

Portal venous pressure and proper graft function in living donor liver transplants in 69 patients from an Egyptian center

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BACKGROUND: Several studies have defined the optimal portal pressure suitable for adequate graft renewal in liver transplantation (LT) but none have studied an Egyptian population to our knowledge.

OBJECTIVES: Determine the level of portal venous pressure (PVP) for adequate graft function, and study the effect of PVP modulation on the outcome of LT in an Egyptian population.

DESIGN: Cross-sectional, prospectively collected data.

SETTING: Liver transplantation unit.

PATIENTS AND METHODS: The study included adult cirrhotic patients who underwent right lobe liver donor living transplantation (LDLT) at our transplantation center. Intraoperative Doppler was performed on all LDLT patients. Two PVP measurements were obtained during the recipient operation: before PV clamping and after graft reperfusion. These PVP measurements were correlated with the results of intraoperative and postoperative Doppler findings and graft function. Mortality in the early postoperative period (<1 month) and development of small-for-size syndrome (SFSS) were recorded.

MAIN OUTCOME MEASURES: PVP, graft injury, and the effect of PVP modulation on the outcome of LT were the primary outcome measures. Secondary outcome measures were to correlate PVP to portal vein hemodynamics and intraoperative mean hepatic artery, peak systolic velocity, and also to correlate PVP with the postoperative graft function and mean postoperative platelet count.

SAMPLE SIZE AND CHARACTERISTICS: 69 adult patients with end-stage liver disease.

RESULTS: Post-reperfusion PVP was lower than pre-clamping PVP. The mean pre-clamping and post-reperfusion values were higher in patients who experienced early mortality and in patients with smaller grafts. A PVP greater than 16.5 mm Hg at the end of the operation predicted the development of SFSS (sensitivity=91.7% and specificity=50.5%). Cases of high PVP that were modulated to a lower level had a smooth and uneventful postoperative outcome.

CONCLUSION: PVP is a significant hemodynamic factor that influences the functional status of the transplanted liver, including the development of SFSS, in the Egyptian population. PVP modulation may improve the outcome of LDLT.

LIMITATIONS: Further study with a larger sample is needed to confirm these results.

CONFLICT OF INTEREST: None.

Liver transplantation (LT) is considered the only curative treatment option for patients with advanced liver disease. However, there are patient to patient differences in systemic and hepatic hemodynamic changes such as the development of collateral circulation, enlarged spleen, or portal vein occlusion.¹ With a fractional graft, changes in hemodynamic parameters become more sophisticated due to the greater probability of small-for-size syndrome (SFSS).¹ SFSS is characterized by postoperative coagulopathy and liver dysfunction.² SFSS is considered a separate clinical entity because of the progressive development of living donor liver transplantation (LDLT). SFSS may be related to a decreased liver parenchymal mass that is inadequate to sustain good graft function.³

Several surgical strategies have been proposed to avoid SFSS by reducing portal blood inflow and portal pressure. In particular, splenic artery ligation and splenectomy have been used without a firm hemodynamic basis for these procedures.⁴ Portal pressure can be determined by puncture of the portal vein (PV) and can be performed during open surgery or via a transhepatic method.⁵ Intraoperative assessment of portal pressure is crucial to assess the need for and type of inflow modification measures. Many transplant centers use an inferior mesenteric vein catheter to determine portal venous pressure (PVP).⁶ Elevation in portal pressure is needed for the regeneration of hepatocytes after partial hepatic excision.⁷ The mechanism of this regeneration is complex including a multiplicity of pathways and cellular proliferation kinetics in the initiation and termination of liver regeneration, growth factors and cytokines, and the capacity of hepatocytes and biliary epithelial cells to function as facultative stem cells for each other.⁸ Several studies have shown that portal vein flow by itself is important in triggering some early changes, including induction of urokinase plasminogen activator gene expression and activation of hepatocyte growth factor.⁸ However, an elevated portal pressure and flow may be harmful to the graft. Several studies have defined the optimal portal pressure suitable for adequate graft renewal that would decrease harm to the graft.⁷

Primary outcome measures of this study were to determine the level of PVP that is adequate for graft regeneration and the reduction of graft injury, and to study the effect of PVP modulation on the outcome of LDLT in an Egyptian population. Secondary outcome measures were to correlate PVP to portal vein hemodynamics: intraoperative mean portal vein velocity (PVV), postoperative mean PVV and intraoperative mean hepatic artery (HA) peak systolic velocity (PSV). Other secondary outcomes were to correlate PVP with the actual

graft-to-recipient weight ratio (GRWR), postoperative graft functions, and mean postoperative platelet count.

PATIENTS AND METHODS

Data was collected prospectively on adult cirrhotic patients who underwent right lobe LDLT at our liver transplantation unit from May 2010 to September 2015. Criteria for inclusion were end-stage liver disease (regardless of indication for LDLT), age from 18 to 60 years, GRWR of >0.8 estimated using preoperative CT volumetric scanning, steatosis of the liver graft not more than 10% percent. Criteria for exclusion were acute liver failure referred for transplantation, PV or hepatic artery complications, and bile leak or biopsy-proven rejection. The protocol was consistent with ethical guidelines of the 1975 declaration of Helsinki,⁹ and approved by the Cairo University Research Ethics Committee. Informed approval was obtained from both the recipient and sound adult living donors.

For preoperative patient evaluation, we used the Child–Pugh score and the Model For End-stage Liver Disease scoring systems for preoperative patient evaluation.¹⁰ Milan criteria were adopted in hepatocellular carcinoma patients.¹¹ The preoperative evaluation included a detailed history and examination and a full investigation of liver function.

Intraoperative ultrasound (US) was performed after the vascular anastomoses and before the biliary anastomosis. Scanning was performed after waiting a few minutes for the early hemodynamic changes after reperfusion to settle. The US unit was a multifrequency 7.5-10 MHz T-shaped convex array transducers with color Doppler and pulsed Doppler capabilities (BK Medical (<https://bkultrasound.com/>)). The BK unit has probes that are small and fit comfortably between the index and thumb fingers, which allows the liver to be palpated and scanned at the same time. The unit was placed to the right side of the patient and lighting conditions were adjusted.

Hepatic vein anastomoses were identified cranially. The PV and the hepatic artery (HA) anastomoses were situated more caudally. The main segmental branches of the HA and PV can be visualized by placing the transducer at the raw surface near the porta hepatis while angling properly. The whole length of the recipient PV was examined for detection of remnants of thrombi. The ratio between the post-anastomotic and pre-anastomotic velocities and the mean PVV were calculated (pre-anastomotic plus post-anastomotic velocities divided by 2). Pulsed Doppler was used to study the vascular anastomoses and hepatic perfusion. Spectral waveforms were obtained at measured angles

of insonation of $<60^\circ$. A longitudinal section of the vessel was obtained, and then the sample volume of the Doppler US system was placed in the middle of the vessel. The smallest possible velocity scale and the lowest possible wall filter were used. The measurements were repeated three times and an average of measurements was taken for each parameter. PVP was measured intraoperatively using a 16, 18 or 20-gauge antithrombotic catheter which was inserted into one of the jejunal or ileal mesenteric veins, an omental vein, the inferior mesenteric vein or the PV itself. The tip of the catheter was positioned in the recipient's mesenteric vein and fixed in place by a ligature. The other end was connected through an extension-arterial line drawn via the surgical wound to a pressure transducer. The normal range for directly measured PVP values was considered 7 to 12 mm Hg. Two readings of the PVP were obtained during the recipient operation: at laparotomy (10 minutes before portal venous clamping), before hepatectomy, and post-reperfusion (10 minutes after graft reperfusion), after vascular anastomoses were completed. Mean portal pressure equals the pre-clamping portal pressure plus post-reperfusion portal pressure divided by 2. If PVP was high (>20 mm Hg), PVP was modulated by splenectomy.

In the postoperative period, patients were followed up for 1 month after the operation (early postoperative period). Postoperative Doppler US was performed with a combined ultrasonic system using a 3.75 MHz convex probe. Waveforms were obtained at measured insonation angles of $<60^\circ$. We measured postoperative PVV, hepatic artery PSV and resistivity index (RI) (peak systolic velocity-end diastolic velocity/peak systolic velocity).

Patients who died within the first month were compared with those who survived the early postoperative period. Patients who developed SFSS during the early postoperative period were compared with those who did not develop SFSS. SFSS was identified according to the Clavien and Kyushu University definitions based on direct hyperbilirubinemia (in the absence of obstructive causes, rejection or CMV infection), coagulopathy and any degree of ascites.¹²

The statistical package IBM SPSS version 21.0 (IBM, Armonk, NY, United States) was used for data entry. Continuous data is summarized by the mean, standard deviation, median, minimum and maximum, after confirming normality. Categorical data is summarized by frequency and relative frequency. The nonparametric Mann-Whitney test was used for comparisons.¹³ Nonparametric Friedman tests were used to compare serial measurements, and Wilcoxon tests and chi-squared (χ^2)

tests were used for categorical data.¹⁴ The Spearman correlation coefficient was used to test for linear relationships between quantitative variables.¹⁵ Receiver operator characteristic curves were used to determine the best cutoff values of PVP for predicting SFSS. A *P* value of $<.05$ was considered to be statistically significant, while that $<.001$ was considered to be highly significant

RESULTS

The study included 69 adult patients with end-stage liver disease, 61 males and 8 females (Table 1). Indications for LDLT are summarized in Table 2. The reasons for liver cirrhosis that necessitated LDLT are summarized in Table 3. Intraoperative clinical data are shown in Table 4. Laboratory data during the early postoperative period are summarized in Table 5.

Early after graft reperfusion, PVP decreased to levels lower than those at baseline in 63 patients and to levels equal to those at baseline in 4 patients, but remained higher than the baseline level by >20 mm Hg in two patients. PVP before PV clamping ranged from 13 to 35 mm Hg with a mean (SD) of 24.9 (3.9) mm Hg. PVP after graft reperfusion ranged from 7 to 27 mm Hg with a mean (SD) of 17.6 (4.93) mm Hg. Mean intraoperative central venous pressure (CVP) ranged from 5.9 to 9.6 mm Hg with a mean (SD) of 7.36 (0.97) mm Hg.

Six patients with a high intraoperative PVP ≥ 20 mm Hg underwent splenectomy, and all had a smooth postoperative course. Thirty-one (45.0%) patients died during the early postoperative period and the remaining 38 survived (Table 6). Apparent causes of death were cardiac arrhythmia in 4 patients, acute rejection in 3 patients, biliary leak in 3 patients, myocardial infarction in 2 patients, pulmonary embolism in 2 patients and hepatic artery thrombosis in 2 patients.

PVP before clamping, after graft reperfusion and in-

Table 1. Demographic characteristics of the patients (n=69).

Variables	Range	Mean	SD
Age (years)	32-63	48.0	6.8
BMI (kg/m ²)	18.9-34.4	26.6	3.5
MELD	11-25	18.62	3.9
Child-Pugh score	7-13	9.56	2.4
Actual graft weight (gm)	800-1100	941.06	94.7
IO graft recipient weight ratio	0.85-1.3	1.00	0.2

BMI: body mass index, MELD: model for end stage liver disease, IO: intra-operative
Normal BMI range: 18.5kg/m² - 25 kg/m² ers

traoperative mean PVP as well as intraoperative CVP were higher in the patients that died, and the results were statistically highly significant (**Table 6**). Fifteen (21.7%) patients developed SFSS during the early postoperative period (**Table 7**). PVP before clamping, after graft reperfusion and mean intraoperative PVP as well as intraoperative CVP were higher in patients who developed SFSS, and the results were a statistically highly

Table 2. Indications for living donor liver transplantation in the study population.

	Number	Percentage
Child A	2	2.9
Child B	11	15.7
Child C	57	81.3
Recurrent hepatic encephalopathy	29	41.4
Recurrent SBP	35	50.0
Refractory ascites	39	55.7
Recurrent GI bleeding	32	45.8

Table 3. Causes for liver cirrhosis in the study population.

Cause of cirrhosis	Number
HCV-related cirrhosis	58
HBV-related cirrhosis	7
Cryptogenic cirrhosis	3
Autoimmune cirrhosis	2

Hepatocellular carcinoma (HCC) was present in 7 patients, 5 post-HCV, 2 post-HBV. HCV: hepatitis C virus and HBV: hepatitis C virus

Table 4. Intraoperative clinical data.

	Mean	Standard Deviation	Median	Minimum	Maximum
Blood (units)	9.5	4.9	8.0	3.0	37.0
Platelets (units)	14.7	7.9	12.0	0.0	42.0
Plasma (units)	9.2	4.7	8.0	0.0	24.0
Cryoprecipitate (units)	.39	0.8	0.0	0.0	4.0
Cold ischemia (minutes)	50.5	16.0	45.0	25.0	106.0
Warm ischemia (minutes)	50.8	16.1	50.0	25.0	100.0
Anhepatic phase (minutes)	109.9	31.7	100.0	60.0	230.0
Intraoperative graft size (g)	913.0	110.3	910.0	500.0	1270.0
Intraoperative GRWR (IO)	1.0	0.2	1.0	0.8	1.5

GRWR: graft-to-recipient weight ratio.

significant. The best cutoff value for the prediction of SFSS (**Figure 1**) was identified using the following parameters: pre-clamping PVP (24.5 mm Hg), with a sensitivity of 83.3% and specificity of 53.5%, and post-perfusion PVP of 16.5 mm Hg, with a sensitivity of 91.7% and specificity of 50.5%. The correlations between the mean PVP (pre-clamping value plus post-reperfusion value divided by 2) and different variables are summarized in **Table 8**. The higher the mean intraoperative PVP, the higher the indices of graft functions.

DISCUSSION

LT is the best strategy for patients with end-stage liver failure. The procedure has evolved from an experimental approach to an almost routine procedure with good survival rates.¹ In the present study, the post-reperfusion PVP was lower than the pre-clamping PVP. These results are in agreement with those of Wu et al, who found that the mean PVP before recipient hepatectomy was significantly higher than the mean PVP after reperfusion.¹⁶ The current study showed that pre-clamping, post-reperfusion and mean PVP were higher in the early mortality group. These results agree with those of Ito et al, who found that patients with an elevated mean PVP demonstrated significantly worse survival. Therefore, elevated PVP was strongly associated with early postoperative mortality after LT.¹⁷ In addition, Ogura et al published a retrospective analysis of 100 transplants with intentional portal pressure control under 20 mm Hg and demonstrated that patients with a higher PVP had higher rates of early postoperative mortality after LT.¹⁸ The current study showed that pre-clamping, post-reperfusion and mean PVP were higher in the SFSS group.

Table 5. Laboratory data during the the early postoperative period.

	Mean	SD	Median	Minimum	Maximum
Hemoglobin (g/dL)	8.9	0.8	8.8	7.0	10.8
Total leucocyte count (10 ³ /μL)	9.8	3.9	9.1	2.2	34.8
Platelets (10 ⁹ /L)	79.2	29.7	73.4	26.8	160.3
CRP	20.5	13.2	17.1	3.4	76.8
AST (U/L)	1.8	1.1	1.6	1.2	12.9
ALT (U/L)	4.9	3.7	4.0	1.0	22.8
GGT (U/L)	3.4	2.8	2.3	0.6	16.0
ALP (U/L)	308.6	924.0	152.6	47.5	10043.9
Total bilirubin (mg/dL)	245.8	240.6	178.0	53.9	2107.6
Direct bilirubin (mg/dL)	204.5	154.9	149.2	35.9	866.6
INR	223.8	160.2	172.6	43.1	806.6
Albumin (g/dL)	2.7	0.3	2.8	1.8	3.3
Creatinine (mg/dL)	1.2	0.5	1.0	0.6	3.0

CRP: C-reactive protein, AST: aspartate aminotransferase, ALT: Alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyltransferase.

Similarly, the review by Rajekar showed that living donor grafts with a portal pressure of more than 20 mm Hg had a greater risk of graft dysfunction and SFSS.¹⁹ In contrast, Lei et al studied LDLT adult recipients. The authors showed that pre-clamping and post-reperfusion PVP were not associated with SFSS development in LDLT.²⁰ The present study showed significant negative correlation between mean PVP and actual GRWR. These results are in agreement with those of Ito et al, who showed that recipients with lower GRWR exhibited a significantly higher PVP.¹⁷ In addition, Man et al measured PVP before and after reperfusion in 40 LDLT patients. The authors found that post-reperfusion portal pressures in the smaller GRWR group were significantly higher than those in the higher GRWR groups.²¹ The current study showed a statistically significant positive correlation between PVP and the intraoperative mean PVV.

This agrees with the study done by Sánchez et al, who found a significant positive relationship between the intraoperative PVV and the mean PVP during LT.²² In contrast, Sainz-Barriga et al analyzed 81 LT procedures and found no correlations between PVV and PVP during LT.²³

The present study showed that there was a statistically significant positive correlation between mean PVP on one side and AST, ALT, ALP, GGT, INR and serum bilirubin on the other side. These results agree with the results obtained by Wu et al, who found that PVP had a

Table 6. Hemodynamic parameters in patients who died versus patients who survived the early postoperative period.

Variables	Died (n=31)	Survived (n=38)	P value
PVP before clamping (mm Hg)	27.1 (3.0)	24.3 (3.9)	<.001
PVP after graft reperfusion (mm Hg)	22.3 (2.9)	16.2 (4.5)	<.001
Mean intraoperative PVP (mmHg)	24.5 (3.2)	19.5 (3.3)	<.001
Mean intraoperative CVP (cm H ₂ O)	10.4 (1.3)	10.0 (1.3)	.049
Mean intraoperative CVP (mmHg)	7.6 (1.0)	7.3 (1.0)	.47

Data are mean (standard deviation). PVP: portal venous pressure; CVP: central venous pressure.

Table 7. Hemodynamic parameters in patients who developed versus patients who did not develop small-for-size syndrome.

Variables	SFSS (n=15)	No SFSS (n=54)	P value
PVP before portal vein clamping (mm Hg)	26.3 (3.0)	24.6 (4.0)	.028
PVP after graft reperfusion (mm Hg)	20.3 (3.4)	16.9 (5.0)	.003
Mean PVP (mm Hg)	23.3 (2.8)	20.7 (4.2)	.003
Mean intraoperative CVP (mm Hg)	7.3 (1.3)	7.4 (0.9)	.532

Data are mean (standard deviation). SFSS: small-for-size syndrome, PVP: portal venous pressure, CVP: central venous pressure.

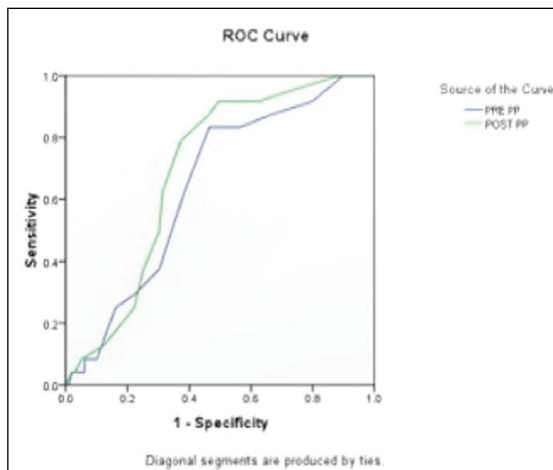


Figure 1. Receiver operating characteristic curve to define a cutoff value of (pre clamping and post re-perfusion) PVP for prediction of SFSS (16.5 mmHg).

Table 8. Correlation between mean intraoperative PVP and indices of graft function.

Variable	r	P value
GRWR (intraoperative)	-0.60	<.001
PVV (intraoperative)	0.43	.03
Mean hepatic artery PSV (intraoperative)	-0.22	.006
AST	0.45	<.001
ALT	0.54	<.001
ALP	0.42	<.001
GGT	0.31	<.001
INR	0.54	<.001
Mean total bilirubin	0.42	<.001
Mean direct bilirubin	0.42	<.001
Mean platelet	-0.39	<.001
Hepatic artery resistive index (postoperative)	0.53	<.001

GRWR: Graft-to-recipient weight ratio, PVP: portal venous pressure, PVV: portal venous velocity, PSV: peak systolic velocity, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, INR: international normalized ratio.

notable correlation with graft functions after LDLT.¹⁶ In parallel with the previous studies, Onoe et al demonstrated that liver functions was significantly improved in the early post-transplantation period in patients with a lower PVP.²³ The results of the present study revealed statistically significant negative correlations between PVP and postoperative platelet count. These results are consistent with the results obtained by Marubashi et al, who found that high PVP was linked with post-transplant thrombocytopenia.²⁴

The present study showed that a PVP above 16.5 mm Hg at the end of the operation may be a predictor for the development of SFSS. In this context, studies were done to determine the level of PVP that could predict the development of SFSS. The study by Chang et al included 34 LDLT patients and noticed that 23 mm Hg was a cutoff value for post-reperfusion PVP, with a sensitivity of 83% and a specificity of 43%.²⁵ In 2010, Ogura et al concluded that a post-reperfusion PVP of <15 mm Hg appeared to be necessary for successful LDLT.²⁶

In the present study, splenectomy was performed in 6 patients in whom portal pressure was equal to or above 20 mm Hg. The portal pressure decreased to a mean of 14.5 mm Hg in these patients, who subsequently experienced a smooth and uneventful postoperative outcome. From this point of view, previous studies were performed to explore the effect of lowering PVP in the presence of relatively small grafts to prevent the development of SFSS, to enhance donor safety and to widen the pool of organ donations. The study by Campos and Botha found that the use of smaller grafts was well tolerated when PVP was adjusted to a goal PVP of less than 15 mm Hg after reperfusion.²⁷

The essential goal of the current study was to focus on the level of PVP that was adequate for proper graft function and the reduction of graft injury, thereby improving the outcome of LT, in an Egyptian population. In addition, we wanted to highlight the effect of PVP modulation on LDLT outcomes. We found that a PVP above 16.5 mm Hg at the end of the operation can be considered a predictor for the development of SFSS (sensitivity was stronger than specificity) (sensitivity=91.7% and specificity=50.5%). A suggested explanation for this is that full portal vein flow has to traverse through a much reduced liver size. The pressure increase in the portal vein effectively shuts down the flow through the portal arterioles and the liver becomes de-

arterialized.²⁸ Of note, a PVP below 16.5 mm Hg alone is not sufficient to prevent graft dysfunction or guarantee a good outcome. A combination of graft size, graft quality, graft inflow and outflow as well as good preoperative recipient health status should be targeted to achieve good postoperative graft functions and a satisfactory outcome. The absence of one or more of these factors increases the risk of graft dysfunction and SFSS.

In LDLT, PVP has a pivotal impact on the outcome. PVP should be maintained within certain limits to enhance proper graft regeneration. If PVP exceeds these limits, it may injure the graft. We propose that PVP should be routinely measured in every recipient who undergoes LDLT.

Although there is no agreement on the best value of PVP, the modulation of PVP may be of great help in LDLT because it may decrease the incidence of SFSS and improve LDLT outcome. Certain maneuvers could be adopted by surgeons to adjust the PVV if it is too low or too high. In this manner, we can maximize the use of PVP to improve both survival and graft function after LDLT.

In this study, we propose that the modification of PVP is an important part of LDLT; the six patients who had an elevated PVP underwent splenectomy and experienced a smooth postoperative outcome. The adoption of PVP modulation may expand the application of LDLT in adults, which may be restricted by graft size and donor integrity. We propose that switching the risk from donor to recipient is an ethically acceptable strategy.

While many studies have determined the cut-off val-

ue of PVP for prevention of SFSS, this is the first Egyptian study to our knowledge. Egyptian demographic characteristics may differ from other populations (taking into account that HCV is the leading cause of cirrhosis in study population (58 out of 69 patients), so we have probably confirmed that the Egyptian population does not differ significantly based on published reports. In addition, the correlation of PVP to mean intraoperative hepatic artery peak systolic velocity is new data. We also correlated PVP to PV hemodynamics, as mean intraoperative and postoperative PVP. This information may help maximize the use of Doppler US in LDLT.

Additional studies like this one are warranted with a larger number of patients to confirm the results, and to address the multiple confounding factors that were not primarily targeted in this study, such as portal flow, preoperative portal hypertension, and overall clinical and nutritional status. Also, further studies are required to compare different methods of portal flow modulations, either surgical (as splenic artery ligation or portal-systemic shunts) or pharmacological and to target other aspects of the graft regeneration power such as functional (hepatobiliary iminodiacetic acid) or radiological assessment (volumetric study).

In conclusion, a PVP greater than 16.5 mm Hg at the end of the operation may be a predictor for the development of SFSS in an Egyptian population. In addition, PVP correlated notably with liver function post-LDLT. PVP is therefore an important hemodynamic factor that can affect graft function. PVP modulation may be a critical aspect of LDLT.

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