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Living donor liver transplantation for patients with portal vein thrombosis: high-volume single center experience

A. ELSARAWY[1], S. AKBULUT[1,2], S. AKTAS[1], H. KILERCIK[3], U. ALKARA[4], S. SEVMIS[1]

[1]Department of Surgery and Organ Transplantation, Faculty of Medicine, Gaziosmanpasa Hospital, Istanbul Yeni Yuzyil University Istanbul, Turkey
[2]Department of Surgery and Liver Transplant Institute, Faculty of Medicine, Inonu University, Istanbul, Turkey
[3]Department of Anesthesiology and Reanimation, Faculty of Medicine, Gaziosmanpasa Hospital, Istanbul Yeni Yuzyil University, Istanbul, Turkey
[4]Department of Radiology, Faculty of Medicine, Gaziosmanpasa Hospital, Istanbul Yeni Yuzyil University, Istanbul, Turkey

Abstract. – OBJECTIVE: End-stage liver disease is commonly associated with portal vein thrombosis (PVT). Lastly, PVT is no longer an absolute contraindication for liver transplantation, and many centers adopt portal vein thrombectomy. PVT imposes special technical difficulties during living donor liver transplantation (LDLT). In this research, the experience with PVT cases during LDLT in a high-volume center is introduced.

PATIENTS AND METHODS: Between January 2018 and July 2023, 312 patients underwent LDLT. After 88 cases were excluded, 224 cases were included, and their incidence of pre-transplant PVT was 16.5% (37/224). Demographic and clinical features, perioperative variables, and post-transplant outcomes of patients with PVT (PVT group, n=37) were compared to patients who had no PVT (non-PVT group, n=187).

RESULTS: According to Yerdel classification, 16, 16, 2, and 3 patients had PVT grade I, II, III, and IV, respectively. Complete venous thrombectomy was accomplished in 34 patients, while for three patients, thrombectomy was not feasible, and graft inflow was established by interposition vascular graft. For portal flow modulation, splenectomy and splenic artery ligation were performed in 7 and 4 patients, respectively, while two patients underwent post-transplant splenic artery embolization. The PVT group had longer operation time ($p<0.001$), longer warm ischemia time ($p=0.031$), longer anhepatic phase ($p<0.001$), and intraoperatively required more than 3 packed RBCs units ($p=0.029$) and ≥1 platelet unit transfusion ($p=0.021$) than the non-PVT group. No statistically significant difference was found between groups in terms of re-exploration ($p=0.954$), post-transplant PVT ($p=0.375$), biliary ($p=0.253$) and arterial complications ($p=0.593$), ICU stay ($p=0.633$), hospital stay ($p=896$), and 30-day mortality ($p=1.000$). Survival analysis showed no statistically significant difference regarding 1-year survival ($p=0.176$) between both groups.

CONCLUSIONS: This study showed that patients with different stages of PVT can successfully undergo LDLT in experienced centers and that they do not differ from patients without PVT in terms of post-transplant complications.

Key Words:
Living donor liver transplantation, Portal vein thrombosis, Thrombectomy, Postoperative complications, Survival.

Abbreviations

AT-III: anti-thrombin III; CIT: cold ischemia time; DDLT: deceased donor liver transplantation; EF: ejection fraction; GRWR: graft-recipient-weight-ratio; HGB: hemoglobin; HRS: hepatorenal syndrome; ICU: intensive care unit; INR: international normalized ratio; LDLT: living donor liver transplantation; LT: liver transplantation; MELD: model for end-stage liver disease; PLT: platelet count; PRBCs: packed red blood cells; PVT: portal vein thrombosis; PV: portal vein; SMV: superior mesenteric vein; WIT: warm ischemia time.

Introduction

Portal vein thrombosis (PVT) is commonly associated with end-stage liver disease, reaching 26% of patients[1,2]. With a better understanding of

Corresponding Author: Sami Akbulut, MD, Ph.D; e-mail: akbulutsami@gmail.com

the clinicopathological nature of PVT, being not necessarily notorious for more advanced or progression of liver disease, many transplant centers are increasingly performing LT for those patients[3]. The advent of portal vein thrombectomy maneuvers, as well as various inflow reconstruction techniques, along with their evolution among the practice of high-volume centers, had expanded the domain of liver transplantation (LT) for cases of PVT that had been doomed beyond transplant surgery in the past years[4]. Living donor liver transplantation (LDLT) is predominantly pursued in regions with low rates of cadaveric donation. The context of living LDLT allows transplant centers to manage nearly all cases of PVT, a scenario that is not always feasible with deceased donor liver transplantation (DDLT). The inherent difficulties of LDLT, namely short inflow vessels, add more surgical complexity in the setting of PVT[1]. In this manuscript, we present our experience with LDLT recipients with pre-transplant PVT.

Patients and Methods

After obtaining the Institutional Review Board (IRB) approval from the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval No.: 2023/5348), the prospectively collected medical records of all patients (n=312) who underwent LT between January 2018 and July 2023 were retrospectively reviewed. The following patients were excluded: pediatric (<18 years) LT (n=62) and deceased donor LT (n=26). The remaining 224 patients met the inclusion criteria for this study. A total of 37 of the patients included in the study had pre-transplant PVT, and these patients were determined to be the case arm of the study. PVT was diagnosed pre-operatively by liver protocol contrast-enhanced multidetector computed tomography (MDCT). The thrombus extent was classified according to the Yerdel classification system[5] into 4 grades: grade I (<50% portal vein stenosis), grade II (>50% stenosis up to complete occlusion of the main portal vein), grade III (complete occlusion of the main portal vein and proximal superior mesenteric vein) and grade IV (extending to distal superior mesenteric vein). The demographic and clinical characteristics, peritransplant features, as well as 30-day mortality, and 1-year survival outcomes were retrieved.

The PVT group (n=37) was compared to the non-PVT group (n=187) to identify significant post-transplant risks and complications. Subgroup analysis of the PVT group among different pathological grades was performed. The following pre- and peri-transplant variables were compared: demographics, pre-transplant hemoglobin (HGB), platelet count (PLT), international normalized ratio (INR), prothrombin time, fibrinogen, albumin, child category, model for end-stage liver disease (MELD) score, previous abdominal surgery, hepatorenal syndrome (HRS), ascites (>1 L encountered upon exploration), graft-recipient-weight-ratio (GRWR), anhepatic phase, cold ischemia time (CIT; min), warm ischemia time (WIT; min), number of intraoperatively given packed red blood cell (PRBCs), PLT units and fresh frozen plasma (FFP) units, volume of intraoperative crystalloids use. Postoperatively, the re-exploration rate, length of intensive care unit (ICU), and hospital stays were compared. The post-operative complications, post-operative 30-day mortality, and one-year post-LDLT survival outcome were compared between both groups.

All patients received a right lobe liver graft, not including the middle hepatic vein, and surgery was performed by the same team of surgery and anesthesia. Recipient hepatectomy was performed without total vascular exclusion, and a portosystemic shunt was not adopted in all patients. Portal vein thrombectomy was performed for all patients by the eversion technique aided by Fogarty catheter retrieval. In three patients, complete thrombectomy was not feasible, and inflow restoration was accomplished using an interposition graft. Graft implantation was performed under partial lateral-caval clamping. All anterior sectoral veins were reconstructed if diameter ≥5 mm with a remarkable flow on the back table, using a dacron graft. An institutional protocol of intraoperative blood transfusion was followed at the discretion of the anesthesiology team. Leucodepleted PRBCs (~250 cc) were transfused if the HGB level dropped below 7 mg/dl in all patients. For patients with renal impairment and cardiac patients, transfusion was adopted if Hb dropped below 8 mg/dl and 10 mg/dl, respectively. An early extubation approach was adopted in all cases.

Tripple immunosuppressive therapy (corticosteroid- tacrolimus- mycophenolate mofetil) was adopted in all cases. Routine postoperative anticoagulant therapy was adopted in all cases based on daily coagulation studies. Postoperative liver Doppler was performed routinely every day in the first postoperative week and then according to the clinical/laboratory profile.

Study Protocol and Ethics Committee Approval

This descriptive and cross-sectional study involving human participants was conducted in accordance with the Ethical Standards of the Institutional and National Research Committee and with the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards. Ethical approval was obtained from the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval No.: 2023/5348). STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline was utilized to assess the likelihood of bias and overall quality for this study.

Statistical Analysis

Statistical analysis was performed using SPSS version 25.0 (SPSS Statistics, IBM Corp., Armonk, NY, USA). Quantitative (continuous; numerical) variables were expressed as Median [95% confidence interval (CI) lower and upper bound] and compared with the Mann-Whitney U test or as mean ±SD and compared using a *t*-test as appropriate. Qualitative (categorical) variables were expressed as number (n) and percentage (%) and compared with the Fischer-exact test. Overall survival was estimated using the Kaplan-Meyer estimate and compared with the log-rank test. A p-value <0.05 was considered statistically significant.

Results

The median (95% CI) age of the study cohort was 53 (52-56) years. The male/female ratio was 141/83. The median (95% CI) BMI was 26.6 (25-9-27.3) kg/m^2. The indications of LDLT were HBV (25%), Non-Alcoholic Steatohepatitis (NASH) (18%), cryptogenic cirrhosis (17%), alcoholic cirrhosis (9%), autoimmune hepatitis with end-stage liver disease (9%), HCV (3%) and other etiologies (19%). The median (95% CI) MELD score was 15 (14-17) points. The median (95% CI) anhepatic phase, CIT, WIT, and operation time were 56 (53-60) min, 42 (41-45) min, 40 (39-42) min, and 6 (6-7) hours, respectively. Most of the patients (n=149, 67%) were within the Child B category, and 48 cases (21%) were within the Child C category. The incidence of pre-transplant PVT was 16.5% (37/224). According to the Yerdel classification – evident in pre-operative imaging and confirmed intraoperatively – 16, 16, 2, and 3 patients had PVT grade I, II, III, and IV, respectively. Complete portal venous thrombectomy was accomplished in 34 patients with subsequent direct native portal vein to graft portal vein inflow restoration, while for the remaining three patients, complete thrombectomy was not feasible, and graft inflow was established as follows: two patients had a cadaveric iliac vein jump graft from a superior mesenteric vein – splenic vein confluence to graft portal vein and the other case had inflow reconstruction from the left gastric (coronary v.) to graft portal vein. The thrombectomy procedure was done *via* the eversion technique[6] and facilitated by the passage of 8 Fr silicon Foley's catheter or Fogarty's catheter beyond the lower limit of the thrombus with gradual upward dragging. During the process of thrombectomy, the superior mesenteric vein/splenic vein confluence had a tear in 4 cases, and the resultant defect was reconstructed by a vein patch harvested from the explanted liver's portal vein and hepatic vein in 2 patients. In the other 2 patients, the defect was reconstructed using a bovine pericardial patch graft. For portal flow modulation, splenectomy and splenic artery ligation were performed in 7 and 4 patients, respectively, while 2 patients underwent post-transplant splenic artery embolization.

Table I shows a comparison between both study groups. The PVT group had significantly lower pre-transplant HGB (p=0.006) and PLT (p=0.004). Patients with PVT showed a higher incidence of HRS (OR=3.2; 95% CI=1.5-6.9; p=0.005). No statistically significant difference between groups in terms of other pre-transplant features, such as age (p=0.475), gender (p=0.110), BMI (p=0.969), underlying causes (p=0.530), Child score (p=0.082), MELD score (p=0.492), presence HCC (p=1.000), albumin (p=0.463), INR (p=0.584), fibrinogen (p=0.135), AT-III (p=0.682), protein S (p=0.085) and protein C levels (p=0.953).

Intraoperatively, The PVT group had longer operative duration (p<0.001), longer WIT (p=0.003), longer anhepatic phase (p<0.001), required more packed RBCs units (OR=2.3; 95% CI=1.1-4.8; p=0.029) and platelets units (OR=4.7; 95% CI=1.4-16.3; p=0.021) than the non-PVT group. There was no statistically significant difference in the incidence of post-transplant PVT (p=0.375), hepatic arterial complications (p=0.593), biliary complications (p=0.253), as well as the rate of post-transplant re-exploration (p=0.954). The ICU stay (p=0.633) and total hos-

Table I. Comparison of both groups in terms of demographics and pre-transplant clinical variables.

Variables*	Non-PVT group (n=187)	PVT group (n=37)	p
Age	53 (52-56)	56 (45-60)	0.475
Gender (M/F)	122/65	19/18	0.110
BMI	26.7 (26.0-27.7)	26.0 (24.5-29.3)	0.969
Etiology			0.530
HBV	49 (26)	8 (22	
NASH	33 (17)	7 (19)	
Cryptogenic	29 (16)	10 (27)	
Alcoholic	19 (10)	2 (5)	
Autoimmune	16 (9)	5 (14)	
HCV	7 (4)	0 (0)	
Others	34 (18)	5 (13)	
MELD Score	14 (14-16)	16 (14-18)	0.492
Child Score			0.082
A	20 (11)	5 (14)	
B	130 (69)	19 (51)	
C	37 (20)	13 (35)	
HCC	40 (21)	8 (22)	1.000
Ascites	165 (88)	33 (89)	0.869
Hepatorenal syndrome	30 (16)	14 (38)	**0.005**
HGB	10.9 (10.4-11.5)	9.4 (8.7-10.4)	**0.006**
PLT count	85 (81-97)	58 (47-73)	**0.004**
Albumin	3.2 (3.1-3.3)	3.1 (2.9-3.5)	0.463
INR	1.4 (1.4-1.5)	1.4 (1.3-1.6)	0.584
Fibrinogen	124 (124-132)	123 (118-124)	0.135
AT-III	53 (49-57)	54 (45-62)	0.682
Protein S	67 (65-72)	64 (61-72)	0.085
Protein C	44 (41-47)	46 (37-54)	0.953

AT-III: anti-thrombin III, BMI: body mass index, HCC: hepatocellular carcinoma, HGB: hemoglobin, INR: international normalized ratio, MELD: model for end-stage liver disease, PLT: platelet, PVT: portal vein thrombosis. *Quantitative variables presented as (median; 95% CI) and qualitative variables presented as n (%).

pital stays (p=0.896) were not significantly different, as well. The postoperative 30-day mortality rates were not different, and the 1-year overall survival rates were as follows (88.4% *vs*. 80.2%; p=0.16). Results are given in Table I, Table II, and Table III. The Kaplan-Meier survival analysis is given in Figure 1.

Subgroup Analysis of the PVT Cases (n=37)

Among the PVT group, the first 20 cases had a longer median duration of anhepatic phase (p=0.048), required more median intraoperative packed RBCs transfusion (p=0.003) and median packed FFPs transfusion (p=0.007) as compared

Table II. Comparison of both groups in terms of peri-operative clinical variables.

Variables*	Non-PVT group (n=187)	PVT group (n=37)	p
>3 PRBCs (package)	58 (31)	19 (51)	**0.029**
>3 FFPs (package)	26 (14)	9 (24)	0.11
>1 Platelets (package)	6 (3)	5 (14)	**0.02**1
Anhepatic phase (min)	54 (51-59)	73 (63-115)	**<0.001**
CIT (min)	42 (41-45)	45 (38-50)	0.407
WIT (min)	39 (37-41)	43 (40-49)	**0.031**
Operation time (hours)	6 (6-7)	7 (7-8)	**<0.001**

CIT: cold ischemia time, FFP: fresh frozen plasma, PRBCs: packed red blood cells, PVT: portal vein thrombosis, WIT: warm ischemia time. *Quantitative variables presented as (median; 95% CI) and qualitative variables presented as n (%).

Table III. Comparison of both groups in terms of post-transplant complications and outcomes.

Parameters	Non-PVT group (n=187)	PVT group (n=37)	p
Re-exploration	29 (15.5)	5 (13.5)	0.954
ICU stay (days)	1 (1-2)	1 (1-2)	0.633
Post-transplant PVT	10 (5)	0 (0)	0.375
Biliary complications	50 (27)	6 (16)	0.253
HA complications	6 (3)	0 (0)	0.593
Hospital stay (days)	14 (14-15)	14 (12-17)	0.896
30-day mortality	10 (5.3)	2 (5.4)	1.000

HA: hepatic artery, ICU: intensive care unit, PVT: portal vein thrombosis. Quantitative variables presented as (median; 95% CI) and qualitative variables presented as n (%).

to the subsequent 17 cases. No statistically significant difference was found in the ICU, hospital stay, and other clinical and biochemical variables between both time periods. None of our cases experienced a recurrence of PVT at a median follow-up time of 23 months after LDLT. There was no statistically significant difference in the incidence of 30-day mortality or the 1-year survival rate among patients with different grades of PVT (Table IV). A further assessment of the 1-year mortality cases (n=7) showed that the cause of death was sepsis in 4 cases, primary graft non-function in 2 cases, and postoperative massive myocardial infarction in the remaining case. Their primary etiologies were: Cryptogenic cirrhosis (3 cases), NASH (2 cases), Chronic HBV, and a case of portal biliopathy. There was no significant correlation between the primary etiology and 1-year survival. A review of the preoperative routine hypercoagulable screening tests (Level anti-thrombin III, protein C, and protein S) did not show a statistically significant correlation, either.

Discussion

Since the first attempt at portal vein thrombectomy in an LT recipient decades ago, this surgical achievement has been revolutionized and paral-

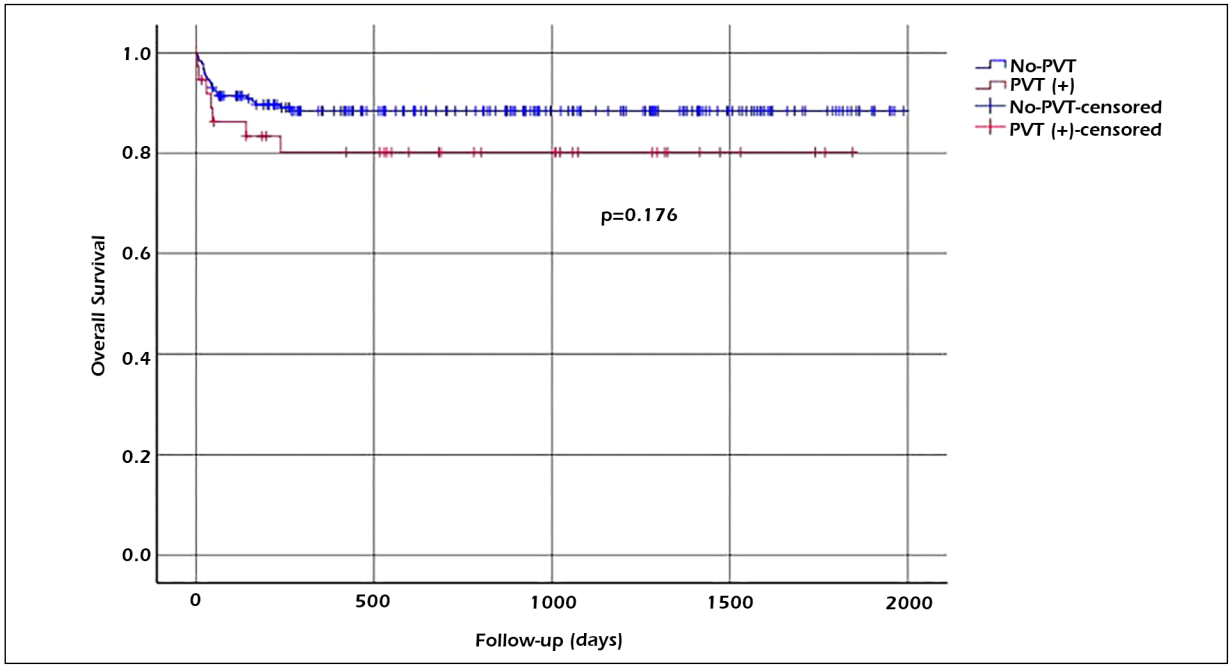

Figure 1. The Kaplan-Meier estimate of 1-year overall survival for the non-PVT *vs.* PVT group (88.4% *vs.* 80.2%). PVT; Portal vein thrombosis.

Table IV. Comparison of first 20 PVT cases and subsequent 17 PVT cases.

Variables	1st group (n=20)	2nd group (n=17)	p
Age	57 (42-63)	51 (42-61)	0.493
BMI	26 (24-28)	26 (24-31)	0.819
MELD Score	17 (14-18)	15 (12-21)	0.869
Anhepatic phase (min)	118 (60-151)	63 (56-73)	0.048
CIT (min)	42 (30-52)	49 (40-53)	0.424
WIT (min)	42 (33-47)	47 (41-53)	0.270
Operation time (hours)	7.5 (7-8)	7 (6-8)	0.308
HGB	9.4 (8.5-10)	9.3 (8.6-12.4)	0.402
PLT count	53 (44-99)	65 (40-79)	0.855
Albumin	3.2 (2.8-3.5)	2.9 (2.8-3.9)	0.819
INR	1.4 (1.3-1.6)	1.4 (1.3-1.8)	0.562
Fibrinogen	124 (109-124)	122 (112-154)	0.771
AT-III	59 (44-67)	49 (40-59)	0.139
Protein S	61 (55-68)	66 (61-76)	0.376
Protein C	44 (35-56)	49 (37-63)	0.703
ICU stay (days)	2 (1-2)	1 (1-1)	0.182
Hospital stay (days)	14 (11-25)	14 (13-23)	0.963
PRBCs (package)	6 (4-8)	2 (2-5)	0.003
FFPs (package)	3 (2-4)	0 (0-2)	0.007
Platelets (package)	0 (0-1)	0 (0-1)	0.354
Post operative PVT	10 (5)	0 (0)	0.150
Biliary complications	50 (27)	6 (16)	0.170
HA complications	6 (3)	0 (0)	0.260
30-day mortality	10 (5.3)	2 (5.4)	0.900

AT-III: anti-thrombin III, BMI: body mass index, CIT: cold ischemia time, FFP: fresh frozen plasma, HA: hepatic artery, HGB: hemoglobin, ICU: intensive care unit, INR: international normalized ratio, MELD: model for end-stage liver disease, PLT: platelet, PRBCs: packed red blood cells, PVT: portal vein thrombosis, WIT: warm ischemia time. Quantitative variables presented as (median; 95% CI) and qualitative variables presented as n (%).

leled by many advancements in portal inflow reconstruction techniques. The surgical short- and long-term outcomes, as well as survival results, have drawn attention to this patient category. The worldwide problem of organ shortage lends to the adoption of LDLT as the only available curative treatment for end-stage liver disease. Though DDLT is not readily available in many regions in the setting of pre-transplant PVT, LDLT would encompass those patients. In our center, the incidence of pre-transplant PVT was 16.5%, with no apparent underlying etiology associated with PVT more than others.

From their experience with 90 LT recipients (88% LDLT) with pre-transplant PVT, Sharshar et al[8] provided a roadmap for the optimum selection of portal inflow reconstruction. For Yerdel grade I and II, thrombectomy was proposed, followed by restoration of portal flow by PV-PV anastomosis or PV-SMV anastomosis *via* interposition graft, respectively. For more advanced grades, they considered non-anatomical inflow reconstructions *via* vicinity shunts or big collaterals. They also considered recipient exploration first for complex PVT to secure the portal inflow status in advance. They achieved complete portal vein thrombectomy in 77% of cases[8]. We adopted a similar stepwise approach based mainly on preoperative imaging and intraoperative meticulous assessment aided by intraoperative Doppler. In our cases, the complete portal vein thrombectomy success rate was 92% with direct PV- PV inflow restoration.

In Aktas et al's study[7], 5 out of 30 cases of PVT had complete (grade III-IV) PVT. They used extra-anatomical inflow reconstruction, either through varico-portal or renoportal inflow restoration *via* cryopreserved cadaveric iliac vein graft. In our three patients presenting with non-feasible complete thrombectomy, we adopted the varicose-portal approach in one case and a jump graft from the SMV-splenic vein confluence in the other 2 patients using the same graft nature.

In a homogenous cohort of LDLT recipients studied by Kamal et al[9], a significant 1-year overall survival was observed between PVT and non-PVT groups. Also, there was a significant surviv-

al difference across different Yerdel grades. In our patients, neither a significant 1-year survival nor a survival difference between different Yerdel grades was observed. However, our results are aligned with the Korean study by Moon et al[10], which shows no difference in 1-year survival between PVT *vs.* non-PVT groups and also no significant survival difference across Yerdel grades. Another recent two-center study from Turkey[11] showed a PVT incidence of 19% among a cohort of 335 LDLT cases; there was no survival advantage found among recipients with earlier Yerdel grades *vs.* more advanced PVT. The difference in survival across centers may be due to different MELD scores and waitlist times, with some patients being transplanted at a more severe disease status.

In our study, the early 30-day surgical mortality of PVT cases was not significantly inferior to their non-PVT counterparts. This finding concurred with the conclusion drawn from the meta-analysis done by Qi et al[12], which stated that the association of PVT with 1-month mortality is not clear. It is also worth mentioning that in this meta-analysis[12], there was no statistically significant decrease in the 1-year survival among PVT patients in studies with high quality data. On the other hand, another meta-analysis by Zanetto et al[13] showed higher 30-day mortality as well as inferior 1-year survival among PVT cases. In the aforementioned study by Kirimker et al[11], there was no statistically significant survival difference at the time points of 30-day, 90-day, or 1 year between recipients with and without PVT. In our opinion, the heterogeneity of studies' cohorts and the existence of many confounding cofactors in this duration (first year after transplant) adds more to this everlasting debate.

In a recent review article by Bhangui et al[1], PVT was considered a major challenge among the surgery and anesthesiology domains during the procedure of resection and flow restoration. However, a more recent multi-center study about how to address a difficult case of LT has excluded all PVT cases from the final analysis[14]. From what had been witnessed in our cases and similar studies of LDLT recipients with PVT, it might be suitable to argue that the presence of grade III or IV PVT should be incorporated into the difficulty grade of end-stage liver cases that are amenable to transplant.

In our study, there was no significant difference in the MELD or Child scores between PVT and non-PVT cases, contrary to previous reports by Kamal et al[9]. This is probably attributed to the fact that all patients had LDLT with less waitlist time than is routinely encountered in DDLT.

The intraoperative transfusion of ≤3 units of packed RBCs during liver transplantation was recently set as a quality benchmark[15]. More than 50% (19/37) of our PVT cases significantly exceeded this benchmark, denoting surgical difficulty and complexity, contrary to 30% in non-PVT. However, of 19 cases, 15 (79%) occurred among the first 20 cases, representing our early experience with PVT in LDLT.

Limitations

Our study has some limitations; firstly, it may present possible confounding bias and unreported intervening factors due to its retrospective nature. The small sample size of our PVT group should be augmented by multicenter data to draw more robust conclusions. Next, intraoperative portal flow hemodynamics were not systemically recorded, and this might have provided insights into intraoperative decision-making. Also, our study cohort was comprised of patients with low median MELD scores compared to other studies, whose short-term outcomes are expected to be better. Finally, there might be an inaccurate estimation of the Yerdel grade intraoperatively among grades II to IV. Future research perspectives regarding PVT include looking forward to a consensus management roadmap in view of the enlarging experience, management of PVT in transplant-deprived regions, and a randomized control study for the best standard of care, especially in grades III and IV patients.

Conclusions

In view of advanced surgical facilities in liver transplant centers, portal vein thrombectomy should be attempted in most cases of PVT and can be safely performed in the setting of LDLT, in view of the steep learning curve. We are adding the already existing significant body of literature denoting non-inferior short-term and 1-year survival outcomes of PVT cases after LT.

ORCID ID
Ahmed Elsarawy: 0000-0002-0299-5473
Sami Akbulut: 0000-0002-6864-7711
Sema Aktas: 0000-0001-9670-8166
Hakan Kilercik: 0000-0003-1624-0124
Utku Alkara: 0000-0002-4574-2767
Sinasi Sevmis: 0000-0001-8728-5472

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Authors' Contributions
Elsarawy A, Akbulut S, Aktas S, Kilercik H, Alkara U, and Sevmis S contributed to the study's concept, design, data collection, data analysis, interpretation, and manuscript writing. Akbulut S, Elsarawy A, Aktas S and Sevmis S wrote the first draft of the manuscript, and all authors commented on previous versions. All authors have approved the manuscript's final version.

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Conflict of Interest
The authors declare no conflict of interest regarding this manuscript.

Informed Consent
The informed consent requirement was waived due to this retrospective analysis.

Availability of Data and Materials
The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval
The study was approved by the Inonu University Institutional Review Board (IRB) for non-interventional studies (Approval No.: 2023/5348).

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