Pérez-González *et al. Egyptian Liver Journal* (2022) 12:28
https://doi.org/10.1186/s43066-022-00192-1

Egyptian Liver Journal

ORIGINAL RESEARCH ARTICLE

Open Access

Budd-Chiari syndrome: epidemiological and clinical characteristics of a case series in Northwest Spain

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Abstract

Introduction: Budd-Chiari syndrome (BCS) is a rare vascular disease of the liver, characterised by occlusion of the venous outflow tract. Cancer, pyogenic liver infection, and prothrombotic haematological conditions are the most frequent causes of BCS. The treatment and prognosis of the disease are closely related to the underlying cause.

Methods: This is a retrospective case-series study performed in Spain, in a health area of around 523,000 inhabitants. Cases were identified in the discharge database of the hospital between 2000 and 2020. Epidemiological, clinical, therapeutic, and prognosis data were obtained from the patient medical records.

Results: A total of 15 cases were identified. Most of them were male patients ($n = 8$, 53.3%) with a median age of 52 years. The most common cause of BCS was cancer ($n = 6$, 40.0%) followed by liver abscesses ($n = 4$, 26.7%). The most frequent clinical course was subacute hepatitis ($n = 8$, 53.3%); 12 of the 15 patients (80%) received anticoagulant treatment, and interventional treatment was carried out in 4 patients (26.7%). Seven patients died within 6 months (46.7%), 6 of them due to progression of the underlying disease, most often cancer; 2 patients (13.3%) developed liver cirrhosis after BCS.

Discussion: The incidence of BCS was low but higher than in other European studies. In addition, this current research showed a different aetiology than previously described. The mortality rate was extremely high and closely related to the underlying disease. The involvement of classic prothrombotic haematological factors was less common than previously described.

Keywords: Budd-Chiari syndrome, Hepatic vein thrombosis, Low molecular weight heparin

Introduction

Budd-Chiari syndrome (BCS) is a vascular disease of the liver characterised by occlusion of the venous outflow tract [1]. This obstruction causes hepatic venous stasis and congestion, producing liver necrosis, hypoxic injury, and fibrosis. BCS can appear in various clinical courses. Firstly, sudden and complete obstruction venous hepatic flow may cause acute or even fulminant ischaemic hepatitis. A second possible clinical course is sub-acute hepatitis, especially in case of incomplete obstruction or cases of slow progression. Third, a smaller group of patients develop liver cirrhosis due to progressive fibrosis and chronic hepatocyte damage.

The incidence and prevalence of BCS is very low [2, 3]. A recent study carried out by Olivier-Hourmand et al. showed its incidence in France was 4.04 cases per million inhabitants [3] and a meta-analysis performed by Li et al. found a pooled annual incidence of 0.469 per million inhabitants [2]. However, we were unable to find any

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studies regarding the incidence or prevalence in Spain. Moreover, most research on BCS to date was conducted in Asian regions (e.g. China, India, etc.), and studies focusing on Western populations are still lacking [2].

Some authors have suggested that BCS should be classified as primary or secondary depending on the nature of the obstruction. Thus, BCS would be considered primary if the obstruction can be attributed to a venous alteration (thrombosis) [4] or as secondary if the obstruction was produced by compression from outside of the vessel such as in the case of tumours or abscesses. Primary BCS is closely related with several prothrombotic conditions such as myeloproliferative disorders, factor V Leiden mutations, protein C deficiency, antiphospholipid syndrome, paroxysmal nocturnal haemoglobinuria, or antithrombin deficiency [5] and a significant number of patients simultaneously have two or more prothrombotic conditions [5]. Secondary BCS is related to neoplasms and infections, such a hydatic cysts or liver abscess.

BCS is diagnosed based on non-invasive imaging such as Doppler ultrasonography (US), computed tomography (CT), or magnetic resonance imaging (MRI) [6], and the presentation on imaging may vary between the stages and clinical course of the disease. Complete occlusion or compression may be seen in acute BCS, while inverted venous flow or collateral venous flow might be present in cases of sub-acute and chronic BCS. Splenomegaly, ascites, and a non-homogeneous liver parenchyma may be detected in cases of chronic BCS. In addition, imaging techniques may reveal the cause of BCS, such as the presence of abdominal tumours or abscesses.

Treatment is based on systemic anticoagulation although other interventions might be necessary depending on the underlying cause. In the case of myeloproliferative disorders, specific treatment should be administered as soon as possible. Surgery may be required to drain purulent collections. Furthermore, cirrhotic patients must be screened for oesophageal varices and hepatocellular carcinoma [7]. Transjugular intrahepatic portosystemic stent-shunt (TIPS) should be considered in several circumstances, such as a complete venous obstruction or acute liver failure [8, 9].

Studies focusing on western populations are lacking, and so research to better understand the differential characteristics of BCS across the world is needed. Thus, the aim of this study was to describe a Spanish case series of BCS, analysing epidemiological, clinical, therapeutic, and prognosis characteristics.

Material and methods

This was a retrospective case-series study undertaken at the Alvaro Cunqueiro Hospital of Vigo, a third level hospital in Northwest Spain. According to the Spanish National Statistical Institute, the population in the health area of Vigo was 523,582 inhabitants in the year 2000. We searched for BCS cases registered in the discharge database of the hospital between the years 2000 and 2020, using code I82 from the International Statistical Classification of Diseases and Related Health Problems (ICD).

BCS was diagnosed by radiological studies (US, CT, or MRI), and epidemiological and clinical data were obtained from the patient medical records. Acute and subacute hepatitis were defined based on the symptoms at onset and in the absence of a pre-existing liver disease. Hepatitis was considered acute if the time between the onset of symptoms and the BCS diagnosis was fewer than 15 days. In contrast, hepatitis was considered subacute if this time was between 15 days and 6 months. Cirrhosis was defined by US, laboratory data (albumin, bilirubin, and prothrombin ratio), and clinical signs (ascites or encephalopathy).

Qualitative variables were expressed with numbers and percentages, while quantitative variables were expressed as the median and interquartile range. To compare the qualitative variables, we used Fisher exact tests. Mann–Whitney *U* tests were performed to compare the quantitative variables, with *p*-values lower than 0.05 being considered significant. Statistical analysis was performed with the Statistical Package for the Social Sciences software (version 22, IBM Corp., Armonk, NY, USA).

Results

A total of 15 BCS cases were identified between the years 2000 and 2020. The estimated incidence rate during the study period was 28.6 cases per million inhabitants, and the median age of the affected patients was 52 years (standard deviation = 20.9); these clinical data are summarised in Table 1. Eight patients (53.3%) were male, and 13 (86.7%) had at least one risk factor for BCS, with neoplasms being the most common (6 cases; 40%). The radiological exam most often performed was CT ($n = 12$; 80.0%) followed by US ($n = 5$; 33.3%) and MRI ($n = 4$; 26.7%). The right suprahepatic vein was the most often affected ($n = 4$; 26.7%) followed by the middle vein ($n = 2$; 13.3%) and left vein ($n = 1$; 6.7%). Two veins were simultaneously affected in 4 cases (26.7%; 2 cases of middle and left veins and 2 cases of middle and right veins). Finally, the three branches were simultaneously thrombosed in 4 patients (26.7%).

Liver abscess aetiology

A liver abscess was found in 4 cases (26.7%), and in 3 of 4 cases, the causative microorganism was also identified. In one case, a 49-year-old male was simultaneously diagnosed of BCS and a pyogenic liver abscess. He received parental antibiotics and systemic anticoagulation with

Table 1 Risk factors and clinical characteristics of the study population

Total number of patients	**15**
Sex, male, *n* (%)	8 (53.3%)
Age in years, median (IQR)	52 (39–75)
Active cancer,*n*(%)	**6 (40.0%)**
Colorectal cancer, *n* (%)	2 (13.3%)
Haematological malignancy, *n* (%)	2 (13.3%)
Hepatocarcinoma, *n* (%)	1 (6.7%)
Ovarian cancer, *n* (%)	1 (6.7%)
Liver abscess, *n* (%)	4 (26.7%)
Prior cirrhosis diagnosis, *n* (%)	2 (13.3%)
Paroxysmal nocturnal haemoglobinuria	1 (6.7%)
Factor V Leiden mutation, *n* (%)	1 (6.7%)
Antiphospholipid syndrome	1 (6.7%)
Clinical debut	
Acute hepatitis, *n* (%)	5 (33.3%)
Subacute hepatitis, *n* (%)	8 (53.3%)
Liver cirrhosis, *n* (%)	2 (13.3%)
Laboratory parameters at diagnosis	
Haemoglobin (g/dL), median (IQR)	11.6 (9.7–13.5)
Platelets ($\times 10^9$/L), median (IQR)	194 (105–226)
International normalised ratio	1.2 (1.1–1.4)
Fibrinogen (mg/dL), median (IQR)	438.5 (331.0–578.0)
Alanine aminotransferase, ALT, (UI/L), median (IQR)	38 (30.3–78.8)
Aspartate aminotransferase, AST (UI/L), median (IQR)	46 (32.0–85.0)
Albumin (mg/dL), median (IQR)	3.0 (2.7–3.6)
Total bilirubin (mg/dL), median (IQR)	1.1 (0.6–2.0)
Diagnostic test performed	
CT	12 (80.0%)
US-Doppler	5 (33.3%)
MRI	4 (26.7%)
Anatomic location	
Right suprahepatic vein	4 (26.7%)
Left, middle, and right suprahepatic veins	4 (26.7%)
Middle suprahepatic vein	2 (13.3%)
Middle and right suprahepatic veins	2 (13.3%)
Middle and left suprahepatic veins	2 (13.3%)
Left suprahepatic vein	1 (6.7%)

IQR, inter-quartile range; *CT*, computerised tomography; *US-Doppler*, Doppler ultrasound; *MRI*, magnetic resonance imaging

Table 2 Therapeutic and prognosis characteristics

Treatment characteristics	
Systemic anticoagulation,*n*(%)	**12 (80.0%)**
LMWH, *n* (%)	11 (73.3%)
Unfractionated heparin, *n* (%)	1 (6.7%)
Chemotherapy	5 (33.3%)
Interventional treatment	4 (26.7%)
Mechanical thrombectomy	2 (13.3%)
TIPS	2 (13.3%)
Outcomes	
Mortality at 6 months	7 (46.7%)
Progression of underlying disease	6 (40.0%)
Progression of cancer	4 (26.7%)
Progression of liver abscess	2 (13.3%)
Unknown cause of death	1 (6.7%)
Progression to cirrhosis	1 (6.7%)

LMWH, low molecular weight heparin; *TIPSS*, transjugular intrahepatic portosystemic shunt

good radiological evolution, and so the abscess was not punctured. In addition, peripheral blood cultures of samples collected from this patient prior to the administration of antibiotics were negative. In the other 3 cases, at least one microorganism was isolated by directly culturing samples from the abscess or peritoneal fluid. Two cases were caused by 2 or more species, including one caused by 2 *Candida* species. Finally, one patient developed a liver abscess due to a Gram-positive coccus, although the species could not be identified.

Prothrombotic conditions

Excluding cancer and infection, other prothrombotic conditions were found in 3 patients; these were a factor V Leiden mutation, paroxysmal nocturnal haemoglobinuria, antiphospholipid syndrome, and systemic lupus erythematosus.

Cancer-related BCS

A total of 6 patients (40%) were diagnosed of cancer, and colorectal neoplasm was the most common, followed by haematological malignancies (one case of leukaemia and another of multiple myeloma). Lastly, two more patients were diagnosed of cancer, a hepatocarcinoma and an ovarian cancer, respectively.

Treatment

The treatments administered are summarised in Table 2. Systemic anticoagulation was started in 12 patients (80%), of which 11 were treated with low molecular weight heparin (LMWH) and one with unfractionated heparin (UH). Two weeks after starting the LMWH, two patients changed from anticoagulation to anti-vitamin K. Three patients (20%) did not receive anticoagulation treatments, one because of a poor prognosis as the result of the underlying cause (advanced hepatocarcinoma). In the second case, only mechanical thrombectomy was performed. Finally, the third patient did not receive anticoagulation because BCS was discovered by coincidence and the medical team decided not to initiate

anticoagulation. In 2 (13.3%) cases, TIPS was performed in addition to the administration of LMWH treatment. No liver transplants were performed in any of the 15 patients.

Radiological interventions

A radiological intervention was performed in 4 patients (26.7%). In 2 cases, a local mechanical thrombectomy was carried out, and a TIPS was conducted in the other 2 patients. The epidemiological and clinical data are summarised in Table 3. Systemic anticoagulation was also prescribed in 3 of these 4 patients. In one case, only mechanical thrombectomy was performed without anticoagulation. Three of the 4 patients died despite the interventions; the cause of death was progression of a neoplasm in 2 cases and the worsening of an abscess in another case. The patient who survived was treated with LMWH plus TIPS.

Outcomes

Seven patients (46.7%) died within the first 28 days of the diagnosis, 5 because of progression of the underlying disease (4 neoplasms and 1 pyogenic abscess). One patient died as the result of acute liver failure (polycythaemia vera was suspected but could not be confirmed). Finally, an 84-year-old female diagnosed with liver cirrhosis died at home, but no cause was given on her medical records. A total of 8 patients survived the first year after the diagnosis of BCS. The causes of BCS among this group were a liver pyogenic abscess in 3 cases (one case was simultaneously diagnosed with colorectal cancer and a polymicrobial liver pyogenic abscess), prothrombotic conditions (one case each of paroxysmal nocturnal haemoglobinuria, a factor V Leiden mutation, and antiphospholipid syndrome), and 2 cases of cancer (one case each of ovarian and colorectal cancer). Finally, no risk factors were found in one case of a 27-year-old male; he developed cirrhosis during the follow-up but is currently alive.

Discussion

Here, we present a case series of BCS, a rare vascular disease of the liver. We found a low incidence rate of 28.6 cases per million inhabitants, which was still higher than that of other European studies [3, 10, 11] at 2–10 cases per million inhabitants [3, 10, 11]. Most of the information available in the academic literature to date comes from case reports or small cohort studies. In our series, cancer was present in 6 of 15 patients (40%), which was higher than previously reported. Most of the studies focused on primary BCS, excluding cases attributed to neoplasms. The relationship between neoplasms and BCS has been previously reported [12, 13], with BCS being related to both solid and haematological cancers. Cancer can cause BCS through various mechanisms, such as direct compression of the hepatic veins, metastases, vessel infiltration, or the induction of venous embolisms. In our series, 4 of the 6 cases of cancer-related BCS were attributed to solid neoplasms located in the abdomen. While hepatocarcinoma has previously been reported as a cause of BCS [14], we found no previous reports of ovarian cancer associated with BCS.

The second most common cause of BCS in our series was liver abscesses. Interestingly, the coexistence of portal vein thrombosis (PVT) and a liver abscess was relatively frequent [15], but BCS secondary to abdominal infections was rarely reported [16]. Only a few such cases have been described, and some of these were attributed to amoebic infections [17], although our case series did not include any of these cases. Amoebic infections, including liver abscesses, are rare in western countries, with most of the reported cases being from low-income regions [18]. Isolation of 2 or more microorganisms, including bacteria and fungi, is common in liver abscesses [19], while the presence of *Candida* spp. and other fungi have previously been reported as a rare cause of liver abscesses [20]. In our case series, two or more microorganisms were isolated from liver or peritoneal samples in 2 patients.

Lastly, prothrombotic factors rather than cancer or infection were detected in 3 patients. Paroxysmal nocturnal haemoglobinuria, a factor V Leiden mutation, and antiphospholipid syndrome have been identified as risk factors for several thrombotic diseases, including BCS [21, 22]. Of note, previous studies showed around a 25% prevalence of mutated factor V in BCS, while in this work, we found a prevalence of only 6.7% [23]. This could perhaps be explained by the distribution of the factor V mutation around the world. In Spain, the prevalence of this mutation in the general population is around 3.3% [24], while in other European countries such as Sweden, it exceeds 10%.

Regarding the treatment of BCS, most of patients received anticoagulation as the primary therapy. There are currently no ongoing clinical trials comparing BCS management options, and so, most information arises from observational studies and clinical experience. Anticoagulation with heparin seems to be the treatment of choice, although no clinical trials have compared UH to LMWH in this context [25]. In addition, no clinical trials have evaluated anti-vitamin K or direct oral anticoagulants in these patients. The second line of BCS management is treatment of the underlying cause. In our case series, 5 out of 6 patients with neoplasms received chemotherapy. Patients with hypercoagulable disorders rather than an infection should receive indefinite anticoagulation unless contraindicated.

Table 3 Main clinical characteristics of the study population

	Sex	Age	Risk factor	Course	Hb (g/dL)	Platelets ($x10^9$/L)	Fg (mg/dL)	Alb (g/dL)	TBIL (mg/dL)	Anticoagulation	Intervention	Outcome
1	Male	68	Suspected polycythaemia vera, not confirmed	Acute hepatitis	19.9	205	294	3.0	9.7	LMWH	TIPS	Died
2	Male	54	Multiple myeloma	Acute hepatitis	10.2	81	608	3.0	2.8	None	Mechanical thrombectomy	Died
3	Male	39	Paroxysmal nocturnal haemoglobinuria	Subacute hepatitis	9.7	66	427	NA	2.1	LMWH	TIPS	Survived
4	Male	21	Leukaemia	Acute hepatitis	15.8	196	301	4.2	1.1	UH	Mechanical thrombectomy	Died
5	Female	78	Hepatocarcinoma	Cirrhosis	12.5	105	325	2.9	0.8	None	None	Died
6	Female	84	Cirrhosis	Cirrhosis	9.6	119	335	2.4	1.4	LMWH[a]	None	Died
7	Female	43	Ovarian cancer	Acute hepatitis	9.3	206	511	2.7	1.1	LMWH	None	Survived
8	Female	73	Liver abscess	Subacute hepatitis	12.1	184	NA	3.3	0.6	LMWH	None	Survived
9	Male	27	Not identified	Subacute hepatitis	13.9	169	450	4.3	2.0	LMWH	None	Survived, developed cirrhosis
10	Female	39	Factor V Leiden mutation	Subacute hepatitis	13.5	226	407	4.6	0.4	None	None	Survived
11	Female	79	Liver abscess	Subacute hepatitis	10.2	464	333	3.3	1.7	LMWH	None	Died
12	Male	75	Colorectal cancer	Acute hepatitis	10.2	194	676	2.3	0.9	LMWH	None	Died
13	Female	29	Antiphospholipid syndrome and systemic lupus erythematosus	Subacute hepatitis	8.9	81	568	3.0	0.3	LMWH[a]	None	Survived
14	Male	51	Colorectal cancer and liver abscess	Subacute hepatitis	11.6	726	715	2.7	0.6	LMWH	None	Survived
15	Male	49	Liver abscess	Subacute hepatitis	12.4	299	465	3.4	0.7	LMWH	None	Survived

Hb, haemoglobin; *Fg*, fibrinogen; *Alb*, albumin; *TBIL*, total bilirubin; *LMWH*, low molecular weight heparin; *UF*, unfractionated heparin; *TIPSS*, transjugular intrahepatic portosystemic shunt

[a] Transition to acenocoumarin after 2 weeks of LMWH

BCS is related to liver cirrhosis through several mechanisms. Firstly, liver cirrhosis has been identified as a risk factor for venous thrombosis (e.g. BCS and portal vein thrombosis). Secondly, liver cirrhosis may develop after BCS as the result of chronic liver damage and fibrosis. In our series, 2 patients were previously diagnosed with liver cirrhosis and another 2 developed cirrhosis after the diagnosis of BCS. According to clinical guidelines, screening for hepatocarcinoma and oesophageal varices is mandatory in both settings [1].

Interventional therapy for BCS is also controversial. No clinical trials have compared different treatments for BCS and most of the data available to date has come from observational studies. The interventional approach has 2 major goals. Firstly is to restore the circulation through thrombosed veins using thrombolytics or by placing a stent. Secondly, in some selected cases, the placement of TIPS or shunts may reduce pressure on hepatic circulation. In our centre, two patients underwent a mechanical thrombectomy, although no clinical trials have yet compared this procedure with the use of thrombolytics. In contrast, the safety and efficacy of TIPS has been demonstrated in several observational cohorts. In our series, this procedure was conducted in 2 patients in combination with LWMH therapy. Finally, in some cirrhotic patients, liver transplant may be indicated, although none of the patients at our centre were referred to the liver transplant unit.

The mortality rate in the first 6 months post-diagnosis was remarkably high in these patients (46.7%) and was closely related to the underlying cause of the BCS. Case-series or cohorts focused on primary BCS found a mortality of between 10 and 20% [4]. However, the mortality rate was higher in secondary BCS, mostly because of the underlying disease [26]. In previous series, cancer-related BCS was less common than primary BCS [27–29] while in our study, secondary BCS was more frequent. Importantly, the incidence, mortality, and causes of BCS seem to vary in different geographical areas, probably in relation to patient age and genetic factors.

Conclusions

BCS had a low incidence in our health area, albeit at higher rates than reported in other European studies. This current case series study indicated a different pattern of risk factors for BCS, with secondary forms being more common than primary forms. Neoplasms and liver pyogenic abscesses were the most common causes of BCS and were more common than classic prothrombotic factors such as factor V Leiden mutations. Mortality rates among patients with BCS were high and were strongly related to the presence of advanced cancer.

Limitations

Our study had several limitations. Firstly, its retrospective design may have caused certain data from the patient medical records to be lost. Secondly, the incidence rate we report here could be due to the low sample size and case distribution. We found 3 cases of BCS each in 2012 and 2013, while none were detected between 2016 and 2020. In addition, this was a single-centre study in a hospital with no liver transplantation unit. All these factors could lead to overestimation of the BCS incidence rate. Finally, the sample size was small due to the low incidence of BCS, and this did not allow us to compare subpopulations, making several comparisons, including contrasting the differences between primary and secondary BCS, inaccurate.

Acknowledgements

In memoriam of Julio Montes Santiago, great physician, remarkable colleague, and inspirational source of several generations of Spanish practitioners.

Authors' contributions

Alexandre Pérez-González: conceived of the presented idea, writing—original draft. Ana Argibay: writing—review and editing. Rut Lorenzo-Castro: writing—review and editing. Ignacio Martín-Granizo: investigation, writing—review and editing. Alberto Rivera-Gallego: project administration. All authors discussed the results and contributed to the final manuscript. The authors read and approved the final manuscript.

Funding

This research did not receive any specific grants from any funding agencies in the public, commercial, or not-for-profit sectors. Alexandre Pérez, the principal investigator, was hired under a Río Hortega contract financed by the Instituto de Investigación Carlos III (ISCIII) with reference number CM20/00243.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by Ethics Committee of Pontevedra-Vigo-Ourense with reference number 2021/286. According to local and national regulations, informed consent was waived due to the retrospective design of the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Received: 10 January 2022 Accepted: 9 April 2022
Published online: 18 April 2022

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