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## Review of Budd-Chiari Syndrome

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## ABSTRACT

This study aims to report the Budd-Chiari syndrome clinical research status and progress that has occurred in over nearly 30 years in China, and emphasize the value of imaging in facilitating the diagnosis of Budd-Chiari syndrome based on more than 2500 cases. Findings on ultrasonography, computed tomography, magnetic resonance imaging, and digital subtraction angiography images are used to propose new Budd-Chiari syndrome types and subtypes. The new subtype classification presented here has important value for guiding interventional treatment. This study also proposes a new concept of anatomical and functional obstruction of hepatic vein that stresses the compensatory value of accessory hepatic vein and azygos vein and describes the risk of manipulation of the communication branch of inferior vena cava obstruction in interventional therapy.

## Introduction

Budd-Chiari syndrome (BCS) is a clinical symptom group of portal vein and/or inferior vena cava (IVC) hypertension resulting from obstruction of the hepatic outflow tract due to obstruction of the small hepatic vein to the IVC at any point along the border with the right atrium. BCS is a potentially life-threatening disease. BCS is considered a rare disease in Western countries, and its prevalence is largely influenced by regional differences. BCS is common in Asian countries such as China, India, and Nepal, and estimated to affect one in 2.5 million people in the West. In the middle and lower reaches of the Yellow River and Huai River in China, there are 6.8–12 cases of BCS per 100,000 people, and more than 20,000 cases of BCS have been identified in China.<sup>1</sup> Anatomical differences in hepatic vein and IVC occlusion are also evident between Western countries and Asia. In the West, hepatic venous thrombosis is more common and venous thrombosis is less prevalent in IVC. In Asia, however, the main cause of hepatic venous outflow tract obstruction is membrane formation, which accounts for up to 70% of all cases. Geographical differences between block position and pathological anatomical differences lead to clinical symptoms, the treatment and prognosis of BCS differ in many ways between the East and West. Following the advances of modern imaging achieved in the hepatic vein, portal vein, IVC, and azygos vein are shown which will replace traditional percutaneous puncture of liver biopsy and autopsy; differences are seen among a huge number of cases and previous reports. Therefore, it is

necessary to recognize cases of BCS.

## Etiology

BCS is classified as primary or secondary according to the exact nature of the hepatic venous outflow tract obstruction. When the lesion outside the hepatic venous outflow tract compresses or infiltrates and blocks the blood flow, it is considered secondary BCS. Examples include primary or metastatic tumors of the liver, leiomyomas, and neoplasms in the IVC. By far, thrombogenesis is the most common etiology of primary BCS in Western countries, with 25%–46% of patients having multiple prethrombotic lesions and a hypercoagulable state. Therefore, primary BCS is considered the result of a unique set of prethrombotic conditions.<sup>2</sup> In China, however, the etiology of BCS is different; in fact, current studies show that primary thrombotic disease is not a common cause of BCS in China. Our study discovered the following:

1. Elevated vascular endothelial growth factor (VEGF) levels in the blood of patients with IVC obstruction;<sup>3</sup>
2. The iodine concentration of groundwater is generally higher in high incidence areas than in low incidence areas;<sup>4</sup>
3. The iodine concentration in blood and urine of BCS patients was higher than that of normal people;<sup>5</sup>
4. Significantly more patients lived in rural areas than in urban areas;

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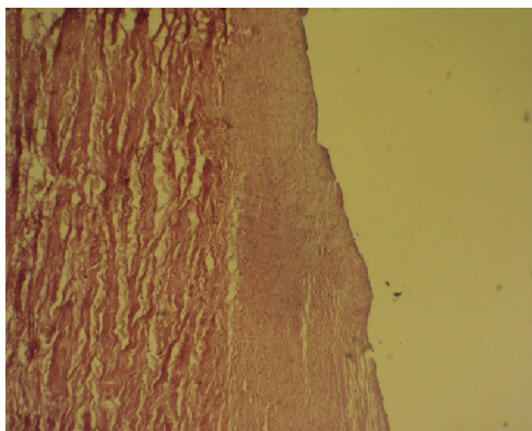


Fig. 1. The endodermis of the inferior vena cava is thickened above the membrane.

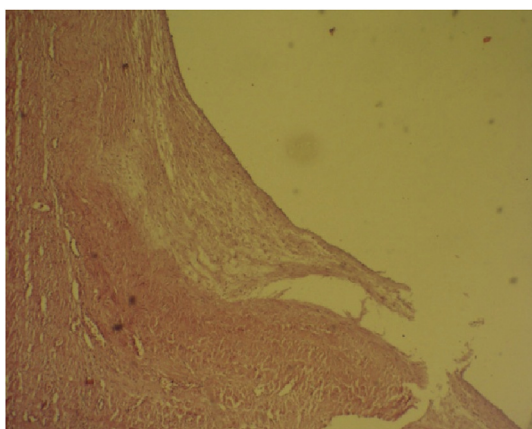


Fig. 2. The membrane of the inferior vena cava is composed of thickened fibrous connective tissue and vascular endothelium.

- 5. The membrane of the hepatic vein and IVC can re-form after being torn by balloon dilation (restenosis);<sup>6</sup>
- 6. The IVC membrane can be re-formed at the original site after surgical membrane resection.<sup>7</sup>

Table 1  
Serum iodine levels in patients with BCS versus controls.

Group	n	serum iodine (µg/L)	Range (min-max)
IVC type BCS	144	347 ± 272.3 <sup>a</sup>	4.3-1095.1
HV type BSS	71	237 ± 231.1 <sup>a</sup>	12.3-937.2
MIX type BCS	18	307 ± 134.4 <sup>a</sup>	72.1-512.7
Control group	60	76.3 ± 25.7	30.2-97.4

Values are given as mean ± SD.

BCS Budd-Chiari Syndrome, IVC Inferior Vane Cava, HV Hepatic Vein, MIX Mixture.

<sup>a</sup> Versus control group (p < 0.05).

Table 2  
T-test results of VEGF concentration value.

Group	Number	Mean value (µg/mL)	Standard error	t-value	P value
VEGF Test	40	23.15	19.27	5.273	<0.001
Control	40	5.63	8.38		

VEGF, vascular endothelial growth factor.



Fig. 3. The swelling of the both lower extremities.

The statistical analysis of the 2590 cases revealed significantly higher rates of hepatic venous obstruction in adolescents younger than 30 years of age than in patients older than 30 years of age.<sup>8</sup> In patients aged 30-79 years, the proportion of IVC obstructions increased with age. In the 60-69 years age group, 256 patients had BCS; of them, 222 had IVC obstruction and 34 had hepatic vein occlusion. In contrast, in the 70-79 years age group, 34 patients had BCS; among them, only one had hepatic vein occlusion (2.9%).

In China, formation of the hepatic vein and IVC membrane is the main cause of obstruction of the hepatic vein and IVC blood flow, but the mechanism of this formation is unclear and may be associated with environmental conditions and genetic abnormalities. Our study of the membrane of the IVC showed that the fibrous connective tissue of the IVC



Fig. 4. The symmetry varicose veins of the both lower extremities.



Fig. 5. The symmetry pigmentation of the both lower extremities.



Fig. 6. The symmetry ulceration of the both lower extremities.



Fig. 7. The varicose veins in the thoracic and abdominal wall.



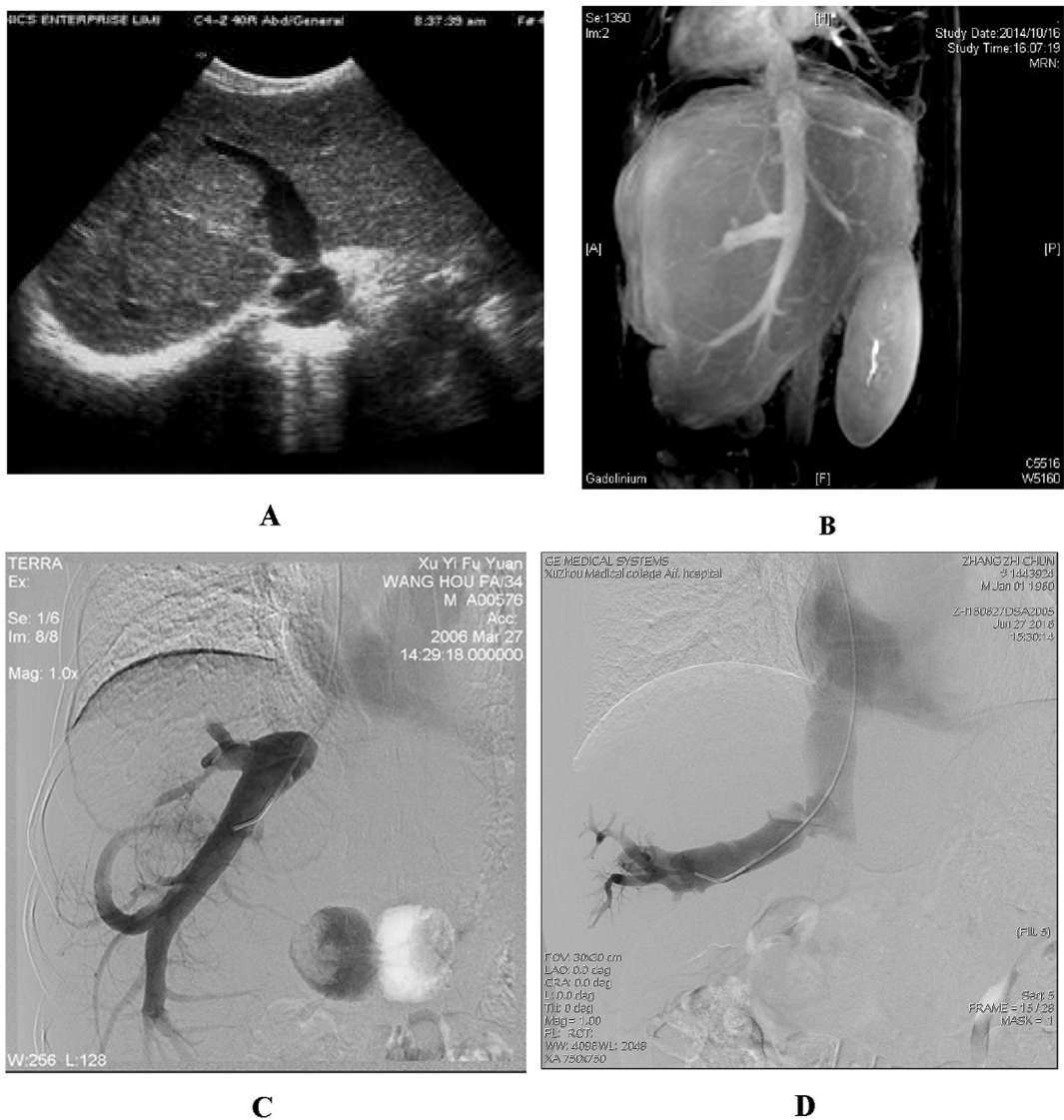
Fig. 8. The varicose veins in the lower back.



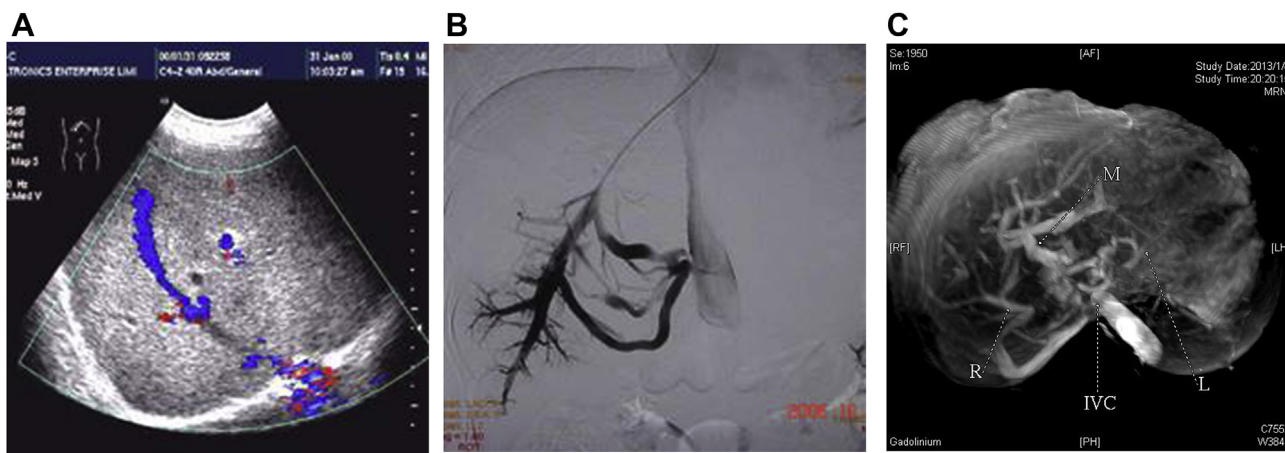
Fig. 9. MRV directly shows the membrane obstruction of hepatic vein ostium and inferior vena cava.



Fig. 10. MRV shows extensive extrahepatic collateral vessels in the inferior vena cava occlusion.



**Fig. 11.** A. The ultrasonography shows the membrane echo of the left hepatic vein ostium  
 B. MRV shows the membrane of the middle hepatic vein ostium  
 C. DSA shows the membranous obstruction of the right hepatic vein ostium  
 D. DSA shows membranous Obstruction of the accessory hepatic vein ostium.



**Fig. 12.** A. The doppler ultrasonography shows segmental obstruction of the right hepatic vein  
 B. DSA showed middle hepatic vein segment occlusion with accessory hepatic vein membranous obstruction  
 C. MRV showed 3 hepatic veins segmental obstruction.

above and below the diaphragm gradually thickened and fused with the endothelium to form the membrane, while the thickened endothelial cells showed no specific changes (Figs. 1 and 2). We conducted the following studies on endothelial hyperplasia of the IVC and found that a high iodine level can cause endothelial hyperplasia.

*Imaging diagnosis*

Chenghao et al. detected the iodine concentrations in the groundwater of 128 patients with membranous obstruction of IVC in Heze, Shandong province, and found that 98.44% of the samples contained iodine concentrations greater than 150 g/L, of which 27.35% were 150–300 µg/L and 71.09% were above 300 µg/L, indicating that the high iodine levels were consistent with the high incidence of BCS.<sup>4</sup>

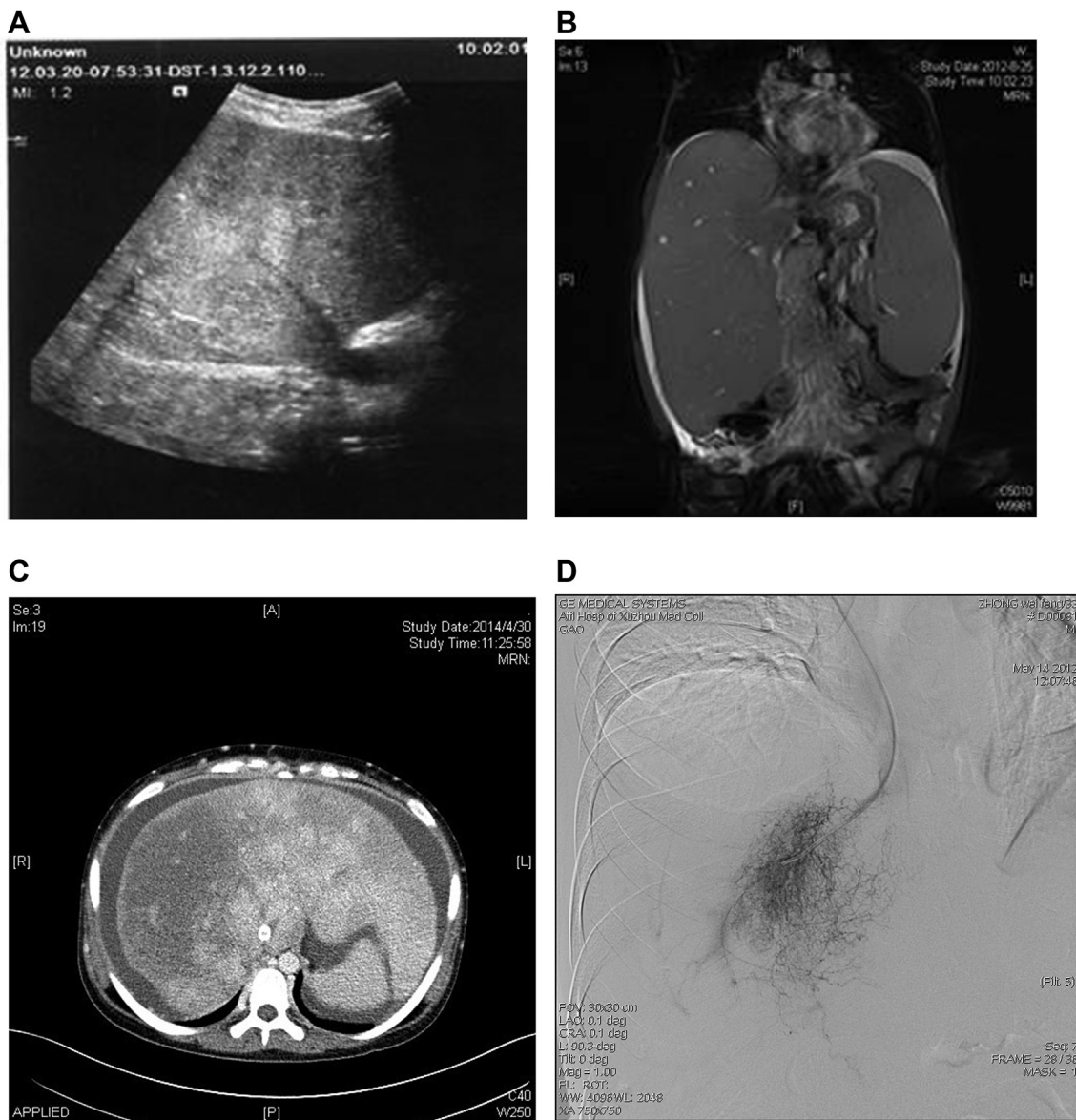
Accordingly, the blood iodine test results of 233 BCS patients reported by Yiping et al. showed that blood iodine levels of BCS patients

were higher than those of the normal population<sup>9</sup> (Table 1).

The results showed that the serum iodine concentration of BCS patients was more than 5 times higher than that of the control group. Accordingly, we tested the urine iodine levels of BCS patients and found that they were also higher than those of the normal population.

Pengfei et al. further studied the culture of umbilical vein vascular endothelial cells and fiber cells with different concentrations of iodide and showed that an iodine concentration of 300–500 mg/L can cause the transition of vascular endothelial cells and fibroblast hyperplasia. Importantly, the iodine concentrations of the drinking water, blood, and urine of BCS patients were consistent with iodine-containing culture medium that could cause vascular endothelial hyperplasia. Therefore, we report here first that a high iodine level (300–500 mg/L) can lead to vascular endothelial cell proliferation.<sup>10–14</sup>

Our study of the IVC membrane found that its tissue structure is fibrous connective tissue in the middle and vascular endothelium in the



**Fig. 13.** A. The ultrasonography showed that the right hepatic vein occlusion that presented a cable-like echo, the middle hepatic vein was unclear, and the left hepatic vein was small  
 B. MR shows hepatosplenomegaly, ascites, hepatic veins is small and exiguity  
 C. The enhanced CT shows liver enlargement, ascites, uneven enhancement, and disappearance of hepatic veins  
 D. DSA showed the disappearance of the main hepatic vein and the small reticular vessels.



Clinical manifestations and diagnosis

Portal hypertension syndrome caused by hepatic venous obstruction manifests similarly to post-hepatitis cirrhosis and drug-induced liver injury and alcoholism; thus, its misdiagnosis is common. The possibility of hepatic vein occlusion should be considered when abdominal distension, hepatosplenomegaly, massive and intractable ascites, gastrointestinal bleeding, and hypersplenism lead to leukopenia and thrombocytopenia in patients with no history of hepatitis, long-term alcoholism, or history of taking non-Yunnan Panax notoginseng.

The clinical manifestations of IVC obstruction involve swelling of the lower limbs (Fig. 3), bilateral lower-extremity varicose veins (Fig. 4), bilateral lower-limb pigmentation (Fig. 5), and pigmentation of the bilateral lower extremities with chronic non-healing ulcers (Fig. 6). Bilateral lower-extremity signs are strong evidence of IVC obstruction, and those higher than the thoracic and abdominal wall skin indicate the longitudinal direction of the varicose veins (Fig. 7), while varicose veins in the back are also strong evidence of IVC obstruction (Fig. 8). Non-specific clinical manifestations of IVC obstruction include weakness, active asthma, irregular menstruation in female patients, habitual abortion, and primary infertility.

Ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) are effective methods for diagnosing hepatic venous and IVC outflow tract obstructions. Doppler US is the preferred examination method, while ultrasonography can display direct signs of IVC and hepatic vein occlusion, i.e. membrane echo of the IVC and hepatic vein openings versus funicular high echo of total lumen occlusion. The occluded distal vessels dilate and thrombus echo, and Doppler US can directly show the obstructed and reverse flow of hepatic vein and IVC. The formation of traffic branches between hepatic veins is an indirect sign of hepatic vein obstruction. Ultrasonography has high sensitivity and specificity for the diagnosis of BCS.

Magnetic resonance angiography (MRA) is superior to CT for displaying the hepatic vein, IVC, azygos vein, and superficial vein in the abdominal wall display. MRA can also directly display the main hepatic vein as well as the IVC membrane and its thickness (Fig. 9), the length of the segmental block, the location and size of thrombus, and the collateral circulation (Fig. 10). MRA is better able than US to show the position, direction, thickness, and quantity of the collateral circulation.

MRI and CT can better observe liver parenchyma to reveal areas of reduced perfusion or necrosis. MRA not only simplifies the diagnosis of BCS, it facilitates interventional treatment planning. The traditional

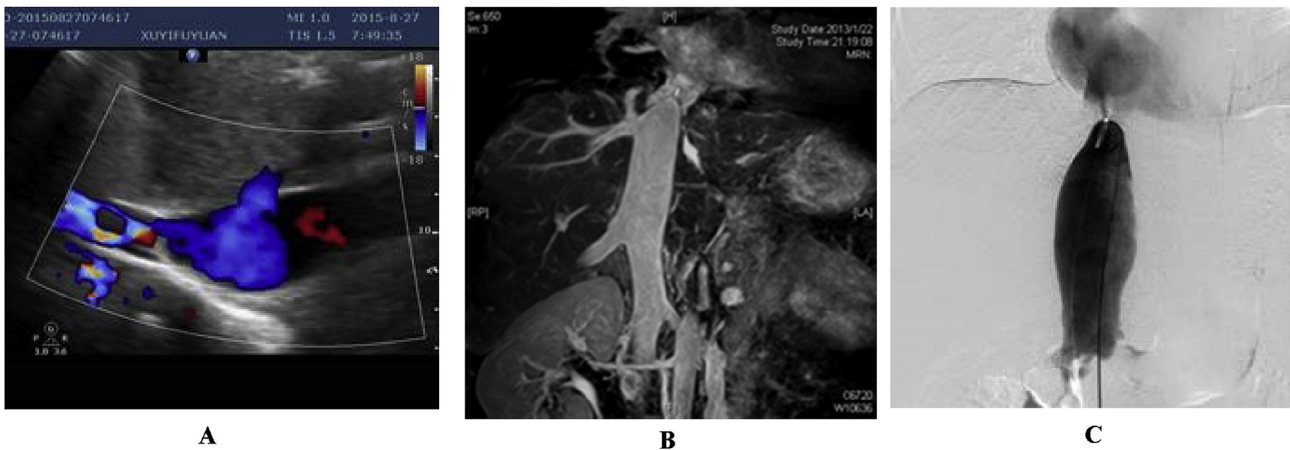


Fig. 15. A. The ultrasonography shows the membranous obstruction of the inferior vena cava with a hole  
 B. MRV shows the membranous obstruction of the inferior vena cava with a hole  
 C. DSA shows the membranous obstruction of the inferior vena cava with a hole.

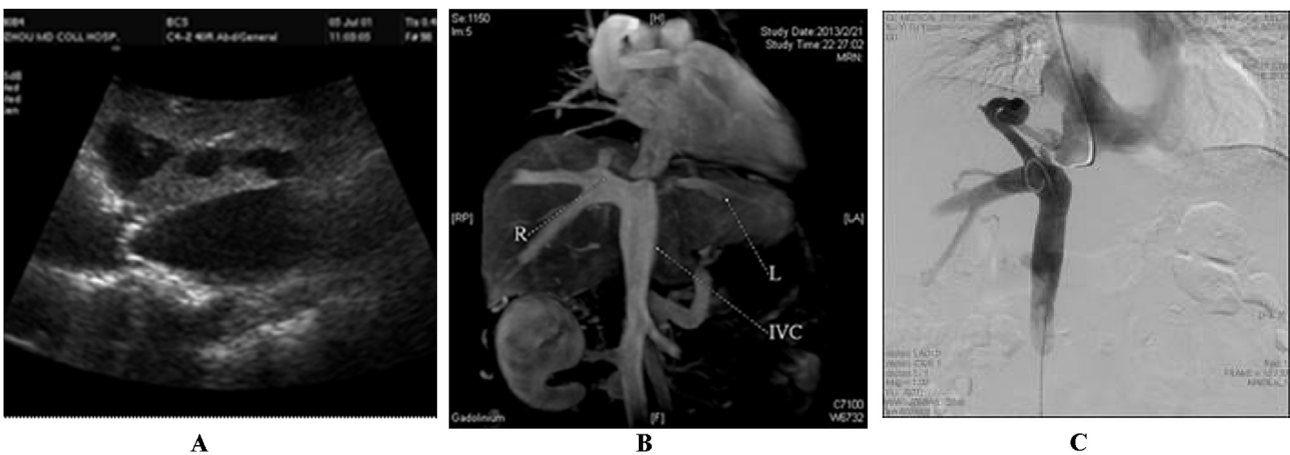
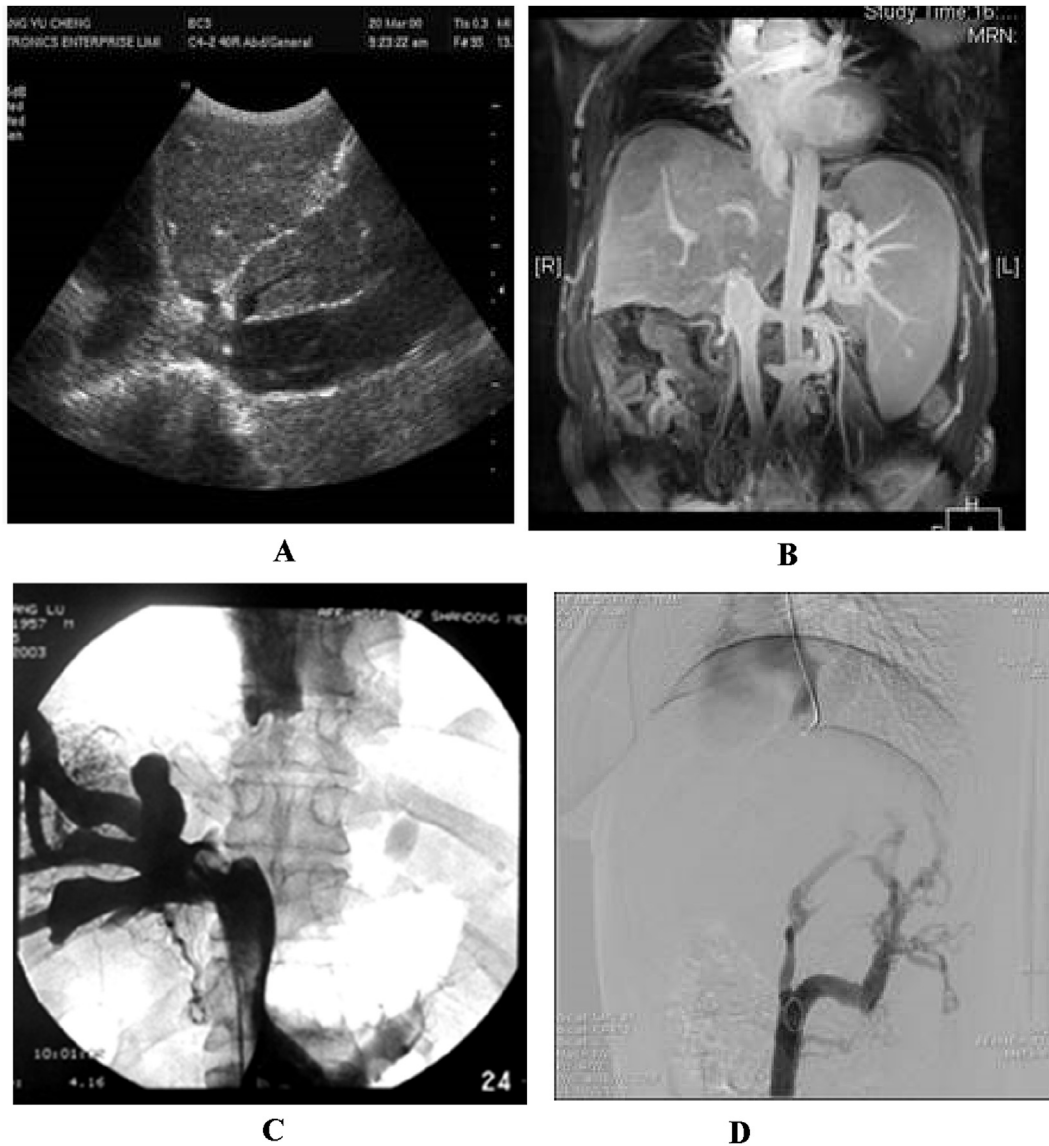


Fig. 16. A. The ultrasonography shows the echo of the membrane of the inferior vena cava  
 B. MRV shows membranous occlusion of the inferior vena cava above the hepatic vein ostium  
 C. DSA shows membranous occlusion of the inferior vena cava above the hepatic vein ostium.



**Fig. 17.** A. The ultrasonography shows the segmental occlusion of the inferior vena cava  
 B. MRV shows the long segmental occlusion of the inferior vena cava  
 C. DSA shows the segmental occlusion of the inferior vena cava  
 D. DSA shows long segmental occlusion of the inferior vena cava

diagnosis of BCS made by percutaneous liver biopsy is challenging, and the definitive diagnosis of BCS can be made only by MRA,<sup>20</sup> so making the diagnosis of BCS by liver biopsy is unnecessary.<sup>2</sup>

*Angiography*

Angiography remains the gold standard for the diagnosis of BCS; its use with US, CT, and MRI is complementary, constituting a complete system of BCS imaging diagnosis. Since it is an invasive angiographic examination, is no longer recommended as a simple diagnostic method but rather as the basis of interventional therapy and for observing the objective indexes for evaluating intervention effects.

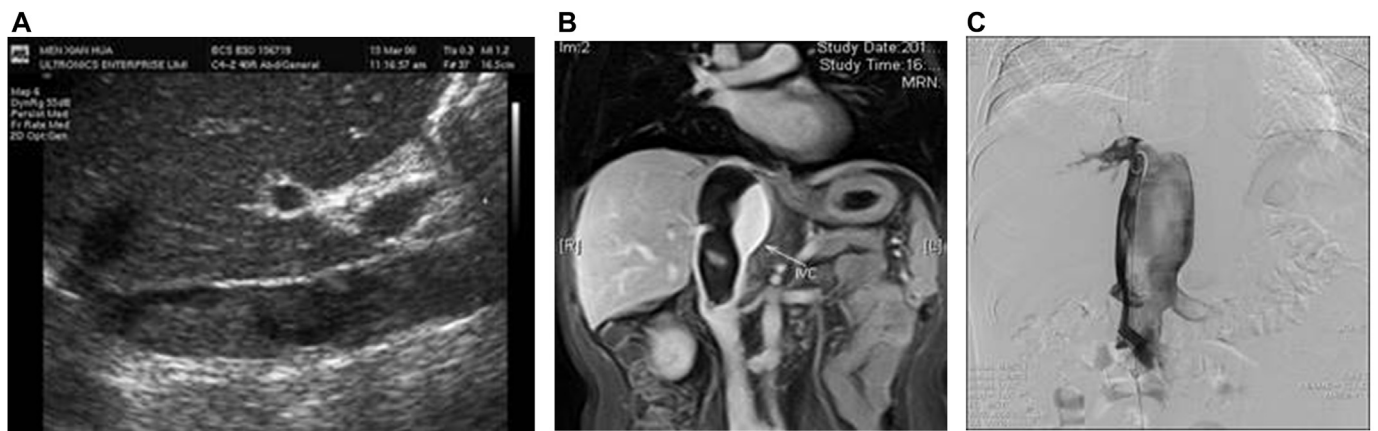
*The definition of membrane and segment obstruction of HV and IVC*

Formation of the IVC and hepatic venous membrane as well as segmental obstruction are unique pathological features of BCS, but in vivo pathological examination can not clearly define the “membrane”

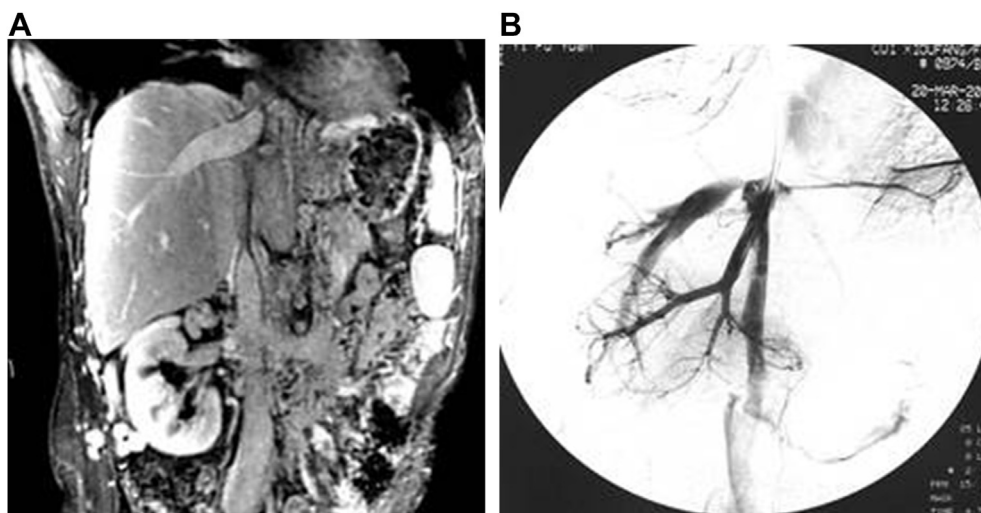
and “segment” at the opening of inferior vena cava and hepatic vein. As a result, there is no definition of the thickness of the membrane and the length of the segment in the literature so far. Our imaging examination found that the length of obstruction of the inferior vena cava varied from 1 mm to 300 mm. Such a big difference made the definition of the membrane and segment unclear. Defining the membrane and segment not only helps unify the diagnostic criteria of various imaging techniques and facilitate their description, but also it promotes subtype classification and which has important clinical value for the selection of interventional therapy. Therefore, it is necessary to define IVC and hepatic venous membrane and segmental obstruction in making the diagnosis of BCS.

In January 2016, we organized interventional radiology, pathology, and imaging diagnosis experts to examine more than 1000 patients with BCS using US, CT, MRI, and digital subtraction angiography images, analyze and discuss the findings, this is first time to create definitions of IVC and hepatic vein membrane and segment. Our definition criteria for inferior vena cava and hepatic venous membrane and segment





**Fig. 18.** A. The ultrasonography shows occlusion of the inferior vena cava with thrombosis.  
 B. MRV shows inferior vena cava occlusion with massive thrombosis.  
 C. DSA shows inferior vena cava occlusion with massive thrombosis.



**Fig. 19.** A. MRV shows the both hepatic vein and inferior vena cava obstructions.  
 B. DSA shows the both hepatic vein and inferior vena cava obstructions.



**Fig. 20.** A. MRV shows the obstructions of the both inferior vena cava and hepatic vein with massive thrombosis.  
 B. DSA shows the obstruction of the both inferior vena cava and hepatic vein with HV thrombosis.

obstruction are as follows: the membrane is below 5 mm, and the segment is above 10 mm.<sup>21</sup>

### BCS types and subtypes

The methods of interventional treatment for BCS differ completely from surgical treatment, so the classification used to guide surgery should not also be used to guide interventional therapy. Here we propose new BCS types and subtypes that can guide interventional therapy based on the fact that imaging has enabled the clear diagnosis of hepatic vein and IVC obstruction using thousands of cases of imaging data. The new classification will promote and standardize the imaging diagnosis and interventional therapy of BCS, which has objective, realistic, and long-term clinical significance.

In 2010, more than 10 experts from a China interventional radiology group engaged in the interventional therapy of BCS formulated an expert consensus on interventional therapy of BCS in China and proposed dividing BCS into three types: hepatic vein occlusion, IVC occlusion, and mixed type,<sup>22</sup> which are still widely used today.

In January 2016, the China Association of Physicians Chamber Vascular Branch of Vena Cava Obstruction committee of experts and domestic interventional radiology, vascular surgery, pathology, and imaging diagnosis experts engaged in BCS research fully discussed the 3 major types and further divided them into 10 subtypes. In the new classification, hepatic vein and IVC occlusion combined with thrombosis was included in the subtype for the first time because it is an objective fact. Interventional therapy can be achieved by thrombolysis. The thrombus is removed by aspiration, and the occluded hepatic and IVC can be safely expanded after thrombus clearance.<sup>23</sup>

The hepatic venous occlusion was divided into four subtypes (Figs. 11–14):

Subtype 1. Membranous occlusion of the hepatic vein/accessory hepatic vein (Fig. 11A–D);

Subtype 2. Segmental occlusion of the hepatic vein (Fig. 12A–C);

Subtype 3. Extensive occlusion of the hepatic vein (Fig. 13A–D); and

Subtype 4. Hepatic vein occlusion with thrombosis (Fig. 14A–D).

IVC obstruction was divided into 4 subtypes as well (Figs. 15–18):

Subtype 1. Membranous obstruction with a hole in the IVC (Fig. 15A–C);

Subtype 2. Membranous occlusion of the IVC (Fig. 16A–C);

Subtype 3. Segmental occlusion of the IVC (Fig. 17A–D); and

Subtype 4. Inferior vena cava obstruction with thrombosis (Fig. 18A–C).

Mixed obstruction of the hepatic vein and IVC was divided into 2 subtypes (Figs. 19 and 20):

Subtype 1. Obstruction of both the hepatic vein and the IVC (Fig. 19A and B); and

Subtype 2. Obstruction of both the hepatic vein and the IVC with thrombosis (Fig. 20A and 20B).

### Subtype classification and choice of interventional therapy

Interventional therapy for BCS includes percutaneous balloon dilation, stent implantation, thrombolysis, transjugular intrahepatic portosystemic shunt, and hepatic venous reconstruction. Interventional therapy can benefit 98% of BCS patients. The technical difficulties of BCS intervention vary widely. For example, interventional treatment of membrane with a hole of the IVC is very easy. However, the recanalization of hepatic vein occlusion or segmentalized IVC occlusion combined with thrombosis, occlusive end with traffic branch formation, and total IVC occlusion is difficult. Our new subtype classification will play a role in guiding treatment plan formulation, instrument preparation, stent preparation, thrombolytic drug preparation, and percutaneous puncture access.

**Table 3**

Correlations between BCS subtype and interventional therapy.

Subtype	Interventional therapy
Membranous obstruction of HV/AHV*	Balloon dilation
Segmental occlusion of hepatic vein	Balloon dilatation + stent
Extensive obstruction of hepatic veins	TIPS, hepatic vein reconstruction
Hepatic vein occlusion with thrombosis	Thrombolysis + balloon dilation
Membrane obstruction with hole in IVC	Balloon dilation
Membranous obstruction of IVC	Balloon dilation
Segmental occlusion of IVC	Balloon dilation + stent
IVC obstruction with thrombosis	Thrombolysis + balloon dilatation/stent
IVC and HV occlusion	Balloon dilatation/stent
IVC and HV obstruction with thrombosis	Thrombolysis + balloon dilatation/stent

AHV Accessory Hepatic Vein, HV Hepatic Vein, IVC Inferior Vane Cava.

### A new point of view

#### 1. Anatomical occlusion and functional occlusion of the left and middle hepatic vein

Xinwei et al. reported that, among the 35 cases of membranous obstruction of IVC, 28 had left hepatic vein and middle hepatic vein obstruction.<sup>24</sup> We observed 1000 cases of IVC obstruction using Doppler US to elucidate the incidence of hepatic vein occlusion. Our results indicated that the incidence of the left and middle hepatic vein occlusion is 79.1%; among the hepatic veins and accessory hepatic vein, multiple traffic teams are formed between the left hepatic veins and middle hepatic vein blood through the traffic back into the IVC, i.e. despite an anatomical obstruction, no functional occlusion is present. Therefore, we can achieve satisfactory clinical results by simply dilating the blocked IVC. Accordingly, when IVC occlusion is accompanied by left hepatic vein occlusion, we consider it an IVC occlusion rather than a mixed obstruction.

#### 2. Accessory hepatic vein(AHV)

The naming of the three major branches of the hepatic vein system (left hepatic vein, middle hepatic vein, and right hepatic vein) is relatively uniform on dissection, while the hepatic veins outside the three hepatic veins have not been named. In Gray's Anatomy, 38th edition, published in 1995, Peter et al. divided the hepatic veins into upper and lower groups. The hepatic veins in the upper group included the left, middle, and right hepatic veins, while the main trunk of the hepatic vein in the lower group was called the accessory hepatic vein.<sup>25</sup> We endorse the term AHV. Our data indicate an incidence of up to 67% of accessory hepatic veins after hepatic vein and IVC occlusion. When hepatic vein obstruction occurs in the upper group, thick traffic branches appear between the AHV and the upper group of the hepatic vein, and the AHV becomes the main hepatic circulation vein (Fig. 18C), playing a role in complete compensation. Moreover, when the hepatic vein and the AHV were blocked, the opening of the AHV had the same value as the opening of the hepatic vein.<sup>26</sup>

#### 3. Location of IVC membrane and hepatic vein opening

The IVC membrane is thought to be located above the hepatic vein openings, leading to hepatic vein blood backflow obstacles. Also, in the original definition of BCS, with the increase in the number of cases, we found that in some cases, the opening of the left hepatic vein is located above the obstruction of the IVC (Fig. 21). This phenomenon was also discovered by vascular surgeon Dr. Xiaoming,<sup>7</sup> and although such cases are rare, this finding challenges the original definition of BCS.

#### 4. Azygos vein and traffic branch

After a hepatic vein obstruction develops, it is easy to establish traffic



Fig. 21. DSA shows that the left hepatic vein ostium is located above the obstruction of the inferior vena cava.

branches between the hepatic veins and the accessory hepatic vein, but it is difficult to establish traffic branches between the intrahepatic and extrahepatic veins, resulting in obvious symptoms and signs of portal hypertension and poor prognosis. The establishment of collateral circulation in vivo and on the body surface after IVC occlusion is more extensive than that of hepatic vein occlusion. Azygos vein is one of the most significant signs of compensatory ability in the posterior collateral circulation of an IVC obstruction. Its lumen can expand to more than 2 cm, which makes it very easy to identify on abdominal CTV or MRV (Fig. 22). Azygos vein dilation is strong evidence for the diagnosis of IVC obstruction. The compensatory ability of azygos vein not only affects the severity of clinical symptoms and signs, it also affects patient survival time since patients can still survive for more than 30 years with good azygos vein compensatory ability.

#### 5. Traffic vessels above the block end

In cases of IVC obstruction, in addition to azygos, the deep and shallow veins of the abdomen and thorax are involved in blood reflux,



Fig. 22. The markedly distensible azygos vein occurs after the inferior vena cava obstruction.



Fig. 23. DSA shows multiple Traffic vessels above the block end.

and relatively small traffic vessels form above the end of IVC obstruction in 5.3% of patients that are difficult to visualize on US, CT, and MRI but visible on digital subtraction angiography (Fig. 23). Special care should be taken when the presence of traffic vessels is detected above the blocking end because these traffic vessels visualized under fluorescence cannot be seen; thus, puncture needles can very easily enter the traffic vessels; thus, the use of large balloon dilation is bound to cause traffic vessel rupture and fatal abdominal cavity hemorrhage. Therefore, for interventional therapy, manipulation of the traffic vessels of an IVC obstruction is potentially dangerous.

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#### Patient consent

Written informed consent was obtained from patients for publication of these case reports and any accompanying images.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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