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ORIGINAL SCIENTIFIC REPORT

Portosystemic Shunts for "Too Small-for-Size Syndrome" After Liver Transplantation: A Systematic Review

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Abstract

Background Portosystemic shunts (PSSs) modulate the portal hyperperfusion against small-for-size syndrome (SFSS) after split or living donor liver transplantation.

Aim To find out the results and the limitations of PSSs against SFSS.

Materials and methods We searched PubMed and Cochrane databanks for systematic review and analyzed the indications, types, morbidities, and survivals of the PSSs at split or living donor liver transplantations.

Results Total 66 patients were assessed in 16 studies. Main indications for PSS were graft recipient weight ratio (GRWRs) <0.8 % and/or portal vein pressure >20 mmHg. Five different types of PSSs were described but hemi-portocaval shunts were the most common one. The incidence of SFSS was 12 %. Overall 90-day, 1-, and 3-year graft survivals were 80, 70, and 47 %, respectively. GRWR <0.65 % was found as the only significant parameter on graft survival. The 90-day, 1- and 3-year graft survivals for GRWR <0.65 and ≥0.65 % patients were 62.5, 42.8, and 30.0 and 95, 94, and 67 %, respectively ($p = 0.03$, $p = 0.01$, and $p = 0.18$).

Conclusion PSSs can modulate the small graft size (GRWR < 0.8 %) and/or portal hypertension (>20 mmHg) after split or living donor liver transplantations sufficiently. However, its protective effect is not unlimited. If the GRWR is below 0.65 %, survival decreases significantly despite PSSs.

Introduction

The limited supply of deceased donor organs is a great problem for patients who are waiting for liver transplantation. Living donor liver transplantation (LDLT) has been adopted to expand the graft pool and it became the main source of liver grafts in some countries where the deceased donation was poor such as Middle East and Asian countries. However, LDLT increased the risk of complications such as small-for-size syndrome (SFSS) that can result in liver failure in the early post-transplant period [1]. Portal hyperperfusion, graft congestion, small functional liver mass, and inability of ingraft response have been considered as the possible causes of SFSS [2]. Based on these pathophysiological features, portosystemic shunts were brought into use to overcome the SFSS after the first description of mesentericoportal disconnection by Boillot in 2002 [3]. By now, different types of shunt procedures have been reported against SFSS during split or living donor liver transplantations and these patients had a large range of graft recipient weight ratios (GRWRs). The aim of the systematic review was to analyze the indications, techniques, results, and limitations of all the published clinical data about the PSSs against SFSS.

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Materials and methods

Electronic searches, PubMed, and Cochrane databases, were scanned lastly in October 04, 2014. The keywords used for searching were [(small for size) AND (transplantation) AND ((shunt) OR (modul*))]. The titles and/or abstracts of the scanned articles were assessed. If the articles met our inclusion criteria, full-text versions were obtained for the second assessment. The references of the selected relevant articles were also cross-checked to decrease the possibility of missing publications. If the selected articles were obviously irrelevant to the aim of this systematic review, they were excluded. Some other studies were also excluded (experimental studies, reviews, letters to editors, studies about different modulation methods except surgical shunts, temporary shunts for unhepatic phase during surgery, duplicated studies, and technical notes not including patient data). The reasons for the exclusion of the studies were recorded in the flow chart (Fig. 1). All the patients in the selected studies were included, irrespective of age, region, and race. No restrictions were made on language, country, or journal. For missing or confusing data, we contacted the authors of the studies via e-mail.

Features of articles, patient demographics, model for end-stage liver disease (MELD) score, graft weight to recipient weight ratio (GRWR), graft volume to estimated standard liver volume (GV/SLV), indications for shunt, types of shunt procedures, presence of small-for-size syndrome (SFSS), and outcomes of patients were enrolled. If the evidence of SFSS was not described or declared in the text, the case accepted as free of SFSS. In almost all studies, the size has been described as GRWR, therefore we focused on GRWR as a marker of graft size. If a non-shunt modulation technique (splenectomy or splenic artery ligation) was made prior to shunt procedure, the portal flow measurements after the non-shunt modulation was accepted as the primary value. If a non-shunt modulation (splenectomy or splenic artery ligation) was made after the shunt procedure, portal flow measurements before the non-shunt modulation was accepted as the last value.

Statistical analysis was performed using SPSS 20.0 for Windows computer software (SPSS Inc., Chicago, IL, USA). For survival analysis, Kaplan–Meier graphs were constructed and log-rank comparison of the groups was used. One-way analysis of variance and unpaired t test were used to compare means and Pearson, Chi-square, and Fisher exact tests were used to compare unpaired parameters. $p < 0.05$ was accepted as statistically significant. To find out a cut-off value for GRWR, receiver operating characteristics (ROC) curve analysis was used.

Results

All of the selected publications were retrospective case series and case reports and reported between 2002 and 2013. The studies were originated from ten centers from seven countries, including 66 cases in 16 articles [3–18]. For missing or confusing data, we reached the

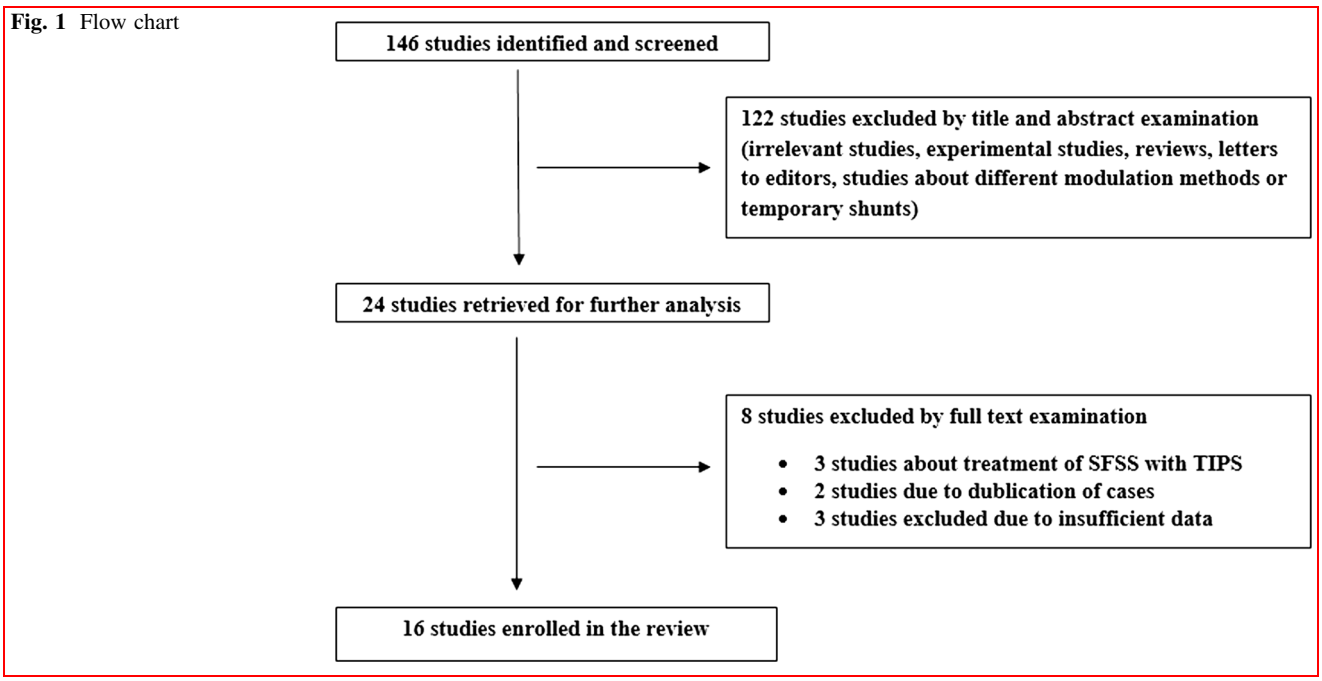

Fig. 1 Flow chart

corresponding authors via e-mail and seven of them replied to us regarding eight studies [3, 7, 8, 10, 12, 13, 17, 18].

All the patients had been accepted as post-transplant SFSS candidate due to low GRWRs (<0.8 %) and/or high portal vein pressure and all these patients had been required a kind of PSS for prevention of SFSS. The most common cause of end-stage liver failure was viral hepatitis. Cryptogenic cirrhosis, primary biliary cirrhosis, autoimmune hepatitis, Budd Chiari syndrome, primary sclerosing cholangitis, Wilson's disease, and acute hepatic failure were the other underlying causes. Demography of the studies and cases are shown in Tables 1 and 2, respectively.

Five different shunt procedures were defined in the reviewed articles.

1. Hemi-portocaval (Fig. 2a): It was the most preferred one (48 cases, 72.7 %) [5–18].
2. Meso-renal: It was between inferior mesenteric vein and left renal vein and performed in end-to-side manner in three cases (Fig. 2b) [4, 13].
3. Meso-caval: This shunt between superior mesenteric vein and inferior vena cava. It was performed in only one case (Fig. 2c) [14].
4. Meso-caval plus mesenteric disconnection (Fig. 2d): It was first described by Boillot and all of the 11 cases in the literature were reported by this author [3, 18].
5. Splenorenal (Fig. 2e): There were three cases, all of them reported by Lauro [9].

Iliac vein, paraumblical vein, contralateral portal branch, and left renal vein were used as the interpositional vascular grafts to perform the shunts. The mean decrease rate in portal venous pressure (PVP) after shunt opening was 30 % for hemi-portocaval shunt (HPCS), 20 % for meso-renal shunt, 27 % for meso-portal shunt plus mesenteric disconnection, and 45 % for splenorenal shunt. There was only one case with meso-caval shunt in which decrease in PVP was 40 % [14].

There was no standard definition for SFSS that was accepted by all the authors. In three studies [3, 11, 15], authors obviously declared that they used the proposed definition of SFSS by Dahm (also called "definition of Clavien") [19]. In the remaining studies, intractable ascites, protracted cholestasis, coagulopathy, renal insufficiency, and tendency to sepsis were also used for the definition of SFSS [5, 7, 9, 14]. The overall incidence of SFSS was 12 % (eight cases). In three cases, dysfunction was reversible. In five cases, it progressed to non-function and two of them resulted in mortality. The remaining three patients underwent re-transplantation.

Portal steal phenomenon (encephalopathy and/or graft dysfunction) is the main complication of a PSS. The direction of the portal flow has great importance due to this potentially fatal complication. There were three studies including the intraoperative assessment of the direction of portal flow by Doppler ultrasonography [7, 11, 15]. But there was no study that evaluate the relative portal flow

Table 1 Demography of the studies and accepted indications to perform portosystemic shunt

Author	Study design	Date	Country	*n*	Accepted indications for shunt procedure[a]
Boillot [3]	Case Report	2002	France	1	GRWR: 0.61
Sato [4]	Case Report	2004	Japan	2	PVP $\geq$ 19 mmHg
Masetti [5]	Case Report	2004	Italy	1	GRWR: 0.3
Takada [6]	Case Report	2004	Japan	2	GRWR $<$ 0.8 % and/or PVP $\geq$ 20 mmHg
Troisi [7]	Retrospective	2005	Belgium	8	GRWR $\leq$ 0.8
Taniguchi [8]	Case Report	2007	Japan	1	GV/SLV: 35.8
Lauro [9]	Retrospective	2007	Italy	4	Small GRWR. High PVP. High PCG
Ikegami [10]	Case Report	2008	Japan	1	%SLV: 23 - High PVF
Yamada [11]	Retrospective	2008	Japan	11	%0.6 $\leq$ GRWR $\leq$ % 1 and PVP $\geq$ 20 mmHg
Oura [12]	Case Report	2008	Japan	1	PVP 28 mmHg versus PVF 2100 ml/dk
Kanazawa [13]	Case Report	2009	Japan	1	PVP $>$ 20 mmHg
Sato [14]	Case Report	2010	Japan	4	PVP $>$ 18 mmHg
Botha [15]	Retrospective	2010	USA	16	GRWR $<$ 0.8 %
Huang [16]	Case Report	2011	China	1	GRWR $<$ 0.8 %
Ravaioli [17]	Case Report	2012	Italy	1	PCG 18 mmHg after SAL
Boillot [18]	Retrospective	2013	France	12	GRWR $<$ 0.8 % and/or PVP $\geq$ 20 mmHg

GRWR graft weight to recipient weight ratio, *PVP* portal venous pressure, *GV* graft volume, *SLV* standard liver volume, *PCG* portacaval gradient, *PVF* portal venous flow, *SAL* splenic artery ligation

[a] If the indication for the shunt procedure is not exactly mentioned in the article, the emphasized parameters were considered as accepted indications

Table 2 Clinical data of the patients

Parameters	n[a]	Values
Male/female	62	36/26
Age (year) (mean ± SD) (range)	61	51.0 ± 10.9 (16–67)
MELD score (mean ± SD) (range)	52	16.8 ± 6.9 (6–49)
Graft types		
Left lobe		48 (72.7 %)
Right lobe		14 (21.3 %)
Left lateral sector		3 (4.5 %)
Right lateral sector		1 (1.5 %)
GRWR (mean ± SD) (range)	63	0.72 ± 0.19 % (0.3–1.3 %)
GV/SLV (mean ± SD) (range)	20	29.8 ± 6.5 (19.0–41.3)
PVP before shunt (mmHg) (mean ± SD) (range)	28	24.9 ± 7.2 (15–47)
PVP after shunt (mmHg) (mean ± SD) (range)	28	16.8 ± 4.9 (8–25)
Rate of decrease in PVP (%) (mean ± SD) (range)	28	31.8 ± 14.6 (8.1–61.5)
PCG before shunt (mmHg) (mean ± SD) (range)	24	17.6 ± 5.2 (8–29)
PCG after shunt (mmHg) (mean ± SD) (range)	24	7.2 ± 3.6 (1–15)
Rate of decrease in PCG (%) (mean ± SD) (range)	24	60.0 ± 17.6 (16.6–91.7)
SFSS (%)	66	8 (12.1 %)
30-day patient/graft survival	49	92 %/90 %
90-day patient/graft survival	36	81 %/75 %
1-year patient/graft survival	32	72 %/65 %
3-year patient/graft survival	20	55 %/40 %

[a] Number of patients with available data

MELD model for end-stage liver disease, *GRWR* graft weight to recipient weight ratio, *GV* graft volume, *SLV* standard liver volume, *PVP* portal venous pressure, *PCG* portacaval gradient, *SFSS* small-for-size syndrome

through the graft vs through the constructed shunt. There were eight cases (12 %) with clinically evident portal steal phenomenon after PSSs [10, 12, 15, 18]. Graft dysfunction due to the portal steal was seen in two patients who had pre-existing unrecognized large spontaneous portosystemic shunts [18]. In the remaining six cases (9.1 %), portal steal was caused by constructed shunts, five cases with hemi-portocaval shunt, and one patient with meso-portal shunt combined with mesenteric disconnection.

After the prophylactic shunt procedure, closing the shunt in time is an important issue for long-term prevention of encephalopathy. Nevertheless, the data about the follow-up for shunt patency were very limited in the majority of the reviewed cases. To shorten the shunt patency, two methods have been suggested. First one was the placement of an endoloop around the shunt intraoperatively and closure of the shunt under fluoroscopic examination (n:1) [8]. Second one was the patent ligamentum teres hepatis as a vein graft to provide a timed spontaneous closure (n:4) [14].

Acute rejection, sepsis, portal venous thrombosis, cardiac failure, and duodenal perforation were the other complications. Three cases of acute rejection were reported in only one study containing eight cases, and fulminant sepsis was seen in one of these cases after steroid treatment [7]. Duodenal perforation and peritonitis was seen in one case at early postoperative period [7]. A patient was died due to cardiac failure on the 9th postoperative day [18]. Portal venous thrombosis was seen in two patients [13, 18]. In one of them, there was accompanying portal steal, who died on the 8th postoperative day, while waiting for re-transplantation [18]. In the other patient with portal thrombosis, the patency was provided with surgical application of urokinase and heparin into the mesenteric venous system [13].

We analyzed the 90-day hospital mortality and survival rates of the shunted patients for each value of GRWR (Fig. 3). ROC curve analysis showed that the GRWR value was a significant variable for 90-day mortality (AUC: 0.710), however the reliability of this variable was not perfect due to wide range of 95 % confidence interval (95 % CI 0.496–0.907) (Fig. 4). The values of GRWR below and above 0.65 % posed a significant difference in 90-day survival ($p = 0.032$; sensitivity: 88 %, specificity: 70 %). When we compared the mean values of MELD scores, recipient's ages, and portal perfusion parameters such as portal venous pressure (PVP) and portacaval gradient (PCG) before and after shunt, there was no significant difference between these two groups. Ninety-day and

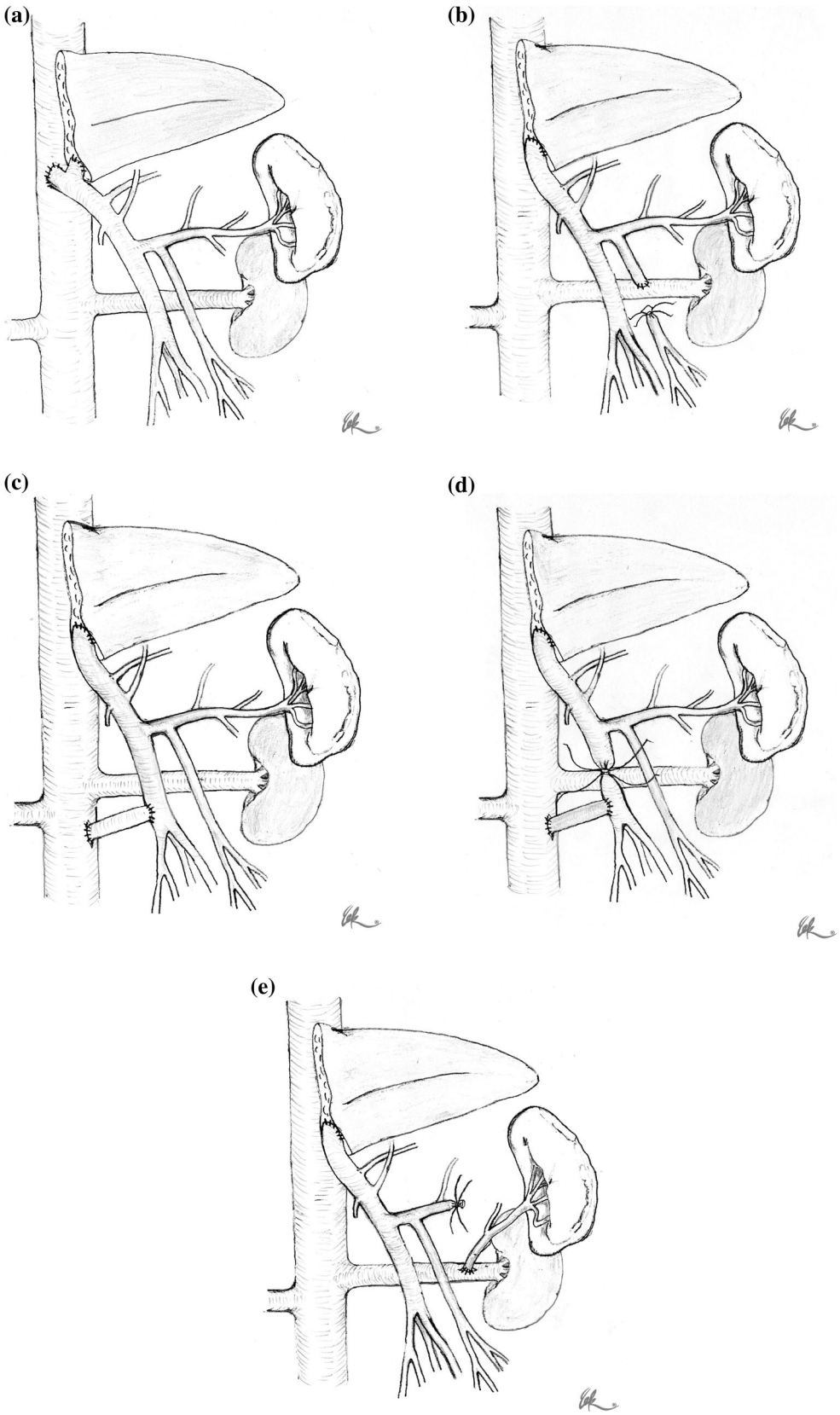

Fig. 2 Types of the portosystemic shunt. **a** Hemi-portocaval shunt for left lobe graft, **b** meso-renal shunt between inferior mesenteric vein and left renal vein, **c** meso-caval shunt between superior mesenteric vein and inferior vena cava, **d** meso-caval shunt plus mesenteric disconnection, **e** splenorenal shunt

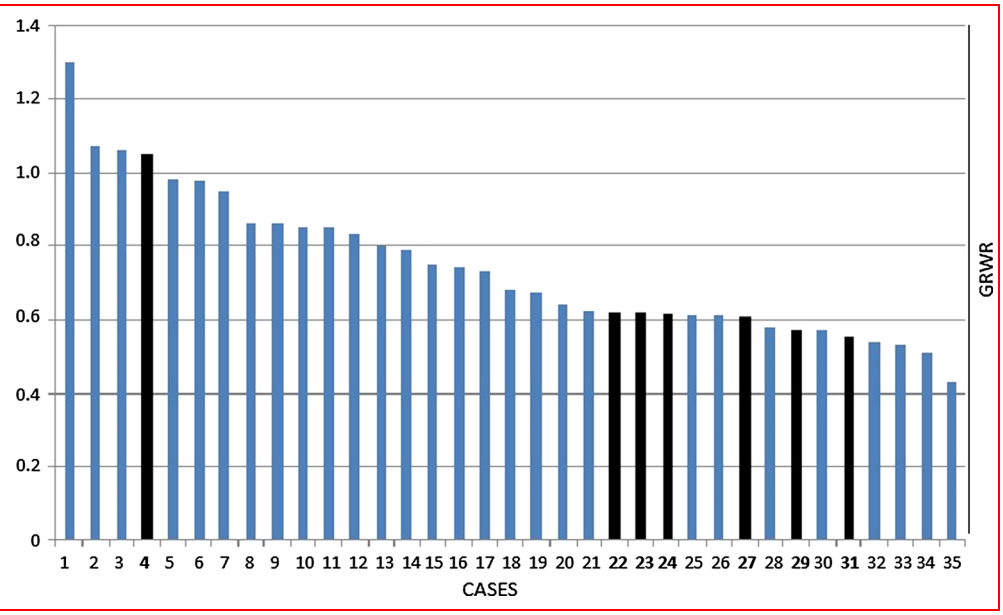

Fig. 3 Ninety-day survival chart. GRWR below 0.65 % was associated with high number of mortal cases in the first 90 days. *Black bars* show mortal cases

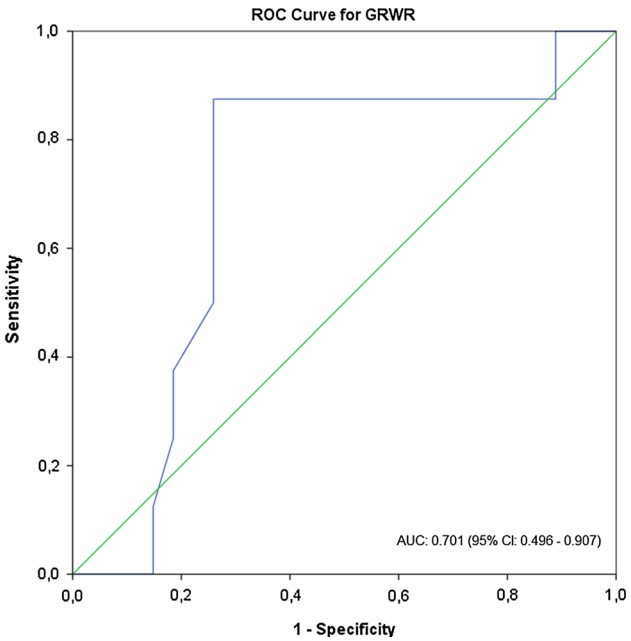

Fig. 4 Receiver operator characteristics curve analysis for relation between GRWR and 90-day survival

1-year survival rates were significantly less in GRWR <0.65 % group despite the PSSs (Table 3; Fig. 5). In patients with GRWR <0.65 %, 90-day survival was 75 and 43 % for HPCS and meso-caval plus mesenteric disconnection, respectively, but the difference was not significant ($p = 0.31$).

We determined that a great majority of the reviewed cases (77.2 %) belong to left-sided liver grafts (left lobe or left lateral sector). Overall, 90-day graft and patient survival for left-sided grafts were 78 %. In all of the mortal cases, the GRWR was below 0.61 %. There was no enough data about the 90-day survival of right lobe grafts. Ninety-day survival was known in only 3 of 15 right-sided grafts. The 90-day graft survival was 82 % in patients with HPCS and 63 % in patients with meso-caval plus mesenteric disconnection. The difference was not significant ($p = 0.39$). There was no sufficient data about other shunt types.

Discussion

Currently split and LDLT has been widely accepted treatment in irreversible liver failure. This development has brought out the importance of the transplanted liver volume. It is still a debate as to how much liver would be enough for the survival of a human. In the last 20 years, the importance of the graft size was evaluated by many authors who tried to define the SFSS. In 1999, Kiuchi et al. [20] reported a decrease in survival, poor bile production, prolonged cholestasis, intractable ascites, and increase in septic complications when the GRWR was <1.0 %. In 2003, Soejima et al. [21] defined the SFSS as having both prolonged functional cholestasis and intractable ascites. In 2005 and 2006, Dahm [19] and Soejima [22] tried to provide a consensus on the definition of SFSS. The definition and the diagnosis of SFSS was based on both prolonged functional cholestasis (total bilirubin level >10 mg/dl on postoperative day 14) without any other definitive causes for cholestasis and intractable ascites (daily production of

Table 3 Comparison of recipients according to the cut-off value of 0.65 % for GRWR

Parameters	No[a]	GRWR < 0.65	No[a]	GRWR ≥ 0.65	*p* value
Number of cases		25		30	
Age (years)	23	50.3 ± 13.7 (16–67)	27	51.1 ± 10.7 (21–66)	0.11
MELD	14	15.3 ± 4.9 (6–21)	19	17.0 ± 9.6 (6–49)	0.55
PSS Types					
Hemi-portocaval	17		22		
Meso-renal	0		1		
Meso-caval	1		0		
Meso-caval + disconnection	7		4		
Splenorenal	0		3		
PVP before shunt (mmHg)	9	26.0 ± 6.6 (17–37.6)	15	24.6 ± 7.7 (15–47)	0.81
PVP after shunt (mmHg)	9	16.8 ± 5.3 (8–23)	15	16.8 ± 5.2 (9–25)	0.99
Rate of decrease in PVP (%)	9	35.5 ± 13.0	15	29.3 ± 14.0 (9–61.5)	0.57
PCG before shunt (mmHg)	10	18.2 ± 4.4 (12–24)	14	17.2 ± 5.8 (8–29)	0.75
PCG after shunt (mmHg)	10	7.8 ± 4.0 (1–15)	14	6.8 ± 3.3 (2–13)	0.25
Rate of decrease in PCG (%)	10	57.4 ± 21.8 (16.6–91.7)	14	60.0 ± 14.6 (38.1–89.6)	0.09
SFSS	25	5 (20 %)	30	3 (10 %)	0.44
30-day patient/graft survival (%)	23	87/82.6	25	96/96	0.33
90-day patient/graft survival (%)	16	62.5/50.0	19	95/95	0.03*
1-year patient/graft survival (%)	14	50/42.8	16	94/94	0.01*
3-year patient/graft survival (%)	10	30/10	9	67/67	0.18*

MELD model for end-stage liver disease, *GRWR* graft weight to recipient weight ratio, *PVP* portal venous pressure, *PCG* portacaval gradient, *SFSS* small-for-size syndrome

* *p* value for comparison of patient survival

[a] Number of patients with available data

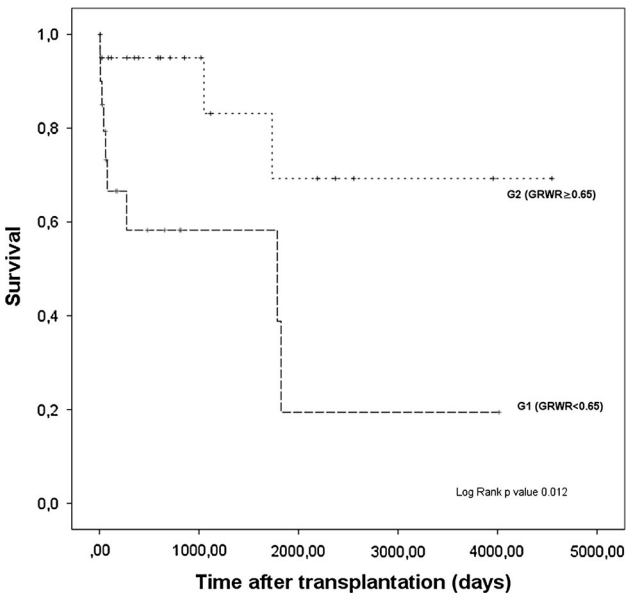

Fig. 5 Kaplan–Meier survival analysis of the groups

ascites >1000 ml at postoperative day 14 or >500 ml at postoperative day 28). Hill et al. [23] used the same parameters with some differences in 2009. In the reviewed articles, Dahm's definition [19] was the main adopted definition, but intractable ascites has still been used as a component of SFSS by many authors. Therefore, it seems that there is still a need for a proper definition of SFSS.

Graft sinusoidal pressure is the major determinant of clinically evident SFSS [10, 24]. Balance of portal venous and hepatic arterial flow are crucial in liver perfusion [25]. High portal blood flow causes a compensatory decrease in hepatic arterial flow (buffering response) [26]. Portal hyperperfusion is a stimulus for rapid regeneration of hepatocytes in the early period after LDLT [27]. However, the regeneration of non-hepatocytes is much slower than the regeneration of hepatocytes. This could explain that rapid volume gain does not mean rapid gain of liver function [28] Hence, persistence of portal hyperdynamic circulation induces hepatic dysfunction [26]. Elevated PVP, especially early in the first week, was associated with higher incidence of bacteremia, cholestasis, prolonged prothrombin time, and intractable ascites, which led to poor outcome [24, 29]. By decelerating the regenerative process, interventions that reduce portal pressure, could therefore improve liver function of the regenerative parenchyma. Based on this mechanism, many treatment modalities and surgical techniques that reduce the portal perfusion have

been developed to prevent or treat the SFSS; such as splenic artery ligation [17, 24, 30], splenic artery embolisation [31, 32], splenectomy [5, 9, 13, 33, 34], intraportal infusions [35], transjugular intrahepatic portosystemic shunts [36], and portocaval or meso-caval shunts [3–18].

Among the modulation methods, PSSs can be expected as the most effective one. Many anastomoses between different branches of the portal and caval systems were identified, however there was a mess in the definition and terminology of the shunts. The data of this review were not sufficient to make a clear comment about the types of the shunts and the outcomes.

The graft size is a critical parameter for graft and patient survival after a living donor or split liver transplantation. Currently, grafts with a GRWR less than 0.8 % are widely regarded as small-for-size grafts [19, 37, 38]. It was previously reported that 90-day survival rates of GRWR $\geq$0.8 and <0.8 % grafts were 93 and 65 %, respectively [20]. In this review, we demonstrated that when a PSS was added, the 90-day survival rates were 95 % and 62.5 % for GRWR $\geq$0.65 and <0.65 %, respectively.

The type of the graft (right or left) is as important as the GRWR on the development of SFSS, graft dysfunction, and graft and patient survival. Tanaka et al. [29] reported that there was no significant difference in 90-day patient survival between GRWR $\geq$0.8 % (81.7 %) and GRWR <0.8 % (86.4 %) in right lobe LDLT, whereas survival of the recipients with GRWR <0.8 % (54.5 %) was significantly lower than that in recipients with GRWR $\geq$0.8 % (82.1 %) in left lobe LDLT. Recently, Lee et al. [39] suggested the GRWR 0.7 % as a safe lower limit without portal inflow modulation in right lobe LDLT but not for left lobe grafts. In this review, most of the patients (77.2 %) had left-sided liver grafts. We analyzed that by constructing a PSS, GRWR can be reduced to 0.65 % without increase in mortality even for the left lobe grafts have a higher donor safety than the right lobe grafts in adult-to-adult living related liver transplantation.

However, it should be kept in mind that most of the reviewed studies were successful case reports, and PSSs have the potential for causing fatal portal steal phenomenon. Although the portal steal is the main complication of shunt procedures, there was no quantitative data in the reviewed articles. Additionally, the fate of the shunts was unknown in most of the cases. According to us, comparison of relative blood flow through portal vein and through shunt can provide reliable and objective data about the risk of portal steal. However, in our view, there is a deficit in literature on this subject. However, left lobe grafts are more prone to SFSS and early graft failure. PSSs by modulating the portal flow can provide sufficient graft and patient survival with the left lobes till the border of 0.65 % GRWR. The mortality and graft loss were significantly high in patients with GRWR <0.65 % when comparing with GRWR $\geq$0.65 % (sensitivity 88 %, specificity 70 %).

There were several limitations of this review. The lack of data on PVP, PCG, and follow-up reduced the reliability of statistical analyses. Some of the major factors affecting outcome of patients with small-for-size grafts (e.g., donor's age, steatosis in graft, anatomic variations in vascular structures, warm/cold ischemia time, presence of cirrhosis, and collateral circulation) were not available in most cases. Additionally, the accepted definitions of SFSS and the parameters for evaluation of portal perfusion were not standard in the studies. Most of the reviewed studies had small number of cases. It should be kept in mind as a warning that PSSs have the potential for causing fatal portal steal phenomenon. Although the portal steal is the main complication of shunt procedures, there was no quantitative data in the reviewed articles. Some surgeons had some degree of success in some recipients with very small grafts. This review is not able to explain the causes of good results with very small grafts, and it should be a subject for future studies.

In conclusion, the definition and the risk factors of SFSS, the parameters measuring portal perfusion, and units of them should be standardized, and long-term follow-up are needed in future studies. This paper has provided the most comprehensive results regarding PSSs performed in LT to decrease the risk of SFSS. The limit level of GRWR can be lowered to 0.65 % by constructing a PSS even with the left-sided grafts.

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Compliance with ethical standards

Conflict of Interests None.

Source of Support None.

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