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The Impact of Portal Vein Thrombosis on Liver Transplant Outcomes: Does Grade or Flow Rate Matter?

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The Impact of Portal Vein Thrombosis on Liver Transplant Outcomes: Does Grade or Flow Rate Matter?

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Background. Portal vein thrombosis (PVT) makes the technical aspect of liver transplantation challenging and also affects outcomes. Our aim was to study impact of PVT grade and postreperfusion portal flow on posttransplant outcomes. **Methods.** Patients who underwent transplantation with PVT between January 2007 and May 2017 were selected (n = 126). Data on grade of PVT and portal vein flow were collected. Patients were classified into 2 groups; low grade (Yerdel Grade I, n = 73) and high grade (Yerdel Grade II or III, n = 53). Using portal flow rate, patients were divided into high flow (≥1000 mL/min, n = 95) and low flow (<1000 mL/min, n = 31). Additional analyses of flow by graft weight and complications were performed. **Results.** Postoperatively, incidence of biliary strictures were significantly greater in high-grade PVT compared with low grade (P = 0.02). Incidence of postoperative portal vein thrombosis was higher in low flow after reperfusion compared with high flow (P = 0.02), as was bile leak (P = 0.02). On identifying factors associated with graft loss, moderate to severe ascites preoperatively, high PVT grade and bile leak were associated with worse graft survival. Subanalysis performed combining grade and flow showed that low grade, high flow had the highest graft survival while high grade, low flow had the lowest (P = 0.006). High-grade PVT with low flow also appeared to be an independent risk factor for biliary complications (P = 0.01). **Conclusions.** In conclusion, biliary complications, especially strictures are more common in high-grade PVT and graft survival is worse in high-grade PVT and low portal flow.

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INTRODUCTION

Orthotopic liver transplantation is the treatment of choice in patients with end-stage liver disease. While a number of studies have been done to examine pretransplant donor and recipient factors that influence posttransplant outcome,[1-3] there have been limited studies examining variables relating to reperfusion and their effects. With the validation of ultrasonic transit time flow measurement devices,[4] we have had a powerful tool to measure portal venous and hepatic arterial blood flow following reperfusion of the liver.[5] It is not only important to detect abnormal flow rates and take measures to correct them but also to have an objective measurement that correlates with outcome, in particular with the portal vein.[6-9]

Portal vein thrombosis (PVT) represents a challenging problem for liver transplant surgeons and recipients as it is known to negatively impact survival.[1] Ideally, we would be able to identify those patients at risk for poor portal flow rates following reperfusion. Previous studies have described ideal portal flow rates in deceased donor liver transplantation[7,8] and one study in particular has detailed the impact of portal flow rates on outcome, specifically in recipients with known PVT.[6] However, there are limited studies that describe a significant relationship between pretransplant PVT grading and postreperfusion portal flow rates and transplant outcome.[10] This becomes significant as new techniques emerge to recanalize the thrombosed portal vein, to establish adequate flow in the pretransplant period, and as we determine which cohort of patients these procedures are necessary.[11] Pretransplant identification of patients at risk for poor portal flow rates may allow us to intervene early to optimize outcomes.

Our hypothesis is that high-grade PVT pretransplant and low portal flow rates following reperfusion are related, and the combination of these 2 factors in particular have an impact on outcome. The aim of this study is to examine the effect of the grade of known pretransplant PVT

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and the portal flow rate following reperfusion on posttransplant outcomes. In addition to graft survival, we also wanted to study related posttransplant complications in this patient population.

MATERIALS AND METHODS

A total of 1042 patients underwent liver transplantation at Henry Ford Hospital between January 2007 and May 2017. Of these, 126 were identified by preoperative computed tomography scan review to have portal vein thrombosis (PVT). Its severity was graded using Yerdel classification.[12] Grading was performed by 1 author (M.D.R.) to ensure consistency.

Demographics such as recipient age, recipient sex, recipient body mass index, model for end-stage liver disease score and donor age were collected for all patients. Intraoperative characteristics such as ischemia times, transplantation technique, biliary anastomosis technique, use of veno-venous bypass, blood and blood product transfusion were also gathered. In addition, intraoperative portal vein and hepatic artery flow rates following reperfusion were measured using a Transonic Systems, Inc. Optima flow-QC transit time flow probe, Model #HT354 (Ithaca, NY). The flow probe measurements at our institution are routinely performed following the arterial reconstruction and before the biliary reconstruction. Postoperatively, the management of all patients with PVT routinely consists of 325 mg acetylsalicylic acid monotherapy, with systemic anticoagulation using warfarin for only those recipients with other indications. We also routinely employ deep venous thrombosis prophylaxis using 5000 Units of subcutaneous unfractionated heparin 3× daily while inpatient once the initial postoperative bleeding risk has subsided.

Two different analyses were performed in our study. The first involved the grade of pretransplant PVT and the second involved portal flow rates after liver reperfusion. Seventy-three patients had Yerdel Grade I, 46 had Grade II, and 7 had Grade III PVT. Based on these grades, the patients were classified into 2 groups; low grade (Yerdel Grade I, n = 73) and high grade (Yerdel Grade II or III, n = 53). Grade IV PVT at our institution is preferentially treated with multivisceral transplantation and therefore there were no patients with grade IV PVT undergoing liver transplant alone. Using portal flow rate, patients were divided into 2 groups; those with high flow (≥1000 mL/min, n = 95) and those with low flow (<1000 mL/min, n = 31). The flow rate of 1000 mL/min was chosen as it was the 25th percentile value of our cohort. Also, portal vein flow rates <1000 mL/min have been shown by Spitzer et al[7] to have a significant negative impact on liver graft survival. We also analyzed a cohort of recipients from January 2007 to May 2017 without known PVT (n = 863) in similar fashion to assess for any impact of portal flow rates on graft survival in this population.

A subanalysis by dividing the patients into 4 groups and combining the previous criteria for PVT grade and portal flow rate was also performed; high flow, low grade (n = 58); high flow, high grade (n = 37); low flow, low grade (n = 15) and low flow, high grade (n = 16). A second subanalysis was performed, which included dividing the patients based on flow per milliliters per 100 grams of liver. Those with flow rate ≥100 mL/min/100 grams were classified as high flow rate (n = 74) and those <100 mL/min/100 grams were classified as low flow rate (n = 37). This flow rate classification was combined with PVT grade classification for comparison; low flow by weight-low grade (n = 38), low flow by weight-high grade (n = 36), high flow by weight-low grade (n = 26), and high flow by weight-high grade (n = 11).

An analysis of risk factors for biliary complications was also performed. Of note, we report data with and without the exclusion of 9 patients who received hepaticojejunostomy (Roux-en-Y biliary reconstruction) from this analysis. PVT grade and portal flow were combined and included in this analysis (low graft with high flow; low grade with low flow; high grade with high flow; high grade with low flow). Other potential risk factors, including recipient and donor characteristics, hepatic artery flow, intraoperative transfusion, and ischemia times were also included in the analysis. We also analyzed a cohort of recipients from January 2007 to May 2017 without known PVT and again excluded those with a Roux-en-Y biliary reconstruction (n = 729). This was done in similar fashion to the PVT cohort to assess for any impact of portal flow rates on biliary complications in this population.

Postoperative outcomes analyzed in these groups included biliary complications, such as bile leaks and anastomotic strictures, rejection rates, both early and late, early allograft dysfunction, postoperative portal vein thrombosis and hepatic artery complications such as stenosis or thrombosis, and length of hospital stay. In addition, usage of preoperative and posttransplant anticoagulation use was compared. Patient and graft survival among all groups was also studied.

Statistical tests used were *t*-test and Mann-Whitney *U* test for continuous variables and chi-square test for categorical variables. Incidence of biliary strictures was compared among the different groups using log-rank test. Cox regression model was used to identify factors that affected graft survival and biliary complications. Survival analysis was performed using Kaplan-Meier method and analyzed using log-rank test. A $P < 0.05$ was defined as statistically significant. This study was performed with approval from the Institutional Review Board.

RESULTS

Grade and Transplant Outcomes

Demographic characteristics were similar in both high-grade PVT and low-grade PVT groups (Table 1). Intraoperative factors such as ischemia times, transplantation techniques, veno-venous bypass use, and transfusion requirements were also similar. Presence of moderate to severe ascites was also similar. Portal flow was also similar in both groups ($P = 0.09$). Portal flow per milliliter per 100 gram liver weight was also similar between both groups ($P = 0.052$). The only difference observed was the technique of biliary reconstruction used. Duct-to-duct versus Roux-en-Y anastomosis was more commonly performed in those with high grade compared with those with low grade PVT (98.1% versus 86.3%, $P = 0.01$). Before implantation, management of PVT in all patients included a thromboendovenectomy and portal vein-to-vein anastomosis except for two patients in whom thromboendovenectomy was followed by anastomosis with a large coronary vein varix.

TABLE 1.

Demographic and intraoperative characteristics among high and low grade PVT groups

Characteristics	Grade I (n = 73)	Grade II or III (n = 53)	*P*
Demographics			
Diagnosis, n (%)[a]			
Hepatitis C	30 (40.1)	18 (34.0)	0.53
Alcoholic related	19 (26.0)	17 (32.1)	0.59
NASH	20 (27.4)	20 (37.7)	0.3
Biliary cirrhosis	8 (11.0)	1 (1.9)	0.11
HCC	17 (23.3)	16 (30.2)	0.51
Others	4 (5.5)	5 (9.4)	0.62
Recipient age, y	56.8 ± 7.6	57.8 ± 7.4	0.47
Recipient sex, M/F	48/25	38/15	0.56
Recipient BMI	29.6 ± 6.6	30.3 ± 5.6	0.51
MELD score	20.3 ± 7.8	22.9 ± 8.2	0.07
Moderate or severe ascites, n (%)	19 (26)	16 (30.2)	0.75
Anticoagulation preop, n (%)	14 (19.2)	12 (22.6)	0.66
Donor age, y	40.3 ± 17.3	42.2 ± 15.2	0.53
Donor liver macrovesicular steatosis >10%, n (%)	4 (5.5)	6 (11.3)	0.47
Donor liver fibrosis (yes), n (%)	13 (17.8)	12 (22.6)	0.66
Intraoperative			
Cold ischemia time, min	333.9 ± 119.5	344.6 ± 111.0	0.61
Warm ischemia time, min	40.5 ± 10.4	40.5 ± 7.3	0.99
Piggyback technique, n (%)	58 (79.4)	46 (86.8)	0.35
Duct-to-duct anastomosis, n (%)	63 (86.3)	52 (98.1)	**0.01**
Venous-venous bypass, n (%)	1 (1.4)	1 (1.9)	1.00
Packed red blood cells, median (25th, 75th)	4 (1, 6)	4 (2, 8)	0.14
Fresh frozen plasma, median (25th, 75th)	6 (3, 10)	8 (4, 14)	0.15
Cell saver, median (25th, 75th)	3 (1, 5)	3 (2, 6)	0.10
Platelets, median (25th, 75th)	0 (0, 2)	0 (0, 6)	0.21
Cryoprecipitate, median (25th, 75th)	1 (0, 5)	2 (0, 10)	0.70
Portal vein flow, L/min	1.4 (1.1–1.89)	1.24 (0.99–1.58)	0.09
Portal flow/liver graft weight, L/min/100 g	89 (67–126)	80 (63–96)	0.052

Bold denotes statistically significant variables.
[a]Multiple diagnoses may overlap.
BMI, body mass index; MELD, model for end-stage liver disease; PVT, portal vein thrombosis.

TABLE 2.

Postoperative outcomes among PVT Grade groups

Outcomes	Grade I (n = 73)	Grade II or III (n = 53)	*P*
Biliary complications, n (%)	22 (30.1)	26 (49.1)	0.04
	21/64 (32.8)[a]	26/53 (49.1)[a]	0.07
Bile leak, n (%)	7 (9.6)	8 (15.1)	0.41
	7/64 (10.9)[a]	8/53 (15.1)[a]	0.5
Biliary stricture, n (%)	16 (21.9)	22 (41.5)	0.03
	15/63 (23.4)[a]	22/53 (41.5)[a]	0.04
Reop for biliary comp, n (%)	7 (9.6)	10 (18.9)	0.19
	6/73 (9.4)[a]	10/53 (18.9)[a]	0.26
Postop early rejection (<3 mo)	5 (6.8)	5 (9.4)	0.74
Late rejection (>3 mo)	14 (19.2)	6 (11.3)	0.32
Postop early allograft dysfunction, n (%)	17 (23.3)	10 (19.9)	0.66
Postop portal vein thrombosis, n (%)	7 (9.6)	12 (22.6)	0.07
Postop hepatic artery stenosis/thrombosis, n (%)	6 (8.2)	0 (0)	0.04
Hospital stay	10 (7, 16)	13 (8, 19)	0.13
Hepatic artery flow, mL/min	400.0 ± 236.9	379.2 ± 171.1	0.59
Anticoagulation after transplant, n (%)	57 (78.1)	45 (84.9)	0.37

[a]Excluded 9 cases with hepaticojejunostomy.
PVT, portal vein thrombosis.

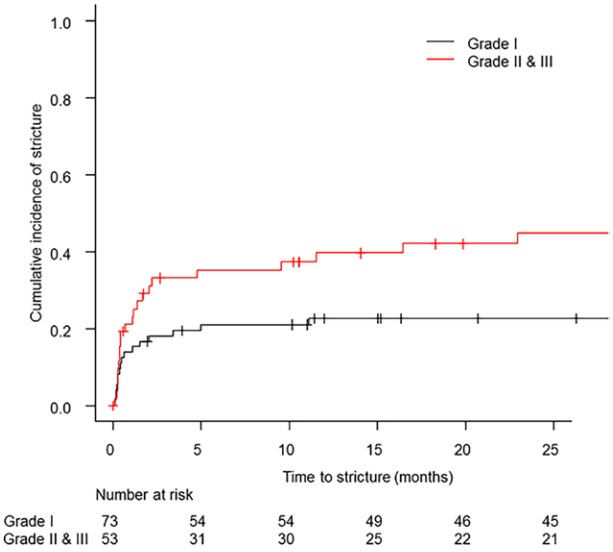

FIGURE 1. Cumulative incidence of biliary strictures among high and low grade groups.

Postoperatively, incidence of biliary complications was higher in the high-grade group compared with the low grade group (P = 0.04, Table 2). Anastomotic biliary strictures were especially more common in the high-grade group compared with the low grade group (41.5% versus 21.9%, P = 0.03). The rates of biliary strictures in particular were also significantly higher when those patients undergoing roux-en-Y hepaticojejunostomy biliary reconstruction were excluded from the analysis (P = 0.04). Cumulative incidence of biliary strictures were also significantly higher in those with high grade compared with low grade PVT (P = 0.02, Figure 1). Incidence of postoperative hepatic artery complications (stenosis or thrombosis) was higher in low grade compared with high-grade group (8.2% versus 0%, P = 0.04). Incidence of postoperative PVT was also higher in the high PVT grade group, but this was not statistically significant (22.6% versus 9.6%, P = 0.07). Other postoperative outcomes such as early allograft dysfunction, bile leak rates, early and late rejection rates, and hospital stay were also similar.

Portal Flow and Transplant Outcomes

Demographic characteristics were similar in both high flow and low flow groups (Table 3). While presence of moderate to severe ascites may be associated with severity of portal hypertension, there was no difference between these 2 groups (P = 0.68). Intraoperative factors such as

TABLE 3.

Demographic and intraoperative characteristics among high- and low-flow groups

Characteristics	High flow (n = 95)	Low flow (n = 31)	*P*
Demographics			
Diagnosis, n (%)[a]			
Hepatitis C	35 (36.8)	13 (41.9)	0.77
Alcoholic related	29 (30.5)	7 (22.6)	0.53
NASH	29 (30.5)	11 (35.5)	0.77
Biliary cirrhosis	6 (6.3)	3 (9.7)	0.82
HCC	24 (25.3)	9 (29.0)	0.86
Others	8 (8.4)	1 (3.2)	0.57
Recipient age, y	56.8 ± 7.6	58.7 ± 7.0	0.18
Recipient sex, M/F	64/31	22/9	0.83
Recipient BMI	29.9 ± 6.5	29.8 ± 4.9	0.93
MELD score	21.5 ± 7.9	20.9 ± 8.6	0.68
Moderate to severe ascites	25 (26.3)	10 (32.3)	0.68
Anticoagulation preop, n (%)	21 (22.1)	5 (16.1)	0.61
Donor age, y	40.7 ± 16.0	43.4 ± 16.3	0.42
Donor liver macrovesicular steatosis >10%, n (%)	6 (6.4)	4 (13.0)	0.22
Donor liver fibrosis, n (%)	17 (17.9)	8 (25.8)	0.48
Intraoperative			
Cold ischemia time, min	334.9 ± 114.7	349.0 ± 119.9	0.56
Warm ischemia time, min	40.8 ± 9.2	39.3 ± 9.0	0.42
Piggyback technique, n (%)	77 (81.1)	27 (87.1)	0.59
Duct-to-duct anastomosis, n (%)	90 (94.7)	25 (80.6)	0.21
Venous-venous bypass, n (%)	1 (1.1)	1 (3.2)	0.43
Packed red blood cells, median (25th, 75th)	4 (2, 6)	4 (1.5, 7.5)	0.96
Fresh frozen plasma, median (25th, 75th)	8 (4, 12)	4 (2, 11)	0.19
Cell saver, median (25th, 75th)	3 (2, 6)	2 (1, 5)	0.41
Platelets, median (25th, 75th)	0 (0, 4)	0 (0, 1.5)	0.22
Cryoprecipitate, median (25th, 75th)	2 (0, 10)	0 (0, 5)	0.45

[a]Multiple diagnoses may overlap.
BMI, body mass index; MELD, model for end-stage liver disease; PVT, portal vein thrombosis.

TABLE 4.

Postoperative outcomes among high- and low-flow groups

Outcomes	High flow (n = 95)	Low flow (n = 31)	*P*
Biliary complications, n (%)	33 (34.7)	15 (48.3)	0.20
	32/90 (35.6)[a]	15/27 (55.6)[a]	0.06
Bile leak, n (%)	8 (8.4)	7 (22.6)	0.052
	8/90 (8.9)[a]	7/27 (25.9)[a]	0.02
Biliary stricture, n (%)	27 (28.4)	11 (35.5)	0.50
	11/27 (40.7)[a]	26/90 (28.9)[a]	0.25
Reop for biliary complications, n (%)	10 (10.5)	7 (22.6)	0.04
	9/90 (10.0)[a]	7/27 (25.9)[a]	<0.001
Postop early rejection (<3 mo)	7 (7.4)	3 (9.7)	0.71
Late rejection (>3 mo)	16 (16.8)	4 (12.9)	0.78
Postop early allograft dysfunction, n (%)	19 (20)	8 (25.8)	0.45
Postop portal vein thrombosis, n (%)	10 (10.5)	9 (29.0)	0.02
Postop hepatic artery stenosis/ thrombosis, n (%)	3 (3.2)	3 (9.7)	0.16
Hospital stay, d	10 (7, 16)	12 (8, 24.5)	0.04
Hepatic artery flow, mL/min	399.4 ± 210.1	365.4 ± 214.9	0.45
Anticoagulation after transplant, n (%)	77 (81.1)	25 (80.6)	1.00

[a]Excluded 9 cases with hepaticojejunostomy.

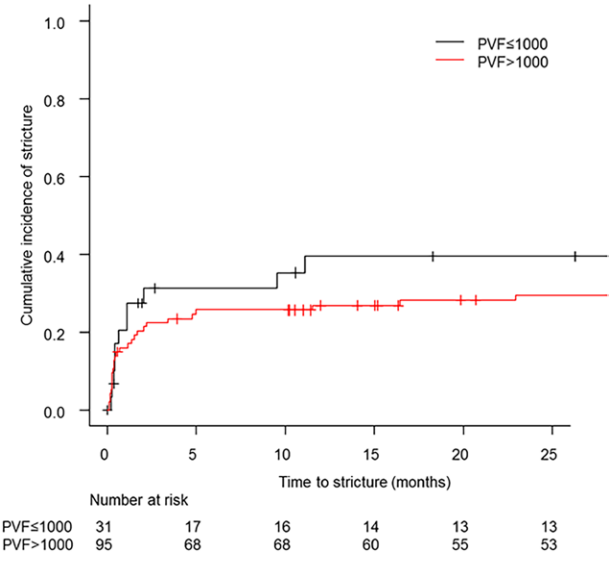

FIGURE 2. Cumulative incidence of biliary strictures among high- and low-flow groups. PVF, portal vein flow.

ischemia times, transplantation techniques, biliary reconstruction techniques, use of veno-venous bypass, and transfusion requirements were also similar.

Postoperatively, incidence of biliary complications was similar in both groups (P = 0.20, Table 4). However, reoperation rate for biliary complications was higher in the low-flow group compared with high flow (22.6% versus 10.5%, P = 0.04). Cumulative rates of biliary strictures between both groups did not reach statistical significance (P = 0.34, Figure 2). Incidence of postoperative PVT was higher in the low-flow group compared with the high-flow group (29.0% versus 10.5%, P = 0.02). Median hospital stay was also longer in the low-flow group (12 versus 10 d, P = 0.04). Other postoperative complication rates such as hepatic artery thrombosis/stenosis, early allograft dysfunction, bile leak rates, and rejection rates were similar.

Flow-grade Subanalysis

On performing a subanalysis by dividing the patients using both flow and grade, we observed that those with high flow and low PVT grade had the highest 5-year graft survival (88.3%) followed by low flow, low grade (72%) and high flow, low grade (68%). The combination of low flow and high PVT grade had the lowest 5-year graft survival (47.7%, P = 0.006, Figure 3).

Flow per Liver Weight Subanalysis

Subanalysis was performed by using both flow by weight and grade, showed that those with high flow by weight and low grade PVT had the highest 5-year graft survival (90.7%), followed by low flow by weight and low grade PVT (88.4%), low flow by weight and high-grade

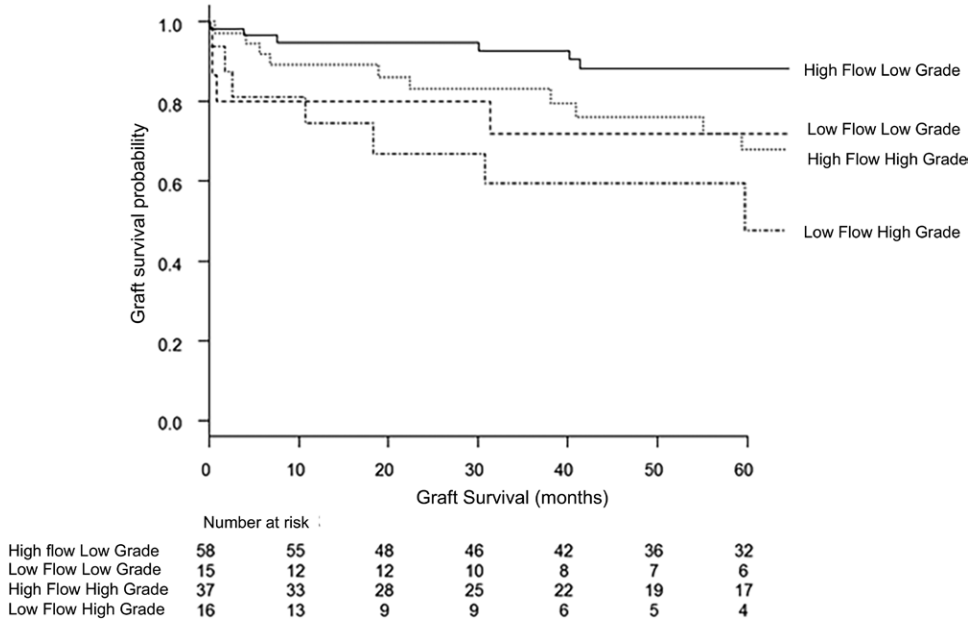

FIGURE 3. Five-y graft survival among the different flow-grade groups.

PVT (64.1%) and finally, high flow by weight with high-grade PVT (57.3%). Patients with high grade regardless of flow by weight had the lowest 5-year survival ($P = 0.02$).

Effect on Graft Survival

On performing a univariate analysis to identify factors associated with graft loss, high PVT grade (hazard ratio [HR]: 2.65; confidence interval [CI]: 1.30-5.43; $P = 0.008$), low flow (HR: 2.27; CI: 1.11-4.64; $P = 0.02$), presence of moderate to severe ascites (HR: 3.34; CI: 1.65-6.78; $P = 0.001$), donor liver macrovesicular steatosis >10% (HR: 3.62; CI: 1.47-8.90; $P = 0.005$), and bile leak (HR: 3.00; CI: 1.35-6.70; $P = 0.007$) were found to be significant risk factors (Table 5). Higher portal flow normalized by liver graft weight was associated with lower risk of liver graft loss (HR: 0.99; CI: 0.98-1.00 [per mL//min/100 g up]; $P = 0.044$). When combining PVT grade and portal flow, the Grade II or III PVT with low portal flow group showed significantly higher risk of graft loss, compared with the group of Grade I PVT with high portal flow (HR: 4.56; CI: 1.70-12.18; $P = 0.003$). On multivariate analysis, moderate to severe ascites (HR: 2.86; CI: 1.32-6.21; $P = 0.008$), Grade II or III PVT with high portal flow (HR: 2.85; CI: 1.11-7.30; $P = 0.03$) and Grade II or III PVT with low portal flow (HR: 4.33; CI: 1.55-12.07; $P = 0.005$ [ref. Grade I PVT with high portal flow]), high PVT grade (HR: 2.69; CI: 1.28-5.65; $P = 0.009$ [ref. Grade I PVT with high portal flow]) and bile leak (HR: 2.40; CI: 1.04-5.53; $P = 0.04$) were independent risk factors for liver graft loss. On performing survival analyses (Figure 4), low grade PVT group had significantly higher 5-year graft survival (85.0%) compared with high-grade PVT group (64.7%, $P = 0.02$). Similarly, high flow group had significantly higher 5-year graft survival (81.8%) compared with low-flow group (59.8%, $P = 0.009$). Upon analyzing a cohort of patients without known PVT, an association of portal flow rates with graft survival was not identified. Similarly, when analyzing the PVT and non-PVT cohorts together, no association of portal flow rate and graft survival was found. In the non-PVT population, 81.6% of patients achieved a target portal flow rate of 1000 mL/min or greater. In the PVT population, 75.4% of patients achieved a target portal flow rate of 1000 mL/min or greater. In those with low grade PVT, 79.5% and 69.8% in those with high-grade PVT were able to achieve a target portal flow rate of 1000 mL/min or greater, respectively. The differences in the ability of these groups to achieve 1000 mL/min target portal flow rate were not found to be statistically significant.

Risk Factor Analysis for Biliary Complications

Possible risk factors for biliary complications were investigated in patients who received duct-to-duct biliary reconstruction. Nine patients who received Roux-en-Y hepaticojejunostomy were excluded from this analysis. The grade II or III PVT group with low portal flow showed a significantly higher risk of biliary complications, compared with the group of grade I PVT with high portal flow (HR: 2.92; CI: 1.32-6.46; $P = 0.008$). Other recipient, donor, and operative factors were not associated with biliary complications. On multivariate analysis, grade II or III PVT with low portal flow remained an independent risk factor (HR: 2.88; CI: 1.28-6.45; $P = 0.01$). This analysis is summarized in Table 6. In a non-PVT cohort, we identified a biliary complication in 39.4% of patients. The rate of bile leak found in this group was 4.3%, and the rate of biliary anastomotic stricture was 36.4%. We were not able to identify a relationship between biliary complications and portal vein flow rates in the non-PVT population.

DISCUSSION

Our study identified an association of known high-grade PVT before transplant and low portal flow rates (<1000 mL/min) postreperfusion with lower rates of graft survival. We did not find that the flow rates per gram of liver mass altered our findings. We also noted a possible association of posttransplant PVT, the need for reoperation

TABLE 5.

Cox regression multivariate analysis of risk factors for liver graft loss

	Univariate analysis			Multivariate analysis		
Risk factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Hepatitis C	0.95	0.45-1.99	0.89			
Alcoholic-related liver disease	1.31	0.63-2.73	0.48			
Nonalcoholic Steatohepatitis	1.53	0.74-3.16	0.25			
Hepatocellular Carcinoma	0.70	0.29-1.70	0.43			
Recipient age <60 y	0.89	0.44-1.81	0.75			
Recipient sex, male	1.3	0.60-2.82	0.51			
Recipient race, non-AA	1.23	0.43-3.54	0.70			
Recipient BMI >30	1.25	0.62-2.52	0.52			
MELD >30	1.55	0.64-3.78	0.33			
Moderate to severe ascites	3.34	1.65-6.78	0.001	2.86	1.32-6.21	**0.008**
Donor age <60 y	0.58	0.26-1.30	0.19			
Donor sex, male	1.36	0.66-2.78	0.40			
Donor race, non-AA	1.34	0.55-3.27	0.51			
Donor liver macrovesicular steatosis (>10%)	3.62	1.47-8.90	0.005	2.52	0.96-6.63	0.06
Donor liver fibrosis	1.00	0.41-2.46	>0.9			
CIT >6 h	1.38	0.69-2.76	0.37			
WIT >40 min	0.61	0.30-1.25	0.18			
Portal flow (low <1000 mL/min)	2.27	1.11-4.64	**0.02**			
Portal flow (continuous, per 100 mL/min up)	0.98	0.91-1.05	0.51			
Portal flow/graft weight (continuous, per 100 mL/min/g up)	0.99	0.98-1.00	**0.044**			
Grade II or III portal vein thrombosis	2.65	1.30-5.43	**0.008**	2.69	1.28-5.65	**0.009**
PVT grade and portal flow						
Grade I with high flow (ref.)						
Grade I with low flow	1.54	0.33-7.29	0.59	1.66	0.35-7.93	0.52
Grade II or III with high flow	2.33	0.95-5.71	0.06	2.85	1.11-7.30	**0.03**
Grade II or III with low flow	4.56	1.70-12.18	**0.003**	4.33	1.55-12.07	**0.005**
Bile leak	3.00	1.35-6.70	**0.007**	2.40	1.04-5.53	**0.04**
Biliary stricture	1.38	0.68-2.81	0.37			
Piggyback technique	0.65	0.29-1.46	0.30			
Anticoagulation pre-Tx	0.52	0.18-1.48	0.22			
Anticoagulation after transplant	0.74	0.32-1.73	0.49			

AA, African American; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; HR, hazard ratio; MELD, model for end-stage liver disease; PVT, portal vein thrombosis; WIT, warm ischemia time.
Bold indicates statistically significant variables.

for biliary complications, and increased hospital length of stay with low portal flow rates. Additionally, we found that posttransplant biliary complications, in particular, biliary strictures, appear to be more common in patients with high-grade pretransplant PVT (Yerdel grade II and III). On multivariate analysis, we found that high-grade pretransplant PVT, low postreperfusion portal vein flow rates, and bile leak may be independent negative predictors for graft survival. Our study includes the largest known cohort of recipients from a single center to examine these variables and outcomes.

There is a known relationship of PVT with early graft loss and perioperative mortality.[1,13] A recent study by Draoua et al from Dallas was the first to show a relationship between portal flow rates after reperfusion and outcome in liver transplantation of recipients with known portal vein thrombosis pretransplant.[6] They found that a PV flow rate of <1300 mL/min was associated with worse graft survival and increased rates of biliary strictures. The graft survival was further decreased when the PV flow rates were <1000 mL/min, which is consistent with previously described literature.[7] Interestingly, they did not discover any significant relationship between the grade of pretransplant portal vein thrombosis and outcome. There was, however, a higher proportion of those patients with higher grade PVT in the low-flow group and there was a higher portion of patients with lower grade PVT in the high flow group. A meta-analysis by Zanetto et al[10] included 44 studies and examined the effects of PVT on mortality. They found a significant increase in 30-day mortality for those patients with Yerdel grade IV PVT (27%) when compared with patients with grade I–III PVT using pooled data from 10 studies. There were 3 studies that were pooled in this analysis to examine partial versus complete PVT, and these results showed a significantly higher 1-year mortality rate with those with complete (42%) as compared with partial (22%) PVT.

Many factors are involved in portal vein flow rate measurement values. A hyperdynamic patient can raise flow rates and to the contrary, a hypovolemic patient may exhibit lower flow rates; there may be extensive collateralization of vessels formed pretransplant by the recipient in their own

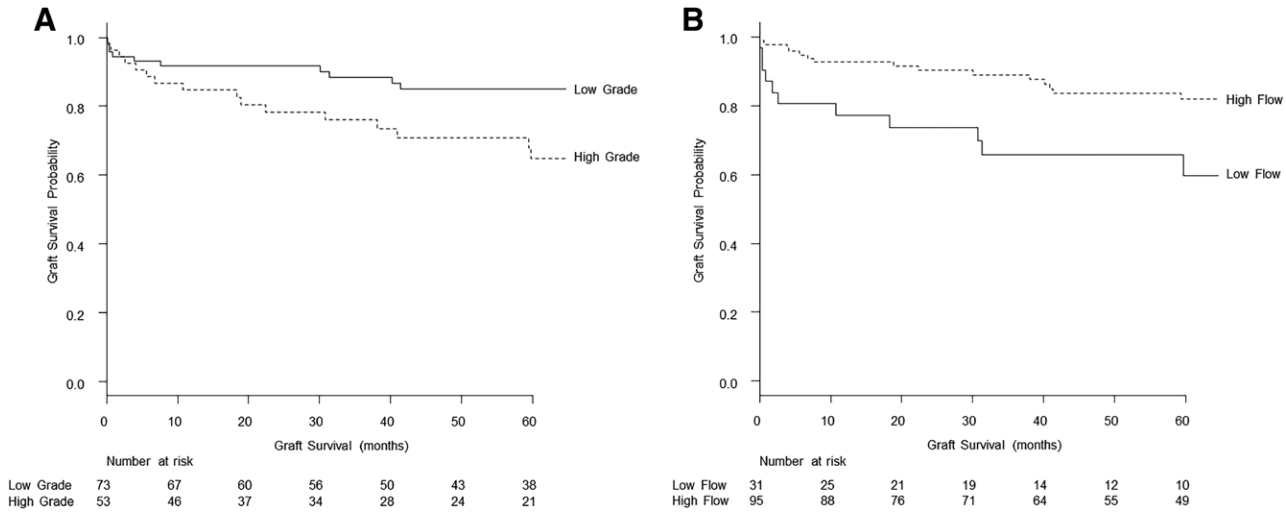

FIGURE 4. Five-y graft survival among (A), the high and low grade groups, and (B), the high- and low-flow groups.

TABLE 6.

Cox regression multivariate analysis of risk factors for biliary complications in patients with duct-to-duct biliary reconstruction

	Univariate analysis			Multivariate analysis		
Risk factors	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
PVT grade and portal flow						
Grade I with high flow (ref.)						
Grade I with low flow	1.67	0.61-4.56	0.32	1.61	0.58-4.47	0.36
Grade II or III with high flow	1.60	0.80-3.19	0.19	1.50	0.75-3.03	0.26
Grade II or III with low flow	2.92	1.32-6.46	**0.008**	2.88	1.28-6.45	**0.01**
Hepatic artery flow, per mL/min	0.72	0.35-1.51	0.39			
Hepatitis C	1.11	0.62-1.97	0.74			
Alcoholic-related liver disease	1.56	0.87-2.82	0.14			
Nonalcoholic steatohepatitis	1.09	0.59-1.99	0.79			
Hepatocellular carcinoma	1.20	0.64-2.24	0.57			
Recipient age 60 y or older	0.83	0.46-1.50	0.54			
MELD >30	1.05	0.70-1.57	0.82			
Moderate to severe ascites	1.13	0.59-2.15	0.71			
Donor age 60 y or older	0.72	0.51-1.02	0.06	1.49	0.72-3.12	0.29
Liver fibrosis	1.23	0.59-2.55	0.58			
Liver macrovesicular steatosis (>10%)	1.42	0.56-3.59	0.46			
CIT >6 h	0.92	0.69-1.23	0.56			
WIT >40 min	0.99	0.74-1.32	0.95			
Without biliary stent	1.09	0.39-3.04	0.88			
Amount autologous red blood cell transfusion						
0–4 units (ref.)						
5–9 units	1.25	0.60-2.63	0.55			
10 units or more	1.44	0.72-2.86	0.31			
Transplant y						
2007–2010 (ref.)						
2011–2013	0.73	0.37-1.45	0.37	0.79	0.39-1.58	0.5
2014–2017	0.47	0.21-1.03	0.06	0.49	0.22-1.10	0.08

CI, confidence interval; CIT, cold ischemia time; HR, hazard ratio; MELD, model for end-stage liver disease; PVT, portal vein thrombosis; WIT, warm ischemia time.
Bold indicates statistically significant variables.

efforts to divert flow around the diseased liver to the systemic circulation; there is always of course the possibility that the intraoperative thromboendovenectomy was not adequate and residual thrombus is preventing adequate flow. Regardless of the cause of low flow rates, based on prior studies it seems that postreperfusion portal flow rates of 1000–1300 mL/min or above are optimal in liver transplantation.[6-8] When faced with low portal flows following reperfusion, it is important to have an algorithm to address this problem. This may involve ligating retroperitoneal or

mesenteric collaterals or considering alternative sources of portal inflow, such as a superior mesenteric vein or the left renal vein. Draoua et al[6] have outlined the algorithm used at their center in their manuscript. There are reports of ligating coronary vein varices to increase the portal flow rates or using an alternative inflow from the left renal vein in the setting of significant splenorenal shunting.[14]

We do not have a stepwise algorithm for flow modulation at our institution, but rather, we prefer to evaluate each case individually. It is our practice to consider flow modulation when the postreperfusion portal flow rates are <1000 mL/min, while also taking into consideration graft volume and cardiac output. We will often ligate retroperitoneal collaterals if significant shunting is seen on preoperative imaging. We have also reported on left renal vein ligation in the setting of large splenorenal shunts to improve portal flow.[15] As a next step, we would consider alternative inflow sources; such as a superior mesenteric vein jump graft, the left renal vein or a coronary vein as inflow.[16] We have extremely rarely used arterialization or portocaval transposition in these patients. We find that a very important aspect to the approach to these patients is to perform a complete thrombectomy if possible, which can be challenging in patients with thrombus extending into the superior mesenteric vein. In these settings, we try to balance complete thrombus removal with patient safety with the understanding that complete thrombectomy is not always possible and in these cases, we typically try to augment flow with with the methods mentioned above. With the alternative scenario of high portal flow with low hepatic arterial flow following reperfusion, we typically prefer intraoperative splenic artery ligation or splenectomy or postoperative splenic artery embolization to modulate flow. Rarely have we used hemiportocaval shunt in this setting, but it is an option. Typically, this scenario is less common in recipients with preoperative PVT.

The relationship between pretransplant PVT grade and outcome was something that our group had interest in exploring further. It is known that PVT affects outcomes in liver transplantation, and it is also clear that low portal flow rates after reperfusion also affect outcomes. A logical assumption when dealing with portal vein thrombosis would be that the degree of PVT may affect portal flow rates, thus affecting outcomes in these cases. There are of course a number of reasons that higher grades of PVT may affect graft survival. First, these patients with extensive PVT are often more ill, with more portal hypertension, hepatic encephalopathy, and debilitation. Second, cases with portal hypertension, extensive collateralization, and cavernous change within the liver hilum, tend to have more blood loss and be significantly more challenging than the routine liver transplant. This may have an impact on the stability of the patient and prolong the hepatectomy and cold ischemia times. These patients also tend to have more significant ascites as well, which likely ties in the severity of the PVT with the findings of higher degree of ascites being associated with graft loss in the multivariate analysis. Additionally, a more extensive PVT may make the portal thromboendovenectomy more difficult and thereby limit flow rates in the portal vein, possibly due to residual thrombus within the portomesenteric system. This factor may explain our finding of higher incidence of postoperative PVT in patients in the low-flow group. With higher grade PVT, therefore, it may make sense that a complete thrombectomy is more difficult to achieve and therefore may impact the portal flow rates following reperfusion. It was this hypothesis that inspired us to examine our experience in greater detail to assess our data for a possible relationship between PVT grade and outcome. When performing this analysis, we found that there was a possible negative impact on survival in those patients with more extensive PVT and that this was likely independent of portal flow rates following reperfusion. It is possible that our findings differ slightly from prior studies due to a larger study population that was examined, as there was a clear trend seen by Draoua et al.[6]

We did find an association between high-grade PVT and incidence of biliary complications posttransplant, in particular, a higher rate of bile duct strictures. This has been shown in the past in other literature.[6] There are studies showing the importance of portal venous blood supply to the bile duct.[17,18] While it is well known that arterial blood supply to the bile duct is critical, the significance of the portal blood supply to the bile duct has perhaps been underestimated. Additionally, we did see a trend toward higher rates of bile leak and reoperation for biliary complications in patients with high-grade PVT. We did find in our multivariate analysis that bile leak may be an independent predictor for graft loss. This relationship may allow for a heightened sense of awareness regarding the possibility of biliary complications in these complex patients and earlier investigation and therapeutic intervention before any potential infection resulting from these problems.

In a separate multivariate analysis of risk factors for biliary complications, we found that grade II or III PVT with resulting low portal flow rates was an independent predictor of biliary complications when those patients undergoing roux-en-Y hepaticojejunostomy were excluded. This suggests that the grade of PVT in combination with the resulting portal flow rates following thrombectomy or endothrombovenectomy may impact the bile duct reconstruction in some way, perhaps related to difficult dissection within the hilum and devascularization of the extrahepatic bile duct. The true causes behind this relationship are not immediately clear, but may be related to recipient and operative factors mentioned above, although there was no significant relationship seen in the captured risk factors used in the univariate analysis. It is also possible that our findings are impacted by sample bias and small sample size as well. Often, cases with high-grade PVT and cavernous changes in the porta hepatis are quite challenging. It is possible that these occasionally prolonged and often difficult cases may contribute to the increased incidence of biliary complications seen in this group. The degree of difficulty of these cases may also account for the finding of an increased incidence of hepatic artery complications seen in the high-grade PVT group. One possible mechanism for the increased incidence of biliary complications may be the partial devascularization of the extrahepatic bile duct while ligating the collaterals within the porta hepatis during a challenging dissection. Interestingly, our biliary complication rates are higher than those reported in the literature. In the analysis of these complications, there does appear to be a trend towards lower complication rates in a more recent era. This may be due to the internal standardization of the biliary reconstruction technique within our group

during this time frame. Additionally, our group has a low threshold for recommending an ERCP and often times in these procedures a stent is placed, which is recorded as a biliary complication in our database.

There are some weaknesses of our study that should be stated. First, this study was performed in a single center via retrospective chart review and the inherent challenges and biases with regard to this type of report should be recognized.[19,20] Second, it should be noted that in the vast majority of cases, we performed a portal thromboendovenectomy, typically using the eversion technique. This is worth mentioning because in some liver transplant programs, especially in grade 3 thrombosis and complete occlusion of the proximal superior mesenteric vein, performing a jump graft is the preferred method for establishing portal inflow.[12,21] However, there are no compelling data to directly compare jump grafts to portal thromboendovenectomy in these particular cases. This concept does warrant consideration as evidenced by our findings that the grade of PVT may impact the portal flow rates following reperfusion. Finally, this is a small subset of all liver transplant recipients across the board and the problem facing those with any PVT, but especially those with higher grade PVT, is quite complex. Therefore, it may be difficult especially with a smaller sample size to elucidate the true meaning and source of the actual risk in these patients. In particular, in these data, it would have been ideal to analyze the effects of grade III PVT as a standalone variable. Unfortunately, the small number of patients with grade III PVT made this challenging and we elected to combine this group with grade II PVT recipients for the data analysis. Therefore, one should interpret these data with caution and taking this factor into consideration.

In conclusion, we believe the grade of preoperative PVT and the portal flow rates after reperfusion may have an impact on outcome in liver transplantation. Additionally, there appears to be a relationship with biliary complications, reoperation, hospital length of stay, and graft survival. The results of our study are significant in the sense that it allows the clinician to be aware of the increased risk of possible complications posttransplant based on the pretransplant PVT grade and the portal flow rates following reperfusion. Additionally, our interventional radiology colleagues are quickly mastering the ability to recanalize an occluded portal vein in conjunction with TIPS before transplant.[11] These patients may represent an opportunity to utilize this intervention more readily for those patients potentially carrying added risk. These patients appear to have excellent outcomes following these procedures. Additional studies are needed to further assess posttransplant complications and portal vein flow rates in these patients. Pretransplant PVT is clearly a complex problem and leads to difficulty intraoperatively, increased postoperative complications and ultimately, decreased graft survival. This is somewhat dependent on the severity of the pretransplant PVT and the ability to perform a complete surgical thromboendovenectomy to establish adequate flow. Our goal is to enable the transplant community to use this knowledge to improve outcomes for recipients based on these and other published data regarding this topic.

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