Thrombotic risk factors in patients with liver cirrhosis: Correlation with MELD scoring system and portal vein thrombosis development

Maria Assunta Zocco1,*, Enrico Di Stasio2, Raimondo De Cristofaro1, Marialuisa Novi1, Maria Elena Ainora1, Francesca Ponziani1, Laura Riccardi1, Stefano Lancellotti1, Angelo Santoliquido1, Roberto Flore1, Maurizio Pompili1, Gian Lodovico Rapaccini1, Paolo Tondi1, Giovanni Battista Gasbarrini1, Raffaele Landolfi1, Antonio Gasbarrini1

1Department of Internal Medicine, Catholic University of Rome, Gemelli Hospital, Largo A. Gemelli 8, 00168 Rome, Italy
2Department of Biochemistry and Clinical Biochemistry, Catholic University of Rome, Rome, Italy

See Editorial, pages 632–634

Background/Aims: Prognostic scores currently used in cirrhotic patients do not include thrombotic risk factors (TRFs). Predicting factors of portal vein thrombosis (PVT) development are still unknown. We wanted to describe TRFs as a function of liver disease severity using the MELD score and assess the role of local and systemic TRFs as predictors of PVT development in cirrhotic patients.

Methods: One hundred consecutive patients with liver cirrhosis were included in the study. TRFs, D-dimers, MELD score, portal vein patency and flow velocity were evaluated in all subjects at baseline and every 6 months thereafter. Variables able to predict PVT development within 1 year were identified by means of multiple logistic regression.

Results: The plasma levels of protein C and antithrombin were lower and the concentration of D-dimers was higher in patients with advanced disease. Plasma levels of antithrombin, protein C and protein S resulted significantly lower in PVT group at univariate analysis, but reduced portal vein flow velocity was the only variable independently associated with PVT development.

Conclusions: Lower concentrations of natural coagulation inhibitors are frequently detected in patients with liver cirrhosis. A reduced portal flow velocity seems to be the most important predictive variable for PVT development in patients with cirrhosis.

Keywords: Thrombotic risk factors; Liver cirrhosis; MELD score; Portal vein thrombosis; Portal flow velocity

1. Introduction

The liver has many haemostatic functions, including the synthesis of most coagulation factors and inhibitors as well as fibrinolytic factors [1,2]. The balance between procoagulant and anticoagulant factors is essential to avoid excessive thrombin generation under physiological conditions [3]. Therefore, it is not surprising that advanced liver disease results in a complex pattern of defects in haemostatic functions in the form of reduced synthesis of coagulation factors, inhibitors, and abnormal clotting factors, abnormalities of fibrinolytic
activity, disseminated intravascular coagulation and platelet function defects [4–7].

Moreover, thrombosis of the intrahepatic veins is frequently observed in cirrhosis and has been associated with its progression [8], while occlusion of small sized intrahepatic veins and sinusoids has been considered a potential triggering factor of liver tissue remodelling [9].

Recently, the prevalence of several genetic and acquired thrombotic risk factors in patients with chronic hepatitis B or C as well as their possible association with necroinflammatory activity and extent of fibrosis has been evaluated [10,11]. It is well known that protein C, protein S and antithrombin (AT) serum levels are decreased in patients with liver disease [12,13] but, to date, few reports are available about the association between the above mentioned and other natural anticoagulant factors produced by the liver and different stages of liver cirrhosis.

Portal vein thrombosis (PVT) is an important complication of cirrhosis, and is mostly associated with the occurrence of hepatocellular carcinoma [14]. The incidence of non-neoplastic PVT in cirrhotic patients is unknown, while its prevalence ranges from 0.6% to 16% [15–17]. Since PVT can be an important source of morbidity and mortality, early detection and treatment for de novo thrombosis is an important issue, especially in patients on the waiting list for liver transplantation [18]. Over the last few years the etiology of PVT has been better defined and large case series have improved our understanding of the natural history of this condition [19]. Male sex, previous abdominal surgery including splenectomy and portocaval shunts, encephalopathy, ascites, past history of bleeding varices, low platelet count, and Child–Pugh class C have been considered predisposing factors to PVT in liver cirrhosis [18,20,21]. Previous sclerotherapy of varices has been shown to be a risk factor in some studies [22,23]; other authors did not confirm this datum [16,24] or have shown that sclerotherapy may only be a trigger factor for PVT in patients with genetic thrombophilia [25,26]. Two studies found antiphospholipid antibodies (APA) in more than half of cirrhotic patients with PVT [27,28] but no relationship was found between anticardiolipin antibodies and PVT in another study [29]. Moreover, inherited (such as the factor V Leiden 1691 G–A mutation and the prothrombin 20210 G–A mutation), or acquired (such as the reduced levels of natural inhibitors of coagulation like protein C, protein S and antithrombin) coagulative defects leading to a hypercoagulable state, have been found in cirrhotic patients with PVT [16,30–34].

On the whole, the occurrence of PVT in liver cirrhosis appears to be a multifactorial complication, in which the involvement of inherited and acquired thrombotic risk factors as well as local anatomical and hemodynamic factors may be involved.

This study was designed to determine whether acquired systemic thrombogenic factors and local factors related to hepatic haemodynamics and portal hypertension might be related to liver disease progression and to the development of PVT.

2. Patients and methods

2.1. Patient population and study design

One hundred consecutive adult patients with cirrhosis (76 men, 24 women) with a median age of 60 years (range 31–81 yrs) were enrolled in the study, which conformed to the ethical standards of the Declaration of Helsinki and was approved by the local ethics committee. Liver cirrhosis was diagnosed by histological examination of liver biopsy or by unequivocal hematocysternial, ultrasound (US) or endoscopic findings suggesting advanced liver disease with portal hypertension. The severity of liver disease was estimated according to Model for End-stage Liver Disease (MELD) scoring system [35].

Patients with patent paraumbilical vein, reversed portal blood flow, known hepatocellular carcinoma or any other malignancy, known hemostatic disorders other than liver disease, bacterial infection, a clinical history of peripheral venous thrombosis, or those who had received any form of antiviral and/or immunomodulatory therapy within the last 6 months were excluded from the study. No patient was taking oral contraceptives, anticoagulation or anti-platelet drugs.

Exclusion criteria were also the presence of the most common inherited coagulation abnormalities (Factor V Leiden and prothrombin (G20210A) genes mutation), as well as, based on familiar screening, antithrombotic protein deficiency (protein C, protein S, antithrombin (AT)). Only 2 patients of the initial population evaluated were affected by Factor V Leiden (heterozygote state) or prothrombin (G20210A – heterozygote state) mutation. Based on this finding, we decided to exclude these patients from further analysis.

The demographic, clinical and laboratory data of the patients enrolled in the study are summarized in Table 1. The following parameters were considered as thrombotic risk factors (TRFs): deficiency in AT, protein S, protein C, presence of lupus anticoagulant (LAC) antibodies, elevated homocysteine and, cryoglobulinemia. TRFs and D-dimer levels were evaluated as functions of a stratified MELD score; an arbitrary cut-off value was set at 13 (usually applied in our institution to select patients for liver transplantation).

The patients were followed up for one year and were evaluated at baseline and every 6 months by liver function tests, D-dimer, TRFs and abdominal Doppler US.

Concerning the development of PVT during follow-up, we evaluated, for their prognostic significance, the clinical and demographic characteristics of patients at baseline. In particular previously described TRFs were analyzed in addition to age, gender, platelet cell count, international normalized ratio (INR), activated partial thromboplastin time (APTT), D-dimer levels, grading of oesophageal varices and MELD score.

PVT was suspected by the occurrence of endoluminal material in the main trunk of portal vein and/or its branches at grey-scale ultrasonography or by the presence of a filling defect at color or power Doppler ultrasonography. In all cases the diagnosis was confirmed by dynamic abdominal computed tomography that also allowed a more precise distinction between partial and complete obstructive thrombosis. Portal cavernoma was defined by the presence of multiple small channels that replaced the thrombosed portal trunk.

The presence and staging of oesophageal varices was evaluated by means of upper endoscopy.

2.2. Blood collection and processing

After informed consent, blood was drawn without stasis by clean venipuncture and collected in vacuum tubes containing 105 mmol/L trisodium citrate as an anticoagulant (Vacutainer; Becton–Dickinson,
Beta2GP1 IgG and IgM ELISA, Instrumentation Laboratory, Milano, enzyme linked immunosorbent assay (ELISA) kits (Imuclone Anti-

Time (dRVVCT – Instrumentation Laboratory Milano, Italy – screen-

LAC antibodies was detected by diluted Russell Viper Venom Clotting

level was below 70%, 64% and 70%, respectively. The presence of

in AT III, protein S, and protein C were diagnosed when the protein

(ELISA). Results appear as a percentage of protein activity. Deficiency

PS) were determined by enzyme-linked immunosorbent assay

chrom AT), protein C (Asserachrom PC), and protein S (Asserachrom

Germany) and following the manufacturer's instructions, AT (Sta-

analyzer STAGO DIAGNOSTIC (Boehringer Mannheim, Mannheim,

cially available reagents from the same company. Using an auto-

meter (TOP, Instrumentation Laboratory Milano, Italy) and commer-

assays. Coagulation tests were performed using an automatic coagulo-

chemistry parameters were measured using commercially available

count, platelets count, prothrombin time (PT) or INR, APTT, clinical

Meylan, France) at a blood anticoagulant ratio of 9:1. Full blood

count, platelets count, prothrombin time (PT) or INR, APTT, clinical

chemistry parameters were measured using commercially available

assays. Coagulation tests were performed using an automatic coagulo-

meter (TOP, Instrumentation Laboratory Milano, Italy) and commerci-

ally available reagents from the same company. Using an auto-

alyzer STAGO DIAGNOSTIC (Boehringer Mannheim, Mannheim,

Germany) and following the manufacturer's instructions, AT (Sta-

chroom AT), protein C (Asserachrom PC), and protein S (Asserachrom

were determined by enzyme-linked immunosorbent assay (ELISA). Results appear as a percentage of protein activity. Deficiency in AT III, protein S, and protein C were diagnosed when the protein level was below 70%, 64% and 70%, respectively. The presence of LAC antibodies was detected by diluted Russell Viper Venom Clotting Time (dRVVCT – Instrumentation Laboratory Milano, Italy – screening and confirm) [36].

Anti-beta2 glycoprotein levels were measured using commercial enzyme linked immunosorbent assay (ELISA) kits (Imuclone Anti-Beta2GP1 IgG and IgM ELISA, Instrumentation Laboratory, Milano, Italy) and were expressed in units, according to the manufacturer's instructions. The dRVVCT assay was performed by a commercial kit ("dRVV test" and "dRVV confirm") using an automatic coagulometer ("Top", Instrumentation Laboratory, Milano, Italy). This test was considered positive if the dRVVCT was >38" and the value of the ratio dRVVCT/dRVV confirm was ≥1.25.

2.3. Doppler measurements

Doppler US examinations were performed using a Color-Power Doppler US scanner Technos (Esaote, Genova, Italy) with a 3.5-

5 MHz convex probe.

All subjects were examined after overnight fasting in a supine posi-

tion after a rest of 15 min in order to avoid any influence of food, pos-

ture and exercise.

The portal vein was examined following current guidelines which

allow a reduction of interobserver variability to non-significant levels

[37]. In particular, care was taken to ensure that the angle of inson-

ation between the Doppler beam and the portal trunk was between

30 and 60°. The doppler study was performed by positioning the sam-

ple volume at about the middle of the portal trunk (between the liver

hilum and the spleno-mesenteric junction) by approaching from the

epigastrium with the probe placed slightly obliquely.

Portal flow velocity was calculated automatically by the instrument

as time averaged maximum velocity, which is the parameter providing

the most reliable and repeatable results [37]. Doppler examinations

were performed by two experienced sonographers (MP, LR) without

prior knowledge of clinical and biochemical status of the study

population. Three blood flow tracings lasting no less than 4 s were

recorded for each vessel and the mean of three was noted as the final

reading.

2.4. Statistical analysis

All data were analysed using the statistical package SPSS 15.0 ver-

sion (SPSS Inc., Chicago, IL). Continuous variables are expressed as

means ± SD, categorical variables are displayed as frequencies. Statis-
tical analysis was performed using the appropriate parametric or not

parametric test (t test or the Mann–Whitney test for comparisons of

continuous variables between groups, corrected p or Fisher’s exact
test for categorical data). Multivariate binary logistic analysis was per-

formed to evaluate the relationship between the development of portal

vein thrombosis and TRFs. The receiver operating characteristic curve

was used to identify the best discriminating value of portal vein flow

velocity at baseline associated with the development of portal throm-

bosis. The coefficients obtained from the logistic regression were also

expressed in terms of odds ratio with 95% confidence intervals. A
two tailed p value less than 0.05 was considered significant.

3. Results

3.1. TRFs and liver dysfunction

Levels of the natural anticoagulant proteins, AT and

protein C were low in the entire group of cirrhotic patients (mean values 52.4% and 42.1%, respectively; normal values: AT, 70–120% and protein C, 70–140%) (Table 1).

Associations of high MELD (defined as ≥13) or low

MELD (<13) with levels or presence of TRFs are pre-

sented in Table 2. Patients with advanced staging had

lower protein C and AT levels (32.1% vs. 54.6%,
p < 0.001 and 42.6% vs. 63.4%, p < 0.001, respectively)

and higher D-dimers levels (2008 ng/ml vs. 520 ng/ml,
p < 0.001) (Fig. 1).

### Table 1

Clinical, biochemical and demographic characteristics of enrolled patients at baseline.

<table>
<thead>
<tr>
<th>Characteristic [normal values]</th>
<th>Patients (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr) 59.5 (11.5)</td>
<td></td>
</tr>
<tr>
<td>Male 76</td>
<td></td>
</tr>
<tr>
<td>Ethiology</td>
<td></td>
</tr>
<tr>
<td>Viral 56</td>
<td></td>
</tr>
<tr>
<td>Alcoholic 28</td>
<td></td>
</tr>
<tr>
<td>Others* 15</td>
<td></td>
</tr>
<tr>
<td>Child-Pugh class</td>
<td></td>
</tr>
<tr>
<td>A (n) 50</td>
<td></td>
</tr>
<tr>
<td>B (n) 25</td>
<td></td>
</tr>
<tr>
<td>C (n) 25</td>
<td></td>
</tr>
<tr>
<td>MELD score 15.1 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Bilirubin (g/dl) [0.3–1.2]</td>
<td>3.7 (5.6)</td>
</tr>
<tr>
<td>Albumin (g/l) [3.4–4.8]</td>
<td>3.1 (0.5)</td>
</tr>
<tr>
<td>Creatinine (mg/dl) [0.7–1.2]</td>
<td>1.3 (1.1)</td>
</tr>
<tr>
<td>Platelet count (×10^3/μl) [140–450]</td>
<td>96.1 (49.9)</td>
</tr>
<tr>
<td>INR [0.8–1.2]</td>
<td>1.37 (0.35)</td>
</tr>
<tr>
<td>Partial thromboplastin time (s) [20–36]</td>
<td>36.4 (8.9)</td>
</tr>
<tr>
<td>Protein C (%) [70–140]</td>
<td>42.1 (19.4)</td>
</tr>
<tr>
<td>Protein S (%) [64–140]</td>
<td>73.1 (20.8)</td>
</tr>
<tr>
<td>Antithrombin (%) [70–120]</td>
<td>52.4 (19.5)</td>
</tr>
<tr>
<td>Homocysteine (μmol/l) [5–15]</td>
<td>10.8 (7.0)</td>
</tr>
<tr>
<td>D-dimer (ng/ml) [278]</td>
<td>1326 (1531)</td>
</tr>
<tr>
<td>LAC antibodies positive Anti-beta2glycoprotein 1 (U/ml) [≥20]</td>
<td>10</td>
</tr>
<tr>
<td>Anti-beta2glycoprotein 1 (U/ml) [≥20]</td>
<td>35 (8) (for samples with anti-beta2GpI ≥ 20 U/ml, n = 13)</td>
</tr>
<tr>
<td>Cryoglobulinemia 12</td>
<td></td>
</tr>
</tbody>
</table>

Quantitative values are expressed as mean (SD). Categorial variables are expressed as frequencies.

* Other: autoimmune or criptogenic cirrhosis.
3.2. Role of TRFs on the development of portal vein thrombosis

Eighty-one out of the 100 patients enrolled completed the study, 6 patients underwent orthotopic liver transplantation and 13 died during follow-up. Eight subjects presented PVT at baseline and were excluded from prognostic evaluation on PVT development. Among the patients evaluated during follow-up (n = 73), 12 developed de novo thrombosis within 1 year. Individual portal flow velocity and thrombus characteristics of these patients are described in Table 3, whereas flow velocity timing changes in patients without PVT are represented in Fig. 2.

The association of TRFs, clinical and demographic characteristics at baseline with PVT development during follow-up is shown in Table 4. As expected, a significant association between PVT development and high MELD score (p = 0.012) was observed. Serum levels of AT, protein C and protein S at baseline resulted significantly lower in patients who developed PVT (p = 0.011, p < 0.001 and p = 0.028, respectively). Similarly,
lowered platelet count was observed in PVT group \((p < 0.001)\).

Concerning haemodynamic parameter, patients with reduced portal vein flow velocity at baseline \((<15 \text{ cm/s})\) showed a significantly higher occurrence of PVT development \((91.7\% \text{ vs. } 19.7\%, p < 0.001)\).

The patients who developed portal thrombosis during follow-up had a mean basal value of portal flow velocity \((11.8 \pm 2.6 \text{ cm/s})\) significantly lower than that of the patients without portal thrombosis \((19.6 \pm 5.7 \text{ cm/s})\) \((p < 0.001)\). Using the receiver operating characteristic curve, 15 cm/s was identified as the best discriminating value in the prediction of portal thrombosis development (sensitivity 85.7\%, specificity 78.0\%). Patients with portal vein flow velocity at baseline <15 cm/s showed a significantly higher occurrence of PVT development \((47.8\% \text{ vs. } 2.0\%, p < 0.001)\).

A multivariate logistic backward regression model was built utilizing previously described variables at baseline associated with the presence of PVT within 1 year. In the final model, reduced flow rate was the only variable independently associated with the development of portal vein thrombosis (OR 44.9, 95% CI 5.3–382.7; \(p < 0.001\)).

4. Discussion

The concern that liver function failure is related to the development of severe coagulopathy is firmly established among hepatologists. This condition is mainly reflected by the prothrombin time (PT) and by APTT prolongation. PT is an excellent marker of liver failure and a strong independent prognostic factor of survival in patients with chronic liver disease. For this reason, new and old models of prognosis for patients with advanced liver disease include PT (or INR) as one of its components [38]. However, recent studies have shown that cirrhotic patients, in addition to diminished

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Demographic, clinical and biochemical data at baseline in patients who developed (PVT) or not (no PVT) portal vein thrombosis within 1 year of observation.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
<td>No PVT ((n = 61))</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.2 (11.3)</td>
</tr>
<tr>
<td>Male</td>
<td>44 (72.1%)</td>
</tr>
<tr>
<td>Ethiology</td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>38 (62.3%)</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>14 (23.0%)</td>
</tr>
<tr>
<td>Others</td>
<td>9 (14.7%)</td>
</tr>
<tr>
<td>MELD score &gt;13</td>
<td>26 (42.6%)</td>
</tr>
<tr>
<td>INR</td>
<td>1.35 (0.36)</td>
</tr>
<tr>
<td>Platelet cell count ((\times 10^3)/l)</td>
<td>103.3 (52.1)</td>
</tr>
<tr>
<td>ATIII</td>
<td>54.7 (19.4)</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>45.9 (18.9)</td>
</tr>
<tr>
<td>Protein S (%)</td>
<td>77.9 (20.0)</td>
</tr>
<tr>
<td>D-dimer (ng/ml)</td>
<td>1038 (1209)</td>
</tr>
<tr>
<td>APPT*</td>
<td>1.21 (0.33)</td>
</tr>
<tr>
<td>LAC positive</td>
<td>8 (13.1%)</td>
</tr>
<tr>
<td>Anti-β2 glycoprotein 1 (U/ml) ([&lt;20])</td>
<td>34 (9)(^b)</td>
</tr>
<tr>
<td>Cryoglobulins positive</td>
<td>10 (16.4%)</td>
</tr>
<tr>
<td>Homocysteine ((\mu)mol/l)</td>
<td>10.1 (4.4)</td>
</tr>
<tr>
<td>Portal flow rate &lt;15 cm/s</td>
<td>12 (19.7%)</td>
</tr>
<tr>
<td>Oesophageal varices</td>
<td></td>
</tr>
<tr>
<td>0/F1</td>
<td>52 (85.2%)</td>
</tr>
<tr>
<td>F2</td>
<td>6 (9.8%)</td>
</tr>
<tr>
<td>F3</td>
<td>3 (4.9%)</td>
</tr>
</tbody>
</table>

Quantitative values are expressed as means (SD). Categorical variables are displayed as frequencies (%). Significant values are expressed in bold.

\(^a\) Results are expressed as a ratio of test to reference coagulation times, using as reference a normal plasma tested in parallel with test plasmas.

\(^b\) Values refer to samples with anti-β2GpI \(>20\) U/ml \((n = 10\) and \(n = 3\), respectively).
hepatic synthesis of clotting factors, also have a profound deficit of natural anticoagulants, such as protein C and AT, which may counterbalance the bleeding tendency caused by the deficiency in procoagulants [3,39].

In a previous study, TRFs were found to be independently associated with the extent of fibrosis in patients with chronic hepatitis [10]. The results obtained in the present study confirm several earlier reports showing that haemostatic tests could be of great practical value in the assessment of hepatocyte function in liver disease [6,13,27,40,41]. Not surprisingly, our study showed that the reduction in the level of antithrombotic proteins is strongly related to the severity of liver cirrhosis according to the MELD scoring system. Moreover, markers of hemostasis activation such as D-dimer were increased in the majority of our patients. D-dimer was significantly higher in patients with MELD ≥ 13, suggesting that the extent of hemostasis activation is related to severity of cirrhosis. The significant negative correlation between levels of D-dimer and both AT and protein C provides further evidence that a hypercoagulation state is due to the loss of the natural anticoagulant proteins.

One possible consequence of the hemostasis activation could be the development of PVT, which is a negative prognostic factor in patients with advanced liver disease [42,43]. Understanding the factors predisposing to PVT would be important in identifying the subgroup of patients at higher risk and may ultimately aid decisions regarding the use and duration of anticoagulation therapy.

As already mentioned, PVT in patients with liver disease is the result of concomitant local, acquired and inherited thrombophilic factors [16,44]. Our study, evaluated prospectively for the first time the role of acquired TRFs and local hemodynamic factors as predictors of PVT development. We found that plasma levels of anticoagulant proteins, such as protein C, protein S and AT, were lower in cirrhotic patients who developed PVT during follow-up than in those without PVT. The association between grading of oesophageal varices and thrombotic events in cirrhotic patients reported by others authors [23] could not be supported by our data. Moreover, no association was found between PVT development and shorted aPTT, which has been previously associated with venous thromboembolism [45]. Conversely, other factors resulted to be related to the development of PVT at least at univariate analysis. The association of low platelet count to PVT has been already found by Francoz et al. [18] and we agree with these authors that in cirrhotic patients the impact of portal hypertension reflected by hypersplenism overcomes the proper effect of low platelet count in preventing PVT occurrence. Furthermore, an important role was played by an advanced disease staging as well as by the reduction of portal flow velocity. These data are not surprising if we consider that PVT is usually a late event in the natural history of liver cirrhosis occurring more frequently in patients with uncompensated disease [21]. This is further confirmed by the epidemiological data showing that the PVT prevalence is about 15% in uncompensated patients submitted to liver transplantation [18,20,46] and is higher than that reported in a series of consecutive outpatients or in hospitalized cirrhotics (7.5–11.2%) who show a minor degree of liver function failure [16,29,47].

Moreover, it is interesting to note that the only factor confirmed at multivariate analysis as predictors of PVT development was the reduced portal flow velocity, thus suggesting that local haemodynamic factors could be more important than systemic anticoagulant deficiency in the pathogenesis of PVT.

It is well known that portal flow velocity is inversely related to Child–Pugh score being lower in patients in class C compared to patients in classes B or A [48] and that when lower than 10 cm/s it is an independent risk factor for patients’ survival [49]. However, we have demonstrated for the first time that the decreased velocity and stagnation of portal blood flow may act as the most important prognostic factor for PVT development. One possible explanation of these results is that the amount of active thrombin generated in the portal circulation, although reduced if compared to a normal condition, is not washed away by an adequate flow. It is reasonable to argue that this effect, together with the presence of reduced levels of protease inhibitors, as shown in the present study, could favour triggering of coagulation and local thrombosis.

Further studies are needed in order to assess the relevance of these parameters in a larger population sample, to identify additional risk factors and to assess the prognostic effect of anticoagulation therapy and portosystemic shunting in patients with established PVT.

Acknowledgements

This work has been supported by an unrestricted grant provided by Fondazione Ricerca in Medicina, Bologna, Italy.

References


