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Advances and Challenges in Budd-Chiari Syndrome Management: A Review of the Literature

ABSTRACT

Budd-Chiari syndrome (BCS) is a medical condition resulting from a partial or complete obstruction of hepatic venous outflow. Epidemiologically, BCS is considered rare; however, its infrequent diagnosis may be attributed to limited diagnostic tools and low clinical awareness. The symptoms experienced by patients can vary widely, ranging from asymptomatic cases to fulminant forms of the disease. Imaging techniques such as Doppler ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) are commonly used to establish the diagnosis. The primary treatment for BCS involves anticoagulant therapy, typically using warfarin or low molecular weight heparin (LMWH). Depending on the patient's clinical status, more invasive therapeutic interventions may also be necessary. This review article aims to enhance clinicians' awareness, from accurate diagnosis to appropriate management of patients with BCS.

Keywords: Budd-Chiari syndrome (BCS), Doppler ultrasonography (US), Hepatic venous outflow, Obstruction, Warfarin

ABSTRAK

Budd-Chiari syndrome (BCS) adalah kondisi penyakit yang disebabkan oleh obstruksi partial atau total pada hepatic venous outflow. Secara data epidemiologi BCS jarang terjadi, tetapi mungkin karena instrumen diagnosis dan kewaspadaan yang rendah sehingga menjadi jarang terdiagnosis. Gejala klinis yang dialami pasien bervariasi, dapat bersifat asimtomatik sampai fulminant. Diagnosis dapat menggunakan batuan pemeriksaan radiologi seperti Doppler ultrasound (US), computed tomography (CT), dan Magnetic Resonance Imaging (MRI). Pengobatan pilihan utama pada BCS adalah penggunaan antikoagulan seperti warfarin dan low molecular weight heparin (LMWH). Sesuai dengan kondisi klinis pasien dapat juga disertai pengobatan dengan tindakan yang lebih invasif. Review article ini diharapkan membantu klinisi untuk meningkatkan kewaspadaan dalam diagnosis hingga tatalaksana pasien dengan BCS.

Katakunci: Budd-Chiari syndrome (BCS), Doppler ultrasonography (US), Hepatic venous outflow, Obstruksi, Warfarin

INTRODUCTION

Budd–Chiari syndrome (BCS) is a disorder caused by partial or complete obstruction of hepatic venous outflow, which may occur at the level of the small hepatic venules, the inferior vena cava, or even the right atrium.^{1,2} This obstruction leads to venous stasis and congestion, resulting in increased sinusoidal pressure and hypoxic damage that affect both hepatocytes and sinusoidal endothelial cells. These pathological changes can cause hepatocyte necrosis, centrilobular fibrosis, nodular regenerative hyperplasia, and may eventually progress to liver cirrhosis. The clinical presentation of BCS varies significantly, ranging from asymptomatic cases to fulminant hepatic failure.²

In many parts of Asia, BCS remains underdiagnosed-primarily due to limited clinical awareness and lack of adequate diagnostic facilities-leading to delays in diagnosis and unreliable epidemiological data.² This review article aims to raise clinical awareness and support healthcare providers in improving the diagnosis and treatment of patients with BCS.

EPIDEMIOLOGY

Global epidemiological data on Budd–Chiari syndrome (BCS) remains limited. A study conducted in Italy between 2002 and 2012 reported 287 hospitalized cases of BCS, with women accounting for 54.4% and a mean age of approximately 50 years.³ In France, a study identified 178 cases of primary BCS, equivalent to a prevalence of 4.04 cases per million population. Of these, 53% were male, with an average age of 40 ± 14 years. Thrombosis was located in the hepatic veins in 121 cases (76.6%), in both the hepatic veins and inferior vena cava in 37 cases (23.4%), and in the portal vein in 5 cases (3.2%). Myeloproliferative neoplasms (MPNs) were the most commonly identified risk factor, present in 48% of cases.⁴ A meta-analysis involving two Asian and four European countries estimated a pooled prevalence of BCS at 11 cases per million population.⁵

CLASSIFICATION

Budd–Chiari syndrome is classified into primary and secondary types based on the underlying cause of hepatic venous outflow obstruction. Primary Budd–Chiari syndrome is

10 characterized by endoluminal obstruction within the hepatic venous outflow tract, most commonly
2 resulting from thrombosis associated with a prothrombotic state, such as hematologic disorders. In
contrast, secondary Budd–Chiari syndrome arises when the obstruction is caused by external
compression or invasion of the hepatic venous system by lesions originating outside the vessel,
such as cysts, tumors, abscesses, or other extrinsic factors.^{6,7}

7 Based on clinical presentation and duration, Budd–Chiari syndrome can be categorized
into acute, subacute, chronic, and fulminant types. Acute BCS typically develops within less than
one month and is characterized by abdominal pain, hepatomegaly, ascites, and the absence of
collateral vein formation. Subacute BCS also presents with a relatively rapid onset; however,
17 symptoms such as ascites and hepatic necrosis tend to be less pronounced due to the development
of collateral venous circulation involving the portal and hepatic veins. Chronic BCS is often
difficult to distinguish from liver cirrhosis, as it commonly presents with complications associated
with cirrhotic progression. Magnetic resonance imaging (MRI) is considered superior in
visualizing and differentiating between acute, subacute, and chronic forms of BCS.^{8–10}

1 Fulminant Budd–Chiari syndrome is a rare clinical condition, believed to result from an
acute obstruction of all three hepatic veins, occurring so rapidly that there is insufficient time for
the development of collateral circulation. It presents with a sudden onset of symptoms, including
ascites, abdominal pain, and features of acute liver failure such as hepatic encephalopathy and
coagulopathy.²

PATHOPHYSIOLOGY

2 Obstruction of hepatic venous outflow leads to elevated sinusoidal pressure and reduced
portal blood flow, thereby exacerbating hepatic congestion. Tissue hypoxia resulting from
impaired perfusion induces hepatocyte necrosis and activates hepatic stellate cells. This process
contributes to the development of fibrosis, and in more severe cases, progresses to congestive
cirrhosis. As a compensatory mechanism, collateral circulation may form to alleviate venous
congestion; however, this adaptation can promote the development of dysplastic nodules and
potentially progress to hepatocellular carcinoma.^{2,11} This pathophysiological mechanism is
illustrated in Figure 1.

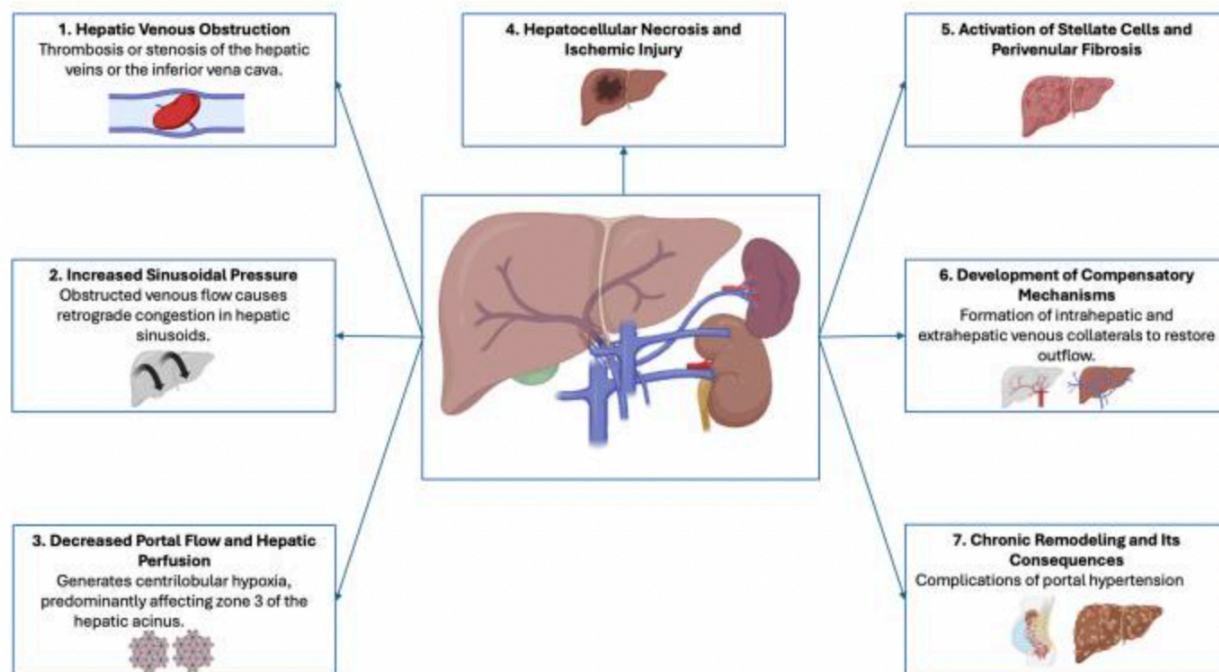


Figure 1. Pathophysiology of Budd-Chiari Syndrome¹¹

The prothrombotic state observed in BCS is associated with various underlying disorders, including protein C or S deficiency, antiphospholipid syndrome, Factor V Leiden mutation, paroxysmal nocturnal hemoglobinuria, prothrombin (PT) gene mutation, antithrombin deficiency, and hyperhomocysteinemia. Among MPNs, polycythemia vera (PV) is the most frequently identified cause of BCS, accounting for approximately 18-43% of cases, followed by essential thrombocythemia (ET), which is implicated in 8-14% of cases.¹¹

CLINICAL MANIFESTATION AND LABORATORY FINDINGS

The clinical manifestations of BCS are highly variable and often nonspecific; up to 20% of cases may present without any symptoms. Symptoms can be categorized based on the site of venous reflux. First, hepatic venous reflux may lead to hepatomegaly, splenomegaly, abdominal pain and distension, ascites, and portal hypertension. Second, reflux involving the inferior vena cava (IVC) may present with bilateral lower extremity edema, varicose veins-including those on the chest wall, abdomen, flanks, and back-along with skin pigmentation and leg ulcers. A third category includes patients exhibiting a combination of both patterns.¹² Most commonly, patients present with a classical triad of abdominal pain, ascites, and hepatomegaly.¹³ Additionally, variceal

bleeding occurs in approximately 5–21% of cases.² Various clinical presentations of Budd–Chiari syndrome are illustrated in Figure 2.

In patients presenting with acute or persistent liver dysfunction, evaluation for possible obstruction of the hepatic venous outflow should be considered. In acute cases, serum transaminase levels are typically elevated, although a rapid decline may also be observed. Laboratory findings such as albumin, bilirubin, and international normalized ratio (INR) may vary depending on the disease course. In cases where MPNs are the underlying cause, splenomegaly is often present, and platelet counts frequently exceed $200,000 \times 10^9$ per liter. In patients with ascites, an elevated serum–ascites albumin gradient (SAAG) may be indicative of Budd–Chiari syndrome.¹⁴

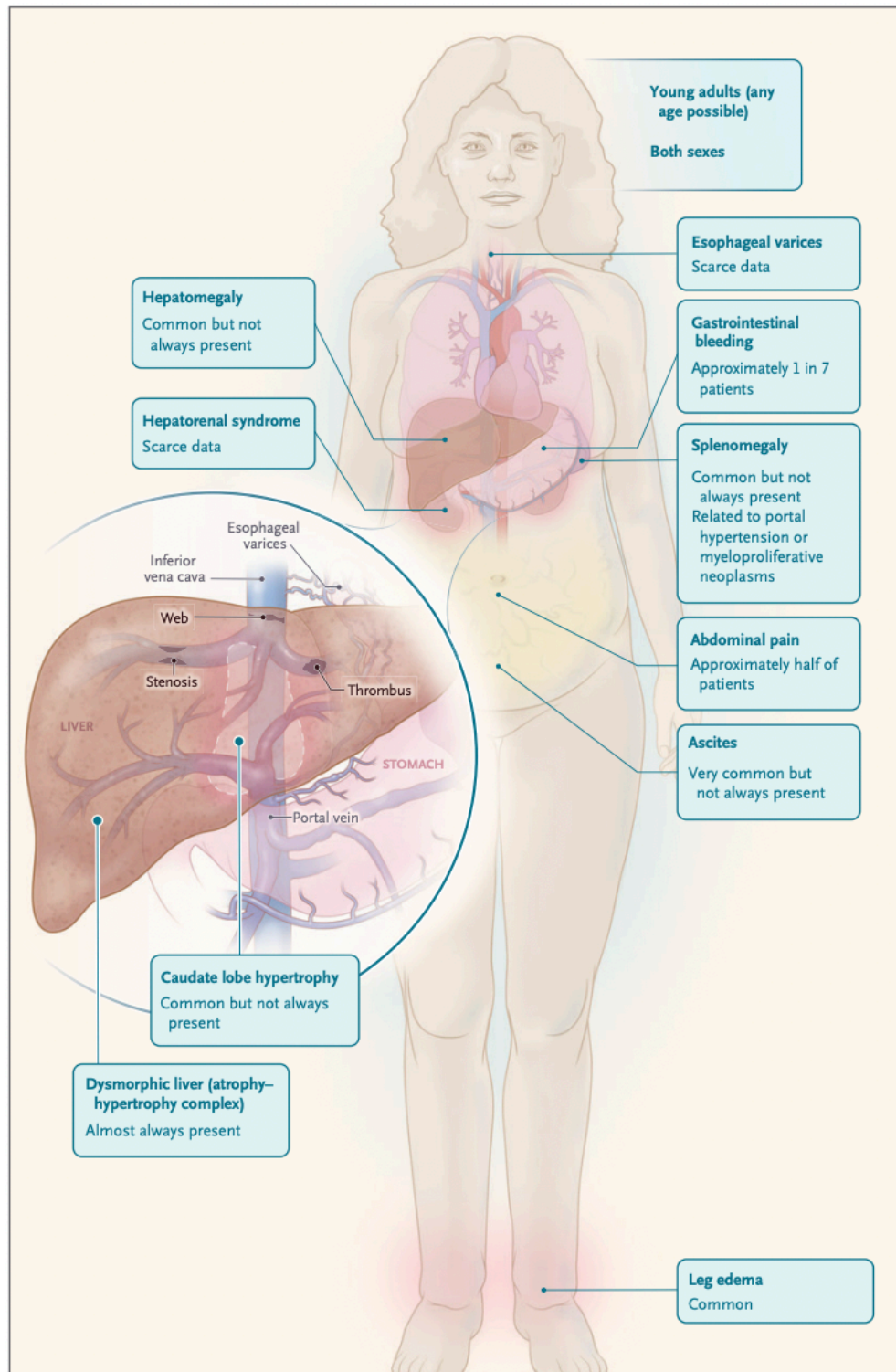


Figure 2. Clinical Manifestation of Budd-Chiari Syndrome¹⁴

DIAGNOSIS

3 Imaging modalities such as doppler ultrasonography (US), computed tomography (CT), and MRI play a crucial role in the diagnosis of BCS. In most cases, non-invasive imaging is sufficient to establish the diagnosis. However, in diagnostically challenging cases, venography and liver biopsy may be considered to confirm the condition.⁷ The characteristic imaging findings associated with BCS are summarized in Table 1.

Ultrasonography (US)

Doppler ultrasonography (US) is considered an appropriate first-line imaging modality for patients with suspected BCS.¹⁵ Its advantages include widespread availability, low cost, and the absence of ionizing radiation.¹⁶ The sensitivity and specificity of Doppler-US for diagnosing BCS are reported to be approximately 87.5% and 85%, respectively. However, its limitations include dependence on operator expertise, technical difficulties in patients with obesity or excessive bowel gas, and a limited ability to provide consistent anatomical detail required for planning endovascular or surgical interventions.²

Computed Tomography (CT)

4 Computed tomography (CT) is one of the most frequently utilized imaging modalities in cases with suspected BCS. CT allows for visualization of vascular abnormalities, hepatic morphological changes, and vascular mapping, which is particularly useful prior to interventional procedures or surgery.¹⁶ Computed tomography imaging can identify the location and extent of venous thrombosis or stenosis and is valuable for delineating vascular anatomy before transjugular intrahepatic portosystemic shunt (TIPSS) placement.¹⁷ Sensitivitas dan spesifisitas CT venography adalah 86,1% dan 97,3%. However, its main limitations include higher cost and reduced reliability in consistently and accurately detecting venous abnormalities.²

Magnetic Resonance Imaging (MRI)

2 Magnetic resonance imaging (MRI) offers higher diagnostic accuracy compared to both CT and Doppler US. Magnetic resonance imaging is a valuable imaging modality as it enables comprehensive assessment of vascular abnormalities, hepatic morphological changes, and detailed mapping of both intrahepatic and extrahepatic vasculature, as well as the evaluation of hepatic

nodules. However, MRI may be challenging to perform in patients with ascites due to the presence of artifacts and the difficulty of maintaining a supine position during the examination.^{15,16}

Table 1. Imaging Findings of Budd-Chiari Syndrome¹⁷

	Acute	Subacute and chronic
Doppler	Thrombosed enlarged hepatic veins	(a) Hepatic venous web, stenosis, occlusion, obliteration (b) Flow in the hepatic veins—absent, turbulent or reversed flow. “Minaret sign” in severe stenosis or occlusion of inferior vena cava (c) Intrahepatic comma-shaped hepatic venous collaterals
CT	(a) Distended vein with filling defect (b) Decreased peripheral parenchymal enhancement with “flip flop” pattern	(a) Altered morphology of liver (b) Extrahepatic collaterals
MRI	(a) Altered T2W signal intensity of vein (b) Non-opacified hepatic vein and inferior vena cava with contrast imaging	(a) Volume redistribution (b) Regenerating nodules

TREATMENT

The current recommended treatment approach for BCS includes lifelong anticoagulation therapy, complemented by various invasive interventions such as angioplasty, TIPS, and liver transplantation.¹⁸ The therapeutic algorithm for BCS can be stratified according to the patient's clinical condition. These treatment pathways are illustrated in Figure 3 and Figure 4.

Medical Therapies

Anticoagulation, as the first-line therapy, should be administered to all patients with BCS. Low-molecular-weight heparin (LMWH) is recommended as the initial treatment for a duration of at least 5-7 days, followed by lifelong warfarin therapy, aiming for an international normalized ratio (INR) target of 2-3. Potential complications, such as bleeding, should be closely monitored. Notably, heparin-induced thrombocytopenia (HIT) occurs more frequently in patients with BCS compared to the general population. In pregnant patients, warfarin is contraindicated, and LMWH is the preferred anticoagulant.²

Direct oral anticoagulants (DOACs) offer the advantage of not requiring regular monitoring, as is necessary with vitamin K antagonists (VKAs), thereby improving convenience and potentially enhancing patient adherence. Although DOACs are not yet broadly recommended as standard therapy for BCS, some studies suggest they are relatively safe and may be beneficial in patients who struggle to maintain a therapeutic INR or require long-term anticoagulation.¹⁹

11

However, data on the use of DOACs in BCS remain limited. While certain reports support their safety, caution is warranted, as DOACs are metabolized in the liver, and there have been cases of hepatic function deterioration associated with their use.²

Thrombolysis

In cases of acute BCS, thrombolysis of the affected hepatic veins may be performed using either pharmacologic agents or mechanical techniques involving balloon catheters.² In carefully selected patients with recent and partial thrombosis, the local administration of thrombolytic agents such as recombinant tissue plasminogen activator (tPA), streptokinase, or urokinase-often in conjunction with angioplasty or stent placement-can facilitate the restoration of hepatic venous outflow.²⁰

Angioplasty Recanalization

Angioplasty recanalization serves to relieve obstruction and improve hemodynamics in hepatic venous outflow. Balloon angioplasty is regarded as the preferred invasive intervention, particularly in symptomatic BCS cases involving membranous or segmental obstruction.² In certain patients, the underlying cause is a partial or localized narrowing of the upper hepatic veins or the suprahepatic segment of the IVC. In such scenarios, percutaneous transluminal angioplasty-with or without stent placement-offers a safe and effective approach to restoring hepatic venous drainage.²¹ The procedure is generally well-tolerated, and successful recanalization may reduce the risk of hepatic dysfunction and the incidence of post-procedural hepatic encephalopathy.²

Transjugular Intrahepatic Portosystemic Shunt (TIPS) and Surgical Shunting

Transjugular intrahepatic portosystemic shunt (TIPS) and surgical shunting are considered secondary treatment options, typically reserved for patients who do not respond to pharmacological therapy and angioplasty recanalization. The presence of hepatic vein obstruction in BCS presents technical challenges for TIPS placement, making the procedure more complex compared to patients with cirrhosis. However, the incidence of hepatic encephalopathy following TIPS is generally lower in BCS patients. Over the past decade, TIPS has emerged as the preferred alternative to surgical shunting, although surgery remains a viable option when TIPS is not feasible. Reported five-year survival rates following TIPS range from 72% to 96%.² In selected

patients awaiting liver transplantation, TIPS may serve as a bridging therapy, potentially improving clinical status and reducing the need for transplantation.²¹

Liver Transplant

Liver transplantation represents the final treatment option for BCS in cases where less invasive therapies have failed. However, it may be considered as a first-line intervention in patients presenting with acute hepatic failure. The 10-year post-transplant survival rate is approximately 68%. Patients with MPNs typically exhibit mature and well-differentiated granulocytes, and as a result, the risk of post-transplant infections is not significantly higher than in patients without MPNs.²¹ Recurrence of BCS following transplantation appears to be low, likely due to the long-term use of anticoagulant therapy after the procedure.²

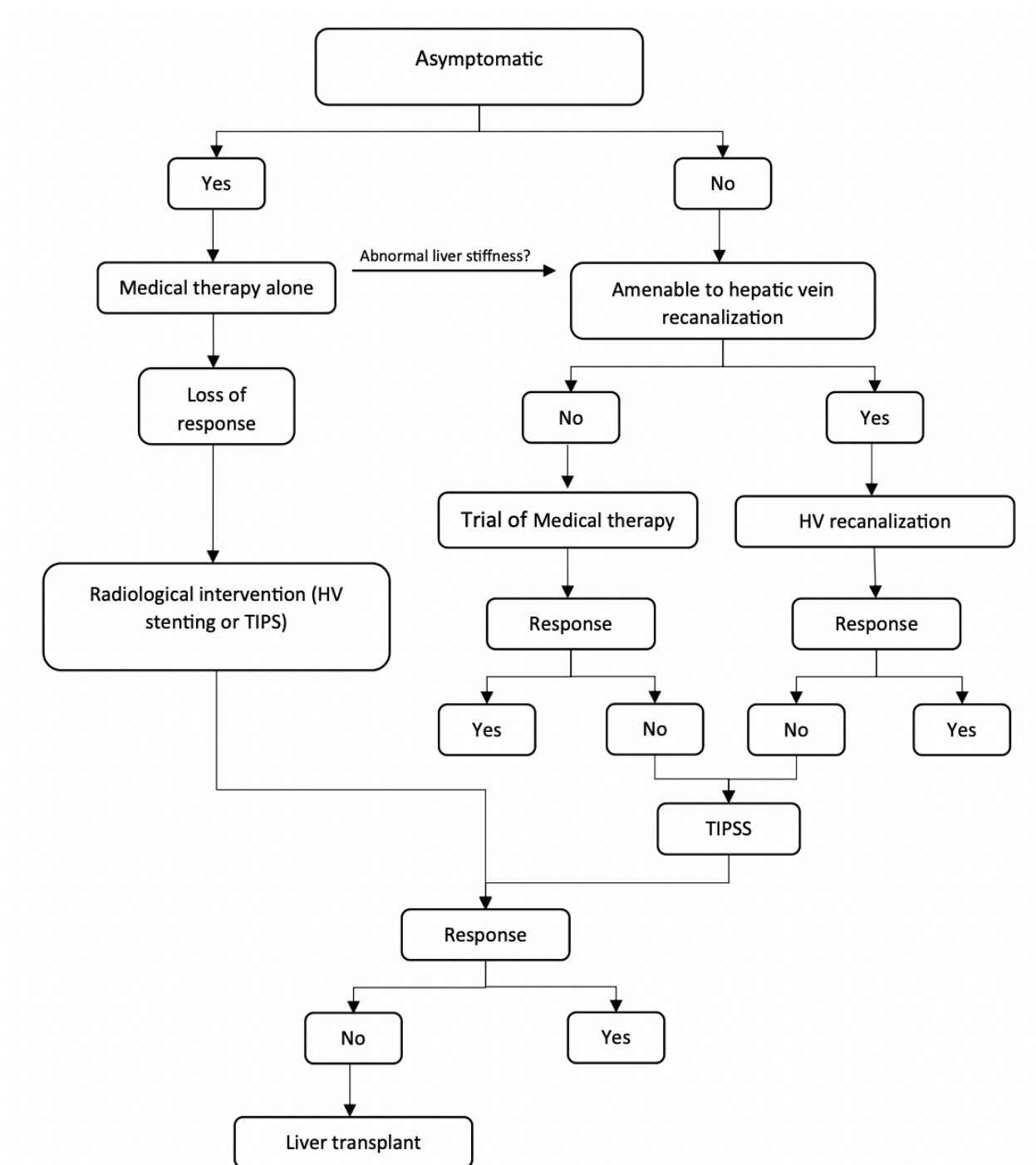


Figure 3. Management strategy for subacute or chronic Budd–Chiari syndrome caused by hepatic vein obstruction²

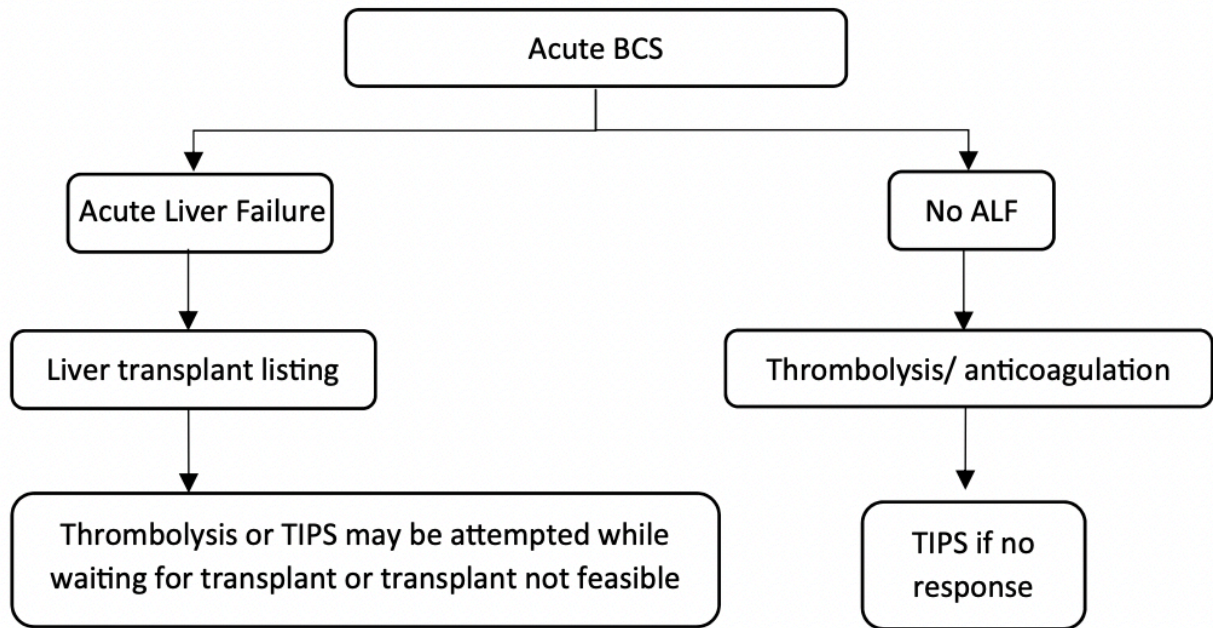


Figure 4. Management strategy for acute Budd–Chiari syndrome²

CONCLUSION

Budd–Chiari syndrome is a condition resulting from partial or complete obstruction of hepatic venous outflow. The clinical presentation varies widely, ranging from asymptomatic cases to fulminant liver failure. Management of BCS should be tailored to the patient's clinical condition and disease severity.