

Budd-Chiari Syndrome: Etiology, management, and outcomes in a study of 35 patients at the Hospital Pablo Tobón Uribe

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Abstract

Budd-Chiari syndrome (BCS) is a rare disorder characterized by the obstruction of the veins of the liver. Both its presentation and therapeutic management are heterogeneous. The following is a retrospective study of patients diagnosed with BCS treated by the hepatology service at the Hospital Pablo Tobón Uribe. The results of the categorical variables are expressed as proportions and the continuous variables as means and ranges. The average age of onset of this disease was 37.7 years and it was not predominant in neither sex. The most common symptoms were abdominal pain (91.4%), ascites (71.4%) and hepatomegaly (60%). Out of 35 patients, 11 (31.4%) had primary hypercoagulability, 7 (20%) had some myeloproliferative disorder, 6 (17.1%) had extrahepatic malignancies —3 with mechanical compression and 3 due to associated hypercoagulability—, and 1 case had a membranous obstruction of the inferior vena cava. 32 patients (91.4%) received anticoagulation as first-line therapy and only 4 were taken to surgery: 2 to angioplasty, 1 to transjugular intrahepatic portosystemic shunt (TIPS) and 1 to orthotopic liver transplantation (OLT). On the other hand, 17 (48.5%) individuals underwent invasive procedures as a second-line therapy, of which 8 (22.8%) underwent angioplasty and stenting, 5 (14.29%) underwent TIPS and 4 needed OLT. The 6 patients who were taken to TIPS did not need liver transplants. Budd-Chiari syndrome remains a rare condition affecting the health of young men and women alike, with a heterogeneous clinical presentation but, in most cases, with a clear trigger where thrombophilic and myeloproliferative disorders predominate. The use of invasive therapeutic measures, especially the early selection of patients who may benefit from TIPS, has changed the natural course and prognosis of this group of patients.

Keywords

Budd-Chiari Syndrome; Hepatic Vein Thrombosis; Thrombosis.

INTRODUCTION

Budd-Chiari syndrome (BCS) is a rare condition caused by the obstruction of the venous flow of the liver. This obstruction may occur anywhere from the hepatic veins to the inferior vena cava. The incidence of this condition is estimated at 1 case per 2.5 million people per year worldwide (1).

Although this syndrome presents with the classical triad of ascites, abdominal pain, and hepatomegaly, in clinical practice it is evident that it is a heterogeneous condition regarding

its presentation and treatment. Patients may have thrombosis associated with primary thrombophilia or a mechanical phenomenon that triggers the obstruction and, in many cases, multiple precipitating factors. Possible treatment choices include anticoagulation and diuretics or invasive radiology procedures, such as thrombolysis, angioplasty or transjugular intrahepatic portosystemic shunt (TIPS), and surgery in the case of portosystemic shunt or liver transplantation (2).

Knowledge about this group of patients is based on small case series, and, in recent years, attempts have been made to

standardize diagnostic criteria, prognostic indicators and step-by-step therapeutic modalities based on the possibilities of success (3).

The following is a series of retrospective cases that describe the clinical, biochemical, and imaging features, as well as the treatment plan and outcomes of patients of all ages diagnosed with BCS and treated at the Hospital Pablo Tobón Uribe.

MATERIALS AND METHODS

This is a retrospective cohort study conducted on a population of patients diagnosed with BCS and treated by the hepatology group of the Hospital Pablo Tobón Uribe in Medellín, Colombia, between January 2010 and November 2018.

BCS was defined as the occlusion of the hepatic venous outflow, for any reason, which can occur in the hepatic veins, the inferior vena cava, or both. Such occlusion may be confirmed using imaging tests (Doppler ultrasound, computed tomography, contrast magnetic resonance imaging, or venography).

Patients with microvascular coronary disease (sinusoidal obstruction syndrome), heart failure, or with a previous history of liver transplantation were excluded. In all patients, general demographic variables, comorbidities, etiology of liver disease, form of presentation, severity according to the MELD (model for end-stage liver disease) score and the Rotterdam score, were analyzed, as well as laboratory characteristics, imaging variables, treatment provided, complications and overall survival.

Results are expressed as continuous variables, described as medians and interquartile ranges (IQR), and categorical variables are presented as absolute numbers and percentages.

RESULTS

During the study period, 35 patients met the inclusion criteria. Distribution by sex was very similar: 18 male patients (51.43 %) and 17 female patients (48.57 %). The average age was 39 years (20-46 years) (**Table 1**).

Some of the risk factors found prior to the onset of the condition included 7 patients (20%) with some type of neoplasm; 6 (17%) with a history of oral contraceptive use; 4 (11,4%) with a history of primary hypercoagulability; 2 pregnant women or in their post-partum period; 2 with a history of sarcoidosis; and 2 cases of local or systemic infection. In 12 cases (34.29 %) no risk factor was reported. It should be noted that 4 patients (11,4 %) presented with more than 1 associated risk factor (**Table 2**). Regarding the clinical presentation and the 3 symptoms classically reported in BCS semiology, 32 patients (91 %) had abdominal pain, 25 (71 %) ascites, and 21 (60 %) hepatomegaly (**Figure 1**).

Only 13 patients (37.14 %) had acute BCS, of which 3 developed criteria for acute liver failure. The remaining cases were subacute or chronic BCS (**Table 1**). Regarding the causes reported after the onset of BCS, 11 patients (31.4 %) had primary hypercoagulability, while 7 (20 %) had some type of myeloproliferative disorder. Furthermore, 6 patients (17,1 %) had extrahepatic neoplasms, 3 presented with mechanical compression of the supra-hepatic veins, and 3 presented with associated hypercoagulability. Membranous obstruction of the inferior vena cava was reported in only 1 case.

Moreover, BCS was found to be secondary to active infection (septic thrombosis) in 1 (2.8 %) of the patients, while 4 (11.42 %) of them were classified under other conditions

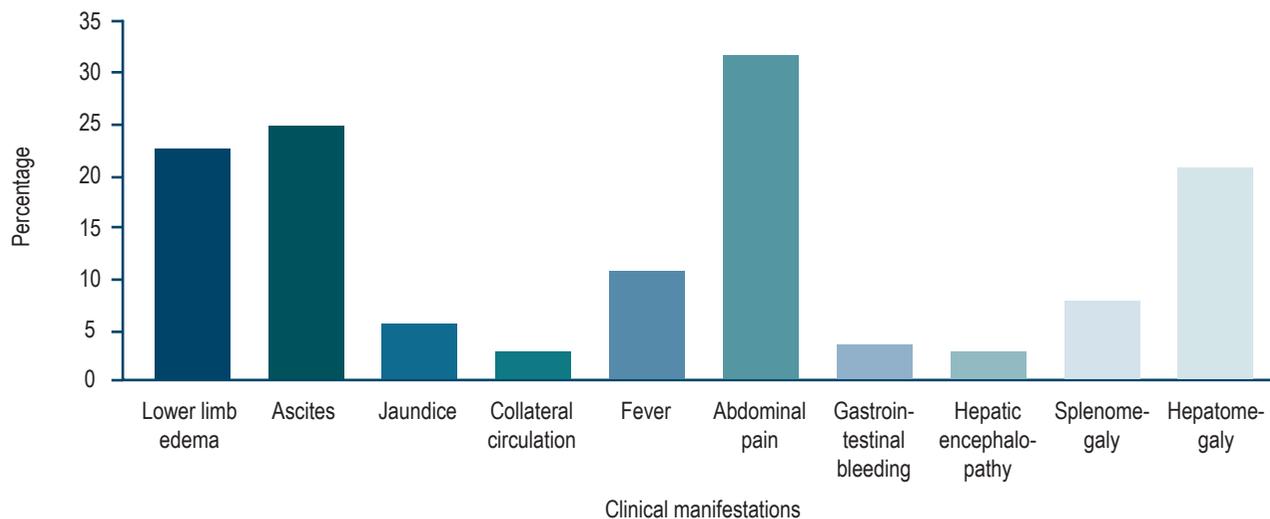


Figure 1. Clinical symptoms. LL: Lower limbs.

Table 1. Clinical features

	Total	Acute	Subacute	Chronic
Total number	35	13	12	10
Demographics				
Male	18 (51.4 %)	7 (53.9 %)	6 (50 %)	5 (50 %)
Female	17 (48.6 %)	6 (46.2 %)	6 (50 %)	5 (50 %)
Age	39 (20-46)	21 (18.5-37)	43.5 (32.5-55.3)	42.5 (32.5-50.5)
BMI	23 (20-26.6)	23 (19.7-25.8)	21.6 (19.2-25.1)	26 (22.1-29.6)
Symptom duration				
<1 month	20 (57.1 %)	13 (100 %)	7 (58.3 %)	0
1- 6 months	8 (22.9 %)	0	5 (41.7 %)	3 (30 %)
> 6 months	6 (17.1 %)	0	0	6 (60 %)
Asymptomatic	1 (2.9 %)	0	0	1 (10 %)
Type				
Primary	32 (91.4 %)	12 (92.3 %)	10 (83.3 %)	10 (100 %)
Secondary	3 (8.6 %)	1 (7.7 %)	2 (16.7 %)	0
Place of obstruction				
Some hepatic vein	7 (20 %)	3 (23.1 %)	2 (16.7 %)	2 (20 %)
Both hepatic veins	15 (42.9 %)	7 (53.84 %)	6 (50 %)	2 (20 %)
Vena cava	2 (5.7 %)	0	0	2 (20 %)
Vena cava and hepatic veins	11 (31.4 %)	3 (23.07 %)	4 (33.33 %)	4 (40 %)
Clinical manifestations				
Edema in LL	23 (65.7 %)	10 (76.9 %)	7 (58.33 %)	6 (60 %)
Ascites	25 (71.4 %)	10 (76.9 %)	8 (66.66 %)	7 (70 %)
Jaundice	6 (17.1 %)	4 (30.8 %)	1 (8.33 %)	1 (10 %)
Collateral circulation	3 (8.6 %)	0	1 (8.33 %)	2 (20 %)
Fever	11 (31.4 %)	8 (61.53 %)	2 (16.66 %)	1 (10 %)
Abdominal pain	32 (91.4 %)	12 (92.30 %)	11 (91.66 %)	9 (90 %)
Gastrointestinal bleeding	4 (11.4 %)	2 (15.38 %)	1 (8.33 %)	2 (20 %)
Hepatic encephalopathy	3 (8.6 %)	3 (23.07 %)	0	0
Splenomegaly	8 (22.9 %)	2 (15.38 %)	2 (16.66 %)	5 (50 %)
Hepatomegaly	21 (60 %)	9 (69.23 %)	5 (41.66 %)	7 (70 %)
Biochemical profile				
Cr	0.9 (0.7-1.2)	1.3 (0.79-1.99)	0.77 (0.62-1.13)	0.9 (0.69-0.98)
Bilirubin \geq 4	1.5 (0.8-2.58)	1.9 (0.82-3.15)	1.35 (0.8-2.1)	1.36 (0.82-2.58)
INR	1.36 (1.14-1.8)	1.8 (1.29-1.95)	1.4 (1.15-1.5)	1.16 (1.0-1.27)
Rotterdam	1.13 (0.25-1.21)	1.16 (0.6-2.15)	1.12 (0.3-1.2)	1.1 (0.2-1.17)
MELD	13 (9-18)	18 (15-27.5)	12.5 (9.3-17.5)	9 (8.5-12.3)
Mortality	8 (22.9 %)	4 (30.8 %)	4 (33.3 %)	0
Days from first symptom to death	43.5 (12.25-95)	12.5 (5.25-26.5)	94 (65-107.25)	0

BMI: Body mass index; LL: Lower limbs; INR: International Normalized Ratio; Cr: Creatinine; MELD: Model for End-stage Liver Disease

such as hypereosinophilic syndrome (n = 1), BCS secondary to catheter-related thrombosis (n = 1), and hepatic sarcoidosis (n = 2). In the remaining 5 cases (14.28 %), no trigger cause was reported (**Table 2**). Overall, 32 cases (91. %) were classified as primary cases associated with thrombosis, while only 3 (8.5 %) were secondary to extrinsic mechanical obstruction.

Table 2. Identified risk factors

Risk factors	n (%)
Any primary thrombophilia	
Factor V Leiden mutation	1 (2.9)
Prothrombin gene mutation	0 (0)
Protein C deficiency	1 (2.9)
Protein S deficiency	0 (0)
Antithrombin deficiency	0 (0)
Any acquired thrombophilia	
Antiphospholipid syndrome	4 (11.43)
Hyperhomocysteinemia	0 (0)
Paroxysmal nocturnal hemoglobinuria	0 (0)
Associated with non-hematologic cancer	6 (17.1)
Lymphoma	2 (5.7)
Myeloproliferative disorder or JAK2 mutation	
Polycythemia rubra vera	4 (11.4)
Essential thrombocytosis	4 (11.4)
Myelofibrosis	1 (2.9)
Not classified	1 (2.9)
Hidden	1 (2.9)
Hormonal factors	
Oral contraceptives	6 (17.1)
Pregnancy/postpartum	3 (8.6)
Systemic conditions	
Connective tissue disorders	2 (5.7)
Sarcoidosis	2 (5.7)
Infections	4 (11.4)
Vasculitis	1 (2.9)
No cause reported	5 (14.3)

On the other hand, in 15 patients (42,86 %) thrombotic involvement of the 3 suprahepatic veins was reported, and in 11 cases (31,4 %) thrombosis occurred in both the suprahepatic veins and the inferior vena cava. Furthermore, in 7 cases (20 %) there was isolated involvement of some of the suprahepatic veins. In 2 (5.7 %) there was an exclusive involvement of the inferior vena cava (**Table 1**).

Regarding the treatment plan, 32 patients (91.4 %) received anticoagulant therapy with full treatment doses. About invasive treatment to improve blood flow through the liver, only 5 were initially treated with invasive procedures: 2 with angioplasty and stenting, 1 with TIPS, and one case of orthotopic liver transplant (OLT) (**Figure 2**).

Regarding patients with clinical deterioration or no response to first-line therapy, 17 (48,5%) underwent invasive procedures, while 8 (22,8%) underwent angioplasty and stenting. In addition, 5 patients (14,9%) required TIPS and 4 were taken to OLT (**Figure 2**). It should be noted that treatment alternatives were defined by the hepatology group and became more complex according to the success of recanalization and decompression. An important finding was that none of the 6 patients who underwent TIPS required liver transplantation.

About the survival of the patients treated by the hepatology service, 8 deaths (22,8 %) were reported, of which only 3 were directly associated with BCS. In the remaining scenarios, deaths were secondary to the progression of underlying conditions.

DISCUSSION

This is one of the largest series of patients diagnosed with BCS published in our country. Firstly, it was possible to observe that this condition affects mainly young patients, since their average age was around the fourth decade of life, and that there is no sex predominance. These findings are comparable with those reported in other series (4). In Colombia, these characteristics had already been described in case reports (5).

It is worth noting that during medical training, BCS is conceived as an acute and severe condition. However, this type of presentation occurs in only one third of cases (34,29 %); most patients present with subacute or chronic BCS. In our case series study, the cardinal symptoms, as described in classical semiology (5), were abdominal pain (91 %), ascites (71.4 %) and hepatomegaly (60 %). These clinical signs are still valid for reaching a diagnosis.

Hepatic venous outflow tract obstruction occurs more frequently in the suprahepatic vein (42.8 %), although it can also occur simultaneously in the suprahepatic vein and

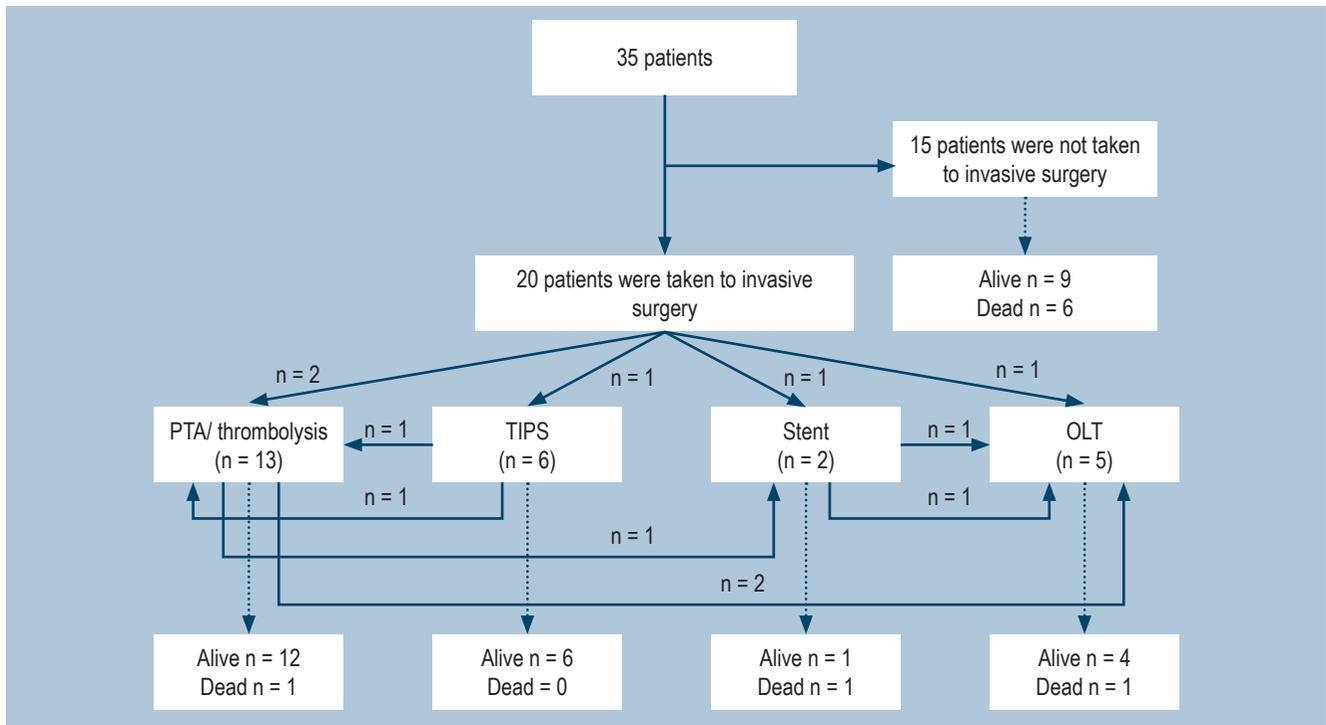


Figure 2. Treatment flowchart. Initially, 1 patient was referred to angioplasty and then received thrombolysis. PTA: percutaneous transluminal angioplasty; TIPS: transjugular intrahepatic portosystemic shunt; OLT: orthotopic liver transplant.

the inferior vena cava (31.4 %). Isolated vein thrombosis (isolated inferior cava or hepatic vein alone) is less common, and most cases (91.4 %) generally are associated with primary causes of thrombosis; extrinsic obstructions were very rare (6).

As reported in previous case series, BCS is associated with primary or acquired thrombophilia and myeloproliferative disorders (6). In the present study, it was not possible to identify the cause of thrombosis in only 5 cases, and some patients had multiple etiologies. Nevertheless, since this is a retrospective study, it is not possible to assure that in all patients the protocol to search for thrombophilia used was the same or that laboratory samples were collected properly at the moment anticoagulation was started.

The most recent studies have proposed and proved, the most efficient treatment to change the prognosis of these patients is definitely one in which decompression and recanalization of the hepatic outflow tract is achieved (7). In our study, 20 patients underwent invasive procedures, which became more complex progressively according to their clinical and biochemical response. It should be noted that this intervention was not carried out based on the guidelines validated by the European Association for the Study of the Liver (8), but rather it was more a methodical

clinical judgment exercise that was performed using the tools available at the time.

Since 2013, we have been stricter in including risk scores to predict therapeutic success and in assessing response earlier, so as not to delay the use of definitive invasive measures that improve prognosis (9). Still, the most important treatment finding is the outstanding result achieved in patients who were taken to TIPS. Despite the few cases, this result is consistent with what is described in current studies (8, 10).

A large part of the treatment alternatives exposed here are not available at all levels of care in the Colombian health system, and most health centers will certainly only have anticoagulation, and even thrombolysis, available. However, it is evident, both in this case series and in larger reports conducted worldwide, that the successful treatment of patients with BCS currently depends on early interventions, as well as on the use of scores that can predict the success of therapies. Another relevant aspect is the selection of patients who, in advance, with the failure of conventional therapies is known. These patients require relieving liver congestion through TIPS or liver transplantation.

The limitations of this study include its retrospective nature and that only the experience of a single medical cen-

ter is reported. Furthermore, the availability of diagnostic and therapeutic tests was not the same for all patients in the study period. Treatment plans were not standardized for anticoagulation and thrombolysis. Also, in the acute phase, most patients received low molecular weight heparins and conventional thrombolytics.

However, some conclusions can be drawn from the results of this series. BCS remains a rare condition, affecting the health of young people, both men and women, with a heterogeneous clinical presentation. In most cases, this con-

dition occurs because there is a clear trigger, particularly thrombophilia and myeloproliferative disorders. The use of invasive therapeutic measures, especially the early selection of patients who may benefit from TIPS, has changed the natural history and prognosis of this group of patients.

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