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Review article: a multidisciplinary approach to the diagnosis and management of Budd-Chiari syndrome

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Summary

Background: Budd-Chiari syndrome (BCS) is a rare but fatal disease caused by obstruction in the hepatic venous outflow tract.

Aim: To provide an update of the pathophysiology, aetiology, diagnosis, management and follow-up of BCS.

Methods: Analysis of recent literature by using Medline, PubMed and EMBASE databases.

Results: Primary BCS is usually caused by thrombosis and is further classified into "classical BCS" type where obstruction occurs within the hepatic vein and "hepatic vena cava BCS" which involves thrombosis of the intra/suprahepatic portion of the inferior vena cava (IVC). BCS patients often have a combination of prothrombotic risk factors. Aetiology and presentation differ between Western and certain Asian countries. Myeloproliferative neoplasms are present in 35%-50% of European patients and are usually associated with the JAK2-V617F mutation. Clinical presentation is diverse and BCS should be excluded in any patient with acute or chronic liver disease. Non-invasive imaging (Doppler ultrasound, computed tomography, or magnetic resonance imaging) usually provides the diagnosis. Liver biopsy should be obtained if small vessel BCS is suspected. Stepwise management strategy includes anticoagulation, treatment of identified prothrombotic risk factors, percutaneous revascularisation and transjugular intrahepatic portosystemic stent shunt to re-establish hepatic venous drainage, and liver transplantation in unresponsive patients. This strategy provides a 5-year survival rate of nearly 90%. Long-term outcome is influenced by any underlying haematological condition and development of hepatocellular carcinoma.

Conclusions: With the advent of newer treatment strategies and improved understanding of BCS, outcomes in this rare disease have improved over the last three decades. An underlying haematological disorder can be the major determinant of outcome.

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1 | INTRODUCTION

Budd-Chiari syndrome (BCS) is defined as an obstruction of the hepatic venous outflow track in the absence of cardiac or pericardial diseases.[1] It is also known as hepatic venous outflow track obstruction (HVOTO). The obstruction causing BCS is usually located in the small or large hepatic veins or in the suprahepatic portion of inferior vena cava (IVC). BCS does not include sinusoidal obstruction syndrome/hepatic veno-occlusive diseases that usually occur in the setting of exposure to toxic plants or therapeutic agents.[2]

BCS was first described in 1845 by a British physician, William Budd, in his seminal work "Diseases of the Liver", where he reported the case of a man with thickened, abnormal hepatic veins who died at King's College Hospital, London.[3] Then, in 1899, an Austrian pathologist, Hans Chiari, while working in Prague, described the clinical and pathological features of hepatic vein outflow obstruction as "obliterating endophlebitis of the hepatic veins".[4]

Significant advances in several areas of BCS have been made in the recent years. The purpose of this article is to provide an update on the practical multidisciplinary team management of this disease, with particular focus on primary BCS. The database search identified a number of publications on BCS from different countries.

2 | EPIDEMIOLOGY

BCS is a rare and potentially life-threatening condition and its prevalence differs geographically. In Western countries the estimated incidence of BCS is one in 2.5 million person-years[5] and it has been relatively consistent over different periods.[6-8] Data from outside of the Western world, however, vary significantly. In Japan, the estimated incidence of BCS was 0.13 per million per year in 1989,[9] whereas in Nepal, BCS accounted for 17% of the patients presenting with chronic liver disease with an incidence of 2.50 per million per year.[10] There is also geographic variation in gender and age at presentation of BCS. In Asia, men are affected more frequently than women with median age at presentation of 45 years. In Europe, women predominate with a relatively younger median age at presentation of 35-38.[11,12] This variation in BCS incidences between Asia and the West could be related to several factors as discussed below.

3 | AETIOLOGY AND PATHOGENESIS

BCS is classified as being primary or secondary, depending on the exact nature of the hepatic venous outflow obstruction. BCS is regarded as secondary BCS, when hepatic flow is obstructed by compression or invasion of a lesion outside the hepatic venous outflow (benign or malignant tumours, cysts, abscess etc.).[12]

BCS is regarded as primary, if flow is obstructed primarily due to a venous anomaly-usually thrombosis.[12] Primary BCS is regarded as the hepatic expression of underlying prothrombotic conditions, in particular blood disorders.[13]

Primary BCS is further classified into three types according to the anatomical location of the venous obstruction. Classical BCS in which the obstruction occurs within the hepatic vein and is more common in women. Hepatic vena cava BCS (HVC-BCS) which involves IVC obstruction with or without involvement of the hepatic veins and is more common in men.[14] The former has potentially more severe outcome than the latter, which has a more chronic evolution and milder symptoms. Small vessel BCS is very rare, in which the hepatic outflow obstruction is limited to the small intrahepatic veins.

In the Western world, classical BCS is the most common form of primary BCS, where the most frequent cause of hepatic vein occlusion is thrombosis due to thrombophilic disorders. Conversely, in Asian population, HVC-BCS is the most common form of primary BCS and is mostly idiopathic or related to anatomical anomalies such as membranous obstruction.[5] HVC-BCS more commonly presents with chronic and less severe symptoms and, therefore, requires a different therapeutic approach than the classical BCS form. The location, size and chronicity are clinically important as these dictate the patient's symptoms and direct the therapeutic approach for patient management.[5]

Irrespective of the cause, obstruction of the hepatic venous outflow track results in increased hepatic sinusoidal pressure and portal hypertension. The hepatic venous stasis and congestion lead to hypoxic damage and ischemic necrosis of adjacent hepatic parenchymal cells.[15] Chronic hepatic congestion leads to sinusoidal thrombosis and pressure, which in turn promote hepatic fibrosis.[16] If hepatic sinusoidal pressure is not relieved by therapeutic interventions or the development of venous collaterals, then nodular regeneration, fibrosis and ultimately cirrhosis occur.[17] BCS-related hepatic fibrosis is predominantly in the central part of the lobule, with central-central bridging and maintenance of vascular relationships, unlike other forms of cirrhosis. Moreover, RNA expression of fibrogenic and angiogenic factors in BCS differs from that of chronic liver disease related to alcohol or viral hepatitis.[18]

Primary BCS is considered a multifactorial disease and multicentre data found a combination of several prothrombotic conditions in 25% to 46% of the patients with BCS,[11,19-21] several times greater than expected in the general population. The discovery of one causal factor should not discourage further investigation to identify other prothrombotic conditions. Multifactorial causes may explain the rarity of BCS.[2]

The prothrombotic conditions found in BCS, in particular the classical type, include: Factor V Leiden mutation, prothrombin (PT) gene mutation, protein C deficiency, protein S deficiency, antithrombin deficiency, antiphospholipid syndrome, hyperhomocysteinemia and paroxysmal nocturnal haemoglobinuria.[22] BCS is also associated with systemic inflammatory diseases, such as Behçet's disease, sarcoidosis, vasculitis and other connective tissue diseases.[22] A detailed description of the frequency of inherited/acquired thrombophilias and risk factors found in patients with BCS compared to those with portal vein thrombosis is summarised by Poisson and colleagues.[23]

3.1 | Myeloproliferative neoplasms (MPNs)

MPNs are a group of clonal haematological diseases originating from mutated haematopoietic stem cells that are predisposed to increased risk of venous and arterial thrombosis. Within this group of diseases polycythemia rubra vera (PV), essential thrombocythaemia (ET) and primary myelofibrosis (MF) are collectively referred to as Philadelphia-negative MPNs.[32]

In Europe, MPNs are the most common aetiology of classical BCS and account for 35%-50% of cases.[11,33-35] This prevalence of MPNs among BCS patients is very high as compared to the pooled annual incidence of MPNs in Europe, which could account for only 2.51 per 100 000.[36] In Norway, recently reported prevalence of PV, ET and MF was 9.2, 8.6 and 3.0 per 10^5 inhabitants, respectively.[37]

Janus kinase 2 (JAK2) V617F mutation is detected in more than half of the patients with MPNs (97% of the patients with PV, 57% with ET and 50% with MF).[38-40] Presence of this mutation has been a diagnostic criterion for MPNs in the 2008 and 2016 WHO guidelines.[41,42] JAK2 V617F positive MPNs are more frequent in BCS than in portal vein thrombosis. Among BCS patients without known pre-exisiting MPN's, the presence of JAK2 V617F mutation is associated with subsequent development of overt MPNs in 41% of BCS. In portal vein thrombosis, JAK2V617F mutation accounts for 28% of cases.[34]

Calreticulin (CALR) is a multifunctional protein that can regulate calcium signalling and protein folding in the endoplasmic reticulum and cytoplasm.[43] Somatic mutations of the CALR gene have been identified in MPN patients lacking the JAK2 V617F mutation.[44] In a large French study of 209 patients with splanchnic vein thrombosis (SVT), CALR mutations were found in 1.9% and represented 5.4% of the patients with an underlying MPN.[45] The reported incidence of CALR mutation in BCS ranges from 0% to 2.9%.[46]

A recent systematic review and meta-analysis of eleven publications (two from Asia) explored the significance of screening for CALR mutations in patients with SVT. The pooled prevalence of CALR mutation in all BCS patients was 1.41%; in patients with MPN it was 2.79%; in BCS with JAK2V617F negative MPN it was as high as 17.22%.[47]

In light of the low prevalence, a French group highlighted that in order to avoid 96% of the unnecessary CALR mutation testing in patients with SVT, it should only be performed in those who have a splenomegaly $\geq$16 cm, a platelet count $>200 \times 10^9$/L and no JAK2 V617F mutation.[23]

It is, therefore, mandatory to screen all BCS patients for underlying MPN mutations even if blood counts are normal, as many have masked polycythaemia. Given its high frequency in MPNs; the JAK2 V617F mutation should be evaluated first, followed by targeted CALR mutation testing. This approach would increase the diagnostic yield of MPNs in patients with BCS and would reduce the need for additional investigations.[45] However, with the increasing use of new technologies all the myeloproliferative mutations can be screened together. Each centre will have its own molecular diagnostic strategy, but increasingly new technology such as next generation sequencing will allow broad screening for the relevant mutations whilst minimising delays in diagnosis.

In contrast to European countries, MPNs are less frequent in BCS patients from China and are only found in 4%-5% of the patients (PV 2% and ET in 1%-2%). JAK2 V617F mutation is found in only 0%-5% of patients diagnosed with primary HVC-BCS.[48-51] The low prevalence of the JAK2 V617F mutation in patients with BCS suggests that MPN might be an uncommon aetiological factor of BCS in China. Pure hepatic vein obstruction and coexistence of splenomegaly and platelet count of greater than 100×10^9/L could be associated with the JAK2 V617F mutation in Chinese BCS patients.[48]

3.2 | Inherited thrombophilia

Inherited thrombophilias are germ line mutations and result in increased thrombosis due to either an impaired neutralisation of thrombin (eg, anti-thrombin deficiency) or failure to control the generation of thrombin (eg, Factor V Leiden, protein C deficiency, protein S deficiency and the G20210A prothrombin gene mutation).[52]

Factor V Leiden is found in 12%-31% of the European BCS patients[33,53,54] and its presence carries a relative risk of 11.3 for developing BCS.[20] In a French study, factor V Leiden was associated with other risk factors for thrombosis in most BCS patients and was found to be a major cofactor of BCS developing during pregnancy.[55]

Notably, compared with Western general population, the factor V Leiden is rare in the Chinese BCS patients.[33]

The G20210A Prothrombin gene mutation is a relatively uncommon (<5%) and is not significantly associated with risk of BCS.[56,57] It was found in 2%-8% of the patients with classical BCS and 0% of the patients with HVC-BCS.[14] Prothrombin mutations are even rarer in the Chinese BCS patients.[34] It is, therefore, necessary that other prothrombotic risk factors should be considered as causing factors for BCS.

Anti-thrombin, protein C and protein S are the most important natural anticoagulant proteins and their deficiencies are closely associated with risk of venous thromboembolism. It is difficult to estimate the actual prevalence of inherited anti-thrombin, protein C and protein S deficiencies in BCS patients[58] as their actual levels may fall due to their consumption in the setting of acute thrombosis; and since these factors are produced in the liver, in patients with liver disease, anti-thrombin, protein C and protein S levels may be depressed according to the severity of liver dysfunction.[58] However, this prevalence is noted to be very low in Europe in a systemic review and meta-analysis.[33,59] Information regarding the prevalence and significance of inherited anti-thrombin, protein C and protein S deficiencies in Chinese BCS patients is lacking.[33]

Given the high frequency of underlying haematological disorders in BCS, haematological expertise is vital for both investigation and treatment.[22]

TABLE 1 Studies using percutaneous recanalisation/angioplasty in BCS

Reference	Study, published year (Country)	Description	No of patients (M/F), Median age/follow-up period	Prognosis/outcomes	Comments
24	Fu, Li, Cui et al, 2015 (China)	Retrospective study of consecutive patients with combined-type (Hepatic vein-cava) BCS, treated with percutaneous recanalization (from December 2007 to August 2014)	N = 62 52 patients underwent single IVC recanalization whereas 8 patients had combined IVC and HV recanalization.	Technical success was achieved in 60 patients. Clinical success was achieved in all of the 60 patients. The cumulative 1-, 2- and 4-y survival rates were 98.3%, 96.5% and 92.7% respectively.	Three patients died during the follow-up. Percutaneous recanalization was suitable for most combined-type BCS patients with excellent short-term survival. Single IVC recanalization was usually enough for decompression in patients with patent AHV. Combined IVC and HV recanalization was performed in patients without patent AHV.
25	Cui, Fu, Li, Xu, 2016 (China)	Retrospective study of consecutive Chinese HV-type BCS from March 2009 to November 2014.	N = 143 111 patients had recanalization of main HV (MHV) and 29 had accessory HV (AHV) recanalization. 136 patients (who had achieved clinical success) were followed for 7-75 mo (mean 33.9 ± 15.3 mo).	Technical success was achieved in 140 of 143 patients (98%). Clinical success was achieved in 136 of 140 these patients (97%). The cumulative 1-, 3- and 6-y primary patency rates were 91.1, 77.4,and 74.0% respectively. The cumulative 1-, 3- and 6-y secondary patency rates were 97.0, 92.4 and 88.8% respectively. The cumulative 1-, 3- and 6-y survival rates were 97.7, 92.2 and 90.0% respectively.	Twenty-eight patients experienced re-obstruction of MHV (n = 24) or AHV (n = 4) at 3 to 36 mo (mean 18.0 ± 11.5 mo) after treatment.
26	Tripathi, Sunderraj, Vemala, 2017 (UK)	Single centre retrospective analysis of BCS patients referred for radiological assessment ± intervention over a 27-y period.	N = 63 patients (out of 155 BCS patients) and were compared to 59 BCS-TIPSS patients. Male: Female ratio 27:36 32 patients had venoplasty alone. 31 had endovascular stents. Mean age, 34.9 ± 10.9 y. Median follow-up, 113.0 mo.	Technical success was 100%, with symptoms resolution in 73%. Cumulative secondary patency at 1, 5, 10 y was 92%, 79%, 79% and 69%, 69%, 64% in the stenting and venoplasty groups respectively. Actuarial survival at 1, 5, 10 y was 97%, 89% and 85%.	10 patients required TIPSS and 8 underwent surgery. When compared to TIPSS, HV interventions resulted in similar patency and survival rates but significantly lower procedural complications (9.5% vs 27.1%) and hepatic encephalopathy (0% vs 18%). Patient age predicted survival following multivariate analysis.
27	Rathod, Deshmukh, Shukla et al, 2017 (Mumbai, India)	Retrospective study of treatment efficacy and safety of radiological intervention (hepatic vein, collateral vein or IVC plasty	N = 190 patients (84 patients had percutaneous recanalization). HV obstruction	Hepatic vein plasty/ stenting was performed in 38 patients; Collateral vein stenting in 3 patients and	Technical success rate of 97.5% and 97.6% was observed in the IVC group and HV/collateral vein group respectively.

(Continues)

TABLE 1 (Continued)

Reference	Study, published year (Country)	Description	No of patients (M/F), Median age/follow-up period	Prognosis/outcomes	Comments
		with or without stenting, or TIPSS) in BCS patients (between January 2008 and June 2014).	was seen in 147 patients, IVC obstruction in 40 patients, concomitant hepatic vein & IVC obstruction in 3 patients. Mean [SD] age = 26.9 [11.5] y; Male = 102;F = 88 Follow-up median duration = 42 (12-88) mo.	complete response was noted in 31 (75.6%) of these 41 patients. 2 patients need TIPSS afterwards. IVC plasty/stenting was performed in 40 patients and 34 (85%) patients showed complete response. Both IVC and HV stenting was done in 3 patients and TIPSS (covered stent) in 106 patients. Overall clinical response was seen in 153 patients (80.5%).	Repeat interventions were required in 19 patients (10.0%) (Including all interventions). Overall complications were noted in nine patients (4.7%).
28	Shalimar, Kedia, Sharma et al, 2016 (Delhi, India)	Analysis of consecutive BCS patients between January 2006 and December 2014 were included.	N = 334 patients Male = 56.6% Median age 24 (3-62) y. 113 patients (33.8%) were lost to follow-up after a mean interval of 12.1 mo. The mean follow-up of the remaining 221 patients was 35.2 mo [median (range): 30 (1-132) mo].	Hepatic vein obstruction alone was seen in 160 patients (48%) – 62 had percutaneous plasty ±stenting; *34 had TIPSS*. Combined hepatic venous- IVC obstruction was noted in 153 (46%) patients- 52 underwent IVC angioplasty alone, 26 had only angioplasty of HV and IVC, 21 IVC angioplasty and HV stenting and 7 had IVC stenting alone. *11 patients had TIPSS*. IVC obstruction alone was observed in 21 patients (6.3%). 20 patients had intervention. Interventional therapy was performed in 233/334 (70%) with 90% overall technical success. Clinical response was complete in 166 (71.2%), partial in 58 (24.9%) and no response in nine (3.9%).	Most of patients (69%) had chronic presentation (over 6 mo duration of symptoms) and were young. Advanced Child class and no response to intervention are associated with poor outcomes on multivariate analysis. Author proposed new simple score – AIIMS HVOO score – that seemed to have better prognostic accuracy (score>3.2 had AUROC 0.78, 95% CI 0.68-0.89) when compared to other prognostic indices. This score needs further validation.
29	Han, Qi, Zhang et al, 2013 (China)	Retrospective study of consecutive Chinese BCS patients treated with percutaneous recanalization, between July 1999 and August 2010.	N = 177 [IVC type = 33 HV type = 50 Combined-type = 40] Median follow-up = 30 mo	Percutaneous recanalization was technically successful in 168 of the 177 patients (95%). 51 of the 168 patients (30%) were treated	Procedure-related complications occurred in seven of the 168 patients (4%). [Hepatic capsule perforation in 2 patients; IVC rupture in one; haematuria related to

(Continues)

TABLE 1 (Continued)

Reference	Study, published year (Country)	Description	No of patients (M/F), Median age/follow-up period	Prognosis/outcomes	Comments
			(range, 0.25-137 mo).	with percutaneous transluminal angioplasty (PTA) alone and 117 (70%) were treated with a combination of PTA and stent placement. The cumulative 1-, 5- and 10-y primary patency rates were 95%, 77% and 58% respectively. The cumulative 1-, 5- and 10-y secondary patency rates were 97%, 90% and 86% respectively. The cumulative 1-, 5- and 10-y survival rates were 96%, 83% and 73% respectively.	heparin use in 3 patients and supraventricular tachycardia in one patient]. 22 patients died during follow-up. Independent predictors of survival included variceal bleeding, increased alkaline phosphatase, increased blood urea nitrogen levels and reocclusion.
30	Fan, Liu, Che et al, 2016 (China)	To evaluate the clinical efficacy and safety of HV angioplasty and TIPSS in the treatment of HV occlusive BCS patients – between May 1995 and December 2014).	N = 60 patients HV angioplasty = 18 patients; Combined HV & IVC angioplasty = 9 (with HV and IVC occlusion). TIPSS = 12 patients (with HV occlusion): Modified TIPSS = 21 (with extensive HV occlusion). Follow-up = 82.25 ± 46.16 mo.	Technical success was achieved in all 60 patients.	Two patients died from hepatic failure during hospitalisation. Three patients underwent re-intervention for stenotic shunt and other three needed repeated dilation of the stenotic HV.
31	Zhang, Fu, Xu et al, 2003 (China)	Retrospective analysis to evaluate the long-term effect of percutaneous stent placement in patients with BCS at a single centre. [From April 1994 to June 2001]	N = 115 patients. 65 males; 50 females. Average age – 37.3 ± 12.7 y (SD, range 17-67) 102 patients had IVC stent placement (85 patients had IVC stent alone), 30 patients had HV stent placement and 17 of them underwent both IVC stent and HV stent.	The successful rates in placing IVC stent and HV stent were 94% (96/102) and 87% (26/30) respectively. 97 patients with 112 stents (90 IVC stents, 22 HV stents) were followed up. 96.7% (87/90) IVC stents and 90.9% (20/22) HV stents remained patent during follow-up periods (mean 49 mo, 45 mo respectively).	Five of 112 stents in the 97 patients developed occlusion. Absence of anticoagulants after the procedure and segmental occlusion before the procedure were related to a higher incidence of stent occlusion.

BCS: Budd-Chiari syndrome; HV: Hepatic vein, IVC: Inferior vena cava, TIPSS: Transjugular-intrahepatic portosystemic stent shunt; LT: Liver transplantation; AHV: Accessory hepatic vein.

3.3 | Acquired factors

Various acquired prothrombotic conditions such as antiphospholipid syndrome, hyperhomocysteinemia and Behçet's disease can contribute to the development of BCS and in particular, paroxysmal nocturnal haemoglobinuria which is typically associated with SVT.

Antiphospholipid syndrome is a prothrombotic disorder that can result in thrombosis of both the venous and arterial circulations. Presence of lupus anticoagulant is associated with the highest risk of developing thrombosis and is more specific for diagnosis of antiphospholipid syndrome than anti-beta 2 glycoprotein-1 antibodies and anti-cardiolipin antibodies.[60] Antiphospholipid syndrome appears to be the third most common prothrombotic factor in classical BCS in the West.[2] Prevalence of antiphospholipid antibodies is estimated to be between 18% and 25%.[11,19] This prevalence seems to be consistent with those reported in one Chinese study of BCS patients, in which antiphospholipid antibodies were positive in 17% (25/145 patients).[49] However, due to the poor specificity of antiphospholipid antibodies in liver disease, a recent systematic review and meta-analysis, suggested that there is insufficient evidence regarding the association between antiphospholipid antibodies and BCS.[61]

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare acquired disorder of haematopoietic stem cells and is diagnosed by flow cytometry of peripheral blood for detection of the CD55 and CD59 deficient clone. Thrombosis is one of the major clinical presentations of this disorder and the majority of thromboses occur in the splanchnic veins, especially the hepatic vein (40.7%).[62] In Europe, PNH accounts for up to 10.5% of the cases of classical BCS.[26,33,63] By comparison, PNH is rare in Asian BCS patients.[64]

Hyperhomocysteinaemia is associated with an increased risk of venous thrombosis in the general population. A systematic review and meta-analysis demonstrated that BCS patients had a significantly higher prevalence of hyperhomocysteinaemia and homozygous MTHFR C677T mutation than healthy controls.[65] In Europe, prevalence of hyperhomocysteinaemia in BCS patients ranges from 11% to 22%[11,66] in published studies, whereas it seems to be double the prevalence in China.[49,50,67]

Behçet's disease is a chronic relapsing systemic inflammatory disease with vasculitis being a major component. BCS has shown to occur in up to 3% of cases of Behcet's syndrome and it often affects the portal vein and IVC.[68]

Many other systemic diseases have been found to be associated with BCS, albeit less frequently, including: inflammatory bowel disease, sarcoidosis, systemic lupus erythematosis, mixed-connective tissue disease, Sjögren's syndrome, nephrotic syndrome and protein-losing enteropathy.[11,22,33,69]

Oral contraceptive (OCP) use was identified in over 30% of female patients with BCS in multicentre European studies.[11,53] The relative risk of hepatic vein thrombosis in OCP users is low, necessitating the consideration of other risk factors for BCS.[20,70,71]

On the other hand, exposure to oral contraceptives has not been evaluated in patients with BCS from Asia. In China, use of oral contraceptives is less than 2%, compared with 30% in Europe.[72,73]

Pregnancy also appears to be a risk factor for classical BCS. However, another underlying condition is usually present in BCS associated with pregnancy. [11,74]

Pregnancy-related BCS is less frequent in China than in Europe. In a meta-analysis, the pooled prevalence of pregnancy-related BCS was 5.0% (95% confidence interval: 3.1%-7.3%) in Europe versus 1.8% (95% confidence interval: 0.4%-4.1%) in China.[75]

Poverty may not be considered a direct cause of BCS. However, hygiene and sanitation situation is often substandard in poverty-stricken regions, thereby leading to a higher frequency of bacterial infections,[76] which can lead to BCS.[77] A significantly higher proportion of poverty is noted in Chinese BCS patients than in controls (51.8% vs. 0.6%).[33] This is also the case in Nepal. Data collected in 1990s showed that nearly 90% of 150 patients with IVC obstruction had low socio-economic status.[10]

4 | CLINICAL PRESENTATION

The clinical presentation of BCS is heterogeneous and ranges from absence of symptoms to fulminant liver failure.[1] The clinical presentation depends on the extent and rapidity of hepatic venous outflow obstruction and the presence of venous collateral circulation to decompress the liver sinusoids. Therefore, BCS can be classified as fulminant, acute, sub-acute or chronic.[15]

Most patients with BCS present with abdominal pain (61%), ascites (83%) and hepatomegaly (67%).[11] Fever, pedal edema and dilated truncal veins (abdominal-wall varices) are also seen in some patients. Abdominal-wall varices are associated with underlying IVC thrombosis and improve with the treatment of thrombosis.[78] Less common clinical manifestations include oesophageal bleeding (5%) and hepatic encephalopathy (9%).[11] About 15% of the patients are asymptomatic owing to preservation of some hepatic venous outflow.[79]

"Clinicopathological dissociation" has been noticed between the acuteness of clinical manifestations and the actual duration of the disease. Most patients presenting with acute manifestations have extensive fibrosis or cirrhosis in liver biopsies, indicating a long-standing process, previously subclinical. Less than 10% of the patients presenting with an acute illness actually have an acute disease process with no evidence of chronicity (fibrosis).[80]

5 | DIAGNOSIS

BCS should be considered in any patient with acute or chronic liver disease, especially presenting with signs or symptoms of hepatic venous outflow obstruction. BCS should always be considered in patients labelled as cryptogenic cirrhosis[81] and in any patient with a known prothrombotic condition presenting with a liver disease.[82]

The diagnosis of BCS is based on the demonstration of a HVOTO[83] and this can be accurately demonstrated on noninvasive imaging such Doppler ultrasonography, computed tomography or

magnetic resonance imaging. It is very important that the radiologist is both experienced and is alerted to the clinical suspicion of BCS.

The presentation on imaging depends on the stage of the disease. Imaging features include: occlusion or compression of the hepatic veins and/or the IVC; stagnant, or inverted venous flow and venous collaterals (called direct signs); and morphological features showing the consequences of outflow obstruction (called indirect signs) such as hypertrophy of unaffected segments (caudate lobe in particular), atrophy of affected segments leading to delayed nodule formation and portal hypertension.[84] Other nonspecific signs such as splenomegaly, inhomogeneous liver parenchyma and ascites can be seen frequently on imaging (Figure 1).[85]

Imaging can also help in the differentiation of primary and secondary BCS as it can identify space occupying lesions or tumours infiltrating the hepatic veins or IVC.[22] Venography is recommended if the diagnosis remains uncertain or for the characterisation of anatomy prior to planning treatment (Figures 2 and 3).[1]

If imaging has failed to demonstrate obstruction of large veins then a liver biopsy (Figures 4–7) can be used in order to assess for small vessel BCS (small hepatic vein occlusion) or veno-occlusive disease (sinusoidal obstructive syndrome).[1] Biopsy usually shows centrilobular congestion, red blood cells within the space of Disse, hepatocyte atrophy or loss of hepatocytes, perisinusoidal fibrosis without inflammatory infiltrates. These histological "vascular" features are found in patients with chronic congestion of any cause (BCS, veno-occlusive disease, or cardiac or pericardial disease). Chronic congestion may lead to "cardiac" cirrhosis, with retention of vascular relationships, but the approximation of the hepatic and portal vessels due to parenchymal collapse. Histological findings do not relate to prognosis, presumably due to the patchy nature of the obstruction and sampling area.[86] Liver biopsy is also useful in excluding secondary BCS due to malignancy.

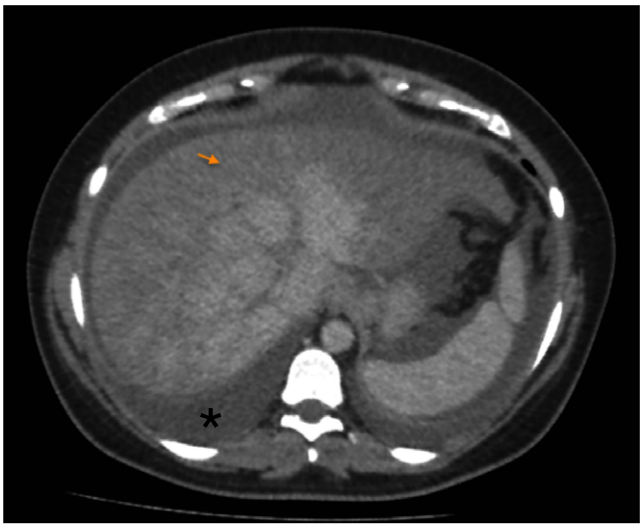

FIGURE 1 Computed tomography scan demonstrating typical findings of Budd Chiari, thrombosed hepatic veins, congested liver and heterogeneous enhancement (arrow), patent portal veins and ascites (asterisk)

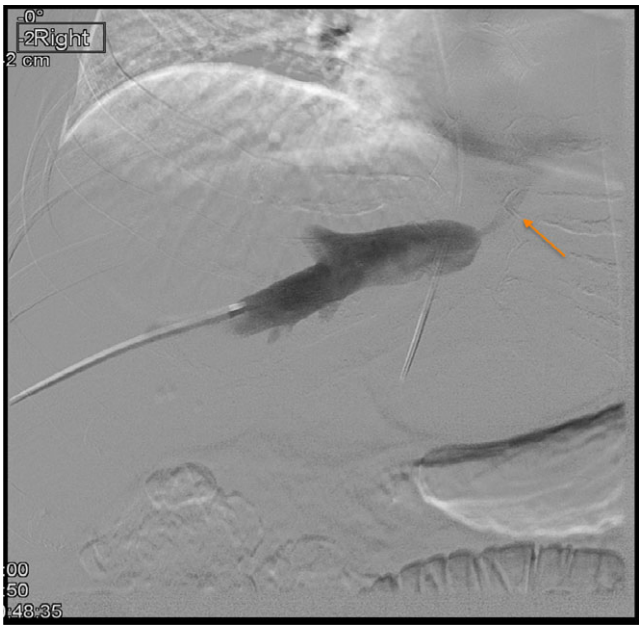

FIGURE 2 Transhepatic venogram showing no flow in hepatic vein (arrow) in patient A

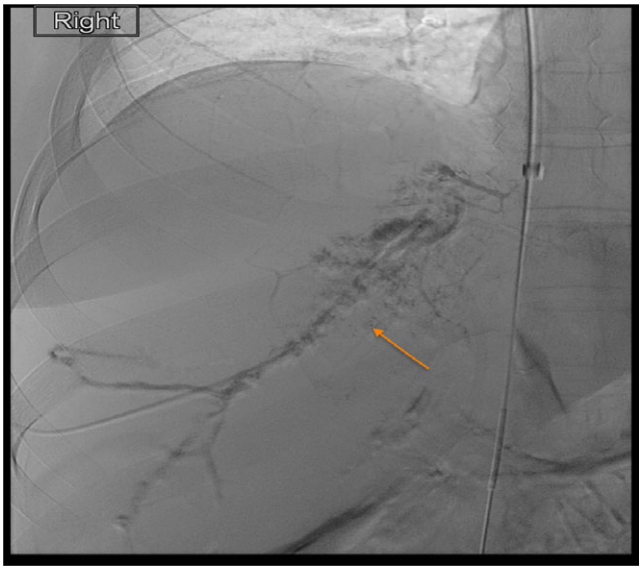

FIGURE 3 Thrombosed hepatic vein (arrow) in patient C

Standard laboratory tests (full blood count, liver and kidney function tests, international normalised ratio [INR]) are helpful in estimating the severity of the disease and predicting mortality. Full blood count and blood film may reflect underlying haematological disorder. Albumin, PT or INR, bilirubin, alanine aminotransferase and creatinine are commonly used prognostic indices in BCS [Child- Pugh, model for end-stage liver disease (MELD), Clichy[87] Rotterdam index,[88] New Clichy[80] and BCS-TIPSS[89]].

Ascitic fluid analysis usually demonstrates high protein count in early BCS (due to high permeability of the sinusoidal wall) with serum ascites to albumin gradient (SAAG) >1.1 g/dl.[22] As discussed

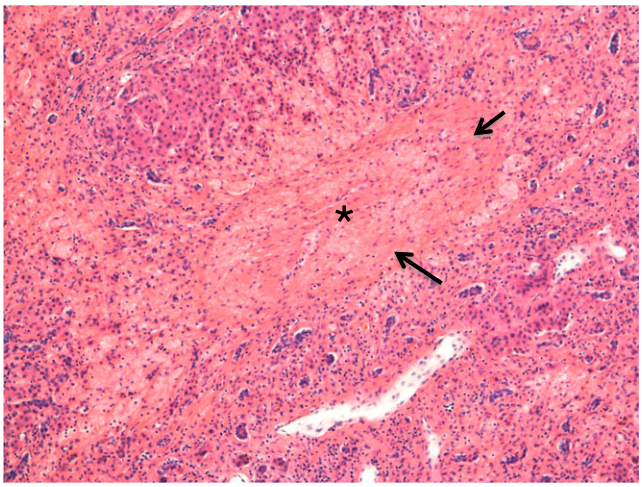

FIGURE 4 Intrahepatic venous occlusion (arrow marks vessel wall and asterisk marks the occluded lumen)

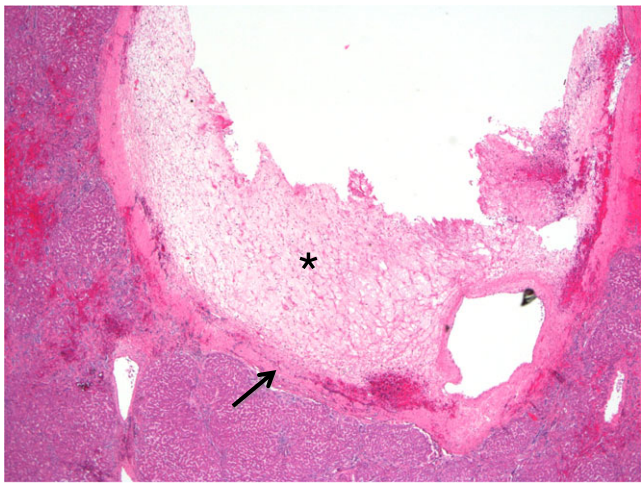

FIGURE 5 Organising thrombus within intrahepatic vein (arrow marks vessel wall and asterisk marks the occluded lumen)

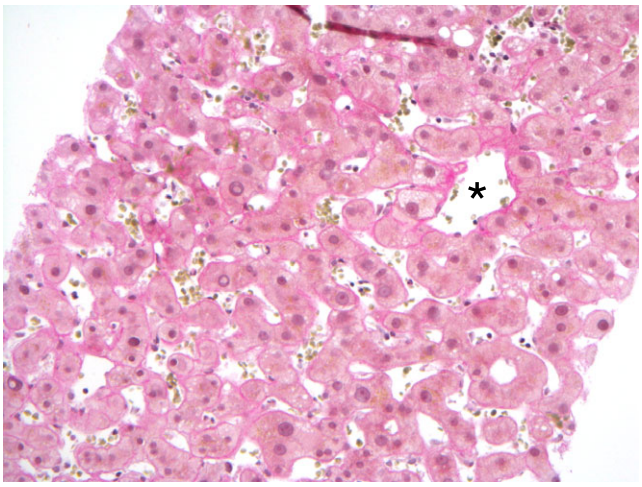

FIGURE 6 HVG stain showing perisinusoidal fibrosis (pink-red staining) with a small hepatic vein present in the top right corner (asterisk)

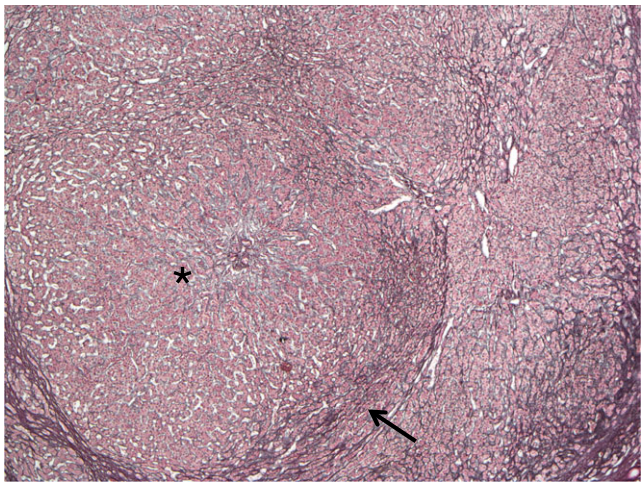

FIGURE 7 Reticulin stain showing advanced nodular regenerative hyperplasia with thin atrophic hepatocyte plates at the periphery (arrow) and expanded hyperplastic plates in the middle (asterisk)

earlier, once diagnosis of BCS is made, a thorough workup should be undertaken to identify multiple underlying prothrombotic risk factors.

6 | SMALL VESSEL BCS

Small vessel BCS is thought to be extremely rare and there is a paucity of literature on the condition.[90-93] It is characterised by hepatic outflow obstruction limited to small intrahepatic veins, with normal radiological appearances of the large hepatic veins. When faced with the latter, clinical suspicion should arise when the triad of ascites, hepato-splenomegaly and abdominal pain remain unexplained. Sinusoidal obstruction syndrome and congestive cardiac disease are excluded from the definition of small vessel BCS.

Cross-sectional imaging may highlight inhomogeneous hepatic parenchymal enhancement after intravenous contrast. However, liver biopsy is often central to establishing the diagnosis, by demonstrating the typical pathological features of BCS (see above).[90] The presence of occlusive thrombi in small hepatic veins has been described in some cases.[94] Moreover, it is recognised that patients with classical BCS can show fresh or organising thrombi in hepatic veins of any size, including small intrahepatic veins.[95] Morphometric analysis of explant livers from patients with BCS demonstrated obliterative lesions affecting small hepatic veins lesions in 67% of the cases.[96]

Sinusoidal obstruction syndrome (SOS, also known as veno-occlusive disease) is a distinct entity characterised by sinusoidal endothelial injury to the "terminal" small hepatic veins (endophlebitis) as a result of a radiation-induced or chemical toxic insult.[97] It may be seen in the context of (neo-) adjuvant chemotherapy (ie oxaliplatin for hepatic metastases and gemtuzumab/ozogamicin for acute myeloid leukaemia) or bone marrow transplantation. Other recognised causes include haematopoietic stem cell transplantation, use of herbal remedies (plant toxins/alkaloids), liver transplantation (LT)

(especially in live-related donation and with azathioprine use) and immunodeficiency. The endothelial injury is mediated by depletion of glutathione and nitric oxide and increased expression of matrix metalloproteinases and vascular endothelial growth factor.[98] The damaged cells are sloughed into the sinusoidal lumen, allowing erythrocytes and leucocytes to leak into the space of Disse. Liver biopsy in SOS shows centrilobular congestion, centrilobular hepatocyte necrosis and occlusion of small hepatic veins with perisinusoidal fibrosis.[97] Although it has been claimed that liver biopsy is able to distinguish SOS from small vessel BCS,[99] in our experience the histological findings in both can be indistinguishable. Close clinical and radiological correlation is therefore required. It is also worth noting that other conditions such as alcoholic and non-alcoholic steatohepatitis[100] and chronic granulomatous disease[101] can also cause small hepatic vein lesions.

7 | TREATMENT

BCS is a life-threatening condition, with high mortality rate without prompt treatment.[102] The management of BCS requires a multidisciplinary approach in all cases with involvement of hepatology, interventional radiology, haematology, histopathology and liver surgery. It is essential that all patients be discussed in a multidisciplinary setting.

Over the past decade, treatment of BCS has been progressively standardised[53,102,103] on the basis of a stepwise approach to control clinical manifestations (such as ascites and variceal bleeding), prevent the extension of venous thrombosis, re-establish venous drainage of the liver and identify and treat the underlying diseases promptly.[1,99] Most recommendations regarding management are based on case reports, retrospective studies and expert opinions.[1,103]

Long-term anticoagulation therapy should be promptly initiated in all BCS patients in the absence of contraindications.[1] Where possible endoscopy should be performed prior to anticoagulation to screen for gastro-oesophageal varices and primary prophylaxis to be offered to reduce the risk of variceal bleeding if indicated. In patients with persistent symptoms, endovascular procedures (thrombolysis, percutaneous transluminal angioplasty, ± stent placement) are performed to restore hepatic blood flow in patients with segmental hepatic vein (HV) or IVC obstruction. Transjugular-intrahepatic portosystemic shunt (TIPSS) or direct intrahepatic porto-caval shunts (DIPS) should be used if angioplasty/stenting is not technically feasible or in presence of severe portal hypertension or persistently deteriorating liver function. LT is the final therapeutic option in severe BCS unresponsive to hepatic venous interventions or TIPSS. LT can also be considered for first line therapy in patients that present with fulminant/acute liver failure.[104] In patients with small vessel BCS, there is no role of percutaneous recanalisation/stenting as portal hypertension is all intrahepatic. These patients should have TIPSS straightaway where indicated (Figure 8).

8 | MEDICAL TREATMENT

Patients with primary classical BCS would require anticoagulant therapy for an indefinite period of time, even after radiological or surgical interventions.[1,103] Anticoagulation alone is sufficient in controlling the mild form of liver disease in about 15% of the patients.[53,105] Low molecular weight heparin is the preferred initial anticoagulant[1] followed by vitamin K antagonists (target INR between 2 and 3). Ascites is managed with diuretics and low salt diet. Underlying prothrombotic conditions should be extensively looked for and be treated promptly.

Recent studies suggest that medical management alone can be appropriate for early classical BCS patients without evidence of significant portal hypertension (ascites, varices), in which 33%-54% of the patients treated with medical management alone showed good outcomes.[14] In contrast, only 0%-7% of the HV-cava BCS patients were treated with medical management alone.[14]

There is obvious concern regarding the use of anticoagulation in the setting of coagulopathy and varices. A high rate of bleeding complications whilst on anticoagulation (50%) has been reported in an old study including 94 consecutive BCS patients diagnosed between 1995 and 2005. However, over half of the bleeding episodes were related to and were likely provoked by an invasive procedure.[106] In contrast to this, the bleeding complications among BCS patients diagnosed between 2005 and 2007 were less frequent (17% of patients). It is likely due to better management of anticoagulation during invasive procedures and adequate pharmacological and endoscopic prophylaxis for portal hypertension-related bleeding.[53]

Primary data show that new oral anticoagulants (NOACs) are effective and safe in patients with SVT and cirrhosis, however, there are no data to support their usage in BCS patients as yet.[107] Caution is however, recommended in patients with liver dysfunction as many NOACs are metabolised by the liver. The use of warfarin is preferable as it is easier to monitor and reverse its effect if over-anticoagulated.

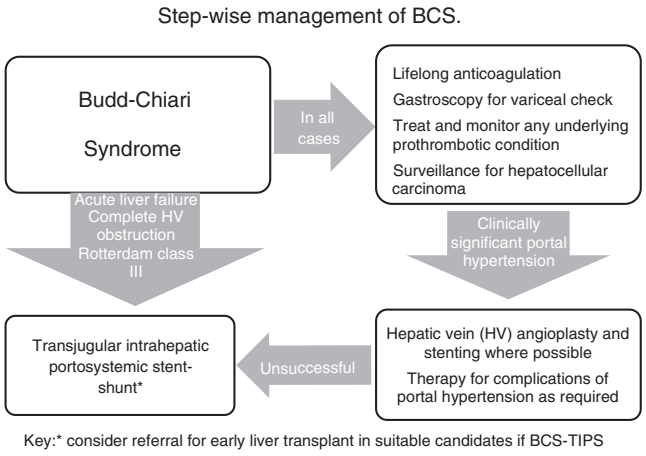

FIGURE 8 Stepwise management of Budd-Chiari syndrome

8.1 | Haematological management

Many JAK2 V617F positive patients have apparent normal blood counts but careful investigation would reveal that a proportion of these have masked polycythaemia, where blood counts may be completely normal due to blood pooling in enlarged spleens. Nuclear medicine red cell mass estimation can confirm suspected polycythaemia. Bone marrow biopsies also help to confirm MPN and MPN subtype. In patients and with overt myeloproliferative disease, BCS patients should be considered as high-risk MPN given the unprovoked thrombosis and therefore should be offered cytoreductive therapy, in addition to long term anticoagulation. Therapeutic options include hydroxycarbamide, alpha-interferons and JAK inhibitors, depending on the MPN sub-diagnosis. In cases where the blood counts are within normal range, the practice is variable, due to lack of data, but some would offer cytoreductive therapy to target a haematocrit and platelet count lower than normal. In many centres, the indication for cytoreduction is personalised depending on individual circumstances. At the pathophysiological level it is increasingly clear that the thrombogenicity of MPN is due to qualitative as much as quantitative changes of blood cells.[108]

Data on the long-term follow-up of BCS with MPN and the influence of MPN on the overall outcome of BCS are limited but likely to be heterogenous and dependent on the MPN subtype. In a recent study that included both BCS and portal vein thrombosis, MF accounted for around 15% and ET and PV each accounted for 37%-38%.[109] Another study showed that a large proportion of BCS had low JAK2 V617F allele burden and mostly normal blood counts suggestive of an early manifestation of MPN.[110] For these patients, the prognosis is likely to be very good. However, for those BCS patients who have MF or advanced PV, the outcome would at the least reflect the prognosis of the MPN subtype. In the case of MF, the prognosis may range from less than 2 years to over 10 years depending on the International Prognostic Scoring System (IPSS) score with a significant risk of leukaemic transformation.

9 | RADIOLOGICAL INTERVENTION

Vascular intervention in BCS aims to relieve hepatic congestion either through correction of obstruction or the creation of a bypass. The aim was to restore the hepatic blood flow to prevent hypoxia and hepatocyte necrosis caused by continued hepatic congestion.

9.1 | Percutaneous recanalisation/Stenting

About one-third of the BCS patients have short-length stenosis of either the hepatic veins or IVC. These patients can be treated with recanalisation by percutaneous angioplasty with or without stenting. HVC-BCS patients have undergone percutaneous recanalisation more frequently as compared to classical BCS patients.[14] Several studies have shown good long-term efficacy and survival-benefit of this procedure (Table 1).[24-31]

In a meta-analysis of over two thousand BCS patients treated by interventional treatment, pooled success rate of percutaneous recanalisation was noted to be 93.1% (95% CI 91.8%-94.3%). The pooled 1-year and 5-years survival rates for recanalisation therapy were 95.9% (95% CI 93.4%-98.3%) and 88.6% (95% CI 82.4%-94.8%) respectively.[111]

Our centre published analysis of 63 BCS patients who underwent venoplasty and compared this to a previously reported series of 59 patients treated by TIPSS.[26] Thirty-two patients were treated with HV venoplasty alone and 31 had endovascular stents placement. Over median follow-up of 113 months, technical success achieved was 100%, with symptom resolution in 73% of patients. Ten patients required TIPSS and 8 underwent surgery when long-term patency was not achieved. Actuarial survival at 1, 5, 10 years was 97%, 89% and 85% respectively. When compared to TIPSS, HV interventions resulted in similar patency and survival rates but significantly lower procedural complications (9.5% vs 27.1%) and hepatic encephalopathy (0% vs 18%).[26] Results supported the stepwise approach to the management of BCS.

Angioplasty has been extensively used in Asia with good long-term outcomes (Table 1).[24,25,27-31,112] Han et al published their experience in 168 Chinese BCS patients undergoing successful percutaneous angioplasty with median follow-up of 30 months. Long-term cumulative primary patency rates were comparable to those of previous studies in Chinese BCS patients.[29] Ten year cumulative secondary patency rate was found to be excellent (86%). Long-term outcomes were excellent in this study group and were comparable to that of European BCS patients undergoing TIPSS and LT.[89,113] However, notably the degree of liver dysfunction in patients in the European series was more severe than that in this study. Reocclusion was independently associated with poor survival in this group and authors recommended percutaneous transluminal angioplasty *combined with* stent placement to decrease the frequency of reocclusion in such patients.

In another Chinese study, absence of anticoagulation after the procedure and segmental occlusion before the procedure were related to a higher incidence of stent occlusion. Authors recommended anticoagulation following percutaneous stent placement in BCS patients especially if by segmental occlusion (Figures 9–11).[31]

9.2 | Transjugular-Intrahepatic portosystemic stent shunt (TIPSS)

For more than two decades, TIPSS has been successfully used for the management of complications of portal hypertension.[114] TIPSS (with bare stents) were first used for the treatment of BCS in the early 1990s[115,116] and it has been shown to be an effective treatment of BCS in subsequent studies.[117-119] Increasing number of *classical BCS* patients have undergone TIPSS and it seems to be most frequent treatment for BCS[12,105,120] in the Western population and LT is only considered when endovascular procedures fail to control the symptoms.[53,102] Polytetrafluoroethylene (PTFE) covered stents

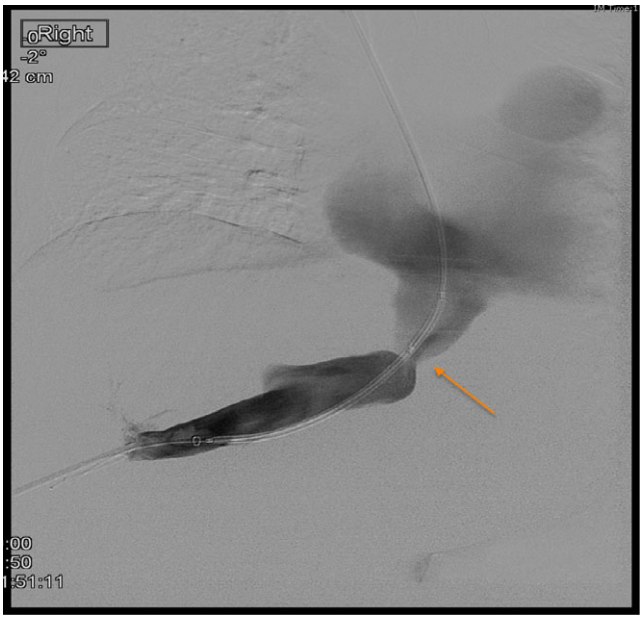

FIGURE 9 Hepatic vein stenosis post-balloon dilatation (arrow) in patient A

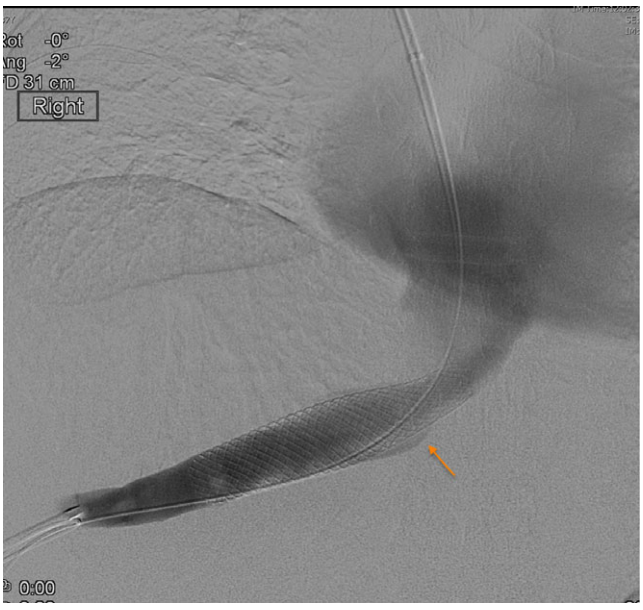

FIGURE 10 Good flow demonstrated after hepatic vein stenting (arrow) in patient A

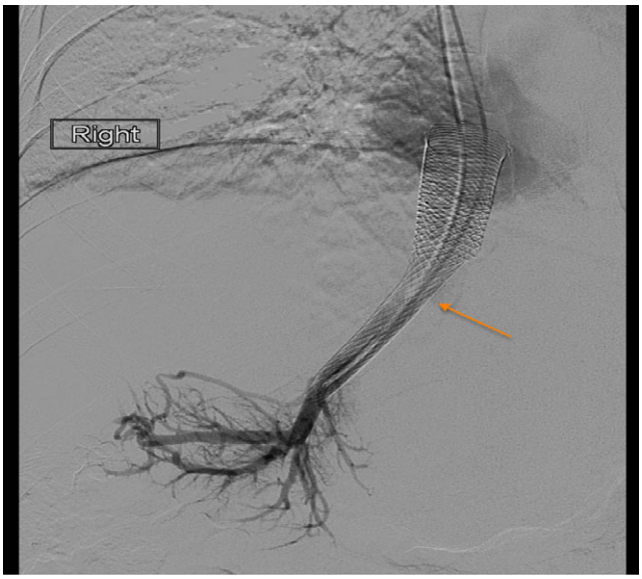

FIGURE 11 Good flow in hepatic vein following stenting (arrow) in patient B

have been increasingly used over the past decade and resulted in increased patency rates.[11,89,121-123]

Given the rarity of BCS, there are no randomised controlled trials precisely identifying the timing and candidates for TIPSS in BCS. The two common indications established for cirrhotic patients with portal hypertension (refractory ascites, recurrent variceal bleeding) are most common indications for TIPSS in BCS patients as well. TIPSS should be considered in cases with diffuse thrombosis of hepatic veins, as it is technically difficult to maintain the long-term HV patency with percutaneous angioplasty ±stenting. TIPSS should also be promptly considered in patients with acute liver failure.[105]

Numerous studies have shown good long-term outcome of TIPSS placement in BCS patients, with high rates of technical success, secondary stent patency and survival (Table 2).[89,123-131]

A systemic review of published literature on TIPSS in BCS patients demonstrated high technical success rates and excellent short- and long-term prognosis of BCS-TIPSS patients.[132]

The reported rate of *TIPSS-related complications* is variable, ranging from 0% to 56% in 16 case series. These complications mainly included liver capsule perforation, IVC and portal vein injury; contrast induced nephropathy and stent migration. TIPSS related deaths were rare. *Shunt dysfunction* appeared to be more frequent in BCS-TIPSS patients due to their prothrombotic states (range 18%-100% in 14 case series). This was more common in patients receiving bare stents than in patients receiving PTFE covered stents.[132] *Hepatic encephalopathy* was previously considered uncommon in BCS-TISS patients, but recent long-term data suggest that nearly 20% of the BCS-TIPSS patients are affected.[26]

In another systematic review with meta-analysis of 2255 BCS patients, assessing the outcomes of interventional treatment for BCS, the reported technical success rate of TIPSS insertion was 96.4%. 1- and 5-year pooled survival rates in TIPSS patients were 87.3% (95% CI = 83.2%-91.3%) and 72.1% (95% CI = 67.2%-77.0%) respectively. The patients with percutaneous recanalisation therapy had a better prognosis than with TIPSS in that metanalysis, but the physical conditions of BCS patients in recanalisation group were usually better than in TIPSS patients. Therefore, authors recommended stepwise management of BCS.[111]

A large multi-centre European study of 124 BCS patients treated with TIPSS, looked at the patients' outcome and factors predicting the outcome after TIPSS.[89] BCS-TIPSS patients had severe liver

TABLE 2 Studies using transjugular-intrahepatic portosystemic stent-shunt (TIPSS) for Budd-Chiari syndrome

Reference	Study, published year & (country)	Description	No. of patients, M:F, follow-up	Prognosis/outcomes	Comments
124	Hayek, Ronot, Plessier et al, 2017 (France)	Retrospective analysis to evaluate the long-term safety, technical success, and efficacy of TIPSS in patients with chronic primary BCS and to determine the predictors of shunt dysfunction (performed between January 2004 and October 2013).	N = 54 (M = 20/F = 34). Mean age, 36 y ±12. Mean follow-up = 56 mo ±41 (interquartile range, 22-92),	Primary and secondary technical success rates were 93% and 98% respectively. Cumulative 1-, 2-, 3-, 5- and 10-y primary patency rates were 64%, 59%, 54%, 45% and 45% respectively. The 10-y survival rate was 76%. 22 patients (42%) experienced at least one episode of TIPSS dysfunction (defined as shunt stenosis greater than 50% and/or portosystemic pressure gradient greater than 12 mm Hg).	Peri-procedural complications occurred in 14 patients (26%) and included inadvertent biliary puncture (*n* = 6), intraperitoneal bleeding (*n* = 3), acute TIPSS thrombosis (*n* = 1), transient marked bradycardia (*n* = 1) and transient respiratory distress (*n* = 3). Early complications occurred in 17 patients (32%) and involved subcapsular haematoma, intraperitoneal bleeding, intrahepatic contrast material extravasation (*n* = 7); acute TIPSS thrombosis (*n* = 6); and TIPSS malposition (*n* = 3) Nine patients required early TIPSS revision. Dysfunction was associated with presence of underlying MPN. Post-TIPSS hepatic encephalopathy was also noticeable.
53	Seijo, Plessier, Hoekstra et al, 2013 (Europe)	Multi-centre prospective study of newly diagnosed BCS patients in nine European countries.	N = 157 patients Median follow-up – 50 mo (range, 0.1-74.0).	88 patients (56%) received at least one invasive intervention. Angioplasty/ thrombolysis = 22 patients, TIPSS = 62, Liver Transplants = 20. Main indications for TIPSS were refractory ascites (69%), liver failure (13%) and variceal bleeding (7%). One, 3- and 5-y actuarial survival and LT-free survival of BCS-TIPSS patients was 88%, 83%, and 72% and 85%, 78% and 72% respectively.	The Rotterdam score was excellent in predicting intervention-free survival. BCS-TIPS PI score was independently associated with survival and LT-free survival.
28	Shalimar, Kedia, Sharma et al, 2017 (India)	Retrospective analysis of consecutive BCS patients undergoing TIPSS (from September 2010 to February 2017).	N = 80 (M = 40; F = 40); Median (range) follow-up – 660 (2-2400) d	The 1-, 3- and 5-y rates for TIPSS stent patency were 89, 81 and 81% respectively and patient survival rates were 93, 89 and 84% respectively. Cumulative encephalopathy-free rates over 1, 3 and 5 y were 91, 86 and 86% respectively.	Eight (10.0%) patients died during follow-up, five within the first year. On multivariate analysis, response to therapy after TIPSS (hazard ratio: 8.37; 95% confidence interval: 1.60-43.82) was independently associated with mortality. The 1-y survival was 97% in patients with complete

(Continues)

TABLE 2 (Continued)

Reference	Study, published year & (country)	Description	No. of patients, M:F, follow-up	Prognosis/outcomes	Comments
					response, compared with 59% in those with incomplete response ($P < 0.004$).
126	Neuman, Anderson, Nielsen et al, 2013 (Denmark)	Retrospective study to evaluate long-term complications and survival in consecutive patients with BCS (from 1997 to 2008).	N = 21 patients; 14 patients had TIPSS Median follow-up time for TIPSS patients- 50 mo (range 15-117 mo)	None of the patients with TIPSS required subsequent liver transplantation during follow-up period. Ascites control was achieved in all TIPSS patients with a marked reduction in the dose of diuretics.	There were no procedure-related complications. 14 TIPSS revisions were needed, mostly of uncovered stents. 1 TIPSS patient died 4 y after the TIPS-procedure, unrelated to BCS.
127	Spiliopoulos, Lalenis, Konstantos et al, 2017 (Greece)	Retrospective, single centre analysis of consecutive patients having TIPSS (between July 2003 and June 2016), due to symptomatic BCS not responding to medical therapy.	N = 27 (M = 10/F = 17). Mean age: 50.8 ± 15.0 y). Mean time follow-up- 46.5 ± 38.7 mo (range 1-139).	Technical success rate was 100%. Clinical success rate was 96.3% (26/27 procedures). Estimated LT-free survival rates (on Kaplan-Meier survival analysis) were 96.3%, 96.3%, 82.5% at 2, 5 and 10 y follow-up respectively. Primary Patency (PP) was 77.4%, 55.3% and 26.3% and re-intervention-free interval was 80.4%, 57.4% and 30.8% at 1, 2 and 8 y follow-up respectively.	1 patient did not experience symptoms relief and died of hepatic insufficiency 1 mo following the TIPSS. Bleeding was seen in 3 (3/27) cases and encephalopathy occurred in 3 patients. Covered stents were correlated with increased survival as compared to bare metal stents (HR: 0.0045; $P = 0.035$) and PP (HR: 0.36; $P = 0.03$). TIPSS achieved high long-term LT- free survival and satisfactory re-intervention rates in patients with symptomatic BCS refractory to anticoagulation.
128	Paladini I, Barbosa et al, 2017	Retrospective study to assess stent patency, overall survival, and long-term results in patients with symptomatic BCS who underwent TIPSS between January 2001 and December 2016.	N = 27 (M = 7; F = 20). Mean age- 34 y (range: 6-62 y). Average follow-up- 49.45 mo (range: 3-218 mo). 5 patients had bare metal stent; 22 had PTFE covered stents.	The success rate for TIPSS was 97%. TIPSS revision was performed in all 5 patients with bare stents and in 14/22 (63%) patients with covered stents.	TIPSS complications were present in 8/27 (30%) patients and included hepatic haematoma (1), sepsis (2), encephalopathy (2), ischemic hepatitis (1), hepatic artery pseudoaneurysm (1) and TIPSS dysfunction in the first 30 days of procedure (3). No deaths were observed. One patient developed cirrhosis and HCC and underwent LT.
129	Qi, Guo, He 2014 (China)	Retrospective study of consecutive Chinese BCS patients treated with TIPSS between December 2004 and June 2012. Patients were classified	N = 51. 39 patients had percutaneous recanalization for 1024 days (0-4574) before TIPSS. Early TIPSS group	The technical success of TIPSS was 100%. 12 patients developed post-TIPSS hepatic encephalopathy (HE) and 25 patients developed stent dysfunction. The	Absence of preoperative HE (HR =0.31; $P = 0.049$) and use of bare stents (HR =0.17; $P = 0.023$) were significantly associated with a lower incidence of post-TIPSS

(Continues)

TABLE 2 (Continued)

Reference	Study, published year & (country)	Description	No. of patients, M:F, follow-up	Prognosis/outcomes	Comments
		as the early and converted TIPSS groups.	(n = 19) has a shorter history of BCS and a lower proportion of prior percutaneous recanalization than converted TIPSS group (n = 32). Main indications were diffuse obstruction of three HVs, liver failure, liver function deterioration, refractory ascites and variceal bleeding.	cumulative 1-y rate of being free of first episode of HE and shunt dysfunction was 78.38 and 61.69% respectively. 12 patients died during the follow-up period. The cumulative 1-, 2- and 3-y survival rates were 84%, 81% and 77% respectively. Survival was similar between early and converted TIPSS groups.	HE. Only the absence of IVC thrombosis (HR = 0.2308, P = 0.015) was significantly associated with a lower incidence of shunt dysfunction and type of stents (bare vs. covered) was not significantly associated with the development of shunt dysfunction (HR = 1.1413;P = 0.775). Absence of IVC thrombosis and BCS-TIPSS score were significantly associated with overall survival.
130	MacNaughtan, Hogan, Tritto et al, 2011 (UK)	Retrospective analysis of BCS patients undergoing TIPSS (between January 1991 and January 2011).	51 patients (M = 20, F = 31) Mean age (at the time of TIPSS insertion)- 40 (±1.96) y	1 y transplant-free survival post-TIPSS insertion was 93%. TIPSS success rate was 88%. The mean number of TIPSS-related interventions was 2.5 (1-10). No patient proceeded to LT.	Local thrombolysis with tissue plasminogen activator was required in three cases.
123	Tripathi D, Macnicholas R, Kothari C, et al 2014 (UK)	A single centre retrospective study of patients undergoing TIPSS using bare or polytertrafluoroethane (PTFE)-covered stents. Between 1996 and 2012.	N = 67 (M = 21, F = 46) Patients with covered stents = 40; patients with bare metal stents = 27. Mean age 39.9 ± 14.3 y. Mean follow-up - 82 mo (range 0.5-184 mo). 9 patients underwent HV dilatation ±stenting prior to TIPSS.	Primary patency rates (76% vs. 27%, $P < 0.001$) and shunt re-interventions (22% vs. 100%, $P < 0.001$) significantly favoured covered stents. Secondary patency was 99%. 6-, 12-, 24-, 60- and 120-mo survival was 97%, 92%, 87%, 80% and 72% respectively.	15% had post-TIPSS hepatic encephalopathy. Two have been transplanted. 6 patients had liver-related deaths. 2 patients developed HCC. The BCS-TIPSS PI independently predicted mortality in the whole cohort, but no prognostic score appeared significant predictor of mortality after subgroup validation.
89	Garcia-Pagan, Heydtmann, Raffa et al, 2008 (Europe)	Study of consecutive BCS patients treated with TIPSS in 6 European centres between July 1993 and March 2006, until death, LT, or last clinical evaluation.	N = 124 (M = 46/F = 78) Mean age (95% CI): 38 (35-40) y. Mean follow-up after the TIPSS was 36.7 mo (range, 0.7-156 mo). Uncovered stents were used in 61 patients (49%), PTFE- covered stents in 48 patients (39%), and both types in 15 patients (12%).	TIPSS patients had severe liver disease reflected by a high Child–Pugh, MELD, Clichy and Rotterdam scores. TIPSS success rate was 93% (124/133). 6 patients died (13%) and 8 (6.5%) required LT during follow-up. One-, 5- and 10-y OLT-free survival rates were 88%, 78% and 69% respectively. One-, 5- and 10-y survival rates were 90%, 84% and 80% respectively.	22 patients (17.7%) had complications associated with TIPSS. Two resulted in deaths. 61 patients (41%) had TIPSS dysfunction. Actuarial probability of TIPSS dysfunction was significantly lower in patients treated with PTFE covered stents than in with bare stents (P 0.001). 4 patients developed recurrent hepatic encephalopathy and all 4 were listed for LT. The

(Continues)

TABLE 2 (Continued)

Reference	Study, published year & (country)	Description	No. of patients, M:F, follow-up	Prognosis/outcomes	Comments
					actuarial probability of developing HE at 1-y post-TIPSS was 21%. BCS-TIPS PI score was proposed with good prognostic ability [AUROC 0.86; 95% CI: 0.72-0.99]. BCS-TIPS PI>7 had 58% sensitivity, 99% specificity, 88% PPV and 96% NPV for death or LT 1-y after TIPSS.
131	He, Zhao, Dai, et al, 2016 (China)	Analysis of feasibility and safety of TIPSS as a treatment for BCS patients with diffuse occlusion of hepatic veins at a single centre. (From January 2007 to December 2010).	N = 91 TIPSS patients (100 patients were included in study). F/M: 66/34 14 patients had acute BCS and 86 patients were included in sub-acute BCS group. 9 patients (2 in acute group and 7 in sub-acute group) received conservative treatment. Follow-up- 5 y	TIPSS was technically successful in all 91 patients (12 in acute group). Mortality rate (during follow-up) was very high (89%) in conservative group (9 patients) who didn't receive TIPSS. Overall 5-y survival rate in TIPSS group was 93.41%.	Acute- BCS patients had a higher rate of jaundice but lower rate of varices and ascites than sub-acute group. Risk of post-TIPSS HE was low (5.49%0. Overall shunt dysfunction was seen in 10.99%. 2 patients in acute BCS died (16.67%) and 4 patients with sub-acute BCS died (5.06%) during follow-up. [2 patients died of non-liver-related aetiologies]. 8/9 patients who didn't undergo TIPSS died of liver failure within 5 mo.
27	Rathod, Deshmukh, Shukla et al, 2017 (Mumbai, India)	Retrospective study of treatment efficacy and safety of radiological interventions in BCS patients at a single centre (between January 2008 and June 2014).	N = 106 patients with TIPSS. Follow-up median duration =45 (13-73) mo.	Technical success for TIPSS was 100%. Primary assisted and secondary patency rate were 95.28% and 100% respectively. Complete response was noted in 83 (78.3%) of TIPSS patients; the rest had partial response.	3 patients died within 1 mo after TIPSS. All three patients were in Child–Pugh class C pre-procedure. Another 5 patients died during follow-up. 5 patients developed hepatic encephalopathy.
119	Rössle, Olschewski, Siegerstetter et al, 2004 (Germany)	Study of patients with severe BCS not responding to medical therapy having TIPSS (between 1991-2001)	N = 35 patients. 11 patients had fulminant/acute BCS (history <2 mo); 13 had sub-acute (<6 mo); and 11 patients had chronic BCS. Bare metal stents =25 patients; PTFE covered stents =8 patients. Mean follow-up =37 ± 29 mo.	TIPSS success rate was 94%. Clinical symptoms and biochemical test results improved significantly during 4 weeks after shunt treatment. The cumulative 1- and 5-y survival rates without LT in all patients were 93% and 74% respectively; and in patients with fulminant/acute disease 91% and 91% respectively (no deaths in this time period).	Three patients died and 2 received Liver transplantation. On the average, 1.4 ± 2.2 revisions per patient were needed during the mean follow-up of 3 y with a 1-y probability of 47%.

BCS: Budd-Chiari syndrome; HV: Hepatic vein, IVC: Inferior vena cava, TIPSS: Transjugular-intrahepatic portosystemic stent shunt; LT: Liver transplantation; HE: Heaptic encephalopathy.

disease reflected by a high Child-Pugh, MELD, Clichy[87] and Rotterdam score (RS).[88] Major indications of TIPSS were refractory ascites (59%), liver failure (22%) and upper gastrointestinal bleeding (9%). The patients had excellent long-term liver transplant-free survival and overall survival. TIPSS was an extremely effective therapy for patients with severe BCS. A new prognostic score - BCS-TIPSS PI was proposed to predict post-TIPSS outcome and it emerged as an effective clinical score at predicting 1-year survival rate after TIPSS (AUROC 0.86; 95% CI: 0.72-0.99). BCS-TIPSS PI > 7 was associated with worse outcome with high specificity and negative predictive value (NPV) for death or LT 1-year after TIPSS; and such patients should be considered for early transplantation.[89]

Seijo et al[53] reported a multicentre prospective study on 157 patients from nine European countries. Patients were followed for a median of 50 months (range, 0.1-74.0). Over 88% of the patients received long-term anticoagulation and 69 patients (44%) did not receive any intervention. Twenty-two patients received angioplasty/thrombolysis. Out of 22 patients who received angioplasty/thrombolysis, 14 (64%) showed poor response and needed further treatment with either TIPSS (12 patients) or liver transplant (2 patients), after a median time of 1.5 months (range, 0.2-19.0).

Sixty-two (39.5%) patients underwent TIPSS. About half of the TIPSS were placed in the first month and 60% in the first 3 months after diagnosis (median time from diagnosis to TIPSS was 1 month (range, 0-38). Patients who underwent TIPSS in the first month had more severe liver disease at diagnosis, reflected by worse Rotterdam PI score.[88] Only four of these BCS-TIPSS patients (6.45%) needed rescue LT, a median of 1.8 months after TIPSS (range, 0.03-13.0). Five year actuarial survival and LT-free survival of BCS-TIPSS patients was 72%. Twenty patients (12.7%) in this study received LT and 60% of the liver transplants were performed in the first 6 months after diagnosis. Fifteen patients who had early liver transplant had severe liver disease at diagnosis (indicated by frequent hepatic encephalopathy, higher RS and class) than the patients who had received TIPSS.[53]

The authors claimed that the approach of close clinical surveillance while reserving TIPSS for those patients who progress or fail to respond to medical treatment did not have a deleterious effect on outcome. RS appeared to be an excellent prognostic value for predicting the need of invasive intervention and should be used early in deciding about type of intervention that is; TIPSS for higher RS and class (class-3). In BCS patients with TIPSS, BCS-TIPSS PI score appeared to be superior to RS for predicting survival at 1 year and could be used for consideration of early LT.

Contrary to wide use of TIPSS in the treatment of BCS patients in Western countries, percutaneous recanalisation is widely applied in most of Chinese BCS patients.[29,31,133-136] This difference in choice of treatment modalities between Western countries and China is primarily because of the disparity in the type of obstruction and risk factors of BCS as discussed before. As stated earlier, majority of western BCS patients have obstruction of hepatic vein alone whereas majority of Chinese BCS patients have combined HV and IVC obstruction.[12,29,31,135] In many of the Chinese studies long-term anticoagulation was not offered.

In a retrospective study of 51 Chinese BCS patients treated with TIPSS, Qi et al reported excellent short-term outcomes.[129] Majority of TIPSS patients (36 patients) had HV-cava BCS type. Importantly, 175 out of 230 patients (76%) with primary BCS presenting during the enrolment period underwent successful percutaneous recanalisation alone. Thirty-nine (76%) out of these 51 patients had percutaneous recanalisation before TIPSS. Nineteen (out of 51) patients had *early TIPSS* (either no prior percutaneous recanalization or percutaneous recanalisation was performed within 3 days before TIPSS). Thirty-two patients had *late or converted TIPSS* (TIPSS was performed >3 days after percutaneous recanalisation) due to the poor response to initial treatment. Compared with the early TIPSS group, the converted TIPSS group had a longer history of BCS and a higher proportion of patients with combined HV-IVC obstruction. Absence of IVC thrombosis and BCS-TIPSS score (<7) was significantly associated with better overall survival. The treatment strategy in this study was consistent with the stepwise strategy used in the West[53] and authors supported use of TIPSS in those Chinese BCS patients in whom percutaneous recanalisation is ineffective or inappropriate (Figures 12–14).[129]

10 | SURGICAL TREATMENT

10.1 | Surgical portosystemic shunts

In the past years, a surgical portosystemic shunting had been traditionally preferred decompressive strategy in BCS patients. However, favourable outcome was only noted with side-to-side porto-caval shunt in patients with HV occlusion alone.[137] Surgical portosystemic shunting did not show survival benefit in BCS patients in several studies and multivariate analyses.[80,87,88,138] Surgical shunts were associated with high perioperative mortality,[139] low late shunt patency[140] and technical difficulties.[141] This modality is, therefore, no longer considered as treatment option and is largely replaced by TIPSS.[53]

10.2 | Liver transplantation (LT)

About 10%-20% of the BCS patients show progressive liver deterioration despite medical management, percutaneous revascularisation and TIPSS. LT is only remaining treatment option in these patients. LT is also a treatment of choice in selected BCS patients who develop hepatocellular carcinoma (HCC) and are within the transplant criteria. Rarely the presentation of BCS is fulminant and patients develop acute liver failure. The initial hospital survival rate in these ALF-BCS patients has historically been poor (37%-40%).[142]

In ALF-BCS patients, anticoagulation should be initiated as soon as the diagnosis is made, even in presence of significant prolongation of the PT time or INR. The therapeutic benefit of early anticoagulation is supported by ALFSG study in which initial hospitalisation survival rates were 100% and 50% in those who had and had not received anticoagulation on admission respectively (P = 0.03).[104]

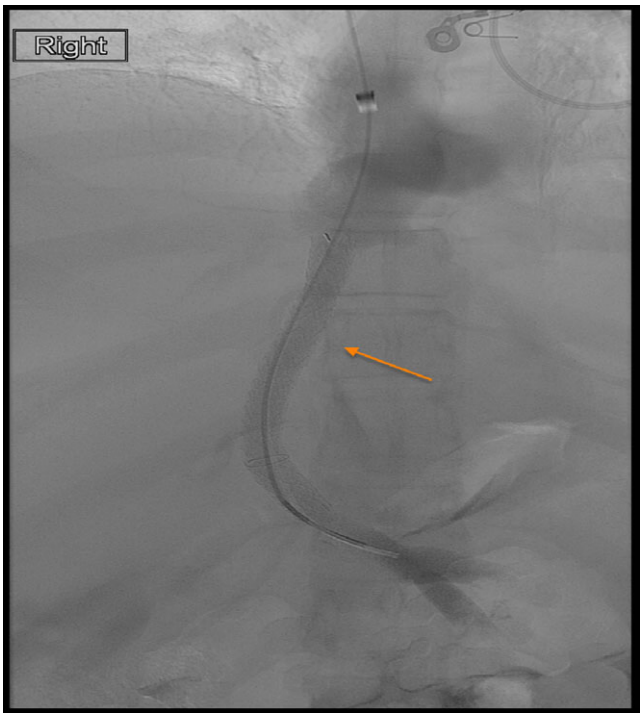

FIGURE 12 Successful direct intrahepatic portosystemic shunt (DIPS) placed in the same patient (arrow) in patient C

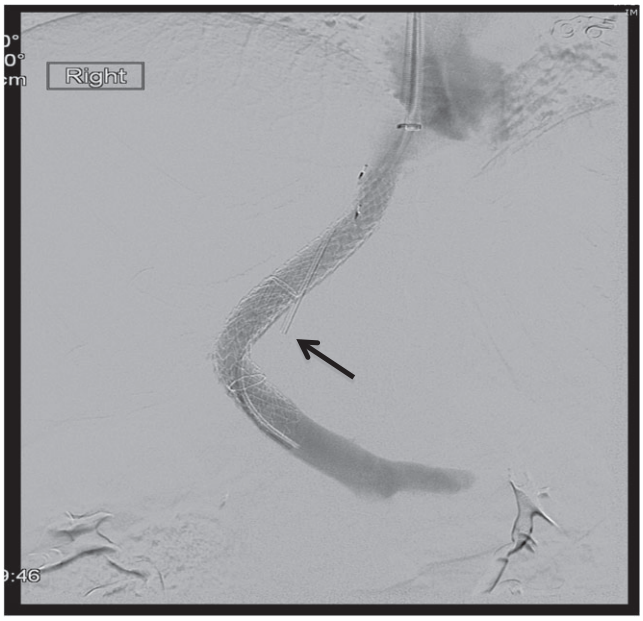

FIGURE 13 DIPS placed into portal vein (arrow), good flow into inferior vena cava and right atrium

Decompression of liver, usually with TIPSS if technically feasible, should be pursued early on while the underlying cause of BCS is being explored. This intervention would buy time during which assessment for clinical improvement can be made. LT is indicated if there is no clinical improvement. Similarly, LT should also be considered early on in ALF-BCS patients, if decompressive procedure is not technically possible (ie due to clot burden).

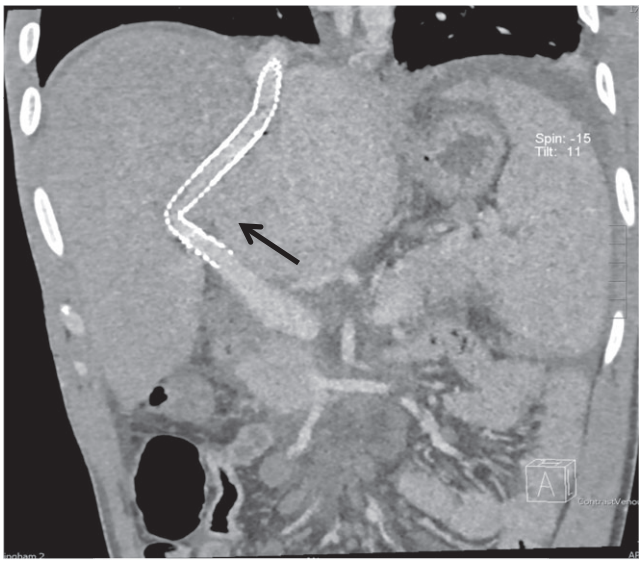

FIGURE 14 Computed tomography scan demonstrates successful DIPS in situ (arrow)

Benefit of LT on survival has been evaluated in a few large retrospective analyses and reported 5-year survival rate was between 71% and 89%.[113,143,144] The survival benefit of LT is most pronounced in BCS patients with worse baseline characteristics (reflected by high RS). The survival rate and graft function after LT in BCS patients are similar[113] or even superior[143] to those transplanted for other indications. Incidence of vascular complications post-LT is noted to be significantly higher in patients with BCS and is influenced by presence of MPN.[145] In a study of 36 BCS-LT patients, 1/3rd developed liver-related thrombotic complications and 10 of them needed re-transplantation.[145] Presence of MPN in BCS-LT patients did not influence 5- and 10-year survival rates in a study and there was no evidence of progression of MPN after LT (secondary to immunosuppressive therapy).[146]

11 | HCC IN BCS

Benign hypervascular regenerative nodules, which can resemble focal nodular hyperplasia, are common in BCS. These are thought to develop following compensatory hypertrophy of areas of liver with altered perfusion.[22]

HCC is a recognised long-term complication of chronic BCS patients. The reported prevalence of HCC in BCS patients is highly variable. A systematic review showed a pooled prevalence of 15.4% (95% confidence interval 6.8%-26.7%), after excluding patients with HCC and concomitant viral hepatitis.[147] Pooled prevalence of HCC in BCS patients with IVC obstruction was 26.5% (95% CI: l4.4%-40.7%). It is worth noting that there was statistically significant heterogeneity among studies in these meta-analyses.[147]

The differentiation between benign large regenerative nodules and HCC in BCS patients is challenging[148,149] and serum alpha-fetoprotein (AFP) seems to be helpful in diagnosing HCC in BCS patients. In a study of 97 consecutive BCS patients, HCC developed in 11 patients during a median follow-up of 5 years with cumulative incidence of 4%. On univariate analyses, male sex ($P = 0.007$) and IVC obstruction ($P < 0.001$) were main risk factors for development of HCC. AFP appeared to be more specific for HCC diagnosis in these patients than with other liver diseases (PPV 100%, NPV 91%, AUROC 0.85).[150]

In a recent study of 348 Egyptian BCS patients, 15 (4.3%) developed HCC. AFP appeared to be good screening test for HCC in this cohort as well (AFP level >24.5 ng/mL had 97.9% specificity).[151] In a Korean study of 67 BCS patients, higher hepatic venous pressure gradient was associated with development of HCC ($P = 0.019$). Fifty four patients included in this study[62] had cirrhosis at the diagnosis of BCS.[152]

Multivariate analyses in larger cohorts to explore relationship between HCC and the underlying causal factors for BCS are needed. Nevertheless, long-term HCC surveillance is warranted in BCS patients (*due to clinicopthological dissociation where many patients presenting acutely have advanced fibrosis or cirrhosis*) and in especially those with cirrhosis and those with IVC obstruction. An algorithm for the management of nodules in BCS patients has been proposed. The presence of liver nodule(s) with a serum AFP level >15 ng/mL is highly suggestive of HCC in BCS patients and biopsy of the largest nodule should be performed to confirm this diagnosis (Figure 15).[153]

12 | PREGNANCY IN BCS

Pregnancy is a hypercoagulable state and is associated with an increased risk of venous thromboembolism.[154] As discussed before, pregnancy alone is unlikely to cause BCS and these patients usually have another thrombotic risk factors.[74]

As primary BCS mainly affects women of childbearing age, pregnancy is an important issue. Several earlier studies reported poor outcome in pregnant women with BCS[155,156] and pregnancy was associated with decompensation of liver disease.[157-159]

Recent experience on pregnancy in women with established BCS has been reported in two relatively larger retrospective European studies.

Rautou et al published experience on 24 pregnancies in 16 women with known and treated BCS, from three European centres.[160] All patients were in stable condition at the time of conception and nine of them had treatment with a portal decompressive procedure previously. At least one causal factor for thrombosis was identified in 14 out of 16 women (88%). Anticoagulation therapy was used during 17 of the pregnancies.

Miscarriage (a spontaneous termination of pregnancy before 20 weeks of gestation) happened in 29% of the pregnancies. One stillbirth occurred after gestation week 20 and all other infants did well despite a high incidence of preterm birth. Maternal outcome was good with no maternal mortality. Three thrombotic events (two related to shunt obstruction) and six bleeding events were recorded.[160]

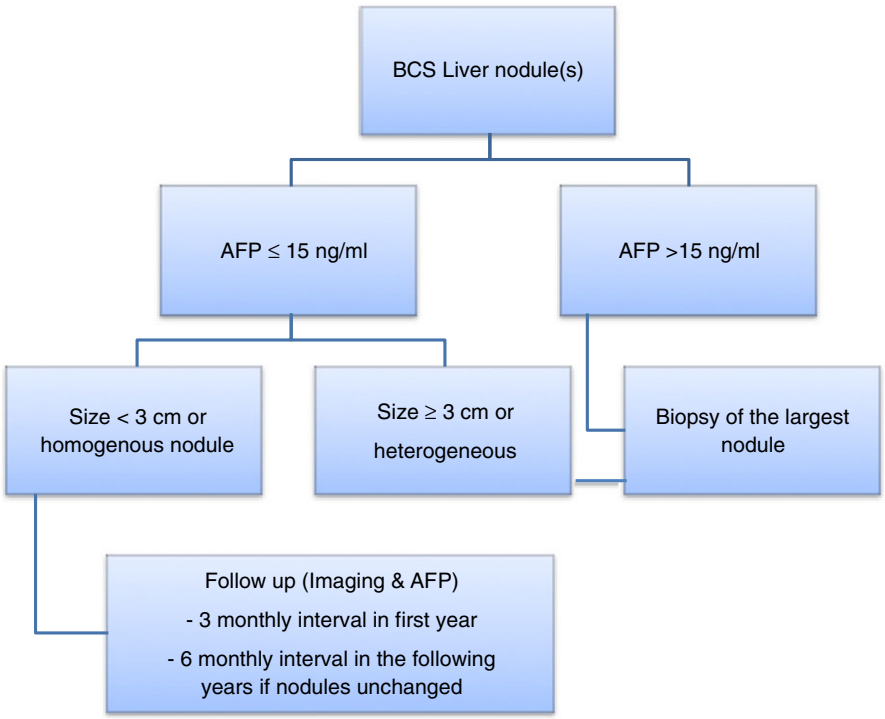

FIGURE 15 Proposed algorithm for the management of hepatic nodules in Budd-Chiari syndrome patients (AFP - alpha-fetoprotein)

We published our experience of 16 pregnancies in seven women with established BCS (from January 2001 to December 2015).[161] At least one causal factor for BCS was identified in six women (86%). Six women had undergone radiological decompressive treatment previously. All patients had anticoagulation and that was continued during pregnancies.

Six foetuses were lost before 20-week gestation in two women. There were nine deliveries over 32-week gestation and one infant was born at 27-week gestation. All infants did well. High incidence of placental disease was noted in our cohort leading to seven (out of 10) births via emergency caesarean section. There were no events of thrombosis and two patients had notable vaginal bleeding in three pregnancies. Two patients were diagnosed with pulmonary hypertension, one during 3rd trimester and the other in the post-partum period. Both of these patients had TIPSS several years before pregnancies. Maternal outcome was good and there was no maternal mortality.[161]

This improved maternal outcome is attributable to improvement in management of BCS over recent years, treatment of the underlying prothrombotic condition, careful anticoagulant therapy and management of pregnancy in centres with greater expertise. Our practice is to screen all BCS patients for pulmonary hypertension during pregnancy, with echocardiography. BCS, therefore, cannot be considered a contraindication to pregnancy in stable patients.

13 | CONCLUSIONS

Multicentre work and advent of new treatment modalities have resulted in increased understanding of BCS and improved long-term outcomes over the last three decades. Different BCS-specific scores have been developed [Clichy[79], Rotterdam[80], New Clichy[72] and BCS-TIPSS[81] scores] following studies in BCS patients. Most of these prognostic indices are valid for transplant-free and invasive therapy-free survivals in BCS patients. However, none of these scores has a sufficient predictive or prognostic accuracy to be used for individual patient management and need further validation in larger studies.[162] Underlying haematological disorders can be the major determinant of outcome in patients with BCS.

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AUTHORSHIP

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Author contributions: FK: collected and analysed data, performed the research, designed and wrote the draft manuscript. All authors performed the research, collected and analysed data, and contributed to the manuscript. DT is the senior author. All authors approved the final version of the manuscript.

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