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Abstract

AIM: To re-examine whether hepatic vein thrombosis (HVT) (classical Budd-Chiari syndrome) and hepatic vena cava-Budd Chiari syndrome (HVC-BCS) are the same disorder.

METHODS: A systematic review of observational studies conducted in adult subjects with primary BCS, hepatic vein outflow tract obstruction, membranous obstruction of the inferior vena cava (IVC), obliterative hepatocavopathy, or HVT during the period of January 2000 until February 2015 was conducted using the following databases: Cochrane Library, CINAHL, MEDLINE, PubMed and Scopus.

RESULTS: Of 1299 articles identified, 26 were included in this study. Classical BCS is more common in women with a pure hepatic vein obstruction (49%-74%). HVC-BCS is more common in men with the obstruction often located in both the inferior vena cava and hepatic veins (14%-84%). Classical BCS presents with acute abdominal pain, ascites, and hepatomegaly. HVC-BCS presents with chronic abdominal pain and abdominal

wall varices. Myeloproliferative neoplasms (MPN) are the most common etiology of classical BCS (16%-62%) with the JAK2V617-F mutation found in 26%-52%. In HVC-BCS, MPN are found in 4%-5%, and the JAK2V617-F mutation in 2%-5%. Classical BCS responds well to medical management alone and 1st line management of HVC-BCS involves percutaneous recanalization, with few managed with medical management alone.

CONCLUSION: Systematic review of recent data suggests that classical BCS and HVC-BCS may be two clinically different disorders that involve the disruption of hepatic venous outflow.

Key words: Budd-Chiari; Hepatic vein outflow tract obstruction; Membranous obstruction of the inferior vena cava; Obliterative hepatocavopathy; Hepatic vein thrombosis

Core tip: With improved diagnostic methods, the terminology for Budd-Chiari syndrome (BCS) has expanded discordantly. This systematic review discusses recent population studies of BCS and proposes the delineation of two clinically unique syndromes.

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INTRODUCTION

Budd-Chiari syndrome (BCS) was originally described as a rare vascular disorder that encompasses an array of symptoms due to obstruction of hepatic blood outflow at the level of the hepatic veins or hepatic portion of the inferior vena cava (IVC)[1]. The symptoms resulting from this type of occlusion of the hepatic outflow, "classical BCS", were first described by Budd[2,3] in 1845 and later by Hans Chiari in 1899. With the advancement of diagnostic and therapeutic techniques, providers have expanded upon these initial characterizations[4]. Historically, identifying the precise location of the obstruction was challenging, leading to the propagation of simplified descriptions. The precise location of the obstruction(s) is however clinically and prognostically significant. As Valla[5] proposed, the clinical manifestations of BCS (the selective group of symptoms that characterize the syndrome) can be explained by the location of the obstruction: Within the hepatic veins *vs* within the IVC at the level of the hepatic ostia. Over time, in order to incorporate novel and more detailed findings associated with BCS, the lexicon has evolved discordantly. The lexicon now includes a myriad of ambiguous terms or eponyms: Budd's disease, Chiari's disease, Chiari's syndrome, Rokitansky's disease, von Rokitansky disease, Hepatic vein outflow tract obstruction, membranous obstruction of the IVC, obliterative hepatocavopathy, Hepatic vena cava disease, Budd-Chiari syndrome with occlusion of hepatic vein, or hepatic vein thrombosis[6-8]. These eponyms have been used at some point during the course of further discovery; this disarray of terms, some of which are unclear and nonspecific, reflects not only the heterogeneous presentation of BCS, but also the possibility of distinct entities within this syndrome.

The currently accepted definition of primary BCS is hepatic outflow obstruction regardless of the cause or level of obstruction[6,9]. The obstruction can range from the small hepatic veins to the orifice of the IVC into the right atrium. Sinusoidal obstruction syndrome is excluded from this definition[6,9]. Secondary BCS is defined as a hepatic venous outflow obstruction due to compression or invasion by extravascular lesions, including benign or malignant diseases such as abscesses, hepatocellular carcinomas, and renal cell carcinomas, or secondary to cardiac or pericardial diseases[6,9].

In 1998, Okuda *et al*[4] proposed that primary hepatic venous thrombosis (classical BCS) and thrombosis of the IVC at the level of the IVC were two separate syndromes. Recent studies continue to suggest a clear division within the definition of "primary BCS" based on the location of the obstructive lesion[4,10]. Obstruction of the hepatic veins or "classical BCS" appears to be more common in Western patient populations and usually has a known etiology[11,12], acute onset of symptoms, and a greater severity of symptoms requiring a different therapeutic approach than obstruction of the IVC at the level of the hepatic veins[4,13,14]. In comparison with "classical BCS", hepatic vena cava (HVC)-BCS appears to be more common in East Asian patient populations, and is more often idiopathic or due to membranous obstruction. HVC-BCS more commonly presents with a chronic onset of less severe symptoms, thus requiring a different therapeutic approach than "classical BCS"[15]. The location, size, and chronicity is clinically important as it dictates the patient's symptoms and directs the therapeutic approach for patient management[10].

Precedence

Historically, hepatic sinusoidal obstruction syndrome (SOS) or veno-occlusive disease was included under the general term BCS[1,16-18]. SOS is specifically defined as obstruction of the sinusoids or hepatic veins resulting from sinusoidal wall injury. Several distinct clinical characteristics differentiate SOS from BCS and the two conditions are now considered separate entities as the distinct etiology and pathophysiology of SOS necessitates different management strategies. SOS is caused by pyrrolizidine alkaloid toxicity, whereas BCS is caused by multifactorial prothrombotic condition(s) or membranous obstruction of the IVC and/or HV[18]. Pyrrolizidine alkaloids include over 150 compounds that

occur naturally in several plant families[18]. Historically, they were ingested in indigenous herbal teas or inadvertently *via* crop contamination in developing countries. Currently, pyrrolizidine alkaloids are used as myeloablative regimens for patients preparing for hematopoietic stem cell transplantation. Thus, SOS almost exclusively affects hematopoietic stem cell transplant patients, while BCS can affect a wide range of patient populations[9]. Clinically, both SOS and BCS can present with abdominal pain, portal hypertension, jaundice, and non-cirrhotic ascites. Management of SOS is challenging and involves preventive measures (avoiding pyrrolizidine alkaloids in susceptible patients) and a few interventional therapeutic options (defibrotide, heparin, shunt procedures, *etc.*). In contrast, management of BCS ranges from medical management (*e.g.*, anticoagulation) to interventional procedures (angioplasty, stents, shunt procedures, *etc.*)[19].

Due to the low incidence of "BCS" in many countries, published data tended to include only small case series. Recently, there have been an increasing number of larger observational studies (both retrospective and prospective), particularly from Asia (China) and Europe. Advancing imaging technologies, such as computed tomography (CT) angiography, magnetic resonance (MR) angiography, Doppler ultrasound (US), and angiography have allowed for better identification and delineation of this disease. This may signal the start of prospective, randomized, controlled therapeutic trials which can differentiate classical BCS from HVC-BCS and their management strategies. Other investigators have suggested various novel classification systems, including those that forego the eponym "Budd-Chiari" altogether[8-16]. However, given that both classical and HVC-BCS reflect an obstruction in hepatic venous outflow, we propose a clarification of the general BCS term into classical BCS and HVC-BCS.

MATERIALS AND METHODS

A systematic literature search yielded 818 results in the PubMed database; 428 in the Scopus database; 18 in the CINAHL database; and 17 in the Cochrane database. All duplicates were removed. After 18 additional studies (from the references within included studies) were added, 1178 study abstracts were screened. Of these, 591 were excluded because of the publication type and/or subject (reviews, case reports including less than 20 patients, non-human studies, or studies not on BCS (*e.g.,* Chiari malformations, acute liver failure, *etc.*). The full text articles of the remaining 587 studies were acquired to determine eligibility.

Inclusion criteria

Clinical trials and observational studies (prospective or retrospective) conducted in predominantly adult subjects with primary BCS were included in this study. All of the included studies needed to explicitly delineate diagnostic methods for BCS (namely standard imaging studies such as US, CT, MR imaging, or venography) and to explicitly describe inclusion and exclusion criteria to ensure the focus on primary BCS (*vs* secondary BCS). For multiple studies published from the same institution(s) within a close time frame, we reviewed years of subject recruitment, methodology specifics, and results. In addition, we also investigated if there were possible overlapping subjects and/or results. Only the most recent eligible studies were included in this review, unless distinctly specific and separate findings were previously reported[20,21].

Of the 587 studies, the following were excluded: 390 were missing key clinical information (*e.g.*, clear inclusion and exclusion criteria) or focused on a subpopulation within the BCS population (*e.g.*, only BCS patients requiring liver transplantation, *etc.*); 71 studies were not limited to primary BCS; 86 studies were not mainly focused on BCS, but rather broader topics associated with BCS (*e.g.*, causes of liver transplantation, *etc.*); 17 studies were older versions of recently published subject populations with similar study aims. Twenty-six studies were included for analysis in this review (Figure 1).

RESULTS

Epidemiology

Many observational studies have recently been published on "BCS" (Table 1). For clarity and compromise, only the terms classical BCS and HVC-BCS will be used to differentiate between the two types of BCS in this review. After considering the location of the obstruction and clinical manifestations of the subjects, studies were grouped as majority-classical BCS or majority-HVC-BCS studies in Table 1. It has previously been suspected that classical BCS is more likely to present in women with a pure hepatic vein obstruction[9,13]. This review continues to support this observation as 13 of the 14 included studies reported a higher incidence of classical BCS in women; 55%-76% of the reported population is female. In addition, recent studies continue to report pure obstruction in the majority of cases 49%-85%. Most studies reported pure hepatic vein obstruction in > 71% of patients (Table 1). Compared with classical BCS, HVC-BCS is more common in men (51%-66%) and more likely to present with an IVC obstruction with or without involvement of the HVs (69%-100%) (Table 1).

Clinical manifestations in classical BCS vs HVC-BCS

Classical BCS typically presents with an acute onset of symptoms with most studies reporting the duration of symptoms < 6 mo (Table 2) with 60%-85% of patients having an acute presentation of symptoms; however, one study from Egypt designated 80% of their 94 patients as chronic, but the definitions of chronic *vs* acute were not explicitly delineated[22]. Classical BCS typically presents with abdominal pain (45%-86% of patients), ascites (76%-100%), and hepatomegaly (43%-83%) (Table 2). In comparison, HVC-BCS typically presents

Table 1 Epidemiology of classical Budd-Chiari syndrome and hepatic vena cava-Budd Chiari syndrome

Ref.	Country	Publication date	Recruitment years	*n*	Age (median)	Gender		Location of obstruction (%)		
						M (%)	F (%)	HV	IVC	Both
Janssen *et al*[27]	The Netherlands	2000	1984-1997	43	40	16 (37)	27 (63)			
Perelló *et al*[40]	Spain	2002	1990-2000	21	36[1]	5 (24)	16 (76)	17 (81)	0 (0)	4 (19)
Colaizzo *et al*[30]	Italy	2008	1997-2006	32	35	9 (28)	23 (72)			
Darwish Murad *et al*[24]	Europe	2009	2003-2005	163	38	70 (43)	93 (57)	80 (49)	4 (2)	79 (48)
Xavier *et al*[31]	Brazil	2010	2000-2008	31	33	11 (35)	20 (65)			
Sakr *et al*[22]	Egypt	2011	2009-2011	94	28.8[1]	36 (38)	58 (62)	70 (74)	3 (3)	16 (17)
Deepak *et al*[29]	India	2011	2006-2009	20	36.6	14 (70)	6 (30)	17 (85)	1 (5)	2 (10)
Rautou *et al*[37]	France	2011	1995-2005	94	38[1]	34 (36)	60 (64)	73 (78)		13 (14)
Raszeja-Wyszomirska *et al*[45]	Poland	2012	2004-2011	20	38	9 (45)	11 (55)			
Westbrook *et al*[32]	United Kingdom	2012	1985-2008	66	36	27 (41)	39 (59)			
D'Amico *et al*[34]	Italy	2013	2005-2011	31	46	14 (45)	17 (55)			
Harmanci *et al*[42]	Turkey	2013	1989-2011	62	42.8[1]	26 (42)	36 (58)	35 (56)	8 (14)	19 (30)
Nozari *et al*[47]	Iran	2013	1989-2012	55	29[1]	22 (40)	33 (60)			
Pavri *et al*[38]	United States	2014	2008-2013	47	42.4	16 (34)	31 (66)			
Faraoun *et al*[25]	Algeria	2015	2008-2012	176	33[1]	75 (43)	101 (57)	125 (71)	0 (0)	51 (29)
De *et al*[23]	India	2001	1992-1998	40	35.2[1]	26 (65)	14 (35)	N/A	23 (72)	9 (28)
Xu *et al*[41]	China	2004	1983-2003	1360	33.2[1]	833 (61)	527 (39)	2 (0)	1358 (100)[2]	
Ebrahimi *et al*[46]	Iran	2011	2002-2008	21	42[1]	11 (52)	10 (48)	6 (29)	12 (57)	3 (14)
Park *et al*[51]	South Korea	2012	1988-2008	67	47	34 (51)	33 (49)	5 (7)	56 (84)	6 (9)
Qi *et al*[35]	China	2013	1999-2011	169	38.3[1]	66 (52)	61 (48)	53 (31)	20 (12)	96 (57)
Cheng *et al*[13]	China	2013	2010-2011	145	46	90 (6)	55 (38)	45 (31)	8 (6)	92 (63)
Qi *et al*[36]	China	2014	2012-2012	25	35.7[1]	14 (56)	11 (44)	4 (16)	0 (0)	21 (84)
Zhou *et al*[26]	China	2014	2006-2010	338	41.7[1]	209 (62)	129 (38)	45 (13)	8 (2)	285 (84)
Gao *et al*[49]	China	2015	2008-2012							
R				98	36[3]	62 (63)	36 (37)	31 (32)	26 (27)	41 (42)
NR				373	45[3]	193 (52)	180 (48)	82 (22)	169 (45)	122 (33)

[1]Mean values; [2]No differentiation between IVC alone *vs* both IVC and hepatic vein; [3]Provided median ages for the two groups separately. R: Recurrence of disease, NR: Non-recurrence of the disease; HV: Hepatic vein; IVC: Inferior vena cava; M: Male; F: Female; N/A: Not available.

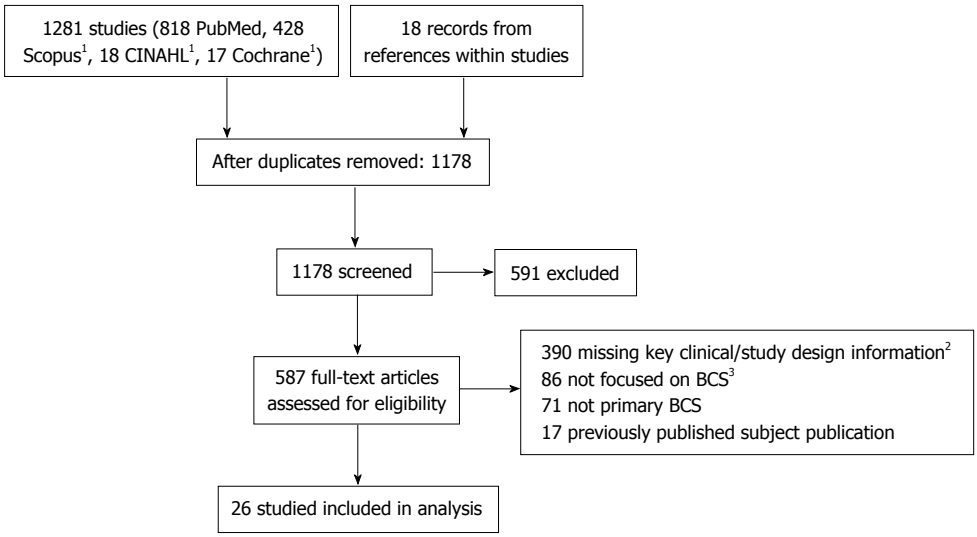

Figure 1 Flow diagram of studies selection. [1]Searches conducted with MEDLINE results removed; [2]Studies missing key clinical information including clear inclusion and exclusion criteria, clear diagnostic parameters, *etc*., and studies that investigated subpopulations (*e.g*., BCS patients requiring liver transplantation, BCS patients without MPN, *etc*.); [3]Studies focused on other categories (*e.g*., causes of liver failure). BCS: Budd-Chiari syndrome; MPN: Myeloproliferative neoplasms.

with chronic onset of symptoms (75%-86% of patients), with an average duration of symptoms prior to diagnosis ranging from 44-96 mo. Nine to seventy percent of patients (most studies reporting < 29%) with HVC-BCS present with abdominal pain, 32%-90% with ascites, and 28%-95% with hepatomegaly. Splenomegaly, abdominal wall varices, lower extremity varices, and discoloration are more commonly associated with HVC-BCS (Table 2)[13,23]. The severity of disease depends upon both the extent of disease (the number of occluded vessels, complete or incomplete occlusion), the presence of associated symptoms (refractory ascites, portal vein thrombosis, *etc*.), and the chronicity of symptoms. Patients with the chronic variation of disease generally have several milder episodes of vague symptoms (abdominal pain or leg swelling), providing sufficient time for

Table 2 Signs and symptoms in classical Budd-Chiari syndrome and hepatic vena cava-Budd Chiari syndrome

	Classical BCS									HVC-BCS						
	Perelló *et al*[40]	Darwish Murad *et al*[24]	Sakr *et al*[22]	Rautou *et al*[46]	Raszeja-Wyszomirska *et al*[45]	Westbrook *et al*[32]	D'Amico *et al*[34]	Harmanci *et al*[42]	Nozari *et al*[47]	De *et al*[23]	Xu *et al*[41]	Ebrahimi *et al*[46]	Qi *et al*[35]	Cheng *et al*[13]	Gao *et al*[49] R *vs* NR	
Country	Spain	Europe	Egypt	France	Poland	United Kingdom	Italy	Sweden	Iran	India	China	Iran	China	China	China	
n (%)	21	163	94	94	20	66	31	62	55	40	1360	21	169	145	98	373
Abdominal pain	18 (86)	99 (61)	78 (83)			36 (55)		28 (45)	33 (60)	28 (70)	122 (9)	5 (29)		30 (21)		
Ascites	18 (86)	135 (83)	80 (85)	73 (78)	20 (100)	57 (87)			42 (76)	30 (75)	914 (67)	19 (90)	95 (56)	77 (53)	76 (78)	224 (60)
Hepatomegaly	9 (43)	109 (67)	78 (83)						33 (60)	38 (95)	1124 (83)	8 (38)		40 (28)	61 (62)	165 (44)
Splenomegaly		85 (52)	48 (51)						19 (34)	26 (65)	683 (50)			113 (78)		
Abdominal wall varices			39 (41)							38 (95)	821 (60)		50 (30)	73 (50)		
Esophageal varices		45 (58)[1]		53 (56)			18 (58)									
Lower extremity edema			46 (49)					28 (45)		28 (70)		14 (67)	86 (51)	76 (52)		
Jaundice	10 (48)		36 (38)						10 (18)	15 (38)	116 (9)					
Encephalopathy	1 (5)	15 (9)	29 (31)	7 (7)		32 (48)						12 (57)	1 (1)			
Bleeding episodes	1 (5)	8 (5)	15 (16)		5 (25)		7 (23)			6 (15)	162 (12)		25 (15)	31 (21)		
Duration of symptoms	1.4[2]	< 1						1-6	6				44	96		
Chronic, > 6 mo		23 (14)	75 (80)[3]					25 (40)	21 (38)	30 (75)				125 (86)		
Acute, < 6 mo		138 (85)	18 (19)					37 (60)	34 (62)					20 (14)		

[1]77 patients underwent EGD; [2]Mean, not median. Most studies reported median duration of symptoms in months; when the median was not available, the mean is reported; [3]No definition of "chronic" was provided. BCS: Budd-Chiari syndrome; HVC: Hepatic vena cava; R: Recurrence of BCS; NR: Non-recurrence of BCS.

the development of collateral vessels[13,24]. In contrast, acute onset and/or significant obstruction (*e.g.*, complete occlusion of several hepatic veins) increases the risk of acute hepatic failure.

Obstruction characteristics

Patients with classical BCS typically have an obstructing thrombus within the hepatic veins (Figure 2)[5,24]. In contrast, patients with HVC-BCS typically have a membranous or segmental obstruction involving the IVC[24] (proximal to the ostia of the hepatic veins), but the obstruction can extend into, or secondarily involve the hepatic veins themselves (Figure 3). Observational studies continue to reflect this difference between classical BCS and HVC-BCS patients; several studies from Europe to northern Africa consistently describe a thrombotic obstruction (87%-95%) limited to the hepatic veins (49%-85%) and rarely describe a membranous obstruction (1%-5%) located at only the IVC (0%-14%). However, in HVC-BCS patients, many studies report a membranous obstruction (30%-61%) only located at the IVC (57%-72%) or both the IVC and HV (63%-84%). Obstructions in HVC-BCS patients are not commonly isolated in the hepatic veins (0%-31%)[24-26]. The development of collateral circulation takes time; given that the chronic form of BCS is more commonly associated with HVC-BCS, it is not surprising that the development of collateral circulation is more typical with HVC-BCS patients (63%-65%) than with classical BCS patients (Table 3).

Etiology

Uncovering the etiology of BCS can be challenging. In classical BCS, however, thrombotic risk factors are consistently identified in the majority of patients[1]. Findings reported in recent studies continue to report myeloproliferative neoplasms [MPN, previously called myeloproliferative disorders (MPD)] as the most common etiology of classical BCS; 9 out of 14 studies found that it is the most common cause of classical BCS affecting 16%-62% of patients, with many reporting between 41%-62% (Table 4). The most commonly observed MPNs include polycythemia vera (PV) and essential thrombocythemia (ET) found in 18%-43% and 6%-14% of classical BCS patients, respectively. The JAK2V617-F mutation is a sensitive marker for MPN and has been observed in 26%-52% of patients with classical BCS[27-34]. In contrast, in several large Chinese studies,

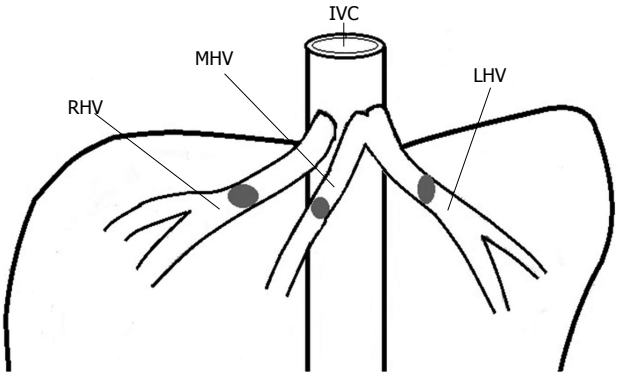

Figure 2 Classical Budd-Chiari syndrome - Occlusions are within the hepatic veins themselves and usually thrombi. RHV: Right hepatic vein; MHV: Middle hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

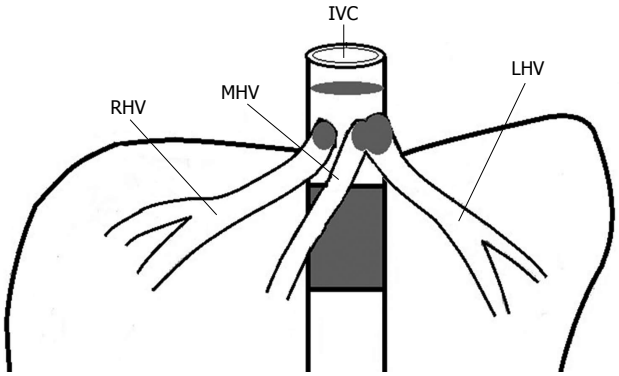

Figure 3 Hepatic vena cava-Budd Chiari syndrome - Occlusions are thin or thick (membranous or segmental) and within the inferior vena cava and occlusion can extend into the hepatic veins and generally involve the ostia to the inferior vena cava. RHV: Right hepatic vein; MHV: Middle hepatic vein; LHV: Left hepatic vein; IVC: Inferior vena cava.

MPN were only found in 4%-5% of patients (PV in 2% and ET in 1%-2%) and the JAK2V617-F mutation in only 0%-5% of patients diagnosed with primary HVC-BCS (Table 4)[13,35,36].

Hereditary prothrombotic conditions such as factor Ⅴ Leiden mutation (FVL), prothrombin (PT) 20210A mutation, protein C deficiency (PCD), protein S deficiency (PSD), antithrombin deficiency (ATD), plasminogen activator inhibitor [PAI-1 (4G-4G)], and the 5,10-methlenetetrahydrofolate reductase enzyme mutation (MTHFRC677T) often also play a significant role in the development of classical BCS. Following MPNs, the FVL mutation is the second most common cause of classical BCS and was found in 2%-53% of patients. Thrombophilic conditions also may contribute to the development of classical BCS. Mutations in PT were found in 2%-8% of patients with classical BCS *vs* 0% of patients with HVC-BCS. PCD, PSD, and ATD were found in 3%-26%, 1%-9% and 3%-15% of patients with classical BCS, respectively, *vs* 0% of patients with HVC-BCS (Table 4). Interestingly, this pattern is not apparent with MTHFRC677T mutations; these mutations were found in 26%-52% of patients with classical BCS and 71%-72% of patients with HVC-BCS. Less common but established prothrombotic or associated conditions further include antiphospholipid antibodies (classical BCS: 3%-29% *vs* HVC-BCS: 0%-17%), hyperhomocysteinemia (10%-18% *vs* 21%-50%), and paroxysmal nocturnal hemoglobinuria (0%-19% *vs* 0%-4%). Several systemic conditions (classical BCS: 5%-24% *vs* HVC-BCS: 1%-19%) including connective tissue disorders such as systemic lupus erythematosus (5%-12% *vs* 1%) are generally associated more frequently with classical BCS. Hormonal factors such as oral contraceptives, pregnancy, or puerperium can also increase the risk of thrombosis as can local insults such as recent surgery. Of these numerous differences between classical BCS and HVC-BCS, one consistent difference is the greater influence of hormonal changes (be it oral contraceptive use or pregnancy) in classical BCS patients (4%-52% of the female population) (Table 4)[29,37-39].

Membranous obstruction of the IVC (and/or HV) is consistently listed as the etiology of a significant number of HVC-BCS patients (52%-61%). In classical BCS patients, membranous obstruction is rare (1%) or rarely explicitly delineated, except in one study of 23 consecutive patients diagnosed with BCS in Germany where 5 patients (22%) were found to have a membranous obstruction of the IVC[24]. Furthermore, despite comprehensive work-up, an etiologic factor is often not identified in HVC-BCS patients (19%-29% *vs* classical BCS: 5%-30%) (Table 4).

Data from recent studies continues to support the possibility of two different types of BCS with separate etiologies: Classical BCS, where thrombophilic risk factors and often multiple concomitant factors are common *vs* HVC-BCS, where thrombophilic risk factors are uncommon, but membranous obstruction and idiopathic hepatic venous outflow obstruction are more common.

Management and outcomes

Treatment and prognosis of BCS depends on a few key factors: Acuity of symptoms, location and extent of the obstruction, and etiology[24]. In 2013, Seijo *et al*[11] outlined a step-wise management approach for BCS patients from the analysis of the extended follow-up data of 157 patients from 9 European countries. This management approach starts with medical management alone (*e.g.*, salt-restriction, anticoagulation, diuretics), including concomitant management of any underlying etiological processes. Diagnostic work-up for classical BCS patients generally includes hematologic work-up for MPN, JAK2V617F mutation screening for MPN[29-31,33], testing for FVL mutation[28], and the aforementioned thrombophilic risk factors. In addition, some studies recommend continued monitoring of JAK2-mutation-positive-patients for occult MPNs[5,9,33]. In general, the medical management of classical BCS patients involves anticoagulation and ascites management with diuretics. Patients with MPN require additional aspirin and cyto-

Table 3 Obstruction characteristics: Location, type, and associated findings

	Classical BCS						HVC-BCS				
	Perelló *et al*[40]	Darwish Murad *et al*[24]	Sakr *et al*[22]	Deepak *et al*[29]	Harmanci *et al*[42]	Faraoun *et al*[25]	De *et al*[23]	Xu *et al*[41]	Ebrahimi *et al*[46]	Cheng *et al*[13]	Zhou *et al*[26]
Country	Spain	Europe	Egypt	India	Turkey	Algeria	India	China	Iran	China	China
n (%)	21	163	94	20	62	176	40	1360	21	145	338
Obstruction location											
HV only	17 (81)	80 (49)	70 (74)	17 (85)	35 (56)	125 (71)	N/A	2 (0)	6 (29)	45 (31)	45 (13)
IVC only	0 (0)	4 (2)	3 (3)	1 (5)	8 (14)	0 (0)	23 (72)	1358 (100)	12 (57)	8 (6)	8 (2)
Both HV and IVC	4 (19)	79 (48)	16 (17)	2 (10)	19 (30)	51 (29)	9 (28)		3 (14)	92 (63)	285 (84)
HV thrombosis	20 (95)				54 (87)	170 (97)		DNS		15 (10)	
IVC thrombosis	3 (14)	DNS	DNS	DNS	27 (44)	DNS		123 (9)			
IVC web/membrane	1 (5)		2 (1)	DNS	DNS	DNS	12 (30)	717 (53)	11 (52)	89 (61)	
Collateral circulation										92 (63)	220 (65)
Benign regenerative nodules										36 (25)[1]	79 (23)

[1]Described as "benign nodules", not benign regenerative nodules. DNS: Study mentions generally, but, does not provide specific counts; BCS: Budd-Chiari syndrome; HV: Hepatic vein; HVC: Hepatic vena cava; IVC: Inferior vena cava.

reductive medications (*e.g.*, hydroxyurea). Patients with autoimmune diseases (*e.g.*, antiphospholipid syndrome, Behçet's disease, *etc.*) require additional corticosteroids and/or immunosuppressive drugs. If patients fail medical management, therapy is then escalated to minimally invasive procedures including percutaneous transluminal angioplasty (PTA) and/or thrombolysis. If patients fail to respond to these measures, developing refractory ascites, variceal bleeding, or liver failure, they are then treated with transjugular intrahepatic portosystemic shunt (TIPS) or other shunt operations[11,40,41], with liver transplantation as a final option[32]. Such an approach appears to result in good long-term survival (Table 5)[11].

Recent studies continue to support that medical management alone can be appropriate for classical BCS patients; 33%-54% of the classical BCS patients treated with medical management alone have good outcomes. In contrast, only 0%-7% of HVC-BCS patients are treated with medical management alone. While both classical and HVC-BCS patients benefit from interventional therapy, the specific interventions are different. Classical BCS patients commonly undergo TIPS (classical BCS: 4%-62% *vs* HVC-BCS: 1%-4.5%) and liver transplantation (9%-55% *vs* 0%-1%). In a study of 62 predominantly classical BCS patients from Turkey, none of the patients underwent liver transplantations, but that was due to a lack of donor availability[42]. In contrast, first line management of HVC-BCS with percutaneous re-canalization (with or without stent deployment) has good outcomes[43]. In one large study from China, Han *et al*[44] found that all 187 consecutively diagnosed primary BCS patients at one institution were eligible for percutaneous recanalization, regardless of the location of the obstruction. Recent studies report that HVC-BCS patients undergo PTA more frequently compared to classical BCS patients (HVC-BCS: 43%-92% *vs* classical BCS: 3%-18%). After percutaneous recanalization, patients are anticoagulated with an international normalized ratio goal of 2-3 for a minimum of 6-8 mo per standard post-endovascular intervention management guidelines[44].

Median follow-up for both classical BCS and HVC-BCS patients were similar (classical BCS: 17-58 mo and HVC-BCS: 12-103 mo). Both groups of patients fared well with their respective management strategies. One-year and five-year survival was 79%-96% and 56%-79% among classical BCS patients, respectively. One-year and five-year survival for HVC-BCS patients was 67%-99% and 75%-86%, respectively (Table 5). Poor prognostic factors for classical BCS patients include: Severe BCS (*e.g.*, ascites requiring diuretics or paracentesis, pleural effusion, higher Clichey Prognositc index score), older age, cirrhosis at diagnosis of BCS, and chronic kidney disease[37,38]. Development of cirrhosis or hepatocellular carcinoma (HCC) are poor prognostic factors for HVC-BCS patients[23].

DISCUSSION

This systematic literature review highlights the numerous differences between classical BCS and HVC-BCS. Despite the growing cognizance of this difference[4,5] and despite

Table 4 Risk factors and/or etiologies of classical Budd-Chiari syndrome and hepatic vena cava-Budd Chiari syndrome

	Classical BCS														HVC-BCS			
	Perelló *et al*[40]	Smalberg *et al*[39]	Colaizzo *et al*[30]	Xavier *et al*[31]	Sakr *et al*[22]	Deepak *et al*[29]	Rautou *et al*[37]	Raszeja-Wyszomirska *et al*[45]	Westbrook *et al*[32]	D'Amico *et al*[34]	Seijo *et al*[11]	Harmanci *et al*[42]	Nozari *et al*[47]	Pavri *et al*[38]	Ebrahimi *et al*[46]	Qi *et al*[35]	Cheng *et al*[13]	Qi *et al*[36]
Country	Spain	Netherlands	Italy	Brazil	Egypt	India	France	Poland	United Kingdom	Italy	Europe	Turkey	Iran	United States	Iran	China	China	China
n (%)	21	40	32	31	94	20	94	20	66	31	157	62	55	47	21	169	145	25
MPN (%)	13 (62)	13 (33)	13 (41)	5 (16)		8 (40)	51 (59)	8 (40)	37 (56)	17 (55)	52 (33)	19 (31)	9 (16)			7 (4)[9]	5 (5)[10]	
JAK2V617-F	N/A	7 (41)		8 (26)	18 (29)[4]	8 (40)			34 (52)							4 (2)	5 (5)[10]	0 (0)
PV	9 (43)										28 (18)			14 (30)		3 (2)	2 (2)[10]	
ET	3 (14)										12 (8)			3 (6)		1 (1)	2 (2)[10]	
FVL	2 (10)	5 (15)	6 (19)	3 (10)	34 (53)[5]	5 (25)	15 (19)	1 (5)	1 (2)	9 (29)	19 (12)	15 (30)	10 (18)	4 (9)		0 (0)	0 (0)[11]	0 (0)
PT 20210A		2 (8)	1 (3)	1 (3)	3 (5)[6]		6 (8)		1 (2)	1 (3)	5 (3)	1 (2)				0 (0)	0 (0)[11]	0 (0)
Protein C deficiency		2 (7)[2]			4 (4)	2 (10)	6 (12)	3 (15)	2 (3)		5 (3)	16 (31)	12 (20)	2 (4)			0 (0)[12]	
Protein S deficiency		2 (7)[2]			1 (1)	1 (5)	5 (9)				3 (2)	5 (10)	3 (6)	1 (2)			0 (0)[12]	
AT deficiency					4 (4)	3 (15)	3 (4)				4 (3)	6 (15)	3 (6)				0 (0)[12]	
PAI-1 (4G-4G)										17 (55)								
MTHFRC677T					31 (52)[6]					8 (26)		19 (39)				96 (71)		18 (72)
HH						2 (10)					29 (18)					64 (50)	30 (21)	
PNH	4 (19)	2 (9)	1 (3)		2 (2)	1 (5)	8 (12)	1 (5)	0 (0)		15 (10)	1 (2)		3 (6)		1 (1)	0 (0)[13]	1 (4)
OCP, pregnancy, or puerperium[1]		13 (52) (OC)[3]	1 (4) (OC)[3]	7 (35)	19 (33)		21 (35) (OC)[3]			4 (24)	35 (39)	4 (11)	3 (9)	2 (6) (OC)[3]			2 (4)	
Systemic diseases or local factors		2 (5)			12 (13)[7]				3 (5)[7]		37 (24)	8 (13)[7]	5 (9) autoimmune		4 (19)[8]	2 (1)	1 (1)	
NAD/idiopathic	1 (5)				8 (9)			6 (30)		2 (6)		6 (10)	10 (18)		6 (29)		28 (19)	
Web/membrane															11 (52)		89 (61)	
MOVC																	6 (4)	
MOVC + HV	1 (5)																60 (41)	
MOHV																	23 (16)	

[1]Percentage of total female patients; [2]Patients on anticoagulation were not tested; [3]Number of women on OC only, no specific information on number of pregnant women; [4]Out of 62 tested; [5]Out of 64 tested; [6]Out of 60 tested; [7]Mainly Behcet's disease; [8]Behcet's disease (2), Hepatitis C (1), Leukemia (1); [9]2 of these 7 patients were diagnosed with latent MPN; [10]In this study, most (105 patients), but, not all were tested; percentages are out of 105; [11]Out of 96 patients were tested; [12]Out of 80 patients tested; [13]Out of 83 patients tested. BCS: Budd-Chiari syndrome; HV: Hepatic vein; HVC: Hepatic vena cava; ET: Essential thrombocythemia; PNH: Paroxysmal nocturnal hemoglobinuria; OCP: Oral contraception; MOVC: Membranous obstruction of IVC; NAD: No associated disease/etiology found; MPN: Myeloproliferative neoplasms; FVL: Factor V Leiden mutation; HH: Hyperhomocysteinemia.

the abundance of recent publications on BCS, there is still a paucity of large, randomized clinical trials with regard to classical and/or HVC-BCS. The vast heterogeneity of these recent publications with regards to recruitment of solely primary *vs* secondary BCS, of solely classical or HVC-BCS, and of patients who have not previously been recruited and described, may lead to disparate and skewed patient populations that preclude certain data analyses and conclusions. Thus, this review specifically sought out studies that recruited BCS subjects that were representative of the indigenous BCS patient population. We attempted to minimize selection bias by excluding studies that focused on a particular subgroup of patients (*e.g.*, BCS patients requiring liver transplantation, exclusion of patients with specific previously diagnosed etiologies, *etc.*). We also attempted to minimize multiple representations of the same patient population by comparing recruitment periods from studies that were similar in geographic location (institution, city, and country) or similar in authorship. The selected studies thereby provide an unadulterated presentation of the differences between classical *vs* HVC-BCS according to geography, patient demographics, location of obstruction, and treatment strategies and outcomes. The examination of these differences is important as they impact the diagnostic work-up and the therapeutic management strategies for individual patients and healthcare communities alike.

Table 5 Management and outcomes in classical Budd-Chiari syndrome and hepatic vena cava-Budd Chiari syndrome

	Classical BCS								HVC-BCS					
	Perelló *et al*[40]		Rautou *et al*[37]	Raszeja-Wyszomirska *et al*[45]	Westbrook *et al*[32]	Harmanci *et al*[42]	Seijo *et al*[11]	Nozari *et al*[47]	Pavri *et al*[38]	De *et al*[23]	Xu *et al*[41]	Ebrahimi *et al*[46]	Park *et al*[51]	Cheng *et al*[13]	Gao *et al*[49]
Country	Spain		France	Poland	United Kingdom	Turkey	Europe	Iran	United States	India	China	Iran	South Korea	China	China
n (%)	21		94	20	66	62	157	55	47	40	1360	21	67	145	471
Medical management	21 (100)		94 (100)	20 (100)	61 (92)	61 (98)	139 (89)	55 (100)	⩾ 40 (85)			12 (57)	32 (48)		
Medical management only (%)[1]	7 (33)						69 (54) 49 (71) alive				0 (0)			4 (3)	31 (7)
Interventional therapy		14 (67)			34 (52)[5]		88 (56) 72 (82) alive	10 (18)		23 (58)	1360 (100) 1318 alive	9 (43)		141 (97)	440 (93)
PTA	1 (5)		17 (18)			2 (3) in IVC	22 (14)			23 (58)		9 (43)	27 (40)	134 (92)	
Shunt operation		2 (10)			32 (48.5)[6]			2 (4)			330 (24)	3 (14)	4 (5.9)		
TIPS[2]		13 (62)	28 (30)	2 (10)		4 (6)	62 (39)[3]	2 (4)	21 (45)				3 (4.5)	1[2]	
Liver transplantation			15 (16)	10 (50)	36 (55)	0 (0)[8]	20[4] (13)	5 (9)	8 (17)		0 (0)			0 (0)[12] 2 (1)[12]	
Median follow-up (in months)	58[13]	38[13]	43	17	40-73[9]	25.2[12]	50		32	56	81.6		103	12	19
Survival	7 (100)	12 (86)	74 (79)	15 (75)			95 (73)	65 mo[10]	37 (79)						
At 1 yr				80%	88%	96%			37 (79)			67%[7]		99%	401 (94)
At 5 yr			74 (79)		56%		95 (73)			75%			86%		
Mortality										10[11]				2 (1)	

[1]Medical management includes anticoagulation, diuretics, and medical treatment of any underlying causes; [2]After PTA failed; [3]Of the 22 patients who initially were treated with PTA/thrombolytics, 12 subsequently underwent TIPS and 2 underwent OLT; [4]Among the 62 patients who underwent TIPS, 4 subsequently underwent OLT; [5]Patients who failed medical management (namely anticoagulation with heparin and warfarin and diuretics) as defined by persistent transaminitis, resistant ascites or worsening hepatic function) moved on to receive stenting, shunting, or TIPS; [6]50% success rate (16/32); [7]Per study, 7 out of 21 patients died before hospital discharge; [8]No patients underwent liver transplantations due to a lack of donor availability; [9]Median follow-up post liver transplantation was 40 mo and median follow-up of patients with MPN was 73 mo; [10]Mean survival time was 65 mo; [11]10 patients died by the 5-yr follow-up period; [12]At the end of the follow-up period, 2 patients were waiting to receive OLT from another hospital; [13]Mean, not median values provided. Interventional therapy includes both endovascular and surgical procedures. OLT: Orthotopic liver transplant; TIPS: Transjugular intrahepatic portosystemic shunt; PTA: Percutaneous transluminal angioplasty; BCS: Budd-Chiari syndrome; HVC: Hepatic vena cava; IVC: Inferior vena cava.

Differentiation between classical and HVC-BCS is important because it dictates what constitutes comprehensive and appropriate diagnostic strategies. Given the likelihood of multiple pro-thrombotic risk factors contributing to the development of classical BCS, recommendations for extensive routine work-up for multiple possible etiologies include testing for MPN; JAK2V617F mutation screening for MPN[42,45]; continued monitoring of JAK2-mutation-positive-patients for occult MPN[5,9,24,31]; further testing for TET2 mutation when the JAK2 screening is negative[32]; FVL mutation[28]; PT 20210A mutation; protein C and S deficiencies; AT deficiency; PAI-1 and MTHFRC677T mutations[24]. Since more than one thrombophilic condition often manifests in classical BCS patients, such an extensive work-up is appropriate, but recent data continues to suggest that those same recommendations may not be appropriate for HVC-BCS patients[24]. For instance, screening for the JAK2V617F mutation is important for classical BCS patients because it has been reported to be a better diagnostic test for MPN when compared to traditional hematologic tests[42]. The JAK2V617F mutation has consistently been found in a significant number of "idiopathic" cases of classical BCS (although this is not observed in "idiopathic" HVC-BCS). In a study of 41 classical BCS patients from England, the JAK2V617F mutation was detected in 58.5% of idiopathic BCS cases[32]. Furthermore, 93% of the patients who later developed latent MPN were positive for the mutation suggesting that the JAK2V617F mutation is a highly sensitive marker to detect overt or covert MPN[33]. Given the possible geographic distribution of classical and HVC-BCS in regions with limited healthcare resources, a clear delineation of standard of care would benefit patients and providers alike. Historically, it has been speculated that there is association between lower standards of living and HVC-BCS. However, a recent prospective study including 53 consecutive BCS patients from Western India found no association between socioeconomic status and location of hepatic venous outflow obstruction although, a correlation between living in mud houses and IVC membranous obstruction was observed[28]. Therefore, according to this review, balancing the costs of diagnostic work-up for numerous potential genetic or acquired pro-thrombotic factors

with the actual benefit the patient may gain should be BCS-type specific.

Treatment and prognosis of BCS depends on a few key factors: Acuity and severity of the symptoms, location and the extent of the obstruction, and etiology of the obstruction[24]. While anticoagulation (initially with heparin and chronically with warfarin) is the initial treatment of choice for both classical BCS and HVC-BCS patients[45], the expected response and course of therapy differs dramatically. Classical BCS patients often present with acute thrombosis of the hepatic veins. This rapid blockage of hepatic venous outflow precludes the ability to adapt *via* the development of collateral circulation. It is not surprising then that acute fulminant liver failure (with its sequelae) is more common among classical BCS patients, thus requiring shunt operations and liver transplantations more frequently than in HVC-BCS patients[13]. In contrast, HVC-BCS patients generally present with chronic symptoms that may lead to the transformation of an old thrombus into a fibrous, membranous obstruction[7,25]. Depending on the thickness and the extent of the obstruction, early interventional therapy (most commonly PTA with or without stent deployment), is very effective and thus more commonly utilized among HVC-BCS patients[13,46]. The thrombotic nature of obstruction observed in classical BCS may explain why these obstructions are more susceptible and responsive to medical management (namely anticoagulation) alone. As noted in two long-term follow up studies by Perelló *et al*[40] and Darwish Murad *et al*[24] (with median follow-ups of 58 and 17 mo respectively) of predominantly classical BCS patients, 33%-44% of patients that were maintained on medical management alone had good outcomes: 100% and 44% (at 12 mo), respectively. In both studies, very few classical BCS patients (5%-9%) required percutaneous recanalization. In HVC-BCS patients, the role of anticoagulation is often adjunctive and temporary; the use of warfarin before angioplasty can improve outcomes in patients with IVC obstruction[47]. Few HVC-BCS patients are managed with medical management alone because of previously reported poor outcomes[38]. In terms of the pathophysiology, Simonetto *et al*[48] recently used a murine model to demonstrate that hepatic venous outflow obstruction as seen in congestive heart failure or veno-occlusive disease led to liver fibrosis not *via* an inflammatory pathway, but *via* sinusoidal thrombosis and mechanical strain, while also showing that anticoagulation may have a beneficial effect in decreasing fibrosis. This aids our understanding of the mechanism by which BCS and HVC-BCS can result in fibrosis, and emphasizes the need for relief of obstruction for proper management. Given the different presentations and treatment courses of the two entities, it would be relevant to further study the pathophysiology of these conditions to better optimize management.

Factors that contribute poor prognosis in classical BCS include: Increasing age, cirrhosis at the time of diagnosis, chronic kidney disease, and portal vein thrombosis[25,38]. The Child-Pugh and MELD scores also play an unclear role in terms of practical management, while asymptomatic patients generally have better prognoses[45,49]. For HVC-BCS patients, factors that contribute to poor prognosis include the development of cirrhosis and HCC. Recent studies have suggested that the risk of developing HCC in HVC-BCS patients (unlike classical BCS patients) is directly attributable to the disease *vs* Hepatitis B or C infections[7]. Furthermore, the incidence of developing HCC in HVC-BCS patients is similar to those of cirrhotic patients[50,51]. These findings suggest that HVC-BCS patients, unlike classic BCS patients, should be routinely monitored for the development of HCC. Specific interventions to address and reduce the high pressure gradient in BCS patients may reduce the risk of HCC development.

In conclusion, clarification in the terminology describing hepatic venous outflow obstruction would enable both clinicians and investigators to identify patients with comparable signs and symptoms, thus enabling the execution of sound (randomized and controlled) and separate research studies on pathogenesis, therapy, and prognosis of what seems to be two different etiologies of Budd-Chiari syndrome. As summarized in this review, recent studies continue to support that classical and HVC-BCS have distinct demographics, characteristics, etiologies, therapeutic strategies, and prognoses. To address gaps in knowledge within classical BCS and HVC-BCS patients, these differences should be acknowledged and future research should be performed on these two conditions separately.

COMMENTS

Background

Budd-Chiari syndrome (BCS) encompasses a wide array of symptoms that are caused by hepatic venous outflow tract obstruction and has been known by many different names. While reviewing the recent literature, this paper delineates the difference between primary hepatic venous thrombosis and thrombosis of the inferior vena cava (IVC), which have both previously been referred to as BCS.

Research frontiers

With the influx of new studies examining the wide spectrum of BCS, there has been a growing argument for the separation of primary hepatic venous thrombosis (classical BCS) and thrombosis of the IVC at the level of the IVC (hepatic vena cava-BCS) given the difference in their etiology and management.

Innovations and breakthroughs

This paper supports the clarification of terminology used to describe hepatic venous outflow obstruction, which will help guide future research and allow for more specific treatment modalities for this condition.

Applications

The evidence presented helps clinicians to understand the difference in etiologies of this syndrome and their influence in the management of the separate entities of this condition.

Terminology

Classical BCS refers to primary hepatic venous thrombosis. HVC-BCS refers to thrombosis of the IVC at the level of the IVC.

Peer-review

This review is well organized and comprehensive, has a good clinical message about BCS, and should be of great interest to the readers.

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