The clinical features, image findings and risk factors of vena cava syndrome in Behçet's syndrome

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Abstract

Objective

To investigate the clinical features, image findings, and potential risk factors of vena cava syndrome (VCS) in Behçet's syndrome (BS).

Methods

We conducted a case-control study in our BS registry database from 2012 to 2021. Fifty-five BS patients with VCS were enrolled in the case group, and two BS patients without VCS were selected as controls for each VCS case using risk-set-sampling. Multivariable logistic regression was used to detect the risk factors of VCS, and the outcome of these patients was also analysed. We also conducted an exploratory study to evaluate spectral computed tomography (CT) imaging in detecting thrombosis in BS patients with inferior VCS (IVCS).

Results

Multivariable logistic regression analysis revealed male gender (OR 11.16, 95%CI 3.34–37.32), early-onset BS (<18 years) (OR 5.57, 95%CI 1.58–19.69), ESR >60 mm/hr (OR 3.83, 95%CI 1.02–12.23) and pathergy reaction (OR 5.10, 95%CI 2.11–12.32) as potential risk factors of VCS in BS patients. For 4 BS patients with IVCS due to thrombosis, spectral CT found better contrast between IVC and thrombi at a low energy level of 40keV using virtual monoenergetic imaging than conventional images at 120kV. With a median follow-up of 3.3 years, the respective estimated 1- and 5-year survival rates were 96.3% and 94.2%, and respective estimated 1- and 5-year relapse-free rates were 93.9% and 78.0%.

Conclusion

Male, early-onset BS, ESR >60 mm/hr, and pathergy reaction are potential risk factors of VCS in BS patients. Spectral CT is valuable in detecting thrombus in vena cava.

Key words

Behçet's syndrome, vena cava, tomography, x-ray computed, patient outcome assessment

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Introduction

Behçet's syndrome (BS) is a systemic vasculitis with recurrent oral and/or genital ulcers and skin lesions as major manifestations (1). It is classified as variable vasculitis involving arteries and veins of all sizes (2, 3). Vena cava, which is also named "central vein", can be anatomically divided into superior vena cava (SVC) and inferior vena cava (IVC). SVC syndrome (SVCS) and IVC syndrome (IVCS) are two rare clinical conditions caused by partial or complete SVC and IVC obstruction. The major causes of SVCS and/or IVCS are malignancies, extrinsic mass compression of vena cava, thrombosis, intravascular devices, etc. (4, 5). SVC and IVC involvement are only seen in about 1-1.5% of BS patients (6, 7), and BS accounts for only 2% of all SVCS causes (4). Although SVCS (n=79) and IVCS (n=69) were reported in a large retrospective cohort study of 5970 BS patients, the detailed clinical characteristics and outcomes of these patients were lacking (7). Given that vena cava is the largest vein system that carries deoxygenated blood from the body into the heart, a well-understanding of the clinical characteristics, management and outcomes of SVCS and/or IVCS in BS patients are of great importance.

Indirect computed tomographic venography (CTV) is an important imaging modality to depict the morphology of the deep venous system and diagnose thrombosis (8, 9). It is also proved that virtual monoenergetic imaging (VMI) at a low energy level (kiloelectron volt [keV]) can improve vessel enhancement and has an advantage in the venous enhancement of CTV (10, 11). Besides, iodine mapping of spectral CT allows material decomposition that isolates iodine density from soft tissue and can differentiate the enhanced venous thrombi such as neoplastic thrombi from bland thrombi (12). Although the exact pathophysiology of thrombosis in BS is still unknown, systemic inflammation seems to play an essential role in it (13). It indicates that spectral CT might detect an enhancement of venous thrombi in BS patients. Therefore, we also conducted an exploratory study to evaluate spectral CT imaging in detecting thrombosis in BS patients with IVCS.

Patients and methods

Patient recruitment and data collection

This retrospective case-control study was based on a registry database of BS patients in our institution from January 2012 to June 2021, and 55 BS patients with newly diagnosed VCS were consecutively included in the case group. All patients fulfilled the 2013 International Criteria for Behçet's Disease (ICBD) (14). Other common causes of VCS, including malignancies, extrinsic mass compression of vena cava, and intravascular devices, were all routinely excluded. Patients' demographics, BS manifestations, laboratory and imaging examinations, and clinical manifestations of patients in the case group due to VCS were thoroughly recorded and analysed. We used risk-set-sampling to select two BS patients without VCS as controls for each VCS case, matched by disease duration (±3 months). and eligible controls were randomly selected. There were no recorded VCS events in the control group during follow-up. We extracted demographic information, BS manifestations, and laboratory examinations of included patients in Table I.

Imaging modalities included Doppler ultrasonography, CT with or without venography, and digital subtraction angiography. A dual-layer spectral detector CT scanner (IQon, Philips Healthcare, USA) was used in 8 patients. Conventional CT, VMI at a low energy level of 40keV and iodine mapping were reconstructed. The CT attenuation and iodine density of IVC at the right renal vein level and thrombus of the IVC were measured. The parameters that represent image quality which were contrast-noise ratio (CNR) and signal-noise ratio (SNR), were calculated using the formula: CNR= (CT attenuation of IVC-CT attenuation of mid-thigh muscle)/SD_{fat}. SNR= CT attenuation of IVC/$SD_{IVC.}$ The enhancement deviation ratio of IVC and thrombus was calculated using the formula: (CT attenuation of IVC-CT attenuation of thrombus)/ CT attenuation of mid-thigh muscle.

We also thoroughly reviewed the treat-

ment and outcome of all the patients. Relapse of the vascular event was defined as a recurrent or newly onset vascular event associated with BS during follow-up (7, 15-16).

The study was approved by the institutional review board of PUMCH (S-443), and written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Statistical analysis

Categorical variables were represented as frequencies and percentages. Normal and non-normally distributed quantitative variables were expressed as mean ± SD and median (IQR). The comparison of continuous variables between the BS with VCS group and the control group was conducted using the t-test and Mann-Whitney U-test for normal and non-normal distributed data, respectively. Categorical data were compared using Chi-squared or Fisher's exact test as appropriate. Univariable and multivariable logistic regression was used to estimate the odds ratio (with a 95% confidence interval) for the risk of developing VCS in BS patients. Variables considered clinically relevant or showed a significant association with VCS in the univariable analysis were entered into the multivariable logistic regressions model. Given the number of events available, variables included in the multivariable logistic model were carefully chosen to ensure parsimony of the final model (Backward LR, entry 0.05, removal 0.10). A two-sided *p*-value <0.05 was defined as a statistically significant difference. Iodine density, CT attenuation and IVC/thrombus enhancement deviation were evaluated using the Wilcoxon signed-rank test. Survival and cumulative risk of relapse analysis were estimated using the Kaplan-Meier curve and Log-Rank test. All data were assessed on the computer using an SPSS 22.0 software package and GraphPad Prism 8.0.

Results

Demographic features

A total of 55 BS patients with VCS were enrolled, suggesting a male predominance (51 males, 4 females). Isolated SVCS and IVCS were diagnosed in 15 and 34 patients, respectively. Six patients had both SVCS and IVCS. The median age at the onset of BS was 23.0 (IQR 19.0–29.0) years, and the median disease duration between BS onset and diagnosis of VCS was 2.8 (IQR 1.0–6.5) years. VCS was the initial presentation for BS in 5 patients.

Table I. Demographic and clinical characteristics of BS patients with and without VCS.

Clinical features	VCS group (n=55)	Control group (n=110)	*P* value
Gender (male)	51 (92.7%)	60 (54.6%)	<0.001
Age at onset (years)	23.0 (19.0-29.0)	34.0 (26.8-45.0)	<0.001
Disease duration	2.8 (1.0-6.5)	2.7 (0.9-6.8)	0.718
ESR (mm/hr)	27.0 (6.0-49.0)	15.5 (7.0-33.0)	0.216
CRP (mg/L)	16.2 (5.8-52.9)	7.2 (1.5-23.0)	0.005
Oral ulceration	55 (100%)	110 (100%)	-
Genital ulceration	36 (65.5%)	83 (75.5%)	0.177
Pseudofolliculitis	23 (41.8%)	40 (36.4%)	0.497
Erythema nodosum	29 (52.7%)	36 (32.7%)	0.013
Pathergy reaction	24 (43.6%)	15 (13.6%)	<0.001
Gastrointestinal involvement	6 (10.9%)	19 (17.3%)	0.283
Ocular involvement	12 (21.8%)	13 (11.8%)	0.091
Joint involvement	6 (10.9%)	11 (10.0%)	0.856
Aortic and/or peripheral artery involvement	5 (9.1%)	17 (15.5%)	0.257
Venous involvement other than vena cava	52 (94.5%)	10 (9.1%)	<0.001
Pulmonary artery involvement	12 (21.8%)	1 (0.9%)	<0.001

*Data expressed in median (IQR) or number (%).

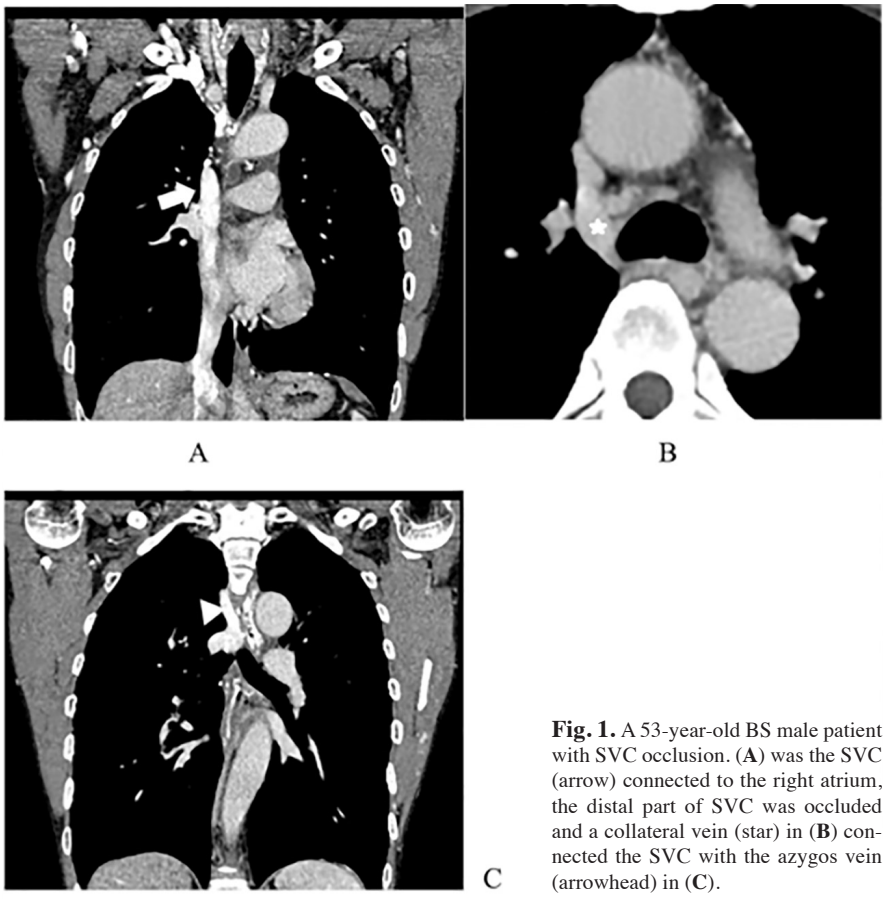

Fig. 1. A 53-year-old BS male patient with SVC occlusion. (**A**) was the SVC (arrow) connected to the right atrium, the distal part of SVC was occluded and a collateral vein (star) in (**B**) connected the SVC with the azygos vein (arrowhead) in (**C**).

Clinical characteristics at presentation

In 21 BS patients with SVCS, facial and/or neck swelling was the most common presentation (18/21, 85.7%), followed by pleural effusion (7/21, 33.3%), upper extremity oedema (5/21, 23.8%), dyspnoea (4/21, 19.0%), chest

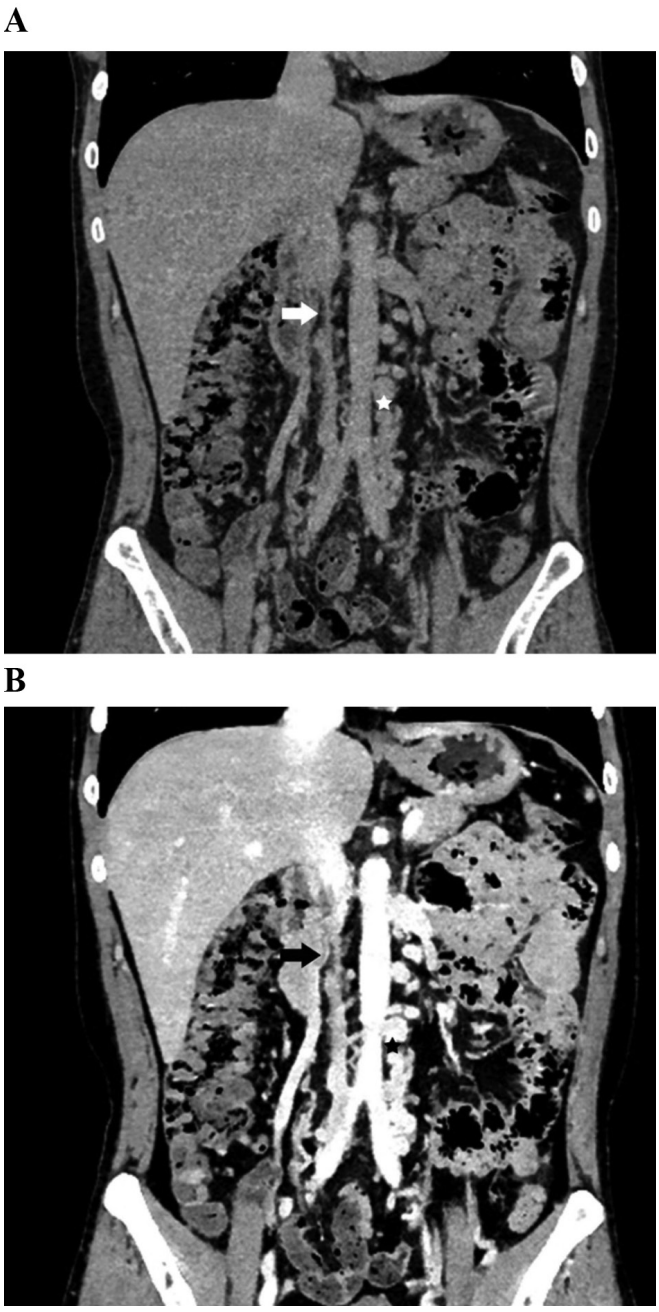

Fig. 2. A 42-year-old BS male patient with IVC stenosis.
(**A**) is CT venography of IVC under 120K, (**B**) is under 40KeV. Arrow indicates the severe IVC stenosis; star shows the collateral circulation from IVC to the left renal vein.

collaterals (3/21, 14.3%), pericardial effusion (2/21, 9.5%). It is worth noting that 2 patients had chylothorax, 1 patient had chylopericardium, and 1 patient had both chylothorax and chylopericardium.

In 40 BS patients with IVCS, lower extremity oedema (22/40, 55.0%) was the most common presentation, followed by abdominal collaterals (13/40, 32.5%), abdominal extension (8/40, 20.0%), jaundice (4/40, 10.0%) and ascites (4/40, 10.0%). Nine patients were also diagnosed with Budd-Chiari syndrome (BCS), while the site of venous obstruction was IVC combined with hepatic veins in 6 patients, IVC alone in 3 patients.

For the other BS manifestations, oral ulceration was presented in all patients, followed by genital ulceration (36/55, 65.4%), erythema nodosum (29/55, 52.7%) and pathergy reaction (24/55, 43.6%). Twelve patients (21.8%) had ocular lesions, 6 patients (10.9%) had gastrointestinal involvement, and 3 patients (5.4%) had ventricular thrombus. Inflammatory markers were significantly elevated in 41 (74.5%) patients when the vena cava involvement developed, the median (IQR) ESR was 27.0 (6.0–49.0) mm/hr, and the median (IQR) CRP level was 16.2 (5.8–52.9) mg/L. The comparison of the clinical characteristics of BS patients with and without VCS is listed in Table I, and the demographic and clinical characteristics of all three subgroups (SVCS, IVCS, SVCS+IVCS) are listed in the supplementary file (Supplementary Table S1).

Vascular involvement

All BS patients with VCS were detected to have vascular thrombosis, occlusion, or stenosis in the SVC (Fig. 1) and/or IVC (Fig. 2). Additionally, fifty-two (94.5%) patients had other sites of venous involvement. In patients with SVCS, deep vein thrombosis (DVT) of the upper extremity and brachiocephalic vein were more common. While in IVCS patients, DVT in the lower extremity and common iliac vein were frequently seen (Table II).

Twelve patients (21.8%) had pulmonary artery involvement (mainly pulmonary thromboembolism, n=11), and 5 (9.1%) patients had aortic and/or peripheral artery involvement.

Risk factors for developing VCS in BS patients

Univariable analysis revealed that male gender ($p<0.001$), BS onset <18 years ($p=0.001$), ESR >60 mm/hr ($p=0.017$), CRP>20 mg/L ($p=0.017$), erythema nodosum ($p=0.014$), pathergy reaction ($p<0.001$) were more common in VCS group compared with the control group in BS patients. Finally, the multivariable logistic regression analysis confirmed that male gender (OR=11.16, 95% CI 3.34–37.32), early-onset BS (<18 years) (OR=5.57, 95% CI 1.58-19.69), ESR >60 mm/hr (OR=3.83, 95% CI 1.02–12.23) and pathergy reaction (OR=5.10, 95% CI 2.11–12.32) were potential risk factors for developing VCS in BS patients (Table III).

Spectral CT imaging evaluation of BS patients with IVCS

For 8 BS patients with IVCS who had received spectral CT imaging evaluation, 5 IVC thrombosis sites were detected in 4 patients, while the other 4

Table II. Vascular involvement of BS patients with VCS.

	SVCS (n=15)	IVCS (n=34)	SVCS and IVCS (n=6)
SVC occlusion/stenosis	5 (33.3)		3 (50.0)
SVC thrombosis	10 (66.7)		3 (50.0)
IVC occlusion/stenosis		9 (26.5)	2 (33.3)
IVC thrombosis		25 (73.5)	4 (66.7)
Involvement of veins adjacent to vena cava			
Brachiocephalic vein thrombosis	5 (33.3)		1 (16.7)
Brachiocephalic vein occlusion/stenosis	1 (6.7)		1 (16.7)
Common iliac vein thrombosis	1 (6.7)	15 (44.1)	2 (33.3)
Common iliac vein occlusion/stenosis		2 (5.9)	
Hepatic vein thrombosis		4 (11.8)	
Hepatic vein occlusion/stenosis		1 (2.9)	
Renal vein thrombosis		2 (5.9)	1 (16.7)
Portal vein occlusion/stenosis		2 (5.9)	
Upper extremity DVT	5 (33.3)		2 (33.3)
Lower extremity DVT		26 (76.5)	3 (50.0)
Great saphenous vein thrombosis		3 (8.8)	
Median cubital vein thrombosis	1 (6.7)		
Internal carotid vein thrombosis	6 (40.0)		2 (33.3)
Internal carotid vein occlusion/stenosis	2 (13.3)		
Subclavian vein occlusion/stenosis	3 (20.0)		
Dural sinus thrombosis		1 (2.9)	1 (16.7)
Aortic and/or peripheral artery involvement			
Subclavian artery thrombosis			1 (16.7)
Common femoral artery thrombosis		1 (2.9)	
Common carotid artery thrombosis		1 (2.9)	
Abdominal aorta thrombosis			1 (16.7)
Aortic arch thrombosis			1 (16.7)
Coronary artery occlusion	1 (6.7)		
Abdominal aorta pseudoaneurysm		1 (2.9)	
Pulmonary artery involvement			
Pulmonary artery thrombosis	2 (13.3)	7 (20.6)	2 (33.3)
Pulmonary artery aneurysm		1 (2.9)	

Data expressed in number (%).

Table III. Univariable and multivariable analysis of clinical and laboratory findings for BS patients with and without VCS.

	Univariable		Multivariable	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Gender				
Female	1.00	-	1.00	-
Male	10.63 (3.59-31.43)	<0.001	11.16 (3.34-37.32)	<0.001
Age at onset				
≥18 years	1.00	-	1.00	-
<18 years	7.40 (2.26-24.21)	0.001	5.57 (1.58-19.69)	0.008
ESR (mm/hr)				
≤20	1.00	0.055	1.00	0.075
20-60	1.12 (0.53-2.35)	0.769	1.39 (0.57-3.40)	0.465
>60	3.26 (1.23-8.63)	0.017	3.83 (1.20-12.23)	0.023
CRP (mg/L)				
≤8	1.00	0.054		
8-20	1.33 (0.55-3.19)	0.524		
>20	2.49 (1.18-5.24)	0.017		
Genital ulceration	0.62 (0.30-1.25)	0.179		
Pseudofolliculitis	1.26 (0.65-2.44)	0.497		
Erythema nodosum	2.29 (1.18-4.45)	0.014		
Pathergy reaction	4.90 (2.29-10.51)	<0.001	5.10 (2.11-12.32)	<0.001
Gastrointestinal involvement	0.59 (0.22-1.57)	0.287		
Ocular involvement	2.08 (0.88-4.94)	0.096		
Joint involvement	1.10 (0.39-3.16)	0.856		

*OR: odds ratio.

patients had IVC occlusion/stenosis without thrombosis. Furthermore, in 4 BS patients with IVCS due to thrombosis, compared to the conventional images at 120kV, the enhancement of IVC and thrombi was strengthened at 40keV (Fig. 3), and the IVC/thrombus enhancement deviation ratio was larger at 40keV (2.2±0.7 *vs*. 1.0±0.2, p=0.043) which means the contrast between IVC and thrombus was more obvious and could facilitate thrombus detection. At 40keV, the CNR (p=0.043) and SNR (p=0.043) were higher than that at 120kV for the much higher CT attenuation and indicated that the image quality at low energy level was better than that at 120kV. Iodine density was 3.0±0.6 mg/ml at IVC and 1.2±0.6 mg/ml at thrombi (p=0.003) (Table IV). Three patients underwent the follow-up spectral CT after 14–24 months, and the thrombi disappeared in 2 patients after treatment.

Treatment before and after the onset of VCS in BS patients

Before the onset of VCS, most patients (44/55, 80.0%) were glucocorticoids (GCs) and immunosuppressant treatment-naive. After the diagnosis of VCS, GCs was used in 50 (90.9%) BS patients, including 34 patients receiving a large dose of GCs (prednisone ≥1mg/kg/d or equivalent dose) and 16 patients receiving a medium dose of GCs (prednisone 0.4–0.6 mg/kg/d or equivalent dose), and then gradually tapered to the maintenance dosage (prednisone ≤10 mg/d or equivalent dose). 47 (85.4%) patients received immunosuppressants, including 4 (7.3%) patients who received a combination of ≥2 immunosuppressants. Cyclophosphamide (CTX) (n=41, 74.5%) was the most commonly used immunosuppressant, and others included mycophenolate mofetil (MMF), cyclosporine A (CsA), and azathioprine. Four severe and/or refractory cases received tumour necrosis factor inhibitors (TNFi), including golimumab in 2 cases, infliximab in 1 case and adalimumab in 1 case.

Fifty patients (90.9%) received anticoagulation treatment (warfarin/rivaroxaban), and one patient received as-

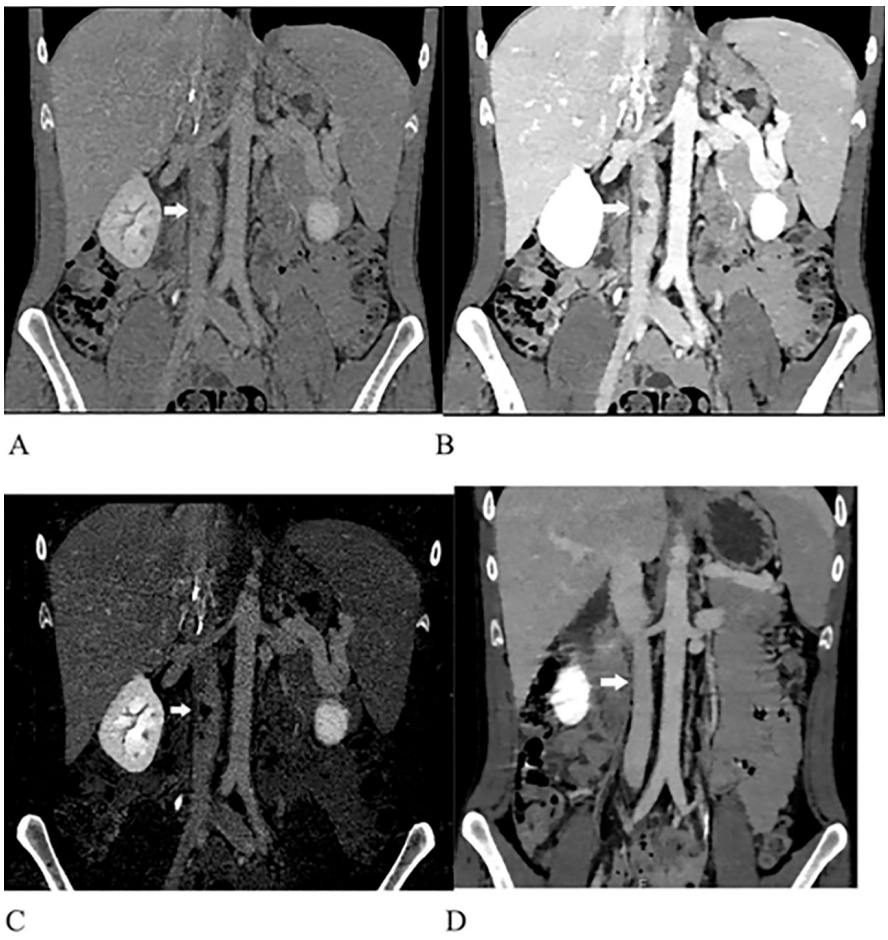

Fig. 3. A 30-year-old BS male patient with IVC thrombosis. **A** and **B** are the curved planar reconstruction (CPR) of CT venography of IVC under 120kV and 40keV. The white arrow indicates the thrombi inside the IVC. It was more obvious in 40keV for the enhancement of IVC was improved by using virtual monoenergetic imaging. **C** was an iodine image. The white arrow indicates the thrombi (iodine density 1.0±0.5mg/mL) was black, as the iodine distribution in thrombi is low. **D** is the CPR of CT venography of IVC of the same patient from the follow up spectral CT examination in 24 months; there was no thrombus in IVC with clinical remission after treatment.

pirin alone. 4 patients at a high risk of bleeding (complicated with aneurysms or oesophageal varices) did not receive anticoagulation or antiplatelet therapy. For patients with IVCS, 6 patients had taken balloon dilation of IVC.

During a median follow-up of 3.3 (IQR 1.4–6.9) years, 47 patients (85.4%) remained stable of vascular events. For 8 patients (14.5%) having a relapse of the vascular event during follow-up, 2 patients had re-occlusion after balloon dilation of IVC, 1 patient had IVC thrombosis, 2 patients had DVT, 1 patient had femoral artery pseudoaneurysm, 1 patient had pulmonary artery aneurysm, 1 patient had iliac artery and right atrium thrombosis. The overall mortality rate was 7.3% (4/55). Of the four patients who died, one patient had haemoptysis and was diagnosed with pulmonary artery aneurysm 5.6 years after the diagnosis of VCS, then he underwent interventional embolisation and died of massive haemoptysis 7.6 years after the diagnosis of VCS; one patient died of haemoptysis caused by pulmonary infection; the other 2 patients died of septic shock. It should be mentioned that 3 out of the 4 death cases had BCS.

The respective estimated cumulative 1- and 5-year survival rates were 96.3% and 94.2%, and respective estimated 1- and 5-year relapse-free rates were 93.9% and 78.0%, respectively. Subgroup analysis showed no significant difference in survival rates and relapse-free rates in 3 subgroups (SVCS, IVCS, SVCS+IVCS) (Fig. 4).

Discussion

Venous involvement is an important clinical manifestation in BS patients, with deep vein thrombosis as a major manifestation (17). However, VCS is a rare complication in BS patients, and our understanding of this condition is still limited. This study has reported a large number of BS patients with VCS in a Chinese cohort with a thorough analysis of the clinical characteristics. We have also reported the outcomes of BS patients with VCS, which is lacking in the previous report (7). To the best of our knowledge, this is also the first study exploring spectral CT imaging in detecting thrombosis in BS patients with IVCS.

In the current study, the development of VCS tends to occur in BS patients with male gender and early-onset (<18 years). We found that facial and/or neck swelling, pleural effusion were common manifestations in BS patients with SVCS, followed by upper extremity oedema, chest collaterals and dyspnoea, similar to previous case reports (18-23). Chylothorax and/or chylopericardium were rare complications in BS patients with SVCS, described in a few studies before, which might occur due to blockage of the lymphatic circulation by subclavian vein thrombosis (24-26). Lower extremity oedema, abdominal collaterals and abdominal extension were presented more frequently in BS patients with IVCS. In a literature review, IVC thrombosis was documented in 91% of BS patients with BCS (27). Unlike BCS with other causes, hepatic venous outflow obstruction in BS is related to the thrombosis of the hepatic and suprahepatic segments of IVC. It can either be isolated or concomitant with hepatic vein thrombosis, and isolated hepatic vein thrombosis is rare (28), which was also confirmed in our study.

BS patients with vascular involvement always had multiple vascular events, and the grouping of vascular manifestations is one of the symptom clusters in BS (29). Our study shows that most BS patients with VCS also had venous involvement other than vena cava, and pulmonary artery involvement was more common in BS patients with VCS, consistent with the previous study (7).

Table IV. Results of the objective analysis of IVC and thrombus at iodine mapping, 120kV and 40keV images for 4 BS patients with IVCS due to IVC thrombosis.

	Region of interest	Iodine density (mg/mL)	120kV (HU)	40keV (HU)	*p*-value
Vascular enhancement	IVC	3.0±0.6	106.5 ± 20.4	290.2 ± 55.3	
CNR	IVC	/	2.7 ± 1.0	11.6 ± 3.3	0.043
SNR	IVC	/	6.5 ± 3.1	12.6 ± 7.2	0.043
Thrombus enhancement	Thrombus	1.2±0.6	52.9 ± 26.7	129.8 ± 59.3	
IVC/thrombus enhancement deviation ratio		/	1.0 ± 0.2	2.2 ± 0.7	0.043

Data expressed in mean ± SD.

The pathophysiology of vascular involvement in BS is still unknown. It is now recognised that inflammation might promote vascular events through neutrophils hyperactivation, endothelial dysfunction, and coagulation disorders (30). Under systemic inflammatory conditions, hyperactivated neutrophils produce reactive oxygen species (ROS) and trigger the release of neutrophil extracellular traps (NETs) at the inflamed vessels, resulting in endothelial dysfunction and tissue injury. Impaired endothelium is a significant cause of vascular obstruction. Meanwhile, damaged endothelial cells also release procoagulant factors and facilitate neutrophils and platelet aggregation, leading to a thrombotic tendency (31). Moreover, increased ROS leads to fibrinogen posttranslational modifications and reduces fibrin susceptibility to plasmin lysis, which augments coagulation (30). For BS patients with vena cava occlusion/stenosis, the image findings of the central vein might be due to thrombus formation, which then recanalises and disappears with changes in the vein walls.

Spectral CT imaging evaluation might be useful in BS patients with VCS. According to the clinical experience, the mean enhancement of IVC was 97HU (32), which requires appropriate scan parameters and timing for optimal venous enhancement. Undiagnosed CTV was found in 3.1–15.2% of cases for unsatisfied contrast opacification of the veins (11). In our study, the CT attenuation of IVC was 290.2±55.3HU at 40keV, which was 2.7 times higher than that at 120kV. The CNR and SNR at 40keV were also higher, which means better image quality in low energy level VMI images. Besides the image quality improvement, the enhancement deviation between IVC and thrombus was larger at 40keV than that at 120kV, which indicated potential better thrombus detection. From the iodine mapping measurement, the iodine density in thrombi of IVC was 1.2±0.6

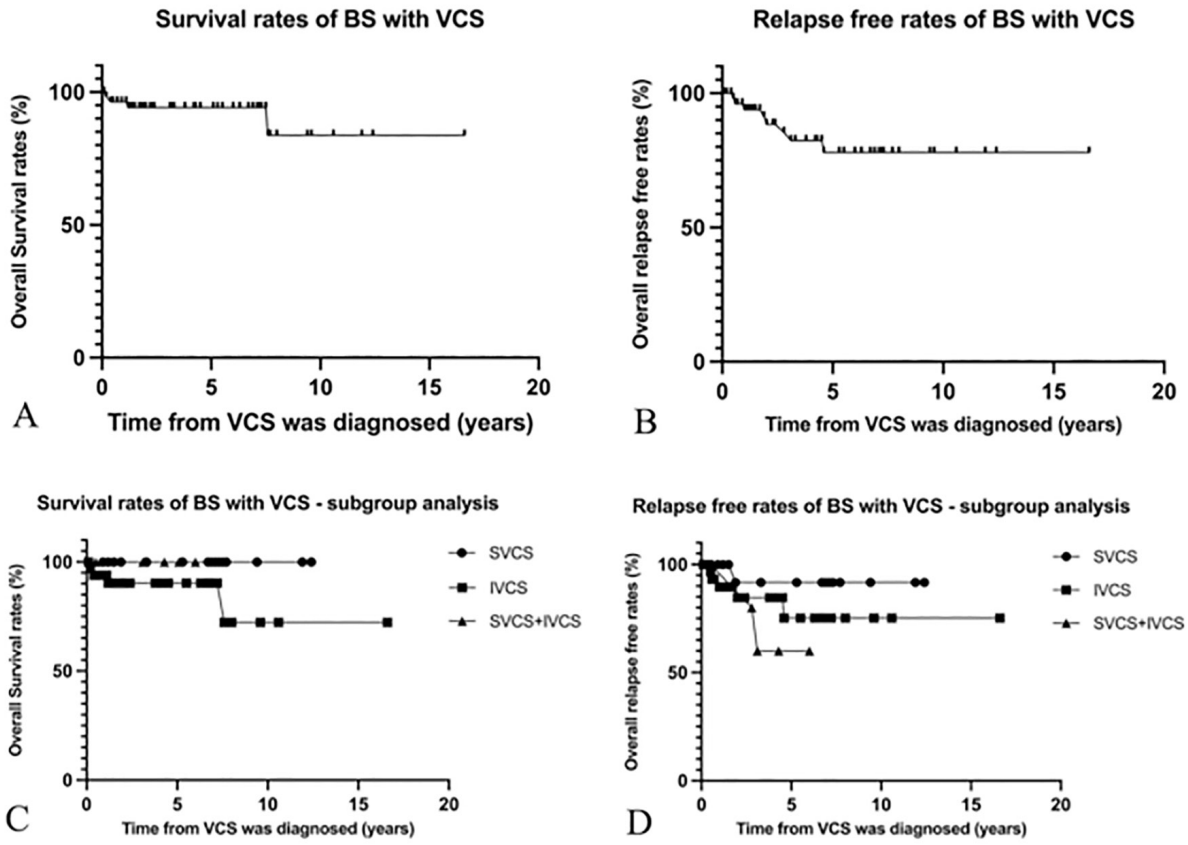

Fig. 4. Kaplan-Meier survival analysis showing overall analysis of survival rates and relapse-free rates in a cohort of 55 BS patients with VCS (**A** and **B**). The curve comparison with the Log-rank test revealed there were no statistical significances of survival rates and relapse-free rates in three subgroups (SVCS, IVCS, SVCS+IVCS) (**C** and **D**).

mg/ml. There have no studies imploring the iodine density of thrombus of IVC on BS. A previous study (12) on neoplastic thrombus iodine density showed that when there was blood supply to thrombus, the iodine density was much higher than bland thrombus. We observed that the iodine density in BS thrombus was higher than bland thrombus (0.92±0.31 mg/mL) (Supplementary file, Figure S1) but lower than neoplastic thrombus (2.67±0.98 mg/mL) showed in the previous study. This pattern might be explained by the different pathophysiological mechanisms of BS and neoplastic thrombus, and the inflammatory thrombus associated with BS should have imaging enhancement.

In our study, active disease patients with skin lesions and higher inflammatory markers are prone to developing VCS, suggesting the critical role of immunosuppressive therapy. Most of our BS patients with VCS received medium to large doses of GCs, while CTX was the most commonly used immunosuppressant, and TNFi was applied in severe and/or refractory cases. Due to the sticky adhesions in the peripheral thrombosis of the venous walls in BS patients rarely cause pulmonary embolism, and anticoagulants could increase the risk of fatal rupture of aneurysms, the use of anticoagulants in BS patients with DVT was controversial (33). In our cohort, anticoagulants were used in most patients with a low risk of bleeding complications. Six patients had received balloon dilation of IVC in our study, and re-occlusion occurred in 2 patients during follow-up. The indication of endovascular and surgical interventions in BS patients with venous thrombosis was controversial because of recurrent infectious or veno-occlusive complications (34).

Given the low incidence of VCS in BS patients, the outcome of VCS in BS has not been well studied. In our study, the respective estimated cumulative 1- and 5-year survival rates were 96.3% and 94.2%, indicating a relatively good outcome. In a recent large retrospective study of BS patients with BCS, 9/61 (14.8%) of BCS patients died during follow-up, and more than half of these patients died of liver failure (35). In our study, although 3 of 4 patients who died had BCS, the main cause was complicated by severe infection and ruptured aneurysm, while VCS and/or BCS were not directly related to mortality. The relatively small number of BCS patients in our study might explain the bias between the two studies. Furthermore, the relapse rate of the vascular event is still high in our cohort, indicating a typically relapsing course of BS, and long-term follow-up are necessary for these patients.

There are some limitations in our study. It is a retrospective study based on a single-centre prospective cohort, and larger-scale prospective multicentre case-control studies are warranted. Spectral CT imaging evaluation was only conducted in 8 BS patients with IVCS, and more data are needed to investigate the value of this technique in BS patients with VCS.

In conclusion, male gender, early-onset BS (<18 years), ESR >60mm/hr and pathergy reaction are potential risk factors of VCS in BS patient. Spectral CT is valuable in detecting thrombus in vena cava and differentiating the property of thrombus.

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