Graft Inflow Modulation in Living Donor Liver Transplantation with a Small-for-Size Graft: A Systematic Review and Meta-Analysis

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Rezumat

Modularea fluxului de grefă în transplantul hepatic de la donator viu cu grefă „small-for-size”: review sistematic și meta-analiză

Intrarea: Grefa „small for size” și, în consecință, sindromul „small for size” (SFSS) este o complicație importantă a transplantului hepatic de la donator viu adult (LDLT). Strategiile optime de prevenire și management intra și postoperator pentru SFSS sunt imprecise. Această cercetare are ca scop elaborarea unei meta-analize care să evaluateze și să comparare strategiile existente de modulare a fluxului portal (MFP). Rezultatul primar este determinarea incidenței SFSS.

Metode: A fost efectuată o căutare sistematică în bazele de date Google Scholar, Embase, PubMed și Cochrane Library. Au fost utilizate atât modele cu efecte fixe, cât și modele cu efecte aleatoare pentru efectuarea meta-analizei.

Rezultate: Douăzeci și cinci de studii au fost selectate dintr-un grup de 830 de studii, dintre care 13 au comparat tehnicile chirurgicale disponibile între cohorte cu și fără MFP și 12 au raportat rezultate ale pacienților care au dezvoltat SFSS în urma LDLT. Incidența SFSS a fost semnificativ mai mică în cohorta MFP decât în cohorta fără modulare a fluxului portal (non-MFP). Supravițuirea globală la un an și rata de re-transplant au fost semnificativ mai bune în cohorta MFP decât în cohorta non-MFP.

Concluzii: La pacienții cu LDLT diagnosticăți în perioada de reperfuzie cu creșterea presiunii și/sau a fluxului venos portal, aplicarea MFP scade semnificativ incidența SFSS și asociază o
Abstract

Introduction: Small-for-size graft and consequently small-for-size syndrome (SFSS) is an important issue for adult living donor liver transplantation (LDLT). The optimal intra- and postoperative prevention and management strategies for SFSS remain unclear. We aimed to analyse and compare the existing strategies of portal inflow modulation (PIM) and conduct a meta-analysis of studies comparing various PIMs. The primary outcome was the incidence of SFSS.

Methods: The Google Scholar, Embase, PubMed, and Cochrane Library databases were systematically searched. Both fixed- and random-effects models were used to perform the meta-analysis.

Results: Twenty-five studies were selected from a pool of 830 studies, of which 13 compared available surgical techniques between cohorts with and without PIM, and 12 reported outcomes of patients who underwent LDLT and developed SFSS. The incidence rate of SFSS was significantly lower in the PIM cohort than in the non-portal inflow modulation (NPIM) cohort. One-year overall survival (OS) and the re-transplantation rate were significantly better in the PIM cohort than in the NPIM cohort.

Conclusions: In LDLT patients diagnosed during the reperfusion period with increased portal venous pressure and/or flow, application of PIM significantly decreased the incidence rate of SFSS and demonstrated significantly better one-year OS.

Key words: small-for-size graft, small-for-size syndrome, portal vein pressure, portal vein flow, portal venous pressure modulation, LDLT transplantation

Introduction

The cornerstone of the living donor liver transplantation (LDLT) strategy is to offer the recipient with certain model for end-stage liver disease (MELD) and Child-Pugh scores a graft of the adequate size and volume (1). The first adult LDLT was performed using left lobe transplants. In 1999, Kiuchi et al. reported that patients who underwent liver transplants with a graft recipient weight ratio (GRWR) < 1.0 demonstrated significantly lower graft survival. The above results were more remarkable in elderly patients. Based on the above findings, the Kyoto group revisited their strategy and started to use right lobe transplants without the middle hepatic vein with a GRWR ≥ 0.8 (2). However, in 1997, the Hong group had already proposed the use of right lobe transplants with the middle hepatic vein to avoid graft dysfunction (3). Consequently, the Kyushu group used transplants with a
lower limit of graft volume/standard liver volume (GV/SLV) of 30% and reported a graft dysfunction rate of 20%, which resulted in a switch to using more right lobe transplants with a lower limit of GV/SLV > 35%, corresponding to a GRWR of 0.7 (4). Furthermore, the Tokyo group proposed a GV/SLV lower limit of 40% because patients transplanted with a GV/SLV < 40% demonstrated poor graft survival (5). Based on the above accumulated evidence, any graft with a GV/SLV < 40% and a GRWR < 0.8 is considered a small-for-size graft (SFSG) (6). A new clinical syndrome called small-for-size syndrome (SFSS) has been described in LDLT patients with SFSG with specific characteristics including prolonged cholestasis, decreased prothrombin time, intractable ascites, and grade 3 or 4 encephalopathy (7,8). Although it is a well-known syndrome after LDLT and its incidence rate is approximately 20%, there is no worldwide acceptable definition for SFSS (8-10).

Seven definitions of SFSS have been proposed thus far. The two most commonly used are those proposed by Soejima et al. and Dahm et al (Table 1) (9-15). Both Western and Asian LDLT centres consider that patients transplanted with grafts with a GV/SLV of 40% or GRWR of 0.8 will demonstrate optimal results without the need for graft inflow modulation (9-15).

There is an ongoing debate on the correlation and inter-relationships of portal venous flow (PVF), portal venous pressure (PVP), and hepatic venous pressure gradient (HVPG) on hyperflow and portal hypertension (PHT) during liver transplantation. Previous studies have reported a negative impact of elevated PVP > 20 mmHg, portal vein flow PVF > 250 ml/min/100 gr graft, and/or HVPG > 15 mmHg on the outcomes of LDLT and hepatic resections (18-20). By contrast, Sainz-Barriga et al. demonstrated that there is no correlation between PVF and PVP that suggest that they should not be used individually to estimate hyperflow and PHT during liver transplantation. In addition, they observed a significant association between central venous pressure (CVP) and PVP. In particular, any elevation of the CVP impacted the PVP value by 60%. Therefore, the estimation of the severity of PHT only on PVP could be misleading. In centres of excellence of LDLT surgery, cut-off values of PVP > 20 mmHg and/or PVF > 250

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**Table 1. Definitions of SFSG, SFSS, DFH, and EAD**

| Author, country, year | Term | Definition |
|----------------------|------|------------|
| Au, Hong Kong, China, 2015 (6) | Small for size graft | Any graft with GRWR<0.8 and or GV/SLV <40% |
| Soejima, Kyushu, Japan 2003 (9) | Small for size syndrome | TB > 5 mg/dl on the 14th postop day combined with intractable ascites (more than 1 litre on the 14th postop day or more than 500 ml on the 28th postop day) |
| Soejima, Kyushu, Japan 2006 (10) | Small for size syndrome | TB > (10 mg/dl or 171 umol/L) on the 14th postop day combined with intractable ascites (more than 1 litre on the 14th postop day or more than 500 ml on the 28th postop day) |
| Dahm, Switzerland, 2005 (11) | Small for size syndrome | Any occurrence two of the following on the three consecutive days (TB >100 umol/L or 5.85 mg/dl, INR>3, encephalopathy grade 3 or 4 |
| Hill, USA, 2009 (12) | Small for size syndrome | Any occurrence of continuous increase of TB up to (10 mg/dl or 171 umol/L) after the 7th postop day, combined with ascites>2 L and INR >1.5 |
| Ikegami, Kyushu, Japan 2012 (13) | Delayed functional hyperbilirubinemia | Any occurrence of TB more than (20 mg/dl or 342 umol/L) for more than 7 consecutive days after the 1st postop week |
| Olthoff, USA, 2012 (14) | Early allograft dysfunction | Any increase of TB> (20 mg/dl or 342 umol/L) or INR>1.6 on the 7th postop day |
| Okamura, Kyoto, Japan, 2018 (15) | Early allograft dysfunction | Any increase of both TB > (10 mg/dl or 171 umol/l) and INR>1.6 on the 7th postop day |

**Abbreviations:**
- GRWR: graft recipient weight ratio
- GV/SLV: graft volume to standard liver volume
- SFSG: small for size graft
- SFSS: small for size syndrome
- DFH: delayed functional hyperbilirubinemia
- EAD: early allograft dysfunction
- TB: total bilirubin
- INR: international normalised ratio

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ml/min/100 gr graft are considered criteria for surgical management of increased PHT (20).

The aetiology of SFSS is multifactorial. Parameters related to the recipient such as MELD and Child-Pugh scores, age, and blood group incompatibility, as well as donor factors such as age, degree of steatosis, WIT, CIT, ischaemia/reperfusion injury, pressure gradients, and adequate inflow and outflow, may contribute to the occurrence of SFSS (21,22).

The aim of the present study was to compare the impact of portal inflow modulation (PIM) strategies with non-modulation strategies in patients with increased PVP or PVF by conducting a systematic review and meta-analysis.

Methods

Literature Search

A systematic search of the literature was conducted in the Google Scholar, Embase, PubMed, and Cochrane Library databases, using full term and MeSH search terms (liver transplantation, living donor liver transplantation, adults, children, portal venous pressure, prophylactic splenic artery embolisation/ligation, portal venous flow modulation, small-for-size graft, and small-for-size syndrome). The literature search included articles published in the last 30 years. This study did not include any human participants or animals and was therefore exempt from ethics approval.

Study Selection and Inclusion and Exclusion Criteria

Articles evaluating the effect of elevated PVP on patients undergoing LDLT were included in the present study. The study population consisted of adults. Abstracts and editorials without original data were excluded.

Data Extraction and Outcomes

Two authors (PG and DA) independently extracted the following summary data from the included studies: name of authors, age, diagnosis, sex, MELD score, ABO incompatibility, graft weight, mean graft volume, EBL, CIT, WIT, PVP at laparotomy, PVF, hepatic arterial flow, septic and vascular complications, retransplantation rate, and 1- and 3-year graft and patient survival rates.

Statistical Analysis

Statistical analyses were conducted using Review Manager software (version 5.3: Cochrane Collaboration, Oxford, England) (23). Heterogeneity was assessed using the I2 test, and cut-off values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity, respectively (24). Where heterogeneity occurred, both fixed- and random-effects models were generated and the conclusions compared, and the random-effects model used when discrepancies were present. Fixed-effects models were used in cases where the I2 value was less than 25%.

Dichotomous variables were analysed on the basis of the odds ratios (ORs) with 95% confidence intervals. For the outcomes considered, the reference categories were selected such that an OR < 1 favoured the PIM cohort. Continuous variables were combined on the basis of the mean difference (MD) and standardised MD. The studies were then combined using the Mantel-Haenszel procedure. For studies that did not report the means and variances of the two groups, these values were estimated from the median, range, and size of the sample, using the technique described by Hozo et al (25). Analysis of the survival benefits was performed using the method described by Palmar et al (26).

In all analyses, the point estimate was considered significant at P < 0.05.

Results

Twenty-five studies were included from an initial pool of 830 studies comprising 3411 patients (8,10,27-49). In 13 retrospective comparative studies comprising 1810
patients, 682 (32%) underwent PIM and 1128 (62%) represented the control cohort who did not undergo PIM (Table 2(27-39). Twelve studies comprising 1601 patients compared the outcomes of LDLT recipients and focused on the cohort of patients who developed SFSS: 178 (11%) out of 1601 patients demonstrated SFSS (Table 3). The definition of the SFSS varied widely: 9 (36%) out of the 25 studies, mainly from Japan, used the definition proposed by Soejima et al., and 11 (44%) out of 25 studies used the definition proposed by Dahm et al. (Tables 1, 2, and 3). Five out of 13 comparative studies monitored PVF (Table 2(27,28,30,34,35). In particular, only two clearly defined that the cut-off level was more than 250 ml/min/100 gr graft (34, 35). All of them reported a significant reduction in PVF after PIM (Table 2). Seven of the 13 comparative studies monitored PVP (29-31,33, 38,39). Only three of them clearly reported a cut-off value of more than 20 mmHg (29,31,36) and one reported a PVP more than 15 mmHg (Tables 2 and 3(38).
| Author, country year | Num. Patients | SFSS Definition | SFSG Definition | Monitored PVP/PVF Col-off value | Initial PVP/PVF PIM vs NPIM | Final PVP/PVF PIM vs NPIM | Portal Infow Modulation | SFSS (n) | Overall Mortality due to SFSS | FU (months) | NOS | Max=9 |
|----------------------|--------------|----------------|----------------|-------------------------------|-----------------------------|-----------------------------|------------------------|----------|-------------------------------|-------------|------|-------|
| Troisi (27) Belgium, 2003 | 13-11 | Graft dysfunction, cholestasis, coagulopathy and massive ascites | GRWR<0.8 | PPF NR | 2600±832 ml/min vs NR | 1700±689 ml/min vs NR | SAL | 3 | 2 | 20±9 | 8 |
| Troisi (28) Belgium, 2005 | 8-5 | Graft dysfunction, cholestasis, coagulopathy and massive ascites | GRWR<0.8 | PFF (ml) | 537±220 vs 401±225 | 190±70 vs NA | Hemiportocaval shunts | 3 | 2 | 22.5±11 | 8 |
| Yoshikuni (29) Japan, 2007 | 44-69 | Bilirubin >10 mg/dl on POD 14" and intractable ascites 8 | GW/SLW<40% | PVP >20 mmHg | 19±4 vs 18±4 | 17±4 vs NA | Splenic embolisation:15, SAL:6 | 31 | 0 | 48 | 8 |
| Umetsu (30) Japan, 2008 | 21-18 | Bilirubin >10 mg/dl on POD 14" and intractable ascites 8 | GRWR<0.8 | PPF NR | NR | Significantly reduced | Splenic artery embolisation:15, SAL:6 | 6 | 1 | NR | 7 |
| Ogura (31) Japan, 2010 | 134-432 | Two of the following on 3 consecutive days; Bilirubin>100 umol/L, INR>2, encephalopathy grade 3 or 4 (9) | GRWR<0.7 | PPF >20 mmHg | 19±5 vs NR | 14±3 vs NR | Splenectomy: PSS | 4 | 2 | 60 | 8 |
| Botha (32) USA, 2010 | 16-5 | Two of the following on 3 consecutive days; Bilirubin>100 umol/L, INR>2, encephalopathy grade 3 or 4 (9) | GRWR<0.8 | PCVG NR | 18(12-25) vs NR | 5(1-5) vs NR | Hemiportocaval shunts | 1 | 1 | 19(6-37) | 7 |
| Goralczuk (33) Gemany, 2011 | 15-7 | Bilirubin >10 mg/dl, intractable ascites and NR >1.5 on POD 14" | GRWR<0.8 | PPF NR | 15 vs 15 | Decreased by 5 vs increased by 4 | Posterior cavography | 5 | NR | 60 | 7 |
| Du (34) China, 2010 | 6-2 | Progressive cholestasis, portal hypertension and abundant ascites | GRWR<0.8 | PPF >250 ml/min/100gr graft | 405(257-554) ml/min/100gr graft vs NR | 196(87-296) ml/min/100gr graft vs NR | SAL, splenectomy | 3 | 1 | NR | 6 |
| Chang (35) Korea, 2014 | 3-31 | Progressive cholestasis, coagulopathy and intractable ascites | GRWR<0.8 | PPF >250 ml/min/100gr graft | 47ml/min/100 gr graft vs NA | 155 ml/min/100 gr vs NA | SAL, splenectomy | 0 | NR | NR | 5 |
| Wang (36) Japan, 2014 | 154-122 | Two of the following on 3 consecutive days; Bilirubin>1000 umol/L, INR>2, encephalopathy grade 3 or 4 (9) | GRWR<0.8 | PPF >20 mmHg | 24.9±4.5 vs 23.9±6.1 | 16.1±4.2 vs 18.4±4.5 | Splenectomy | 39 | NR | 4.5±3.3 years | 7 |
| Emond (37) USA, 2017 | 52-222 | Two of the following on 3 consecutive days; Bilirubin>1000 umol/L, INR>2, encephalopathy grade 3 or 4 (9) | GRWR<0.8 | NA | NA | NA | SAL, splenectomy, PSS | 16 | 2 | 36 | 7 |
| Badawy (38) Japan, 2017 | 88-76 | Two of the following on 3 consecutive days; Bilirubin>1000 umol/L, INR>2, encephalopathy grade 3 or 4 (9) | GRWR<0.8 | PPF >15 mmHg | 19±5 vs 19±7 | 13±3 vs 12±2 | Splenectomy | 2 | 0 | 80 | 7 |
| Yao (39) Japan, 2018 | 128-128 | Bilirubin>10 mg/dl on POD 14" and intractable ascites 8 | GRWR<0.8 | PPF NR | 221(11-35) vs 17(6-36) | 18(16-27) vs 12(3-15) | Splenectomy | 52 | NR | 120 | 7 |
| Total 1810 pts | 682(38%) | 1138(62%) | 5(38%) definitions ref No 9 | 4(31%) definitions ref No 8 | Splenectomy: 8 SAL:5 HPC:2 PSS:2 Spl Embolisation:1 Post cavaoplasty:1 | 165 | 11 | HQ=11 |
### Table 3. Study characteristics of non-comparative studies

| Author, country year | Num. Patients (No of SFSS) | SFSS Definition | SFSG Definition | Portail Venous Pressure Modulation | Overall Mortality due to SFSS | NOS |
|----------------------|---------------------------|-----------------|-----------------|-----------------------------------|------------------------------|-----|
| Takahasi (40) Japan, 2018 | 37 (NR) | Bilirubin>5mg/dl or ascites>1/L/day on POD14 | GRWR<0.8 | Splenectomy | NR | 8 |
| Kanekar (41) India, 2017 | 42(6) | Two of the following on 3 consecutive days; Bilirubin>100 umol/L, INR>2, encephalopathy grade 3 or 4 | GRWR<0.8 | None underwent PIM | NR | 7 |
| Osman (42) Egypt, 2017 | 129(7) | Two of the following on 3 consecutive days; Bilirubin>100 umol/L, INR>2, encephalopathy grade 3 or 4 | GRWR<0.8 | Splenectomy ± PSS | 7 | 7 |
| Ikegami (43) Japan, 2016 | 207(21) | Bilirubin>20mg/dl within one month of transplantation | GV/SLV<35% | Splenectomy | 12 | 7 |
| Shimazu (44) Japan, 2016 | 48(0) | Two of the following on 3 consecutive days; Bilirubin>100umol/L, INR>2, encephalopathy grade 3 or 4 | GRWR<0.8 | None underwent PIM | 0 | 7 |
| Salman (45) Egypt, 2016 | 123(24) | Two of the following on 3 consecutive days; Bilirubin>100 umol/L, INR>2, encephalopathy grade 3 or 4 | GRWR<0.8 | NA | NR | 7 |
| Liu (46) China, 2016 | 246(17) | Bilirubin>171 umol/L (>10mg/dL), with or without ascites > 1L on POD 14th | GRWR<0.8 | NA | NR | 7 |
| Vasavada (47) Taiwan, 2014 | 186(22) | Bilirubin >5 mg/dl, on POD 14th and intractable ascites | GRWR<0.8 | SAL, splenectomy | NR | 7 |
| Sanchez-Cabus (48) Spain, 2013 | 45(0) | Two of the following on 3 consecutive days; Bilirubin>100 umol/L, INR>2, encephalopathy grade 3 or 4 | GRWR<0.8 | NA | 0 | 7 |
| Ishizaki (49) Japan, 2012 | 54(0) | Two of the following on 3 consecutive days; Bilirubin>100 umol/L, INR>2, encephalopathy grade 3 or 4 | GRWR<0.8 | NA | 0 | 7 |
| Soejima (10) Japan, 2012 | 312(47) | Bilirubin >10 mg/dL on POD 14th and intractable ascites | GV/SLV<35% | Splenectomy | 0 | 7 |
| Sanefuji (8) Japan, 2010 | 172(34) | Bilirubin >5 mg/dl, on POD 14th and intractable ascites | GV/SLV<40% | Splenectomy ± PSS | NR | 7 |
| Total | 1601(178) | 6 (50%) definitions Ref 9 5(42%) definitions Ref 8 | Splenectomy:4 Spl/my±PSS:2 SAL:1 | 19 | HD:12 |

SAL: splenic artery ligation, GRWR: graft-to-recipient-weight ratio, SFSS: small-for-size-syndrome, SFSG: small for size graft, NOS: Newcastle-Ottawa scale, PSS: portal-systemic shunts, POD: postoperative day, intractable ascites: ≥ 1000mls/day on POD 14th or 500mls on POD 28th, GW/SLW: graft weight/standard liver weight, GV/SLV: graft volume/standard liver volume, PIM: portal inflow modulation, NA: nonapplicable

8: Reference No: 8 Soejima Y, et al. 9: reference No: 9 Dahm, et al.

Splenectomy was used in 8/13 (61.53%) retrospective comparative studies to modulate portal inflow, five (38.46%) used splenic artery ligation, two used portosystemic shunts in combination with splenectomy and splenic artery ligation, two used hemi-portocaval shunts alone, one each used splenic artery ligation and posterior cavoplasty (Tables 2 and 3). The overall perioperative mortality secondary to SFSS occurrence was 21% and was reported in 15 out of 25 studies (Tables 2 and 3) (10,27-32,34,37,38,42-44,48,49).

Meta-analysis was conducted using the data from the 13 comparative studies (27-39). There was no evidence of statistically significant differences in the demographic characteristics and ABO incompatibility between the donors and recipients. Moreover, graft characteristics such as graft weight and mean graft volume were not different between
Table 4. Outcome of interests of studies comparing Portal inflow modulation vs non-modulation

| Outcome of Interest | Number of studies and patients | Statistical method, estimated effect, 95% CI | p-value | I² (%) |
|---------------------|--------------------------------|------------------------------------------|---------|--------|
| Recipient Age (27-31,33,34,36-38) | 10,1499 | MD=1.65(-1.20, 4.50) | 0.26 | 95 |
| Recipient’s Gender (Male) (29-31,33,36-38) | 7, 1454 | OR=1.03(0.62, 1.30) | 0.81 | 0 |
| MELD score (28-31,38-39) | 7, 1445 | MD=-0.00(-1.16, 1.16) | 1.00 | 77 |
| Donor’s Age (29-31,36-38) | 6, 1432 | MD=1.66(-5.96, 4.28) | 0.22 | 93 |
| Donor’s Gender (male) (29,31,36-38) | 5, 1393 | OR=0.69(0.45, 1.06) | 0.09 | 65 |
| ABO incompatible (29,31,36,38) | 4, 1119 | OR=1.91(0.76, 4.79) | 0.17 | 63 |
| Graft weight (gr) (28-31,37,38) | 7, 1177 | MD=-44.99(-67.65, 42.81) | 0.66 | 99 |
| Mean Graft volume (ml) (27,30,36) | 3, 339 | MD=-12.42(-67.65, 42.81) | 0.66 | 88 |
| GRWR ratio (%) (27-34,37,38) | 10, 1244 | MD=-0.00(-1.16, 1.16) | 1.00 | 77 |
| EBL (ml) (27-30,33,38) | 7, 995 | MD=-6(-8.88, 56.41) | 0.85 | 96 |
| CIT (min) (27-30,33,38) | 6, 3675 | MD=-0.05(-10.16, 11.24) | 0.92 | 63 |
| WIT (min) (28-36,33,38) | 5, 462 | MD=-1.05(-7.32, 5.22) | 0.74 | 76 |
| PVP at lap/my (mmHg) (29,36,38) | 3, 553 | MD=-2.14(-0.62, 4.91) | 0.13 | 87 |
| HAF (ml/min) (27,36) | 2, 300 | MD=-29.81(-75.84, 16.23) | 0.20 | 91 |
| SFSS (27,28,30,32,34,36,38) | 7, 545 | OR=0.28(0.16, 0.51) | <0.001 | 0 |
| Sepsis (27-29,38,39) | 5, 570 | OR=1.14(0.58, 2.21) | 0.71 | 30 |
| PV thrombosis (27,28,36,38,39) | 5, 733 | OR=2.07(0.77, 5.60) | 0.15 | 24 |
| HA Thrombosis (27,36,38) | 3, 464 | OR=1.23(0.17, 8.75) | 0.84 | 31 |
| Retransplantation (27,28,32) | 3, 58 | OR=0.15(0.03, 0.71) | 0.02 | 0 |
| 1-OS (27,29,30) | 3, 703 | HR=0.51(0.27,0.95) | 0.03 | 0 |
| 1-GS (28,37,38) | 3, 451 | HR=0.75(0.30, 1.89) | 0.55 | 35 |
| 3-GS (37,38) | 2, 438 | HR=0.97(0.51,1.83) | 0.93 | 25 |
| 1-PS (28,29,30,33,37,38) | 6, 512 | HR=0.92(0.56, 1.51) | 0.73 | 0 |
| 3-PS (29,30,37,38) | 4, 794 | HR=1.03(0.75, 1.40) | 0.86 | 7 |

MELD: model for end-stage liver disease, GRWR: graft recipient weight ratio, EBL: estimated blood losses, HA: hepatic artery thrombosis, CIT: cold ischemic time, PVP: portal venous pressure, PVF/GW: portal venous flow/ graft weight ratio, HAF: hepatic artery flow, SFSS: small-for-size-syndrome, OS: overall survival, GS: graft survival, PS: patient survival, P: portal vein, OR: odds ratio, MD: mean difference, HR: hazard ratio, PIM: portal inflow modulation, NPIM: non-portal inflow modulation, lap/my: laparotomy.

Three studies including 58 patients reported retransplantation rate. There was evidence that retransplantation was performed significantly less in the PIM cohort (2.7%) compared to the NPIM cohort (28.5%), (OR = 0.15 (0.03, 0.71), p = 0.02) (Table 4).

In three studies including 703 patients, one
year overall survival (OS) was significantly better in the PIM cohort than in the NPIM cohort (HR = 0.51 (0.27, 0.95), p = 0.03) (Table 4). Twenty-three of the 25 studies scored more than 7 points on the Newcastle-Ottawa scale (NOS) assessment and were classified as of high quality (Tables 2 and 3).

**Primary Outcome**

There was evidence that the incidence rate of SFSS was significantly lower in the PIM cohort (5.5%) than in the PIM cohort (16.7%), (OR = 0.28 (0.16, 0.51), p<0.001) (Fig. 2 Table 4).

**Discussion**

To the best of our knowledge, this is the first meta-analysis to assess the use of PIM in LDLT patients with increased PVP or flow in the reperfusion phase.

It has been reported that the incidence rate of SFSS in cases with a GRWR < 0.8 varies widely between 0% and 43%. In contrast, in grafts with a GRWR > 1.0, the incidence ranges between 0 and 5%(8). In the present study, there was evidence of a lower incidence rate of SFSS in the PIM cohort (5%) than in the NPIM cohort (16.7%). This finding is optimistic because it is comparable to recipients with a GRWR > 1.0. Therefore, a detailed analysis was conducted to define the parameters, factors, and conditions that contributed to the production of the above results.

It has been reported that donor age, female sex, and MELD score are risk factors for graft failure and consequent graft loss (50). Furthermore, patients with MELD scores between 14 and 25 typically have the most survival benefits from LDLT (50). In the present study, the recipients' age, sex, and MELD score did not demonstrate significant differences. Of note, the MELD scores of the PIM and NPIM cohorts were 16 (14-23) and 17 (13-20), respectively. These scores demonstrate that patients were carefully selected for LDLT and that selection bias may have influenced the results. Donors' ages in the PIM and NPIM cohorts were 40 (36-45) and 36 (34-47), respectively, which was a non-significant difference. It has been reported that donors aged > 45 years may have a negative impact on the outcomes (50-52).

There is evidence that ABO-incompatible liver grafts can trigger hyper-acute rejection mediated by anti-ABO antibodies (51). In the present study, there were no differences in ABO-incompatibility between the PIM and NPIM cohorts.

It has been reported that a GRWR < 0.8 has a major impact on the increased occurrence of SFSS(9). In the present study, both PIM and NPIM cohorts included patients with GRWRs < 0.8 (Tables 1 and 2). However, there was evidence that the PIM cohort included patients with significantly lower GRWRs than the NPIM cohort (Table 4). This finding supports the effectiveness of surgical techniques on the modulation of elevated PVP.
and/or PVF. In particular, four studies used only splenectomy (29,36,38,39), three used either SAL or splenectomy (34,35,37), two HPCS only (28,32), two splenectomies and/or portosystemic shunts (31,37), one study SAL and/or splenic artery embolisation (30), one only SAL (29), and one posterior cavoplasty (33). Recent guidelines by the international liver transplantation society recommend close monitoring of PVP, PVF, and hepatic artery haemodynamics to diagnose early occurrence of SFSS. They also recommend the use of SAL/embolisation and/or any portosystemic shunts to prevent and manage SFSS. Notably, they did not mention splenectomy in the above recommendations (52). Splenectomy was used as a modulation technique mainly by the Kyoto and Kyushu LDLT teams, while other LDLT centres are reluctant to use it because of major complications such as post-splenectomy sepsis, portal and splenic thrombus, and bleeding complications. Recently, Moon et al. reported that splenic devascularisation efficiently alleviated increased PVP; moreover, there was evidence that the splenic devascularisation cohort demonstrated shorter operative time and less postoperative complications and mortality compared to the splenectomy cohort (53). In the present study, further detailed subgroup analysis of the surgical interventions in the meta-analysis was technically not feasible due to the lack of data. Furthermore, the heterogeneity of the applicable surgical techniques was high in studies conducted in different institutions, and some sample sizes were underpowered. Therefore, heterogeneity, learning curve, and institutional and underpowered sample bias may have influenced the above results.

The EBL parameter demonstrates the operative safety of the intervention and the level of the learning curve. Our analysis demonstrated no differences between the interventional and control cohorts (\textit{Table 4}). Furthermore, there were no differences in portal vein, hepatic artery thrombosis, and sepsis incidence rates between the interventional and control cohorts. These findings further support the safety of the applied interventions. However, only five studies reported data for sepsis and portal vein thrombosis and three reported hepatic artery thrombosis: therefore, underpowered sample and institutional bias might have influenced the results.

Overall perioperative mortality due to SFSS occurrence was reported in 15/25 studies (\textit{Tables 2 and 3}) (10,27-32,34,37,38,42-44,48,49). A previous systematic review on both LDLT and hepatectomies reported an overall mortality of 21% (16). In the present study, the overall mortality in LDLT patients secondary to SFSS was 21% and ranged from 5% to 40%, and no significant differences were detected between the PIM and NPIM cohorts. The most common cause of death in both cohorts was sepsis (27,28,32,34,35).

Retransplantation is a treatment option in cases of irreversible graft failure after LDLT. This decision is based on operative risk and the possibility of long-term survival benefits. Age, creatinine levels, and urgency of retransplantation are associated with poor prognosis (54). Retransplantation was reported in only three studies including 58 patients; there was evidence that significantly fewer re-transplantations were performed in the PIM cohort (2.70%) than in the NPIM cohort (29%) (\textit{Table 6}) (27,38,32). Sepsis was the most common cause of death. However, the above results should be treated cautiously because underpowered samples may have influenced the results.

For the first time, we estimated and compared overall graft and patient survival between the PIM and NPIM cohorts. The lower incidence rate of SFSS and the lack of differences in the incidence rates of portal vein, hepatic artery thromboses, and septic complications reflected the significantly better one-year OS of the PIM compared to the NPIM cohort (\textit{Table 4}). However, the above result included data from only three studies including 703 patients: therefore, underpowered samples might have influenced the results. Furthermore, PIM resulted in a lower incidence rate of SFSS, but the 1- and 3-year graft and patient survival were not different between the two cohorts.
Based on the evidence that PIM is mainly necessary during the critical period of graft regeneration, researchers have found that the main limitation of surgical techniques is the permanent modification of the portal venous inflow (55). In recent years, research has focused on the pharmacological modulation of PVP and/or PVF with somatostatin, due to its ease of use and reversibility. Somatostatin is a natural peptide hormone located within and outside the liver and acts through five types of somatostatin receptors (SSTRs), and its effects are predominantly inhibitory. Somatostatin, by inducing vasoconstriction in the portomesenteric vasculature, can decrease PVP and/or PVF in a dose-dependent manner (56). It has been reported that somatostatin may attenuate acute shear stress injury due to portal hypertension and consequently positively impact small-for-size liver graft survival (57). Recently, Troisi et al. reported that somatostatin may reduce the hepatic venous portal gradient in patients with clinically significant portal hypertension without influencing arterial supply to the liver graft (58).

A previous systematic review based on 12 studies including 449 patients demonstrated that the mortality, morbidity, and retransplantation rates ranged from 0% to 33%, 17% to 70%, and 0% to 25%, respectively. The PIM cohort demonstrated an actuarial survival rate of 84% at five years (59). The present systematic review was based on 25 studies including 3411 patients, with an additional meta-analysis conducted on 24 patient and graft variables. In particular, there was new evidence that demonstrates that the SFSS rate was significantly lower in PIM compared to the NPIM cohort. The retransplantation rate was significantly lower in the PIM compared to the NPIM cohort, and one year OS was significantly better in the PIM cohort compared to the NPIM cohort.

The present study underlines the importance of definition in medicine (60). Liver transplant surgeons from centres of excellence in LDLT urgently need to collaborate to define a new worldwide acceptable definition of SFSS.

The results of this study should be interpreted in the context of its limitations. The studies analysed were conducted in single centres over a long period of time, and their follow-up periods varied widely. Moreover, they did not use a single definition for SFSS and the indications for modulation, and consequently, the applied interventions varied widely. Therefore, national, institutional, selectional performance, follow-up, and underpowered sample bias might have influenced the results. In addition, further subgroup analysis of the types of graft inflow modulation was technically not feasible because the majority of the variables consisted of a small number of studies with small sample sizes (Table 4).

Conclusion

In conclusion, the interventional cohort included patients with significantly lower GRWR and demonstrated a significantly lower incidence rate of SFSS, a significantly lower retransplantation rate, and a better one year OS than the control cohort. Therefore, in cases of increased PVP, HPVG, and PVF, surgical modulation of the graft inflow can be safely applied.

Conflict of Interest

All authors declare that they have no conflicts of interest to disclose.

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