The Management of Portal Vein Thrombosis after Adult Liver Transplantation: A Case Series and Review of the Literature

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Abstract

**Background:** Portal vein thrombosis (PVT) after adult liver transplantation (LT) is a rare but serious complication with no consensus on the ideal treatment. We report a case series and a comprehensive review of the literature on PVT after LT to discuss the therapeutic options.

**Methods:** The clinical data of 360 adult patients (≥18 years of age) that underwent LT from January 2015 to January 2018 were reviewed, and a comprehensive search of PubMed and Web of Science was conducted. Patients diagnosed with PVT after LT were identified, and relevant risk factors and therapies were analyzed.

**Results:** Among the 360 patients, seven (2.69%) developed PVT after LT. The onset of PVT within one week after LT was found in six patients (85.71%). Four of these seven patients with PVT received systemic anticoagulation (low molecular weight heparin and warfarin) therapy. Minimally invasive interventional therapies combined with systemic anticoagulation (heparin and warfarin) were applied to three patients, two of whom died because of severe abdominal hemorrhage and liver failure. In the 29 cases reported in the literature, minimally invasive interventional therapy combined with anticoagulation or sclerotherapy were the most used methods (19/29). Systemic anticoagulation was administered to three patients, surgical operation (thrombectomy; portosystemic shunt and retransplantation) was performed for seven patients. Among these 29 patients, four eventually died.

**Conclusions:** In conclusion, interventional therapy combined with systemic anticoagulation is a good choice for the management of PVT after LT, and in our experience, systemic anticoagulation alone can also have a positive effect for early PVT patients.

Background

The establishment of uncompromised inflow and adequate venous outflow are critical for a successful liver transplantation (LT) procedure. However, the prognosis after LT can be marred by serious vascular complications including hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT), which can significantly increase posttransplant mortality[1, 2].

PVT can be more detrimental to the graft and patient survival than HAT after LT because an alternative portal inflow is difficult to establish[3]. PVT is a rare complication with a reported incidence of 3% to 7% in patients who have undergone LT and is somewhat higher in children[4, 5]. A diagnosis of PVT after LT usually depends on follow-up ultrasonography and the manifestation of hepatic dysfunction or portal hypertension involving variceal hemorrhage, splenomegaly, and hypersplenism[6-9]. Several predisposing factors are considered relevant to post-LT PVT formation, including preoperative PVT in the recipient, previous portosystemic shunts or splenectomy, hypercoagulable state, technical issues during the LT, vein graft and conduit availability, and pediatric transplantation[10-13].

The management of PVT aims to relieve the presenting symptoms and maintain normal liver function. Reported therapeutic options for PVT include systemic anticoagulation, management of portal hypertension with sclerotherapy of bleeding varices and portosystemic shunt, minimally invasive interventional therapies, surgical thrombectomy and retransplantation[14, 15]. However, with only a few articles available to guide medical options, the ideal treatment of PVT after LT has not been defined. Here, we report a case series and a comprehensive review of the literature on PVT after LT to discuss the therapeutic options. Incidence, risk factors, clinical features, and treatment outcomes are described.

Methods

**Clinical case series**

The medical records of all adult patients (18 years of age or older) who received donor organs after cardiac death (DCD) and who underwent LT at the First Affiliated Hospital, Xi’an Jiaotong University from January 2015 to January 2018 were reviewed. The clinical data of these recipients were collected including demographic features, perioperative laboratory values, postoperative complications and PVT management after LT. Patients diagnosed with PVT after LT were identified, and relevant risk factors were analyzed including surgical history and the presence of PVT before LT. Written consent was given by the patients for their information to be stored in the hospital database and used for research. This study was approved by the First Affiliated Hospital of Xi’an Jiaotong University Ethics Committee.

**Review of the literature on PVT after LT**

We performed a comprehensive search of PubMed and Web of Science from their inception to January 31, 2018 to identify all available articles that discussed the management of PVT after LT in adult patients. We combined search keywords for “portal vein thrombosis” (or “PVT”), “vascular complication”, “adult” and “liver transplantation” (or “LT”). All case reports and case series discussing PVT after LT in adults were included. A secondary search of the bibliography of each included article was also undertaken. Excluded studies were those with insufficient data. Abstracts, review articles, editorials, and letters were also excluded. Relevant data including patient demographics, clinical symptoms, management and outcomes were extracted from the included publications.

**Statistical analysis**

Continuous data with normal distributions were reported as the means ± standard deviations (SD). Abnormal distribution variables were expressed as medians and ranges. Categorical data were reported as frequencies and percentages. All statistical analysis was performed using IBM SPSS (version 20.0).
Results

Clinical case series

There were 260 adult patients who underwent LT from January 1 2015 to January 1 2018 at the First Affiliated Hospital of Xi'an Jiaotong University. Among these patients, seven (2.69%) developed PVT after LT, with a male-to-female ratio of 2:5. The mean age was 54.74 ± 9.68 years (Median: 50.0; Range: 44.0–57.0). The etiology included HBV-related liver cirrhosis in four patients, hepatic carcinoma post-HBV infection in one patient, and autoimmune liver disease in two patients.

Of these seven patients, the onset of PVT formation occurring within one-week posttransplantation in six patients (85.71%). Two of these six patients experienced a liver function injury, the remaining four patients were asymptomatic, which was confirmed by ultrasonography. PVT was found 3 months after LT in one patient, a 57-year-old woman who was readmitted with upper gastrointestinal tract bleeding. Pretransplantation PVT was found in six patients (Yerdel stage I: 3; stage II: 1; stage III: 2). Two patients (28.57%) had undergone a splenectomy before LT.

Four of these seven patients received systemic anticoagulation in the form of low molecular weight heparin and warfarin therapy. All of them were in good clinical condition after a median follow-up duration of 17.6 months (range: 5.7–36.4 months). Minimally invasive interventional therapy combined with heparin and warfarin systemic anticoagulation was applied to the remaining three patients. Two of these three patients died because of severe abdominal hemorrhage and liver failure. A summary of the case series is provided in Table 1.

| Patient | Age (years) | Gender | Etiology | MELD Score | Pre-OLT PVT (Yerdel stage) | Post-OLT PVT | PV T onset (days) | Treatment | Prognosis |
|---------|-------------|--------|----------|------------|-------------------------|-------------|------------------|-----------|-----------|
| 1       | 52          | Female | HBV-Liver Cirrhosis - HCC | 30 | yes/III | Main PV; SMV | 2 | Anticoagulation | Alive |
| 2       | 44          | Female | HBV-Liver Cirrhosis | 33 | yes/III | Main PV | 7 | Anticoagulation | Alive |
| 3       | 44          | Female | HBV-Liver Cirrhosis | 23 | yes/III | Main PV | 1 | Anticoagulation | Alive |
| 4       | 50          | Female | Autoimmune Liver Disease | 16 | yes/III | Main PV; SMV | 1 | Percutaneous transhepatic angioplasty thrombolysis + anticoagulation | Alive |
| 5       | 57          | Female | Autoimmune Liver Disease | 22 | 0 | Main PV | 90 | Anticoagulation + percutaneous transhepatic portal venous thrombolytic therapy | Dead |
| 6       | 55          | Male | HBV-Liver Cirrhosis | 11 | yes/III | Main PV; SMV | 1 | Transjugular transhepatic portal vein puncture thrombolytic + anticoagulation | Dead |
| 7       | 46          | Male | HBV-Liver Cirrhosis | 12 | yes/III | Main PV; SMV | 1 | Anticoagulation | Alive |

Abbreviations: HBV, Hepatitis B virus; MELD, Model for end-stage liver disease; Pre-OLT, Pre-orthotopic liver transplantation; PV, Portal vein; SMV, Superior mesenteric vein.

Review of the Literature on PVT after LT

A total of 21 articles that reported one or more cases, which included a total of twenty-nine cases of post-LT PVT formation in adult LT recipients[2, 3, 10–12, 16–31]. The characteristics of the reported cases are summarized in Table 2. Among these twenty-nine cases, the etiologies for LT were liver malignancies in four cases (13.79%), primary sclerosing cholangitis in five cases (17.24%), post-infection liver cirrhosis in six patients (20.69%), alcoholic cirrhosis in seven patients (24.14%), and other benign liver disease in seven patients (24.14%, Table 3). The median age was 48.0 years (range: 23.0–72.0 years), and 55.17% were male. The time to PVT onset from LT ranged from 2 days to 10 years, and the median follow-up was 12 months (range: 1.5–60 months) (Table 3). Among these 29 patients, splenectomy was performed in five patients, TIPS or splenorenal shunts was placed in three patients, and coronary vein steals were reported in two patients. Data on pretransplantation PVT status was reported in ten of the included twenty-nine cases, four of which (40.00%) reported pretransplantation PVT. In total, thirteen (44.83%) of the twenty-nine patients had relevant risk factors that may have predisposed them to the formation of PVT after LT (Table 2).
| Author           | Year | Country | Patients | Etiology of LT                                      | Type of LT | PVT diagnosis | Pre-LT PVT | Surgery history                                      | Other risk factors |
|------------------|------|---------|----------|----------------------------------------------------|------------|---------------|------------|-----------------------------------------------------|-------------------|
| George et al     | 1988 | USA     | 1        | Primary Sclerosing Cholangitis                      | OLT        | US            | NP         | Proximal Choledochoduodenostomy                     | NP                |
| Khan et al       | 2014 | USA     | 2        | Cholangiocarcinoma; Alcoholic Cirrhosis            | OLT + PBLT | US + CT + MRI | NP         | Pancreatoduodenectomy (one patient)                 | Hypercoagulat state (one patient) |
| Gill et al       | 2009 | UK      | 1        | Cryptogenic Cirrhosis                              | OLT        | US + CT       | Yes        | Splenectomy                                         | NP                |
| Koo et al        | 2008 | Korea   | 1        | Alcoholic Cirrhosis                                | OLT        | US + CT       | No         | NP                                                  | Coronary vein steal |
| Kensinger et al  | 2014 | USA     | 1        | Reformed ethanol abuse                             | OLT        | US + CT       | NP         | TIPs                                                | NP                |
| Cherukuri et al  | 1998 | USA     | 2        | HCV + Primary sclerosing cholangitis; Postinfectious cirrhosis | OLT + ReLT | US            | NP         | Splenorenal shunt (one patient); LT                 | NP                |
| Bakthavatsalam et al | 2001 | USA   | 1        | Autoimmune Hepatitis                               | OLT        | US            | Yes        | NP                                                  | NP                |
| Barriga et al    | 2004 | Italy   | 1        | HBV Liver Cirrhosis                                | PBLT       | US            | No         | Splenectomy                                         | NP                |
| Guckelberger et al | 1999 | Germany | 1        | HBV Liver Cirrhosis                                | OLT        | US + MRI      | No         | Cholecystectomy                                     | NP                |
| Brown et al      | 2013 | USA     | 1        | HCV + Alcohol Abuse                                | PBLT       | US + CT       | NP         | Splenectomy                                         | NP                |
| Lodhia et al     | 2010 | USA     | 3        | Alcoholic Cirrhosis; Cryptogenic Cirrhosis; Primary Sclerosing Cholangitis | OLT        | MRI           | NP         | Proctocolectomy (one patient)                       | NP                |
| Haska et al      | 1993 | USA     | 1        | Postinfectious Cirrhosis                           | ReLT       | US            | No         | LT                                                  | Coronary vein steal |
| Kawano et al     | 2016 | Japan   | 1        | HCC                                                | Living-donor LT | CT     | No         | Splenectomy                                         | NP                |
| Jeng et al       | 2014 | China   | 2        | HCC; Alcoholic Cirrhosis                           | Living-donor LT | CT     | NP         | NP                                                  | NP                |
| Kobayashi et al  | 2012 | Japan   | 1        | Autoimmune hepatitis                               | Living-donor LT | Endoscopy | NP         | Splenectomy                                         | NP                |
| Janette et al    | 1994 | USA     | 3        | Alcoholic Cirrhosis; Drug abuse + postnecrotic cirrhosis,Autoimmune hepatitis | OLT        | US + Arterial portography | NP         | Distal splenorenal shunt (one patient)               | NP                |
| Daniel et al     | 1997 | USA     | 1        | Primary sclerosing cholangitis                      | OLT        | US + CT       | NP         | NP                                                  | NP                |
| Eric et al       | 1990 | USA     | 2        | Cholangiocarcinoma; Primary sclerosing cholangitis | OLT + ReLT | CT + SMA portography | NP         | Chemotherapy; Choleodochojejunostomy; LT             | NP                |
| Bhattacharjya et al | 1999 | UK     | 1        | Cryptogenic cirrhosis                              | PBLT       | US            | Yes        | NP                                                  | NP                |
| Baccarani et al  | 2001 | Italy   | 1        | HCV Cirrhosis                                      | PBLT       | US            | No         | NP                                                  | NP                |
| Ciccarelli et al | 2001 | Belgium | 1        | HCV Cirrhosis                                      | OLT        | US            | Yes        | NP                                                  | NP                |

Abbreviations: LT, Liver transplantation; OLT, Orthotopic liver transplantation; ReLT, Re-transplantation; PBLT, Piggyback liver transplantation; HCV, Hepatitis C virus; HCC, Hepatocellular carcinoma; US, Ultrasonography; CT, Computed Tomography; MRI: Magnetic resonance imaging; SMA, Superior mesenteric artery; PVT, Portal vein thrombosis; NP, Not reported.
Table 3: Characteristics and treatment of reported cases of PVT after adult liver transplantation

| Variables                        | PVT after LT (n = 29) |
|----------------------------------|-----------------------|
| Age (years)                      | 48 (23–72)            |
| Gender (male/female)             | 16/13                 |
| PVT position                     |                       |
| Main PV                          | 11 (36.93%)           |
| Partial PV                       | 3 (10.34%)            |
| PV + SMV                         | 4 (13.79%)            |
| PV + SMV + Splenic vein          | 5 (17.24%)            |
| Onset time post-transplant       |                       |
| ≤30 days                         | 18 (62.07%)           |
| >30 days                         | 11 (37.93%)           |
| Treatment                        |                       |
| Anticoagulation/Non-Treatment    | 3 (10.34%)            |
| Anticoagulation + Interventional therapy | 16 (55.17%) |
| Interventional therapy + Sclerotherapy | 3 (10.34%) |
| Anticoagulation + Surgical thrombectomy | 1 (3.45%) |
| Surgical thrombectomy + interventional therapy | 4 (13.79%) |
| Portosystemic shunt              | 1 (3.45%)             |
| Retransplantation                | 1 (3.45%)             |
| Follow-up duration (months)      | 12 (1.5–60)           |
| Mortality                        | 4 (13.79%)            |

Abbreviations: LT, Liver transplantation; PVT, Portal vein thrombosis; PV, Portal vein; SMV, Superior mesenteric vein.

Of the reported twenty-nine cases, eighteen cases (62.07%) were diagnosed within 30 days post-LT, and ultrasonography was the first choice for monitoring PVT formation after LT. The symptoms of these cases for evaluation are shown in Fig. 1. Injury to liver function was the most frequent manifestation (12/29), and five of twenty-nine cases were asymptomatic. Regarding the therapeutic choices for PVT after LT, minimally invasive interventional therapy combined with systematic anticoagulation or sclerotherapy were the most frequently used methods (19/29; Table 3). Among these nineteen patients, four eventually died. Two patients died of liver-related complications (one due to bleeding and one due to multiple organ failure). The remaining two patients died of rejection after discontinuing immunosuppression drugs and fungal brain abscess. In the other ten patients, systemic anticoagulation was applied to three, and surgical operation (thrombectomy; portosystemic shunt and retransplantation) was performed in seven patients. All patients were in good condition during the follow-up duration.

Discussion

Portal vein thrombosis following adult liver transplantation is an uncommon complication. Preoperative recipient portal vein thrombosis was considered to be a primary risk factor predisposing recipients to PVT formation after LT[17]. Shaked and Busuttil[32] found that two of 33 preoperative PVT patients developed PVT following LT, and Davidson et al.[33] reported that the incidence of rethrombosis was approximately 21% in patients with preoperative PVT. These findings are in accordance with our results. Among the 260 LT patients at our institution, 51 (19.61%) had PVT before LT. The incidence of rethrombosis was 9.80% (5/51), which is much higher than its incidence in patients without pre-LT PVT (0.96%). In our current case series, six of seven patients who developed PVT following LT had preoperative PVT. The study of Shaked and Busuttil also found that the incidence of PVT was highest among patients with pre-existing pathologies of the portal vein including chronic active hepatitis, hypercoagulable states, trauma or previous dissection of the porta hepatis, and splenectomy[32]. Other factors include technical problems such as misalignment or excessive vessel length, ongoing rejection, liver fragment transplantation, using venous conduits in PVT, portosystemic shunts and decreased portal flow from stenosis[4, 34–40]. In our institution, two of twenty (10%) patients who had undergone a splenectomy before LT developed PVT after LT. Of the remaining 240 patients without splenectomy before LT, only five (2.08%) developed post-LT PVT. In terms of reported cases, thirteen (44.83%) of the twenty-nine patients had relevant risk factors including preoperative PVT (4/29), splenectomy (5/29), portosystemic shunts (3/29), coronary vein steal (2/29) and living-donor liver transplantation (3/29).

PVT can occur early or late after LT. Early PVT was defined as PVT detected within 30 days of LT. Late PVT was defined as PVT detected more than 30 days after LT or as early PVT persisting after 30 days[41]. In our current case series, 85.71% (6/7) of patients were diagnosed with early PVT. Among the cases included in the literature review, 62.07% were confirmed within 30 days. The clinical manifestation may differ between early and late phase PVT. PVT formation early after LT may present as mild or severe graft dysfunction, variceal bleeding, encephalopathy and, rarely, bowel infarction requiring immediate
intervention. Liver function injury was the most frequent symptom in our study. Bakthavatsalam et al. reported that early PVT formation was associated with high morbidity and mortality following LT[18]. Patients with late phase PVT after LT may present with liver dysfunction, or portal hypertension, or asymptomatic for the development of collateral circulation could reestablish portal flow to the liver[42]. Collateral circulation developed in one patient in our study, which played an important role in the patient's recovery of graft function. Because several patients were asymptomatic, ultrasonography examination played an important role in the diagnosis of postoperative PVT.

The treatment strategies for PVT after LT should depend on clinical manifestations and laboratory tests. Reported therapies range from systemic anticoagulation with heparin to transjugular or percutaneous transhepatic catheter-based thrombolysis to portosystemic shunts, surgical thrombectomy and retransplantation[30, 43, 44]. However, optimal treatment guidelines for posttransplantation PVT have yet to be defined. Currently, interventional radiological procedures are becoming attractive alternatives to surgical thrombectomy or retransplantation for the management of PVT following LT due to the minimal invasiveness, low rates of complications, and high success rates associated with these techniques[45]. In the reviewed literature, interventional radiology therapy combined with systemic anticoagulation (55.71%) were the most frequently chosen methods in the management of PVT. However, the technical difficulty of percutaneous access or cannulation of a portal vein with thrombosis limits the application of interventional therapy. It was also reported that potential anastomotic disruption was a risk for the application of interventional procedures in the early posttransplant period[3].

In our experience, systematic anticoagulation should be used immediately for PVT patients with stable liver function. If the hepatic artery is present without stenosis or thrombosis, systematic anticoagulation with careful monitoring is a good option. In addition, an interventional radiology procedure is also a good choice if the thrombus remains unchanged after anticoagulation. However, the manipulation of percutaneous access or cannulation of the portal vein should be performed carefully to avoid the potential risk of anastomotic disruption and bleeding. In the present cases, four patients received anticoagulation treatment and recovered uneventfully. One patient died of uncontrolled bleeding following transjugular transhepatic portal vein puncture thrombolytic. For patients with PVT formation more than 30 days posttransplantation, anticoagulation and interventional treatment can also be chosen for thrombolytic if the collateral circulation has already formed and symptoms are mild.

There are several limitations of our study due to the limited number of cases. Because of the characteristics of case reports or series, the risk factors of posttransplant PVT formation cannot be fully analyzed. In addition, owing to the selection biases of retrospective cases, mortality may be underestimated.

Conclusions

In summary, the management of PVT following LT should depend on the clinical symptoms and the patient's condition. Interventional therapy combined with systemic anticoagulation is always a good choice, and in our experience, systemic anticoagulation alone can also have a positive effect on early PVT patients. For the effects of conservative treatment and surgery such as thrombectomy, portosystemic shunts or retransplantation, further prospective studies with larger sample sizes are needed.

Abbreviations

PVT: portal vein thrombosis
LT: liver transplantation
HAT: hepatic artery thrombosis
DCD: donor organs after cardiac death
SD: standard deviations

Declarations

Ethics approval

This retrospective study was approved by the institutional review board of the First Affiliated Hospital, Xi'an Jiaotong University. Written consent was given by the patients for their information to be stored in the hospital database and used for research. All treatment strategies and indications for surgery were discussed by a multidisciplinary board. Prior to surgery, all patients had been informed of the necessity of surgery and the potential for perioperative complications, they all agreed to surgery and gave informed consent.

Consent for publication

Consent form for publication was obtained by all the patients, and written consent was given by all participants for their personal or clinical details along with any identifying images to be published in this study.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.
Competing interests
The authors declare that they have no competing interests.

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Author contributions
All authors helped to perform the research; QS.L. and WW.L. manuscript writing, performing data analysis; T.M., Y.W. and XM.L. literature review, performing data analysis; YY.Y., JH.S. and M.T. contribution to writing the manuscript, drafting conception; XG.Z., Y.L. and B.W. contribution to writing the manuscript, drafting conception and study design.

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Figures
Figure 1

The symptoms of the reported cases with post-LT portal vein thrombosis.