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Budd-Chiari syndrome (BCS) is a rare disorder that is characterized by hepatic venous outflow obstruction. The aim of this study was to assess determinants of survival and to evaluate the effect of portosystemic shunting. In this international multicenter study, 237 patients with BCS, diagnosed between 1984 and 2001, were investigated. Univariate, multivariate, and time-dependent Cox regression analyses were performed. Overall survival at 1, 5, and 10 years was 82% (95% CI, 77%–87%), 69% (95% CI, 62%–76%), and 62% (95% CI, 54%–70%), respectively. Encephalopathy, ascites, prothrombin time, and bilirubin were independent determinants of survival. A prognostic classification combining these factors could identify three classes of patients (classes I–III). The 5-year survival rate was 89% (95% CI, 79%–99%) for class I, 74% (95% CI, 65%–83%) for class II, and 42% (95% CI, 28%–56%) for class III. Anticoagulants were administered to 72%; only for patients in class I was this associated with a trend toward improved survival (relative risk [RR], 0.14; 95% CI, 0.02–1.21). Portosystemic shunting was performed in 49% of the patients (n = 117); only for patients in class II, time-dependent analyses suggested an improved survival (RR, 0.63; 95% CI, 0.26–1.49). In conclusion, at the time of diagnosis, patients with BCS can be classified into good (I), intermediate (II), and poor (III) prognostic classes, according to simple baseline clinical and laboratory parameters. Our results suggest an improved survival after surgical portosystemic shunting for patients with an intermediate prognosis (class II). (HEPATOLOGY **2004;39:500–508.**)

Budd-Chiari syndrome (BCS) comprises a group of disorders characterized by hepatic venous outflow obstruction. The site of obstruction is either in the hepatic veins or the suprahepatic inferior vena cava.[1] BCS is a rare disorder that occurs predominantly in young adults and affects more women than men. Overall, 5-year survival varies from 50% to 80% in different series.[2–4]

Clinically, a classical triad of hepatomegaly, ascites, and abdominal pain is found in many patients.[2,5] However, the clinical course may differ markedly between patients. Some patients exhibit clinical signs of portal hypertension, such as variceal bleeding and refractory ascites with relatively intact hepatic function.[4,6] Others have liver failure, including hepatic encephalopathy, jaundice, and biochemical signs of severe hepatocellular dysfunction, at presentation. The most important cause of BCS in Western countries is thrombotic obstruction of the hepatic veins.[7] It is now believed that an inherited predisposition and an acquired thrombogenic stimulus may converge in the pathogenesis of BCS.[5,8] Main treatment options include the long-term use of anticoagulants, surgical portosystemic shunting (PSS),[9–11] transjugular intrahepatic portosystemic shunting (TIPS),[12] and orthotopic liver transplantation.[13] Other treatment methods are thrombolysis[14] and percutaneous hepatic vein balloon angioplasty.[15]

Abbreviations: BCS, Budd-Chiari syndrome; PSS, portosystemic shunting; TIPS, transjugular intrahepatic portosystemic shunting; ALT, alanine aminotransferase; INR, international normalized ratio; ULN, upper limits of normal value; RR, relative risk; CI, confidence interval.

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Received June 5, 2003; accepted November 21, 2003.

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Published online in Wiley InterScience (www.interscience.wiley.com).

DOI 10.1002/hep.20064

Several studies have been published on the cause, clinical manifestations, prognosis, and interventions in BCS.[4–6,9,10,14,16–20] However, the results vary widely, and unequivocal conclusions cannot be drawn. Little is known about factors that may be of relevant predictive value for the survival of BCS patients. Because of its rarity, most studies on BCS are case reports or contain limited numbers of patients. Small series are hampered by the lack of sufficient statistical power to control for baseline characteristics when survival or the effect of therapy is evaluated. Institutional experience and preferences as well as patient selection play a major role in the choice of treatment.[21] This creates a large degree of heterogeneity between study populations. Most studies on the effect of therapeutic interventions, in particular PSS, do not report selection criteria nor do they control for differences in baseline characteristics between patients who do or do not undergo PSS. Furthermore, many studies do not adjust for the time-interval between diagnosis and the procedure, which easily could lead to a response-time bias.

The aim of the present study was to identify independent prognostic markers for survival of BCS patients and to evaluate the effect of PSS on survival, controlled for these prognostic markers as well as for the time-interval between diagnosis and procedure. We conducted a large collaborative, multicenter study in which baseline characteristics of BCS patients were evaluated in multivariate models.

Patients and Methods

Patients. Patients were derived from the computerized diagnosis registration systems of all Dutch academic hospitals, the Mayo Clinic (Rochester, MN), Hôpital Beaujon (Clichy, France), and Hôpital Louis Mourier (AP-HP, Colombes, France). All participating hospitals serve as tertiary referral centers. Part of the study population from France was described previously by Zeitoun et al.[16] and from the Mayo Clinic by Tsiotos et al.[22] By means of a standardized review of the medical charts, all patients consecutively diagnosed with BCS between January 1984 and January 2001 were identified using the following key words: Budd-Chiari syndrome, hepatic outflow obstruction, hepatic vein thrombosis, vascular liver disease, hepatic vein, inferior vena cava, portal vein, and thrombosis. BCS was defined as hepatic venous outflow obstruction and its manifestations, regardless of the cause and regardless of the level of the obstruction from the small hepatic veins to the entrance of the inferior vena cava into the right atrium.[1] Hepatic outflow obstruction caused by congestive heart disease and sinusoidal obstruction syndrome (veno-occlusive disease) were considered separate disease entities. These patients were not included in our study. The diagnosis of BCS was established by Doppler ultrasound, computerized tomography, magnetic resonance imaging, or venography.[1] Histologic or nonspecific radiologic features suggestive of BCS were not considered diagnostic. Date of diagnosis was defined as the date of first evidence of BCS on radiologic imaging. Diagnosis could be made either at the participating center or at a smaller regional hospital before referral to the participating center. In both cases, the first available data were used as baseline data. Data on patient characteristics at the time of diagnosis, type of treatment during follow-up, and clinical outcome were collected from patient records in structured, uniform data forms. If necessary, patients or general physicians were approached to complete follow-up data. All patients were followed up from the date of diagnosis until death, orthotopic liver transplantation, study closure (January 1, 2001), or, in case of loss to follow-up, the date of last visit.

Clinical Assessment. The choice of variables to be used in the analyses was based on known prognostic factors in hepatologic disorders in general and BCS in particular, as well as on clinical experience with relevant factors.

The following characteristics, present at the time of diagnosis, were evaluated for their prognostic significance: age, sex, ascites, hepatomegaly, splenomegaly, variceal hemorrhage, hepatic encephalopathy, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, site of outflow obstruction (hepatic veins, vena cava inferior, or combination), portal vein thrombosis, liver cirrhosis, Child-Pugh score, prothrombin time, platelet count, and serum levels of bilirubin, albumin, alanine aminotransferase (ALT), alkaline phosphatase, sodium, creatinine, and hemoglobin. Ascites, hepatomegaly, and splenomegaly were assessed by abdominal ultrasonography or other radiographic methods. Presence of esophageal varices and variceal hemorrhage was confirmed by radiologic or endoscopic examination. Underlying myeloproliferative disorders were confirmed by bone marrow examination to include only overt forms.[23] Hepatic encephalopathy was evaluated by the Glasgow Coma Scale. The Child-Pugh score was calculated for those with complete data on degree of ascites and encephalopathy, the prothrombin time, and serum levels of bilirubin and albumin at the time of diagnosis ($n = 190$).

Therapeutic interventions during follow-up were assessed. For portosystemic shunting (including TIPS), the interval between the date of diagnosis and date of shunting was determined to allow time-dependent analysis of the effect on survival.

Statistical Analysis. Transplantation-free survival rates were calculated by means of the Kaplan-Meier method. Univariate survival analyses of the effect of patient characteristics were based on comparison of survival curves by the log-rank test, including trend analysis for ordered variables. Statistically significant variables, as well as other clinically relevant variables (age, site of obstruction, ALT levels) were introduced into a multivariate Cox's proportional hazards analysis, with stratification for country. By means of stepwise backward elimination, a final model was constructed comprising variables that were significantly and independently (*i.e.*, controlled for other variables) related to survival. Next, these prognostic markers were included as variables in a linear equation to create a BCS prognostic formula, in which the logarithm of the corresponding rate ratios (*i.e.*, the regression coefficients of the proportional hazards model) was used as a coefficient. Accordingly, all patients were classified into groups based on their prognostic scores, and survival curves were compared.

Because PSS was performed during the follow-up, the effect of portosystemic shunting on survival was analyzed in an extended Cox's proportional hazard model, in which shunting was included as a time-dependent covariate. This meant that at t = 0, no patient had received a PSS (all "not performed"). At the time a patient received PSS (t = x), this variable was scored as "performed." In this way, the period that patients had lived up to the moment of PSS was calculated as "nonshunted survival period" in the Cox analysis.

For all Cox models, the assumption of proportional hazards was investigated for each variable by studying the ln(-ln)plot and by entering portosystemic shunting as a time-dependent variable multiplied by the logarithm of time. All analyses were carried out in SPSS for Windows, version 10.1.1 (SPSS, Chicago, IL). The level of statistical significance was set at $P < .05$.

Table 1. Patient Characteristics at the Time of Diagnosis in 237 Patients With Budd-Chiari Syndrome

Characteristic	Obtained Data
Age (yrs)*	35 (13-76)
Male/female (%)	78/159 (33/67)
Myeloproliferative disorders (%)	54 (23)
Polycythemia rubra vera	45
Essential thrombocythemia	9
Paroxysmal nocturnal hemoglobinurea (%)	12 (5)
Clinical manifestations (%)	
Ascites	199 (84)
Hepatomegaly	181 (76)
Splenomegaly	120 (51)
Encephalopathy	24 (10)
Variceal bleeding	19 (8)
Site of outflow obstruction (%)	
Hepatic veins	147 (62)
Inferior vena cava	17 (7)
Combined hepatic veins and inferior vena cava	73 (31)
Membranous obstruction of inferior vena cava (%)	9 (4)
Portal vein obstruction	34 (14)
Serum levels	
Albumin (g/L)*	34 (13-57)
Bilirubin (μmol/L)*	28 (3-301)
Platelet count ($\times$10E6/L)*	265 (10-896)
ALT ($\times$ULN†)*	1.0 (0.1-86.7)
Alkaline phosphatase ($\times$ULN†)*	1.1 (0.3-16.3)
Hemoglobin (mmol/L)*	8.1 (3.5-13.0)
Sodium (mmol/L)*	137 (121-145)
Creatinin (μmol/L)*	80 (35-469)
Prothrombin time: INR $>$ 2.3 (%)‡	43 (26)
Cirrhosis at liver biopsy (%)§	11 (8)
Child Pugh classification	
Child A	45 (24)
Child B	103 (54)
Child C	42 (22)

Abbreviations: ALT, alanine aminotransferase; INR, international normalized ratio.

*Median (range).

†ULN, Upper limits of normal value; corrected for intercenter variation in normal values.

‡In the French sample, the Quick-time was used as a measure for the prothrombin time. A Quick time value between 100% and 44% was assumed to be equal to an INR $\leq$2.3. A Quick time less than 44% was equal to an INR $>$ 2.3.

§One hundred thirty-eight patients underwent a liver biopsy.

Results

Two hundred eighty-two patients with the diagnosis of BCS were identified in our institutions. Patients with hepatic outflow obstruction resulting from malignancy (n = 35), patients with BCS after liver transplantation (n = 3), and patients diagnosed at autopsy (n = 7) were excluded. This left a total of 237 patients who were eligible for analysis.

Patient characteristics at the time of diagnosis are shown in Table 1. Patient inclusion per year from 1984 until 2001 showed a homogeneous distribution (mean, 14; range, 7–23). The sample included 73 Dutch, 76 American, and 88 French patients with no statistically significant difference in survival; 5-year survival was 73% (95% CI, 62%–84%), 61% (95% CI, 50%–72%), and 72% (95% CI, 61%–83%), respectively. Between countries, the number of idiopathic cases, the surgical intervention rate, and reasons for exclusion were comparable. Median age was 35 years (range, 13–76 years), and 67% of the patients were female. In 54 patients (23%), an overt myeloproliferative disorder was present, including polycythemia rubra vera (n = 45) and essential thrombocytosis (n = 9). Paroxysmal nocturnal hemoglobinuria was present in 12 cases. Ascites (84%) and hepatomegaly (76%) were the most prevalent clinical symptoms. Eleven patients were asymptomatic. Median Child-Pugh score was 8 (range, 5–14). At liver biopsy (n = 138), evidence

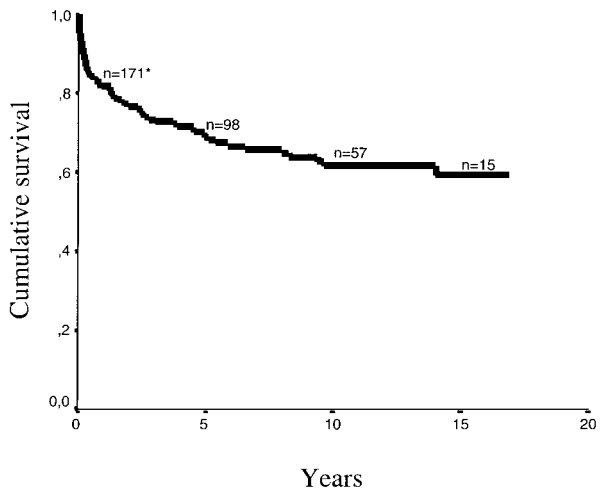

Fig. 1. Overall survival in 237 patients with Budd-Chiari syndrome. Survival rates at 1, 5, 10, and 15 years were 82% (95% CI, 77%–87%), 69% (95% CI, 62%–76%), 62% (95% CI, 54%–70%), and 59% (95% CI, 51%–68%), respectively. *Numbers represent patients at risk at 1, 5, 10, and 15 years, respectively.

for cirrhosis was found for 11 patients. The hepatic outflow obstruction was located in the hepatic veins in 62%, the inferior vena cava in 7%, and both in 31% of the cases. Thirty-four patients (14%) had combined BCS and extrahepatic portal vein thrombosis.

Survival. Follow-up ranged from 2 days to 203 months (median, 44 months). During follow-up, 52 patients (22%) died and 29 (12%) underwent orthotopic liver transplantation. Twenty patients were lost to follow-up. Causes of death were liver failure (n = 17), postoperative multiorgan failure (n = 12), sepsis (n = 4), newly developed malignancy (n = 2), cardiovascular disease (n = 3), cerebrovascular accident (n = 2), variceal bleeding (n = 1), and combinations (n = 3). For 8 patients, information on cause of death could not be retrieved. Survival rates were 82% (95% CI, 77%–87%), 69% (95% CI, 62%–76%), and 62% (95% CI, 54%–70%) at 1, 5, and 10 years, respectively (Fig. 1).

Prognostic Factors. Univariate analyses showed that ascites ($P = .03$), encephalopathy ($P < .001$), Child-Pugh score ($P < .001$), prothrombin time ($P < .001$), and serum levels of sodium ($P = .03$), creatinine ($P = .01$), albumin ($P = .02$), and bilirubin ($P < .001$) were significantly related to survival (Table 2).

These variables, as well as age, serum levels of ALT, and site of outflow obstruction, were introduced into a multivariate Cox regression analysis, stratified by country. Variables were selected by using a stepwise backward elimination technique. The final Cox model showed that encephalopathy ($P < .001$), ascites ($P = .08$), prothrombin time ($P = .02$), and serum levels of bilirubin ($P = .07$) were independent prognostic markers for survival for 205 patients with complete data on these variables (Table 3).

Several tests for interaction between these markers did not alter the results (data not shown). In addition, adding quadratic effects of continuous variables did not modify the results (data not shown).

The predictors obtained from the multivariate Cox's analysis were included in a linear prognostic formula in which the coefficients were equal to the regression coefficients of the proportional hazard model (Table 3). The equation was as follows:

$$1.27 \times \text{encephalopathy} + 1.04 \times \text{ascites} + 0.72 \times \text{prothrombin time} + 0.004 \times \text{bilirubin}.$$

Ascites and hepatic encephalopathy were scored as present (1) or absent (0) and prothrombin time as higher (1) or lower (0) than 2.3 INR. Bilirubin was included as a continuous variable for which the risk increased with 0.004 per μmol/L. The total score (*i.e.*, the sum of item scores) ranged from 0.02 to 4.03. Because the frequency distribution of total scores was not homogeneous, we decided to transform the linear equation into an index in which the upper and lower quarters of the frequency distribution were taken as the extremes. Consequently, three classes of patients could be distinguished: class I represented a total score between 0 and 1.1 (n = 55), class II between 1.1 and 1.5 (n = 95), and class III a total score of 1.5 and higher (n = 55). Five-year survival rates for the 205 patients with complete data were 89% (95% CI, 79%–99%) for class I, 74% (95% CI, 65%–83%) for class II, and 42% (95% CI, 28%–56%) for class III (Fig. 2).

Interventions. Overall, 171 patients of 237 (72%) were treated with anticoagulants. Thirty-nine patients (16%) were managed medically with diuretics, paracentesis, or both only for control of their ascites. Peritoneovenous shunting (Denver/Leveen) was performed in eight patients (3%), percutaneous transluminal angioplasty or stenting was performed in seven patients (3%), and surgical thrombectomy or angioplasty was performed in three patients (1%). One hundred seventeen patients (49%) underwent PSS during follow-up. In all participating centers, indications for PSS were refractory ascites, deterioration of liver function, or both. The distribution of PSS in the different classes of the prognostic model was as follows: 16 patients in class I (29%), 52 in class II (55%), and 33 in class III (60%). The type of PSS was mesocaval in 42 cases (36%), portocaval in 35 (30%), mesoatrial in 10 (9%), mesoinnominate in 6 (5%), splenorenal in 4 (3%), cavoatrial in 2 (1%), and portoatrial in 1 (1%). In 17 patients (15%), a TIPS procedure was performed. In 16 cases (14%), shunt failure occurred; this was followed by revision in seven patients (all after TIPS

Table 2. Univariate Survival Analyses of Characteristics at the Time of Diagnosis in 237 Patients With Budd-Chiari Syndrome

	Numbers	5-Year Survival (%)	95% CI	*P* Value		Numbers	5-Year Survival (%)	95% CI	*P* Value
Age (yrs)*					Cirrhosis at liver biopsy				
>35	121	69	60-78	.43	Present	11	37	5-69	.22
≤35	116	68	59-77		Absent	127	65	56-74	
Sex					Missing	99	78	68-87	
Male	78	66	55-77	.56	Albumin (g/L)*				
Female	159	70	62-78		<34	117	60	50-70	.02
Ascites					≥34	99	79	70-88	
Present	199	66	59-73	.03	Missing	21	70	47-93	
Absent	38	84	69-99		Bilirubin (μmol/L)*				
Hepatomegaly					>28	119	54	44-64	<.001
Present	181	70	63-77	.76	≤28	109	82	74-90	
Absent	47	65	51-79		Missing	9	§	§	
Missing	9	§	§		ALT (×ULN†)*				
Splenomegaly					>1.0	85	66	55-77	.08
Present	120	63	54-72	.17	≤1.0	108	75	66-84	
Absent	104	74	65-83		Missing	44	61	45-76	
Missing	13	§	§		Sodium (mmol/L)*				
Encephalopathy					≤137	113	64	55-73	.03
Present	24	27	6-48	<.001	>137	105	75	66-84	
Absent	213	73	66-80		Missing	19	57	28-87	
Variceal bleeding					Creatinin (μmol/L)*				
Present	19	71	49-93	.93	>80	119	60	50-70	.01
Absent	218	69	62-76		≤80	103	74	66-82	
Site of outflow obstruction					Missing	15	§	§	
Hepatic veins	147	63	54-72	.09	Prothrombin time‡				
Inferior vena cava	17	56	28-84		INR >2.3	167	42	25-59	<.001
Combined hepatic veins and inferior vena cava	73	82	73-91		INR ≤2.3	43	75	68-82	
					Missing	27	75	58-93	
Portal vein thrombosis					Child-Pugh classification				
Present	34	56	36-76	.42	Class A	45	89	79-99	<.001
Absent	203	71	40-78		Class B	103	67	57-77	
Myeloproliferative disorder					Class C	42	45	29-61	
Present	54	71	58-84	.92	Missing	47	74	60-88	
Absent	183	68	61-75						
Paroxysmal nocturnal hemoglobinurea									
Present	12	44	13-75	.18					
Absent	225	70	63-77						

NOTE. Comparison of Kaplan-Meier survival curves is based on log-rank testing.

*Cut-off points were based on the median.

†ULN, upper limits of normal value; corrected for intercenter variation in normal values.

‡In the French sample, the Quick-time was used as a measure for the prothrombin time. A Quick time value between 100% and 44% was assumed to be equal to an INR ≤2.3. A Quick time lower than 44% was equal to an INR > 2.3.

§Because of the small numbers in the missing category, no survival rates could be calculated.

procedure), a second surgical PSS in five patients, and other forms of therapy in four patients. One patient required a third revision of the TIPS. Of all shunted patients, 26 died (22%) and 10 (9%) underwent orthotopic liver transplantation, 5 of whom died. Of the nonshunted patients, 19 (16%) died and 19 (16%) were transplanted, 2 of whom died.

Benefit of Anticoagulation and Portosystemic Shunting. The use of anticoagulants to prevent further development of thrombosis did not yield a significant beneficial effect on survival in our total population (relative risk [RR], 1.05; 95% CI, 0.62–1.76). Results did not alter when the group on anticoagulants in combination with PSS was taken as a separate category (RR, 0.80; 95% CI, 0.61–1.05). Subanalysis of the effect of anticoagulants on survival for the three classes suggested improved survival for patients in class I (RR, 0.14; 95% CI, 0.02–1.21), but not for those in class II (RR, 0.88; 95%CI, 0.39–2.01) and class III (RR, 1.3; 95% CI, 0.50–3.04).

For the analyses on the efficacy of PSS, only the first shunting procedure was taken into account. One hundred six of the 117 shunted patients (91%) underwent a PSS procedure within the first year of diagnosis (median, 1 month; range, 0–132 months). We performed a time-

Table 3. Results of Multivariate Cox Regression Analysis for 205 Budd-Chiari Syndrome Patients With Complete Data

Variable	*P* Value	Risk Ratio	95% CI	Prognostic Classification Item-Score*
Encephalopathy	<.001			
Present		3.58	1.87-6.86	1.27
Absent				
Ascites	.08			
Present		2.83	0.87-9.22	1.04
Absent				
Prothrombin time	.02			
INR >2.3		2.05	1.13-3.70	0.72
INR ≤2.3				
Bilirubin (μmol/L)†	.07	1.004	1.00-1.01	0.004

*The prognostic classification is based on these four variables. The equation is as follows: 1.27 × encephalopathy + 1.04 × ascites + 0.72 × prothrombin time + 0.004 × bilirubin. The item-scores are equal to the natural logarithm of the corresponding risk ratios.

†Bilirubin was included as a continuous variable.

dependent Cox regression analysis in which, during the follow-up, patients were switched to the shunted group at the time of PSS. In the total population, the Cox assumption for proportional hazards was evaluated by investigating the consecutive effects of shunting within 1 month after diagnosis (n = 63), shunting between 1 to 6 months (n = 39), and shunting after 6 months (n = 15). As is shown in Table 4, mortality risk increased as PSS was performed later during follow-up. Therefore, analysis of the effect of PSS in the overall population was not feasible. When reevaluating the proportionality assumption for the three different prognostic classes, only class II patients exhibited an equal mortality risk of PSS after prolonged follow-up. In this class, time-dependent Cox analysis showed a tendency toward improved survival (RR, 0.63; 95% CI, 0.26–1.49), which is shown in Fig. 3.

Table 4. Survival in Relation to PSS (n = 117), According to the Interval Between Diagnosis and Shunting Using a Cox Analysis Testing for Proportionality

Interval Between Diagnosis and PSS (months)	*P* Value	Relative Risk	95% CI
<1 (n = 63)	.83	1.07	0.57-2.00
1-6 (n = 39)	.002	3.05	1.53-6.09
>6 (n = 15)	.009	4.15	1.42-12.12

A separate analysis assessing survival in relation to the type of shunt showed similar results for surgical shunting as for TIPS procedures (data not shown).

Discussion

There is a large variation in results of studies on BCS in terms of clinical presentation, effects of therapy, and survival. Because the prevalence of BCS is only approximately 1:100,000, controlled prospective studies are extremely difficult to perform. We carried out a multicenter cohort study in which data were obtained using standardized and predefined criteria. The present study reports on 237 patients newly diagnosed with nonmalignant BCS. This therefore is the largest cohort described until now. The large sample size enabled us to perform extensive survival analyses with control for possible confounding factors. Data were collected by using structured data forms and attempts were made to retrieve missing data on clinical outcome by contacting patients or their physicians. An international multicenter study like the

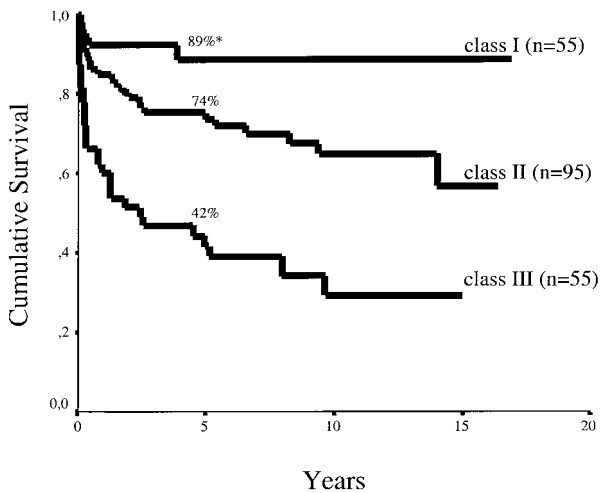

Fig. 2. Survival for class I (n = 55), class II (n = 95), and class III (n = 55), according to the prognostic classification. $P_{trend} < .0001$, $P_{class\ I\ vs.\ II} = .013$, $P_{class\ II\ vs.\ III} = .0001$. *5-year survival rates.

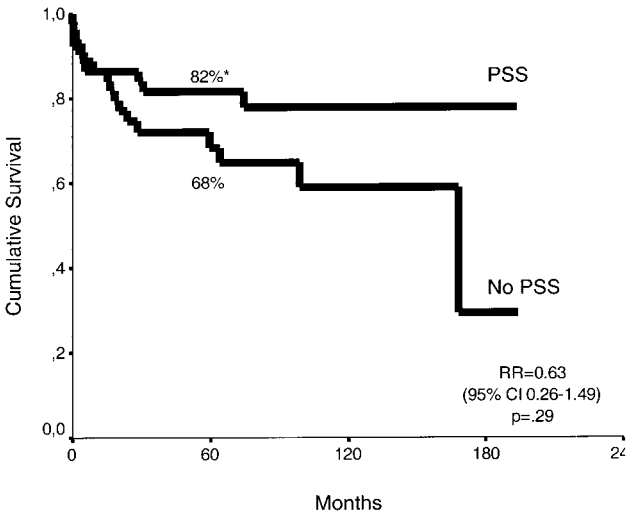

Fig. 3. Survival in class II (n = 95) according to PSS. At the time of shunting, patients were censored from the non-PSS group and included in the PSS group (t = 0 is time of shunting). During the follow-up, 52 patients (55%) underwent a PSS. *P* values are derived from the Cox's time-dependent regression analysis. *5-year survival rate.

present study could be hampered by crossnational variation in patient characteristics and institutional differences in therapeutic interventions. However, by introducing stratification for country in multivariate analyses, the effects of this variation as well as that of other possible confounding factors were minimized.

In the present study, 5-year survival was 69%, which is slightly higher than results from other series with long-term follow-up.[7,16] This could be because in recent years, improvement in availability and techniques of diagnostic tools has contributed to earlier recognition of BCS patients.[19,24] Furthermore, most of our patients were treated with anticoagulants, which, in addition to better identification of underlying prothrombotic factors,[22] has been reported to contribute to the improvement in prognosis of BCS.[16]

The aim of the present study was to assess prognostic determinants of survival in BCS patients. We identified four important factors that are independently associated with survival: encephalopathy, ascites, prothrombin time, and serum level of bilirubin. A prognostic classification, based on these factors, identified three classes of patients with good prognosis (class I; 5-year survival rate, 89%), intermediate prognosis (class II; 5-year survival rate, 74%), and poor prognosis (class III; 5-year survival rate, 42%).

Only two other studies used multivariate analysis for prognostic factors in BCS. The first was conducted in France among 120 BCS patients diagnosed between 1970 and 1992.[16] In that study, response of ascites to diuretics, the Child-Pugh score, age, and serum creatinine seemed to be of significant value for the prognosis of BCS. A prognostic index based on these factors dichotomized 85 patients into a good prognostic group (5-year survival, 95%) and a poor prognostic group (5-year survival, 62%), whereas overall 5-year survival was only 65%. In the second study, these results were evaluated in an independent sample of 69 patients.[25] The original index was extended with an additional factor, representing acute, chronic, or acute-on-chronic BCS. However, a recent review of an expert panel on BCS has stated that at the present time, no consensus has been reached on the classification into acute and chronic disease, because scientific arguments for this classification are still lacking.[1] Both prognostic studies also assessed the effect of PSS and did not show a beneficial effect on survival, even after control for prognostic class.

In comparison with these previous prognostic studies, the current study further optimizes prognostic modeling for BCS in several ways. First, our study includes a larger population of 237 patients, enabling analyses with more statistical power. In addition, it allowed the identification of three distinct prognostic groups, including a group with a considerably poor prognosis (class III; 5-year survival, 42%), for which liver transplantation may be the only life-saving procedure. Second, our study involves recently diagnosed patients (between 1984 and 2001) who were treated according to current therapeutic standards. Both previous studies did not evaluate the effect of TIPS, because only surgical shunting procedures were investigated. In our study, 17 patients underwent a TIPS procedure. Results of comparative analyses revealed no effect of type of shunting on survival. Other recent studies have demonstrated positive results of this new approach in terms of short-term survival.[12,13,26] TIPS is less invasive and therefore probably associated with a lower procedural mortality than PSS.[27] Long-term follow-up studies are needed to assess the place of TIPS in the treatment of BCS. Third, our prognostic classification includes simple clinical parameters that are easily available at diagnosis. In contrast, both previous classifications include response of ascites to treatment, thereby precluding its use at the time of diagnosis. Comparison of our index, using baseline variables only, with the previous index including a time- and treatment-dependent ascites score, therefore was not feasible. Fourth, the previous studies did not evaluate the effect of PSS in a time-dependent analysis. As is indicated by our results, the effect of shunting may not be equal over time, and appropriate control for this factor is needed to avoid response-time bias. In our time-dependent analysis, we found for class II a trend toward improved survival in patients with a PSS as compared with patients who were treated otherwise (RR, 0.63; 95% CI, 0.26–1.49). In fact, this class represented the largest subgroup (n = 95). These results suggest that for a reasonable group of patients, PSS may be an effective treatment. Other studies, mostly case series from surgical units, report on high survival rates after PSS with 5-year survival of 57%[11] to 94%.[9,10] However, most of these studies do not provide data on patient selection criteria, which play a major role in the long-term results of treatment,[21] nor do they take account of differences in time-point of shunting within the clinical course of patients.

Another well-known and widely used classification in liver diseases is the Child-Pugh score. Our prognostic classification, including encephalopathy, ascites, prothrombin time, and bilirubin, but not albumin, closely resembles this score. However, addition of albumin to this model showed that albumin did not have a significant impact on survival (data not shown). In addition, discriminative analyses (using the Akaike information criteria) demonstrated that our prognostic model was superior to the Child-Pugh score in predicting the outcome in patients with BCS (data not shown).

It is known that in BCS, a variety of histopathologic features can be found, ranging from centrilobular congestion and necrosis to venoportal or venocentric cirrhosis.[28] However, the prognostic role of histologic examination is probably limited. Previously, no significant association was found between findings at histologic examination and survival in 45 BCS patients.[3] This can be explained partly by the expected inhomogeneous distribution of liver cell lesions, which may lead to sampling errors of biopsy specimens. Histopathologic findings also were not predictive for early or late shunt patency and survival among patients undergoing PSS.[22] In this study, hepatocellular function and the time between onset of clinical symptoms and diagnosis, rather than results of histologic analysis, were suggested to be the crucial factors in choice of therapy. Given its relatively low predictive value and the fact that only limited numbers of liver biopsies have been performed at the time of diagnosis, the prognostic value of histologic analysis was not assessed in the present study.

Although a large randomized study has never been performed, nearly all studies suggest that the administration of anticoagulants will prevent extension of thrombosis and may induce recanalization.[4,24,29] In our study, most patients (72%) received anticoagulants. Overall, we could not detect a significant effect on survival when we compared patients treated with or without anticoagulants. Only for patients in class I was there a trend toward improved survival (RR, 0.14; 95% CI, 0.02–1.21). Because the reason to withhold anticoagulants often was unknown, this result should be interpreted with caution.

As others have stressed, orthotopic liver transplantation is an effective salvage procedure in the cases of acute fulminant or end-stage liver failure.[30–32] Without transplantation, these patients most likely would have had a poor outcome. For this reason, we have used transplantation-free survival as the outcome measure. Because the decision to perform liver transplantation might have been based on variables from our prognostic classification, we assessed whether our results would alter if only death was considered as endpoint. For this analysis, patients who received a liver transplantation (n = 29) were censored at time of intervention. We found that our prognostic classification remained a valuable tool to predict real survival ($P < .001$).

In conclusion, major prognostic factors for BCS are prothrombin time, serum bilirubin levels, and the presence of hepatic encephalopathy and ascites. A prognostic classification combining these factors divides patients into three groups with a good (class I), intermediate (class II), or poor (class III) prognosis. This classification, based on simple clinical and laboratory parameters, is a useful tool for assessment of disease severity at the time the diagnosis of BCS is established and before any form of therapy has been instituted. After adjustment for the time-interval between diagnosis and PSS, a trend toward improved survival was found for class II patients undergoing PSS. These results suggest that, in contrast to findings from other studies, shunting may well be valuable for a large subgroup of patients. Prospective studies are needed to confirm these results and to evaluate the effect of derivative therapy further in patients with BCS.

Acknowledgment: The authors thank other investigators who participated in this study: T.J. Tang (Erasmus Medical Center, Rotterdam), W.C.J. Hop (Erasmus Medical Center, Rotterdam), J. Meinardi (University Hospital, Groningen), S.H. van Uum (University Hospital St. Radboud-Nijmegen, currently University Hospital Saskatoon), R.A.F.M. Chamuleau (Academic Medical Center, Amsterdam), C.M.J. van Nieuwkerk (Free University, Amsterdam), S. Escolano (Groupe Hospitalier Pitié-Salpêtrière, Paris), and E. Rodgers (Mayo Clinic and Foundation). We also thank the reviewers for their valuable comments. Dr. H.L.A. Janssen is a Clinical Fellow of the Netherlands Organization for Scientific Research (NWO).

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