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ORIGINAL ARTICLE

The histological grading of fibrosis in Budd-Chiari syndrome: A chronic liver disease, different from others

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Abstract

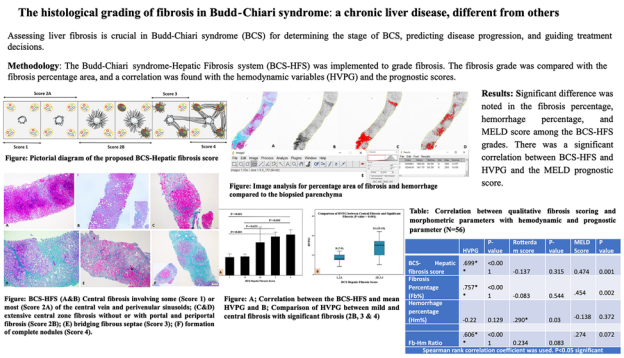
Introduction Budd-Chiari syndrome (BCS) is an uncommon disease caused by hepatic venous outflow obstruction. They can result in centrilobular fibrosis, nodular regenerative hyperplasia and cirrhosis. Assessing liver fibrosis is crucial for determining the stage of BCS, predicting disease progression and guiding treatment decisions. Although this pathology has been known for decades, no useful grading system was assigned. This study aims to introduce a histologic fibrosis grading system for BCS patients.

Methodology All patients from 2017 to 2022 (Sanjay Gandhi Postgraduate Institute of Medical Sciences [SGPGIMS]), Lucknow diagnosed with BCS for whom liver biopsy was performed were included in the study. The Budd-Chiari syndrome-Hepatic Fibrosis system (BCS-HFS) was implemented to grade fibrosis. The fibrosis grade was compared with the fibrosis percentage area and a correlation was found with the hemodynamic variables (hepatic venous pressure gradient [HVPG]) and the prognostic scores.

Results There were 56 patients with BCS. The median age was 27 years, with a male-female ratio of 1.8:1. There was a significant difference in the fibrosis percentage, hemorrhage percentage and model for end-stage liver disease (MELD) score among the BCS-HFS grades ($p < 0.05$). There was a significant correlation between BCS-HFS and HVPG ($\rho = 0.699$, $p < 0.001$) and the MELD prognostic score ($\rho = 0.474$, $p < 0.001$).

Conclusion BCS-HFS is applicable for grading fibrosis in BCS. It can help in uniform histopathology reporting and for further prospective and comparative studies.

Graphical abstract



	HVPG	P-value	Rotterdam score	P-value	MELD Score	P value
BCS- Hepatic fibrosis score	.699**	<0.001	-0.137	0.315	0.474	0.001
Fibrosis Percentage (f%)	.757**	<0.001	-0.083	0.544	.454	0.002
Hemorrhage percentage (Hm%)	-0.22	0.129	.290*	0.03	-0.138	0.372
Fb-Hm Ratio	.606**	<0.001	0.234	0.083	.274	0.072

Spearman rank correlation coefficient was used. P<0.05 significant

Keywords Budd-Chiari syndrome · Fibrosis · Hemorrhage · Hepatic vein · Hepatocytic atrophy · Histopathology · HVPG · Liver biopsy · MELD · Prognosis

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Introduction

Budd-Chiari syndrome (BCS) is an uncommon heterogeneous clinical disease caused by hepatic venous outflow obstruction. It can involve small hepatic venules up to the entrance of the inferior vena cava (IVC) into the right atrium. It can be classified into primary BCS, caused by thrombosis and secondary BCS, caused due to compression by space-occupying lesions or invasion by malignancy or parasites [1]. The true incidence of the disease is unknown, given the few studies and the limited number of patients. The diagnosis can often be made clinically and by radiological demonstration of outflow obstruction. However, patients with obstruction of intrahepatic veins may have normal findings on imaging and need liver biopsy for a definitive diagnosis [2].

The pathophysiological consequences include obstruction of hepatic veins and hepatic damage by retrohepatic hypertension. Due to the increase in sinusoidal pressure, ischemia and hepatocellular necrosis occur, especially in the perivenular area. They can result in centrilobular fibrosis, nodular regenerative hyperplasia and cirrhosis in the later course of the disease [1].

There have been various attempts to determine parameters or combinations of parameters that may predict prognosis in BCS patients. Significant fibrosis is one of the important prognostic factors [3–5]. Transient elastography (fibroscan) is a non-invasive imaging technique that assesses liver stiffness, providing information about the degree of liver fibrosis. Congestion, altered liver anatomy caused by the obstruction of hepatic veins, obesity, ascites, altered blood flow and hepatomegaly can make obtaining accurate liver stiffness measurements challenging.

Liver biopsy remains the gold standard for assessing liver fibrosis, diagnosing other liver pathologies and determining the extent of liver cell damage and inflammation. This information is crucial for determining the stage of BCS, predicting disease progression and guiding treatment decisions. Liver biopsy findings can assist in tailoring treatment strategies for BCS. In cases of advanced fibrosis or cirrhosis, liver transplantation may be considered a treatment option [6, 7].

Analyzing liver biopsies in the BCS setting remains difficult, as no widely accepted scoring systems are used to stage fibrosis in BCS. Most related studies used the METAVIR (Meta-analysis of Histological Data in Viral Hepatitis) scoring system, which is assigned for chronic hepatitis, a portal-based pathology. However, it is essential to note that this system may not fully capture the specific characteristics of fibrosis in Budd-Chiari syndrome. In BCS, the progression to cirrhosis first involves the central vein and zone 3 of the hepatic lobule with congestive injury followed by sinusoidal fibrosis. Later, these changes evolved to central-to-central and central-to-portal bridging fibrosis with regenerative nodules.

Additionally, unlike most other liver processes, BCS can result in heterogeneous fibrosis [8–11]. This raises our concern about the reproducibility of histopathological observations and a unified fibrosis grading system in BCS. This study aims to introduce a histologic fibrosis grading system for patients with BCS. Although this pathology has been known for decades, no useful grading system facilitates prospective and comparative studies. Therefore, communicating accurate information to clinicians regarding liver fibrosis is potentially hampered. Given the extensive involvement of sinusoids by fibrosis, we have also quantified the percentage of fibrosis as a gold standard measure of fibrosis.

Methods

Patient selection

This retrospective analysis was conducted from January 2017 to December 2022 at the Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences (SGPGIMS), Lucknow, a referral tertiary care hospital in northern India. All patients diagnosed with BCS for which liver biopsy was performed were included in the study. The study material was restored from the archives and contained no risk to patients. Clinical, laboratory and other medical records were retrieved from the hospital information system. Fifty-nine cases of BCS were retrieved from the pathology department archives from a total of 2623 liver biopsies. The 56 patients meeting these search parameters were filtered using a specific inclusion criterion (≥ 11 portal tracts): We excluded the patients having inadequate biopsy (< 11 portal tracts) and those having mixed pathologies, i.e. non-alcoholic steatohepatitis (NASH), alcoholic steatohepatitis (ASH) or autoimmune hepatitis (AIH) and steatosis ~ 20% of hepatocytes, regardless of the etiology. Fifty-six patients met the inclusion criteria and three were excluded: one had viral/alcoholic hepatitis, one had significant steatosis ($> 20\%$) and one had an inadequate biopsy. There were 56 patients available for final analysis. Shear-wave elastography (Fibroscan) was performed on Aixplorer® and SuperSonic Imagine (Aix-en-Provence, France) with XC6-1 (single crystal curved) convex. Trans-jugular liver biopsy was taken with the Tru-Cut 18 G needle (2–4 passes) at the time of hepatic venous/IVC recanalization or DIPS procedure. Hepatic venous and right atrial pressure measurements were done in cases of hepatic venous or IVC occlusions pre and post-balloon dilatation/stenting. In seven patients, the HVPG values were missing. The correlation between the BCS hepatic fibrosis score and HVPG values will be determined for 49 patients.

Clinical details

All clinical, laboratory and radiological details at the time of biopsy were obtained from the hospital information system (HIS), an electronic medical record of our institution. The performance of severity indexes such as the Child-Pugh classification, model of end-stage liver disease/pediatric end-stage liver disease (MELD/PELD) (< 12 years) and Rotterdam score were calculated [12].

Histopathological details

Biopsy tissue containing at least 11 complete portal tracts was an adequate biopsy specimen. Tissue sections stained with hematoxylin and eosin (H&E), Masson's Trichrome (MT), orcein and Gomori's reticulin stain were re-evaluated for histological features, including sinusoidal dilatation, hepatocytic atrophy, fibrosis and congestion. Semiquantitative grading was performed for sinusoidal dilatation, hepatocytic atrophy [13] and fibrosis. ImageJ software was used to calculate a quantitative morphometric assessment of fibrosis and hemorrhagic areas.

Sinusoidal dilatation was scored from 0 to 3

- Score 0: No sinusoidal dilation
- Score 1 (mild): Focal and zone 3, but the overall liver acinar arrangement remains maintained
- Score 2 (moderate): Most of the zone 3 areas and there may be some compression of surrounding liver cells
- Score 3 (severe): Involves zone 3 and zone 2 with compression of liver tissue and acinar disarray

Hepatocytic atrophy was scored from 0 to 3

- 0: No atrophy
- 1: Mild atrophy (slight reduction in the size of hepatocytes)
- 2: Moderate atrophy (moderate reduction in the size of hepatocytes)
- 3: Severe atrophy (hepatocytes exhibit significant shrinkage and loss of cellular mass)

We designed a simplified BCS hepatic fibrosis score based on the pathogenesis of the disease and a prior literature review [14–17].

Budd-Chiari syndrome-Hepatic Fibrosis score (BCS-HFS)

The BCS hepatic fibrosis score was developed to grade the stage of liver disease in BCS patients. Based on the pattern of fibrosis, scores of 0, 1, 2A, 2B, 3 and 4 may be assigned as follows [17, 18] (Fig. 1).

0: No fibrosis;

- 1: Mild fibrosis, involving a few of the central vein and perivenular sinusoids
- 2A: Mild fibrosis, involving most of the central vein and perivenular sinusoids
- 2B: Extensive sinusoidal fibrosis or Grade 1/2A fibrosis with portal and periportal fibrosis
- 3: Bridging fibrosis; centro-central or porto-central
- 4: Cirrhosis

Stage 2B, 3 and 4 fibrosis were considered advanced fibrosis. The BCS hepatic fibrosis score was developed to grade the stage of liver disease in BCS patients. The pictorial diagram of BCS-HFS staging system (Fig. 1) was shared between the dedicated hepatopathologists (NN, CB) as a reference image and the biopsies were graded accordingly. The interobserver agreement was 92.8%. The consensus was made with discussion, where the opinion differed.

Quantification of fibrosis and congestion

Quantitative assessment of fibrosis and congestion by computerized morphometry and image analysis was performed. Images of Masson Trichrome-stained slides were taken in live mode with the Plan Achromat lens

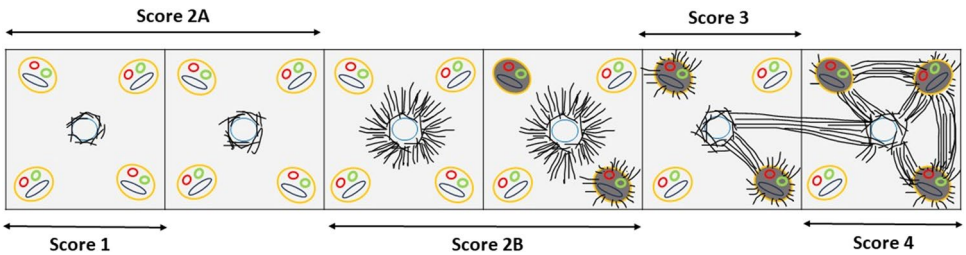

Fig. 1 Pictorial diagram of the proposed Budd-Chiari syndrome (BCS) hepatic fibrosis score: score 0, no fibrosis; score 1, central fibrosis involving some of the central vein; score 2A, central fibrosis, involving most of the central vein and sinusoidal fibrosis; score 2B, extensive central zone and perisinusoidal fibrosis without portal and periportal fibrosis or perivenular fibrosis along with portal and periportal fibrosis; score 3, central-to-portal or central-to-central bridging fibrous septae; score 4, cirrhosis

of an Olympus DP26 microscope with a color camera (U-TVO.63XC) attached and saved in high-resolution (2448 × 1920 pixels) tiff format—correction of images through the adjustment for contrast and brightness conversion of images into 16 bits. The image was processed into a binary image to outline the fibrosis. Process the image through binary and water-shading of the outlined area. The threshold was set to 137–145. Compared to the total parenchymal area in the biopsy, the percentages of the fibrosis area and congestion area were calculated in the 16-bit 2/3 image and 16-bit 3/3 image, respectively. The average of all consecutive areas at 20 × was considered the final value for each biopsy (Fig. 2).

Statistical analysis

STATA 18.0 software (StataCorp. 2023; Stata Statistical Software: Release 18. College Station, TX, USA: StatCorp LLC) was used for statistical analysis. The normality assumption for continuous variables was tested using the Shapiro-Wilk test. As the data was non-parametric, the median and interquartile range were used to present demographic and clinical information. Data with proportions were expressed as percentages. Kruskal-Walli's test was used to compare continuous variables and Fisher's exact test was used for the categorical variables. A Spearman rank correlation test was used between qualitative fibrosis scoring and various outcome factors. All tests were two-tailed and considered significant at the 5% level.

Results

Basic attributes and biochemical parameters

There were 56 patients with BCS in this series, of which seven (12.5%) were acute and 49 (87.5%) were diagnosed with chronic BCS. The mean age of BCS patients varied from 2 to 70 years (25.7 ± 15.0; median 27 years), with a male–female ratio of 1.8:1 (36 males and 20 females). The most common clinical features were ascites (51; 91.1%) followed by esophageal varices (34; 60.8%) and gastrointestinal (GI) bleeding (8; 14.3%). Most patients (48/56; 85.7%) had normal or mildly elevated bilirubin levels (1.2–2.5 mg/dL).

BCS hepatic fibrosis score, clinico-radiological variables and prognostic scores

Of 56 BCS patients, six were grade 1 (10.7%), 14 were grade 2A (25%), seven were grade 2B (12.5%), 20 were grade 3 (35.7%) and the remaining nine patients were grade 4 (16.1%). None of the patients had a fibrosis score of 0 (Fig. 3). The percentages of fibrosis in the corresponding fibrosis grades 1, 2A, 2B, 3 and 4 were 4.0 (1.7, 8.6), 4.2 (3.1, 5.5), 10.9 (4.4, 14.3), 9.1 (7.4, 14.5) and 16.4 (11.8, 22.4), respectively.

Demographic, laboratory and radiological variables were compared among the BCS hepatic fibrosis scores of the study patients. Fibroscan values, fibrosis percentage and hemorrhage percentage significantly differed among BCS grades ($p < 0.05$). All other variables were statistically equal between grades ($p > 0.05$). BCS hepatic fibrosis scores were compared to MELD, pediatric end-stage liver disease

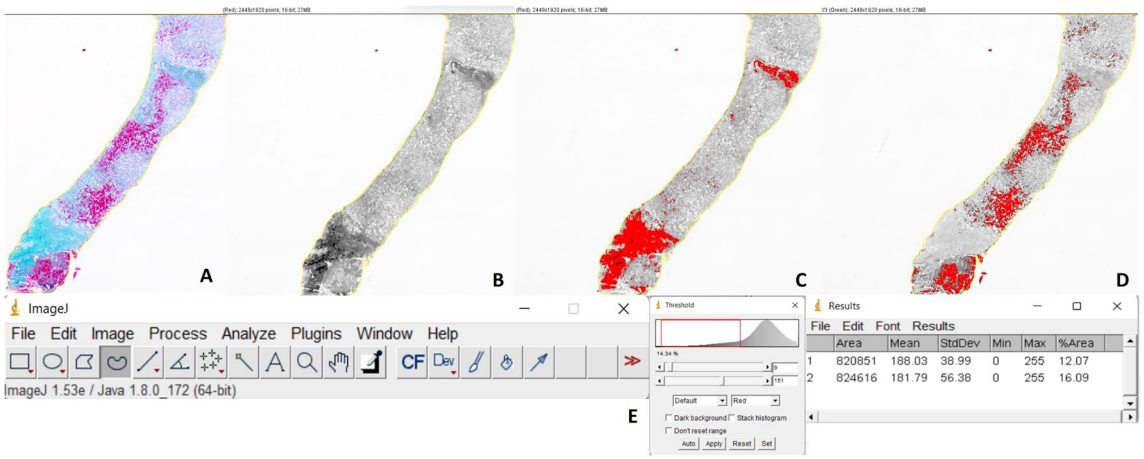

Fig. 2 Image analysis for percentage area of fibrosis and hemorrhage compared to the biopsied parenchyma. **A** Displaying Masson Trichrome-stained slide of liver biopsy and the selection of the total biopsied parenchyma. **B**, **C**, **D** Process the image through binary into red, green and blue (RGB) stacks and water-shading the outlined area by setting the threshold values. **E** The percentage of fibrosis area (1) and hemorrhage area (2) were counted

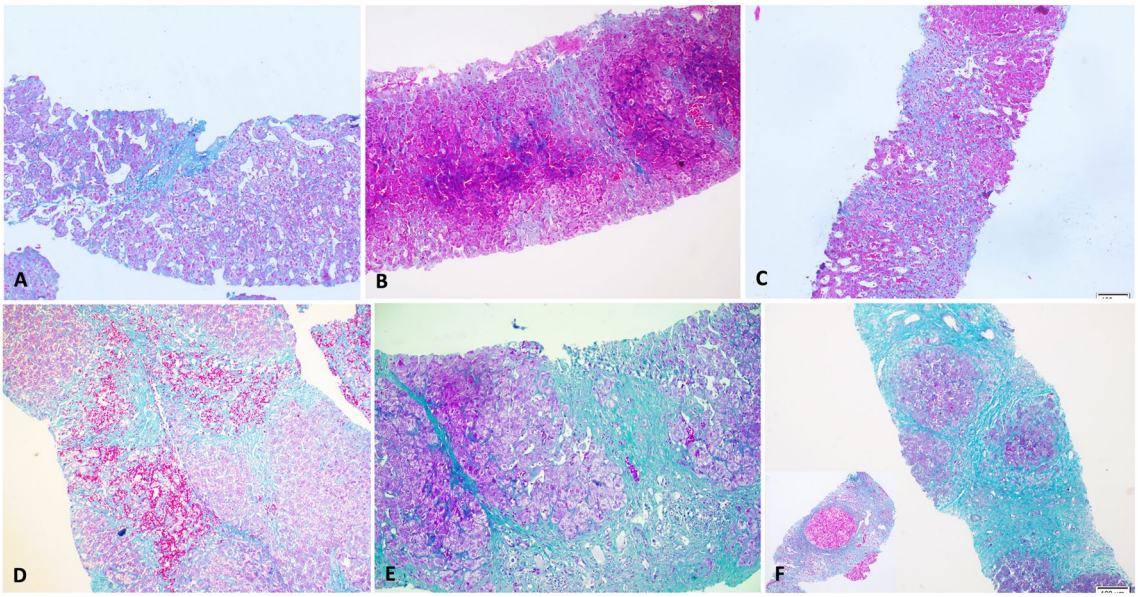

Fig. 3 Budd-Chiari syndrome (BCS) hepatic fibrosis score based on Masson's Trichome staining. Fibrosis involving some of the central vein (**A** grade 1; MT; 100×). Fibrosis involving most of the central veins (**B** grade 2A; MT; 100×). Extensive perisinusoidal fibrosis without portal fibrosis (**C** grade 2B; MT; 100×) and with portal fibrosis (**D** grade 2B; MT; 100×). Bridging fibrous septae (**E** grade 3; MT; 200×) and formation of complete nodules (**F** grade 4; MT; 100×)

Table 1 Demographic data and the laboratory parameters among the different Budd-Chiari syndrome fibrosis score categories ($n=56$)

Demographic and Laboratory Data	Budd-Chiari syndrome-Hepatic Fibrosis score (BCS-HFS)						
	1	2A	2B	3	4	Total	Test
N	6.0 (10.7%)	14.0 (25.0%)	7.0 (12.5%)	20.0 (35.7%)	9.0 (16.1%)	56.0 (100.0%)	
Age	19.5 (9.0, 31.0)	25.0 (15.0, 32.0)	22.0 (10.0, 66.0)	23.5 (15.0, 30.0)	37.0 (27.0, 45.0)	25.0 (15.0, 32.5)	0.2
T Bil	1.7 (0.9, 3.3)	1.2 (0.8, 1.6)	1.1 (0.7, 2.5)	1.2 (0.8, 1.9)	2.1 (1.4, 2.3)	1.3 (0.9, 2.2)	0.5
D Bil	0.9 (0.4, 1.9)	0.5 (0.4, 1.6)	0.4 (0.3, 0.9)	0.6 (0.4, 0.8)	0.9 (0.7, 1.1)	0.7 (0.4, 1.1)	0.4
SGOT (AST)	47.5 (26, 55)	47.0 (39.0, 108.0)	42.0 (34.0, 62.0)	39.5 (31.0, 57.0)	42.0 (33.0, 43.0)	42.0 (32.5, 59.5)	0.3
SGPT (ALT)	22.5 (14.0, 36.0)	43.0 (38.0, 52.0)	47.0 (24.0, 65.0)	35.5 (28.0, 46.5)	30.0 (23.0, 32.0)	36.5 (27.5, 47.0)	0.0
Albumin	3.4 (3.0, 4.0)	3.8 (3.2, 4.2)	4.0 (3.4, 4.2)	4.0 (3.4, 4.4)	3.6 (3.3, 3.9)	3.9 (3.2, 4.3)	0.6
Fibroscan	34.5 (21.0, 58.0)	39.0 (18.0, 54.0)	45.0 (24.0, 54.0)	65.0 (44.0, 75.0)	72.0 (44.0, 75.0)	45.0 (33.0, 73.5)	0.1
Rotterdam score	1.1 (1.0, 1.8)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	0.4
Child–Pugh score	7.5 (6.0, 8.0)	6.0 (5.0, 8.0)	7.0 (6.0, 8.0)	7.5 (7.0, 8.0)	7.0 (6.0, 9.0)	7.0 (6.0, 8.0)	0.4
MELD	15.5 (15.0, 17.0)	17.0 (12.5, 19.0)	21.0 (14.5, 25.0)	22.0 (18.0, 28.0)	24.0 (20.0, 29.0)	20.0 (16.5, 25.5)	**0.001**
PELD	11.5 (6.0, 17.0)	17.5 (13.0, 22.0)	19.0 (13.0, 20.0)	13.0 (7.0, 17.0)		15.0 (10.0, 19.5)	0.5
HVPG	8.0 (7.0, 9.0)	8.5 (8.0, 10.0)	15.0 (7.0, 17.0)	12.0 (10.0, 16.5)	16.0 (15.0, 19.0)	10.5 (8.0, 16.0)	**< 0.001**
Fibrosis %	4.0 (1.7, 8.6)	4.2 (3.1, 5.5)	10.9 (4.4, 14.3)	9.1 (7.4, 14.5)	16.4 (11.8, 22.4)	7.6 (4.5, 14.2)	**< 0.001**
Hemorrhage %	2.3 (1.0, 4.7)	3.2 (1.5, 5.6)	0.7 (0.4, 0.8)	1.2 (0.8, 1.8)	2.2 (1.3, 2.6)	1.4 (0.9, 2.6)	**< 0.001**

Data has been presented in the median and interquartile range. Multiple comparisons by Bonferroni corrections were done. For fibroscan grade 2A and 3, for fibrosis% grade 1 and 4 as well as 2A to 2B, 3 and 4 were significant. p value < 0.05 was significant. *T Bil* total bilirubin, *D Bil* direct bilirubin, *SGOT* serum glutamic-oxaloacetic transaminase, *AST* aspartate aminotransferase, *SGPT* serum glutamic pyruvic transaminase, *ALT* alanine aminotransferase, *MELD* model for end-stage liver disease, *PELD* pediatric end-stage liver disease, *HVPG* hepatic venous pressure gradient

Table 2 Budd-Chiari syndrome fibrosis score and the grading of the histological findings ($n=56$)

	BCS hepatic fibrosis score						*p* value
	0	1	2A	2B	3	4	
Sinusoidal dilatation							
0	0	0	0	0	2 (66.7)	1 (33.3)	0.291
1	0	3 (13.6)	3 (13.6)	5 (22.7)	9 (40.9)	2 (9.10)	
2	0	1 (6.7)	4 (26.7)	2 (13.3)	6 (40)	2 (13.3)	
3	0	2 (12.5)	7 (43.8)	0	3 (18.8)	4 (25)	
Hepatocytic atrophy							
0	0	1 (5)	2 (10)	5 (25)	10 (50)	2 (10)	**0.045**
1	0	4 (23.5)	3 (17.6)	2 (11.8)	5 (29.4)	3 (17.6)	
2	0	0	5 (38.5)	0	4 (30.8)	4 (30.8)	
3	0	1 (16.7)	4 (66.7)	0	1 (16.7)	0	

Fisher's exact test was used. $p<0.05$ significant

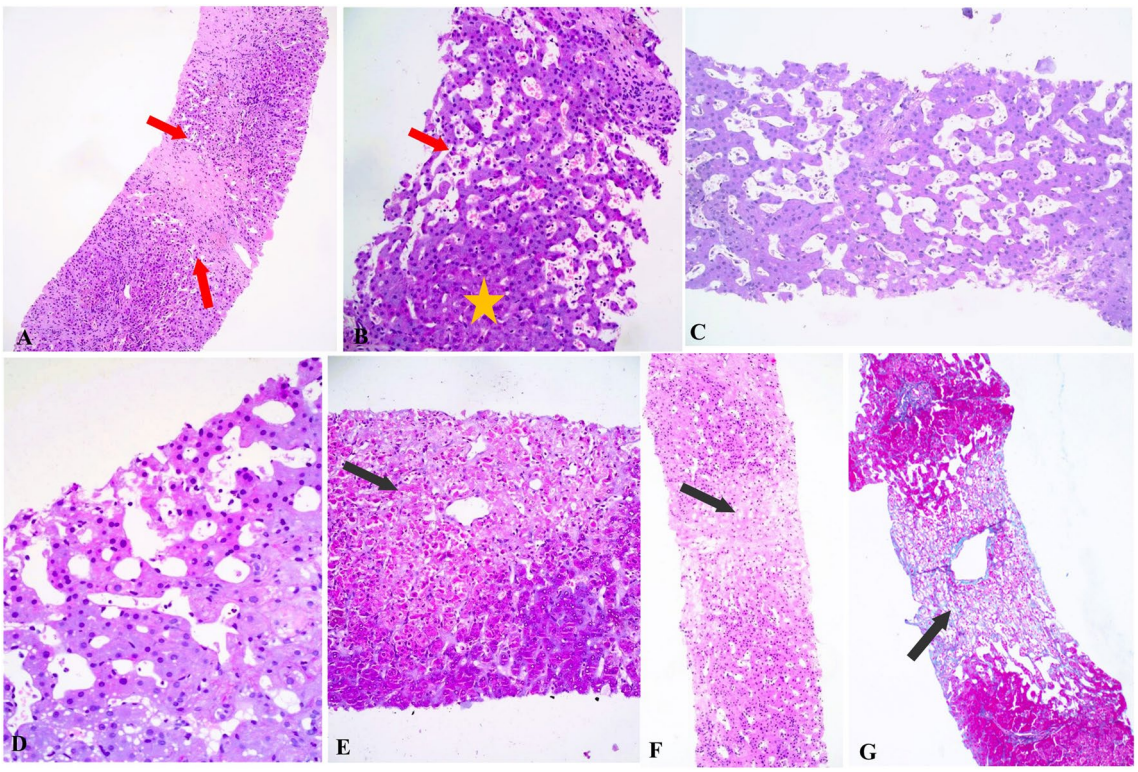

Fig. 4 Histological features of Budd-Chiari syndrome showing mild, moderate and severe sinusoidal dilatation marked with an arrow and unremarkable sinusoids are marked with a star (**A**, **B**, **C**; H&E stain; 100×, 100×, 200×). Mild, moderate and marked hepatocytic atrophy is also demonstrated (**D**, **E**, **F**; H&E stain; 200×, 100×, 100×)

(PELD), Child-Pugh and Rotterdam scores and only the MELD score was significant (Table 1).

BCS hepatic fibrosis score and histological findings

The association of BCS scoring with sinusoidal dilatation and hepatocytic atrophy was evaluated. The BCS-HFS did not correlate significantly with sinusoidal dilatation, but it was significantly associated with hepatocellular atrophy (Table 2, Fig. 4).

BCS hepatic fibrosis score, morphometric parameters and hemodynamic variables

Spearman correlation coefficients were calculated between hepatic fibrosis score, fibrosis percentage,

fibrosis-to-hemorrhage ratio, hemodynamic variables HVPG and Rotterdam prognostic score. The BCS hepatic fibrosis score, percentage fibrosis and fibrosis-to-hemorrhage ratio were significantly correlated with HVPG ($\rho = 0.699$, $p < 0.001$; $\rho = 0.757$, $p < 0.001$; $\rho = 0.606$, $p < 0.001$). The MELD prognostic scores were significantly correlated with the BCS hepatic fibrosis score and fibrosis percentage area ($\rho = 0.474$, $p < 0.001$; $\rho = 0.454$, $p < 0.002$). The Rotterdam score did not correlate with any of the above parameters ($\rho = -0.137$, $p = 0.315$ and $\rho = -0.083$, $p = 0.544$). The percentage of the hemorrhage area in liver biopsies significantly correlates with the Rotterdam prognostic score. However, the correlation was poor ($\rho = 0.290$, $p = 0.03$) (Table 3, Fig. 5).

Discussion

In the Asian population, patients affected are commonly in their third or fourth decade of life. They are widely male and have inferior vena cava blockage or a combination of inferior vena cava and hepatic vein blockage [19]. The patients in our study had a median age of 27 years and were predominantly males. Most BCS patients present with a chronic clinical course (87.5%); however, in a small number of cases, liver function deteriorates rapidly and has an acute or fulminant presentation [20, 21].

The presence of venous collateral circulation and the extent and rapidity of hepatic venous outflow obstruction determine the clinical presentation. It manifests most commonly with ascites, lower limb edema, abdominal pain, esophageal varices and hepatomegaly [22, 23]. Less common include hepatic encephalopathy, hepatorenal syndrome and resistant ascites [2, 24, 25].

Histological examination is commonly recommended, but its role in managing the disease and predicting the outcome remains controversial [26]. To determine hepatic reserve and function, it is crucial to stage liver fibrosis accurately in BCS. Mukund et al. [6] found the need for a comprehensive algorithm considering both venous occlusion and the stage of liver disease while deciding treatment for BCS. They have given a simplified algorithm for the management of BCS. The BCS may be further categorized into three sub-groups (BCS-A–C) depending upon the severity of hepatic fibrosis and accordingly, treatment may be offered and follow-up may be designed [26]. Darwish Murad et al. found standardizing fibrosis staging difficult in BCS due to heterogeneous collagen deposition and perisinusoidal involvement. They performed a multicentric study and concluded that in contrast to inflammatory hepatopathies (including viral,

Table 3 Correlation between qualitative fibrosis scoring and morphometric parameters with hemodynamic parameter and prognostic parameter ($n = 56$)

	HVPG	*p*-value	Rotterdam score	*p*-value	MELD score	*p* value
BCS hepatic fibrosis score	.699**	**< 0.001**	−0.137	0.315	0.474	**0.001**
Fibrosis percentage (Fb%)	.757**	**< 0.001**	−0.083	0.544	.454	**0.002**
Hemorrhage percentage (Hm%)	−0.22	0.129	.290*	**0.03**	−0.138	0.372
Fb-Hm ratio	.606**	**< 0.001**	0.234	0.083	.274	0.072

Spearman rank correlation coefficient was used. $p < 0.05$ significant

BCS Budd-Chiari syndrome, *MELD* model for end-stage liver disease, *HVPG* hepatic venous pressure gradient

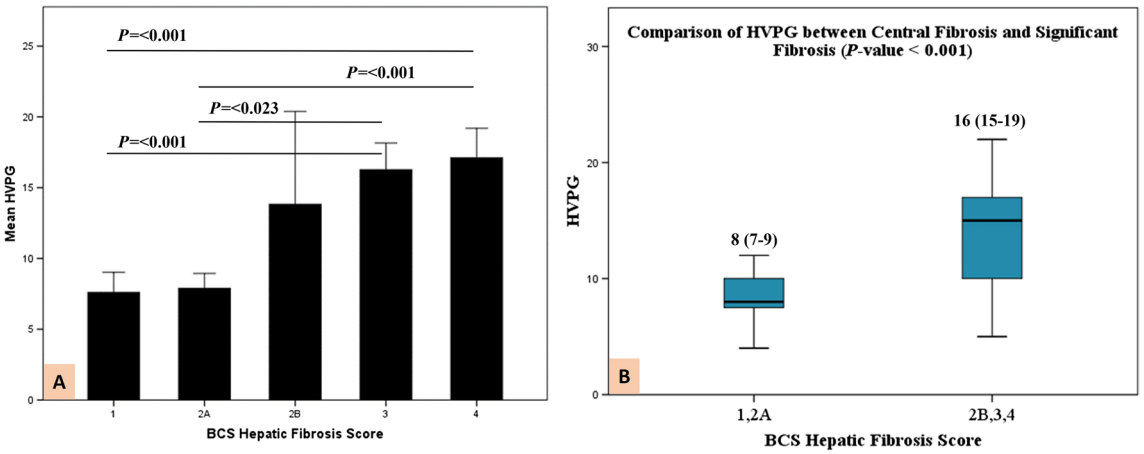

Fig. 5 **A** Correlation between the Budd-Chiari syndrome (BCS) hepatic fibrosis score and mean hepatic venous pressure gradient (HVPG) and **B** comparison of HVPG between mild and central fibrosis with significant fibrosis (2B, 3, and 4)

alcoholic and non-alcoholic fatty liver disease [NAFLD] whose fibrosis staging systems and serum biomarkers of fibrosis have been validated), these tools have been recognized as unreliable in vascular obstructive diseases [2, 3, 8]. Zeitoun et al. found that the Child-Pugh score was a valuable prognostic factor in BCS, whereas histological variables did not predict survival [5].

Evidence suggests that even liver biopsy, hailed as the gold standard for fibrosis assessment, may not accurately stage fibrosis and predict clinical outcomes in hepatic outflow obstructive diseases [8]. A gold standard for estimating fibrosis is the percentage of fibrosis within the liver parenchyma. Compared to the gold standard amount of fibrosis, the proposed BCS fibrosis scoring is highly significant. Fibrosis percentage and BCS-HFS grade were significantly correlated with the MELD prognostic score. End-stage liver disease (ESLD) has been scored objectively by the model for end-stage liver disease (MELD), which is widely accepted. However, it has never been evaluated for BCS. Darwish Murad et al. found that MELD has a discriminative ability to predict survival in BCS patients. They compared the discriminative ability of MELD in BCS ($n = 237$) vs. other chronic liver diseases ($n = 281$) [27]. Rotterdam score does not find a significant correlation, as is a score for early three-month survival and primarily for acute BCS.

Hepatic congestion contributes to liver fibrosis through various mechanisms. The increased sinusoidal pressure and subsequent liver cell injury due to congestion can trigger inflammation and activation of hepatic stellate cells. These cells are the primary cells producing scar tissue (collagen) in the liver. Over time, fibrosis can progress and lead to septa and nodules, ultimately resulting in cirrhosis. The ratio of congestion to fibrosis in BCS may vary between individuals and at different stages of the disease. Congestion may be more prominent in the early stages and fibrosis might be minimal. However, as the disease progresses, fibrosis becomes more significant and dominates liver pathology. Histopathological examination of liver tissue obtained through liver biopsy can provide information about congestion and fibrosis in BCS. It is worth noting that the exact quantification or ratio of congestion to fibrosis is not typically reported or utilized in clinical practice. The fibrosis-to-hemorrhage ratio was significant for BCS-HFS and correlated with HVPG values and the MELD score. Transient elastography (TE) measurements of liver stiffness can be altered by altered liver anatomy, thrombosis and ischemia in patients with BCS and are not found to be significantly correlated with the BCS hepatic fibrosis score or the percentage fibrosis [28]. This fibrosis-to-hemorrhage ratio might help assess the treatment response or follow-up of the patient after the radiological intervention. Follow-up fibroscans were not included in our study.

Other histopathologic observations demonstrate that sinusoidal dilatation and centrilobular hepatocyte atrophy correlate well with the fibrosis scoring system. However, the correlation was significant only for hepatocytic atrophy. These findings are similar to the study by Gonzalez et al., who identified 23 specimens of BCS and 26 specimens of congestive hepatopathy (CH). Sinusoidal dilatation was insignificant, whereas centrilobular dropout or marked hepatocytic atrophy was significant in BCS compared to CH [17].

Measuring the HVPG in BCS can provide important information about portal hypertension and its impact on the liver. It is calculated by measuring the pressure difference between the IVC and the portal vein. This pressure gradient reflects the resistance to blood flow within the liver. This resistance is influenced by factors such as the extent of liver damage and fibrosis. Since fibrosis increases hepatic vascular resistance, it ultimately leads to portal hypertension. Several studies have compared liver stiffness (LS) directly against invasive hepatic venous pressure gradient (HVPG) and found an excellent direct correlation between LS and HVPG [28–30]. The BCS hepatic fibrosis score, fibrosis percentage and fibrosis-to-hemorrhage ratio proposed in the current study correlate well with HVPG, a hemodynamic variable.

Additionally, those with portal fibrosis (2B, 3, 4) had significantly higher HVPG than those without portal fibrosis (0, 1, 2A), as shown in Fig. 5. The correlation of the two variables could provide helpful information for physicians when diagnosing and managing patients with portal hypertension. These findings support the validity of this score as an effective indicator of the severity of BCS. Therefore, secondary portal vein obstruction can alter the central and reverse lobulation pattern to a more veno-portal distribution, mimicking other forms of chronic liver injury, as described in the seminal work by Tanaka and Wanless [31].

To conclude, BCS-HFS is applicable to grade fibrosis in BCS. It can help in uniform histopathology reporting and for further prospective and comparative studies. Utilization of the BCS-HFS and other morphometric parameters (percentage fibrosis and fibrosis-to-hemorrhage ratio) as indicators of disease severity may be considered. This BCS-HF score correlates well with hemodynamic parameters that reflect liver injury and the MELD prognostic score, supporting its utility as a valuable indicator of disease severity.

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Data availability Data is available on request.

Declarations

Conflict of interest NN, RY, GP, ZH, CB, RV, NK and PM declare no competing interests.

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