Transplant International

ORIGINAL ARTICLE

Long term outcomes and complications of reno-portal anastomosis in liver transplantation: results from a propensity score-based outcome analysis

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SUMMARY

Diffuse splanchnic vein thrombosis (DSVT) remains a serious challenge in liver transplantation (LT). Reno-portal anastomosis (RPA) has previously been reported as a valid option for management of patients with DSVT during LT. The aim of this study was to evaluate post-transplant renal function and surgical outcomes of patients with DSVT who underwent RPA during LT. Between January 2005 and December 2017, 1270 patients underwent LT at our institution, including 16 with DSVT managed with RPA (RPA group). We compared renal function and surgical outcomes in these patients to outcomes in 48 propensity score (PS)-matched patients without thrombosis (control group), using a 1:3 matching model. The two groups had similar rates of postoperative portal vein thrombosis (PVT), renal dysfunction as measured by estimated glomerular filtration rate (eGFR), and overall postoperative complications (Clavien grade III), although the RPA group had a higher incidence of postoperative upper gastrointestinal (GI) bleeding (31.3% vs 4.2%; $P = 0.009$) that had no clinical consequence. There were no significant differences in five-year graft and patient survival rates between the groups ($P = 0.133$ and $P = 0.166$, respectively). RPA is an established technique in the management of patients with DSVT during LT, with comparable outcomes to patients without thrombosis. Our report is the first to demonstrate similar surgical outcomes, including long-term renal function, in LT recipients with or without RPA.

Transplant International 2021; 34: 1938–1947

Key words
diffuse splanchnic vein thrombosis, kidney function, liver transplant, portal vein thrombosis, reno-portal anastomosis

Received: 14 January 2021; Revision requested: 29 April 2021; Accepted: 11 May 2021; Published online: 31 August 2021

doi:10.1111/tri.13920

Introduction

Portal vein thrombosis (PVT) entails a wide variety of conditions and can potentially impact the entire porto-spleno-mesenteric axis. It can range from a nonocclusive single branch thrombus to a diffuse occlusive thrombus involving the portal, splenic and mesenteric veins [1–3].

PVT is often encountered during liver transplantation (LT), with reported incidences ranging from 2% to 26% [4, 5]. While a single-vessel nonocclusive thrombus can be managed easily, a diffuse splanchnic vein thrombosis (DSVT) (Yerdel Grade 4) [5] presents a significant challenge, involving complete thrombosis of the main portal vein (PV) and the proximal and distal superior mesenteric vein [1].

PV inflow is essential to preserve liver graft viability [6]. PVT management varies depending on the anatomy and extent of the thrombosis [7–10]. Options range from PV thrombectomy and meso-portal jump graft, for single-vessel thrombosis, to arterialization of the PV, porto-caval hemi-transposition, reno-portal anastomosis (RPA) and full multi-visceral transplant for patients with diffuse splanchnic thrombosis. These procedures may result in complications but are the only options that make LT possible in patients with DSVT [11].

When RPA is chosen as an alternative source of graft inflow in DSVT, it is generally constructed by sewing the left renal vein with the graft PV, either in an end-to-end or side-to-end fashion, with or without an interposition graft. The RPA provides adequate portal inflow in patients with spontaneous or surgical splenorenal shunt (SRS) [11, 12]. To date, however, data regarding the long-term outcomes following RPA procedures are lacking. Furthermore, post-transplant renal function in LT recipients with RPA has not been well studied.

Herein we compare short- and long-term outcomes of patients with DSVT and SRS transplanted using RPA and patients without PVT who underwent conventional LT.

Patients and methods

Study design and patient selection

From January 2005 to December 2017, 1270 LTs were performed at Cleveland Clinic Foundation (Cleveland, Ohio, USA). The study was reviewed and approved by the Institutional Review Board (IRB) of Cleveland Clinic Foundation. The obtaining of informed consent or its exemption occurred following the guidelines of the Declaration of Helsinki, specific national legislations and local IRB recommendations. Patient records and information were anonymized and de-identified before analysis.

In 16 recipients with DSVT (Yerdel Grade 4 PVT), portal flow was established via an RPA with an interposed venous graft (reno-portal group). In all cases, a spontaneous SRS was evident on pretransplant computed tomography (CT) and/or magnetic resonance imaging (MRI). All patients in the RPA group underwent CT or MRI of the liver every 6 months while on the transplant waiting list in order to have an up-to-date map of the portal system including the patency of the splenic vein.

We compared these patients with a control group of 48 propensity score-matched patients without PVT who underwent LT during the same period.

Our primary aim was to analyze the safety and feasibility of the RPA and its impact on kidney function. The secondary aim was to compare short- and long-term outcomes between the two groups.

Clinical and demographic data

Recorded donor data included Donor Risk Index (DRI), cold ischemia time (CIT), and liver weight. Also recorded were type of donor (donation after cardiac death, donation after brain death) and type of LT (split or whole liver).

Preoperative data collected on recipients included sex, age, model for end-stage liver disease (MELD) score, liver disease etiology, presence of portal hypertension complications (ascites, variceal bleeding, and hepatic encephalopathy), estimated glomerular filtration rate (eGFR), and findings on CT scan performed within 6 months before LT (i.e., PV patency and presence of SRS).

Operative data included warm ischemia time (WIT), type of venous reconstruction, use of bypass, operative time, and transfusion requirement. Graft hemodynamic data included intraoperative flow measurements (PV flow, hepatic artery flow (HAF) and augmented HAF after PV clamping), and Doppler ultrasound (DUS) flow measurements at last follow-up, that is, resistive index, portal flow velocity and hepatic artery (HA) peak systolic velocity. Intraoperative HA and PV flow were measured before bile duct anastomosis using a transit time flow-meter (VeriQ system, Medistim A/S, Oslo, Norway), after which the PV was clamped to assess the augmentation of the HAF [13].

Table 1. Patients characteristics

	Control group (n = 48)	Reno-portal group (n = 16)	P
Recipient factor			
Age, year	57 (39–72)	61 (23–70)	0.630
Sex, female	9 (18.8)	5 (31.3)	0.312
MELD	19.5 (6–43)	16.5 (7–31)	0.681
Primary LD			
Hepatitis C	10 (20.8)	5 (31.3)	0.498
Hepatocellular carcinoma	17 (35.4)	5 (31.3)	1.000
Alcoholic	5 (10.4)	1 (6.3)	1.000
NASH	6 (12.5)	4 (25.0)	0.252
PBC or PSC	2 (4.2)	2 (12.5)	0.258
Ascites	35 (72.9)	12 (75.0)	1.000
Variceal bleeding	14 (29.2)	10 (62.5)	0.035
Hepatic encephalopathy	35 (72.9)	11 (68.8)	0.756
Donor factor			
Donor risk index	1.77 (1.21–3.09)	1.92 (1.11–2.88)	0.757
CIT, min	426 (97–628)	430 (323–566)	0.828
Donation after cardiac death	6 (12.5)	1 (6.3)	0.669
Split liver	4 (8.3)	1 (6.3)	1.000
Graft weight, gr	1699 (656–2650)	1575 (870–2305)	0.606
Operative factor			
WIT, min	44 (14–80)	39 (29–70)	0.628
Venous reconstruction			0.157
Conventional bicaval	12 (25)	1 (6.3)	
Piggyback	36 (75)	15 (93.7)	
Bypass	2 (4.2)	1 (6.3)	1.000
Operative time, min	484 (264–1200)	530 (389–686)	0.325
Transfusion			
RBC, ml	2004 (0–19425)	1375 (0–22005)	0.608
FFP, ml	936 (0–5000)	675 (0–8300)	0.824
PLT, ml	475 (0–5000)	248 (0–7500)	0.723
Cryo, ml	100 (0–4000)	0 (0–625)	0.370

Postoperatively, we recorded alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and international normalized ratio (INR) on days 1, 3 and 7; hospital and intensive care unit (ICU) length of stay; surgical complications graded by Clavien–Dindo class [14]; in-hospital mortality, portal hypertension, length of follow-up; and tacrolimus trough level at 1, 3, 6, 12, 24, and 36 months, and 24-h urine protein excretion at 1 and 3 years. Early allograft dysfunction (EAD) was defined as the presence of one or more of the following: bilirubin ≥10 mg/dl on day 7, INR ≥1.6 on day 7, and ALT or AST >2000 IU/l within the first 7 days [15]. Primary nonfunction (PNF) of a transplanted liver within 7 days of implantation is defined (according to United Network for Organ Sharing criteria) by AST ≥3000 and at least one of the following: INR ≥2.5, arterial pH ≤7.30 or venous pH ≤7.25 or lactate ≥4 mmol/l [16]. Postoperative ascites was defined as a buildup of abdominal fluid after abdominal drain removal. Post-transplant encephalopathy was identified based on clinical records indicating an overt clinical impairment of cognitive function.

Surgical approach

RPA was introduced at our institution as a salvage procedure for patients for whom PV thrombectomy had failed. Our technique has evolved over time. Early in our experience, the left renal vein (LRV) was identified and isolated in the left retroperitoneal space next to the ligament of Treitz (proximal isolation). The venous conduit was brought to the hepatic hilum primarily via a tunnel obtained bluntly by dissection of the anterior wall of the intrarenal vena cava during hepatectomy or, less optimally, via a transmesocolic route. Presently, however, dissection of the left vein is achieved by caudal mobilization of the soft tissue on the anterior wall of the vena cava (exposed during hepatectomy) until the LRV is reached at its insertion with the inferior vena cava (distal isolation). This maneuver is facilitated by

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Table 2. Graft hemodynamics

	Control group (n = 48)	Reno-portal group (n = 16)	P
Intraoperative Flow measurement			
Portal flow (ml/min)	1449 (595–3664)	1200 (378–1940)	0.091
Hepatic artery flow (ml/min)	259 (80–1200)	260 (142–770)	0.851
Total flow (ml/min/100 g)	114.6 (50.8–245.4)	98.4 (61.8–196.3)	0.122
PV (ml/min/100 g)	98.9 (34.1–238.5)	82.6 (42–180.5)	0.1273
HAF (ml/min/100 g)	15.7 (4.0–87.9)	15.8 (7.5–54.0)	0.9315
US liver measurements POD7			
Resistive index	0.76 (0.32–1.41)	0.76 (0.3–0.89)	0.875
Portal flow velocity (cm/s)	39.8 (0–106)	43.5 (17–76)	0.561
Hepatic artery flow velocity (cm/s)	81 (23–303)	57.5 (37–130)	0.053

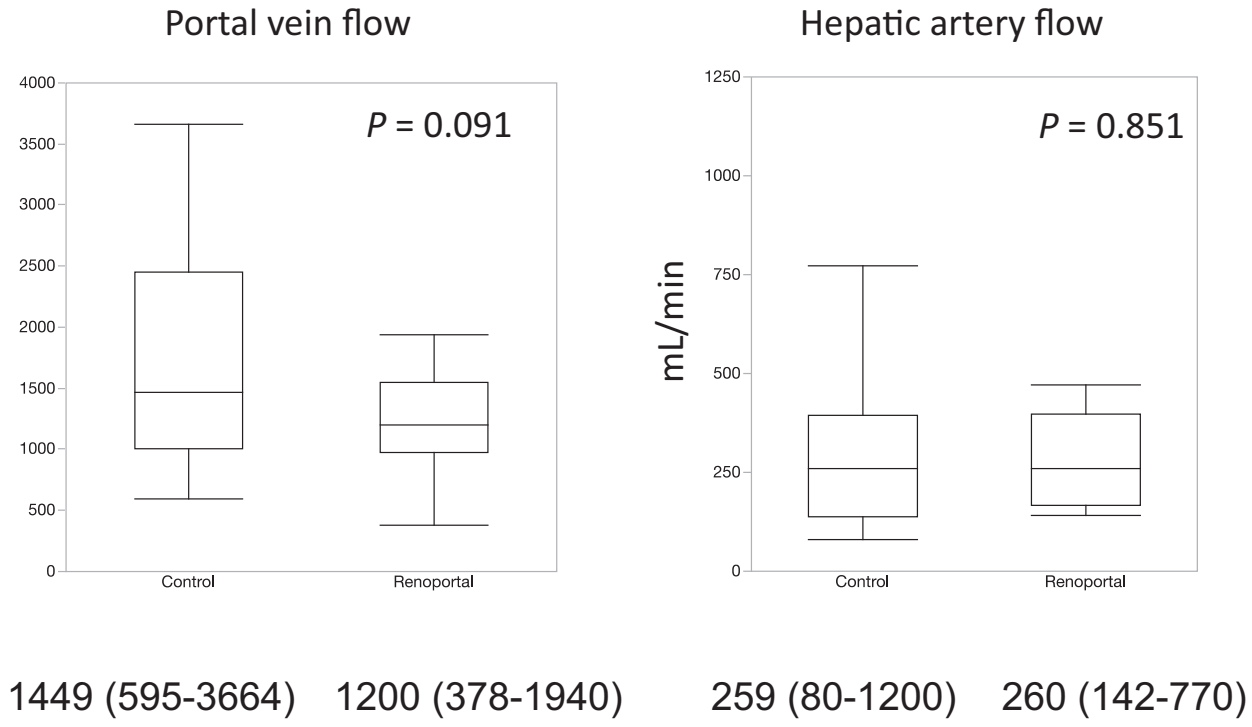

Figure 1 Intraoperative Portal Vein and Hepatic Artery Flows in RPA group and control group. These changes include the intraoperative flow measurement to assess the physiology of portal flow in reno-portal patients (which is the sum of the LRV flow and the flow added by the existing portosystemic shunt).

the early transection of the recipient's thrombosed PV along with the rest of the hilar structures. A Satinsky clamp can be placed on the anterior wall of the inferior vena cava to create traction cranially and toward the operating surgeon. This allows easier and more proximal dissection of the LRV. Regardless of the technique used, the LRV is mobilized for 2 to 2.5 cm proximally to its confluence with the vena cava. Importantly, the presence of a retroaortic LRV should always be determined preoperatively to avoid its dangerous and difficult distal isolation.

Postoperative management

After LT, all patients were transferred to the ICU. DUS, blood tests and close clinical surveillance were performed daily until POD 7. DUS included assessment of the arterial resistive index, PV velocity and HA peak systolic velocity. All patients received a triple immunosuppressive regimen including corticosteroids, mycophenolate mofetil, and tacrolimus, with anti-thymocyte globulin on days 0 and 2 if serum creatinine was initially >1.5 mg/dl. Deep venous thrombosis prophylaxis

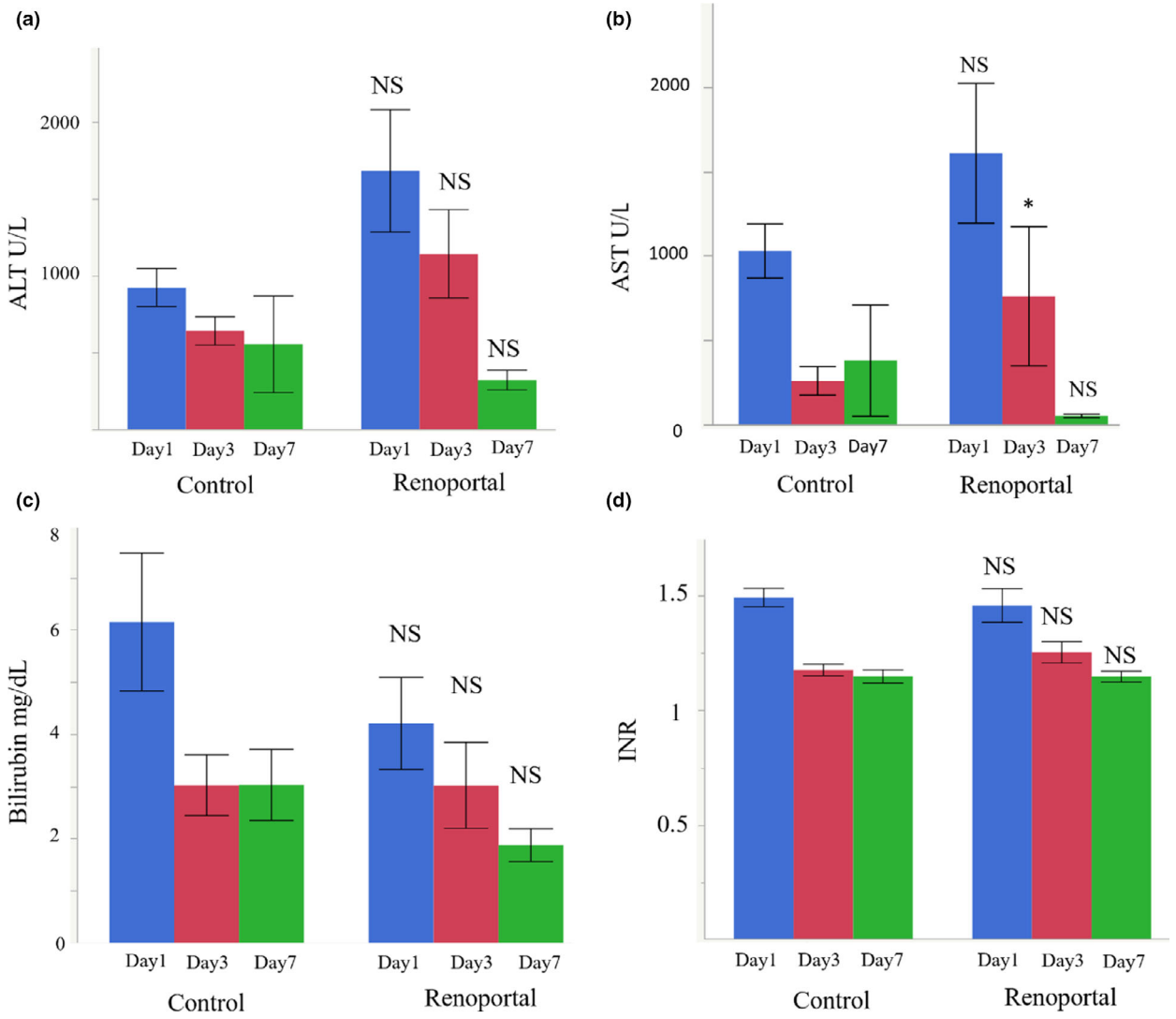

Figure 2 Post-transplant levels of ALT (a), AST (b), bilirubin (c) and INR (d) at 1, 3, and 7 days after transplantation in RPA and control groups. ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio.

included compression stockings, early mobilization and administration of anticoagulation. No anticoagulation was used to prevent PVT after LT, but all patients received indefinite low-dose aspirin therapy.

After discharge, patients visited our outpatient clinic every fortnight for the first 2 months and then once every 3 months. Follow-up consisted of physical examination, liver function tests and DUS. CT-guided angiography was performed in the event of abnormal PV flow at DUS to assess vascular patency. eGFR was measured at 1, 3, 6, 12, 36 and 60 months.

Statistical analysis

The Propensity Score (PS) model was calculated considering the following variables as covariates: age, sex, DRI, MELD score, pretransplant eGFR, and length of follow-up. Treated patients and controls were matched using nearest neighbor matching based on the individual PS with a caliper set at 0.2 and with a 1:3 matching model. In order to correct imbalance in the outcome analysis, weight adjustment was used.

Continuous variables were expressed as a median with range and compared with Wilcoxon rank sum test; categorical variables were expressed as percentages and were compared with the Fisher's exact test.

Means and standard deviations were used to summarize eGFR at various time points. Linear mixed modelling was used to assess for statistically significant interactions between groups (control vs. reno-portal) and whether changes in eGFR across time (baseline, 1, 3, 6, 12, 36 and 60 months) differed between groups. In

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Table 3. Surgical outcomes

	Control group (n = 48)	Reno-portal group (n = 16)	P
Follow-up duration (days)	1058 (737–4036)	1529 (750–3529)	0.530
Length of hospital stay (days)	9 (5–82)	12 (1–69)	0.125
Length of ICU stay (days)	4 (2–13)	3 (0–28)	0.775
In-hospital mortality	0 (0)	0 (0)	NA
Surgical complication			
Hepatic artery thrombosis	1 (2.1)	0 (0)	1.000
Hepatic artery stenosis	1 (2.1)	1 (6.3)	0.441
Hepatic vein stenosis	0 (0)	1 (6.3)	0.250
Portal vein thrombosis	2 (4.2)	0 (0)	1.000
Bile leak	1 (2.1)	1 (6.3)	0.441
Biliary anastomotic stricture	10 (20.1)	5 (31.3)	0.498
Graft dysfunction			
Primary nonfunction	1 (2)	0 (0)	1.000
Early allograft dysfunction	2 (4.2)	0 (0)	1.000
Postoperative complications			
Upper GI Bleeding	2 (4.2)	5 (31.3)*	0.009
Postoperative Ascites	14 (29.2)	7 (43.8)†	0.360
Hepatic Encephalopathy	9 (18.8)	1 (6.3)	0.429

*Single episode, self-limited, no intervention required.

†Two out of 7 patients were treated sccessfully by proximal splenic artery embolization.

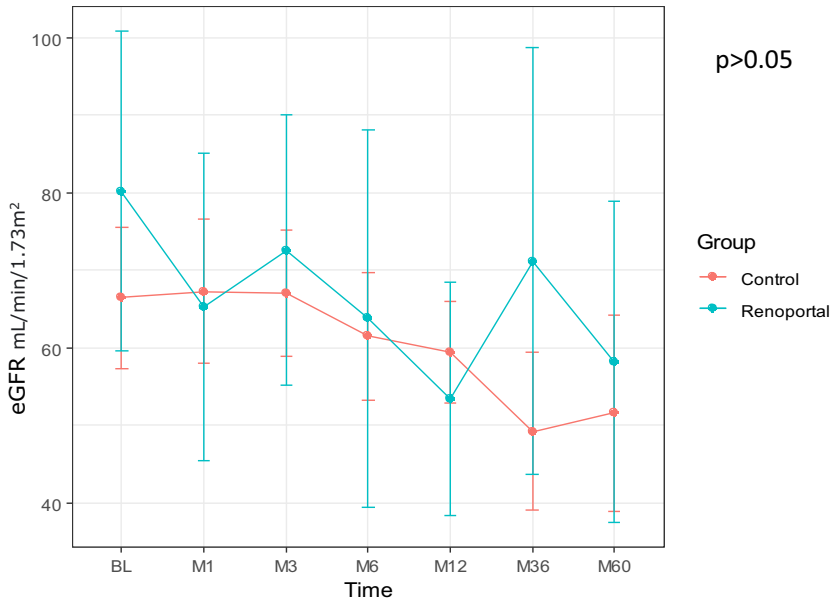

Figure 3 Linear mixed modeling; change in eGFR across time between RPA group and control group (mean ± 95% CI). eGFR, estimated glomerular filtration rate.

our model, group was a between-subjects variable while time was a within-subjects variable. Linear mixed modelling does not exclude participants with one or more missing data points, which results in higher statistical power.

The significance of fixed effects was assessed using the F-statistic (F). Type III sum of squares test was used. Type III tests are obtained by comparing a model in which only the tested effect is excluded with the full model (containing all effects). Model fit was assessed by inspecting the residuals histogram and fitted vs. residuals scatter plot.

Pairwise post hoc comparisons were used to compare eGFR at various time points within each group (paired

Table 4. Post hoc comparison of eGFR between groups. No significance difference between both groups at any of the time points was found

	Control $N = 48$	Reno-portal $N = 16$	P
BL	66.4 (31.6)	80.2 (38.8)	0.212
M1	67.3 (29.3)	65.2 (32.7)	0.844
M3	67.0 (23.1)	72.6 (27.3)	0.538
M6	61.4 (21.6)	63.8 (29.2)	0.840
M12	59.4 (18.7)	53.4 (21.0)	0.430
M36	49.2 (24.7)	71.2 (26.2)	0.102
M60	51.6 (23.6)	58.1 (24.7)	0.544

Data was summarized using Mean (SD).

t-test) and between groups at each time point (independent samples t-test). P values were adjusted for false discovery rate.

Graft and patient survival between the groups were analyzed using the Kaplan–Meier curve and compared by a log-rank test. Statistical significance was set at $P < 0.05$.

The statistical analyses were conducted using the JMP version 12 (SAS Institute Inc., Cary, NC, USA) and the STATA 15 software program (Stata Corp, College Station, TX, USA).

Results

Donor and recipient demographic data were similar between the RPA and control groups (Table 1). Preoperatively, only the incidence of variceal bleeding was significantly different (62.5% in the RPA group vs 29.2% in the control group, $P = 0.035$). Four split LT were performed in the control group and one in the RPA group ($P = 1.000$). Six DCD grafts were used in the control group and one in the RPA group ($P = 0.669$). Intraoperative data were similar between the groups. Median warm ischemia time was 44 min (range, 14–80 min) in the control group and 39 min (range, 29–70 min) in the RPA group ($P = 0.628$). Median operative time was 484 min (range, 264–1200 min) in the control group and 530 min (range, 389–686 min) in the RPA group ($P = 0.325$).

Graft hemodynamics are shown in Table 2. Median intraoperative PV flow was 1449 ml/min (range; 595–3664) in the control group and 1200 ml/min (range, 378–1940 ml/min) in the RPA group ($P = 0.091$) (Figure 1). Median total flow per 100 g of hepatic parenchyma was 114.6 ml/min/100 g (range, 50.8–245.4 ml/min/100 g) in the control group and 98.4 ml/min/10 0g (range, 61.8–196.3 ml/min/100 g) in the RPA group ($P = 0.122$). Median portal vein velocity at post-transplant day 7 was 39.8 cm/s (range, 34.1–238.5 cm/s) in control group and 43.5 cm/s (range, 17–76 cm/s) in the RPA group ($P = 0.561$).

Post-transplant liver function

Peak cytolysis (AST) was initially higher in the RPA group, although the difference was only statistically significant on POD 3. The evolution of AST, ALT, total bilirubin, and INR was identical in both groups (Figures 2a–d).

Post-transplant outcomes

Surgical outcomes are shown in Table 3. One case of PNF was observed in the control group ($P = 1.000$). Median ICU and hospital stays were 4 and 9 days, respectively, for the control group and 3 and 12 days, respectively for the RPA group. There was no significant difference in the rates of HA thrombosis, HA stenosis, PV thrombosis, bile leaks and biliary anastomotic strictures in the two groups. Biliary strictures were the most frequent surgical complication in both groups, with an incidence of 20.1% in the control group and 31.3% in the RPA group ($P = 0.498$); all were managed with endoscopic stent placement. None of the 16 recipients with RPA experienced PV thrombosis. High-grade postoperative complications (Clavien grade IIIb) were reported in two patients (12.5%) in the RPA group (one bile leak and one case of intra-abdominal bleeding); none were observed in the control group ($P = 0.06$).

Rates of postoperative ascites and hepatic encephalopathy were comparable between the groups. We observed a statistically significant difference in the incidence of postoperative upper GI bleeding (4.2% in the control group vs 31.3% in the RPA group, $P = 0.009$); all cases were self-limited.

Post-transplant renal function

Renal function deteriorated in both groups during follow-up. Linear mixed modelling analysis showed no statistically significant interaction between time and group, indicating similar changes in eGFR with time ($P > 0.05$) (Figure 3). Furthermore, pairwise comparisons did not reveal any statistically significant difference in eGFR between both groups at any of the time

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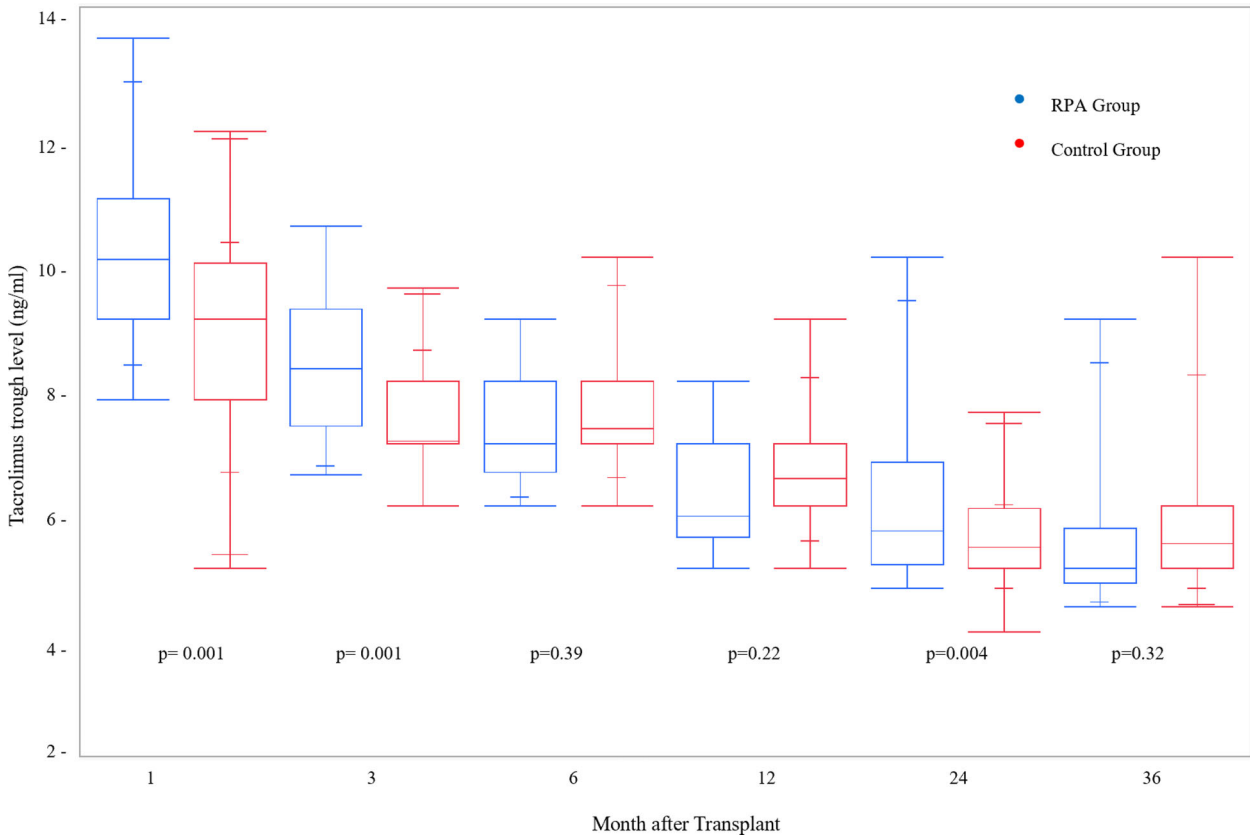

Figure 4 Trough levels of tacrolimus at 1, 3, 6, 12, 24, and 36 months after LT in RPA group and control group.

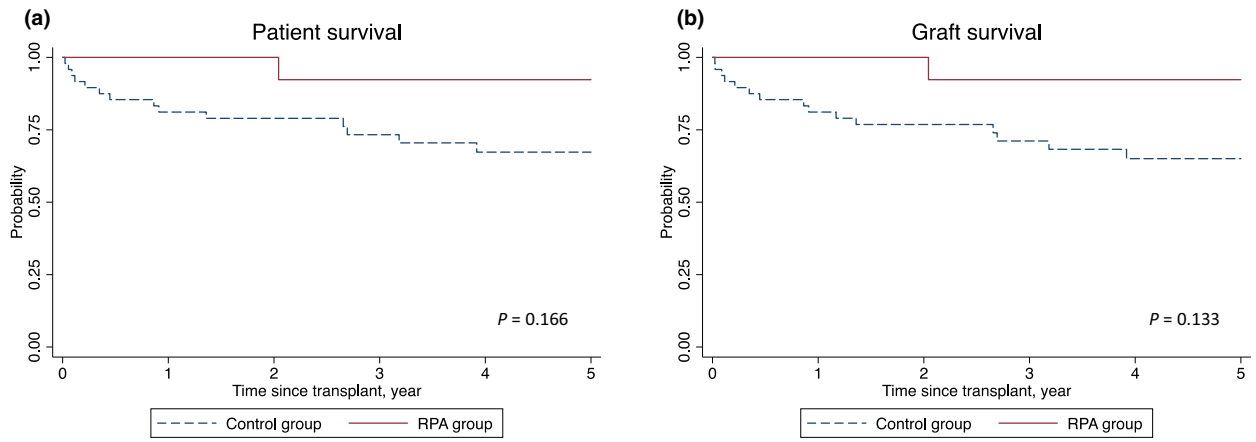

Figure 5 Kaplan–Meier curves of patient (a) and graft (b) survival rates within five years after transplantation.

points ($P > 0.05$ for all pairwise comparisons). Pairwise comparison between groups and within groups are depicted in Table 4. The median tacrolimus trough levels at 1, 3, 6, 12, 24, and 36 months in the two group are reported in Figure 4. The median tacrolimus level was statistically significant higher in the RPA group at 1, 3, and 24 months after LT. The median 24-h urine protein excretion (gm/24 h) at 1 year was 0.45 gm (range, 0.25–0.55 gm) in the RPA group and 0.47 gm (range, 0.22–0.66 gm) in the control group ($P = 0.460$), and at 3 years it was 0.52 gm (range, 0.29–0.67) in the RPA group and 0.51 ($P = 0.521$) in the control group.

Patient and graft survival

Patient and graft survival were comparable in the two groups (see Figure 5a,b), with slightly lower patient and graft survival in the control group ($P = 0.166$ and

$P = 0.133$, respectively). Five-year patient and graft survival rates were 86.5% and 86.5%, respectively in the RPA group and 67.3% and 65.0%, respectively, in the control group.

Discussion

To date, although approximately 66 cases of RPA have been described in the literature, most of them are in case reports [12,17–25]. To our knowledge, the current study is one of the largest case series from an experienced transplant institution. We herein report short and long-term surgical outcomes of 16 LT recipients who underwent RPA for DSVT in comparison with a propensity score-matched cohort. Our findings demonstrate that RPA for LT recipients with DSVT can be performed safely and provides satisfactory surgical outcomes. Furthermore, the current study suggests that RPA may not affect long-term renal function. This is the first report showing comparable long-term renal function in patients undergoing RPA for DSVT and patients undergoing conventional LT.

Although the most recent systematic literature review of RPA for DVST in LT found a 5% incidence of PV rethrombosis [11], none of the 16 patients in our cohort developed PV rethrombosis. Furthermore, we did not observe PNF in the RPA group. Because insufficient PV flow could be a risk factor for the development of PV thrombosis or PNF, adequate PV flow should be secured after implantation of the liver graft. In our cohort, intraoperative PV flow measurement (median 1200 ml/min) was performed in all patients, and results were similar in the RPA group and the control group (median 1449 ml/min). This finding suggests that the left renal vein blood flow granted an almost physiologic PV inflow to the transplanted liver. Because the presence of an adequate spontaneous or surgical SRS is necessary for securing sufficient PV flow after the RPA procedure, full understanding of portal vascular anatomy and portal hemodynamics is mandatory for successful LT with RPA.

In the aforementioned systematic literature review, the authors reported a 3% incidence of variceal bleeding, a 27.3% incidence of postoperative ascites and an 18.2% incidence of transient renal dysfunction after RPA in LT recipients; in all cases, the latter two complications resolved within three months post-transplant [11]. In the current study, we observed a 31.3% (5/16) incidence of upper GI bleeding and a 43.8% (7/16) incidence of postoperative ascites. All cases of upper GI bleeding consisted of a single self-limited episode that didn't require intervention. We attributed the bleeding to a temporary backflow from the SRS in the context of a post-transplant vascular pressure readjustment. In the RPA group, seven patients developed postoperative ascites but only two required splenic artery embolization. Ascites resolved in all cases within 3 months. In cases in which the portal hypertension is not fully relieved after RPA, splenic artery embolization may help reduce complications [26,27].

The detrimental effect of RPA on renal function is also of concern, because it is thought that RPA may cause left kidney congestion. In the current study, short and long-term renal functions were comparable in the RPA group and the control group. Decompression of portal hypertension might prevent renal dysfunction arising from left kidney congestion.

We observed a slightly longer operative time in the study group, likely a direct consequence of the time required for the RPA to be constructed and anastomosed to the liver PV. In cases in which the graft PV is not long enough for direct anastomosis, the use of an appropriate interposition graft may be required. In our cohort, the donor's iliac vein was most commonly used as an interposition graft. In patients undergoing RPA for DSVT, a number of collaterals can be seen as well as large SRS, which may be preserved during LT. Therefore, the appropriate use of interposition graft may avoid the unnecessary dissection of left renal vein, which may result in less blood loss. In the current study, transfusion requirements were the same in both groups.

The retrospective nature of this study and the scarce number of cases may limit the generalizability of our findings, although we attempted to reduce the selection bias by propensity matching. The rarity of the condition, the limited number of centers performing these procedures and the availability of different technical solutions to restore the PV flow make it difficult to obtain definitive data on the best technique to restore PV flow in case of DSVT.

Conclusion

The current study confirms the safety and feasibility of RPA for restoration of graft PV flow in patients with DSVT who require LT. In this limited cohort, RPA was a simple, safe and effective revascularization technique, with surgical and medical outcomes to comparable to those in patients without thrombosis undergoing conventional LT. Splenic artery embolization could represent a valid tool in case of complications from unresolved portal hypertension after RPA. We suggest that RPA be considered an alternative approach to cavo-portal hemi-transposition or multi-visceral transplant in patients with DSVT and SRS.

Transplant International 2021; 34: 1938–1947

Funding

No funding has been received for the conduction of the current study.

Conflicts of Interest

The authors have no financial or proprietary interest in the subject matter or materials discussed in the manuscript.

Authorship

GD: conceptualized the idea and design of the study. HM, AS, TDU, KH, BE, MF, FA, LDP, CM and CQ: participated in data collection and data analysis interpretation. GD, LDP and AS: wrote the article. All authors participated in the revision of the article and in the approval of the final draft.

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