Portal vein thrombosis with cirrhosis: is it an indication for early liver transplantation?

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Introduction
Portal vein thrombosis (PVT) is an independent risk factor for perioperative mortality and graft loss but not long-term outcomes in patients with cirrhosis after LT.
The aim of this study was to assess the effect of timing of Living Donor Liver Transplantation (LDLT) on early results in patients with cirrhosis with PVT and decompensated liver (early vs. late). This was a retrospective study.
Patients and methods
This study included 24 patients with cirrhosis with PVT who underwent LDLT between January 2015 and June 2017 in Ain Shams University Hospitals. Fifteen patients were Child C and Model for End stage Liver Disease (MELD) more than 15 (group A) at time of transplantation and nine patients were transplanted early (Child B and MELD <15) owing to other indications, for example, Hepato Celluluar Carcinoma (HCC) (group B). Comparisons were done between both groups regarding operative data and perioperative mortality.
Results
Both groups were comparable in age, sex, etiology of liver disease, and presence of HCC. Operation in group B was easier than in group A, with statistically significant difference regarding operative time (7.4±1.2 vs. 10±2.1 h, *P*=0.002), need for blood transfusion (55.6 vs. 100%, *P*=0.005), and amount of blood transfusion [2 U (0–6) vs. 3 U (1–10) (*P*=0.048)]. Blood loss was only significantly lower in group B at 1900 ml (700–2600) versus 3000 (1000–6000) in group A (*P*=0.073). No statistically significant differences in ICU stay (*P*=0.570), hospital stay (*P*=0.432), and perioperative mortality (22.2 vs. 26.7%) were observed in group B and group A (*P*=0.562).
Conclusion
LDLT in patients with cirrhosis with PVT is technically more feasible when done early (Child B and MELD <15), but this is not associated with better outcome. PVT in patients with cirrhosis is not an indication for early transplantation.

Keywords:
indication, LDLT, portal vein thrombosis with cirrhosis

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Introduction

The prevalence of portal vein thrombosis (PVT) varies from 5 to 20% in patients with cirrhosis [1]. Notably, most patients have Child–Pugh classes A and B [2]. The development of PVT is associated with a decreased portal flow caused by splanchnic vasodilatation and the liver architectural derangement [3]. Furthermore, there is presence of systemic thrombotic risk factors and changes of the coagulation and anticoagulation factors in liver cirrhosis [4]. In the past, Liver Transplantation (LT) was forsaken for patients with PVT. Currently, however, PVT is no longer a contraindication owing to the development of various surgical and medical strategies. In a retrospective analysis of 21 673 LT recipients using the United Network for Organ Sharing registry, the presence of PVT was identified as an independent risk factor for post-transplant early mortality [5]. PVT is a risk factor for early mortality and graft loss but not long-term outcomes in patients undergoing LT [6]. The aim of this study was to compare the early results (90 days) of Living Donor Liver Transplantation (LDLT) in patients with PVT transplanted early (Child B and Model for End stage Liver Disease, MELD <15) and patients transplanted late (Child C and MELD >15).

Patients and methods

Patients

Between January 2015 and June 2017, 112 LDLT were done in Ain Shams Centre for Organ Transplantation. Twenty-four (21.4%) patients had PVT either diagnosed

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preoperatively by radiology or was an incidental intraoperative discovery. Of the 24 patients, 15 were transplanted for end-stage liver disease (Child C and MELD score >15) and nine patients were transplanted for other indications, mostly Hepato Celluluar Carcinoma (HCC) (Child B, or MELD <15). For patients with HCC, exclusion of malignant PVT depends on the relation of tumor to portal vein, lack of vascularization of the thrombus in arterial phase of triphasic computed tomography (CT), and absence of disruption of vessel wall or arteriovenous fistula. Ultrasound (US)-guided biopsy and pathological assessment is the most accurate form of examination but is invasive and carries a high risk of complication in such patients, so it is avoided in this study.

Preoperative workup

All patients undergoing transplant were subjected to the following:

(1) Full clinical assessment.
(2) Laboratory investigations: complete blood count, coagulation profile, liver function tests, kidney function tests, lipid profiles, diabetes profile, serum electrolytes, viral markers, tumor markers, and assessments for bilharzias, autoimmune disease, and metabolic liver disease. All patients with PVT diagnosed preoperatively were investigated for hypercoagulable state with protein C, protein S, antithrombin III, lupus anticoagulant, anticadiolipin IgG and IgM, factor V Leiden mutation, prothrombin G20210A mutation, JAK2V617F mutation, and MTHFR C677T gene mutation.
(3) Radiological investigations: triphasic pelviabdominal CT with portography, venography, and arteriography. Bone scan and CT chest were done for HCC staging.
(4) Endoscopy: upper gastrointestinal endoscopy and colonoscopy.
(5) Medical consultations: cardiology, chest, psychological, ENT, dental, gynecological consultations, and others according to patient condition.
(6) Calculation of MELD and Child score.

Only two cases of known patients with PVT had pretransplant trial of management of PVT with anticoagulant. Thrombolysin or transjugular intrahepatic portosystemic shunt was not done in any patients.

Intraoperative

All patients were treated with portal vein eversion thrombectomy with adequate flow and direct anastomosis of recipient portal vein with donor portal vein. There was no need for any other treatment options (jumping graft, renoportal with graft, portocaval hemitransposition, or portal vein arterialization).

At the end of the operation, if portal vein velocity by Doppler US was less than 50 (steel phenomenon), ligation of collateral was done (one patient) or exposure of left renal vein with clamping and re-measure PV velocity, if increased ligation of left renal vein at its termination in inferior vena cava were done (five patients).

Postoperative workup

(1) All patients with PVT started anticoagulation with enoxaparine therapeutic dose (1 mg/kg/12 h) as soon as the patient's condition allows (INR <2, platelet count $>30\times10^9$/l, and drain color to be serous). In patients with renal impairment, dose adjustment was done. In patients without increased systemic risk of hypercoagulable state, enoxparine was continued for 1 month. For patients with systemic risk, enoxparine was continued for 1 month and then shifted to oral anticoagulant (warfarin), and follow-up was done to maintain INR between 2 and 3 forever.

Early workup (first 3 months)

(1) Follow-up included laboratory investigation and Doppler US daily for 2 weeks, then twice weekly for 2 weeks, and then once weekly for 2 months.
(2) For patients with incidental discover of PVT intraoperatively, investigations for inherited or acquired risk of hypercoagulable state were done, including protein C, protein S, antithrombin III, lupus anticoagulant, anticadiolipin IgG and IgM, factor V Leiden mutation, prothrombin G20210A mutation, JAK2V617F mutation, and MTHFR C677T gene mutation.

Later (after 3 months)

(1) Follow-up laboratory investigation and US every 2–4 weeks were done according to patient's demands.
(2) Follow-up of tumor markers every 3 months and abdominal CT every 6 months was done for patients transplanted for HCC.

This study involves follow-up of 24 patients with PVT who underwent LDLT at Ain Shams University Hospitals. These patients were classified into two groups:

(1) Group A: patients with Child C and MELD up to 15.
(2) Group B: patients with Child B and MELD less than 15.

Comparison between the two groups was done using the following:

(1) Preoperative data.
    (a) Demographic data.
(2) Operative data.
    (a) Blood loss.
    (b) Cell saver and blood transfusion.
    (c) Operative time.
(3) Short-term results.
    (a) Perioperative mortality (90 days).

Statistical analysis

Data were collected, revised, coded, and entered to the statistical package for the social sciences (IBM SPSS) version 20. The comparisons between the two groups with qualitative data were done by using χ^2-test and/or Fisher exact test, which was used instead of χ^2-test when the expected count in any cell was found less than 5.

The comparisons between two independent groups regarding quantitative data with parametric distribution were done by using independent *t*-test.

The comparison between two independent groups regarding quantitative data with nonparametric distribution was done by using Mann–Whitney *U*-test.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *P*-value was considered significant as the following:

(1) $P>0.05$: nonsignificant.
(2) $P<0.05$: significant.
(3) $P<0.01$: highly significant.

Results

This study include patients transplanted between January 2015 and June 2017 with PVT (24/112 patients, 21.4%). PVT was diagnosed either preoperatively by radiology or was an incidental discovery intraoperatively. Group A included 15 patients of 24 who were transplanted for end-stage liver disease (Child C and MELD score >15) and group B included nine patients transplanted for other indication, for example, HCC and refractory ascites but were still early regarding Child and MELD (Child B, or MELD <15).

Group A included 12 (80%) male and three (20%) female patients in comparison with nine (100%) male with no female patients in group B, which was statistically not significant ($P=0.151$). The median age in group A was 55 years (ranging between 35 and 62 years) and 59 years (ranging between 34 and 68 years) in group B (statistically not significant $P=0.446$).There was no statistical significant difference regarding etiology of liver disease. All patients in group A were transplanted owing to HCV, whereas seven (77.8%) patients of nine in group B were because of HCV, one (11.1%) patient was owing to autoimmune hepatitis, and one (11.1%) patient was owing to cryptogenic cirrhosis (statistically not significant, $P=0.162$). Overall, 40% of the patients in group A and 33% in group B had HCC at the time of transplantation (statistically not significant, $P=0.744$) (Table1).

Comparison was done between both groups regarding operative data, and there was a statistically significant difference in operative time and blood transfusion (incidence and amount). Blood loss was lower in group B at 1900 ml (range between 700 and 2600) than in group A at 3000 ml (range between 1000 and 6000), but the difference tended to be significant but not statistically significant ($P=0.073$). Blood transfusion happened in all patients (100%) in group A but only in five (55.6%) patients in group B (statistically high significant, $P=0.005$), and also the number of unit of blood was higher (3 U, ranging between 1 and 10 U) in group A than in group B (2 U, ranging between 0 and 6 U) (statistically significant, $P=0.048$). Cell salvage (autologous blood transfusion) was done in all patients of both groups except patients transplanted for HCC (40% in group A and 33.3% in group B) (statistically not significant, $P=0.744$). The median amount of blood retransfused was 800 ml (0.0–3000 ml) in group A versus 700 ml

Table 1 Comparison between demographic data of the patients

	Group A (Child C, MELD >15) [*n* (%)]	Group B (Child B, MELD <15) [*n* (%)]	*P*
Age	55 (35–62)	59 (34–68)	0.446
Sex			
Female	3 (20.0)	0 (0.0)	0.151
Male	12 (80.0)	9 (100.0)	
Etiology of cirrhosis			
HCV	15 (100.0)	7 (77.8)	0.162
AIH	0 (0.0)	1 (11.1)	
Cryptogenic	0 (0.0)	1 (11.1)	
HCC			
Negative	9 (60.0)	6 (66.7)	0.744
Positive	6 (40.0)	3 (33.3)	

AIH, auto immune hepatitis. This table shows no statistically significant difference between the groups regarding age, sex, etiology of liver disease, and HCC incidence.

(0.0–1250 ml) in group B (statistically not significant, *P*=0.411). The mean operative time was 10±2.1 h in group A in comparison with 7.4±1.2 h in group B (statistically highly significant, *P*=0.002) (Table 2).

Postoperative data of both groups regarding ICU and hospital stay were nearly similar. Mean ICU stay was 6 days in both group A (ranging between 5 and 12 days) and group B (ranging between 4 and 8 days) (*P*=0.570). The median hospital stay in group A was 28 days (ranging between 21 and 46 days), which was slightly higher than group B at 24 days (ranging between 20 and 38 days) (*P*=0.432) (Table 2).

There was no significant difference in early postoperative mortality between both groups (*P*=0.562). Four patients of 15 (26.7%) died early in group A. Two patients died owing to portal vein rethrombosis. One of them showed very early occlusion, on day 2. Patient explored with thrombectomy and good intraoperative Doppler followed by rethrombosis within 3 days. The other presented with sudden deterioration with marked elevation of liver enzymes on day 14 postoperatively. The patient needed vasopressor and mechanical ventilation, with Doppler showing complete occlusion of portal vein and inhomogenous graft. One patient died of hepatic artery (HA) thrombosis, and last one died of uncontrolled sepsis (pneumonia with bilateral patches). In group B, two patients of nine (22.2%) died of portal vein rethrombosis and HA thrombosis. The patient with portal vein rethrombosis was explored with thrombectomy and collateral ligation, but had unsatisfactory weak portal flow. The patient with HA thrombosis was explored twice with reconstruction of HA anastmosis with re-occlusion within less than 12 h between transplantation procedure and each exploration (Table 2).

Discussion

The prevalence of PVT in patients with cirrhosis ranges from 5 to 20%. This heterogeneity is owing to the different diagnostic modalities used in different studies (autopsy, surgery, and US) and the exclusion or inclusion of HCC. The severity of liver dysfunction might influence the incidence of PVT in liver cirrhosis [1]. In a prospective study by Zocco *et al.* [3], 49% (36/73) of patients with PVT had MELD score of more than 13.

In our study, incidence of PVT was 21.4% (24/112 patients). Nine (37.5%) patients were Child B and MELD less than 15 and 15 (62.5%) patients were Child C and MELD more than 15.

Song *et al.* [7] showed that the packed red blood cell transfusion amount of PVT group was not different from that of no-PVT group, unlike most publications where the transfusion requirement and operation time was significantly greater in the PVT group compared with no-PVT group [8–10].

In our study, the procedure technically was more easier in group B with low Child and MELD in comparison with group A with higher Child and MELD score with less operative time (7.4±1.2 vs. 10±2.1 h, *P*=0.002), need for blood transfusion (55.6 vs. 100%, *P*=0.005),

Table 2 Intraoperative and postoperative data of both groups

	Group A (Child C, MELD >15) [*n* (%)]	Group B (Child B, MELD <15) [*n* (%)]	*P*
Blood loss [median (range)] (ml)	3000 (1000–6000)	1900 (700–2600)	0.073[a]
Blood transfusion			
Yes	15 (100)	5 (55.6)	0.005[b]
No	0 (0)	4 (44.4)	
Blood transfusion (U)	3 (1–10)	2 (0.0–6)	0.048[a]
Cell salvage			
Yes	9 (60)	6 (66.7)	0.744[b]
No	6 (40)	3 (33.3)	
Cell salvage [median (range)] (ml)	800 (0.0–3000)	700 (0.0–1250)	0.411[a]
Operative time (h)	10±2.1	7.4±1.2	0.002[a]
ICU stay (days)	6 (5–12)	6 (4–8)	0.770[a]
Hospital stay (days)	28 (21–46)	24 (20–38)	0.432[a]
Perioperative mortality (90 days)			
Living	11 (73.3)	7 (77.8)	0.562[b]
Dead	4 (26.7)	2 (22.2)	
Cause of death			
HAT	1 (25)	1 (50)	0.431
PVT	2 (50)	1 (50)	
Sepsis	1 (25)	0 (0)	

HAT, hepatic artery thrombosis; PVT, portal vein thrombosis. [a]Mann–Whitney U-test. [b]Fisher's exact test.

and amount of blood transfusion [2 U (0–6) in group B vs. 3 U (1–10) in group A] (P=0.048).

PVT was associated with worse outcomes after LT, especially with high Yerdel grade (III and IV) in which thrombosis extended below the splenic and superior mesenteric veins confluence [11]. However, some single-center studies have described no effect on survival, particularly if physiological portal vein reconstruction is achieved [12–14]. Despite the debate about LT results in patients with PVT, LT carries a favorable survival benefit in these patients [15].

In our study, perioperative mortality in all patients was 25% (six patients out of 24 patients) which is definitely high. Comparison between the effects of different grades on survival was very important but was not applicable owing to the small sample size. Unfortunately, better general condition of patients when transplanted early (Child B, MELD <15) was not associated with better outcome. Perioperative mortality was nearly similar (26.7% in group A vs. 22.2% in group B, P=0.562).

In LDLT for patients with PVT, not only PV-related complications but also HA-related complications are prone to develop because HA injury can often occur during dissection of hepatic hilum when pericholedochal varix or cavernous transformation of hepatic hilum is present, and alternative available arterial inflow vessels or interposing fresh cadaveric iliac artery that have small branches corresponding to graft HA are usually absent. Particularly in patients with extensive PVT, including grades 3 and 4, we have to perform meticulous dissection to reduce HA injury such as direct arterial wall injury or intimal dissection from mural hematoma propagation [16].

In our study, two patients (33% of mortality) died owing to HA problems, with one in each group: One of them may be related to technical problem, but the other was related to hypercoagulable state with recurrent rapid rethrombosis even after reconstruction twice.

Conclusion

Living donor liver transplantation in patients with cirrhosis with PVT is technically more feasible when done early (Child B and MELD <15), but this is not associated with better outcome. PVT is not an indication for early transplantation.

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Conflicts of interest

There are no conflicts of interest.

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