Incidence and Recurrence of Portal Vein Thrombosis in Cirrhotic Patients

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Cirrhosis has been long considered a risk factor for bleeding due to the co-existence of the so-called 'coagulopathy'.[1,2] More recently, however, compelling evidences have been provided on the occurrence of thrombotic events in the portal and systemic circulation.[3–5] Portal vein thrombosis (PVT) is predominantly observed in patients with moderate to severe liver failure with a variable prevalence ranging from 0.6 to 25%.[6–8]

Only few studies have provided a longitudinal assessment of the PVT incidence and its sequelae, including recurrence and survival.[9–14] Due to the variability of PVT incidence and the paucity of data regarding recurrence and survival,[15–20] we prospectively analysed the incidence and the recurrence of PVT in the population of Portal vein thrombosis Relevance On Liver cirrhosis: Italian Venous thrombotic Events Registry (PRO-LIVER), a multi-centre study,[8] which involved 43 enrolling centres in Italy (ClinicalTrials.gov Identifier: NCT01470547).

The presence of PVT at baseline was assessed with Doppler ultrasound examination.

By pre-set study criteria, PVT was first suspected when solid endoluminal material was detected in the main trunk of the portal vein and/or its branches, and it was confirmed by demonstration of a filling defect on the Doppler examination. Occlusive/complete PVT was defined by a thrombus leaving no channel for blood flow. Otherwise, PVT was considered non-occlusive/incomplete.

In case of death, the circumstances and likely cause(s) were recorded.

Survival curves were formally compared using the log-rank test. Cox proportional hazards analysis was used to calculate the adjusted relative hazards of outcome events by each clinical variable.

Stochastic level of entry into the model was set at a *p*-value of 0.10, and interaction terms were explored for all the variables in the final model.

Demographics and clinical characteristics of the population have been previously reported.[8]

Seven hundred and fifty-three cirrhotic patients were followed up for a median of 21 (interquartile range [IQR]: 6.7–24) months yielding 1,008 patient-years of observation.

* *The list of PRO-LIVER Collaborative Group appears in the Supplementary Appendix.*

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During the observational period, 61 (8%) patients developed PVT (52% symptomatic): 36 (59%) of these were free from PVT at baseline and were considered as a new event (15.8 [9.4–21.0] months), 25 (41%) occurred in patients who displayed PVT at baseline and were, thus, classified as a recurrence (16.0 [12.0–24.0] months). The incidence rate of PVT was 6.05 per 100 patient-years in all patients, 4.1 per 100 patient-years in those without PVT at admission and 18.9 per 100 patient-years in those with PVT at admission.

Among the 25 patients who displayed PVT recurrences, 7 (28%) were reported to take anticoagulants ($n = 5$, 20%) or anti-platelets ($n = 2$, 8%) at baseline.

Complete thrombosis was detected in 15 (25%) patients; as for the location, in 33 (54%) patients PVT occurred only in the main trunk or one of its branches, while obstruction of more than one portal vein branches was present in 28 (46%) patients; an extension of thrombosis to the mesenteric–splenic veins was reported in 15 (24%) patients.

Table 1 Clinical and laboratory characteristics in cirrhotic patients experienced portal vein thrombosis during the follow-up

Variables	Patients without PVT ($N = 692$)	Patients with new incident PVT ($N = 36$)	Patients with recurrent PVT ($n = 25$)	*p*-Value
Age (mean ± SD), years	64.5 ± 12.1	62.1 ± 13.5	62.1 ± 13.5	0.516
Male sex, *n* (%)[a]	463 (67)	31 (86)	19 (76)	0.038
Aetiology				0.651
Alcohol, *n* (%)	170 (25)	7 (19)	9 (36)	
Viral, *n* (%)	308 (44)	15 (42)	9 (36)	
NASH/metabolic, *n* (%)	40 (6)	2 (6)	1 (4)	
Autoimmune, *n* (%)	17 (2)	0 (0)	1 (4)	
Mixed, *n* (%)	91 (13)	9 (25)	2 (8)	
Others/unknown, *n* (%)	66 (9)	3 (8)	3 (12)	
Child–Pugh score				0.314
Class A, *n* (%)	365 (53)	15 (42)	17 (68)	
Class B, *n* (%)	236 (34)	14 (42)	7 (28)	
Class C, *n* (%)	91 (13)	6 (17)	1 (4)	
MELD score, median (IQR)	10 (8–14)	10 (8–14)	11 (8–11)	0.576
Baveno score				0.391
Compensated, *n* (%)	406 (59)	17 (47)	15 (60)	
Decompensated, *n* (%)	286 (41)	19 (53)	10 (40)	
Ascites				0.696
Absent, *n* (%)	429 (62)	19 (53)	16 (64)	
Responsive to diuretic therapy, *n* (%)	196 (28)	13 (36)	8 (32)	
Refractory, *n* (%)	67 (10)	4 (11)	1 (4)	
Encephalopathy[a]				0.044
Absent, *n* (%)	590 (85)	24 (69)	22 (88)	
Mild, *n* (%)	90 (13)	11 (31)	3 (12)	
Moderate to severe, *n* (%)	12 (2)	1 (3)	0 (0)	
HCC, *n* (%)	139 (20)	9 (25)	4 (16)	0.672
Albumin, (gr/L)	3.4 ± 0.6	3.5 ± 0.7	3.4 ± 0.4	0.752
Bilirubin, (mg/dL)	2.2 ± 3.3	2.4 ± 3.8	1.2 ± 0.5	0.287
PT-INR	1.30 ± 0.34	1.33 ± 0.22	1.28 ± 0.17	0.818
Serum creatinine (mg/dL)	0.95 ± 0.64	0.92 ± 0.42	0.93 ± 0.27	0.933
Platelet count ($\times 10^3$/L)[b]	116 ± 66	82 ± 43	88 ± 44	0.001
Platelet count tertiles[a]				
≥ 126 ($\times 10^3$/L)	240 (35)	5 (14)	5 (20)	0.001
76–125 ($\times 10^3$/L)	240 (35)	9 (25)	7 (28)	
≤ 75 ($\times 10^3$/L)	212 (30)	22 (61)	13 (52)	

Abbreviations: HCC, hepatocellular carcinoma; IQR, interquartile range; MELD score, Model for End-stage Liver Disease score; NASH, non-alcoholic steatohepatitis; PT-INR, prothrombin time-international normalized ratio; PVT, portal vein thrombosis; SD, standard deviation.
[a]Chi-square trend.
[b]Analysis of variance.

►**Table 1** reports the clinical characteristics of the patients according to the presence or not of PVT during the follow-up period; patients experiencing PVT had lower platelet count and previous PVT.

Cox multivariable model showed that previous PVT (hazard ratio [HR]: 4.22, 95% confidence interval [CI]: 2.49–7.15, $p < 0.001$) (►**Fig. 1A**) and being in the third lower tertile of platelets count (vs. the first) (HR: 3.52, 95% CI: 1.71–7.23, $p = 0.001$) were significantly and independently associated with the occurrence of PVT.

During the study, 145 (19%) died (median [IQR] follow-up = 9.87 [3.6–16.3] months). Multivariable models demonstrated that only age (HR: 1.03, 95% CI: 1.02–1.05, $p < 0.001$), hepatocellular carcinoma (HR: 2.11, 95% CI: 1.49–2.98, $p < 0.001$), Child–Pugh classes B (HR: 5.61, 95% CI: 3.60–8.75, $p < 0.001$) and C (HR: 11.46, 95% CI: 6.95–18.88,

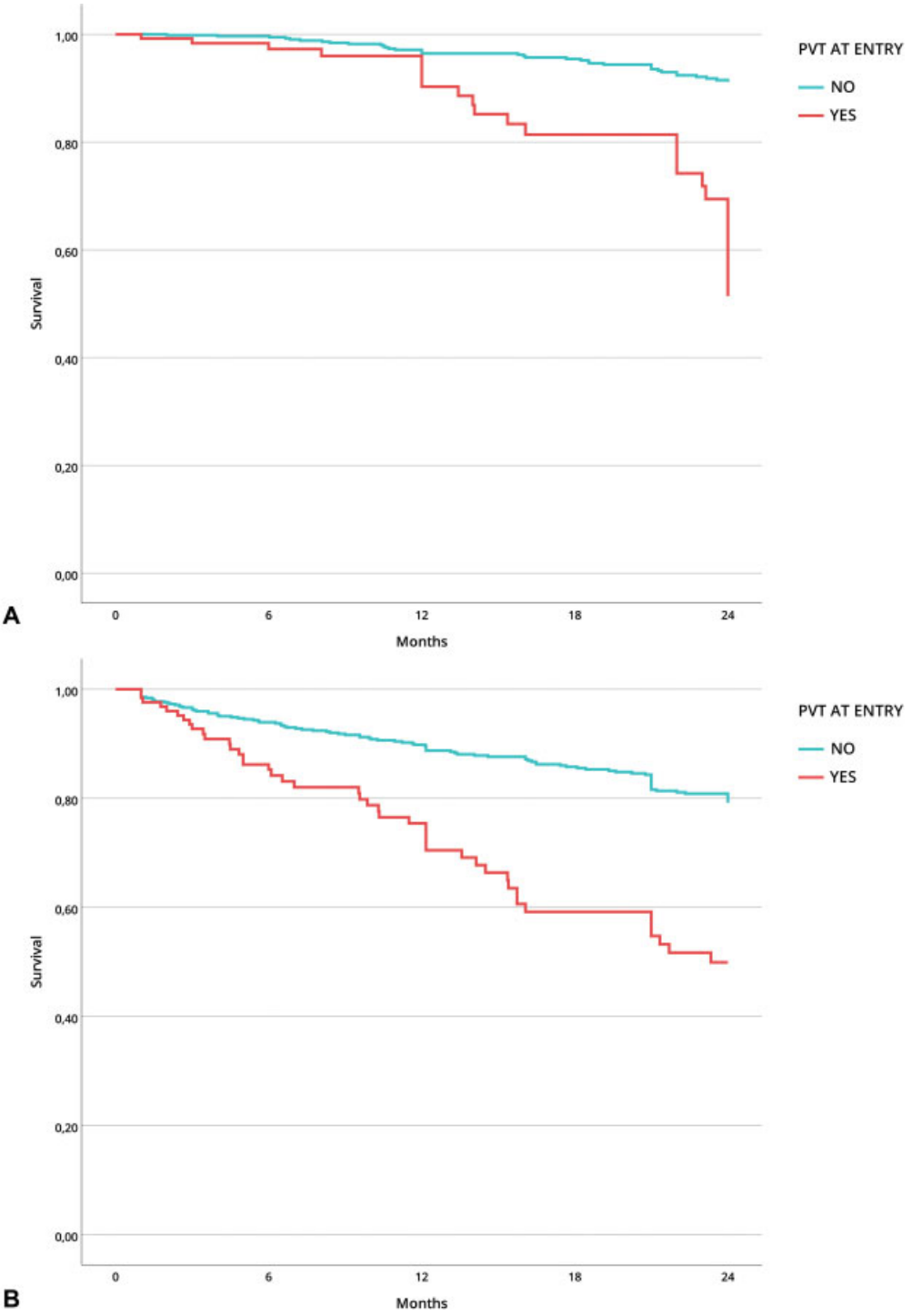

Fig. 1 (**A**) Survival free from portal vein thrombosis (PVT) in patients according to previous PVT at admission. Log-rank: 53.342; $p < 0.001$. (**B**) Cumulative survival according to previous PVT at admission. Log-rank: 37.578; $p < 0.001$.

$p < 0.001$) and PVT at the entry (HR: 1.70, 95% CI: 1.18–2.45, $p = 0.004$) (►**Fig. 1B**) remained statistically significant as independent predictors of death.

This study shows that in cirrhosis PVT is a risk factor for PVT recurrence and low survival.

Previous analysis of PVT incidence in cirrhotic population was limited to patients with low to moderate cirrhosis and it was associated to an annual risk in average of 2%.[9] In this study, including patients with low to severe cirrhosis, the annual PVT incidence rate was 6.05%. This incidence, however, changes when a previous PVT is reported at the admission. Thus, the annual rate of PVT was much higher in patients with a history of PVT indicating that PVT per se carries a risk for recurrences. It is noteworthy that in the multivariable regression analysis, not only previous PVT, but also low platelet count independently predicted the occurrence of PVT event. This paradoxical association could reflect the platelet over-activation and consumption and consequent low platelet count due to a rapid platelet turnover.[21]

During the follow-up, the survival rate of our population was 80.7%, which is consistent with other reports on this setting.[11,20] In addition to the known association between hepatocellular carcinoma and liver failure versus low survival, we found that PVT at entry was per se an independent predictor of low survival. However, we have no element to suggest that PVT is a factor favouring low survival or is a mere reflection of disease severity as data regarding the mortality cause were incomplete.

The study has implications and limitations. The study shows that cirrhosis is complicated by a high rate of PVT and that previous PVT is an independent predictor not only of PVT recurrence but also of low survival. The study opens potentially novel therapeutic scenarios as the association between PVT and poor outcomes would provide a rationale to plan interventional trials with anti-thrombotic drugs. A recent meta-analysis on this topic[22] suggested a potential usefulness of anticoagulants in improving outcomes of PVT but randomized controlled trials are necessary to support this finding. The PRO-LIVER study has been performed in a single country, enrolling only Caucasians, limiting the generalizability of the findings to cirrhotic patients from other countries or ethnic groups.

In conclusion, PVT is a frequent complication of cirrhosis and its early diagnosis would be helpful to identify patients at risk of poor clinical outcomes.

Conflict of Interest
None declared.

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