Is Portal Venous Pressure or Porto-systemic Gradient Really A Harbinger of Poor Outcomes After Living Donor Liver Transplantation?

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Background: Portal hyperperfusion as a cause of small for size syndrome (SFSS) after living donor liver transplantation (LDLT) remains controversial. Portal venous pressure (PVP) is often measured indirectly and may be confounded by central venous pressure (CVP). **Methods:** In 42 adult cirrhotics undergoing elective LDLT, PVP was measured by direct canulation of portal vein and porto systemic gradient (PSG) was obtained after subtracting CVP from PVP. None underwent portal inflow modulation. SFSS was looked in 27 patients after excluding 15 with technical complications. **Results:** Clinical features of SFSS found in 6 patients, 5 with graft recipient weight ratio (GRWR) > 0.8% and PVP < 20 mm of Hg. One with GRWR < 0.8% could truly be labeled as SFSS. Incidence of SFSS was not higher in patients with elevated PVP > 20 mm of Hg (14.3% vs 0%, $P = 0.259$) or PSG > 13 mm of Hg (33.3% vs 0%, $P = 0.111$). Intensive care unit (ICU) stay was longer in patients with elevated PVP (14.55 vs 9.13 days, $P = 0.007$) and PSG (16.8 vs 9.72 days, $P = 0.009$). There was no difference in graft functions, post-operative complications and mortality in first month post-LDLT. **Conclusion:** Elevated PVP or PSG increased morbidity but neither predicted SFSS nor affected survival. (J CLIN EXP HEPATOL 2017;7:235–246)

The demand for liver transplantation has continued to increase in the last three decades and has far outpaced the supply of organs from deceased donors. The entire evolution of living donor liver transplantation (LDLT) for adult recipients rests on two principles—donor safety and ensuring an adequately sized graft for the recipient. The size of the graft is most often limited by the concern for donor safety. Small for size syndrome (SFSS) refers to the clinical syndrome caused by a partial liver graft that is too small to sustain metabolic demands in the recipient. Portal hyperperfusion as measured by portal venous pressure (PVP) has been proposed to be a cause of SFSS after implantation of a

reduced size liver graft and a potential contributor to poor outcomes after LDLT. Measurement of PVP is often indirect and not standardized. Moreover elevated central venous pressure (CVP) may confound the measured values of PVP. A porto systemic gradient (PSG) obtained by subtracting CVP from PVP may be more representative of graft injury occurring from portal hyperperfusion. This prospective study was performed to assess whether elevated PVP or PSG can predict poor recipient outcomes, especially SFSS.

MATERIALS AND METHODS

Patients

A prospective observational study was conducted at Amrita Institute of Medical Sciences, Kochi, Kerala, India from September 2014 to August 2015. Patients over 18 years of age undergoing elective LDLT during the period of study were included. Patients undergoing ABO incompatible LDLT, LDLT for fulminant hepatic failure, pediatric LDLT and patients with previous porto systemic shunt or splenic artery ligation or splenectomy, patients with portal vein thrombosis (PVT) or anomalies and patients with Budd Chiari syndrome were excluded from the study. Clearance from the Institutional Ethical Committee was taken prior to commencement of the study. Informed consent was taken from the patients prior to inclusion in the study. Disease severity in the recipients was assessed using Child Turcot Pugh (CTP) score and Model for End Stage Liver Disease (MELD) score.

Keywords: graft recipient weight ratio, cirrhosis, small for size syndrome

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Abbreviations: BAL: bronchoalveolar lavage; CTP: Child Turcot Pugh; CVP: central venous pressure; GRWR: graft to recipient weight ratio; HAT: hepatic artery thrombosis; INR: International Normalized Ratio; LDLT: living donor liver transplant; MELD: Model for End Stage Liver Disease; MHV: middle hepatic vein; N: total number; P: probability value; PNF: primary non-function; PSG: porto systemic gradient; PVP: portal venous pressure; PVT: portal vein thrombosis; ROC: receiver operating characteristics; SD: standard deviation; SGOT: serum glutamate oxaloacetate transaminase; SGPT: serum glutamate pyruvate transaminase; SFSS: small for size syndrome

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Donors and Grafts

All patients included in the study received right lobe grafts. Graft steatosis was assessed using liver attenuation index obtained from the plain computed tomography (CT) scan of the donor and a value less than 5 was defined as graft steatosis.¹ A good outflow was ensured by taking the grafts with middle hepatic vein or reconstructing segment V and VIII veins.

Operation and Portal Venous Pressure Measurement

Main portal vein was cannulated using 24 gauge anti thrombotic canula before the native liver was dissected and was connected to pressure sensor. Three pressure readings were recorded and their mean was calculated. A PSG was obtained by subtracting CVP from PVP. At the end of bench work for the graft, graft recipient weight ratio (GRWR) was calculated after measurement of the graft weight. Second set of pressures were recorded after reperfusion and completion of all vascular graft anastomoses, again via canulation of main portal vein.

None of the patients underwent portal inflow modulations.

Post-Operative Care and Immunosuppression

A daily record of patient's vital parameters, Glasgow coma scale, urine output, and drain output (ascites) was maintained. The status of the graft vasculature was assessed using Doppler ultrasound scans done every 24 h for first 4 days, then on 7th, 14th, 21st and 30th day or earlier if clinically indicated. In cases where equivocal findings were noted on Doppler ultrasound, CT angiogram was performed. The standard peri-operative antibiotic prophylaxis consisted of piperacillin-tazobactam and fluconazole. In cases with preoperative positive culture reports, appropriate culture sensitive antibiotics were administered in the peri-operative period. Other drugs and supportive medications including N-acetyl cysteine and ursodeoxycholic acid were also administered. Blood investigations were performed according to the routine protocol followed for LDLT patients. Cultures (ascitic fluid/urine/blood/bronchoalveolar lavage [BAL] or sputum) were obtained on post-operative day 3 and 5 or as clinically indicated.

Triple immunosuppression was administered in the post-operative period consisting of steroids, tacrolimus and either azathioprine or mycophenolate mofetil. The target whole blood trough level of tacrolimus was 6–10 ng/ml in the first month following LDLT.

Primary End Point: Small for Size Syndrome Dahm–Clavien Definition²

Presence of two of the following on three consecutive days in the first post-operative week in a small for size graft

(GRWR < 0.8%) after exclusion of technical (arterial/portal occlusion/outflow congestion/bile leak), immunological (rejection), infectious (cholangitis, sepsis) factors

1. Bilirubin > 5.85 mg%
2. INR > 2
3. Encephalopathy grade 3 or 4

Secondary End Points

Graft functions measured using the peak, mean and median levels of bilirubin, transaminases (SGOT, SGPT), INR. Post-LDLT ascites, peak levels of creatinine, profound deterioration of renal functions, lactates in the first 30 post-operative days.

Profound deterioration of renal function was defined as post-operative renal dysfunction with rise in serum creatinine more than two times the baseline value, or urine output less than 0.5 ml/kg/h for 12 h,³ or the need for renal replacement therapy was also assessed.

Other variables compared were complications like outflow occlusion (hepatic vein thrombosis), hepatic artery thrombosis (HAT), PVT, primary non-function (PNF), post-operative bleeding, requirement of transfusions, bile leak, positive blood cultures, time spent on ventilator, intensive care unit (ICU) and hospital and mortality in first 30 days of LDLT.

PNF was defined as irreversible loss of graft function requiring emergency re-transplantation during the first 10 days after the initial liver transplantation. It is characterized by AST $\geq$ 2000 UI/L, INR $\geq$ 3.0 or acidosis (pH $\leq$ 7.3 and/or lactate concentration $\geq 2 \times$ normal), in the absence of a vascular thrombosis.

Post-operative bleeding was defined as drop in hemoglobin by 2 g% during any 24-h period requiring blood transfusion or reoperation.

Statistical Analyses

For assessment of end points patients were divided in to two groups using their PVP (cut-off of 20 mm of Hg).⁴ For assessment using PSG, no reference value was available to segregate patients in to two groups. A receiver operating characteristics (ROC) curve was plotted for PSG values for SFSS. A cut-off of 13 mm of Hg was obtained with sensitivity of 100%, specificity 92.3%, area under curve 0.98 (Figure 1). Statistical analysis was performed using Mann Whitney test for continuous data, Fischer's exact test for categorical data using IBM SPSS software version 20.

RESULTS

A total of 99 liver transplantations were performed during the period of study (September 2014 to August 2015). Fifty five patients met the inclusion criteria of which 45 consented for pressure measurements, however readings could be obtained in 42 of these as operating surgeons did not cannulate portal vein for concern for worsening of intra op

Diagonal segments are produced by ties.

Figure 1 ROC curve for PSG values.

bleeding in 3. Secondary endpoints were assessed in 42 patients. Primary endpoint was measured in 27 patients after excluding 15 patients with other potential causes for graft dysfunction (4 had bile leak, 4 had outflow occlusion, 4 had HAT, 1 had non-flow limiting thrombus in anterior sectoral portal vein and 2 had MHV thrombosis who subsequently also developed bile leak). No portal inflow modulation was performed for any of the patient included in the study (Figure 2).

Etiology of Liver Disease (Tables 1 and 2)

Most common etiology of cirrhosis was ethanol related. In patients with portal pressures >20 mm of Hg, 5 (71.4%) had ethanol related cirrhosis, 1 (14.3%) had cryptogenic cirrhosis and 1 (14.3%) had HCC. In patients with $PVP \leq 20$ mm of Hg, 9 (45%) had ethanol related cirrhosis, 5 (25%) had cryptogenic cirrhosis, 3 (15%) had HCC, 2 (10%) were HBV related and 1 (5%) had cirrhosis related to autoimmune hepatitis.

Severity of Liver Disease (Tables 1 and 2)

CTP score: In patients with $PVP > 20$ mm of Hg, 6 (85.7%) had CTP score of C and 1 (14.3%) had CTP score of B. In patients with $PVP \leq 20$ mm of Hg, 18 (90%) were having CTP score of C and 1 (5%) patient each were having CTP score of A and B.

MELD score: Mean MELD score of patients in $PVP > 20$ mm of Hg was 21.71 (95% CI 16.4–26.9) and

Figure 2 Diagram showing the flow of participants through the study.

of patients with $PVP \leq 20$ mm of Hg was 23.4 (95% CI 20–26.71). The difference between the Mean MELD scores of PVP groups was not significant ($P = 0.575$).

Mean MELD score of patients in $PSG > 13$ mm of Hg was 18.6 (95% CI -1.26 to 38.59) and of patients with $PSG \leq 13$ mm of Hg was 23.5 (95% CI 20.77–26.33). The difference between the Mean MELD scores of PSG groups was not significant ($P = 0.244$).

Donor Variables (Tables 1 and 2)

Donor Age

Mean age of donors in patients with $PVP > 20$ mm of Hg was 41.2 years (95% CI 32–48.33) and in patients with $PVP \leq 20$ mm of Hg was 34.6 years (95% CI 30.95–38.57). The difference in the mean age of donors between PVP groups was not significant ($P = 0.122$).

Table 1 Comparison of Demographic, Disease and Graft Variables Between PVP Groups.

Factor	Portal venous pressure after implant (N)	Mean	SD	95% confidence interval for mean		P value
				Lower bound	Upper bound	
Age (years)	≤20(20)	47.25	11.68	41.73	52.67	0.406
	>20(7)	51.14	5.95	45.63	56.65	
Sex (M:F %)	≤20(20)	95:5				1.0
	>20(7)	100:0	–		–	
Etiology (ethanol:others %)	≤20(20)	45:55				0.385
	>20(7)	71.4:28.6	–		–	
MELD score	≤20(20)	23.4	7.06	20	26.71	0.575
	>20(7)	21.71	5.64	16.4	26.9	
GRWR (%)	≤20(20)	0.91	0.21	0.81	1.02	0.275
	>20(7)	0.81	0.21	0.61	1.01	
Liver attenuation index	≤20(20)	9.6	9.5	5.05	14.26	0.467
	>20(7)	6.4	11.0	–3.86	16.66	
Donor age (years)	≤20(20)	34.6	9.11	30.95	38.57	0.122
	>20(7)	41.2	10.37	32.86	48.33	

GRWR: graft recipient weight ratio.

MELD: Model for End stage Liver Disease

PVP: portal venous pressure.

SD: standard deviation.

P: probability.

N: number of patients.

Table 2 Comparison of demographic, Disease and Graft Variables Between PSG Groups.

Factor	Portal systemic gradient after implant (N)	Mean	SD	95% confidence interval for mean		P value
				Lower bound	Upper bound	
Age (years)	≤13(24)	48.13	11.12	43.38	52.78	0.854
	>13(3)	49.33	4.16	38.99	59.68	
Sex (M:F %)	≤13(24)	95.8:4.2				1.0
	>13(3)	100:0	–		–	
Etiology (ethanol:others %)	≤13(24)	50:50				1.0
	>13(3)	66.7:33.3	–		–	
MELD score	≤13(24)	23.5	6.47	20.77	26.23	0.244
	>13(3)	18.6	8.02	–1.26	38.59	
GRWR (%)	≤13(24)	0.9	0.22	0.8	1.0	0.356
	>13(3)	0.78	0.02	0.73	0.82	
Liver attenuation index	≤13(24)	8.5	10.24	4.11	12.97	0.742
	>13(3)	10.6	7.66	–8.42	29.62	
Donor age (years)	≤13(24)	35.3	9.84	31.48	38.95	0.135
	>13(3)	44.3	2.08	42	46	

GRWR: Graft recipient weight ratio.

MELD: Model for End stage Liver Disease.

PSG: porto systemic gradient.

SD: standard deviation.

P: probability.

N: number of patients.

Mean age of donors in patients with PSG > 13 mm of Hg was 44.3 years (95% CI 42–46) and in patients with PSG ≤ 13 mm of Hg was 35.3 years (95% CI 31.48–38.95). The difference in the mean age of donors between PSG groups was not significant ($P = 0.135$).

Graft Steatosis (Liver Attenuation Index)

Mean liver attenuation index of grafts in patients with PVP > 20 mm of Hg was 6.4 (95% CI –3.86 to 16.66) and in patients with PVP ≤ 20 mm of Hg was 9.6 (95% CI 5.05–14.26). The difference was not statistically significant ($P = 0.467$).

Mean liver attenuation index of grafts in patients with PSG > 13 mm of Hg was 10.6 (95% CI –8.42 to 29.62) and in patients with PSG ≤ 13 mm of Hg was 8.5 (95% CI 4.11–12.97). The difference was not statistically significant ($P = 0.742$).

Graft Recipient Weight Ratio

Minimum GRWR in patients with PVP > 20 mm of Hg was 0.56% (mean 0.81%, 95% CI 0.61–1.01%) and 0.49% in those with PVP ≤ 20 mm of Hg (mean 0.91%, 95% CI 0.81–1.02%). The difference in mean GRWR between the PVP groups was not significant ($P = 0.275$).

The difference in GRWR between the PSG groups was not significant (PSG > 13 mm of Hg, mean GRWR 0.78%, 95% CI 0.73–0.82%) (PSG ≤ 13 mm of Hg, mean GRWR 0.9%, 95% CI 0.8–1.0%) ($P = 0.356$).

Small for Size Syndrome

A combination of hyper bilirubinemia and coagulopathy of values defined for SFSS was found in 6 patients. Of these 6 patients, 5 had a GRWR > 0.8% and also PVP < 20 mm of Hg. Of 27, only 1 patient truly satisfied criteria for SFSS.

The incidence of SFSS was not significantly higher in patients with PVP > 20 mm of Hg (14.3%) as compared to those with PVP ≤ 20 mm of Hg (0) ($P = 0.259$).

Incidence of SFSS was also not higher in patients with PSG > 13 mm of Hg (33.3%) as compared to those with PSG ≤ 13 mm of Hg (0) ($P = 0.111$).

Graft Recipient Weight Ratio and Portal Pressure

Patients with small grafts (GRWR < 0.8%) did not have significantly higher portal pressure (mean PVP 18.38 mm of Hg, 95% CI 15.67–21.2) as compared to those with larger grafts (GRWR > 0.8%) (mean PVP 16.83 mm of Hg, 95% CI 15.14–18.46) ($P = 0.328$).

Post-Operative Graft Function (Tables 3–6)

Serum Bilirubin

There was no statistically significant difference in serum bilirubin levels in the first month of LDLT in patients with PVP > 20 mm of Hg (mean 5.94 mg%, 95% CI 3.07–8.8)

when compared to those with PVP ≤ 20 mm of Hg (mean 5.41 mg%, 95% CI 3.84–6.98) ($P = 0.721$).

There was no statistically significant difference in serum bilirubin levels in the first month of LDLT in patients with PSG > 13 mm of Hg (mean 5.94 mg%, 95% CI 2.52–9.34) when compared to those with PSG ≤ 13 mm of Hg (mean 5.5 mg%, 95% CI 4.0–6.99) ($P = 0.818$).

Serum Transaminases

Serum Glutamate Oxaloacetate Transaminase: There was no significant difference in mean serum SGOT levels in the first month of LDLT in patients with PVP > 20 mm of Hg (mean 285.24 U/L, 95% CI 30.6–539.8) when compared to those with PVP ≤ 20 mm of Hg (mean 171.6 U/L, 95% CI 59.3–283.8) ($P = 0.321$).

There was a trend toward lower mean serum SGOT levels in the first month of LDLT in patients with PSG ≤ 13 mm of Hg (mean 164 U/L, 95% CI 70.92–257.2) when compared to those with PSG > 13 mm of Hg (mean 444.13%, 95% CI –119.04 to 1007.3) ($P = 0.054$). Peak SGOT levels also showed a trend toward a lower serum level in patients with PSG < 13 mm of Hg (527.93 U/L vs 1342 U/L, $P = 0.064$).

Serum Glutamate Pyruvate Transaminase: There was no significant difference in mean serum SGPT levels in the first month of LDLT in patients with PVP > 20 mm of Hg (mean 378.75 U/L, 95% CI 114.07–643.41) when compared to those with PVP ≤ 20 mm of Hg (mean 254.79 U/L, 95% CI 108.78–400.79) ($P = 0.368$).

There was no statistically significant difference in mean serum SGPT levels in the first month of LDLT in patients with PSG > 13 mm of Hg (mean 500.22 U/L, 95% CI –172.7 to 2319) when compared to those with PSG ≤ 13 mm of Hg (mean 255.21 U/L, 95% CI 268.5–830.3) ($P = 0.165$).

International Normalized Ratio

There was no significant difference in mean serum INR levels in the first month of LDLT in patients with PVP > 20 mm of Hg (mean 2.33, 95% CI 1.63–3.01) when compared to those with PVP ≤ 20 mm of Hg (mean 1.94, 95% CI 1.66–2.21) ($P = 0.189$).

There was a trend toward lower mean serum INR levels in the first month of LDLT in patients with PSG ≤ 13 mm of Hg (mean 1.95, 95% CI 1.7–2.18) when compared to those with PSG > 13 mm of Hg (mean 2.65, 95% CI 1.07–4.21) ($P = 0.065$). Median INR levels also showed a trend toward improvement in patients with PSG < 13 mm of Hg in first month of transplantation (1.75 vs 2.47, $P = 0.077$).

Post-Operative Ascites (Tables 3–6)

There was no significant difference in mean volume of drain output (ascites) in the first month of LDLT in patients with PVP > 20 mm of Hg (mean 1.12 L, 95% CI

Table 3 Assessment of PVP and Secondary Endpoints.

Factor	Portal pressure after implant (N)	Mean	SD	95% confidence interval for mean		P value
				Lower bound	Upper bound	
Peak bilirubin (mg%)	≤20(30)	10.53	7.31	7.7997	13.2643	0.376
	>20(12)	13.16	11.27	5.9958	20.3225	
Mean bilirubin (mg%)	≤20(30)	5.41	4.20	3.8403	6.9813	0.721
	>20(12)	5.94	4.50	3.0767	8.8000	
Median bilirubin (mg%)	≤20(30)	5.05	4.09	3.5210	6.5820	0.822
	>20(12)	5.36	3.89	2.8915	7.8352	
Peak SGOT (U/L)	≤20(30)	557.24	944.288	204.6403	909.8463	0.380
	>20(12)	861.67	1145.673	133.7410	1589.5924	
Mean SGOT (U/L)	≤20(30)	171.60	300.512	59.3909	283.8171	0.321
	>20(12)	285.24	400.673	30.6636	539.8147	
Median SGOT (U/L)	≤20(30)	99.35	181.67	31.5149	167.1884	0.406
	>20(12)	160.92	284.112	-19.5993	341.4327	
Peak SGPT (U/L)	≤20(30)	561.42	903.639	223.9991	898.8475	0.477
	>20(12)	781.42	878.383	223.3186	1339.5148	
Mean SGPT (U/L)	≤20(30)	254.79	390.999	108.7896	400.7924	0.368
	>20(12)	378.75	416.557	114.0792	643.4141	
Median SGPT (U/L)	≤20(30)	205.55	299.863	93.5744	317.5156	0.360
	>20(12)	313.88	436.333	36.6425	591.1075	
Peak INR	≤20(30)	3.60	1.359	3.0899	4.1048	0.329
	>20(12)	4.06	1.385	3.1785	4.9382	
Mean INR	≤20(30)	1.94	0.731	1.6685	2.2142	0.189
	>20(12)	2.33	1.089	1.6348	3.0186	
Median INR	≤20(30)	1.77	0.802	1.4655	2.0648	0.342
	>20(12)	2.07	1.183	1.3167	2.8199	
Peak ascites (L)	≤20(30)	1.78	1.295	1.2989	2.2658	0.513
	>20(12)	2.05	0.842	1.5153	2.5847	
Mean ascites (L)	≤20(30)	1.04	0.739	0.7638	1.3160	0.722
	>20(12)	1.12	0.507	0.8014	1.4460	
Median ascites (L)	≤20(30)	1.05	0.857	0.7299	1.3701	0.714
	>20(12)	1.15	0.602	0.7681	1.5328	
Peak creatinine (mg%)	≤20(30)	1.433	0.592	1.2121	1.6546	0.160
	>20(12)	1.784	0.97	1.1672	2.4011	
Peak lactate in first week	≤20(30)	3.95	3.31	2.68	5.19	0.533
	>20(12)	4.65	3.20	2.78	6.72	
Number of transfusions	≤20(30)	2.60	4.45	0.94	4.26	0.647
	>20(12)	3.33	5.123	0.08	6.59	
Number of days on respirator	≤20(30)	1.33	1.184	0.89	1.78	0.287
	>20(12)	2.0	2.86	0.18	3.82	
Length of ICU stay (days)	≤20(30)	9.13	3.92	7.67	10.60	0.007
	>20(12)	14.55	8.178	9.05	20.04	
Length of hospital stay (days)	≤20(30)	20.53	8.13	17.50	23.57	0.163
	>20(12)	24.27	4.98	20.93	27.62	

INR: International Normalized Ratio.

ICU: intensive care unit.

SGOT: serum glutamate oxaloacetate transaminase.

SGPT: serum glutamate pyruvate transaminase.

SD: standard deviation.

P: probability.

L: liters.

U/L: units/liter.

Table 4 Assessment of PVP and Secondary Endpoints.

Factor	Category	Portal pressure ≤ 20	Portal pressure > 20	P value
Profound deterioration of renal function	No	29 (96.7%)	10 (83.3%)	0.192
	Yes	1 (3.3%)	2 (16.7%)	
Blood culture	Negative	22 (73.3%)	10 (83.3%)	0.696
	Positive	8 (26.7%)	2 (16.7%)	
Urine culture	Negative	26 (86.7%)	10 (83.3%)	1.0
	Positive	4 (13.3%)	2 (16.7%)	
BAL/sputum culture	Negative	27 (90%)	7 (58.3%)	0.031
	Positive	3 (10%)	5 (41.7%)	
Post-operative bleeding	No	22 (73.3%)	5 (41.7%)	0.078
	Yes	8 (26.7%)	7 (58.3%)	
PNF	No	29 (96.7%)	11 (91.7%)	0.495
	Yes	1 (3.3%)	1 (8.3%)	
Bile leak	No	24 (80%)	12 (100%)	0.159
	Yes	6 (20%)	0	
HAT	No	28 (93.3%)	10 (83.3%)	0.565
	Yes	2 (6.7%)	2 (16.7%)	
MHV thrombosis	No	27 (90%)	9 (75%)	0.329
	Yes	3 (10%)	3 (25%)	
PV thrombosis	No	29 (96.7%)	12 (100%)	1.0
	Yes	1 (3.3%)	0	
Mortality	No	26 (86.7%)	8 (66.7%)	0.195
	Yes	4 (13.3%)	4 (33.3%)	

BAL: bronchoalveolar lavage.

HAT: hepatic artery thrombosis.

MHV: middle hepatic vein.

PNF: primary non-function.

PV: portal vein.

P: probability.

0.8–1.44) when compared to those with PVP ≤ 20 mm of Hg (mean 1.04 L, 95% CI 0.76–1.31) ($P = 0.722$).

There was no statistically significant difference in mean volume of drain output (ascites) in the first month of LDLT in patients with PSG > 13 mm of Hg (mean 1.01 L, 95% CI 0.64–1.37) when compared to those with PSG ≤ 13 mm of Hg (mean 1.07 L, 95% CI 0.82–1.31) ($P = 0.833$).

Post-Operative Renal Function (Tables 3–6)

Peak creatinine level was not significantly different in patients with PVP > 20 mm of Hg (mean 1.78 mg%, 95% CI 1.16–2.40) as compared to those with PVP ≤ 20 mm of Hg (mean 1.43 mg%, 95% CI 1.21–1.65) ($P = 0.160$).

Peak creatinine level was not significantly different in patients with PSG > 13 mm of Hg (mean 1.32 mg%, 95% CI 0.83–1.82) as compared to those with PSG ≤ 13 mm of Hg (mean 1.56 mg%, 95% CI 1.31–1.82) ($P = 0.461$).

Incidence of profound deterioration of renal dysfunction in first month of LDLT was also not different between

PVP groups (16.7% vs 3.3%, $P = 0.192$) and PSG groups (0% vs 8.3%, $P = 1.0$).

Lactates in First Week of Living Donor Liver Transplantation (Tables 3–6)

Peak lactate level in first week of LDLT was not significantly different in patients with PVP > 20 mm of Hg (mean 4.65 mmol/L, 95% CI 2.78–6.72) as compared to those with PVP ≤ 20 mm of Hg (mean 3.95 mmol/L, 95% CI 2.68–5.19) ($P = 0.533$).

Peak lactate level in first week of LDLT was not significantly different in patients with PSG > 13 mm of Hg (mean 6.08 mmol/L, 95% CI 2.22–10.12) as compared to those with PSG ≤ 13 mm of Hg (mean 3.83 mmol/L, 95% CI 2.78–4.89) ($P = 0.989$).

Post-Operative Ventilation and Length of Intensive Care Unit Stay (Tables 3–6)

There was no significant difference in the requirement of post-operative ventilation in number of days in the first

Table 5 Assessment of PSG and Secondary Endpoints.

Factor	PSG (N)	Mean	SD	95% confidence interval for mean		P value
				Lower bound	Upper bound	
Peak bilirubin (mg%)	≤13(36)	10.9	7.76	8.2726	13.5257	0.484
	>13(6)	13.58	13.14	−0.2112	27.3778	
Mean bilirubin (mg%)	≤13(36)	5.5	4.423	4.0025	6.9956	0.818
	>13(6)	5.94	3.25	2.5261	9.3473	
Median bilirubin (mg%)	≤13(36)	5.12	4.22	3.6858	6.5450	0.922
	>13(6)	5.29	2.42	2.7424	7.8409	
Peak SGOT (U/L)	≤13(36)	527.93	867.446	234.4236	821.4264	0.064
	>13(6)	1342.0	1506.443	−238.9151	2922.9151	
Mean SGOT (U/L)	≤13(36)	164.06	275.275	70.9210	257.2006	0.054
	>13(6)	444.13	536.464	−119.0418	1007.3085	
Median SGOT (U/L)	≤13(36)	95.88	166.587	39.4202	152.3326	0.119
	>13(6)	243.33	397.807	−174.1397	660.8064	
Peak SGPT (U/L)	≤13(36)	549.46	830.224	268.5564	830.3713	0.186
	>13(6)	1073.13	1187.202	−172.7259	2319.0593	
Mean SGPT (U/L)	≤13(36)	255.21	363.011	268.5564	830.3713	0.165
	>13(6)	500.22	561.853	−172.7259	2319.0593	
Median SGPT (U/L)	≤13(36)	208.55	281.274	113.3821	303.7207	0.199
	>13(6)	404.17	606.75	−231.8701	1040.2034	
Peak INR	≤13(36)	3.62	1.31	3.1712	4.0638	0.198
	>13(6)	4.40	1.57	2.7429	6.0538	
Mean INR	≤13(36)	1.95	0.680	1.7223	2.1827	0.065
	>13(6)	2.65	1.492	1.0793	4.2107	
Median INR	≤13(36)	1.75	0.745	1.4972	2.0014	0.077
	>13(6)	2.47	1.599	0.7890	4.1443	
Peak ascites (L)	≤13(36)	1.85	1.22	1.4358	2.2653	0.913
	>13(6)	1.91	0.93	0.9238	2.8929	
Mean ascites (L)	≤13(36)	1.07	0.719	0.8296	1.3163	0.833
	>13(6)	1.01	0.35	0.6410	1.3770	
Median ascites (L)	≤13(36)	1.1	0.84	0.8125	1.3822	0.711
	>13(6)	0.97	0.31	0.6358	1.2976	
Peak creatinine (mg%)	≤13(36)	1.56	0.75	1.3107	1.8249	0.461
	>13(6)	1.32	0.47	0.8347	1.8220	
Peak lactate in first week	≤13(36)	3.83	3.07	2.78	4.89	0.989
	>13(6)	6.08	3.94	2.22	10.12	
Number of transfusions	≤13(36)	2.81	4.76	1.19	4.42	0.119
	>13(6)	2.83	3.65	−1.00	6.67	
Number of days on respirator	≤13(36)	1.28	1.08	0.91	1.64	0.029
	>13(6)	3.0	3.95	−1.14	7.14	
Length of ICU stay (days)	≤13(36)	9.72	4.86	8.08	11.37	0.009
	>13(6)	16.8	8.7	6.00	27.60	
Length of hospital stay (days)	≤13(36)	21.14	7.86	18.48	23.80	0.372
	>13(6)	24.40	4.15	19.24	29.56	

INR: International Normalized Ratio.

ICU: intensive care unit.

SGOT: serum glutamate oxaloacetate transaminase.

SGPT: serum glutamate pyruvate transaminase.

SD: Standard deviation.

P: probability.

L: liters.

U/L: units/liter.

Table 6 Assessment of PSG and Secondary Endpoints.

Factor	Category	PSG ≤ 13	PSG > 13	P value
Profound deterioration of renal function	No	33 (91.7%)	6 (100%)	1.0
	Yes	3 (8.3%)	0	
Blood culture	Negative	27 (75%)	5 (86.3%)	1.0
	Positive	9 (25%)	1 (13.7%)	
Urine culture	Negative	31 (86.1%)	5 (86.3%)	1.0
	Positive	5 (13.9%)	1 (13.7%)	
BAL/sputum culture	Negative	31 (86.1%)	3 (50%)	0.071
	Positive	5 (13.9%)	3 (50%)	
Post-operative bleeding	No	25 (69.4%)	2 (33.3%)	0.164
	Yes	11 (30.6%)	4 (66.7%)	
PNF	No	35 (97.2%)	5 (83.3%)	0.268
	Yes	1 (2.8%)	1 (16.7%)	
Bile leak	No	30 (83.3%)	6 (100%)	0.569
	Yes	6 (16.7%)	0	
HAT	No	34 (94.4%)	4 (66.7%)	0.091
	Yes	2 (5.6%)	2 (33.3%)	
MHV thrombosis	No	31 (86.1%)	5 (83.3%)	1.0
	Yes	5 (13.9%)	1 (16.7%)	
PV thrombosis	No	35 (97.2%)	6 (100%)	1.0
	Yes	1 (2.8%)	0	
Mortality	No	30 (83.3%)	4 (66.7%)	0.319
	Yes	6 (16.7%)	2 (33.3%)	

BAL: bronchoalveolar lavage.

HAT: hepatic artery thrombosis.

MHV: middle hepatic vein.

PNF: primary non-function.

PV: portal vein.

P: probability.

month of LDLT in patients with PVP > 20 mm of Hg (mean 2.0 days, 95% CI 0.18–3.8) when compared to those with PVP ≤ 20 mm of Hg (mean 1.33 days, 95% CI 0.89–1.78) ($P = 0.287$).

However those with PSG > 13 mm of Hg required longer post-operative ventilation (mean 3 days, 95% CI –1.14 to 7.14) as compared to those with PSG ≤ 13 mm of Hg (mean 1.28 days, 95% CI 0.91–1.64) ($P = 0.029$).

Length of ICU stay was significantly longer in patients with PVP > 20 mm of Hg (mean 14.55 days, 95% CI 9.05–20.4) as compared to those with PVP ≤ 20 mm of Hg (mean 9.13 days, 95% CI 7.67–10.6) ($P = 0.007$) and also in patients with PSG > 13 mm of Hg (mean 16.8 days, 95% CI 6–27.6) as compared to those with PSG ≤ 13 mm of Hg (mean 9.72 days, 95% CI 8.08–11.37) ($P = 0.009$).

Length of Hospital Stays (Tables 3–6)

There was no significant difference in number of days spent in hospital after LDLT by patients with

PVP > 20 mm of Hg (mean 24.27 days, 95% CI 20.93–27.62) when compared to those with PVP ≤ 20 mm of Hg (mean 20.53 days, 95% CI 17.5–23.57) ($P = 0.163$).

There was no significant difference in number of days spent in hospital after LDLT by patients with PSG > 13 mm of Hg (mean 24.4 days, 95% CI 19.24–29.56) when compared to those with PSG ≤ 13 mm of Hg (mean 21.14 days, 95% CI 18.48–23.8) ($P = 0.163$).

Hepatic Artery Thrombosis, Portal Vein Thrombosis, Outflow Occlusion (Tables 3–6)

There was no statistically significant difference in the incidence of vascular complications namely HAT (6.7% vs 16.7%, $P = 0.565$), PVT (1% vs 0%, $P = 1.0$), outflow occlusion (MHV thrombosis 10% vs 25%, $P = 0.329$) between the PVP groups.

There was no statistically significant difference in the incidence of vascular complications namely HAT (5.6% vs 33.3%, $P = 0.565$), PVT (1% vs 0%, $P = 1.0$), outflow

occlusion (MHV thrombosis 13.9% vs 16.7%, $P = 1.0$) between the PSG groups.

Biliary Complications (Tables 3–6)

Incidence of bile leak was not significantly higher in patients with PVP > 20 mm of Hg (0% vs 20%, $P = 0.159$), or in patients with PSG > 13 mm of Hg (0% vs 16.7%, $P = 0.569$).

Sepsis (Tables 3–6)

Incidence of respiratory infections (positive BAL/sputum cultures) was higher in patients with PVP > 20 mm of Hg (41.7% vs 10%, $P = 0.031$).

However there was a trend toward increase in incidence of respiratory infections in patients with PSG > 13 mm of Hg (50% vs 13.9%, $P = 0.071$).

Incidence of blood stream infections (positive blood cultures) however was not significantly different in PVP groups (16.7% vs 3.3%, $P = 0.192$) or in PSG groups (13.7% vs 25%, $P = 1.0$).

Post-Operative Bleeding and Need for Transfusion of Blood and Blood Products

Incidence of post-operative bleeding or need for transfusion of blood and blood products was not significantly different in PVP groups (58.3% vs 26.7%, $P = 0.08$) or in PSG groups (66.7% vs 30.6%, $P = 0.164$).

Primary Non-Function (Tables 3–6)

Incidence of PNF of the graft liver was not significantly different in PVP groups (3.3% vs 8.3%, $P = 0.495$) or in PSG groups (2.8% vs 16.7%, $P = 0.268$).

Mortality in First Month Post-Living Donor Liver Transplantation (Tables 3–6)

Mortality was 13.3% in patients with PVP $\leq$ 20 mm of Hg as compared to 33.3% in those with PVP > 20 mm of Hg, however difference was not statistically significant ($P = 0.195$).

Mortality was 16.7% in patients with PSG $\leq$ 13 mm of Hg as compared to 33.3% in those with PSG > 13 mm of Hg, however difference was not statistically significant ($P = 0.319$).

DISCUSSION

In early days of liver transplantation liver graft dysfunction was the terminology used to describe the combination of hyper bilirubinemia and coagulopathy. In the absence of technical or immunological complications, in deceased donor liver transplantation (DDLT) where whole liver graft is used, graft dysfunction was attributed to poor quality of liver graft, poor retrieval or poor liver

preservation. In contrast, grafts from living donors have excellent quality, controlled retrieval and very short cold ischemia times. Despite this, initial graft dysfunction did seem to occur in LDLT.

Kiuchi et al. analyzed 276 LDLT recipients and found significantly worse graft survival for patients with GRWR < 0.8%.⁴ Thus inadequate size of the graft was considered as the reason for graft dysfunction and SFSS terminology was frequently used to describe dysfunction in smaller grafts. However, SFSS is difficult to differentiate from other complications resulting in graft dysfunction, most importantly sepsis. There is no concrete consensus to accurately define of SFSS, and hence its exact incidence, risk factors, appropriate preventive and therapeutic strategies and prognosis remain largely undetermined.

Initial days of LDLT to ensure donor safety, majority of right lobe grafts were harvested without middle hepatic vein. Reconstruction of sectoral veins was performed only if the diameters of the veins were > 5 mm. It was in this cohort of patients a GRWR of at least 0.8% was recommended to avoid graft dysfunction. Subsequently Liu et al. from Hong Kong group published use of right lobe grafts with middle hepatic vein.⁵ Due to excellent outflow from the middle hepatic vein, grafts with GRWR < 0.8% performed very well in their series. Koreans took middle path of harvesting right lobe grafts without middle hepatic vein and aggressively reconstructing venous tributaries of segment V and VIII using conduits to form a neo middle hepatic vein.⁶ With these modifications over the last decade it was realized that even a GRWR < 0.8% was sufficient for recipient metabolic demand. Ben-Haim et al. showed that GRWR as low as 0.6% can be used in patients with Child's A cirrhosis.⁷ In our series of 42 cases all grafts were harvested either with middle hepatic vein or were reconstructed on bench to form a neo middle hepatic vein.

Grafts with GRWR > 0.8% at times can exhibit SFSS. It can be attributed to graft steatosis. However in good quality grafts with adequate volume and good outflow, additional factors were explored to explain graft dysfunction. Hyperperfusion through portal vein leading to injury to hepatic vasculature and parenchyma thus came in to picture as an etiologic factor to explain graft dysfunction and SFSS. So if PVP is very high a graft with good GRWR can get damaged vice versa even a small sized graft can survive if PVPs are normal.

Hyperperfusion injury occurs immediately after graft reperfusion and inflow modulation was advised at the time of transplantation itself. Hence PVP was used by many centers as objective criteria to guide portal inflow modulation in the form of splenectomy, splenic artery ligation or porto caval shunts to protect grafts from hyperperfusion injuries.

Ito Takashi et al. in their series of 79 cases of LDLT showed patients with small grafts (GRWR < 0.8%) displayed significantly higher PVP than recipients of larger

grafts (GRWR > 0.8%).⁸ Portal pressure was measured in their series via canulation of Inferior mesenteric vein that allowed them to maintain continuous access to measure PVP subsequently for initial 14 days of LDLT. However in our series of 42 cases of LDLT there was no statistically significant difference in PVP in patients with small grafts as compared to those with larger grafts (18.38 vs 16.83 mm of Hg, $P = 0.328$). We measured PVP by direct canulation of portal vein however there were no measurements of PVP subsequently.

None of the patients in our study underwent portal inflow modulation. We found only 1 patient who met all the criteria for SFSS that is combination of hyperbilirubinemia and coagulopathy in small for size graft (GRWR < 0.8%). We noticed that the incidence of SFSS was not significantly higher in patients with elevated PVP. This was in contrary to the findings by Ito et al.⁸ who described poor patient survival attributable, at least in part, to SFSS in patients with PVP > 20 mm of Hg. Perhaps this may partly be due to the fact that CVP may have confounded the PVP values.

Prior to reperfusion of the graft during the recipient hepatectomy large volume fluids could have been given which may falsely elevate PVP. In order to obviate this confounding factor, in our study we also calculated PSG by subtracting CVP from PVP. However, elevated PSG also did not show any statistical correlation for development of SFSS.

We found that GRWR cut off of 0.8% did not protect from development of SFSS. A combination of hyper bilirubinemia and coagulopathy of values defined for SFSS was found in 6 patients. Of these 6 patients, 5 had a GRWR > 0.8% and also PVP < 20 mm of Hg. Although we assessed other factors like recipient MELD, graft steatosis, donor age; there were no specific reasons to explain impaired graft function in these patients. Perhaps immunologic factors or loss of hepatocyte function due to reperfusion injury could have contributed to occurrence of SFSS.

In our study patients with elevated PVP > 20 mm of Hg had significantly longer length of ICU stay. However there were no significant differences in graft function, volume of post-transplant ascites, post-operative blood stream infections, vascular complications, post-operative bleeding and requirement of transfusions, biliary complications, hospital stay or mortality. Longer length of ICU stay probably was related to higher incidence of respiratory infections in these patients. However Ito et al.⁸ in their series of 79 cases of LDLT showed elevated PVP early in the first week (days 0–4) was associated with higher incidence of bacteremia, cholestasis, prolonged prothrombin time and ascites.

We also noticed similar findings in patients with PSG > 13 mm of Hg who had longer length of ICU stay which can be explained by longer requirement of post-operative ventilation. Correlation between elevated PVP or PSG and increased incidence of respiratory infections or

longer requirement of post-operative ventilation remains an unsettled issue.

Limitation of our study was the smaller sample size of 42 patients. However we cannot disregard the fact that even patients with high PVP or PSG did well without any inflow modulation. Likewise in majority of patients (5 out of 6) who had combination of hyper bilirubinemia and coagulopathy of values defined for SFSS, PVP was < 20 mm of Hg.

Other limitation of the study was single point measurement of PVP before and after implantation. We did not measure PVP subsequently in the post-operative period. Nevertheless, the critical point to measure PVP to predict SFSS is peri-operative. It is known that any portal inflow modulation after a few days may be futile attempt as damage would have already occurred. Thus, post-reperfusion PVP is the critical value in predicting or managing SFSS.

Our follow up was also limited for 1 month. But SFSS and its complications should manifest in first month and hence it's unlikely that the follow up was inadequate to report SFSS.

CONCLUSIONS

PVP > 20 mm of Hg did not predict SFSS.

Use of PSG of > 13 mm of Hg could not foresee SFSS either.

SFSS occurred in patients with low PVP and normal GRWR as well suggesting a multi factorial etiology for its development.

Elevated PVP or PSG increased the morbidity of recipients but they did not appear to affect their survival.

Larger prospective studies with uniform criteria for defining SFSS and measuring PVP are necessary before PVP and PSG can be used to guide treatments for SFSS outside clinical trials.

CONTRIBUTION BY AUTHORS

Dr. Amol Vijay Kanetkar: contributed in study design, performed the study, collected and analyzed the data and wrote the paper.

Dr. Dinesh Balakrishnan: contributed in study design, performed the study and helped in writing the paper.

Dr. Sudhindran S: designed the study, helped in statistical analysis and writing the paper.

Dr. Puneet Dhar: helped in analysis of data and writing the paper.

Dr. Unnikrishnan Gopalakrishnan, Dr. Ramachandran Menon and Dr. Othiyil Vayoth Sudheer also helped in performing the study.

CONFLICTS OF INTEREST

The authors have none to declare.

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