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*Original Article*

# The etiology of chronic splanchnic vein thrombosis in adults: a two-center analysis

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**Abstract:** Portal vein thrombosis (PVT) and Budd-Chiari syndrome (BCS) are rare vascular disorders with both well-recognized and less commonly identified etiologies. Objectives: This study aims to investigate the etiologies of portal vein thrombosis (PVT) and Budd-Chiari syndrome (BCS), thereby enhancing improving early detection and management strategies for these conditions. A retrospective review was undertaken to identify the etiologies of PVT and BCS. Methods: A detailed clinical evaluation was performed and all underlying diseases, such as MPD, and related conditions (e.g. surgery) associated with thrombosis were recorded. Results: The study comprised a total of 73 patients, with 58 diagnosed with PVT and 15 with BCS. Of these patients, 56 (76.7%) had at least one underlying disease. The most prevalent underlying diseases in patients with PVT were cirrhosis (32/58, 55.2%), myeloproliferative disease (3/58, 5.2%), malignancy (4/58, 6.9%), and rheumatological conditions (4/58, 6.9%). For BCS, 11/15 patients (73.3%) had at least one predisposing condition, including cirrhosis in six cases. Congenital causes were identified in 16/58 cases of PVT (27.6%), in 7/15 cases of BCS (46.7%). Thirty-two patients had previously undergone gastrointestinal surgery (PVT 24/58, BCS 8/15); surgery was the sole etiology in 15/73 patients (20.5%). Homocysteinemia was common (PVT 20/58, BCS 5/15). A multitude of rare etiologies were identified, including paroxysmal nocturnal haemoglobinuria, Crohn's disease, nephrotic syndrome, drug therapies, pregnancy, JAK2 mutation, and elevated factor VIII or fibrinogen. Conclusions: The presence of a wide range of diverse frequent-infrequent etiologies of congenital or acquired splanchnic vein thrombosis in this cohort underscores the necessity for the implementation of appropriate diagnostic strategies in a broad spectrum of at-risk patients.

**Keywords:** Splanchnic vein thrombosis, portal vein thrombosis, Budd-Chiari syndrome

## Introduction

Splanchnic vein thrombosis (SVT) is an uncommon form of venous thrombosis, which includes portal vein thrombosis (PVT) and thrombosis of the hepatic venous system (Budd-Chiari syndrome [BCS]) [1]. These conditions which share many risk factors and clinical features. PVT is an unusual thrombotic condition which obstructs the portal vein and its tributaries. In cases of chronic, partial PVT, where the portal vein is not fully occluded, the condition is often clinically silent but can also lead to various possible sequelae such as variceal hemorrhage and intestinal ischemia [2, 3], and the potentially life-threatening complications of ischemic hepatitis, liver failure or small intestinal infarction. Partial PVT can also progress to complete occlusion, with associated complications such as intestinal infarction, which can result in a high rate of mortality and postoperative problems. Chronic PVT can induce portal hypertension, or lead to decompensation in cirrhotic patients. While PVT is rare in the general population, it has a higher prevalence in three main categories of patients. These are patients with (i) cirrhosis and portal hypertension, or other chronic liver diseases, (ii) local hepatobiliary, pancreatic or gastrointestinal primary or secondary malignancies and (iii) myeloproliferative

disorders (MPD) or other including such as major abdominal infections or inflammation (e.g. inflammatory bowel disease) [4]. As the severity of cirrhosis increases, so too does the risk of PVT. In well-compensated disease, the risk is less than 1%, but in advanced cases it can reach as high as 16% [2, 5]. Furthermore, multiple prothrombotic risk factors are common and can compound the risk for PVT [6]. A large analysis of autopsy data from a single centre suggested that cirrhosis increases the risk for PVT five-fold, but that the risk is increased 17-fold in the presence of concurrent hepatic cancer [7]. This finding is corroborated by a large registry analysis study, which reported a 36% incidence of PVT among patients undergoing transplantation for concurrent cirrhosis and hepatocellular carcinoma [8]. In a significant minority of patients, the etiology remains unknown; however, the proportion of these cases has decreased in recent years due to the identification and detection of more prothrombotic states [6].

BCS is a group of disorders of hepatic vein outflow characterized by thrombosis at various levels from the hepatic veins to the suprahepatic inferior vena cava [9]. The manifestations of BCS are heterogeneous. Symptoms such as abdominal pain, ascites and hepatomegaly occur frequently, but patients may also present with acute liver failure [10]. As a hepatic manifestation of underlying prothrombotic conditions, the etiology of BCS shows substantial overlap with that of PVT, except that BCS secondary to cirrhosis is uncommon [11]. BCS is typically caused by relatively uncommon profibrotic disorders, including MPD and inherited or acquired thrombophilia conditions [12].

In addition to the well-recognized etiological factors of SVT, certain widespread conditions such as Crohn's disease can occasionally cause PVT or BCS and, conversely, certain rare prothrombotic diseases, such as Behçet's disease and paroxysmal nocturnal haemoglobinuria (PNH), have been shown to carry a high level of risk [13]. The complex interplay of factors and the significant prevalence of asymptomatic cases necessitate meticulous documentation of various etiologies in PVT and BCS, along with a comprehensive diagnostic approach, to ascertain underlying causes in these patients and initiate targeted management. A retrospective study was undertaken to determine the etiology of chronic PVT and BCS in a consecutive cohort of adult patients in Turkey.

## Materials and methods

### *Patient selection*

The present retrospective study identified all patients over the age of eighteen with PVT and BCS who were managed at Mersin University Hospital and Cukurova University Hospital in Turkey during the period 2010-2015 were identified. The diagnosis of both conditions was based on abdominal color Doppler ultrasonography performed in supine, fasting patients (GE Healthcare LOGIC P6, Aurora, OH, USA). A detailed clinical evaluation was performed and all underlying diseases, such as MPD, and related conditions (e.g. surgery) associated with thrombosis were recorded. Follow-up data for a minimum period of one year were available for all cases. Individuals under the age of eighteen, for whom demographic information was not available, those for whom etiological examinations were incomplete, and subjects who have a follow-up period of less than one year were excluded from the study. The study was approved by the Clinical Research Ethics Committee of Mersin University (date and decision no: 2023/197).

### *Laboratory investigations*

In all cases, with the exception of those patients suffering from cirrhosis, nephrotic syndrome or those receiving anticoagulant/antiaggregant therapy, the following parameters were measured: protein C, protein S, antithrombin III activity, factor VIII and fibrinogen levels. Antiphospholipid antibodies (anticardiolipin IgG and IgM, and anti-La antibodies), factor V Leiden mutations (R506Q), PG20210A mutation, *JAK2* V617F mutations and homocysteine levels were documented in all patients. All patients were assessed for the presence of PNH, using flow cytometry with fluorescein-labeled proaerolysin (FLAER) assay of granulocytes and red blood cells.

Protein C and protein S activity (Clotting Assay Bioclot Pr C/Pr S, Biopool AB, Umea, Sweden), antithrombin III activity (Stachrom ATIII, Diagnostica Stago, Asnières-sur-Seine,

**Table 1.** Underlying diseases in patients with portal venous thrombosis (PVT) or Budd-Chiari syndrome (BCS), n (%)

| Underlying diseases | PVT (n=58) | BCS (n=15) |
|---|---|---|
| Any underlying disease | 45 (77.6) | 11 (73.3) |
| Cirrhosis | 32 (55.2) | 6 (40.0) |
| Myeloproliferative disease | 3 (5.2) | 1 (6.7) |
| Polycythemia *vera* | 1 (1.7) | 1 (6.7) |
| Primary myelofibrosis | 1 (1.7) | 0 (0.0) |
| Essential thrombocytosis | 1 (1.7) | 0 (0.0) |
| Malignancy | 4 (6.9) | 0 (0.0) |
| Hepatoma | 1 (1.7) | 0 (0.0) |
| Cholangiocellular carcinoma | 1 (1.7) | 0 (0.0) |
| Colon adenocarcinoma | 1 (1.7) | 0 (0.0) |
| Multiple myeloma | 1 (1.7) | 0 (0.0) |
| Rheumatological conditions | 4 (6.9) | 2 (13.3) |
| Scleroderma | 2 (3.4) | 0 (0.0) |
| Behçet's disease | 0 (0.0) | 1 (6.7) |
| Ankylosing spondylitis | 1 (1.7) | 0 (0.0) |
| Familial mediterranean fever | 1 (1.7) | 0 (0.0) |
| Rheumatoid arthritis | 0 (0.0) | 1 (6.7) |
| Other | 2 (3.4) | 2 (13.3) |
| Paroxysmal nocturnal hemoglobinuria | 1 (1.7) | 1 (6.7) |
| Crohn's disease | 0 (0.0) | 1 (6.7) |
| Nephrotic syndrome | 1 (1.7) | 0 (0.0) |

France), anticardiolipin IgG and IgM (Imulyse ACA, Biopool, Sweeden), and anti-La antibodies (Bioclot LA, Biopool AB, Umea, Sweden), were measured using commercial kits. The presence of the Factor V Leiden (R506Q) and PG20210A mutations was detected by the amplification of the related genes by polymerase chain reaction (PCR) (LightCycler 480 Instrument II, Roche Life Science). The *JAK2* V617F mutation was analyzed by real-time PCR reaction (RT-PCR). The assessment of fibrinogen and FVIII levels was conducted through the utilisation of the Destiny Plus™ - Medium Throughput Haemostasis Analyser (Tcoag Ireland Ltd, Bray, Ireland). The homocysteine level was measured by high performance liquid chromatography (HPLC; Agilent GC Systems, Ratingen, Germany) using Chromsystems kit.

The data are presented separately for patients with PVT or BCS. All analyses were descriptive.

*Statistical analysis*

IBM SPSS v.22 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) is a software program used for statistical data evaluation. Descriptive statistics were calculated as mean and standard deviation or the median, minimum and maximum values for numerical data, as appropriate. Frequency and percentage values were used for categorical data.

## Results

*Demographic information*

The cohort consisted of 73 patients, including 58 with PVT and 15 with BCS. The median age of the cohort was 46 years (range 18-82 years).

*Risk factors*

Risk factors identified included cirrhosis, surgery, and homocysteinemia. A comprehensive analysis of the cohort's thrombotic risk factors is provided in **Tables 1** and **2**.

*Analysis results*

A total of 73 patients were identified with PVT or BCS and were included in the study. Of these 58 (79.5%) had PVT and 15 (20.5%) had BCS. The cohort included 40 females and 30 males, with a median age of 46 years (range 18-82 years). In total, 56/73 patients (76.7%) had an underlying acquired disease (**Table 1**). More than half of the patients with PVT had cirrhosis (32/58, 55.2%) (**Table 1**). In addition to these primary conditions, other predisposing diseases were identified in more than one patient with PVT. These included MPD (3/58, 5.2%), malignancy (4/58, 6.9%), and rheumatological conditions (4/58, 6.9%) (**Table 1**). Crohn's disease and nephrotic syndrome were each present in a single patient. In the subgroup with BCS, 11/15 patients (73.3%) had an underlying disease, most frequently cirrhosis (6/15, 40.0%) (**Table 1**).

Underlying events or acquired conditions related to PVT or BCS is summarized in **Table 2**. Surgery (24/58, 41.4%) and homocysteinemia (20/58, 34.5%) predominated in patients with

**Table 2.** Underlying events, concomitant medications, or acquired conditions related to portal venous thrombosis (PVT) or Budd-Chiari syndrome (BCS), n (%)

| Underlying Events | PVT (n=58) | BCS (n=15) |
|---|---|---|
| Surgery | 24 (41.4) | 8 (53.3) |
| Intestinal surgery | 7 (12.1) | 3 (20.0) |
| Cholecystectomy | 4 (6.9) | 2 (13.3) |
| Splenectomy | 6 (10.3) | 0 (0.0) |
| Gynaecologic surgery | 3 (5.2) | 2 (13.3) |
| Vascular surgery | 3 (5.2) | 0 (0.0) |
| Renal surgery | 1 (1.7) | 0 (0.0) |
| Hepatic surgery | 0 (0.0) | 1 (6.7) |
| Drug therapy | 6 (10.3) | 0 (0.0) |
| Oral contraceptive | 4 (6.9) | 0 (0.0) |
| Roaccutane | 1 (1.7) | 0 (0.0) |
| Etanercept | 1 (1.7) | 0 (0.0) |
| Other | 36 (62.1) | 13 (86.7) |
| Pregnancy[a] | 2 (3.4) | 0 (0.0) |
| *JAK2* V617F mutation | 2 (3.4) | 3 (20.0) |
| Homocysteinemia | 20 (34.5) | 5 (33.3) |
| Elevated factor VIII | 8 (13.8) | 3 (20.0) |
| Elevated fibrinogen | 4 (6.9) | 2 (13.3) |

[a]None of the gynaecologic surgical procedures was related to pregnancy.

PVT (**Table 2**). Previous surgery was also frequent in cases of BCS (8/15, 53.3%). Of the 32 cases in which surgery had taken place prior to SVT, it was the sole cause in 15/73 patients (20.5%) and had occurred in conjunction with one or more other causes in the remaining 17 cases (17/73, 23.2%). Five patients (two PVT, three BCS) who developed thrombosis due to a *JAK2 V617F* mutation, three of whom (one PVT, two BCS) did not have MPD.

In this study, a congenital cause was identified in 16/58 cases of PVT (27.6%) and in 7/15 cases of BCS (46.7%). Factor V Leiden heterozygous mutation was the most common congenital cause of PVT, with protein C or protein S deficiency being frequent causes in both diseases (**Table 3**).

No patient had been diagnosed with omphalitis, sepsis or a history of abdominal trauma. The presence of antiphospholipid syndrome was excluded in the present cohort, as indicated by the absence of anticardiolipid and anti-La antibodies. In addition, in 8.2% of cases (n=6), no discernible cause was detected (two PVT, four BCS).

Cavernous transformation of the portal vein, a mass-like network of collateral veins around the portal vein, occurred in 34 patients with PVT (58.6%), of whom nine (26.5%) had a congenital cause.

## Discussion

An analysis of this series of patients managed at two centers in Turkey provides additional insight into the complex and wide-ranging etiologies in PVT and BCS. The findings confirm cirrhosis as the most frequent causal factor in PVT [14]. Indeed, in our series, more than half of all patients with PVT had cirrhosis. The pattern of non-cirrhosis thrombophilic etiologies was broadly similar to previous reports which examined cases of PVT in the absence of liver disease [15]. The incidence of overt MPD was lower in our cohort than expected, based on data previously published by other researchers [11, 16]. This discrepancy may be attributable to differing diagnostic criteria, a topic which remains the matter of debate in the setting of SVT. In a large single-center study of autopsy data [7], the incidence of cirrhosis among PVT patients was lower, and the rate of malignancy was higher, than in our population. It can be hypothesised that these differences are likely to reflect higher mortality rates among patients with cirrhosis and malignancies. Therefore, their preponderance in autopsy data may be indicative of their significance when compared to hormonal or inherited thrombophilic causes. Another consecutive case series has reported a similar variety of thrombotic risk factors, both congenital and acquired, in patients with BCS to those observed in this study [11].

Etiologies in our population included several relatively rare inflammatory or prothrombotic diseases known to increase the risk for SVT. The presence of Behçet's disease, a chronic systemic inflammatory condition, in our region was not unexpected, given its prevalence along the historical Silk Road trade route [17]. The identification of Behçet's disease as a potential cause of BCS in a single patient is of significance to our research. One case of PVT and one case of BCS were caused by the rare prothrombotic condition PNH, which was diagnosed only after onset of SVT as part of the

**Table 3.** Congenital causes of portal venous thrombosis (PVT) or Budd-Chiari syndrome (BCS), n (%)

| Congenital Causes | PVT (n=58) | BCS (n=15) |
|---|---|---|
| Any congenital cause | 16 (27.6) | 7 (46.7) |
| Factor V Leiden heterozygous mutation | 7 (12.1) | 1 (6.7) |
| *G20210A* prothrombin gene mutation | 5 (8.6) | 2 (13.3) |
| Protein C deficiency | 6 (10.3) | 4 (26.7) |
| Protein S deficiency | 6 (10.3) | 3 (20.0) |
| Antihrombin III deficiency | 3 (5.2) | 3 (20.0) |

investigation into etiologic factors. PNH, in which uncontrolled complement activation leads to intravascular hemolysis, is considered the most severe acquired thrombophilic state. BCS, and to a lesser extent PVT, are established complications of PNH, and are associated with a high risk of mortality [18]. It is also important to be aware that relatively routine diseases, such as the inflammatory conditions Crohn's disease and nephrotic syndrome, are also infrequent causes of PVT or BCS. Omphalitis, defined as inflammation of the umbilical cord stump in the neonate, is a rare cause of PVT and portal vein hypertension [19] but was not observed within the confines of our population. Similarly, although abdominal trauma [20] has been implicated in PVT and BCS on very rare occasions, it did not contribute to the condition in this cohort of patients.

The diversity of thrombophilic risk factors in this cohort highlights the importance of a complete investigation of thrombophilia. A thrombophilia screening protocol include the assessment of protein C, protein S, antithrombin III, the factor V Leiden mutation, the factor VIII level, the JAK2 mutation, homocysteine levels, and a variety of additional assays. However, the rarity of SVT and the relatively low number of published case series with varying inclusion criteria and diagnostic protocols make it difficult to establish the true prevalence of inherited prothrombotic disorders in PVT [7, 15]. In our population under scrutiny, the prothrombotic factor V Leiden mutation was identified as the most prevalent congenital cause, thereby substantiating its established correlation with both PVT and BCS [21]. Protein C, protein S and antithrombin III were not measured in patients with cirrhosis since lower levels of these factors can occur secondary to parenchymal liver disease, lowering the observed incidence of deficiency syndromes in our cohort. A series that excluded patients with cirrhosis found that protein C and protein S deficiencies were the most prevalent inherited prothrombotic conditions in PVT [15].

The JAK2 V617F mutation has recently attracted substantial attention, given its profound association with thrombogenesis, which is mechanically implicated through endothelial damage, increased blood cell adhesion, and facilitation of neutrophil extracellular trap formation [22]. It has been established that JAK2 V617F-mutated myeloproliferative neoplasms (MPN) are characterised by the unregulated proliferation of bone marrow progenitors, which in turn results in an elevated risk of SVT [23]. Polycythemia vera (PV), a myeloproliferative neoplasm characterized by an increased red blood cell mass and increased risk of thrombosis [24]. As a result, the diagnosis of MPD as a cause of SVT has increased and PVT can now be the first detected symptom of such disorders [6]. Consistent with published data [25-27], *JAK2* V617F was frequent in patients with BCS in our series (20.0%) but the incidence was strikingly low (3.4%) in patients with PVT. This contrasts with other studies which have observed *JAK2* V617F in 20-43% of PVT cases [28-30], but lower rates (0-10%) are not unknown [31, 32]. Interestingly, three patients had the *JAK2* V617 mutation without MPD, as has been reported previously in patients with SVT and normal peripheral blood counts [28, 33, 34]. *JAK2* V617F screening represents a useful component of the diagnostic workup for SVT, and should not be restricted to patients with known MPD.

SVT is a rare but well-known complication after abdominal surgery. In our series of patients, surgery was the sole cause of SVT in 20% of patients, and a contributory factor in a further 23%. PVT can be caused by local injury to the portal vein axis following intraabdominal surgical procedures such as laparoscopic splenectomy or colectomy, pancreatic surgery, portal systemic shunts and devascularization. A recent study observed a 10-fold increase in PVT after splenectomy in patients with liver cirrhosis [35], and PVT has been reported in up to

50% of patients after splenectomy [36]. Surgical complications are a less frequent cause of BCS. The choice of surgical technique can affect the risk for SVT. A recent analysis of 116 cases has concluded that splenorenal shunt with pericardial devascularization reduces the risk for postoperative PVT in comparison with splenectomy or selective devascularization in cirrhotic patients with portal hypertension [37]. Biomarkers can also be used to determine the risk for SVT after surgery: platelet count is the standard marker but novel molecular markers, such as the fibrin degradation product D-dimer [38], may have a better predictive value to guide prophylactic treatment decisions.

The risk of SVT is increased in patients with antiphospholipid syndrome, and current guidelines recommend the routine screening for antiphospholipid antibodies in patients with SVT [39].

Furthermore, the risk of developing splanchnic vein thrombosis in the early stages of acute pancreatitis (AP) is significant, and may affect up to a quarter of patients [40]. However, antiphospholipid syndrome and AP was not detected in our cohort, possibly due to the small number of cases.

Although limited by a small population size, these findings demonstrate the multifactorial etiology of SVT. Awareness of the risk of PVT or BCS in patients with various congenital or acquired prothrombotic conditions - including rare disease conditions which carry a high risk - may help to trigger appropriate diagnostic procedures and avoid progression to fatal complications in undetected cases.

## Conclusion

This study highlights the importance of identifying etiological factors in PVT and BCS for better management and prevention. Future studies with larger cohorts are needed to confirm these findings and explore potential therapeutic interventions.

## Disclosure of conflict of interest

None.

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