Retrospective Cohort Study

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Portal vein thrombosis and liver transplantation: management, matching, and outcomes. A retrospective multicenter cohort study

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Background and aims: Besides the increased risk of perioperative morbidity, graft failure, and mortality, the majority of PVT are diagnosed at liver transplantation (LT). Improving preoperative management and patient selection may lead to better short-term and long-term outcomes and reduce the risk of a futile LT. The authors aimed to identify predictors of adverse outcomes after LT in patients with nonmalignant portal vein thrombosis (PVT) and improve donor to recipient matching by analyzing the results of the Italian cohort of LT recipients.

Methods: Adult patients who underwent LT in Italy between January 2000 and February 2020 diagnosed with PVT pre-LT or at time of LT were considered eligible for inclusion. Based on a survey encompassing all 26 surgeons participating in the study, a binary composite outcome was defined. Patients were classified as having the composite event if at least one of these conditions occurred: operative time more than 600 min, estimated blood loss greater than 5000 ml, more than 20 ICU days, 90 days mortality, 90 days retransplant.

Results: Seven hundred fourteen patients were screened and 698 met the inclusion criteria. The analysis reports the results of 568 patients that fulfilled the criteria to enter the composite outcome analysis. Overall, 156 patients (27.5%) developed the composite outcome. PVT stage 3/4 at transplant and need for any surgical correction of PVT are independent predictors of the composite outcome occurrence. When stratified by PVT grade, overall survival at 1-year ranges from 89.0% with PVT grade 0/1 to 67.4% in patients with PVT grade 3/4 at LT ($P < 0.001$). Nevertheless, patients with severe PVT can improve their survival when identified risk factors are not present.

Conclusions: Potential LT candidates affected by PVT have a benefit from LT that should be adequately balanced on liver function and type of inflow reconstruction needed to mitigate the incidence of adverse events. Nonetheless, the absence of specific risk factors may improve the outcomes even in patients with PVT grades 3–4.

Keywords: donor selection, LT, nonmalignant PVT, organ allocation, physiological reconstruction, portal hypertension

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Introduction

Portal vein thrombosis (PVT) is a multifactorial condition that arises both in cirrhotic and noncirrhotic patients, that poses critical challenges in the intraoperative management to restore an adequate inflow toward the liver, with significant impact on liver transplant (LT) outcomes. Male sex, BMI >40 Kg/m^2, diabetes mellitus, metabolic syndrome, nonalcoholic steatohepatitis, autoimmune hepatitis, hepatocellular carcinoma (HCC), and transjugular intrahepatic porto-systemic shunt (TIPS) have been previously identified as predictors of pretransplant PVT[1]. Prevalence of PVT in the overall cohort of cirrhotic patients at evaluation or at the time of transplantation ranges from 5 to 26%, with the majority of patients presenting with a partial thrombosis[2]. Patients presenting with PVT are at higher risk of 30 days mortality after LT compared to cirrhotic patients without a PVT, and in particular patients with a complete PVT show lower 1-year survival rates compared to those with partial thrombosis[3]. Moreover, patients with pretransplant PVT are at higher risk of graft failure, and PVT recurrence, especially when a grade 3 or 4 is present[4]. Mortality has been reported to be as high as 17.5% in pretransplant patients with complete PVT[1]. Intraoperative management of the PVT varies according to PVT extension and require accurate preoperative planning in case of diffuse PVT[5]. Nevertheless, several series reported that up to 50% of PVT are diagnosed at the time of LT, with potential harmful consequences on patient safety[2,6]. The modern approach to PVT is based on moving the target of reconstruction at LT toward a physiological inflow rather than a strictly anatomical conception[7–9]. The definition of a physiological inflow implies that the splanchnic venous blood is directed to the liver graft, including all those nonanatomical reconstructions obtained using porto-systemic shunts. This kind of reconstruction allows to overcome pre-LT portal hypertension (PHT), which on the contrary persists after LT whenever a nonphysiological reconstruction is performed[8]. Furthermore, tackling such a distorted portal circulation, presence, site, and entity of hepatofugal collaterals have to be considered key factors aiming at restoring a post-transplant 'physiologic' splanchnic hydrodynamics. This also explains why the complexity of reconstructions correlates with LT outcomes more than traditional PVT classifications in some series[10]. Despite the relevant impact on post-LT morbidity, predictors of outcomes capable to improve organ allocation and timing of LT in patients with PVT are yet to be defined. We decided to perform a multicenter study to obtain a snapshot of the results achieved so far in the management of patients with PVT undergoing LT on a nationwide basis, and to identify preoperative predictors of short-term outcomes in order to improve organ allocation and patients' prioritization policies on the waiting list.

Methods

A consensus meeting involving surgeons and hepatologists has been held annually for the last 5 years during the annual national congress of the Italian Society of Organ Transplantation (SITO) in the context of the 'SITO continuous consensus conference platform', to update allocation policies and discuss implementations of the Italian LT network. This was needed due to recent government decree that promoted the major national scientific societies to promulgate guidelines on their specific clinical practice to increase the quality of healthcare across the country and limit the spread of medico-legal disputes. In this context, a national study on the role of PVT was launched by SITO to evaluate the impact of this condition in the Italian LT activity.

HIGHLIGHTS

- Liver transplant in the setting of portal vein thrombosis can be performed without falling in the futility area with 5 years overall survival that exceeds 70% globally.
- Patients are at statistically significant risk to develop the composite outcome after liver transplant when presenting with a portal vein thrombosis stage 3/4 and a direct anastomosis is not feasible.
- Renoportal anastomosis and porto-caval hemi-transposition are the only two reconstruction strategies associated with an increased incidence of 90 days mortality.

Patient selection

Adult patients (age >18) who underwent LT in Italy between January 2000 and February 2020 diagnosed with nonmalignant PVT pre-LT or at time of LT were considered eligible for inclusion in this study. Pediatric LT and combined transplants were excluded. Patients without PVT at LT were considered eligible to enter the study only if an effective downstaging in the interval between listing and LT was demonstrated (anticoagulation therapy or TIPS placement). PVT stage was assessed according to the Yerdel classification that divides PVT in four grades: grade 1 is a minimally or partially thrombosed portal vein (PV), in which the thrombus is mild or, at the most, confined to $<50\%$ of the vessel lumen with or without minimal extension into the superior mesenteric vein (SMV); grade 2 is a $>50\%$ occlusion of the PV, including total occlusions, with or without minimal extension into the SMV; grade 3 is a complete thrombosis of both PV and proximal SMV (Distal SMV is open); grade 4 is a complete thrombosis of the PV and proximal as well as distal SMV[11].

Data collection

The study was performed according to the Strengthening The Reporting Of Cohort Studies in Surgery (STROCSS) guidelines[12] (Supplemental Digital Content 1, http://links.lww.com/JS9/C10) and all institutions obtained their respective approvals according to their local centers requirements. Center volume was calculated on the mean case load of LT during the last decade, and was stratified in three groups, namely <40, 40–80, and >80 cases/year. Preoperative characteristics included sex, age at transplant, liver disease, general comorbidities, presence of HCC, BMI, Child-Pugh (CPT) and signs of PHT (varices, splenomegaly, presence of splenorenal shunts). Grade of PVT at listing and at LT were compared to evaluate the efficacy of PVT downstaging in patients that underwent anticoagulation therapy or TIPS placement. Intraoperative data including operative time (OT), estimated blood loss (EBL), donor age, and type. Reconstruction strategies included thrombectomy, anatomic (SMV to PV) jump graft or conduit, extra-anatomic (mesenteric varices to PV) physiological direct anastomosis, extra-anatomic jump or conduit, renoportal anastomosis, porto-caval hemi-transposition, and small intestine transplant. Postoperative course data included in-hospital stay, ICU days, morbidity

according to Clavien–Dindo, 90 days mortality, postoperative bleeding, sepsis and rethrombosis, retransplantation and, finally, patient and graft survival. Patients receiving liver grafts from donors after cardiac-death (DCD) and living donors (LD) were excluded from the analysis.

Study outcome and statistical analysis

Composite endpoints are often used to assess complex outcomes in surgical studies, combining several variables into a single measure for a more comprehensive evaluation of the impact of surgical interventions on patient health.

To develop such an instrument, we conducted a survey among all the 26 surgeons actively involved in the study, to establish a consensus on its definition and structure.

The survey led to the formulation of a binary composite endpoint, encompassing five perioperative and postoperative key variables: OT, blood loss, ICU stay, mortality and retransplant.

Patients were categorized as having the composite event if they met any of the following conditions: OT exceeding 600 min, EBL over 5000 ml, more than 20 days in ICU, mortality within 90 days, or a retransplant within 90 days.

The consensus for these variables varied, with a minimum agreement of 88% for the ICU stay cut-off, and a maximum consensus of 100% for the EBL cut-off.

Univariable logistic regression models were performed to evaluate the association between patients and surgical characteristics with the composite outcome. The variables with *P*-value smaller than 0.10 at univariable analysis were included in a multivariable logistic model.

The overall survival (OS) was also considered an endpoint of primary interest. OS function was estimated using the Kaplan–Meier method. The log-rank test was used to assess differences among groups.

Kruskal–Wallis test for continuous variables and Fisher's exact test for categorical variables were performed to assess differences in the distribution of perioperative and postoperative outcomes among the levels of PVT stage at transplant.

χ^2 test, Fisher's exact test, and Cochran-Armitage trend test were used to evaluate the association between 90 days mortality and selected variables.

A *P*-value <0.05 was considered statistically significant in all the analyses.

All the analyses were performed with the statistical software SAS 9.4 (SAS Institute).

Results

Records of 714 patients were received from 14 out of 22 Italian LT Centers that voluntarily joined the study: University of Modena and Reggio Emilia, University of Padua, University of Turin, Papa Giovanni XXIII Hospital of Bergamo, Niguarda Hospital of Milan, ISMETT of Palermo, University of Marche, University of Verona, University of Milan, San Camillo-Forlanini General Hospital of Rome, University of Udine, Sapienza University of Rome, University of Rome Tor Vergata and Fondazione IRCCS Istituto Nazionale Tumori of Milan. After initial screening, 16 cases did not meet the inclusion criteria reported above and therefore were excluded from the analysis. In particular, 13 patients did not have any PVT at listing nor at LT, and 3 were lost at follow-up. Therefore, 698 patients were included in the study. After initial review, 114 patients were missing data to enter the composite outcome analysis, and 16 were DCD or LD grafts, so 568 patients from twelve centers were ultimately included in the analysis (Fig. 1).

Population characteristics

Median age was 57 (IQR 51–62), with a prevalence of male patients (73.1%), and a median BMI of 25.1 Kg/m^2 (IQR 23.2–27.4). Liver failure resulted the most frequent independent leading cause of transplant (48.1%), followed by HCC in 37.3% of cases, consistently with the 81.3% rate of CPT B–C patients. Almost half the population (44%) received anticoagulation and 20.8% underwent TIPS placement. However, only 27.9% of patients with PVT had a successful downstaging of the thrombosis before LT (Table 1) (Supplementary Table 1, Supplemental Digital Content 2, http://links.lww.com/JS9/C11).

Surgical outcomes

The surgical approaches adopted are reported at the bottom of Table 1. In 62.7% of cases a thrombectomy was required to restore an adequate inflow to the liver, while 3.5% had an anatomic reconstruction with the interposition of a jump graft. Conversely, 1.9% of cases required an extra-anatomic reconstruction, whether with the interposition of a conduit or not. Finally, eight patients (1.4%) had a reconstruction with a reno-portal anastomosis (RPA), all in presence of a splenorenal shunt. Lastly, 17 cases (3%) of purely nonphysiological reconstructions were performed with a porto-caval hemi-transposition (PCHT). This complex procedure was chosen as an upfront strategy in 13 cases. In four cases it was performed at the end of LT due to the insufficient portal flow after thrombectomy. Of note, in two cases it was constructed as a rescue for acute rethrombosis, respectively, overnight after LT in one case and on postoperative day 5 (POD) after thrombectomy and direct anastomosis in the second case. No cases of small intestine transplant were reported in this series. Finally, 180 patients (31.7%) underwent direct PV resection and reconstruction.

Table 2 summarizes short-term and long-term outcomes. Median OT was 407 min (IQR 340–480), with median EBL of 1400 ml (IQR 560–2500). Median ICU stay was 4 days (IQR 2–6), with median overall hospital stay of 18 days (IQR 12–30) and incidence of morbidity > 3a of 24.6%. Mortality at 30 days was 7.9% and reached 13.4% at 90 days after LT. Rethrombosis occurred in 7.9% of cases, with a re-LT rate at 90 days of 4.4%.

Supplementary Table 2 (Supplemental Digital Content 2, http://links.lww.com/JS9/C11) summarizes the major outcomes by PVT stage according to Yerdel classification at LT (grade 0/1, grade 2, grade 3/4).

Composite outcome

Distribution of each of the five endpoints making up the composite outcome plus the composite outcome itself, according to PVT stage at LT, are depicted in Figure 2. Overall, 156 patients (27.5%) developed the composite outcome: 59 (21.5%), 62 (29.4%), and 35 (42.2%) among patients with G0/1, G2 and G3/4 PVT stage at LT, respectively. At the univariable analysis several factors were significantly correlated with the prevalence of the composite outcome (Table 3). In particular Center volume > 80 (vs. <40:

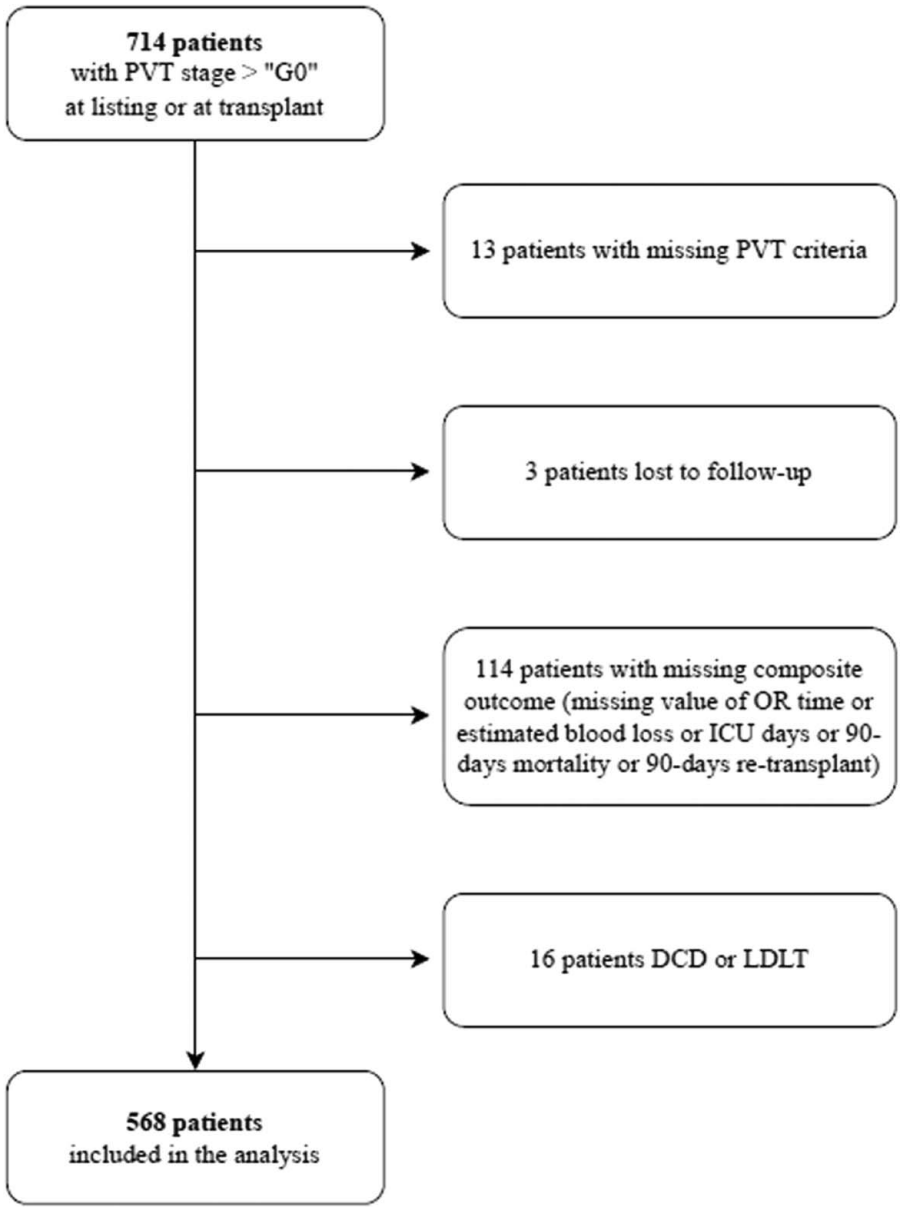

Figure 1. Study flow-chart.

OR = 0.53, 95% CI: 0.33–0.88, $P = 0.013$), variations of MELD score of 5 points (OR = 1.3, 95% CI: 1.15–1.48, $P < 0.001$), CPT stage C (vs. A: OR = 2.66, 95% CI: 1.53–4.65, $P < 0.001$), liver failure as a leading cause of transplant (vs. HCC: OR = 1.70, 95% CI: 1.13–2.56, $P = 0.012$), PVT grade 2 at transplant (vs. G0/1: OR = 1.52, 95% CI: 1.00–2.29, $P = 0.048$), PVT grade 3 or 4 at transplant (vs. G0/1: OR = 2.66, 95% CI: 1.58–4.48, $P < 0.001$), use of PCHT as a reconstruction strategy (OR = 6.78, 95% CI: 2.35–19.6, $P < 0.001$), and the need for any portal flow reconstruction strategy different from direct portal anastomosis (OR = 0.51, 95% CI: 0.33–0.78, $P = 0.002$) showed a statistically significant correlation. At multivariable analysis PVT stage 3/4 at transplant and need for a surgical correction of PVT were confirmed as independently associated to the composite outcome.

Survival

Figure 3 shows OS and its stratification according to PVT stage at transplant. 1-year OS is 82.9% (95% CI: 79.5–85.8%) and reached 72.0% (95% CI: 67.9–75.6%) at 5 years (OS at 2 and 3 years are 79.4 and 75.5%, respectively). When stratified by PVT grade, OS at 1-year ranged from 89.0% (95% CI: 84.7–92.2%) with PVT grade 0/1 to 67.4% (95% CI: 56.2–76.4%) in patients with PVT grade 3/4 at LT (OS at 1, 2, 3, and 5 years are for G0/1 89.0%, 86.0%, 82.6%, 77.3%; for G2 81.0%, 78.0%, 74.2%, 72.3%; for G3/4 67.4%, 61.0%, 55.1%, 53.0%, respectively, $P < 0.001$). Notably, 90 days mortality had a general incidence of 13.4% and resulted to be significantly associated to PVT stage at LT (90 days mortality was 8.0, 13.7, and 30.1% among patients with G0/1, G2 and G3/4 PVT stage at LT, respectively; $P < 0.001$) (Supplementary Table 2,

Table 1

Demographic, clinical, and surgical characteristics ($N = 568$).

Variable	Level	Overall ($N = 568$)
Center volume, *N* (%)	< 40 cases (5 centers)	90 (15.8)
	40–80 cases (3 centers)	105 (18.5)
	> 80 cases (4 centers)	373 (65.7)
Year of transplant, *N* (%)	2000–2010	137 (24.1)
	2011–2020	431 (75.9)
Age, median (Q1–Q3)		57 (51–62)
Sex, *N* (%)	Female	153 (26.9)
	Male	415 (73.1)
Presence of HCC, *N* (%)		253 (44.5)
MELD, median (Q1–Q3)		15 (12–20)
Child, *N* (%)	Child A	106 (18.7)
	Child B	268 (47.2)
	Child C	194 (34.2)
BMI, median (Q1–Q3)		25.1 (23.2–27.4)
Presence of shunts, *N* (%)		119 (21.0)
Leading cause of transplant, *N* (%)	PVT	11 (1.9)
	HCC	212 (37.3)
	Liver failure	273 (48.1)
	Other	72 (12.7)
PVT stage at listing, *N* (%)[a]	G0	17 (3.6)
	G1	193 (40.5)
	G2	180 (37.8)
	G3	70 (14.7)
	G4	16 (3.4)
Days between imaging and transplant, median (Q1–Q3)[b]		155 (49–404)
Days between listing and transplant, median (Q1–Q3)[c]		112 (35–290)
Treated with anticoagulation therapy, *N* (%)		250 (44.0)
TIPS performed, *N* (%)		118 (20.8)
PVT stage at transplant, *N* (%)	G0	56 (9.9)
	G1	218 (38.4)
	G2	211 (37.1)
	G3	64 (11.3)
	G4	19 (3.3)
PVT downstaged at transplant, *N* (%)[a]		133 (27.9)
Donor age, median (Q1–Q3)		62 (50–73)
Thrombectomy, *N* (%)		356 (62.7)
Extra-anatomic direct anastomosis, *N* (%)		11 (1.9)
Extra-anatomic jump, *N* (%)		2 (0.4)
Anatomic jump, *N* (%)		20 (3.5)
Renoportal anastomosis, *N* (%)		8 (1.4)
Hemicaval transposition, *N* (%)		17 (3.0)
Direct anastomosis, *N* (%)		180 (31.7)

[a]Missing 92.
[b]Missing 52.
[c]Missing 60.

Supplemental Digital Content 2, http://links.lww.com/JS9/C11). Ninety-days mortality was also associated to any portal flow reconstruction strategy different from direct portal anastomosis ($P = 0.008$), RPA ($P = 0.014$), cavo-portal transposition ($P < 0.001$), and center volume ($P < 0.001$), while successful downstaging and other technical solutions for portal inflow reconstruction had no significant correlations (Supplementary Table 3, Supplemental Digital Content 2, http://links.lww.com/JS9/C11). In panel C (including patients with PVT stage at transplant G0/1/2) and D (including patients with G3/4) of Figure 3, OS is stratified according to the presence of at least one of the risk factors identified as significantly associated with composite outcome at univariable analysis. Here, we can appreciate that the presence of at least one of these risk factors has the effect to reduce the expected OS even in patients with a more favorable PVT grade (0/1/2) in a statistically significant fashion ($P = 0.022$). Consistently, it seems that patients could improve their survival despite a more severe PVT if these factors are not present (although this result is not statistically significant, with $P = 0.067$).

Table 2

Outcome variables ($N = 568$).

Variable	Level	Overall ($N = 568$)
OR time (min), median (Q1–Q3)		407 (340–480)
OR time (min), *N* (%)	≤ 600	527 (92.8)
	> 600	41 (7.2)
Estimated blood loss (ml), median (Q1–Q3)		1400 (560–2500)
Estimated blood loss (ml), *N* (%)	≤ 5000	514 (90.5)
	> 5000	54 (9.5)
ICU stay (days), median (Q1–Q3)		4 (2–6)
ICU stay (days), *N* (%)	≤ 20	524 (92.3)
	> 20	44 (7.7)
90 days mortality, *N* (%)		76 (13.4)
90 days re-transplant, *N* (%)		25 (4.4)
Composite outcome observed, N (%)[a]		156 (27.5)

[a]'Observed' if: OR time > 600 min or estimated blood loss > 5000 ml or ICU days > 20 or 90 days mortality = Yes or 90 days re-transplant = Yes.

Discussion

The present study shows that LT in the setting of PVT can be performed without falling in the futility area with 5 years OS that exceeds 70% globally, and that remains above 50% even in the group of PVT stage 3/4. Therefore, those patients should not be denied the opportunity to receive a LT, although some specific risk factors for adverse outcomes can be highlighted. Interestingly, we identified through a consensus among the transplant centers the variables to build a composite outcome: OR time longer than 10 h, more than 5 l of blood loss, the event of

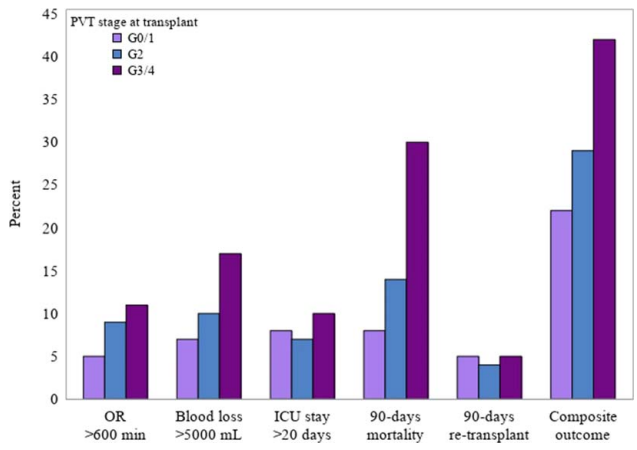

Figure 2. Frequency distribution of outcomes by PVT stage at transplant.

Table 3

Results from univariable and multivariable logistic regression models to evaluate the association between patients and surgical characteristics and composite outcome (*N* = 568).

			Univariable analysis			Multivariable analysis		
Variable	**Level**	**Composite outcome / Tot (%)**	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Overall	–	**156/568 (27)**	—	—	—			
Center volume	< 40 cases	32/90 (36)	Ref.	—	—	Ref.	—	—
	40–80 cases	39/105 (37)	1.07	0.60–1.92	0.82	1.59	0.84–3.01	0.16
	> 80 cases	85/373 (23)	0.53	0.33–0.88	**0.013**	0.61	0.36–1.03	0.062
Year of transplant	2000–2010	38/137 (28)	Ref.	—	—			
	2011–2020	118/431 (27)	0.98	0.64–1.51	0.93			
Age	+ 10 years		1.01	0.82–1.26	0.90			
MELD	+ 5		1.30	1.15–1.48	< **0.001**	1.08	0.92–1.28	0.35
Child	Child A	21/106 (20)	Ref.	—	—	Ref.	—	—
	Child B	58/268 (22)	1.12	0.64–1.96	0.70	0.85	0.46–1.57	0.61
	Child C	77/194 (40)	2.66	1.53–4.65	< **0.001**	1.64	0.83–3.24	0.15
Shunts preformed	No	121/449 (27)	Ref.	—	—			
	Yes	35/119 (29)	1.13	0.72–1.76	0.59			
Leading cause of transplant	HCC	47/212 (22)	Ref.	—	—	Ref.	—	—
	PVT	4/11 (36)	2.01	0.56–7.15	0.28	1.52	0.40–5.84	0.54
	Liver failure	89/273 (33)	1.70	1.13–2.56	**0.012**	1.60	0.96–2.66	0.069
	Other	16/72 (22)	1.00	0.53–1.91	0.99	0.86	0.43–1.71	0.66
PVT stage at listing	G0/1	47/210 (22)	Ref.	—	—			
	G2	54/180 (30)	1.49	0.94–2.34	0.088			
	G3/4	27/86 (31)	1.59	0.91–2.78	0.11			
	Missing	28/92						
Anticoagulation therapy	No	96/318 (30)	Ref.	—	—			
	Yes	60/250 (24)	0.73	0.50–1.06	0.10			
TIPS performed	No	125/450 (28)	Ref.	—	—			
	Yes	31/118 (26)	0.93	0.59–1.47	0.74			
PVT stage at transplant	G0/1	59/274 (22)	Ref.	—	—	Ref.	—	—
	G2	62/211 (29)	1.52	1.00–2.29	0.048	1.06	0.67–1.67	0.82
	G3/4	35/83 (42)	2.66	1.58–4.48	< **0.001**	1.95	1.11–3.44	**0.021**
PVT downstaging at transplant	No	100/343 (29)	Ref.	—	—			
	Yes	28/133 (21)	0.65	0.40–1.04	0.075			
	Missing	28/92						
Donor Age	+ 10 years		1.05	0.94–1.17	0.40			
Thrombectomy	No	50/212 (24)	Ref.	—	—			
	Yes	106/356 (30)	1.37	0.93-2.03	0.11			
Extra-anatomic direct anastomosis	No	152/557 (27)	Ref.	—	—			
	Yes	4/11 (36)	1.52	0.44–5.27	0.51			
Extra-anatomic jump	No	155/566 (27)	Ref.	—	—			
	Yes	1/2 (50)	2.65	0.16–42.6	0.49			
Anatomic jump	No	150/548 (27)	Ref.	—	—			
	Yes	6/20 (30)	1.14	0.43–3.01	0.80			
Renoportal anastomosis	No	152/560 (27)	Ref.	—	—			
	Yes	4/8 (50)	2.68	0.66–10.9	0.17			
Hemicaval transposition	No	144/551 (26)	Ref.	—	—			
	Yes	12/17 (71)	6.78	2.35–19.6	< **0.001**			
Direct anastomosis	No	122/388 (31)	Ref.	—	—	Ref.	—	—
	Yes	34/180 (19)	0.51	0.33–0.78	**0.002**	0.58	0.36–0.94	**0.026**

Only variables with $P < 0.10$ at univariable analysis were included in multivariable analysis. To avoid multicollinearity, 'PVT stage at listing' and 'PVT downstaging' were excluded, and only 'PVT stage at transplant' was included. Among surgical approach variables, only the binary variable 'Direct anastomosis' was included.
Bold values are statistically significant.

death or retransplant at 90 days and ICU stay prolonged over 20 days. Notably, the analysis showed that patients are at statistically significant risk to develop the composite outcome after LT when presenting with a PVT stage 3/4 and a direct anastomosis is not feasible. In addition, and importantly enough, we provided evidence that absence of recipient related risk factors like a MELD score > 25, compromised liver function with CPT score C and acute liver failure as leading indication to transplant are associated to comparable survival rates between all the PVT stages. Therefore, our analysis provides a tool for better donor-recipient matching and safer organ allocation.

Patients should be carefully informed that their condition of PVT is related to increased risk of adverse perioperative events, though they still have a survival benefit from LT in expert centers. Management of nontumoral PVT is in fact a major challenge in LT candidates, since both physiological understanding and high

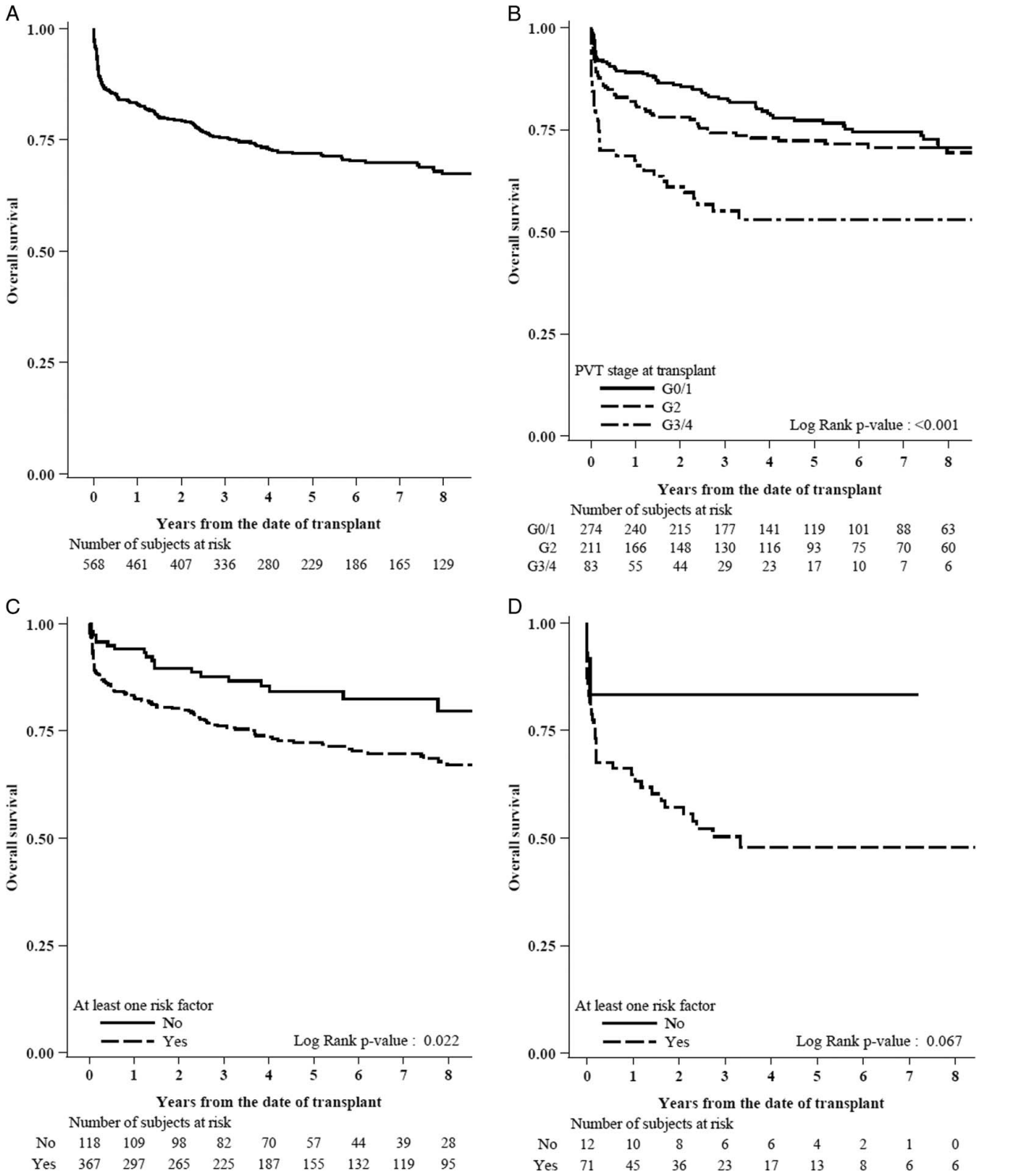

Figure 3. Overall survival [A, median FU (Q1–Q3) in years: 3.9 (1.7–7.7)] and overall survival by PVT stage at transplant (B). Overall survival by risk groups, among patients with PVT stage at transplant G0/1/2 (C) and patients with G3/4 (D). Patients had 'At least one risk factor' if: 'Center volume' <80 or 'MELD' > 25 or 'Child' = 'C' or 'Leading cause of transplant' = 'Liver failure' or 'Hemicaval transposition' = 'Yes' (variables significantly associated with composite outcome at univariable analysis).

demanding surgical skills are required for the appropriate management. In a meta-analysis comparing 20.425 patients with PVT to 417.144 without, risk of mortality was reported higher in stage 3 and 4 PVT (HR 1.59, 95% CI: 1.00–2.51, and HR 2.24, 95% CI: 1.45–3.45, respectively), with 1.33% of rethrombosis and a significant risk of graft loss in patients with PVT[4]. Notably, overall outcomes of our series show that the higher is the PVT stage, the higher is the risk of longer OT, in-hospital stay,

postoperative complications and mortality, in a statistically significant fashion. Nevertheless, it should be mentioned that the type of reconstruction plays a major role in the postoperative outcomes. Bhangui and colleagues recently reported a novel classification of PVT, which is based on the concept of physiological inflow restoration to liver[8]. This requires an accurate preoperative study that becomes essential to identify existing porto-systemic shunts and plan the most appropriate reconstruction strategy. Nonetheless, the majority of cases of PVT are still diagnosed intraoperatively, with potential harms for the patient and suboptimal surgical approach[6,13]. For example, known mesenteric shunts can be used as inflow source directed to the liver by constructing a direct anastomosis to the graft PV, or with the interposition of a conduit[14]. Consistently, a renoportal anastomosis can achieve good post-LT outcomes, even comparable to the outcomes of patients without PVT, when performed in presence of significant spontaneous splenorenal shunts[15,16]. In line with this, PCHT is a reconstruction strategy that can be adopted as a rescue strategy in selected cases, again taking advantage from the presence of splenorenal shunts. However, persistence of high splanchnic vascular bed resistances makes such a technique a nonphysiologic solution. In fact, besides several attempts to mitigate its negative hemodynamic impact[17], its infrequent use and lack of standardization and persistent splanchnic hypertension, are often cause of severe complications. In addition, the potential for an increased flow escape through vertebral and retzius growing collaterals in the middle long-term post-transplantation, may induce a progressive portal flow reduction with increased risk of late thrombosis. To mitigate the long terms post-transplant consequences of an unresolved portal hypertension, a latero-terminal collateral-portal anastomosis in adjunct to PCHT has been described to promote a progressively developing drainage of the splanchnic circulation into the donor portal flow[18]. However, this is a technically demanding solution only exceptionally adoptable.

Our results show that RPA and PCHT are the only two reconstruction strategies associated with an increased incidence of 90 days mortality ($P = 0.014$ and <0.001, respectively, see Supplementary Table 3, Supplemental Digital Content 2, http://links.lww.com/JS9/C11), which is in line with the complexity of these procedures and with the severity of patients, bearing in mind that PCHT was used as a rescue in 23.5% of cases.

Overall, data on prognostic impact of center volume, technical solution chosen, and donor-recipient match strongly suggest a policy of centralization in high volume centers for those cases with a high-grade portal thrombosis diagnosed before transplantation.

No case of multivisceral transplantation (MVT) has been reported in this series. However, it is has been shown that results after intestine transplant and MVT are improving overtime, although postoperative complications are up to 56% (including severe diarrhea and graft vs. host disease), with 5 years OS around 60%[8,19–21].

Management of anticoagulation in patients with PVT is another crucial point, since it requires to balance the risk of bleeding with that of PVT progression, especially in patients with previous history of variceal bleeding[22,23]. Most importantly, successful anticoagulation is associated with a lower rate of decompensation and with improved survival in cirrhotic patients[24]. Anticoagulation therapy should be considered in patients without cirrhosis and with recent PVT to prevent the development of chronic PVT and reduce the risk of intestinal ischemia, while in patients with cirrhosis it should be tailored according to patient-specific characteristics and to the expected benefit[25]. JAK-2 (Janus Kinase 2) and CALR (Calreticulin) mutations along with presence of antiphospholipid antibodies should be tested in patients with PVT in absence of major provoking factors[25]. Low-molecular weight heparin is usually preferred since it seems to prevent both PVT and liver decompensation[26]; however, also warfarin and novel anticoagulants can be used. Our series showed that less of 50% of the included patients underwent pre-LT anticoagulation therapy, reaching an effective downstaging in 27% of cases, confirming the lack of homogeneity in pre-LT management of patients affected by PVT. A possible explanation of why not all the PVT responded to anticoagulation therapy may be found in the thrombus structure itself. In fact, a recent work demonstrated that approximately one third of the examined PV thrombi in patients with cirrhosis consists of intimal fibrosis with an additional fibrin-rich thrombus[27]. Postoperative management of anticoagulation in the series was very homogeneous, with use of low-molecular weight heparin dosed according to patient-weight in all cases. Therefore, no correlation with the incidence of rethrombosis could be highlighted, although the study lacks data on duration of postoperative anticoagulation.

This study has some other limitations, namely its retrospective design, the wide time interval and the differences of perioperative patient management from each center. Moreover, we could not have figures about the risk of list drop-out related to the presence and progression of PVT due to the lack of data of patients that did not underwent LT. Lastly, we lack a centralized revision of preoperative imaging for homogeneous definition of preoperative PVT stage. Nevertheless, it represents a large national sample, providing generalizable data that help transplant centers to identify LT candidates affected by PVT at higher risk of severe complications, to improve donor-recipient matching and, therefore, to potentially mitigate the risk of post-LT adverse outcomes on an evidence-based strategy.

Conclusions

Potential LT candidates affected by PVT have a benefit from LT that should be adequately balanced on liver function and type of inflow reconstruction needed to mitigate the incidence of adverse events. Although postoperative complications and 90 days mortality are significantly increased in patients affected by PVT stage 3/4, yet 5 years OS exceed 50% even in these complex scenarios and can get even better in absence of risk factors in the recipient. Allocation policies should be carefully balanced to guarantee to these patients an optimal timing to maximize the benefit of LT.

Ethical approval

The study was performed according to Strengthening The Reporting Of Cohort Studies in Surgery (STROCSS) guidelines and after Institutional Review Board 'AVEN' approval for data collection (protocol number 215/2013/OSS/AOUMO), all institutions obtained their respective approvals according to their local centers requirements.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

F.D.B., P.M., and U.C.: concept and design; P.M., R.B., F.T., S.C., A.L., D.P., D.N., P.V., D.D., N.G., V.C., Q.L., L.T., and M.B.: data collection; S.F., V.B., P.M., S.D.S.: data analysis; F.D.B., P.M., S.D.S., S.F., and V.B.: interpretation of the results; F.D.B. and P.M.: manuscript drafting; U.C., S.D.S., S.F., V.B., V.M., G.T., M.R., U.B., G.M. E., L.C., A.C., M.V., S.G., L.D.C., M.C., and R.R.: critical revision.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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Data availability statement

Data are available upon request to the corresponding author for comparative studies.

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