World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i43.16236

World J Gastroenterol 2014 November 21; 20(43): 16236-16244
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

RETROSPECTIVE STUDY

Budd-Chiari syndrome: A single-center experience

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Received: April 5, 2014 Revised: May 30, 2014
Accepted: July 11, 2014
Published online: November 21, 2014

Abstract

AIM: To investigate challenges, risk factors, prognostic indicators, and treatment outcomes associated with Budd-Chiari syndrome (BCS) at a tertiary care center.

METHODS: A retrospective cohort study was conducted at the University of Pennsylvania in patients with a diagnosis of BCS or hepatic vein thrombosis. All patients receiving care at the University of Pennsylvania, and who had at least 2 clinical encounters in the University of Pennsylvania Health system from January 1, 2008 to September 10, 2013 were eligible for study inclusion. Data were extracted from the electronic medical record of each patient, and recorded in a secure Research Electronic Data Capture database. Logistic regression analyses were applied to identify predictors of outcome of liver transplant (LT) or death.

RESULTS: Between January 1, 2008 and September 10, 2013, forty-seven patients were identified. Median age was 42.4 years. Thirty-one (66.0%) were women. A majority were Caucasian (68.1%). At diagnosis, 43 (91.5%) patients had ascites, 27 (57.4%) patients had a hematologic disorder associated with a hypercoagulable state and 26 (55.3%) had cirrhosis. Forty (85.1%) patients were on anticoagulation (AC), 30 (63.8%) of whom were maintained on warfarin. Two patients (4.3%) underwent thrombolytic therapy. A transjugular intrahepatic portosystemic shunt (TIPS) was placed in 21 (44.7%) patients, 19 (90.5%) of whom were also on AC. Twenty-one (44.7%) received AC alone. Over a median of 974 d, 8 (17.0%) patients received LT, and 10 (21.3%) died. The median time from listing to death was 26 mo [interquartile range (IQR) = 16, 65)]. TIPS with AC was utilized more frequently in younger patients (P = 0.02). Age, cirrhosis and chronic kidney disease (CKD) were significant predictors of LT or death.

CONCLUSION: AC alone was employed as frequently as TIPS with AC, though the latter was used more frequently in younger patients with polycythemia vera. There were no significant differences in treatment outcome regardless of the therapeutic intervention employed. Significant predictors of poor prognosis included age, cirrhosis and CKD.

Key words: Budd-Chiari syndrome; Transjugular intrahepatic portosystemic shunt; Liver transplantation; Anticoagulation; Hepatic vein thrombosis

Core tip: Budd-Chiari syndrome (BCS) is a challenging disease with a spectrum of clinical manifestations. It is evident from our experience that this condition has heterogeneous causes. Once specific prognostic factors are considered, treatment courses should be determined on a case-by-case basis but are most consistently instituted in a stepwise fashion. Moreover, in certain patients with visible hepatic decompensation,

systemic anticoagulation may need to be fortified with portal decompression procedures such as transjugular intrahepatic portosystemic shunt earlier in the disease process. The liver transplant waitlist mortality was 15.6%; therefore, it is evident that BCS patients have high mortality despite being considered candidates for liver transplantation.

Pavri TM, Herbst A, Reddy R, Forde KA. Budd-Chiari syndrome: A single-center experience. *World J Gastroenterol* 2014; 20(43): 16236-16244 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i43/16236.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i43.16236

INTRODUCTION

Budd-Chiari syndrome (BCS) is characterized by occlusion of the hepatic venous outflow tract that may occur from the terminal branches of the hepatic venules to the level of the right atrium[1,2]. Regardless of the etiology of obstruction, the early stages of BCS are characterized by a reduction in outflow from the liver[1,3]. Consequently, venous stasis and congestion result in hypoxic liver injury. These mechanisms contribute to the development of hepatocyte necrosis in the centrilobular regions of the liver lobule, progressive centrilobular fibrosis, and ultimately, cirrhosis[4]. The pathophysiology of BCS is therefore consistent with the established clinical manifestations, which include ascites, abdominal pain, and tender hepatomegaly[5]. Unfortunately, though the pathophysiology of the condition is well understood and there are multiple therapeutic options including transjugular intrahepatic portosystemic shunt (TIPS) placement and liver transplantation (LT), BCS still results in excess morbidity and mortality.

The primary goals of therapy for BCS are to alleviate hepatic congestion and ameliorate liver injury and its sequelae[6,7]. The cornerstone of therapy is systemic anticoagulation (AC) and in select cases may include local thrombolytic therapy[1]. Other therapeutic modalities include insertion of a TIPS or surgical decompression of the portal system, both of which alleviate elevated hepatic sinusoidal pressure[8,9]. There is controversy surrounding the efficacy of systemic AC in the treatment of BCS, and it has been shown that this form of therapy must often be supplemented by other treatment modalities such as portosystemic shunting[10]. Additionally, the insertion of a TIPS appears to be a highly successful intervention, which may delay or eliminate the need for LT[11,12]. In a single European study, the insertion of a TIPS in symptomatic BCS patients was associated with low morbidity and mortality, while providing long-lasting resolution of the clinical manifestations of BCS and higher transplant-free survival[13]. It has been suggested that a stepwise approach to managing BCS is optimal[14]. AC and other medical therapies are recommended as first line treatment. While revascularization or placement of a TIPS are suggested if there is no response to medical therapy, LT is indicated as a "rescue" therapy, shortly after which AC should be instituted to prevent recurrent thrombosis[15]. Due to the heterogeneous nature of BCS progression, data in the literature support an individualized approach to treatment and encourage a selective, cautious approach to invasive procedures[16].

Identifiable predictors of prognosis after a diagnosis of BCS is established are also important in determining appropriate treatment strategies. Previously established indicators of prognosis include rapidity and extent of hepatic vein occlusion, severity of underlying liver disease, and presence of hepatic decompensation[1]. Additional prognostic factors include age, Child-Pugh (CP) score, presence of ascites, serum creatinine, and the presence of features indicating acute injury superimposed on chronic lesions at the time of diagnosis[17]. In order to better understand the current therapies employed and their associated outcomes, as well as other potential prognostic factors in BCS, a retrospective cohort study was undertaken in patients presenting to the University of Pennsylvania with a diagnosis of BCS. This study aimed to characterize a carefully selected cohort of BCS patients at a tertiary care center, to elucidate the risk factors for BCS, identify predictors of prognosis, and evaluate treatment response.

MATERIALS AND METHODS

All patients diagnosed with BCS or hepatic vein thrombosis, as determined by the inclusion of an International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code consistent with the diagnosis (453.0) in the electronic medical record, receiving their care at the University of Pennsylvania, and having at least 2 clinical encounters in the University of Pennsylvania Health system from January 1, 2008 to September 10, 2013 were eligible for study inclusion. All subjects were at least 18 years of age at the date of data collection. Subjects less than 18 years of age were excluded from the study due to lack of access to their electronic medical records. The Hospital of the University of Pennsylvania comprises an active hepatology practice, a large and experienced interventional radiology group, as well as a robust LT program, thus providing a fitting setting for this study.

In order to determine the treatment outcomes of patients who presented with BCS, an extensive chart review was performed for all potential subjects identified from the electronic medical record review. Data were collected and recorded on the following variables: (1) demographics including age, gender, and race; (2) BCS risk factors including hypercoagulable states (Factor V Leiden, protein C deficiency, protein S deficiency and presence of G20210A prothrombin gene mutation), hematologic disorders, malignancies and oral contraceptive exposure; (3) medical comorbidities; (4) laboratory data on the date of diagnosis and at the date closest to the date of data collection; (5) histology data from liver biopsy and/or

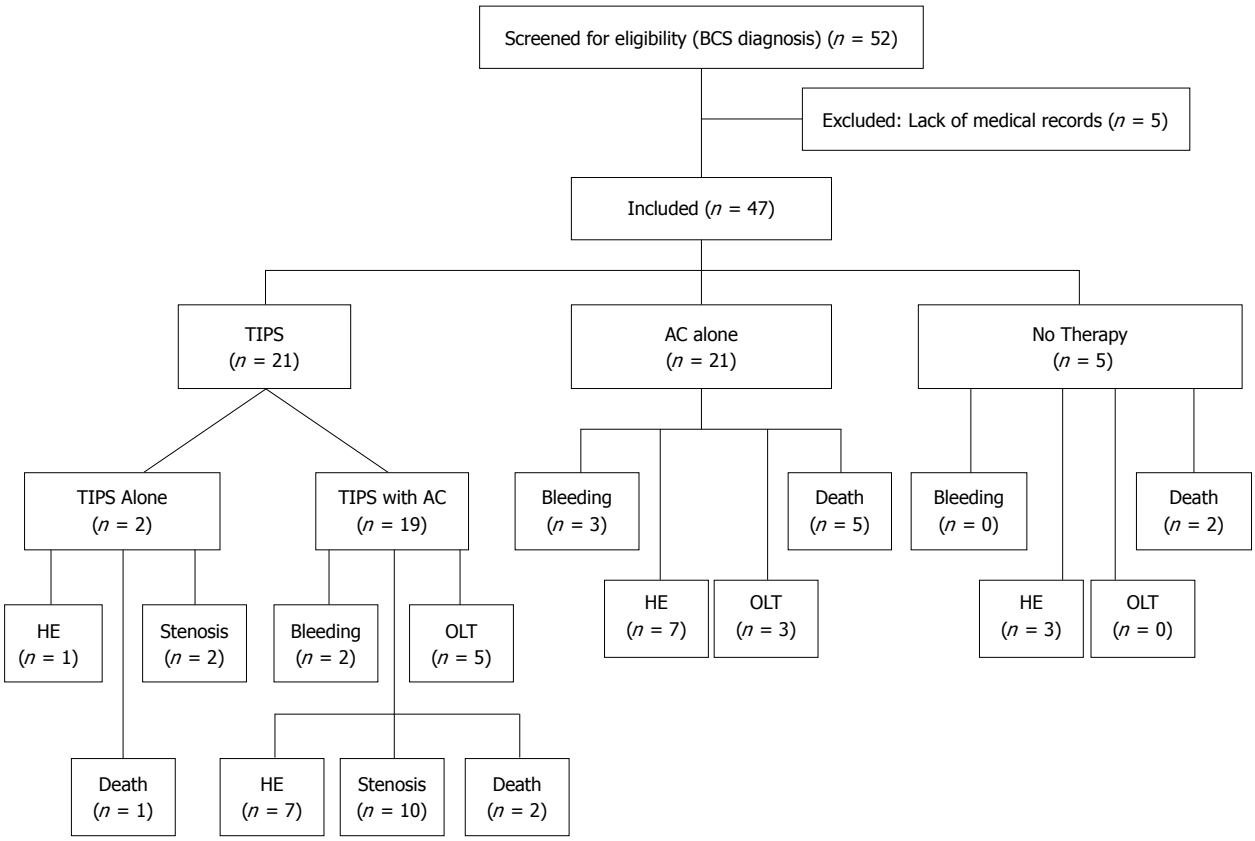

Figure 1 Treatment and outcomes. BCS: Budd-Chiari syndrome; TIPS: Transjugular intrahepatic portosystemic shunt; AC: Anticoagulation; HE: Hepatic encephalopathy; OLT: Orthotopic liver transplantation.

explant samples; (6) clinical data including symptoms associated with BCS on the date of diagnosis and at the date closest to the date of data collection; (7) treatment modality rendered; and (8) treatment outcomes including gastrointestinal bleeding, TIPS complications, LT and death.

Statistical analysis

Descriptive statistics were performed on the entire BCS cohort, including review of disease risk factors, clinical manifestations at presentation, treatment modalities employed and treatment outcomes observed. Those patients receiving AC alone were compared to those receiving TIPS or other types of portosystemic shunting to determine differences in their response to therapy. Additionally, predictors of outcome, as determined by need for LT, and/or death, were assessed. χ^2 analysis and Fishers exact testing as appropriate were used to compare categorical variables. *T*-tests and Wilcoxon rank sum testing were used to compare continuous variables. Logistic regression was used to identify predictors of LT or death. Kaplan-Meier curves were constructed to determine survival stratified by transplant status and by treatment modality employed. Log rank statistics were utilized to compare Kaplan-Meier curves. A P value of < 0.5 was the prespecified level of significance. Stata 12.1 (College Station, TX) was utilized for all statistical analyses. The protocol was approved by the Institutional Review Board at the University of Pennsylvania.

RESULTS

Forty-seven patients were identified as having a diagnosis of either BCS or hepatic vein thrombosis (Figure 1). The mean age of the cohort was 42.4 years [interquartile range (IQR) = 32.1, 52.1]; 31 (66.0%) were women. The racial distribution indicated a Caucasian majority (Table 1). The clinical manifestations and hematological risk factors present at diagnosis are described in Table 1. In our population of patients at the University of Pennsylvania, the prevalence of BCS exceeded population-based predictions, as an estimated 0.98% (47/4800) of patients who had clinic encounters during the study's 5-year period were diagnosed with BCS.

With regard to treatment, 40 (85.1%) patients were on systemic AC; 21 (52.5%) of whom were on heparin, 30 (75.0%) on warfarin, and 13 (32.5%) on both. Only 4 (8.5%) were on aspirin. Hydroxyurea, an antineoplastic drug that is used in the treatment of polycythemia vera (PV), was utilized in 13 (27.7%) patients. The patients' symptoms were generally better controlled when compared to the date of diagnosis. Regarding ascites, 43 had it at diagnosis, 29 had it post-treatment, and only 17 had the presence of ascites at both time points. While 27 patients were noted to have hepatomegaly at diagnosis, only 7 had it post-treatment, and 6 patients had it at both

Table 1 Clinical and laboratory characteristics *n* (%)

Clinical or laboratory feature	Entire cohort (*n* = 47)	TIPS with anticoagulation (*n* = 19)	Anticoagulation alone (*n* = 21)	*P* value
Age (yr) (Median, IQR)	42.4 (31.1, 52.1)	33.3 (29.7, 45.8)	46.9 (39.5, 57.3)	0.01
Gender				
Male	16 (34.0)	6 (31.6)	7 (33.3)	0.91
Race/Ethnicity				
African-American	11 (23.4)	5 (26.3)	3 (14.3)	0.69
White	32 (68.1)	12 (63.2)	16 (76.2)	
Other	4 (8.5)	2 (10.5)	2 (9.5)	
Hispanic/Latino	2 (4.3)	2 (10.5)	0 (0.0)	0.22
Comorbidities				
Alcohol	2 (4.3)	0 (0.0)	1 (4.8)	1.00
Anemia	9 (19.1)	2 (10.5)	6 (28.6)	0.24
Cerebrovascular accident	1 (2.1)	1 (5.3)	0 (0.0)	0.47
Coronary artery disease	2 (4.3)	1 (5.3)	1 (4.8)	1.00
Chronic kidney disease	10 (21.3)	6 (31.6)	2 (9.5)	0.12
Chronic obstructive pulmonary disease	0 (0.0)	0 (0.0)	0 (0.0)	
Congestive heart failure	1 (2.1)	0 (0.0)	1 (4.8)	1.00
Cirrhosis	26 (55.3)	13 (68.4)	8 (38.1)	0.05
Diabetes mellitus	8 (17.0)	1 (5.3)	4 (19.0)	0.34
Hypercholesterolemia	2 (4.3)	1 (5.3)	1 (4.8)	1.00
Peripheral vascular disease	0 (0.0)	0 (0.0)	0 (0.0)	
Risk factors				
Essential thrombocytosis	3 (6.4)	2 (10.5)	1 (4.8)	0.60
Factor V leiden mutation	4 (8.5)	1 (5.3)	2 (9.5)	1.00
Oral contraceptive use	2 (4.3)	2 (10.5)	0 (0.0)	0.23
Paroxysmal nocturnal hemoglobinuria	3 (6.5)	1 (5.3)	2 (9.5)	1.00
Protein C deficiency	2 (4.26)	1 (5.3)	1 (4.8)	1.00
Protein S deficiency	1 (2.1)	0 (0.0)	1 (4.8)	1.00
Polycythemia vera	14 (29.8)	9 (47.4)	4 (19.0)	0.09
Laboratory tests				
(Median, IQR) or (mean ± SD)				
Albumin (g/dL)	2.9 ± 0.5	3.1 ± 0.6	2.7 ± 0.5	0.07
Alkaline phosphatase (U/L)	131 (98, 161)	131 (98, 177)	116 (96, 160)	0.69
Alanine aminotransferase (IU/L)	59 (36, 119)	76 (55, 190)	52 (39, 87)	0.11
Aspartate aminotransferase (IU/L)	67 (42, 113)	78 (54, 221)	66 (37, 96)	0.33
Bilirubin, total (mg/dL)	1.6 (1.2, 2.9)	1.7 (1.2, 4.0)	1.5 (0.9, 2.1)	0.42
Creatinine (mg/dL)	0.9 (0.6, 1.3)	0.8 (0.6, 1.2)	0.9 (0.6, 1.4)	0.80
Hemoglobin (mg/dL)	13.4 ± 2.7	14.5 ± 2.1	12.3 ± 2.9	0.02
International normalized ratio	1.7 (1.3, 2.2)	1.7 (1.4, 2.2)	1.5 (1.2, 2.6)	0.66
Platelet count (THO/μL)	217 (97, 329)	262 (181, 376)	173 (80, 238)	0.05
Disease severity (Diagnosis)				
Child-Pugh (CP) score	9.2 ± 1.5	9.3 ± 1.3	8.9 ± 1.8	0.49
Model for end stage liver disease	17.1 ± 6.2	16.7 ± 4.9	18.9 ± 7.3	0.63
Rotterdam score				
I	22	10	10	1.00
II	0	0	0	
III	11	5	4	
Follow-up time (d) (Median, IQR)	974 (393, 2697)	1101 (386, 2697)	834 (190, 1791)	0.36

TIPS: Transjugular intrahepatic portosystemic shunt; IQR: Interquartile range.

times. For edema, 15 presented at diagnosis, 13 at the date of data collection, and 2 at both time points. Only 2 (4.3%) patients underwent thrombolytic therapy alone. In the cohort, 21 (44.7%) patients received a TIPS procedure and 8 (17.0%) received LT. Although all of the patients who received a TIPS presented with ascites, only 13 (61.9%) of the 21 patients who received TIPS had resolution of their ascites. Within the TIPS cohort (n = 21), variceal hemorrhage occurred in 6 (28.6%) patients prior to the intervention and in 1 (4.76%) post-TIPS. Stenosis was the major complication observed in this cohort, occurring in 12 (57.1%) of the patients who received a TIPS. Eleven (52.4%) patients had one or more TIPS revisions. Hepatic encephalopathy was seen in 38.1% of patients post-TIPS.

Ten (21.3%) patients died during a median follow-up of 974 d (IQR = 393, 2697). Of the patients who died during follow-up, 6 (60%) were male, 3 (30%) had a TIPS placed, 8 were evaluated for LT, 5 had been listed for transplantation but died while waiting, and none underwent LT. The median time from listing to death was 26 mo (IQR = 16, 65). The transplant-free survival rate was 94.4% at 1 year post-diagnosis, 74.8% at 3 years, and 69.5% at 5 years (Figure 2). Of those who were transplanted, all survived until the end of the follow-up period (Figure 2). The survival rates for the TIPS with AC co-

Table 2 Treatment and outcomes *n* (%)

Outcome	Entire cohort (*n* = 47)	TIPS with anticoagulation (*n* = 19)	Anticoagulation alone (*n* = 21)	*P* value
Anticoagulation	40 (85.1)	19 (100.0)	21 (100)	
Time to anticoagulation (d) (Median, IQR)	23 (0, 249)	28 (1, 91)	7 (0, 906)	0.92
TIPS	21 (44.7)	19 (100.0)	0 (0)	
Bleeding	5 (10.6)	2 (10.5)	3 (14.3)	1.00
Hepatic encephalopathy	18 (38.3)	7 (36.8)		
TIPS stenosis[1]	12 (57.1)	10 (52.6)		
Resolution of ascites[1]	13 (61.9)	12 (63.2)		
Variceal hemorrhage[1,2]	1 (4.76)	1 (5.26)		
Liver transplantation	8 (17.0)	5 (26.3)	3 (14.3)	0.44
Time to liver transplantation (d) (Median, IQR)	11101 (295, 2021)	947 (519, 1561)	1863 (295, 3628)	0.48
Death	10 (21.3)	2 (10.5)	5 (23.8)	0.41
Time to death (d) (Median, IQR)	811 (686, 1142)	1030 (919, 1142)	686 (107, 789)	0.05

[1]These outcomes represent those observed in the post-TIPS setting (at date of data collection); [2]For variceal hemorrhage, data were unknown for 6 patients in the entire cohort, and for 3 patients in the TIPS with AC cohort, in the post-TIPS setting. TIPS: Transjugular intrahepatic portosystemic shunt; IQR: Interquartile range; AC: Anticoagulation.

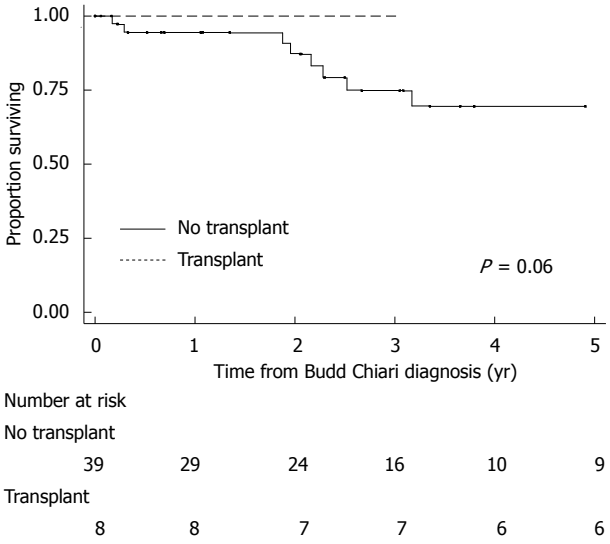

Figure 2 Kaplan-Meier estimate of mortality: Effect of transplant status.

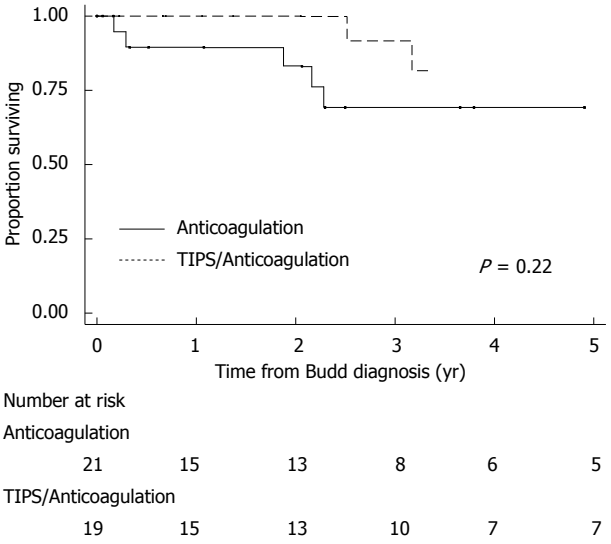

Figure 3 Kaplan-Meier estimate of mortality: Effect of transjugular intrahepatic portosystemic shunt + anticoagulation *vs* anticoagulation alone. TIPS: Transjugular intrahepatic portosystemic shunt.

hort were 100% at 1 year post-diagnosis, 91.7% at 3 years, and 81.5% at 5 years. The survival rates over time for the cohort treated with AC alone were lower: 89.5% at 1 year, and 69.2% at 3 and 5 years following diagnosis (Figure 3). These differences were not statistically significant.

The vast majority of patients who underwent a TIPS procedure were also on AC, while 44.7% of patients received AC alone (Table 2). Patients receiving TIPS and AC were compared to patients who received AC alone (Tables 1 and 2). In general, patients who had a TIPS placed and were on AC were significantly younger ($P = 0.02$) and tended to be enriched with PV ($P = 0.09$), reflecting underlying contributing factors or conditions associated with BCS (Table 1). There were no differences between treatment subgroups in the severity of liver disease at the time of diagnosis as determined by the CP or Model For End-Stage Liver Disease (MELD) scores. Additionally, there were no differences in time to institution of AC between groups. Of the 8 (17.0%) patients who required LT, 5 had a TIPS placed and 3 were on AC alone (Table 2). In univariable analysis, age, cirrhosis and the presence of chronic kidney disease (CKD) were significant predictors of LT or death (Table 3). These were found to be significant predictors of poor prognosis in multivariable analysis as well (Table 3). There was no significant difference in mortality in those undergoing TIPS with AC *vs* those on AC alone.

DISCUSSION

Our study validated previously recognized underlying risk factors associated with BCS, including various hypercoagulable states. Further, we evaluated predictors of poor outcome and assessed the effectiveness of current treat-

Table 3 Predictors of liver transplant and death

Predictor	Univariable odds ratio (95%CI)	Univariable *P* value	Multivariable odds ratio (95%CI)	Multivariable *P* value
Age	1.04 (1.00-1.09)	0.090	1.06 (1.00-1.12)	0.062
Ascites (Diagnosis)	1.96 (0.19-20.4)	0.570		
Chronic kidney Disease	10.80 (1.95-59.77)	0.006	7.67 (1.20-48.96)	0.031
CP score (Diagnosis)	0.79 (0.49-1.28)	0.339		
Cirrhosis	8.18 (1.92-34.84)	0.004	6.25 (1.19-32.72)	0.030
Creatinine (Diagnosis)	1.76 (0.60-5.14)	0.300		
MELD score	0.96 (0.85-1.08)	0.489		
TIPS Placement	0.95 (0.26-3.42)	0.935		

MELD: Model For End-Stage Liver Disease; TIPS: Transjugular intrahepatic portosystemic shunt; CP: Child-Pugh.

ment modalities employed in BCS. Established predisposing factors for BCS include hematologic and hepatic metabolic abnormalities, chronic myeloproliferative disorders, malignancies, and oral contraceptive use. In terms of underlying causes of BCS, prothrombotic disorders predominate in the West, whereas the etiology is often idiopathic or possibly even congenital in Asia[18,19]. In our cohort, we observed that polycythemia vera was the most common risk factor for hypercoagulability, predisposing nearly one third of our cohort to vascular thrombosis (Table 1). With respect to predictors of prognosis, more invasive therapy in the form of TIPS placement was not significantly associated with an outcome of either LT or death, though there was a trend towards a decreased rate of death in those treated with TIPS and AC when compared to AC alone. The time to institution of AC and the time to placement of TIPS were not shown to be predictive of prognosis. In multivariable analysis, increasing age, the presence of cirrhosis at diagnosis, and chronic kidney disease were found to be significantly associated with poor prognosis. Unfortunately, no other factors, such as bilirubin or markers of disease severity, were associated with outcome in this modern cohort. Previously suggested predictors of prognosis include age, CP score, MELD score, an established diagnosis of cirrhosis and presenting features including the presence of ascites and elevated creatinine[13,20].

Though patients were treated with a number of strategies, AC was employed prior to the institution of invasive therapies in more than 50% of cases, indicating a stepwise approach to treatment. Placement of a TIPS was applied more frequently in younger patients and in those with PV but did not appear to be utilized frequently in patients with more severe disease. When TIPS was combined with AC, time to death was lengthened when compared to AC alone. TIPS in the absence of AC was performed in only 2 patients, thus a comparison with this subgroup was not statistically feasible. Historically, TIPS has been recommended as a viable and effective treatment option for both management of portal hypertension and refractory ascites[21,22]. In terms of resolving ascites, a success rate of over 90% has been noted in the pretransplant population, irrespective of etiology of liver disease[23]. However, in the cohort described, relief of ascites post-TIPS only occurred in 61.9% of patients. We speculate that the therapeutic response to TIPS in BCS patients is limited by a variety of factors, such as underlying medical conditions, severity of liver dysfunction as defined by MELD score at the time of shunt placement, and technical challenges in placing a shunt in the presence of hepatic vein thrombosis. In theory, a successful TIPS is attainable in the majority of patients with BCS; however, previous studies have reported that the procedure is more straightforward in non-BCS patients with cirrhosis[20].

BCS is a rare condition, with a reported prevalence of approximately 0.13-0.36 patients per million per year in population-based and registry-based data[18]. However, current estimates of the prevalence of this disease are lacking. The moderately high prevalence of BCS we observed reflects the composition of patients at a tertiary care center, and underscores the fact that BCS patients require coordinated specialty care that may be difficult to obtain outside of tertiary care centers. The high mortality rate and low rate of transplantation seen in this cohort raise important concerns regarding waitlist mortality, contraindications for LT, and transplant-free survival rates (Tables 4 and 5). A 2008 international study by Garcia-Pagán *et al*[20] reported 1- and 5-year orthotopic liver transplantation (OLT)-free survival rates of 88% and 78%, respectively, in a cohort of 124 patients with BCS. In comparison, our cohort demonstrated 1- and 5-year OLT-free survival rates of 94.4% and 69.5%, respectively. In this cohort, the waitlist mortality was 15.6%; thus, it is evident that BCS patients have high mortality despite being considered candidates for LT. Moreover, of the 10 patients who died, half had contraindications to LT, such as metastatic cancer and coronary artery disease (Table 4).

The highly recommended stepwise treatment regimen for BCS involves AC, remediation of risk factors, diuretics and prophylaxis for complications of portal hypertension, followed by thrombolysis with angioplasty for venous stenosis if indicated, TIPS, and ultimately LT. This strategy has been associated with 5-year survival rates of nearly 70%[24,25]. A 2013 study by Fitsiori *et al*[13] showed that after placement of a TIPS 93% of BCS patients were symptom- and OLT-free throughout a mean follow-up of 38.1 mo. However, we did not demonstrate a reduction in need for LT after TIPS placement. This may have been in part due to our small sample size. The results suggest that the management and survival of

Table 4 Characteristics of patients who died after diagnosis of Budd-Chiari syndrome

Study ID	Age at death	Gender	Race	Ethnicity	Evaluated for LT? (Y/N)	Listed for LT? (Y/N)	Contraindication for LT? (Y/N) If "Yes," specify	Time from listing to death (mo)	LT? (Y/N)	Cause of death
1	49	F	Black or AA	Not hispanic or Latino	Y	Y	N	26	N	Unknown
2	61	M	White	Not hispanic or Latino	N	N	Y; HCC with extensive vascular invasion and lung metastasis	N/A	N	Unknown
3	49	M	White	Not hispanic or Latino	Y	Y	N	65	N	Metastatic colon cancer
4	59	M	White	Not hispanic or Latino	Y	N	Y; poor LT candidate due to ESRD, history of CAD, and kidney/pancreas transplant	N/A	N	Vertebral osteomyelitis of the lumbar spine, MRSA bacteremia
5	34	M	White	Not hispanic or Latino	Y	Y	Y; Testicular cancer	12	N	Metastatic testicular cancer
6	34	M	White	Not hispanic or Latino	Y	Y	N	72	N	Hypercapnic respiratory failure, pneumonia
7	67	F	Black or AA	Not hispanic or Latino	Y	N	N (in transplant evaluation stage at date of death)	N/A	N	Severe sepsis
8	52	F	Other	Not hispanic or Latino	Y	N	Y; HCC with secondary malignant neoplasm of the lung	N/A	N	Liver failure, metastatic HCC
9	42	F	White	Not hispanic or Latino	N	N	Y; Breast cancer	N/A	N	Metastatic breast cancer
10	69	M	White	Not hispanic or Latino	Y	Y	N	16	N	Renal failure, liver failure, possible sepsis

LT: Liver transplantation; AA: African American; HCC: Hepatocellular carcinoma; CAD: Coronary artery disease; ESRD: End-stage renal disease; MRSA: Methicillin-resistant Staphylococcus aureus; F: Female; M: Male; Y/N: Yes/No; N/A: Not available.

Table 5 Comparison of alive and deceased cohorts *n* (%)

	Patients who died (*n* = 10)	Patients who survived (*n* = 37)
Age at date of death (yr) (Median, IQR)	48.5 (41.3, 59.7)	39.5 (32.1, 48.8)
Gender		
Male	6 (60)	10 (27)
Female	4 (40)	27 (73)
Race/Ethnicity		
African-American	2 (20)	9 (24)
White	7 (70)	25 (68)
Other	1 (10)	3 (8.1)
Hispanic/Latino	0 (0)	2 (5.4)
Treatment and management		
Anticoagulation alone	5 (50)	16 (43)
TIPS alone	1 (10)	1 (2.7)
TIPS with AC	2 (20)	17 (46)
Evaluated for LT	8 (80)	19 (51)
Listed for LT	5 (50)	32 (86)
LT	0 (0)	8 (22)
No therapy	2 (20)	5 (14)

LT: Liver transplantation; AC: Anticoagulation; TIPS: Transjugular intrahepatic portosystemic shunt; IQR: Interquartile range.

patients with BCS could be ameliorated if treatment options such as LT were more easily and rapidly available to patients who do not benefit from or worsen clinically after TIPS placement. Despite access to optimal resources and clinical care, treatment challenges persist in the management of both pre- and post-transplant patients with BCS. The patients in our cohort who did not survive primarily had advanced liver disease in addition to underlying conditions that rendered them poor candidates for surgical and/or interventional radiology procedures, such as extrahepatic malignancies and end-stage renal disease.

This retrospective study demonstrated an alarmingly high mortality rate (21.3%) in a modern BCS cohort in the LT era. The results raise valid concerns about the management and treatment of BCS, a rare and understudied disease process. Lacking in the literature are prospective randomized controlled trials comparing treatment outcomes in BCS, leaving a reliance on clinical expertise and individualized treatment plans for effective management of this condition[26,27]. In view of the results of this and other studies, it is clear that BCS is a challenging disease with a spectrum of etiologies and clinical manifestations. Once specific prognostic factors are considered, treatment course should be determined on a case-by-case basis but is most consistently instituted in a stepwise fashion[28]. Moreover, in certain patients with visible hepatic decompensation, systemic AC may need to be fortified with more invasive treatment modalities, such as TIPS, earlier in the disease progression in order to allevi-

ate symptoms and restore synthetic function.

COMMENTS

Background

Budd-Chiari syndrome (BCS) is a rare vascular disorder of the liver, caused by an occlusion of the hepatic vein, which requires a stepwise approach to treatment. Many studies have investigated potential prognostic indicators, in the hopes of guiding treatment strategies for this understudied disease. However, due to the lack of prospective, multi-center randomized controlled trials, management remains a challenge.

Research frontiers

In the area of BCS research, the most pressing need is to determine independent indicators of prognosis, in order to stratify patients based on need for invasive treatments, and manage them accordingly. Now that the pathophysiology of BCS is better understood, the main objectives of research pertaining to the disorder are to enhance treatment outcomes and reduce morbidity and mortality associated with the syndrome.

Innovations and breakthroughs

As an observational, retrospective cohort study, the results corroborate the previously established predictors of prognosis in BCS patients. This single-center experience at a tertiary care center highlights the need for multi-center prospective studies examining risk factors and treatment outcomes for this disease.

Applications

This study's results indicate that further investigation is required in order to identify independent prognostic factors and treatment algorithms for this understudied disease. This study also showed that TIPS is a useful treatment modality for BCS patients, and it should be applied earlier in the disease progression.

Peer review

The authors examined risk factors and predictors of prognosis regarding the rare disorder of BCS. The analyzed series of forty-seven patients is representative of the commonly observed risk factors and outcomes of patients with this syndrome. The results suggest that invasive treatment modalities such as TIPS may have a constructive role early in the disease process in order to improve hepatic synthetic function and reduce the risk of need for liver transplantation and/or death.

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P- Reviewer: Ranieri G, Soares RLS **S- Editor**: Ding Y
L- Editor: A **E- Editor**: Ma S

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ISSN 1007-9327