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Original Article

Exploring the Occurrence and Determinants of Post-Reperfusion Syndrome in Living Donor Liver Transplantation

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ABSTRACT

Background: Post-reperfusion syndrome (PRS) during liver allograft reperfusion is characterized by hemodynamic instability, including hypotension, bradycardia, and arrhythmias. The incidence and risk factors of PRS are primarily studied in cadaveric liver transplantation. This study aims to estimate the incidence of PRS and identify associated factors in living donor liver transplantation (LDLT).

Objective: To estimate the incidence of PRS and evaluate factors associated with its development in LDLT.

Methods: We prospectively observed 70 adult patients with chronic liver disease who underwent LDLT between August 2020 and March 2022. Patients were categorized into two groups: those who developed PRS (PRS group) and those who did not (non-PRS group).

Results: PRS occurred in 26 of 70 recipients (37.1%). The PRS group had significantly higher mean MELD scores, lower preoperative fibrinogen levels, and longer graft cold ischemia times (p= 0.027, p= 0.015, p= 0.045, respectively). These patients also experienced greater intraoperative blood loss and required more blood product transfusions. Postoperatively, the PRS group had longer mechanical ventilation times, a prolonged vasopressor requirement, and higher peak bilirubin levels in the first 7 days (p= 0.009, p= 0.001, p= 0.002, respectively).

Conclusion: PRS is associated with more severe liver disease, greater intraoperative blood loss, and higher blood product transfusions. Postoperatively, patients with PRS had longer mechanical ventilation, prolonged vasopressor use, and elevated bilirubin levels.

KEYWORDS: End-stage liver disease; Liver transplantation; Reperfusion; Living donor

INTRODUCTION

Orthotopic liver transplantation (OLT) is the treatment of choice for patients with end-stage liver disease (ESLD). OLT comprises three phases: 1) the dissection phase, which involves separating adhesions and mobilizing the liver; 2) the anhepatic phase, during which the native liver is removed and a vascular bed is created for the new liver; and 3) the neohepatic or reperfusion phase [1]. The reperfusion phase, which is the transition from the anhepatic to the neohepatic phase, is the most critical component of the surgery. During reperfusion of the allograft liver, significant hemodynamic instability is observed in the form of post-reperfusion syndrome (PRS), which can result in extreme hypotension, bradycardia, or arrhythmias. Post-reperfusion syndrome was originally described by Aggarwal *et al.* in 1987 as cardiovascular collapse after reperfusion of the new liver graft [2]. Aggarwal *et al.* defined PRS as a greater than 30% decrease in mean arterial pressure (MAP) from its baseline value before reperfusion, lasting for at least 1 minute and occurring within the first 5 minutes of reperfusion of the liver graft.

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More recently, Hilmi *et al.* expanded and classified PRS into mild and significant categories 1) Mild PRS, defined by a less than 30% decrease in MAP and/or heart rate, lasting for less than 5 minutes, and responsive to an intravenous bolus dose of calcium chloride (1 gram) and/or adrenaline (≤100 μg) without the need to start a continuous infusion of vasopressors. 2) Significant PRS, defined by a greater than 30% drop in MAP and/or heart rate, asystole or hemodynamically significant arrhythmias, or the need for a continuous infusion of vasopressors during the intraoperative period and continuing throughout the postoperative period. Another version of significant PRS includes prolonged (lasting >30 minutes) or recurrent (reappearing within 30 minutes after resolution) fibrinolysis, which requires treatment with anti-fibrinolytic agents [3].

The incidence of PRS varies among different studies, ranging from 8% to 53% [4]. Some reports suggest a high incidence of 77% [5]. The exact mechanisms and etiology of PRS are complex, multifactorial, and not fully understood. The immediate severe hemodynamic effects of PRS may result from the heart and vasculature being transfused from the new graft with a large bolus of acidotic, hyperkalemic, cold fluid containing other vasoactive agents. Release of various pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-2 (IL-2), and interleukin-8 (IL-8) from the donor's liver due to prior ischemia [6, 7], and the recipient's immune system also produces various inflammatory cytokines such as kallikrein, bradykinin, chemokines, and activated complements [7]. PRS can cause dramatic cardiovascular and metabolic derangements that can influence the recipient's outcome and survival [8].

The data and literature on PRS are mainly based on cadaveric orthotopic liver transplantation rather than living donor liver transplantation. Hence, this study aimed to estimate the incidence of PRS and evaluate the factors associated with PRS in living donor liver transplantation.

MATERIALS AND METHODS

Following approval from the institutional ethics committee (IEC/2021/83/MA10), we prospectively observed all consecutive adult patients (18–65 years old) with chronic liver disease who underwent living donor liver transplantation at the Institute of Liver and Biliary Sciences, New Delhi, between August 2020 and May 2022. Patients with acute liver failure, acute-on-chronic liver failure, severe cardiac dysfunction, or those under the age of 18 (pediatric patients) were excluded. Written informed consent was obtained from all participants. A standard anesthesia protocol was followed, as briefly described below. Fentanyl (2 μg/kg), propofol (2 mg/kg), and rocuronium (1 mg/kg) were used to induce anesthesia and facilitate endotracheal intubation. Anesthesia was maintained with a 50% oxygen-air mixture, sevoflurane at 0.8–1.0 minimum alveolar concentration, and infusions of fentanyl and cis-atracurium. Intravenous fluids (PlasmaLyte ATM) and vasopressors were titrated to maintain a mean arterial pressure (MAP)≥ 65 mmHg and stroke volume variation (SVV) less than 13%. Monitoring and correction of coagulopathy were based on thromboelastography™. Arterial blood gas, blood glucose, and ionized calcium levels were serially monitored and treated accordingly. The target hematocrit was 24%. Postoperatively, all patients were transferred to the intensive care unit (ICU) for further management.

Post-reperfusion syndrome (PRS) was defined as a greater than 30% decrease in MAP from the baseline value before reperfusion, lasting at least 1 minute and occurring within the first 5 minutes of liver graft reperfusion. Patients were divided into two groups: PRS and non-PRS. Various preoperative, intraoperative, and postoperative factors associated with PRS were evaluated.

PRS was managed with incremental boluses of phenylephrine 100 μg if the heart rate was > 80 bpm, or adrenaline 10 μg if the heart rate was < 80 bpm, to maintain hemodynamic stability. Severe hypotension (an abrupt decrease in MAP below 40 mmHg) was immediately

Table 1: Preoperative liver transplant recipient-related data.

Variables	PRS group (n=26)	Non-PRS group (n=44)	P-value
Age (years)	44.31 ± 8.11	46.93 ± 10.7	0.284*
Sex (male/female)	23(88.46%)/3(11.54%)	37(84.09%)/7(15.91%)	0.614§
BMI (kg/m²)	26.53 ± 4.42	24.81 ± 4.43	0.123*
MELD-Na	24.35 ± 4.92	21.07 ± 6.32	0.027*
Hb (gm/dL)	8.75 ± 1.64	9.35 ± 1.77	0.166*
Creatinine (mg/dL)	0.67 ± 0.18	0.72 ± 0.19	0.250*
Platelet (x1000)	57.5 (40-96)	80 (46.75-109.25)	0.238†
INR	2.25 ± 1.0	1.89 ± 0.76	0.086*
T. Bilirubin (mg/dL)	3.26 (2.10, 6.35)	2.51 (1.60, 6.45)	0.179†
Fibrinogen (mg/dL)	121.96 (80.88, 144.93)	152.55 (107.4, 199.83)	0.015†
Albumin (mg/dL)	3.22 ± 0.53	2.97 ± 0.69	0.120*

Data are presented as mean ± SD, median (Q1, Q3) or n (%).
*Independent t-test, †Mann Whitney test, §Chi-square test
Abbreviations: BMI: Body mass index, MELD: Model for end-stage liver disease, Hb: Hemoglobin.

treated with incremental boluses of 10 µg adrenaline. Phenylephrine and adrenaline boluses were repeated until the blood pressure showed an increasing trend, at which point they were discontinued. Persistent hypotension was managed using a titrated infusion of noradrenaline and vasopressin, with a target MAP> 65 mmHg.

Data Collection

Recipient characteristics included demographic data, the Model for End-Stage Liver Disease (MELD) score, preoperative laboratory variables, donor characteristics (age, sex, and BMI), surgery-related variables (duration of the anhepatic phase, total duration of surgery, total blood loss, and total blood products transfused), and graft-related variables (graft-to-recipient weight ratio, cold ischemia time, warm ischemia time, and right or left lobe). The anesthetic monitoring system recorded all hemodynamic data (mean arterial pressure, heart rate, systemic vascular resistance, and cardiac output) and retrieved it intraoperatively to assess hemodynamic changes. The occurrence of PRS and the dose of rescue vasopressor boluses administered during reperfusion were also recorded.

Postoperative variables included the time to extubate, duration of vasopressor requirement, serum bilirubin, AST, ALT, INR, and creatinine levels (up to 7 days), as well as the length of ICU and hospital stay and any other complications.

Ethical Considerations

The current study was approved by the institutional ethics committee (IEC/2021/83/MA 10) of Institute of Liver and Biliary Sciences, New Delhi, India.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 21.0, IBM Corporation, Chicago, USA. All continuous data were expressed as mean ± SD or median (interquartile range), as appropriate. Categorical data were expressed as number (percentage). The Kolmogorov-Smirnov test was used to assess the normality of the data. Continuous data were analyzed using either the independent t-test or the Mann-Whitney test, depending on the normality of the data. Categorical data were analyzed using the Chi-square test or Fisher's exact test, as appropriate. A p-value of less than 0.05 was considered statistically significant.

Table 2: Donor characteristics.

Variables	PRS group (n=26)	Non-PRS group (n=44)	P-value
Donor age (years)	36.69 ± 11.43	33.18 ± 10.16	0.187*
Donor sex (male/female)	10(34.46%)/16(61.54%)	20(45.45%)/24(54.54%)	0.568§
Donor BMI (kg/m2)	24.54 ± 3.57	24.31 ± 2.56	0.759*

Data are presented as mean ± SD and n (%).
*Independent t-test, §Chi-square test
Abbreviations: BMI: Body mass index

RESULTS

A total of 82 patients underwent OLT during the study period. Of these, 12 patients were excluded from the study: 6 due to acute liver failure and another 6 due to pediatric liver transplants. Finally, 70 adult patients who underwent OLT were assessed during the study period.

Post-reperfusion syndrome occurred in 26 of the 70 recipients (37.1%). The patients were divided into two groups: the PRS group (n= 26), who developed PRS intraoperatively, and the non-PRS group (n= 44). The demographic characteristics between the two groups were comparable (Table 1). The mean MELD Na score was 24 in the PRS group, which was significantly higher than in the non-PRS group (MELD Na= 21, p= 0.027). There was no significant difference in the etiology of liver disease between the two groups.

Among the preoperative laboratory values, patients in the PRS group had significantly lower fibrinogen levels compared to those in the non-PRS group. The median fibrinogen level (mg/dL) in the PRS group was 121.9 (80.88, 144.93), compared to 152.55 (107.4, 199.83) in the non-PRS group (p= 0.015), as shown in Table 1. The donor characteristics, such as donor age, sex, and BMI, were comparable between the two groups (Table 2).

Regarding intraoperative surgery and anesthesia-related variables, the median cold ischemia time (minutes) was significantly higher in the PRS group (92 [77.75, 119]) compared to the non-PRS group (81 [64.25, 92.25], p= 0.045). The median blood loss (mL) in the PRS group was 2250 (1520, 4000), compared to 1810 (1300, 2400) in the non-PRS group, which was significantly higher (p= 0.031). Patients in the PRS group also received significantly more blood products than those in the non-PRS group. The incidence of fibrinolysis was comparable between the two groups (Table 3).

Among the postoperative outcomes, the median duration of mechanical ventilation required postoperatively was significantly longer in the PRS group (p= 0.009). The time required to taper vasopressors was also significantly longer in the PRS group (p= 0.001). The peak bilirubin level during the first 7 days after liver transplantation (LT) was significantly higher in the PRS group [8.34 (5.23, 11.63) vs. 4.97 (3.55, 9.58), p= 0.022]. All other postoperative outcomes were comparable between the two groups (Table 4).

DISCUSSION

The overall incidence of post-reperfusion syndrome (PRS) in our study was 37.4%, which is substantially lower compared to the prevalence of PRS reported in previous studies, which ranged from 32% to 65% [2, 8, 9]. We believe that differences in the patient populations, variations in surgical and anesthesia techniques, and the methods used to detect PRS (including underdiagnosis of PRS, particularly when analyzing data retrospectively) may account for this discrepancy. In our study, PRS was evaluated prospectively, and each patient's hemodynamic data during the reperfusion period was recorded by a multiparameter hemodynamic monitor and reviewed every 30

Table 3: Intraoperative data of liver transplant recipients.

Variables		PRS group (n=26)	Non-PRS group (n=44)	P-value
CIT (min)		92 (77.75, 120)	81 (64.25, 92.25)	0.045†
WIT (min)		25 (20.25, 30.5)	25.5 (21, 29.5)	0.808†
Duration of an-hepatic phase (min)		106 (74.75, 153.0)	90 (62.75, 143.5)	0.556†
Temporary Portocaval shunt [n (%)]	Yes	17 (65.38%)	30 (68.18%)	0.810§
	No	9 (34.61%)	14 (31.81%)	
Graft lobe [n (%)]	Right	23 (88.46%)	35 (79.54%)	0.514§
	Left	3 (11.54%)	9 (20.45%)	
GRWR		0.90 ± 0.17	0.95 ± 0.22	0.239*
Blood loss		2250 (1520, 4000)	1810 (1300, 2400)	0.031†
PRBC (unit)		4 (3, 10)	3 (2, 4)	0.048†
FFP (unit)		2.5 (0.25, 4)	0 (0, 2)	0.006†
Cryoprecipitate (unit)		4 (0, 8)	0 (0, 5)	0.028†
SDPC (unit)		0 (0, 1)	0	0.020†
Incidence of fibrinolysis		2 (7.6%)	1 (2.27%)	0.280§

Data are presented as mean ± SD, median (Q1, Q3) or n (%).
*Independent t-test, †Mann Whitney test, §Chi-square test
Abbreviations: CIT: Cold ischemia time, WIT: Warm ischemia time, GRWR: Graft recipient weight ratio, PRBC: Packed red blood cells, FFP: Fresh frozen plasma, SDPC: Single donor platelet

seconds at the end of surgery. This approach made it more likely to detect PRS compared to previous studies that relied on retrospective chart reviews.

Upon analyzing the patients with and without PRS, we found that the MELD score was significantly higher in those who experienced PRS. Patients in the PRS group also had significantly lower preoperative serum fibrinogen levels, and they experienced significantly higher blood loss and blood product transfusions. The increased use of packed red blood cell (PRBC) transfusions could be attributed to surgical difficulties or may reflect the severity of liver disease, particularly with hypofibrinogenemia. Patients with end-stage liver disease typically have fibrinogen deficiency and other coagulation abnormalities, which worsen as liver cirrhosis progresses [10]. In line with our study, Chung *et al.* showed that patients in the PRS group had significantly higher MELD scores, more blood loss, and required more blood transfusions than the non-PRS group [11]. Hilmi *et al.* also reported that patients with severe PRS required more PRBC, fresh frozen plasma (FFP), and cryoprecipitate transfusions intraoperatively [3]. Khosravi *et al.* similarly found that blood loss and blood product use were significantly higher in patients with PRS [12].

The only significant graft-related factor identified in our study was the duration of cold ischemia. Although the cold ischemia time was within acceptable limits for both groups, the PRS group had significantly longer cold ischemia times. While major graft insults occur during reperfusion, the initial insult begins during cold ischemia, due to mitochondrial dysfunction and cellular membrane damage [13-15]. Oxidative stress during reperfusion leads to Kupffer cell activation, microvascular dysfunction, and neutrophil activation [16, 17]. Ischemic reperfusion injury may or may not be the cause of hemodynamic changes immediately after reperfusion, and the relationship between ischemia-reperfusion injury (I/R) and PRS remains unclear [18].

We also analyzed immediate postoperative outcomes in patients who experienced PRS.

Table 4: Post-operative liver transplant recipient data.

Variables	PRS group (n=26)	Non-PRS group (n=44)	P-value
Duration of mechanical ventilation (hours)	16 (12-36.5)	12.75 (12-14)	0.009†
Time taken to taper vasopressors (hours)	17 (15-20)	14 (12.5-15)	0.001†
Peak bilirubin (mg/dl)	8.34 (5.23, 11.63)	4.97 (3.55, 9.58)	0.022†
Peak AST (U/L)	168 (123.8, 336.8)	185 (125.5, 324)	0.961†
Peak ALT (U/L)	170 (115.8, 276.5)	166.2 (131.25, 298.5)	0.874†
AKI [n (%)]	11 (42.31%)	14 (31.82%)	0.376§
Graft rejection [n (%)]	3 (8.57%)	5 (14.29%)	0.71‡
ICU stay (days)	10 (6-24.75)	10.5 (7-16.25)	0.951†
Hospital stay (days)	32.5 (25.25-59)	29.5 (22-40.75)	0.355†

Data are presented as median (Q1, Q3) or n (%).
†Mann Whitney test, §Chi-square test, ‡Fisher's exact test
Abbreviations: AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AKI: Acute kidney injury, ICU: Intensive care unit

Among these variables, the PRS group required a longer duration of mechanical ventilation and vasopressor support postoperatively. However, there was no significant difference in the ICU or hospital length of stay, nor in the incidence of other complications. This may be due to multiple factors affecting postoperative outcomes beyond reperfusion. In a study by Fayed *et al.*, a prolonged duration of mechanical ventilation was observed in patients with severe PRS, but there were no significant differences in ICU stay, hospital stay, or other postoperative complications [19]. Hilmi *et al.* also found that ICU length of stay and days on a ventilator were greater in patients with PRS [3]. In our study, peak bilirubin levels during the first seven days after liver transplantation (LT) were significantly higher in the PRS group. However, there was no significant difference in peak aspartate transaminase (AST) or alanine transaminase (ALT) levels during the same period. This is consistent with a previous study by Chung *et al.*, which also observed significantly higher peak bilirubin levels during the first five days after liver transplantation [11]. They similarly found no significant relationship between PRS and ICU stay, hospital stay, or postoperative complications.

One limitation of our study is the small sample size. The confounding factors influencing PRS are numerous, and thus, our results may be affected by various unaccounted recipient and donor conditions, comorbidities, and surgical and anesthesia variables.

In conclusion, during living donor liver transplantation, the severity of liver disease is associated with an increased risk of PRS. Intraoperative blood loss and blood product transfusions were higher in patients who experienced PRS. Postoperative outcomes were comparable between both groups, except for the peak bilirubin levels in the immediate postoperative period. Further prospective studies are needed to identify the risk factors for PRS in living donor liver transplantation.

CONFLICT OF INTEREST: None declared.

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