Original article

Outcomes of Living Donor Liver Transplant Recipients Receiving Grafts with the Graft-to-Recipient Weight Ratio less than 0.6%: A Matched Pair Analysis.

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Authorship

Hajime Matsushima, Akihiko Soyama, and Takanobu Hara conceptualized the idea and design of the study. Hajime Matsushima, Akihiko Soyama, Takanobu Hara, Yasuhiro Maruya, Takuro Fujita, Hajime Imamura, Tomohiko Adachi, Masaaki Hidaka, and Susumu Eguchi participated in data collection, analysis, and interpretation. Hajime Matsushima wrote the article. All authors participated in revising the article and approving the final draft.

Running title

Living donor liver transplantation with very small grafts

Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CNI, calcineurin inhibitor; EAD, early allograft dysfunction; GRWR, graft-to-recipient weight ratio; GV, graft volume; GW, graft weight; INR, international normalized ratio; iRHV, inferior right hepatic vein; MELD, Model for End-Stage Liver Disease; MHV, middle hepatic vein; LDLT, living donor liver transplantation; SFSS, small-for-size syndrome; SLV, standard liver volume

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ABSTRACT

We sometimes experience living donor liver transplantation (LDLT) involving very small grafts with graft-to-recipient weight ratio (GRWR) <0.6% when the actual graft size is smaller than predicted. The outcomes in this situation have not been fully investigated. The present study aimed to determine the graft outcomes of LDLT with GRWR <0.6%. We retrospectively reviewed 280 cases of adult LDLT performed at our institution between January 2000 and March 2021. In our institution, the lower limit for graft volume/standard liver volume ratio was 30%. The patients were divided into two groups according to the cutoff value of 0.6% for actual GRWR. Graft survival and surgical outcomes including small-for-size syndrome (SFSS) were compared between the groups using propensity score matching (PSM) analysis. Risk factors associated with SFSS in recipients with GRWR <0.6% were also evaluated. Fifty-nine patients received grafts with GRWR <0.6%. After PSM, similar graft survival rates were observed for GRWR <0.6% (n = 53) and GRWR ≥0.6% (n = 53) (P = 0.98). However, patients with GRWR <0.6% had a significantly worse 3-month graft survival rate (86.8% versus 98.1%, P = 0.03) and higher incidence of SFSS (P < 0.001) than patients with GRWR ≥0.6%. On multivariate analysis, Model for End-Stage Liver Disease score and donor age were associated with SFSS in patients with GRWR <0.6%. The same factors were also associated with graft survival. In conclusions, although similar overall graft survival rates were observed for LDLT with GRWR <0.6% and GRWR ≥0.6%, GRWR <0.6% was associated with an increased risk of SFSS. Appropriate donor and recipient selection is important for successful LDLT with very small grafts.

INTRODUCTION

Living donor liver transplantation (LDLT) has been developed worldwide as an alternative to deceased donor liver transplantation to overcome the shortage of cadaveric donor organs.[1] Living donor grafts are generally obtained from high-quality donors. However, small-for-size grafts with insufficient hepatic mass and vascular bed can have low synthetic and metabolic capacities and cause parenchymal injury through portal hyperperfusion, leading to the development of small-for-size syndrome (SFSS).[2,3] Nevertheless, because the use of small grafts potentially enhances donor safety and expands the donor pool, some transplant centers have attempted to use small grafts for LDLT.

Most transplant centers have arbitrary requirements for graft-to-recipient weight ratio (GRWR) ≥0.8% or graft weight/standard liver volume (GW/SLV) 30%–40%.[4-6] Because several studies revealed similar graft survival rates for LDLT using small grafts with GRWR <0.8% and larger grafts with GRWR ≥0.8%,[7-9] some transplant centers in Japan and the United States have set the minimal GRWR requirement to 0.6%.[10-12] At our institution, the preoperative graft volume (GV) estimated by 3D volume analysis is required to be >30% of SLV. However, there is a potential risk for overestimation of graft size prior to transplantation, resulting in the procured partial liver graft having a smaller volume than predicted. Consequently, some transplant centers, including our institution, have experienced LDLT using very small grafts with GRWR <0.6% by accident rather than by intent. Although several studies found inferior graft outcomes after LDLT using grafts with GRWR <0.6% compared with larger grafts with GRWR ≥0.6%,[9,13] the clinical evidence for this category remains unsatisfactory due to the limited experience of LDLT with very small grafts. In the present study, we report our findings for the outcomes of adult LDLT in the largest experience to date of LDLT involving very small grafts with GRWR <0.6%. We also investigated the risk factors for SFSS in our cohort.

PATIENTS AND METHODS

Study population and variables

The study analyzed data for adult LDLTs performed between January 2000 and March 2021 at Nagasaki University Hospital. The study was approved by the Ethics Committee of Nagasaki University Hospital (Approval no. 20012022-2) and conducted in accordance with the Declaration of Helsinki. Pediatric recipients and retransplant cases were excluded. Selected demographic and clinical variables were extracted from a prospectively maintained database. These variables included sex, age, body mass index (BMI), diagnosed liver diseases, Model for End-Stage Liver disease (MELD) score at the time of transplantation, Child–Pugh grade, medical condition at the time of transplantation, presence of portal vein thrombosis, comorbidities, donor age, ABO incompatibility, graft type, estimated GV, actual graft weight, GRWR, estimated GV/SLV, GW/SLV, and operative factors including operative time, blood loss, blood transfusion, warm and cold ischemia times, and splenectomy. SLV was calculated using the formula reported by Urata et al.[14] Graft weight was measured on the back table before graft implantation. GRWR was calculated using the actual weight of the graft and the recipient's body weight at the time of transplantation.

Graft selection, surgical procedure, and immunosuppression

Preoperative GV estimation and graft selection were performed as described previously.[15,16] We set the lower limit of GV/SLV at 30% and selected left lobe graft with middle hepatic vein (MHV) as our first choice. The predicted donor liver remnant volume was required to be >30% of the total donor liver volume. These criteria for donor selection did not vary over the study period. Since 2011, we have performed hybrid living donor surgery for both right and left hepatectomies.[17] In recipient surgery using a right lobe graft, which usually lacks the MHV,

the MHV was reconstructed if the drainage volume of segment 5 or 8 was expected to exceed 100 mL.[18-20] In cases with a right lobe graft that contained the inferior right hepatic vein (iRHV), the iRHV was reconstructed when its diameter exceeded 5 mm.[21] As we described previously,[22,23] splenectomy was indicated when the platelet count at the time of transplantation was <50,000 /μL due to hypersplenism. Because we started to perform splenectomy based on donor age, GV/SLV, and portal venous pressure after graft implantation in April 2021, splenectomy with intent to modulate the portal inflow was not performed during the study period.

Immunosuppression was standardized with calcineurin inhibitors (CNIs) as maintenance therapy. In cases with ABO incompatibility, the recipient received an anti-CD20 antibody (rituximab: 375 mg/m^2) at 14 days before transplantation. In patients who retained a high anti-ABO antibody titer (>64 times) after anti-CD20 antibody treatment, plasma exchange was additionally conducted. Mycophenolate mofetil was added to the standard maintenance protocol in ABO-incompatible cases and patients with impaired renal function for the sake of CNI-sparing.

Study groups and assessed outcomes

Because GRWR has been used worldwide for graft selection, we analyzed the associations between actual GRWR and graft outcomes, instead of using GW/SLV. A strong positive correlation was observed between actual GRWR and GW/SLV (Supplementary Figure 1). The patients were divided into two groups based on graft size: group S, containing cases with GRWR <0.6%, and group L, containing cases with GRWR ≥0.6%. The distributions of actual GRWR in the two groups are shown in Supplementary Figure 2. The main study outcomes were graft and patient survival rates. The incidence rates of early allograft dysfunction (EAD) and SFSS were also compared between the groups. Furthermore, because development of SFSS

was reported to increase the mortality rate at 3 months,[2,9,24] we compared the 3-month survival rates between group S and group L. To evaluate the degree of ischemia/reperfusion injury and early graft function, the serum levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and international normalized ratio (INR) within 7 days after transplantation were reviewed. EAD was defined as described previously.[25] SFSS was determined as described by Dahm et al.[26] and Soejima et al.[27] The risk factors for SFSS in recipients of small grafts with GRWR <0.6% were also examined.

Statistical analysis

Data for continuous variables were expressed as median and interquartile range (IQR), while data for categorical variables were expressed as number of cases and percentage. Differences in data for categorical variables were evaluated using the Pearson χ^2 test or Fisher exact probability test as appropriate. Differences in data for continuous variables were evaluated using the Wilcoxon rank sum test. Overall graft and patient survival rates were estimated using the Kaplan–Meier method and a log-rank test. Possible risk factors associated with overall graft survival, including GRWR, were analyzed using a multivariate Cox regression analysis. Because development of SFSS is of particular concern for LDLT with small grafts, the 3-month graft survival rates were also evaluated. For comparisons of the graft outcomes between group S and group L, a 1:1 propensity score matching model was built using a caliper of 0.20. The propensity scores were calculated based on recipient factors (age, BMI, MELD score, Child–Pugh grade, ABO incompatibility, medical condition at the time of transplantation, splenectomy during LT) and donor age. To identify risk factors for SFSS in LDLT with GRWR <0.6%, a multivariate regression analysis was performed. All statistical analyses were performed using JMP Pro version 16 software (SAS Institute Inc., Cary, NC). Values of $P < 0.05$ were considered to indicate statistical significance.

RESULTS

A total of 299 LDLTs were performed at Nagasaki University during the study period. Of these, 12 pediatric recipients (<18 years of age) and 7 retransplant cases were excluded, and the remaining 280 adult LDLTs were enrolled in the study. The actual GRWR (median, 0.78 [IQR, 0.64–0.95]; mean, 0.81 [SD, ±0.24]) was significantly smaller than the estimated GRWR (median, 0.86 [IQR, 0.71–1.04]; mean, 0.91 [SD, ±0.26]) ($P < 0.001$) (Figure 1A, B). The relationship between estimated GRWR and actual GRWR was linear ($r = 0.85$, $P < 0.001$) (Figure 1C). Of the 280 patients, 59 (21.1%) received small grafts with actual GRWR <0.6%. Risk factors associated with overall graft survival were analyzed using a Cox regression model (Supplementary Table 1). Recipient age, donor age, and intraoperative blood loss were identified as independent factors, while GRWR <0.6% was not associated with graft survival.

The demographic characteristics of the patients in group S (GRWR <0.6%, n = 59) and group L (GRWR ≥0.6%, n = 221) are summarized in Table 1. Before propensity score matching, the median BMI in group S was significantly higher than that in group L (26.3 kg/m^2 versus 22.6 kg/m^2, $P < 0.001$). In addition, the donor age in group S was significantly younger than that in group L (33 years versus 40 years, $P = 0.01$), and splenectomy was performed more frequently in group S than in group L (62.7% versus 38.5%, $P < 0.001$). The propensity score matching model selected 53 patients for each group. After propensity score matching, all variables except for graft type and graft weight were well balanced between the groups.

Graft and patient survival rates

Before propensity score matching, the overall graft survival rates in group S were 84.8% at 1 year, 76.1% at 3 years, and 65.9% at 5 years, and comparable to the rates of 79.6% at 1 year, 73.6% at 3 years, and 68.1% at 5 years in group L ($P = 0.68$) (Figure 2A). Similarly, the patient

survival rates in group S were 84.8% at 1 year, 77.8% at 3 years, and 69.8% at 5 years, and comparable to the rates of 81.5% at 1 year, 75.4% at 3 years, and 69.5% at 5 years in group L (P = 0.63) (Figure 2B). Moreover, the 3-month graft and patient survival rates did not differ significantly between the two groups (86.4% versus 88.2%, P = 0.75, and 86.4% versus 89.6%, P = 0.52, respectively) (Figure 2C, D). After propensity score matching, there were no significant differences in the overall graft and patient survival rates between the groups (Figure 3A, B). However, group S had significantly poorer 3-month graft and patient survival rates than group L (86.8% versus 98.1%, P = 0.03, and 86.8% versus 100%, P = 0.01, respectively) (Figure 3C, D).

Surgical complications and early graft function including EAD and SFSS

Surgical complications and early graft function, including EAD and SFSS, were compared in the matched cohort. Regarding surgical complications, there were no significant differences between the two groups (Table 2). The trends for AST, ALT, bilirubin, and INR are shown in Supplementary Figure 3. AST and ALT at postoperative day 7 were higher in group L than in group S, while bilirubin at postoperative day 4 was significantly higher in group S than in group L. Furthermore, INR at postoperative days 4 and 7 was significantly higher in group S than in group L. EAD was more frequently observed in group S compared with group L (45.3% versus 20.8%, P < 0.01) (Table 2). The incidence rates of SFSS defined by Dahm et al.[26] and Soejima et al.[27] were significantly higher in group S than in group L (20.8% versus 1.9%, P < 0.01, and 32.1% versus 13.2%, P = 0.02, respectively). The amounts of ascites at postoperative days 14 and 28 in group S were significantly higher than the amounts in group L (P < 0.001 and P < 0.01, respectively). The 90-day mortality rate was significantly higher in group S than in group L (13.2% versus 0%, P = 0.01).

Factors associated with SFSS after LDLT using grafts with GRWR <0.6%

Because patients who developed SFSS defined by Dahm et al.[26] or Soejima et al.[27] had inferior graft and patient survival rates compared with patients who did not develop SFSS (Supplementary Figure 4), we analyzed the risk factors for SFSS in recipients of grafts with GRWR <0.6%. Among the 59 patients, 25 patients developed SFSS as defined by Dahm et al. and/or Soejima et al. The demographic characteristics of the patients who did and did not develop SFSS are shown in Table 3. The median MELD score at the time of transplantation was significantly higher in patients who developed SFSS than in patients who did not (19 versus 14, $P < 0.01$). The donor age was also significantly higher in patients who developed SFSS than in patients who did not (40 years versus 33 years, $P = 0.03$). Finally, the intraoperative blood loss during surgery was significantly greater in patients who developed SFSS than in patients who did not (7,600 mL versus 3,970 mL, $P = 0.01$). On multivariate analysis, MELD score (hazard ratio [HR]: 3.55 per 10 increase, $P < 0.01$) and donor age (HR: 1.75 per 10-year increase, $P = 0.02$) were independently associated with development of SFSS (Table 4).

Graft survival according to MELD score and donor age in recipients of very small grafts with GRWR <0.6%

Because MELD score and donor age were found to be associated with SFSS, we further investigated the impacts of these factors on graft survival. A cut-off value for MELD score was determined using the HRs obtained in a Cox regression model (Supplementary Figure 5) as described previously.[28,29] Because the impacts of donor age on graft outcomes after LDLT have been extensively explored in a number of previous studies with larger cohorts, the cut-off value for donor age was set at 50 years by reference to these studies.[9,10,16,30-32] Recipients with MELD score ≥20 had poorer graft survival than recipients with MELD score <20 (Figure 4A).

The graft survival rate in recipients with donor age ≥50 years was inferior to that in recipients with donor age <50 years (Figure 4B). The combination of MELD score and donor age was employed to stratify the overall graft survival rates in recipients of very small grafts with GRWR <0.6% (Figure 4C). Recipients with MELD score <20 and donor age <50 years showed better graft survival (88.2% at 1 year, 88.2% at 3 years, and 81.3% at 5 years) than the recipients with MELD score ≥20 and donor age ≥50 years.

DISCUSSION

LDLT has become an established treatment for end-stage liver diseases, especially in countries facing severe deceased donor shortages. Owing to concerns regarding SFSS and compromised recipient outcomes, the majority of LDLT centers in North America are reluctant to use left lobe grafts, which are usually smaller than right lobe grafts.[33,34] However, because several studies revealed that use of left lobe grafts is safer for donors, several LDLT centers in Japan and the United States are currently utilizing grafts from the smaller left lobe with excellent recipient outcomes.[9,10,12,27] The threshold of GRWR has been a matter of debate for safe expansion of left lobe graft availability, and a lower limit of GRWR ≥0.8% has been used in most transplant centers in consideration of the increased risk of SFSS. However, recent studies showed that smaller grafts with GRWR <0.8% could be used safely, and some transplant centers consider that GRWR can be reduced to 0.6% with an appropriate donor-recipient pairings.[9,10,12,30,35] Although several studies reported inferior graft survival rates in LDLT with actual GRWR <0.6% compared with GRWR ≥0.6%,[9,36] the outcomes in this population have not been fully established due to the limited experience. Herein we have presented the largest series of adult LDLTs involving small grafts with actual GRWR <0.6%. We conducted a comparative study of the outcomes between recipients with GRWR <0.6% and GRWR ≥0.6% using a propensity score matching analysis and found similar overall graft and patient survival

rates. However, it should be noted that the incidence rates of EAD and SFSS were significantly higher in patients with GRWR <0.6%, and the 3-month graft survival rates in recipients with GRWR <0.6% were inferior to the rates in recipients with GRWR ≥0.6%. Further analyses revealed that increased MELD score and donor age were associated with the risk of SFSS and impaired graft survival.

In a recent report, accumulated evidence showed that transplantation outcomes were multifactorial and that graft size did not solely affect graft fate.[37] Ben-Haim et al.[38] reported their early experiences of LDLT with small grafts. They found that graft size did not affect the outcomes in patients with Child–Pugh class A, while small grafts were associated with unfavorable outcomes in more seriously ill patients with Child–Pugh class B or C.[38] These findings were confirmed by subsequent studies, in which the MELD score was used as a surrogate marker for disease severity. Ikegami et al.[39] reported that MELD score ≥19 was a high-risk factor for SFSS in LDLT with a left lobe graft. Other studies from Western countries found that MELD score, but not graft size, predicted the risk of SFSS,[7] and indicated that lowering of actual GRWR to 0.6% may be possible in patients with MELD score <20.[34] Consistent with these studies, the present study identified MELD score as a predictive factor for SFSS in cases with GRWR <0.6%. Because a sufficient GV is considered essential to meet the metabolic demands of ill patients, size-disease severity adjustment may be a key to achieving successful LDLT. Another important factor that determined the graft outcomes in our cohort was donor age. In LDLT with small-for-size grafts, satisfactory liver regeneration, particularly during the early phase after transplantation, is important to overcome graft dysfunction caused by SFSS. Previous studies revealed that aging reduces the capability for liver regeneration through gene signaling pathways.[40,41] Therefore, to minimize the risk of SFSS, use of grafts from older donors should be avoided, particularly in small-for-size grafts.

Despite the lack of relationship between GRWR and overall graft survival in the

present study, the propensity score matching analysis revealed that the 3-month graft survival rate was poorer for small grafts with GRWR <0.6% than for larger grafts with GRWR ≥0.6%. Meanwhile, the 1-year graft survival rate for GRWR <0.6% was 84.8%, which was similar to the rate for GRWR ≥0.6%.[9] A previous study in Hong Kong also demonstrated favorable graft survival in 39 patients with GRWR <0.6%, with a 1-year graft survival of 92.3%.[35] These outcomes may be attributable to the donor and recipient demographic characteristics. Indeed, the median donor age was 33 years for recipients with GRWR <0.6% in our cohort, and the median age was even younger in the Hong Kong study at 31 years. Furthermore, the MELD score was 15 in the present study, compared with 16.1 in the Hong Kong study. Meanwhile, an experienced LDLT center in North America reported the outcomes of 12 patients with actual GRWR <0.6%, which was smaller than predicted.[12] In that study, the outcomes were excellent, with a 1-year graft survival rate of 94%. Of note, all of the donors in that study were aged <50 years, and the median age was 35 years (range, 25–46 years). Furthermore, the MELD score was >20 in only two patients (16.7%). In another study, the Kyoto group reported that the 1-year graft survival rate for recipients with GRWR <0.6% was <70%.[9] However, that previous study included more seriously ill patients with a median MELD score of 20 and grafts from older donors with a median age 41 years compared with our 59 patients. Taken together, the present findings highlight the importance of appropriate donor-recipient selection for successful LDLT with very small grafts.

Another potential treatment strategy for optimizing graft outcomes is the use of portal inflow modulation. Surgical and pharmacological portal flow modulations are considered to mitigate the risk of SFSS.[10-12,42-45] However, the indications for use of portal inflow modulation remain controversial.[46] At our center, splenectomy was not performed with the aim of achieving portal inflow modulation based on portal pressure or flow measurements during the study period. However, splenectomy was performed in 62.7% of patients with

GRWR <0.6%, compared with 38.5% of patients with GRWR ≥0.6%, based on platelet count <50,000 /μL secondary to hypersplenism. Given that spleen size, as a surrogate for portal hypertension, is associated with portal hemodynamics,[47,48] the higher rates of splenectomy potentially contributed to the similar graft survival rates in patients with GRWR <0.6% and GRWR ≥0.6%. Since we changed our policy in April 2021 based on our previously published data,[16] splenectomy is indicated for patients with small-for-size grafts, taking disease severity, donor age, and portal vein pressure after reperfusion into consideration. Further studies to determine the effects of the new strategy on outcomes in this patient category are currently underway. It should be noted that optimal venous outflow is as important as inflow modulations.[12] Although the venous anatomy of right lobe grafts can vary widely due to absence of the MHV and presence of the iRHV, right lobe grafts did not increase the risk of SFSS in patients with GRWR <0.6% (Table 3). One possible explanation for this is that the MHV or iRHV was reconstructed in 3 of 6 recipients receiving a right lobe graft with GRWR <0.6% based on our policy. Unfortunately, one of these patients developed SFSS and died from sepsis within 3 months after transplantation, but the other two patients survived for >10 years without development of SFSS. Therefore, we believe that securing optimal venous outflow of with MHV or iRHV reconstruction is important for enhancing functional graft size, especially in small-for-size right lobe grafts.

The present study has several limitations. First, it was a retrospective study based on a single-center experience. Therefore, case-by-case bias potentially exists in the graft selection with consideration of various recipient and donor factors. As shown in Table 1, donor age was younger and splenectomy was performed more frequently for grafts with GRWR <0.6% than for grafts with GRWR ≥0.6%. Although the propensity score matching succeeded in eliminating such heterogeneities between the groups for comparison, a selection bias was possible. Second, precise data on graft hemodynamics, including portal flow volume and portal

vein pressure, were not available in the present study. Further studies are required to assess the effects of graft hemodynamics and portal inflow modulations on the outcomes of grafts with GRWR <0.6%. In addition, we focused on the actual GRWR based on previous studies.[7-13,35-37] Given that we did not intend to utilize small grafts with GRWR <0.6% in our policy, favorable outcomes of LDLT with GRWR <0.6% could be regarded as fortuitous. Therefore, our data do not necessarily encourage the use of smaller grafts. Considering that overestimation can occur during pretransplant evaluation of graft size, accurate estimation of graft size is particularly important to optimize graft outcomes as well as appropriate donor-recipient selection.

In conclusion, our results showed similar overall graft survival rates for very small grafts with GRWR <0.6% and larger grafts with GRWR ≥0.6%. However, short-term graft survival was poorer in recipients with GRWR <0.6% than in recipients with GRWR ≥0.6%, with an increased risk of EAD and SFSS. The use of small grafts with GRWR <0.6% should not be indicated for high-risk patients with MELD score ≥20 and donor age ≥50 years.

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FIGURE LEGENDS

Figure 1. (A, B) Distributions of estimated GRWR (A) and actual GRWR (B). (C) Relationship between estimated GRWR and actual GRWR.

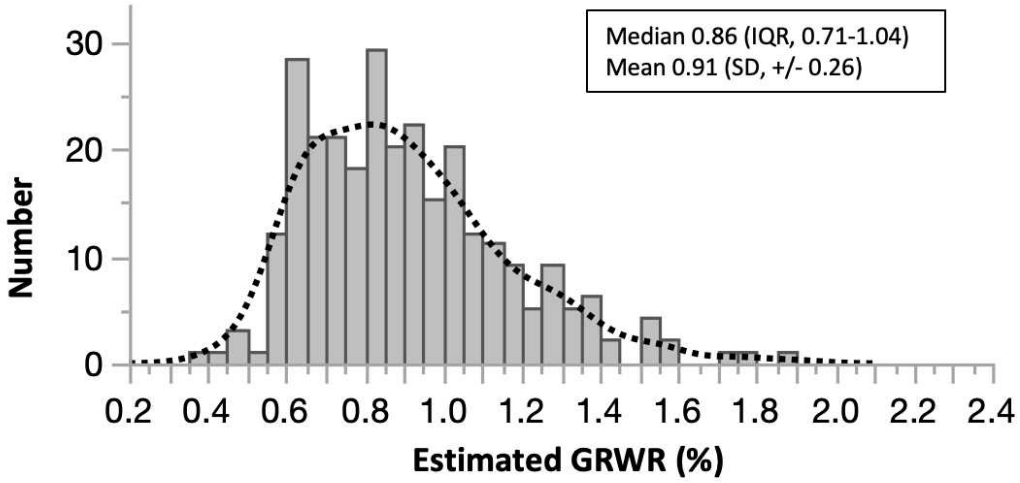
Figure 2. Kaplan–Meier curve analyses in group S and group L. In the entire cohort, there were no significant differences in the overall graft (A) and patient (B) survival rates between group S and group L ($P = 0.68$ and $P = 0.63$, respectively), and also no significant differences in the 3-month graft (C) and patient (D) survival rates between group S and group L ($P = 0.75$ and $P = 0.52$, respectively).

Figure 3. Kaplan–Meier curve analyses for group S and group L in the matched cohort. The overall graft (A) and patient (B) survival rates were comparable between group S and group L ($P = 0.98$ and $P = 0.88$, respectively), but the 3-month graft (C) and patient (D) survival rates in group S were significantly poorer than the rates in group L ($P = 0.03$ and $P < 0.01$, respectively).

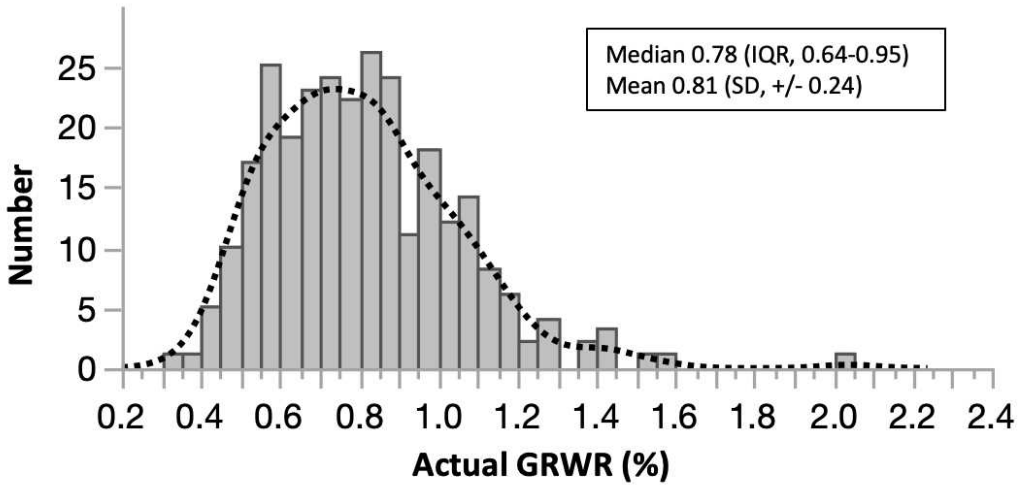
Figure 4. (A, B) Relationships between graft survival and MELD score (A) and donor age (B) in recipients of grafts with GRWR <0.6%. (C) Relationship between graft survival and the combination of MELD score and donor age.

Figure 1

A


Median 0.86 (IQR, 0.71-1.04)
Mean 0.91 (SD, +/- 0.26)
Number
30
20
10
0
0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4
Estimated GRWR (%)

B


Median 0.78 (IQR, 0.64-0.95)
Mean 0.81 (SD, +/- 0.24)
Number
25
20
15
10
5
0
0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4
Actual GRWR (%)

C

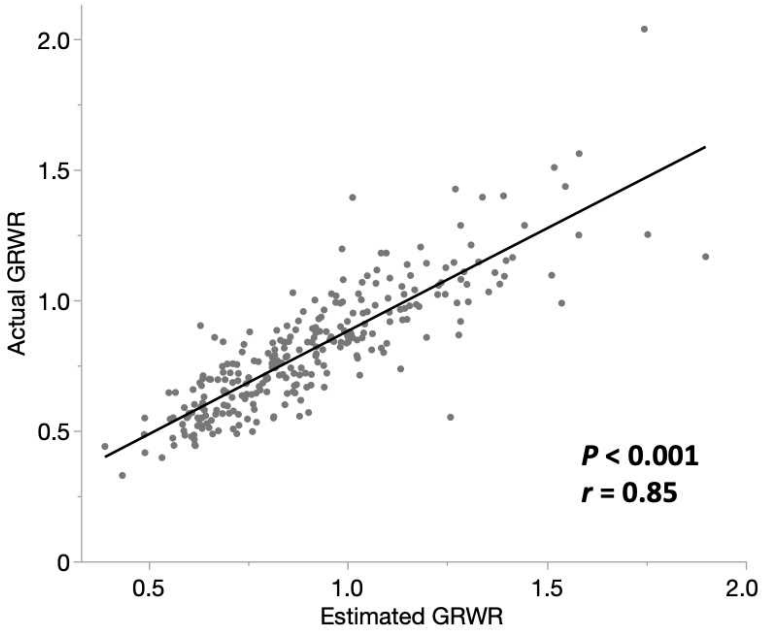

Actual GRWR
2.0
1.5
1.0
0.5
0
0.5 1.0 1.5 2.0
Estimated GRWR
P < 0.001
r = 0.85

Figure 2

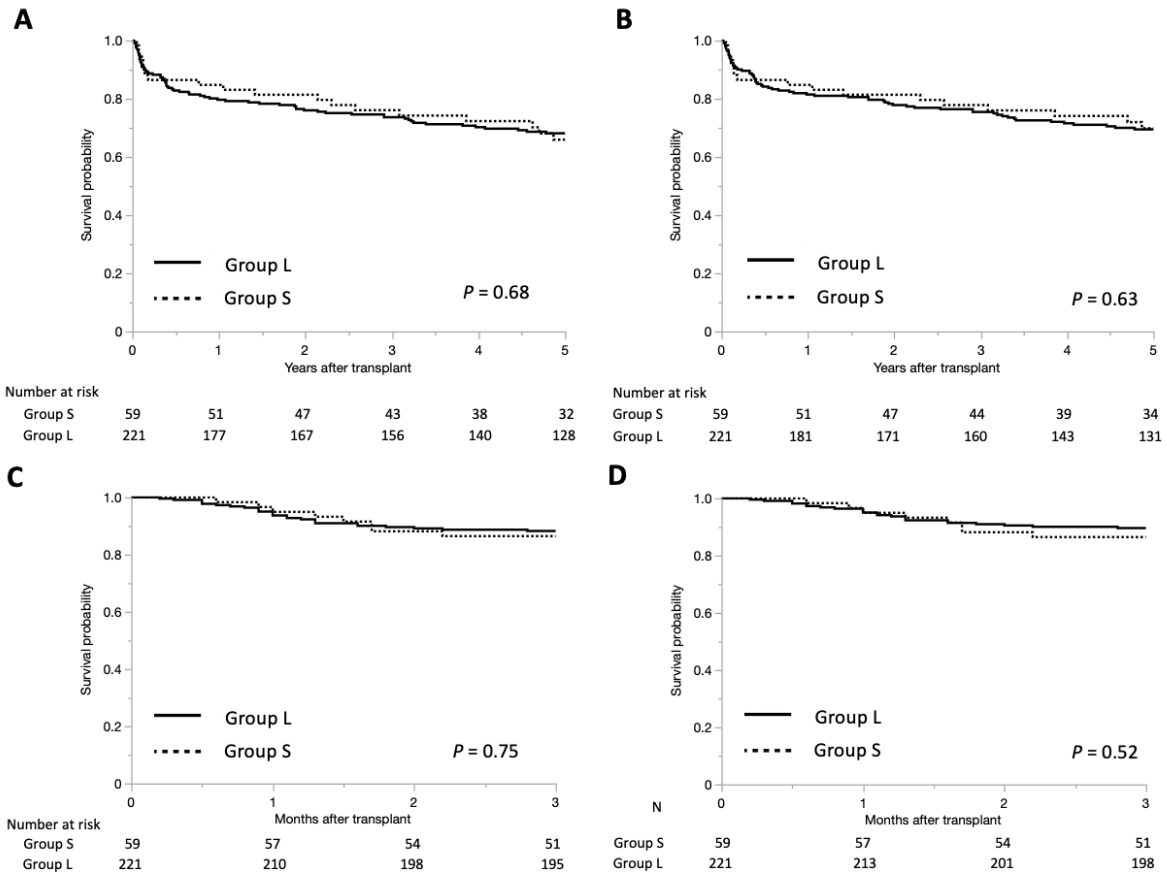

A
Survival probability
1.0
0.8
0.6
0.4
0.2
0
0
1
2
3
4
5
Years after transplant
Group L
Group S
P = 0.68
Number at risk
Group S 59 51 47 43 38 32
Group L 221 177 167 156 140 128
B
Survival probability
Years after transplant
Group L
Group S
P = 0.63
Number at risk
Group S 59 51 47 44 39 34
Group L 221 181 171 160 143 131
C
Survival probability
Months after transplant
Group L
Group S
P = 0.75
Number at risk
Group S 59 57 54 51
Group L 221 210 198 195
D
Survival probability
Months after transplant
Group L
Group S
P = 0.52
N
Group S 59 57 54 51
Group L 221 213 201 198

Figure 3

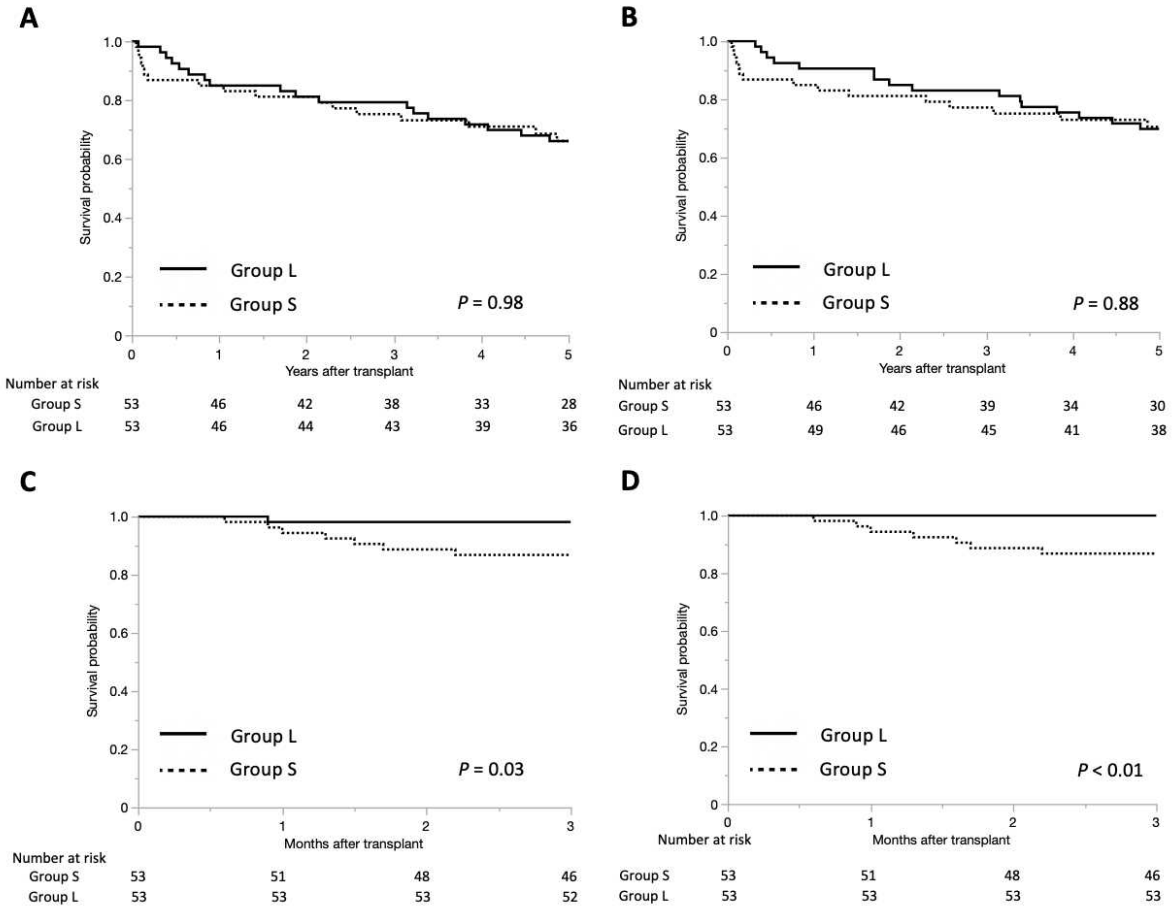
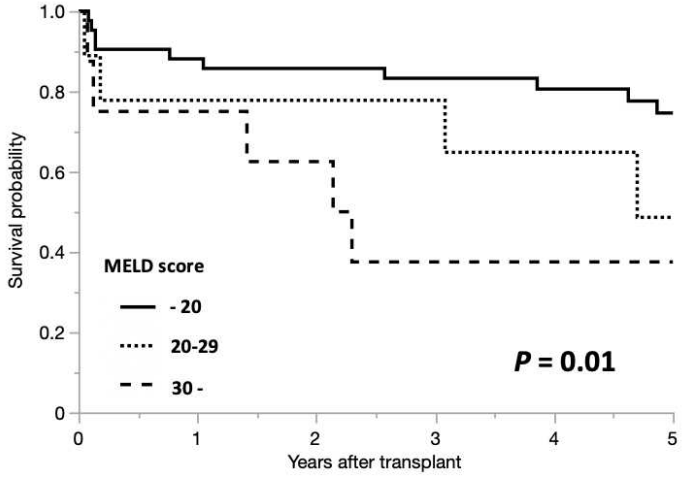
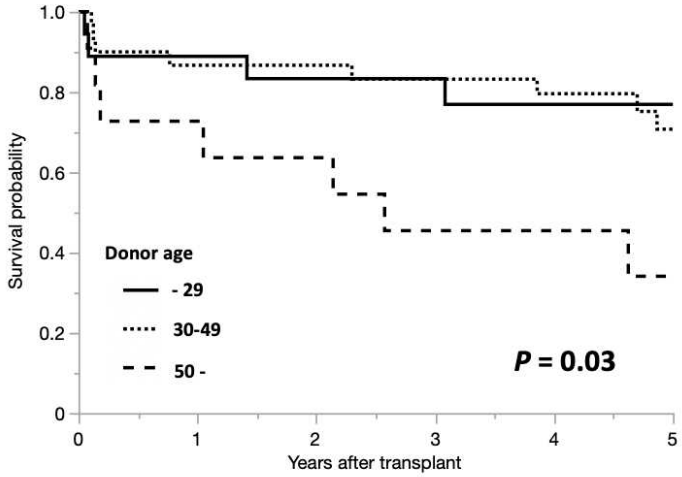

A
Survival probability
1.0
0.8
0.6
0.4
0.2
0
Group L
Group S
P = 0.98
0 1 2 3 4 5
Years after transplant
Number at risk
Group S 53 46 42 38 33 28
Group L 53 46 44 43 39 36
B
Survival probability
Group L
Group S
P = 0.88
Years after transplant
Number at risk
Group S 53 46 42 39 34 30
Group L 53 49 46 45 41 38
C
Survival probability
Group L
Group S
P = 0.03
0 1 2 3
Months after transplant
Number at risk
Group S 53 51 48 46
Group L 53 53 53 52
D
Survival probability
Group L
Group S
P < 0.01
Number at risk
Months after transplant
Group S 53 51 48 46
Group L 53 53 53 53

Figure 4

A


1.0
0.8
0.6
0.4
0.2
0
Survival probability
MELD score
- 20
20-29
30 -
P = 0.01
0
1
2
3
4
5
Years after transplant

B


1.0
0.8
0.6
0.4
0.2
0
Survival probability
Donor age
- 29
30-49
50 -
P = 0.03
0
1
2
3
4
5
Years after transplant

C

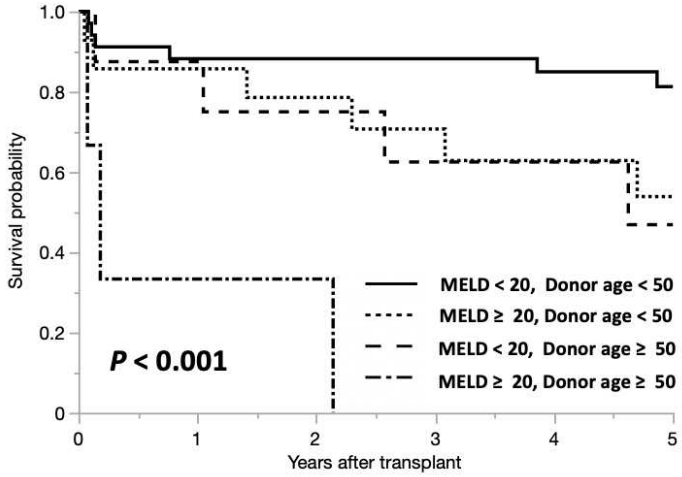

1.0
0.8
0.6
0.4
0.2
0
Survival probability
P < 0.001
MELD < 20, Donor age < 50
MELD ≥ 20, Donor age < 50
MELD < 20, Donor age ≥ 50
MELD ≥ 20, Donor age ≥ 50
0
1
2
3
4
5
Years after transplant

Table1. Patient characteristics according to GRWR

	Before matching			After matching		
	Group S **GRWR < 0.6% (n=59)**	**Group L** **GRWR ≥ 0.6% (n=221)**	***P***	**Group S** **GRWR < 0.6% (n=53)**	**Group L** **GRWR ≥ 0.6% (n=53)**	***P***
Recipient age, y	57 (50-63)	57 (52-62)	0.78	58 (50-65)	59 (53-64)	0.75
Sex, female	24 (40.7%)	96 (43.4%)	0.70	21 (39.6%)	24 (45.3%)	0.56
Body mass index	26.3 (24.4-27.9)	22.6 (20.8-25.5)	**< 0.001**	26.0 (23.9-27.3)	26.3 (23.5-29.7)	0.50
Diagnosis						
Hepatocellular carcinoma	29 (49.2%)	86 (38.9%)	0.16	27 (50.9%)	28 (52.8%)	0.85
Hepatitis B	12 (20.3%)	35 (15.8%)	0.41	9 (17.0%)	6 (11.3%)	0.40
Hepatitis C	26 (44.1%)	68 (30.8%)	0.06	23 (43.4%)	24 (45.3%)	0.85
PBC,PSC,AIH	7 (11.9%)	35 (15.8%)	0.45	7 (13.2%)	7 (13.2%)	1
Alcohol-related cirrhosis	6 (10.2%)	42 (19.0%)	0.11	5 (9.4%)	8 (15.1%)	0.37
NASH	9 (15.3%)	21 (9.5%)	0.20	9 (17.0%)	7 (13.2%)	0.59
Fulminant hepatic failure	2 (3.4%)	12 (5.4%)	0.74	2 (3.8%)	2 (3.8%)	1
MELD score	15 (13-22)	16 (12-23)	0.85	15 (13-20)	16 (11-20)	0.56
Child-pugh grade C	38 (64.4%)	134 (60.6%)	0.60	34 (64.2%)	29 (54.7%)	0.323
Pretransplant Medical condition, ICU	5 (8.5%)	22 (10.0%)	0.73	4 (7.6%)	2 (3.8%)	0.68
Portal vein thrombosis at the time of transplant	6 (10.2%)	26 (11.8%)	0.73	4 (7.6%)	7 (13.2%)	0.34
Comorbidity						
Hypertension	9 (15.3%)	32 (14.5%)	0.81	9 (17.0%)	9 (17.0%)	1
Diabetes mellitus	13 (22.0%)	68 (30.8%)	0.19	12 (22.6%)	16 (30.2%)	0.38
Donor age, y	33 (27-45)	40 (31-53)	**0.01**	33 (27-46)	36 (27-49)	0.76
ABO incompatibility	9 (15.3%)	41 (18.6%)	0.56	7 (13.2%)	9 (17.0%)	0.59
Graft type (left lobe)	53 (89.8%)	105 (47.5%)	**< 0.001**	48 (90.6%)	23 (43.4%)	**< 0.001**
GRWR, %	0.54 (0.49-0.56)	0.84 (0.72-0.99)	**< 0.001**	0.54 (0.49-0.56)	0.81 (0.68-0.97)	**< 0.001**
Graft weight, g	366 (328-414)	514 (423-620)	**< 0.001**	360 (321-408)	567 (483-650)	**< 0.001**
GW/SLV, %	29.5 (27.4-32.1)	44.5 (38.4-52.6)	**< 0.001**	28.8 (27.0-31.4)	45.5 (39.4-54.2)	**< 0.001**
Operation time, hr	13.4 (11.7-14.6)	13.5 (12.0-15.4)	0.51	13.3 (11.7-14.6)	13.5 (12.1-15.3)	0.28
Blood loss, mL	6343 (2930-9201)	6543 (3889-11500)	0.30	5684 (2865-9002)	6400 (4248-10790)	0.38
Transfusion						
Red blood cells, U	14 (4-26)	14 (6-27)	0.43	14 (5-25)	14 (4-24)	0.94
Fresh-frozen plasma, U	20 (5-30)	20 (8-30)	0.78	20 (0-30)	20 (5-28)	0.93

Platelets, U	20 (0-20)	20 (10-30)	0.30	20 (0-20)	20 (0-30)	0.66
Warm ischemia time, min	40.5 (35.8-48.3)	40 (36-48)	0.77	41 (36-48)	44 (37-51)	0.27
Cold ischemia time, min	102.5 (64.8-119.5)	100 (75-127)	0.85	101 (62-121)	111 (83-127)	0.41
Splenectomy	37 (62.7%)	85 (38.5%)	< **0.001**	31 (58.5%)	29 (54.7%)	0.70
Transplant era			0.12			0.49
2000-2004	1 (1.7%)	26 (11.8%)		1 (1.9%)	4 (7.6%)	
2005-2009	17 (28.8%)	56 (25.3%)		16 (30.2%)	17 (32.1%)	
2010-2015	25 (42.4%)	77 (34.8%)		21 (39.6%)	21 (39.6%)	
2016-2021	16 (27.1%)	62 (28.1)		15 (28.3%)	11 (20.8%)	

GRWR, graft-to-recipient weight ratio; NASH, nonalcoholic steatohepatitis; MELD, model for end-stage liver disease; GW, graft weight; SLV, standard liver volume

Table 2. Surgical outcomes according to GRWR

	Group S (n=53)	**Group L (n=53)**	***P***
Hepatic artery thrombosis	0 (0%)	2 (3.8%)	0.50
Portal vein thrombosis	7 (13.2%)	7 (13.2%)	1
Biliary complications	12 (22.6%)	9 (17.0%)	0.47
Acute cellular rejection	17 (32.1%)	20 (37.7%)	0.54
Clavien-Dindo complications (grade ≥ IIIb)	27 (51.9%)	26 (49.1%)	0.77
Early allograft dysfunction	24 (45.3%)	11 (20.8%)	< **0.01**
Small-for-size syndrome by Dahm et al.	11 (20.8%)	1 (1.9%)	< **0.01**
Small-for-size syndrome by Soejima et al.	17 (32.1%)	7 (13.2%)	**0.02**
Daily amount of ascites on day 14, mL	860 (129-2229)	0 (0-1085)	< **0.001**
Daily amount of ascites on day 28, mL	0 (0-830)	0 (0-0)	< **0.01**
Hospital stay, day	47 (37-72)	46 (37-68)	0.84
90-day mortality	7 (13.2%)	0 (0%)	**0.01**

GRWR, graft-to-recipient weight ratio

Table 3. Univariate analysis of factors assciated with SFSS in graft with GRWR<0.6%

	SFSS - (N=34)	SFSS + (N=25)	*P*
Recipient age, y	59 (52-65)	53 (44-62)	0.06
Body mass index	26 (25-28)	26 (24-29)	0.71
MELD score	14 (12-18)	19 (14-30)	**<0.01**
Child-pugh grade C	21 (61.8%)	17 (68.0%)	0.62
Pretransplant medical condition, ICU	1 (2.9%)	4 (16.0%)	0.15
Portal vein thrombosis at the time of transplant	4 (11.8%)	2 (8.0%)	1
Donor age, y	33 (24-36)	40 (30-54)	**0.03**
ABO incompatibility	5 (14.7%)	4 (16.0%)	1
Graft type (left lobe)	31 (91.2%)	22 (88.0%)	0.69
Operation time, hr	13.1 (11.6-14.1)	14.0 (12.8-15.6)	0.07
Blood loss, mL	3970 (2610-8212)	7600 (5115-16750)	**0.01**
Warm ischemia time, min	40 (36-48)	44 (35-50)	0.61
Cold ischemia time, min	94 (61-116)	110 (94-148)	0.05
Splenectomy	23 (67.7%)	14 (56.0%)	0.36

SFSS, small-for-size syndrome; GRWR, graft-to-recipient weight ratio; MELD, model for end-stage liver disease

ICU, intensive care unit

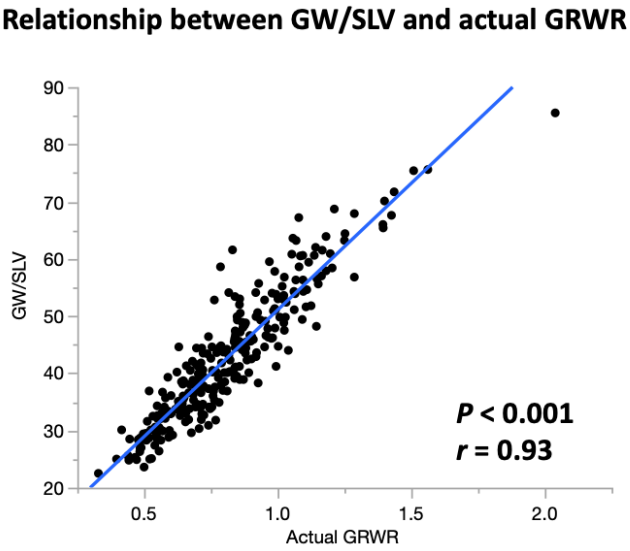
Table 4. Multivariate analysis of factors associated with SFSS in graft with GRWR<0.6%

Variables	OR (95% CI)	*P*
MELD score, per 10 increase	3.55 (1.28-9.85)	< 0.01
Donor age, per 10 years old increase	1.75 (1.07-2.86)	0.02
Blood loss, per 100 mL increase	1.01 (0.99-1.02)	0.249

SFSS, small-for-size syndrome; GRWR, graft-to-recipient weight ratio; OR, odd ratio

MELD, model for end-stage liver disease

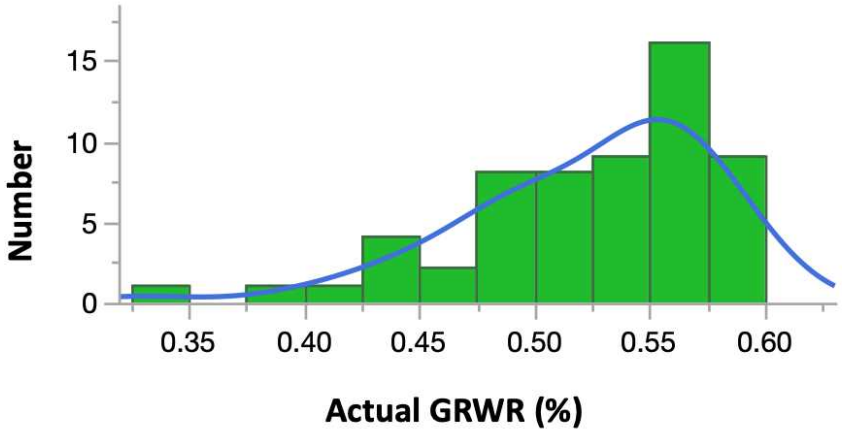
Supplementary figure 1



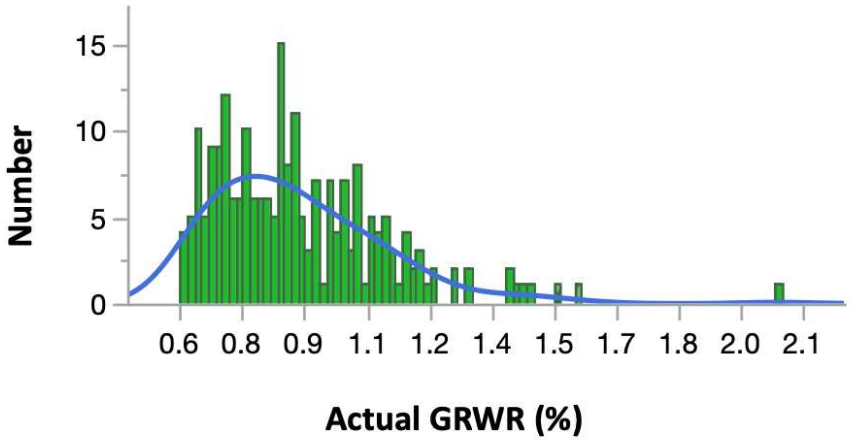
Supplementary figure 2

Distributions of GRWR for group S (A) and L (B)

A

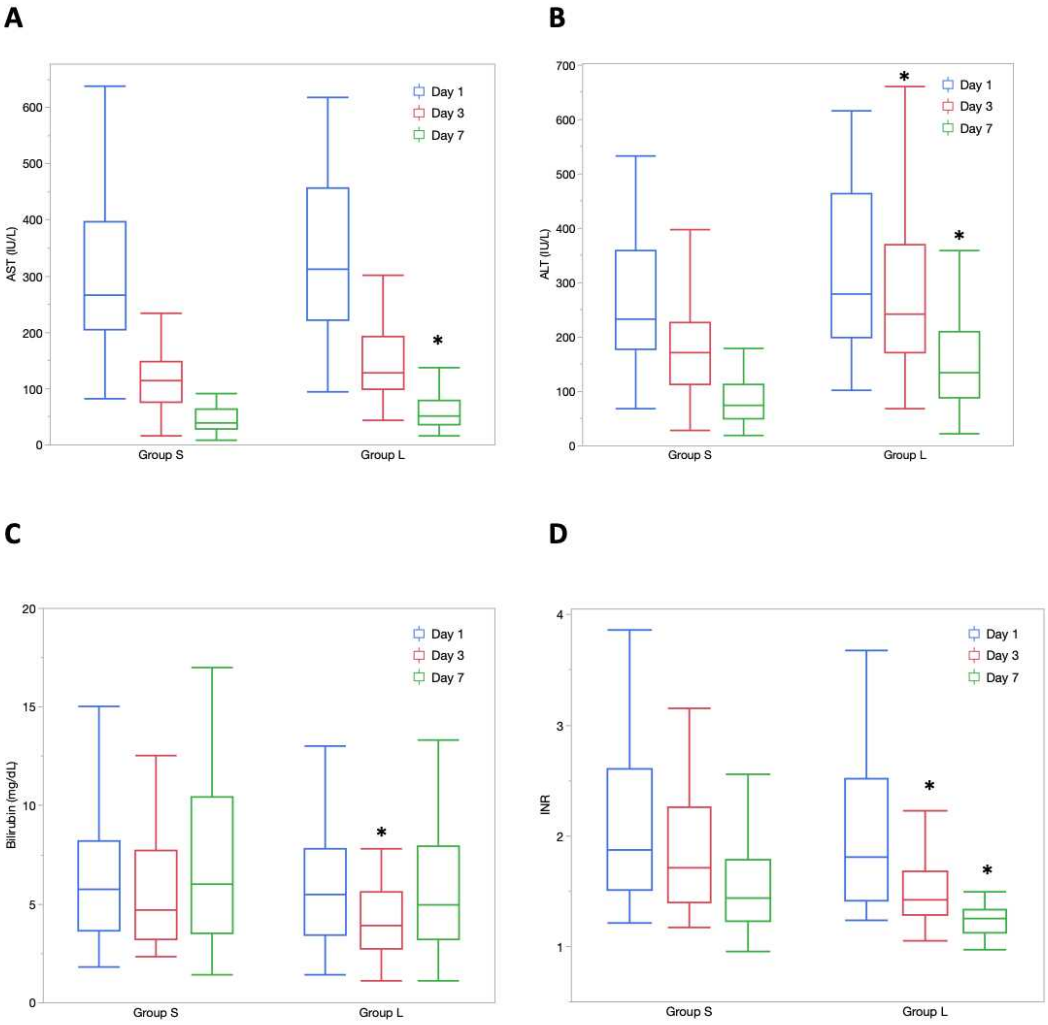


B



Supplementary figure 3

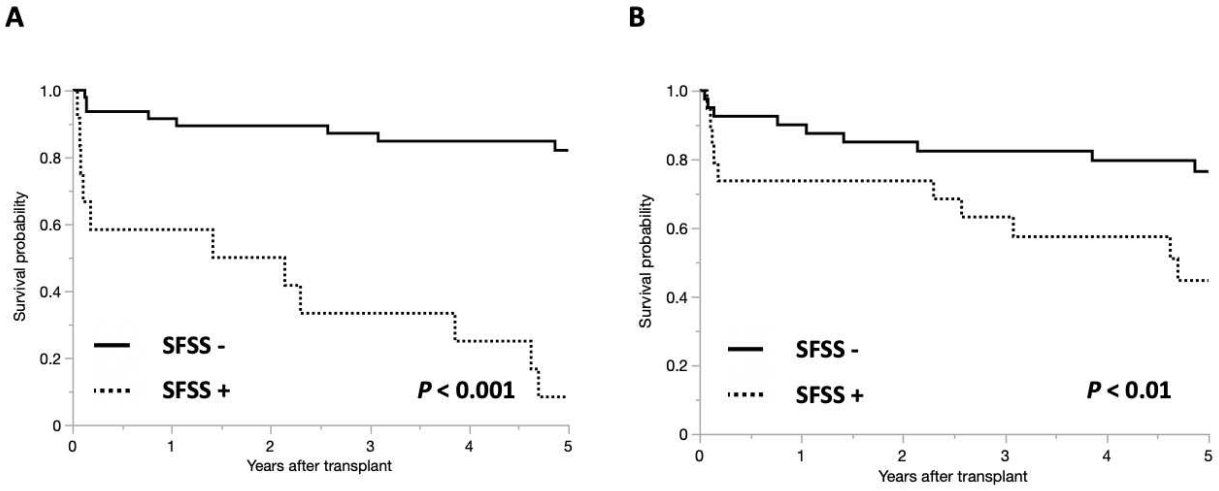
Biochemical recovery after LDLT including AST (A), ALT (B), bilirubin (C), and INR (D)



*: Differences between group S and L are significant ($P < 0.05$)

Supplementary figure 4

Graft survival according to the development of SFSS defined by Dahm et al (A) and Soejima et al (B)



Supplementary figure 5