

Original Article

Studies on Budd-chiari syndrome complicated with hepatocellular carcinoma: most patients without inferior vena cava obstruction

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Abstract: Background: To investigate the characteristics of Budd-Chiari syndrome (B-CS) types, rate of HCC complicated by different types of B-CS and values of CTA in diagnosis of B-CS and HCC complicated by B-CS. Material and Methods: 494 patients with B-CS were analyzed retrospectively. All patients underwent CTA, which was used to assess the accuracy of diagnosing B-CS and the rate of HCC complicated by various kinds of B-CS. Digital subtraction angiography (DSA) and pathological examination were used as gold standard. Results: Among 494 patients diagnosed by DSA, there were 21 (4.3%) cases of inferior vena cava type, 80 (16.2%) cases of hepatic vein type and 393 (79.6%) cases of hepatic vein combined with inferior vena cava complex type. The accuracy of diagnosing B-CS by CTA was 86.6% (428/494), in which the accuracy of diagnosing inferior vena cava type was 85.7% (18/21), 83.8% (67/80) for hepatic vein type and 87.3% (343/393) for complex type. The rate of HCC complicated by B-CS was 12.8% (63/494), among which inferior vena cava type was 4.8% (1/21), hepatic vein type was 11.3% (9/80) and complex type was 13.5% (53/393). There were no statistic differences between these three types ($P=0.459$). The accuracy of diagnosing HCC by CTA was 82.5% (52/63). Conclusion: B-CS in patients from China's Yellow River basin is mainly hepatic vein combined with inferior vena cava complex type, which is more likely to be complicated by HCC. CTA plays an important role in diagnosing B-CS and HCC complicated by B-CS.

Keywords: Budd-chiari syndrome, hepatocellular carcinoma, computed tomographic angiography, incidence

Introduction

Budd-Chiari syndrome (B-CS) is a global disease with relatively low incidence, which refers to obstruction happens at any part between hepatic vein and joint of inferior vena cava and right atrium. It may result in portal hypertension and/or inferior vena cava hypertension syndrome, including splenomegaly, hydroperitoneum, low extremity edema, varicose vein on the thoracoabdominal wall and esophageal and gastric, etc [1-3]. Incidence of B-CS appear to be regional, with hepatic vein thrombosis predominant in western countries, while membranous obstruction of inferior vena cava (MOVC) are common in Asian countries like China, Japan and India [1, 3]. Therefore, there are enormous differences between eastern and western countries in condition of recovery and treatment. It was well-known, however, some patients may lead to hepatocellular carcinoma

(HCC) during the development of B-CS, which will significantly decrease their survival rates [4]. Research shows that 0.7% HCC cases were caused by B-CS [5]. Among different reports, the rate of HCC in B-CS patients varies from 2.0% to 51.6%, and the accumulative incidence rate can reach 17.6% [6]. In most studies, however, B-CS complicated with HCC is mainly MOVC, while hepatic venous obstruction is extremely rare.

In clinic, B-CS can be simply divided into inferior vena cava obstructive type (IVC type), hepatic venous obstructive type (HV type) and hepatic vein combined with inferior vena cava complex type. Different kinds of B-CS have different clinical manifestation [1]. At present, hepatic venous obstruction and/or obstruction of the hepatic portion of the inferior vena cava diagnosed by venous angiography are deemed as gold standard [7, 8], while confirmed diagnosis

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Table 1. Basic information of 494 patients with B-CS

| Parameters | Value | Percentage |
|-------------------------------------|-----------|------------|
| Gender | | |
| Male | 279 | 56.5% |
| Female | 215 | 43.5% |
| Age (years old) | 46.6±11.6 | |
| Types of B-CS | | |
| IVC type | 21 | 4.3% |
| HV type | 80 | 16.2% |
| One main hepatic vein obstruction | 9 | 11.3% |
| Two main hepatic vein obstruction | 17 | 21.3% |
| Three main hepatic vein obstruction | 54 | 67.5% |
| Complex type | 393 | 79.6% |
| One main hepatic vein obstruction | 32 | 8.1% |
| Two main hepatic vein obstruction | 73 | 18.6% |
| Three main hepatic vein obstruction | 288 | 73.3% |

Table 2. The accuracy of diagnosing B-CS by CTA

| Parameters | CTA positive number | Total number | Percentage |
|--------------|---------------------|--------------|------------|
| B-CS | 428 | 494 | 86.6% |
| IVC type | 18 | 21 | 85.7% |
| HV type | 67 | 80 | 83.8% |
| Complex type | 343 | 393 | 87.3% |

of HCC depends on pathological examinations. As a significant image tool, computed tomographic angiography (CTA) is valuable in diagnosing B-CS and complicated HCC. Considering obvious regional varieties of B-CS incidence, we analyzed clinical data of 494 B-CS patients from China's Yellow River basin (mainly Henan Province) and further investigated the lesion characteristic and its complication with HCC, so we can deepen the understanding of the disease further more.

Material and methods

Ethics

This study has been approved by Medical Ethics Committee of the First Affiliated Hospital of Zhengzhou University and was conducted under all patients' informed consent.

Patient selection

Patients treated in the First Affiliated Hospital of Zhengzhou University from July 2011 to June 2014 were involved in this study. They were all

from Yellow River basin (mainly Henan Province) and were examined by CTA initially on admission and confirmed to have B-CS after digital subtraction angiography (DSA) examination. The diagnosis of HCC depended on biopsy and pathological examination of surgical specimens. None of the patients was selected by sex or age.

Examination methods

CTA examination: all patients underwent scanning by a GE LightSpeed 64-slice CT scanner. Tube potential was 120 Kv; tube current was under automatic milliamperage setting (240 mA~500 mA); pitch was 0.984:1, and bed speed was 39.37 mm/rot; scanning speed was 0.8 s/360°; slice thickness and interlayer distance was 5.0 mm, and collimating width was 64×0.625 mm. After plain scanning for abdomen, 100 ml nonionic iodinated contrast (Omnipaque, 350 mg/ml or Ultravist, 370 mg/ml) was injected via the antecubital vein (3 ml/s). Then triple-phase enhanced scanning (time delay: 25 s~30 s, 65 s~75 s, 130 s~140 s) was used. Collected data were reconstructed standardly with a thickness of 0.625mm and an interval of 0.625 mm. Adw4.4 workstation (Advantage Windows 4.4, GE Medical Systems) was used for post-processing, including VR, MinIP, MIP, MPR, MPVR, etc. to display vessels and liver parenchyma.

DSA examination: Siemens Hicor digital angiography system was used for observation after inferior vena cavography with femoral vein or internal jugular vein puncture, then hepatic vein or accessory hepatic vein angiography was carried out, percutaneous transhepatic venography was also carried out when necessary.

Pathologic examination: Patients with hepatic lesions were demonstrated by liver biopsy or surgical resection. All samples were fixed by 4% formalin solution, routine embedded in paraffin, serial sliced with thickness of 4 μm, stained with HE and observed under light microscopic.

Outcome assessments

Enhanced CT scanning and CTA were assessed by one attending doctor and one senior doctor, who would make a diagnosis consensus of vas-

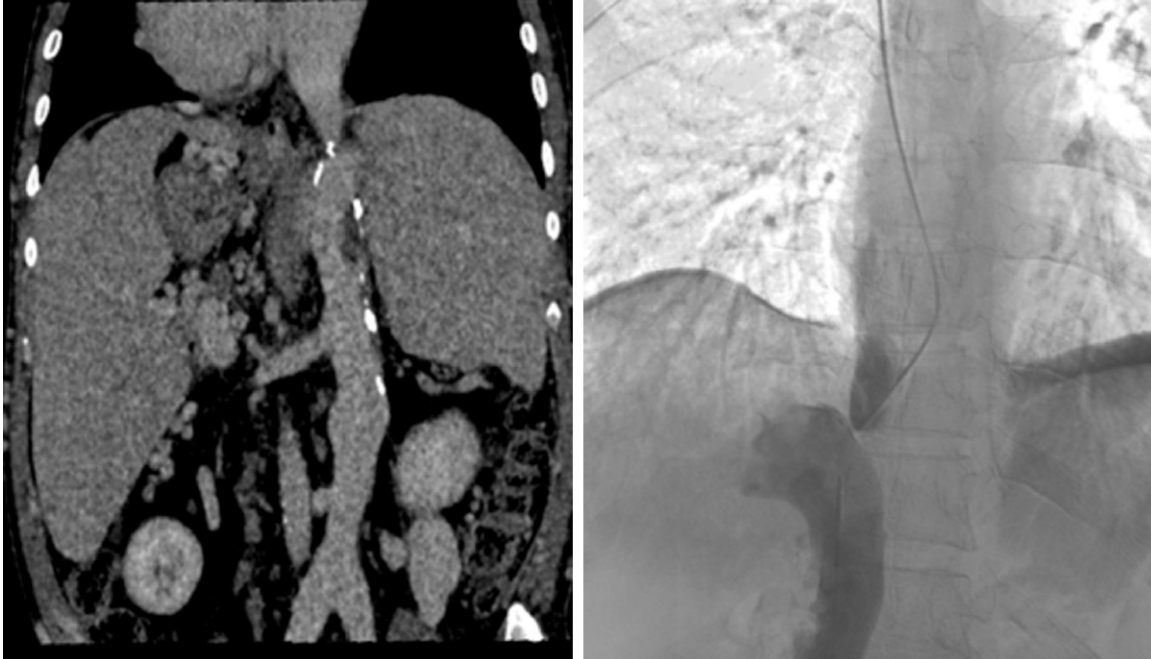


Figure 1. Membranous occlusion were both confirmed by CTA (vascular reconstruction image) and DSA (femoral vein and jugular vein combined radiography) in one patient, indicating that CTA can reflect the vessel obstruction conditions in patients with B-CS well and has relatively high accuracy of diagnosis.

cular lesions and focal liver lesions. DSA examination was conducted by one associate senior doctor or one attending doctor, who would make a diagnosis of vessel obstruction. Pathological diagnosis of liver neoplasm was completed by one attending doctor and one senior doctor.

Data analysis

SPSS 17.0 software was used to analyze the data. Enumeration data were shown in ratio, and measurement data were presented by $\bar{x} \pm s$. Chi-square test was used to HCC risk differences of various types of B-CS. $P < 0.05$ was deemed as statistical significance.

Results

General information

Among 494 patients, there were 279 male patients and 215 female patients (1.3:1). The average age were 46.6 ± 11.6 years old (ranging from 5 to 79 years old).

B-CS types

There were 21 cases of IVC type (4.3%), 80 cases of HV type (16.2%), and 393 cases of

complex type (79.6%). The patients with complex type were significantly more than that with IVC or HV type. Among 80 cases of HV type, there were 9 cases with one main hepatic vein obstruction (11.3%), 17 cases with two main hepatic vein obstruction (21.3%) and 54 cases with three main hepatic vein obstruction (67.5%). Of all 393 cases of complex type, there were 32 cases with one main hepatic vein obstruction (8.1%), 73 cases with two main hepatic vein obstruction (18.6%) and 288 cases with three main hepatic vein obstruction (73.3%) (**Table 1**). Compared with DSA, the diagnostic accuracy rate of CTA was 86.6% for B-CS, while it was 85.7% (18/21), 83.8% (67/80), and 87.3% (343/393) for IVC type, HV type, and complex type, respectively (**Table 2**). The imaging features of B-CS demonstrated by DSA and CTA were shown in **Figure 1**. Additionally, communicating branches of hepatic vein and open accessory hepatic veins were observed in most patients by CTA (**Figure 2**).

HCC diagnosis

Of all the 494 patients, pathological examination revealed that there were 63 cases (12.8%) complicated with HCC, among which were one case of IVC type (1.6%), 9 cases of HV

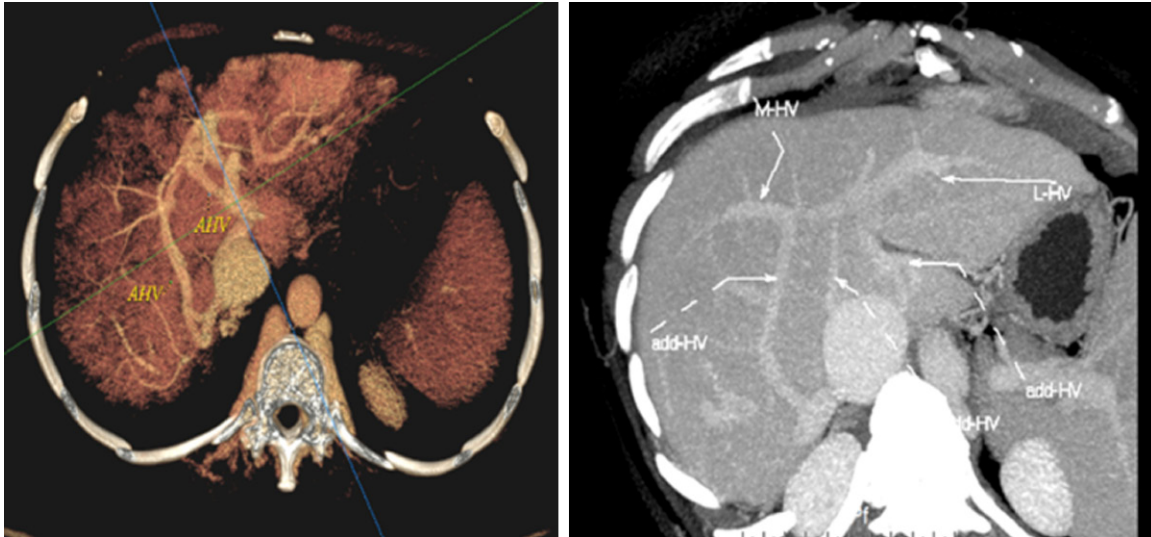


Figure 2. Main hepatic vein obstruction, extensive communicating branches and abundant open accessory hepatic veins were observed by CTA in B-CS patients, and blood in liver flowed into inferior vena cava through these compensatory collateral circulations to remit liver congestion.

Table 3. The rate of HCC complicated by different types of B-CS

| Parameters | Number of complicated HCC | Total number | Percentage |
|--------------|---------------------------|--------------|------------|
| B-CS | 63 | 494 | 12.8% |
| IVC type | 1 | 21 | 4.8% |
| HV type | 9 | 80 | 11.3% |
| Complex type | 53 | 393 | 13.5% |

type (14.3%), and 53 cases of complex type (84.1%), respectively. For different types of B-CS, the complication rates with HCC were 4.8% (1/21), 11.3% (9/80), and 13.5% (53/393) for IVC type, HV type, and complex type, respectively. The complication rate with HCC for complex type was significantly higher than that for other two kinds, but there was no statistical differences among these three types ($P=0.459$) (Table 3).

Among all the 63 HCC cases confirmed by pathological examinations, there were 52 cases were initially identified by CTA with an accuracy rate of 82.5% (52/63). The pathological features of HCC on CTA are demonstrated by Figures 3 and 4.

Discussion

Types of B-CS

The cause and pathogenesis of B-CS are still unclear at present, and a number of alternative

mechanisms of B-CS have been proposed, such as congenital abnormality, mutant on Factor V Leiden, myeloid proliferation disease, thrombosis etc [3, 9-13]. However, there has been no unequivocal hypothesis about the pathogenesis of B-CS to date. Furthermore, Chinese patients with B-CS don't have so many coagulation diseases like westerners [14, 15], indicating there are differences in the pathogenesis of B-CS between Chinese and westerners.

There were several types of B-CS and the characteristics of B-CS have significant differences in different regions. For instance in western countries, B-CS is mostly caused by hepatic vein obstruction, while MOVOC is the major cause in Asian countries [1, 3]. In China, B-CS appears more frequently on the middle and lower catchment of the Yellow River and Huai River, including Henan, Jiangsu, Shandong province, etc [2, 3]. Our results demonstrated that the inferior vena cava obstruction wasn't the major type of B-CS in patients from Henan province. Among the 494 patients who were diagnosed as B-CS by DSA, 79.6% patients (393/494) were complex type of hepatic vein and inferior vena cava obstruction. Only in 4.3% patients (21/494), obstruction was observed in inferior vena cava, of which the occurrence rates were even lower than that in hepatic vein obstruction patients (16.2% (80/494)). Besides, among the hepatic vein obstruction and mixed obstruction patients, three major hepatic vein

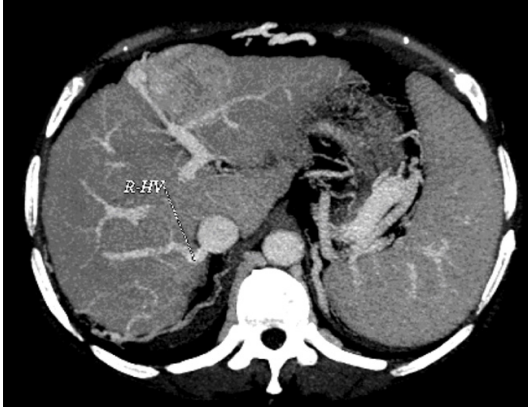


Figure 3. Left liver lobe complicated with HCC (diameter: 5 cm) was found through CTA in a B-CS patient. Due to hepatic vein outflow tract obstruction, tumor still showed high density during venous phase, without typical characteristics of fast in fast out.

branches obstruction were observed in most of them (67.5% and 73.3%, respectively) and only a few patients suffered from one or two branches obstruction. He Xiao et al. [16] reported that among 567 B-CS patients from Henan province who were examined by abdominal ultrasound, the occurrence rates of mixed obstruction, inferior vena cava obstruction and hepatic vein obstruction were 81.3%, 1.94% and 16.75%, respectively, which were consistent with our results.

Obviously, B-CS patients in this study mainly suffered from mixed obstructions and even extensive obstructions in multiple branches of major hepatic vein, which were not consistent with many other studies. It could be speculated that those different results were associated with the regionality of B-CS, and further studies were required to investigate whether the obstruction types and lesion ranges of B-CS would change with the prolongation of disease duration.

B-CS complicated with HCC

So far, B-CS has been regarded as one of unequivocal risk factors of HCC, in this study, 12.8% B-CS patients (63/494) were complicated with HCC, which was consistent with others' results. Some foreign researchers reported that the morbidity of HCC were higher in MOVC patients and almost hadn't been observed in hepatic vein obstruction patients, which suggested the close relation between MOVC and

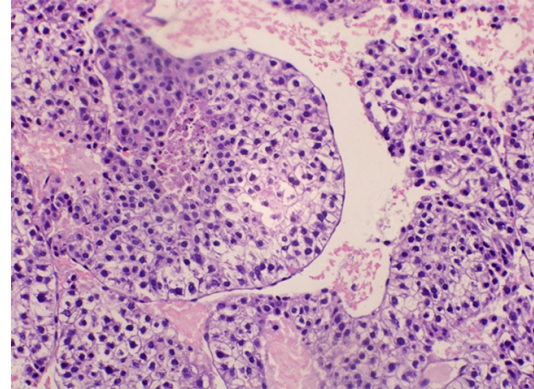


Figure 4. HCC confirmed by pathological examination: mild abnormality of carcinoma cell were observed under microscope with evident nucleus and increased split phase ($\times 400$).

secondary HCC [17-23]. In general, the reason may be that acute or sub-acute injuries could be generally observed in hepatic vein obstruction, but in contrast, inferior vena cava obstruction always appeared as chronic or latent injury which was caused by chronic congestion hypoxia in liver.

Nevertheless, our study hadn't confirmed this viewpoint. Among 63 B-CS complicated with HCC patients, the morbidity of inferior vena cava obstruction was 1.6% (1/63), which was significant lower than that in hepatic vein obstruction (14.3% (9/63)) and mixed obstruction group (84.1% (53/63)). Also, the morbidity of B-CS complicated with HCC in inferior vena cava obstruction, hepatic vein obstruction and mixed obstruction group were 4.8% (1/21), 11.3% (9/80), 13.5% (53/393), respectively. Since statistical differences of the morbidity of secondary HCC hadn't been observed in three kinds of obstructions ($P=0.459$), we could not expect the risk of HCC was higher in inferior vena cava obstruction patients.

The reasons why extensive obstructions in hepatic vein cause chronic hepatic injury even result in HCC but can't induce acute or sub-acute hepatic failure in a short time is not fully understood. In our respects, extensively established communicating branches in or out of liver and the compensatory dilation of accessory hepatic veins may be the explanations. Previous studies showed that the extensively established communicating branches and compensatory dilation of accessory hepatic

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veins were important characteristics in B-CS patients [7, 8], and these collateral circulations were important compensatory mechanisms, which could relieve the obstruction in hepatic vein outflow tract. Although one or multiple branches of hepatic veins were blocked, hepatic blood on the control region of obstructed vascular could flow back to heart via other hepatic or accessory hepatic veins, which would largely relieve the congestion of liver. However, for the hepatic congestion can't be relieved completely, HCC will occur eventually because of the chronic injury in patient's liver.

B-CS diagnosed by CTA

Up to now, DSA is still the gold standard of the diagnosis of B-CS [7, 8]. Because of the characteristics of high expensive, invasiveness, operation inconvenience, and unclear demonstration of vascular wall or surrounding tissues, angiography hasn't been widely applied in clinics, so it's unsuitable to regard angiography as a routine examination. In contrast, the characteristics of non-invasive, easy to operate, high temporal and spatial resolution, as well as the application of several reconstructions of vascular technologies such as VR, MIP, MPR etc. make CTA a special method to diagnose B-CS.

CTA is performed to diagnose B-CS majorly depends on findings which indicate the obstruction of hepatic veins outflow tract. In addition, some indirect signs such as enlargement of caudate lobe, open of accessory hepatic vein, communicating branches established between hepatic veins, and collateral circulation established outside the liver etc. are also important evidences to diagnose B-CS. Based on these signs, we can increase the diagnostic accuracy of B-CS [7, 8, 24, 25]. In our study, the accuracy rate of CTA in diagnosing B-CS was 86.6% (428/494), and the accuracy rates of CTA in diagnosing inferior vena cava, hepatic vein and mixed obstruction were 85.7% (18/21), 83.8% (67/80), and 87.3% (343/393), respectively, which demonstrated a promising diagnostic value. As for the false negative results conducted by CTA, cirrhosis nodules of liver and enlargement of caudate lobe which could result in the compression stenosis on hepatic vein and inferior vena cava can't be recognized clearly by CTA might be the possible reasons. Besides, changes in hepatic hemodynamics of B-CS were different from those in other disease.

Therefore, it was important to choose the suitable scanning duration of delay-stage. Furthermore, with the application of new CTA technologies, the diagnostic accuracy of CTA could be increased [26].

B-CS complicated with HCC diagnosed by CTA

When compared with DSA, another advantage of CTA conducted in B-CS patients is manifesting the changes in morphology and function, which can recognize the potential hepatic diseases. Although the confirmation of HCC still depends on the pathological examination, the diagnostic accuracy of CT on diagnosing B-CS is extremely high, which is associated with the special imaging characteristics [27]. Whereas Moucari et al [19]. reported that among the 15 hepatic carcinoma nodules which were observed in 11 B-CS complicated with HCC patients, fourteen nodules were found owning abundant blood supply during the arterial phase. Only 4 hepatic carcinoma nodules in 3 patients demonstrated the imaging characteristics of "fast-in, fast-out". Because there were obstructions in B-CS complicated with HCC patient's hepatic vein outflow tract, during the venous phase of enhanced scanning, contrast media couldn't be eliminated from liver like HCC resulted from other diseases. This would lead to the relatively high or equal density imaging of carcinoma during the portal venous and delayed phase, and thus the classical imaging characteristics of "fast-in, fast-out" couldn't be observed easily. This also caused troubles in differentiating the hepatic carcinoma lesions with regenerative nodules and decreased the accuracy rate of CTA in some degree. In this study, among the 63 B-CS patients who were confirmed with secondary HCC, only 52 patients were successfully recognized by CTA and the diagnostic accuracy rate was only 82.5%, which may be correlated with the atypical image features of HCC complicated by B-CS.

However, image features such as unilateral irregular nodules with a big mass were observed in B-CS complicated with HCC [23, 28]. Besides, there were regeneration nodules in B-CS patients. Although these nodules may be misdiagnosed as HCC, they actually have their own image features on CT [29, 30], and these features may improve the diagnostic accuracy of CT on HCC.

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Although this study revealed the distinct features of B-CS and B-CS complicated with HCC in patients from China's Yellow River Basin, there were some limitations should be noted: 1) because no permanent staff were assigned to conduct the DSA, CTA and pathological examinations, there might be minor personal errors in diagnosing B-CS. 2) no further analysis was conducted on the specific types and severity of vascular obstructions, and no profound investigations were employed on the reconstructions of collateral circulations and accessory hepatic vein expansion, so we could not clarify their correlations.

Conclusions

Our study did demonstrate that CTA was a promising tool in diagnosing B-CS and its complication with HCC. More importantly, obstruction of inferior vena cava is not common in patients with B-CS and B-CS complicated with HCC from China's Yellow River basin, however, B-CS of complex type was more common. These findings would definitely extend our experience and knowledge in diagnosing and treating the disease, and thus improve patients' survival quality.

Disclosure of conflict of interest

None.

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