Budd-Chiari Syndrome:

New insights in Pathogenesis, Management and Prognosis

Sarwa Darwish Murad

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Success has taste only
when you fight for it

Fawzi Darwish Murad

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Abstract

Budd-Chiari Syndrome is a rare, challenging clinical condition which is characterised by a hepatic venous outflow obstruction, usually caused by a thrombotic occlusion at the level of the small hepatic veins until the entrance of the inferior vena cava into the right atrium. It affects usually young adults, mostly female.

The classical clinical presentation is a triade of abdominal pain, hepatomegaly and ascites, but usually, there are large inter-individual differences ranging from asymptomatic cases to patients with portal hypertension or even liver failure. Budd-Chiari syndrome can be classified in a primary form, typified by an endoluminal lesion of mostly thrombotic origin, and a secondary form, characterised by an extravascular lesion invading or compression the lumen.

The aetiology is complex and multifactorial, and usually consists of a combination of underlying inherited and acquired thrombophilia. Among the main causes are myeloproliferative disorders, Factor V Leiden mutation, prothrombine gene mutation and deficiencies of natural coagulation inhibitors, but also antiphospholipid syndrome and use of oral contraceptives. The outflow obstruction, resulting in increased sinusoidal pressure causes centrilobular congestion and ischaemia, with a decrease in portal inflow.

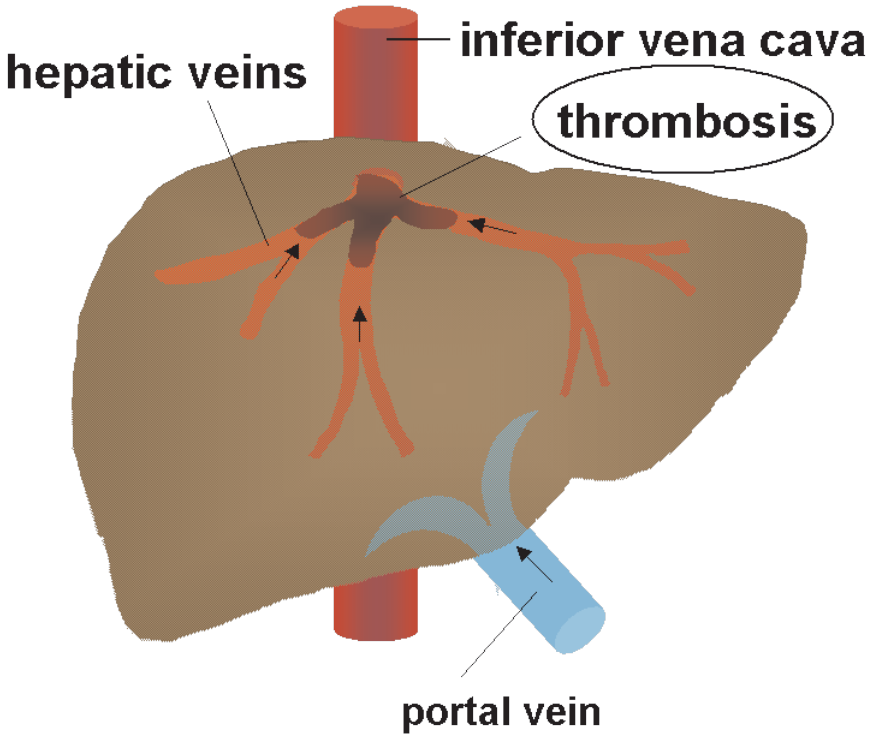
Therapeutic options range from conservative measures to derivative procedures and eventually liver transplantation. Anticoagulation seems mandatory to prevent further ungoing thrombosis but should be used with caution when there is a history of variceal bleeding. Hepatic vein angioplasty, vascular stents and thrombolysis can be attempted in patients with a short history of thrombosis. Surgical portosystemic shunting was commonly used in the past as a derivative procedure to convert the portal vein from an inflow to an outflow tract. The rationale for this type of shunting is decreasing since the introduction of the TIPS, which shows promising results in the treatment of Budd-Chiari Syndrome, especially when covered stents are used. Liver transplantation is reserved for patients with end-stage liver disease.

The overall 5-year survival in Budd-Chiari Syndrome currently ranges from 64-69%. Age, renal function and the Child-Pugh score and its components appear to be of prognostic value to assess disease severity in terms of survival probabilities.

Introduction

Budd-Chiari Syndrome is a rare clinical disorder caused by the obstruction of hepatic veins or the inferior vena cava [1, 2] (figure 1). It presents with abdominal pain, hepatomegaly, ascites, and leads to severe congestion and necrosis, which can result in fibrosis and ultimately cirrhosis. Sometimes liver function deteriorates rapidly, leading to acute liver failure [3-5]. The extension of the hepatic vein or inferior vena cava obstruction is variable and expressed in different clinical courses.

Figure 1
Hepatic outflow obstruction caused by thrombosis in Budd-Chiari Syndrome.



Historical perspective

In 1845, Budd described several cases of intrahepatic abscesses that involved one of the hepatic veins and resulted in thrombosis [6]. Budd did not describe the clinical picture of hepatic vein occlusion. In 1899, Chiari collected cases in whom the occlusion was thought to be due primarily to inflammation of the wall of the large hepatic veins [7]. He established occlusion of hepatic veins as a disease entity, independent of an associated liver disorder and he presumed the disease to be syphilitic in origin. The described occlusion was limited to the hepatic vein ostia. Subsequently, the entity was identified as obliterating endophlebitis and characterised as Chiari's disease or syndrome, or Budd-Chiari disease or syndrome. Thompson and Turnbull reported in 1921 on hepatic vein obstruction associated with a fibrous diaphragm in the intrahepatic vena cava. In contrast to Chiari, they strongly supported the view that the disease

can be explained on the basis of thrombosis alone, and they rejected the syphilitic origin [8]. In 1929, Oppenheimer recognised the association with polycythemia rubra vera, a myeloproliferative disorder which is nowadays considered a major cause for BCS [9]. In 1959, Parker distinguished symptomatic and asymptomatic hepatic vein occlusion and related the latter to the fact that some large hepatic veins remain patent [3]. He concluded that although the vascular lesions can be explained in terms of thrombosis alone, initial endophlebitis couldn't be excluded. In the sixties and seventies numerous reports from Asia and South Africa were published on primary involvement of the hepatic portion of the inferior vena cava usually associated with partial or complete hepatic vein obstruction [2].

Terminology and definition

Several authors have challenged the term Budd-Chiari syndrome (BCS) as ambiguous and attempted to introduce other nomenclatures [1, 2] (Table 1). Although important for our understanding of BCS, most of these nomenclatures have not entered clinical practice. The term Budd-Chiari syndrome has been retained because it is more concise than other terminologies ever proposed to designate the whole spectrum of disorders encompassed by the present definition [10]. Budd-Chiari syndrome is defined as: hepatic venous outflow obstruction and its manifestations, regardless of the cause and regardless of the level of obstruction from the small hepatic veins to the entrance of the inferior vena cava into the right atrium.

According to this definition, two entities bearing many pathophysiological and clinical similarities with BCS are excluded:

- Heart diseases impairing hepatic venous outflow. Right-sided congestive heart failure can be very difficult to distinguish from BCS. This applies particularly to constrictive pericarditis predominantly involving the juxtacaval pericardium, as well as right atrial myxoma obstructing the entrance of inferior vena cava.
- Veno-occlusive disease (VOD), also referred to as sinusoidal obstruction syndrome, is defined as a non-thrombotic obstruction of central and/or sublobular hepatic veins by concentric luminal narrowing due to subendothelial edema or fibrosis. Veno-occlusive disease occurs in relation to application of toxic agents and is, at present, encountered almost exclusively in association with bone marrow transplantation [11]. The epidemiology, cause, pathophysiology, treatment and prognosis of veno-occlusive disease are such distinct from other forms of hepatic venous outflow obstruction that it should be considered a separate disease entity [12]. With the exception of veno-occlusive disease as defined above, obstruction limited to the small veins is generally due to thrombosis, allergic phlebitis or granulomatous involvement, all reported causes of obstruction affecting the large hepatic veins [13]. Although the manifestations of BCS are sometimes difficult to distinguish from those of veno-occlusive disease, the context is different. When liver imaging shows no signs of large vein obstruction, the differentiation between small vein thrombosis and veno-occlusive disease can be made by means of liver biopsy.

Table 1
Previously reported terms given to the entity Budd-Chiari syndrome or its subsets.

Endophlebitis obliterans hepatica
Chiari's disease
Budd-Chiari's syndrome
Veno-occlusive disease
Thrombosis of the hepatic veins
Membranous obstruction of inferior vena cava
Coarctation of inferior vena cava
Obliterative/occlusive hepatocavopathy
Obstruction of the hepatic veins
Hepatic venous outflow obstruction/block

Classification

Obstruction of the hepatic venous outflow tract is classified according to its location: small hepatic veins, large hepatic veins, inferior vena cava and combined obstruction of large hepatic veins and inferior vena cava (Table 2) [1]. This classification can be used in the absence of pathological examination of the venous outflow tract, which should be preferred in future clinical investigations [14]. In general, the site of obstruction is easily determined through non-invasive imaging (Doppler-ultrasound, magnetic resonance, computed tomography) or conventional venography.

There is currently no consensus on the classification of disease severity (fulminant versus non-fulminant) and disease duration (acute, subacute and chronic). To be clinically useful, such a classification should be based on factors influencing prognosis and factors, which guide physicians in their management of the disease. These factors should ideally be extracted from studies based on large retrospective or prospective data sets. A purely descriptive stratification for disease severity should be used in clinical studies until such a prognostic classification is validated. In previous classifications, duration of symptoms, rate of disease progression, severity of manifestations, and the age of venous or hepatic lesions have been variously used to differentiate among fulminant, acute, subacute or chronic disease [5, 13, 15-19]. The prognostic value of these categories has not been assessed. It is well known that the disease can either have a long insidious course or a rapid downhill course. Furthermore, the apparent age of the macroscopic and microscopic damage to the liver may differ from the apparent duration of symptoms. Several cases with a recent clinical onset have been associated with marked liver fibrosis, suggesting a long preclinical course [3]. Recent thrombosis superimposed on older lesions probably explains the acute clinical onset in these patients.

Table 2
Classification of Budd-Chiari syndrome according to the site of obstruction [10]

Designation	Definition
Small hepatic veins	Veins that cannot be shown clearly on hepatic venograms or by ultrasound studies; they include terminal hepatic veins (central veins), intercalated veins, and interlobular veins
Large hepatic veins	Veins that are regularly demonstrable on hepatic venograms and ultrasound studies; segmental branches of hepatic veins are generally included
Inferior vena cava	A segment of the IVC which extends from the entry level of the right, middle, and left hepatic veins to the junction between the IVC and the right atrium
Combined obstruction	Combination of obstruction in the large hepatic veins and inferior vena cava

Clinical features

Two-third of the patients with BCS are female and most of them are diagnosed at an age of 20 to 40 years. Most patients present with obstruction of the hepatic veins, sometimes combined with obstruction of the inferior vena cava (Table 3). Membranous obstruction of the vena cava is rarely seen in western patients, but much more prevalent in middle- or east Asia, and in Africa.
Clinically, a classical triad of hepatomegaly, ascites and abdominal pain is found in many patients. However, the clinical course may show marked inter-individual differences. Some patients exhibit clinical signs of portal hypertension, such as variceal bleeding and refractory ascites with relatively intact hepatic function. Others present with liver failure, including hepatic encephalopathy, jaundice and biochemical signs of severe hepatocellular dysfunction (Table 4). Common laboratory findings are represented in table 5.

It is important to recognize that BCS is not always a severe disease requiring aggressive treatment. Lack of long-term prognostic studies of unselected patients has limited our knowledge about the real prevalence of the different clinical forms of the syndrome. BCS is considered asymptomatic when there are no signs of abdominal pain, ascites, hepatomegaly, edema, encephalopathy and gastro-intestinal bleeding, nor a history of any of them [20]. The diagnosis of asymptomatic BCS in these patients is often made in the course of a routine examination, e.g. in patients with myeloproliferative syndrome.

Table 3
Site of outflow obstruction in a western population with Budd-Chiari syndrome (n=237) [71].

Site of outflow obstruction (%)	
Hepatic veins	147 (62)
Inferior vena cava	17 (7)
Combined hepatic veins and inferior vena cava	73 (31)
Membranous obstruction of inferior vena cava	9 (4)
Portal vein obstruction	34 (14)

Table 4
Patient characteristics at the time of diagnosis in patients with Budd-Chiari Syndrome [71].

Characteristic	%
ascites	84%
hepatomegaly	76%
splenomegaly	51%
abdominal pain	53%
jaundice	21%
leg edema	15%
fever	18%
encephalopathy	10%
variceal bleeding	8%

Table 5
Common laboratory findings in patients with Budd-Chiari Syndrome.

Laboratory test	Change in BCS
Aminotransferases	Mild increase (x 1-5 ULN) in the majority of patients. May occasionally be high (up to 100 x ULN), particularly so in the fulminant form.
Bilirubin	Mild increase usual.
Prothrombin time	Moderate decrease usual. Marked decrease in the fulminant form.
Hematocrit	May be low, normal or high. Suggest polycythemia vera when increased.
Platelet count	May be low, normal or high. Suggest primary myeloproliferative disorders when high normal or frankly increased.
White blood cell count	May be low, normal or high. Increased counts in the absence of infection may be seen in patients with underlying myeloproliferative disorders.

Aetiology

An extensive systematic investigation for the aetiology should always be initiated once the diagnosis has been confirmed. BCS can be classified into a primary and a secondary type (Table 6). Primary BCS is defined as hepatic outflow obstruction caused by the presence of an endoluminal vascular lesion within the hepatic veins. In western countries, this lesion is usually caused by thrombosis in the presence of a hypercoagulable state, which is either an acute event or a chronic development. In developing countries such as India, China, Nepal and South-Africa, a thin membrane (i.e. web) occluding the inferior vena cava is much more prevalent. Okuda and colleagues have proposed a different nomenclature for IVC thrombosis as they believe significant differences exists between "classical BCS" and IVC thrombosis [2, 21]. Patients with so-called obliterative hepatocavopathy exhibit a more insidious clinical presentation with remarkable subcutaneous abdominal dilated veins and have often infection-associated causes. However, hypercoagulable states and prothrombotic disorders are difficult to diagnose in developing countries. Furthermore, Valla et al. reported on patients with short-segment stenosis, defined as smooth tapering of the hepatic venous lumen over a maximum length of 4 cm, which could also manifest in a membranous obstruction of the hepatic veins at the ostia [22]. In this study, the authors concluded that this condition is the result of previous caval thrombosis and should therefore not be considered as separate etiological entity. Therefore, nowadays hepatic vein thrombosis as well as IVC thrombosis are still both considered manifestations of BCS.

Secondary BCS is caused either by a malignancy or parasitic mass invading the vascular lumen, or by extrinsic compression of the hepatic veins and/or inferior vena cava by lesions in the vicinity of the vessel, such as abscesses, cysts or solid tumors. In practice, BCS is regarded as primary when no causes of secondary obstruction can be found by radiological imaging techniques.

Table 6
Classification of Budd-Chiari syndrome according to etiology [10].

Designation	Definition
Primary	Hepatic venous outflow obstruction originating from endoluminal venous lesion (thrombosis, webs, endphlebitis)
Secondary	Hepatic venous outflow obstruction originating from a lesion outside the venous system (tumor, abcsess, cysts). The lesion can obstruct outflow by invading the lumen or by extrinsic compression.

Many current studies underline the complex multifactorial pathogenesis of BCS, in which inherited thrombophilia creates a predisposition for thrombosis and acquired thrombotic stimuli are needed to cause clinically manifest hepatic vein thrombosis. Concurrence of several prothrombotic risk factors is present in more than 25% of the patients [23, 24]. Since a combined etiology is common, identification of a single cause should not preclude investigation of other etiological factors. An overview of the main etiological factors is presented in table 7.

Table 7

Most common underlying thrombophilia in recent series of patients with BCS. Data are derived from studies in the Netherlands [23], India [29], France [24] and Israel [30]

Etiological factor	%	Hazard Ratio for BCS (95% CI)
Inherited		
Factor V Leiden mutation	26	11.3 (4.6-26.5)
Prothrombin gene mutation	5	2.1 (0.4-9.6)
Protein C deficiency	9	6.8 (1.9-24.4)
Protein S deficiency	6	4.4 (2.2-20.6)
Antithrombin deficiency	4	4.4 (2.1-10.9)
MTHFR mutation	12	-
Acquired		
Myeloproliferative disorders	45	-
Occult	36	-
Classic	9	-
Antiphospholipid syndrome	5	-
Oral contraceptive use	60	2.4 (0.9-6.2)

The most predominant inherited prothrombotic cause of BCS is Factor V Leiden (FVL) mutation, which is present in 23-31% of the patients [25, 26] and of which the prevalence is significantly higher in BCS than in controls [23, 25]. FVL mutation is a point mutation in the Factor V gene (G1691A). Factor V plays an important role in promoting the conversion of prothrombin in thrombin. However, FVL exerts its thrombogenic effect mainly when combined with other prothrombotic factors, as protein C or S deficiency or use of oral contraceptives. Furthermore, patients with BCS and FVL mutation appear to present significantly more frequent with acute ischaemic forms and ALT levels of higher than 50 times the upper limit of normal value, than patients with BCS without FVL [26]. However, mortality rates were not different.

Prothrombin gene mutation is a point mutation (G20210A) in the factor II gene leading to increased levels of prothombin and can be detected by PCR analysis. Prothrombin gene mutation is present in 5-6% of the patients with BCS with a relative risk of 2.1 as compared to controls [23, 24].

A mutation in the methylene tetrahydrofolate reductase gene (i.e. MTHFR C677T mutation) results in hyperhomocysteinemia, a condition associated with arterial and venous thrombosis. The diagnosis is made by either PCR (mutation) or the methionine tolerance test. In BCS, hyperhomocysteinemia was found to be 2.7 times more prevalent than in controls [27].

Other inherited thrombogenic disorders are deficiencies in the natural coagulation inhibitors. Protein C deficiency is present in 13-20% of patients with BCS [24, 28] and the relative risk of BCS in patients with protein C deficiency is 6.8 [23]. For protein S deficiency, association with BCS is less strong, as it was only present in 6-7% in series from India [28, 29] but it was absent in patient series from western countries [23, 24]. The same accounts for antithrombin deficiency, which is only reported in 4% in Indian series [29]. The diagnosis of inherited deficiencies in protein C, protein S and antithrombin in patients with BCS is difficult because acquired deficiencies can develop in the event of liver failure, acute thrombosis and anticoagulant therapy. Therefore, decreased levels of coagulation inhibitors are of significance only when associated with normal or slightly reduced levels of other liver-dependent coagulation factors such as factor II, V,VIII and X. Family studies can provide useful additive information and vitamin K deficiency needs to be ruled out as a cause of these deficiencies.

Myeloproliferative disorders, including polycythemia rubra vera, essential thrombocytosis and myelofibrosis, consitute the most common etiological factors for BCS, being present in about 25% when classic diagnostic criteria are used [23, 24], but in 45-53% when occult and latent forms are considered [30, 31]. Careful evaluation of the peripheral blood pattern for evidence of a primary myeloproliferative disorder (increased blood cell count, increased hematocrit) may be followed by determination of total red cell mass and serum erythropoietin, and bone marrow biopsy. In addition, culture of bone marrow or peripheral blood progenitors for assessment of spontaneous erythroid colony formation may support the diagnosis of a primary occult myeloproliferative disorder when no changes in the peripheral blood examinations are found. Noteworthy is that sometimes an increased red blood cell mass can also be observed within the course of BCS, i.e. secondary polycythemia vera, in the presence of increased erythropoietin levels, but as yet, this phenomena remains unexplained [32].

Antiphospholipid syndrome, defined by presence of high levels of anticardiolipin antibodies (IgG and IgM) and lupus anticoagulant antibodies, is the second most common acquired prothrombotic risk factor for BCS, being present in 20% of patients with BCS [33]. However, IgG anticardiolipin antibodies were also elevated in patients with liver cirrhosis of other origin, suggesting a secondary effect [34].

Paroxysmal nocturnal haemoglobinuria [35] and Behçet's disease [36] are other forms of acquired thrombophilia reported to be associated with BCS. Diagnoses of these diseases are made by respectively flow cytometry (for paroxysmal nocturnal haemoglobinuria) and assessment of the criteria of the International Study Group for Behçet's disease.

Use of oral contraceptives, especially of the first and second generation, was shown to be more prevalent in patients with BCS as in controls [37], with a comparable association as with other thrombotic diseases. Pregnancy-related BCS is common in Eastern countries [5] but very rare in the West. Local factors predisposing for thrombosis, like inflammation and infection related diseases (e.g. pancreatitis, gastrointestinal disorders) or abdominal interventions, are occasionally reported and of minor importance in BCS.

Pathogenesis and haemodynamic changes

After obstruction of the hepatic outflow tract, continuing blood inflow from the hepatic artery and portal vein into the sinusoids results in an increase of sinusoidal pressure upstream of the occlusion and subsequent centrilobular congestion and ischaemic changes in the pericentral area with loss of hepatocytes and necrosis. Outcomes of this course are either massive necrosis resulting in acute liver failure, or the process of fibrotic changes, resulting in cirrhosis. As would be expected, sinusoids surrounding the portal tract do not become affected until very late in the course and hence, overall liver function remains intact for a long time. Hemodynamically, an increase in the sinusoidal pressure is suggested to lead to 1) decreased portal flow due to small pressure gradient between the sinusoids and portal vein and 2) compensatory increased flow in the hepatic artery with, when sinusoidal pressure exceeds portal pressure, stagnant or even reversed (i.e. hepatofugal) flow in the portal vein. However, circumstantial evidence for this mechanism is lacking at the present time.

Diagnosis

Since the disease can deteriorate rapidly, the need to obtain the correct diagnosis is usually urgent. The diagnosis of BCS should be suspected under the following circumstances:
(a) simultaneous presence of ascites, liver enlargement and upper abdominal pain;
(b) signs of chronic liver disease, particularly when intractable ascites contrasts with mildly altered liver function tests;
(c) liver disease in a patient known to have a prothrombotic disorder;
(d) fulminant hepatic failure in the presence of liver enlargement and ascites;
(e) chronic liver disease which remains unexplained after alcoholism, chronic viral hepatitis B or C, autoimmunity, iron overload, Wilson's disease, and alpha-1 antitrypsin deficiency have been excluded.
These circumstances, although suggestive, are not sufficient to make a diagnosis of BCS. This is established only upon demonstration of an obstructed hepatic venous outflow tract.

Figure 2
Diagnostic Work-up for patients with Budd-Chiari Syndrome [10].

Step	Diagnostic Method
1	Doppler-ultrasound
	⬇
2	Magnetic resonance imaging Computed Tomography
	⬇
3	Venography & transvenous biopsy
	⬇
4	Liver explant

Radiographic evaluation

In the clinical setting, various imaging modalities are available for investigating the gross hepatic vascular anatomy: ultrasound (US), magnetic resonance imaging (MRI), computed tomography (CT) and X-ray venography (Figure 2). US combined with Doppler imaging has a diagnostic sensitivity of more than 75% and should be the first line of investigation [38, 39]. Hepatic veins devoid of flow signal, collateral hepatic venous circulation, a spider-web appearance usually located in the vicinity of the hepatic vein ostia, and stagnant, reversed or turbulent flow can all be indicative of BCS [40, 41]. Lack of visualization or tortuosity of the hepatic veins at real-time ultrasonography is common but not specific for BCS because such features can also be seen in advanced cirrhosis. A distinctive feature of BCS, however, is the association with intrahepatic or subcapsular hepatic venous collaterals.

When it is technically difficult to obtain an adequate sonographic evaluation or when the diagnostic features cannot be demonstrated, CT or, preferably, MRI should be performed as a second line of investigation [42]. With the combination of these imaging procedures, the diagnosis will remain uncertain only in a small minority of cases. Uncertainty is likely to occur mainly in patients with cirrhosis.

MRI allows good evaluation of the hepatic veins and the inferior vena cava. Inhomogeneous parenchymal enhancement after intravenous contrast injection is suggestive but not diagnostic of BCS. Parenchymal changes, such as atrophy-hypertrophy complex, parenchymal infarction or extinction and focal nodular hyperplasia can be visualised as well. The sensitivity and specificity of MRI needs to be further clarified. MRI has several advantages above other radiological modalities in being devoid of (nefro) toxicity and being unaffected by body habitus and being operator-independent. CT also shows inhomogeneous contrast distribution (figure 3, 4). Compared to MRI, CT has reduced sensitivity for investigating hepatic veins and the contrast used could lead to reduced renal function.

The third line of investigation should be retrograde cannulation (transjugular or transfemoral) of the hepatic veins for venography with or without liver biopsy. Venography is useful in the assessment of the extent of outflow obstruction and also allows for pressure measurements, while the concurrent liver biopsy yields data that is useful not only for confirming the diagnosis of BCS but also for ruling out other disorders such as veno-occlusive disease and cirrhosis of other etiologies [43]. Typically, venography delineates the obstruction and shows gross hepatic collaterals or a spider web (i.e. tiny venous channels opacified from the catheter tip in the wedge position). The disadvantage of venography is that it is often impossible to cannulate the hepatic veins in the presence of a (thrombotic) occlusion, and that the procedure usually requires the use of considerable amounts of iodine-containing contrast medium. Currently, direct hepatic vein puncture through the transcapsular route has been successfully performed in experienced centres.

Figure 3
CT image of a patient with acute Budd-Chiari Syndrome. Note the marked hepatomegaly and congestive parenchymal changes

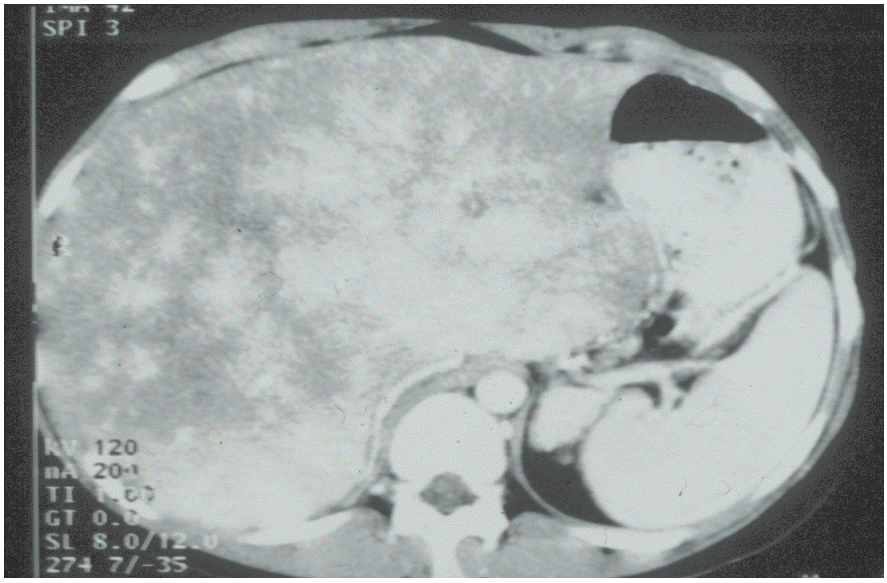
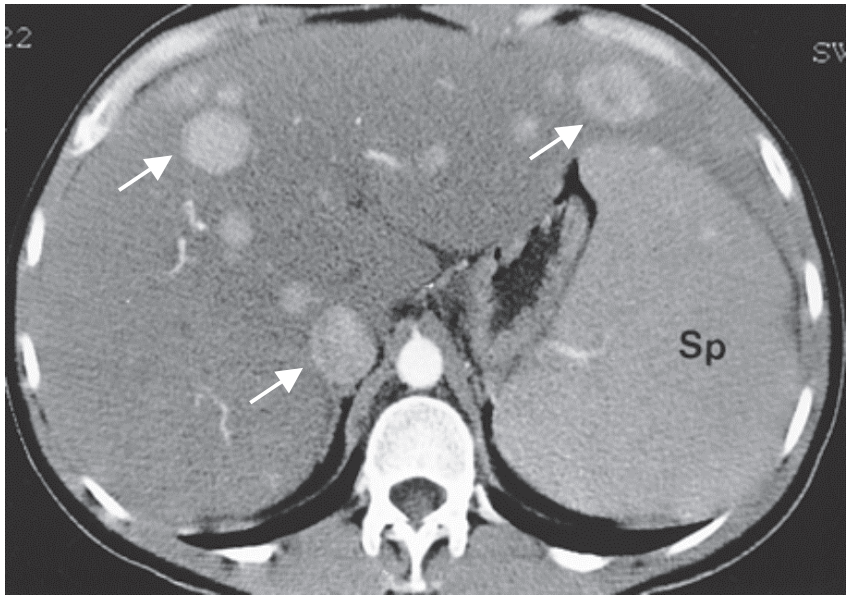


Figure 4
CT image of a patient with Budd-Chiari type nodules (arrows)



Liver biopsy

Although a liver biopsy can help in the diagnosis of BCS, its value in the assessment of disease severity and prognosis is limited [14, 44]. This is probably due to sample variation, which is caused by the inhomogeneous distribution of the disease characteristics within the liver. Liver histology therefore should not be considered essential to assess liver injury in patients with an already established diagnosis of BCS. Laboratory and radiological investigations, in addition to being safer, are probably better in providing prognostic information and in guiding therapy.

The combination of Doppler-ultrasound and magnetic resonance imaging allow optimal delineation of venous obstruction for therapeutic decisions. Venography with pressure measurements, in particular, should be performed when radiological or surgical shunting is considered. A major, as yet unanswered issue is how to take the degree of liver dysfunction into account when choosing the type of medical or surgical therapy. The uncontrolled non-randomized studies performed thus far do not allow this issue to be answered satisfactory [19, 45, 46].

Therapy

Therapeutic options in BCS are diverse, ranging from a conservative attitude to the need for urgent liver transplantation. Therapy in BCS as yet is far from being evidence-based, as controlled studies have never been performed. Consequently, therapeutic guidelines must be based on case series, clinical experience and expert opinion. Therapeutic choices are influenced considerably by local facilities and expertise. Hence, the treatment of this syndrome is associated with uncertainties and difficulties. Attempts to concentrate management in (academic) centers with specific expertise should therefore be strongly encouraged. This policy is likely to improve patient care and hence, prognosis and is essential for facilitating proper scientific research.

General considerations

A well-accepted general principle in the therapy of BCS is that patients should receive treatment for underlying diseases. Although based on circumstantial evidence, therapy with anticoagulation should always be considered because underlying prothrombotic states are often present and recent improvement in the prognosis of BCS has coincided with the generalized use of anticoagulation [44]. In addition, there are no reports of severe bleeding in patients with BCS who received anticoagulation, and there is proven efficacy of anticoagulation in other forms of thrombosis. For symptomatic patients, anticoagulation should be combined with diuretics or paracentesis for ascites and with pharmacological or endoscopic therapy of varices when there is a history of gastro-intestional bleeding due to portal hypertension. Patients with ascites, variceal bleeding or signs of liver failure should be followed closely.

Those who do not improve or develop severe or recurrent complications despite medical treatment should be considered for stenting, Transjugular Intrahepatic Portosystemic Shunt (TIPS) insertion, or surgical portosystemic shunting. The timing of these procedures is one of the greatest challenges in managing BCS. In particular, it is often difficult to decide whether in a given clinical situation the effect of conservative therapy can be awaited or whether an invasive procedure aimed at restoration of the hepatic outflow block would be preferable. For instance, a patient may present with local occlusions of the hepatic veins that seem amenable to dilatation and/or stenting. However, when this is associated with only mild clinical manifestations, which may be controlled with medical therapy alone, the best therapeutic strategy remains unclear and highly dependent on individual preferences.

Liver transplantation should be considered when there is progression of liver dysfunction despite previous therapies or when patients have subacute or acute liver failure [47].

Clearly, the eventual therapeutic choice may be influenced by local expertise in specific intervention techniques. At present, there are no clear end-points for defining failure of a given treatment and thus the need for more definitive intervention. Many studies of therapeutic interventions, particularly surgical shunts, have been published [19, 45, 48]. However, the scientific value of the published data is unsatisfactory. Data on selection criteria, proportion of patients not suitable for the studied procedures and long-term follow-up are often not mentioned. Therefore, conclusive information obtained from such studies is limited. Nevertheless, these studies provide important information that can be used in the design of future studies.

Hepatic vein angioplasty and stenting

In patients with short segment stenosis [22] or occlusion of the hepatic veins with significant patent segments, it is desirable to overcome the obstruction between hepatic vein remnants and the inferior vena cava by means of balloon angioplasty with or without stenting [49-52]. This approach will re-establish hepatic venous outflow via the physiological route. Use of thrombolysis may enhance the success rate of these procedures [49, 53-56]. Thrombolysis may be effective particularly when locally infused, in the presence of a short history of thrombosis or when combined with a successful radiological procedure [56]. If the veins cannot be entered via the transjugular route, then transhepatic puncture of hepatic vein remnants can be considered. The predictive factors for restenosis are still unknown. Therefore, the indications for stenting – at the time of initial angioplasty or after recurrence – remain unclear. After failure of angioplasy or stenting a surgical portosystemic shunt or TIPS should be considered.

Shunt procedures

The rationale for surgical portosystemic shunting is to convert the portal vein into an outflow tract of the liver [57]. It is evident that this cannot be accomplished with end-to-side porto-caval anastomoses. There is controversy as to the superiority of side-to-side porto-caval versus mesocaval shunts in the management of BCS. The latter were introduced because of the difficulty to perform a portocaval shunt in the presence of a hypertrophied caudate lobe [58]. In addition, mesocaval shunting can be achieved at some distance from the portal vein, thereby increasing the feasibility of subsequent liver transplantation. Complete obstruction of the inferior vena cava or its compression by the caudate lobe adds to the difficulty of deciding to perform a surgical portosystemic shunt [59]. Patients with severe forms of BCS have the potential to benefit from decompression of the liver by means of a surgical shunt. However, the surgical mortality in such high-risk patients may surpass the benefit of the shunt.

In the past decade, TIPS implantation has been increasingly used as an alternative derivative procedure. The technique of TIPS has been described extensively but requires refinement and special expertise in BCS because the hepatic vein obstruction makes the procedure more difficult [60-62]. In most patients it is possible to cannulate the remaining hepatic vein stump and to direct a needle through the liver parenchyma towards the right intrahepatic branch of the portal vein. When no hepatic vein remnants are found, ultrasound-guided puncture in the liver can be performed directly through the intrahepatic portion of the inferior vena cava. As the liver in BCS is usually large, the intrahepatic parenchymal tract bridged by the stent is typically longer than in patients with cirrhotic liver disease. At least in theory, TIPS has advantages over a surgical shunt when there is marked enlargement of the caudate lobe and compression or thrombosis of the inferior caval vein as this may result in caval vein pressures exceeding portal venous pressure. TIPS implantation functionally results in a portocaval shunt because it enables retrograde (hepatofugal) blood flow through intrahepatic portal veins radicles. Many centers nowadays prefer TIPS to surgical shunts because the procedure-related morbidity and mortality are lower and results seem comparable or even superior to surgical shunting [63, 64]. An additional factor leading to increased popularity of TIPS is that expertise with surgical shunt procedures has considerably decreased worldwide. Also in patients presenting with severe hepatic failure, TIPS has been proposed as the preferred initial treatment [65], but further studies should determine whether in this situation transplantation would be the better option [63]. Recent studies convincingly show that TIPS implantation using newly developed covered stents significantly

reduces the incidence of shunt dysfunction, a previously common complication [66-68]. This is of paramount importance in BCS, since this condition is often associated with increased thrombotic tendency. Future long-term studies have to show whether this treatment modality should become the first line therapy in BCS.

Liver transplantation

Orthotopic liver transplantation should be considered as effective treatment for rapidly progressive BCS after failure of conventional treatment or portosystemic shunting [69, 70]. Early mortality is related mainly to infections whereas late mortality is usually related to recurrent BCS or thrombosis of the inferior vena cava or portal vein, despite anticoagulation. Morbidity is related mainly to portal and arterial thrombosis, haemorrhage under anticoagulant therapy and ischaemic bile duct lesions. Since most patients with BCS exhibit important risk factors for thrombosis, anticoagulation is probably best continued after transplantation. How long to continue anticoagulation is at present unclear. The European Liver Transplant Association (ELTA) collected the results for BCS patients transplanted from 1998 using the European Liver Transplantation Registry. These data show a 5-year survival rate of 76%. Recipient age had no impact on survival, neither did the condition under which transplantation was performed (emergency or elective). The results, however, were negatively influenced by renal failure pre-transplantation and by the time interval between diagnosis and transplantation.

Prognosis

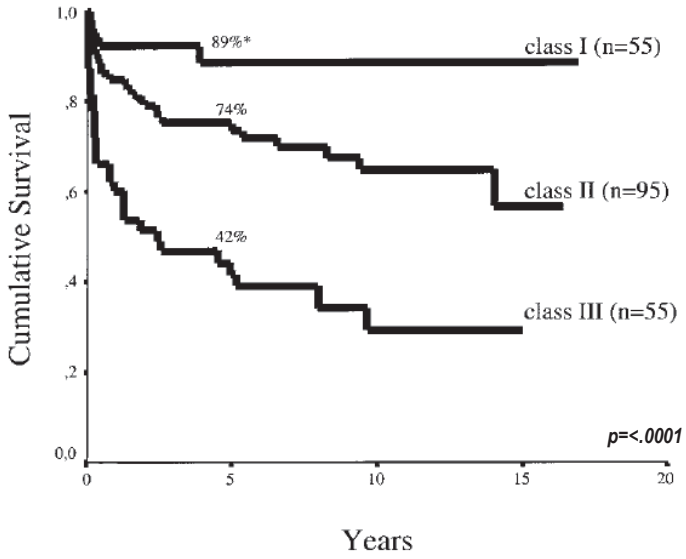
The natural course of BCS is largely unknown. In previous studies in which the disorder was recognised only at an advanced stage and therapeutic options were limited, first-year mortality was up to 60%. Main causes of death are variceal bleeding due to portal hypertension, complications associated with chronic ascites and liver failure. During the last decades, medical as well as derivative treatment options have expanded, the disease is recognised earlier and hence, outcome has gradually improved. Noteworthy is that, in accordance with the clinical presentation and the aetiology of BCS, prognosis is heterogeneous, difficult to predict and to a large extent dependent on type of treatment.

Current large longitudinal studies have reported 1-, 5- and 10-year survival rates of 77-82%, 64-69%, and 57-62%, respectively [44, 71]. Highest mortality rates are within the first 12-24 months. Furthermore, both multivariate cohort studies have determined independent prognostic factors, which influence long-term survival.

In the French study by Zeitoun et al. of 120 patients, the response of ascites to diuretics, Child-Pugh score, age, and serum creatinine levels were found to be of prognostic value and an index composed of these factors could distinguish excellent and poor prognostic groups [44]. In the same study, portosystemic shunting did not show a significant influence on survival after correcting for other predictive factors in multivariate analyses. This is in contrast to previous surgical case series, which have reported survival rates as high as 94% [19]. However, most of these studies did not provide data on patient selection criteria.
In another study, performed at our own institution among 237 patients, a prognostic classification, composed of the factors ascites, encephalopathy, prothrombin time and bilirubin levels, could subdivide patients in 3 classes with good, intermediate and poor prognosis (figure 5) [71]. In the same study, efficacy of different therapeutic options were compared between the classes by using time-dependent analyses. Patients in the good prognostic class were most likely to benefit from medical management with anticoagulation alone. Patients in the intermediate class were the only ones who showed a tendency to benefit from portosystemic shunting. The latter finding is remarkable and offers possibilities for the selected use of derivative procedures, including TIPS. In the poor prognostic class, neither medical management nor shunt procedures were adequate, suggesting that orthotopic liver transplantation may be the only treatment option for these patients with end-stage liver disease [70, 72].

In contrast to clinical parameters, liver histology was not related to survival in BCS and may therefore have limited prognostic value [14]. Concurrent portal vein thrombosis (PVT) is present in about 25% of patients with BCS [73]. Prognosis in these patients with combined pathology appears poor with 5-year survival rates of 23-57%. The presence of an occluded portal vein in addition to obstructed hepatic veins clearly puts an additional strain on the already marginal therapeutic options for patients with BCS.

Figure 5
Survival in patients with Budd-Chiari Syndrome according to the prognostic classification (p<.0001) [71]



Points to remember:

- Budd-Chiari syndrome is defined as hepatic venous outflow obstruction and its manifestations, regardless of the cause and regardless of the level of obstruction from the small hepatic veins to the entrance of the inferior vena cava into the right atrium.
- Sinusoidal obstruction syndrome (also veno-occlusive disease) is not considered Budd-Chiari syndrome.
- Primary Budd-Chiari syndrome is defined as hepatic venous outflow obstruction originating from an endoluminal venous lesion (thrombosis, webs, endphlebitis), while secondary Budd-Chiari syndrome is characterised by a lesion outside the venous system, with invasion or compression of the lumen (tumor, abcsess, cysts).
- The classical triad of symptoms consists of ascites, hepatomegaly and abdominal pain.
- Diagnosis is usually made by Doppler Ultrasound, followed by MRI or CT.
- Liver histology can confirm the diagnosis, but is hampered by a heterogeneous distribution of lesions. Therefore, the prognostic value is limited.
- Anticoagulation is always indicated in patients with Budd-Chiari syndrome, unless absolute contra-indications exist (history of repeated variceal bleeding).
- TIPS is the shunting procedure of first choice.
- Liver transplantation is performed as salvage treatment for end-stage disease.
- Prognosis is poor in the absence of treatment. With adequate therapy, 5-year survival is about 70%.

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II

Early Changes of the Portal Tract on Micro-CT Images in a Newly Developed Rat Model for Budd-Chiari Syndrome

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Abstract

Background and aim

The effect of increased sinusoidal pressure on the portal tract in Budd-Chiari Syndrome (BCS) is as yet not elucidated. Our aim was to investigate portal changes in a newly developed rat model for BCS.

Methods

We created an outflow obstruction in Sprague-Dawley rats (n=6) by diameter reduction of the inferior vena cava. Left and right liver lobes, with portal vein contrast, were scanned using a Micro-CT, and volumes of the portal tree and liver parenchyma were computed by the ANALYZE software program.

Results

Portal branching density was significantly lower in BCS than shams and decreased over time ($P<0.01$). There was a significant drop in volume of both parenchyma and portal tree in the left, but not right lobes. At 6 weeks post-surgery, perfusion-index (i.e. ratio between both volumes) became equal to (left) or even higher than (right) shams, suggesting a new equilibrium with preserved portal perfusion. Histological findings were consistent with those observed in humans.

Conclusions

As early as day 2, a significant loss of peripheral portal branches was seen, which progressed over time. Inter-lobar differences in vascular abnormalities suggest compensatory mechanisms. Despite a decrease in both liver and portal vein volume, relative portal perfusion appeared spared.

Introduction

Budd-Chiari Syndrome (BCS), a hepatic venous outflow obstruction mostly attributable to thrombosis, can be located anywhere from the small hepatic veins until the entrance of the inferior vena cava into the right atrium [1]. BCS is uncommon, and has a broad spectrum of symptoms, etiological factors, radiological findings and clinical outcomes, the latter varying from compensated disease to liver failure and death. So far, the pathogenesis and sequence of vascular changes following BCS are poorly understood.

The portal vein accounts for 75-78% of total hepatic flow [2]. In BCS, the obstruction of the hepatic veins causes increased sinusoidal and portal pressure and eventually portal hypertension. However, the hemodynamic changes, usually called 'hyperdynamic circulatory syndrome', observed in portal hypertension following cirrhosis, are not present in BCS [3], indicating a different pattern of circulatory changes. So far, these changes have only been studied in radiological studies inducing temporary hepatic vein occlusion [4], and histological studies in explanted livers of transplanted patients [5]. These studies showed impairment of the portal perfusion, indicated by deceased velocity rates and a change of portal flow direction from hepatopetal to hepatofugal or even stagnant flow. However, in order to study the true effects on both structure and volume of the portal venous tract, an animal model is needed.

Of all animal models, the rat model is the most logical choice, as it not only applies to most of the general considerations for feasibility of using animal models, as described by Mullen et al. [6], but also, the anatomy of the rat liver closely resembles that of human [7], Indeed, in the past, several rat models of hepatic outflow obstruction have been developed [8,9]. However, all were only used to investigate the histological consequences of outflow obstruction. Therefore, we developed a rat model, in which we evaluated by micro-CT imaging the actual structural and volume changes occurring within the portal vein following BCS at time points representing acute and sub-acute conditions.

Material and Methods

Animals

Six male Sprague-Dawley rats were used. To mimic conditions occurring in acute and sub-acute BCS, rats were sacrificed at 2 days and 6 weeks after surgery, respectively. Within each group, 2 operated rats and 1 sham rat were included. The study was executed with approval of the Mayo Clinic Institutional Animal Care and Use Committee.

Creation of hepatic outflow obstruction

All rats were denied food overnight and anaesthetized with an intraperitoneal injection of Sodium Pentobarbital (40 mg/kg). The rat was supported with head up at an angle of 30° to allow gravity to lower the intra-abdominal organs. A 2.5 cm abdominal mid-line incision was made, the diaphragm was pulled up and the falciform ligament was cut to expose the suprahepatic inferior vena cava (IVC). Subsequently, the IVC and an adjacent glass tube (diameter 1.3 mm) was tightly ligated using a 3-0 silk thread according to a technique previously described [8]. Several attempts revealed that a diameter reduction of 50% of the original size of the IVC was sufficient to create an acute hepatic venous obstruction without undesirable effects for the venous return of the lower body part. The muscle and skin were closed in layers and Buprenorphine (0.1-0.5 mg/kg) was used as post-operative analgesic. Sham surgery included the same steps, but without ligature of the IVC. All animals were fed ad libitum and received humane care in compliance with the Institution's guidelines for care and use of laboratory animals in research.

Specimen preparation

At 2 days and 6 weeks, rats were anaesthetized with intraperitoneal injected Nembutal (40 mg/kg), a laparotomy was performed and the rats were euthanized by exsanguinations following an incision in the right atrium. The portal vein was ligated to allow cannulation and was subsequently infused with a heparinized 0.9% saline solution to prevent clotting. The IVC was cut and cannulated to facilitate flushing out of any residual blood in the hepatic vasculature using a Syringe Infusion Pump (22, Harvard Apparatus) until homogenous bleaching of the liver occurred.

Subsequently, the portal vein was injected with a yellow low-viscosity radiopaque polymer compound (Microfil® MV-122; Flow Tech, Inc., Carver, MA, USA). In order to prevent filling of the hepatic veins, injection was ceased as soon as the opacified portal veins reached the peripheral surface of the liver. The liver was resected into a right, left and middle lobe and fixed in 10% formalin solution, followed by immersion in successively increased concentrations of glycerin solutions. The left and right lobes were suspended in a plastic cylinder and imbedded in Bioplastic Liquid Casting Plastic (Aldon Corp. Avon, NY, USA) and used for micro-CT scanning. Middle lobes were prepared for histology, using Hematoxylin and Eosin (H&E), Masson Trichrome and Reticulin staining. Slides were investigated by 2 independent pathologists (SCA and PEZ).

Micro-CT scanning and image analyses

The micro-CT scanner used was previously described in more detail [10,11]. Its resolution is more than ten times higher than in regular CT scanners (it depicts details at 40 μm versus 500 μm). Specimens were rotated at angular increments of 0.49º, providing 721 views in 360º to create 3-Dimensional projection images. A reconstruction program created volume images up to 1024^3 voxels and a modified Feldkamp's filtered back-projection algorithm was used to convert data into a 16-bits gray scale [12]. The ANALYZE software package (version 4.0, Biomedical Imaging Resource, Mayo Clinic, Rochester, MN, USA) was used for quantitative analyses of the images, providing volume rendering methods to visualize the 3-D architecture of the portal tree. Two computational methods were employed to measure volumes. First, seeded region growth algorithm was applied to extract voxels representing the opacified vascular lumen, based on the steep difference in grayscale value, to measure the *volume of the portal vein* (V_{pv}). This method also served to subtract all perfusion-related artifacts (i.e. noise) from the true observed tree. Second, homotopic morphological thickening was a technique used to define *volume of the liver perfused* (V_t). It involves computational thickening of the selected supplying (i.e. root) vascular tree in 3 dimensions in a number of iterations until the liver surface was reached.

Statistical analyses

In each micro-CT image, we counted in 5 representative fields of 4 x 4 millimeter hepatic tissue the number of visible portal branches (*branching density*). With the ANALYZE software, V_{pv} as well as V_t was computed at every significant bifurcation from the main vascular stem. The ratio between $V_{t\ and}$ V_{pv} was calculated to indicate the relative perfusion per each square millimeter (mm^3) of portal vein volume; we called this the *perfusion index*. Computations were limited to 5 branching levels. Mann-Whitney-U tests were used to compare the number of portal branches per field between BCS rats and shams, and to compare changes in volumes in BCS and sham rats over time. To control for multiple testing (3 comparisons), □ was set at 0.01 (i.e. Bonferroni correction).

Results

Macroscopy and histology

Marked ascites formation was noted in both BCS rats at 6 weeks post-surgery, but not in shams or BCS rats at 2 days post-surgery. At laparotomy, we noted extensive abdominal wall bleeding and the presence of abdominal collaterals in BCS rats, whereas this was not observed in the shams. Liver specimens in experimental BCS rats sacrificed after 2 days were enlarged and discolored due to congestion, and after 6 weeks marked hepatomegaly and necrotic streaks in the peripheral blunt edges of the liver surface were observed (fig 1). Centrilobular congestion and sinusoidal dilation was the main histological feature at 2 weeks post-surgery (fig 2b). However, at 6 weeks, more extensive pathology, including centrilobular necrosis, portal inflammation, peri-central, peri-portal and bridging fibrosis and wall thickening of the central veins was observed, in addition to the formation of inadequate peri-portal veins and a few regenerative nodules (fig 2c). At both time-points, the portal veins contained only contrast without frank thrombosis. Completely normal liver morphology and architecture were seen in shams (fig 2a).

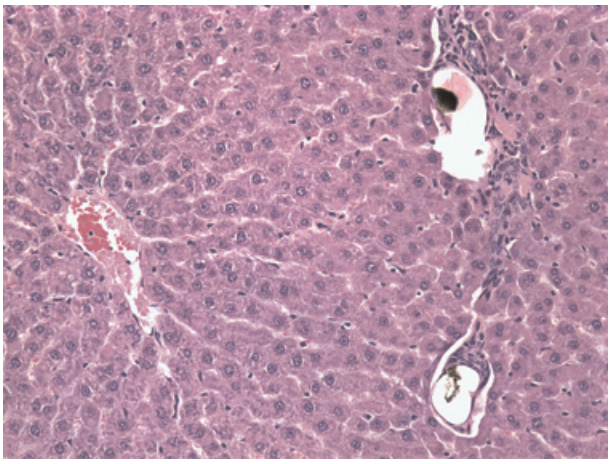
Figure 1

Macroscopy of liver at 6 weeks post-operative. Note the congested liver and marked necrotic streaks in the periphery of the liver surface.

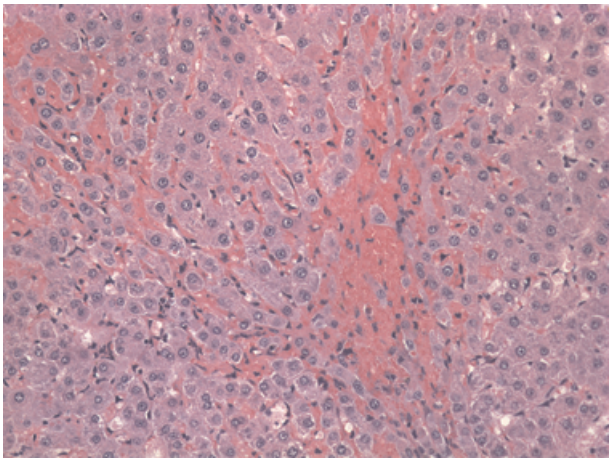
Figure 2

Histology showed normal architecture in shams (2a; H&E stain, original magnification 20x), marked sinusoidal congestion and pressure atrophy of the peri-central hepatic cords at 2 days post-surgery (2b; H&E stain; original magnification 10x); and delicate centro-central bridging fibrosis at 6 weeks post-surgery (2c; Masson trichrome stain; original magnification 20x).

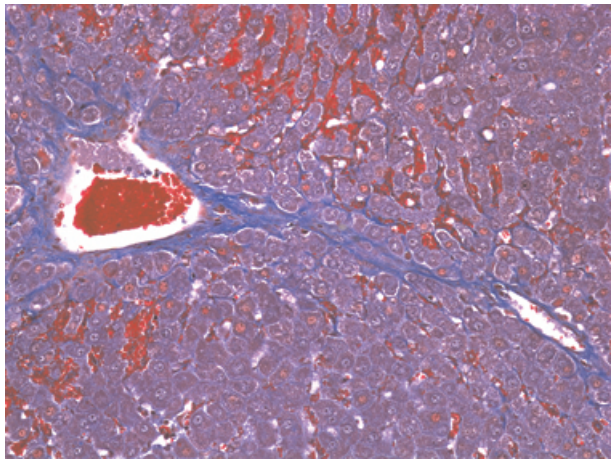
2a



2b)



2c)



3-Dimensional CT images

Micro-CT imaging analyses revealed a gradual loss of small portal branches in BCS rats over time (fig 3). Median numbers of portal branches are presented in table 1. For both the left and right lobe, a significant decrease in number of portal branches was observed at 6 weeks post-surgery, as compared to 2 days post-surgery and shams (all $P<0.01$). In addition, significant differences existed between right lobes of BCS rats at 2 days and 6 weeks post-surgery ($P<0.01$).

Volume measurements

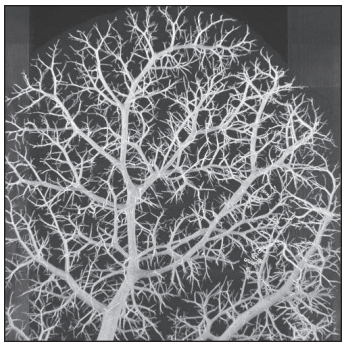
At 2 days after ligation, we found lower V_{pv} and V_t in BCS rats than in shams, but the difference was not statistically significant. For left lobes, loss of parenchyma (decreased by 20%) was more pronounced than loss of vascular supply (a decrease of 10%), reflecting in a significant decrease in the perfusion index. This observation suggested that the liver tissue was relatively under-perfused. The opposite was true for right lobes, in which an increase in perfusion index was seen. Here, the decrease in tissue volume of 11% was proportionally lower than that of portal venous volume (20%), but this failed to reach statistical significance (P=0.06).

At 6 weeks post-surgery, marked discrepancy developed between the left and right lobe. For left lobes, the decline in both V_{pv} as V_t continued and was significantly different from shams or at 2 days post-surgery. However, now the perfusion index increased and approached the level found in shams, thereby possibly indicating a new equilibrium in which the remaining liver tissue was adequately perfused. In contrast, for right lobes, V_{pv} and $V_{t\ were}$ higher at 6 weeks than at 2 days following ligation and were also higher than in shams. As is shown in table 1, V_t increased two-fold, implying possible development of hypertrophy. Hence, the relative perfusion index was significantly higher than in shams, indicating functional compensatory mechanisms.

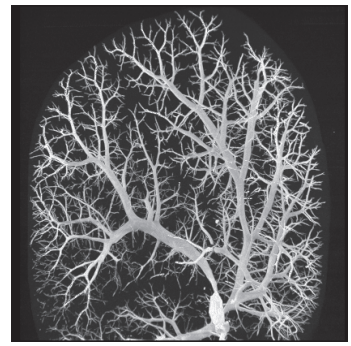
Figure 3

Three-dimensional micro-CT images of the portal tract of shams (3a), BCS rats at 2 days post-surgery (3b) and BCS rats at 6 weeks post-surgery (3c). Note that the spherical objects in figure 3b left and 3c right are perfusion-related artifacts, which were not included in the computation of these vascular volumes.

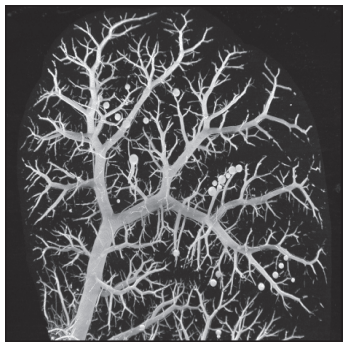
3a) left



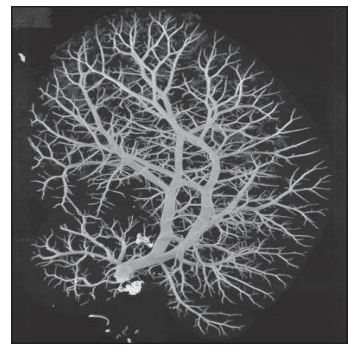
3a) right



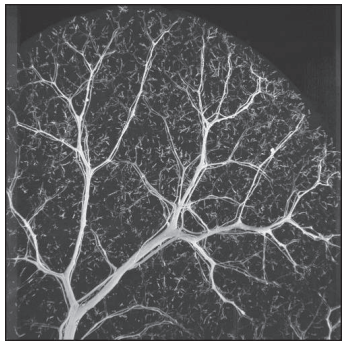
3b) left



3b) right



3c) left



3c) right

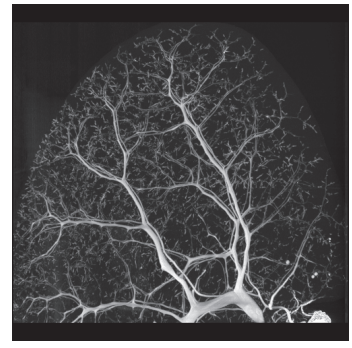


Table 1

Number of portal branches per area of 4 by 4 mm, volume of the portal vein (V_{pv}), volume of the perfused liver tissue (V_t) and perfusion index (V_t /V_{pv} ratio) per lobe for BCS rats and shams. Represented values are medians (interquartile range). Level of statistical significance is set at P<0.01.

	Branches (N)	V_{pv} (mm3)	V_t (mm3)	V_t /V_{pv} ratio (%)
Left lobes				
Shams	77 (47-140)	20 (11-21)	557 (437-823)	38 (27-41)
2 days post-surgery	50 (43-54)	18 (12-22)	444 (365-545)	27 (24-31)
6 weeks post-surgery	13 (9-18)	7 (4-12)	274 (193-397)	42 (31-55)
2 days vs. shams	P=0.14	P=0.94	P=0.13	P=0.01
6 weeks vs. shams	P<0.001	P=0.01	P=0.003	P=0.26
2 days vs. 6 weeks	P<0.001	P=0.008	P=0.008	P=0.02
Right lobes				
Shams	83 (60-121)	5 (2-13)	130 (70-136)	25 (24-31)
2 days post-surgery	40 (33-53)	4 (1-8)	116 (43-288)	42 (25-53)
6 weeks post-surgery	17 (8-31)	7 (3-10)	272 (165-386)	41 (40-47)
2 days vs. shams	P<0.001	P=0.29	P=0.65	P=0.06
6 weeks vs. shams	P<0.001	P=0.91	P=0.09	P<0.001
2 days vs. 6 weeks	P<0.001	P=0.29	P=0.04	P=0.76

Discussion

The pathogenesis of BCS and changes in the hepatic vasculature following BCS are poorly understood. In particular, the portal vein is of interest since it undergoes structural and functional changes, together with the hepatic artery to compensate for the diminished outflow. In this study, we developed a rat model that mimicked vascular changes occurring in BCS, 2 days and 6 weeks after obstruction, representing acute and sub-acute conditions. We evaluated changes in the portal vein by 3-dimensional Micro-CT contrast images.

In our rat model, we created a partial outflow block of the IVC. This can be compared with the clinical situation of BCS with an occlusion in the IVC, a condition that occurs in association with hepatic vein thrombosis in 16-31% of patients [13,14]. Unfortunately, a model in which hepatic vein thrombosis is induced locally without immediate sacrifice of the rat is as of yet not available and not feasible. However, the macroscopic and histological findings of our rat model were consistent with those observed in humans with BCS [15,16]. At 2 days post-operative, liver specimen were enlarged and significant centrilobular congestion was found. After 6 weeks, centrilobular necrosis, peri-portal veins and fibrosis became apparent, which reflected more long-term changes. Therefore, our current model using partial IVC occlusion was able to mimic the clinical situation in BCS, and is as of yet the most feasible model approaching the human clinical situation of BCS.

The results of the Micro-CT analyses suggest the following sequence of vascular changes. At 2 days post-surgery, branching density was evidently diminished, and both volume of the portal vein and the liver tissue decreased in both lobes. However, in the left lobe, the loss of tissue was more pronounced while in the right lobe loss of venous volume was more remarkable. There, our findings at day 2 were consistent with a combination of relative hypo-perfusion of the liver parenchyma in the left, but hyper-perfusion in the right lobe. At 6 weeks post-operatively, both volumes declined even further in the left lobe, implying both portal loss and atrophy of the liver tissue. However, a new equilibrium appeared to have been established in which the tissue, although atrophied, showed preserved perfusion. In the right lobe on the other hand, a reciprocal increase in both the volume of the portal vein as well as liver tissue occurred, indicating hypertrophy and hyper-perfusion, most likely to compensate for the changes in the left lobe.

The severe loss of portal branches in the left lobes is in accordance with results from several other studies. Gronczewski et al. [17] showed that partial IVC occlusion led to a decrease in portal flow by tracer experiments in guinea pig models. Furthermore, in transplanted patients with recent onset BCS disturbed portal inflow and obliterative portal venopathy were found, while patients with long-standing disease showed increased arterial influx and a variable degree of atrophy in one of the liver lobes [5]. Temporary occlusion of the hepatic veins leads to an immediate decrease in maximum peak velocity of the portal vein and disappearance of Doppler signal, indicating that the changes occur very soon after the occlusion [4].

In our model, marked inter-lobar vascular differences were present. While the left lobes appeared seriously affected, the right lobes seemed to compensate with a greater-than-normal hepatic perfusion. Most studies on the atrophy/hypertrophy complex of liver lobes after venous

occlusion are performed in animal models of portal vein ligation [18,19]. Rocheleau et al. showed that there was an inverse relationship between the vascular changes in the left and right lobes following left portal stenosis [2]. This was also reflected in the weight of the two lobes, with the left lobe being atrophied and the right hypertrophied, resulting in a similar total liver weight. However, their model differed from ours since in our model, the stenosis was at the level of the IVC and therefore theoretically affected both lobes equally. The question of why in our experiment the left lobe specifically is affected and the right is not, is difficult to answer from this pilot study. However, a few possible explanations can be hypothesized. The first explanation is related to the anatomy of the rat liver, which differs from the human livers in two ways. First, in rats 67% of the total portal flow goes to the left lobe, which is much larger than the right lobe, while in humans the opposite is true [2]. Secondly, the hepatic vein of the rat bifurcates unequally; the left vein bifurcates at an angle of 90º, while the right vein is a straight continuum of the main trunk [7]. Taking both observations together, one can speculate that a partial stenosis at the level of the IVC leads to a larger relative outflow block for the left than for the right hepatic vein. In other words, the majority of the remaining outflow preferentially goes through the right hepatic vein, making the right lobe the most likely lobe for compensation, and the left lobe the more susceptible lobe. The second explanation is more close to changes observed in the human liver. Patients with BCS are known to form intra- or extra-hepatic venous collaterals, which offer compensatory outflow for the obstructed regions, and/or exhibit changes in the hepatic artery, known as the Hepatic Artery Buffer Response (HABR) [20]. However, in the current experiment we did not evaluate changes in the hepatic artery, nor could we opacify the hepatic veins searching for collaterals. We believe that future studies should focus on these possible compensatory mechanisms to further elucidate this phenomenon.

Our study has a few limitations. First, the comparison between the two different time- points is inter-subject rather than intra-subject. This is due to the fact that for computerized visualization of the complete vascular tree, the whole liver organ needed to be resected. However, there is little reason to suspect that our results would be altered if we looked for the changes over time within the same subject. Second, we only collected data at 2 days and 6 weeks, and not at intermediate intervals. However, the choice of these time-points was based on the study by Akiyoshi et al. [8] who showed in their rat model of congestive liver fibrosis that fibrosis develops after 6 weeks and necrotic changes after 24 hours. As we were most interested in the acute and sub-acute changes following BCS, we decided to choose similar intervals. However, we believe that intermediate data would be very interesting to observe small consecutive steps in future studies with larger study sample size. Third, there are several micro- and macro-anatomic differences between rat and human livers that could affect the translation of these findings to the human situation. It is for instance known that in rats two caudate lobes are present with one vascular supply whereas in men there is one caudate lobe with two separate ramuli caudates [7]. Therefore, despite the intriguing effects of IVC occlusion on the caudate lobe in humans with BCS, we decided not to analyze this lobe in our rats. Another difference is that in rats, the left and middle hepatic vein can enter the IVC either separately or in conjuncture via the truncus communis, whereas the right hepatic veins are homologous to the right hepatic vein in men. This is the reason why we chose not to ligate the hepatic veins separately, but to ligate above the insertion of the hepatic veins, namely the IVC itself. Finally, in rats, different anatomical and functional relations exist between the portal, sinusoidal, and central venous bed. However, in the current study, we were only interested in the gross changes of the portal venous tree, and

detailed information regarding these microscopic relations was beyond the scope of our investigation.

In conclusion, in this first rat model for Budd-Chiari syndrome, a significant loss of peripheral portal branches was found on Micro-CT images in BCS rats as compared to shams. Changes occurred as early as 2 days after hepatic outflow obstruction. Hepatic vasculature was not equally affected among the lobes, suggesting inter-lobar compensatory mechanisms. Despite a decrease in both liver and portal vein volumes, which could be explained by atrophy and loss of portal branches, overall portal perfusion appeared relatively spared.

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III

Myeloproliferative Disease in the Pathogenesis and Survival of Budd-Chiari Syndrome

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Abstract

Background and objectives

Several issues regarding myeloproliferative diseases (MPD) in Budd-Chiari syndrome (BCS) exist that need to be clarified. The aim of this study was to evaluate multifactorial aetiology in BCS patients with MPD, to assess potential added value of the JAK2 mutation in the diagnostics of MPD in BCS and to determine the survival of MPD patients in BCS.

Design and methods

All patients referred to a university hospital with primary, non-malignant BCS between January 1980 and January 2006 were included in this study (n=40). In addition to standard MPD work-up, JAK2 mutation analysis was performed in 17 patients.

Results

MPD was present in 33% of the patients. In two patients suspect for Essential Thrombocythemia, who failed to meet WHO criteria, JAK2 mutation analysis led to the identification of MPD. In 38% of patients with MPD additional pro-thrombotic factors were present. Ten-year survival was 92% (95% CI, 78%–100%) in patients with MPD versus 53% (95% CI, 28%–79%) in patients without MPD (*P*=0.18).

Interpretation and conclusions

The multifactorial aetiology in BCS patients with MPD highlights the necessity of extensive screening for other underlying pro-thrombotic conditions. JAK2 mutation analysis is of diagnostic importance in patients with BCS. Survival of BCS patients did not differ significantly between individuals with and without MPD.

Introduction

Budd-Chiari syndrome (BCS) is a rare disorder caused by obstruction of the hepatic veins or the suprahepatic inferior vena cava and is associated with one or more underlying pro-thrombotic conditions in at least 75% of the patients (1). Myeloproliferative diseases (MPD) are the most important aetiological factor (2).

Several issues regarding MPD in BCS exist that need to be clarified. First, studies showing multifactorial aetiology in BCS patients with MPD are scarce and number of included patients in these studies are low (3, 4). Second, some BCS patients are labelled as having so-called occult MPD when criteria for MPD are not fulfilled, but in whom bone marrow culture show spontaneous erythroid colony formation (EEC). These patients may subsequently develop overt MPD. Recently, a clonal mutation in the JAK2 tyrosine kinase (JAK2V617F) is reported in a high proportion of patients with MPD and its role in BCS has not yet been fully determined (5). Third, there are no studies that address survival of BCS patients with MPD.

The aim of this study was to evaluate multifactorial aetiology in BCS patients with MPD, to assess potential added value of the JAK2 mutation in the diagnostics of MPD in BCS and to determine the survival of MPD patients in BCS.

Methods

Patients

Between January 1980 and January 2006, all patients referred to our hospital with primary, non-malignant Budd-Chiari Syndrome (BCS) were included in this study. BCS was defined as hepatic venous outflow obstruction at any level from the small hepatic veins to the junction of the inferior vena cava and the right atrium (1). Patients were followed up from date of diagnosis until death, study closure (January 1, 2006), or, in case of loss to follow up, the last date of visit. Patients were evaluated for pro-thrombotic conditions including coagulation disorders, MPD, and paroxysmal nocturnal haemoglobinuria (PNH). Other potential aetiological factors were collected by chart review. For patients included before 1996, the diagnostic evaluation has been reported. For patients included after 1996, plasma and DNA was stored and informed consent was obtained to perform studies on prothrombotic factors. The medical ethical committee approved these studies.

Coagulation assays

Venous blood samples were collected in 3.2% sodium citrate (final concentration). Plasma was centrifuged at 2000 g for 10 min at 4 ºC. Routine coagulation assays were performed immediately, or plasma was frozen at –80 °C. Genomic DNA was isolated from the white cell fraction of citrated blood, using the salt concentration standard procedure.

Antithrombin, protein C and protein S activity were measured by standard clotting assays. Free protein S levels were assessed using an ELISA (Biopool, Umeå, Sweden). In case of potential liver failure, the presence of hereditary deficiencies in antithrombin, protein C and S was only diagnosed if there was a clear isolated deficiency of either coagulation inhibitor in comparison to other coagulation tests and liver synthesis markers such as albumin. In patients on long-term oral anticoagulant treatment, protein C and S levels were not determined. Factor V Leiden mutation and prothrombin gene variant were assessed by PCR. The presence of lupus anticoagulant was tested by an APTT based and a diluted PT assay. Anticardiolipin antibodies (aCL) were tested by ELISA and values above the 95th percentile were considered a significant increase. Diagnosis of antiphospholipid antibodies (APA) was made if lupus anticoagulant or aCL was present on two or more occasions according to recently published guidelines (6). Diagnosis of paroxysmal nocturnal hemoglobinuria (PNH) was based on flow cytometric analysis.

Diagnostic work-up and diagnostic criteria for MPD

MPD was classified according to the current WHO guidelines (7-10). Total red blood cell (RBC) mass was determined as described before (11). A value above 125% of the theoretical value was considered a significant increase (12). If RBC mass was not measured, a significant increase was defined as a hemoglobin level above 18.5 g/dl in men or 16.5 g/dl in women (7, 10). Spontaneous erythroid colony formation (EEC) was determined in clonogenic assays as described earlier (13).

JAK2 mutation was determined in patients of whom DNA was available. High-molecular-weight peripheral blood DNA was isolated and the quality was verified by amplification of exon 11 of the FLT3 gene, using FLT3-11F 5'-CAATTTAGGTATGAAAGCC-3' and FLT3-11R 5'-

CAAACTCTAAATTTTCTCT-3'. Subsequently, two independent PCR reactions were performed using an allele-specific forward primer JAK2-ASP 5'-TTTTAAATTATGGAGTATATT-3'in combination with reverse primers GJAK2MUT1 5'-TATAACTGAATAGTCCTACAGTG-3' or GJAK2MUT2 5'-GTTGAACCTGCCATAATCTC-3'. PCR were performed on 50ng DNA (250μM dNTP, 15 pmol primers, 2mM MgCl2, Taq polymerase and 1x buffer (Invitrogen LT, Breda, The Netherlands)). Cycling conditions: 1x 5'94^{0}C, 35x 1'94^{0}C, 1'54^{0}C (FLT3) or 61.5^{0}C (JAK2 mutation), 1'72^{0}C, and 1x 7'72^{0}C.

Statistical analysis

Results are expressed as median ± SD. All tests were 2-tailed with the level of significance set at $P<0.05$. Comparison between patients with and without MPD were performed using the non-parametric Mann-Whitney U test for continuous variables and the Chi-square test for categorical variables. Survival rates were calculated by means of the Kaplan-Meier method and comparison of survival functions was based on log-rank testing. Statistical analyses were carried out in SPSS 11.5.0 for Windows (SPSS, Chicago, IL).

Results

Patient characteristics

Forty patients with primary, non-malignant BCS were identified in our hospital. Median age was 28.4 years (18.4-53.3) and 26 patients (65%) were female. In nine patients (23%) additional portal vein thrombosis (PVT) was present.

Underlying disorders

Coagulation disorders were found in 14 patients (35%). APA were detected at diagnosis of BCS in ten patients. Four patients had APA that was confirmed after 12 weeks. In six patients aCL or lupus anticoagulant was measured only once. Only patients in whom APA were confirmed were regarded as having APA. Oral contraceptives were used in 13 patients (52%). In four patients (10%) no underlying disorder could be found. Other prothrombotic factors are shown in table 1.

MPD in BCS

Twenty-nine patients underwent complete diagnostic work-up for MPD, and in 21 of these EEC were also performed. Eleven patients did not undergo a bone marrow biopsy nor was an EEC performed, mostly because of absence of peripheral blood count abnormalities and clinical features of MPD (n=8). This latter group of patients, who were not suspect for having a primary haematological disorder, did not undergo bone marrow biopsy since they were worked-up earlier in our study period and biopsies were not yet part of the routine diagnostic work-up for BCS. However, most of these patients were already diagnosed with another eligible cause for BCS. Screening for the JAK2 mutation could be performed in 17 patients (43%).

The results of MPD work-up are shown in table 2. Eleven patients were diagnosed with MPD according to current WHO criteria. Two other patients, who were suspect for MPD (high platelet counts), but failed to meet WHO criteria, had a positive JAK2 mutation and were therefore classified as MPD. MPD was present in 13 BCS patients (33%). In two of these patients, MPD had existed for a considerable period prior to the development of BCS (9 and 11 years). BCS was the first clinical presentation of MPD in eleven MPD patients.

Comparison of baseline characteristics between patients with (n=13) and without (n=27) MPD were as follows: median age (35.7 years vs. 29.6 years, P=0.10) and male:female ratio (44%:56% vs. 59%:41%. n.s.). Combined BCS-PVT was observed in nine patients, all without MPD. In five MPD patients (38%) additional pro-thrombotic factors were present, indicating multifactorial aetiology. Of these patients, three (23%) had one additional risk factor and two (15%) had two additional risk factors (table 2). Multifactorial aetiology was present in six patients (22%) of the patients without MPD.

The JAK2 mutation was identified in seven out of the 17 tested BCS patients (41%). None of the ten patients without the JAK2 mutation were diagnosed with MPD according to WHO criteria. The JAK2 mutation was present in two patients with clinical MPD showing spontaneous EEC, while absent in a third showing an isolated spontaneous EEC.

Table 1

Aetiological factors in 40 patients with primary, non-malignant Budd-Chiari syndrome[a]

	N	%[b]
Myeloproliferative disease	13	33
Coagulation disorder	14	35
Protein C deficiency[c]	2	7
Protein S deficiency[c]	2	7
Factor V Leiden mutation	5	15
Homozygote	2	6
Heterozygote	3	9
Prothrombin gene variant	2	8
Homozygote	0	0
Heterozygote	2	8
Antiphospholipid antibodies[d]	4	11
Anticardiolipin antibodies IgM/IgG	4	11
Lupus anticoagulant	1	3
Plasminogen deficiency	1	3
Others	21	53
Oral contraceptive use	13	52
Paroxysmal nocturnal hemoglobinuria	2	9
Auto-immune[e]	5	13
Ulcerative colitis	1	3
Abdominal surgery	1	3
No underlying disorder	4	10

[a]Patients can have more than one aetiological factor simultaneously.
[b]Percentage of tested patients; not all investigations could be performed in the individual patients.
[c]Patients treated with oral anticoagulants or hepatic failure during diagnostic work-up were excluded in this analysis.
[d]Diagnosis of antiphospholipid antibodies was made if lupus anticoagulant or aCL was present and confirmed after 12 weeks.
[e]Auto-immune diseases: Behcet's disease (n=1), Sjögren's disease (n=1), systemic lupus erythematosus (n=2) and mixed connective tissue disease (n=1).

Table 2

The diagnostic criteria in 13 patients with Myeloproliferative Disease (MPD) in primary, non malignant BCS

Pat. no	Sex	Age	Hb	Ht	RBC	Spl.meg-	Platelets	WBC	Epo	EEC	JAK2	Retic. fibrosis	BM Iron	Bone marrow biopsy/ morphology	Addiitional RF
			g/dl	*%*	*ml/kg*		*10E9/L*	*10E9/L*	*mU/mL*						
Polycythemia vera															
1[a]	F	49.9	16.3	43	21.1	+	273	25.0	327	-	NA	+	-	Panmyelosis, especially erythroid line, dysplastic megakaryocytes, clustering	None
2	F	46.3	17.4	51	33.9	+	361	10.2	19	NA	+	+	-	Panmyelosis, dysplastic megakaryocytes, clustering	None
3	M	40.2	18.4	54	NA	+	112	16.5	5	NA	NA	+	-	Erythroid and megakaryocytic hyperplasia, dysplastic megakaryocytes, clustering	None
4	F	46.9	12.6	42	39.2[b]	+	418	10.6	NA	NA	+	+	-	Panmyelosis, dysplastic megakaryocytes, clustering	None
5	M	26.0	17.3	41	34.6	+	472	9.7	10	+	+	+	-	Erythroid and megakaryocytic hyperplasia	None
6	M	27.4	17.3	47	41.3	+	328	4.6	12	+	+	-	-	Panmyelosis, dysplastic megakaryocytes dysplastic megakaryocytes, clustering	None
Essential thrombocythemia															
7	F	29.5	14.2	45	29.5	-	520	4.9	NA	+	NA	-	+	Erythroid and megakaryocytic hyperplasia, dysplastic megakaryocytes	OCC
8	F	36.8	9.2	27	NA	-	629	16.0	NA	NA	+	-	-	Megakaryocytic hyperplasia and dysplasia, clustering	Protein C def., OCC
9	F	46.6	11.8	37	26	-	596	3.6	NA	NA	NA	+	-	Megakaryocytic hyperplasia and dysplasia, clustering	None
10	F	35.9	11.0	39	NA	-	497	9.8	23	+	NA	+	-	Erythroid and megakaryocytic hyperplasia, dysplastic megakaryocytes	OCC, SLE
11[e]	F	20.9	11.3	38	NA	-	445	7.3	15	-	+	-	+	Megakaryocytic hyperplasia and dysplasia	OCC
12[e]	M	21.8	15.8	43	26.7	+	450	16	3	-	+	-	+	Megakaryocytic hyperplasia and dysplasia	None
Chronic myeloproliferative disease, unclassifiable															
13	F	36.9	14.4	39	30.0	+	215	23	30	+	NA	-	-	Erythroid and megakaryocytic hyperplasia, dysplastic megakaryocytes, clustering	OCC

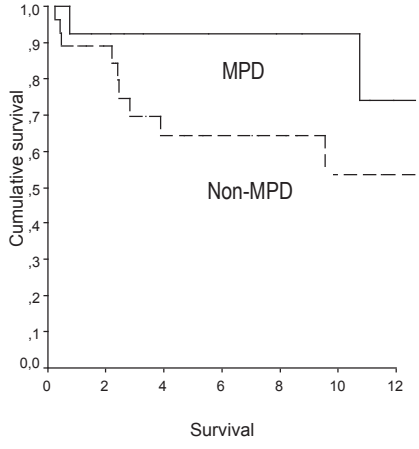
[a]Patient 1 was diagnosed with MPD despite an elevated erythropoietin level, as it has been shown that this does not exclude MPD (9).
[b]>25% above mean normal predicted value.
[c]In none of the patients' bone marrow collagen fibrosis was present.
[d]OCC (oral contraceptives), SLE (systemic lupus erythematosus).
[e]Patients 11 and 12 were suspect for MPD based on high platelet counts, which was later confirmed by positive JAK2 mutation.

Follow-up

Overall mean follow-up was 7.1 ± 6.9 years (8.2 ± 6.6 years in patients with MPD and 6.5 ± 7.1 years in patients without MPD). Only two patients were lost to follow-up, one in each group. One patient without, and three patients with MPD underwent liver transplantation. Eleven patients (28%) died during follow-up, of which two had MPD. In both patients, cause of death was not MPD, but newly developed epitheloid abdominal sarcoma after liver transplantation (n=1) and liver failure (n=1). Causes of death in patients without MPD were liver failure (n=3), sepsis (n=3), cardiovascular disorders (n=1), variceal bleeding (n=1) and mesenteric vein thrombosis (n=1). Both patients with MPD died in the first year after diagnosis and hence the survival rates in patients with MPD at 1, 5, and 10 years remained constant at 92% (95% CI, 78%–100%). Survival rates in patients without MPD at 1, 5, and 10 years were 89% (95% CI, 77%–100%), 64% (95% CI, 44%–85%) and 53% (95% CI, 28%–79%), respectively (figure 1). There was no significant difference in survival between the two (P=0.18). None of the patients without MPD clinically developed MPD during follow-up.

Figure 1

Survival in non-MPD patients (n=27) and MPD patients (n=13) with primary, non-malignant Budd-Chiari syndrome. Survival rates in patients with MPD at 1, 5, and 10 years were 92% (95% CI, 78%–100%), with number of patientzs at risk being 12, 8 and 5, respectively. Survival rates in patients without MPD at 1, 5, and 10 years were 89% (95% CI, 77%–100%), 64% (95% CI, 44%–85%) and 53% (95% CI, 28%–79%), with number of patients at risk being 24, 11 and 5, respectively.



Discussion

In this study we evaluated a large group of 40 consecutive patients diagnosed with primary, non-malignant BCS at our hospital, thereby focussing on multifactorial aetiology, the potential added value of the JAK2 mutation in MPD diagnostics and survival of MPD patients in BCS.

We found a prevalence of MPD of 33%, which is in line with the prevalence of 23%-49% when conventional criteria for diagnosis of MPD are used (PVSG/WHO) (14, 15). None of our BCS patients without MPD at diagnosis developed MPD during follow-up.

Several studies have shown the coexistence of multiple pro-thrombotic factors in BCS patients with MPD (3, 4). Our results showed that in 38% of the patients with MPD additional risk factors were present. These results highlight the necessity of extensive screening for additional pro-thrombotic conditions.

Recently, a clear association between MPD and a somatic point mutation of the JAK2 tyrosine kinase (JAK2 V617F) has been described (5). The acquired mutation in JAK2 is found in most patients with PV and is seen in half of the patients with ET and CIMF (5). This mutation has recently been shown to occur in 59% of BCS patients and is reported to be of use in the characterization of occult MPD in BCS (16). Our study showed a JAK2 mutation prevalence of 41%. Interestingly, the JAK2 mutation led to the identification of two patients with MPD who failed to meet WHO criteria. This, combined with the report by Patel et al., suggests that JAK2 mutation analysis should be included in standard MPD work-up in BCS patients. One patient was diagnosed with MPD despite an elevated erythropoietin level, as it has been shown that this does not exclude MPD (17). Unfortunately, this patient died during follow-up, making JAK2 analysis impossible.

To date, survival in BCS patients with MPD has not yet been systematically investigated. In our study, 10-years survival was 92% for BCS patients with MPD. It has been suggested that a shortened survival in MPD patients with additional BCS is primarily related to complications of hepatic dysfunction and portal hypertension, and not to complications of MPD. Indeed, the two BCS patients with MPD died of causes unrelated to MPD. Our results showed no statistically significant difference in survival between BCS patients with and without MPD. However, it should be noted that in the 27 BCS patients without MPD, a wide range of pro-thrombotic factors were present that differ in nature and prognosis, varying from oral contraceptive use, homozygote factor V Leiden mutation to PNH (18). Since individual prevalences of these etiological factors are low, comparative sub-group analysis was not possible. It has been shown that more extensive thrombosis in the splanchnic area is associated with poorer survival (19). PVT was only present in patients without MPD in our BCS population, which may account for the slightly lowered survival of these patients in our study. In addition, three patients with and one patients without MPD underwent liver transplantation, which may have affected survival rate in favour of MPD patients.

In conclusion, we report MPD in 33% of our BCS patients. In 38% of the patients with MPD, additional pro-thrombotic factors were present. Our study clearly confirms the importance of

JAK2 mutation analysis in patients with BCS. Long term follow-up did not show a significant difference in survival between patients with and without MPD.

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IV

Genetic Variation in Thrombin-Activatable Fibrinolysis Inhibitor (TAFI) is associated with the Risk of Splanchnic Vein Thrombosis

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Abstract

Background and Aims

Splanchnic vein thrombosis (SVT) has been associated with a hypercoagulable state. TAFI may contribute to a hypercoagulable state and therefore we were interested in the role of TAFI in SVT. Since the disease is frequently associated with liver insufficiency, which affects plasma levels of TAFI, we studied the role of variation in the TAFI gene in SVT.

Patients and Methods

In a multicenter case-control study on 118 patients with SVT (39 Budd-Chiari syndrome and 85 portal vein thrombosis) and 118 population-based controls, the relationship of SVT with single nucleotide polymorphisms (SNPs) and haplotypes in the TAFI gene (−438G/A, Ala147Thr, Thr325Ile and 1583A/T) was determined.

Results

The risk for SVT was decreased (OR 0.2, 95% CI 0.1-0.7) in 147Thr/Thr homozygotes and slightly, but not significantly, increased in carriers of the 325Ile allele (OR 1.6, 95%CI 0.9-2.7). Haplotype analysis confirmed that the Ala147Thr SNP has the strongest association with risk of SVT.

Conclusions

Genetic variation in the TAFI gene is associated with risk of SVT, suggesting a role for TAFI in the pathogenetic mechanism of SVT.

Introduction

Splanchnic vein thrombosis (SVT) is thrombosis of the hepatic veins and of the portal venous system. It includes the Budd-Chiari syndrome (BCS), which is characterized by occlusion of hepatic outflow at the level of hepatic venules, large hepatic veins or inferior caval vein (1) and portal vein thrombosis (PVT) (2). PVT often occurs in conditions leading to decreased portal flow, such as cirrhosis or malignancies, abdominal surgery and infections. Both BCS and PVT have been observed in association with acquired or hereditary hypercoagulable conditions, such as myeloproliferative disorders and antiphospholipid syndrome or factor V Leiden mutation and prothrombin mutation (2-4).

Thrombin-activatable fibrinolysis inhibitor (TAFI) (5), also known as plasma procarboxypeptidase R (6), procarboxypeptidase U (7) and procarboxypeptidase B (8), is the precursor of a carboxypeptidase that potently attenuates fibrinolysis. Activated TAFI (TAFIa) suppresses fibrinolysis by removing carboxy-terminal lysine residues from partially degraded fibrin polymers, preventing the binding of the fibrinolytic components plasminogen and tissue-type plasminogen activator (9, 10). By this mechanism, TAFI stabilizes the fibrin clot and makes the clot more resistant to lysis. Indeed, elevated plasma TAFI antigen levels are associated with a mildly increased risk for venous thrombosis (11, 12) and for recurrent venous thromboembolism (13). The TAFI concentration in plasma is partly genetically determined, and several genetic variants have been reported that are associated with plasma TAFI levels, such as the –438G/A (rs#2146881) (14, 15) single nucleotide polymorphism (SNP) in the TAFI promoter region which is of interest because promoter SNPs may affect the transcription rate and because this SNP is associated with risk of venous thrombosis (14). Also SNPs that result in amino acid changes and may affect the TAFI function are of interest, such as the Thr325Ile (1040C/T, rs#1926447) which results in a TAFI isoform with altered antifibrinolytic activity (16) and the Ala147Thr (505G/A, rs#3742264).These SNPs have also been associated with TAFI levels and venous thrombosis risk (14). Also the 1583A/T (rs#1087) has a strong association with TAFI plasma levels (17). However, the associations between these SNPs and risk of splanchnic vein thrombosis are still unknown.

In patients with liver disease, the role of TAFI in determining the risk of SVT can not be clearly determined, since plasma levels are strongly affected by the disease. Therefore, we focused on studying genetic variation, which is an important determinant of TAFI levels and not affected by the disease. SVT is frequently seen in patients with pre-existent liver disease, but may also result in a reduced liver synthesis capacity, as is seen in patients with BCS. Therefore, we studied the role of TAFI in SVT by determining the contribution of variation in the TAFI SNPs that have been reported to be functional on SVT in a multicenter case-control study.

Methods

Subjects

A total of 118 patients, 39 patients with BCS and 85 patients with PVT of whom six patients had both BCS and PVT, were enrolled in the study. These patients, identified in seven academic hospitals in the Netherlands between July 1997 and February 2003, underwent a full screening for thrombogenic disorders. Details of the procedure have been published previously (3). Part of this previously reported patient population (n = 105) is included in this study. Briefly, diagnostic criteria for BCS and PVT were partial or complete obstruction of hepatic outflow or the portal vein, respectively, as documented by appropriate radiographic abdominal imaging (Doppler ultrasonography, computed tomography, magnetic resonance imaging or venography) or laparotomy. Patients with veno-occlusive disease or with hepatic outflow obstruction caused by congestive heart failure were excluded. Patients alive were asked to visit the hospital in which they were registered for blood sampling, at the same time enabling investigators to complete the questionnaire with information on previous thrombotic events, familial thrombosis, acquired risk factors of thrombosis, and the use of anticoagulants at the time of venipuncture. The population-based control group consisted of 118, sex- and age matched (≤ 5 years difference) healthy subjects who had no history of venous thromboembolism and did not use coumarin derivatives, and were partners or friends of the patients. The study was approved by the ethical committee of each participating hospital and the participants gave their informed consent before entering the study.

Methods

We selected four SNPs in the TAFI gene that comprehensively describe the DNA sequence variation of the TAFI gene, including the promoter and 3' UTR region. The four haplotype-tagging SNPs were selected on the basis of the linkage disequilibrium map of the TAFI locus provided by the SeattleSNP project (http://pga.gs.washington.edu/) and the HAPMAP project (www.hapmap.org) to study the total common genetic variation. Since there are several SNPs that tag a specific haplotype, we selected SNPs based on their potential functionality as described in the introduction. Blood was collected in tubes containing 3.2% trisodium citrate (9:1 vol/vol) using a Vacutainer system (Becton Dickinson, Plymouth, UK). The blood was centrifuged for 30 min at 2000g at 4° C and genomic DNA was isolated from the white cell fraction using standard procedures. Analysis of the SNPs in the TAFI gene (–438G/A (dbSNP rs#2146881), Ala147Thr (505G/A, dbSNP rs#3742264), Thr325Ile (1040C/T, dbSNP rs#1926447) and 1583A/T dbSNP rs#1087)) was performed using polymerase chain reaction (PCR) with subsequent restriction enzyme digestions as described previously (18). Briefly: the PCR mixture (25 µL) contained: 50 ng genomic DNA, 37.5 pM of each primer, 1.5 mM of each dNTP (Pharmacia), 2.5 µL buffer (15 mM MgCl2 500 mM KCl 100 mM TrisHCl, pH 8.3) and 1.25 U Taq DNA polymerase (Boehringer Mannheim). The PCR conditions were: 4 min 95° C of initial denaturation, followed by 32 cycles of 1 min of denaturation at 94° C, 1 min annealing at 58 and 62° C resp and 2 min of elongation at 72° C. The PCR products were digested with their specific restriction enzymes for 180 min at 37ºC and analyzed on a 2.5% agarose gel. The laboratory staff was not aware of the patient or control status.

Statistical analysis

Patients with both BCS and PVT were included in the analyses of both diseases. The data are presented as means ± standard deviation (SD). Allele frequencies were calculated by gene counting and for each SNP the deviation from Hardy-Weinberg equilibrium was tested in controls using a χ^2 test with one degree of freedom. The association between TAFI SNPs and SVT was investigated by logistic regression, using the genotypes with the highest frequency (–438GG, 147Ala/Ala, 325Thr/Thr and 1583A/A) as reference groups (14).

Haplotypes present in the population were inferred by means of the haplo.em function of the program Haplo Stats (http://cran.r-project.org/src/contrib/Descriptions/haplo.stats.html), which computes maximum likelihood estimates of haplotype probabilities (19, 20). Haplotype reconstruction resulted in seven haplotypes with frequencies > 2%. The most common haplotype (G-Ala-Thr-A) served as the reference category.

The association between TAFI gene haplotypes and SVT was investigated by (weighted) logistic regression using the haplo.glm function of the program Haplo Stats (19-21). The probability for each haplotype pair in each individual was assigned and then an individual's phenotype was directly modeled as a function of each inferred haplotype pair, weighed by their estimated probability, to account for haplotype ambiguity. Using haplo.score, we computed simulation P-values for each haplotype to account for multiple testing. Details on the background and theory of score statistics can be found in Schaid et al. (21) The number of simulations was set at 1000.

A value of $P < 0.05$ was considered statistically significant. Except for the haplotype analyses, all statistical analyses were performed using the Statistical Package for Social Science for windows, version 10.1 (SPSS Inc. Chicago, Illinois, USA).

Results

The characteristics of the 118 patients with SVT (39 patients with BCS and 85 patients with PVT) and 118 controls are summarized in table 1. Fifty-four (46%) of the SVT patients and controls were male and the mean age of SVT patients and controls was 51 years.

Table 1
Characteristics of patients with Splanchnic Vein Thrombosis (SVT), Budd-Chiari syndrome (BCS), Portal vein thrombosis (PVT) and healthy controls

	SVT n = 118	BCS n = 39	PVT n = 85	Controls n = 118
Age (y)	51 (18-81)	43 (18 - 66)	53 (24 – 81)	51 (17 - 77)
Male	54 (46%)	14 (36%)	42 (49%)	54 (46%)
Oral anticoagulation	47 (40%)	30 (77%)	21 (25%)	-
Inherited thrombophilia	27 (23%)	11 (28%)	17 (20%)	NA
Myeloproliferative disorders	27 (23%)	13 (33%)	15 (18%)	-
PNH	3 (3%)	1 (3%)	2 (2%)	NA
Lupus anticoagulant	4 (3%)	4 (10%)	-	NA
Anti-cardiolipin antibodies	5 (4%)	3 (8%)	2 (2%)	NA
Biopsy documented cirrhosis	15 (13%)	6 (15%)	10 (12%)	NA
History of pancreatitis	9 (8%)	-	9 (11%)	-
Infection	15 (13%)	3 (9%)	14 (16%)	-
Inflammatory bowel disease	3 (3%)	2 (5%)	2 (2%)	-
Autoimmune disease	10 (8%)	5 (13%)	5 (6%)	-
Previous abdominal surgery	39 (33%)	10 (26%)	30 (35%)	NA
Cancer	2 (2%)	-	2 (2%)	-
Oral contraceptives	24 (38%)	14 (56%)	14 (33)	12 (19)
Antithrombin activity levels (%)	92.1 ± 22.5	99.4 ± 23.8	91.0 ± 18.7	104.2 ± 13.5

Data are presented as mean (range). Inherited thrombophilia is defined as Factor V Leiden mutation, Prothrombin mutation, Protein C deficiency, Protein S deficiency or Antithrombin deficiency. Myeloproliferative disorders include Polycythemia vera, Essential thrombocythemia, Myelofibrosis, MPD Unclassified. hemoglobinuria. Infection at time of diagnosis: liver viral, liver bacterial, cholecystitis/cholangitis, omphalitis, intestinal with(out) abcess, elsewhere abdominal, extra-abdominal, sepsis eci. Previous abdominal surgery: Splenectomy, Cholecystectomy, and other abdominal surgery. Oral contraceptive use % of women at time of diagnosis. PNH: paroxysmal nocturnal, NA: not available.

The distributions of the –438G/A, Ala147Thr, Thr325Ile and 1583A/T TAFI SNPs were in Hardy-Weinberg equilibrium in the control group.

Subjects with the 147Thr/Thr genotype had a lower risk of SVT (OR 0.2, 95% CI 0.1-0.7) compared with the reference group of subjects with the 147Ala/Ala genotype, with an intermediate risk (OR 0.9, 95% CI 0.5-1.5) for the heterozygotes (table 2). Subjects with the 325Thr/Ile genotype had a higher risk of SVT (OR 1.8, 95% CI 1.0-3.0) than subjects with the 325Thr/Thr genotype. Carriers of the 325Ile allele also had a slightly increased risk (OR 1.6; 95% CI 0.9-2.7). Subjects with the –438GA genotype showed an OR of 1.6 (95% CI 0.9-2.7) as compared to subjects with the –438GG genotype. The 1583A/T polymorphism was not associated with risk of SVT (table 2).

In the subgroup of BCS subjects with the 147Thr/Thr genotype had also somewhat, although not significantly, lower risk of vein thrombosis with an OR of 0.2 (95% CI 0.02-1.3) compared with subjects with the 147Ala/Ala genotype, and an OR of 1.2 (95% CI 0.6-2.5) for the heterozygotes. The associations between the other TAFI SNPs and BCS was similar to those in the total group. Subjects with the 325Thr/Ile genotype had an OR for BCS of 1.3 (95% CI 0.6-2.9) when compared with subjects with the 325Thr/Thr genotype. Subjects with the –438GA genotype showed an OR of 1.5 (95% CI 0.7-3.3) when compared with the subjects with the –438GG genotype. Subjects with the 1583AT genotype showed an OR of 1.4 (95% CI 0.7-3.0) when compared with the subjects with the 1583AA genotype.

In the PVT subgroup, the associations between the TAFI SNPs and risk of vein thrombosis were similar to those in the total SVT group. Subjects with the 147Thr/Thr genotype had a lower risk of PVT (OR 0.3, 95% CI 0.1-0.8) than subjects with the 147Ala/Ala genotype, with an intermediate risk (OR 0.9, 95% CI 0.5-1.6) for the heterozygotes. Subjects with the 325Thr/Ile genotype showed an OR of 1.7 (95% CI 1.0-3.1) when compared with subjects with the 325Thr/Thr genotype. In subjects with the –438GA genotype the OR for PVT was 1.4 (95% CI 0.8-2.5) when compared with subjects with the –438GG genotype. Subjects with the 1583AT genotype showed an OR of 1.5 (95% CI 0.8-2.9) when compared with the subjects with the 1583AA genotype.

Since the TAFI SNPs are in high linkage disequilibrium, we also analyzed the association between TAFI haplotypes and risk of SVT, using the most common haplotype (G-Ala-Thr-A) as reference (figure 1). The haplotype analysis confirmed that the Ala147Thr SNP has the strongest association with risk of SVT. The risk of SVT was significantly lower for the G-Thr-Thr-A haplotype (-438G/147Thr/325Thr/1583A, OR 0.1, 95% CI 0.03-0.6) and also somewhat, although not significantly, lower for the A-Thr-Thr-T haplotype (OR 0.3, 95% CI 0.06-1.5), when compared with the common G-Ala-Thr-A haplotype. There was a clear SNP-SNP interaction, since no association with risk was seen for the G-Thr-Thr-T haplotype. In the BCS and PVT subgroups a similar trend, although not significantly, was observed for the G-Thr-Thr-A haplotype as compared to the common G-Ala-Thr-A haplotype.

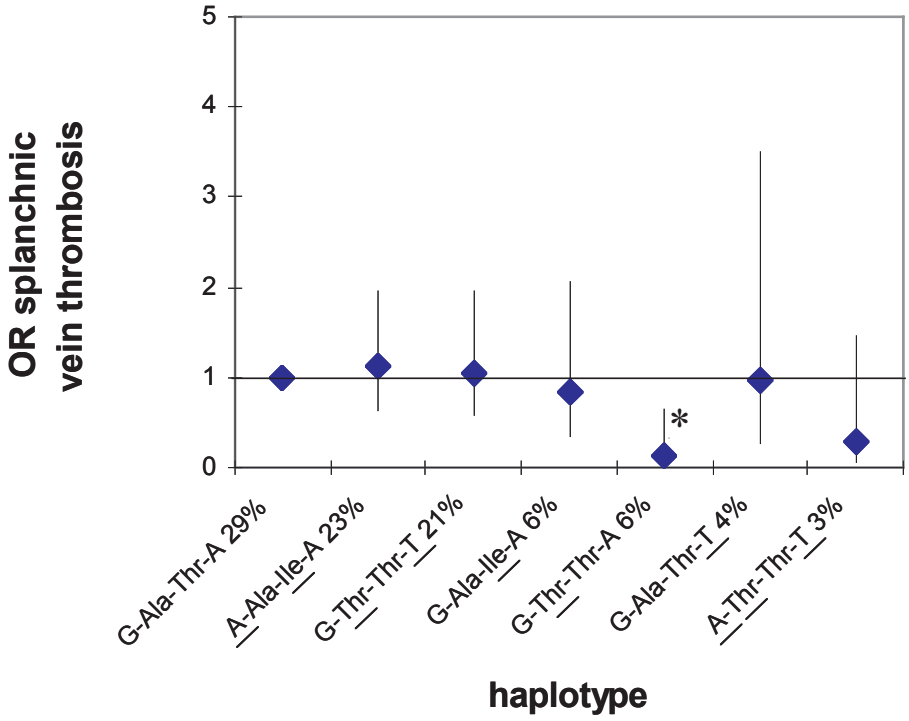
Table 2
Associations between TAFI genotypes and risk of SVT

	Genotype distribution patients (n=118)		Genotype distribution controls (n=118)		OR (95% CI)
-438G/A*					
GG	48	(42%)	60	(52%)	1
GA	58	(51%)	46	(40%)	1.6 (0.9-2.7)
AA	8	(7%)	10	(9%)	1.0 (0.4-2.7)
GA & AA	66	(58%)	56	(48%)	1.5 (0.9-2.5)
A-allele (freq)	0.32		0.28		
Ala147Thr*					
Ala/Ala	58	(50%)	48	(41%)	1
Ala/Thr	54	(46%)	50	(43%)	0.9 (0.5-1.5)
Thr/Thr	5	(4%)	18	(16%)	0.2 (0.1-0.7)
Ala/Thr & Thr/Thr	59	(51%)	68	(59%)	0.7 (0.4-1.2)
Thr-allele (freq)	0.27		0.37		
Thr325Ile*					
Thr/Thr	40	(34%)	53	(45%)	1
Thr/Ile	69	(59%)	52	(44%)	1.8 (1.0-3.0)
Ile/Ile	9	(8%)	13	(11%)	0.9 (0.4-2.4)
Thr/Ile & Ile/Ile	78	(66%)	65	(55%)	1.6 (0.9-2.7)
Ile-allele (freq)	0.37		0.33		
1583 A/T*					
AA	47	(41%)	48	(58%)	1
AT	60	(52%)	45	(45%)	1.4 (0.8-2.4)
TT	8	(7%)	7	(7%)	1.2 (0.4-3.5)
AT & TT	68	(60%)	52	(52%)	1.3 (0.8-2.3)
A-allele (freq)	0.33		0.30		

*Genotype with highest TAFI antigen level was considered as reference. TAFI, thrombin-activatable fibrinolysis inhibitor; SVT, splanchnic vein thrombosis; OR, odds ratio; CI, confidence interval

Figure 1

The effect of thrombin-activatable fibrinolysis inhibitor (TAFI) haplotypes on risk of splanchnic vein thrombosis (SVT) in patients versus controls expressed as odds ratio's. The alleles in the haplotype are given in the following polymorphism order: -438G/A, Ala147Thr (505G/A), Thr325Ile (1040C/T) and 1583A/T. Asterisk indicate haplotype, whose average effect is significantly different from the group with the most common haplotype (G-Ala-Thr-A) which served as the reference category.



Discussion

Our study indicates that SNPs in the TAFI gene are associated with the risk of SVT. Both the Ala147Thr and Thr325Ile SNPs are associated with risk of SVT.

We selected four haplotype-tagging SNPs in the TAFI gene to study the total common genetic variation (covering 92% of the genetic variation). Since there are several options for SNPs tagging a haplotype, we selected SNPs based on their potential functionality in order to learn more about the different mechanisms that may underlie associations with SVT. The -438G/A and 1583A/T were selected because they are associated with the TAFI concentration, and the –438G/A is located in the promoter region and may therefore affect synthesis regulation (16, 17). The Ala147Thr SNP was also selected because of its association with TAFI concentration and with the risk of arterial thrombosis and because the amino acid substitution may affect functionality of TAFI (22, 23). The Thr325Ile SNP was selected because this SNP encodes for two different isoforms of TAFI, with a difference in activity and half-life and because it also correlates with TAFI concentration (16).

We considered BCS and PVT as one entity (splanchnic vein thrombosis) as has been done in previous studies (24, 25) because a common pathway, that leads to a hypercoagulable condition, is expected.

In our study, the 147Thr/Thr genotype was significantly associated with decreased risk of SVT and the risk for SVT was slightly, but not significantly, increased in carriers of the 325Ile allele (OR 1.6, 95%CI 0.9-2.7). Previously, the Ala147Thr and theThr325Ile SNPs were reported to be strongly associated with TAFI antigen levels (15, 26). However, from previous findings it has become clear that this association is mostly due to the genotype-dependent antibodies that are used in these assays (26). When using assays that did not have this problem, it has been shown that the 147Ala and 325Ile alleles are still associated with lower TAFI antigen levels but that the relationship is less strong (15). It is therefore expected that the genotypes that are associated with SVT in our study are the genotypes that are associated with the lowest TAFI antigen levels. A recent study by Martini and coworkers (14) reported also that carriers of the 505G (147Ala) allele have an increased risk of DVT. In contrast, previous studies reported an association between high levels of TAFI and risk of deep venous thrombosis (11) which suggests that the relation between genotypes and risk may not be via the TAFI concentration in plasma per se, but may be related to a change in functional aspects of TAFI.

TAFI can circulate in different isoforms, and the activated form of TAFI of the 325Ile isoform has a half-life of 15 min while that of the 325Thr variant is 8 min. Furthermore, the antifibrinolytic potential of the 325Ile isoform was 30-60% greater than the 325Thr variant (27). The ability of TAFIa 325Ile variant to release twice as much lysine during fibrinolysis as the 325Thr variant may shift the balance towards coagulation instead of fibrinolysis in these patients albeit the lower antigen levels. This may partially explain the increased risk of SVT in carriers of the 325Ile-allele.

Because there is a high degree of linkage disequilibrium, it is not possible to estimate the contribution of the individual SNPs by analyzing the SNPs separately in the univariate analysis.

Therefore, we also studied the effects of haplotypes, in order to estimate the effects of the SNPs combined in one model. This haplotype analysis indicates that the Ala147Thr SNP has the strongest effect on risk of SVT. Mechanistic studies have so far shown little effect of the Ala147Thr SNP on the antifibrinolytic potential of TAFIa (27). A possible explanation could be that there is linkage disequilibrium between the Ala147Thr with a yet unknown regulatory factor of TAFI.

The haplotype analysis assumes additivity of the effects of the alleles. We see some, but not strong, gene-dose effects and therefore it is not completely clear whether this assumption is completely valid. Larger studies are needed to elucidate more detailed the interaction between the alleles.

The strength of our study is that we determined TAFI genetic variations, performed haplotype analysis to assess the pathogenetic importance of TAFI in SVT and that our study is therefore not affected by an effect of the disease on TAFI levels. In addition, this study is performed in a group of patients with SVT that is unique and large considering that SVT is a rare disease. Our study had a case-control design, which means that only patients who survived the SVT were included, and since BCS is fatal in 20% of the cases within 2 years when treated in specialized centers (28) the true association between TAFI and SVT may have been underestimated.

In conclusion, the present study describes a relationship between TAFI gene SNPs, including haplotype analysis and risk of SVT, where subjects carrying TAFI “lowering alleles” had a higher risk of SVT which suggests that TAFI plays a role in the development of splanchnic vein thrombosis.

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V

Risk Factors, Management and Outcome of Budd-Chiari Syndrome

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Abstract

Background

Budd-Chiari Syndrome (BCS) is characterised by hepatic venous outflow obstruction. Because of the low incidence previous studies have been focussed on prevalent patients and were small in sample size. Our aim was to prospectively investigate risk factors and current trends in management and outcomes .

Methods

From October 2003 to October 2005, incident patients with BCS were identified in nine European countries. Diagnosis was exclusively based on radiological imaging. Obstruction due to sinusoidal obstruction syndrome, malignant and cardiac causes were excluded. Blood samples and radiographical studies were collected for centralized work-up. Patients were systematically followed until death, study closure or last visit.

Results

Of 210 patients identified in 39 hospitals, 163 (93 females; median age 38) were eligible for analysis. Median follow-up was 17 months (range 0.1-31). More than one risk factor was present in 46% of the patients. Myeloproliferative disorders were found in 49%. V617F-JAK2 mutation was detected in 29%. Patients were mainly treated with anticoagulation (n=140, 86%), TIPS (n=56, 34%) and/or liver transplantation (n=20, 12%). Only 3 patients underwent surgical portosystemic shunting. Eighty patients (49%) were managed non-invasively. One and two-year survival rates were 87% (95% CI 82-93) and 82% (95% CI 75-88), respectively. Time to intervention was determined by ascites, encephalopathy, albumin, ALT and creatinine levels.

Conclusions

This study on BCS shows an excellent short-term survival with management aimed at minimal invasiveness. TIPS appears to have replaced surgical shunting. Myeloproliferative disorders were often present in BCS patients and should always be tested for.

Introduction

Budd-Chiari Syndrome (BCS) is a rare, but clinically challenging disorder defined as an obstruction of hepatic venous outflow, anywhere from the small hepatic veins to the suprahepatic inferior vena cava[1]. In the Western world thrombosis is the most common cause. Although the classic presentation is that of a previously healthy young woman who presents with sudden onset of abdominal pain, ascites and hepatomegaly, many variations to this presentation exist. The etiology is frequently related to an underlying prothrombotic disorder. Previous studies have suggested that one-fourth of patients have coexistence of multiple risk factors[2,3]. Therapeutic options include medical management with anticoagulants and diuretics, as well as invasive procedures, such as thrombolysis, Percutaneous Transluminal Angioplasty (PTA), radiological (Transjugular Intrahepatic Portosystemic Shunting (TIPS)) and surgical portosystemic shunting, and Orthotopic Liver Transplantation (OLT)[4,5].

Due its low incidence, estimated at 1 in 2.5 million per year[6], our current knowledge on etiology and prognosis is based on small studies of prevalent cases, i.e. a mix of patients who developed the disease recently or longer ago. This gives rise to survival bias as well as a distorted view on current treatment modalities and their effect, compounded by scarcity of recent data[7-10]. There is an important need for knowledge on the current aspects of BCS, obtained in a large multicentric cohort of recently diagnosed patients and treated according to most recent recommendations. Therefore, we performed a large prospective cohort study in patients with BCS.

Methods

Study design

This was a prospective multicenter follow-up study of incident patients with BCS, identified in academic and large regional hospitals in nine European countries, enrolled from October 2003 to October 2005 and followed until May 2006 (study closure), death or, in case of loss to follow-up, date of last visit. The study was conducted with approval from all national, and- if necessary- local ethical committees. All patients agreed by completion of a written informed consent.

BCS was defined as previously described[1]. Sinusoidal obstruction syndrome (previously known as veno-occlusive disease) was excluded from this definition.

All consecutive newly diagnosed patients with BCS were enrolled in the study if they met the following inclusion criteria: 1) evidence for BCS was unambiguous and established by radiographic imaging (Ultrasound (US), Computerised Tomography (CT), Magnetic Resonance Imaging (MRI) or Venography); and 2) patient was older than 16 years. Patients were excluded if outflow obstruction occurred in the setting of congestive heart failure, liver transplantation, or a (hepatobiliary) malignancy.

Data acquisition

To harmonise patient management all participating centers received guidelines at the start of this study on follow-up and general indications for invasive procedures, such as portosystemic shunting and liver transplantation. Data were collected at baseline, week 1 to 4, month 2, 3, 6, 9, 12, 18 and 24, at death, and at significant clinical events. These were defined as 1) clinical deterioration (i.e. any new hospital admission and/or first development or recurrence of massive ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, variceal bleeding and/or hepatic encephalopathy; 2) new radiographic liver study, and 3) new BCS-related intervention. All data were obtained by a standardised review of the medical charts by a single investigator per country using a structured questionnaire. Data were periodically reviewed and monitored by a single investigator (SDM) for purposes of data quality assessment. Copies of the original imaging studies were collected and scored by one radiologist per country, with special expertise in vascular liver disease.

Risk factors at diagnosis

At diagnosis, plasma and DNA samples were obtained following a uniform protocol and sent to a central laboratory (Hôpital Beaujon, Clichy, France) for standardized thrombophilia assessment. Patients were screened for the following underlying disorders: Factor V G1691A mutation (factor V Leiden); prothrombin gene G20210A mutation; protein S, protein C or antithrombin deficiency; myeloproliferative disorders and JAK2 V617F mutation; antiphospholipid antibodies, hyperhomocysteinemia and MTHFR C677T mutation; paroxysmal nocturnal hemoglobinuria (PNH) and Behçet's disease. In view of the possibility of an acquired deficiency of the natural anticoagulant proteins (C, S and antithrombin) due to hepatocellular dysfunction and concomitant use of anticoagulation and/or oral contraceptives, a deficiency was only considered hereditary if 1) only one of the three proteins was deficient (i.e. isolated deficiency); 2) the abovementioned drugs were not used; and 3) bilirubin level was lower than 2 times the upper limits of normal (ULN). In addition, for protein S deficiency, concurrent presence of Factor V Leiden mutation or anticardiolipin IgG antibodies were excluded, since these can influence

protein S levels. An expert (FWL) who was not involved in data analysis reviewed each case individually.

Statistical analyses

The primary endpoint was death. Secondary outcomes included time to transplantation or death (i.e. transplantation-free survival), and time to any invasive therapeutic intervention or death (i.e. intervention-free survival). Between-groups comparison was based on Chi-square testing, independent sample T-tests or Mann-Whitney-U tests. Actual and transplantation-free survival rates were calculated by means of the Kaplan Meier method and compared by log rank testing. Cox regression analysis was utilized to find predictors of intervention-free survival. Statistical significance was set at $P<0.05$. All statistical analyses were conducted in SPSS, version 14.0.0, Chicago, IL.

Results

Baseline characteristics and risk factors

Baseline characteristics and risk factors are summarised in table 1 and 2. A total of 210 patients were identified in 39 hospitals. Forty-seven patients were excluded because the date of diagnosis fell outside the study period (n=16); the diagnosis of BCS was not confirmed (n=14); there was an underlying malignancy (n=7); and other reasons (n=10). Thus, the total number of eligible patients was 163. Median age at diagnosis was 38 years (range 16-83), 93 patients (57%) were female, and the majority was Caucasian (87%). Median follow-up time was 17.1 months (range 0.1-31).

The prominent clinical features of BCS were ascites (83%), hepatomegaly (67%) and abdominal pain (61%). Half of the patients had a recent (i.e. <1 months) onset of symptoms. In 5 patients, all asymptomatic, BCS was found incidentally. In total, 227 imaging studies were performed to establish the diagnosis of which ultrasound was the most commonly used technique (n=88, 39%), followed by CT (n=82, 36%), MRI (n=36, 16%) and venography (n=21, 9%). Hepatic outflow obstruction involved the hepatic veins in 49%, the inferior vena cava (IVC) in 2% and both in 49%. In only 2 patients, the IVC was occluded by a membrane. Concurrent obstruction in the portal venous system was found in 30 patients (18%), including portal vein (n=11), superior mesenteric vein (n=2), splenic vein (n=2), and combinations (n=15). Thirty-nine patients (24%) underwent liver biopsy at diagnosis. Main histological features were sinusoidal congestion (n=25, 64%), hepatocellular necrosis (n=13, 33%) and fibrosis (n=23, 59%), often with significant heterogeneity within the same specimen. Evidence of cirrhosis was present in 7 patients (18%).

In total 160 patients (98%) were screened for underlying prothrombotic disorders (table 2). In 135 of 160 patients (84%), at least one thrombophilic disorder was identified. About half of the patients had more than one of these risk factors (74 of 160 patients (46%)). The most common underlying disease was a myeloproliferative disorder (MPD), which was found in 49% of the patients who underwent bone marrow biopsy (n=93, 57%), red cell mass measurement (n=29, 18%) and/or colony cultures (n=41, 25%). The JAK2 V617F mutation was found in 35 of 121 tested patients (29%), of whom 27 showed a mutational load lower than 50% and 4 showed a mutational load above 75% (in 4 patients mutational load could not be calculated). Twenty-eight of the 35 JAK2-positive patients already had MPD features on bone marrow biopsy, whereas in the others biopsy was negative (n=4) or not performed (n=3).

Factor V Leiden mutation was found in 12% (n=18) and prothrombin gene mutation in 3% (n=5) of patients. Hyperhomocysteinemia, defined as elevated plasma levels of homocysteinemia or the presence of a homozygous MTHFR C677T mutation (genotype 677TT) was detected in 28 (22%) patients. In addition, concurrent risk factors were present in 14 of 18 (78%) with Factor V Leiden mutation, in 5 of 5 (100%) with prothrombin gene mutation and in 22 of 28 (79%) with hyperhomocysteinemia. Isolated protein C, protein S and antithrombin deficiency was present in 4% (n=5), 3% (n=3) and 3% (n=3), respectively.

Table 1

Clinical characteristics at time of diagnosis in 163 patients with BCS.

Clinical Characteristic	**N (%)**
Onset of symptoms prior to diagnosis	
< 1 mo	82 (50)
1-6 mo	56 (34)
> 6 mo	23 (14)
undetermined	2 (1)
Abdominal pain	99 (61)
Ascites	135 (83)
Hepatic encephalopathy	15 (9)
Esophageal varices [1]	45 (58)
Gastrointestinal bleeding	8 (5)
Hepatorenal syndrome (type I [2])	12 (7)
Clinicopathological presentation [3]	43 (26)
acute	33 (20)
chronic	87 (53)
acute-on-chronic	
Radiographic finding [4]	
Hepatomegaly	109 (67)
Splenomegaly	85 (52)
Caudate lobe hypertrophy	118 (72)
Location of outflow obstruction	
hepatic veins	80 (49)
inferior vena cava	4 (2)
both	79 (49)
Number of hepatic veins involved:	
1	15 (9)
2	15 (9)
3	129 (79)
Portal vein occlusion	30 (18)
Laboratory testing (unit)	**Median (range)**
ALT (ULN)	1.42 (0.3-294.4)
Albumin (g/l)	34 (17-51)
Bilirubin (μmol/l)	31 (4-325)
Prothrombin time [5]	
seconds	18.1 (11.4-61.7)
INR	1.4 (1.0-10.9)
Quick time (%)	64 (7-100)
Creatinine (μmol/l)	79.6 (36-589)

[1] 77 patients underwent gastroduodenoscopy

[2] type I Hepatorenal syndrome was defined as at least 50% lowering of the creatinine clearance to a value below 20 ml/min or at least 2-fold increase of serum creatinine to level of 221 μmol/l in less than two weeks.

[3] According to predefined criteria [11], acute was defined as abdominal pain, ALT above 5 x ULN and liver cell loss at biopsy (if available); chronic as previous symptoms and / or hospitalisations, splenomegaly, atrophy/hypertrophy complex of liver lobes and centrilobular fibrosis or cirrhosis at biopsy (if available), acute-on-chronic as both acute and chronic characteristics

[4] radiographic findings are analyzed such that preference was given to MRI, followed by CT, US, and venography findings in that order. In other words, if for one patient multiple radiological reports were available, findings obtained by a MRI study was considered superior to CT and so on.

[5] excluded are patients under anticoagulation at time of diagnosis (n= 20)

Table 2

Risk factors in 163 patients with BCS.

Etiology	Positive / total nr. tests (%)
Inherited thrombophilia [1]	30 / 154 (19)
Factor V Leiden G1691A mutation	18 / 147 (12)
Prothrombine gene G20210A mutation	5 / 144 (3)
Protein C deficiency [2]	5 / 117 (4)
Protein S deficiency [2, 3]	3 / 109 (3)
Antithrombin deficiency [2]	3 / 110 (3)
Acquired thrombophilia [1]	67 / 153 (44)
Antiphospholipid antibodies	37 / 150 (25)
Hyperhomocysteinemia [4]	28 / 129 (22)
Paroxysmal nocturnal hemoglobinuria	15 / 70 (19)
Myeloproliferative disorder and/or JAK2 mutation [5]	56 / 143 (39)
Myeloproliferative disorder	50 / 103 (49)
Polycythemia vera	27
Essential thrombocytosis	9
Idiopathic myelofibrosis	2
Unclassified MPD	11
Occult (i.e. negative biopsy but positive cultures)	1
JAK2 V617F mutation	35 / 121 (29)
Hormonal risk factors (females only) [1]	35 / 93 (38)
Oral contraceptives use	31 / 93 (33)
Pregnancy 3 months prior to diagnosis	6 / 93 (6)
Other (systemic) risk factors [1]	32 / 163 (20)
Connective tissue disease	10
Inflammatory bowel disease	8
Behçet's disease	4
Sarcoidosis	2
Vasculitis	1
Dehydration	5
Other [6]	9

[1] the group prevalence represents the presence of at least one of the factors in the following list

[2] deficiencies of natural anticoagulants were only considered true if they were tested in the absence of anticoagulation and/ or oral contraceptives, and isolated low values were found on only one of the natural anticoagulant in the absence of liver dysfunction (i.e. bilirubin level < 2ULN).

[3] additional exclusion criteria applied to Protein S deficiency were Factor V Leiden mutation and anticardiolipin IgG antibodies.

[4] hyperhomocysteinemia was defined as the presence of either elevated plasma levels of homocysteinemia (>15 mol/l) or a homozygous MTHFR C677T mutation

[5] based on the evidence of MPD on bone marrow biopsy and/or spontaneous colony formation on cultures and/or presence of JAK2 mutation

[6] other risk factors considered were intra-abdominal infection, sepsis or spontaneous bacterial peritonitis

Management

Thirteen patients (8%) received no treatment directed at the venous obstruction or its manifestations (figure 1). Ten of these patients had no (n=3) or mild (n=7) symptoms and nearly normal bilirubin levels (median 19 μmol/l). All survived and remained ascites-free with a median follow-up of 22.7 months (range 6.8-31.0). The remaining three patients without BCS treatment had severe liver failure and all of them died within five months (range 1.6-4.4). The majority of patients however, received treatment with anticoagulation (n=140; 86%) and diuretics (n=100; 61%). Twenty patients were already using anticoagulation with a median time of 27 days before diagnosis of BCS for previous thrombotic events (n=11) or suspected but unconfirmed BCS before the final diagnosis was made (n=9; median 1 day). Of all anticoagulated patients, only 5 (8%) developed variceal bleeding, all non-fatal.

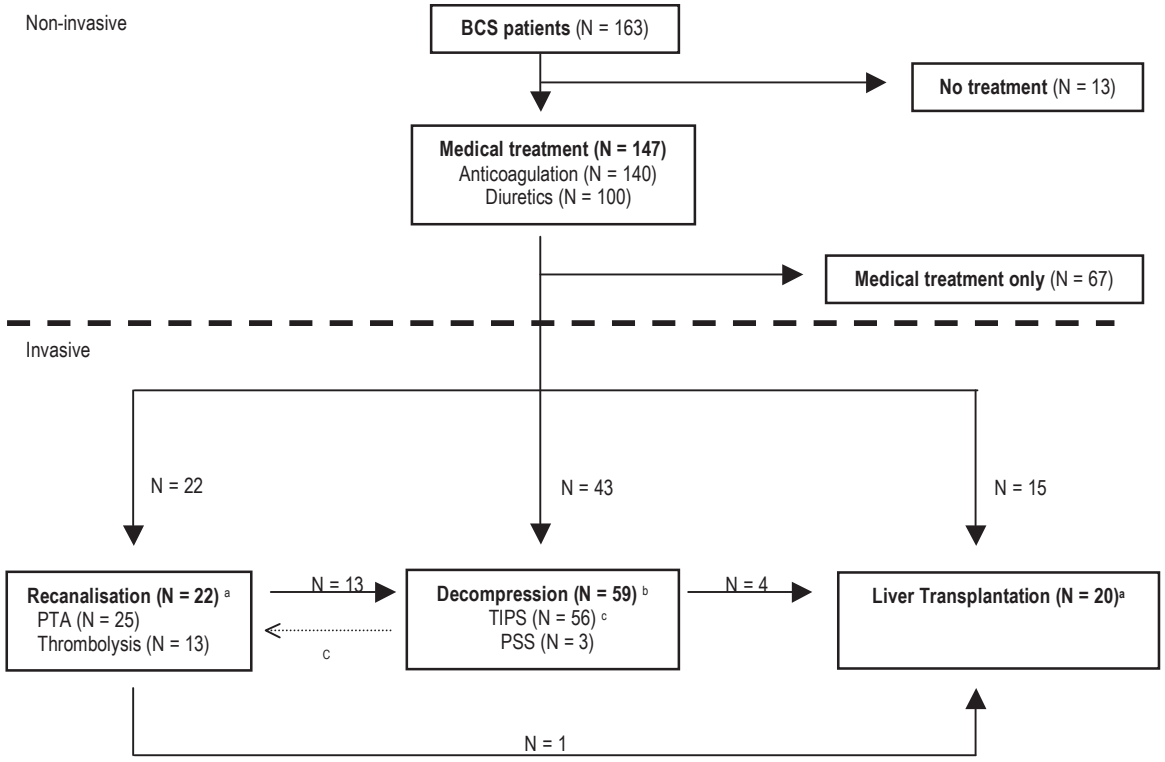
Twenty-two patients underwent thrombolysis (n=10) and/or percutaneous transluminal angioplasty (PTA; n= 14) as initial invasive procedure. Immediate recanalisation of the vein(s) was achieved in 40% of those undergoing thrombolysis and in 57% of the patients undergoing PTA. Thirteen patients required subsequent TIPS and one patient deteriorated rapidly and needed liver transplantation 2.8 months later.

TIPS was attempted in 64 patients (39%) and was successfully implanted in 56 (34%). Main indications for TIPS were refractory ascites (64%), liver failure (13%) and variceal bleeding (5%). We observed no significant differences in clinical parameters between patients in whom TIPS was successful, and those in whom it was not, indicating that failure of placement was largely due to technical issues (data not shown). The approach of the TIPS procedures was through the hepatic vein remnant in 49% and transcaval in 51%. Shunt dysfunction occurred in 9 patients (18%) and was successfully treated by TIPS revision in all cases. Polytetrafluoroethylene (E-PTFE) covered stents were used in 63% (n=35) with a patency rate of 85%. After TIPS, three patients (5%) required OLT. In contrast to TIPS, surgical shunting - all side-to-side portocaval - was only performed in 3 patients (2%). Thrombosis of the surgical shunt occurred in 1 patient, who died two months later. The second shunted patient continued to have refractory ascites and was transplanted after 9.8 months. The third remained transplant-free.

Twenty patients (12%) underwent OLT. The indications for OLT were the following: fulminant or rapidly progressive liver failure (n=8), absence of response on previous intervention (n=5), rescue treatment for fulminant failure after failed attempt of TIPS (n=2), intractable variceal bleeding (n=2), refractory ascites (n=2) and hepatopulmonary syndrome (n=1). One patient died immediately after OLT due to multi-organ failure (i.e. the patient with failure of TIPS placement) and one patient died 6.6 months post-OLT due to ovarian sarcoma, which became evident only after OLT. All 18 surviving patients were alive and symptom-free at a median follow-up of 19 months post-OLT (range 1.1-30.2).

Figure 1

Treatment flowchart for 163 patients with Budd-Chiari Syndrome. [a] patients can have had more than one procedure; [b] three patients received no medical treatment prior to decompression; [c] nine patient underwent revision of TIPS by recanalisation procedures.

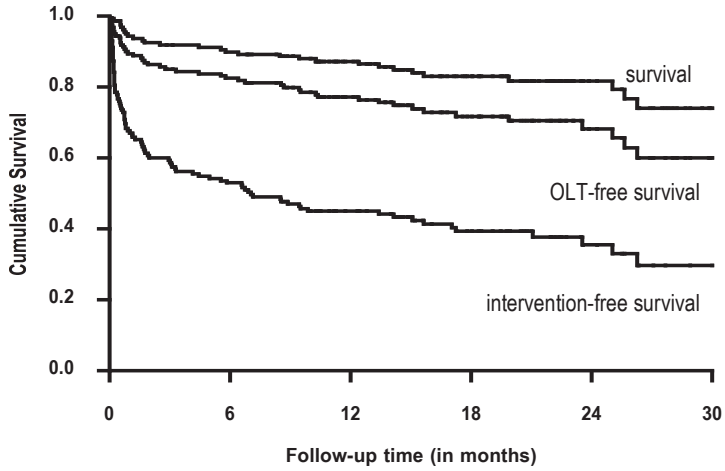


Survival and Prognostic Indicators

Fourteen patients were lost to follow-up after a median of 17.4 months, and 29 patients died with a median of 5.5 months after diagnosis (range 0.1-26.3). Main causes of death were liver failure (n=8), multi-organ failure (n=4) and GI bleeding (n=2). Median follow-up for the surviving population was 19.3 months (range 0.3-31). Overall survival was 90% (95%CI 85-94) at 6 months, 87% (95% CI 82-93) at 12 months and 82% (95% CI 75-88) at 24 months. Transplantation-free survival rates were 83% (95% CI 77-88), 77% (95% CI 71-84), and 68% (95% CI 60-77) at 6, 12 and 24 months, respectively. Survival without invasive intervention was 52% (95% CI 44-59), 44% (95% CI 36-52) and 35% (95% CI 26-44) at 6,12 and 24 months, respectively (figure 2).

Figure 2

Cumulative probability to remain free of death (i.e. overall survival), free of liver transplantation or death (i.e. OLT-free survival) and free of invasive interventions (including PTA, thrombolysis, TIPS, surgical shunting and OLT) or death (i.e. intervention-free survival) in 163 patients with BCS.



Patients at risk (per 3 months)	0	3	6	9	12	15	18	21	24	27	30
Actuarial survival	163	145	141	133	118	94	77	58	36	24	12
OLT-free survival	163	135	130	120	103	80	65	47	28	19	10
Intervention-free survival	163	92	82	70	59	46	36	25	15	8	5

Further exploration by univariate analyses revealed that patients who underwent invasive interventions were those with ascites and hepatic encephalopathy, higher levels of bilirubin, prothrombin time, ALT, and creatinine, and lower levels of albumin at diagnosis (table 3). Patients with an MPD were also at increased risk to undergo a procedure. However, this was no longer the case after we adjusted for liver-related parameters in the multivariate regression analysis. Eventually, ascites, encephalopathy, albumin, ALT and creatinine remained as independent indicators of invasive interventions.

Table 3

Results of univariate and multivariate Cox modelling for invasive intervention-free survival for 163 patients with BCS. Only predictors (i.e. baseline characteristics) with a statistical significant association (i.e. P <0.01) or important demographics are shown. Total number of events is 100.

	Univariate Cox model			Multivariate Cox model[1]		
Predictors	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
Age (per 10 y)	1.08	0.95-1.22	0.27	-	-	NS
Sex			0.11	-	-	NS
male	1.38	0.93-2.05				
female	1.0					
Ascites			<0.001			0.001
present	12.43	3.92-39.36		7.91	2.43-25.78	
absent	1.0					
Hepatic encephalopathy			<0.001			0.043
present	3.89	2.22-6.81		2.04	1.02-4.06	
absent	1.0					
Thrombophilia			0.007	-	-	NS
inherited and/or acquired	0.58	0.34-0.99				
MPD and/or JAK2 mutation[2]	1.18	0.70-1.98				
other	1.0					
Bilirubin (per 10 μmol/l)	1.05	1.02-1.09	<0.001	-	-	NS
Albumin (per 1 g/l)	0.95	0.93-0.97	<0.001	0.97	0.94-1.00	0.046
Prothrombin time (per 1 INR)[2]	1.23	1.07-1.42	<0.001	-	-	NS
ALT (per 1 ULN)	1.01	1.01-1.02	<0.001	1.01	1.00-1.01	0.025
Creatinine (per 10 μmol/l)	1.06	1.04-1.08	<0.001	1.05	1.02-1.08	<0.001

[1] in the multivariate cox model, complete data was obtained for 154 patients with 93 events.

[2] includes patients with only MPD/JAK2 (n=18) or in combination with inherited and/or acquired thrombophilia (n=36)

[3] if prothrombin time was expressed other than in INR (i.e. in seconds or in % Quick time) then this was converted into INR assuming a normal value of 10 seconds. Also, patients with anticoagulation at diagnosis (n=20) were excluded.

Discussion

We present a prospective cohort study of newly diagnosed patients with BCS, conducted in 9 countries throughout Western Europe. Previous studies have been performed in single tertiary referral centers and have all been retrospective in nature. As a result of our study design, we have minimized selection and information bias and limited problems related to incomplete data. We followed patients for a maximum of 2.8 years which allowed us to capture most significant events, since the vast majority of interventions and deaths occur within the first 2 years after diagnosis8-13. Moreover, all established therapeutic options were available in the participating centers.

The prevalence of Factor V Leiden mutation was only 12% in our predominantly Caucasian population. This is in contrast to earlier studies on BCS (22%-31%)2,3,14,15, and resembles the proportion described in venous thrombosis (12%-19%)16,17. The discrepancy with those earlier studies is most likely explained by selection bias. Since the prevalence in Caucasians is 5-8%18, Factor V Leiden is only a moderate risk factor for BCS. The prevalence of the prothrombin gene mutation (3% in our study versus 2% in healthy individuals19) and hyperhomocysteinemia20 hardly exceeded population frequencies, hence these variables were weak risk factors at most. The majority of these patients had at least one other identifiable cause, indicating that in conjunction with other prothrombotic disorders, thrombophilia potentially plays a significant role in the pathogenesis of BCS.

In 46% of our BCS patients there was more than one risk factor. This is almost twice as high as previously reported2,3 and is most likely related to our near-complete etiological work-up. We still were unable to detect a cause in 16% of patients which signifies the need for future exploration of new factors, e.g. in the fibrinolytic pathway.

Myeloproliferative disorders comprise the most prevalent underlying disease (49%), in line with previous findings21,22. Despite the initial hesitation of performing invasive diagnostic tests for MPD, we believe that every patient with BCS should undergo a bone marrow assessment, since concurrent hypersplenism, occult gastrointestinal bleeding or hemodilution can mask peripheral blood abnormalities23,24. The recently discovered JAK2 V617 mutation was found in only 29% of our patients. This is in sharp contrast to recent publications which reported prevalences as high as 40-59%21,25,26. However, these retrospective studies were performed on stored samples and conducted in specialised hepatology and/or hematology centers, whereas we tested JAK2 on samples of incident patients, regardless of previous MPD testing.

Our data indicate that management focused on early interventions, yet with the lowest possible invasiveness, yields excellent results. Nearly half of our patients were managed without a radiological or surgical therapeutic intervention. Time to these interventions, used as a proxy for clinical deterioration, appeared to be determined by the same factors earlier found to be related to patient survival8,10 (i.e. ascites, encephalopathy, albumin, ALT and creatinine levels). We observed excellent short-term survival rates, which were similar if not higher than those observed in earlier retrospective series, where more aggressive interventions were applied 8, 10.

TIPS was the most frequently used invasive intervention (n=56), whereas only 3 patients received a surgical portosystemic shunt. This observation illustrates the temporal change in management, as surgical shunting was previously mainstay of therapy (applied in 50-68% in a large earlier series8,10). The frequently feared complication of TIPS occlusion appears to have diminished to the background, as e-PTFE covered stents provide excellent patency27,28. Despite the absence of evidence from randomised studies - an impossibility in such a rare disease - we believe that TIPS provides excellent outcome for patients with BCS and should be the treatment of choice for those patients with refractory ascites and progressive liver function abnormalities.

In conclusion, this international prospective cohort study on BCS shows an excellent 1- and 2-year survival of over 80% with a management aimed at minimal invasiveness with anticoagulation and TIPS, and with transplantation as a salvage procedure. Surgical shunting, only a decade ago the treatment of choice, appears to have lost its place in the management of BCS. Myeloproliferative disorders are highly associated with BCS and should always be tested for.

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VI

Long-term outcome of covered and uncovered Transjugular Intrahepatic Portosystemic Shunt (TIPS) in Budd-Chiari syndrome

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Abstract

Background

Clinical outcome of covered versus uncovered TIPS for patients with Budd-Chiari Syndrome (BCS) is as yet largely unknown.

Objective

To compare patency rates of bare and polytetrafluoroethylene(PTFE)-covered stents, and to investigate clinical outcome using four prognostic indices (Child-Pugh score, Rotterdam BCS index, modified Clichy score, and Model for End-Stage Liver Disease).

Methods

Consecutive patients with BCS who had undergone TIPS between January 1994 and March 2006 were evaluated in a retrospective review in a single center.

Results

Twenty-three TIPS procedures were performed on sixteen patients. Primary patency rate at 2-years was 12% using bare and 56% using covered stents (P=0.09). We found marked clinical improvement at three months post-TIPS as determined by a drop in median Child-Pugh score (10 to 7, P=0.04), Rotterdam BCS index (1.90 to 0.83, P=0.02), and modified Clichy score (7.77 to 2.94, P=0.003), but not in MELD (18.91 to 17.42, P=0.9). Survival at 1 and 3 years post-TIPS was 80% (95% CI 59%-100%) and 72% (95% CI 48%-96%). Four patients (25%) died and one required liver transplantation.

Conclusions

TIPS using PTFE-covered stents show better patency rates than bare stents in BCS. Moreover, TIPS leads to improvement in important prognostic indicators for survival of patients with BCS.

Introduction

Budd-Chiari Syndrome (BCS) is caused by the obstruction of hepatic venous outflow at any level from the small hepatic veins to the junction of the inferior vena cava (IVC) and the right atrium [1]. It is an uncommon disorder occurring in 1/100,000 of the general population worldwide [2]. Nonetheless, if left untreated, BCS may lead to liver dysfunction and liver failure requiring liver transplantation in advanced cases [3]. Prognosis of patients with BCS is difficult to predict. Besides the established classifications to assess the extent of liver dysfunction, such as the Child-Pugh score [4] and the MELD score [5], attempts have been made to develop more BCS-specific prognostic models. The Clichy score, developed by Zeitoun et al. [6] and later modified by Langlet et al. [7] indicated that patients with high age, Child-Pugh score and creatinine levels and an acute-on-chronic type of lesion have the worst predicted outcome. The Rotterdam BCS index, previously developed by our group, included high baseline bilirubin and prothrombin levels, as well as the presence of ascites and encephalopathy as predictors of poor survival [8].

Therapeutic options for patients with BCS include anticoagulation, portosystemic shunting (placement of transjugular intraheptic portosystemic shunt [TIPS] or surgical shunt) and orthotopic liver transplantation (OLT) [1]. Because there are no randomized controlled trials to guide therapy for BCS, recommendations are derived from uncontrolled studies and clinical experience. The choice of treatment depends upon the cause, the anatomic location and extent of the thrombosis, and the condition of the liver [9]. In practice, experience at individual centers may also influence the choice of therapy [10].

TIPS can be a useful treatment option for patients with BCS uncontrolled by medical therapy. Perelló et al. have shown that TIPS was effective in decreasing portal hypertension, improving liver function, reducing transaminase levels and controlling ascites [11]. However, one of the limitations of TIPS is the development of TIPS stenosis over time. As a consequence, polytetrafluoroethylene (PTFE)-covered stents were introduced in attempt to address this problem. One recent study has demonstrated that PTFE-covered stents have a lower dysfunction rate, a lower number of re-interventions and fewer prosthesis requirements as compared to bare stents for the TIPS treatment of BCS patients [12].

Studies reporting on the long-term treatment response to TIPS using PTFE-covered stents versus bare stents in BCS have been relatively few. Therefore, the goal of the present study was to describe the experience at our hospital - the institution that serves as a referral center for BCS in the Netherlands. We investigated the long-term treatment response from patients receiving TIPS placement for the management of BCS. Specifically, our study focused on: (1) investigating the difference in primary patency rates between bare stents and PTFE-covered stents, and (2) evaluating the long-term clinical outcome of patients, as determined by the four existing prognostic indices (Child-Pugh score, Rotterdam BCS index, modified Clichy score and the Model for End-Stage Liver Disease [MELD score]).

Patients and Methods

Patients

Between January 1994 and March 2006, all consecutive patients who were diagnosed with BCS and had undergone TIPS placement at our center were identified by means of a search in the computerized hospital registration system. The following inclusion criteria were used: radiological proof of BCS (by Doppler ultrasound/computerized tomography/magnetic resonance imaging or venography) and age older than 16 years. Excluded from the study were patients who exhibited hepatic outflow obstruction due to congestive heart failure, patients with sinusoidal obstruction syndrome [13], patients with underlying malignancy or patients who developed BCS after OLT.

Methods

We obtained a complete set of demographic, clinical, radiological and laboratory data for each patient by a systemic review of the medical records and the hospital computer database. The starting time of analysis was the day of the TIPS procedure. Patients were followed up until the study closure date (31 March 2006) or until liver transplantation or death. Patients lost to follow-up before the study closure date were included until the day they were last known to be alive.

Primary TIPS patency period was determined by the interval between the date of first TIPS placement and the date of first TIPS dysfunction to allow time-dependent analysis of the effect on primary TIPS patency. Similarly, primary assisted TIPS patency period was determined by the interval between the day of the respective TIPS revision and the date of subsequent TIPS occlusion. In both cases, TIPS dysfunctions were confirmed by radiological investigation and TIPS patency times were censored at death, surgical shunt procedure, OLT or at study closure date.

PTFE-covered stent (Viatorr Endoprothesis, WL Gore & Associates, Arizona, USA) was first used in BCS patients in October 2002 at our hospital. Prior to this date, BCS patients who underwent TIPS received various types of self-expandable bare stents (Wallstent, Boston Scientific, Massachusetts, USA; Memotherm stent, Angiomed, Karlsruhe, Germany; SMART stent, Cordis – Johnson & Johnson, Florida, USA). The covered-stent group included patients who had received only the PTFE-covered stent type and thus in whom the total portosystemic tract was fully covered by PTFE. In contrast, the bare-stent group consisted of patients who had received either bare stents alone or both bare and covered stents placed in one procedure.

Four prognostics indices - Child-Pugh score, the Rotterdam BCS index, the modified Clichy score and the MELD score [4, 7, 8, 14] - were calculated using the previously published formulae for each patient at three separate time-points. For the MELD model, the scientific version was used, which allowed a range above or below the usual range of 6-40 when MELD is used in the setting of liver transplantation. The 3 time-points included pre-TIPS, 3 months post-TIPS, and at last follow-up. In order to avoid potential effects of other treatments on the scoring parameters of the prognostic indices, the clinical and laboratory values used to calculate the scores for the pre-TIPS time-point were those recorded before the patients were stabilized with treatments such as albumin or systemic anticoagulants. All pre-TIPS assessments were performed within 2 weeks prior to TIPS. The 3 months post-TIPS time-point was defined as the

3-month follow-up radiological assessment of TIPS, or death or OLT, whichever came first. The last evaluation performed on each patient beyond 3 months post-TIPS and up until the study closure date was considered as the last follow-up.

Statistical Analysis

All continuous variables were summarized by medians and ranges. Non-parametric Wilcoxon signed-rank tests were used for comparisons of pre-TIPS to post-TIPS data in case of continuous variables and McNemar tests in case of categorical variables. For comparing data between the two stent-type groups (bare and covered), we used non-parametric Mann-Whitney U-tests for continuous variables and Fisher's Exact test for categorical variables. Survival as well as TIPS patency were estimated by the Kaplan-Meier method. The SPSS 12.0 statistical package (SPSS Inc., Chicago, IL) was used for data analysis.

Results

Clinical Data

Seventeen consecutive patients with BCS treated with TIPS between January 1994 and March 2006 at our center were included in the current study initially. However, in one patient shunt insertion was not successful because her liver appeared to be too firm for the needle and therefore no puncture of the liver parenchyma could be performed. Thus, this left a total of 16 patients that were eligible for analyses.

Patient characteristics at the time of TIPS are summarized in Table 1. Median age of patients at time of TIPS was 31 years (range 19–50). The 15 patients who survived at least a week following TIPS had a median follow-up of 29 months (range 1-110 months). The etiological factors for BCS identified in our patients included: myeloproliferative disorders (n=4), antiphospholipid syndrome (n=5), thrombogenic disorders (n=3), oral contraceptives (n=6), Behçet's Disease (n=1), and idiopathic (n=1). Three patients had more than one of these risk factors.

In the bare-stent group, 6 patients received bare stents alone and 2 received a combination of bare and covered stents. The covered-stent group consisted of 8 patients and all received only covered stents. Characteristics between the bare-stent and covered-stent group showed a similar distribution and no statistically significant difference was found for the variables presented in Table 1. Of all the clinical risk scores, the largest absolute discrepancy was found for the MELD score. This was due to one outlier to the lower extreme in the bare and one outlier to the upper extreme in the covered stent group. Again, the difference was not statistically significant.

Technical Details on TIPS

In three patients (19%), the shunt was created via the normal hepatic vein to portal vein route whereas in the other 13 patients (81%), TIPS was placed via the transcaval route. In 10 of the 16 patients, the stent was placed accurately with no evidence of immediate complications. However, six patients experienced technical complications from the procedures: 3 with perforation of the liver capsule, 1 with biliary duct puncture, 1 with bleeding complication at the site of TIPS requiring fresh frozen plasma transfusions and 1 with migration of the stent from its original tract. The median number of stents inserted per procedure in a patient was 2 (range 1–3), and was similar between the bare- and the covered-stent groups ($P>0.05$). The clinical course of the bare-stent group and the covered-stent group is depicted in Figure 1. In total, 23 TIPS procedures were performed on the 16 patients. Anticoagulation was given to all patients pre- and post-TIPS.

Table 1

Patient Characteristics pre-TIPS for 16 patients with BCS who underwent TIPS placement.

Characteristics	Observed Data (N (%))		
	Total Patients (N=16)	Bare Stent# (N=8)	Covered Stent (N=8)
Demographics			
Age at BCS Diagnosis (yrs)*	31 (18 – 50)	29 (24 – 38)	32 (18 – 50)
Age at time of TIPS (yrs)*	31 (19 – 50)	29 (24 – 38)	32 (19 – 50)
Female	10 (62)	5 (62)	5 (62)
Etiology			
Myeloproliferative disorder	4 (25)	2 (25)	2 (25)
Antiphospholipid syndrome	5 (31)	3 (38)	2 (25)
Thrombogenic disorders	3 (19)	3 (38)	0 (0)
Clinical Manifestations			
Ascites	16 (100)	8 (100)	8 (100)
Hepatomegaly	15 (94)	7 (88)	8 (100)
Encephalopathy	2 (12)	2 (25)	0 (0)
Edema	8 (50)	4 (50)	4 (50)
Splenomegaly	7 (44)	3 (38)	4 (50)
Variceal bleeding	2 (12)	0 (0)	2 (25)
Site of outflow obstruction			
Right hepatic vein	15 (94)	8 (100)	7 (88)
Middle hepatic vein	16 (100)	8 (100)	8 (100)
Left hepatic vein	15 (94)	8 (100)	7 (88)
Inferior vena cava	11 (69)	5 (62)	6 (75)
Portal vein obstruction	3 (19)	2 (25)	1 (12)
Serum levels**			
Total bilirubin (µmol/L)*	45 (17 – 297)	30 (17 – 297)	56 (25 – 155)
Albumin (g/L)*	30 (21 – 44)	28 (23 – 44)	32 (21 – 39)
Alkaline phosphatase (U/L)*	158 (48 – 499)	164 (75 – 393)	158 (48 – 499)
ALT (U/L)*	66 (12 – 1793)	32 (12 – 1793)	111 (30 – 408)
Platelet count (10E9/L)*	213 (24 – 373)	233 (24 – 369)	150 (101 – 373)
Hemoglobin (mmol/L)*	8.7 (5.6 – 11.9)	8.6 (5.6–9.9)	9.0 (6.8 – 11.9)
Creatinine (µmol/L)*	78 (44 – 172)	70 (44 – 172)	82 (49 – 152)
INR*	2.2 (1.0 – 9.4)	1.6 (1.0 – 5.2)	4.5 (1.3 – 9.4)
Prognostic Indices			
Child Pugh Score*	10 (6 – 14)	9.5 (6 – 14)	11 (9 – 13)
Rotterdam BCS Index*	1.90 (1.11– 4.22)	1.87 (1.11 – 4.22)	1.93 (1.19 – 2.38)
Modified Clichy Score*	7.77 (2.87 – 9.01)	7.32 (2.87 – 9.01)	8.04 (5.95 – 8.68)
MELD Score*	18.91 (0.83 – 41.93)	14.83 (0.83 – 32.76)	26.98 (12.00 – 41.93)

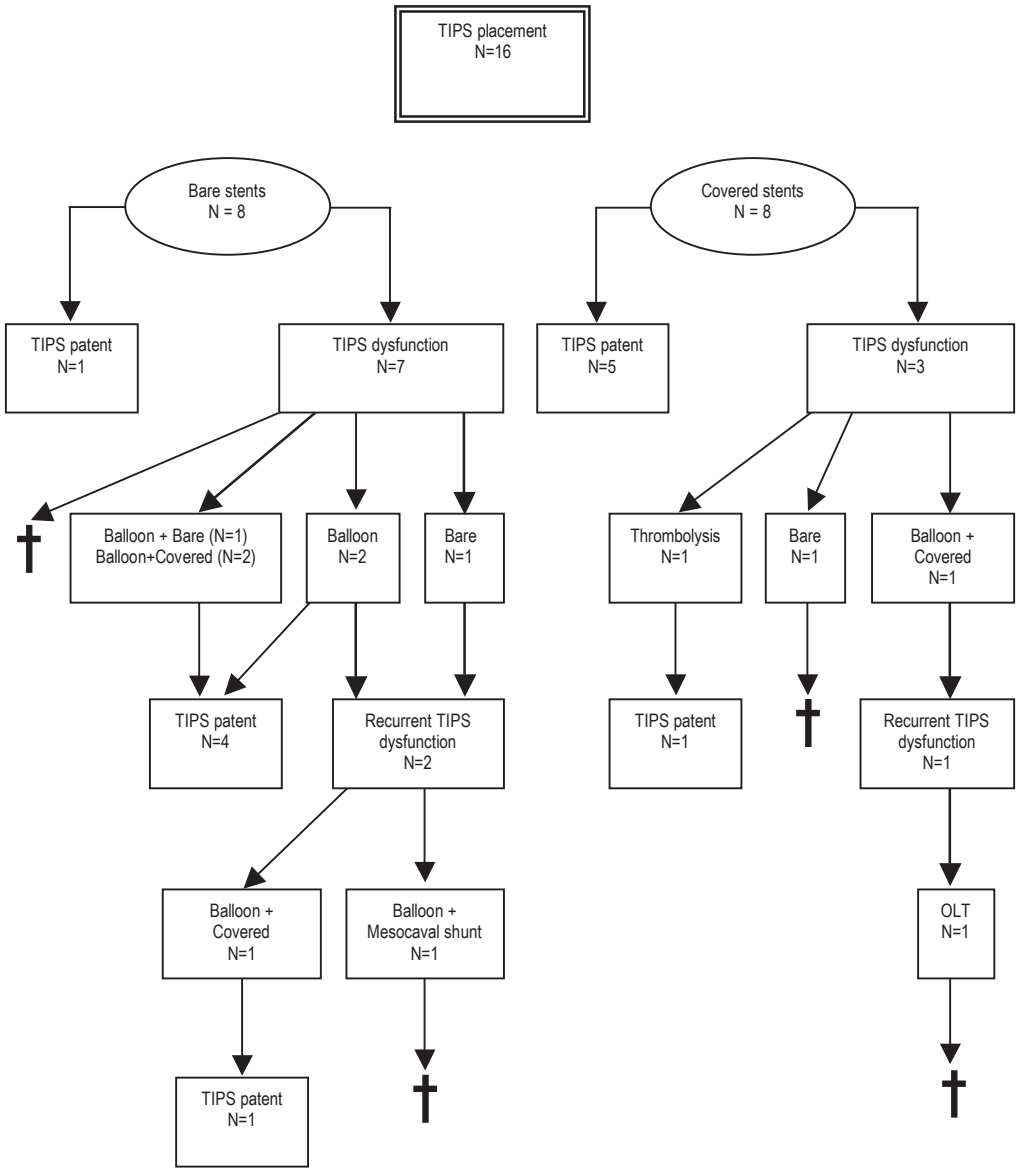
* median (range)

No statistically significant differences were found between the bare and covered stent group (i.e. P-value was >0.05 for all variables)

** Normal lab values: albumin 35 – 50 g/L, total bilirubin < 17 µmol/L, Alkaline phosphatase <120 U/L, ALT < 41U/L, platelets 150-370 10E9/L, hemoglobin 8.6 – 10.5 mmol/L, creatinine 65 – 115 µmol/L

Figure 1

Clinical course of the bare-stent and PTFE-covered stent groups. Definitions of abbreviations and symbols: Bare=bare stent, Covered=covered stent, Balloon=balloon dilatation and † = death.



Survival

Overall cumulative survival rates at 1 year and 3 years post-TIPS were 80% (95% CI, 59–100%) and 72% (95% CI, 48–96%), respectively. Mean survival time was 81 months (95% CI, 57–105 months). The overall mortality rate was 25% (n=4). Three patients died due to variceal bleeding, multi-organ failure and liver failure secondary to sepsis, and these occurred 2 days, 2 months and 26 months post-TIPS, respectively. In the fourth patient, TIPS malfunction occurred at 1.5 months after the procedure and subsequently liver transplantation was required. At 6.5 months after OLT, she died of epithelioid ovarian sarcoma which was diagnosed at a post–mortem examination. No other patient was transplanted.

TIPS Patency

Shunt dysfunction was observed more frequently in the bare-stent group than in the covered-stent group (2-year primary patency rate was 12% versus 56%, respectively. Mean TIPS patency period was 11 months (95% CI, 0-25 months) for the bare-stent group and 27 months (95% CI, 14–39 months) for the covered-stent group.

On the analysis comparing primary TIPS patency with primary assisted TIPS patency, we found in general that the primary assisted TIPS patency rates were higher than the primary patency rates for any given time interval post-TIPS. The cumulative proportion of patients with primary TIPS patency at 6 and 12 months post-TIPS were 47% (95% CI, 21-73%) and 39% (95% CI, 14-65%) respectively whereas the cumulative proportion of patients with assisted TIPS patency at 6 months and 12 months post TIPS revisions were 89% (95% CI, 68–100%), and 76% (95% CI, 47–100%) respectively.

Clinical Improvement

The results of the biochemical parameters (i.e. hemoglobin, platelets, INR, total bilirubin, albumin, creatinine, and ALT), and clinical manifestations (i.e. presence or absence of ascites and encephalopathy) assessed pre- and post-TIPS are summarized in Table 2. Most changes pointed in the direction of clinical and biochemical improvement post-TIPS.

When comparing data for the prognostic indices obtained pre-TIPS with the follow-up results at 3 months post-TIPS and at last follow-up, we found marked statistically significant improvement in the Child-Pugh scores (P=0.04 and P=0.02, respectively), and in the modified Clichy scores (P=0.003 and P=0.007, respectively). For the Rotterdam BCS index, there was also a significant difference between pre-TIPS and at post-TIPS follow-ups (P=0.02 at 3-month follow-up and P=0.05 at last follow-up). However, no statistically significant difference in the MELD scores between pre-TIPS and post-TIPS scores at both follow-up time-points were found. This is presented in more detail in Figure 2.

Table 2

Biochemical parameters (median, range) and clinical manifestations (N, %) assessed pre-TIPS, at 3-month follow-up and at final follow-up. Patients without complete follow-up (n=6) are excluded from the analysis.

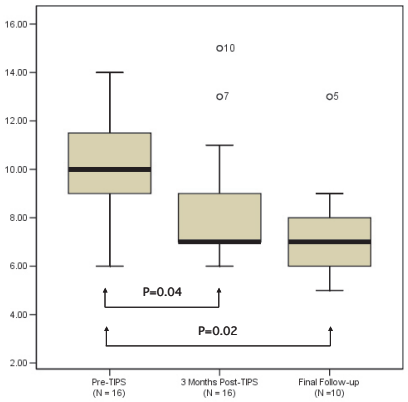
	Pre-TIPS (N=10)	3 Months Post-TIPS (N=10)		Final Follow-up (N=10)	
			P		*P*
Serum levels					
Hemoglobin (mmol/L)	7.7 (5.6 – 9.0)	7.4 (6.1 – 8.4)	0.54	8.6 (4.9 – 10.1)	0.31
Platelets (10^9/L)	223 (62 – 369)	283 (88 – 372)*	0.37	231 (96 – 381)*	0.59
INR	1.7 (1.0 – 7.1)	2.85 (1.9 – 5.4)	0.06	2.7 (1.4 – 4.2)	0.15
Total bilirubin (µmol/L)	32 (17 – 155)	22 (11 – 58)	0.14	22 (10 – 559)	0.39
Albumin (g/L)	30 (23 – 40)	40 (38 – 45)	0.01	42 (21 – 46)	0.04
ALT (U/L)	64 (12 – 1793)	50 (25 – 80)	0.48	39 (21 – 54)	0.33
Creatinine (µmol/L)	64 (44 – 172)	63 (48 – 100)	0.39	68 (45 – 175)	0.52
Clinical manifestations					
Ascites	10 (100%)	2 (20%)	0.01	1 (10%)	0.01
Encephalopathy	1 (10%)	0 (0%)	0.01	0 (0%)	0.01

*N=9 tested

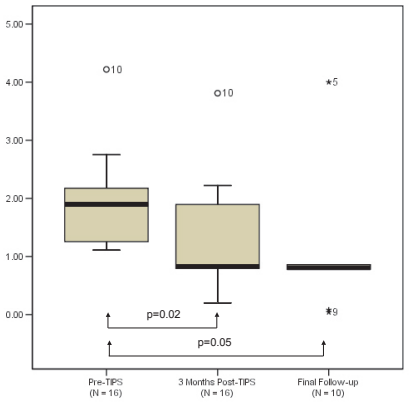
Figure 2

Comparisons of pre-TIPS to post-TIPS scores for prognostic indices (Child-Pugh scores, Rotterdam BCS index, modified Clichy score and MELD score) obtained pre-TIPS, within 3 months post-TIPS and at last follow-up. The numbers appeared beside the extreme values (marked with an open circle) refer to the patient identification numbers.

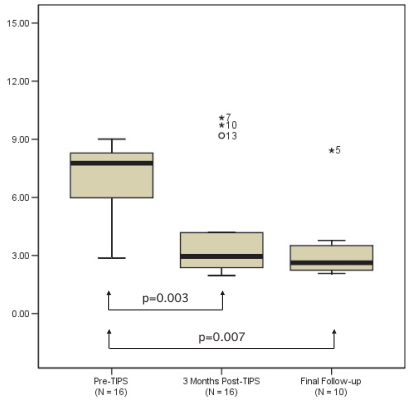
(a) Child-Pugh Score



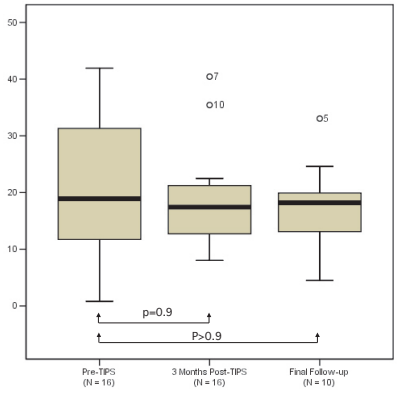
(b) Rotterdam BCS index



(c) Modified Clichy Score



(d) MELD Score



Discussion

The use of TIPS as a treatment option for BCS has steadily increased in the recent years as the quality of the stent-grafts is improved and the imaging techniques associated with this procedure become more sophisticated.

It has been shown from previous studies that the outcome of TIPS in terms of survival and TIPS patency can be markedly variable. The series from Perelló et al. (n=21, mean follow-up 4 years), Mancuso et al. (n=14, mean follow-up 20 months) and Rössle et al. (n=33, mean follow-up 37 months) showed a mortality rate of 5%, 28% and 9% respectively [11, 15, 16]. Our series of 16 patients with a median follow-up of 29 months (range 1-110 months) has an overall mortality of 25% which is comparable to the Mancuso's series but higher than the other two series. With respect to TIPS patency, we found 39% of patients with primary TIPS patency at 12 months which is just lower than the 1-year probability of 47% for shunt revision-free reported in Rössle's series.

Our data show a trend towards better primary TIPS patency in the covered-stent group than the bare stent group (1-year patency rate was 12% versus 75% for bare and covered stent group respectively). This is in line with findings from the study by Hernandez-Guerra et al., who showed a primary patency rate at 1 year of 19% in the bare-stent group compared with 67% in the covered stent group [12]. However, the comparison made between the two stent types may not be totally equitable in our series. This is because most of the patients in the bare-stent group received their TIPS at the earlier period of the study and management of patients with BCS might have changed over time due to our increasing understanding of the underlying pathogenesis of BCS. Also, although we found none of the baseline characteristics to be significantly different between both groups, there were still absolute differences between some characteristics, of which MELD was the most pronounced. Indeed, the difference in initial MELD scores between the covered and bare stent group was largely due to one outlier to the upper extreme in the covered and one to the lower extreme in the bare stent group, which in small sample sizes can have a detrimental effect on the estimate. However, the difference was in favour of the bare stent group, which only underlines the beneficial outcome we found in the covered stent group.

Most studies to date have focused on survival and dysfunction rates. However, we were able to demonstrate a marked clinical improvement in patients receiving a TIPS. The median pre-TIPS Child-Pugh score of our patients was 10, which dropped to a score of 7 at 3 months post-TIPS and at the last follow-up. These data translated to an average improvement of Child-Pugh class C to B. Nevertheless, one has to take into account that the Child-Pugh score has been used mainly for assessing the risk of mortality in patients with cirrhosis and not for BCS specifically. A better prognostic tool for BCS may be the Rotterdam BCS index which was developed using data from a population of 237 patients with BCS [8]. We observed a median improvement of 1.06 points in the Rotterdam BCS index at 3-month follow-up (i.e., an improvement from Class III to II) in our series. This has important clinical relevance as we learned from the study by Murad et al. [8], who reported on five-year survival rates of 89% (95% CI, 79%-99%) for class I, 74% (95% CI, 65%-83%) for class II and 42% (95% CI, 28%-56%) for class III. With regard to the modified Clichy score, it has been reported that patients with a score of >5.1 (high risk

group) have a worse prognosis than those with a score of <5.1 (low risk group), represented by a five-year survival rate of 65% as compared to a rate of close to 100% for the low risk group [7]. We found our patients to have a median pre-TIPS score of 7.77 and a drop in post-TIPS scores to 2.94 and 2.62 at 3 months post-TIPS and at last follow-up respectively.
In contrast to the positive findings described above, we did not find any improvement in the MELD score post-TIPS at neither of the follow-up periods. This may be due to the fact that MELD consists only of biochemical parameters (serum bilirubin, INR, and serum creatinine), which usually are only mildly altered in BCS.

We are aware that there are several limitations in our study. Firstly, there is a potential underestimation of the prognostic scores determined at the last follow-up time-point as they did not take into account those 6 cases which had either died or did not have a follow-up beyond 3 months. Therefore, the results at the last follow-up can only be interpreted as an improvement in the prognosis of only those who have had survived at least 3 months after TIPS. Secondly, as in most other retrospective series with large follow-up time span, our study may have been affected by bias created by a difference in practice over time. However, only 3 out of our 16 patients received TIPS prior to 2000, while TIPS became standard practice in the mid-nineties. So although the possibility of bias is present, the magnitude of it is estimated to be very low. Lastly, an inherent limitation of this study is that the number of patients and events were low. Consequently, a type II error could well be present due to low statistical power. Nevertheless, despite the low sample size, the present study provides, for the first time, evidence that TIPS does improve the clinical and biochemical parameters that are critical prognostic factors for survival as determined by the three prognostic indices (Child-Pugh score, Rotterdam BCS index, and modified Clichy score). Obviously, larger prospective controlled studies are necessary in order to draw definitive conclusion about whether TIPS has true survival benefit and to address the fundamental question regarding the role of TIPS in replacing or at least delaying patients' need for liver transplantation.

In conclusion, TIPS is a safe and technically feasible treatment option for patients with BCS. The procedure leads to improvement in those clinical and biochemical parameters that have important prognostic relevance. This clinical improvement is observed at short term follow-up and its effect is sustained over time. Covered stents appear to provide better results than bare stents but large prospective studies with longer period of follow-up are needed to confirm our findings.

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VII

Determinants of Survival and the Effect of Portosystemic Shunting in Patients with Budd-Chiari Syndrome

Sarwa Darwish Murad, Dominique-Charles Valla, Piet C. de Groen, Guy Zeitoun, Judith A.M. Hopmans, Elizabeth B. Haagsma, Bart van Hoek, Bettina Hansen, Frits R. Rosendaal, and Harry L.A. Janssen

Hepatology, 2004; 39(2): 500-508.

Abstract

Background and rationale

Budd-Chiari syndrome is a rare disorder, characterized by hepatic venous outflow obstruction. The aim of this study was to assess determinants of survival and to evaluate the effect of portosystemic shunting.

Methods

In this international multicenter study, 237 patients with Budd-Chiari syndrome, diagnosed between 1984 and 2001, were investigated. Univariate, multivariate and time-dependent Cox regression analyses were performed.

Results

Overall survival at 1, 5 and 10-years was 82% (95% CI 77-87), 69% (95% CI 62-76) and 62% (95% CI 54-70), respectively. Encephalopathy, ascites, prothrombin time and bilirubin were independent determinants of survival. A prognostic classification combining these factors could identify three classes of patients (class I-III). The 5-year survival rate was 89% (95% CI 79-99) for class I, 74 % (95% CI 65-83) for class II and 42% (95% CI 28-56) for class III. Anticoagulants were administered to 72%; only for patients in class I this was associated with a trend towards improved survival (RR=0.14, 95% CI 0.02- 1.21). Portosystemic shunting was performed in 49% of the patients (n=117); only for patients in class II, time-dependent analyses suggested an improved survival (RR=0.63, 95% CI 0.26-1.49).

Conclusion

In conclusion, at the time of diagnosis, patients with BCS can be classified into good (I), intermediate (II) and poor (III) prognostic classes, according to simple baseline clinical and laboratory parameters. Our results suggest an improved survival after PSS for patients with an intermediate prognosis (class II).

Introduction

Budd-Chiari syndrome (BCS) comprises a group of disorders characterized by hepatic venous outflow obstruction. The site of obstruction is either in the hepatic veins or the supra-hepatic inferior vena cava [1]. BCS is a rare disorder, which occurs predominantly in young adults and affects more women than men. Overall, five-year survival varies from 50 to 80 % in different series [2-4].

Clinically, a classical triad of hepatomegaly, ascites and abdominal pain is found in many patients [2, 5]. However, the clinical course may differ markedly between patients. Some patients exhibit clinical signs of portal hypertension, such as variceal bleeding and refractory ascites with relatively intact hepatic function [4, 6]. Others present with liver failure, including hepatic encephalopathy, jaundice and biochemical signs of severe hepatocellular dysfunction. The most important cause of BCS in Western countries is thrombotic obstruction of the hepatic veins [7]. It is now believed that an inherited predisposition and an acquired thrombogenic stimulus may converge in the pathogenesis of BCS [5, 8]. Main treatment options include the long-term use of anticoagulants, surgical portosystemic shunting (PSS) [9-11], transjugular intrahepatic portosystemic shunting (TIPS) [12] and orthotopic liver transplantation (OLT) [13]. Other treatment modalities are thrombolysis [14] and percutanous hepatic vein balloon angioplasty [15].

Several studies have been published on etiology, clinical manifestations, prognosis and interventions in BCS [4-6, 9, 10, 14, 16-20]. However, the results vary widely and unequivocal conclusions cannot be drawn. Little is known about factors, which may be of relevant predictive value for the survival of BCS patients. Due to its rarity, most studies on BCS are case-reports or contain limited numbers of patients. Small series are hampered by the lack of sufficient statistical power to control for baseline characteristics when survival or the effect of therapy is evaluated. Institutional experience and preferences as well as patient selection play a major role in the choice of treatment [21]. This creates a large degree of heterogeneity between study populations. Most studies on the effect of therapeutic interventions, in particular portosystemic shunting do not report selection criteria nor do they control for differences in baseline characteristics between patients who do or do not undergo PSS. Furthermore, many studies do not adjust for the time-interval between diagnosis and the procedure, which could easily lead to a response-time bias.

The aim of the present study was to identify independent prognostic markers for survival of BCS patients and to evaluate the effect of PSS on survival, controlled for these prognostic markers as well as for the time-interval between diagnosis and procedure. We conducted a large collaborative multicenter study in which baseline characteristics of BCS patients were evaluated in multivariate models.

Materials and methods

Patients

Patients were derived from the computerized diagnosis registration systems of all Dutch academic hospitals, the Mayo Clinic (Rochester, MN., U.S.A.), Hôpital Beaujon (Clichy, France) and Hôpital Louis Mourier (AP-HP, Colombes, France). All participating hospitals serve as tertiary referral centers. Part of the study population from France was described previously by Zeitoun et al [16] and from the Mayo Clinic by Tsiostos et al. [22]. By means of a standardized review of the medical charts, all patients consecutively diagnosed with Budd-Chiari syndrome (BCS) between January 1984 and January 2001 were identified using the following key words: Budd-Chiari syndrome, hepatic outflow obstruction, hepatic vein thrombosis, vascular liver disease, hepatic vein, inferior vena cava, portal vein and thrombosis. BCS was defined as hepatic venous outflow obstruction and its manifestations, regardless of the cause and regardless of the level of the obstruction from the small hepatic veins to the entrance of the inferior vena cava into the right atrium [1]. Hepatic outflow obstruction caused by congestive heart disease and sinusoidal obstruction syndrome (veno-occlusive disease) were considered separate disease entities. These patients were not included in our study. The diagnosis of BCS was established by Doppler ultrasound, Computerized Tomography, Magnetic Resonance Imaging or venography [1]. Histological or non-specific radiological features, suggestive of BCS, were not considered diagnostic. Date of diagnosis was defined as the date of first evidence of BCS on radiological imaging modalities. Diagnosis could be made either at the participating center or at a smaller regional hospital before referral to the participating center. In both cases, the first available data were used as baseline data. Data on patient characteristics at the time of diagnosis, type of treatment during follow-up and clinical outcome were collected from patient records in structured, uniform data forms. If necessary, patients or general physicians were approached to complete follow-up data. All patients were followed from the date of diagnosis until death, orthotopic liver transplantation, study closure (January 1st, 2001) or, in case of loss to follow-up, the date of last visit.

Clinical assessment

The choice of variables to be used in the analyses were based on known prognostic factors in hepatological disorders in general and BCS in particular, as well as on clinical experience with relevant factors.

The following characteristics, present at the time of diagnosis, were evaluated for their prognostic significance: age, sex, ascites, hepatomegaly, splenomegaly, variceal hemorrhage, hepatic encephalopathy, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, site of outflow obstruction (hepatic veins, vena cava inferior or combination), portal vein thrombosis, liver cirrhosis, Child-Pugh score, prothrombin time, platelet count and serum levels of bilirubin, albumin, alanine aminotransferase (ALT), alkaline phosphatase, sodium, creatinine, and hemoglobin. Ascites, hepatomegaly and splenomegaly were assessed by abdominal ultrasonography or other radiographic methods. Presence of esophageal varices and variceal hemorrhage was confirmed by radiological or endoscopic examination. Underlying myeloproliferative disorders were confirmed by bone marrow examination to include only overt forms [23]. Hepatic encephalopathy was evaluated by the Glasgow Coma Scale. The Child-Pugh

score was calculated for those with complete data on degree of ascites and encephalopathy, the prothrombin time and serum levels of bilirubin and albumin at the time of diagnosis (n=190).

Therapeutic interventions during follow-up were assessed. For portosystemic shunting (including TIPS), the time-interval between the date of diagnosis and date of shunting was determined to allow time-dependent analysis of the effect on survival.

Statistical analysis

Transplantation-free survival rates were calculated by means of the Kaplan Meier method. Univariate survival analyses of the effect of patient characteristics were based upon comparison of survival curves by the logrank test, including trend analysis for ordered variables. Statistically significant variables, as well as other clinically relevant variables (age, site of obstruction, ALT levels) were introduced into a multivariate Cox's proportional hazards analysis, with stratification for country. By means of step-wise backward elimination, a final model was constructed comprising variables which were significantly and independently (i.e. controlled for other variables) related to survival. Next, these prognostic markers were included as variables in a linear equation to create a BCS prognostic formula, in which the logarithm of the corresponding rate ratios (i.e. the regression coefficients of the proportional hazards model) were used as coefficients. Accordingly, all patients were classified into groups based on their prognostic scores and survival curves were compared.

As PSS was performed during the follow-up, the effect of portosystemic shunting on survival was analyzed in an extended Cox's proportional hazard model, in which shunting was included as time-dependent covariate. This means that at t=0, no patient has received a PSS (all "not performed"). At the time a patient receives a PSS (t=x), this variable is scored as "performed". In this way, the period that patients have lived up to the moment of PSS was calculated as "non-shunted survival period" in the Cox analysis.

For all Cox models, the assumption of proportional hazards was investigated for each variable by studying the ln(-ln)plot and by entering portosystemic shunting as a time-dependent variable multiplied by the logarithm of time. All analyses were carried out in SPSS for Windows, version 10.1.1 (SPSS, Chicago, IL). The level of statistical significance was set at $p<0.05$.

Results

Two hundred eighty-two patients with the diagnosis of BCS were identified in our institutions. Patients with hepatic outflow obstruction due to a malignancy (n=35), patients with BCS after liver transplantation (n=3) and patients diagnosed at autopsy (n=7) were excluded. This left a total of 237 patients who were eligible for analysis.
Patient characteristics at the time of diagnosis are shown in table 1. Patient inclusion per year from 1984 till 2001 showed a homogeneous distribution (mean 14, range 7-23). The sample included 73 Dutch, 76 American and 88 French patients with no statistically significant difference in survival (5-year survival 73% (95% CI 62-84), 61% (95% CI 50-72) and 72% (95% CI 61-83), respectively). Between countries, the number of idiopathic cases, surgical intervention rate and reasons for exclusion were comparable. Median age was 35 years (range 13-76 years) and 67% of the patients were female. In 54 patients (23%), an overt myeloproliferative disorder was present, including polycythemia rubra vera (n=45) and essential thrombocytosis (n=9). Paroxysmal nocturnal hemoglobinurea was present in 12 cases. Ascites (84%) and hepatomegaly (76%) were the most prevalent clinical symptoms. Eleven patients were asymptomatic. Median Child-Pugh score was 8 (range 5-14). At liver biopsy (n=138), evidence for cirrhosis was found for 11 patients. The hepatic outflow obstruction was located in the hepatic veins in 62%, the inferior vena cava in 7% and both in 31% of the cases. Thirty-four patients (14%) had combined BCS and extra-hepatic portal vein thrombosis.

Survival

Follow-up ranged from 2 days to 203 months (median: 44 months). During follow-up, 52 patients (22%) died and 29 (12%) underwent an orthotopic liver transplantation. Twenty patients were lost to follow-up. Causes of death were liver failure (n=17), postoperative multi-organ failure (n=12), sepsis (n=4), newly developed malignancy (n=2), cardiovascular disease (n=3), cerebrovascular accident (n=2), variceal bleeding (n=1) and combinations (n=3). For 8 patients, information on cause of death could not be retrieved. Survival rates were 82% (95% CI 77-87), 69% (95% CI 62-76) and 62% (95% CI 54-70) at 1, 5 and 10 years, respectively (figure 1).

Table 1

Patient characteristics at the time of diagnosis in 237 patients with Budd-Chiari Syndrome

	Obtained data
Age (years)*	35 (13-76)
Male/female (%)	78/159 (33/67)
Myeloproliferative disorders (%)	54 (23)
polycythemia rubra vera	45
essential thrombocythemia	9
Paroxysmal nocturnal hemoglobinurea (%)	12 (5)
Clinical manifestations (%)	
ascites	199 (84)
hepatomegaly	181 (76)
splenomegaly	120 (51)
encephalopathy	24 (10)
variceal bleeding	19 (8)
Site of outflow obstruction (%)	
hepatic veins	147 (62)
inferior vena cava	17 (7)
combined hepatic veins and inferior vena cava	73 (31)
Membranous obstruction of inferior vena cava (%)	9 (4)
Portal vein obstruction	34 (14)
Serum levels	
albumin (g/l)*	34 (13-57)
bilirubin (μmol/l)*	28 (3-301)
platelet count (x10E6/l)*	265 (10-896)
ALT (xULN†)*	1.0 (0.1-86.7)
alkaline phosphatase (xULN†)*	1.1 (0.3-16.3)
hemoglobin (mmol/l)*	8.1 (3.5-13.0)
sodium (mmol/l)*	137 (121-145)
creatinine (μmol/l)*	80 (35-469)
prothrombin time: INR >2.3 (%)#	43 (26)
Cirrhosis at liver biopsy (%)¶	11 (8)
Child Pugh classification	
Child A	45 (24)
Child B	103 (54)
Child C	42 (22)

* Median (range)

† ULN= Upper limits of normal value; corrected for inter-center variation in normal values.

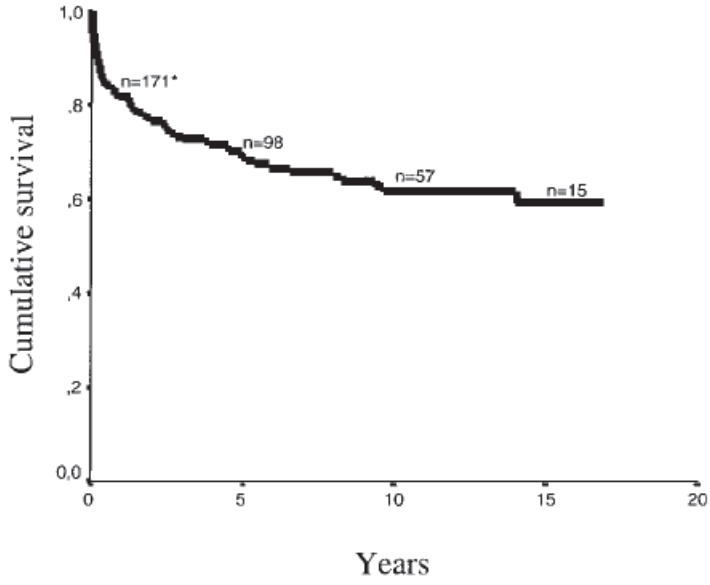
In the French sample, the Quick-time was used as a measure for the prothrombin time. A Quick time value between 100 and 44 % was assumed to be equal to an INR≤2.3. A Quick time lower than 44 % was equal to an INR>2.3.

¶ 138 patients underwent a liver biopsy

Figure 1

Overall survival in 237 patients with Budd-Chiari syndrome. Survival rates at 1, 5, 10 and 15 years were 82% (95 % CI 77-87), 69% (95 % CI 62-76), 62% (95 % CI 54-70) and 59% (51-68%) respectively.

** Numbers represent patients at risk at 1, 5, 10 and 15 years, respectively.*



Prognostic factors

Univariate analyses showed that ascites (p=.03), encephalopathy (p<.001), Child-Pugh score (p<.001), prothrombin time (p<.001), and serum levels of sodium (p=.03), creatinine (p=.01), albumin (p=.02) and bilirubin (p<.001) were significantly related to survival (table 2).

These variables, as well as age, serum levels of ALT and site of outflow obstruction, were introduced into a multivariate Cox regression analysis, stratified by country. Variables were selected by using a stepwise backward elimination technique. The final Cox model showed that encephalopathy (p<.001), ascites (p=.08), prothrombin time (p=.02) and serum levels of bilirubin (p=.07) were independent prognostic markers for survival for 205 patients with complete data on these variables (table 3).

Several tests for interaction between these markers did not alter the results (data not shown). In addition, adding quadratic effects of continuous variables did not modify the results (data not shown).

Table 2

Univariate survival analyses of characteristics at the time of diagnosis in 237 patients with Budd-Chiari syndrome.

	Categories	*N*	5-y surv %	95 % CI	***P***
Age (years)¶	> 35	121	69	60-78	.43
	≤ 35	116	68	59-77	
Sex	Male	78	66	55-77	.56
	Female	159	70	62-78	
Ascites	Present	199	66	59-73	.03
	Absent	38	84	69-99	
Hepatomegaly	Present	181	70	63-77	.76
	Absent	47	65	51-79	
	missing	9	*	*	
Splenomegaly	Present	120	63	54-72	.17
	Absent	104	74	65-83	
	missing	13	*	*	
Encephalopathy	Present	24	27	6-48	<.001
	Absent	213	73	66-80	
Variceal bleeding	Present	19	71	49-93	.93
	Absent	218	69	62-76	
Site of outflow obstruction	Hepatic veins (HV)	147	63	54-72	.09
	Inferior vena cava (IVC)	17	56	28-84	
	Combined HV and IVC	73	82	73-91	
Portal vein thrombosis	Present	34	56	36-76	.42
	Absent	203	71	40-78	
Myeloproliferative disorder	Present	54	71	58-84	.92
	Absent	183	68	61-75	
Paroxysmal nocturnal haemoglobinurea	Present	12	44	13-75	.18
	Absent	225	70	63-77	
Cirrhosis at liver biopsy	Present	11	37	5-69	.22
	Absent	127	65	56-74	
	missing	99	78	68-87	
Albumin (g/l)¶	< 34	117	60	50-70	.02
	≥ 34	99	79	70-88	
	missing	21	70	47-93	
Bilirubin (µmol/l)¶	> 28	119	54	44-64	<.001
	≤ 28	109	82	74-90	
	missing	9	*	*	
ALT (xULN†)¶	> 1.0	85	66	55-77	.08
	≤ 1.0	108	75	66-84	
	missing	44	61	45-76	
Sodium (mmol/l)¶	≤ 137	113	64	55-73	.03
	> 137	105	75	66-84	
	missing	19	57	28-87	
Creatinine (µmol/l)¶	> 80	119	60	50-70	.01
	≤ 80	103	74	66-82	
	missing	15	*	*	
Prothrombin time	INR >2.3	167	42	25-59	<.001
	INR ≤2.3	43	75	68-82	
	missing	27	75	58-93	
Child Pugh classification	Class A	45	89	79-99	<.001
	Class B	103	67	57-77	
	Class C	42	45	29-61	
	missing	47	74	60-88	

¶ Cut-off points were based on the median.
† ULN= Upper limits of normal value; corrected for inter-center variation in normal values.
# In the French sample, the Quick-time was used as a measure for the prothrombin time. A Quick time value between 100 and 44 % was assumed to be equal to an INR≤2.3. A Quick time lower than 44 % was equal to an INR>2.3.
* Due to small numbers in the missing category, no survival rates could be calculated.

Table 3

Results of multivariate Cox regression analysis for 205 Budd-Chiari patients with complete data.

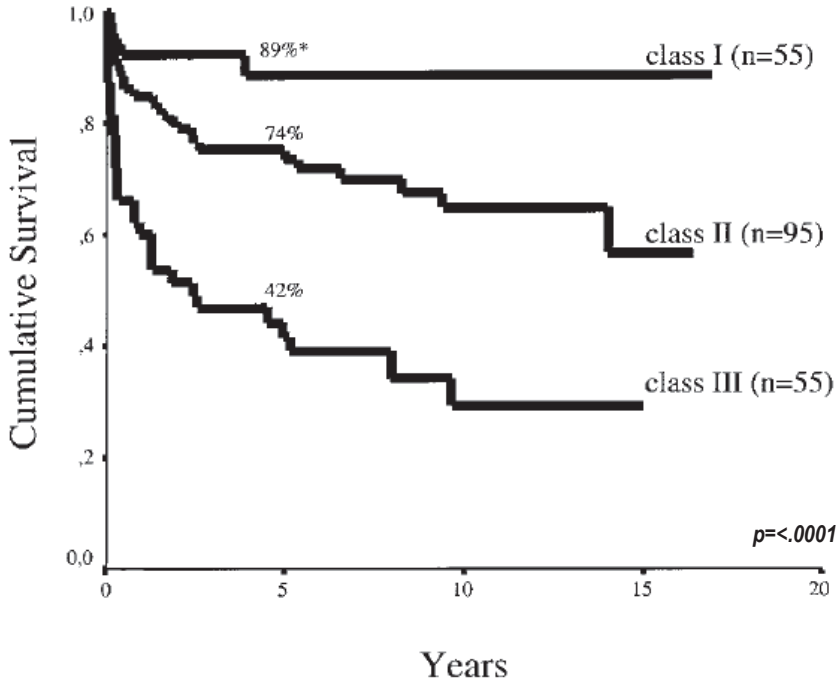
Variable	P-value	Risk Ratio	95 % CI	Prognostic classification item-score¶
Encephalopathy	<.001			
Present		3.58	1.87-6.86	1.27
Absent				
Ascites	.08			
Present		2.83	0.87-9.22	1.04
Absent				
Prothrombin time	.02			
INR >2.3		2.05	1.13-3.70	0.72
INR ≤2.3				
Bilirubin (μmol/l)†	.07	1.004	1.00-1.01	0.004

¶ The prognostic classification is based on these four variables. The equation is as follows:
1.27*encephalopathy + 1.04*ascites + 0.72*prothrombin time + 0.004*bilirubin.
The item-scores are equal to the natural logarithm of the corresponding risk ratios.
† Bilirubin was included as a continuous variable.

The predictors obtained from the multivariate Cox's analysis were included in a linear prognostic formula, in which the coefficients were equal to the regression coefficients of the proportional hazard model (Table 3). The equation was as follows:
*1.27*encephalopathy + 1.04*ascites + 0.72*prothrombin time + 0.004*bilirubin.*
Ascites and hepatic encephalopathy were scored as present (1) or absent (0) and prothrombin time as higher (1) or lower (0) than 2.3 INR. Bilirubin was included as a continuous variable for which the risk increased with 0.004 per μmol/l. The total score (i.e. sum of item-scores) ranged from 0.02 to 4.03. Since the frequency distribution of total scores was not homogeneous, we decided to transform the linear equation into an index, in which the upper and lower quarter of the frequency distribution were takes as the extremes. Consequently, 3 classes of patients could be distinguished: class I represented a total score between 0 and 1.1 (n=55), class II between 1.1 and 1.5 (n=95) and class III a total score of 1.5 and higher (n=55). Five-year survival rates for the 205 patients with complete data were 89% (95% CI 79-99) for class I, 74% (95% CI 65-83) for class II and 42% (95% CI 28-56) for class III (figure 2).

Figure 2

Survival for class I (n=55), II (n=95) and III (n=55), according to the prognostic classification. P_{trend} *<.0001,* $P_{class\ I\ vs\ II}$ *=.013,* $P_{class\ II\ vs\ III}$ *=.0001.*
** 5-year survival rates.*



Interventions

Overall, 171 patients of 237 (72%) were treated with anticoagulants. Thirty-nine patients (16%) were managed medically with diuretics and/ or paracenthesis only, for control of their ascites. Peritoneovenous shunting (Denver/ Leveen) was performed in 8 (3%), percutaneous transluminal angioplasty or stenting in 7 (3%) and surgical thrombectomy or angioplasty in 3 patients (1%). One hundred and seventeen patients (49 %) underwent portosystemic shunting (PSS) during follow-up. In all participating centers, indications for PSS were refractory ascites and/or deterioration of liver function. The distribution of PSS in the different classes of the prognostic model was as follows: 16 patients in class I (29%), 52 in class II (55%) and 33 in class III (60%). The type of PSS was meso-caval in 42 cases (36%), porto-caval in 35 (30%), meso-atrial in 10 (9%), meso-innominate in 6 (5%), spleno-renal in 4 (3%), cavo-atrial in 2 (1%) and porto-atrial in one (1%). In 17 patients (15%), a TIPS procedure was performed. In 16 cases (14%), shunt failure occurred; this was followed by revision in 7 (all following TIPS procedure), a second surgical PSS in 5 and other forms of therapy in 4 patients. One patient required a third revision of the TIPS. Of all shunted patients, 26 died (22%) and 10 (9%) underwent orthotopic liver transplantation, 5 of whom died. Of the non-shunted patients, 19 (16%) died and 19 (16%) were transplanted, 2 of whom died.

Benefit of anti-coagulation and portosystemic shunting

The use of anticoagulants in order to prevent further development of thrombosis did not yield a significant beneficial effect on survival in our total population (RR=1.05, 95% CI 0.62-1.76). Results did not alter when the group on anticoagulants in combination with PSS was taken as a separate category (RR=0.80, 95% CI 0.61-1.05). Sub-analysis of the effect of anticoagulants on survival for the three classes suggested improved survival for patients in class I (RR=0.14, 95% CI 0.02-1.21) but not for those in class II (RR=0.88, 95%CI 0.39-2.01) and class III (RR=1.3, 95% CI 0.50-3.04).

For the analyses on the efficacy of PSS, only the first shunting procedure was taken into account. One-hundred-six of the 117 shunted patients (91%) underwent a PSS procedure within the first year of diagnosis (median 1 month; range 0-132). We performed a time-dependent Cox regression analysis, in which during the follow-up, patients were switched to the shunted group at the time of PSS. In the total population, the Cox assumption for proportional hazards was evaluated by investigating the consecutive effects of shunting within one month after diagnosis (n=63), shunting between 1 to 6 months (n=39), and shunting after 6 months (n=15). As is shown in table 4, mortality risk increases as PSS is performed later during follow-up. Therefore, analysis of the effect of PSS in the overall population was not feasible. When re-evaluating the proportionality assumption for the three different prognostic classes, only class II patients exhibited an equal mortality risk of PSS after prolonged follow-up. In this class, time-dependent Cox analysis showed a tendency towards improved survival (RR=0.63, 95% CI 0.26-1.49), which is shown in figure 3.

A separate analysis assessing survival in relation to the type of shunt showed similar results for surgical shunting as for TIPS procedures (data not shown).

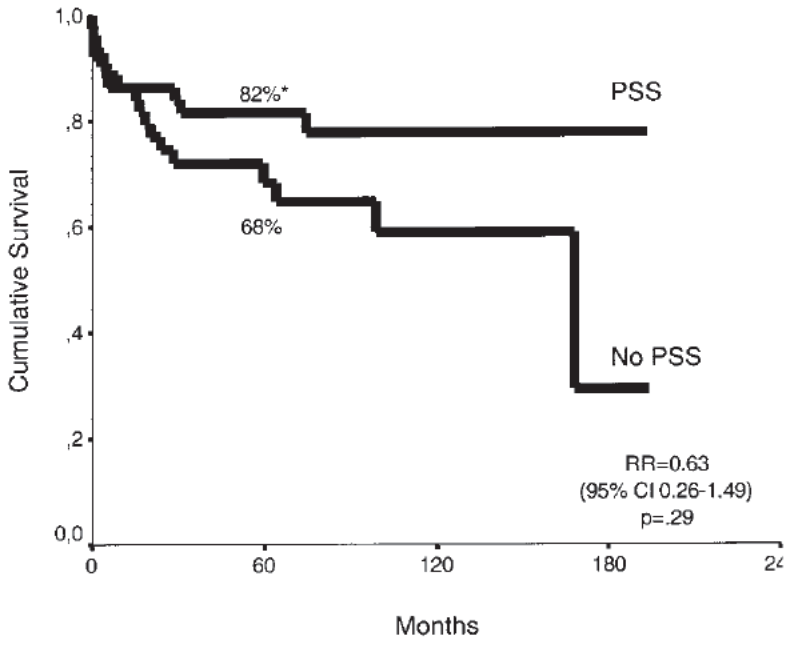
Table 4

Survival in relation to PSS (n=117), according to the interval between diagnosis and shunting. Cox analysis testing for proportionality.

Interval diagnosis-PSS	p-value	Relative Risk	95 % CI
< 1 month (n=63)	.83	1.07	0.57-2.00
1-6 months (n=39)	.002	3.05	1.53-6.09
> 6 months (n=15)	.009	4.15	1.42-12.12

Figure 3

Survival in class II (n=95), according to PSS. At the time of shunting, patients were censored from the non-PSS-group and included in the PSS-group (t=0 is time of shunting). During the follow-up, 52 patients (55%) underwent a PSS. P-values are derived from the Cox's time-dependent regression analysis.



Discussion

There is a large variation in results of studies on Budd-Chiari Syndrome in terms of clinical presentation, effects of therapy and survival. Since the prevalence of BCS is only about 1:100,000, controlled prospective studies are extremely difficult to perform. We carried out a multicenter cohort study, in which data were obtained using standardized and predefined criteria. The present study reports on 237 patients newly diagnosed with non-malignant BCS. This is therefore the largest cohort described until now. The large sample size enabled us to perform extensive survival analyses with control for possible confounding factors. Data were collected by using structured data forms and attempts were made to retrieve missing data on clinical outcome by contacting patients or their physicians. An international multicenter study like the present study could be hampered by cross-national variation in patient characteristics and institutional differences in therapeutic interventions. However, by introducing stratification for country in multivariate analyses, the effects of this variation as well as that of other possible confounding factors were minimized.

In the present study, 5-year survival was 69%, which is slightly higher than results from other series with long-term follow-up [7, 16]. This could be due to the fact that in recent years, improvement in availability and techniques of diagnostic tools has contributed to earlier recognition of BCS patients [19, 24]. Furthermore, the majority of our patients were treated with anticoagulants, which, in addition to better identification of underlying prothrombotic factors [22], has been reported to contribute to the improvement in prognosis of BCS since 1985 [16].

The aim of the present study was to assess prognostic determinants of survival in BCS patients. We identified four important factors, which are independently associated with survival: encephalopathy, ascites, prothrombin time and serum level of bilirubin. A prognostic classification, based on these factors, identified 3 classes of patients with good (class I, 5-year survival rate 89%), intermediate (class II, 5-year survival rate 74%) and poor prognosis (class III, 5-year survival rate 42%).

There are only two other studies using multivariate analysis for prognostic factors in BCS. The first was conducted in France among 120 BCS patients, diagnosed between 1970 and 1992 [16]. In that study, response of ascites to diuretics, the Child-Pugh score, age and serum creatinine appeared of significant value for the prognosis of BCS. A prognostic index based on these factors dichotomized 85 patients into a good (5-year survival 95%) and a poor prognostic group (5-year survival 62%), while overall 5-year survival was only 65%. In the second study, these results were evaluated in an independent sample of 69 patients [25]. The original index was extended with an additional factor, representing acute, chronic or acute-on-chronic BCS. However, a recent review of an expert panel on BCS has stated that at the present time, no consensus has been reached on the classification into acute and chronic disease, as scientific arguments for this classification are still lacking [1]. Both prognostic studies also assessed the effect of PSS, and did not show a beneficial effect on survival, even after control for prognostic class.

In comparison to these previous prognostic studies, the current study further optimizes prognostic modeling for BCS in several ways. First, our study includes a larger population of 237

patients, enabling analyses with more statistical power. In addition, it allowed the identification of three distinct prognostic groups, including a group with a considerably poor prognosis (Class III, 5-year survival 42%), for which liver transplantation may be the only life saving procedure. Second, our study involves recently diagnosed patients (between 1984 and 2001) who were treated according to current therapeutic standards. Both previous studies did not evaluate the effect of TIPS, as only surgical shunting procedures were investigated. In our study, 17 patients underwent a TIPS. Results of comparative analyses revealed no effect of type of shunting on survival. Other recent studies have demonstrated positive results of this new approach in terms of short-term survival [12, 13, 26]. TIPS is less invasive and therefore probably associated with a lower procedural mortality than PSS [27]. Long-term follow-up studies are needed to assess the place of TIPS in the treatment of BCS. Third, our prognostic classification includes simple clinical parameters, which are easily available at diagnosis. In contrast, both previous classifications include response of ascites to treatment, thereby precluding its use at the time of diagnosis. Comparison of our index, using baseline variables only, with the previous index including a time- and treatment-dependent ascites score, was therefore not feasible. Fourth, the previous studies did not evaluate the effect of PSS in a time-dependent analysis. As is indicated by our results, the effect of shunting may not be equal over time and appropriate control for this factor is needed to avoid response-time bias. In our time-dependent analysis, we found for class II a trend towards improved survival in patients with a PSS as compared to patients who were treated otherwise (RR= 0.63, 95% CI 0.26-1.49). In fact, this class represented the largest subgroup (n=95). These results suggest that for a reasonable group of patients, PSS may be an effective treatment. Other studies, mostly case series from surgical units, report on high survival rates following PSS with 5-year survival of 57% [11] to 94% [9, 10]. However, most of these studies do not provide data on patient selection criteria, which play a major role in the long-term results of treatment [21], nor do they take account of differences in time-point of shunting within the clinical course of patients.

Another well-known and widely used classification in liver diseases is the Child-Pugh score. Our prognostic classification, including encephalopathy, ascites, prothrombin time and bilirubin, but not albumin, closely resembles this score. However, addition of albumin to this model showed that albumin did not have a significant impact on survival (data not shown). In addition, discriminative analyses (using the Akaike Information Criteria) demonstrated that our prognostic model was superior to the Child-Pugh in predicting the outcome in patients with BCS (data not shown).

It is known that in BCS, a variety of histopathological features can be found, ranging from centrilobular congestion and necrosis to veno-portal or veno-centric cirrhosis [28]. However, the prognostic role of histology is probably limited. Previously, no significant association was found between findings at histological examination and survival in 45 BCS patients [3]. This can be partly explained by the expected inhomogeneous distribution of liver cell lesions, which may lead to sampling errors of biopsy specimens. Histopathological findings were also not predictive for early or late shunt patency and survival among patients undergoing PSS [22]. In this study, hepatocellular function and the time between onset of clinical symptoms and diagnosis, rather than histology, were suggested to be the crucial factors in choice of therapy. Given its relatively low predictive value and the fact that only limited numbers of liver biopsies have been performed at the time of diagnosis, the prognostic value of histology was not assessed in the present study.

Although a large randomized study has never been performed, nearly all studies suggest that the administration of anticoagulants will prevent extension of thrombosis and possibly induce recanalisation [4, 24, 29]. In our study, the majority of patients (71%) received anticoagulants. Overall, we could not detect a significant effect on survival when we compared patients treated with or without anticoagulants. Only for patients in class I, there was a trend towards improved survival (RR=0.14, 95% CI 0.02-1.21). Since the reason to withhold anticoagulants was often unknown, this result should be interpreted with caution.

As others have stressed, orthotopic liver transplantation is an effective salvage procedure, in the case of acute fulminant or end-stage liver failure [30-32]. Without transplantation these patients would most probably have had a poor outcome. For this reason, we have used transplantation-free survival as the outcome measure. Since the decision to perform liver transplantation might have been based on variables from our prognostic classification, we assessed whether our results would alter if only death was considered as endpoint. For this analysis, patients who received a liver transplantation (n=29) were censored at time of intervention. We found that our prognostic classification remained a valuable tool to predict real survival ($p<.001$).

In conclusion, major prognostic factors for the BCS are the prothrombin time, serum bilirubin levels, and the presence of hepatic encephalopathy and ascites. A prognostic classification combining these factors divides patients into three groups with a good (class I), intermediate (class II) or poor (class III) prognosis. This classification, based on simple clinical and laboratory parameters, is a useful tool for assessment of disease severity at the time the diagnosis of BCS is established, and before any form of therapy has been instituted. After adjustment for the time-interval between diagnosis and PSS, a trend towards improved survival was found for class II patients undergoing PSS. These results suggest that, in contrast to findings from other studies, shunting may well be valuable for a large subgroup of patients. Prospective studies are needed to confirm these results and to further evaluate the effect of derivative therapy in patients with BCS.

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VIII

Can MELD Be Used To Predict Prognosis in Patients with Budd-Chiari Syndrome?

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Abstract

Background

MELD is a widely accepted and objective scoring system for end-stage liver disease (ESLD), but has never been evaluated in Budd-Chiari Syndrome (BCS). Our aim was to investigate whether MELD can be used to predict survival in patients with BCS.

Methods

Patients with BCS (n=237) were obtained from a large international study. Patients with ESLD (n=281) were used to compare the discriminative ability of MELD in BCS versus other chronic liver diseases. MELD and Rotterdam BCS index, a recently developed prognostic index for BCS, were calculated using standard equations. Receiver Operating Characteristic curves and c-statistics were used to assess models' ability to predict 1-year survival.

Results

Median MELD was 12.5 (range –7.4 to 43.4) for BCS and 11.3 (-3.0-49.5) for ESLD (P=0.12). C-statistic of MELD in BCS was 0.695 (95% CI 0.59-0.80), in contrast to 0.848 (95% 0.80-0.90) in ESLD. Survival was significantly poorer in ESLD than in BCS (P<0.001). C-statistic of the Rotterdam BCS index was 0.760 (95% 0.67-0.85). Correlation between MELD and Rotterdam BCS index was 0.61 and most of the discrepancy existed in BCS patients with high prevalence of ascites and encephalopathy, and preserved liver function. Addition of ascites and encephalopathy to MELD improved the c-statistic to 0.751 (95% CI 0.65-0.85).

Conclusion

In conclusion, MELD showed a sub-optimal discriminative ability to predict survival in BCS. This was explained by the highly variable degree of liver dysfunction and hence clinical outcome in BCS in contrast to ESLD.

Introduction

Budd-Chiari syndrome (BCS) is a complex disease entity, which is characterised by hepatic venous outflow obstruction. The obstruction, in the western world usually caused by thrombosis, can be located anywhere from the small hepatic veins to the entrance of the inferior vena cava into the right atrium [1-3]. Although a large spectrum of etiological factors exists, most patients share an underlying tendency to develop thrombosis, either hereditary or acquired.

Even though prognosis of BCS remains moderate to poor, survival has improved since 1985 with the increased use of anticoagulation as maintenance therapy [4]. Due to the rarity of the disease, large studies using multivariate analyses for evaluating potential prognostic indicators are exceptional. Recently, our group evaluated the prognostic value of several clinical and laboratory parameters in a follow-up study on 237 patients with BCS; to date the largest series described [5]. Based on multivariate modelling, a prognostic index was developed, which was composed of the following variables: ascites, encephalopathy, prothrombin time and bilirubin. According to this index, patients with good, intermediate and poor prognosis can clearly be distinguished. This index is referred to as the Rotterdam BCS index. It has been designed specifically for patients with BCS and is strengthened by the combination of both clinical as well as laboratory parameters, with a potential use in therapeutic decision making. The rarity of the disease and the novelty of the model, however, have so far precluded testing of its external validity in an independent, large-sized patient population.

The Model for End-Stage Liver Disease (MELD) is a widely accepted objective scoring system for patients with chronic liver disease. It was initially developed to predict survival in patients undergoing TIPS [6], but is now widely used as a prognostic model for patients with end-stage liver disease of various origins [7]. It is a continuous score, composed of 3 laboratory parameters; serum creatinine, bilirubin and INR. MELD has been validated frequently and appears to accurately predict short-term survival in most decompensated liver diseases [8-10]. Therefore, it has become the primary tool for organ allocation on the liver transplantation waiting list in the United States for all types of liver diseases, regardless of the etiology [11]. Unlike most other hepatic diseases, BCS is a condition marked by a considerable variability in disease severity as well as prognosis. The use of MELD as a prognosticator of BCS has as yet never been investigated.

Therefore, the aim of the current study was to investigate whether the MELD score can be used to predict prognosis in patients with BCS.

Methods

Budd-Chiari Syndrome patient population

Consecutive patients, diagnosed with non-malignant BCS, in the period between January 1984 and January 2001, were identified by means of a systematic search through computerised hospital registration systems in all academic hospitals in the Netherlands (8 in total), the Mayo Clinic College of Medicine (Rochester, MN) in the USA, and Hôpital Beaujon (Clichy) and Hôpital Louis Mourier (AP-HP, Colombes) in France, all of which serve as tertiary referral centers. Diagnosis of BCS was made by radiological imaging alone, and based on the currently used definition [1, 2], thereby excluding hepatic outflow obstruction due to congestive heart failure or sinusoidal obstruction syndrome (previously Veno-Occlusive Disease). The present study population has been described in more detail previously [5]. The total study population consisted of 237 patients, (Netherlands n=73 (31%); United States n=76 (32%), France n=88 (37%)). Patient information was retrieved from the date of diagnosis until death, Orthotopic Liver Transplantation (OLT), study closure (i.e. January 1st 2001) or date of last visit.

Hospitalized end-stage liver disease (ESLD) patient population

In order to assess the discriminative ability of MELD in BCS in comparison to that in ESLD of various origin, we used the study population previously described by Kamath et al. [7]. This study population consisted of patients, hospitalized for decompensated liver disease at the Mayo Clinic between January 1994 and January 1999. Patients were identified by a computerized diagnostic index and included in the study if they were over 18 years of age and there was an unambiguous diagnosis of cirrhosis. Patients were excluded if they had hepatocellular carcinoma, recent alcohol use (i.e. less than 1 month before hospitalization), severe cardiopulmonary disease, sepsis or renal disease. The total number of eligible patients in this cohort was 281. The underlying cause of cirrhosis was alcoholic liver disease in 84 (30%), viral hepatitis in 59 (21%), primary biliary cirrhosis in 37 (13%) and primary sclerosing cholangitis in 6 (2%) patients. In the remaining 95 patients (34%), a variety of other causes existed including Non Alcoholic Fatty Liver Disease, hemochromatosis, and autoimmune hepatitis. Patients were followed up from the first day of hospitalization until death or date of last follow-up. None of the patients underwent liver transplantation.

MELD and Rotterdam BCS index

All clinical data were collected at time of diagnosis. Since MELD became the primary tool for liver transplant allocation in the USA in February 2002 - thus after the inclusion period of our patients (1984-2001)- MELD scores had never been assessed in any of the patients with BCS, and hence had never affected therapeutic decision making, including OLT. Therefore, baseline data were used to calculate the MELD score in retrospect only for the purpose of this study. The MELD score was calculated according to the original description, namely: 9.57 * ln (creatinine) + 3.78 * ln (bilirubin) + 11.2 * ln (INR) + 6.43 [11]. To take advantage of the full range of the score, we did not impose upper and lower limits of laboratory values (allowing MELD scores below 6 and over 40). Data on creatinine (in mg/dl) and bilirubin levels (in mg/dl) were available in 222 (94%) and 228 (96%) of the BCS patients, respectively. INR, on the other hand, was not readily available for all patients for two reasons: 1) INR was introduced in 1999, and thus in the years before, prothrombin time (PT) was only measured in seconds, and 2) international differences exist in ways to measure PT. In total, INR was measured in 95 (40%), the Quick time (expressed

in %) in 87 (37%) and the PT (in seconds) in 48 (20%) patients. The Quick time was subsequently converted to INR by dividing 100% by the Quick time value, assuming a normal value of PT of 10 seconds (i.e. 100/Quick time * 1.0). For 14 patients (6%) with PT in seconds, the ISI (International Sensitivity Index) of the used thromboplastin reagent was known and the INR could be calculated using the formula previously described: INR = $(PT/PT_n)^{ISI}$, assuming a normal value of PT of 10 seconds [12]. Because of variation in timing of blood sampling, 34 patients did not have a prothrombin time recorded within 24 hours after diagnosis. The missing values for these patients were subsequently imputed by survival modeling by using two independent predictors of INR, being white blood cell count (regression coefficient=0.22; P=0.002) and bilirubin (regression coefficient=0.13; P=0.005). For 7 patients, the imputation could not be done as these parameters were also missing. Hence, INR was available in a total of 230 (97%) patients and MELD could finally be calculated for 213 BCS patients (90%) with complete data on all its components. In ESLD patients, MELD could be calculated for the complete dataset.

The Rotterdam BCS index was assessed according to the previously described equation: 1.27 * encephalopathy + 1.04 * ascites + 0.72 * prothrombin time + 0.004 * bilirubin [5]. Encephalopathy and ascites are scored as present (1) or absent (0), prothrombin time as lower (0) or higher (1) than an INR of 2.3 and bilirubin is included on a continuous scale, expressed in mol/l. The Rotterdam BCS index could be calculated for 205 BCS patients (87%) with available data on these components. As previously described, patients were categorized according to their scores into low (< 1.1; n=55), intermediate (1.1-1.5; n=95) and high (> 1.5; n=55) classes [5].

Statistical analyses

Considering the severe condition of patients with BCS in the pre-transplant phase (OLT is mostly used as rescue treatment in case of fulminant or progressive liver failure), we assumed OLT to be equal to death in all our analyses (i.e. both are endpoints). Hence, transplantation-free survival was calculated from date of diagnosis (BCS) or hospitalization (ESLD) until OLT, death, study closure or date of last visit. The Kaplan Meier method was employed to calculate cumulative survival rates and log rank testing was used for between-groups comparison. Cox's proportional hazards model was utilized to calculate the independent effect of each variable on the outcome. Before applying Cox models, the assumption of proportional hazards was evaluated and shown to be valid.

Patients were stratified into high, intermediate and low MELD classes according to the 33rd and 67th percentile of MELD scores among the events. To assess the ability of MELD to predict survival in patients with BCS or ESLD, our analyses were performed by measuring the concordance (c) statistic, which is equal to the area under the Receiver Operating Characteristic (ROC) curve [13]. The outcome of interest was 1-year survival. A c-statistic between 0.8 and 0.9 was interpreted as excellent discriminative ability and a test with c-statistics of 0.7 and higher as a clinical useful tool. Correlation analyses included measurement of the Pearson correlation coefficient (for the continuous scores) and the Kappa statistic (for the between-classes agreement). In all analyses, a P-value of 0.05 or less was considered statistically significant.

Results

Median follow-up for 237 patients with BCS was 44 months (range 2 days-203 months), and in this period, 29 underwent OLT (12%) and 52 patients died (22%), of whom 7 post-OLT. For the 281 patients who were hospitalized for ESLD, median follow-up was 17.2 months (range 0.03-67.3) and 129 patients died (45%). Table 1 presents baseline data for both patient groups. Patients with ESLD were significantly older than patients with BCS (median age 60.6 versus 34.5 years; P<0.001); the gender of patients with BCS was mostly female (67%) whereas patients with ESLD were more likely to be male (54%, P<0.001).

Table 1

Comparison of baseline data for 237 patients with Budd-Chiari syndrome versus 281 patients with End-Stage Liver Disease (ESLD). P-values are based on Chi-square testing (for categorical variables) or Mann-Whitney-U testing (for continuous variables).

	Budd-Chiari Syndrome (n=237)	End-Stage Liver Disease (n=281)	P-value
Age[1]	34.5 (13-76)	60.6 (20-93)	<0.001
Gender (M/F)	78/159	153/128	<0.001
Creatinine[1] (mg/dl)	0.91 (0.40-5.30)	1.00 (0.30-14.0)	<0.001
Bilirubin[1] (mg/dl)	1.61 (0.15-17.60)	1.50 (0.20-62.10)	0.99
INR[1]	1.54 (0.76-7.69)	1.30 (0.90-5.56)	<0.001
Albumin[1] (g/dl)	3.4 (1.3-5.6)	3.0 (1.6-4.9)	<0.001
Ascites (%)	199 (84)	115 (43)	<0.001
Encephalopathy (%)	24 (10)	51 (19)	0.006
Cirrhosis at biopsy (%)	11 (8*)	281 (100)	<0.001
MELD score[1]	12.5 (-7.4-43.4)	11.3 (-3.0-49.5)	0.12
Child-pugh score[1]	8 (5-14)	7 (5-14)	0.12
Deaths (%)[2]	52 (22%)	129 (45%)	0.001

[1] all continuous variables are expressed as median (range)

* total number of biopsies performed in patients with BCS was 138.

[2] deaths include only real deaths, not OLT

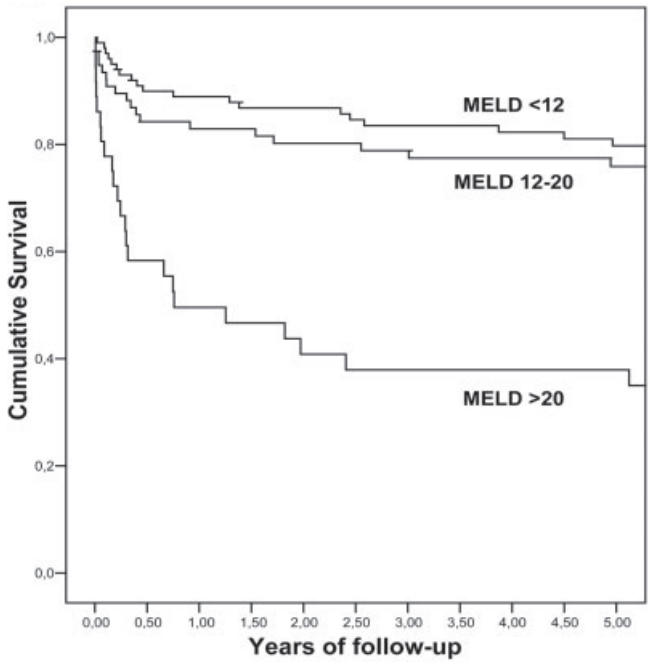
MELD in BCS

To evaluate whether we could use the original equation of the MELD score in patients with BCS we calculated the regression coefficients for each of the individual components in a multivariate Cox model and compared that to the original model. All of the components appeared significantly associated with survival and the corresponding regression coefficients were 0.69 for $\log_e$ creatinine (95% CI 0.01-1.38; *P*=0.047), 0.44 for $\log_e$ bilirubin (95% CI 0.12-0.75; *P*=0.006) and 0.65 for $\log_e$ INR (95% CI 0-1.3; *P*=0.054). With the multiplication by 10, later introduced by Kamath et al. [7] for ease of use, these coefficients fall within the confidence interval of those in the original MELD model.

Median MELD score was 12.45 (range -7.36 to 43.4). Univariate Cox regression analysis showed a significant association between the MELD score and survival (Odds Ratio [OR] 1.08; 95% CI 1.05-1.11; P<0.001). Low MELD was defined as MELD <12 (n=100), intermediate MELD as MELD 12-20 (n=77) and high MELD as MELD >20 (n=36). Mortality rates for these MELD classes were 22%, 27% and 64% (P<0.001); and five-year survival rates were 80% (95% CI 72%-88%), 76% (95% CI 66%-86%) and 38% (95% CI 32%-54%) respectively. There was a significant difference in survival between high and low MELD (P<0.001) and between high and intermediate MELD (P<0.001), but not between low and intermediate MELD (P=0.53; figure 1a). For 1-year mortality, the c-statistic of MELD in BCS was 0.695 (95% CI 0.589-0.802).

Figure 1a

Transplantation-free survival in which patients were stratified according to the MELD score into low (<12), intermediate (12-20) and high (>20) MELD. Survival for patients with BCS with complete data on MELD (n=213). Two-way comparison between low (n=100) versus intermediate (n=77) MELD, low versus high (n=36) and intermediate versus high showed a P-value of 0.53, <0.001 and <0.001, respectively. P_{trend} was <0.001.



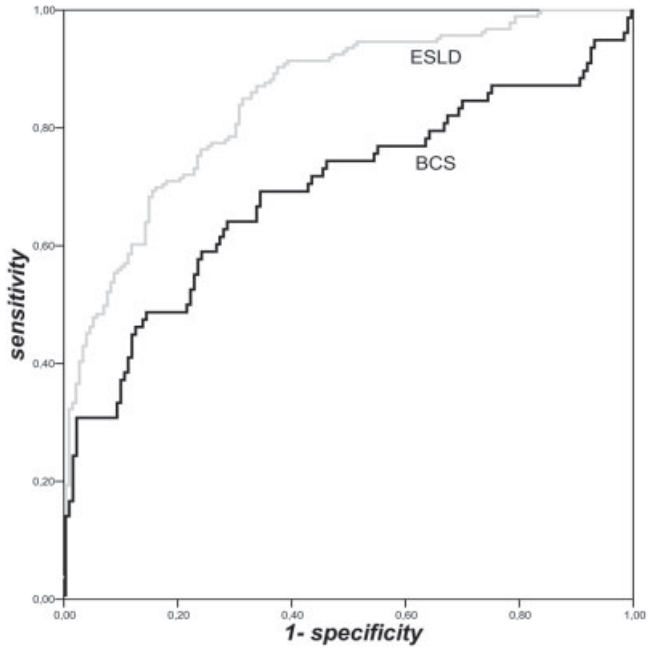
Results did not alter when we performed separate analyses with only patients with a directly measured INR (n=95; C-statistic MELD = 0.726; 95% CI 0.55-0.90), thereby confirming that our indirect method of obtaining an INR (by conversion or imputation) had not significantly affected our results. Furthermore, 171 patients (72%) used anticoagulation during their clinical course. Although INR measurement was performed at time of diagnosis, so inherently prior to initiation of therapy, we performed analyses to rule out the possibility that for some, INR sampling was affected by vitamine K antagonists administered prior to diagnosis. We compared the INR levels between all patients once treated with anticoagulation and patients who never received anticoagulation and found no statistical difference between both groups (mean INR 1.81 versus 1.66, respectively; P=0.18).

MELD in BCS versus ESLD

Median MELD in ESLD was 11.3 (range –3.0 to 49.5) and the 1-year mortality c-statistic was 0.848 (95% CI 0.799-0.897). Thus, MELD showed a better discriminative ability in the prediction of mortality for ESLD than for BCS (figure 2).

Figure 2

Receiver Operating Characteristic (ROC) curves showing the accuracy of MELD to predict 1-year mortality in BCS (black line) versus ESLD (gray line). C-statistics was 0.695 for MELD in BCS and 0.848 for MELD in ESLD.



This difference in c-statistic could not be explained by a difference in the actual MELD scores in both disease entities (P=0.12). However, when we compared survival, patients with ESLD were found to have a significant poorer prognosis than patients with BCS; 5-year survival rate was 44% (95% CI 35%-52%) in ESLD versus 69% (95% CI 62%-76%) in BCS (P<0.001). Patients with ESLD had a 2.3 fold increased risk of death as compared to BCS. This difference remained significant even after adjusting for the MELD score and age in a multivariate Cox model (table 2). In other words, given the same MELD score and age, patients with BCS showed considerably higher survival rates. This is further illustrated by figure 1b presenting the association of the three MELD classes in ESLD. As opposed to the association of MELD classes and survival in BCS (figure 1a), BCS patients showed significantly better survival rates than patients with ESLD for each MELD class (all P<0.01). Results were unaltered when we looked at survival irrespective of liver transplantation (data not shown).

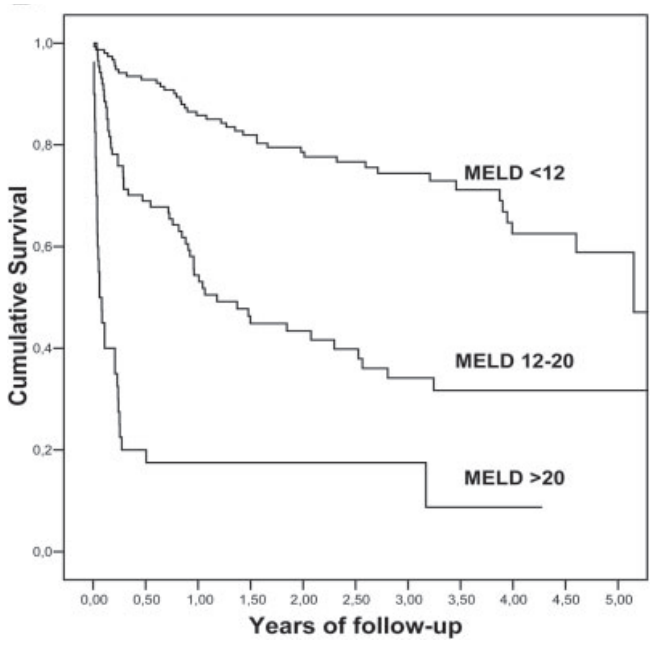
Table 2

Multivariate Cox model for 213 patients with BCS and 281 with ESLD. The difference in survival between patients with ESLD and BCS was independent of differences in MELD score or age. Total number of events (i.e. death/OLT) was 196 (129 in ESLD versus 67 in BCS).

Variable	Regression coefficient	Regression coefficient standard error	Risk ratio	P-value
ESLD*	0.838	0.197	2.312	<0.001
MELD	0.106	0.008	1.112	<0.001
Age	0.014	0.005	1.014	0.009

* reference is BCS.

Figure 1b
Transplantation-free survival in which patients were stratified according to the MELD score into low (<12), intermediate (12-20) and high (>20) MELD for patients with BCS.



MELD and Rotterdam BCS index

Median score of the Rotterdam BCS index was 1.16 (range 0.02-4.03). The c-statistic of the Rotterdam BCS index for prediction of 1-year mortality was found to be 0.760 (95% CI 0.670-0.850). In order to explain the difference with MELD, we evaluated the correlation between both scoring systems (figure 3). Absolute agreement between the corresponding classes of MELD and Rotterdam BCS index was found in 102 patients (53%). However, large discrepancies existed in 23 patients (11%) who had low (section a; n=7) or intermediate MELD (b; n=16) but high Rotterdam score. All these patients suffered from ascites (100%) and 8 (35%) had encephalopathy, explaining the high Rotterdam score. Also, in the 48 patients (25%) with low MELD and intermediate Rotterdam score (c), ascites was present in 45 (94%) and encephalopathy in 3 (6%). The six patients with high MELD but intermediate Rotterdam score (d) all had ascites (100%) and none had encephalopathy. Finally, of the 15 patients (4%) with intermediate MELD but low Rotterdam score (e), only 5 (33%) had ascites and none of them had encephalopathy. There were no patients with high MELD and low Rotterdam score. Pearson's correlation coefficient (r) for the continuous scores was 0.61 (P<0.001) and Kappa for between-classes agreement was 0.29.

These results suggested that the discrepancy between the two scores was largely due to the use of clinically important variables (ascites and encephalopathy) in the computation of the Rotterdam BCS index but not in the MELD score MELD. Table 3 shows the results of the univariate and multivariate regression models incorporating MELD, ascites, encephalopathy and albumin. The multivariate analysis suggest that the effect of ascites on survival iuivalent to that of a 17 point rise in MELD. Similarly, the effect of encephalopathy was that of a 16 MELD points rise. When implementing this in a modified MELD model, the c-statistic improved to a value of 0.751 (95% CI 0.654-0.847), thereby closely approaching that of the Rotterdam BCS index. The ROC curve of this model, as well as that of MELD and the Rotterdam BCS index are shown in figure 4.

Figure 3

Correlation between the MELD score and the Rotterdam BCS index (n=194). Pearson correlation coefficient=0.61, Kappa=0.29.

Lines represent the separate cut-off scores (i.e. 1.1 and 1.5 for the Rotterdam BCS index; and 12 and 20 for the MELD score). The inserted letters represent the following sections in which discrepancy exists: a= low MELD, high Rotterdam BCS index; b= intermediate MELD, high Rotterdam BCS index; c= low MELD, intermediate Rotterdam BCS index; d= high MELD, intermediate Rotterdam BCS index; e= intermediate MELD, low Rotterdam BCS index. Solid dots represent death or OLT.

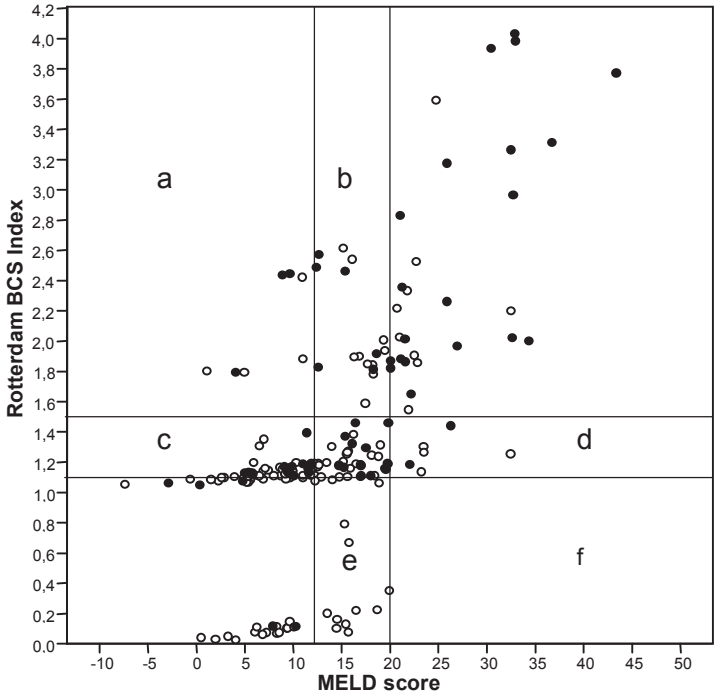


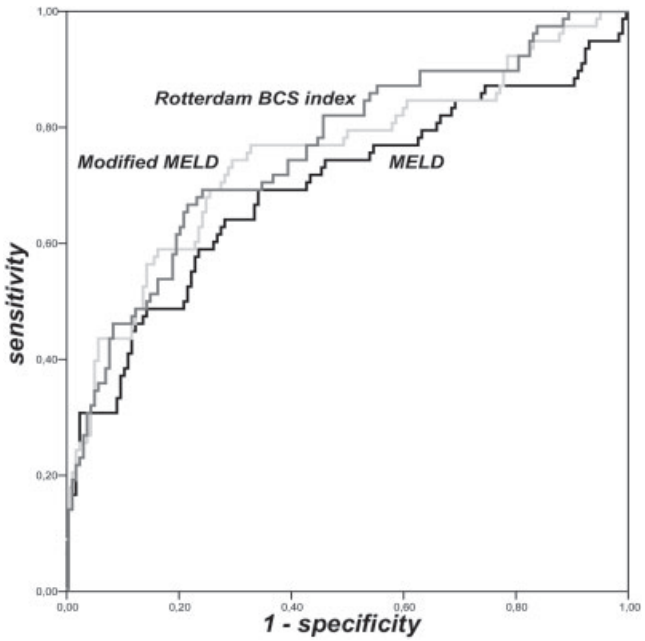
Table 3

Univariate and multivariate Cox regression models with MELD, clinical parameters of the Rotterdam BCS index (i.e. ascites and encephalopathy) and albumin, fitted for 202 BCS patients with complete data. In total, 67 events (i.e. death or OLT) occurred.

	Univariate Cox model			*Multivariate Cox model*		
Variable	Regression coefficient (B)	Standard error of B	P-value	Regression coefficient (B)	Standard error of B	P-value
MELD	0.078	0.015	<0.001	0.059	0.016	<0.001
Ascites	1.164	0.464	0.012	1.019	0.525	0.052
Encephalopathy	1.312	0.277	<0.001	0.946	0.321	0.003
Albumin	-0.29	0.016	0.070	-	-	-

Figure 4

Receiver Operating Characteristic (ROC) curves showing the accuracy of MELD (black line), the Rotterdam BCS index (dark gray line) and the modified MELD (light gray line) to predict transplantation-free survival after 1 year. C-statistics was 0.695 for MELD, 0.760 for the Rotterdam BCS index and 0.751 for modified MELD.



Discussion

In this study we evaluated the prognostic accuracy of the MELD score in patients with Budd-Chiari syndrome. MELD appears to have lower prognostic value in patients with BCS, than in patients with ESLD. In addition, the MELD score exhibited poorer discriminative ability than the previously developed Rotterdam BCS index in patients with BCS. Improvement of MELD by adding ascites and encephalopathy increased the prognostic ability of MELD, but did not surpass the Rotterdam BCS index.

Prognosis for patients with BCS has generally been difficult to predict due to the large variability in clinical presentation and disease course, as opposed to end stage liver disease, which usually has a more predictable course. In addition, the diverse therapeutic modalities such as anticoagulation, angioplasty, and TIPS may in part reverse the vascular pathophysiology of BCS and prevent further damage, resulting in excellent long-term survival. TIPS, in particular, has been used with increased frequency and has shown excellent results in terms of control of portal hypertension [14, 15]. However, at the time of data collection for the current study, TIPS was scarcely used since experience was not as widespread as it is the case to date (only 17 patients underwent TIPS [5]) and therefore, our data did not allow us to examine its effect in detail. All these therapeutic measures for BCS, however, are frequently used on empirical grounds rather than based on the individual patient's clinical condition and therapeutic needs. Therefore, we believe that a simple, yet powerful prognostic model is of the utmost importance to aid both in determining the need for intervention and in the accurate prognostication of patients with BCS.

MELD has been validated in various forms of end-stage liver diseases, demonstrating good- to-excellent prognostic value in this patient group [7]. Unlike the Child-Pugh score, MELD is a continuous measure which allows quantification of mortality risks. In addition, it contains objective laboratory parameters and is not limited by a ceiling effect. It instead uses statistically derived coefficients to give appropriate weights to variables according to their relative importance.

However, in our patient population with BCS, the prognostic value of MELD appeared to fall in the lower range (c-statistic was just below 0.7). Indeed, MELD was associated with lower discriminative ability to predict 1-year mortality in BCS than in ESLD. Also, within the BCS patient population, MELD showed lower ability to prognosticate patients than the Rotterdam BCS index did. There are two possible explanations for this observation. The first lies in the fact that MELD has been designed and validated for the prediction of short-term outcome of patients with end-stage cirrhosis being enlisted for liver transplantation. Indeed, the patient cohort upon which the MELD score was developed included predominantly patients with advanced hepatocellular synthetic dysfunction owing to cirrhosis following viral hepatitis or cholestatic liver disease [7]. BCS, on the other hand, can exhibit a large variability in liver function, related to a variable degree of vascular pathology, hepatocellular necrosis and atrophy. This was reflected by the significantly higher survival rates in patients with BCS, as compared to ESLD in our study. In line with our findings, others have also demonstrated that MELD may indeed perform less well in patients with relatively well-compensated liver disease, such as patients undergoing elective TIPS [16, 17] and non-transplant cirrhotic patients [18, 19].

The second explanation is that the presence or absence of ascites and encephalopathy did not provide additional prognostic information to MELD, and therefore is not incorporated in the MELD model. This is likely explained by the fact that in ESLD, ascites and encephalopathy are merely a reflection of the advanced degree of hepatocellular dysfunction and presence of fibrosis, the former which is already assessed in the MELD score. In BCS, liver function is generally less impaired and hence less predictive. Indeed, ascites and encephalopathy can present early in the course of BCS in the absence of advanced fibrosis and liver dysfunction, as was shown in our correlation analysis. Ascites and encephalopathy therefore reflect the effect of vascular pathology, and the subsequent development of focal hepatocellular necrosis, rather than that of fibrosis and cirrhosis. In BCS, these parameters indicate severe disease and predict higher mortality risks. Although Transjugular Intrahepatic Portosystemic shunting is nowadays regarded as initial derivative treatment of choice, and many successes have been booked since its introduction [14, 15], a proportion of patients develop TIPS dysfunction, fail to respond or eventually go on to develop liver failure which can only be reversed by liver transplantation. Therefore, the abovementioned discrepancy between both scores is of major clinical importance since using only the MELD score as scoring system will exclude otherwise severely ill patients (i.e. classified as high Rotterdam BCS index with a predicted 5-year survival of 42% [5]) from the liver transplantation list. This is further supported by our finding that the MELD score did perform better when these clinical parameters were added to the model, approaching the accuracy of the Rotterdam BCS index. Our findings are consistent with previous studies, which have suggested that clinical parameters could have important additive prognostic information in certain hepatic disorders [19].

The limitations of our study include those common to other retrospective studies. More particular for our study, we were challenged in first, the availability of INR, and second, the possible influence on INR of anticoagulation use. Regarding the former, INR availability was initially hampered by variability in exact timing or method of the measurement of prothrombin time. However, we implemented multiple methods to recalculate the INR from other indicators of prothrombin time and we showed that by doing so, our conclusion regarding the accuracy of MELD was unaltered. With regard to the latter, we investigated and confirmed our suspicion that anticoagulation had not affected baseline INR measurements by performing comparative analyses between INR levels in the total group with anticoagulant management, and the group of patients never treated by anticoagulation. Indeed, there was no significant difference in INR between the two. Thus, if INR had been measured in some patients who possibly received vitamin K antagonists prior to establishment of the diagnosis, it is highly unlikely that it had an immediate effect on the INR obtained shortly after diagnosis. The last limitation relates to the fact that the Rotterdam BSC index has previously been developed using the same patient population as the current one. This could have resulted in statistical over-fitting of the Rotterdam model, as compared to MELD, and therefore inherently higher model performance in the former. Statistical techniques assessing the internal validation of the Rotterdam BCS index could have provided us with more information regarding the accuracy of the model's performance and the extent of over-fitting, but this was precluded by our relatively small study sample. However, the finding that the MELD model improved considerably when we added clinical parameters was based on independent multivariate analysis. Even if the accuracy of the Rotterdam BCS index suffered from overestimation, this cannot explain the improvement achieved in the modified MELD model.

In conclusion, the prognostic accuracy of MELD appeared lower in BCS than in ESLD. Furthermore, MELD showed a sub-optimal discriminative ability to predict mortality in BCS, as compared to the recently developed Rotterdam BCS index. MELD, although excellent in predicting mortality in chronic liver diseases, appears less useful as a prognostic model for patients with BCS. To date, prognostication of patients with BCS remains thus an unresolved issue. Future large independent studies with external validation of the several existing models should reveal the most accurate prognostic model for this disease. However, in the absence of better models as of yet, the Rotterdam BCS index appears the most appropriate prognostic index for patients with BCS.

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IX

Early mortality in patients with Budd-Chiari Syndrome: Who are at risk? Results from the European Network for Vascular Disorders of the Liver (EN-Vie)

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Submitted for Publication

Abstract

Background

We prospectively studied mortality n incidents cases of Budd-Chiari Syndrome (BCS) with a focus on the first 2 years after diagnosis during which time the vast majority of patient deaths occur. In addition, we examined the validity of a previously established prognostic model, the Rotterdam BCS index (RBI), in the identification of high-risk patients.

Methods

We designed the first prospective international observational study of 163 incident cases of BCS between 2003-2006. We analysed mortality patterns and compared patients who died early with survivors. The validity of the RBI, consisting of encephalopathy, ascites, bilirubin and prothrombin time, was measured by the area under the Receiver Operating Curve (C-statistic).

Results

Mortality was highest in the first 2 months (n=12; 41% of all deaths). Patients who died early were of older age ($p<0.001$), had higher RBI scores ($p<0.001$) and elevated creatinine levels ($p=0.03$). The c-statistic of the RBI for early mortality was 0.84. Adding age and creatinine to the RBI improved the model's c-statistic to 0.92. There was a stepwise decline in 2-month survival rates as RBI scores increased from 0-5 (100%), 5-7 (88%), 7-9 (73%) and 9 and above (25%; $P_{trend}<0.001$). Patients who died later in the follow-up resembled patients with early mortality in age and renal function, but had better liver function and lower RBI scores. RBI score obtained at 2 months was still able to predict late mortality (c-statistic 0.78).

Conclusion

The first 2 months compose the most crucial time in the disease course of BCS. Early mortality is accurately predicted by the RBI. Obtaining the RBI score at diagnosis as well as during follow-up is a useful tool for the identification of patients at risk of death.

Introduction

Budd-Chiari Syndrome (BCS) is a challenging disease entity resulting from an outflow obstruction at the level of the hepatic veins or the inferior vena cava [1]. It occurs in the context of a variety of disorders, the majority thrombogenic in origin, of which the most important ones include myeloproliferative diseases and genetic prothrombotic mutations, such as Factor V Leiden, prothrombine gene mutation and, more recently, the JAK2 mutation [2-4]. The classical presentation includes ascites, hepatomegaly and abdominal pain, but many variations in symptoms and the severity exist.

The clinical course of BCS is profoundly heterogeneous and to a large extent unpredictable. A handful of retrospective follow-up studies have reported that mortality is highest in the first 2 years after diagnosis [5-9], but none have evaluated specifically what determines early mortality. Considering the rarity of BCS (in one study, incidence is was found to be 1 per 2.5 million [10]), these retrospective reviews spanned many years and therefore did not assess survival within shorter time intervals (such as the first few months after diagnosis). Therefore, it is unknown whether there are differences between early and late mortality.

In a previous attempt to classify the prognosis of patients with BCS in a meaningful way, a large multicenter retrospective study was performed with 237 patients in 2004 [6]. This resulted in a prognostic index, composed of ascites, encephalopathy, bilirubin and prothrombin time, later referred to as the Rotterdam BCS index [11]. In the disease-specific prediction of mortality, it appeared superior to the MELD score [11]. However, the index has never been externally validated in an independent patient population.

Therefore, we aimed to determine the most crucial time in the natural history of BCS and to investigate the external validity of the Rotterdam BCS index to identify high-risk patients. This study was conducted as part of the first prospective observational follow-up study of 163 incident patients with BSC in nine European countries, entitled EN-Vie (European Network for Vascular Disorders of the liver).

Methods

Study design, patient population, data collection

The present study was a prospective, international follow-up study of incident patients with Budd-Chiari Syndrome (BCS). Diagnosis was restricted to the currently used definition of BCS [1], which was confirmed radiographically, and in patients older than 16 years of age. Enrolment occurred between October 2003 and October 2005 and follow-up was from date of diagnosis until May 2006 (study closure) or death. Details on study design and hospital participation are extensively described elsewhere [12]. In summary, a total of 210 patients were identified nationwide in 30 academic and 9 regional hospitals in France, Spain, the Netherlands, Great Britain, Germany, Italy, Belgium, Portugal and Switzerland. After exclusion of 47 patients (reasons: date of diagnosis fell outside the study period (n=16); incorrect diagnosis of BCS (n=14); underlying hepatobiliary malignancy (n=7); and others (n=10)), a total number of 163 eligible patients were used for analysis.

Data collection occurred at date of diagnosis (i.e. baseline) and during follow-up at regular time intervals (including week 1, 2, 3, 4, and month 2, 3, 6, 9, 12, 18 and 24), at death, end of follow-up, and at significant intermediate clinical events (i.e. clinical deterioration, new radiological imaging, or initiation of a new intervention).

All data were obtained by a systematic review of the medical charts and reported on a uniform, standardized clinical record form (CRF) by one single investigator per country. All CRF's underwent multiple cycles of data verification, review, correction and re-review, to ensure validity of the data inserted in the database. Data collected at each visit included patient symptoms, physical findings, laboratory and radiographic data, type and outcome of interventions, and mortality.

The Rotterdam BCS index

Prior to the current study, a collaborative project was executed between Erasmus Medical Center (Rotterdam, the Netherlands), Hopital Beaujon (Clichy, France) and the Mayo Clinic (Rochester, MN, USA) in which 237 patients were analysed in a retrospective fashion to identify predictors of long-term (median 44 months) survival. Eventually, the following prognostic index was created: RBI = 1.27 x encephalopathy + 1.04 x ascites + 0.72 x Prothrombin time + 0.004 x bilirubin level [6]. Encephalopathy and ascites were scored as 1 (present) or 0 (absent), and prothrombin time measured in INR as equal to or lower than 2.3 (0) or higher than 2.3 (1). The score calculated for a relatively healthy patient, with no ascites or encephalopathy, INR ≤ 2.3 and bilirubin levels within normal limits (i.e. 17 μmol/l), would be 0.07. This index was later referred to as the Rotterdam BCS index [11] (RBI).

In the current study, we assessed the RBI score for each patient at diagnosis and at study intervals, if clinical data were present. Also, we recalculated the index score by combining the individual results of the index variables, to ensure that the manually inserted scores were correct. If data on variables were missing at diagnosis, imputation was done by taking the first available results (i.e. first observation carried forward; usually that of the next CRF at week 1).

Statistical analyses

The primary outcome of interest was mortality. Patients, who were lost to follow-up before study closure or death, were censored at date of last visit. Temporal patterns in mortality were assessed to determine what the most crucial time in the natural history of patients with BCS is, subsequently defined as '*early mortality*'. Comparison between patients who died during that early period, and patients who survived, were based on Chi-square testing (for categorical variables) and Mann-Whitney-U testing (for non-parametric continuous variables). Patients who were lost to follow-up prior to completion of that period were excluded from analysis. The validity of the RBI in predicting early mortality was measured by the area under the Receiver Operating Characteristic (ROC) Curve, as expressed in the concordance (c-) statistic [13]. The c-statistic ranges from 0 to 1, in which a value of 0.5 equals chance, a value above 0.7 represents a reliable model, and a value above 0.8 equals an excellent model. Variables, not represented by the RBI and found to be significantly different among survivors and non-survivors, were added one by one to the RBI in a multivariate Cox proportional hazards regression analysis. Beta-coefficients of the significant variables were used to calculate the relative weights of these variables and added to the RBI. Survival rates were calculated with the Kaplan Meier method and compared through log rank testing.

The level of statistical significance was set at $P<0.05$. All statistical analyses were conducted in SPSS (version 14.0.0, Chicago, IL, USA).

Results

What is the most important period in the natural history of BCS?

Of the total 163 patients with a median follow-up of 17.1 months (range 0.1-31), 29 patients (18%) died within a median of 5.5 months after diagnosis (range 0.1-26.3). Overall survival rates were 90% (95%CI 85-94) at 6 months, 87% (95% CI 82-93) at 12 months and 82% (95% CI 75-88) at 24 months.

During follow-up, 20 patients (12%) underwent OLT with a median of 1.7 months (range 0.1-23.5) and 56 patients (34%) underwent TIPS placement with a median of 0.8 months (range 0-21.1) after diagnosis. Plotting the frequency of these significant events (i.e. TIPS, OLT and death) against time revealed that the majority of these events took place within the first 2 months (69%, 55% and 41%, respectively; figure 1). Thus, the first 2 months was the most crucial period in the disease course of BCS.

Figure 1

Temporal patterns of mortality (total n=29), liver transplantation (total n=20) and TIPS procedures (total n=56). Results are expressed per percentage of totals.

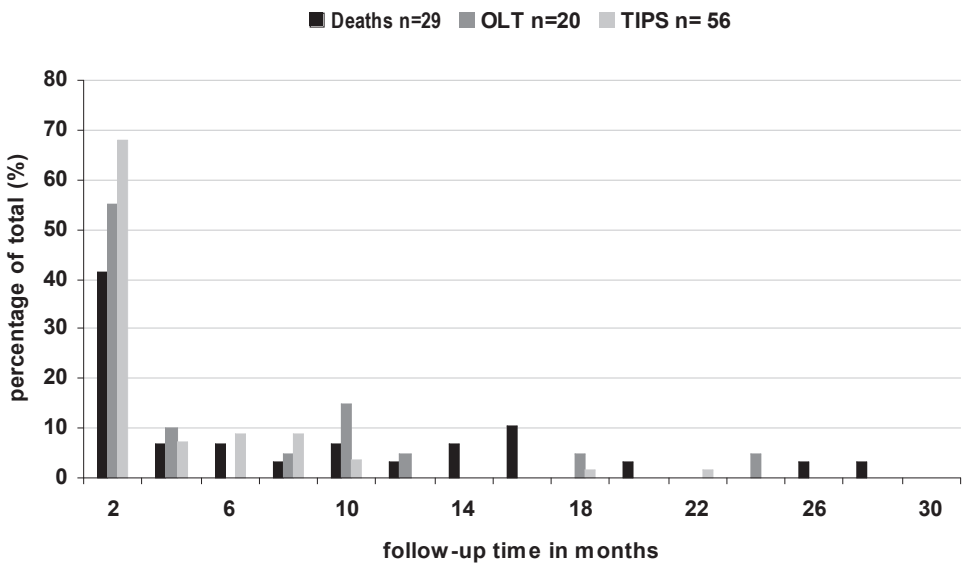


Table 1

Comparison of baseline characteristics and interventions between patients who died within the first 2 months (n=12) and patients who survived the first 2 months (n=147). Patients who were lost to follow-up (n=4) are not included in the analysis. P-values are based on Chi-square testing for categorical variables and Mann-Whitney U testing for continuous variables. Numbers represent actual numbers (%) for categorical variables and median values (range) for continuous variables.*

Characteristic	Early death (n=12)	Survivors (147)	P-value
Demographics			
Sex (female)	5 (42)	87 (59)	0.24
Age at diagnosis*	53 (33-71)	36 (16-84)	<0.001
Clinical data			
Onset of symptoms			#
- < 6 months	12 (100)	23 (16)	
- ≥ 6 months	0 (0)	122 (83)	
Ascites	12 (100)	119 (81)	#
Hepatic encephalopathy	5 (42)	9 (6)	<0.001
Gastro-intestinal bleed	0 (0)	8 (5)	#
Hepatorenal syndrome	4 (33)	6 (4)	<0.001
Asymptomatic at diagnosis	0 (0)	5 (3)	#
Radiographic data			
Type of BCS:			0.39
- isolated HV occlusion	5 (42)	73 (50)	
- isolated IVC occlusion	1(8)	3 (2)	
- combined HV and IVC	6 (50)	71 (48)	
Splanchic vein (i.e. PV/SMV/SV) involvement	4 (33)	26 (18)	0.18
Collaterals formation	5 (42)	67 (46)	0.79
Laboratory data			
Bilirubin (μmol/l)*	82 (5-286)	30 (6-325)	0.001
INR*	2.0 (1.2-3.4)	1.4 (1.0-10.9)	0.003
ALT (ULN)*	13.6 (0.4-128.3)	1.2 (0.3-294.4)	0.02
Albumin (g/l)*	32 (17-36)	34 (16-53)	0.03
Creatinine (μmol/l)*	124 (44-535)	79 (36-589)	0.03
Prognostic data			
Rotterdam BCS index score*	2.00 (1.06-3.45)	1.15 (0.02-3.57)	<0.001
Treatment data			
Anticoagulation	7 (58)	119 (81)	0.06
Percutaneous Transluminal angioplasty (PTA)	0 (0)	12 (8)	#
Thrombolysis	0 (0)	12 (8)	#
Surgical shunting	1 (8)	2 (1)	0.09
Transjugular Intrahepatic Portosystemic Shunting (TIPS)	2 (17)	35 (24)	0.57
Liver transplantation	1 (8)	9 (6)	0.76

Abbreviations: 'HV' Hepatic Veins; 'IVC' Inferior Vena Cava; 'PV' Portal Vein; 'SMV' Superior Mesenteric Vein; 'SV' Splenic Vein; 'INR" International Normalized Ratio (unit for Prothrombin time).

Statistical comparison is not valid because of null cells.

What are the differences between patients who died in the first 2 months and those who survived?

We compared baseline characteristics, clinical and biochemical parameters, as well as treatment modalities between patients who died within the first 2 months (n=12; 7%) and patients who survived the first 2 months (n=147; 90%). We excluded 4 patients who were lost to follow-up before 2 months. This is presented in table 1. Statistical comparison of both groups showed that patients who died early were significantly older ($p<0.001$), had significantly more often encephalopathy ($p<0.001$) and hepatorenal syndrome ($p<0.001$) at diagnosis and laboratory testing showed higher levels of bilirubin ($p=0.001$), INR ($p=0.003$), ALT ($p=0.02$) and creatinine ($p=0.03$) and significantly lower levels of albumin ($p=0.03$). Also, all patients who died early had ascites at presentation and were diagnosed within 6 months of onset of symptoms. None were asymptomatic at presentation or had a GI bleed. Interestingly, there were no significant differences in treatment modalities, although none of the patients with early mortality received thrombolysis or a percutaneous transluminal angioplasty. Finally, the baseline RBI score, obtained for 158 (99%) eligible patients, was significantly higher in the group with early mortality ($p<0.001$). We also assessed the RBI score at time of death (n=12) and compared this to the RBI obtained at 2-month follow-up for the patients who survived. The latter was available for 125 patients (85%) within a median follow-up time of 46 days (range 4-65). The median RBI score was 3.48 (range 1.05-5.65) at time of death. In contrast, the median RBI score in patients who survived the first 2 months was 1.13 (range 0.02-3.10; $p <0.001$).

Causes of death were liver failure (n=7), GI bleed (n=1), sepsis (n=1), post-operative multiorgan failure (n=1; after OLT) and cardiopulmonary failure (n=1). One patient, only started on anticoagulation, died after 6 days of unknown reasons and no autopsy was available.

How well is the RBI at diagnosis able to discriminate between patients who are at high risk and those who are at lower risk for early mortality and can its validity be further improved by addition of other variables?

The ROC curve for the RBI to predict 2-month mortality in 158 patients is shown in figure 2a. The C-statistic of the model was 0.84 (95% CI 0.71-0.97), thereby indicating that the RBI is a very reliable indicator for early mortality.

Of all those parameters found to be significantly different between patients who died and those who survived the first 2 months, only age, creatinine, ALT, albumin and hepatorenal syndrome were not represented by the RBI. Therefore, we added these variables one by one to the RBI in a multivariate Cox analysis of 2-month mortality. Addition of albumin ($p=0.26$), ALT ($p=0.33$) and hepatorenal syndrome ($p=0.95$) did not make an independent contribution to the RBI in the prediction of early mortality. However, both age ($p=0.003$) and creatinine ($p=0.03$) remained significantly associated with early mortality and this effect was independent of the RBI ($p<0.001$). Therefore, we added both variables to the RBI in the multivariate model presented in table 2.

Figure 2 a

Receiver Operating Characteristic (ROC) curve for) original Rotterdam BCS index to predict early mortality (n=12). This was calculated for 158 patients with BCS. C-statistic respresents area under the ROC curve.

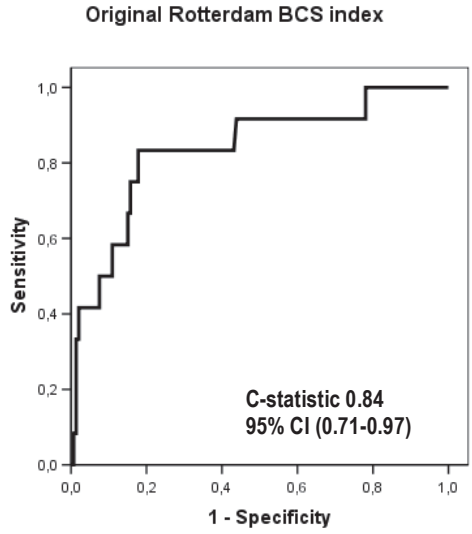


Table 2

Results from the multivariate Cox analysis with Rotterdam BCS index, age at diagnosis and creatinine levels at diagnosis for 158 patients with complete data. Results are per increments of 1 point (Rotterdam BCS index), 1 year (age) or 1 μmol/l (creatinine).

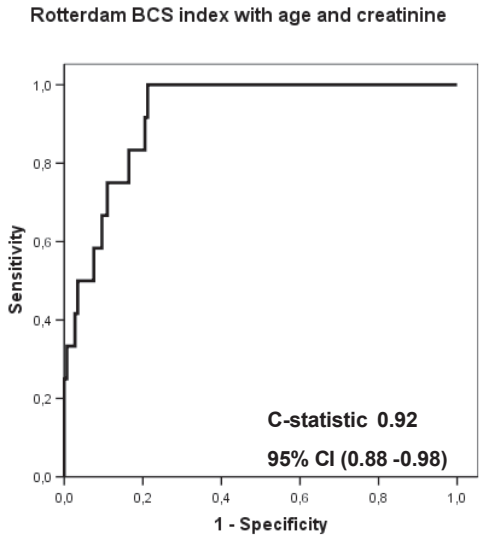
Variable	β coefficient	P-value	Hazard ratio	95% CI
Rotterdam BCS index	1.036	0.004	2.82	1.39 - 5.73
Age at diagnosis	0.068	0.001	1.07	1.03 - 1.12
Creatinine	0.007	0.006	1.002	1.00 - 1.01

Modified Rotterdam BCS index = RBI + 0.07 x age + 0.01 x creatinine

Based on the ratio of the beta-coefficients in this model, we calculated that for each year increase in age, the RBI score would be increased with 0.07 and for each μmol/l increase in creatinine levels, the score would increase by 0.007 points.
Therefore, the modified RBI equation is as follows:
1.27 x encephalopathy + 1.04 x ascites + 0.72 x Prothrombin time + 0.004 x bilirubin + 0.07 x age + 0.007 x creatinine.

The modified RBI had a median value of 4.6 (range 2.1-10.9). The ROC of this modified RBI is shown in figure 2b. The C-statistic of this model was found to be 0.92 (95% CI 0.88-0.98) and therefore this model dramatically improved the predictive value of the original RBI.

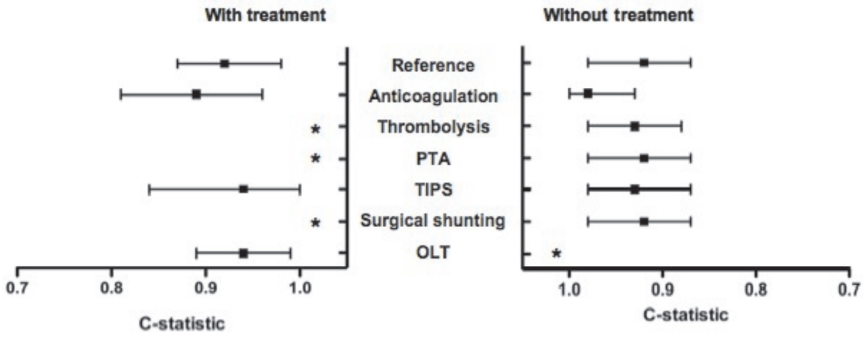
Figure 2b
Receiver Operating Characteristic (ROC) curve Rotterdam BCS index, including age and creatinine, to predict early mortality (n=12). This was calculated for 158 patients with BCS. C-statistic respresents area under the ROC curve.



Is the validity of the modified RBI to predict 2-month mortality biased by the type of treatment patients received early in their disease course?
We performed ROC analyses of the modified RBI, stratified for the type of treatment given. The results of all c-statistics in the strata are presented in figure 3. This showed that the c-statistic of the modified RBI was not dependent on the type of treatment patients received as all confidence intervals overlapped. As it can be seen in the figure, there were no deaths amongst patients receiving thrombolysis or PTA and there was only 1 death each in patients who underwent shunting or OLT, and therefore, ROC analysis could not be performed in these strata.

Figure 3

Area under the Receiver Operating Characteristic Curve (C-statistics with 95% CI) for prediction of 2 months mortality by the Modified Rotterdam BCS index, stratified by intervention. Asterisks (*) indicate that there were 1 or less events in the strata and therefore the C-statistic cannot be computed.



What is the relationship between the modified RBI score and mortality risks?

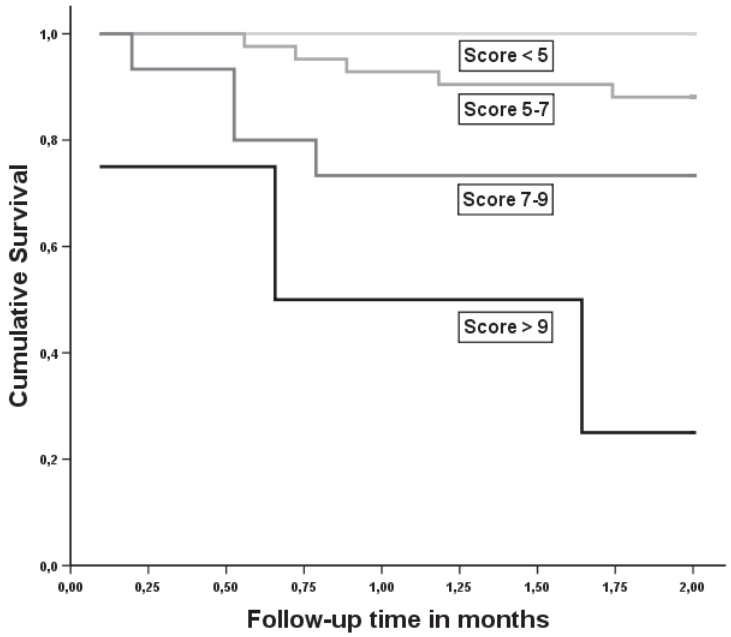
The median value for the modified RBI at diagnosis among patients who died in the first 2 months was 7.43 (range 5.74-10.89) in contrast to 4.46 in those who survived (range 2.14-9.10; p<0.001). The relationship between early mortality and the modified RBI score is represented by the Kaplan Meier curve in figure 4. Here, we found that a score of 5 or lower (n=97) indicated 100% 2-month survival; a score between 5 and 7 (n=42; n=5 deaths) was associated with a 2-month survival of 88% (95% CI 78%-98%); a score between 7 and 9 (n=15; n= 4 deaths) with 73% (95% CI 51%-96%); and a score above 9 (n=4; n=3 deaths) suggested very poor survival rate of 25% (95% CI 0%-66%; P_{trend}<0.001). Obviously, number of events per group is low.

Are there differences between patients who died in the first 2 months (i.e. early mortality) and those who died thereafter (i.e. late mortality)?

We compared the 12 patients who died early with the 17 patients who died later in the disease course of BCS (after a median of 12.4 months; range 2.5-26.3). Those who died later were of similar age (*P*=0.72) and sex distribution (*P*=0.98) as patients who died early. Also, there were no differences in radiographic characteristics (all *P*>>0.05). Alike early mortality, patients with late mortality all had ascites at diagnosis and none were asymptomatic. However, patients with late mortality had significant lower bilirubin (median 39.5; p=0.04), lower INR (median 1.6; p=0.07) and lower ALT levels (median 1.46; p=0.03). Interestingly, the RBI score was significantly lower in the late mortality group (median 1.2, range 1.11-2.26; p = 0.01). Causes of death in the late mortality group were liver failure (n=1), GI bleeding (n=1), post-operative multi-organ failure (n=1), cardiopulmonary failure (n=1), previous extra-hepatic malignancy (n=1) and new hepatobiliary malignancy (n=1). Four death causes did not fall in any of these categories, and for 7 patients the cause of death was unclear.

Figure 4

Kaplan Meier Survival Curve for the new Rotterdam BCS index, classified into score ≤ 5 (total n=97; n=0 deaths), score > 5 and ≤ 7 (total n=42; n= 5 deaths), score > 7 and ≤ 9 (total n=15; n= 4 deaths), and score >9 (total n=4; n=3 deaths). Excluded are patients who were lost to follow-up prior to 2 months (n=4). Comparison revealed P_{trend} <0.001; score < 5 versus all other scores (P<0.001); 5-7 versus > 9 (P<0.001); 7-9 versus > 9 (P=0.08); 5-7 versus 7-9 (P=0.13).



Can the modified RBI also predict late mortality?

We selected all patients who survived the first 2 months (n=147). Of these, 122 patients (83%) had data on the RBI score between 40 and 100 days after diagnosis. We subsequently recalculated age at time of collection of the RBI and obtained creatinine values (available for n=124) to calculate the modified RBI score. This was available for 121 patients. In these, 15 patients died after 2 months (thus 2 deaths were excluded from the analyses because of missing RBI data). The ROC analysis of this modified RBI to predict late mortality showed a c-statistic of 0.78 (95% CI 0.66-0.89). This suggests that although the modified RBI was much stronger in the prediction of early mortality, scores obtained after the initial crucial time can still be used to reliably predict late mortality.

Discussion

This first prospective international observational study shows that the most crucial time in the disease course of patients with Budd-Chiari Syndrome is the first 2 months after diagnosis. During these months, patients have the highest risk of mortality, and receive most of their treatments. Early mortality was associated with a higher RBI score. The validity of the RBI in predicting early mortality was excellent, but improved further with the addition of age and creatinine to the model. This modified RBI not only predicted early mortality with high accuracy, but the effect was also found to be independent on treatment. Finally, the modified RBI appeared also a valid tool to predict late mortality when obtained later during the follow-up.

Mortality in BCS was generally described in previous retrospective series to be highest within the first two years after diagnosis [5-9]. Indeed, most of these studies have analysed long-term survival and presented mortality data with 2-, 3- or 5-year increments. The current prospective study therefore was founded on these observations and was designed to follow patients over a 2,5 years period after diagnosis. However, as our results show, it is actually the first 2 months that are of crucial importance. This is a new finding that has not been adequately described previously. Interestingly, we found significant differences in clinical and biological parameters between patients who survived and those who died during the first 2 months. It appears that ascites, encephalopathy, hepatorenal syndrome, elevated bilirubin, creatinine, ALT and INR and lowered albumin levels were more prevalent in the patients who died early. This is largely consistent with the prognostic predictors found in the aforementioned studies [6-8].

The original RBI, derived from our previous retrospective study [6], appeared an excellent tool to predict early mortality in this independent prospective study (c-statistic 0.84). Not only was the RBI score significantly higher in the group with early mortality, also the RBI continued to climb in this group, whereas it remained stable during the 2-month follow-up for the survivors. We were able to improve the performance of the RBI further by the addition of new independent predictors of mortality: age and creatinine. Both are known survival determinants [8]. Since we found that increase in c-statistic from 0.84 to 0.92 clinically relevant, we decided to continue further analysis with this modified RBI. Although number of deaths in each score group was low, and statistical significance could not always be obtained, it appeared that patients with a score lower than 5 were all alive at 2 months, whereas 2-month survival rates declined as scores became higher (i.e. 88% for score 5-7 versus 73% for 7-9 versus 25% for score higher than 9).

The clinical applicability of this modified RBI becomes evident as one considers that in this study, only 1 patient of those twelve who died had received a liver transplant. Obviously, treatment decisions in the current observational study were not randomized nor dictated by the investigators and were therefore dependent on the local expertise, preference, and availability of the several modalities. The median modified RBI score at diagnosis of those who died within the first 2 months, was 7.53 (range 5.7-10.9). One can therefore argue that if at the time of diagnosis it was known that these patients were at high risks of early mortality, liver transplantation might have been considered earlier, leading potentially to a better outcome (10-year post transplantation is 68%-83% [14, 15]).

Comparison between early and late mortality taught us that there are certain characteristics which are shared by all patients who died, early or late. All had ascites, none was asymptomatic and all were of high age (above 50) and had poor renal function. However, the patients who died late differ from those who died early by lower laboratory levels (e.g. bilirubin, INR, and ALT) as well as RBI scores, which were actually within the same range as the 2-month survivors. Another observation was that although some data was missing on death causes, the majority of early mortality was liver-disease related while the late mortality had a more heterogeneous mix of causes. Obviously, these abovementioned variables were collected at diagnosis, and thus are subject to change during follow-up. However, a score such as the RBI can be obtained at any time and we have shown that the RBI at 2 months is still of predictive value for late mortality (c-statistic = 0.78).

One can question why use this RBI and why not use other models in the prediction of BCS? Traditionally, the Child-Pugh score [16], reflecting a stepwise severity scale of ascites, hepatic encephalopathy, prothrombin time, bilirubin and albumin levels, has been used as a general indicator of liver disease severity. Although designed for cirrhosis, in earlier days it was also used in the prognostication of BCS. Major limitations however include the ceiling effect of using categorized laboratory values, its design for cirrhosis patients, and the fact that the respective variable weights were not statistically driven, but rather arbitrary chosen. The currently most used general measure of liver dysfunction is the MELD score, which reflects bilirubin, creatinine and INR levels [17, 18]. It has been validated in a variety of cirrhotic liver diseases and is nowadays the primary tool for liver transplant allocation in the USA [19]. However, in our previous study, we have compared the RBI scoring system with that of MELD and shown that MELD performs suboptimal in patients with BCS [11]. Finally, Zeitoun et al. had identified four prognostic parameters in a population of 85 patients and created a prognostic model, nowadays known as the Clichy risk score [8]. This score includes information on age, serum creatinine, response of ascites to treatment, and the Child-Pugh score. By summing individual scores, patients were classified into an excellent prognostic class (i.e. PI ≤ 5.4) or a poor prognostic class (i.e. PI >5.4), with 5-year survival rates of 95% and 62%, respectively. Later, another component was added to this risk score; the so-called clinicopathological form, which reflected a worse outcome for those patients with an 'acute-on-chronic' presentation [20]. The major drawbacks of this model include the fact that it cannot be assessed at diagnosis, since the ascites variable is treatment-dependent, and the use of histological parameters (sampling errors are common in BCS [7]). In contrast, the RBI is a simple tool, readily available at diagnosis and thereafter, specifically designed, and now externally validated, in patients with BCS, and able to predict early as well as late mortality, depending on when it is measured. We therefore believe that the RBI has a place in daily clinical practice, not only to aid in the identification of high-risk patients, but also in the triage of therapies.

Our study has several limitations. First, although it was prospectively performed, it still is an observational study. As a result there were limitations to how much data we could collect. We were dependent on local physicians to comply with our general recommendations for follow-up intervals, as well as the quality of the hospital data systems to record data. Also, we could not interfere in therapeutic decision-making. However, often regarded as a limitation, well-executed prospective studies are not always suboptimal compared to randomized clinical trials [21]. Another advantage of observational studies is that it is able to describe the clinical course of a disease

within the complexity of daily practice, rather than within an artificially sub-selection of patients and conditions. Furthermore, considering the rarity of BCS, randomization of any sort is practically not feasible. The second limitation is related to the fact that overall the mortality rate of BCS in our study is low; only 29 of 163 patients died (18%). This led to statistical limitations in comparative analyses, but did not interfere with the c-statistic, since that is independent on the frequency of outcomes. The fact that overall survival in patients with BCS has increased over the last few decades has ben described previously and this has been attributed to the generalized use of anticoagulation [8]. To obtain more events, longer follow-up would be needed, although the yield is doubtful, since we showed that after the initial 2 months the mortality rate per year significantly declined with time. The third limitation is the amount of missing clinical data, including causes of death. Despite our extensive data quality validation system in which data were only inserted in the database after multiple queries, this however remains an inherent problem of observational studies.

In conclusion, in this first prospective multinational observational study, we found the first 2 months to be the most crucial time in the disease course of patients with BCS. Early mortality was associated with a higher RBI score. The modified RBI, including ascites, encephalopathy, bilirubin, prothrombin time, age and creatinine, appeared an excellent tool to predict early mortality. Even if obtained later during follow-up, the model was able to adequately predict late mortality. This could be of major clinical importance in both the identification of high-risk patients as well as triaging of treatments in patients with BCS.

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Pathogenesis and Treatment of Budd-Chiari Syndrome combined with Portal Vein Thrombosis

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Abstract

Objectives

Combined Budd-Chiari Syndrome and Portal Vein Thrombosis (BCS-PVT) is a challenging clinical condition with as yet unknown outcome. The aim of the present study was to investigate aetiology, treatment options and prognosis of patients with BCS-PVT.

Methods

Patients, diagnosed with non-malignant BCS between 1984 and 2001, were identified in a large international study, and classified into isolated BCS (n=204), BCS-PVT without spleno-mesenteric vein thrombosis (SMVT; n=15) and BCS-PVT with SMVT (n=18).

Results

Multifactorial aetiology was present in 58% of patients with combined BCS-PVT. Number of etiological factors increased significantly with the extent of thrombosis (p=0.002). Main treatment options included anticoagulation and portosystemic shunting, of which extended TIPS showed the most beneficial results. Five-year survival was 59% (95% CI 39-80%) in BCS-PVT versus 85% (95% CI 76-88%) in isolated BCS (p=0.11). Survival tended to be worse in BCS-PVT patients with SMVT as compared to patients without SMVT (RR=3.47, p=0.11).

Conclusions

In BCS, extension of thrombosis into the splanchnic venous bed was significantly related to the number of etiological factors, and was associated with poor outcome. These results strongly support a liberal use of anticoagulants, which so far had been widely debated. Alternatively, derivative shunt procedures appear difficult, yet not impossible.

Introduction

Budd-Chiari syndrome (BCS) is characterised by hepatic venous outflow obstruction located at the level of the small hepatic veins up to the junction of the inferior vena cava with the right atrium (1, 2). The occlusion of the veins, mostly caused by a thrombosis, leads to increased sinusoidal pressure and ischemic necrosis. When symptomatic, BCS is characterised by abdominal pain, ascites, hepatomegaly and, in case of massive necrosis, acute liver failure (3). Hereditary, as well as acquired thrombophilia, have been identified as etiological factors in a majority of patients and combinations of risk factors are common (4-6).

Extrahepatic portal vein thrombosis (PVT) is characterised by thrombotic occlusion in the main, left or right portal vein. Portal hypertension with bleeding from esophageal varices is the predominant clinical manifestation. Similar to BCS, underlying thrombophilia is usually present. However, unlike BCS, local risk factors and decreased flow also play an important role (7, 8). The management of PVT is usually confined to prevention and treatment of variceal bleeding by beta blocking agents and endoscopic therapy.

In at least 50% of explant livers after transplantation for severe BCS, histological signs of intrahepatic obstructive portal venopathy have been found (9). The presence of acute thrombi in the intrahepatic portal branches was associated with parenchymal infarcts and a short pre-transplant course, thereby indicating subfulminant liver disease. The development of PVT in patients with hepatic outflow obstruction was suggested to be caused by a combination of underlying thrombophilia and reduced portal flow (9, 10).

As yet, little is known about the aetiology, clinical course and management of these patients with combined pathology. It is hypothesized that in BCS, extension of thrombosis in other splanchnic veins is more frequently associated with severe and complex thrombophilic aetiology, and that the prognosis of patients with combined BCS-PVT is worse than patients with isolated BCS. Therefore, the aim of the present study was to investigate aetiology, treatment options and prognosis of patients with BCS-PVT and to compare them with patients with isolated BCS.

Methods

Patients

Consecutive patients diagnosed with BCS between January 1984 and January 2001 were identified by means of a search in computerised diagnosis registration systems of all eight academic hospitals in the Netherlands, the Mayo Clinic (Rochester, MN) in the USA and Hôpital Beaujon (Clichy) and Hôpital Louis Mourier (AP-HP, Colombes) in France. The participating hospitals all serve as tertiary referral centers and part of the study population from France (11) and the USA (12) has been described previously. Key words, used to identify patients included: Budd-Chiari syndrome, hepatic outflow obstruction, hepatic vein thrombosis, vascular liver disease, hepatic vein and inferior vena cava. The current definition of BCS was used (1). Diagnosis was based on characteristic features at Doppler Ultrasound, computerised tomography (CT), magnetic resonance imaging (MRI) or venography. The total study population has been described in more detail previously (13). Additional data has been collected for the purpose of the current study.

All medical records and radiology reports present at time of diagnosis of BCS were examined to find patients with concurrent PVT. PVT was defined as partial or complete occlusion of the extra-hepatic portal vein, and the diagnosis was established by radiological imaging modalities.

Clinical data

Predefined clinical data at the time of diagnosis were collected by a standardised review of medical charts by two of the authors (HJ and SDM) and uniform structured data forms were completed. These clinical data included data on patient demographics, clinical symptoms and signs, laboratory values and location of thrombosis. The Child-Pugh score, as well the Rotterdam prognostic score were assessed for all patients with complete data on the corresponding variables. The Rotterdam score was recently developed by our group to classify patients at baseline into good (class I), intermediate (II) and poor (III) prognostic classes according the following formula: *1.27*encephalopathy + 1.04*ascites + 0.72*prothrombin time + 0.004*bilirubin* (13).

Search for etiological factors included: hereditary thrombophilia (i.e. Factor V Leiden mutation, prothrombin gene mutation, and inherited deficiency for protein C, protein S or antithrombin), acquired hypercoagulability (i.e. myeloproliferative disorders, anticardiolipin antibodies, lupus anticoagulant antibodies, paroxysmal nocturnal haemoglobinurea, Behçet disease, use of oral contraceptives and pregnancy), local risk factors (abdominal infections, systemic inflammatory diseases, and abdominal or extra-abdominal surgery), case history of thrombosis and family history of thrombotic events or hereditary thrombophilia. Deficiencies of protein C, protein S and antithrombin were only considered primary when isolated, i.e. when the levels of other liver-dependent coagulation factors were normal; hence, liver dysfunction was ruled out as a cause for secondary deficiency. Myeloproliferative disorders were confirmed by bone marrow examination, and consequently only overt forms were included (14). Since all patients had BCS, we did not consider BCS or BCS-related cirrhosis as a local risk factor for PVT in our analyses. According to the location of the obstruction, patients with combined BCS-PVT were classified into two groups: patients with additional splenic and/or superior mesenteric vein thrombosis

(referred to as BCS-PVT with SMVT) and patients without SMVT (referred to as BCS-PVT without SMVT).

Statistics

In this cohort study, all patients were followed from date of diagnosis until death, study closure (January 1st, 2001) or, in case of loss to follow-up, the date of last visit. Survival was calculated by means of the Kaplan Meier method and the log rank test was used for comparison between groups. Comparison of baseline characteristics was based on χ^2 tests (for categorical variables), and Mann-Whitney U tests or Kruskal-Wallis tests (for continuous variables). Cox regression analyses were employed to calculate relative hazard risks. Statistical significance was set at a p-value of 0.05 or less. All analyses were performed in SPSS for Windows, version 10.1.1 (SPSS, Chicago, IL, USA).

Results

In a total sample of 282 patients diagnosed with BCS between 1984 and 2001 (13), 42 patients (15%) with combined BCS-PVT were identified. Exclusion criteria were underlying malignancy (n=7), and also diagnosis at post-mortem examination since etiological investigations as well as follow-up data were not available (n=2). This left a total of 33 eligible patients, among which were 11 Dutch (33%), 15 American (46%) and 7 French (21%). There was no significant difference in survival between countries (p=.85).

Using the same in- and exclusion criteria, 204 patients with isolated BCS could be identified in the total sample. There were no significant differences in demographic characteristics, clinical manifestations, laboratory findings or prognostic indicators between patients with combined BCS-PVT (n=33) and patients with isolated BCS (n=204) at the time of diagnosis (table 1).

Clinical manifestations

Median age at diagnosis was 37 years (range 18-76) and 70% was female. The main clinical symptoms and laboratory results for combined BCS-PVT are presented in table 1. There were 4 asymptomatic patients. Only 3 patients (9%) presented with variceal haemorrhage as a result of portal hypertension. Sequelae of hypersplenism (thrombocytopenia and/ or leucopenia) were present in 9 patients (27%). Median Child-Pugh score was 8 (range 5-12) in 28 and median Rotterdam prognostic score was 1.16 (range 0.02-3.37) in 30 patients with complete data.

Characteristics of the obstruction

All patients with BCS-PVT had occlusion of the hepatic veins and the portal vein. The portal vein was occluded completely in 28 patients (82%) and partially in 5 (18%). Eleven patients (33%) also exhibited thrombosis of the inferior vena cava. Eighteen patients (55%) showed additional thrombosis in the splenic vein (n=8), superior mesenteric vein (n=2) or both (n=8), and were subsequently classified as BCS-PVT with SMVT. There were 15 patients without SMVT (45%).

Table 1

Baseline factors, present at time of diagnosis in patients with combined BCS-PVT (n=33) and isolated BCS (n=204). P-values are derived from the χ^2 test (for categorical variables) or the Mann-Whitney U test (for continuous variables).

Baseline characteristics	BCS-PVT	Isolated BCS	p-value
Demographics (%)			
Age[a]	37 (18-76)	34 (13-76)	.62
Male/female	10/23 (30/70)	68/136 (33/67)	.73
Country:			.09
The Netherlands	11 (33)	62 (30)	
United States	15 (46)	61 (30)	
France	7 (21)	81 (40)	
Clinical manifestations (%)			
Ascites	28 (85)	171 (84)	.88
Hepatomegaly	26 (79)	155 (79)	.97
Splenomegaly	18 (55)	102 (53)	.86
Variceal bleeding	3 (9)	16 (8)	.81
Encephalopathy	3 (9)	21 (10)	.83
Laboratory findings[a]			
Albumin (g/l)	33 (19-57)	34 (13-54)	.95
ALT (xULN)[b]	1.0 (0.1-21.0)	1.0 (0.1-86,7)	.95
Bilirubin (μmol/l)	29 (5-149)	27 (3-301)	.82
Alkaline phosphatase (xULN)[b]	1.1 (0.4-3.1)	1.2 (0.3-16.3)	.18
Platelet count (x10E9/l)	291 (42-652)	224 (10-896)	.22
Haemoglobin (mmol/l)	7.9 (4.1-11.2)	8.2 (3.5-13.0)	.34
Sodium (mmol/l)	137 (124-145)	137 (121-145)	.95
Creatinin (μmol/l)	71 (44-469)	80 (35-393)	.13
Prothrombin time (%)[c]			.64
INR ≤ 1.7	21 (68)	108 (60)	
INR 1.8-2.3	4 (13)	35 (19)	
INR > 2.3	6 (19)	37 (21)	
Prognostic indicators (%)[d]			
Child Pugh Score			.38
Class A	7 (27)	38 (23)	
Class B	16 (62)	88 (53)	
Class C	3 (11)	39 (24)	
Rotterdam prognostic classification			.32
Class I	10 (33)	45 (26)	
Class II	10 (33)	85 (48)	
Class III	10 (33)	45 (26)	

[a] Median (range)

[b] ULN= Upper limits of normal value; corrected for inter-center variation in normal values.

[c] In the French sample, the Quick-time was used as a measure for the prothrombin time. A Quick time value between 100 and 54 was assumed to be equal to an INR ≤ 1.7, 54-44 % to an INR 1.8-2.3, and 44% and lower to an INR > 2.3.

[d] The Child-Pugh score and the Rotterdam prognostic classification could only be calculated for patients with complete data on the corresponding factors (n=26, and n=30, respectively).

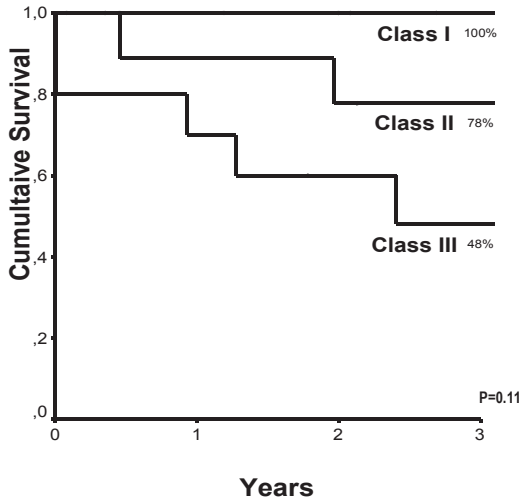
Survival

Median follow-up was 32 months (range 2 days- 184 months) and 10 patients died (30%), of whom 6 in the first 2 years. Median survival was 19 months and median age at death was 47 years (range 25-76). Overall, 1-, 3- and 5-year survival rates were 87% (95% CI 75-99%), 75% (95% CI 59-91%) and 59% (95% CI 39-80%), respectively. According to the Rotterdam prognostic score, 3-year survival rates were 100% (all alive) for class I, 78% (95% CI 51-100%) for class II and 48% (95% CI 33-63%) for class III (p=0.11; figure 1). The hazard of death increased nearly twofold per each class (RR=1.96, 95% CI 0.83-4.67).

Patients with combined BCS-PVT tended to have worse prognosis than patients with isolated BCS (RR=1.73; 95% CI 0.87-3.46), but this trend was not statistically significant (p=0.11). Five-year survival was 59% (95% CI 39-80%) and 85% (95% CI 76-88%), respectively (p=0.11, figure 2a). Patients with additional SMVT showed a trend towards lowered survival, as compared to patients without SMVT (RR=3.47, p=0.11). Number of deaths was 8 (44%) and 2 (13%), and 5-year survival was 48% (95% CI 22-74%) and 76% (95% CI 45-100%), respectively (p=0.09; figure 2b).

Figure 1

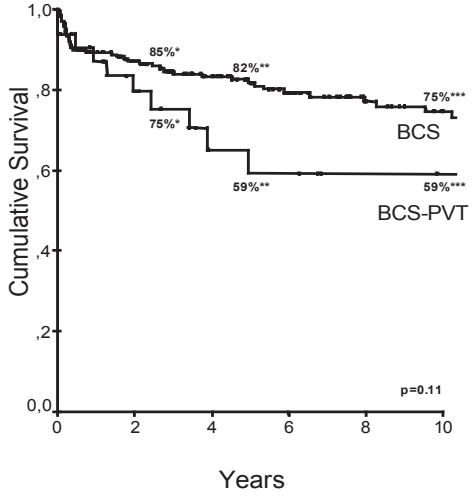
Survival for class I (n=10), class II (n=10) and class III (n=10) of the Rotterdam prognostic classification. Numbers represent 3-year survival rates.



Numbers at risk				
Class I	10	8	6	4
Class II	10	8	7	6
Class III	10	7	5	4

Figure 2a

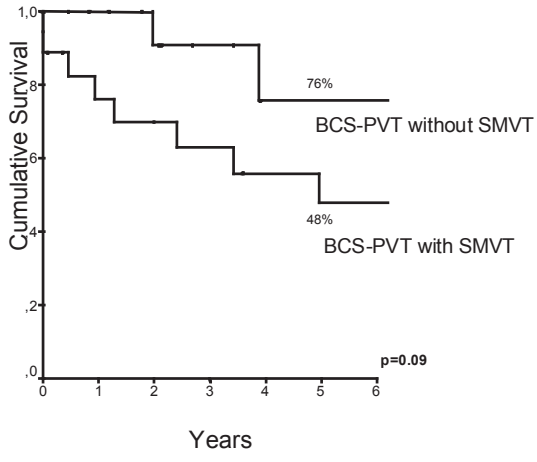
Overall survival in patients with isolated BCS (n=204) and patients with combined BCS-PVT (n=33). Numbers represent survival rates at 3-year (*), 5-year (**) and 10-years (***).



Numbers at risk						
Isolated BCS	203	149	119	91	65	54
BCS-PVT	33	21	11	10	7	6

Figure 2b

Survival analysis for patients with combined BCS-PVT without spleno-mesenteric vein thrombosis (SMVT; n=15) and patients with BCS-PVT with SMVT (n=18). Numbers represent 5-year survival rates.



Numbers at risk							
BCS-PVT without SMVT	15	13	10	7	4	4	4
BCS-PVT with SMVT	18	12	10	9	7	7	6

Aetiology

In combined BCS-PVT, aetiology was unknown in 8 (24%), unifactorial in 6 (18%) and multifactorial in 19 patients (58%). Systemic hypercoagulability was present in 64% (hereditary: n=4, acquired: n=14; combined n=3). In 3 patients, only local precipitating factors were present (9%). A combination of an underlying systemic etiological factor superimposed by a local factor was present in 9 patients (27%). The prevalence of etiological factors is presented in table 2.

The number of etiological factors differed significantly between patients with isolated BCS, BCS-PVT without SMVT and BCS-PVT with SMVT and increased stepwise as thrombosis was more extended (p=0.002). Median number of etiological factors was 1.0 (0-95th percentile 0-4), 2.0 (0-95th percentile 0-3) and 3.0 (0-95th percentile 0-7), respectively (p=0.05). Multifactorial aetiology, defined as presence of two or more risk factors, was present in 38% of patients with isolated BCS, 53% in patients with BCS-PVT without SMVT and 61% in patients with BCS-PVT with SMVT (p=0.08, figure 3).

Table 2

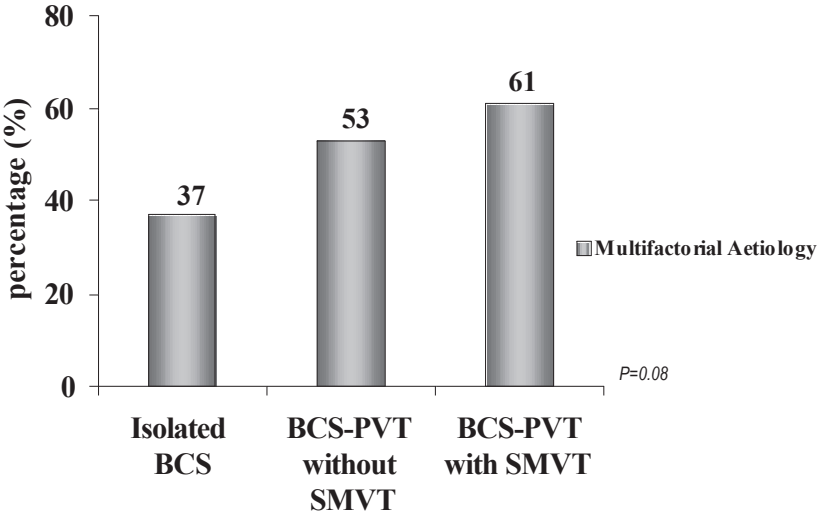
Prevalence of etiological factors in 33 patients with combined BCS-PVT. Patients can have more than one risk factor.

Etiological factor	N	Specifications
Acquired thrombophilia	21	Polycythemia rubra vera (n=7), essential thrombocythosis (n=2), not-classified myeloproliferative disorder (n=1), anticardiolipin antibodies (n=1)[a], paroxysmal nocturnal hemoglobinurea (n=3), Behçet's disease (n=1), oral contraceptive use (n=5), pregnancy (n=1)
Hereditary Thrombophilia	15	Protein C deficiency (n=5), Protein S deficiency (n=1), Anti-thrombin deficiency (n=3), Factor V Leiden mutation (n=2)[a], Prothrombin gene mutation (n=4)[b]
Local risk factors[c]	15	Abdominal surgery (n= 7), abdominal infection (n=3), extra-abdominal surgery (n=2), Inflammatory Bowel Disease (n=2), polycystic liver disease (n=1)
Other risk factors	15	History of other thrombotic events (n=8), family history of thrombosis (n=4), family history of inherited thrombophilia (n=2), vasculitis (n=1)

[a] Number of patients tested: n=18
[b] Number of patients tested: n=9
[c] Excluding BCS or BCS-related cirrhosis as local risk factor

Figure 3

Multifactorial aetiology (i.e. 2 or more risk factors) in patients with isolated Budd-Chiari Syndrome (BCS; n=204), patients with combined BCS-PVT without SMVT (n=15) and patients with BCS-PVT with SMVT (n=18).



Therapy and Clinical Outcome

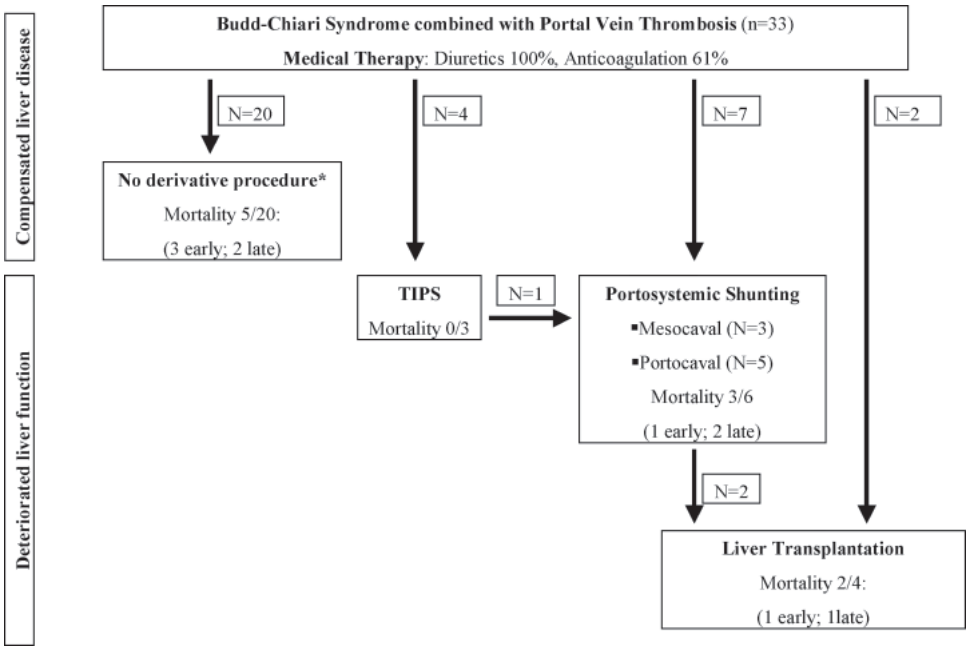
Treatment options and clinical outcome for BCS-PVT are summarised in figure 4.

Medical management

All patients received diuretics and/ or paracenthesis for control of their ascites. Anticoagulants were administered to 20 patients (61%). Reasons to refrain the other 13 patients from anticoagulation were: history of or presentation with upper variceal bleeding (n=3), spontaneous elevated INR (n=2), absence of underlying thrombophilia (n=4) and immediate start with invasive therapy (n=2). In 2 patients, only aspirin was given. Of 8 patients, treated solely with anticoagulants, 2 died of acute (1 day) and chronic (15 months) liver failure. In the medical treated group without anticoagulation, 1 patient died due to chronic liver failure after 4 years. In 12 patients (60%), anticoagulant therapy was combined with radiological or surgical procedures.

Figure 4

Treatment options and clinical outcome in 33 patients with BCS-PVT. Early deaths represent deaths within 30 days after the procedure.
This includes Leveen shunting (n=4, mortality 2/4) and partial hepatectomy (n=1, alive).



Transjugular intrahepatic portosystemic shunt (TIPS)

TIPS was performed in 4 patients (12%) with refractory ascites. To overcome the problem of inserting a TIPS in an occluded portal vein, the standard technique was extended by thrombolysis one day prior to TIPS (n=1) or balloon pull-through thrombectomy (n=2). These patients were alive and well at 4-43 months. In the fourth patient, the emergency TIPS was unsuccessful and a rescue surgical portocaval shunt procedure was attempted. Nevertheless, this patient died immediately after surgery of recurrent massive bleeding.

Surgical portosystemic shunting (PSS)

In all participating centers, the indication for PSS was intractable ascites and/or deteriorating liver function. PSS was performed in 7 patients as primary treatment. Of these, 3 received a mesocaval shunt; in 1 patient, the shunt occluded after a week and the patient died 2 months thereafter; a second patient died of liver failure after 28 months and the third patient survived up to 15 years. A side-to-side portocaval shunt could be attempted in 3 patients because of partial PVT and in 1 patient by performing peri-operative thrombectomy of the portal vein. Post-surgery, shunt occlusion occurred in 1 patient who subsequently underwent liver transplantation and died 1 week post-transplantation. Inferior vena cava thrombosis occurred in another patient, which was treated by percutaneous balloon angioplasty and stenting, followed by liver transplantation (alive and well at 132 months). The shunt remained patent in the other 2 patients, who were alive at 14 and 25 months of follow-up, respectively.

Orthotopic Liver Transplantation (OLT)

Two patients (6%) who presented with acute liver failure (Child Pugh score 12 and 8, and Rotterdam prognostic class III and II, respectively) went for primary OLT. Patency of the portal vein was restored by peri-operative thrombectomy in 1 patient and she was alive at 21 months after diagnosis. The other patient died due to graft failure after 40 months. As mentioned, OLT was performed as rescue treatment in 2 patients, of whom 1 died.

Other

A peritoneovenous shunt was carried out in 4 patients, of which 2 died. A partial hepatectomy was performed in 1 patient with BCS-PVT due to polycystic liver disease and this patient was alive at 32 months of follow-up.

Discussion

BCS and PVT both preclude the normal hepatopetal blood flow and result in an increase in vascular resistance and eventually portal hypertension. In BCS, this is usually manifested by hepatomegaly and ascites, while in PVT, most patients develop oesophageal and/or gastric varices, which may lead to massive gastrointestinal bleedings. Although BCS and PVT are considered separate disease entities, there is a considerable overlap in aetiology. In both disorders, hypercoagulability is a major predisposing factor. Yet, systemic risk factors predominate in BCS whereas local risk factors, e.g. cirrhosis, abdominal tumours, inflammatory diseases and surgery, predominate in the pathogenesis of PVT. Applying Virchow's triad for the development of thrombosis, a reduced portal flow in BCS, the presence of systemic hypercoagulability and injury of the vessel wall by adjacent structures may converge in the pathophysiology of combined BCS-PVT. To date, no longitudinal study has been able to unravel the complete pathogenic mechanism.

The present study describes the largest cohort of patients with combined BCS-PVT described so far. Ascites, abdominal distension and hepatosplenomegaly were mostly present, while liver tests were only mildly altered. In contrast to isolated PVT, in which variceal bleeding is the most common presenting symptom (15, 16), only 3 patients with BCS-PVT presented initially with upper GI bleeding. This can be explained by the fact that medical attention is driven by the more severe presentation of BCS, which is usually prominent before significant varices are formed.

Coexistence of multiple etiological factors was present in 58%. Previously, 26-28% of patients with BCS and 14-37% of patients with PVT were reported as having multiple risk factors (5, 6). Our finding may indicate that in combined BCS-PVT, the complex interaction between inherited, acquired and local predisposition is even more pronounced. Moreover, a striking finding in our study was that the number of etiological factors was significantly associated with the extension of thrombosis in the splanchnic bed ($p=0.002$).

Prognosis in patients with BCS-PVT was poor as compared to patients with isolated BCS (5-year survival 59% versus 85%). Likewise, prognosis in BCS-PVT with SMVT was worse than in BCS-PVT without SMVT (48% versus 76%). These results, although not statistically significant, suggest that survival is related to the extent of thrombosis. This trend is in line with findings from the only other clinical study on combined BCS-PVT, in which 5-year survival rates were 23% for 13 patients with BCS-PVT and 64% for 38 patients with isolated BCS (17). The even poorer outcome of those patients could partly be ascribed to selection of severe cases with signs of liver failure (encephalopathy was present in 46%), but also to the higher prevalence of thrombosis in the superior mesenteric or splenic vein (46%). The multicenter approach of our study and the longer follow-up period allowed a larger sample size, and a reflection of the current therapeutic standards.

Anticoagulation was administered to the majority of our patients. We could not assess the independent effect of anticoagulation on survival. However, the fact that extended thrombosis (i.e. BCS-PVT with SMVT) was associated with 1) a higher prevalence of thrombophilia and 2) a worse prognosis, suggests that anticoagulant therapy may be important not only to potentially recanalize the occluded vein, but also to prevent extension of thrombosis and hence, to reduce

mortality. This hypothesis is supported by data from several small retrospective series in BCS and PVT (18, 19). Condat et al. (18) showed that anticoagulation significantly reduced the risk of recurrent thrombosis, but did not increase the risk of upper variceal haemorrhage, thereby refuting the main argument to withhold anticoagulants. Furthermore, anticoagulation appeared to result in (partial) recanalisation in 93% (20). Although based on circumstantial evidence, we believe that anticoagulants should be administered to all patients with combined BCS-PVT, and in particular to patients with underlying thrombophilia.

TIPS was performed in 4 of our patients of whom only one died, after surgical shunting. Several modifications have been employed to overcome the technical difficulties associated with the presence of both hepatic and portal vein thrombosis. Patency was temporarily restored by local infusion of thrombolytic agents and balloon pull-through thrombectomy, recently also described in a few case-reports and small series (21-24). Although the numbers are limited, these findings suggest that portal vein thrombosis is not an absolute contraindication for TIPS and an extended TIPS procedure should be attempted as first line derivative treatment for patients who do not respond to medical therapy.

Surgical shunts, such as mesocaval and portocaval shunts, were attempted as initial treatment in 7 patients, of whom 3 died. In BCS, the role of PSS remains inconclusive. Two multivariate studies failed to show a beneficial effect on survival (11, 25) and in our own series, PSS only appeared beneficial for a subgroup of patients with intermediate prognosis (13). Therefore, we believe that surgical shunting should be used with caution.

In conclusion, prognosis in patients with combined BCS-PVT is poor, in particular if there is extension of thrombosis in the splenic and/or superior mesenteric vein. There was a significant association between the number of etiological factors and degree of extension of thrombosis, indicating a higher prevalence of multifactorial aetiology in patients with multiple sites of thrombosis. Therefore, anticoagulation seems warranted in patients with combined BCS-PVT, not only to treat underlying thrombophilia but also to potentially prevent further extension of thrombosis in the splanchnic venous bed. Derivative procedures appear difficult, yet not impossible, and require modifications to the standard technique. An extended TIPS by additional thrombolysis or balloon pull-through angioplasty appeared to have the best outcome, but these results have to be confirmed in larger series.

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XI

Acute Portal Vein Thrombosis: A Prospective Multicenter Follow-up Study

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Abstract

Background & Aims

Current recommendations for early anticoagulation in acute portal vein thrombosis unrelated to cirrhosis or malignancy are based on limited evidence. The aim of this study was to prospectively assess the risk factors, outcome and prognosis in patients managed according to these recommendations.

Methods

We enrolled 105 patients with acute thrombosis of the portal vein, or its left or right branch. Laboratory investigations for prothrombotic factors were centralized. Thrombus extension and recanalization were assessed by expert radiologists.

Results

A local risk factor was identified in 22% of patients, and one or several general prothrombotic conditions in 53%. Anticoagulation was given to 101 patients. After a median of 245 days, the portal vein and its left or right branch were patent in 41% of anticoagulated patients (*versus* 14% initially), the splenic vein in 75% (*versus* 58% initially), and the superior mesenteric vein in 69% (*versus* 40% initially). No recanalization occurred after 6 months. Failure to recanalize the portal vein was independently related to the presence of ascites (hazard ratio 3.2, 95% confidence interval 1.3-8) and an occluded splenic vein (hazard ratio 3.2, 95% confidence interval 1.3-7.6). Gastrointestinal bleeding and intestinal infarction occurred in 9 and 2 patients, respectively. Two patients died from causes unrelated to thrombosis or anticoagulation therapy.

Conclusion

Recanalization occurs in one third of patients receiving early anticoagulation for acute portal vein thrombosis, while thrombus extension, intestinal infarction, severe bleeding and death are rare. Alternative therapy should be considered when ascites and splenic vein obstruction are present.

Introduction

Acute portal vein thrombosis (PVT) is characterized by the recent development of a thrombus in the portal vein or its left or right branches.[1, 2] Extension to mesenteric venous arches causes intestinal infarction, with a reported mortality of up to 50%.[3, 4] Without recanalization, a cavernoma develops, associated with a permanent risk of potentially fatal gastrointestinal bleeding, recurrent thrombosis, or biliary obstruction.[1, 5, 6] Therefore recanalization is a major goal for the treatment of acute PVT and often a pressing challenge because most PVT cases are recognized at the acute stage.[7] Expert panels have recommended early anticoagulation therapy for acute PVT.[2] However, these recommendations are based on small retrospective cohort studies performed over several decades.[8-10]

The aim of this study was to prospectively assess (a) patient characteristics of those presenting with acute non-cirrhotic, non-malignant PVT; (b) the incidence and predictive factors of recanalization in patients managed according to recent recommendations; and (c) the incidence of disease- and treatment-related complications.

Methods

Patients and management

Between October 2003 and October 2005, incident cases of acute PVT were enrolled in 7 European countries (Belgium, France, Germany, Italy, Netherlands, Spain, and Switzerland). Diagnostic criteria were imaging evidence of solid material in the portal vein lumen or in its left or right branch, and the absence of porto-portal collaterals. In case of disagreement, diagnostic procedures were ranked in the following order of decreasing accuracy: computerized tomography, magnetic resonance imaging, and Doppler-ultrasound. Patients with cirrhosis or abdominal malignancies were excluded on the basis of history, clinical and laboratory findings, and imaging of the liver, bile ducts, pancreas and other abdominal organs based on a central review of imaging studies.

Patients were managed by their referring specialists in contact with national coordinating centers. Protocol recommendations included (a) a comprehensive evaluation of local and general risk factors for thrombosis; (b) blood sampling for centralized plasma and DNA storage; (c) early initiation of heparin therapy followed by oral anticoagulation targeting an INR of 2 to 3; (d) 6-months of anticoagulation therapy, prolonged to long-term if a permanent prothrombotic disorder was found and/or the mesenteric vein was obstructed; (e) clinical, laboratory and radiological follow-up examinations. However, the final choice of the type and duration of anticoagulation treatment was left to the judgment of the referring specialist.

Definitions

Date of diagnosis corresponded to the date of the imaging study where diagnostic criteria were met after centralized review. Radiological images were collected and reviewed by expert radiologists during a centralized national review. The following segments were examined: portal vein, right and left portal vein branches and terminal segment of the superior mesenteric and splenic veins. Patency was defined as visualization of a completely normal venous segment; obstruction as the presence of solid material in the vascular lumen or obliteration of the normal lumen; and recanalization as the normal appearance of a previously obstructed segment. Cavernoma was defined as the presence of clear porto-portal collaterals. A diagnosis of mesenteric infarction was based on evidence in a pathology specimen.

Follow-up and data collection

Patients were followed from the date of diagnosis until death, study closure (May 1st 2006), or the date of the last visit. Clinical, laboratory and radiological data were collected at diagnosis, at predefined intervals (1, 3, 6, 12, 18, 24 months), and during significant clinical events. Blood samples were obtained for centralized etiological work-up. Risk factors for thrombosis were investigated as previously reported.[11, 12] All collected data were confirmed by national and international experts before freezing for analyses.

Endpoints

Endpoints included: (i) patency of the portal vein trunk and at least one of its main right or left branches as a result of recanalization or lack of extension; (ii) patency of the superior mesenteric and splenic veins; and (iii) bleeding, intestinal infarction or death.

Statistical analyses

Quantitative variables are expressed as mean (± standard error), or median and range, and qualitative variables as absolute and relative frequencies. Comparisons between groups of quantitative and qualitative variables were made by the Wilcoxon and χ^2 test, respectively. Recanalization rates were assessed using Cox models. Independent predictive factors for lack of recanalization were assessed with Cox model regression. Overall survival rates were assessed by the Kaplan-Meier method. Comparisons of recanalization rates with risk factors were made by the log rank test. All tests were two-sided and p values < 0.05 was considered significant. Data handling and analysis were performed with SPSS 12.0 (SPSS Inc., Chicago, Illinois, USA).

The study was approved by all national and, if necessary, local ethics committees. All enrolled patients agreed to participate by completing a written informed consent form after receiving complete oral and written information.

Results

Patient characteristics at diagnosis

One hundred and five patients were enrolled and followed-up for a median of 245 days (range 0-904 days): 8 in Belgium, 4 in Germany, 17 in Italy, 43 in France, 20 in the Netherlands, 8 in Spain, and 5 in Switzerland. The main features at diagnosis are presented in Table 1. Most patients had a fever or elevated C reactive protein levels, with or without an inflammatory focus. Three patients presented with variceal bleeding but with no cavernoma or evidence of cirrhosis, alcoholic or nonalcoholic fatty liver disease, viral hepatitis, metabolic syndrome, excess iron, autoimmune liver disease, Wilson's disease or alpha-1 antitrypsin deficiency. Intrahepatic obliterative portal venopathy was identified in one of these 3 patients.

Table 1

Clinical and radiological characteristics of 105 patients with APVT at diagnosis

Gender – Female/Male	52/53
Age – Median (range)	49 (16-84)
Abdominal pain – N (%)	96 (91)
Fever	55 (52)
Ascites – N (%)	42 (40)
Small volume ascites* – N (%)	36(34)
Clinical ascites – N (%)	6(6)
Splenomegaly at imaging – N (%)	40 (38%)
Hepatomegaly at imaging – N (%)	26 (25%)
Variceal bleeding – N (%)	3 (3)
Prothrombin ratio - % – Median (range)	83 (27-114)
Serum bilirubin - µmol/L– Median (range)	15 (2-207)
ALT – Median (range)	46(13-1484)
Serum creatinine - µmol/l – Median (range)	76 (28-163)
Haemoglobin - mmol/l Median (range)	8 (3-12.5)
Leucocytes - 10^9/l Median (range)	9.3 (1-34)
Platelets - 10^9/l Median (range)	274(55-949)
CRP - UI Median (range)	53 (1-529)
Elevated CRP or fever – N (%)	89(85)

*Only visible at imaging

Table 2

*Causal factors identified at diagnosis in 105 patients with acute PVT. *patients may have 2 local factors*

	N tested	N positive	N positive/ N tested (%)
Myeloproliferative disease	105	24	23
JAK 2 positive	85	17	16
Antiphospholipid syndrome	93	9	10
Protein C deficiency	88	1	1
Protein S deficiency	86	6	7
Antithrombin deficiency	92	2	2
Prothrombine gene mutation	102	15	15
Factor V Leiden	102	4	4
Homozygous MTHFR mutation	82	9	11
Hyperhomocysteinemia	72	8	11
0/1/2/3 prothrombotic disorders		49/44/10/2	47/42/9/2
Connective tissue disease	105	5	4
Hormonal contraception or replacement	53	23	44
Personal history of deep vein thrombosis	105	14	13
Family history of deep vein thrombosis	105	23	22
Local factor*	105	23	22
Pancreatitis		8	8
Cholecystis or cholangitis		6	6
Liver abscess		5	5
Gastritis		3	3
Inflammatory bowel disease		1	1
Diverticulitis		1	1
CMV hepatitis		1	1
Abdominal trauma		1	1
General prothrombotic disorder among patients with a local factor		9	39
No causal factor		25	24

* Patients may have 2 local factors

As shown in Table 2, at least one general risk factor for venous thrombosis (excluding exogenous oestrogens or progestatives and systemic inflammation) and local factors were found in 42% and 22% of patients, respectively. Obliterative portal venopathy [13] was found in four of the 17 patients who underwent liver biopsy; and pure nodular regenerative hyperplasia, small duct sclerosing cholangitis without fibrosis, and bacterial cholangitis was found 1 each. The remaining 10 patients had histologically normal liver and bile ducts.

Portal venous obstruction at diagnosis

Obstruction of the portal vein or of its two branches was found in 90 patients (86%). The 15 remaining patients had only a single obstructed portal vein branch (with or without splenic or superior mesenteric vein obstruction). The splenic vein or the superior mesenteric vein were obstructed in 44 (41%) and 61 (58%) patients, respectively. Complete obstruction of the portal vein, superior mesenteric vein and splenic vein was found in 29 patients (28%).

Treatment

Anticoagulation was administered to 101 patients (95%) for a median duration of 235 days (range 7 to 937 days). Median interval from first symptoms to start of treatment was 13 days (range 0 to 140 days), and from diagnosis to treatment 1 day (range -7 to 76 days). Initial treatment was heparin in 88 patients (unfractionated heparin in 25 patients, low molecular weight heparin in 63), and vitamin K antagonists in 13. A transjugular intrahepatic portosystemic shunt was inserted in 1 patient who also received anticoagulation treatment and thrombolysis.

Outcome in the 101 patients receiving anticoagulation

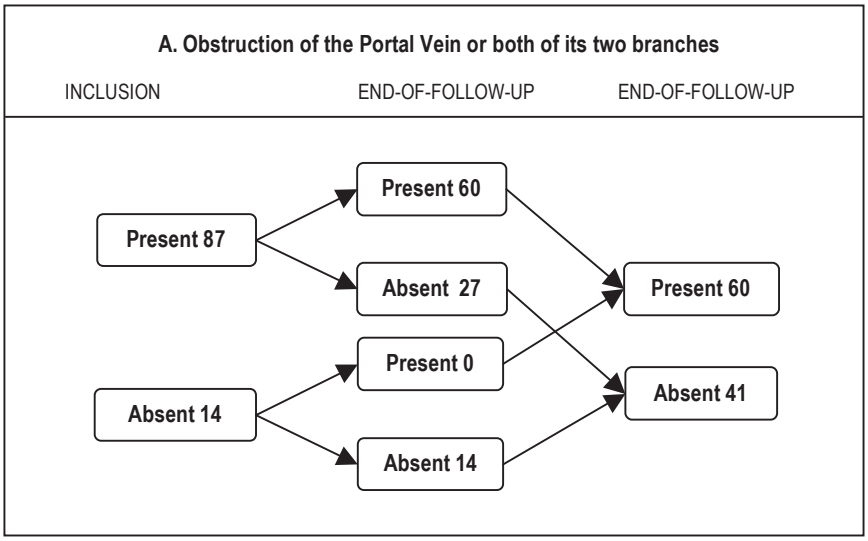
Patency of portal venous segments at the end of follow-up.

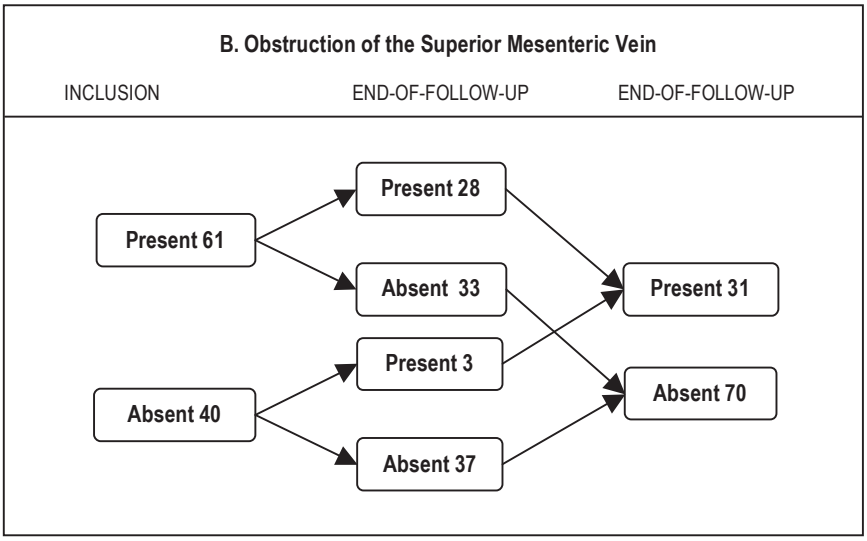
Figure 1 shows the outcome of venous obstruction compared to initial findings. Compared to baseline, the prevalence of obstruction decreased by 32 % for the portal vein or its 2 main branches; 48% for the splenic vein; 50% for the superior mesenteric vein; and 43% for simultaneous obstruction of the portal vein, right and left portal vein branches, superior mesenteric and splenic veins. The portal venous system was completely patent in 18 patients. A portal cavernoma developed in 40 patients.

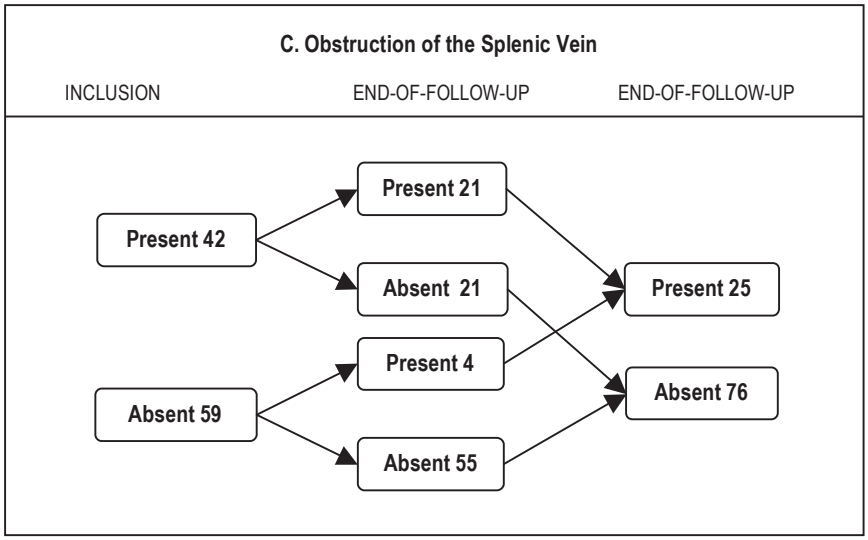
None of the 14 patients with obstruction of a single portal vein branch developed obstruction of the portal vein or both branches. Extension to the superior mesenteric vein or splenic vein developed in 3 and 4 patients, respectively. Progression occurred after diagnosis, but before anticoagulation was begun in all 3 patients with extension to the splenic vein, and in 1 of the 4 with extension to the superior mesenteric vein.

Figure 1

Distribution of obstructed venous segments at diagnosis and at the end-of follow-up in 101 patients receiving anticoagulation therapy. 1A - Portal vein or both its branches. 1B - Superior mesenteric vein. 1C - Splenic vein







Recanalization of the portal vein trunk and/or main branches.

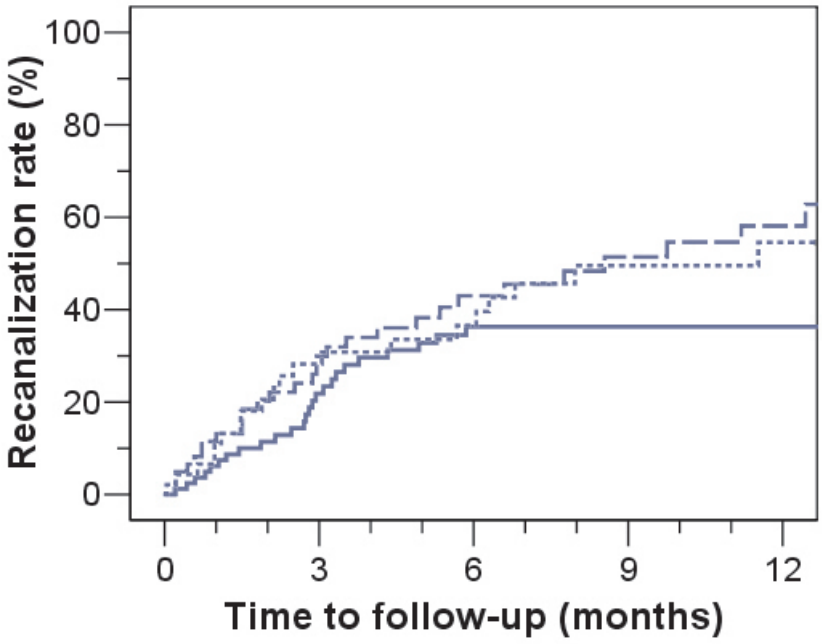
Figure 2 shows that the 1-year recanalization rate was 34% in the 87 patients with initial obstruction of the portal vein or both branches. Recanalization did not occur in any of the patients 6 months after anticoagulation treatment was initiated. Univariate analysis showed that factors predicting failure of recanalization were ascites detected clinically or at imaging [hazard ratio (HR) 3.7, 95% confidence interval (CI) 1.5-9.1]; the presence of the V617F-JAK2 mutation (HR 2.1, 95% CI 1.2-3.8), elevated alkaline phosphatase (HR 1.2, 95% CI 1.1-3), elevated serum gamma-glutamyl transferase (HR 1.1, 95% CI 1.1-1.2), duration of anticoagulation therapy (HR 1.1, 95% CI 1.001-1.006), splenic vein obstruction (HR 3.6, 95% CI 1.1-8.7), superior mesenteric vein obstruction (HR 2,.4,95% CI 1.1-5). The outcome did not differ according to the type or number of thrombotic risk factors or the type of anticoagulation treatment (heparin-based and initiated within 7 days of first symptoms in 27 patients, or otherwise in 61 patients). The only independent factors found at multivariate analysis were ascites (assessed clinically or at imaging) (HR 3.2, 95% CI 1.3-8) and splenic vein obstruction (HR 3.2, 95% CI 1.3-7.6). Figure 3 shows that recanalization did not occur in any of the 20 patients with both splenic vein obstruction and ascites.

Recanalization of splenic vein or mesenteric veins.

Figure 2 shows that the 1-year recanalization rate was 58% for the superior mesenteric vein, and 50% for the splenic vein. There was no apparent plateau in recanalization over time for these two veins. Patient characteristics were not significantly different in those with recanalization and those without (data not shown).

Figure 2.

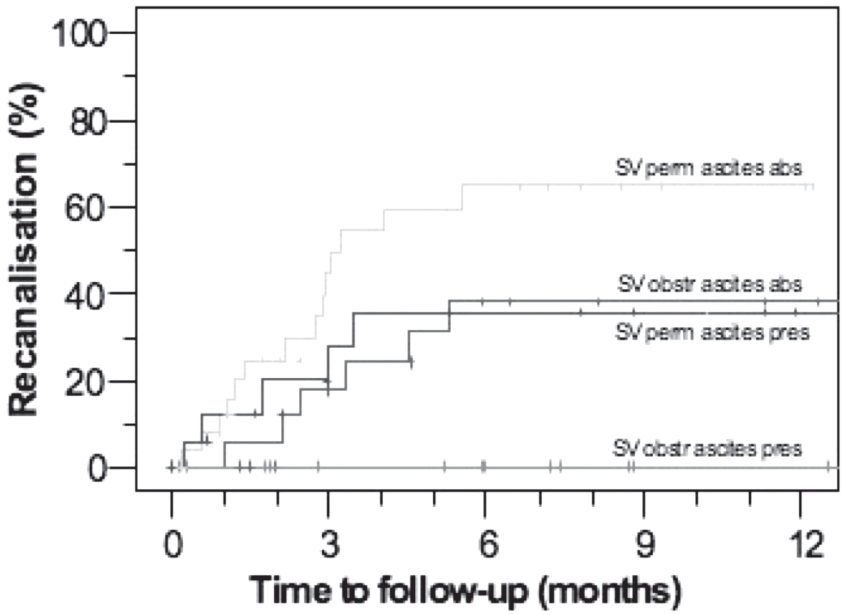
Recanalization rate in anticoagulated patients with initial obstruction of the extrahepatic portal vein or both its main branches (N = 87), superior mesenteric vein (N = 61), or splenic vein (N = 42)



Patients at risk					
Months	0	3	6	9	12
Portal vein (solid line)_	87	51	36	22	18
Splenic vein (completely dotted line)	42	28	21	13	12
Mesenteric vein (partly dotted line)	61	36	23	16	12

Figure 3

Cumulative rate of recanalization of complete extrahepatic portal vein obstruction according to whether splenic vein was obstructed (SV obstr) or permeable (SV perm), and whether ascites was present (ascites pres) or absent (ascites abs) at imaging. (Analysis on 89 patients because 2 patients had missing data)



Outcome in the 4 patients not receiving anticoagulation therapy

Two patients who did not receive antithrombotic therapy had no recanalization. The V617F-JAK2 mutation was retrospectively detected in 1 while the lupus anticoagulant was found in the other; obstructed segments were the right portal vein and the splenic vein in one patient, and both portal vein branches in the other. The 2 remaining patients had acute pancreatitis as the only cause of portal vein obstruction. One received aspirin without recanalization; the other did not receive any antithrombotic therapy and fully recovered with a patent portal venous system.

Bleeding, intestinal infarction and death in patients receiving anticoagulation therapy

Bleeding occurred in 9 out of 101 patients (gastrointestinal in 5, nasal in 2, intra-abdominal in 1, bone marrow biopsy-related hematoma in 1). Although bleeding required transfusion or a prolonged hospital stay in 5 patients, there were no mortalities. Two patients who developed mesenteric infarction 6 and 12 days after beginning anticoagulation underwent 140cm- and 40cm-long intestinal resection, respectively. Both patients survived with good clinical outcome. Two patients died, 1 from sepsis 14 months after diagnosis; and 1 from cholangiocarcinoma, undetectable upon review of initial CT scan, and diagnosed 6 months after PVT.

Discussion

This study in one-hundred prospectively enrolled patients with acute PVT clarifies the etiology and outcome of anticoagulation therapy in this disease. The extrahepatic portal vein was completely blocked in approximately 90% of patients who were at risk of permanent portal hypertension. Furthermore, two thirds of the patients had superior mesenteric vein involvement and were thus at of risk intestinal infarction.

Previous retrospective studies have identified local factors in 25% of acute PVT patients. The results in this prospective study were similar (22%) thus the reason that thrombosis develops in this particular vein remains unanswered in most patients**.** However, this study suggests that intrahepatic vascular disease is an underestimated risk factor for acute PVT. [14] Obliterative portal venopathy or nodular regenerative hyperplasia was found in 4% of all patients and 30% of those who underwent liver biopsy. In these patients, acute PVT presented with ruptured esophageal varices or other well known abdominal symptoms.

A general risk factor for venous thrombosis was identified in 42% of patients. These results confirm those of retrospective studies[10-12, 15, 16] and the predominance of myeloproliferative diseases (23% of patients), G20210A prothrombin gene mutation (15%), and antiphospholipid syndrome (10%) were also similar to previous results. Only 13% of patients had a local factor without a general risk factor, and 24 % had no identified factor. These results support the recommendation that all acute PVT patients - with or without local factors - should be investigated for prothrombotic disorders and considered for early anticoagulation without waiting for test results.

A randomized controlled trial of anticoagulation for acute PVT is not realistic due to the rarity and heterogeneity of this disorder. This study has clarified the overall outcome of early anticoagulation therapy using homogeneous inclusion criteria and endpoints. Protocol recommendations were closely followed, so only 4 patients did not receive anticoagulation treatment. The main findings were a very low rate of extension, and a marked rate of recanalization. None of the 14 patients with initial thrombus of one main portal vein branch had extension to the trunk or other branches. Extension into the superior mesenteric or splenic vein was only observed in 3 patients, most of whom began anticoagulation later. Furthermore, the incidence of intestinal infarction was only 3% in patients with superior mesenteric vein obstruction. This is similar to results in a medical series of 33 patients treated with early anticoagulation [10], but much lower than in unselected or surgical patients (20-50%) who did not all receive anticoagulation.[4]

Although a recovered patency of the portal vein and at least one main branch was reached in one third of patients receiving anticoagulation therapy, obstruction of the portal vein or both of its 2 main branches persisted until the end of follow-up in the rest. The latter patients will probably develop permanent portal hypertension because no recanalization occurred between 6 and 12 months after anticoagulation began. Indeed, a portal cavernoma had already developed in 40% of patients by the end of follow-up. Thus, early anticoagulation is less effective in inducing recanalization of complete extrahepatic portal vein obstruction than in preventing extension to or from the portal vein.

Nevertheless, recanalization rates approached 60% in superior mesenteric and splenic veins. This outcome is clinically significant because a preserved mesenteric vein is a major predictor of long term survival.[17] Moreover, recanalization of these veins steadily increased during follow-up. Further studies are needed to assess whether anticoagulation should be maintained until recanalization of these veins. Finally, the absence of PVT related deaths in this cohort is remarkable, especially because most of these patients had extensive portal venous thrombosis at inclusion.[17]

In patients with acute PVT, the baseline risk of bleeding can be increased by portal hypertension and intestinal ischemia. Although five percent of our patients had major bleeding there were no bleeding-related deaths. It should be noted that this rate of severe bleeding is similar to that from deep-vein thrombosis at other sites.[18]

Additional or alternative therapeutic options should be considered to increase the recanalization rate, but current options include high risk procedures. Pharmacological or instrumental thrombolysis have recently been proposed by a direct, percutaneous transhepatic approach to the portal vein, or by superior mesenteric artery catherization.[4, 19-21] These invasive, poorly evaluated procedures should only be considered for patients with the least chance of recanalization during anticoagulation therapy. Hence, the simple and powerful independent predictors of recanalization identified in this study are an important clinical tool. Patients with a combination of splenic vein obstruction and ascites have very little chance of recanalization during anticoagulation therapy and could be candidates for alternative treatment. However, the low mortality rate of chronic PVT should also be considered when deciding on invasive therapy during acute stage PVT.[1]

In conclusion, this study supports early anticoagulation of patients with acute PVT because of the high prevalence of permanet risk factors for venous thrombosis; the limited number of cases with thrombus extension or intestinal infarction; the high rate of splanchnic vein recanalization; and the low rate of severe bleeding.

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XII

SUMMARY AND DISCUSSION

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SUMMARY AND DISCUSSION

Budd-Chiari Syndrome (BCS) is a rare disease entity with many challenges. It is most accurately defined as “hepatic venous outflow obstruction and its manifestations regardless of the cause and level of obstruction which can be located anywhere from the small hepatic veins to the entrance of the inferior vena cava into the right atrium”. In two third of the cases, the patient is female and in her reproductive age. The classical clinical presentation is the triad of ascites, hepatomegaly and abdominal pain, but many variations to this presentation exist. In general, patients develop these symptoms in the absence of severe liver dysfunction, in other words, the usual liver function parameters poorly correlate with disease activity. The disease is usually detected by Ultrasound, CT, MRI and combinations thereof. Venography is the golden standard but this is rarely performed nowadays. The hepatic venous outflow obstruction is usually caused by thrombosis in the outflow tract, and is seen in association with many thrombogenic conditions, including inherited and acquired forms of thrombophilia. Before 2000, the management of BCS included long-term anticoagulation, diuretics, thrombolysis with or without angioplasty and surgical portosytemic shunting. Liver transplantation is reserved for those with progressive liver failure despite maximal treatment or for patients with fulminant liver failure (**CHAPTER I**).

Following hepatic venous outflow obstruction, created by partial ligation of the inferior vena cava in rats, many changes occur on the microvascular as well as macrovascular level (**CHAPTER II**). In the earlier stage after the obstruction, centrilobular congestion and sinusoidal dilatation occurs and the liver enlarges, clinically evident as hepatomegaly. This is accompanied by a decrease in intravascular volume of the portal veins secondary to a collapse of the small peripheral portal branches. The effective liver tissue volume decreases too, but to a lesser degree and therefore several areas remain relatively under-perfused. In a later stage, centrilobular necrosis as well as fibrosis and regeneration nodules develop. At this stage, the portal intravascular volume decreases further, but now the degree to which the liver tissue volume is lost equals that of the portal volume loss and therefore a new equilibrium is reached in which the remaining liver tissue is relatively well-perfused.
This pilot study has much potential for the future. Using this animal model, one can think of dynamic studies such as those using contrast CT or even dynamic MRI at smaller time intervals while the rat is kept alive. Of great interest would be to do similar experiments but this time by studying the hepatic artery instead. I also think there is room for refinement of the experimental steps, and larger sample sizes. Overall, this study has helped us in increasing our so far premature understanding of the pathophysiological changes occurring in the liver and its vasculature.

The etiology of BCS is variable but almost always involves an increased tendency to develop thrombosis. The most prevalent underlying diseases leading to BCS are myeloproliferative disorders (MPD). We have shown that the prevalence ranges from 33% (**CHAPTER III**) to as high as 49% (**CHAPTER V**) in the era in which spontaneous erythroid colony formation and the JAK-2 mutation count as one of the confirmatory criteria. Survival in patients with BCS and MPD is not determined by the underlying disease, and does not significantly differ from patients without MPD, and thus with other etiological factors. Considering this high prevalence, patients with (suspected) BCS should always undergo investigation for MPD, including peripheral blood

tests and smear, bone marrow biopsy and/or nuclear studies for determination of red cell mass (in polycythemia vera). Vice versa, one may suggest that patients with MPD should be closely followed for development of BCS, although the incidence thereof is much lower.
Other less common etiological factors include Factor V Leiden mutation (12%-15%), Prothombin gene mutation (3%-8%), Protein C (4%-7%), Protein S (3%-7%) and Antithrombin deficiency (3%). Use of oral contraceptives is present in 33%-52% of all female patients.
Interestingly, 38% of BCS patients with MPD appeared to also have other pro-thrombotic factors simultaneously (**CHAPTER III**). Indeed, multifactorial etiology was present in 46% of all BCS patients included in the EN-Vie study (**CHAPTER V**). This finding underlines the importance of completing the full set of diagnostic studies for all thrombogenic disorders, even if one factor has been found already. One may state that this would not change management as most of these conditions are similarly, i.e. with anticoagulation. This is true. Yet, there are other reasons for obtaining this information, such as for prognostic purposes as well as for counseling patients regarding family planning.

Despite all efforts to find an underlying cause with the conventional tests for thrombophilia, in about 10%-16% of patients, no cause can be identified. There are, obviously, two mechanisms leading to thrombosis; one is the increased production (i.e. thrombogenesis) and one is the decreased break-down (i.e. fibrinolysis). The markers involved in the fibrinolysis are thusfar not as extensively studied as those involved in the thrombogenesis. We therefore sought to investigate the role of TAFI (thrombin-activatable fibrinolysis inhibitor), a factor that is known to potently attenuate fibrinolysis, in the pathogenesis of the Budd-Chiari Syndrome (**CHAPTER IV**). Indeed, TAFI antigen levels have previously been associated with a mildly increased risk for venous thrombosis. Since TAFI, as many other coagulation factors is produced in the liver, measuring antigen levels alone would be misleading. Therefore we investigated the prevalence of different genetic variants in a case-control setting of 118 patients with either Budd-Chiari syndrome or portal vein thrombosis (since both diseases carry a similar thrombogenic pattern) versus healthy individuals. Results from this study suggest that the 147Thr/Thr (lowering both functionality and antigen levels of TAFI) and 325Thr/Ile (increasing half-life and antifibrinolytic activity of TAFI) genetic variants are associated with decreased and increased risk of thrombosis, respectively. The relationship between concentration on the one hand and functionality on the other, may not be as linear as expected and further research is required to elucidate the true direction of association. In fact, we are currently investigating the role of several fibrinolytic factors (including plasminogen activator inhibitor 1 (PAI-1), TAFI, tissue-type plasminogen activator (t-PA) antigen and factor XIII) in a case-control study of 101 patients with BCS and healthy controls. Preliminary results thereof look promising and have the potential to further unravel the complex interaction between coagulation, fibrinolysis and venous thrombosis in the liver.

In the days before the flight of interventional radiology, the only definitive therapy for BCS was a surgical shunt, in which an anastomosis was created between the portal vein or mesenteric vein and the inferior vena cava in order to bypass the obstructed liver veins. This however, was associated with high operative mortality rates, although in many (selected) surgical series, surprisingly high survival rates were reported. In our retrospective case series of 237 patients from 1984 to 2001, we found that 49% of patients underwent surgical shunting (**CHAPTER VII**), but we failed to find a significant survival benefit. Relative mortality risks increased from 1.07 if

the shunting was performed within one month after diagnosis to 4.15 if it was done after six months. Only in a subgroup of patients, with intermediate severity and risks, a small benefit in survival was found although statistical significance was not reached. In simple words, patients who had less severe disease would survive regardless of shunting, patients who had most severe disease would die regardless of surgery, and those inbetween may potentially benefit from shunting.

In the late nineties Transjugular intrahepatic shunting (TIPS), initially used as a bridge treatment for patients with cirrhosis awaiting liver transplantation, founds it's use in the treatment of BCS. Associated with lower intra-operative mortality, we, as have others, have shown that TIPS leads to marked improvement in clinical condition of patients with BCS (**CHAPTER VI**). Also, since the use of stents coated with polytetrafluoroethylene (PTFE), primary patency rates have remarkably improved (56% versus 12% in bare stents), a finding of value in BCS patients who already have an increased thrombosis risk to begin with. The combination of low morbidity and mortality with excellent clinical outcome has nowadays made TIPS the most attractive treatment of choice for patients with BCS. In fact, in our prospective study (EN-Vie) of 163 patients diagnosed between 2003 and 2005, we found that in contrast to the extremely infrequent utility of surgical shunting (only 2%), TIPS was the most frequently used therapeutic modality (34%) (**CHAPTER V**). These data reflect the current trend towards using the least invasive management first. Given the fact that survival in this study is markedly higher than survival in the earlier studies, this approach now has set ground.

Unfortunately, in none of the studies performed were we able to demonstrate a clear and significant survival benefit for any of the treatment modalities used. Indeed, earlier studies from different research groups could also not show any significant improvement in outcome. This is mostly attributable to low sample sizes. Due to this rarity and large heterogeneity in BCS, randomized clinical trials have never been performed and we are pessimistic as to whether this can ever be achieved. Until that time, all the evidence we have is collected from observational and descriptive studies. Although not as "hard" an evidence, these non-controlled results still provide us with enough information, which supported by clinical judgment and experience, can result in appropriate medical decisions.

Prognosis in BCS had always been difficult to predict due to the large variability in clinical presentation and disease course. Some patients have minimal symptoms and do well on medical management alone while others present with fulminant liver failure, which, if not timely treated by liver transplantation, often results in death. How does a physician know upfront which of these patients need close observation and aggressive management because of high mortality risks? This is a question we have tried to answer in three studies, two on our retrospective study population (n=237) and one in the prospective study population (EN-Vie, n= 163).

First, we aimed to find independent predictors of transplantation-free survival by multivariate Cox regression analysis (**CHAPTER VII**). Taking into consideration many known and unknown risk factors for patient death, we were able to find four independent predictive factors for survival, which are the presence of ascites (scored as absent (0) versus present (1)), presence of encephalopathy (scored as absent (0) versus present (1)), serum bilirubin levels (in μmol/l) and the prothrombin time (scores as INR below (0) or above (1) 2.3)). Combining these factors in a linear prediction model, we were able to find three significantly different classes of patients, with excellent (class I; 5-yr survival 89%), intermediate (class II, 5-yr survival 74%) and poor (class III; 5-yr survival 42%) prognosis. These variables, which are readily available at diagnosis, can

guide clinicians with regards to intensity of follow-up and perhaps management of patients with BCS, although the latter is still a matter of debate. This classification was later referred to as the Rotterdam BCS index.
Although the variables of the Rotterdam BCS index are readily available at diagnosis, it does make use of subjective clinical parameters, and uses dichotomous rather than continuous variables. Also, the score was derived from a retrospective sample, and due to the rarity of the disease, was never again validated in a new series of patients. The most well-known and used liver scoring system of current times is the Model for End-stage Liver Disease (MELD). This model does have the advantage of using only objective (laboratory) parameters, and allows for quantification of mortality risks. Also, it has been tested in many different cirrhosis data sets and has proven its validity in most of the liver diseases, in particular in the short-term mortality prediction. Therefore, we were interested to investigate whether MELD was able to accurately predict mortality in patients with BCS (**CHAPTER VIII**). In this study, we compared the discriminative ability (expressed as the area under the Receiver Operating Characteristic (ROC) curve or c-statistic) of MELD in our 237 patients with BCS with that in 281 patients with end-stage liver disease (ESLD) due to other causes. To our surprise, though excellent in ESLD, MELD was found to perform sub-optimally in patients with BCS (c-statistic 0.848 versus 0.695, respectively). Moreover, comparison of MELD with the now *internally* validated Rotterdam BCS index showed that the Rotterdam BCS index had a higher predictive ability (c-statistic 0.760). Correlation analyses of MELD and the Rotterdam BCS index indeed revealed that the discrepancy is most likely due to those subjective clinical parameters, ascites and encephalopathy, which appear to have a major role in the prognosis in patients with BCS. As mentioned earlier, patients with BCS can have severe ascites and encephalopathy in the setting of nearly normal liver function tests. Therefore the MELD can underestimate the disease severity. Further exploration indeed revealed that adding these variables to the MELD made the c-statistic increase to a level equal to the Rotterdam BCS index.

Mortality in BCS has always been described to be highest within the first two years after diagnosis. This had formed the basis of our 2,5 year follow-up in the EN-Vie study. But all previous retrospective series had spanned many follow-up years to include sufficient number of patients, and crude 1 or 2 year mortality rates were not further divided into mortality per month. We were interested to see when within these 2,5 years, mortality was actually highest (**CHAPTER IX**). The results of our study indicated that the greatest burden in terms of morbidity and mortality is within the first two months after diagnosis. We labeled this 'early mortality'. The main characteristics of patients with earlier mortality were older age, higher Rotterdam BCS indices and elevated creatinine levels. Discriminative (ROC) analysis of the Rotterdam BCS index, which this time was equal to the *external* validation of the model, showed an excellent c-statistic of 0.84 in the prediction of early mortality. Adding age and creatinine levels to the index improved it even further (0.92). Even interim Rotterdam BCS index scores obtained after two months were adequately predicting late mortality (0.78). However, one must take into consideration that the total number of patient deaths was 29 in the whole follow-up, of which 12 were early deaths and thus used as endpoints in our analyses. This means that the number of events was low and therefore overestimation of our results may have occurred. Obviously, many more studies are needed to further establish this index as a reliable tool in the prognostication of patients with BCS.

Extension of the thrombotic process from the hepatic veins or inferior vena cava into the splanchnic venous bed is a feared complication in patients with BCS. Yet, the combination is present in 15 (**CHAPTER X**) to 18% (**CHAPTER V**) of patients. Indeed, we showed that patients with combined BCS and Portal Vein Thrombosis (PVT) have poorer survival rates than patients with isolated hepatic thrombosis (5-year survival 59% versus 85%, respectively; **CHAPTER X**). Survival decreased further when the thrombosis also involved the splenic or superior mesenteric veins. Moreover, we found an interesting trend towards higher rate of multifactorial etiology in those with extended thrombosis. Intestinal infarction is a rare yet serious potential result of splanchnic thrombosis. It also attenuates treatment options since although TIPS in an occluded PVT is certainly possible, yet poses more of a challenge to the radiologist. Liver transplantation without the portal vein stump is extremely difficult and sometimes impossible.

In our EN-Vie study of 100 incident patients with PVT, isolated or combined with splenic and/or mesenteric vein thrombosis (**CHAPTER XI**), we found that in more than half of the patients who received early anticoagulation for VPT, recanalization occurred and no new thrombus extension had developed. The results of this study combined with that of the previous study (**CHAPTER X**) very strongly argue for early institution of anticoagulation in all patients with BCS, PVT or combinations, not only in an attempt for recanalization but also to prevent further extension and hence worse outcome. Also, the main therapy for most of the (thrombogenic) etiological factors is anticoagulation. Many times, however, this argument has been counteracted by the fear for inducing life-threatening bleeding from varices, which are not uncommon findings in patients with portal hypertension. However, the rate of bleeding after anticoagulation was only 8% in patients with BCS (**CHAPTER V**) and 9% in patients with PVT (**CHAPTER XI**), and all were non-lethal. Therefore as the benefits appear to outweigh the risks, increasing evidence exists that anticoagulation should be the mainstay of therapy in all patients with BCS.

SAMENVATTING EN DISCUSSIE

Budd-Chiari Syndroom (BCS) is een zeldzaam en complex ziektebeeld. De huidige definitie luidt als volgt: “Het BCS is een veneuze afvloed belemmering van de lever en de gevolgen daarvan, ongeacht de oorzaak en niveau van de afsluiting, welke zich vanaf de kleine hepatische venen tot aan de inmonding van de vena cava inferior in het rechter atrium kan bevinden”. Ongeveer tweederde van de patiënten betreft een vrouw in haar vruchtbare leeftijd. De klassieke presentatie bestaat uit een triade van ascites, hepatomegalie en buikpijn, maar er bestaan vele varianten hierop. In het algemeen is er weinig correlatie tussen de ernst van de symptomen en de biochemische parameters in het bloed, m.a.w. patiënten kunnen symptomen ontwikkelen in de afwezigheid van afwijkende lab waarden. Het ziektebeeld wordt meestal opgespoord met behulp van abdominale echografie en/of CT en/of MRI scans. Venografie wordt nog steeds als gouden standaard beschouwd maar in de praktijk wordt het zelden meer gebruikt. De veneuze afvloed belemmering wordt meestal veroorzaakt door de aanwezigheid van een trombose, en wordt vaak gezien in combinatie met vele onderliggende trombogene oorzaken, welke zowel aangeboren of verworven kunnen zijn. Voor het jaar 2000 bestond het klinisch-therapeutisch beleid uit een combinatie van anticoagulantia, diuretica, trombolyse met/zonder angioplastiek en chirurgische portosystemische shunting. Lever transplantatie is uitsluitend gereserveerd voor diegenen die ondanks maximale therapie progressief leverfalen ontwikkelen, of voor patiënten met fulminant leverfalen (**HOOFDSTUK I**).

Na het creëren van een veneuze uitvloed belemmering in ratten door een partiële afsluiting van de vena cava inferior vinden er vele veranderingen op zowel micro-vasculair als macro-vasculair niveau plaats (**HOOFDSTUK II**). In de vroege fase (i.e. 2 dagen) na de afsluiting zwelt de lever op (hepatomegalie) en zien we de ontwikkeling van centrilobulaire congestie en verwijding van de sinusoiden in histologische preparaten. Dit gaat gepaard met een vermindering van het intravasculair volume van de portale venen als gevolg van verlies van de kleine perifere vaten. Het effectieve leverweefsel volume vermindert ook, echter in mindere mate, en daarom blijven bepaalde gebieden relatief minder van bloed voorzien. In de late fase (i.e. 6 weken) zien we de ontwikkeling van centrilobulaire necrose en fibrose als ook regeneratie nodules. In deze fase daalt het intravasculaire volume nog verder maar dit maal is de mate van leverweefsel verlies gelijk aan die van de portale vaten, waardoor een nieuw evenwicht ontstaat waarbij het resterende leverweefsel relatief nog voldoende wordt doorbloedt.
Deze pilot studie heeft veel potentie voor de toekomst. Met dit proefdiermodel kan men bijvoorbeeld in de toekomst dynamische studies uitvoeren met contrast CT of zelfs MRI waarin men kan werken met kleinere tijdsintervallen en gebruik makend van levende proefdieren. Bovendien is het interessant om daarnaast ook de hepatische arterie te bestuderen. De studie laat veel ruimte over voor verbetering, zowel op het gebied van de technische details en experimentele stappen als het aantal proefdieren. Desalniettemin heeft deze studie ons een stapje verder geholpen in ons onderontwikkelend begrip van de pathofysiologische verandering welke plaatsvinden in de lever en de lever vasculatuur na het ontstaan van het Budd-Chiari syndroom.

De etiologie van het Budd-Chiari syndroom is erg variabel, maar de gemeenschappelijke factor van alle oorzaken is de verhoogde neiging tot het vormen van trombose. De meest voorkomende onderliggende oorzaak voor het Budd-Chiari syndroom zijn de myeloproliferatieve

ziektebeelden (MPD). In onze studies hebben we aangetoond dat de prevalentie van MPD in het Budd-Chiari syndroom varieert tussen 33% (**HOOFDSTUK III**) en 49% indien we de recentelijk gevonden JAK 2 mutatie als diagnostisch criterium gebruiken (**HOOFDSTUK V**). De overleving van patiënten met BCS en MPD wordt niet bepaald door de onderliggende oorzaak en is niet significant verschillend van de overleving van BCS patiënten zonder MPD en dus met andere onderliggende oorzaken. Gezien dit feit moeten in onze opinie alle patiënten met (een vermoedelijk) BCS altijd een volledig onderzoek voor MPD ondergaan, inclusief perifere bloed testen en uitstrijk, een beenmerg biopt en/of nucleaire testen voor het bepalen van het rode bloed cel volume (in polycythemia vera). Vice versa kan men ook beredeneren dat patiënten met MPD intensief moeten worden vervolgd voor de ontwikkeling van het BCS, alhoewel de associatie hier veel zwakker is en de uitvoering ingewikkelder.
Overige, minder prevalente, oorzaken zijn Factor V Leiden mutatie (12%-15%), Prothrombine gen mutatie (3%-8%), Proteïne C (4%-7%), Proteine S (3%-7%) en Antitrombine deficiëntie (3%). Ongeveer 33%-52% van alle vrouwelijke patiënten gebruiken orale anticonceptie.
Het is interessant dat 38% van alle patiënten met BCS en MPD naast MPD ook andere pro-trombotische aandoeningen hebben (**HOOFDSTUK III**). Multi-factoriele etiologie (i.e. het voorkomen van meer dan één risicofactor) was aangetoond in 46% van alle patiënten in onze EN-Vie studie (**HOOFDSTUK V**). Deze bevinding benadrukt het belang van het voltooien van een complete trombofilie screening in alle patiënten, zelfs als er al één oorzakelijke factor gevonden is. Men kan beargumenteren dat dit echter geen invloed heeft op het klinisch-therapeutisch beleid aangezien het merendeel van deze ziekten op dezelfde manier wordt behandelt, namelijk met anticoagulantia. Dit is correct. Echter, er zijn vele andere redenen te bedenken waarom dit toch van belang is, zoals voor prognose bepaling en als leidraad voor discussies ten aanzien van erfelijkheid en gevolgen voor gezinsplanning.
Ondanks al onze pogingen tot de opsporing van een oorzakelijke factor kunnen we in 10%-15% van de gevallen geen oorzaak vinden met al onze conventionele trombofilie testen. Uiteraard zijn er twee mechanismen welke kunnen leiden tot de vorming van trombose: aan de ene kant is er verhoogde aanmaak (i.e. trombogenese) en aan de andere verminderde afbraak (i.e. fibrinolyse). De factoren betrokken bij de fibrinolyse zijn echter veel minder vaak onderzocht. Daarom waren wij geïnteresseerd in de rol van TAFI (i.e. thrombin-activatable fibrinolysis inhibitor) -een factor betrokken bij de remming van de fibrinolyse- in de pathogenese van het BCS (**HOOFDSTUK IV**). In eerdere studies in veneuze (niet-hepatische) trombose werden TAFI antigeen concentraties geassocieerd met een licht verhoogd risico voor trombose. Aangezien TAFI, net als de meeste andere coagulatie factoren, in de lever wordt aangemaakt (en dus afhankelijk is van de lever functie) kozen we niet voor de meting van de antigeen concentraties. We hebben daarom de prevalentie van verschillende genetische varianten bestudeerd, in een case-control setting binnen een populatie van 118 patiënten met BCS of vena portae trombose (VPT) en 118 gezonde controlepersonen. De resultaten van dit onderzoek tonen aan dat de 147Thr/Thr (welke leidt tot verlaging van de functionaliteit en antigeen concentraties van TAFI), en de 325Thr/Ile (welke leidt tot een grotere halfwaardetijd en anti-fibrinolytische activiteit) genetische variaties geassocieerd zijn met een respectievelijk verlaagd (147Thr/Thr) en een verhoogd (325Thr/Ile) risico voor trombose. De relatie tussen de concentratie aan de ene kant en functionaliteit aan de andere is waarschijnlijk niet zo lineair als verwacht en verder onderzoek is hier noodzakelijk om dit verder uit te diepen. Wij zijn op dit moment daarom bezig met het onderzoeken van de rol van andere factoren betrokken bij de fibrinolyse (i.e. plasminogen activator inhibitor 1 (PAI-1), TAFI, tissue-type plasminogen activator (t-PA) antigen en factor XIII)

in een case-control studie van patiënten en gezonde controlepersonen uit de EN-Vie studie. De voorlopige resultaten zijn veelbelovend en hebben de potentie om meer inzicht te genereren in de complexe interactie tussen trombogenese, fibrinolyse en het ontstaan van veneuze trombose in de lever.

In de dagen vóór de enorme groei van de interventie radiologie was the enige definitieve behandeling optie voor het BCS de chirurgische shunting procedure waarin een anastomosis werd gecreëerd tussen het portale vaatbed en de vena cava inferior met als gevolg dat de ge-occludeerde lever venen werden omgeleid. Dit was echter geassocieerd met een hoge operatie mortaliteit, hoewel dit werd tegengesproken in vele (geselecteerde) chirurgische case series; hierin werden opvallend hoge overlevingskansen aangehaald. In onze retrospectieve series van 237 patiënten met het BCS tussen 1984 en 2000 werd chirurgische shunting in 49% van de gevallen uitgevoerd (**HOOFDSTUK VII**). Echter in deze studie vonden wij geen statistisch significant overlevingsvoordeel. Relatieve mortaliteit risico's namen toe van 1,07 wanneer de operatie was uitgevoerd binnen één maand na diagnose tot 4,15 als het na zes maanden werd uitgevoerd. Slechts in een subgroep van patiënten met een redelijke prognose en ziekte ernst (zie later voor deze classificatie) was chirurgische shunting geassocieerd met een lagere mortaliteit, echter dit was niet significant. Met andere woorden, patiënten met een minder ernstig ziektebeeld overleven waarschijnlijk toch wel, onafhankelijk van de behandeling; patiënten met het meest ernstig ziektebeeld hebben een slechte prognose ondanks welke behandeling dan ook en de middengroep zou misschien wat voordeel kunnen hebben.
In de jaren negentig werd de Transjugulaire intrahepatische shunting (TIPS) procedure in steeds grotere mate gebruikt voor patiënten met lever cirrose maar later ook voor patiënten met het BCS. In het begin functioneerde TIPS als een overbrugging procedure naar een lever transplantatie. Al gauw bleek dat de operatie mortaliteit vele malen kleiner was dan de chirurgische shunting terwijl tegelijkertijd een goed klinische effect werden bereikt. In onze lokale studie toonden we aan dat TIPS leidt tot een belangrijke verbetering van de klinische status van patiënten met het BCS, als gemeten in belangrijke graadmeters van lever functie en symptomatologie (**HOOFDSTUK VI**). Vóór de introductie van de polytetrafluoroethylene (PTFE) had TIPS als grote nadeel de ontwikkeling van stent occlusie, welke relatief vaak werd gezien. Wij vonden echter een significante verbetering van de doorlaatbaarheid van de stents met de gecoate stents (56% versus 12% met de conventionele stents). Dit is met name van belang voor patiënten met het BCS, die van nature al een hoge trombose neiging vertonen. De combinatie van lage morbiditeit en mortaliteit getallen en de uitstekende klinische resultaten hebben geleid tot een toename in het gebruik van TIPS in het BCS. Onze prospectieve EN-Vie studie met patiënten gediagnosticeerd tussen 2003 en 2005 (en dus een aantal jaar later) laat deze trend dan ook duidelijk zien: TIPS was de meest voorkomende therapie keuze (34% van alle patiënten) en chirurgische shunting was slechts uitgevoerd in 3 patiënten (2%) (**HOOFDSTUK V**). Deze resultaten reflecteren ook de actuele trend aan binnen het klinisch beleid van patiënten met BCS, gericht op de minst invasieve therapie. Deze benadering blijkt zijn vruchten af te werpen aangezien de overlevingskansen hedentendage veel gunstiger zijn dan een tweetal decennia geleden.
Helaas konden wij, net als andere onderzoekers, geen significant overlevingsvoordeel vinden voor welk therapeuticum dan ook. Dit is voornamelijk te wijten aan de steekproefgrootte, welke vaak ontoereikend is. Vanwege de zeldzaamheid en de grote heterogeniteit van het BCS zijn er nog nooit gerandomiseerde klinische trials uitgevoerd en we zijn pessimistisch of dit ooit in de

toekomst kan worden bereikt. Alle kennis die we tot nu toe hebben verworven is verkregen door middel van observationele en descriptieve studies. Ondanks het feit dat de 'evidence' hier niet heel hard is, leveren deze ongecontroleerde studies ons toch genoeg informatie welke tezamen met klinische kennis, ervaring en gezond verstand toch kan resulteren in correcte medische beslissingen.

De prognose van patiënten met het BCS is altijd moeilijk te bepalen geweest door de grote heterogeniteit in klinische presentatie en ziektebeloop. Sommige patiënten hebben weinig symptomen en doen het goed op enkel medicamenteuze behandeling terwijl anderen zich presenteren met fulminant lever falen, welke indien niet tijdig behandelt met lever transplantatie, vaak resulteert in het overlijden van de patiënt. Hoe weet een arts van tevoren welke van deze patiënten hoge mortaliteit risico's hebben en dus striktere controle en een meer agressieve behandeling nodig hebben? Dit was de vraag die we trachtten te benantwoorden in drie studies, twee gebaseerd op onze retrospectieve data (n=237) en één op onze prospectieve EN-Vie data (n=163). Onze eerste doelstelling was om onafhankelijke predictoren te vinden van transplantatievrije overleving middels multivariabel Cox regressie analyse (**HOOFDSTUK VII**). We namen vele bekende en onbekende risicofactoren voor overleving mee in de analyses en uiteindelijk vonden we een set van vier onafhankelijke predictoren voor overleving. Deze zijn: ascites (gescoord als 0 (afwezig) en 1 (aanwezig)); hepatische encephalopatie (gescoord als 0 (afwezig) en 1 (aanwezig)); bilirubine waarden (uitgedrukt op een continue schaal in μmol/l) en protrombine tijd, uitgedrukt in INR (gescoord als kleiner dan (0) of groter dan (1) 2,3). Daarna hebben we deze factoren gecombineerd in een lineair predictie model, waarmee we drie verschillende patiënten categorieën konden onderscheiden: patiënten met een uitstekende (Class I, 5-jaars overleving 89%), gemiddelde (Class II, 5-jaars overleving 74%) en slechte (Class III, 5-jaars overleving 42%) prognose. Deze factoren, welke beschikbaar zijn ten tijde van de diagnose, kunnen als leidraad dienen voor de frequentie van controles en misschien ook voor de te geven behandeling, alhoewel het laatste nog ter discussie staat. Deze classificatie werd later de Rotterdam BCS index genaamd.
Ondanks het feit dat deze factoren simpel en makkelijk beschikbaar zijn, zijn twee van de vier subjectief (in plaats van louter objectief) en drie van de vier dichotoom (in plaats van continu), en dit is niet altijd wenselijk. Bovendien was de score berekend met behulp van retrospectieve data, en gezien de zeldzaamheid van het ziektebeeld, niet extern gevalideerd op een nieuwe dataset. De meest bekende en gebruikte lever score systeem van deze tijd is de MELD (Model for End-stage Liver Disease). Dit model maakt alleen gebruik van subjectieve (laboratorium) factoren en kwantificeert (in plaats van categoriseert) mortaliteit risico's. Daarnaast is deze score vele malen extern gevalideerd in cirrose (maar geen BCS) data, met name op het gebied van predictie van korte termijn mortaliteit. Daarom waren wij geïnteresseerd te onderzoeken in welke mate MELD mortaliteit in patiënten met het BCS kan voorspellen (**HOOFDSTUK VIII**). In deze studie vergeleken we de voorspellende waarde (uitgedrukt in area under the Receiver Operating Characteristic (ROC) curve, oftewel c-statistic) van MELD in onze 237 patiënten met het BCS met dat in 281 patiënten met zogenaamd *end-stage liver disease* (ESLD) (i.e. laatste fase van lever falen door andere oorzaken dan BCS). Tot onze verbazing bleek MELD, welke een uitstekende voorspellende waarde heeft in ESLD, suboptimaal te functioneren als predictief model voor BCS (c-statistic 0,848 versus 0,695, respectievelijk). Verder vergeleken we de voorspellende waarde van MELD in BCS met de Rotterdam BCS index. Dit betekende tegelijkertijd dat de Rotterdam BCS index nu *intern* gevalideerd werd. De resultaten toonden aan

dat de Rotterdam BCS index een betere voorspellende waarde had dan MELD (0,760). Correlatie analyses van MELD met de Rotterdam BCS index toonden dat deze discrepantie met name te wijten was aan juist de afwezigheid van de twee subjectieve factoren ascites en encephalopathie, welke blijkbaar een belangrijke rol hebben in de voorspelling van de prognose van patiënten met het BCS. Zoals eerder gezegd, patiënten met BCS kunnen deze complicaties van portale hypertensie hebben zonder veel afwijkende laboratorium waarden. Daardoor kan de MELD score de werkelijke prognose van patiënten onderschatten. Verder onderzoek toonde aan dat de voorspellende waarde van MELD verbeterde toen we deze variabelen toevoegden aan de MELD. De c-statistic van dit gewijzigd model was gelijk aan die van de Rotterdam BCS index.

De voorgaande studies in BCS hebben aangetoond dat de mortaliteit het hoogst is in de eerste twee jaar na diagnose. Dit gegeven vormde de basis voor de 2,5 jaar follow-up periode in onze EN-Vie studie. Echter, alle voorgaande studies hadden het nadeel dat vanwege de zeldzaamheid van het ziektebeeld, vele jaren van follow-up nodig waren om voldoende aantallen patiënten te onderzoeken. Daarom werd mortaliteit vaak in grote tijdsintervallen (bijv 3 en 5 jaar intervallen) bekeken. In onze EN-Vie studie, waarin we in negen landen incidente gevallen van BCS includeerden in een veel kortere tijdsspan, konden we de moraliteit wat gedetailleerder in kaart brengen. We wilden onderzoeken welk tijdsinterval het meest belangrijks was qua mortaliteit en morbiditeit (**HOOFDSTUK IX**). Het bleek dat dit de eerste twee maanden van diagnose betrof; we noemden dit 'vroege mortaliteit'. De meest belangrijke karakteristieken van patiënten met vroege mortaliteit waren: oudere leeftijd, hogere Rotterdam BCS index score en hogere creatinine waarden. ROC analyse van de Rotterdam BCS index toonde een uitstekende c-statistic van 0,84 voor de voorspelling van vroege mortaliteit. Dit betekend tegelijkertijd de externe validatie van onze index. De toevoeging van leeftijd en creatinine waarden aan de Rotterdam BCS index leidde tot zelfs hogere c-statistic van 0.92. We hebben ook onderzocht of de score verkregen twee maanden na diagnose een voorspellende waarde had voor de late mortaliteit. Dit bleek inderdaad het geval, maar met een lagere c-statistic van 0,78. Echter, bij de interpretatie van deze resultaten men moet rekening houden met het feit dat het totaal aantal overleden patiënten gedurende de hele follow-up periode 'slechts' 29 was (18%), waarvan er 12 patiënten met vroege mortaliteit waren. Daarom kan er een zekere mate van overschatting opgetreden zijn. Uiteraard is er nog veel meer onderzoek nodig om de rol van de Rotterdam BCS index verder te valideren.

Uitbreiding van de trombose van de hepatische venen of vena cava inferior naar het splanchnische veneuze vaatbed is een gevreesde complicatie in patiënten met het BCS. Toch komt dit in 15% (**HOOFDSTUK X**) tot 18% (**HOOFDSTUK V**) van de gevallen voor. We hebben aangetoond dat patiënten met de combinatie van BCS en vena portae trombose slechtere overlevingskansen hebben dan patiënten met geïsoleerde BCS (5-jaar overleving is 59% versus 85%, respectievelijk; **HOOFDSTUK X**). De overleving daalde nog meer indien de trombose ook de vena lienalis of de vena mesenterica superior trof. Bovendien vonden we een interessante associatie tussen het aantal aanwezige etiologische factoren en de uitbreiding van de trombose. Verder is mesenterische ischaemie en infarcten is nog een andere een zeldzame maar ernstige complicatie van splanchnische trombose. De uitgebreidheid van de trombose heeft ook een nadelig effect op de therapeutische mogelijkheden, aangezien TIPS in een geoccludeerde vena portae weliswaar mogelijk is, maar wel een meer gecompliceerde procedure wordt. Lever

transplantatie wordt uitermate bemoeilijkt door de afwezigheid van een doorlaatbare vena porta stomp.
In onze EN-vie studie hebben we ook onderzoek gedaan naar patiënten met een vena portae trombose, met of zonder lienalis of mesenterica trombose (**HOOFDSTUK XI**). In 100 incidente patiënten met vena portae trombose vonden we dat in meer dan de helft van de patiënten die meteen werden behandelt met anticoagulantia, ofwel recanalisatie optrad ofwel geen verdere uitbreiding van de trombose plaats vond. De resultaten van deze studie, gecombineerd met de resultaten in onze vorige BCS studie (**HOOFDSTUK X**), pleitten voor een vroegtijdige start van anticoagulantia in alle patiënten met BCS, VPT of combinaties hiervan, niet alleen als een poging tot recanalisatie, maar ook om verdere uitbreiding en dus een slechtere prognose, te voorkomen. Bovendien is anticoagulantia de hoeksteen van behandeling voor veel van de (pro-thrombotische) etiologische factoren. Echter in het verleden is deze redenering vaak tegengesproken door de vrees om met anticoagulantia bloeding te veroorzaken, met name uit slokdarm- of maagspataderen (i.e. varices), welke niet zelden complicaties zijn van portale hypertensie. Echter wij vonden dat de prevalenties van bloedingen na anticoagulantia erg laag waren (8% in BCS (**HOOFDSTUK V**) en 9% in VPT (**HOOFDSTUK XI**)) en dit was nooit levensbedreigend. Er bestaat dus steeds meer wetenschappelijk bewijs dat anticoagulantia tot de meest belangrijke behandelingen moet worden gerekend in het therapeutisch beleid van patiënten met het BCS.

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WORDS OF GRATITUDE

EN-Vie has been an extremely gratifying project during which time I had the honor and privilege to work very closely with world-renowned experts in the field of vascular liver disorders. Having said that, the most amazing part still was the fact that each and everyone involved was so incredibly dedicated so as to turn this small and severely under-budgeted study in a field that was of interest only to a few fanatics, into a clinically useful and satisfying project. The strong relationships that were build over our common struggles and our almost daily E-mail communications were enforced in our semi-annual meetings in Paris. I think none of the EN-Vie investigators will ever forget the dinners (or the menu ;) at the tiny restaurant L'Epoque in the picturesque dark streets of Paris.

I would like to start by thanking Dominique Valla, the coordinator of the EN-Vie study who was our leader in every way possible. Dear Dominique, I cannot thank you enough for your supervision and guidance. I was so nervous before I first met you in Clichy, as I had read all your articles and now I was to meet you in person. Your sympathetic personality however melted that fear away in minutes and you convinced me right there to work for EN-Vie. I have learned so much from you and am deeply honored that you will be member of my PhD committee. Thank you very very much.

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I am extremely delighted that my parents-in-law have come over from Mytilene to join us today. You are so special to me. Efgaristo para poli!

The most important things in life are not to be measured in papers or impact factors, nor in grants or awards, but in the quality of human interactions and in the surprises you sometimes find along the way. I have learned to accept that life does not follow rules or schedules, but has its own logic. This is how I, during a brief visit for one of my studies at the Mayo Clinic, met the man who changed my life forever. Kostas, life with you has been like a dream that never ends. You have the gift to turn every day into a special one. I am extremely proud of how hard we, against all odds, have worked to make our fairly tale come true. We now often wonder what the 'happily ever after' really means. Well, this is it. Let's enjoy.
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CURRICULUM VITAE

Sarwa Darwish Murad werd geboren op 25 juli 1979 te Bagdad, Irak. Op tweejarige leeftijd werd ze gedwongen haar geboorteland te verlaten en een vierjarig verblijf in Teheran, Iran volgde. Op zesjarige leeftijd zette ze haar eerste voet op Hollandse bodem en belande ze in Winterswijk, een pittoresk dorpje in de Achterhoek. Op elfjarige verhuisde het gezin naar de randstad. Ze behaalde haar VWO diploma op de O.S.G. Ring van Putten te Spijkenisse. In 1997 startte ze haar Geneeskunde studie aan de Erasmus Universiteit te Rotterdam. In haar tweede studiejaar besloot ze naast geneeskunde, een Master of Science opleiding te volgen op het gebied genaamd Health Services Research. Hier kwam ze voor het eerst in aanraking met het wetenschappelijk onderzoek, en met name de epidemiologie en public health trokken haar aan. Ze voltooide een afstudeeronderzoek naar etnische verschillen in probleem gedragingen bij adolescente jongeren. Een plezierig onderdeel van de Master studie was dat ze een maand aan de Harvard School of Public Health in Boston mocht studeren. Gedurende haar geneeskunde opleiding was ze met name geïnteresseerd in de Maag-, Darm- en Leverziekten. Ze startte daarop een nieuw onderzoek, ditmaal een Europese studie naar vasculaire leverziekten, de EN-Vie studie genaamd. Dit vormde de start van haar promotieonderzoek welke beschreven is in dit proefschrift. Haar oudste co-schap deed ze op de afdeling Gastroenterology and Hepatology van de Mayo Clinic. Ze voltooide haar artsendiploma in 2004 en begon officieel als artsonderzoeker op de MDL afdeling aan het Dijkzigt ziekenhuis, welke snel werd opgedoopt tot Erasmus MC. Gedurende de drie volle jaren die daarop volgde heeft ze het genoegen gehad met verschillende instituten samen te mogen werken, zowel nationaal als internationaal. De studie werd mede gesponserd door de Mozaiek beurs die ze in 2004 in ontvangst mocht nemen. Sinds 1 juli 2007 is ze werkzaam als resident in de Department of Internal Medicine in de Mayo Clinic School of Graduate Medical Education en woont ze samen met haar echtgenoot in Rochester, MN, USA. Over een aantal jaar hopen zij samen terug te keren naar Nederland voor de voortzetting van haar opleiding tot Maag-, Darm- en Leverarts.

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