Editorial

Portal vein thrombosis and cirrhosis—old wine, new wine

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Portal vein thrombosis (PVT) has been classically defined as the obliteration of portal venous flow due to partial or complete thrombus formation within the lumen of the vein. The diagnosis of PVT can be divided into two broad headings of clinical and radiological assessments. Clinically, patients could present with acute abdominal symptoms with catastrophic consequences, worsening portal hypertension complications or be completely asymptomatic. Radiologically, PVT can be diagnosed when there is presence of thrombus formation in the portal vein in the presence of/or absence of Porto-portal collateral formation (also referred to as cavernoma). Recently, we defined PVT as a syndrome in which the presence of a thrombus in the portal vein or its branches presents either as an incidental finding on abdominal imaging; or with a myriad of acute abdominal signs and symptoms that represent complications of portal hypertension; or a composite of both acute abdominal and portal hypertensive manifestations in the presence or absence of cirrhosis and/or malignancy (1). This anatomico-functional definition and subsequent new classification of PVT in cirrhosis (*Table 1*) encompasses occurrence, consequences and associations and could be more suited for singularity in studies (2). In patients with cirrhosis, cross-sectional estimates for PVT have ranged between 0.6% and 26% (3). However, the prevalence is dependent on many factors such as age, presence and etiology of underlying hepatic and extrahepatic diseases and velocity of portal venous blood flow. Child Pugh class A and B cirrhotics have one and five-year PVT development of 4.6% and 10.7%, respectively. Cirrhosis increases the relative risk of developing PVT by more than seven-fold above that seen in general population (4). Multiple studies have shed light on predictors of PVT in cirrhosis—Child class B and C, prior PVT, pro-thrombotic state and large portosystemic shunts, hepatocellular carcinoma (HCC), thrombosis of other systemic veins, recent surgical, endoscopic or invasive interventions of the abdomen and portal flow velocity <15 cm/sec (5). PVT is seen to occur in 35% of cirrhotic patients with HCC and has a distinct effect on natural history and prognosis in this cohort (6).

In the journal of *Internal Medicine and Emergency*, Violi *et al.* on behalf of the Italian Society of Internal Medicine, undertook the 'PVT Relevance on Liver cirrhosis: Italian Venous Thrombotic Events Registry' (PRO-LIVER) study to understand the prevalence, and predictors of PVT in cirrhosis (7). A total of 802 consecutive cirrhotic patients were enrolled and 753 consecutive cirrhotic patients were included in the analysis. Chronic viral hepatitis and alcoholic liver disease were predominant etiologies. Around half of the patients belonged to Child Pugh class B and C and 57% of patients were compensated as per Baveno IV scoring. HCC was seen in 20% and 17 patients had a transjugular intrahepatic portosystemic shunt insertion prior to study enrolment. PVT was detected in 126 patients (17%), main trunk or branch occlusion in 81 patients (64%), while >1 branch PVT was present in 45 patients (36%); mesenteric or splenic vein thrombosis involvement was reported in 27 patients (21%). The authors further classified PVT as per Yerdel grading based on anatomical site of occlusion. Asymptomatic PVT was seen in 43% of patients and clinical manifestation were seen in 51% of cases that included refractory ascites, upper gastrointestinal bleeding and acute encephalopathy. Initiation of this study is highly commendable, but falls short of novel findings

Table 1 New classification of portal vein thrombosis [modified from (1)]

Site of portal vein thrombosis
Type 1: trunk only
Type 2: branch only; 2a, one branch; 2b, both branches
Type 3: trunk and branches
Degree of portal venous system occlusion
O: occlusive: no flow visible in portal vein lumen on imaging/Doppler study
NO: non-occlusive: flow visible in portal vein lumen through imaging/Doppler study
Duration and presentation
R: recent (first time detected in previously patent portal vein, presence of hyperdense thrombus on imaging, absent or limited collateral circulation, dilated portal vein at the site of occlusion)
Ch: chronic (no hyperdense thrombus; previously diagnosed PVT on follow-up, portal cavernoma and clinical features of portal hypertension)
As: asymptomatic
S: symptomatic: features of acute PVT (with or without acute bowel ischemia) or features of portal hypertension
Extent of portal vein system occlusion
S: splenic vein
M: mesenteric vein
SM: both
Type and presence of underlying liver disease
Cirrhotic, non-cirrhotic liver disease, post-liver transplant, hepatocellular carcinoma, local malignancies and associated conditions

PVT, portal vein thrombosis.

that are practice changing. An in-depth analysis of the study methodology, enrolment pattern and associated patient characteristics is important in understanding ways to improve on follow up. As the authors rightly suggest, the most important limitation is the cross-sectional nature of the study. Analytical cross-sectional studies have limited ability to draw valid conclusions about any association or possible causality because risk factors and outcomes are measured simultaneously (8).

Hence it is difficult to ascertain whether the disease or the exposure came first, and confirmation requires further rigorous studies. This is very noticeable while analysing the patient characteristics and PVT. The authors state that their study supported previous findings that indicate PVT occurs frequently in cirrhosis whatever the etiology. However, the influence of the etiology of cirrhosis on the development of PVT in reality, insufficiently studied and neither chronic viral hepatitis alcoholic liver disease was found to be predictive of PVT in previous studies, in contrast to the study in discussion. A large study inclusive of patients evaluated for liver transplantation has shown that 6.3% had a diagnosis of PVT, in particular when cirrhosis was related to non-alcoholic steatohepatitis (NASH), the enrolment of whom in the current study was limited (only 4%) (9). In a recent study by Ruiz *et al.*, an increased risk of PVT was associated with patients of autoimmune hepatitis on the liver transplantation waiting list and in such patients post-transplant (10). Internal medicine departments were highly represented in the study enrolment that could have affected real life representation of cirrhosis patients with PVT. The authors discuss the possible mechanisms that could lead to PVT in cirrhosis—from prothrombotic state to low grade endotoxemia, but fail to assess these in their cohort of patients. Hypercoagulable state in cirrhosis could be due to decreased protein C and elevated factor VIII levels as shown by prior studies. A recent study by Carnevale *et al.* provided evidence that lipopolysaccharide derived from intestinal microbiota stimulated endothelial

cells resulting in an increase in systemic levels of factor VIII (11). This highlights the role of gut microbiome in hypercoagulability and portal vein thrombotic events in cirrhosis and is an interesting area of further research and therapy. Amitrano and colleagues showed that more than two-thirds of cirrhotic patients with PVT have inherited thrombophilic disorders. The prothrombin gene 20210A mutation is associated with a five times increased risk of developing PVT and in cirrhosis patients with PVT, methyl-tetrahydrofolate reductase C677T and Factor-V-Leiden mutations and are more frequently detected than in those without PVT. But the strength of such associations is still a matter of debate (12). Prior history of resolved PVT was found to be a strong predictor of PVT in the study by Violi and co-workers. Four percent of patients without PVT had a prior PVT event in comparison to 20% with PVT (P<0.001). This aspect is novel to PVT in cirrhosis, and has been proposed by us as one of the major characteristics for development of a pre-test probability for PVT prediction in patients with cirrhosis, similar to that is in use for deep vein thrombosis. The consequences of repeated episodes of PVT on the natural history of cirrhosis is unknown. In the current study, the authors did not look at survival outcomes in their patients with PVT with regards to the significant associated factors. This remains to be seen in the ongoing PROLIVER prospective study and its subsequent analysis. Progression of PVT was not associated with hepatic decompensations, increase in mortality, and need for liver transplantation, in cirrhotic patients with non-malignant PVT as was shown by Nery *et al.* and recently by Borjas-Almaguer and colleagues (5,13).

The authors suggest that treatment of PVT and subsequent outcomes is an unmet need. Patients with PVT can have an increase in refractory acute variceal bleeding and poor survival after liver transplantation. Patency of portal vein is pertinent for liver-transplantation candidates; as end-to-end portal vein anastomosis is shown to be associated with better outcomes after liver transplantation compared to other surgical techniques (14,15). The Baveno VI consensus recommends anticoagulation in potential liver-transplantation candidates with PVT or in case of progressive PVT. This could translate to facilitation of liver transplantation and reduction in posttransplant morbidity and mortality. Five-day treatment failure or 6-week mortality has not been reported in patients with upper GI bleeding under anticoagulation and till date, no deaths directly related to anticoagulation has been documented in cirrhotic patients with PVT. Screening endoscopy and standard prophylaxis (primary or secondary) of variceal bleeding, are necessary prior to initiation of anticoagulation. For non-transplant candidates, there are no recommendations to date (16). Violi *et al.* suggested that the validation of the PVT using a computed tomography (CT) scan would be useful. This is important with regards to the new anatomico-functional classification of PVT in which CT modality can help delineate between recent and chronic PVT based on density of thrombus, and assess outcomes subsequently. The authors do not assess other important predictors or associations of PVT in cirrhosis—such as the reduction in portal blood flow velocity to <15 cm/sec on Doppler ultrasound, use of non-selective betablockers and presence or the development of large portosystemic collaterals (with volume of flow >400 mL/min and velocity of blood flow >10 cm/sec in the largest collateral).

Inclusion of patients with HCC and PVT is not ideal for studies that aim to look at natural history of cirrhosis with non-malignant PVT. Zanetto *et al.* in a recent study showed that PVT incidence was 24% and 11% in patients with and without HCC, respectively. In patients with PVT and HCC, PVT occurred in almost 50% of Child class A patients. A Cox multivariate analysis confirmed HCC and increased Maximal Clot Firmness on Thromboelastography and Functional Fibrinogen (FIBTEM®) to be independently associated with increased PVT risk (17). In patients with HCC related PVT (tumoral) and in those with HCC and bland PVT, striking outcomes in natural history remains to be seen and would require distinct study protocol inclusion and methodology for clear assessment.

Finally, in patients with chronic PVT who develop recent progression of thrombotic event, leading to worsening of liver failure or portal hypertensive complications—a syndrome of acute on chronic PVT—leading to acute on chronic liver failure could be included in future prospective trials. This patient group is not yet well defined and could become a distinct cohort that requires revision in/or new treatment recommendations.

The study by Violi *et al.* lack effectiveness in defining novel associations and predictors of PVT in cirrhosis and do not add to practice changing aspects in current clinical Hepatology. However, the ongoing large prospective PROLIVER study and it's results and conclusions will hopefully shed light on controversial and novel aspects of cirrhosis and PVT, if guided by current recommendations, proper enrolment methodology, tenacious and sonorous analysis and subsequent changes in definitions in understanding of the disease.

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References

1. Sarin SK, Philips CA, Kamath PS, et al. Toward a comprehensive new classification of portal vein thrombosis in patients with cirrhosis. Gastroenterology 2016;151:574-7.e3.
2. Von Köckritz L, De Gottardi A, Trebicka J, et al. Portal vein thrombosis in patients with cirrhosis. Gastroenterol Rep (Oxf) 2017;5:148-56.
3. Tsochatzis EA, Senzolo M, Germani G, et al. Systematic review: portal vein thrombosis in cirrhosis. Aliment Pharmacol Ther 2010;31:366-74.
4. Ogren M, Bergqvist D, Bjorck M, et al. Portal vein thrombosis: prevalence, patient characteristics and lifetime risk: a population study based on 23,796 consecutive autopsies. World J Gastroenterol 2006;12:2115-19.
5. Nery F, Chevret S, Condat B, et al. Causes and consequences of portal vein thrombosis in 1,243 patients with cirrhosis: results of a longitudinal study. Hepatology 2015;61:660-7.
6. Woo HY, Heo J. New perspectives on the management of hepatocellular carcinoma with portal vein thrombosis. Clin Mol Hepatol 2015;21:115-21.
7. Violi F, Corazza RG, Caldwell SH, et al. Portal vein thrombosis relevance on liver cirrhosis: Italian Venous Thrombotic Events Registry. Intern Emerg Med 2016;11:1059-66.
8. Sedgwick P. Cross sectional studies: advantages and disadvantages. BMJ 2014;348:g2276.
9. Stine JG, Shah NL, Argo CK, et al. Increased risk of portal vein thrombosis in patients with cirrhosis due to non-alcoholic steatohepatitis. Liver Transpl 2015;21:1016-21.
10. Ruiz P, Sastre L, Crespo G, et al. Increased risk of portal vein thrombosis in patients with autoimmune hepatitis on the liver transplantation waiting list. Clin Transplant 2017.
11. Carnevale R, Raparelli V, Nocella C, et al. Gut-derived endotoxin stimulates factor VIII secretion from endothelial cells. Implications for hypercoagulability in cirrhosis. J Hepatol 2017;67:950-6.
12. Amitrano L, Guardascione MA, Brancaccio V, et al. Risk factors and clinical presentation of portal vein thrombosis in patients with liver cirrhosis. J Hepatol 2004;40:736-41.
13. Borjas-Almaguer OD, Cortez-Hernández CA, González-Moreno EI, et al. Portal vein thrombosis in patients with cirrhosis: just a common finding or a predictor of poor outcome? Ann Hepatol 2016;15:902-6.
14. Francoz C, Belghiti J, Vilgrain V, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. Gut 2005;54:691-7.
15. D'Amico G, De Franchis R; Cooperative Study Group. Upper digestive bleeding in cirrhosis. post-therapeutic outcome and prognostic indicators. Hepatology 2003;38:599-612.
16. de Franchis R; Baveno VI Faculty. Expanding consensus in portal hypertension: report of the Baveno VI Consensus Workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.
17. Zanetto A, Senzolo M, Vitale A, et al. Thromboelastometry hypercoagulable profiles and portal vein thrombosis in cirrhotic patients with hepatocellular carcinoma. Dig Liver Dis 2017;49:440-5.

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