

Budd-Chiari syndrome: current perspectives and controversies

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Abstract. – Budd-Chiari syndrome (BCS) is a rare disorder caused by hepatic venous outflow obstruction with a wide spectrum of etiologies. Clinical manifestations are so heterogeneous that the diagnosis should be considered in any patients with acute or chronic liver disease. Therapeutic modalities for BCS have improved dramatically during the last few years. The concept of a step-wise treatment strategy has been established, including anticoagulation, thrombolysis, percutaneous recanalization, transjugular intrahepatic portosystemic shunt, surgery and liver transplantation. However, this strategy is primarily based on experts' opinions and retrospective case series, rather than prospective randomized trials. Furthermore, an earlier use of TIPS has been proposed in selected cases because of a relatively high mortality from BCS patients who underwent medical therapy alone. Herein, we review the advances in the classification, etiology, clinical presentation, diagnosis and treatment of BCS.

Key Words:

Budd-Chiari syndrome, Etiology, Diagnosis, Treatment; review.

Introduction

Budd-Chiari syndrome (BCS) is defined as hepatic venous outflow obstruction at any levels from the small hepatic veins (HV) to the junction of the inferior vena cava (IVC) and the right atrium, regardless of the cause of obstruction¹⁻³. However, hepatic venous outflow obstructions caused by hepatic veno-occlusive disease/sinusoidal obstruction syndrome and cardiac disorders should be excluded from this definition. This is because veno-occlusive disease/sinusoidal obstruction syndrome refers to the obstruction of sinusoids or central hepatic veins due to toxic in-

jury of the sinusoidal wall⁴. Given that BCS can lead to potentially life-threatening liver failure and portal hypertension-related complications¹⁻⁴, early diagnosis and treatment should be worthwhile. In the recent years, the number of publications regarding BCS has been remarkably increased⁵. This paper aims to review the advances in the classification, etiology, diagnosis and treatment of primary BCS. BCS secondary to malignant tumors, especially hepatocellular carcinoma, is not considered as primary BCS. Their mechanisms should be mainly tumor invasion.

Classifications

According to the potential causes, BCS can be classified as two groups: primary and secondary. BCS is considered primary when obstruction of the hepatic venous outflow tract is the result of an endoluminal venous lesion (i.e., thrombus or web). BCS is considered secondary when hepatic venous outflow obstruction originates from a lesion outside the venous system (tumor, abscess, cysts). The lesions can obstruct outflow by invading the lumen or by extrinsic compression.

According to the clinical manifestations, BCS can be divided into two groups: asymptomatic and symptomatic. BCS is considered asymptomatic when there are no remarkable signs⁶. About 15%-20% of BCS patients are asymptomatic. The major compensation mechanism should be the spontaneous development of large intra- or extra-hepatic and portosystemic collaterals⁷. By comparison, most of BCS patients are symptomatic. They include abdominal pain, ascites, jaundice, hepatomegaly, edema, encephalopathy and/or gastrointestinal bleeding.

According to the location of obstruction, BCS is briefly classified as three types: pure obstruction of HVs, pure obstruction of IVC, and com-

bined obstruction of HVs and IVC⁸. Pure IVC or combined IVC/HV obstruction is common in Asian countries⁹, whereas pure HV obstruction is frequent in Western countries. Given the nature of obstruction, BCS is further classified as two major groups: (1) HV and/or IVC obstruction or thrombosis; and (2) HV and/or IVC webs.

Etiology

One or more underlying prothrombotic conditions are observed in at least 75% of patients with primary BCS^{10,11}. The systemic prothrombotic conditions are divided into acquired and inherited types. Acquired causes primarily include myeloproliferative neoplasms (MPNs), hyperhomocysteinemia, paroxysmal nocturnal hemoglobinuria (PNH) and Behçet's syndrome, etc. Inherited causes primarily include factor V Leiden mutation, G20210A prothrombin gene mutation and inherited protein C, protein S, and antithrombin deficiencies.

BCR-ABL negative MPNs, including polycythemia vera, essential thrombocythemia, and idiopathic myelofibrosis, are the most common acquired causes of primary BCS^{12,13}. The prevalence of MPNs is about 50% in BCS patients¹⁴. Because JAK2 V617F mutation is found in about 80% of patients with polycythemia vera and 50% of patients with essential thrombocythemia or idiopathic myelofibrosis, routine screening for JAK V617F mutation is very valuable to establish an early diagnosis of MPNs in BCS patients. Numerous observational studies and meta-analyses confirm that the JAK2 V617F mutation can be detected in 30-50% of BCS patients¹⁵⁻¹⁹. However, it should be noted that MPNs are rare in Chinese patients with BCS²⁰⁻²⁴. These findings suggest that MPNs may not be a major etiology of BCS in China.

By comparison, hyperhomocysteinemia, PNH, and Behçet's syndrome appear to be relatively rare etiologies of BCS. However, several important points should be clearly recognized. First, a systematic review and meta-analysis suggests that hyperhomocysteinemia with homozygous MTHFR mutation may be associated with the occurrence of BCS²⁵. However, the relevant evidence originates from very limited data. Second, PNH is an extremely rare condition²⁶⁻²⁸. However, the presence of hepatic vein thrombosis is extraordinarily high in patients with PNH²⁹. Third, Behçet's syndrome is a well-recognized cause of BCS^{30,31}. However, this is frequently observed in Turkey³²⁻³³, but not in other countries³⁴. Some ad-

ditional acquired risk factors should be clearly recognized, such as oral contraceptive use and pregnancy³⁵⁻³⁸.

Factor V Leiden mutation and prothrombin G20210A gene mutation are considered as the most common inherited prothrombotic factors in BCS patients³⁹⁻⁴². However, a recent systematic review and meta-analysis suggests that the factor V Leiden mutation is associated with an increased risk of BCS, but not the prothrombin G20210A mutation^{43,44}. Thus, routine screening for prothrombin G20210A mutation in BCS patients is questioned. Additionally, both gene mutations were hardly observed in Chinese patients with BCS. To our knowledge, only few patients with familial BCS presented with factor V Leiden mutation⁴⁵.

Inherited protein C, protein S, and antithrombin deficiencies are also considered as the major risk factors for BCS. However, their roles are ambiguous, because chronic liver diseases often obscure the recognition of these deficiencies. Recently, a systematic review and meta-analysis confirms that inherited protein C, protein S, or antithrombin deficiencies should significantly increase the risk of BCS⁴⁶. Accordingly, the measurement of protein C, protein S, or antithrombin concentrations should be regularly performed in BCS patients and their first-degree relatives.

Besides, the coagulation and fibrinolysis abnormalities are found. In our recent study, the patients with BCS had significantly higher factor VIII levels and significantly lower factor V, VII, IX, X, XI, XII, protein C and antithrombin levels than healthy controls. This finding suggests an imbalance of pro- and anti-coagulation factors in BCS patients⁴⁷. Additionally, a slightly increased fibrinolytic potential was observed in BCS patients⁴⁸.

Diagnosis

A diagnosis of BCS should be considered in all patients with acute or chronic liver disease, especially when common causes for liver disease have been ruled out. In other words, the patency of HV and IVC may be considered as a part of routine evaluation of liver diseases.

Imaging tests play a crucial role in the early diagnosis of BCS and assessment of location of obstruction⁴⁹⁻⁵¹. There are various imaging modalities for the investigation of hepatic vascular patency, such as Doppler ultrasound, MRI and computed tomography. Doppler ultrasound has a

diagnostic sensitivity of over 85% and should be the first choice of imaging investigation^{52,53}. The major signs of BCS include no blood flow signal in the hepatic veins, intra- or extra-hepatic collateral circulation, a spider-web appearance located adjacently to the hepatic vein ostia and stagnant, and reversed or turbulent blood flow^{54,55}. Computed tomography (CT) or MRI should be considered, if a sonographic evaluation is technically difficult or if the imaging features of BCS in the sonography are ambiguous (Figure 1). However, it should be noted that the sonography is advantageous over CT in detecting the membranous lesions with IVC thrombosis and the lesions in the HV openings⁵⁶.

Non-invasive imaging tests are at most cases sufficient for the diagnosis of BCS. However, if they are inadequate, the venography and liver biopsy should be further considered. Venography is useful for the accurate assessment of extension

and location of outflow obstruction and measurement of HVs pressure. Liver biopsy is also useful for the exclusion of veno-occlusive disease⁵⁷.

Treatment

Currently, a step-wise treatment strategy has been proposed and widely adopted^{11,58,59}. The treatment strategy is primarily based on the response to previous therapy and aims at minimal invasiveness. It can provide an excellent long-term survival with a 5-year survival rate of over 80%^{58,59}. The major treatment options include anticoagulation, thrombolysis, percutaneous recanalization, transjugular intrahepatic portosystemic shunt (TIPS), surgery and liver transplantation. Furthermore, the underlying etiology of BCS should be corrected.

All patients should receive anticoagulant therapy regardless of clinical symptoms^{60,61}. The major reasons why asymptomatic patients with BCS

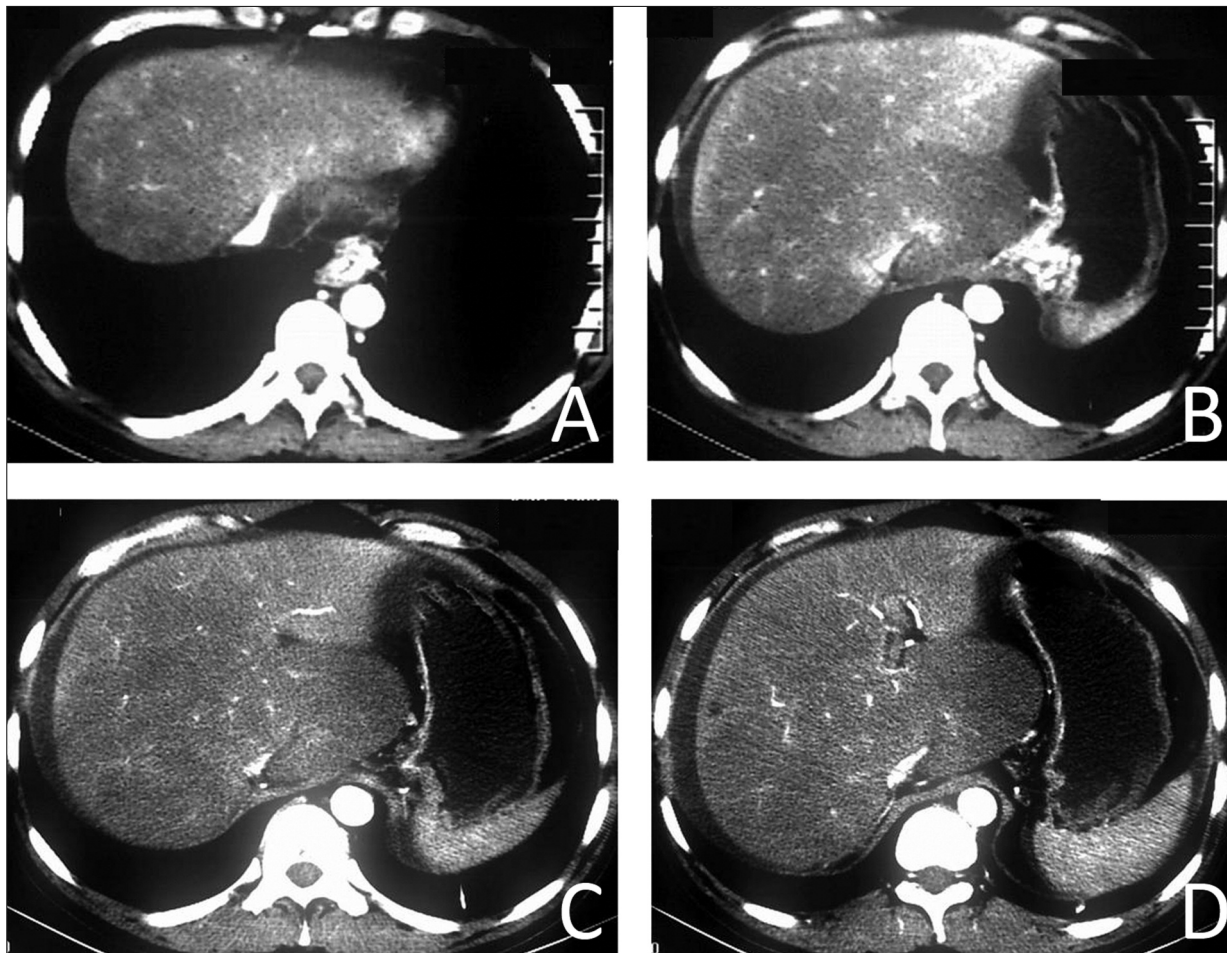


Figure 1. The characteristics of Budd-Chiari syndrome in contrast-enhanced CT scan: hepatic vein is not clearly displayed, inferior vena cava is compressed, and liver congestion.

should receive anticoagulant therapy include (1) prothrombotic states are frequently observed in BCS and potentially increase the occurrence and recurrence of venous thrombosis; and (2) the prognosis of BCS is improved with the use of anticoagulation⁶². In symptomatic patients with BCS, anticoagulation should be prescribed in combination with diuretics and paracentesis for ascites and in combination with pharmacological and endoscopic therapy for the management of portal hypertension-related bleeding. At present, no definitive conclusions regarding the risk of bleeding after anticoagulation in BCS could be achieved. Given the benefit of anticoagulation in BCS, we recommend that anticoagulation therapy should be initiated after active bleeding is completely controlled.

The major indication for balloon angioplasty with or without stenting should be short segmental stenosis or occlusion within the HVs and IVC⁶³⁻⁶⁵ (Figure 2). In some experienced centers, balloon angioplasty is also employed for long segmental stenosis or occlusion within the HVs and IVC or old IVC thrombosis. Additionally, if there were compensatory but obstructed accessory HVs, recanalization of accessory HVs should be considered for the treatment of long-segment HV obstruction⁶⁶. The adjunctive use of thrombolytics may increase the rate of venous recanalization. Local catheter-directed thrombolytic therapy in combination with balloon angioplasty is preferred for the treatment of BCS with HV or IVC thrombosis^{67,68}. If the veins cannot be entered via a transjugular route, percutaneous transhepatic puncture of hepatic vein remnants can

be considered. Whether stent placement should be performed at the time of initial angioplasty or after recurrence remains unclear. Recently, our study found that balloon angioplasty combined with stent placement should be recommended to decrease the frequency of re-occlusion and its associated mortality⁶³. Certainly, the retrospective nature of our study may restrict our conclusions. Thus, further prospective randomized controlled trials should be warranted.

Hepatic venous outflow obstruction may be circumvented by different forms of shunt from the portal vein or superior mesenteric vein to the IVC or right atrium according to the locations of obstruction. Generally, shunt surgery should be indicated for the failure of angioplasty combined with stenting and severe portal hypertension-related complications (i.e., refractory ascites and recurrent variceal bleeding). With the improvement of interventional radiological techniques, TIPS has gradually replaced surgical shunts for BCS patients (Figure 3)⁶⁹⁻⁷³. TIPS can be technically successful in BCS patients with portal, splenic, and superior mesenteric vein thrombosis⁷⁴. Furthermore, the advent of covered stents can prolong the patency of TIPS⁷⁵.

Liver transplantation should be indicated for rapidly progressive BCS after the failure of conventional treatment and/or portosystemic shunting. The outcome of transplantation has remarkably improved over the years. The 5-year survival rate of BCS after liver transplantation can reach up to 75%^{76,77}. Prior TIPS does not compromise the results of liver transplantation. Early mortality of liver transplantation is related to in-

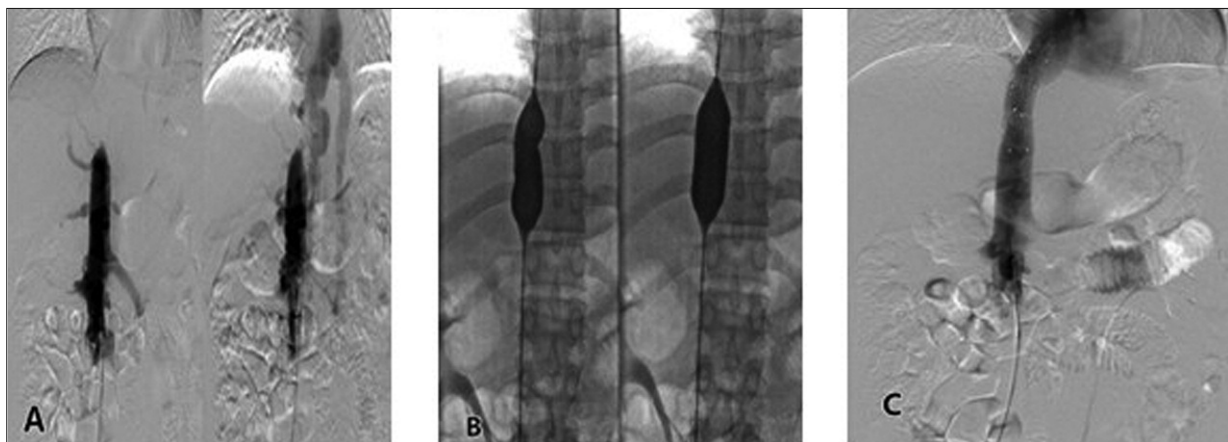


Figure 2. Balloon angioplasty and stent placement for Budd-Chiari syndrome. **A**, An inferior vena cava angiogram demonstrates a long-segmental inferior vena cava obstruction. **B**, The obstruction was dilated with balloon. **C**, The inferior vena cava was recanalized and the collateral vessels disappeared after stent placement.

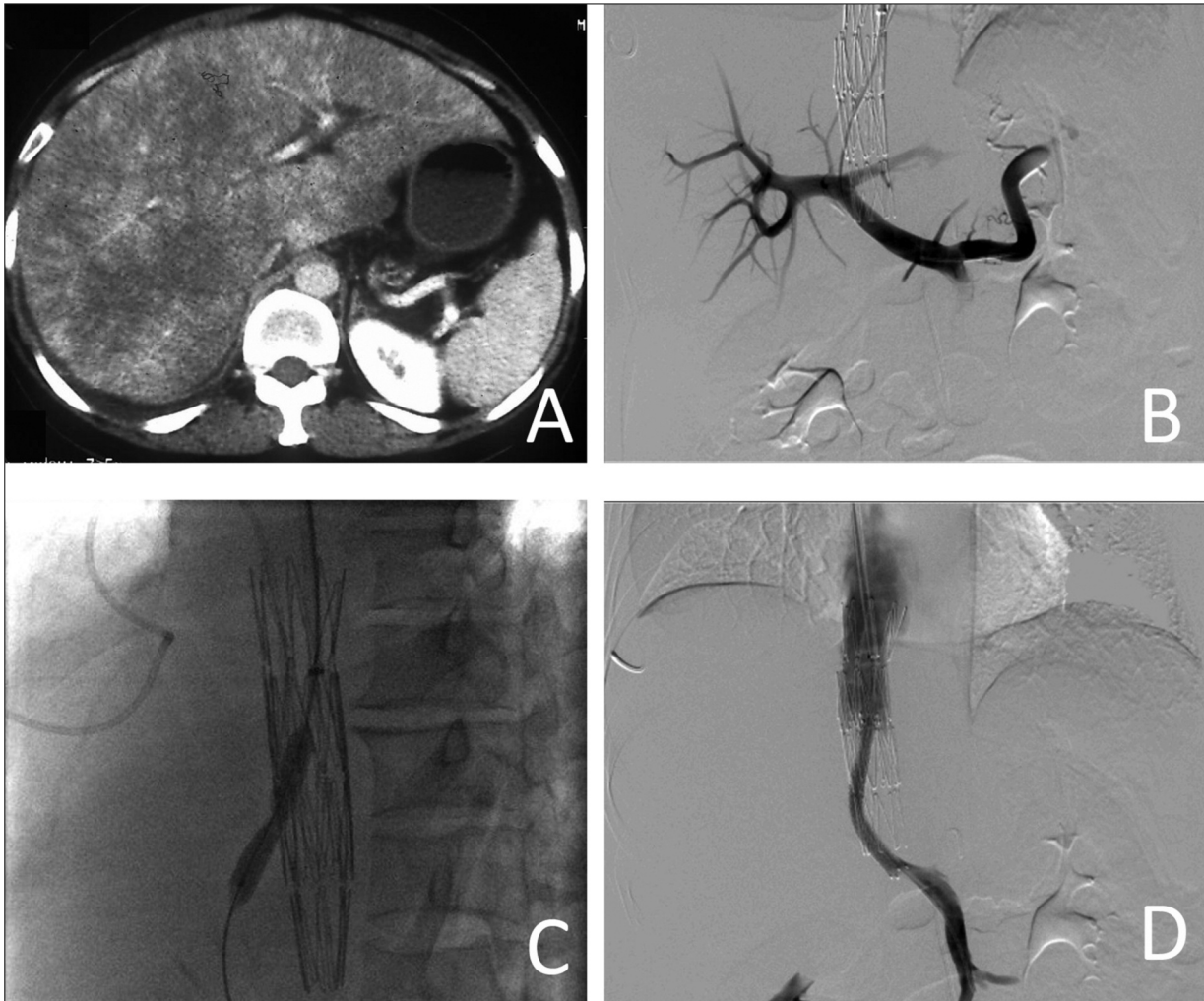


Figure 3. A transjugular intrahepatic portosystemic shunt was placed through the strut of inferior vena cava stent. **A**, CT demonstrated liver congestion. Hepatic vein and inferior vena cava were not clearly displayed. **B**, The portal vein was punctured through the strut of inferior vena stent. **C**, The puncture tract was dilated by balloon. **D**, A TIPS stent was inserted. And then, a venography showed that both inferior vena cava and TIPS stent were patent.

fections and late mortality is related to recurrent BCS. Given that BCS often has a prothrombotic state, long-term anticoagulation after liver transplantation should be maintained.

Controversies

Despite a step-wise treatment strategy is widely employed in West, the selection of treatment modalities for BCS might be different between China and Western countries⁷⁸. In China, the survival benefit after percutaneous recanalization alone is very significant in most of BCS patients⁷⁹. By contrast, only a small proportion of patients will undergo TIPS or liver transplanta-

tion. Accordingly, whether or not a Western treatment algorithm can be extrapolated to Chinese BCS patients needs to be explored.

The accurate timing of performing a TIPS remains under debate. Traditionally, TIPS is recommended in severe cases, such as diffuse hepatic venous occlusion that cannot be recanalized and liver failure or hepatic function deterioration. However, an earlier use of TIPS may be necessary in selected cases because of a relatively high mortality from BCS patients who underwent medical therapy alone⁸⁰⁻⁸². Accordingly, whether or not the indications of TIPS can be shifted into an earlier time in BCS patients should be validated⁸³.

Conclusions

BCS is a life-threatening hepatic vascular disorder. With the advancement of new therapeutic strategy, the prognosis of BCS has gradually improved⁸⁴. In West, the etiology of BCS is clearly identified in most of patients, and a step-wise treatment strategy has been effectively established. However, the etiological distribution and treatment selection are different between West and China⁸⁵. Further studies are warranted to clarify the potential etiology of BCS in China. Additionally, the accurate timing of aggressive treatments should be well defined in future.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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