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# Clinical characteristics and risk factors of hepatocellular carcinoma development in Budd-Chiari syndrome patients after endovascular treatment ☆

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ABSTRACT

*Background and Aims:* Endovascular treatment has improved Budd-Chiari syndrome (BCS) patient outcomes, but patients remain at risk for developing hepatocellular carcinoma (HCC). We aimed to analyse the characteristics and risk factors for HCC development in BCS patients after endovascular treatment.
*Methods:* Clinical data of BCS patients who had received endovascular treatment were retrospectively reviewed. Characteristics of BCS patients who developed HCC post-treatment were compared with those without HCC development. Univariable and multivariable Cox regression analyses were used to determine the risk factors.
*Results:* We enrolled 302 BCS patients. HCC was confirmed in 31 patients after treatment. Early-stage tumours were the most common (11/31, 35.5 %) according to the Barcelona Clinic Liver Cancer staging system. A serum alpha fetoprotein (AFP) cut-off level of > 15.7 ng/mL showed a sensitivity of 69.3 % and specificity of 97.4 % for detecting HCC in these patients. The presence of preoperative liver cirrhosis (hazard ratio (HR)=4.677; $P = 0.043$) and postoperative restenosis (HR=6.867; $P < 0.001$) were independent risk factors associated with HCC development in BCS patients after endovascular treatment.
*Conclusion:* HCCs that develop after endovascular treatment in BCS patients are often detected at an early stage. Preoperative liver cirrhosis and postoperative restenosis were independent risk factors for HCC development in these individuals.


## 1. Introduction

Budd-Chiari syndrome (BCS) is primarily characterized by hepatic venous outflow obstruction. Unlike in Western countries, most BCS cases in Asian countries have chronic presentation [1–4]. Prolonged hepatic congestion can lead to exacerbated hepatocellular hypoxia, hepatocyte necrosis, and fibroproliferation, which is believed to be one mechanism of cirrhosis [4,5]. Hepatocellular carcinoma (HCC) can subsequently arise from this foundation [5]. Previous reports have extensively demonstrated that endovascular treatment for BCS can improve liver function and reduce the progression of liver failure. However, BCS patients remain at high risk for developing HCC, with a pooled prevalence of 15.4 % [6,7].

The reported risk factors associated with HCC in the context of BCS have varied within the literature because of small sample sizes and sporadic cases, with most studies only considering preoperative situations [8–10]. Additionally, research focusing on the clinical characteristics and risk factors for HCC development after endovascular treatment in BCS was limited. In this study, we analysed clinical data from BCS patients who had received endovascular treatment to explore the characteristics and risk factors for postoperative HCC development in these individuals.

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## 2. Materials and methods

### 2.1. Patient population

This retrospective study was approved by our Institutional Review Board. All patients provided written informed consent before treatment. Because of the retrospective nature of the study, the Institutional Review Board waived the requirement for informed consent from the patients for participation in the study. We retrospectively reviewed the clinical data of 415 BCS patients that were collected between January 2017 and March 2023. The inclusion criteria were as follows: (1) patients aged between 18 and 80 years; (2) primary BCS; and (3) initial endovascular treatment in our centre that resulted in successful recanalization. The exclusion criteria were as follows: (1) secondary BCS caused by factors such as tumours or trauma; (2) pre-existing HCC or other malignancies before endovascular treatment for BCS; (3) history of previous surgical or interventional treatment for BCS; (4) concurrent cardiac or renal insufficiency; and (5) patients lost to follow-up or with a follow-up $<$ 1 year after initial endovascular treatment.

A diagnosis of primary BCS was established using systematic abdominal ultrasonography, with magnetic resonance angiography (MRA) or computed tomography angiography (CTA) used as a secondary examination to confirm the diagnosis before treatment. Finally, angiography was performed in all patients to identify the obstruction site of the inferior vena cava (IVC) and hepatic vein (HV). BCS patients were mainly classified into three types: (1) IVC type, manifesting as an obstruction of the IVC with patent HVs; (2) hepatic type, manifesting as an obstruction of at least one HV with patent IVC; and (3) mixed type, manifesting as an obstruction of the IVC and at least one HV. Liver cirrhosis was diagnosed using the typical presentations on abdominal ultrasound, CT, and MRI scans. These presentations included a change in liver volume, imbalance of the left and right liver lobe sizes, wavy or serrated hepatic capsule, widened hepatic fissure, uneven echo or density signal of the liver, dilatation of the portal vein, and collateral circulation [11].

### 2.2. Endovascular treatment procedure and strategy

Under local anaesthesia, catheterization and angiography were simultaneously performed via the right femoral and right internal jugular vein approach, then the occlusion site of the IVC, HV, or accessory HV (if present) was assessed. For IVC type and HV type cases, recanalization of the veins was first conducted with balloon dilation alone, followed by stent placement if the obstructed lumen diameter contracted by $>$50 %. For mixed type cases, IVC recanalization was only needed if at least one large and patent HV or accessory HV (diameter $>$ 5 mm) was identified. Otherwise, both IVC and HV recanalization were performed using the above stepwise strategy. In cases with accompanying fresh thrombosis, a thrombolytic catheter was initially inserted for thrombolysis, followed by balloon angioplasty and/or stent placement after thrombus clearance. Trans-jugular intrahepatic portosystemic shunt (TIPS) was performed in patients with extensive HV occlusion. The specific procedural details are referenced from our previous publications [12–15].

### 2.3. Follow-up and outcome assessments

All patients underwent follow-up every 3 to 6 months post-treatment or whenever symptoms recurred. Follow-up included clinical symptoms, abdominal colour Doppler ultrasound, and laboratory test results, including serum alpha fetoprotein (AFP) levels ($\leq$ 9 ng/mL was considered normal), coagulation function, liver function, and kidney function. If vascular restenosis or intrahepatic nodules were indicated by ultrasound, then further evaluation using CTA or MRA was conducted. Patients were followed up until first HCC diagnosis or the end of the study period. In the event of vascular restenosis during follow-up, timely balloon angioplasty and/or stent placement was performed to restore vessel patency.

Technical success of endovascular treatment was defined as successful recanalization of the IVC and at least one patent HV or accessory HV, with significant improvement or stabilization of the BCS clinical symptoms. HCC diagnosis was confirmed by pathological evaluation with percutaneous biopsy in patients with progressive intrahepatic nodules and without contraindications. Otherwise, the imaging diagnosis was used according to guidelines on HCC management [16]. The clinical features of HCC in BCS patients after endovascular treatment were recorded, including tumour number, size, location, and staging following the Barcelona Clinic Liver Cancer (BCLC) system. The patients were divided into two groups according to whether they developed HCC or not (HCC group vs. non-HCC group).

## 3. Statistical analysis

Normally distributed quantitative data are presented as the mean $\pm$ standard deviation and were compared using the independent-samples *t*-test. Non-normally distributed quantitative data are presented as the median (interquartile range) and were compared using the Mann-Whitney U test. Categorical data are presented as a ratio (or percentage) and were compared using the chi-square test or Fisher's exact test. Using electronic callipers, the tumour size was measured as the maximum diameter of the largest targeted tumour. Receiver operating characteristic (ROC) curve analysis was used to assess the sensitivity and specificity of the AFP values for predicting HCC development, with the threshold corresponding to the maximum Youden Index considered as the optimal cut-off point. Comparisons between two groups of baseline variables and treatment outcomes were then performed. A Cox regression analysis was used to analyse the risk factors for developing HCC after endovascular treatment in BCS patients. Baseline variables and treatment outcomes were first investigated by a univariate Cox regression analysis. Candidate variables with a *P*-value $<$ 0.05 in the univariate analysis were considered in the multivariate adjusted model. *P*-values $<$ 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

## 4. Results

### 4.1. BCS treatment outcomes

According to the inclusion and exclusion criteria, 302 BCS patients were ultimately included in this study (Fig. 1). The baseline characteristics of all 302 patients are summarized in Supplemental Table 1. Initial technical success was achieved in all patients in this study. Among the 38 patients with HV type BCS, recanalization of the main HV was performed in 35 cases. Only two patients underwent recanalization of the accessory HV by balloon dilation, while one patient underwent TIPS. Among the 12 patients with IVC type and 252 patients with mixed type, all received recanalization of the IVC, with simultaneous dilation of the main HV in 65 cases and of the accessory HV in 31 cases. In addition, 156 of the patients with mixed type did not undergo HV recanalization because of the presence of a large and patent accessory HV. No patients experienced any major intraoperative or postoperative complications, such as vascular rupture, cardiac tamponade, or stent displacement.

The patients in this study were followed up for a median of 52.5 (22.0–75.2) months. A total of 59 patients experienced

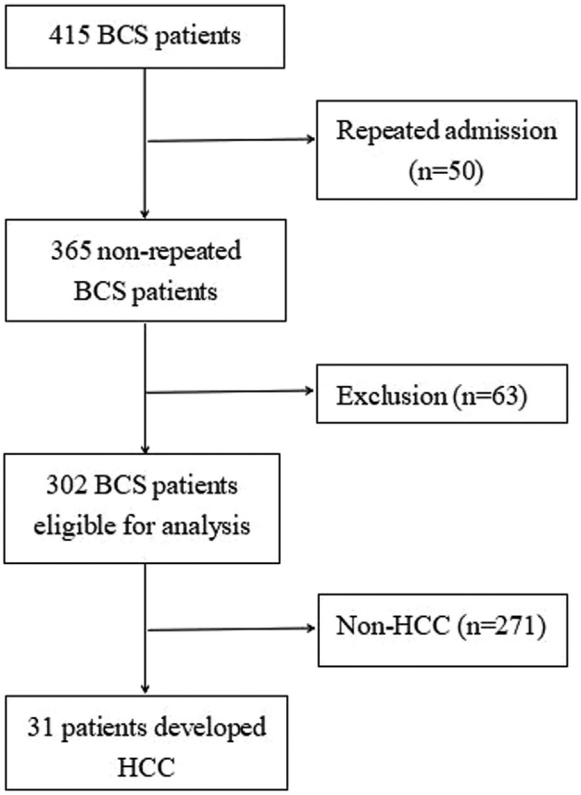


**Fig. 1.** Flowchart of the review of study patients. Abbreviations: BCS, Budd-Chiari syndrome; HCC, hepatocellular carcinoma.

restenosis, with 48 of them undergoing another balloon dilation and/or stent placement. Subsequent IVC and HV patency was again achieved. The other 11 patients refused further intervention. All patients survived throughout the follow-up period.

**Table 1**
Characteristics of 31 patients with hepatocellular carcinoma (HCC) after endovascular treatment for Budd-Chiari syndrome (BCS).

| Characteristic | Datum |
|---|---|
| Age at HCC diagnosis | 51.8 ± 9.9 |
| Child-Pugh Class at HCC diagnosis, n A/B/C | 20/10/1 |
| Tumour location, n (%) | |
| Right lobe | 12 (38.7) |
| Left lobe | 7 (22.6) |
| Both | 12 (38.7) |
| Tumour type, n (%) | |
| Single | 15 (48.4) |
| Multiple | 16 (51.6) |
| BCLC stage, n (%) | |
| 0-Very early stage | 6 (19.4) |
| A-Early stage | 11 (35.5) |
| B-Intermediate stage | 9 (29.0) |
| C-Advanced stage | 5 (16.1) |
| D-Terminal stage | 0 (0) |

Abbreviations: BCLC, Barcelona Clinic Liver Cancer.

### 4.2. HCC development and characteristics

HCC was identified in 31 patients after endovascular treatment of BCS in this study. There was histological confirmation in 20 patients with percutaneous liver biopsy and clinical diagnosis in 11 patients using typical imaging features (Fig. 2). All of these patients displayed clinical features of liver cirrhosis upon HCC diagnosis. The median duration between the primary treatment of BCS and HCC diagnosis was 65 (26–81) months. In this study, the cumulative 1-, 3-, and 5-year HCC incidence rates were 0.3 %, 4.7 %, and 7.7 %, respectively.

The clinical features of the 31 HCC patients diagnosed after endovascular treatment for BCS are shown in Table 1. Hepatitis B virus surface antigen (HBsAg) was positive in one patient (3.2 %), while no patients were positive for hepatitis C virus infection. The

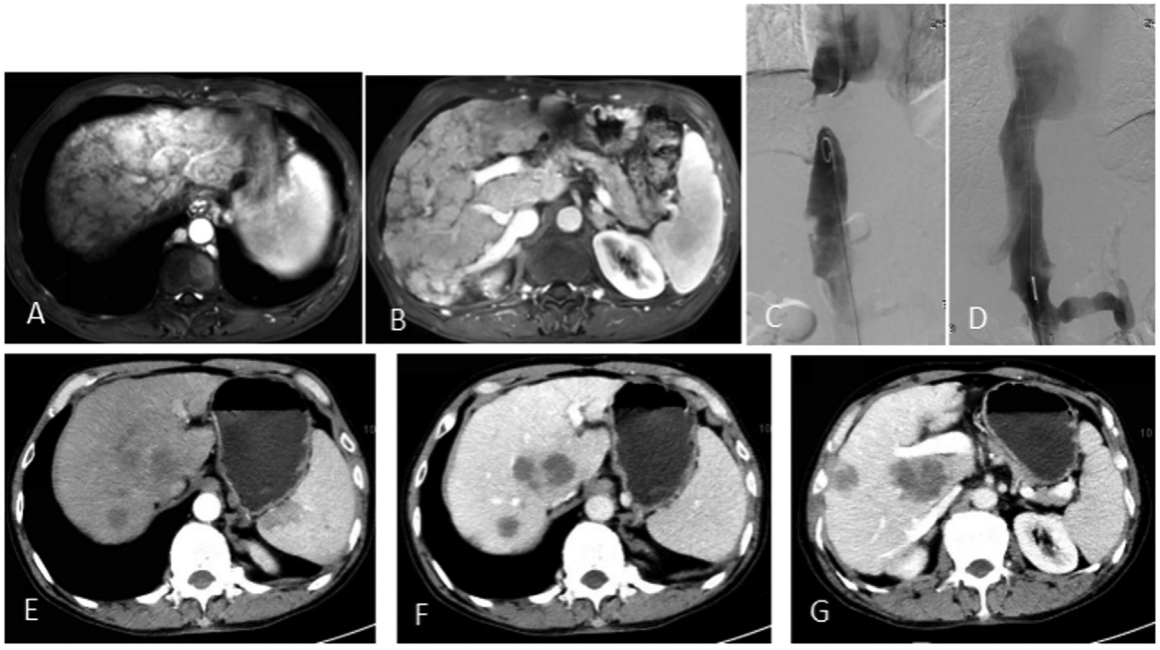


**Fig. 2.** Endovascular treatment and hepatocellular carcinoma (HCC) development in a 66-year-old man with Budd-Chiari syndrome (BCS). (A, B) Magnetic resonance angiography performed before treatment showed obvious liver cirrhosis and mixed type BCS. The inferior vena cava (IVC) and three main hepatic veins (HVs) showed occlusion with the presence of a large accessory HV. (C, D) The patient only underwent IVC recanalization because of a patent accessory HV. (E, F, G) Enhanced computed tomography images of the same patient three years after treatment, which showed multiple HCC lesions on the right side of the liver, with heterogeneous enhancement on the arterial phase and washout on the delayed phase.

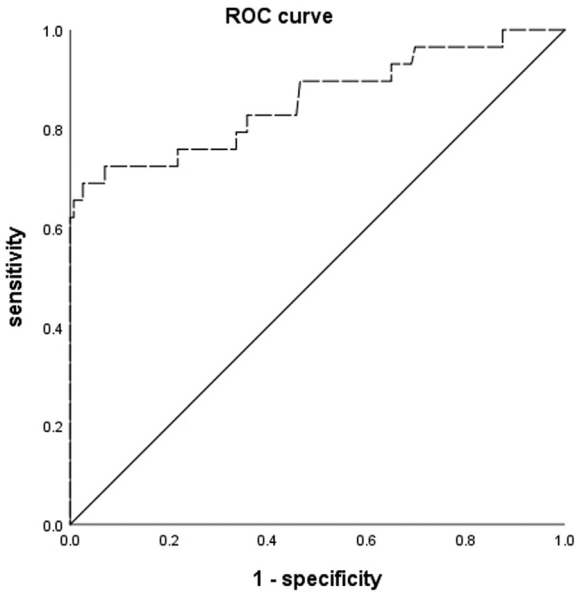


**Fig. 3.** Receiver operating characteristic (ROC) curve analysis for using the serum alpha fetoprotein (AFP) value for detecting hepatocellular carcinoma (HCC). AFP levels showed an adequate discrimination capacity (area under the ROC curve (AUC) value of 0.857, $P < 0.001$).

tumour size ranged from 1.1 to 11.9 cm (mean 4.2 ± 3.4 cm) in these patients. Among them, six patients were at very early stage, 11 at early stage, nine at intermediate stage, and five at advanced stage. In the HCC group ($n = 31$), the serum AFP levels showed a wide range, with a median level of 204.1 (5.7–1246.5) ng/mL. Among these patients, eight (25.8 %) had AFP levels within the normal range (< 9 ng/mL). In the non-HCC group ($n = 271$), the serum AFP levels were normal in 247 (91.1 %) patients, with a median level of 3.9 (2.7–5.8) ng/mL. There was a highly significant difference between the two groups ($Z = 6.314$, $P < 0.001$). An ROC analysis of the serum AFP levels for HCC detection indicated that the area under the ROC curve (AUC) value was 0.857 (95 % confidence interval (CI): 0.765–0.948, $P < 0.001$). A serum AFP cut-off level of > 15.7 ng/mL showed a sensitivity of 69.3 % and specificity of 97.4 % for HCC detection after endovascular treatment in BCS patients (Fig. 3). Among the patients with HCC in this study, 21 were treated with transarterial chemoembolization, five with microwave ablation, and two with surgical resection. The remaining three patients refused aggressive intervention and only received conservative treatment.

### *4.3. Risk factors for HCC in BCS patients after endovascular treatment*

The data were compared between the HCC group and non-HCC group for clinical characteristics before primary endovascular treatment and treatment outcomes, as presented in Table 2. There were no significant differences in sex, age at BCS diagnosis, type of BCS, baseline Child-Pugh Class, prognostic index, endovascular strategies, or the number of occluded main HVs after treatment between the two groups. However, the comparisons of serum albumin levels, serum total bilirubin levels, presence of antithrombin deficiency, preoperative liver cirrhosis, preoperative oesophageal varices, diameter of accessory HV, and postoperative restenosis showed significant differences between the two groups. The univariate analysis showed that the risk factors for HCC development in BCS patients who underwent endovascular treatment were increased serum total bilirubin (TBIL) levels at baseline, positivity for HBsAg, preoperative liver cirrhosis, splenomegaly, oesophageal varices, a large accessory HV diameter, and postoperative restenosis. Spearman correlation analysis showed a clear colinearity between preoperative liver cirrhosis and TBIL ($P = 0.033$), while TBIL was not included in the multivariable analysis. The multivariate analysis showed that both the presence of preoperative liver cirrhosis and postoperative restenosis were significant factors associated with HCC development in BCS patients who underwent endovascular treatment (Table 3, Fig. 4).

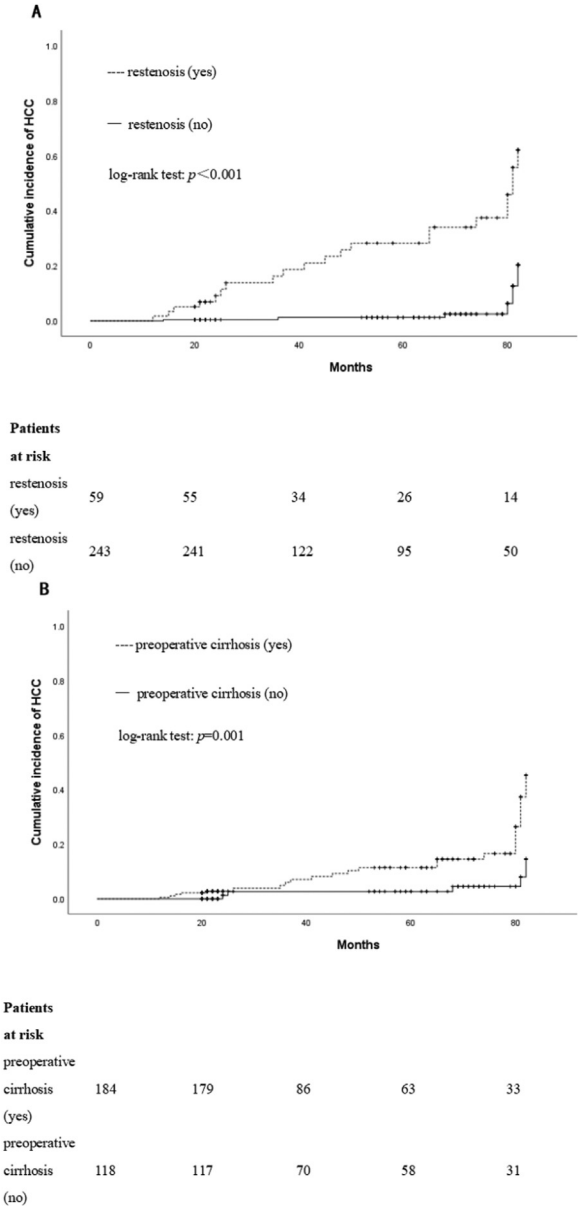


**Fig. 4.** Kaplan-Meier curves for hepatocellular carcinoma (HCC) development after endovascular treatment for Budd-Chiari syndrome (BCS), stratified by (A) restenosis (yes/no) and (B) preoperative cirrhosis (yes/no).

## 5. Discussion

This study included a large case series of 302 Chinese patients with BCS who underwent endovascular treatment, focusing on their characteristics and risk factors for developing HCC post-treatment. We found that the HCCs occurring after endovascular treatment in BCS patients were frequently detected at an early stage, with a balanced distribution of HCC nodules across hepatic lobes. The cumulative 1-, 3-, and 5-year HCC incidence rates in our BCS cohort were 0.3 %, 4.7 %, and 7.7 %, respectively. Ele-

**Table 2**
Comparisons between the hepatocellular carcinoma (HCC) group and Non-HCC group for baseline clinical and imaging features and treatment outcomes.

| Variable | HCC group ($n$ = 31) | Non-HCC group ($n$ = 271) | $P$ value |
|---|---|---|---|
| Sex, n | | | 0.942 |
| Male/female | 16/15 | 138/133 | |
| Age (years) | 46.7 ± 11.6 | 49.9 ± 13.2 | 0.193 |
| Type of BCS, n (%) | | | 0.225 |
| IVC type | 3 (9.7) | 9 (3.3) | |
| HV type | 4 (12.9) | 34 (12.5) | |
| Mixed Type | 24 (77.4) | 238 (84.1) | |
| Laboratory test | | | |
| AST, U/L | 31.6 ± 15.4 | 28.0 ± 14.9 | 0.208 |
| ALT, U/L | 26.2 ± 20.1 | 23.2 ± 16.2 | 0.345 |
| Albumin, g/L | 38.8 ± 7.6 | 41.8 ± 6.5 | 0.017* |
| TBIL, μmol/L | 52.5 ± 85.1 | 31.0 ± 29.7 | 0.004* |
| Creatinine, μmol/L | 58.3 ± 21.7 | 56.0 ± 12.1 | 0.381 |
| Prothrombin time, s | 15.3 ± 4.0 | 14.0 ± 5.4 | 0.191 |
| International normalized ratio | 1.3 ± 0.2 | 1.2 ± 0.5 | 0.663 |
| Child-Pugh Class, n | | | |
| A/B/C | 18/10/3 | 167 /93/11 | 0.370 |
| MELD score | 15.5 ± 9.0 | 14.6 ± 4.5 | 0.342 |
| New Clichy score | 3.5 ± 0.8 | 3.6 ± 1.0 | 0.619 |
| Positive for HBsAg, n (%) | 1 (3.2) | 1 (0.4) | 0.195 |
| Underlying etiological factors, n (%) | | | |
| JAK2 V617F mutation | 1 (11.1) | 7 (5.2) | 0.414 |
| Antithrombin deficiency | 18 (62.1) | 77 (42.1) | 0.035* |
| Positive anticardiolipin antibodies | 0 (0) | 4 (3.7) | 0.502 |
| Hyperhomocysteinaemia | 4 (36.4) | 18 (19.6) | 0.182 |
| Imaging features, n (%) | | | |
| Liver cirrhosis | 26 (83.9) | 158 (58.3) | 0.006* |
| Combined thrombosis | 7 (22.6) | 43 (15.9) | 0.341 |
| Caudate lobe enlargement | 11 (35.5) | 68 (25.1) | 0.151 |
| Splenomegaly | 22 (71.0) | 156 (57.6) | 0.105 |
| Oesophageal varices | 14 (45.2) | 27 (10.0) | <0.001* |
| Presence of accessory HV | 23 (74.2) | 165 (60.9) | 0.104 |
| Diameter of accessory HV, mm | 9.1 ± 2.5 | 7.5 ± 2.3 | 0.006* |
| Endovascular treatment, n (%) | | | |
| Balloon dilation alone | 25 (80.6) | 232 (85.6) | 0.306 |
| Stent placement | 5 (16.1) | 39 (14.4) | 0.483 |
| TIPS | 1 (3.2) | 0 (0) | 0.147 |
| Number of occluded main HVs after treatment, n (%) | | | 0.421 |
| None | 0 (0) | 14 (5.2) | |
| One main HV | 4 (12.9) | 38 (14.0) | |
| Two main HVs | 9 (29.0) | 95 (35.1) | |
| Three main HVs | 18 (58.1) | 124 (45.8) | |
| Postoperative restenosis | 21 (67.7) | 38 (14.0) | <0.001* |

Abbreviations: BCS, Budd-Chiari syndrome; IVC, inferior vena cava; HV, hepatic vein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; MELD, model of end-stage liver disease; TIPS, Trans-jugular intrahepatic portosystemic shunt.
* Variable had a significant difference between two groups.

vated serum TBIL levels at baseline, a positive HBsAg status, preoperative liver cirrhosis, splenomegaly, oesophageal varices, a large accessory HV diameter, and postoperative restenosis were associated with HCC risk, as suggested by the univariate analysis. Notably, postoperative restenosis was identified as the sole independent risk factor for HCC development by the multivariate analysis.

The HCC incidence in BCS patients was reportedly similar to that in patients with other etiologic cirrhosis [9,17]. Park et al [18]. showed that the cumulative 5-year probability of developing HCC was 18.5 % in BCS patients in South Korea without considering the treatment options. Another retrospective study in China showed an HCC occurrence rate of 12.8 % at the initial time of BCS diagnosis [19]. Our study showed a lower cumulative 5-year HCC incidence rate (7.7 %) following endovascular treatment than these previous studies, suggesting that restoring hepatic venous flow can partially mitigate, but not eliminate, the risk of HCC. Among the 31 BCS patients with HCC in our study, the majority presented with early-stage disease (11/31, 35.5 %) by BCLC staging, followed by the intermediate stage (9/31, 29.0 %). No patient had terminal stage disease at the time of diagnosis. Following endovascular treatment, the patients typically underwent regular follow-ups, including imaging and serum biomarker evaluations, which could enable the timely identification of disease progression. This surveillance strategy likely played a key role in the early detection of HCC, highlighting the effect of proactive management rather than solely reflecting the natural history of the disease. One recent study highlighted the importance of close monitoring for HCC in BCS patients and suggested that regular imaging and serological assessments could facilitate the early detection of HCC, enabling timely interventions [20]. These findings are consistent with those of our study, emphasizing the pivotal role of early detection in BCS patient management. Moreover, serum AFP levels have been previously shown to be useful for discriminating HCC in BCS patients [7], which was also supported by our results. Additionally, we further proposed a serum AFP cut-off value of 15.7 ng/mL for detecting HCC in BCS patients post-endovascular treatment, with a sensitivity of 69.3 % and specificity of 97.4 %.

For the specific characteristics of HCC associated with BCS, sex predominance is controversial. Our current data did not show a significant difference in sex distribution between the HCC and non-HCC groups following endovascular intervention for BCS. Three studies demonstrated that BCS patients who developed HCC were predominately male [8–10], while others identified female sex as a risk factor associated with HCC development in BCS patients

**Table 3**
Univariable and multivariable analyses for HCC development.

| Variables | Univariable Cox model | | | Multivariable Cox model | | |
|---|---|---|---|---|---|---|
| | HR | 95 %CI | *P* value | HR | 95 %CI | *P* value |
| Sex (male) | 0.849 | 0.419–1.719 | 0.650 | | | |
| Age (per 1 year increase) | 0.997 | 0.973–1.022 | 0.836 | | | |
| Type of BCS (IVC type) | 0.666 | 0.196–2.258 | 0.514 | | | |
| Type of BCS (HV type) | 0.776 | 0.268–2.224 | 0.640 | | | |
| Type of BCS (Mixed type) | 1.451 | 0.619–3.405 | 0.392 | | | |
| AST (per unit increase) | 1.013 | 0.992–1.033 | 0.224 | | | |
| ALT (per unit increase) | 1.011 | 0.992–1.029 | 0.261 | | | |
| Albumin (per unit decrease) | 0.959 | 0.919–1.002 | 0.062 | | | |
| TBIL (per unit increase) | 1.005 | 1.000–1.009 | 0.038 | | | |
| Creatinine (per unit increase) | 1.011 | 0.983–1.040 | 0.430 | | | |
| Prothrombin time (per unit increase) | 1.009 | 0.960–1.061 | 0.723 | | | |
| INR (per unit increase) | 0.853 | 0.335–2.170 | 0.738 | | | |
| Child-Pugh score (per unit increase) | 1.050 | 0.833–1.324 | 0.679 | | | |
| MELD score (per unit increase) | 1.006 | 0.935–1.082 | 0.877 | | | |
| New Clichy score (per unit increase) | 0.975 | 0.688–1.380 | 0.886 | | | |
| Positive for HBsAg (present vs absent) * | 17.109 | 2.167–135.101 | 0.007 | 0.000 | 0.000 | 0.988 |
| JAK2 V617F mutation (present vs absent) | 0.391 | 0.044–3.455 | 0.399 | | | |
| Antithrombin deficiency (present vs absent) | 1.973 | 0.928–4.192 | 0.077 | | | |
| Positive anticardiolipin antibodies (present vs absent) | 0.044 | 0.000–167.067 | 0.457 | | | |
| Hyperhomocysteinaemia (present vs absent) | 1.546 | 0.450–5.313 | 0.489 | | | |
| Preoperative liver cirrhosis (present vs absent) * | 4.466 | 1.712–11.646 | 0.002 | 4.677 | 1.052–20.800 | 0.043 |
| Preoperative thrombosis (present vs absent) | 1.361 | 0.583–3.177 | 0.476 | | | |
| Preoperative caudate lobe enlargement (present vs absent) | 1.896 | 0.906–3.969 | 0.090 | | | |
| Preoperative splenomegaly (present vs absent) * | 3.779 | 1.659–8.610 | 0.002 | 1.730 | 0.532–5.631 | 0.362 |
| Preoperative oesophageal varices (present vs absent) * | 5.218 | 2.596–10.598 | 0.000 | 1.676 | 0.573–4.898 | 0.345 |
| Preoperative presence of accessory HV (present vs absent) | 2.007 | 0.895–4.500 | 0.091 | | | |
| Diameter of accessory HV (per unit increase if present) * | 4.489 | 1.184–17.020 | 0.027 | 4.407 | 0.640–30.369 | 0.132 |
| Treatment method (balloon dilation alone) | 1.244 | 0.507–3.052 | 0.634 | | | |
| Treatment method (stent placement) | 0.654 | 0.249–1.714 | 0.387 | | | |
| Treatment method (TIPS) | 3.960 | 0.506–31.000 | 0.190 | | | |
| Postoperative restenosis (present vs absent) * | 7.662 | 3.606–16.282 | 0.000 | 6.867 | 2.457–19.192 | 0.000 |

Abbreviations: BCS, Budd-Chiari syndrome; IVC, inferior vena cava; HV, hepatic vein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; MELD, model of end-stage liver disease; TIPS, Trans-jugular intrahepatic portosystemic shunt; HR, hazard ratio; CI, confidence interval.
* Variables included in the multivariable analysis.

[17,21,22]. A report by Xu et al [23]. suggested that oestrogen levels can promote cell proliferation and the cell cycle, while inhibiting apoptosis, in hepatoma cells of BCS-associated HCC in vitro, supporting the notion that BCS-associated HCC was predominant in female patients. Pascale et al [24]. indicated that multiple genes and signalling pathways play pivotal roles in HCC progression and may be influenced by various circumstances. Therefore, we hypothesize that, in the context of BCS, genetic factors and hormone levels may interact with haemodynamic restoration post-endovascular treatment, potentially affecting sex differences in the risk of developing HCC. This possibility warrants further investigation in future studies.

Previous studies have shown a predominance of solitary right-lobe HCC nodules in BCS patients [8,17]. However, our study showed that the frequency of HCC was 38.7 % in the right lobe, 22.6 % in the left lobe, and 38.7 % in both lobes of the liver. These observations could have been from persistent imbalanced intrahepatic congestion and chronic fibrosis in BCS patients after varying degrees of hepatic outflow recovery.

The univariate analysis in this study identified several associated risk factors for HCC development in BCS patients after endovascular treatment. Elevated TBIL levels and HBsAg positivity indicated underlying hepatic dysfunction and viral hepatitis, which have been widely recognized as contributing to HCC development. Nevertheless, HBsAg positivity is not common in BCS patients [9]. HBsAg positivity was only observed in two patients (one in the HCC group and one in the non-HCC group) in our study. Sakr et al [10]. reported that oesophageal varices were detected in 100 % of their BCS-associated HCC cases, and they observed progressive liver disease and portal hypertension in their cases. In another study, Wester et al [25]. described how cirrhosis preceded HCC in all BCS patients. Similarly, all patients in our study experienced liver cirrhosis at the time of HCC diagnosis. Moreover, the incidences of liver cirrhosis and oesophageal varices at baseline were significantly higher in the HCC group than in the non-HCC group (83.9 % vs. 58.3 % and 45.2 % vs. 10.0 %, respectively). Interestingly, our results demonstrated that the presence of an accessory HV with a large diameter is also a risk factor for HCC progression in postoperative BCS patients. Previous studies have shown that a single accessory HV with a diameter $\geq$ 5 mm could effectively drain the liver from a substantial intrahepatic collateral circulation [26,27]. However, our findings suggest that a larger accessory HV diameter indicates a pathological adaptation to prolonged congestion and is insufficient for preventing cirrhosis progression and HCC development in BCS.

Notably, our findings indicated that preoperative liver cirrhosis and postoperative restenosis were the most important risk factors for HCC development, as suggested by the multivariate analysis. Restenosis occurred in 67.7 % of patients in the HCC group compared with only 14.0 % in the non-HCC group, which was statistically significantly different. These results are consistent with those reported by Paul et al., which showed that the failure to restore hepatic venous outflow was associated with HCC development in BCS patients during subsequent follow-up [28]. Prolonged and intensified hepatic congestion caused by restenosis may exacerbate intrahepatic fibrosis and create a microenvironment conducive to carcinogenesis. Therefore, taking measures to reduce the incidence of vascular restenosis as much as possible may help decrease HCC development in BCS patients.

One limitation of the present study is its retrospective design. Most patients (60.9 %) in our cohort had combined liver cirrhosis at baseline. Therefore, the incidence of HCC following endovas-

cular treatment in our study could have been overestimated in certain patients. Additionally, because of the diverse HCC treatment approaches associated with BCS and relatively brief follow-up period of our patient cohort after HCC development, this study did not analyse the patients' survival outcomes. Despite these limitations, this study provides important insights by examining a large sample size of BCS patients who underwent endovascular treatment, as well as by identifying the specific characteristics and risk factors for HCC development in such patients after treatment.

In conclusion, even after the successful endovascular treatment of BCS, the possibility of HCC development remains. The majority of the patients in our study were at the early HCC tumour stage when the disease was detected. We found that the main risk factors for developing HCC after endovascular treatment in our BCS patient cohort were the presence of preoperative liver cirrhosis and postoperative restenosis. Therefore, strategies to mitigate the risk of restenosis should be prioritized to reduce the incidence of HCC and improve BCS patient outcomes. Longitudinal studies with an extended follow-up are required to evaluate survival outcomes.

## Declaration of competing interest

All authors have no conflict of interest to declare.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2025.02.008.

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