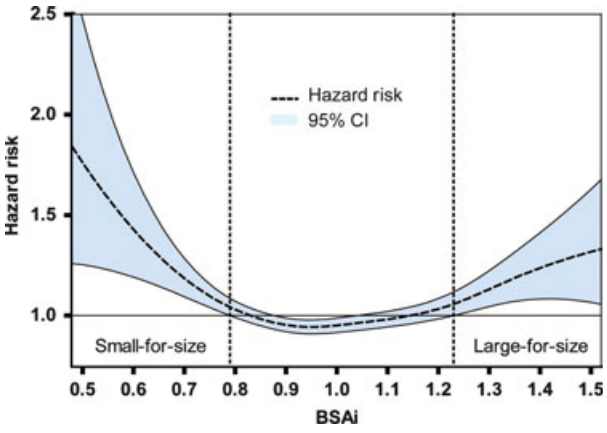
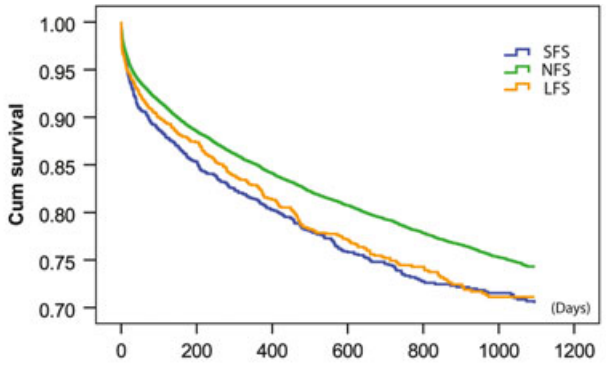


Figure 1 Body surface area index and hazard risk of graft failure. *N* = 24 509. Blurred area represents 95% confidence intervals of hazard risk related to each BSAi value. Hazard risk is significantly increased (both upper and lower 95% confidence interval becomes above 1.000) if BSAi is below 0.78 or over 1.24.

presented here shows that the size mismatch has a bidirectional impact on graft survival with a progressive increase in the risk of graft failure toward both the ends of the size mismatch spectrum, SFS to LFS. We provided the evidence that the SFS graft with BSAi less than 0.78 is significantly associated with an increased risk of graft failure in adult deceased liver transplant (Table 2). In addition, we provided the evidence that larger grafts with BSAi greater than 1.24 have an increased risk of graft failure.

Until now, it was totally unknown how small or large a whole liver graft relative to recipient size must be in order to produce the 'SFS' or 'LFS' syndrome in deceased whole liver transplant cases. A small-for-size graft (SFS) graft has a relatively high vascular resistance because of a relatively smaller vascular network [14–16]. Impaired tissue oxygenation may aggravate ischemia/reperfusion injury, and is associated with PNF and acute rejection in the early postoperative period [17–20]. In addition, small liver grafts often lead to concomitant pulmonary and renal failure, and frequently can lead to death of the recipient in the absence of retransplantation [21,22]. Other consequences of the 'SFS' syndrome include high incidence of vascular thrombosis and biliary complications. There is evidence to suggest that "portal hyperperfusion" is a causal factor in graft injury associated with SFS in live donor liver transplant [23]. High portal flow causes congestion and leads to sinusoidal endothelial cell and Kupffer cell injury with release of inflammatory cytokines [24]. In contrast, a large graft may be subjected to graft compression with consecutive graft necrosis if the abdomen is primary closed or increased rate of infectious complications in case of use prosthetic mesh because of its larger volume, which result in delayed recovery of hepatic function and, in the worst case scenario, massive hepatic necrosis and PNF, the so-called 'LFS syndrome' Cary, NC, USA [1,3].

In live donor liver transplant, the recommended minimal functional remnant liver volume following extended hepatectomy is $\geq$25% in normal liver, and $\geq$40% in injured liver with moderate to severe steatosis, cholestasis, fibrosis, cirrhosis, or following chemotherapy. [6,25] Also, a living donor graft of less than 40–50% of SLV, corresponding to a GWRBW of 0.8–1.0%, is associated with worse outcome. [1] These thresholds are less well-defined for deceased whole liver transplant mainly because of technical and time



		SFS	NFS	LFS	Overall
BSAi		<0.78	0.78-1.24	>1.24	
N.		1,713	21,399	1,393	24,505
	Time of Occurrence (Days)¶				
PNF	-	23 (1.3%) *	169 (0.8%)	9 (0.6%)	201 (0.8%)
Primary Graft Failure (A.)	30 [1-1070]	62 (4.3%) **	520 (3.0%)	38 (3.3%)	620 (3.1%)
Vascular Thrombosis (B.)	26 [1-1070]	47 (2.7%) ***	310 (1.4%)	17 (1.2%)	374 (1.5%)
Biliary Complication (C.)	180 [2-1054]	23 (1.3%)	201 (0.9%)	13 (0.9%)	237 (1.0%)
Acute Rejection (D.)	203 [1-1064]	22 (1.3%)	194 (0.9%)	18 (1.3%)	234 (1.0%)
Infection (E.)	195 [4-1070]	13 (0.8%)	128 (0.6%)	10 (0.7%)	151 (0.6%)
Total (A+B+C+D+E)		167 (9.7%)	1,353 (6.3%)	96 (6.9%)	1,616 (6.6%)
Retransplantation	-	179 (10.5%) ****	1,786 (8.3%)	139 (10.0%) *****	2,104 (8.5%)

Figure 2 Cumulative effect of size mismatch on 3-year graft survival and incidences of post-transplant complications in newly defined three size mismatch groups. (Upper) Graft survival was analyzed by the Kaplan–Meier Survival Model with Generalized Wilcoxon analysis. $N = 1713$ in small-for-size, $N = 21\ 399$ in normal-for-size, and $N = 1393$ in LFS. Three-year graft survivals were 71.2% in small-for-size, 74.2% and 71.1% in LFS group (small-for size vs. normal-for-size $P < 0.001$ and LFS vs. normal-for-size $P < 0.001$). (Lower) Also, incidence of post-transplant primary nonfunction (PNF), primary graft dysfunction, vascular thrombosis, biliary complications, acute rejection, and infection as well as retransplantation of those three groups were analyzed by Pearson chi-square (χ^2) test with *post hoc* Tukey test. *Compared to NFS: $P = 0.036$, ** Compared to NFS: $P = 0.007$, ***Compared to NFS: $P < 0.001$, LFS: $P = 0.002$, **** Compared to NFS: $P < 0.001$, ***** Compared to NFS: $P = 0.046$, ¶ data were shown in median value with range. LFS, large-for-size; NFS, normal-for-size; and SFS, small-for-size.

constraints [26–30], and three dimensional CT scan, which is becoming a standard way for volumetric assessment of the donor liver, and is required to calculate size mismatch in live donor liver transplant, but is often difficult to perform in deceased donors before organ procurement. It is believed that even larger graft volume is necessary because of the added risk factor of brain death on graft function and longer preservation injury. Using the indices to quickly and reliably predict size mismatch, the previously undetected effect of size-mismatched transplant on the graft outcome as well as safe size mismatch range can be investigated in deceased liver transplant.

Our generalized additive model with smoothing splines showed that size mismatch has a bidirectional impact on graft survival, which can be explained on the basis that size mismatch has not been considered a risk factor for graft survival because regression models assume linear correlation cannot detect a bidirectional size mismatch effect, a similar problem to the effects of hypo- or hyper-natremia [31]. In addition, we found that to prevent SFS related decrease in graft survival, more than 78% of liver volume is required, which is much higher than the 40–50% threshold for live donor liver transplant. Likewise, to prevent LFS related decrease in graft survival, the graft liver volume needs to be less than 124% of the recipients. On the basis of these findings, we redefine 'SFS'as BSAi of less than 0.78 and 'LFS' of greater than 1.24.

Using these new criteria of 'SFS'and 'LFS', we showed in this study that high incidence of PNF, primary graft dysfunction, vascular thrombosis, and retransplantation in the SFS group compared with the NFS group, which is consistent with those prior studies and hypotheses. Three-year graft survivals were significantly lower in the SFS and the

Table 3. Baseline characteristics of donors and recipients among three size mismatch groups.

Variables	SFS Mean ± SEM	NFS Mean ± SEM	LFS Mean ± SEM	Group comparisons SFS vs. NFS	SFS vs. LFS	NFS vs. LFS
Recipient	–	–	–	–	–	–
Demographic	–	–	–	–	–	–
Age (years)	53.5 ± 0.2	53.8 ± 0.1	53.0 ± 0.3	0.505	0.373	0.022
Laboratory values at transplant	–	–	–	–	–	–
Creatinine (mg/dl)	1.5 ± 0.0	14 ± 0 1	1.3 ± 0.0	<0.001	<0.001	0.123
Prothrombin Time- International Normalized Rat	1.9 ± 0.0	1 9 ± 0 0	2.0 ± 0.0	0.525	0.706	0.131
Sodium (mEg/dl)	136.0 ± 0.1	136 0 ± 0 0	136.0 ± 0.1	0.982	0.739	0.520
Total bilirubin (mg/dl)	8.8 ± 0.3	8 3 ± 0 1	9.5 ± 0.3	0.151	0.200	0.001
MELD score	22.1 ± 0.2	21 2 ± 0 1	22.2 ± 0.3	0.001	0.984	0.002
Donor	–	–	–	–	–	–
Demographic	–	–	–	–	–	–
Age (years)	38.7 ± 0.4	42.2 ± 0.1	41.9 ± 0.4	<0.001	<0.001	0.772
Donor quality	–	–	–	–	–	–
Donor Risk Index*	1.53 ± 0.01	1.51 ± 0.00	1.52 ± 0.01	0.247	0.924	3.515
Donor Cause of Death	–	–	–	–	–	–
Anoxia	20.0%	18.8%	20.1%	0.380	0.997	0.437
CerebroVascular Accident	44.7%	42.1%	42.2%	0.071	0.311	1.000
Warm ischemia time (min)	41.1 ± 1.1	41.9 ± 0.3	41.9 ± 1.2	0.734	0.897	0.998
Donor after cardiac death	5.6%	5.3%	4.6%	0.770	0.353	0.478
Expanded Donor Including Brain Dead and DCD	24.0%	27.0%	25.0%	0.010	0.015	0.012
Cold Ischemia Time (h)	7.3 ± 0.1	7.1 ± 0.0	7.1 ± 0.1	0.295	0.284	0.796
Macro-Steatosis	–	–	–	–	–	–
Mild (<30%)	25.4%	30.4%	34.7%	<0.001	<0.001	0.001
Moderate (30–60%)	0.6%	0.9%	1.4%	0.380	0.032	0.100
Severe (>60%)	0.2%	0.1%	0.3%	0.976	0.686	0.421

Data are means ± SEM.
*Donor risk index without height [12].

LFS group, which is also in line with other clinical studies in live donor liver transplant (Fig. 2a). Retransplantation following graft failure is risky for several reasons; patient and graft survival rates are worse than for a primary transplant; the procedure is more expensive; requires longer ICU and hospital stays; and in the context of organ shortage, retransplantation inevitably denies organs to first-time recipients. In fact, an annual savings of more than $50 million would be achieved, and the number of patients who could receive livers would be increased, if the number of retransplants performed presently could be reduced by half. [32] BSAi helps to identify the recipient group who carries high risks for graft failure, primary graft dysfunction, and vascular thrombosis after transplant. Therefore BSAi, the index to quickly and reliably predict size mismatch related co-morbidities and graft outcome, has an important value in deceased liver transplant.

BSA is frequently used to standardize measures of biological function with respect to variations in body size and conformation based on metabolic demands. As previously reported, caloric needs, total body water, and extracellular water are more closely associated with BSA than body weight at any age group [33]. BSA has been widely used to estimate metabolic demand based on weight and height, and can be used as a predictor of hepatic steatosis [34,35]. In addition, BSA has been used to estimate liver volume, such as standard liver volume (SLV (ml) = 706.2 × BSA (m^2) + 2.4) and has formed the basis for the determination of size mismatch [4,34]. Reported evidence has also shown that there is a significant correlation between SLV and graft weight with recipient body weight [GWRBW = graft weight (kg)/recipient body weight (kg)] [1], which is another index used clinically to predict the outcome related to size mismatch in live donor liver transplant. The SLV ratio between donor and recipient is a widely accepted method to predict the outcome related to size mismatch in live donor liver transplant. As such, we assessed the correlation of BSAi with SLV. BSAi was well correlated with the SLV ratio between donor and recipient, as shown in our previous report.

Large-for-size group had a worse 3-year graft survival, but the early graft failure rate such as vascular thrombosis,

PNF, and primary graft dysfunction) were essentially the same as the NFS. The survival curve indicates that initial graft survival runs between NFS and SFS with similar declining curve, but there was a further decline in the survival curve starting around 200 days after transplant. As a result, the final 3-year survival was same as that of the SFS group. We found that biliary complications, acute rejection, and infection were relatively late complications in liver transplant (commonly after 180 days after transplant) and the incidence of acute rejection in the LFS was higher when compared with the NFS. The higher incidence of acute rejection may be associated with further decline in the survival curve around 200 days after transplant. We speculated that this observation may be associated with higher percentages of steatosis in larger graft, graft compression with consecutive graft necrosis if the abdomen is primary closed or increased rate of infectious complications in case of use prosthetic mesh. Further investigation is warranted for morbidity and mortality in the LFS group.

Lastly, currently majority of commonly used statistical tools assume the linear relationship between response variable and covariates, which is called as likelihood-based regression models, including the normal linear regression model, the logistic regression model for binary data, and Cox's proportional hazards model for survival data [13]. Such assumptions may force the fitted relationship away from its natural path at critical points, resulting in underestimating the effect of those variables. Some of donor and recipient variables namely pretransplant sodium, and index variables for size mismatch have nonlinear effect on graft outcome, by meaning that those variables have a higher hazard risk for graft outcome toward both higher (hypernatremia or LFS) and lower (hyponatremia and SFS) ends [31]. Unavailability of statistical tools for such variables may be, at least in part, attributed to underrecognition of the importance of the issue related to pretransplant sodium as well as size mismatch in the field of liver transplant. To overcome this issue, we employed generalized additive models (GAMs) instead of conventional parametric regression model. GAMs are a method of fitting a smooth relationship between two or more variables through a scatterplot of data points. GAMs are extremely flexible and do not require any *a priori* assumption about the relationship between response variable and covariates, and is therefore particularly useful where the relationship between the variables is expected to be of a complex form, not easily fitted by standard linear or even non-linear models. This state-of-the-art GAM model has become popular in medical research [31,36,37]. In this study, continuous and natural relationship between size mismatch and graft survival as well as cut-off for SFS and LFS are successfully determined by GAMs.

We are aware that our study has some limitations. The primary limitation is its retrospective nature. For example, SFS in full size cadaveric graft may be attributed to technical failure secondary to graft rotation/displacement with consecutive vascular complication (thrombosis, outflow obstruction). More detailed analysis of vascular complication may unveil that technical issue, but complete dataset for those details was not available from this national database. Further investigation is warranted regarding the complication related to SFS cadaveric transplant. Second, fluid excess (ascites and oedema) is universal in end-stage liver disease. Fluid excess causes weight-to-height parameters, such as percentage ideal body weight, BMI, and BSA, to be underestimated, and the BSA of the recipient may not accurately reflect liver volume in these situations. Third, we found that steatosis is higher in the LFS group. Hepatic macrosteatosis is a known significant risk factor for graft survival and the higher percentages of steatosis may be, at least in part, attributed to lower graft survival in the LFS group. To minimize the effect of steatosis on graft survival, the donor macro- and micro-steatosis were included in the initial multivariate model. Lastly, size-mismatched liver transplant may urgently undergo to save the life of sicker patients under the condition of limited donor availability in deceased liver transplant, which may affect the outcome of patients. To exclude the potential confounding effect of severity of liver disease, recipient demographic variables were included in the multivariable model. Although confounding effect of recipient condition may still exists together with other studies from clinical and animal model of size-mismatched liver transplant, size-mismatched transplant has a significant impact on the postoperative graft outcome. BSAi can be used to make a decision whether to proceed with size-mismatched transplant for the sicker group of patients when only size-mismatched donor is available. If the recipient outcome with size-mismatched transplant outweighs the recipient outcome without transplant, use of significantly size-mismatched organ can be justified. The hazard risk of graft failure related to each BSAi value provided in Table 2 will aide to quickly determine the risk related to those size-mismatched liver transplants.

Authorship

KF: designed research, performed research, collected data, analyzed data and wrote the paper. YY, SN and EP: designed research and wrote the paper. TH: wrote the paper. KA: analyzed data and wrote the paper.

Funding

This research project was funded by the Department of Anesthesiology, Perioperative Medicine and Pain Management, University of Miami Miller School of Medicine, Miami, Florida, USA.

Acknowledgements

This work was supported in part by Health Resources and Services Administration contract 234-2005-370011C. The content is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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