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Revisiting the Prognostic Influences of Donor-Recipient Size Mismatch in Deceased Donor Liver Transplantation

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Background. Liver transplantation (LT) outcomes are influenced by donor-recipient size mismatch. This study re-evaluated the impact on graft size discrepancies on survival outcomes. **Methods.** Data from 53 389 adult LT recipients from the United Network for Organ Sharing database (2013–2022) were reviewed. The study population was divided by the body surface area index (BSAi), defined as the ratio of donor body surface area (BSA) to recipient BSA, into small-for-size (BSAi < 0.78), normal-for-size (BSAi 0.78–1.24), and large-for-size (BSAi > 1.24) grafts in deceased donor LT (SFSD, NFSD, and LFSD). Multivariate Cox regression and Kaplan-Meier survival analyses were conducted. **Results.** The frequency of size mismatch in deceased donor LT increased over the past 10 y. SFSD had significantly worse 90-d graft survival ($P < 0.01$), and LFSD had inferior 1-y graft survival among 90-d survivors ($P = 0.01$). SFSD was hazardous within 90 d post-LT because of vascular complications. Beyond 1 y, graft size did not affect graft survival. LFSD risk within the first year was mitigated with lower model for end-stage liver disease (MELD) 3.0 scores (<35) or shorter cold ischemia time (<8 h). **Conclusions.** The negative impacts on donor-recipient size mismatch on survival outcomes are confined to the first year post-LT. SFSD is associated with a slight decrease in 90-d survival rates. LFSD should be utilized more frequently by minimizing cold ischemia time to <8 h, particularly in patients with MELD 3.0 scores below 35. These findings could improve donor-recipient matching and enhance LT outcomes.

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INTRODUCTION

Liver transplantation (LT) is the best treatment for end-stage liver disease.[1] In LT, donor-recipient matching is known to be crucial for enhancing survival rates after the transplant.[2] Size mismatch between donor and recipient is an important part of donor-recipient matching and has been carefully examined in living donor LT (LDLT). In LDLT, size mismatch is defined using the graft-to-recipient weight ratio (GRWR). Small-for-size and large-for-size syndromes have been mitigated by maintaining a GRWR of 0.6%–4.0% through preoperative donor liver volume calculations using 3-dimensional imaging.[3,4] Size mismatch in DDLT has also been shown to correlate with poorer GS.[5-7] However, GRWR is usually not feasible at the time of deceased liver allocation. Although it is not always precise, liver volume is known to correlate with height and weight. Therefore, body surface area (BSA) or the standard total liver volume (sTLV), a linear regression of liver volume based on BSA, is used as an alternative to the graft volume.[8,9]

The safety threshold for size match in DDLT proposed by previous studies, the donor-to-recipient BSA ratio (BSA index) of 0.78 to 1.25, is generally narrower than the GRWR range of 0.6%–4.0% used in LDLT, as shown in Table 1.[3-7,10] The implications of small-for-size grafts in DDLT (SFSD) and large-for-size grafts in DDLT (LFSD) might be different from those in LDLT. Moreover, few studies have explored the differences between SFSD and LFSD. Small-for-size syndrome occurs when the graft cannot meet the recipient's functional and metabolic needs, whereas large-for-size syndrome arises from inadequate blood supply to the graft.[6] The two

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TABLE 1.

Median height and weight of donors and recipients, and corresponding BSA index, sTLV ratio, and GRWR

	Donor		Recipient				
	Height (cm)	Weight (kg)	Height (cm)	Weight (kg)	BSA index	sTLV ratio	GRWR (%)
SFSD	162.0	60.0	180.0	107.0	0.74	0.63	1.19
NFSD	173.0	81.6	173.0	84.4	0.99	0.98	1.98
LFSD	178.0	105.0	163.0	63.1	1.30	1.49	3.16

BSA was calculated by Du Bois's formula and sTLV was calculated by Vauthey's formula (Du Bois, Vauthey). BSA index is the ratio of donor BSA to recipient BSA, and sTLV ratio is the ratio of donor sTLV to recipient sTLV. Since graft weight is not obtained in the UNOS database, GRWR was calculated by the donor sTLV divided by the recipient weight.
BSA, body surface area; GRWR, graft-to-recipient weight ratio; LFSD, large-for-size grafts in deceased donor liver transplantation; NFSD, normal-for-size grafts in deceased donor liver transplantation; SFSD, small-for-size grafts in deceased donor liver transplantation; sTLV, standard total liver volume; UNOS, United Network for Organ Sharing.

are clinically distinct groups and identifying the differences in clinical outcomes between the SFSD and LFSD could benefit clinical practice in DDLT.

Large-scale research from US and UK national registry databases has consistently shown the negative impacts of size mismatches in DDLT.[5,11,12] However, the detailed effects on short- and long-term GS and the specific donor/recipient subgroups least affected by size mismatches are not fully understood. This study aimed to look into the effects of SFSD and LFSD on short-term and long-term outcomes after LT and identify candidates best suited for size-mismatched grafts using US national registry data.

MATERIALS AND METHODS

Study Population

The study utilized data from the United Network for Organ Sharing (UNOS) database between 2013 and 2022. The study cohort consisted of 72 078 adults (aged 18 and above), who underwent deceased donor LT. After excluding split/partial LT, multiorgan transplants, status 1 patients, retransplantations, and procedures involving donors after circulatory death, 54 236 patients remained. All patients with incomplete basic donor/recipient characteristics for donor age, donor sex, donor height, donor weight, race, cause of death, cold ischemia time (CIT), recipient age, recipient sex, recipient height, recipient weight, model for end-stage liver disease (MELD) 3.0 score, pretransplant medical condition, history of previous abdominal surgery, and portal vein thrombosis were excluded, leaving 53 389 patients (98.4% of total). As Fukazawa et al. previously reported, the BSA index (BSAi) was used to define graft size mismatch, categorizing grafts as SFSD if BSAi ≤ 0.78, normal-for-size grafts in DDLT (NFSD) if 0.78 < BSAi < 1.24, and LFSD if BSAi ≥ 1.24.[5] The Du Bois formula calculated the BSA, and the BSAi was determined by the ratio of donor BSA to recipient BSA.[13] Regarding macrosteatosis, of 53 389 grafts in the cohort, 29 765 (55.8%) patients had missing data; thus, macrosteatosis was categorized as ≥30%, <30%, or no biopsy performed. Regarding ascites, the degree of ascites was categorized as absent, slight, moderate, or unknown in the UNOS database. The causes of graft loss/patient death were identified by the following terms as previously described: "grf_fail_cause_ostxt, cod, cod_ostxt" and considered variables "pri_grf_fail, pri_non_func, vasc_thromb, hepatic_art_thromb, other_vasc_thromb, biliary, diffuse_cholang, hep_denovo, hep_recur, recur_disease, rej_acute, rej_chronic, infect."[14]

The primary objective was to assess variations in graft survival (GS) at two endpoints (90 d and 5 y post-LT) among three graft types: SFSD, NFSD, and LFSD. The secondary objective was to evaluate variations in hazard ratios (HR) of GS or conditional GS (cGS) in these groups at three endpoints: 90-d GS, 1-y cGS in patients whose graft survived no <90 d, and 5-y cGS in patients whose graft survived no <1 y. This analysis revealed the effects of size mismatch on short-term and long-term outcomes after LT. The third outcome was to analyze the causes of graft loss/patient death in each group at 2 intervals: 90-d and 1 y in 90-d survivors. Additionally, the impact on the MELD 3.0 score and CIT on the survival outcomes of SFSD and LFSD was investigated. All the analyses were conducted with the approval of the institutional review board at Stanford University (No. 69532).

Statistical Analyses

Statistical analyses were conducted using R 4.3.1 (https://cran.r-project.org/). Donor and recipient demographics were presented as frequencies with percentages or median values with interquartile ranges (IQR). Differences between categorical values were assessed using the chi-square test, whereas continuous values were analyzed using the Mann-Whitney *U* or Kruskal-Wallis tests as appropriate. GS was evaluated using the Kaplan-Meier method, with the Log-rank test assessing differences. GS was calculated from the time of transplant until either death, graft loss, or the last recorded follow-up. Multivariate Cox proportional hazard models identified HRs of LT involving SFS or LFS grafts. These models were adjusted for several confounders: donor age, cause of donor death, graft macrosteatosis, CIT, recipient age, MELD 3.0 score, pretransplant medical condition, history of previous abdominal surgery, and portal vein thrombosis. Propensity score matching was employed to balance the cohort and compare GS among different graft types by adjusting for the same variables and donor/recipient gender. The restricted cubic spline (RCS) method was employed to visualize how the BSA index impacts LT outcomes at different intervals post-LT. The HR of RCS was adjusted uniformly with the aforementioned variables. Additionally, as a sensitivity analysis, Kaplan-Meier survival curves were depicted in the cohorts stratified by donor-recipient gender combinations and by the degree of ascites. Statistical significance was established below a *P* value of 0.05.

RESULTS

Baseline Characteristics

Our study cohort consisted of 53 389 LT, out of which 4248 (8.0%), 45 706 (85.6%), and 3435 (6.4%) were SFSD,

NFSD, and LFSD grafts, respectively. The ratio of SFSD and LFSD slightly increased over the study period, with LFSD nearly reaching the rate of SFSD after 2020 (Figure 1). The baseline characteristics of these groups are detailed in Table 2. In the SFSD group, compared with the NFSD and LFSD groups, there was a significantly lower proportion of male donors (34.8% versus 61.3% and 73.2%; $P<0.01$) and a significantly higher proportion of male recipients (80.7% versus 67.1% and 40.1%; $P<0.01$). Donors in the SFSD group were also shorter and lighter, with fewer having >30% macrosteatosis in liver biopsies (162.0 cm versus 172.7 cm and 178.0 cm; 60.0 kg versus 81.6 kg and 105.3 kg; 2.4% versus 4.2% and 6.2%; all $P<0.01$), whereas recipients in this group were taller and heavier (180.0 cm versus 172.7 cm and 162.6 cm; 107.4 kg versus 84.4 kg and 63.1 kg; all $P<0.01$). In contrast, the LFSD group exhibited opposite trends. Furthermore, donors in the SFS group were more likely to die from cerebrovascular disease (35.1% versus 31.4% and 27.3%; $P<0.01$). Other characteristics were similar across the groups.

Graft Survival at 90 d and 5 y Post-LT and Conditional Graft Survival

The Kaplan-Meier survival plots mapping GS for 3 graft types at 90 d and 5 y post-LT are presented in Figure 2A,B. The 90-d or 5-y GS of SFSD was significantly worse than the NFSD or the LFSD: 93.7% versus 95.5% and 95.3%, $P<0.01$ at 90 d, 78.0% versus 79.6% and 79.5%, $P=0.01$ at 5 y. Kaplan-Meier plots for 5-y GS showed that the curves for SFSD and NFSD were parallel after 90 d. The LFSD curve initially followed a downward trend similar to the SFSD after 90 d until around 360 d, after which it deviated and approached the NFSD curve. To elucidate this trend, cGS was analyzed, restricting the study population to those who survived the initial 90 d, 1 y, or 3 y (Figure 2C-F). The LFSD group showed inferior 1-y cGS at 90 d post-LT, or 1-y GS of 90-d survivors, than the other 2 groups. Beyond 1 y, there were no statistical differences in GS between the 3 groups, although the survival curve for LFSD seemed superior to the other 2 groups. This pattern remained similar after propensity score matching between the SFSD and NFSD groups (Figure S1, SDC, http://links.lww.com/TXD/A708) and between the LFSD and NFSD groups (Figure S2, SDC, http://links.lww.com/TXD/A708). Graphical description of the propensity score model is shown in Figure S3 (SDC, http://links.lww.com/TXD/A708). In addition, a similar pattern of survival curves was observed when the study population was stratified by donor-recipient gender combinations (Figure S4, SDC, http://links.lww.com/TXD/A708) and by the degree of ascites (Figure S5, SDC, http://links.lww.com/TXD/A708).

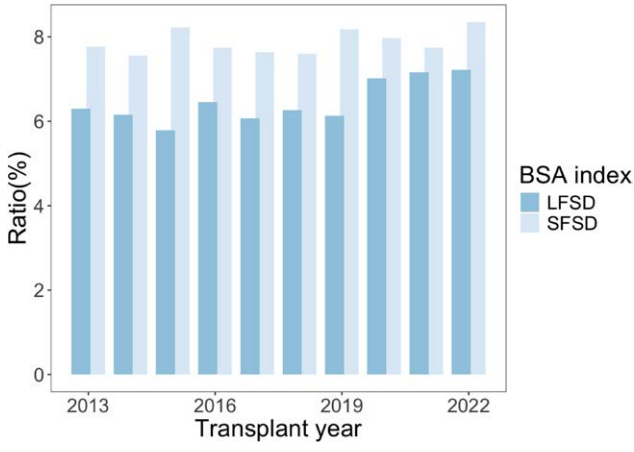

FIGURE 1. Trends in the ratio of size-mismatched grafts over the study period. The ratio of SFSD and LFSD gradually increased over the 10-y study period. LFSD, large-for-size grafts in deceased donor liver transplantation; SFSD, small-for-size grafts in deceased donor liver transplantation.

HRs of Graft Failure at Different Intervals Post-LT

The multivariate Cox regression analyses of 90-d GS, 1-y cGS in 90-d survivors, and 5-y cGS in 1-y survivors are shown in Table 3. SFSD was a significant prognostic factor for 90-d GS (HR, 1.44; 95% CI, 1.27-1.64; $P<0.01$), and LFSD was significantly hazardous between 90 d and 1 y post-LT (HR, 1.28; 95% CI, 1.08-1.51; $P<0.01$). SFSD and LFSD were not significantly hazardous at other intervals. Other factors such as macrosteatosis were significantly hazardous until 90 d, and intensive care unit stay before transplant or portal vein thrombosis were consistently hazardous throughout the 3 intervals. To elucidate the impact on the BSA index on GS in a continuous fashion, RCS curves were depicted (Figure 3A-C). The curve for 90-d GS showed that the adjusted HR increases as the BSA index deviates from 1.0, with a sharper increase when the BSA index <1.0. The curve for 1-y cGS for 90-d survivors was more symmetrical, whereas the curve for 5-y cGS for 1-y survivors showed a flat trend.

Cause of Graft Loss/Patient Death After LT

Among patients whose graft failed within 1 y, the causes of graft loss/patient death cause were recorded in most patients (3995/4336 patients, 92.1%). The common causes of graft loss and patient death, stratified by graft type and 2 time intervals (within 90 d or from 90 d to 1 y post-LT), are shown in Table 4. For graft failure within 90 d, vascular complications were more frequent in the SFSD group (22.3% versus 13.6%/8.8% in NFSD/LFSD, $P<0.01$). Within vascular complications, hepatic artery thrombosis (HAT) showed similar trends, occurring more frequently in the SFSD group (19.3% versus 9.9%/6.9% in NFSD/LFSD, $P<0.01$). To further assess the impact on BSAi on vascular complications, we divided the SFSD group further into 4 quantiles (group 1: BSAi <0.6958, group 2: $0.6958 \le$ BSAi <0.7361, group 3: $0.7361 \le$ BSAi <0.7606, and group 4: BSAi ≥ 0.7606). The causes of graft loss/patient death within 90 d in each subgroup are shown in Table S1 (SDC, http://links.lww.com/TXD/A708). Although the relationship was not perfectly linear, there was a noticeable trend where lower BSA index values were associated with higher rates of HAT and vascular complications. The incidence of these complications was highest in group 1, which had the lowest BSA index within the SFSD group, and was higher in the other groups compared with those in the NFSD or LFSD groups, as shown in Table 4.

From 90 d to 1 y post-LT, respiratory failure was more common in the LFSD group (14.9% versus 8.7%/9.3% in NFSD/SFSD, $P=0.04$), whereas multiple organ failure was more common in the SFSD group (12.0% versus 7.1%/4.7% in NFSD/LFSD, $P=0.04$). Additionally, causes of patient death and causes of graft loss requiring retransplantation were separately analyzed (Tables S2 and S3, SDC, http://links.lww.com/TXD/A708). Most graft losses requiring retransplantation

TABLE 2.

Baseline donor and recipient characteristics

(%) or [IQR]	SFS (n = 4248)	NFS (n = 45706)	LFS (n = 3435)	*P*
Donor characteristics				
Age, y	41.0 [26.0, 56.0]	44.0 [30.0, 56.0]	41.0 [30.0, 54.0]	<0.01
Sex, male	1480 (34.8)	28029 (61.3)	2515 (73.2)	<0.01
Height, cm	162.0 [155.0, 168.0]	172.7 [165.0, 178.0]	178.0 [172.0, 184.0]	<0.01
Weight, kg	60.0 [51.1, 68.5]	81.6 [70.0, 95.0]	105.3 [91.0, 123.6]	<0.01
BMI, kg/m^2	22.7 [20.0, 25.8]	27.5 [24.0, 31.8]	33.3 [28.7, 39.4]	<0.01
BSA, m^2	1.6 [1.5, 1.8]	2.0 [1.8, 2.1]	2.2 [2.1, 2.4]	<0.01
Macrosteatosis				<0.01
>30%	101 (2.4)	1924 (4.2)	213 (6.2)	
<30%	1439 (33.9)	18408 (40.3)	1539 (44.8)	
No biopsy	2708 (63.7)	25374 (55.5)	1683 (49.0)	
Cause of death				<0.01
Anoxia	1667 (39.2)	18123 (39.7)	1491 (43.4)	
CVD	1492 (35.1)	14353 (31.4)	938 (27.3)	
Head Trauma	990 (23.3)	12175 (26.6)	924 (26.9)	
Others	99 (2.3)	1055 (2.3)	82 (2.4)	
CIT, h	5.9 [4.7, 7.3]	5.8 [4.7, 7.2]	5.8 [4.6, 7.1]	0.03
Recipient characteristics				
Age, y	56.0 [48.0, 63.0]	58.0 [50.0, 64.0]	58.0 [49.0, 64.0]	<0.01
Sex, male	3429 (80.7)	30660 (67.1)	1377 (40.1)	<0.01
Height, cm	180.0 [172.7, 185.4]	172.7 [165.1, 180.0]	162.6 [157.5, 170.2]	<0.01
Weight, kg	107.4 [92.5, 123.4]	84.4 [72.9, 97.5]	63.1 [55.3, 72.6]	<0.01
BMI, kg/m^2	33.5 [29.1, 38.2]	28.4 [24.9, 32.5]	23.7 [21.0, 26.8]	<0.01
BSA, m^2	2.3 [2.1, 2.4]	2.0 [1.8, 2.1]	1.7 [1.6, 1.8]	<0.01
Medical condition				<0.01
ICU	655 (15.4)	6121 (13.4)	507 (14.8)	
Hospitalized	1012 (23.8)	9937 (21.7)	860 (25.0)	
Home	2581 (60.8)	29648 (64.9)	2068 (60.2)	
Previous abdominal surgery	1842 (43.4)	21448 (46.9)	1727 (50.3)	<0.01
Portal vein thrombosis	597 (14.1)	6558 (14.3)	485 (14.1)	0.83
MELD score	25.0 [16.0, 33.0]	23.0 [15.0, 31.0]	25.0 [17.0, 31.0]	<0.01
BSA index	0.7 [0.7, 0.8]	1.0 [0.9, 1.1]	1.3 [1.3, 1.4]	<0.01

Continuous variables: median [IQR]; categorical variable: number (%).

BSA, body surface area; BMI, body mass index; CIT, cold ischemia time; CVD, cerebrovascular disease; ICU, intensive care unit; LFSD, large-for-size grafts in deceased donor liver transplantation; MELD, model for end-stage liver disease; NFSD, normal-for-size grafts in deceased donor liver transplantation; SFSD, small-for-size grafts in deceased donor liver transplantation.

within 90 d were because of vascular complications and primary nonfunction. Vascular complications were more common in SFSD group, and primary nonfunction was more common in LFSD group.

Impact of MELD 3.0 Score and CIT on Survival Outcomes of SFSD/LFSD

The overall study population was stratified by MELD 3.0 score and CIT. In each cohort, the RCS curve was depicted to show how the changing BSA index impacts 1-y GS (Figure 4A-D). The curves indicate that in the MELD 3.0 ≥ 35 group and the CIT ≥8 h group, the adjusted HR increased as the BSA index deviated from 1.0. In contrast, in the MELD 3.0 < 35 group and the CIT <8 h group, an increase in the BSA index beyond 1.0 was not associated with an increase in the adjusted HR, although the decrease in the BSA index from 1.0 was associated with an increased adjusted HR.

DISCUSSION

This study aimed to re-evaluate the impact on graft size discrepancies on short-term and long-term survival outcomes using a national database. Previous reports have highlighted the negative effects of graft size mismatch in LT using national registries.[5,11,12] However, the impact on size mismatch at different time intervals has not been thoroughly examined, and recent single-center studies have raised questions about its significance.[15,16] In this context, our analysis found that the frequency of size mismatch in DDLT has slightly increased in the past 10 y. For short- or long-term outcomes, SFSD was hazardous within 90 d post-LT because of vascular complications, and LFSD was hazardous from 90 d to 1 y post-LT because of respiratory failure. Beyond 1 y post-LT, graft size did not affect GS. Furthermore, our investigation into the impacts of MELD 3.0 or CIT revealed that the risk of LFSD is minimal if MELD 3.0 < 35 or CIT < 8 h.

The analysis of the frequency of size mismatch revealed that it gradually increased over the past 10 y, with LFSD steadily increasing after 2020 (Figure 1). LT candidates with smaller BSA experience longer wait times and higher waitlist mortality than others,[17] and the increasing prevalence of LFSD might reflect the fact that these candidates have had to rely on livers from donors with larger BSA than themselves. This trend would not be concerning if the outcomes of size-mismatched grafts were comparable to those of size-matched grafts; however, this was not the case.

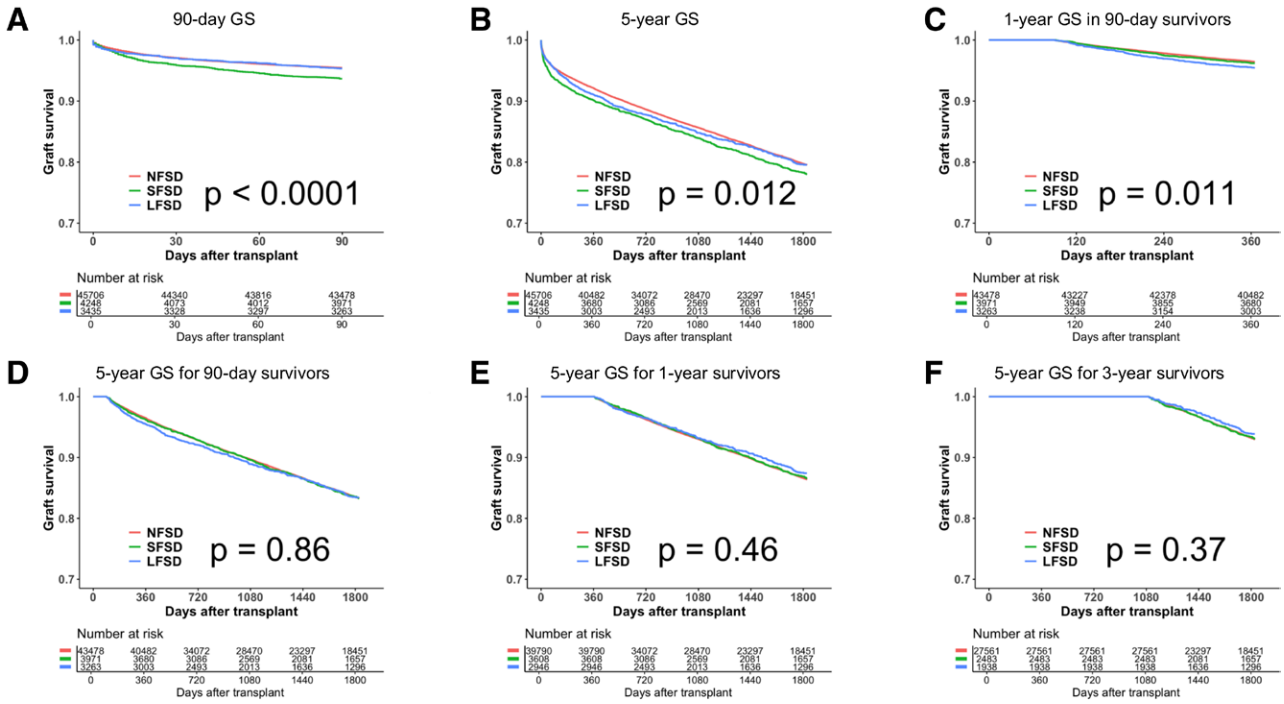

FIGURE 2. The Kaplan-Meier survival curve for liver transplantation among three different graft sizes. Each plot represents the GS using SFSD, NFSD, and LFSD grafts at different time intervals post-LT: 90-d GS (A), 5-y GS (B), 1-y GS in 90-d survivors (C), 5-y GS in 90-d survivors (D), 1-y survivors (E), and 3-y survivors (F). GS, graft survival; LFSD, large-for-size grafts in deceased donor liver transplantation; NFSD, normal-for-size grafts in deceased donor liver transplantation; SFSD, small-for-size grafts in deceased donor liver transplantation.

TABLE 3.

The risk factors of graft survival

	90-d GS			1-y cGS at 90-d			5-y cGS at 1-y		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Donor characteristics									
Age/y	1.00	1.00-1.01	0.07	1.01	1.01-1.01	<0.01	1.01	1.00-1.01	<0.01
Cause of death (reference: head trauma)									
Anoxia	0.95	0.86-1.05	0.33	1.04	0.92-1.17	0.53	1.01	0.95-1.08	0.74
CVD	1.18	1.06-1.32	<0.01	1.06	0.93-1.21	0.39	1.01	0.94-1.08	0.86
Others	1.12	0.86-1.46	0.40	0.92	0.65-1.29	0.63	0.88	0.74-1.05	0.17
Macrosteatosis (reference: <30%)									
>30%	1.60	1.35-1.89	<0.01	1.21	0.97-1.51	0.09	0.85	0.74-0.97	0.02
No biopsy	0.94	0.86-1.02	0.14	1.00	0.90-1.1	0.93	0.95	0.90-1.01	0.08
CIT > 6h	1.30	1.20-1.41	<0.01	1.13	1.03-1.24	<0.01	1.04	0.99-1.09	0.13
Recipient characteristics									
Age/y	1.01	1.01-1.01	<0.01	1.03	1.02-1.03	<0.01	1.02	1.01-1.02	<0.01
Medical condition (reference: home)									
ICU	2.10	1.86-2.37	<0.01	1.90	1.64-2.21	<0.01	1.42	1.30-1.54	<0.01
Hospitalized	1.17	1.04-1.31	0.01	1.34	1.17-1.54	<0.01	1.15	1.07-1.24	<0.01
Previous abdominal surgery	1.31	1.21-1.41	<0.01	1.04	0.95-1.14	0.37	1.05	1.00-1.10	0.05
Portal vein thrombosis	1.53	1.39-1.69	<0.01	1.32	1.17-1.48	<0.01	1.18	1.10-1.26	<0.01
MELD score, per point	1.00	1.00-1.01	0.26	1.00	0.99-1.01	1.00	1.00	0.99-1.00	<0.01
BSA index (reference: NFSD)									
SFSD	1.44	1.27-1.64	<0.01	1.13	0.95-1.34	0.15	1.05	0.96-1.15	0.28
LFSD	1.00	0.85-1.18	0.97	1.28	1.08-1.51	<0.01	1.03	0.93-1.14	0.54

BSA, body surface area; cGS, conditional graft survival; CIT, cold ischemia time; CVD, cerebrovascular disease; GS, graft survival; ICU, intensive care unit; LFSD, large-for-size grafts in deceased donor liver transplantation; MELD, model for end-stage liver disease; NFSD, normal-for-size grafts in deceased donor liver transplantation; SFSD, small-for-size grafts in deceased donor liver transplantation.

The Kaplan-Meier survival curves and multivariate Cox regression model revealed the impact of size mismatch at different time periods after LT (Figure 2). The analyses indicate that size mismatch affects GS only within the first year after LT. This aligns with other reports suggesting that donor factors, such as age, hepatectomy time, and macrosteatosis, primarily impact short-term survival outcomes after LT.[18-20] Furthermore, SFSD and LFSD were hazardous during

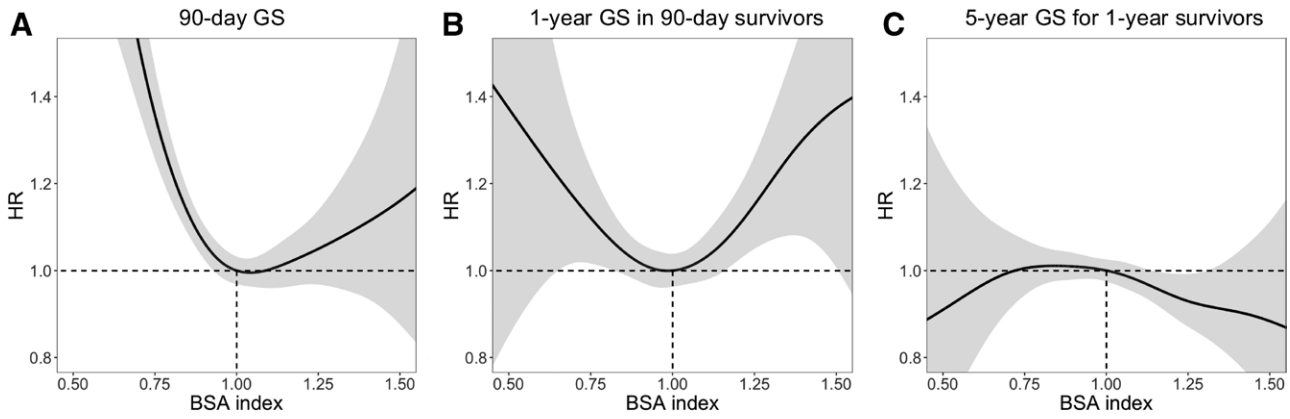

FIGURE 3. RCS Curves for the impact of BSA index on graft survival at different time intervals post-LT. This figure shows RCS curves assessing the impact of increasing BSA index for 90-d GS (A), 1-y GS for 90-d survivors (B), and 5-y GS for 1-y survivors (C). The adjusted hazard ratio was set to 1.0 when BSA index is 1.0. Gray shadows indicate the 95% confidence intervals. BSA, body surface area; GS, graft survival; RCS, restricted cubic spline.

TABLE 4.

Causes of graft loss and patient death at different intervals

	90 d				90 d- 1 y			
%	SFSD	NFSD	LFSD	*P*	SFSD	NFSD	LFSD	*P*
n	269	2069	160		150	1540	148	
Infection	31 (11.5)	275 (13.3)	24 (15.0)	0.57	20 (13.3)	295 (19.2)	34 (23.0)	0.10
Cardiovascular	56 (20.8)	417 (20.2)	45 (28.1)	0.06	17 (11.3)	179 (11.6)	13 (8.8)	0.58
Vascular complications	60 (22.3)	282 (13.6)	14 (8.8)	<0.01	7 (4.7)	47 (3.1)	2 (1.4)	0.25
HAT	52 (19.3)	204 (9.9)	11 (6.9)	<0.01	6 (4.0)	39 (2.5)	2 (1.4)	0.35
Primary non function	33 (12.3)	266 (12.9)	20 (12.5)	0.96	0 (0.0)	4 (0.3)	0 (0.0)	0.68
Multiple organ failure	15 (5.6)	159 (7.7)	13 (8.1)	0.44	18 (12.0)	109 (7.1)	7 (4.7)	0.04
Malignancy	1 (0.4)	12 (0.6)	0 (0.0)	0.58	21 (14.0)	248 (16.1)	16 (10.8)	0.20
Respiratory failure	10 (3.7)	100 (4.8)	6 (3.8)	0.61	14 (9.3)	134 (8.7)	22 (14.9)	0.04
Recurrence of original liver disease	1 (0.4)	8 (0.4)	0 (0.0)	0.73	3 (2.0)	33 (2.1)	1 (0.7)	0.48
Cerebrovascular	8 (3.0)	145 (7.0)	9 (5.6)	0.04	3 (2.0)	67 (4.4)	5 (3.4)	0.34
Biliary complications	10 (3.7)	51 (2.5)	2 (1.2)	0.27	7 (4.7)	65 (4.2)	3 (2.0)	0.41
Rejection	4 (1.5)	20 (1.0)	1 (0.6)	0.64	9 (6.0)	64 (4.2)	10 (6.8)	0.23
GVHD	2 (0.7)	41 (2.0)	3 (1.9)	0.36	2 (1.3)	27 (1.8)	5 (3.4)	0.33
Intraoperative death or bleeding	4 (1.5)	62 (3.0)	7 (4.4)	0.20	0 (0.0)	0 (0.0)	0 (0.0)	NA
Renal failure	1 (0.4)	3 (0.1)	0 (0.0)	0.59	2 (1.3)	9 (0.6)	3 (2.0)	0.11
PTLD	0 (0.0)	0 (0.0)	0 (0.0)	NA	2 (1.3)	15 (1.0)	1 (0.7)	0.85
Miscellaneous	14 (5.2)	109 (5.3)	8 (5.0)	0.99	4 (2.7)	87 (5.6)	9 (6.1)	0.29
Unspecified	19 (7.1)	119 (5.8)	8 (5.0)	0.62	21 (14.0)	157 (10.2)	17 (11.5)	0.33

GVHD, graft-versus-host disease; HAT, hepatic artery thrombosis; LFSD, large-for-size grafts in deceased donor liver transplantation; NA, not available; NFSD, normal-for-size grafts in deceased donor liver transplantation; PTLD, post-transplant lymphoproliferative disorder; SFSD, small-for-size grafts in deceased donor liver transplantation.

different phases after LT: SFSD within the initial 90 d and LFSD from 90 d to 1 y post-LT (Table 3; Figure 3). To understand why SFSD and LFSD were hazardous during specific periods after LT, the causes of graft loss and patient death were investigated.

The analysis of causes of death/graft loss showed that the SFSD group was more likely to die from vascular complications within 90 d, whereas the LFSD group was more likely to die from respiratory complications between 90 d and 1 y (Table 4). Although graft size mismatch for SFSD in DDLT is much smaller than for small-for-size grafts in LDLT, the observed findings are consistent with previous reports in LDLT, possibly because of the hepatic artery buffer effect of portal hyperperfusion, which lowers hepatic artery flow.[21-23] It is worth noting that after portal flow modulation in LDLT, increased arterial flow was also observed, although its relation to the incidence of HAT has not been reported.[24] Supporting this hypothesis, our analysis revealed that graft failure because of HAT was more common in SFSD. In contrast, there were fewer vascular complications in LFSD, aligning with the idea that hepatic artery flow is preserved because of portal hypoperfusion. The high incidence of respiratory complications in LFSD may be because of graft-induced compression of the diaphragm and rib cage.[9] Primary nonfunction was likely more common in LFSD because of the compression of a large graft by the rib cage, and LFSD is a known risk factor for EAD.[6] Thus, SFSD and LFSD cause specific complications at different times. We then tried to identify candidates best suited for size-mismatched grafts, particularly considering MELD 3.0 score or CIT.

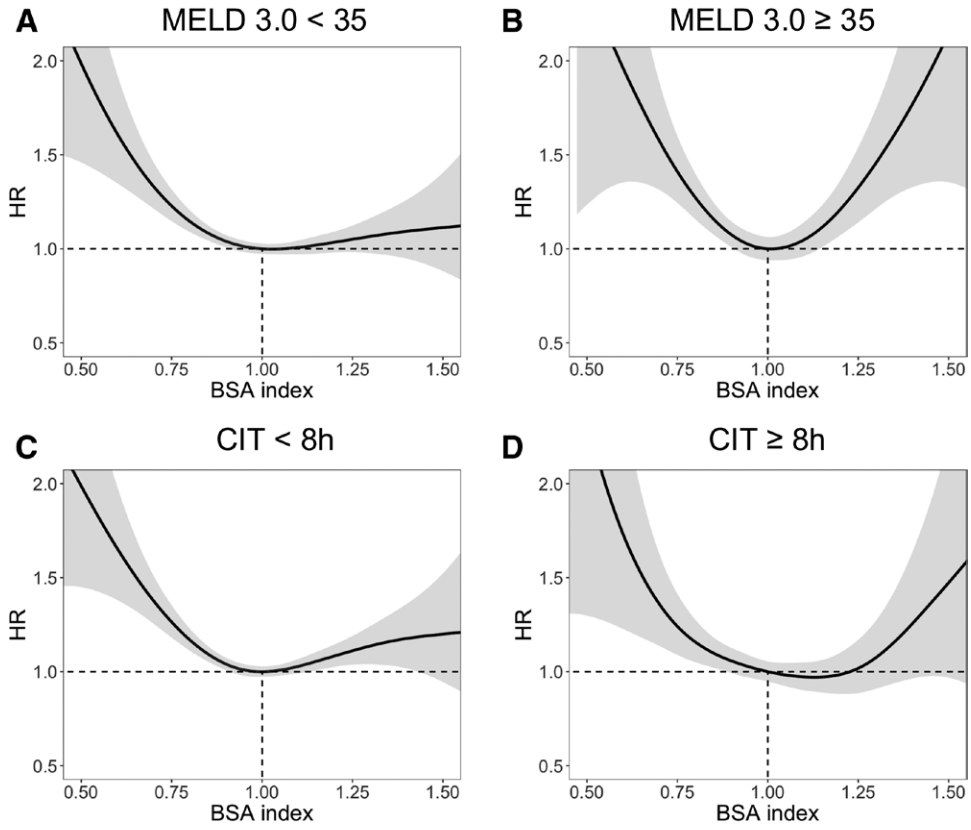

FIGURE 4. RCS Curves for the impact of BSA index on graft survival in MELD 3.0 or CIT-stratified groups. This figure shows RCS curves assessing the impact of increasing BSA index for patients with MELD 3.0 < 35 (A), MELD 3.0 ≥ 35 (B), CIT < 8 h (C), and CIT ≥ 8 h (D). The adjusted hazard ratio was set to 1.0 when BSA index is 1.0. Gray shadows indicate the 95% confidence intervals. BSA, body surface area; CIT, cold ischemia time; GS, graft survival; MELD, Model for End-Stage Liver Disease; RCS, restricted cubic spline.

Differences in the significance of size mismatch by MELD 3.0 or CIT group were analyzed: for SFSD, the risk increased with decreasing BSA across all groups (Figure 4). However, for LFSD, the risk increased with increasing BSA only in candidates with MELD 3.0 ≥ 35 or CIT ≥ 8 h. In candidates with MELD 3.0 < 35 or CIT < 8 h, the risk did not increase with increasing BSA. This discrepancy might be explained by the pathophysiology of early allograft dysfunction (EAD), which is more common in LFSD because of ischemic reperfusion injury triggered by portal hypoperfusion.[8] High MELD 3.0 or longer CIT is also associated with a higher risk of EAD,[8,25-30] suggesting that the risk of EAD in LFSD might vary between different MELD 3.0 or CIT groups. Future studies are needed to test this hypothesis, as it was not possible to evaluate the frequency of EAD in the UNOS database. Nevertheless, this finding is promising for patients with small BSA who have had fewer transplantation opportunities. Utilizing LFSD might be key to increasing transplant opportunities for these patients. On the other hand, SFSD was uniformly hazardous. The median donor height in the SFSD group was 162.0 cm, and median donor weight was 60.0 kg (Table 1). If these livers were preferentially allocated to patients with small BSA, the BSA index would not be small, and the graft would be NFSD. This approach would also benefit patients with small BSA, as BSA is known to be a major source of sex disparity in waitlist mortality.[31]

This study has several limitations. First, as a retrospective national registry study, there is inevitably some degree of variability in reporting between centers or regions. Additionally, the causes of graft loss/patient deaths had some missing values. Second, the three graft types in this study had several notable differences, such as donor and recipient gender and macrosteatosis. However, our results did not change after controlling for macrosteatosis, and the survival curve pattern was similar between different donor-recipient gender matches (Figure S4, SDC, http://links.lww.com/TXD/A708). Third, weight and BSA are overestimated in patients with ascites, and one might argue that the BSA index is not a uniformly trustworthy surrogate for graft size mismatch. However, the ascites-stratified analysis revealed a similar pattern of hazard in SFSD/LFSD between patients with moderate ascites or slight or no ascites (Figure S5, SDC, http://links.lww.com/TXD/A708). Additionally, the differences in GS rates between the SFSD group and other groups at 90 d and 5 y were small, so we do not intend to recommend entirely refraining from using SFSD. However, it is important to acknowledge the nearly 2% difference in 90-d outcomes observed in the national database of >50 000 LTs.

In conclusion, US national registry analysis showed that the negative impacts of donor-recipient size mismatch on survival outcomes are limited to within 1 y post-LT, with SFSD being hazardous in the first 90 d and LFSD in the 90-d to 1-y period. SFSD suffered from vascular complications in the first 90 d, whereas LFSD suffered from respiratory failure in the subsequent period until 1 y post-LT. Further, LFSD was only hazardous in cases with MELD 3.0 ≥ 35 or CIT ≥ 8 h. Although SFSD is generally safe to use, consideration

should be given to the minor decrease in 90-d survival rates. LFSD should be utilized more frequently by minimizing CIT to <8 h, especially in patients with MELD 3.0 < 35. Our findings could significantly enhance donor-recipient matching.

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