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ORIGINAL ARTICLE

SMALL FOR SIZE SYNDROME IN ADULT-TO-ADULT LIVING DONOR LIVER TRANSPLANTATION: A REVIEW OF THE LATEST LITERATURE

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Summary

Living donor liver transplantation (LDLT) has emerged as a popular solution to address the organ shortage, driven by ethical considerations and its increasing demand over the last decade. Nonetheless, in the contest of this innovative technique the emergence of small-for-size syndrome (SFSS) poses a significant challenge, stemming from inadequate liver remnant size to meet postoperative metabolic demands. This can significantly impact the outcomes for both donors and recipients of LDLT. Addressing this challenge necessitates a comprehensive evaluation of the donor, graft, and recipient. Our systematic review, conducted in adherence to PRISMA guidelines, identified 15 articles meeting eligibility criteria. SFSS manifests post-liver transplantation when the transplanted liver fails to meet the recipient's metabolic needs during the recovery phase from end-stage liver disease. Clinical signs, laboratory findings, and Doppler assessments are necessary for diagnosis to facilitate timely interventions and prevent irreversible graft damage. Preventive strategies encompass meticulous donor-recipient selection, precise surgical techniques, and diligent postoperative care. These findings underscore the imperative for ongoing research and the formulation of effective preventive measures to optimize the success of LDLT and enhance patient outcomes.

Key words: small for size syndrome, liver transplant, graft-to-recipient weight ratio, living donor liver transplantation

Abbreviations

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BMI: body mass index
CT: computed tomography
EAD: early allograft dysfunction
GRWR: graft-ratio-weight-ratio
HA: hepatic artery
HABR: hepatic arterial buffer response
HV: hepatic vein
INR: international normalized ratio
LDLT: living donor liver transplantation

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MELD: model of end-stage liver disease
OPTN: organ procurement and transplantation network
PRISMA: preferred reporting items for systematic reviews and meta-analyses
PV: portal vein
PVP: portal vein pressure
PVF: portal vein flow
PNF: primary non-functioning
PV: portal vein
PSV: peak systolic velocity
SFSG: small for size graft
SFSS: small for size syndrome

INTRODUCTION

Since 1994, there has been a growing trend in the utilization of living donor liver transplantation (LDLT) as a solution to the organ shortage due to ethical considerations [1]. The critical assessment of both the donor and graft is essential to reduce the risks associated with small-for-size syndrome (SFSS), a potentially harmful condition that can negatively impact both the graft and recipient [2]. During donor evaluation, a thorough understanding of potential risk factors can help prevent this complication. Timely recognition during transplant allows for actuate strategies to minimize portal vein hyper-flow. At last, updates in treatment strategies can reduce the impact of SFSS on postoperative short- and long-term course [3].
This review provides a brief examination of the syndrome, including its diagnosis, risk factors, and preventive strategies.

MATERIALS AND METHODS

Study selection

This is a systematic review adhering to the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [4]. The MEDLINE registry (https://pubmed.ncbi.nlm.nih.gov) was searched using the following string: (((small for size syndrome) AND ((liver transplant) OR (living donor living transplant) OR (GRWR))). Data extraction was performed on November 22nd 2023. Two authors (G.D.L and S.M.) independently screened publication titles, abstracts, and full-text articles. Publication year, country, study type, number of patients, definition of SFSS, incidence of SFSS, and short- and long-term complications were extracted from the articles meeting the eligibility criteria.

Eligibility criteria

We only included research published in English from 2017 onwards that specifically deals with SFSS following liver transplantation. The inclusion criteria for the study were: retrospective or prospective studies related to SFSS, focusing on risk factors, prevention, and treatment. To maintain consistency in the study, papers exploring SFSS in Eastern populations, as living donor liver transplant prevalence in these regions is distinct, were excluded. Additionally, pre-clinical studies, reviews, letters to the editor, surveys, case reports, abstracts, and small case series were excluded. Furthermore, duplicates and partially duplicate series were also removed from the study.

RESULTS

After initially identifying 187 papers, we excluded 2 papers in foreign languages, 2 duplicates, and 15 comments before screening. In the first screening, 48 papers were excluded due to a lack of relevance to the study's intended scope. Additionally, 34 articles were excluded as review articles, 10 as case reports, and 18 as pre-clinical studies. Furthermore, 35 studies were excluded due to their focus on East Asia populations. This thorough selection process resulted in 23 papers that were assessed for eligibility. In the end, 15 articles were identified as meeting the eligibility criteria for this review. A detailed PRISMA Flowchart summarizes the entire process (Fig. 1). As summarized in Table 1, most of the studies come from Egypt and India, which can be explained by the shortage of deceased donors in these countries. The population analyzed ranges from 13 patients to 665, with the age between the studies seeming to be more homogeneous, with a weighted mean and SD of 50.21 +/-12.77.

Definition and incidence

SFSS is a condition that occurs after liver transplantation when the transplanted liver fails to meet the recipient's metabolic needs during the recovery phase from end-stage liver disease. This happens when the functional capacity of the transplanted liver is not enough to meet the metabolic requirements of the recipient after the transplantation [2,5-7]. Most papers defined SFSS with a graft-to-recipient weight ratio (GRWR) below 0.8, with only one article defining it for a GRWR of below 0.6. The incidence of SFSS ranged from 0.27% to as high as 22.76% [8].

Diagnostic criteria and clinical features

In order to accurately diagnose SFSS, a combination of clinical, laboratory, and imaging parameters is required. While clinical presentation and laboratory findings are important, imaging studies such as Doppler ultrasound can provide valuable information on the hemodynamics and morphology of the graft. A timely diagnosis is crucial in preventing irreversible graft damage and improving chances of recovery.

Various groups have proposed different diagnostic criteria for SFSS. Dahm et al. characterized SFSS as the occurrence of at least two of the following criteria persisting for three consecutive days, following the exclusion of vascular or biliary complications, infections, or rejection episodes: bilirubin levels exceeding 5.85 mg/dl, an international normalized ratio (INR) higher than 2, and the presence of encephalopathy graded at 3 or 4, all within the initial postoperative week [7]. According to Kyushu et al., SFSS is conversely diagnosed by the combination of a total bilirubin level exceeding 10 mg/dl on postoperative day 14, without any other clear cause for cholestasis, and a daily ascites production exceeding 1000 mL on postoperative day 14, or more than 500 mL on postoperative day 28 [9].

Attention must be paid to differentiating SFSS from other syndromes that may arise after transplantation since each one of them implies different approaches:

- early allograft dysfunction (EAD): is defined by the presence of one or more of the following variables: Bilirubin exceeding 10 mg/dL on postoperative day 7; INR surpassing 1.6 on postoperative day 7; or aminotransferase level (AST) exceeding 2000 IU/mL within the initial 7 postoperative days [10];
- primary nonfunction (PNF): is an irreversible and extreme form of EAD when the extent of cellular damage is not compatible with survival, necessitating early retransplantation or resulting in death [11]. The Organ Procurement and Transplant Network (OPTN) considers PNFas an indication for urgent relisting within 7 days post-transplant when AST is > 3000 IU/L and one of the criteria for coagulopathy (INR > 2.5) or acidosis (arterial pH < 7.3 or venous pH < 7.25 or lactate > 4.0 mmol/L) is met [12].

Salman et al. analyzed the ultrasound Doppler changes after LDLT in the hepatic artery (HA) assessing the peak systolic velocity (PSV), portal vein (PV) waveform and velocity, and the shape of the hepatic veins (HV). The patients underwent flow assessment every 12 hours for the first 7 days. Patients who experienced SFSS displayed a higher PV velocity and lower HA - PSV (p value < 0.001). This underscores the utility of Doppler as a valuable tool for the early detection of the syndrome [13].

Risk factors

SFSS has a multifactorial etiology and its development in the postoperative period can be influenced by various risk factors including recipient preexistent status, graft factors, graft volume, and intraoperative factors:

- recipient preexistent factors: body mass index (BMI), model of end-stage liver disease (MELD), and aspartate aminotransferase (AST), were found to be significantly higher in patients who developed SFSS after living donor liver transplantation (LDLT) in the retrospective study by Abdallah et al [14]. In addition, Fujiki et al identified the MELD score as an independent risk factor for SFSS [8]. On the other hand, another study on 134 patients showed that MELD and Child-Pugh scores did not affect the SFSS rate. In the same analysis, portal hypertension before LDLT was identified as a risk factor for SFSS [15];
- graft factors: the studies conducted by Abdallah and Shoreem found a correlation between graft steatosis exceeding 10% and the onset of SFSS. Left lobe grafts were more at risk of developing SFSS [14,15]. Conversely, Ikegami et al. demonstrated that appropriate matching of selected left lobe donors (i.e., age < 48y) with selected recipients (MELD < 19) can lead to acceptable outcomes [16];
- graft volume and donor-recipient liver selection: graft volume is universally recognized as one of the most important variables correlated to the development of SFSS [3]. This is especially true in living donor liver transplantation, where the disparity between the dimensions of the graft and the weight of the donor is greater [17]. Graft-ratio-weight-ratio (GRWR) is the most used parameter to define a graft as "small for size". Literature lacks of consensus on the lower limit values of GRWR to avoid SFSS. Currently "small for size grafts" are defined as those with a GRWR below 0.8% or approximately 40% of the standard recipient liver volume [3]. The definition is supported by several studies, including Abdallah's research, which identifies a GRWR of less than 0.8 as a risk factor for the development of SFSS [14]. In some other studies, identified during the literature review, a small graft is defined if

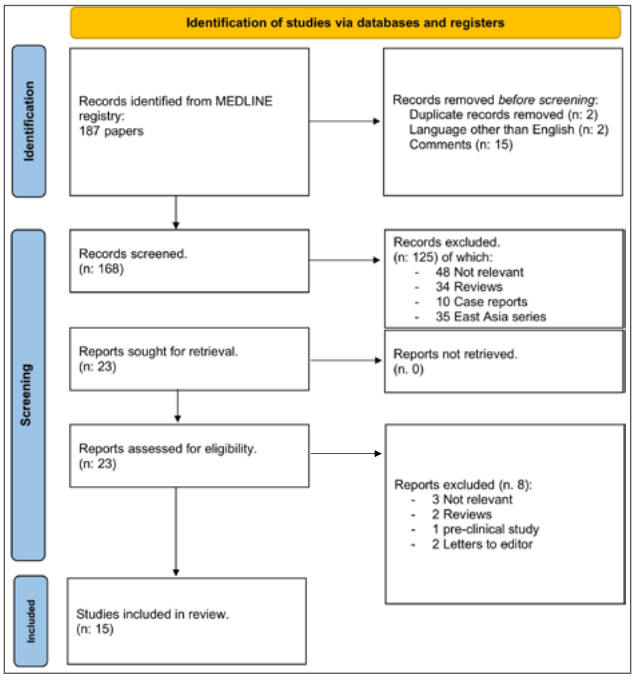

Figure 1. PRISMA flow-chart of the systematic review.

Table I. Summary of the included studies' key characteristics.

Author [ref]	Year	Country	Study type	Population (n)	Age [mean +/- SD]	Primary outcome	SFSS	Small graft definition
Shaw B et al. [1]	2017	U.S.	Retrospective	43	55 +/- 12.5	Validation of a non-weight-based formula to estimate ideal liver volume	9 (21%)	GV/SLV < 0.33
Kanetkar et al. [2]	2017	India	Prospective	27	48.29 +/- 10.92	Impact of PVP and porto-systemic gradient on outcomes in liver transplant	1 (0.27%)	GRWR < 0.8
Shoreem et al. [3]	2017	Egypt	Retrospective	174	46.5 +/- 8.1	Analyse the incidence, risk factors, prevention, treatment, and outcome of SFSS after LDLT	20 (11.5%)	GRWR 0.8-1
Goja et al. [4]	2018	India	Retrospective	665	48.47 +/- 16.82	Postoperative outcomes in RLG	14 (2.1%)	GRWR 0.8-1
Sethi et al. [5]	2018	India	Retrospective	200	41.69 +/- 9.44	LDLT outcomes in GRWR < 0.8%	7 (12%)	GRWR < 0.8
Sholkamy et al. [6]	2018	Egypt	Cross-sectional	69	48 +/- 6.8	Determine the level of portal venous pressure (PVP) for adequate graft function, and study the effect of PVP modulation on the outcome of LT	15 (21.7%)	GRWR < 0.8
Wahab et al. [7]	2018	Egypt	Retrospective	500	55+/- 13.5	evaluate the experience of LDLT in HCV endemic area	6 (1.2%)	GRWR < 0.8
Agarwal et al. [8]	2019	India	Retrospective	147	48.93 +/- 8.74	Determine a minimum absolute weight graft predicting good outcomes	14 (9.52%)	GRWR < 0.8
Soin et al. [9]	2019	India	Retrospective	287	49.3+/- 9.1	Evaluate the outcomes of LD LT with SFSG	8 (2.7%)	GRWR < 0.8%
Iesari et al. [10]	2019	Belgium	Retrospective	64	50.2 +/- 18.22	LDLT outcomes on a single center	3 (4.7%)	GRWR < 0.8%

Table I. *continues.*

Author [ref]	Year	Country	Study type	Population (n)	Age [mean +/- SD]	Primary outcome	SFSS	Small graft definition
Abdallah et al. [11]	2020	Egypt	Retrospective	110	48.8 +/- 6.9	Evaluate perioperative effectors, which can increase the risk of SFSS following adult LDLT	23 (20.9%)	GRWR < 0.8%
Kisaoglu et al. [12]	2021	Turkey	Retrospective	13	52.2 +/- 9.6	Analyzing the effect of portal flow augmentation during LDLT	2 (15.3%)	GRWR < 0.8%
Salman et al. [13]	2021	Egypt	Retrospective	123	48.7 +/- 7.58	Study the early postoperative doppler changes after adult-to-adult LDLT	28 (22.76%)	GRWR < 0.8%
Tourky et al. [14]	2021	Egypt	Retrospective	145	46.9 +/- 17.53	Assess different intraoperative factors that may predict early death after adult-to-adult LDLT.	29 (20%)	GRWR < 0.8%
Fujiki et al. [15]	2022	U.S. and UAE	Retrospective	130	57.54+/- 5.9	Study surgical strategies effects on small graft LDLT	1 (0.8%)	GRWR < 0.6%

LDLT: living donor liver transplant; GRWR: graft recipient weight ratio; GV: graft volume; PVP: portal vein pressure; RLG: right liver graft; SFSG: small-for-size graf; SFSS: small for size syndrome; SLV: standard liver volume.

the GRWR is less than < 0.8 [19], while others consider a graft small even with a ratio between 0.8 and 1 [15]. Recently, Wong et al. showed that GRWR can be safely lowered to 0.6% after careful recipient selection, resulting in excellent outcomes [20]. On the other hand, a study by Sethi, involving 200 patients undergoing LDLT, found no statistically significant difference between patients with GRWR less than 0.8 and those with 0.8 or more (p = 0.247). Furthermore, the study revealed that SFSS syndrome can also develop in normal-sized grafts [21]. Since achieving an optimal GRWR doesn't always consistently prevent SFSS, some researchers suggest that the recipient's weight might not always reflect the true adequacy of the graft. For example, Agarwal suggested excluding the GRWR parameter due to its susceptibility to recipient weight variations. Recipient weight in cirrhotic patients is influenced by ascites, edema, and sarcopenic status. In their study, they determined a cutoff of 643 grams, which demonstrated the optimal balance of specificity (77.8%) and sensitivity (51.2%) for predicting favorable outcome [22]. Shaw et al. [2] sought to validate a formula based not on weight but on the utilization of CT scan based thoraco-abdominal circumferences to calculate the optimal volume for each recipient, termed the standard liver volume (SLV). Through an analysis of their dataset, they classified a graft as "small" if the ratio of Graft Volume to SLV was < 0.33. Using this cut-off, they achieved favorable outcomes in terms of postoperative complications, particularly a low incidence of SFSS. However Ct measured Graft Volume/SLV is frequently overestimated of 20% in comparison to the real weight measured on the back table [23];

- intraoperative factors: intraoperative factors that can determine or influence SFSS include various surgical and procedural elements during liver transplantation. These factors may impact the balance between the size of the transplanted liver graft and the recipient's needs,

potentially leading to complications associated with SFSS. The predominant mechanism in SFSS is considered sinusoidal shear stress, primarily induced by elevated portal vein pressure (PVP) and/or portal vein flow (PVF). These factors contribute to graft over-perfusion, leading to disturbances in hepatic microcirculation. Thus, high portal vein inflow is considered one of the biggest risk factors in developing SFSS [3]. Regarding this subject, Abdallah et al. conducted measurements using a catheter in the superior mesenteric vein at preclamping, and post-reperfusion and calculated the mean portal vein pressure (PVP). Subsequently, in their data analysis, they determined that the mean portal pressure at preclamping (22.5 mmHg), post-reperfusion (17.5 mmHg), and the overall mean PVP (20.5 mmHg) showed sensitivities of 95.7, 91.3, and 95.7%, along with specificities of 87.4, 88.9, and 89.7%, respectively, in predicting SFSS [14]. In addition, Sholkamy et al. analyzed also the PVP before, and after graft reperfusion and mean PVP in 69 patients undergoing LDLT. The best cutoff values for the prediction of SFSS were pre-clamping PVP 24.5 mm Hg, with a sensitivity of 83.3% and specificity of 53.5%, and post-perfusion PVP of 16.5 mm Hg, with a sensitivity of 91.7% and specificity of 50.5% [24]. Conversely, in a prospective study by Kanetkar involving 42 patients undergoing LDLT, six patients met the criteria for SFSS. Among them, five exhibited PVP greater than 20 mmHg and GRWR exceeding 0.8%. However, no statistically significant differences were observed in SFSS development between patients with PVP greater than 20 mmHg and those with PVP less than 20 mmHg (Vijay Kanetkar et al., 2017). These findings suggest that the occurrence of SFSS is influenced by multiple factors, extending beyond elevated PVP and GRWR, as it can manifest in patients with normal PVP and GRWR. At last, according to the series of Shoreem, there was no correlation between SFSS development and cold and warm ischemia time [15].

PREVENTION AND TREATMENT

Proactive prevention of SFSS entails meticulous donor-recipient selection, precise surgical techniques, and post-operative management strategies.

As mentioned before, careful donor recipient selection in terms of graft volume and GRWR is mandatory to prevent the development of SFSS.

Considering the theory of hyper-perfusion [6], another strategy to mitigate the risk of SFSS involves assessing hemodynamics, particularly portal flow [14,24]. This evaluation can occur preoperatively, considering the patient's degree of portal hypertension, conducting ultrasound or invasive assessments of portal flows, and studying the presence and impact of portosystemic shunts [25].

Intraoperative monitoring of hemodynamics and portal flow can also guide surgical decisions to mitigate SFSS risk [24,26]. Advances in portal flow modulation [27], such as splenic artery ligation and hemi-portocaval shunt creation [28] demonstrate to mitigate the SFSS risk in certain cases. Another strategy may include liver outflow modulation: Goja et al. [26] demonstrate the effectiveness of the middle hepatic vein venoplasty in LDLT in preventing SFSS and early allograft dysfunction.

Considering the expansion of Living Donor Liver Transplantation (LDLT) to adult recipients and the broadening of transplantability criteria in recent years, studies have emerged to investigate the feasibility of employing auxiliary grafts. The objective is to facilitate less complex donor procedures and avert the risk of Small for Size Syndrome (SFSS). This strategic shift acknowledges the need for innovative approaches to ensure the viability of liver transplants in adult recipients while mitigating the potential complications associated with size disparities between the graft and the recipient. The exploration of auxiliary grafts represents a proactive step in adapting transplantation protocols to evolving clinical demands, aiming to optimize outcomes and expand the pool of viable donors in the context of LDLT [29].

SFSS treatment

Once the Small Size Syndrome (SFSS) has manifested, unfortunately, the options available to reduce the risk of catastrophic consequences are limited. The literature primarily delineates therapeutic strategies based on symptomatology. These strategies involve the assertive administration of albumin and diuretics to counteract significant ascitic production, complemented by the extensive use of antibiotics to reduce the risk of sepsis [5,30].

None of the articles extracted from the review process singularly focus on postoperative symptomatic treatment; instead, they predominantly engage in discourse concerning strategies aimed at averting the onset of SFSS. Few authors propose postoperative ligation [31] or embolization of the splenic artery [8] when arterial ligation or splenectomy does not coincide with transplantation. This procedure can be performed once SFSS is suspected or as described by Fujiki et al., after sonographically detecting a reduction in hepatic arterial blood flow due to hepatic arterial buffer response [HABR].

Some preclinical studies and rare clinical investigations focus on the pharmacological treatment of portal hyperperfusion and the consequent shear stress and HABR. Somatostatin and its analogs appear to effectively PVP by inducing a direct splanchnic vasoconstriction effect and inhibiting gut-derived vasodilatory peptides (glucagon, VIP, substance P) [32]. The protective effect of continuous somatostatin infusion in the initial postoperative period has been demonstrated in both pig and murine models [33-35]. Somatostatin use has also been described in clinical

practice [36,37] showing promising effects in ameliorating the consequences of SFSS. Other therapeutic options may include beta-blockers [38,39], which reduce cardiac output and portal venous flow, as well as prostaglandin E1 [PGE1] and prostacyclin [PGI2], which appear to improve hepatic circulation and prevent small graft congestion [40,41]. If pharmacological treatment and postoperative portal flow modulation fail, the only other viable option is retransplantation [30].

CONCLUSIONS

The use of living donations has gained more attention, making SFSS a well-recognized phenomenon. Although safety is a top priority in LDLT, it is important to understand the risk factors, causes, and treatment of SFSS to improve recipient outcomes. Fortunately, although it is still difficult to completely prevent SFSS in patients receiving small grafts, its incidence has decreased significantly in recent years. This positive trend is due to a better selection of donor-recipient matches, the development of new techniques to prevent SFSS, and improved postoperative management. It is crucial to recognize and diagnose SFSS in a timely manner to implement interventions that can prevent irreversible damage to the graft, thus improving the chances of recovery.

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Conflict of interest statement

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Author contributions

AL, RDC, PR: conceptualisation, visualization; AL, RDC, MS, PR: methodology, software formal analysis; AL, RDC: validation; MS, GDL: investigation, data curation; LDC: resources; PR: writing-original draft preparation, writing-review and editing; AL, RDC, PR, LDC: supervision.
All authors have read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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