Small-For-Size Living Related Liver Transplantation

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Introduction

- Type of Primary graft dysfunction following liver transplantation
- Incidence is approximately 20% (2019)

- SFSS is a condition where a small liver graft exhibits primary dysfunction within the first postoperative week, even when other causes like vascular obstruction, biliary leak, sepsis, and immune rejection are ruled out.

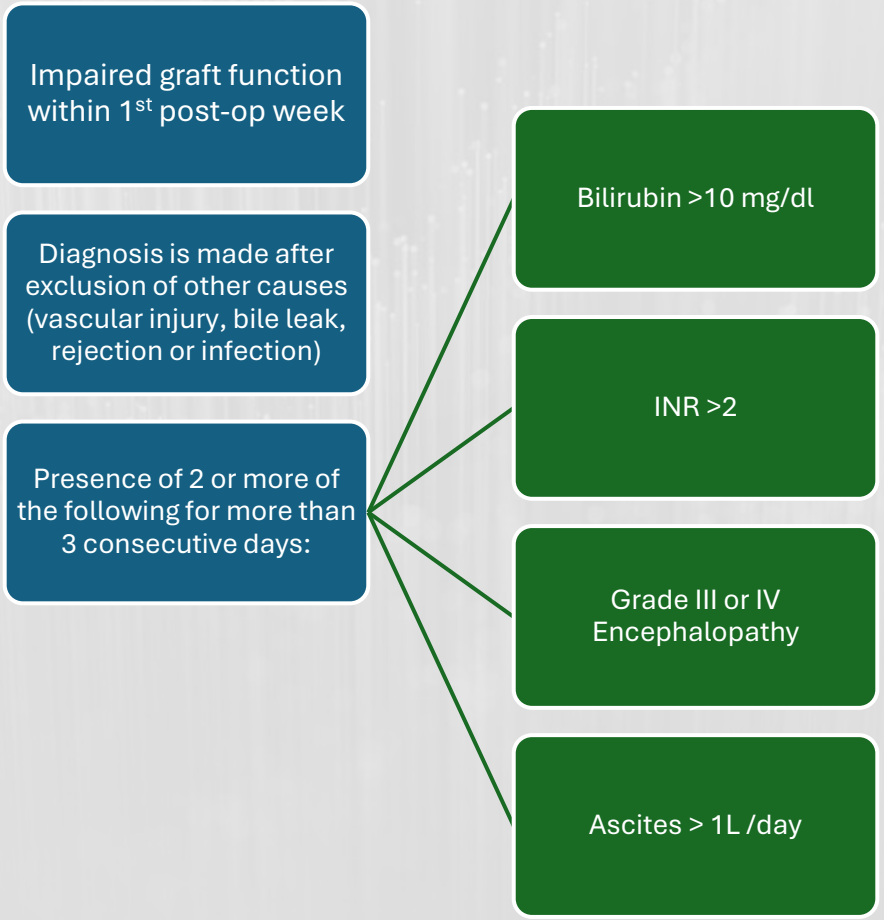
- SFSS occurs when a small graft is unable to meet the functional demands of the recipient, leading to liver failure with symptoms like coagulopathy, ascites, prolonged cholestasis, and encephalopathy, and can also lead to pulmonary and renal failure.

(A systematic review of small for size syndrome after major hepatectomy and liver transplantation, Riddiough, Georgina E. et al., HPB, Volume 22, Issue 4, 487 – 496)

Definition of SFSS

- A commonly accepted definition of SFSS:
- Small-for-size dysfunction (SFSD): Dysfunction of a small partial liver graft with a graft-to-recipient weight ratio (GRWR) less than 0.8%, occurring within the first postoperative week, and ruling out other causes.

Characteristics



SFSS grading and management according to ILTS-iLDLTG-LTSI Consensus Conference 2023

- Kirchner VA, Shankar S, Victor DW 3rd, et al. Management of Established Small-for-size Syndrome in Post Living Donor Liver Transplantation: Medical, Radiological, and Surgical Interventions: Guidelines From the ILTS-iLDLT-LTSI Consensus Conference. *Transplantation*. 2023;107(10):2238-2246. doi:10.1097/TP.0000000000004771

Grade	POD 7	POD 14	Graft Loss (%)	Treatment
A-pre-SFSS	T. Bil > 5 mg/dL	T. Bil > 5 mg/dL T. Bil > 5 mg/dL or ascites 1 L/d	< 9%	Supportive care, pharmacologic GIM
B-portal hypertensive phase	T. Bil > 10 mg/dL or INR > 1.6	T. Bil > 10 mg/dL and ascites 1 L/d	9–26%	Supportive care,, pharmacologic GIM, IR/surgical GIM
C-liver failure phase	T. Bil > 10 mg/dL and INR > 1.6	T. Bil > 20 mg/dL	59–77%	Supportive care,, pharmacologic GIM, IR/surgical GIM, possible liver retransplant

GIM graft inflow modulation; *INR* international normalized ratio; *IR* interventional radiology; *T.Bil* total bilirubin

Pathophysiology of SFSS

Portal Hyperperfusion

● Occurs when a smaller liver receives the same volume of portal venous blood flow as a full-sized liver.

● Significantly elevated portal venous pressure (PVP), especially in small grafts with a GRWR less than 0.8%.

● Elevated PVP can persist for up to two weeks after surgery, compared to non-SFSS grafts.

● PVP greater than 20 mmHg is associated with worse graft survival at six months (38% vs 85%).

●Portal hyperperfusion results in:

- Sinusoidal congestion
- Endothelial dysfunction
- Impaired liver function

Contributing Factors

Venous Congestion: Inadequate drainage of blood from the graft through hepatic veins exacerbates the congestion caused by portal hyperperfusion.

Arterial Hypoperfusion: Insufficient blood supply through the hepatic artery compromises graft function and regeneration.

Graft Size Mismatch: In some cases, the graft's volume is simply insufficient to handle the recipient's metabolic needs, even with optimal blood flow.

Risk Factors

Graft-Related Factors

- **GRWR below 0.8%** is a key indicator of inadequate graft size relative to the recipient's body weight, increasing the risk of SFSS.
- **Impaired venous outflow**, often due to surgical technique, can worsen congestion and contribute to SFSS.
- **Steatosis exceeding 30%** in the donor liver, particularly macrovesicular steatosis, compromises the graft's functional capacity and elevates SFSS risk.
- **Prolonged ischemia time** during organ retrieval and transplantation heightens the risk of damage to the graft, making it more susceptible to SFSS.

Risk Factors

Donor-Related Factors

- **Abnormal liver function tests** in the donor raise concerns about pre-existing liver issues that could negatively impact graft function and increase SFSS susceptibility.
- **Prolonged donor ICU stay (over five days)** suggests a compromised health status, potentially affecting graft quality and raising the risk of SFSS.

Risk Factors

Recipient-Related Factors

- **Advanced liver disease (Child-Pugh grade C, MELD >19)** increases SFSS vulnerability due to pre-existing portal hypertension and diminished capacity to compensate for a small graft.
- **Pre-existing portal hypertension**, regardless of the cause, amplifies the stress on a small graft, making SFSS more likely.

Prevention of SFSS

Donor and Recipient Selection

- Careful donor selection is essential, aiming for:
  - **Younger donors** who generally have healthier livers, resulting in improved graft function. (<48 years old)
  - **Donors with normal liver function tests** indicating a healthy liver and minimizing the risk of graft dysfunction.
  - **Donors with a short ICU stay**, signifying a less severe health condition and potentially better graft quality.

Prevention of SFSS

- Graft size should be carefully matched to the recipient's needs:
  - **GRWR should ideally be at least 0.8%,** or even higher for recipients with significant portal hypertension.
  - **Graft quality, particularly the degree of steatosis, should be thoroughly evaluated**, especially for larger recipients.
  - **Recipient age and MELD score** should be considered, as these factors influence the capacity for graft regeneration.
- **Dual grafts** can be considered when a single suitable graft is unavailable.

Prevention of SFSS

Surgical Techniques for Prevention

Reducing Portal Inflow

- **Modulation of splenic artery flow** is crucial, as this artery significantly contributes to portal blood flow. Techniques include:
  - **Splenic artery ligation:** Completely blocking the artery to drastically reduce portal inflow.
  - **Splenic artery banding:** Partially constricting the artery to allow controlled flow reduction.
- **Portacaval shunts** can be created to divert a portion of portal blood flow, relieving pressure on the graft. These shunts connect the portal vein to the inferior vena cava.

Prevention of SFSS

Improving Venous Outflow

- **Surgical techniques are employed to optimize blood drainage from the graft**. These include:
  - **Enlarging the anastomosis between the graft's hepatic veins and the recipient's veins** to facilitate better outflow.
  - **Reconstructing multiple hepatic veins** to ensure adequate drainage from various graft segments. This may involve the middle hepatic vein, veins from segments 5 and 8, the right hepatic vein, and the inferior right hepatic vein.
  - **Performing posterior cavoplasty**, a procedure to widen the inferior vena cava opening where hepatic veins drain, to improve outflow

Treatment of Established SFSS

Supportive care & Prevent other complications

Pharmacologic Graft Inflow Modulation

Interventional Radiology

Surgical Graft Inflow Modulation

Re-Transplant

Treatment of Established SFSS

Supportive Care

- **ICU management is crucial for monitoring and supporting patients with SFSS**. This includes:
  - Diligent monitoring of fluid balance, electrolytes, and nutritional needs.
  - Correction of any coagulopathy (bleeding disorders).
  - Prompt treatment of complications, such as infections or organ dysfunction.

Treatment of SFSS (Medications)

Pharmacological agents to reduce portal flow/pressure

Agents	Mechanism of reducing portal hypertension
SST ([a]octreotide)	Induces splanchnic vasoconstriction via SSTR-2, inhibits stellate cell contraction, and decreases intrahepatic resistance via SSTR-1
Beta-blockers	Reduce cardiac output via β1 blockade Induces splanchnic vasoconstriction via β2 blockade
Vasopressin ([a]terlipressin)	Induces splanchnic vasoconstriction via vasopressin receptor (V_{1a} receptor)
PGE1 PGI2 ([a]iloprost)	PGE1 activates PGE1 receptor and PGI2 activates prostacyclin IP receptor, both lead to upregulation of cyclic adenosine monophosphate and subsequent vasodilation

[a]Synthetic analogs have differential affinity for receptors compared to their natural compounds, which may affect physiological response.
PGE1, prostaglandin E1; PGI2, prostacyclin; SST, somatostatin; SSTR, somatostatin receptor.

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A1 Pharmacological Interventions for Management of Established SFSS

Recommendations

- *Early intervention with SST might be considered to decrease PVP in patients with SFSS.*
  *(Level of evidence: **Moderate**; Strength of recommendation: **Moderate**)*
- *PGE1 and beta-blockade may also be considered to improve SFSS.*
  *(Level of evidence: **Low**; Strength of recommendation: **Weak**)*

A2 Standardized Protocol of Pharmacological Interventions for Management of Established SFSS

Recommendations

- *Adequate trough levels of immunosuppressive medications should be maintained in the setting of SFSS*
  *(Level of Evidence: **Moderate**; Strength of Recommendation: **Strong**)*

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Treatment of SFSS

Surgical and Radiological Interventions

- **When medical management proves insufficient, procedures may be required**:
  - **Revision of anastomoses** can address technical issues hindering outflow.
  - **Portacaval shunt creation** might become necessary to divert portal blood flow.
  - **Splenectomy**, though typically a last resort, can significantly reduce portal inflow.
  - **Interventional radiology techniques** offer less invasive options for managing portal hypertension, such as transhepatic portography and TIPS

B1 IR Techniques (SAE, Splenic Embolization) in the Postoperative Setting

Recommendations

- *Proximal versus distal embolization of the splenic artery can be effective to mitigate Grade B SFSS (portal hypertensive phase).*
  *(Level of evidence: **Low**; Strength of recommendations: **Moderate**)*

B2 The Indications and Techniques for Surgical Interventions in the Postoperative Setting

Recommendations

- *Surgical intervention can be beneficial to those with Grade B SFSS (portal hypertensive phase) that have failed to respond to medical therapy and IR techniques.*
  *(Level of evidence: **Low**; Strength of recommendation: **Moderate**)*
- *SAL/splenectomy is beneficial and recommended as surgical treatment choice in posttransplant Grade B SFSS cases that fail IR interventions.*
  *(Level of evidence: **Low**; Strength of recommendation: **Moderate**)*

B3 The Best Modality for Evaluation of Response to Treatment in SFSS

Recommendations

- *We suggest the use of the following factors to evaluate the response to treatment in SFSS: recovery of liver function (tests), decrease in ascites, and improvement of urine output/renal function.*
  *(Level of evidence: **Low**; Strength of recommendation: **Moderate**)*

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Treatment of SFSS

Retransplantation

- **In severe, unresponsive SFSS cases, re-transplantation is the only viable solution.**

- Indicators of a high risk of graft loss and potential need for re-transplantation include:

  - Persistent high bilirubin (> 10 mg/dL) and prolonged clotting times (INR > 1.6) by postoperative day 7.

  - Isolated bilirubin > 20 mg/dL by postoperative day 14.

C1 Criteria for Retransplantation

Recommendations

- *When medical/IR/surgical interventions fail in SFSS, re-LT should be considered. The decision to retransplant should be based upon the overall clinical situation considering persistent hyperbilirubinemia (total bilirubin >10 mg/dL) with coagulopathy (INR >1.6) or isolated hyperbilirubinemia (>20 mg/dL); ascites; rising ammonia; dysfunction of other organs and absence of sepsis.*
  *(Level of Evidence: **Low**; Strength of recommendations: **Moderate**)*

C2 Timing of Retransplantation

Recommendations

- *Based upon the relatively good outcome for patients with segmental graft dysfunction/SFSS, it might be reasonable to avoid re-LT in the first 2 wk to allow for graft regeneration and/or recovery, except in the situation of Grade C SFSS in which re-LT is recommended given the significant risk of graft failure.*
  *(Level of Evidence: **Low**; Strength of recommendations: **Moderate**)*

C3 Type of Grafts for Retransplant

Recommendations

- *Type of graft will depend on*
  i. Availability of DD grafts
  *(Level of Evidence: **Moderate**; Strength of recommendations: **Moderate**)*
  ii. Availability of a potential living donor
  *(Level of Evidence: **Low**; Strength of recommendations: **Weak**)*

C4 Priority for Retransplant

Recommendations

- *While continued waitlist mortality and dropout for primary LT exist due to increasing demand and insufficient organ supply, ethical principles of utility and justice should be considered when offering re-LT.*

*(Level of Evidence: **Low**; Strength of recommendations: **Moderate**)*

- *In most instances, based on patients with SFSS are already prioritized based on their disease severity status and we would advocate higher prioritization where geographically possible.*
  *(Level of Evidence: **Low**; Strength of recommendations: **Weak**)*

C5 Retransplantation Futility

Recommendations

- *Criteria for the futility of re-LT in SFSS following LDLT may be similar for re-LT for other indications.*
  *(Level of Evidence: **Moderate**; Strength: **Moderate**)*
- *Re-LT should be proposed with caution in patients with concomitant significant renal dysfunction and increasing pressor requirements and avoided in patients with ongoing sepsis or untreated infection (especially with multidrug resistant organisms).*
  *(Level of Evidence: **Moderate**; Strength: **Moderate**)*

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Conclusions

- SFSS is a mismatch between the patient's metabolic needs and the graft function
- SFSS is not uncommon and increases mortality early post LDLT
- Early recognition and treatment is essential for a better outcome
- Management is multi-disciplinary using different modalities
- Prevention is KEY

Thank You!!