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PRO: Portal Vein Thrombosis Impacts Liver Transplantation Outcomes

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KEY POINTS

- Portal vein thrombosis (PVT) characteristics impact liver transplantation (LT) outcomes. Occlusive PVTs and/or those extending to the superior mesenteric vein (SMV) result in suboptimal short-term and long-term LT outcomes compared with those without PVT.
- Nonphysiological surgical reconstruction of the portal vein (PV) during LT results in higher surgical complications and postoperative morbidity and mortality.
- The management of PVT during LT requires surgical expertise and greater resource utilization.

PVT remains a common problem in patients with cirrhosis, with an estimated prevalence rate in those awaiting

LT of 2% to 26%,^{1,2} which is thought to parallel the prevalence of disease in all patients with cirrhosis.³ Previously considered a contraindication to LT, the presence of non-malignant PVT no longer precludes transplantation, as indicated by a 1985 report detailing successful revascularization,⁴ but peritransplant outcomes in those with PVT still remain inferior compared with those without PVT, particularly in patients with complete occlusion of the PV or use of nonphysiological vascular reconstruction.^{3,5,6}

Data from single-center and database studies reveal that pretransplant PVT amplifies early (90-day) and later (1-year) graft failure and patient mortality. Among pediatric recipients, the risk of 30-day mortality is increased almost 3-fold.⁷ Similarly, an increased hazard of death at

Abbreviations: CI, confidence interval; HAT, hepatic artery thrombosis; HR, hazard ratio; LT, liver transplantation; NA, not applicable; NASH, nonalcoholic steatohepatitis; OR, odds ratio; PV, portal vein; PVT, portal vein thrombosis; SMV, superior mesenteric vein; UNOS, United Network for Organ Sharing.

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30 days posttransplant among those with PVT has been reported in a single-center study, and increased 90-day graft and patient mortality in those with PVT at LT when analyzing United Network for Organ Sharing (UNOS) data.⁸

In cirrhosis, sluggish portal flow caused by increased intrahepatic resistance, combined with prothrombotic and inflammatory factors, creates an environment for PVT formation.^{1,3} It can be characterized radiographically based on lumen obstruction and chronicity, as well as intraoperatively according to the Yerdel classification, which describes clot extent into the venous system and lumen patency (Fig. 1).^{5,9} Restoration of portal flow is a requisite for adequate allograft function. Routine surgical technique for PVT during LT is an eversion thrombectomy (thrombus is extracted) or thrombendvenectomy (clot and adherent intima are removed) combined with an end-to-end anastomosis between the donor and

recipient PV.^{3,6,9} However, the clot characteristics dictate the operative approach, because more extensive clots require PV resection, ligation of portosystemic shunts, or creation of jump grafts using donor vessels, recipient vessels, or synthetic grafts.^{3,6,9}

Those with higher Yerdel grade, particularly grade 3 or 4, have a higher rate of morbidity and mortality with LT because of the complexity of the surgical operation; these operations often require challenging reconstructions, which are often nonphysiological (arterialization of PV, cavoportal hemitransposition, renoportal anastomosis).⁵ Nonphysiological vascular reconstructions have also been described with reports of aneurysmal dilation,³ rethrombosis of veins, unresolved portal hypertention,¹⁰ and increased morbidity and mortality.^{3,6,10} For example, in a single-center cohort of 1379 liver transplant recipients, Hibi et al.¹⁰ reported the 1-year patient survival

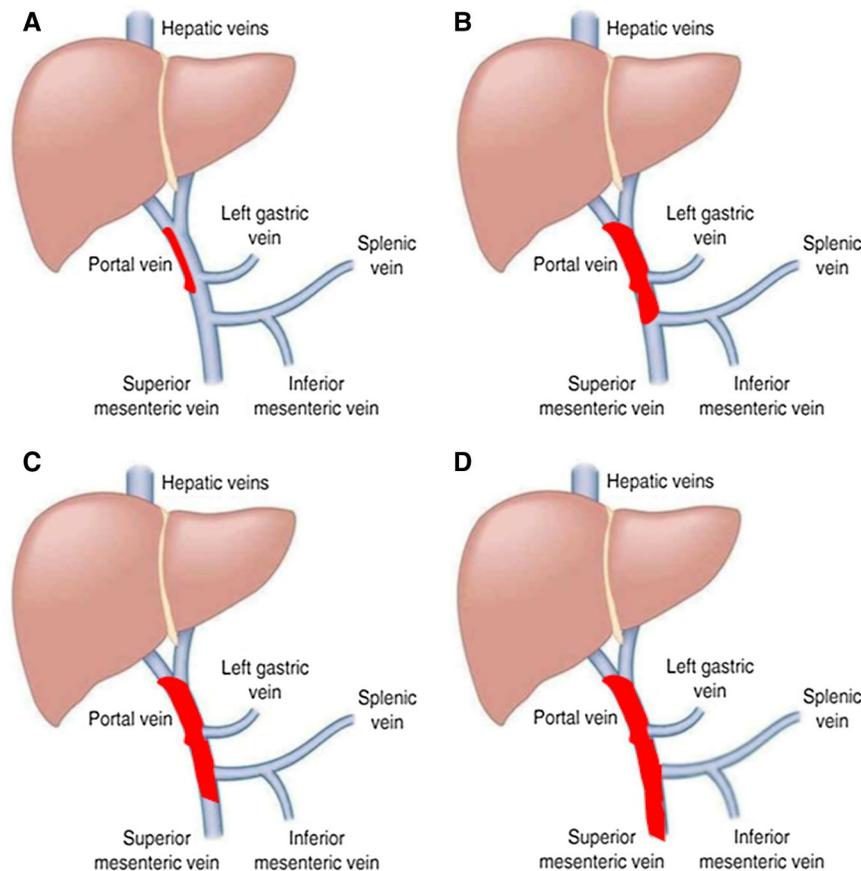


FIG 1 Diagram of Yerdel classification. (A) Grade 1: thrombus at main PV affecting less than 50% of the lumen with or without minimal extension into SMV. (B) Grade 2: thrombus at PV affecting more than 50%, including complete thrombosis with or without minimal extension into the SMV. (C) Grade 3: complete PVT plus thrombosis extending to the proximal SMV with patent distal SMV. (D) Grade 4: complete PVT plus complete thrombosis of the SMV (proximal and distal). Adapted with permission from *Liver Transplantation*.⁹ Copyright 2016, American Association for the Study of Liver Diseases.

TABLE 1. SUMMARY OF SELECTED STUDIES ASSESSING OUTCOMES IN LT RECIPIENTS WITH PVT

Study	Population	PVT Prevalence, n (%)	PVT Characteristics	Key Findings
Yerdel et al. (2000) ⁵	Retrospective, single-center cohort of 779 adults undergoing LT from 1987 to 1996	63 (8.1%)	Yerdel grade 1: 24 (38%) Yerdel grade 2: 23 (37%) Yerdel grade 3: 6 (9.5%) Yerdel grade 4: 10 (15.5%)	<ul style="list-style-type: none"> Higher resource utilization (increased transfusion requirements, need for hemodialysis) and postoperative complications (primary nonfunction, rethrombosis) in recipients with PVT compared with those without PVT. There was no difference in 5-year posttransplant survival rates between recipients with grade 1 PVT compared with those without PVT (both 86%). 5-Year graft survival rate of grades 2-4 PVT was significantly different compared with those without PVT (52% versus 76.3%; $P < 0.0004$). 5-Year patient survival rate of grades 2-4 PVT was significantly different compared with those without PVT (55% versus 84.2%; $P < 0.0001$).
Englesbe et al. (2010) ²⁰	Retrospective, single-center cohort of 3295 adults undergoing LT from 1995 to 2007	148 (4.5%)	Only occlusive PVT included	PVT was associated with an increased risk for mortality at 30 days compared with those without PVT (OR, 7.39; 95% CI: 2.39-22.83; $P < 0.0001$).
Suarez-Aracho et al. (2010) ¹⁴	Nonocclusive PVT excluded Retrospective, single-center cohort of 617 patients undergoing LT from 1991 to 2008	48 (7.8%)	Nonocclusive: 28 (58.3%) Occlusive: 20 (41.7%)	<ul style="list-style-type: none"> Greater patient mortality at 1 year in those with any type of PVT compared with those without PVT (29.1% versus 16.5%; $P < 0.05$). 1-Year patient mortality was significantly different among recipients with occlusive PVT compared with those without PVT (45% versus 16.5%; $P < 0.01$). No significant difference in 1-year patient mortality in those with nonocclusive PVT compared with those without PVT (17.8% versus 16.5%; $P < 0.8$). Increased blood product utilization in patients with PVT compared with those without (15.4 versus 11 units; $P < 0.05$).
Ravaioli et al. (2011) ¹¹	Retrospective, single-center cohort of 889 patients undergoing LT +/- dual organ transplant from 1998 to 2008	91 (10.2%)	Nonocclusive: 51 (56%) Occlusive: 40 (44%)	<ul style="list-style-type: none"> Although 1-year patient mortality was similar between those with and without PVT, there was a marked difference between 1-year and 5-year mortality in those with occlusive PVT versus nonocclusive PVT early in the study (1998-2002) compared with later (2003-2008) in the study. When comparing all recipients with occlusive PVT versus nonocclusive PVT during the entire study period, there was no difference in 1-year and 5-year patient mortality. PVT associated with increased risk for 30-day (HR, 2.9; 95% CI: 1.6-5.3; $P = 0.001$) and overall posttransplant mortality (HR, 1.7; 95% CI: 1.1-2.4; $P = 0.01$).
Watts et al. (2011) ⁷	Retrospective UNOS database review of 3630 children undergoing LT (deceased or live donation) from 2001 to 2007	136 (3.7%)	NA	
Hibi et al. (2014) ¹⁰	Retrospective, single-center cohort of 1379 adults undergoing LT from 1998 to 2009 Grouped recipients into three categories: 1. No PVT group 2. PVT: physiological revascularization group 3. PVT: nonphysiological revascularization group	174 (12.6%)	Nonocclusive: 91 (52.3%) Occlusive: 83 (47.7%)	<ul style="list-style-type: none"> 27% of recipients with occlusive PVT underwent reconstruction with nonphysiological portal inflow (PVT: nonphysiological revascularization group). 97% of recipients with nonocclusive PVT underwent PV reconstruction with physiological portal inflow (PVT: physiological revascularization group). PVT: nonphysiological revascularization group had longer hospital stays, increased need for hemodialysis, and increased rate of rethrombosis. 1-, 5-, and 10-year patient survival rates were significantly lower in the PVT nonphysiological revascularization group than both of the other groups (PVT: physiological revascularization and no PVT group).
Ghahril et al. (2016) ⁸	Retrospective UNOS database review of 48,570 adults undergoing LT from 2002 to 2013	3321 (6.8%)	NA	PVT associated with increased 90-day graft loss (OR, 1.72; 95% CI: 1.51-1.97; $P < 0.001$) and mortality (OR, 1.7; 95% CI: 1.45-1.99; $P < 0.001$).
Agbim et al. (2019) ¹⁹	Retrospective UNOS database review of 3689 adults with NASH undergoing LT from 2002 to 2013	450 (12.2%)	NA	NASH recipients with PVT had increased risk for graft loss (HR, 1.37; 95% CI: 1.15-1.63; $P < 0.001$) and overall death (HR, 1.31; 95% CI: 1.05-1.63; $P < 0.001$) compared with NASH recipients without PVT.

rate in recipients with nonphysiological PV reconstructions was 64% compared with 87% ($P = 0.002$) in those without PVT. Similarly, a 2018 meta-analysis revealed recipients with occlusive PVT had a 5-fold higher 30-day mortality rate compared with those with nonocclusive PVT.² Furthermore, patients with diffuse thrombosis of splanchnic vessels remain particularly at risk for such complications and may be candidates for multivisceral transplantation, which remains complicated by high intestinal rejection rates.^{3,10} As surgical innovation and experiences advance with time, it is possible that outcomes may improve, as suggested by an Italian study, which reported a notable difference between patient mortality in those with occlusive PVT compared with nonocclusive PVT as surgical technique evolved.¹¹ Table 1 summarizes outcomes in select studies.

The presence of PVT causes increased resource utilization in terms of operative time, blood product utilization, length of stay, and surgical complications.^{5,12-14} Kim et al.¹² noted that in liver transplant candidates undergoing living donor LT with right lobe grafts, those with PVT had an increased amount of packed red blood cell requirement, longer intensive care unit stays, and bleeding compared with those without PVT. Increased resource utilization was more pronounced among those with occlusive PVT compared with nonocclusive PVT.^{10,12} In addition, rethrombosis,^{5,10} dialysis utilization, and infectious complications are increased in those with PVT.⁵

Furthermore, analysis of the UNOS database demonstrates recipients with pretransplant PVT have an increased risk for development of hepatic artery thrombosis (HAT) and subsequent graft loss. This was independent of recipient, donor, and surgical factors, and the authors postulate that this occurs because of ongoing endothelial impairment.¹⁵ In addition, the same authors noted those with pretransplant PVT who receive allografts from donors considered high risk, as defined by a donor risk index >1.7 , were more likely to have graft loss as a result of posttransplant HAT.¹⁶ In general, suboptimal organs do not tolerate prolonged cold and warm ischemic times well, which may occur in the setting of complex vascular reconstructions required for PVT.¹ Overall, this underscores that thoughtful consideration and clinical equipoise are required regarding donor and recipient selection, particularly in a landscape where organ scarcity abounds and wait-list mortality is high.

The art of balancing recipient and donor criteria rings particularly true because the LT candidate and recipient population has evolved from patients with hepatitis C to patients with nonalcoholic steatohepatitis (NASH),¹⁷ who often have many cardiometabolic comorbidities. Notably, patients with cirrhosis caused by NASH who are undergoing LT are more likely to have PVT,¹⁸ and patients with NASH with PVT have inferior posttransplant outcomes.¹⁹ At present, the management of PVT in candidates awaiting LT is not uniform,⁹ but given the less-than-favorable posttransplant outcomes in LT candidates with PVT coupled with changing dynamics in recipient demographics and the organ shortage, future endeavors are needed to outline best PVT treatment and perhaps prevention strategies to enable successful posttransplant results.

In conclusion, although innovation in surgical techniques has lowered the threshold to perform LT in candidates with PVT, these patients, particularly those with occlusive and PVT extending into mesenteric veins, continue to have suboptimal outcomes. Clot characteristics clearly influence outcomes, as indicated by a recent meta-analysis,² and surgical management requires considerable skill, which develops with time.¹¹

CORRESPONDENCE

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