# Preventing Small-for-size Syndrome in Living Donor Liver Transplantation: Guidelines From the ILTS-iLDLT-LTSI Consensus Conference

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**Abstract.** Small-for-size syndrome (SFSS) is a well-recognized complication following liver transplantation (LT), with up to 20% developing this following living donor LT (LDLT). Preventing SFSS involves consideration of factors before the surgical procedure, including donor and recipient selection, and factors during the surgical procedure, including adequate outflow reconstruction, graft portal inflow modulation, and management of portosystemic shunts. International Liver Transplantation Society, International Living Donor Liver Transplantation Group, and Liver Transplant Society of India Consensus Conference was convened in January 2023 to develop recommendations for the prediction and management of SFSS in LDLT. The format of the conference was based on the Grading of Recommendations, Assessment, Development, and Evaluation system. International experts in this field were allocated to 4 working groups (diagnosis, prevention, anesthesia, and critical care considerations, and management of established SFSS). The working groups prepared evidence-based recommendations to answer-specific questions considering the currently available literature. The working group members, independent panel, and conference attendees served as jury to edit and confirm the final recommendations presented at the end of the conference by each working group separately. This report presents the final statements and evidence-based recommendations provided by working group 2 that can be implemented to prevent SFSS in LDLT patients.

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Living donor liver transplantation (LDLT) has increased worldwide over the past 2 decades with significant improvements in overall outcomes.[1,2] However, approximately 20% of recipients still develop small-for-size syndrome (SFSS), a well-recognized complication of LDLT.[3] There is increasing evidence to suggest that SFSS is a multifactorial syndrome, precipitated by various perioperative factors in a small-for-size graft (SFSG) setting.[4] The hemodynamic alterations which SFSG sustain following reperfusion damage the hepatocytes, affect sinusoidal endothelial integrity, and cause dampening of hepatic arterial buffer response leading to arterial hypoperfusion, and resultant ischemic injury to the graft.[3,5]

The understanding and analysis of the several perioperative factors involved in the occurrence of SFSS, including donor and recipient selection, intraoperative and postoperative managements, are essential to prevent and manage SFSS (Figure 1). Better understanding of SFSS pathophysiology associated with surgical and medical advances in its management have incrementally improved the outcomes of patient who suffer from SFSS, but there are currently no consensus on the best strategies that should be adopted to prevent SFSS. In this International LT Society-International LDLT Group-Liver Transplant Society of India Consensus Conference working group report, current available literature on the prevention of SFSS in LDLT is summarized. The aim of these recommendations, approved by the International LT Society-International LDLT Group-Liver Transplant Society of India, is to provide guidance in donor and recipient selection, and in the surgical and medical management aiming at preventing SFSS.

The recommendations were graded according to the Grading of Recommendations, Assessment, Development, and Evaluation system.[6,7] Given the paucity of literature for some of the individual scientific questions, a modified Grading of Recommendations, Assessment, Development, and Evaluation approach was applied when reporting effect size narratively. Effect sizes of reported results and potential limitations (risk of bias, imprecision, indirectness, inconsistency, and publication bias) were considered when rating the quality of evidence from very low to high. Accordingly, the quality of the evidence was rated as low, moderate, or high and the strength of the recommendation was rated as weak, moderate, or strong.

## DONOR SELECTION

### Donor Age

In most LDLT programs, acceptable living donor age for right lobe (RL) donation is between 18 and 60 y, with few centers going beyond 60 y, an age group associated with increased risks to the donor.[8–10] It is well reported that the future liver remnant (FLR) posthepatectomy should be ≥30% of the whole liver volume for donors younger than 35 y and ≥35% for donors older than 35 y.[8,11,12] The reason for larger FLR in older donors is due to the lower regenerative potential (declining hepatic progenitor

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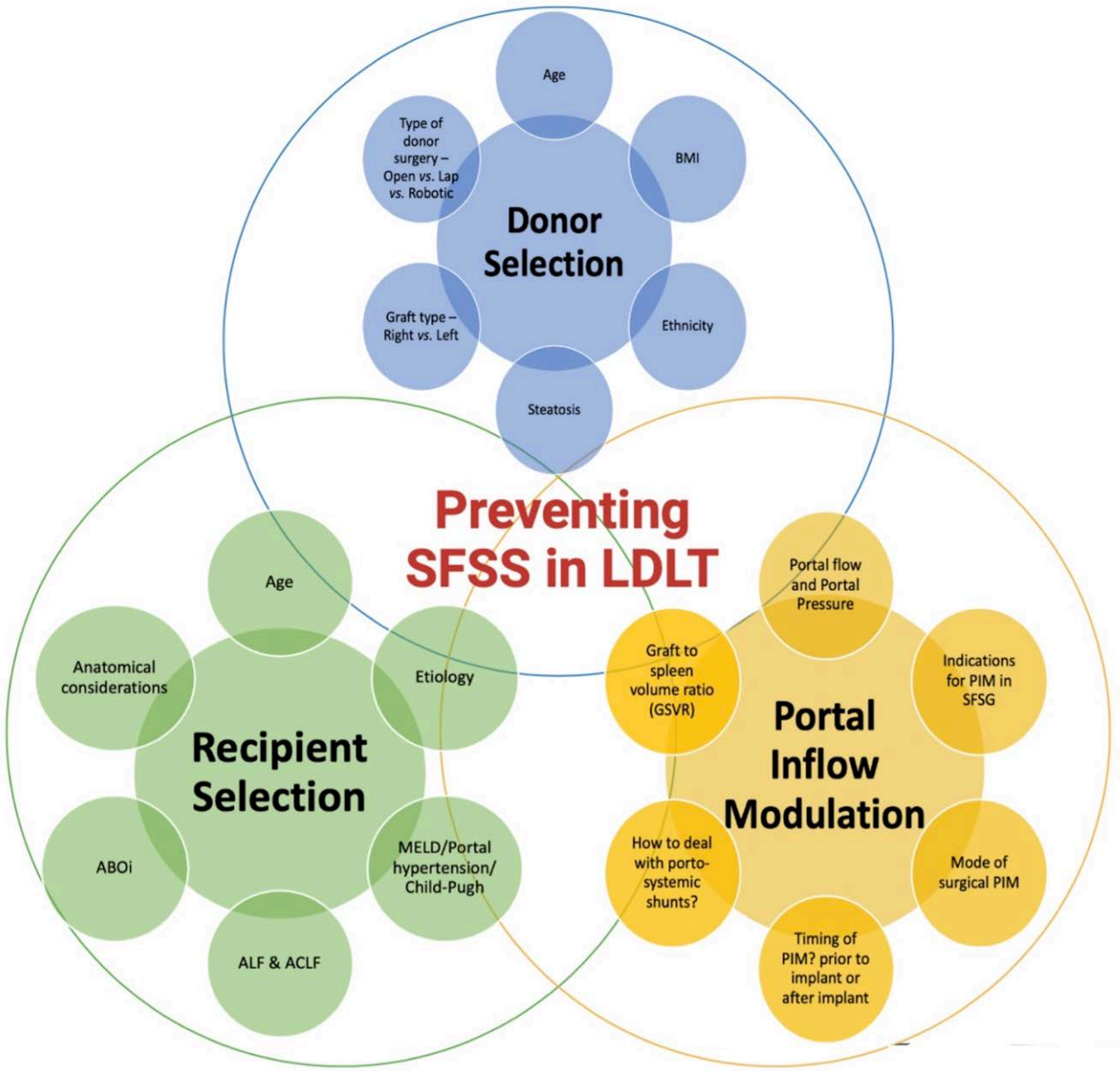


**FIGURE 1.** Factors to be considered for preventing SFSS in LDLT. ABOi, ABO incompatibility; ACLF, acute-on-chronic liver failure; ALF, acute liver failure; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; PIM, portal inflow modulation; SFSG, small-for-size graft; SFSS, small-for-size syndrome.

population) and higher resistance (lower compliance) of hepatic parenchyma adding substantial risk to donor and recipient recovery.[13–15] Donor age is a well-known prognostic factor for recipient morbidity and mortality in adult-to-adult LDLT, with optimal donor age cutoff for good recipient outcomes reported as 46.5 y.[16,17] Grafts from donors >45 y have higher risk of SFSS and inferior graft survival, especially in combination with steatotic graft, lower graft-to-recipient weight ratio (GRWR), high-acuity recipient, intraoperative portal venous pressure (PVP) >19 mm Hg, and ABO incompatibility (ABO-i)[18–23] (**Table S1, SDC,** http://links.lww.com/TP/C858). Older grafts have also been implicated in failed portal inflow modulation (PIM), because these grafts tolerate PVP >15 mm Hg more poorly when compared with the younger grafts.[24] However, donor age on its own has not been shown to be associated with SFSS, but for the safety of the donor and recipient, it is pertinent to adhere to the strict donor selection and recipient pairing of the grafts to prevent SFSS.

### Recommendations

It is recommended to avoid a combination of older donor (age ≥45 y) and SFSG because it may increase the risk of SFSS (strength of recommendation: strong; level of evidence: moderate)

## Donor BMI and Steatosis

Obesity is associated with an increased risk of hepatic steatosis and with the increased prevalence of obesity, hepatic steatosis is the most common cause of rejection of potential liver donors.[25,26] Although body mass index (BMI), a simple index of weight-for-height, is commonly used to determine overweight and obesity,[27] multiple studies have shown negative results regarding whether the

BMI can be an absolute criterion for obesity.[28–30] To date, several studies have investigated the safety of liver donation in live liver donors with high BMI and outcome of their recipients.[31–33] The most representative study from the Toronto group in 2017 demonstrated that the use of graft with macrosteatosis <10% from donors with a BMI >30 kg/m$^2$ had no negative impact on short-term and long-term outcomes of LDLT.[33] This means that donor's high BMI alone doesn't increase the risk of SFSS, suggesting that the degree of steatosis is more important for SFSS.

Percutaneous core needle biopsy is no longer universally performed to investigate macrosteatosis in live donors because of its invasiveness, potential adverse events, and inconsistent results.[34–36] Most centers perform liver biopsy only on very selected potential donors for assessing the degree of steatosis and prefer to routinely use the CT liver attenuation index or a combination of MRI-based proton density fat fraction and magnetic resonance spectroscopy.[37–39] According to previous studies, routine percutaneous core needle biopsy on potential living liver donors reported 76% of donors having macrosteatosis when their BMI is >28 kg/m$^2$.[40,41] The acceptable range of hepatic steatosis in LDLT varies and is dependent on factors such as donor age, graft type and volume, and preoperative recipient condition.[42] Most centers have a macrosteatosis cutoff of 10% for RL donation because anything more than that has shown to cause increased release of inflammatory cytokines, inhibition of the capacity to differentiate steatotic hepatocytes, loss of early regenerative potential, poor tolerance to ischemia-reperfusion injury and hence overall increased risk of early allograft dysfunction, SFSS, morbidity, and mortality.[19,38,43–45] Use of grafts with macrosteatosis up to 20% is not absolutely contraindicated.[46,47] However, because safety issues of RL donors with significant hepatic steatosis remain to be elucidated, it is recommended to avoid donor graft with macrosteatosis >20% in combination with SFSG because of the increased risk of SFSS. An elegant single center study using well-selected RL grafts (adequate FLR in donor and adequate GRWR in recipient), with up to 20% macrosteatosis showed no compromise in graft function and outcomes in the recipient, and the donor[46] (**Table S2, SDC,** http://links.lww.com/TP/C858).

In recent studies, weight loss interventions have shown to reduce the macrosteatosis, in living donor candidates with high BMI or significant macrosteatosis, thereby reducing the risk to both the donor and recipient.[47–49] A randomized controlled trial (RCT) demonstrated superior liver regeneration in live liver donors and decreased early allograft dysfunction in recipients, when simple lifestyle measures including customized low calorie diet and exercise regime was carried out for 2 wk before live donation surgery.[50] It is important that donors with BMI >30 kg/m$^2$ be counseled about the increased risk of graft failure in the recipient and advised weight loss interventions prior to be considered for donation.

### Recommendations

It is recommended to avoid donor graft with macrosteatosis >20% in combination with SFSG because it may increase the risk of SFSS (strength of recommendation: strong; level of evidence: low).

## RL Versus LL Graft

Smaller-size grafts can enhance donor safety and expand donor availability; however, they also cause SFSS, which is associated with high mortality and morbidity.[23,51–54] In humans, RL liver volume comprises 45%–80% and the left lobe (LL) liver volume comprises 20%–45% of the total volume.[55] Selecting between RL and LL grafts require balancing the risks of donor morbidity, which may be related to FLR size, against the recipient's risks of mortality and morbidity, related to dysfunction from a small graft.[56–59] Donor morbidity has been reported in the range of 24%–30%, with no significant difference between RL and LL donors. The comparable outcomes between RL and LL donation, has prevented a "left-shift," with RL-LDLT still preferred because of recipient operation being technically less challenging, with less vascular complications, better regeneration, and overall better short- and long-term graft and patient survival.[60] This can be explained by the good outcomes from RL grafts providing minimum absolute graft weight of 650 g, despite a GRWR of <0.8.[61]

**TABLE 1.**

**SFSS comparing RL versus LL grafts**

| Author and year | Type of study | Country | N | Outcome(s) |
|---|---|---|---|---|
| Acuna et al, 2022[60] | Systematic review and metanalysis | Multiple | 1829 | 9/67 studies included data on SFSS; 1313 RL (51 SFSS, 3.9%) vs 516 LL (61 SFSS, 11.8%). RL-LDLT less likely to develop SFSS (RR = 0.47; 95% CI, 0.30-0.74; $I^2$ = 0%). |
| Jo et al, 2022[52] | Retrospective, single center | Republic of Korea | 118 | Comparable outcomes for donor and recipients of LL graft and RL graft |
| Fujiki et al, 2022[62] | Retrospective, multicenter | USA/UAE | 130 | In LL graft, splenectomy and augmented venous outflow are recommended to reduce the risk of SFSS |
| Wong et al, 2021[53] | Retrospective, single center | China | 545 | Reduced SFSS and improved survival in RL graft recipients |
| Agarwal et al, 2019[61] | Retrospective, single center | India | 147 | 19.4% death in group with graft weight <650 g, compared with 7% death in patients with graft >650 g |
| Halazun et al, 2016[51] | Retrospective, single center | USA | 214 | SFSS in LL graft 5.4% vs 0% in RLG ($P$ = 0.003); overall LL graft outcomes comparable to RL graft outcomes and didn't affect graft or patient survival |

CI, confidence interval; GRWR, graft-to-recipient weight ratio; LDLT, living donor liver transplantation; LL, left lobe graft; MELD, model for end-stage liver disease; MVA, multivariate analysis; OR, odds ratio; RL, right lobe graft; RR, relative risk; SFSS, small-for-size syndrome.

A recent meta-analysis of 25 230 donors, reported RL donors were more likely to experience any complication (RR = 1.35; 95% confidence interval [CI], 1.18-1.59; $I^2$ = 53%; 28 studies; 12 359 patients), major complication (RR = 1.63; 95% CI, 1.30-2.05; $I^2$ = 19.4%; 22 studies; 13 075 patients), and stayed longer in hospital (SMD, 1.48; 95% CI, 1.20-1.83; 20 studies; 9823 patients). Importantly, because of their larger graft volume, average mean RL graft 675 g (range, 461–994 g) versus LL graft 437 g (range, 283–519 g), the RL-LDLT recipients were less likely to develop SFSS (RR = 0.47; 95% CI, 0.30-0.74; $I^2$ = 0%; 9 studies; 1829 patients)[60] (Table 1).

### Recommendations

When there is borderline graft volume for LL grafts, RL graft should be considered during donor selection as recipients are less likely to develop SFSS (strength of recommendation: strong; level of evidence: moderate).

### Type of Surgery (Open Versus Lap Versus Robotic)

Minimally invasive donor hepatectomy has significant advantages to the donor, and the recipient outcomes have reported to be safe and, comparable to the grafts from open surgery.[63,64] A recent systematic review of 31 studies concluded a marginal benefit in estimated blood loss and length of hospital stay in favor of pure laparoscopic donor hepatectomy and robotic donor hepatectomy, when compared with open procedure.[65] Technological advancements in robotic platform with its superb optical system, wide range of motion and tremor-free instrumentation, has made significant progress in donor hepatectomies, but the complexity of these procedures limits them to transplant centers with high volume and experience.[66–69] In a retrospective observational study, the SFSS rate was 6.6% in robotic (n = 102) and 4.6% in open (n = 152) RL donor hepatectomy, which was not statistically significant.[70] Although there is currently no evidence to suggest that minimally invasive donor hepatectomy impacts on the SFSS in the recipients, caution should be exercised in selecting these donors because an SFSG in this setting may also be associated with additional graft factors, including longer donor warm ischemia time, short vessels, and potentially higher biliary complications.[71–73]

As part of the donor factors, the working group also reviewed the evidence for donor ethnicity as a variable influencing SFSS. Although there are reports that Eastern population when compared with the Western have a higher percentage of body fat for a specified BMI (different BMI cutoff compared with west), higher rates of hepatic macrosteatosis, lean (nonobese) nonalcoholic fatty liver disease, lower liver regenerative potential, different transplant indications, and recipient acuity, there is currently no evidence to suggest that the donor ethnicity has an impact on SFSS in the recipient.[2,74–76]

## RECIPIENT SELECTION

### Recipient Age

Although the age of the donor clearly predicts the development of SFSS, the recipient age does not seem to. Two retrospective studies reported that recipient age is a risk factor for SFSS on multivariate analysis (MVA).[22,77] Ikegami et al reported that recipient age >53 y old is a risk factor for SFSS, but this difference with younger donors (<53 y) was not statistically significant on MVA ($P$ = 0.07).[22] Conversely, Uchiyama et al found that recipient age <45 y old and donor age >48 y old were significant risk factors ($P$ < 0.01 and $P$ < 0.03, respectively) for SFSS.[77] Other single center studies and systematic reviews have not found association between recipient age and development of SFSS.[18,19,44,78] It can be safely concluded that recipient age alone is not a risk factor for SFSS.

### ABO-i

Few studies identify ABO-i as potential risk factor for SFSS. In a retrospective study performed on 121 LDLT patients, the ABO-i graft was a risk factor for SFSS on univariate analysis (UVA; $P$ = 0.07) but was not significant on MVA (odds ratio [OR] = 2.02, 95% CI, 0.75-5.47, $P$ = 0.17).[18] A large retrospective study reported significantly higher rate of SFSS in ABO-i LDLT with smaller grafts (0.6 ≤ GRWR < 0.8), when compared with larger grafts (GRWR ≥ 0.8) [20.4% versus 10.7%, respectively, $P$ = 0.011]; however, there was no difference in graft survival between the 2 groups. In keeping with older donor age and risk of SFSS, this study confirmed that the graft survival was inferior for small ABO-i grafts when compared with large ABO-i grafts at a donor age cutoff of ≥50 y.[79] Similarly, Yao et al in a large single center retrospective study reported ABO-i as a risk factor for failed PIM, thereby increasing the risk of SFSS and early graft loss (hazard ratio = 3.67; $P$ = 0.20). The authors went onto identify a subgroup of high-risk recipients (ABO-i/or donor age ≥45 y) who according to their algorithm needed PIM, and those ABO-compatible and young donors (age <45 y) can avoid PIM, even if PVP ≥15 mm Hg.[24] A meta-analysis of 12 comparative studies did not demonstrate ABO-i to increase the risk of SFSS.[80] It can be inferred from the available literature that ABO-i on its own does not increase the risk of SFSS but can do in combination with other factors such as donor age and recipient acuity.

### Cause of Liver Disease

Based on available studies, cause of underlying liver disease does not seem to be a risk factor for SFSS in experienced high-volume centers. Retrospective studies have shown SFSS to be more frequent in patients with cholestatic liver disease (UVA $P$ < 0.01)[23] and hepatocellular carcinoma recipients with BMI ≤30 kg/m$^2$ (UVA $P$ = 0.037)[44] but not on MVA. Few other studies have shown no correlation between the cause of liver disease and risk of SFSS.[18,22]

### MELD, Portal Hypertension, and Child-Pugh Scores

Preoperative model for end-stage liver disease (MELD) score has been described as a risk factor for SFSS, but not all studies have reported this association.[18,77,81–83] In most studies, MELD cutoff of 19 seems to reflect high-acuity recipient, with higher risk for SFSS,[19,45,77] except in 1 study which reported a MELD >26 as a significant predictor of SFSS.[84] Alim et al only accepted grafts with >0.8 GRWR in recipients with MELD >20 and suggested that the GRWR can be decreased even to 0.6 if the MELD score is below 20, donor age <45 y, and there are no signs

**TABLE 2.**

**SFSS in relation to recipient MELD/portal hypertension/Child-Pugh**

| Author and year | Type of study | Country | N | Outcome(s) |
|---|---|---|---|---|
| Wong et al, 2021[81] | Retrospective, single center | China | 545 | MELD not associated with graft or patient survival |
| Toshima et al, 2021[44] | Retrospective, single center | Japan | 694 | Child-Pugh C associated with SFSS in BMI<30 patients |
| Abdallah et al, 2020[19] | Retrospective, single center | Egypt | 110 | MELD > 19 significant predictor of SFSS |
| Macshut et al, 2019[18] | Retrospective, single center | Japan | 121 | MELD not associated with SFSS. Child-Pugh C associated with SFSS on MVA |
| Yao et al, 2018[24] | Retrospective, single center | Japan | 319 | Risk factors for graft loss higher in patients with PVP>15 mm Hg/Child-Pugh C (OR 1.31) |
| Shoreem et al, 2017[45] | Retrospective, single center | Egypt | 174 | MELD predictor of SFSS on UVA, but not MVA. Portal hypertension associated with SFSS on UVA, not on MVA |
| Chok et al, 2017[82] | Retrospective, single center | China | 54 | MELD not associated with survival |
| Sethi et al, 2017[83] | Retrospective, single center | India | 226 | MELD not associated with SFSS |
| Uchiyama et al, 2016[77] | Retrospective, single center | Japan | 321 | MELD not associated with SFSS |
| Alim et al, 2016[85] | Retrospective, single center | Turkey | 649 | They only accepted MELD > 20 if GRWR > 0.8 |
| Ikegami et al, 2016[22] | Retrospective, single center | Japan | 207 | MELD >19 significant predictor of SFSS |
| Marubashi et al, 2015[86] | Retrospective, single center | Japan | 138 | MELD significant predictor of SFSS |
| Chan et al, 2010[86] | Retrospective, single center | China | 322 | MELD predictor of SFSS on UVA, not on MVA |
| Selzner et al, 2009[84] | Retrospective, single center | Canada | 271 | MELD >26 significant predictor of SFSS |

BMI, body mass index; GRWR, graft-to-recipient weight ratio; LDLT, living donor liver transplantation; LL, left lobe graft; MELD, model for end-stage liver disease; MVA, multivariate analysis; OR, odds ratio; PVP, portal venous pressure; SFSS, small-for-size syndrome; UVA, univariate analysis.

of macrosteatosis within the graft.[85] Marubashi et al proposed a formula to estimate the minimum graft size to control the risk of SFSS based on standard liver volume and MELD score.[86] Conversely, in some studies MELD score predicted SFSS on UVA but not on MVA, again confirming that SFSS is a multifactorial syndrome.[45,87] Based on the evidence available, it can be concluded that patients with high MELD scores may need larger grafts to prevent SFSS (Table 2).

Portal hypertension has been associated with SFSS in some studies because it may lead to portal hyperperfusion, which is an important factor for the damage to SFSG. Patients with higher MELD scores are likely to have a higher PVP.[45] Decompensation including bleeding, encephalopathy and ascites, presented similarly in SFSS and non-SFSS patients.[19]

In the study by Macshut et al, MELD was not identified as a risk factor for SFSS, but Child-Pugh C class recipients were associated with a higher risk of SFSS development (OR 7.44; $P$ = 0.013). Interestingly, this did not translate into allograft loss.[18] Similarly, in the study by Toshima et al, Child-Pugh Class C was the only preoperative recipient factor associated with SFSS development in recipients with BMI <30 kg/m$^2$.[44] Therefore, MELD score alone does not increase risk for SFSS but does increase risk in combination with a SFSG.

### Recommendations

It is recommended to a*void a combination* of higher MELD (>19) and SFSG to reduce the risk of SFSS (strength of recommendation: moderate; level of evidence: moderate).

## Acute Liver Failure

Despite high MELD scores in acute liver failure (ALF) patients, PVP may only be mildly or moderately increased and therefore may not increase the risk of SFSS. In 2 large cohorts of ALF patients receiving a LDLT, no higher rates of SFSS were described.[88,89] A retrospective study from Kyoto >20 y ago, demonstrated higher incidence of SFSS in ALF patients receiving a LL-LDLT.[90] Conversely, a study from Kyushu around the same time demonstrated higher incidence of SFSS in cirrhotic patients when compared with those with fulminant liver failure.[91]

## Acute-on-Chronic Liver Failure

In comparison to ALF, acute-on-chronic liver failure (ACLF) patients do have high PVP, because they have underlying cirrhosis.[92] Therefore, considerations on management can be similar to those made for patients with decompensated cirrhosis with high MELD scores. Additionally, sepsis and systemic inflammatory response syndrome are known risk factors for SFSS in these patients.[83] Patients with ALF or with ACLF typically present with multiorgan failure and systemic inflammation, with or without sepsis, which can be the main driver of SFSS in these patients. Based on limited evidence, it can be concluded that both ALF and ACLF per se are not risk factors for SFSS if the graft volume is adequate.[93] Their metabolic requirement is higher, so risk of SFSS may become higher with SFSG, and in the presence of sepsis and systemic inflammatory response syndrome.[94]

## Graft Anatomic Considerations

A good venous outflow is as important as vascular inflow for a successful LDLT.[95] A congested liver segment contributed to graft weight rather than actual graft function.[96,97] Therefore, it is crucial to ensure every segment of a SFSG is functional.[83] An unimpeded venous outflow also has synergistic effects on portal hemodynamics and helps to alleviate PVP and reduce effects of excess portal venous flow (PVF).[98–100] In an RCT comparing types of RL graft, there was no difference in SFSS rate

when extended RL graft [ie, division of middle hepatic vein (MHV) beyond segment 8 vein] was compared with modified RL graft (SFSS 7.0% versus 11.6%; $P = 0.46$).[98] In another RCT comparing native right portal vein versus polytetrafluoroethylene for neo-MHV reconstruction, there was no difference in SFSS rate depending on the type of conduit (1.6% versus 1.7%; $P = 1.000$).[101] An interesting study on a large cohort from China clarified if MHV needs to be reconstructed routinely. They reported that if the GRWR is >0.86, then MHV does not need to be reconstructed. They also go onto suggest that if GRWR <0.8 (even up to 0.5), SFSS can be prevented when MHV reconstructed.[102] Recent data does suggest that a selective and tailored approach to RL outflow reconstruction is crucial to maintain graft function in SFSG[45,99,103] (**Table S3, SDC,** http://links.lww.com/TP/C858).

Few centers take caudate lobe along with LL graft for LDLT because of the ease of transection. However, caudate adds to only 2%–9% (approximately) of graft volume, and hence not recommended.[104,105] If the caudate lobe is included in the graft, there is evidence to suggest that it may not need separate drainage.[106,107]

There is currently no evidence to suggest that multiple arteries or bile ducts increase the risk of SFSS. Handling of multiple arteries in LDLT has been well reported, but there are no reports to suggest that ligation of the less significant artery increases the risk of SFSS.[108,109] Similarly, multiple ducts may increase the risk of biliary complications, which might complicate postoperative recovery and push a low-GRWR graft to SFSS, but per se multiple ducts does not influence the risk of SFSS.[110–112]

### Recommendations

In the setting of RL SFSG, an optimum reconstruction of anterior sector outflow and inferior hepatic vein(s) is recommended (strength of recommendation: strong; level of evidence: strong).

## PIM

Various pharmacological, radiological, and surgical treatments aimed at reducing the portal inflow to smaller grafts may help in ameliorating the effects of the high portal pressure and have been collectively termed as PIM or portal flow modulation or graft inflow modulation.[5,113–117] These modulation techniques can be used either on its own or more often in combination.[118,119] Radiological PIM[120,121] are almost always done as a desperate measure in the post-transplant period in the setting of already established SFSS, whereas pharmacological and surgical modulation are in most instances used as preventive measure. Surgical PIM is a relatively nascent subject and little consensus exists on how inflow modulation can be applied to successfully prevent SFSS, allograft dysfunction and graft failure.[113]

### Portal Pressure and Portal Flow

The pathophysiology of the development of SFSS is multifactorial. Although the graft size has long been implicated as the major culprit for SFSS, portal hypertension, and hyperdynamic splanchnic circulation play a key role in the development of SFSS.[80] There is enough evidence to suggest that high PVP on a SFSG can cause sinusoidal shear stress, hepatic microcirculatory disturbances, hepatocyte functional insufficiency, over-regeneration of the hepatocytes, hepatocellular damage and death. Furthermore, portal hyperperfusion when coupled with insufficient venous outflow, decreases the arterial perfusion, with a reduced capacity to regenerate, resulting in impaired liver function.[122,123] PVP is measured via direct cannulation of the PV or its tributaries such as inferior mesenteric vein or other mesenteric veins. It must be noted that high central venous pressure can influence portal pressure, and PVP values in this setting can be erroneous. Most studies suggest that a PVP of <15 mm Hg seems to be ideal to avoid graft damage,[124–126] but there is some evidence that even 15–20 mm Hg may not increase the risk of SFSS.[80,119,127] There is certainly enough evidence to suggest that PVP >20 mm Hg is counterproductive[91,93] (Table 3).

In contrast to PVP which measures the resistance to the portal flow in the liver, the PVF refers to the amount of blood coursing through the portal system of the liver. Similar to pressure, the hyperdynamic splanchnic state seen in cirrhotics can significantly increase the PVF. Flow is said to double to what is observed in healthy individuals due to the loss of splanchnic vascular tone and altered hemodynamics.[133,134] Although increased PVF is one of the triggers for the regeneration of the liver graft, excessive flow damages the graft, impairs recovery, and leads to SFSS.[135,136] PVF is measured using the doppler ultrasound or specialized flow meters. However, the accuracy of these probes has been called into question due to the alteration in flow values with even slight change in probe size, thereby questioning their reliability.[131,137] A PVF above 250 mL/min/100g of liver tissue has been noted by some authors to negatively impact the graft,[94,95] whereas others claim that flows even up to 300–360 mL/min/100g of liver tissue do not cause significant graft damage.[94]

There is currently no evidence to suggest correlation between PVP and PVF, with PVP measurement preferred in most LDLT centers because of the ease of obtaining the measure, better reproducibility and reliability, and overall cost-effectiveness. Sainz-Barriga et al suggested that PVP or PVF should not be used on its own to estimate increased portal hypertension or flow during liver transplantation, the reasons being that high PVP (>20 mm Hg) were found across spectrum of PVF, and in 3% of patients with low PVP (<20 mm Hg), there was high flow (>270 mL/min/100g of liver tissue).[130] Intraoperative decision on employing measures to modulate the graft inflow may require evaluation of both PVP and PVF parameters and must be correlated closely with the central venous pressure.[130,138,139] There is a definite need for standardization of techniques to measure the PVP and PVF because these intraoperative numbers guide the pharmacological or surgical PIM.

### Recommendations

Routine measurement of portal pressure and/or flow in the setting of SFSG is recommended (strength of recommendation: strong; level of evidence: moderate).

### Indications for PIM in SFSG

PVP and PVF are metrics, which can be used to assess the relative state of portal hyperperfusion. An absolute number for pressure or flow is not universally accepted. It

**TABLE 3.**

**SFSS in relation to portal pressure and flow values**

| Author and year | Type of study | Country | N | Outcome(s) |
|---|---|---|---|---|
| Gavriilidis et al, 2022[78] | Systematic review and meta-analysis | Multiple | 1810 | Application of PIM significantly reduced the incidence of SFSS when PVP was high |
| Soin et al, 2019[119] | Retrospective | India | 287 | PVP maintained <15–18 mm Hg along with good venous outflow has good results in SFSG |
| Troisi et al, 2017[80] | Systematic review | Multiple | 449 | Ideal portal pressure <20 mm Hg |
| Osman et al, 2016[124] | Prospective | Egypt | 76 | Pressure cutoff 15 mm Hg is appropriate for prevention of SFSS |
| Hori et al, 2014[125] | Retrospective | Japan | 155 | PVP <15 mm Hg in SFSG gives good results |
| Asencio et al, 2013[128] | Systematic review | Spain | – | Portal flow >250 mL/min/100 g requires PIM |
| Kaido et al, 2011[129] | Retrospective | Japan | 52 | GRWR <0.8 with a target PVP <15 mm Hg |
| Sainz-Barriga et al, 2011[130] | Prospective | | 81 | Portal flow >4 times in donor (>360 mL/min/100 g) is risk factor for graft failure. No correlation between flow and pressure. 3% of patients with low pressures (<20) have high flow (>270 mL/min/100 g) |
| Chan et al, 2011[131] | Prospective | China | 46 | Portal flow and pressure correlates well prior to explant. No correlation after implantation. |
| Ogura et al, 2010[126] | Retrospective | Japan | 134 | PVP <15 mm Hg associated with better graft parameters |
| Jiang et al, 2009[132] | Prospective | China | 18 | PVF should be maintained below 300 mL/min/100 g |
| Yagi et al, 2006[127] | Prospective | Japan | 28 | Graft function better when PVP <20 mm Hg |

GRWR, graft-to-recipient weight ratio; GV/SLV, graft volume/standard liver volume; PIM, portal inflow modulation; PVF, portal venous flow; PVP, portal venous pressure; SFSG, small-for-size graft; SFSS, small-for-size syndrome.

is generally accepted that pressure >20 mm Hg correlates with the development of graft dysfunction and therefore keeping PVP <20 mm Hg is recommended.[80,113,119,127,140] Kaido et al reported their experience with small grafts (GRWR of 0.6) in combination with PVP control (targeting final portal pressures below 15 mm Hg). They showed that survival and incidence of complications of recipients of small grafts and standard-size grafts was similar when pressures were kept below 15 mm Hg.[129]

With respect to portal flow the ideal PVF for partial grafts has been varyingly interpreted to be ranging from twice the perfusion observed in the full-size grafts (260 mL/min/100g of liver tissue) to 4 times the baseline flows observed in the healthy donor (360 mL/min/100g of liver tissue).[130] Nonetheless most studies have identified a cut of 250 mL/min/100g of liver tissue as the cutoff value for PVF.[78,113,128,130,137,141–144] (**Table S4, SDC,** http://links.lww.com/TP/C858). The window of ideal portal flow is still an evolving concept that needs further scientific rigor.

Based on the evidence available, we conclude that, in SFSG, portal pressure (>15 mm Hg) and/or portal flow (>250 mL/min/100g of liver tissue) increases the risk of SFSS, early graft loss and overall poor outcome. However, the question does arise whether the indication to modulate portal inflow be decided at the preoperative assessment and planning stage, rather than intraperatively. There is some evidence that graft-to-spleen-volume-ratio (GSVR) may guide decision on the need for PIM.[145–149] Gyoten et al reported that GSVR <0.95 predicts PVP of >20 mm Hg.[150] Cheng et al reported a GSVR of <0.60 was highly associated with post-transplant elevated PVF.[149]

### Recommendations

In the setting of SFSG, portal pressure >15 mm Hg and/or portal flow >250 mL/min/100g of liver tissue, PIM is recommended (strength of recommendation: moderate; level of evidence: moderate).

## Choosing the Type of Surgical PIM

Over the years, several modalities have been developed to reduce the PVP and/or PVF. The basic tenet is to either reduce the blood flow into the portal vein through modulation of splenic inflow or to divert the portal flow by creating portosystemic shunts. Of the modalities described, splenic artery ligation (SAL), splenectomy, and hemiportocaval shunts (HPCS) are the most commonly performed,[78,113,114,151] and splenic devascularization preferred in very few centers.[151,152]

Initially described by Troisi et al, SAL has been shown to reduce the PVP along with an increase in the hepatic artery flow.[114,153,154] The reduction in pressure is due to the reduction in the splenic outflow.[155] The striking feature of proximal SAL is that it is a simple and easily performed procedure with possibly the lowest morbidity compared with other procedures.[113,137,156,157]

Nevertheless, the reduction in PVP is modest and may be temporary.[5,80,142] It could be argued that in significantly increased PVP or PVF, SAL may be inconsequential. SAL has also been used to increase the hepatic artery flow when found to be low (<100 mL/min),[113,158] and the mechanism behind this is by reducing splenic steal of the hepatic blood flow.

From the evidence available it can be concluded that, as a first line measure for PIM, SAL offers a simple, yet effective modality to control modest increase in the PVP/PVF after implantation of partial grafts (**Table S5, SDC,** http://links.lww.com/TP/C858).

### Recommendations

Splenic artery ligation as the first line of surgical PIM is recommended (strength of recommendation: strong; level of evidence: moderate).

A number of centers use splenectomy as a means to reduce the PVP and/or PVF.[14,78,159] Splenectomy was increasingly being performed prior to the advent of direct-acting antiviral agents as part of interferon therapy for hepatitis C infection. It results in high gradient fall in PVF

as the splenic component accounts for up to 52% of the total portal blood flow.[154,160] However, splenectomy as a modality for PIM has not gained universal acceptance because of the increased risk of complications such as bleeding, thrombosis of the splenic vein and portal vein, septic complications, and pancreatic leak.[161–166] It must, however, be noted that some of the large volume LDLT centers continue to perform splenectomy and consider this as the first modality in reducing portal flow.[14] In the current age of advanced surgical techniques using instrumentations such as vessel sealing devices and vascular staplers, splenectomy could be performed without significantly increased risk of technical complications in those with expertise[14,62,159,167,168] (**Table S6, SDC,** http://links.lww.com/TP/C858).

### Recommendations

Splenectomy is recommended as another effective modality of PIM but may be associated with increased morbidity (strength of recommendation: moderate; level of evidence: moderate).

HPCS work by diverting a significant amount of the portal flow away from the graft liver and as such can produce a quick and large fall in the PVP and/or PVF.[119,136,137] Troisi et al reported significant and persistent reduction of the portal inflow to >50% of the initial values when HPCS was used.[136] Such a large reduction associated with HPCS may lead to graft hypoperfusion and steal leading to graft dysfunction, both in the short term and long term after transplant.[169] Several technical considerations regarding creation of HPCS are yet to be standardized, including the type of conduit, size of conduit, timing of HPCS, and prophylactic closure of HPCS after the graft regeneration. The shunt can be created directly from the left/right branch of the portal vein to the inferior vena cava or using a conduit (recipient portal vein, cryopreserved veins, or synthetic grafts).[170] Soin et al recommend a conduit with a graft size of 8–10 mm and a length of 10–20 mm.[119,136] Using synthetic grafts with fixed diameter can ensure that the diversion cannot exceed predefined values, as may occur with autologous grafts. The timing of shunt creation is a matter of debate because some suggest doing this after explant and before graft implantation with native portal vein or cryopreserved vein, because of the technical ease and also allows reduction of PVP and/or PVF, before graft is reperfused.[119] However, others consider creating the shunt only after measuring the post-implantation PVP and/or PVF values. Furthermore, it is unclear whether these shunts should be taken down in the long term to prevent ongoing portal steal from the graft and complications such as recurrent hepatic encephalopathy and liver atrophy.[171–173] In most cases, complications pertaining to the shunt can be tackled with ligation of the shunt either by surgical exploration or by endovascular techniques[113] (**Table S7, SDC,** http://links.lww.com/TP/C858).

### Recommendations

Hemiportocaval shunt is recommended for surgical PIM in exaggerated portal hypertension but may come at risk of portal steal and graft hypoperfusion (strength of recommendation: moderate; level of evidence: moderate).

## Timing of PIM

Size of the liver graft, PVP, and/or PVF and compliance are among the most important factors for the development of injurious portal hypertension in the recipient.[124,127,156,174–176] Although preimplantation PVP/PVF parameters can shed light on the degree of portal hypertension, it may not correlate with the postimplantation pressures/flow.[130] The compliance and the ability of the graft to take up the portal blood can significantly alter the post-implantation pressure/flow. Performing graft inflow modulation based on the pressure/flow parameters after reperfusion is probably ideal because it allows consideration of the graft compliance, which is a crucial factor and may decrease or increase PVP/PVF parameters after reperfusion. The postreperfusion parameters also consider the outflow of the graft, which may accommodate the high flow and may prevent damage to the graft from hyperperfusion. Majority of centers perform PIM after measuring PVP and/or PVF "after" reperfusion, because it allows reassessment of need, as well as the modality of PIM based on graft hemodynamics.[78,80,113] Center to center variation however does exist and some centers routinely prefer to base the decision on PIM on dissection phase (preimplantation) pressures/flow parameters[119] (**Table S8, SDC,** http://links.lww.com/TP/C858).

### Recommendations

It is recommended that PIM be performed after reperfusion of graft, and this should be guided by the portal pressure and/or flow measurements (strength of recommendation: moderate; level of evidence: low).

## How to Deal With Spontaneous Portosystemic Shunts?

Many patients with end-stage liver disease have spontaneous portosystemic shunts (SPSS). The presence of such shunts may be beneficial because explant hepatectomy can be performed with minimal blood loss because of shunting of blood from the portal circulation. After reperfusion, SPSS may divert blood away from the portal system and reduce the hyperperfusion of the graft, thereby reducing the risk of SFSS.[118,177] SPSS are present in about 20%–35% of transplant candidates, with a recent review on the intraoperative management of SPSS concluding that there was heterogenous management of SPSS during LT, with very little consensus.[178,179] The pathophysiology of the development of SFSS is postulated to be related to the increased portal flow and associated shear stress it causes on a small graft. Consequently, it may seem counterintuitive to ligate the SPSS in SFSG because it may worsen the hyperdynamic circulation. However, the size of these shunts and their long-term status could alter the portal hemodynamics following implantation. A large, persistent SPSS can divert the flow (hepatofugal) after transplantation leading to portal steal syndrome, with consequent graft hypoperfusion and dysfunction.[180–182] Intraoperative cine portography to identify large shunts and their flow patterns after implantation can help in the management of these shunts. Lee et al uses intraoperative cine portography to identify SPSS intraoperatively and ligates shunts >10 mm to prevent postoperative portal steal syndrome.[183,184] Simultaneous measurement of the PVP and/or PVF parameters upon clamping of the SPSS can help identify patients in whom the ligation of SPSS can

cause disastrous elevation in the PVP and/or PVF.[180] In all other cases, to prevent portal steal, large SPSS (>10 mm) should ideally be ligated. Decision to ligate the shunts versus leaving them undisturbed needs to be carefully weighed after considering all factors because ligation probably gives a more controlled situation of portal hemodynamics, and reduces the need for re-exploration or radiological interventions in the post-transplant period for SPSS with steal[118] (**Table S9, SDC,** http://links.lww.com/TP/C858).

### Recommendations

SPSS can cause graft hypoperfusion in the setting of SFSG. We recommend intraoperative portal pressure and/or flow measurements to guide management of these shunts. Further PIM may be required after ligation of shunt to prevent hyperperfusion (strength of recommendation: moderate; level of evidence: low).

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