Long-term Outcome and Analysis of Dysfunction of Transjugular Intrahepatic Portosystemic Shunt Placement in Chronic Primary Budd-Chiari Syndrome[1]

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Purpose: To evaluate the long-term safety, technical success, and efficacy of transjugular intrahepatic portosystemic shunt (TIPS) in a series of patients with Budd-Chiari syndrome (BCS), and to determine the predictors of shunt dysfunction.

Materials and Methods: From 2004 to 2013, all patients with primary BCS referred for TIPS placement were included in the study. The primary and secondary technical success rates and the number and types of early (ie, before day 7) complications were noted. Factors associated with dysfunction were analyzed with uni- and multivariate analyses. Survival was analyzed with Kaplan-Meier curves.

Results: Fifty-four patients (34 women [63%]; mean age, 36 years ± 12 [standard deviation]) were included. Twenty-eight patients (52%) had myeloproliferative neoplasms. The mean Model for End-Stage Liver Disease score was 14.5 ± 4. The most frequent indication for TIPS was refractory ascites (50 of 54; 93%). Primary and secondary technical success rates were 93% and 98%, respectively. Early complications occurred in 17 patients (32%). After a mean follow-up of 56 months ± 41 (interquartile range, 22–92), 22 patients (42%) experienced at least one episode of TIPS dysfunction (median delay between administration of TIPS and first episode of dysfunction, 10.8 months). Cumulative 1-, 2-, 3-, 5-, and 10-year primary patency rates were 64%, 59%, 54%, 45%, and 45%, respectively. Dysfunction was associated with a myeloproliferative neoplasm (hazard ratio, 8.18; 95% confidence interval: 1.45, 46.18; $P = .017$), more than two initial stents (hazard ratio, 3.90; 95% confidence interval:1.16, 13.10; $P = .027$), and the occurrence of early complications (hazard ratio, 11.34; 95% confidence interval: 1.82, 70.69; $P = .009$). The 10-year survival rate was 76%.

Conclusion: TIPS placement in patients with chronic primary BCS was associated with a nonnegligible rate of early complications and required endovascular revision or revisions in 42% of patients. Nevertheless, secondary patency was close to 100%, and long-term survival was good.

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Primary Budd-Chiari syndrome (BCS) is a rare vascular disorder that involves hepatic venous outflow impairment at any level between the small hepatic veins and the right atrium (1,2). Primary forms of BCS are associated with prothrombotic states, mostly myeloproliferative neoplasms. Without treatment, BCS is a life-threatening condition, with mortality rates that range from 70% to 90% (1,2).

Over the past decade, treatment of BCS has been progressively standardized (1–3) on the basis of a step-wise algorithm to correct clinical manifestations such as ascites or variceal bleeding, prevent the extension of venous thrombosis, and re-establish venous drainage of the liver. First-line long-term anticoagulation therapy is required for all patients. In patients with persistent symptoms, endovascular procedures that include thrombolysis, percutaneous transluminal angioplasty, or stent placement are performed to restore venous patency whenever possible. When there are no hepatic vein stumps, or in case of unsuccessful endovascular stent placement, transjugular intrahepatic portosystemic shunt (TIPS) or direct intrahepatic portocaval shunts are used (4,5). TIPS were first used for the treatment of BCS in the early 1990s (6,7) with bare stents. However, over the past decade, stents coated with polytetrafluoroethylene have been used, which resulted in increased patency rates (8–12). This technique is now a very important treatment for BCS, and liver transplantation is only considered when endovascular procedures fail or symptoms persist (2,3).

Several case reports and case series (8,12–21) evaluated the short- and long-term outcome of BCS patients treated with TIPS, with only one published European multicentric study (10) (Table E1 [online]). Studies have shown that the long-term outcome is good, with low mortality rates. To that end, most studies (10,12,19) focused on factors associated with patient survival. Nevertheless, a major drawback of TIPS placement is stent dysfunction, resulting in recurrence of clinical symptoms or complications and requiring subsequent, and sometimes repeated, endovascular procedures with dilation, restenting, and recanalization by mechanical or pharmacologic thrombolysis to restore TIPS patency. Other than the type of stent that is used (ie, bare or covered), very little data exist on the risk factors of TIPS dysfunction (19). Therefore, the purpose of our study was to evaluate the long-term safety, technical success, and efficacy of TIPS in a series of patients with BCS and to determine the predictors of shunt dysfunction.

Advances in Knowledge

- Dysfunction was associated with a myeloproliferative neoplasm (hazard ratio, 8.18; 95% confidence interval:1.45, 46.18; P = .017), more than two initial stents (hazard ratio, 3.90; 95% confidence interval: 1.16, 13.10; P = .027), and the occurrence of early complications (hazard ratio, 11.34; 95% confidence interval: 1.82, 70.69; P = .009).
- After a mean follow-up of 56 months ± 41 (standard deviation), 22 patients (42%) experienced at least one episode of transjugular intrahepatic portosystemic shunt (TIPS) dysfunction (median delay between TIPS placement and the first dysfunction, 10.8 months).
- The cumulative 1-, 2-, 3-, 5-, and 10-year primary patency rates were 64%, 59%, 54%, 45%, and 45%, respectively.
- The cumulative 1-, 2-, 3-, 5-, and 10-year survival rates were 96%, 88%, 83%, 83%, and 76%, respectively.

Implications for Patient Care

- In patients with primary Budd-Chiari syndrome, TIPS placement is associated with a fairly high rate of early complications that require endovascular revision or revisions in a fairly high number of the patients.
- The secondary permeability rate after endovascular TIPS revision was close to 100%, and long-term survival was good.
- Patients with myeloproliferative neoplasms, early complication or complications, and more than two initial stents should be closely followed up.

Materials and Methods

Patients and Definitions

This retrospective study was performed between January 2004 and October 2013 in the radiology department of a tertiary referral hospital for vascular liver diseases. The study was approved by the local institutional review board, with a waiver of informed consent. All consecutive patients with primary BCS referred for a TIPS procedure were included.

Diagnosis of BCS was on the basis of criteria established by the European Network for Vascular Disorders of the Liver (En-Vie) and defined at the Baveno V Consensus meeting (22) as hepatic venous outflow obstruction at any level between the small hepatic veins and the junction between the inferior vena cava and the right atrium. BCS was diagnosed with a combination of color Doppler ultrasonography

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Abbreviations:
BCS = Budd-Chiari syndrome
TIPS = transjugular intrahepatic portosystemic shunt

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Guarantors of integrity of entire study, G.H., M.R., A.P., A.S., M.A.R., M.Z., V.V.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, G.H., M.R., A.P., A.S., M.A.R., P.E.R., D.V.; clinical studies, G.H., M.R., A.P., A.S., M.A.R., M.Z., D.V.; experimental studies, G.H., A.S., M.A.R.; statistical analysis, G.H., M.R., M.A.R.; and manuscript editing, G.H., M.R., M.A.R., M.Z., P.E.R., D.V., V.V.

Conflicts of interest are listed at the end of this article.

(US), computed tomography (CT), and/or magnetic resonance (MR) imaging. All patients were discussed during a multidisciplinary board meeting that included diagnostic and interventional radiologists, hepatic surgeons, pathologists, and hepatologists.

TIPS were indicated in patients who were ineligible for, or did not respond to, conservative medical treatment or venous recanalization (10,18). Our center followed the classic indications of TIPS in BCS: *(a)* variceal bleeding confirmed at endoscopy; *(b)* liver failure defined as an international normalized ratio greater than 1.5 and hepatic encephalopathy that had developed within 6 months before TIPS or hepatic dysfunction, defined as a persistent increase in total bilirubin level for 1 week with a maximum total bilirubin level greater than 3.0 mg/dL; and *(c)* refractory ascites defined as ascites that could not be treated with diuretics (23).

Baseline and follow-up demographic and clinical and laboratory data were obtained from medical records, including the etiologic cause of BCS, the history of BCS before TIPS, and a previous endovascular procedure, if performed. Clinical presentation (ie, acute, acute on chronic, or chronic) was noted (24). Acute features included acute right upper quadrant abdominal pain, ascites, jaundice, and serum alanine aminotransferase five or greater times the upper limit of normal values. Chronic features included previous hospitalization for unexplained symptoms that regressed spontaneously and that were later related to BCS, splenomegaly, or atrophy and/or hypertrophy of liver segments (24). The Child-Pugh score (25), the Model for End-Stage Liver Disease score (26), the BCS TIPS prognostic index (3), and the Rotterdam score (27) were all also calculated.

During the study period, a total of 54 patients (34 women; 63%) with chronic primary BCS referred for TIPS placement were included in our study. The median delay between the initial diagnosis of BCS and TIPS placement was 9 months (interquartile range, 2–23 months). Table 1 summarizes the baseline clinical and laboratory patient characteristics. The mean age of patients in our study cohort was 36 years ± 12 (standard deviation; age range, 15–67 years).

Table 1

Baseline Patient Characteristics

Parameter	Result
Patients (n = 54)	
Male	20 (37)
Female	34 (63)
Mean age*†	36 ± 12 (15–67)
Etiologic cause of BCS‡	
Myeloproliferative neoplasm	28 (52)
Coagulopathy disorders	14 (26)
Antiphospholipid syndrome	7 (13)
Paroxysmal nocturnal hemoglobinuria	3 (6)
Other	2 (4)
No cause	9 (17)
Clinical presentation§	
Acute/chronic	12 (22)
Subacute	1 (2)
Chronic	41 (76)
Previous treatment	
None	47 (87)
Yes	7 (13)
Mean time delay before TIPS creation (d)*	50 ± 80
Right hepatic vein angioplasty	2 (4)
Left hepatic vein angioplasty	2 (4)
Inferior vena cava angioplasty	2 (4)
Mesenteric caval shunt	1 (2)
Indication for TIPS placement‡	
Refractory ascites	50 (93)
Liver dysfunction	17 (31)
Upper GI bleeding	4 (7)
Hepatorenal syndrome	3 (6)
Major pleural effusion	4 (7)
Mesenteric caval shunt thrombosis	1 (2)
Failure of previous endovascular treatment	1 (2)
Obstruction of main hepatic veins	
One main hepatic vein obstructed	1 (2)
Two main hepatic veins obstructed	4 (7)
Three main hepatic veins obstructed	49 (91)
Associated IVC thrombosis	3 (6)
Portal vein thrombosis	
Main portal vein	3 (6)
Right portal vein	3 (6)
Left portal vein	1 (2)
Baseline biology	
AST > normal	42 (78)
Mean ULN†	2.5 (0.5–14.2)
ALT > normal	26 (48)
Mean ULN†	1.9 (0.4–17.1)
AP > normal	40 (74)
Mean ULN†	2.2 (0.6–7.2)
GGT > normal	50 (93)
Mean ULN†	3.8 (0.7–12.5)
Total bilirubin > N	46 (85)
Mean ULN†	2.9 (0.5–14.8)
Rotterdam Class	
1	3 (6)
2	41 (76)
3	10 (19)
Mean MELD*†	14.5 ± 4 (6–25)
Mean INR*†	1.46 ± 0.32 (1–3)
Mean platelet count 10^9/mL*†	2.19 ± 1.28 (0.31–5.96)
BCS TIPS PI	
Mean*†	4.4 ± 1.0 (2.7–7.2)
Mean Child-Pugh score*†	9.3 ± 1.6 (6–13)

Note.—Data in parentheses are percentages unless otherwise indicated. ALT = alanine aminotransferase, AP = alcalin phosphatase, AST = aspartate aminotransferase, GGT = γ gutamyl transferase, GI = gastrointestinal, INR = international normalized ratio, IVC = inferior vena cava, MELD = Model for End-Stage Liver Disease, PI = prognostic index , ULN = upper limit of normal values.

* Data are ± standard deviations.

† Data in parentheses are range.

‡ Several patients had multiple causes or TIPS indications.

§ According to the criteria established by the European Network for Vascular Disorders of the Liver (En-Vie) and defined at the Baveno V Consensus meeting.

Table 1 *(continues)*

TIPS Procedure

All patients underwent multiphasic contrast agent–enhanced CT examinations of the liver before TIPS placement to identify any focal liver masses that suggested hepatocellular carcinoma, to analyze morphologic changes in the liver, and to evaluate the passage of a TIPS needle through the caudate lobe to prevent extrahepatic puncture when the direct transcaval approach was considered. All procedures were performed with general anesthesia by transjugular approach by an experienced interventional radiologist (M.R., M.A.R., M.Z., or A.S., each with more than 10 years of experience in the field of liver diseases) with the assistance of a second operator (a senior resident, fellow, or interventional consultant). As part of the medical treatment of BCS, all patients received anticoagulation therapy before the procedure. This was stopped during the procedure, with a target international normalized ratio of less than 2. The procedures were performed with fluoroscopic and US guidance. US guidance is routinely used in our department for TIPS procedures because it offers excellent real-time control of the puncture site and needle progression. This is even more important in patients with BCS because most punctures are performed by a transcaval approach and most livers show major morphologic changes (eg, segment I hypertrophy or caval compression).

Intraabdominal fluid drainage was conducted before the procedure if ascites or pleural effusion was abundant. After introduction of a 10-F sheath into the inferior vena cava, initial cavography was performed to assess the presence of thrombosis or compression of the inferior vena cava. Selective catheterization of the hepatic veins remnants was systematically attempted with 4-F or 5-F catheters to confirm occlusion of the hepatic veins and localize the stumps. When the segment of a hepatic vein proximal to the inferior vena cava or a large collateral was viewed, the puncture was performed by using this vein. In the absence of a residual hepatic vein or in case of a so-called spider web appearance, the transcaval approach was chosen.

Punctures were performed by using a transjugular liver access set (Rösch-Uchida; Cook Medical, Bloomington, Ind). Portal venography was then performed. The intrahepatic tract was dilated with a balloon catheter that was 8 mm in diameter (Mustang; Boston Scientific, Natick, Mass). Stents were then deployed to cover the entire intrahepatic tract and were then dilated with a balloon catheter that was 10 mm in diameter (Mustang; Boston Scientific). From 2004 to 2005, the TIPS procedure was performed with both uncovered and covered self-expanding stents (Wallstent and Wallgraft, Boston Scientific; Fluency, Bard Incorporated, Karlsruhe, Germany). An uncovered stent was deployed to cover the entire tract, with the distal portion of the stent placed in the main portal vein. A second covered stent was then placed inside the first one via an 11-F sheath to cover the intraparenchymal portion of the tract. This stent combination accounted for one stent in our analysis. After 2005, the TIPS procedure was performed with expanded polytetrafluoroethylene-covered self-expanding nitinol stent grafts (Viatorr; W. L. Gore and Associates, Flagstaff, Ariz). Therefore, none of the patients was treated with bare stents alone. Stents were 10 mm in diameter and between 40 and 100 mm in length depending on the patient's anatomy and the length of the tract, measured by a graduated pigtail catheter. When the first stent did not cover the entire tract between the inferior vena cava (or the hepatic stump) and the portal vein, additional stents were deployed to increase the total length of the TIPS. The mean hepatic venous portal gradient was calculated by measuring inferior vena cava and portal vein pressures before and after TIPS placement in all patients. Postoperative low-molecular-weight heparin (ie, 8000–12 000 units twice a day on the basis of patient weight) was administered until the patient was clinically stable and TIPS were shown to be patent at follow-up US on day 5–7. Warfarin was then prescribed to all patients and the international normalized ratio was monitored monthly, with a target value between 2 and 3.

Primary technical success was defined as satisfactory TIPS placement with a final hepatic venous portal gradient that was less than 12 mm Hg after a first attempt. A second attempt was systematically made in case the first procedure failed, and success corresponded to secondary technical success. Complications were recorded in all patients and they corresponded to any adverse events that occurred either during (periprocedural complication) or up to 7 days (early complication) after the procedure. Patients underwent regular follow-up color Doppler US imaging during their hospital stay (days 1, 3, and 5–7) and at specific intervals (1, 3, 6, and 12 months after TIPS and then yearly thereafter or whenever symptoms recurred).

Follow-up and TIPS Revisions

Patients were followed up until death, the end of the study period (December 15, 2014), or the date of the last visit if the patient was lost to follow-up. Follow-up data were obtained from the medical records or by a telephone interview of the patients or their family members when necessary (G.H. and M.R.).

TIPS revision was planned in the presence of any evidence of shunt dysfunction: *(a)* absence of flow in the shunt at color Doppler US imaging or combined velocity criteria (peak intrashunt velocity, ≥250 cm/sec; maximum velocity in the portal third of the shunt, ≤50 cm/sec; or maximum portal vein velocity ≤ two-thirds of the baseline value) (28) or hepatofugal to hepatopetal flow in the intrahepatic portal branches; *(b)* recurrence or new occurrence of variceal bleeding; and *(c)* recurrence or new occurrence of ascites. These cases were all confirmed by portography with pressure measurements. Shunt dysfunction was defined as shunt stenosis greater than 50% and/or portosystemic pressure gradient greater than 12 mm Hg. The cause and number of TIPS revisions during the study period were noted for each patient. For

each revision, the type of procedure (ie, thromboaspiration, local thrombolysis, angioplasty, or need for additional stent placement) and the delay between TIPS placement and revision or between two revisions were noted. Survival time corresponded to the delay between the date of TIPS procedure and death, the end of the study period, or the most recent visit. Primary patency time corresponded to the delay between TIPS placement and the need for the first TIPS revision.

Statistical Analysis

Quantitative and qualitative variables were presented as medians and ranges or means ± standard errors with the range and numbers with percentages, respectively. Quantitative and qualitative variables were compared by using an independent sample *t* test or a one-way analysis of variance and the χ^2 or Fisher exact test, respectively. The cumulative rates of freedom from shunt dysfunction and of being alive were assessed with Kaplan-Meier curves. If patients underwent liver transplantation, survival rates were censored at the date of liver transplantation. A two-tailed *P* value less than .05 was considered to indicate statistical significance. All statistical analyses were performed by using statistical software (SPSS 20.0; SPSS, Chicago, Ill).

Results

The main etiologic causes of BCS were myeloproliferative neoplasms (28 of 54; 52%), coagulation disorders (14 of 54; 26%), antiphospholipid syndrome (seven of 54; 13%), and paroxysmal nocturnal hemoglobinuria (three of 54; 6%). Most patients presented with chronic (41 of 54; 76%) or acute on chronic (12 of 54; 22%) BCS.

Mean baseline Model for End-Stage Liver Disease, Child-Pugh, and BCS TIPS prognostic index scores were 14.5 ± 4 (range, 6–25), 9.3 ± 1.6 (range, 6–13), and 4.4 ± 1.0 (range, 2.7–7.2), respectively, with three (6%), 41 (76%), and 10 (19%) of 54 patients with Rotterdam class 1, 2, and 3, respectively. At baseline imaging, the three hepatic veins were completely obstructed in 49 patients (91%), and three patients (6%) had associated inferior vena cava thrombosis.

The main indication for TIPS placement was refractory ascites (50 of 54; 93%). Seven of the 54 patients (13%) underwent previous treatment, including hepatic vein angioplasty (*n* = 6) and surgical mesenteric caval shunts (*n* = 1). The mean interval between the previous treatment and TIPS placement was 50 days ± 80.

TIPS Procedure and Early Complications

Table 2 summarizes the TIPS procedure details and early complications.

TIPS placement was technically successful in 50 of 54 patients after a first attempt (primary technical success rate, 93%) (Fig 1). In the four remaining patients, another attempt was made and was successful in three patients, which led to a secondary technical success rate of 98% (53 of 54). In the remaining patient, TIPS placement was a failure, and the patient underwent successful emergency liver transplantation. The shunt was created from the inferior vena cava or one of the hepatic vein remnants in 49 (92%) and four (8%) patients, respectively. The puncture was made in the right, main, and left portal vein in 40 (75%), eight (15%), and five (10%) of the patients, respectively. Most TIPS were placed by using self-expanding stents (W. L. Gore and Associates) (*n* = 48; 91%). Respectively, one, two, three, and four stents were used to complete the TIPS procedure in 19 (36%), 26 (49%), seven (13%), and one (2%) patients. The hepatic venous portal gradient decreased from a mean 21.4 mm Hg ± 6.7 to 6.7 mm Hg ± 3.8. No portosystemic venous collaterals underwent embolization during the procedures.

Periprocedural complications occurred in 14 patients (26%) and included inadvertent biliary puncture (*n* = 6), intraperitoneal bleeding (*n* = 3 with one with acute hemorrhagic shock), acute TIPS thrombosis (*n* = 1), transient and marked bradycardia (*n* = 1), and transient respiratory distress (*n* = 3). All complications were

Table 2

Details of the TIPS Procedure and Early Complications

Parameter	Result
Technical success	
Primary	50 (93)
Secondary	53 (98)
No. of stents at first TIPS placement*	
1	19 (36)
2	26 (49)
3	7 (13)
4	1 (2)
Type of stents	
Gore stents with or without additional stents	48 (91)
Combination of non-Gore stents	6 (9)
Mean HVPG (mm Hg)†	
Before procedure	21.4 ± 6.7
After procedure	6.7 ± 3.8
Periprocedural complications	
None	40 (74)
Minor complications	
Acute TIPS thrombosis‡	1 (2)
Bleeding	3 (6)
Bradycardia	1 (2)
Respiratory distress	3 (6)
Biliary puncture	6 (11)
Early complication§	17 (32)
Minor complications	
Bleeding	7 (14)
Pleural effusion	1 (2)
Encephalopathy	1 (2)
Kidney infection	1 (2)
Ascites superinfection	1 (2)
Cardiac dysfunction	1 (2)
Major complications	
Acute TIPS thrombosis	6 (11)
Stent placement	2 (4)
Angioplasty	2 (4)
Thromboaspiration	1 (2)
In situ thrombolysis	2 (4)
Malposition	3 (6)

Note.—Data in parentheses are percentages. Early complications were those that occurred less than 7 days after the procedure. HVPG = hepatic venous portal gradient.

* One stent refers here to either one covered and bare stent (Viatorr) or to the combination of a bare stent with a second covered stent deployed within.

† Data are ± standard deviation.

‡ Successfully managed during the procedure.

§ Patients could have more than one complication.

Figure 1

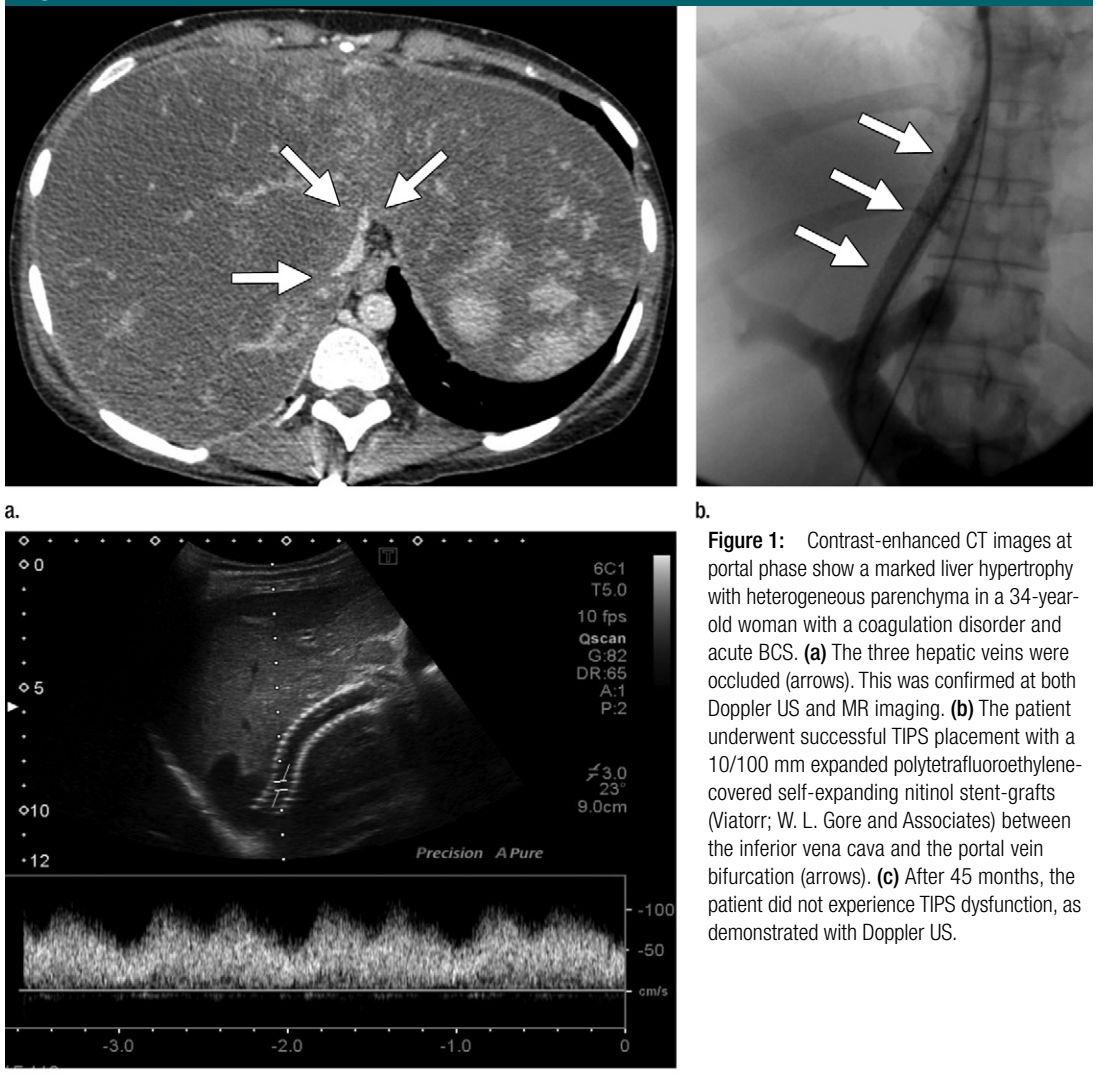

Figure 1: Contrast-enhanced CT images at portal phase show a marked liver hypertrophy with heterogeneous parenchyma in a 34-year-old woman with a coagulation disorder and acute BCS. **(a)** The three hepatic veins were occluded (arrows). This was confirmed at both Doppler US and MR imaging. **(b)** The patient underwent successful TIPS placement with a 10/100 mm expanded polytetrafluoroethylene-covered self-expanding nitinol stent-grafts (Viatorr; W. L. Gore and Associates) between the inferior vena cava and the portal vein bifurcation (arrows). **(c)** After 45 months, the patient did not experience TIPS dysfunction, as demonstrated with Doppler US.

successfully managed by conservative treatment.

Early complications (ie, <7 days after the end of the procedure) occurred in 17 patients (31%) and mainly involved bleeding because of subcapsular hematoma, intraperitoneal bleeding, or intrahepatic contrast material extravasation (n = 7); acute TIPS thrombosis (n = 6); and TIPS malposition, in which the proximal tip of the TIPS did not reach the inferior vena cava (n = 3). Nine patients required early TIPS revision with a combination of angioplasty (n = 2), thromboaspiration (n = 1), in situ thrombolysis (n = 1), and new stent placement (n = 5) to obtain stent patency. All revisions were technically successful.

Shunt Dysfunction

After a mean follow-up of 56 months ± 41 (interquartile range, 22–92), 22 patients (42%) experienced TIPS dysfunction (Table 3, Fig 2). After exclusion of the nine early TIPS revisions because of early complications, the median interval between TIPS placement and the first dysfunction was 10.8 months (interquartile range, 5–21.5 months). Initial symptoms of dysfunction were recurrent (n = 14) or persistent ascites (n = 2), abdominal pain (n = 2), decreased diuresis (n = 2), and kidney failure (n = 2). The estimated cumulative 1-, 2-, 3-, 5-, and 10-year primary patency rates were 64%, 59%, 54%, 45%, and 45%, respectively (median primary patency duration or time to transplantation, 46 months [interquartile range, 19–89 months]; Fig 3). When patients who underwent liver transplantation were censored, these 1-, 2-, 3-, 5-, and 10-year primary patency rates were 64%, 59%, 55%, 55%, and 55%, respectively (median of primary patency duration was not reached). All first TIPS dysfunctions occurred within the first 27 months.

Table 3

Follow-up Characteristics

Parameter	Result
Mean duration of follow-up*†	55.8 ± 40.9 (22–92)
Patients with >12 months follow-up	50 (93)
Lost to follow-up	10 (19)
Death	9 (17)
Liver transplantation	7 (13)
Hepatocellular carcinoma	3 (9)
Liver dysfunction	3 (9)
TIPS technical failure	1 (2)
Mean delay, TIPS to liver transplantation (mo)*	48 ± 42
Final patency	51 (96)
Median duration of patency (mo)†	46 (19–89)
TIPS dysfunction	22 (42)
No. of TIPS dysfunctions	
1	15 (28)
2	3 (6)
3	2 (4)
5	1 (2)
6	1 (2)
First dysfunction (*n* = 22)	
Mean delay, TIPS to first dysfunction (mo)*†	5.7 ± 7.3 (0–9.6)
Mean delay, TIPS to first dysfunction, early complications excluded (mo)*†	13.5 ± 11.3 (5–21.5)
Cause	
TIPS thrombosis	12 (55)
Malposition	3 (14)
TIPS stenosis	3 (14)
Low-flow velocity	4 (18)
Second dysfunction (*n* = 7)	
Mean delay, first to second dysfunction (mo)*†	22 ± 33 (0.7–26.8)
Cause‡	
TIPS thrombosis	3 (43)
Malposition	1 (14)
TIPS stenosis	2 (28)
Low-flow velocity	3 (43)
Third dysfunction (*n* = 4)	
Mean delay, second to third dysfunction (mo)*†	22 ± 28.6 (6.3–30)
Cause‡	
TIPS thrombosis	1 (25)
Malposition	1 (25)
Low-flow velocity	4 (100)
Fourth dysfunction (*n* = 2)	
Mean delay, third to fourth dysfunction (mo)*†	13.8 ± 3.4 (11.4–16.2)
Cause	
TIPS stenosis	1 (50)
Low-flow velocity	1 (50)
Fifth dysfunction (*n* = 2)	
Mean delay, fourth to fifth dysfunction (mo)*†	22 6 3.9 (19.1–24.6)
Cause	
TIPS stenosis	1 (50)
Low-flow velocity	1 (50)
Sixth dysfunction (*n* = 1)	
Mean delay, fifth to sixth dysfunction (mo)	1.4
Cause	
Low-flow velocity	1 (100)

Note.—Data in parentheses are percentages unless otherwise indicated.

* Data are ± standard deviation.

† Data in parentheses are interquartile range.

‡ The sum may exceed the number of patients because of coexistent causes.

During the same study period, eight patients underwent 10 angiographic examinations for suspected TIPS dysfunction because of a new episode of ascites (*n* = 10) and abnormal US findings (*n* = 3). Angiography findings were normal and dysfunction was excluded.

Fifteen (28%), three (6%), two (4%), one (2%), and one (2%) patients had one, two, three, five, and six TIPS dysfunctions, respectively. Causes of TIPS dysfunction are described in Table 3. All dysfunctions led to TIPS revision by balloon angioplasty alone or in combination with endovascular procedures, including new stent placement. No cutting balloons were used. Two procedures were technical failures. At the end of follow-up, 51 of 53 patients (96%) who received a TIPS, including those who underwent transplantation, had a patent TIPS. The final secondary patency rate was not different between patients with and patients without myeloproliferative neoplasm (*P* = .378) (Fig 4). Symptoms regressed after the TIPS revision in 19 of 22 patients. Symptoms recurred despite TIPS revision in the three remaining patients. These three patients died. One patient had a TIPS endoprothesis infection confirmed with fluorine 18 fluorodeoxyglucose positron emission tomography, another had a hepatic aneurysm rupture unrelated to endovascular procedures, and one had multiorgan failure. Finally, symptoms persisted in two patients, with no TIPS dysfunction (gradient, <10 mm Hg), and both died (one after liver transplantation and the other while on the waiting list).

At univariate analysis, patients with shunt dysfunction more frequently had a myeloproliferative neoplasm (77% vs 35%; *P* = .005), more frequently required more than two stents (*P* = .004), and had more early complications (55% vs 12%; *P* = .005) (Table 4). All patients with more than two initial stents (*n* = 8) experienced TIPS dysfunction, compared with 31% (14 of 45) of those with one or two stents (*P* < .001). All patients with a shunt dysfunction had an international normalized ratio between 2 and 3.5 in the month preceding dysfunction. There was no correlation between

Figure 2

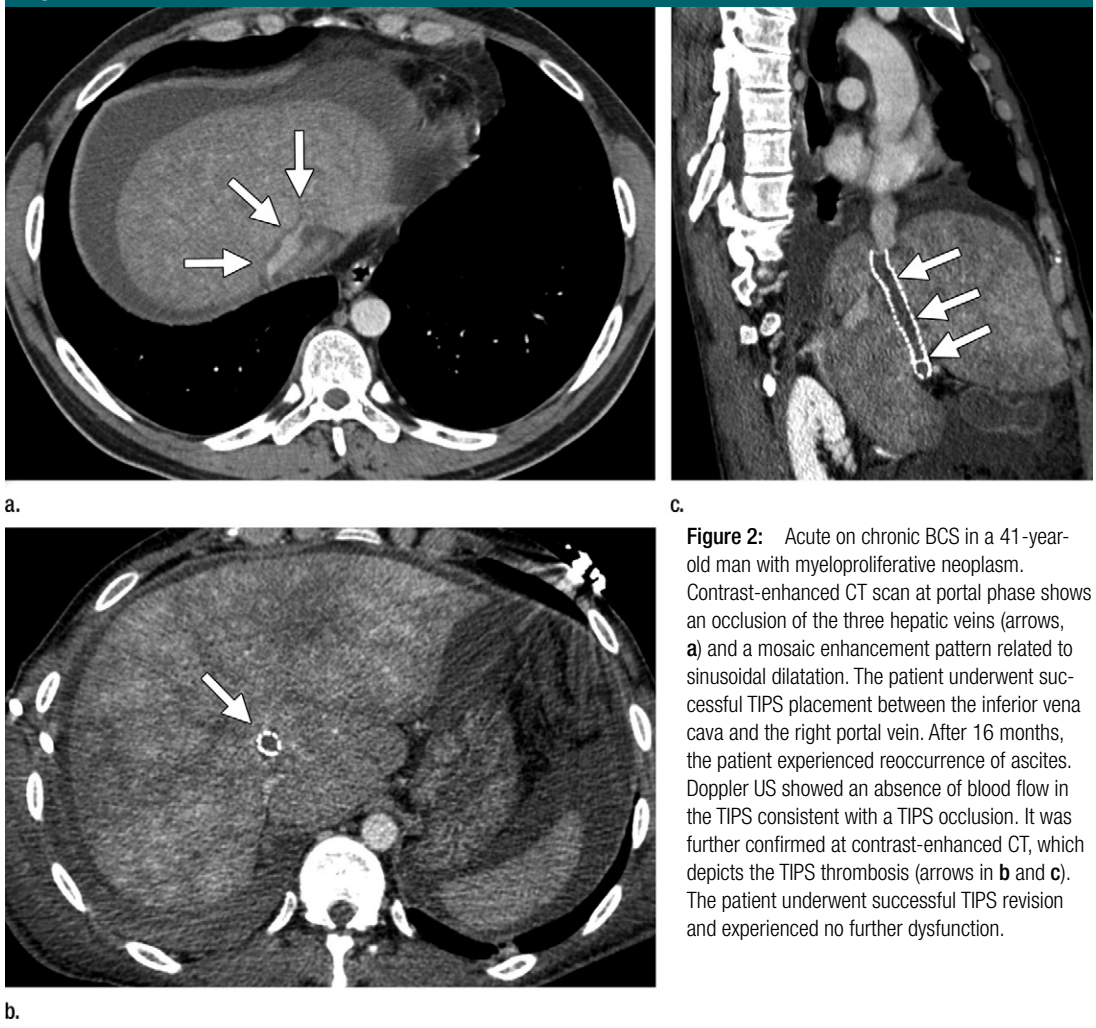

Figure 2: Acute on chronic BCS in a 41-year-old man with myeloproliferative neoplasm. Contrast-enhanced CT scan at portal phase shows an occlusion of the three hepatic veins (arrows, **a**) and a mosaic enhancement pattern related to sinusoidal dilatation. The patient underwent successful TIPS placement between the inferior vena cava and the right portal vein. After 16 months, the patient experienced reoccurrence of ascites. Doppler US showed an absence of blood flow in the TIPS consistent with a TIPS occlusion. It was further confirmed at contrast-enhanced CT, which depicts the TIPS thrombosis (arrows in **b** and **c**). The patient underwent successful TIPS revision and experienced no further dysfunction.

international normalized ratio values and shunt dysfunction.

Multivariate analysis showed that a myeloproliferative neoplasm (hazard ratio, 8.18; 95% confidence interval: 1.45, 46.18; P = .017), more than two initial stents (hazard ratio, 3.90; 95% confidence interval: 1.16, 13.10; P = .009), and the development of early complications (hazard ratio, 11.34; 95% confidence interval: 1.82, 70.69; P = .020) were associated with TIPS dysfunction.

Follow-up

At the end of the study period, 50 patients (93%) had more than 12 months of follow-up and 10 patients (19%) were lost to follow-up. The mean follow-up time of the patients who were lost to follow-up was 52.2 months ± 23.7.

In patients with refractory ascites and after exclusion of TIPS dysfunction, eight (15%) patients had recurrent (n = 6) or persistent (n = 2) ascites, which was transient in three patients. Five patients with recurrent or persisting ascites died, including three of liver failure, one after massive bleeding because of a hepatic artery aneurysm, and one after undergoing liver transplantation. Liver failure worsened in four patients after TIPS; three (17%) underwent liver transplantation and one died before liver transplantation. None of the patients had recurrent variceal bleeding after TIPS placement.

Acute encephalopathy developed in eight patients (15%) within 1 month after TIPS insertion: one patient had grade 4, three patients had grade 3, and four patients had grade 2. Hepatic encephalopathy was transient in three patients and did not recur. Hepatic encephalopathy recurred once in two patients, and more than twice in three patients.

Thirteen patients (25%) had late episodes of encephalopathy, and all had an identified triggering factor (eg, diuretics, infection, or medical treatment); two patients had grade 4, four

Figure 3

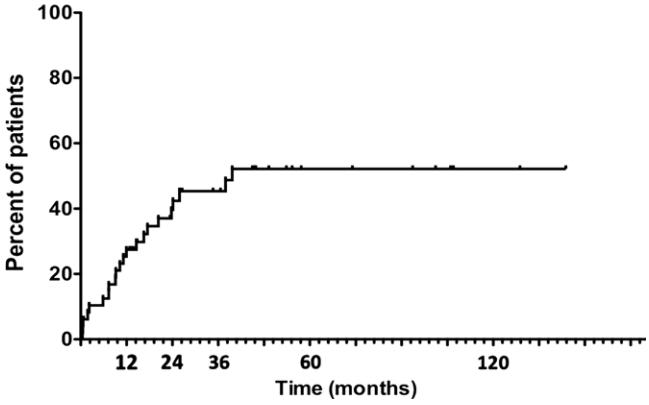

Figure 3: Graph shows the cumulative rate of first TIPS dysfunction in all patients including those who underwent transplantation (patients who underwent liver transplantation were censored at the time of the liver transplantation).

Figure 4

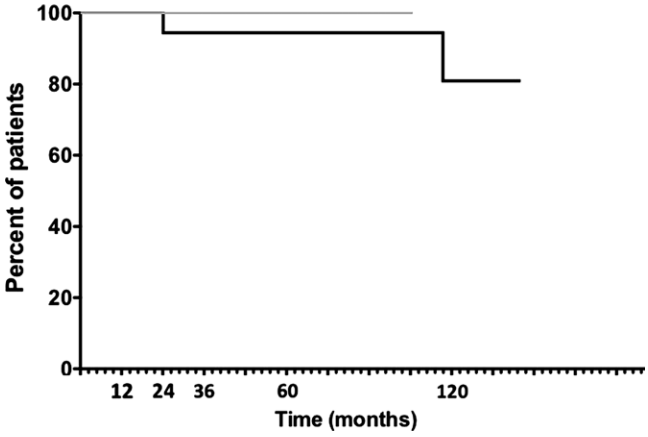

Figure 4: Graph shows estimated cumulated rates of secondary TIPS patency (patients who had liver transplant were censored at the time of the liver transplantation) for patients with myeloproliferative neoplasms (gray line) and those without myeloproliferative neoplasm (black line). There was no significant difference between the two populations ($P = .378$).

patients had grade 3, five patients had grade 2, and two patients had grade 1. Hepatic encephalopathy recurred more than twice in three patients and required administration of rifaximin (Normix; Alfa Wassermann, Alanno, Italy), which stabilized the situation.

Seven patients (11%) underwent liver transplantation for hepatocellular carcinoma ($n = 3$), liver dysfunction ($n = 3$), and technical failure of TIPS placement ($n = 1$). The mean delay between TIPS and liver transplantation was 48 months ± 42. Overall, nine patients died (17%). None of the deaths was related to TIPS dysfunction. The cumulative 1-, 2-, 3-, 5-, and 10-year overall survival rates were 96%, 88%, 83%, 83%, and 76%, respectively. No factor was associated with death (all $P > .05$).

Discussion

Our study shows the good long-term results and outcome of TIPS placement in patients with BCS, with a high rate of technical success, secondary stent patency, and fairly low mortality. However, one-third of the patients had early complications, and 42% had at least one TIPS dysfunction. Both technical and clinical factors appeared to be risk factors of TIPS dysfunction, including the presence of a myeloproliferative neoplasm.

Technical success rate was high because TIPS placement was unsuccessful in only one patient. Since it was first introduced, numerous studies have shown that TIPS procedure is a technical success in most patients when performed by experienced teams (29,30). This means that the procedure is highly feasible even when there are no patent hepatic veins, as in most of the patients in our study. However, the complication rate was fairly high; 26% of patients experienced periprocedural complications and 32% of patients experienced early complications, and most of the complications were related to the TIPS procedure. This is consistent with previous data. In a recent meta-analysis, Qi et al (29) reported complication rates ranging from 0% to 56%, but all larger studies report rates above 20% (10,12,15,18). There are numerous different reported complications including capsule perforation, venous injury, or kidney failure, but bleeding is one of the most important (31,32). This was also the most frequent complication in our study along with acute stent thrombosis. This may be because a longer hepatic parenchymal tract needs to be stented during the TIPS procedure in BCS patients than in patients with cirrhosis, and because all patients received anticoagulation therapy before the procedure. Indeed, the rate of complications is higher than that in TIPS placement for other causes, such as refractory ascites because of cirrhosis (around 9% [33,34]). Nevertheless, in our experience, all periprocedural and early complications could be treated with a conservative approach, and none of the patients died of procedure-related complications.

Around 40% of the patients had TIPS dysfunction, including close to 15% of patients with more than one episode after a mean of 13.5 months. This rate is high, but similar to recently published series (12,19). It is also slightly higher than rates reported in patients who received TIPS for refractory ascites because of cirrhosis (ie, around a third of the patients [33,34]), probably because of the underlying prothrombotic condition of patients with primary BCS. It has been clearly demonstrated (8,10,14,15,18) that an important risk factor for TIPS dysfunction is the type of stent used because shunt dysfunction is less frequent in patients with covered stents than in those with bare stents. This was not true in our study, probably

Table 4

Comparison of Patients with or without TIPS Dysfunction

Parameter	Total No. of Patients	TIPS Dysfunction ($n = 22$)	No TIPS Dysfunction ($n = 31$)	*P* Value	Multivariate Analysis	
					Hazard Ratio*	*P* Value
Patients	53					
Male	19	8 (36)	11 (35)	.587		
Female	34	14 (64)	20 (65)	…		
Mean age (y)†		34 ± 11	36 ± 12	.557		
Clinical presentation‡						
Acute/chronic	12	5 (23)	7 (23)			
Subacute	1	0	1 (3)	.696		
Chronic	41	17 (77)	23 (74)			
Etiologic cause of BCS§						
Myeloproliferative syndrome	28	17 (77)	11 (35)	.005	8.18 (1.45, 46.18)	.017
Coagulation disorders	14	6 (27)	8 (26)	.910		
Antiphospholipid syndrome	7	3 (14)	4 (13)	.623		
Paroxysmal nocturnal hemoglobinuria	3	2 (9)	1 (3)	.371		
Other	2	0	2 (6)	.337		
Unknown	9	4 (18)	5 (16)	.845		
Previous treatment	7					
Mean delay with TIPS (d)†		111 ± 153	32.5 ± 38	.006		
Right hepatic vein angioplasty	2	0	2 (3)			
Left hepatic vein angioplasty	2	1 (5)	1 (3)	.460		
Inferior vena cava angioplasty	2	0	2 (6)			
Mesenteric caval shunt	1	1 (5)	0			
Indication for TIPS placement§						
Refractory ascites	50	19 (86)	31 (94)			
Liver dysfunction	17	5 (23)	12 (39)			
Upper GI bleeding	4	2 (9)	2 (6)			
Hepatorenal syndrome	3	1 (5)	2 (6)	.643		
Major pleural effusion	4	2 (9)	2 (6)			
Mesenteric caval shunt thrombosis	1	1 (5)	0			
Failure of previous endovascular treatment	1	1 (5)	0			
No. of hepatic veins involved‖						
1	1	0	1 (3)			
2	4	3 (14)	1 (3)	.268		
3	48	19 (86)	29 (94)			
Associated IVC thrombosis	3	3 (14)	0	.066		
Portal vein thrombosis						
Main	3	2 (9)	1 (3)			
Right branch	3	2 (9)	1 (3)	.339		
Left branch	1	1 (5)	0			
Baseline biology						
AST > normal	42	15 (68)	27 (87)	.348		
ALT > normal	26	8 (36)	19 (61)	.074		
AP > normal	39	13 (59)	26 (84)	.061		
GGT > normal	50	19 (86)	31 (100)	.067		
Total bilirubin > normal	45	16 (73)	29 (94)	.054		
Rotterdam class						
1	3	1 (5)	2 (6)			
2	40	12 (55)	28 (90)	.208		
3	10	6 (27)	4 (13)			
Mean MELD score		16 ± 4	14 ± 5	.242		
Mean INR		1.48 ± 0.38	1.44 ± 0.35	.665		

Table 4 *(continues)*

Table 4 (continued)

Comparison of Patients with or without TIPS Dysfunction

Parameter	Total No. of Patients	TIPS Dysfunction ($n = 22$)	No TIPS Dysfunction ($n = 31$)	*P* Value	Multivariate Analysis	
					Hazard Ratio*	*P* Value
Platelet count (10^9/mL)						
Baseline		2.34 ± 1.40	2.10 ± 1.23	.503		
At 12 months		1.84 ± 1.26	2.04 ± 0.93	.504		
BCS TIPS prognositic index						
Mean		4.4 ± 0.9	4.4 ± 1.1	.994		
Mean Child-Pugh score		9.2 ± 1.4	9.5 ± 1.6	.641		
Technical success						
Primary		22 (100)	30 (97)	.585		
Secondary		22 (100)	31 (100)	…		
No. of stents						
1	19	6 (27)	13 (42)			
2	26	8 (36)	18 (58)	.004	3.90 (1.16, 13.10)	.027
3	7	7 (32)	0			
4	1	1 (5)	0			
Type of stents						
Gore stents with or without additional stents#	47	21 (95)	26 (84)			
Combination of non-Gore stents	6	1 (5)	5 (16)	.220		
Mean HVPG (mm Hg)						
Before procedure		22.7 ± 6.2	20.6 ± 7.0	.302		
After procedure		7.2 ± 4.9	6.4 ± 3.1	.532		
Complications						
Periprocedural complications	8	3 (14)	5 (16)	.703		
Early complications at <7 days	15	12 (55)	3 (10)	.005	11.34 (1.82, 70.69)	.009
Follow-up						
Death		5 (23)	4 (13)	.464		
Liver transplantation		2 (9)	5 (16)	.508		
Final patency		20 (91)	31 (100)	.168		

Note.—Data in parentheses are percentages. ALT = alanine aminotransferase, AP = alcalin phosphatase, AST = aspartate aminotransferase, GGT = γ gutamyl transferase, GI = gastrointenstinal, HVPG = hepatic venous portal gradient, INR = international normalized ratio, IVC = inferior vena cava, MELD = Model for End-Stage Liver Disease, ULN = upper limit of normal values.

* Data in parentheses are 95% confidence intervals.

† Data are ± standard deviation.

‡ According to the criteria established by the European Network for Vascular Disorders of the Liver (En-Vie) and defined at the Baveno V Consensus meeting.

§ Several patients had multiple causes or TIPS indications.

‖ Determined by using a combination of preprocedural US, CT, and MR imaging.

One patient had TIPS failure and was not included in follow-up analysis.

because our patients were treated with covered stents (associated or not with an underlying bare stent). This allowed us to identify other factors associated with TIPS dysfunction that are important as covered stent use becomes increasingly frequent. A myeloproliferative neoplasm, more than two initial stents, and the development of early complications were associated with TIPS dysfunction. The two latter variables may indicate that the risk of dysfunction is higher with a long parenchymal pathway. The association between myeloproliferative neoplasms and TIPS dysfunction was not known. They have been associated with the risk of acute portal vein thrombosis in the general population (35,36) and, more importantly, with the risk of recurrent thrombosis in patients treated with liver transplantation in BCS (37,38). Patients with these clinical and technical risk factors should probably be more closely monitored with Doppler US imaging.

Studies that focused on the risk factors of TIPS dysfunction are rare. Qi el al (19) identified inferior vena cava thrombosis as a possible risk factor. This was not identified in our series, but these authors reported on Chinese patients who are more prone to associated inferior vena cava thrombosis or occlusion than are patients in Western countries (39). It is important to note that all TIPS dysfunctions were successfully revised in our study, which led to a high rate of secondary patency.

Interestingly, there was not a difference in terms of dysfunction between acute and chronic BCS presentation. This is probably explained by the fact that TIPS creation is more driven by symptoms than the presentation itself. However, the number of acute presentations was probably too small to draw any valid conclusions.

The mortality rate in our study was 17%. This is in the range of recent series (0%–36%) (10,12,19,29). Indeed, the short- and long-term prognosis for patients with primary BCS treated with TIPS placement is good (10,18,29,30). In our study, the causes of death were not related to stent complication. This is also similar to published data because shunt occlusion or acute shunt thrombosis leads to death in very few patients. Unlike data reported by Garcia-Pagán et al (10), no other factors associated with death were identified, including age, international normalized ratio, or bilirubin level. This is also true for most published studies, because the prognostic analysis was only performed in a latter large multicenter study (10) and a few single-center studies (12). This is probably because the limited number of deaths prevents a sufficiently powerful statistical analysis. Thirteen percent of the patients underwent liver transplantation. In most patients, the indications for liver transplantation were not related to TIPS dysfunction, but to the presence of hepatocellular carcinoma or liver dysfunction. In other large series, liver transplantation was mainly indicated for liver failure, recurrent hemorrhage, or TIPS dysfunction (10,18).

Our study is limited by its single center and retrospective design. Nevertheless, our institution is a referral center for vascular liver diseases, and patient exploration and follow-up are closely performed. We identified the overall length of the TIPS as a risk factor of dysfunction. Dysfunction may also be associated with its configuration (eg, angulation and plication of stent graft material). This was not considered in our study because we felt it was difficult to objectively describe. Nevertheless, this should be considered when following patients. Our study shows the results of TIPS creation according to the multistep management reported by Plessier et al (18). This strategy was validated by the multicenter study reported by Seijo et al (3) and endorsed by the European Association for the Study of the Liver guidelines on vascular liver diseases (40). Therefore, the possible benefit of earlier TIPS creations in the course of the disease cannot be drawn from our results, nor is that of other treatments, namely hepatic veins percutaneous transluminal angioplasty, considered alone. However, our strategy is supported by several published studies and is valid for the patients when considering the present results.

In conclusion, TIPS placement in patients with primary BCS was associated with a fairly high rate of early complications, and endovascular revision or revisions were required in 42% of patients. Our study identified the technical and clinical factors associated with TIPS obstruction, especially myeloproliferative neoplasms. Nevertheless, the secondary patency rate was close to 100%, and long-term survival was good.

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