

**Selective Splenectomy Centered on Graft-to-Spleen Volume Ratio is a Practical
Option in Living Donor Liver Transplantation to Prevent Early Allograft
Dysfunction: A Prospective Validation Study**

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Graphical Abstract

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Abstract

Background:

While simultaneous splenectomy (SPX) is an option in selected cases of living donor liver transplantation (LDLT) to protect graft function, graft-to-spleen volume ratio (GSVR) may serve as a new determinant of SPX. A prospective validation study was conducted to test our institutional strategy of SPX based mainly on GSVR, which has been employed since 2019.

Methods:

This prospective study enrolled 141 LDLT recipients from 2019 to 2024. The indication for SPX was $\text{GSVR} \leq 0.70$ and high-risk patients (ABO-incompatibility or donor age ≥ 45 years) with a final portal venous pressure $>15\text{mmHg}$. Surgical outcomes related to

graft function were evaluated and compared between the group with SPX (n = 51), the group without SPX (n = 90), and the historical control group without SPX despite GSVR of ≤ 0.70 (from 2007 to 2018, n = 33). The risk factors for early allograft dysfunction (EAD) in the modern era were also investigated.

Results:

Low GSVR indicated 88.2% (45 out of 51) of SPX in the prospective cohort. The historical group (no-SPX despite GSVR ≤ 0.70) showed an increased incidence of EAD with post-transplant thrombocytopenia, cholestasis, coagulopathy, and massive ascites. In contrast, these adverse events decreased significantly after introducing the new selective SPX protocol, with comparable results between the SPX and no-SPX groups in the prospective cohort. The Model for End-stage Liver Disease (MELD) score was the only indicator of EAD in the multivariable analysis after 2019.

Conclusions:

Selective SPX centered on GSVR is a feasible and practical option in LDLT to screen out high-risk recipients and improve their graft function for EAD prevention.

1 | Introduction

Simultaneous splenectomy (SPX) in liver transplantation (LT) is mainly performed in Asian countries where living donor LT (LDLT) is more common than deceased donor LT. The positive aspects of SPX include the prevention of portal hypertension (PHT) and small-for-size syndrome (SFSS)^{1,2}. On the other hand, it may negatively affect some surgical outcomes, such as operative time, blood loss, and portal vein thrombosis formation³. Therefore, due to accumulated evidence and concerns about complications, it is currently reserved for selected cases rather than all cases^{2,4,5}. In 2018, our group demonstrated that SPX for portal venous pressure (PVP) modulation is not necessarily required in all recipients and should be limited to grafts from either ABO-incompatible or older donors². In 2019, we also identified a low graft-to-spleen volume ratio (GSVR) ≤ 0.70 as a new indication for SPX, and an algorithm for SPX considering PVP and GSVR was proposed⁵.

Ever since its association with PHT was first reported⁶, few studies have been conducted to investigate the clinical impact of GSVR on post-LDLT outcomes other than PHT^{7,8}. In 2019, we clarified that spleen preservation with extremely low GSVR, that is, the imbalance between a small partial liver graft and a large spleen volume,

would lead to hypersplenism after LT. Hypersplenism may be associated with persistent post-LT thrombocytopenia, which may inhibit liver regeneration^{9,10}, and graft dysfunction represented by hyperbilirubinemia, coagulopathy, and massive ascites⁵. The concept of GSVR has made us aware of a previously unknown risk factor. In other words, if we focus only on PHT and graft size, there would be a population that cannot be saved with the conventional surgical indications for SPX.

As best practices need to be updated and existing evidence is derived only from retrospective analyses, the validity of selective SPX should be investigated in a prospectively accumulated cohort. The aims of this prospective study were 1) to summarize and review our 6-year experience with a new surgical strategy for simultaneous SPX in LDLT and 2) to elucidate the risk factors for LDLT in the modern era.

2 | Patients and methods

2.1 | Study population

The treatment algorithm and patient population are summarized in Figure 1.

Based on the evidence acquired from previous retrospective studies from our institution^{2,5}, SPX was limited to (i) cases with a GSVR ≤ 0.70 mL/mL and (ii) high-risk cases (ABO-incompatibility or donor age ≥ 45 years with post-reperfusion PVP > 15 mmHg (Figure 1A). The application of SPX for each recipient was determined preoperatively by GSVR and intraoperatively by PVP. As the new algorithm became effective in January 2019, data were prospectively collected from patients undergoing primary LDLT at Kyoto University Hospital from January 2019 to October 2024 (Figure 1B). Patients with prior SPX before LT ($n = 3$), SPX performed for splenic artery aneurysm ($n = 3$), abandoned SPX due to surgical difficulty ($n = 3$), and technical error with complicated anastomosis of the hepatic artery ($n = 1$) were excluded.

A historical cohort of primary LDLT recipients from January 2007 to December 2018 was used for comparison. Prior to 2018, SPX was performed for various reasons, including hepatitis C virus, blood group incompatibility, aneurysm, and PVP > 15 mmHg after reperfusion¹. Based on the objective of this study, only patients with both low GSVR and preserved spleen in the historical cohort were included in the analysis, as they would be the candidates for SPX according to the current algorithm. In

the end, we enrolled 141 recipients in the prospective cohort and 33 in the historical cohort.

2.2 | Study design

The patient groups analyzed in this study are also shown in Figure 1B. First, to confirm the feasibility of the current algorithm, post-LT outcomes, including graft function and surgical complications, were compared between patients without SPX (Group I, n = 90) and with SPX (Group II, n = 51) in the prospective cohort. Second, current risk factors for early allograft dysfunction (EAD) were evaluated in the prospective cohort (n = 141). Finally, the same variables were compared between patients with low GSVR and SPX in the prospective cohort (Group III, n = 45) and patients with no-SPX despite low GSVR (Group IV, n = 33) in the historical cohort.

All study protocols were approved by the Ethics Committee of Kyoto University (approval number: R1473-8), and all procedures were conducted in accordance with both the Declarations of Helsinki and Istanbul. This research received a waiver of informed consent.

2.3 | Evaluation of GSVR

GSVR was calculated by dividing the estimated graft volume in milliliters by the estimated spleen volume in milliliters before surgery. Three-dimensional graft and recipient spleen images were generated using SYNAPS VINCENT software (Fujifilm Medical Co. Ltd, Tokyo, Japan). All preoperative CT images were obtained within 1 month before LT.

Although we used the actual graft weight in grams in the previous retrospective analysis, we used the estimated graft volume here for the following reasons. First, they are compatible as the median ratio of the estimated graft volume (mL) to actual graft weight (g) was 1.01 (interquartile range (IQR), 0.95-1.06) in the prospective cohort. Second, the treatment plan can be discussed in advance and the operation can be performed seamlessly if the indications are decided before surgery.

2.4 | PVP measurement

An 18-gauge catheter was inserted through a small jejunal vein branch at the beginning of the surgery to monitor the PVP. The tip of the catheter was positioned in the recipient's portal vein. The PVP was monitored continuously and recorded at 3 time points: (1) at the time of catheter insertion (initial), (2) after portal venous reflow of the graft (reflow), and (3) at the end of the surgery (final). The catheter was removed prior to abdominal closure.

2.5 | The execution of SPX and shunt ligation

In general, SPX was performed when PVP decreased with the goal of reducing blood loss; during the anhepatic phase in cases with temporary portocaval shunts (TPCSs) and after reperfusion in cases without shunt creation. TPCS was considered when PVP after liver removal exceeded the initial PVP.

Ligation of portosystemic shunts was performed after graft implantation. Only large spontaneous portosystemic shunts, such as splenorenal shunts and gastric/esophageal varices (collateral vessels), if present, were ligated to prevent portal venous steal phenomenon after transplantation. If PVP was elevated >15 mmHg after shunt ligation, SPX was added in high-risk patients according to the SPX algorithm.

Although our institution reported the initial results of permanent hemi-portocaval shunt before ¹¹, the practice was suspended in 2009 due to unsatisfactory outcomes with difficulty in regulating the direction of venous flow.

No other interventions were performed to further modulate PVP, including splenic artery ligation (SAL) and pharmacological agents.

2.6 | Immunosuppression

Immunosuppressive regimens consisting of tacrolimus or cyclosporine and mycophenolate mofetil (MMF), in addition to low-dose steroids, were started within 24

hours of LDLT in all patients. ABO-incompatible recipients received rituximab more than 2 weeks prior to LT and MMF preoperatively ¹².

2.7 | Definitions

Bacterial infection was identified according to the Centers for Disease Control and Prevention's National Healthcare Safety Network surveillance definitions ¹³. A definition of EAD was based on postoperative day 7 laboratory values, determined as serum total serum bilirubin (T-Bil) greater than 10 mg/dL or international normalized ratio (INR) greater than 1.6 ^{14,15}. Early graft loss (EGL) was defined as re-LT or mortality during the first 90 days after LT.

2.8 | Statistical analysis

Continuous variables are presented as medians with ranges or IQRs where appropriate. Categorical variables are presented as numbers and percentages. Comparisons were made using the Mann-Whitney U test for continuous variables and the χ^2 test or Fisher exact test for categorical variables, as appropriate. The multivariable logistic regression model was used to analyze significant factors predicting EAD. Any variable with a *P* value <0.10 in univariable analysis was considered a candidate for multivariable analysis. Odds ratios (ORs) and 95%

confidence intervals (CIs) were calculated for each variable. Graft survival was estimated using the Kaplan-Meier method and compared using the log-rank test. To investigate the potential impact due to an unmeasured confounder in the comparison between prospective and historical cohorts, we calculated the E-value which represents the minimum strength of association required for an unmeasured confounder to explain away an estimated effect.¹⁶ A *P* value of <0.05 was considered statistically significant. SAS version 9.4 and JMP 18.0 (SAS Institute, Cary, NC) were used for all statistical analyses.

3 | Results

There were 77 males (54.6%) and 64 females (45.4%), and the median age was 54 years (range, 19-70). The median donor age was 46 years (range, 20-65). The causes of LDLT were as follows: autoimmune hepatitis (31.9%), alcoholic liver disease (24.8%), non-alcoholic steatohepatitis (NASH) (14.9%), hepatocellular carcinoma or cholangiocarcinoma (7.8%), biliary atresia (7.1%), viral hepatitis (2.8%), acute liver failure (4.3%), and other (6.4%). Concurrent SPX was performed in 51 patients (36.2%). The indications for SPX were GSVR (*n* = 45) and PHT (*n* = 6). Median follow-up was 27.5 months (range, 0.4-77.0).

3.1 | The feasibility of the new protocol for SPX in the prospective cohort

The results of the comparisons between Group I (no-SPX) and Group II (SPX) are shown in Table 1. The SPX group had more patients with autoimmune hepatitis ($P = 0.004$), indicating that chronic liver disease is prone to cause splenomegaly. Smaller graft-to-recipient weight ratio (GRWR) ($P = 0.004$), longer operative time ($P = .01$), and more operative blood loss ($P = 0.002$) were observed in the SPX group. Regarding outcomes, although SPX was associated with an increased incidence of splenic vein thrombosis (SPVT) ($P < .001$) and pancreatic fistula (PF) ($P = 0.005$), the incidence of other complications, including bacteremia, rejection, EAD, and EGL, were comparable. All SPVTs were well controlled with anticoagulation therapy. All PFs were successfully treated without reoperation. Temporal changes in PVP are shown in Figure 2. PVP decreased as the procedure progressed (Fig. 2A). The SPX group had higher initial ($P = 0.03$) and post-reflow PVP ($P = 0.001$) but comparable final PVP, because 68.6% (35/51) of the SPX were performed after reperfusion. We further divided the SPX group into 2 groups based on the timing of SPX: anhepatic phase ($n = 16$) or post-reperfusion ($n = 35$) (Fig. 2B). Some PVP data for PVP after SPX are missing because most SPX were performed for low GSVR, not for PHT. In the subgroup with SPX during the anhepatic phase, the PVP after SPX was very low due to TPCS. In the subgroup with

SPX after reperfusion, SPX could reduce the median PVP from 18 to 14 mmHg ($P = 0.006$). No differences in post-LT outcomes were observed according to the timing of SPX (Supplementary Table 1, <http://links.lww.com/LVT/A958>).

To follow the operative course in detail, the chronological changes of platelet count, T-Bil, alanine aminotransferase, and ascites in the first month after LT are shown in Figure 3A-E. While the platelet count increased significantly in the SPX group, no statistical differences existed between the changes in the other parameters in the first month after LT. Overall cumulative graft survival was also comparable by the group as follows: No-SPX, 97.7% and SPX, 100% at 1 year; No-SPX, 94.5% and SPX, 97.4% at 2 years ($P = 0.45$, Fig. 3F).

3.2 | Risk factor assessment for EAD in the prospective cohort

Background characteristics were compared based on the presence of EAD in the prospective cohort (Supplementary Table 2, <http://links.lww.com/LVT/A958>).

Patients who developed EAD had higher model for end-stage liver disease (MELD) scores ($P = 0.01$) and increased blood loss during LT ($P = 0.02$).

Twelve variables, including recipient and donor factors, were analyzed using logistic regression analysis (Table 2). While univariable analyses showed that MELD

score and GRWR were potential predictors of EAD, multivariable analyses identified MELD score as an independent predictor (OR 1.69, 95% CI 1.17-2.51; $P = 0.006$). The MELD score had an area under the curve of 0.734 and a cut-off score of 21 (sensitivity: 72.73%, specificity: 75.38%, data not shown) was suggested by receiver operating characteristic curve analysis to predict EAD. When this cohort was stratified according to MELD score with a threshold of 21, recipients with MELD score ≥ 21 had a significantly higher incidence of EAD (21.4% (6/28) vs. 4.4% (5/113), $P = 0.008$, Supplementary Fig. 1A, <http://links.lww.com/LVT/A958>). In these patients, delayed platelet count recovery and delayed decrease in T-bil were observed, possibly due to the higher baseline values of these parameters before LT (Supplementary Fig. 1B-F, <http://links.lww.com/LVT/A958>).

3.3 | The therapeutic effect of SPX on low GSVR based on comparison to the historical cohort

To focus on the impact of SPX on cases with low GSVR, 6 patients who underwent SPX for PHT in the prospective cohort were excluded from the analysis. The results of the comparisons between Group III (low GSVR with SPX in the prospective cohort) and Group IV (low GSVR without SPX in the historical cohort) are shown in

Supplementary Table 3, <http://links.lww.com/LVT/A958>. The historical cohort included more patients with viral hepatitis ($P = 0.01$), reflecting the transition of primary disease in LT over decades. Although other patient backgrounds were comparable, low GSVR without SPX was associated with an increased incidence of EAD (78.8% vs. 4.4%, $P < 0.001$; risk ratio 17.73, E-value = 34.95). Spleen preservation was also associated with adverse laboratory findings. While the platelet counts gradually increased in the SPX group after the first week post-LT, no recovery was observed in the no-SPX group for 1 month and it remained extremely low with a median value that never exceeded $100 \times 10^3/\text{mL}$ (Fig. 4A). The spleen-preserved group also had significantly higher INR, T-Bil, and amount of ascites immediately after LT, and the difference persisted for 1 month (Fig. 4B-E).

4 | Discussion

The efficacy of our new protocol of selective SPX was successfully validated, which can appropriately select high-risk patients and improve their outcomes. While the retrospective study demonstrated the potential risk of spleen preservation in low GSVR⁵, the current prospective study confirmed that SPX in low GSVR is a promising option to prevent EAD. Although the concept of GSVR may serve as a new standard in LDLT, several issues need to be discussed.

A scheme illustrating our concept of GSVR is shown in Figure 5A. We believe that two pathologies can be caused by an imbalance between a small graft and a large spleen immediately after LDLT: PHT and hypersplenism. A large part of both pathologies may overlap, but some cases would need individual evaluation. PVP modulation is performed to prevent SFSS, while GSVR-based SPX aims to treat hypersplenism (not PHT). Although the frequency of SPX for PHT in the current protocol is low (6 out of 51, 11.8%) compared to low GSVR (88.2%), patient selection based on GSVR alone may miss some patients who will have PHT and vice versa. By using both parameters, we do not want to leave any high-risk patient untreated.

We have constantly reviewed our practice and refined surgical strategies to improve LDLT outcomes, as summarized in Figure 5B. Since 2007, we have used SPX as a main portal inflow modulation in adult-to-adult LDLT¹. Our research in sarcopenia highlighted the frailty of LDLT recipients and led to adjustments in patient selection criteria. An outbreak of multidrug-resistant *Pseudomonas aeruginosa* in our hospital further necessitated these restrictions, leading to the implementation of a requirement that recipients must be ambulatory without assistance in 2013¹⁷. In 2016, we further developed the criteria by using 3 parameters of body composition: skeletal muscle mass, muscle quality, and visceral adiposity¹⁸. Candidates must have at least one parameter

within the normal range to undergo LDLT. Then, in 2019, we initiated a new protocol for SPX with GSVR and PVP for selected recipients based on retrospective analyses ^{2,5}. Thanks to these efforts, the outcome of primary LDLT at Kyoto University has improved significantly over the decades (Fig. 5C-D). Since EGL is no longer a major complication due to advances in LDLT nowadays (Fig. 5D), future clinical practice should focus on reducing EAD. The incidence of EAD has decreased over time but remains high at 17-32% in recent reports ¹⁹⁻²². Our current result of 9.3% (14 of 151 after 2019) is lower than these institutions (Fig. 5C). Although GSVR or SPX alone cannot guarantee the success of LDLT, screening out patients with low GSVR may have great potential to reduce the incidence of EAD at these other institutions.

Recipients with low GSVR are at significant risk for EAD (Fig. 5C). They consistently developed it more frequently than the overall population (Era 1: 36.4% vs. 56.3%, Era 2: 29.8% vs. 47.8%). While the change in the incidence of EAD between Era 1 and Era 2 (after the introduction of the sarcopenia criteria) was not pronounced, the decrease after the introduction of GSVR in 2019 was significant not only in the whole population ($P < 0.001$), but also in the population with low GSVR ($P < 0.001$). In particular, the rate in the population with low GSVR became comparable to that in the whole population in Era 3 (9.3% vs. 10.4%). These facts suggest that the conventional

protocol for SPX and body composition assessment failed to screen out some high-risk patients, i.e. low GSVR without PHT. At the same time, it indicates that the current protocol is more sophisticated with GSVR as a key factor. Therefore, we strongly recommend the measurement of GSVR in centers performing LDLT. Since the frequency of encountering recipients with low GSVR <0.70 would be around 30%, this means that a significant number of patients are at potential risk of developing EAD due to this pathology.

Another finding also supports the validity of our GSVR-based protocol.

Although excluded from the study population, there were 3 cases in which SPX was abandoned due to high surgical difficulty (severe adhesion or inflammation), although SPX was indicated for low GSVR during the prospective study period (Fig. 1).

Surprisingly, all patients developed EAD (Table 3). Although one case of antibody-mediated rejection (AMR) was included, we cannot draw any conclusions about the causality between SPX and AMR in the present study because the incidence of AMR is very low (1.9% (10/539) overall and 7.8% (10/128) in the ABO incompatible subgroup after 2008). It is difficult to speak of a "what if" scenario because GSVR is not the only determinant, but the possibility that SPX would have protected graft function cannot be excluded.

One of the important roles that SPX plays in the treatment of low GSVR is the prevention of thrombocytopenia caused by hypersplenism, which has been reported to be an important predictor of graft function in LT with a cut-off of 50,000 to 60,000/ μ L on day 5^{23,24}. Platelet counts typically reach a nadir between day 5 and day 7 post-LT due to increased consumption but return to preoperative levels by day 14^{5,24,25}. While the recipients with normal GSVR had an elevated median platelet count exceeding 100,000/ μ L by day 14 (Fig. 2A), the value did not change from the pre-LT levels or exceed 100,000/ μ L for more than 1 month in recipients with low GSVR and preserved spleen (Fig. 3A). Consistent with thrombocytopenia, other adverse events also persisted including cholestasis, coagulopathy, and ascites (Fig. 3B-3E). In contrast, the low GSVR with SPX group showed a steady increase in platelet counts and a reduction in these adverse events.

GSVR can coexist with GRWR instead of replacing it because they represent different pathologies: the risk of hypersplenism and SFSS, respectively. Currently, we use GRWR only to determine graft size and try to keep it above 0.6. While recent evidence shows that cases with GRWR <0.80 have acceptable outcomes²⁶, smaller grafts should be used with caution as many centers select younger donors or apply PVP modulation for these small grafts²⁷⁻²⁹. Indeed, GRWR<0.70 showed an increased

incidence of EAD (18.2% (4/22) vs. 5.9% (7/119), $P = 0.07$) after 2019 in our cohort (Supplementary Figure 2, <http://links.lww.com/LVT/A958>). In the future, along with low GSVR, we must continue to explore an optimal intervention to improve the function of ultra-low GRWR grafts.

The surgical risks of SPX cannot be ignored as an increased incidence of complications was observed, including blood loss, SPVT, and PF. Other groups have reported similar findings^{3,4}. At our institution, SPX is performed using a vessel sealing device for dissection around the spleen and a vascular stapler for the splenic hilum when portal pressure is decreased to reduce blood loss (during the anhepatic phase with TPCS or after reperfusion). Blood loss remains high even with these efforts, but few recent publications in the field of LDLT show that operative blood loss is a risk for EAD or graft loss. As for PF, while the incidence rate was 9.8%, we didn't see any serious complications such as aneurysms or reoperations. Transgastric drainage is now available and management is becoming less invasive and safer. Finally, SPVT is difficult to prevent. The median time to diagnosis of SPVT in our prospective cohort was 9 days (interquartile range, 7-14). A review article including all types of SPX procedures shows similar results with 8-12 days³⁰. We believe that the etiology of SPVT after SPX in LDLT is not thrombocytosis, as platelet counts are usually very low

in the first 2 weeks after surgery⁵. Rather, blood stasis or the surgical manipulation itself may play a more important role. Thus, close follow-up is required for SPVT so that it does not extend to the portal vein. To sum up, whereas these complications are treatable, we must be prepared to manage them appropriately.

Because untreated splenomegaly can not only cause PHT and thrombocytopenia immediately after LT but also persist long-term and even cause fibrosis³¹, we consider SPX the most radical solution. However, the utility of less invasive alternatives needs to be discussed. First and foremost, we are in no way forcing SPX on other transplant surgeons. If centers performing LDLT are not comfortable with it, they can adjust the GSVR above 0.70 by selecting larger grafts. GSVR could serve as an index not only for SPX, but also for graft selection as well as GRWR. Second, other surgical interventions, such as SAL or splenic embolization, can also be applied.

Although the effect of SAL on PVP will persist for at least 2 weeks³², its effect on platelet levels, which is our focus here, has not been demonstrated; the extent to which SAL has a therapeutic effect on persistent hypersplenism after LT remains unclear.

Besides, a recent randomized control trial showed that SAL aimed at PVP reduction didn't reduce the rate of EAD in adult LDLT³³, which discourages us from using it as an alternative. Regarding post-LT splenic artery embolization, which is a treatment

option for refractory thrombocytopenia and ascites after LDLT, there is a risk of leaving patients who are known to be at high risk of developing EAD without pretreatment. If a patient has refractory thrombocytopenia or ascites requiring additional embolization, he or she probably already has EAD, and we find it ethically difficult to prioritize avoiding surgical complications over EAD prevention. Third, pharmacological therapy would be another option. Somatostatin (continuous infusion)³⁴ and prostaglandin E1 (intraportal infusion)³⁵ are candidates, but the evidence to date is for inflow modulation, and its efficacy is unknown because it has not been used for the purpose of preventing thrombocytopenia due to hypersplenism. Overall, the current level of evidence is not strong enough for us to pursue any technique other than SPX at this time. However, considering the fact that patients who could not be splenectomized for technical reasons despite low GSVR developed EAD without intervention (Table 3), we think it is reasonable to introduce the alternatives in these patients first to study their effects in a prospective way. Our point is that patients with low GSVR should not be left untreated.

We acknowledge several limitations of this study. First, using the historical cohort as a comparison in a prospective study is not typical. We intended to highlight the risk patients with low GSVR possess when the spleen is preserved and the benefits SPX will bring, as these specific adverse events have diminished since 2019. Although

patient characteristics did not differ except for some comorbidities (Supplementary Table 3, <http://links.lww.com/LVT/A958>) and E-value is relatively high, unmeasured confounding cannot be excluded during the evolution of LT over the years. Therefore, the analyses should be interpreted with caution. Second, this study missed the opportunity to measure platelet-derived factors, such as platelet-derived growth factor and vascular endothelial growth factor, to support the theory that platelets contribute to liver regeneration. Instead, we tried to find a suitable rodent model of severe splenomegaly plus thrombocytopenia, but splenic vein ligation or long-term administration of CCl₄ was not sufficient to mimic this clinical situation because of its mild degree of splenomegaly^{36,37}. Further efforts are needed to prove the underlying mechanism. Finally, the cut-off value of 0.70 may not be absolute. Although we set this threshold based on the first quartile of the overall distribution in 349 patients in the previous study⁵, there is no other working definition of GSVR in the clinical setting, except for a recent study that found a cut-off of around 1.00 in pediatric LDLT to be appropriate for predicting PHT, impaired graft function, and poor graft survival⁸. As this was a single-institution experience, the efficacy of our practice needs to be verified by external cohorts. As more research is done on this topic, optimal cut-off values may be found, just as the threshold for GSVR is getting lower and lower^{26,38}.

To date, various prognostic factors have been reported in LDLT, such as sarcopenia, old donor age, low platelet count, and high PVP^{2,18,24,39,40}. Our continuous efforts show that we are on the right track to overcome these difficulties with our surgical strategy as shown in Figure 5B. With the current LT and SPX indications, previously known risk factors are no longer relevant and only a very basic parameter, the MELD score, has been identified as an indicator of EAD. This result is reasonable because T-bil and INR levels are criteria for EAD as well as components of the MELD score. Patients with higher MELD scores often have more severe cholestasis and coagulopathy before LT, which may persist or take longer to resolve after LT. This would mean that perioperative treatment strategies are already being established in LDLT and more focus should be placed on expanding the donor pool. Our country has a chronic shortage of living donors, and candidates inevitably spend long on the waiting list until their general condition deteriorates. There are still many problems to be solved, but it is necessary to change the indications so that LT can be performed earlier while the general condition is maintained.

In conclusion, GSVR-centered selective SPX is a feasible and practical option in LDLT that improves graft function in high-risk recipients. There is no doubt that low GSVR is closely related to EAD, which should be addressed. We sincerely hope that as

this indicator becomes more widespread and research on this topic continues, surgical strategies in the LT field will be further revised.

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ACCEPTED

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Figure 1Outline of the current study.

(A) Indication of SPX in Kyoto University since 2019.

* The low-risk group includes grafts from both ABO-compatible/identical donors and young donors aged <45 years, and the high-risk group includes grafts from either ABO-incompatible donors or older donors aged ≥45 years.

(B) Patient population flow diagram.

LT, liver transplantation ; GSVR, graft-to-spleen volume ratio; PVP, portal venous pressure; SPX, splenectomy

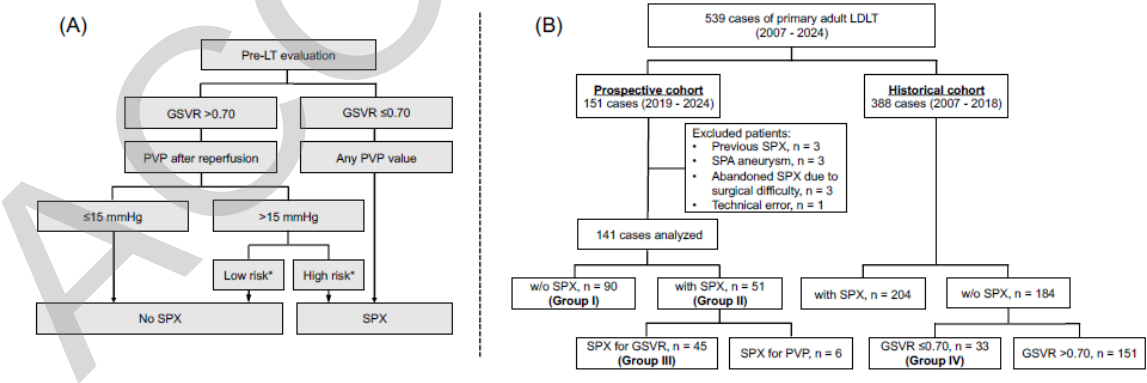


Figure 2Time-series changes in the portal venous pressure

(A) According to whether SPX was performed (n = 141)

(B) According to the timing of SPX (n = 51)

$P < 0.05$

SPX, splenectomy

¹ After SPX in the anhepatic phase

² After SPX after reperfusion

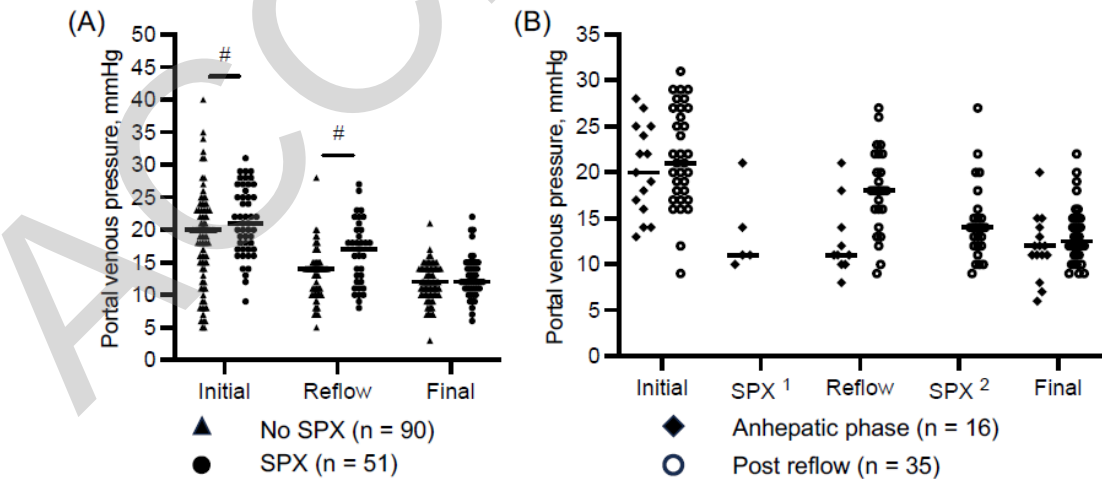


Figure 3 Outcomes are comparable between the SPX and no-SPX groups in the prospective cohort.

(A) Platelet counts

(B) International normalized ratio

(C) Alanine aminotransferase

(D) Total bilirubin

(E) Ascites

(F) Graft survival according to the execution of SPX

$P < 0.05$

SPX, splenectomy

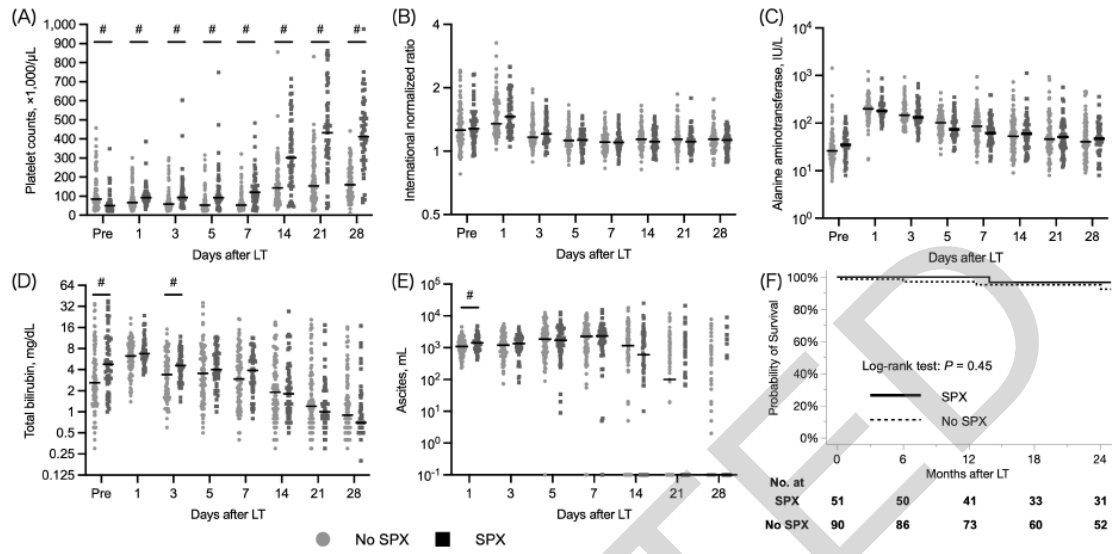


Figure 4 Outcomes in patients with low GSVR and preserved spleen in the historical cohort are worse than those with low GSVR and SPX in the prospective cohort.

(A) Platelet counts

(B) International normalized ratio

(C) Alanine aminotransferase

(D) Total bilirubin

(E) Ascites

$P < 0.05$

SPX, splenectomy

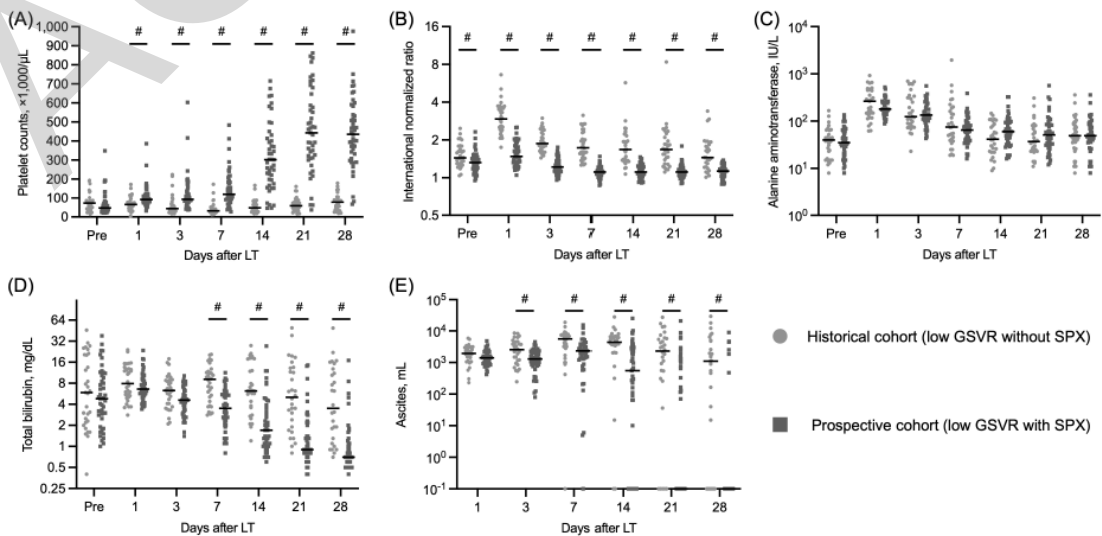


Figure 5 The history of strategical modification in LDLT at Kyoto University.

(A) Concept of GSVR

(B) Changes in treatment strategies

(C) Changes in the frequency of EAD in primary LDLT

(D) Changes in the frequency of EGL in primary LDLT

* The high-risk group includes grafts from either ABO-incompatible donors or older donors aged ≥ 45 years.

** Candidates must have at least one parameter within the normal range to undergo LDLT. The cut-off value for each body composition is as follows: low SMI: $< 40.31 \text{ cm}^2/\text{m}^2$ for men and $< 30.88 \text{ cm}^2/\text{m}^2$ for women, high IMAC > -0.358 for men and > -0.229 for women, and high VSR: > 1.325 for men and > 0.710 for women.

GSVR, graft-to-spleen volume ratio; PHT, portal hypertension; PVP, portal venous pressure; SPX, splenectomy; LDLT, living donor liver transplantation; SMI, skeletal mass index; IMAC, intramuscular adipose tissue content; VSR, visceral to subcutaneous adipose tissue area ratio; EAD, early allograft dysfunction; EGL, early graft loss

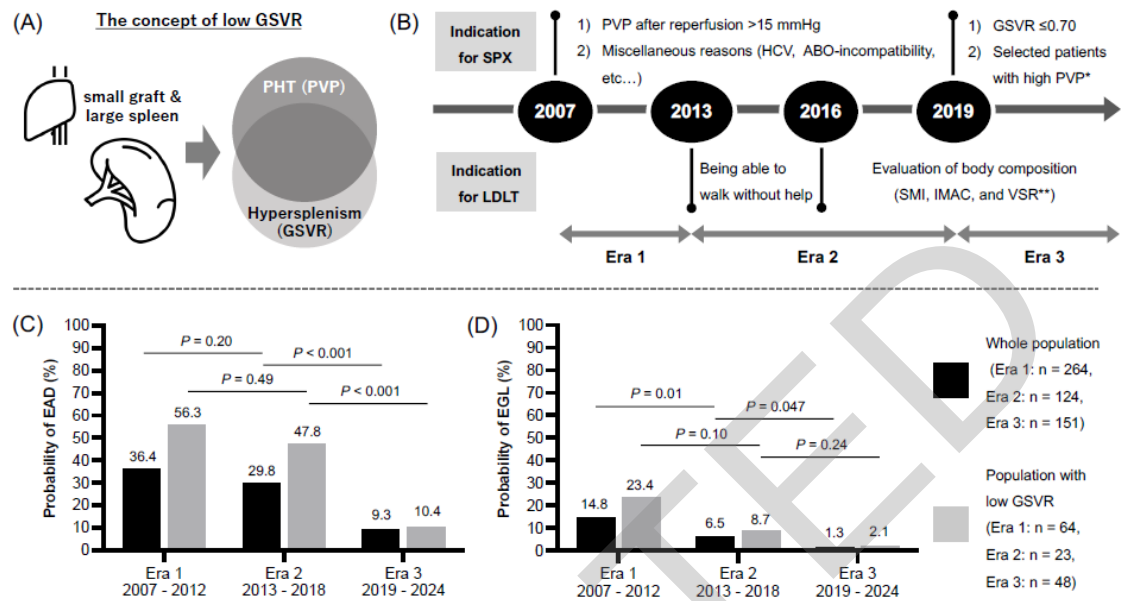


Table 1

Clinical characteristics of recipients, donors, and posttransplant outcomes in the prospective cohort (2019-2024)

Variables	Total n = 141	No-SPX group n = 90	SPX group n = 51	<i>P</i> value
Recipient factors				
Age, y	54 (42-60)	56 (45-62)	54 (40-59)	0.06
Female	64 (45.4)	43 (47.8)	21 (41.2)	0.45
Liver disease				0.00
AIH/PBC/PSC	45 (31.9)	21 (23.3)	24 (47.1)	4
Alcoholic	35 (24.8)	24 (26.7)	11 (21.6)	0.50
NASH	21 (14.9)	14 (15.6)	7 (13.7)	0.77
Cancer ^a	11 (7.8)	10 (11.1)	1 (2.0)	0.06
Biliary atresia ^a	10 (7.1)	5 (5.6)	5 (9.8)	0.50
Hepatitis B/C ^a	4 (2.8)	3 (3.3)	1 (2.0)	1.00
Acute liver failure ^a	6 (4.3)	6 (6.7)	0 (0)	0.09
Others ^a	9 (6.4)	7 (7.8)	2 (3.9)	0.49
Child-Pugh C	87 (61.7)	56 (62.2)	31 (60.8)	0.87
MELD score	14 (10-19)	13 (10-19)	14 (10-20)	0.32
Spleen volume, mL	593 (318-805)	383 (217-599)	843 (676-1126)	1
GSVR	1.08 (0.63-2.02)	1.58 (1.10-2.86)	0.58 (0.49-0.69)	<.001
Donor factors				
Age, y	55 (34-55)	46 (34-54)	49 (33-56)	0.40
Right lobe graft	84 (59.6)	59 (65.6)	25 (49.0)	0.06
Graft weight, g	585 (430-665)	597 (436-685)	570 (420-635)	0.09
GRWR, %	0.89 (0.75-1.05)	0.95 (0.75-1.09)	0.82 (0.73-0.92)	0.004
ABO incompatibility	26 (18.4)	16 (17.8)	10 (19.6)	0.79
Surgical factors				
Operation time, min	722 (640-865)	705 (638-823)	768 (677-932)	0.01
CIT, min	82 (54-117)	80 (53-113)	94 (60-125)	0.13
WIT, min	35 (29-46)	35 (29-44)	37 (31-46)	0.21
Blood loss, mL	4704 (2430-	4008 (1941-	5670 (3000-	0.00

	7150)	6148)	10600)	2
Initial PVP, mmHg	20 (16-24)	20 (14-23)	21 (17-25)	0.03
Post-reperfusion PVP, mmHg	14 (11-17)	14 (10-15)	17 (12-20)	0.00
Final PVP, mmHg	12 (10-14)	12 (10-14)	12 (11-15)	1
Operative outcomes				0.12
Splenic vein Thrombosis	13 (9.2)	0 (0)	13 (25.5)	<.001
Portal vein thrombosis ^a	3 (2.1)	1 (1.1)	2 (3.9)	0.30
Pancreatic fistula ^a	5 (3.5)	0 (0)	5 (9.8)	0.00
Biliary leakage ^a	11 (7.8)	7 (7.8)	4 (7.8)	5
Bacteremia	16 (11.4)	11 (12.2)	5 (9.8)	1.00
Acute rejection	54 (38.3)	31 (34.4)	23 (45.1)	0.66
Reoperation	14 (9.9)	10 (11.1)	4 (7.8)	0.21
Early allograft dysfunction ^a	11 (7.8%)	8 (8.9)	3 (5.9)	0.53
Early graft loss ^a	1 (0.7%)	1 (1.1)	0 (0)	0.75
				1.00

Data are presented as the medians (interquartile range) or n (%).

AIH, autoimmune hepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; NASH, non-alcoholic steatohepatitis; MELD, model for end-stage liver disease; GSVR, graft-to-spleen ration; GRWR, graft-to-recipient weight ration; CIT, cold ischemia time; WIT, warm ischemia time; PVP, portal venous pressure

^a Fisher exact test was applied. Other comparisons were performed using the Pearson χ^2 test for categorical variables.

Table 2

Multiple logistic regression analysis assessing risk factors for early allograft dysfunction in the prospective cohort (n = 141)

Variables	Univariable analysis		Multivariable analysis	
	OR (95%CI)	<i>P</i> value	OR (95%CI)	<i>P</i> value
Recipient age	0.98 (0.94-1.03)	0.41		
Child-Pugh C	1.72 (0.47-8.14)	0.24		
MELD score, by 5	1.74 (1.21-2.55)	0.003	1.69 (1.17-2.51)	0.006
GSVR	0.97 (0.50-1.52)	0.92		
Donor age	1.00 (0.95-1.05)	0.85		
Right lobe	0.54 (0.15-1.90)	0.34		
GRWR, by 0.1 %	0.71 (0.46-1.01)	0.06	0.73 (0.44-1.07)	0.11
ABO incompatibility	0.98 (0.14-4.12)	0.98		
Blood loss, by 500 mL	1.03 (0.99-1.06)	0.17		
CIT	1.00 (0.99-1.01)	0.17		
WIT	0.99 (0.93-1.04)	0.68		
Final PVP	0.93 (0.72-1.18)	0.55		

MELD, model for end-stage liver disease; CIT, cold ischemia time; WIT, warm

ischemia time; PVP, portal venous pressure; OR, odds ratios; CI, confidence interval

Table 3

The details of patients in which splenectomy was abandoned despite low GSVR

No.	Age / sex	Liver disease	MELD / Child-Pugh score	GSVR (graft volume / spleen volume in mL)	GRWR	Donor age, y	Graft lobes	Blood type compatibility	Plt, / μ L (day 7)	INR (day 7)	T-bil, mg/dL (day 7)	EAD	Outcome
1	60 / M	ALD	8 / 11	0.57 (740 / 1290)	0.90 %	55	Right	Incompatible	22,000	1.02	12.0	Yes	Mortality due to AMR
2	53 / M	NASH	12 / 12	0.69 (700 / 1011)	0.82 %	55	Right	Identical	43,000	1.19	13.2	Yes	Discharge home
3	46 / F	Congenital liver fibrosis	9 / 6	0.55 (410 / 747)	0.89 %	45	Left	Compatible	22,000	1.45	15.3	Yes	Rehabilitation facility

ALD, alcoholic liver disease; NASH, non-alcoholic steatohepatitis; MELD, model for end-stage liver disease; GSVR, graft-to-spleen ration; GRWR, graft-to-recipient weight ratio; Plt, platelets; INR, international normalized ratio; T-bil, total bilirubin; EAD, early graft dysfunction; AMR, antibody-mediated rejection