Transjugular Intrahepatic Portosystemic Shunt for Acute Variceal Bleeding in Patients with Viral Liver Cirrhosis: Predictors of Early Mortality

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OBJECTIVE. The purpose of our study was to assess the predictors of early mortality after the creation of transjugular intrahepatic portosystemic shunts (TIPS) for acute variceal bleeding in patients with viral liver cirrhosis.

MATERIALS AND METHODS. Seventy-three patients (56 men and 17 women; mean age, 51.3 years) with viral liver cirrhosis who underwent TIPS placement for acute variceal bleeding were studied. Multiple covariates, including demographic, clinical, and biochemical parameters, were included in univariate and multivariate analyses to determine their association with early (30-day) mortality.

RESULTS. During the follow-up period (mean, 35 months 3 days), shunt dysfunction occurred in 33 patients (45.2%). Forty-three patients (58.9%) died, and 23 patients (31.5%) died within 30 days of TIPS. Early death was predicted independently by hyperbilirubinemia (> 3 mg/dL; $p = 0.004$; odds ratio, 10.6) and elevated serum creatinine level (> 1.7 mg/dL; $p = 0.018$; odds ratio, 12.0).

CONCLUSION. Hyperbilirubinemia and elevated serum creatinine level are predictive of early mortality after TIPS creation for acute variceal bleeding in patients with viral liver cirrhosis.

The transjugular intrahepatic portosystemic shunt (TIPS) is a well-established therapy for patients with liver cirrhosis complicated by acute or recurrent variceal bleeding that is refractory to endoscopic therapy and intractable ascites [1–4]. However, TIPS are associated with high early mortality; the 30-day mortality rate ranges from 25% to 30% [1–4]. Many authors have investigated prognostic factors accurately predicting survival after TIPS placement [5–13]. Several factors predictive of poor survival have been recognized: hyponatremia, hyperbilirubinemia, elevated serum alanine aminotransferase, advanced liver disease, emergent TIPS placement, and coexisting renal insufficiency [5–13].

To date, most studies about TIPS have been from Western countries, and most patients included in these studies had alcoholic liver cirrhosis [1–13]. However, in Asian countries, hepatitis virus carriers are reported to be 5–20% of the population, and viral hepatitis is the main cause of liver cirrhosis [14, 15]. Viral liver cirrhosis is different from alcoholic liver cirrhosis in many aspects such as histologic and morphologic changes, disease progression, treatment options, and incidence of hepatocellular carcinoma (HCC) [16–18]. Therefore, it is inappropriate to apply the Western data to patients with viral liver cirrhosis, especially in hepatitis virus–endemic areas. However, a few studies from Asian countries have investigated prognostic factors of TIPS in patients with viral liver cirrhosis. We performed this study to assess the prognostic factors for early mortality after TIPS placement for acute variceal bleeding in patients with viral liver cirrhosis. To our knowledge, this is the first English-language article from a hepatitis virus–endemic area that describes the prognostic factors after TIPS placement.

Materials and Methods

Study Population

This retrospective study was approved by the review board of our institution. The medical records of 111 consecutive patients who underwent TIPS placement in our institution between June 1991 and January 2002 were reviewed to verify the cause of liver disease and indication for TIPS and to obtain all relevant clinical and laboratory data. Thirty-eight patients were excluded because of their cause of liver cirrhosis (alcoholic [$n = 23$] and cholestatic [$n = 1$] liver disease) or elective TIPS (recurrent variceal

bleeding [$n = 10$] and intractable ascites [$n = 4$]). Emergent indications for TIPS was defined as a patient requiring blood products within 24 hr of TIPS creation, hemodynamic instability, balloon tamponade, or obvious continued bleeding [6].

The patient cohort consisted of 56 men and 17 women with a mean age of 51.3 years (range, 27–85 years). The causes of liver disease were hepatitis B ($n = 63$) and hepatitis C ($n = 10$) virus. According to the modified Child-Pugh classification, 15 patients had class A liver disease, 20 patients class B, and 35 patients class C. The remaining three patients had insufficient data to classify them. Ten patients had documented HCC before TIPS creation that had been treated with transcatheter arterial chemoembolization (TACE, $n = 9$) or percutaneous ethanol injection ($n = 1$). In four patients, HCC was detected on pre-TIPS CT and treated with TACE within 7 days after TIPS placement.

TIPS Procedure

TIPS were created using a technique described elsewhere [1–4]. The TIPS was usually created between the right hepatic vein and the right portal vein ($n = 40$), or, in patients with a small right hepatic vein, between the middle hepatic and the right portal veins ($n = 17$). In 16 cases, the shunt was created between the middle hepatic and the left portal veins ($n = 10$) or between the left hepatic and left portal veins ($n = 6$) because of right portal vein thrombosis ($n = 8$) or an unfavorable location of the HCC ($n = 8$). Shunt tracts were dilated with 10-mm angioplasty balloons (Boston Scientific/Medi-Tech) and lined with various commercially available stents: Wallstents (Boston Scientific/Medi-Tech, $n = 49$), Niti-S (Taewoong, $n = 17$), Memotherm (Angiomed, $n = 4$), and Gianturco Z stent (Cook, $n = 3$). Stents of 10-mm-diameter ($n = 55$) and 8-mm-diameter ($n = 10$) were used. Stent size was not recorded in the remaining eight patients. The goal of the procedure was to reduce the portosystemic pressure gradient (PPG, measured between the portal vein and right atrium) to less than 12 mm Hg, which was achieved in 45 of 69 patients (four patients did not have hemodynamic measurements recorded).

Follow-Up

Doppler sonography was performed before discharge, at 3–4 months intervals, and whenever shunt dysfunction was suspected clinically. Shunt dysfunction was suspected on Doppler sonography if the calculated peak velocity in the shunt was less than 60 cm/sec or reversal of flow was shown on color flow imaging of the draining hepatic vein or portal vein [19]. Results from Doppler sonography were confirmed with angiography. Stenosis was defined on angiography if there was a 50% or greater narrowing of the lumen or

the portosystemic gradient was 12 mm Hg or greater.

Patients were followed up from their date of TIPS placement until death, liver transplantation, or study closure. The date of the last clinic visit or liver transplantation defined the follow-up period for all surviving patients. If no clinic visits were recorded in the medical records, the patients or their families were contacted by telephone ($n = 9$) and a brief interview was conducted to determine the patient's clinical course after TIPS creation.

Statistical Analysis

Sixteen variables related to clinical or biochemical data were included in the analysis. Continuous variables were dichotomized on the basis of the existing literature [10–12]: albumin level (< 2.8 vs ≥ 2.8 mg/dL), prothrombin time (PT; < 60 vs $\geq 60\%$), total bilirubin level (> 3 vs ≤ 3 mg/dL), serum creatinine level (> 1.7 vs ≤ 1.7 mg/dL), alanine aminotransferase (ALT) level (> 70 vs ≤ 70 IU/L), aspartate aminotransferase (AST) level (> 70 vs ≤ 70 IU/L), WBC (> 8 vs $\leq 8 \times 10^3/\mu L$), platelet count (> 120 vs $\leq 120 \times 10^3/\mu L$), and PPG before ($> 18$ vs ≤ 18 mm Hg) and after (> 12 vs ≤ 12 mm Hg) TIPS placement. Categoric variables included sex, cause of liver disease (hepatitis B vs C), comorbid conditions (hypertension, diabetes, and HCC; presence vs absence), and route of TIPS (right portal vein vs left portal vein).

The univariate association between individual prognostic factors and early mortality (30 days) was tested using Fisher's exact test or the Student's *t* test as appropriate, and multiple logistic regression was used to test the significance of factors adjusted for one another. For all analyses, a *p* value of less than 0.05 and a 95% confidence interval that did not span unity were considered the thresholds of statistical significance.

Patient data were censored at time of death, liver transplantation, or last follow-up. Kaplan-Meier analyses were performed to estimate time to death, and the log-rank test was used to determine whether differences were significant. All analyses were conducted with SPSS for Windows (Microsoft) version 10.0 software (SPSS).

Results

Outcomes of TIPS Placement

TIPS were successfully created in all the 73 patients. The characteristics of the patients are shown in Table 1. The mean pre- and post-TIPS portosystemic pressure gradients were 26.5 and 10.2 mm Hg, respectively. Variceal bleeding stopped in 61 (83.6%) of 73 patients after creation of the TIPS, and 12 patients continued to bleed. In the 12 patients, shunt occlusions due to acute thrombosis were detected in four patients but they refused

further treatment. In the remaining eight patients, the shunts were patent on Doppler sonography. One patient underwent splenorenal shunt surgery, and the remaining 11 patients died of persistent bleeding. In one patient, hemoperitoneum developed after TIPS placement that contributed to accelerated multiorgan failure, and the patient died 2 days after TIPS placement.

The mean and median times of follow-up were 35 months 3 days and 23 months 6 days (range, 2 days–136 months). Shunt dysfunction occurred in 33 patients during the follow-up period. Shunt occlusion due to acute thrombosis occurred in nine patients. Five patients were successfully treated with aspiration thrombectomy and balloon angioplasty. The remaining four patients refused further intervention. Shunt stenoses developed in 24 patients, which were detected by rebleeding ($n = 13$), Doppler sonography ($n = 9$), and recurrent ascites ($n = 2$). Rebleeding developed within 6 months in seven patients (29.2%) and within 12 months in 12 patients ($n = 50\%$). Fifteen patients underwent percutaneous shunt revision with balloon angioplasty. Additional stents were required in six patients for sufficient coverage of the hepatic venous end of the shunt tract. Primary and secondary patency rates of the TIPS tract were 61.3% and 76.4% at 1 year, 49.3% and 72.0% at 2 years, and 42.9% and 68.9% at 3 years, respectively.

Forty-three patients died during the follow-up period; 23 (31.5%) of them died within the first 30 days after TIPS placement. The causes of 30-day mortality included uncontrolled bleeding ($n = 11$), multiorgan system failure ($n = 7$), liver failure ($n = 3$), renal failure ($n = 1$), and adult respiratory distress syndrome ($n = 1$). The causes of death beyond 30 days were progressive liver failure ($n = 7$) followed by sepsis with shock ($n = 4$), recurrent variceal bleeding ($n = 3$), renal failure ($n = 3$), gastric ulcer bleeding ($n = 1$), and unknown ($n = 2$). Overall survival rates were 71.1% at 1 year, 61.2% at 2 years, 49.5% at 3 years, and 35.4% at 5 years.

Determinants of Early Mortality

In univariate analyses, serum albumin level, total bilirubin level, PT, and serum creatinine level were associated with 30-day mortality (Table 2). The 30-day mortality rate of patients with serum albumin level < 2.8 mg/dL was 46.2% (30/65) versus 13.8% (9/65) for ≥ 2.8 mg/dL ($p = 0.019$). In patients with a PT $< 60\%$, the 30-day mortality rate was 55.7% (34/61) compared with 14.8% (9/61) in

patients with a PT of ≥ 60% (p = 0.001). Thirty-day mortality rates in patients with total bilirubin levels > 3 and ≤ 3 mg/dL were 56.5% (13/23) and 20% (9/45), respectively (p < 0.001). The 30-day mortality rates in patients with creatinine levels > 1.7 and ≤ 1.7 mg/dL were 55.6% (10/18) and 23.4% (11/47) (p < 0.001). In multivariate analysis, only two variables retained independent predictive value: total bilirubin level and creatinine level (Table 3). Figures 1 and 2 show Kaplan-Meier survival estimates between patients with hyperbilirubinemia and the remaining group (p = 0.001 by log-rank test) and between patients with elevated creatinine level and the remaining group (p = 0.001 by log-rank test).

Discussion

In the past decade, TIPS placement has become a widely used, validated therapy for patients with portal hypertension [1–4]. Although accepted indications of TIPS include recurrent variceal bleeding, portal hypertensive gastropathy, refractory ascites or hydrothorax, and Budd-Chiari syndrome, acute variceal bleeding is the most established indication, with little debate about TIPS efficacy [1–4].

When TIPS is used as rescue therapy in acute variceal bleeding, early (1-month) mortality rates range from 28% to 48%, which are significantly higher than those after elective TIPS placement (11–26%) [5–13]. Although numerous studies have evaluated factors that affect patient survival after elective TIPS placement [5–9], only three articles have analyzed predictors of early death after emergent TIPS placement for acute variceal bleeding [10–12]. Banares et al. [10] found that hepatic encephalopathy before TIPS placement, ascites before TIPS placement, and a serum albumin level lower than 2.7 g/L were independently related to 30-day mortality. Sanyal et al. [11] reported that aspiration and grade IV encephalopathy were independent predictors of early death. Finally, Patch et al. [12] found six variables were related to early mortality: moderate or severe ascites, need for ventilation, WBC, platelet count, partial thromboplastin time, and creatinine. Those authors obtained a prognostic index score combining the six variables that was prospectively validated in another series of patients [12]. However, evaluation of encephalopathy and ascites is somewhat subjective and likely to be affected by concomitant medical therapies. Therefore, we did not include these factors in the analyses for prognostic factors. For the same reason, individual components of Child-Pugh classification were included in the analyses instead of the classification itself.

In our study, elevated serum bilirubin and creatinine levels were independent predictors

TABLE 1: Demographic, Clinical, and Biochemical Characteristics of Study Population

Characteristic	No.	%	Mean (SD)
Demographic			
Age (yr)	73[a]	100.0	51.3 (9.9)
Men	56	76.7	
Cause of cirrhosis			
Hepatitis B virus	63	86.3	
Hepatitis C virus	10	13.7	
Child-Pugh score	63[a]	86.3	9.1 (3.0)
Child-Pugh classification			
A	15	20.5	
B	20	27.4	
C	35	47.9	
Comorbid conditions			
Hypertension	13	17.8	
Diabetes	10	13.7	
Hepatocellular carcinoma	13	17.8	
Biochemical			
Albumin (g/dL)	65[a]	89.0	2.7 (0.5)
AST (IU/L)	55[a]	75.3	59.7 (10.5)
ALT (IU/L)	55[a]	75.3	43.5 (11.4)
Total bilirubin (mg/dL)	68[a]	93.2	3.9 (6.4)
Prothrombin (%)	61[a]	83.6	60.4 (17.6)
WBC ($\times 10^3/\mu L$)	59[a]	80.8	8.1 (2.1)
Platelet count ($\times 10^3/\mu L$)	60[a]	82.2	120 (32)
Serum creatinine (mg/dL)	65[a]	89.0	2.7 (1.5)
PPG (mmHg)			
Before TIPS	65[a]	89.0	26.5 (6.5)
After TIPS	65[a]	89.0	10.2 (3.1)

Note—SI unit conversion: albumin and hemoglobin, × 10 g/L; bilirubin, × 17.1 μmol/L; creatinine, × 88.4 μmol/L. PPG = portosystemic pressure gradient (measured between portal vein and right atrium), TIPS = transjugular intrahepatic portosystemic shunt, AST = aspartate aminotransferase, ALT = alanine aminotransferase.
[a]Number of patients available for each variable.

TABLE 2: Univariate Analysis for Early Mortality After Creation of Transjugular Intrahepatic Portosystemic Shunt

Predictor of Early Mortality	p	Odds Ratio	95% CI
Serum albumin, < 2.8 vs ≥ 2.8 g/dL	0.019	5.152	1.311–20.245
Prothrombin, < 60% vs ≥ 60%	0.001	7.362	2.149–25.215
Total bilirubin, > 3 vs ≤ 3 mg/dL	0.007	5.041	1.582–16.270
Serum creatinine, > 1.7 vs ≤ 1.7 mg/dL	0.009	10.200	1.775–58.623

Note—CI = confidence interval.

TABLE 3: Multivariate Analysis for Early Mortality After Creation of Transjugular Intrahepatic Portosystemic Shunt

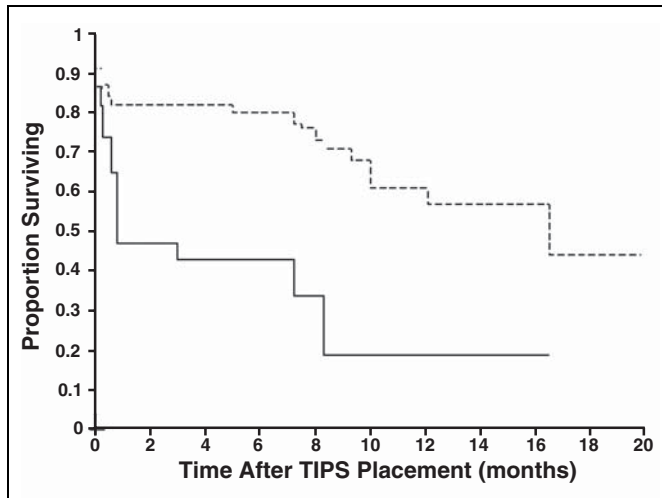| Independent Predictor of Early Mortality	p	Odds Ratio	95% CI
Total bilirubin > 3 mg/dL	0.004	10.609	2.082–54.056
Serum creatinine > 1.7 mg/dL	0.018	11.997	1.526–94.345

Note—CI = confidence interval.

Fig. 1—Kaplan-Meier survival curves based on serum bilirubin level show significantly higher mortality rate in patients with hyperbilirubinemia (> 3 mg/dL [*n* = 23], *solid line*) (*p* = 0.001 by log-rank test) than in those without. Dotted line indicates bilirubin level ≤ 3 mg/dL (*n* = 45).
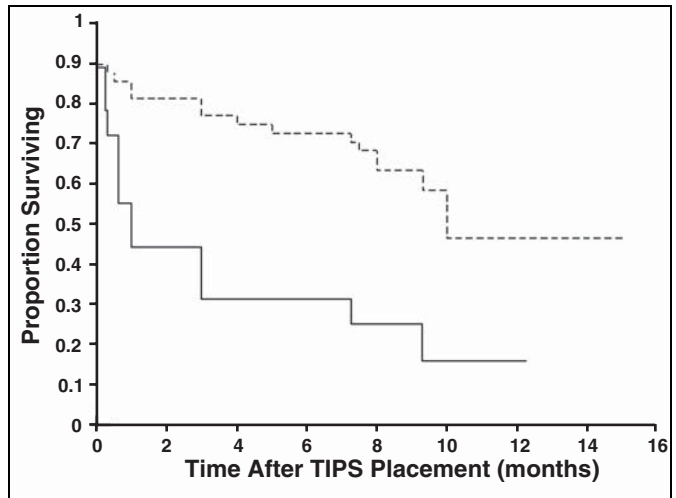

Fig. 2—Kaplan-Meier survival curves based on serum creatinine level show significantly higher mortality rate in patients with elevated serum creatinine level (> 1.7 mg/dL [*n* = 18], *solid line*) (*p* = 0.001 by log-rank test) than in those without. Dotted line indicates serum creatinine level ≤ 1.7 mg/dL, *n* = 47.

of early death. In patients with bilirubin > 3 mg/dL and creatinine > 1.7 mg/dL, the risk of early death was 10.6 and 12.0 times greater than in patients with bilirubin ≤ 3 mg/dL and creatinine ≤ 1.7 mg/dL, respectively. Patients with these risk factors had a very high rate of early mortality.

Hyperbilirubinemia has been a frequently designated predictor of early mortality in other studies. Rajan et al. [6], after reviewing 220 patients, reported independent association of the total bilirubin level with early mortality, with the odds ratios of 4.4 in acute variceal bleeding and 7.1 in recurrent bleeding, respectively. Chalasani et al. [7] found that total bilirubin level ≥ 3.0 mg/dL had an independent effect on 30-day mortality (relative risk, 5.4). That study included patients who had TIPS placed for variceal bleeding and those who had TIPS placed for intractable ascites. These results are not astonishing because the serum bilirubin level reflects hepatic synthetic dysfunction in chronic and acutely diseased metabolic states.

In our study, elevated serum creatinine level was another independent factor of early mortality after TIPS placement. The association of an elevated creatinine level with poor survival has been suggested in both emergent and elective TIPS placement [5, 12, 13]. Patch et al. [12] proposed that an elevated serum creatinine level is independently associated with early mortality after TIPS placement in patients with acute variceal bleeding. Russo et al.

[13], in a multivariate analysis of outcomes of TIPS placement for variceal bleeding and intractable ascites, reported elevated serum creatinine level was the strongest predictor of 30-day mortality. Therefore, we think that elevated serum bilirubin and creatinine levels are important predictors of early mortality in both emergent and elective TIPS placement.

In our study, 31.5% (23/73) patients died within 1 month after TIPS creation. The most common cause of early mortality was persistent variceal bleeding (11/23 patients) despite successful TIPS creation. Ten of the 11 patients had hyperbilirubinemia (> 3 mg/dL), and eight had an elevated serum creatinine level (> 1.7 mg/dL). In these patients, therefore, decompression of portal hypertension is insufficient, and embolization of the varix itself may be needed for immediate control of variceal bleeding. We had four early deaths in patients with acute thrombotic shunt occlusions. Some investigators speculated that the influx of bile into the shunt may stimulate thrombosis and suggested the use of a covered stent-graft to avoid direct bile–shunt contact [20, 21]. In a recent study in which a polytetrafluoroethylene-covered stent-graft was used for the TIPS, only one early shunt occlusion occurred in 71 patients [22].

Recently, in Western countries, TIPS placement has been used in candidates for liver transplantation as a bridge to transplantation [23, 24]. TIPS placement may prolong the waiting period in such candidates and fa-

cilitate surgery by the reduction of portal pressure and obliteration of collaterals. However, because liver transplantation has not yet been widely performed in Asia [25], TIPS has been accepted in Asian countries as a definite and permanent treatment for portal decompression. Therefore, precise prediction and meticulous survey for TIPS dysfunction are no less important than those for early mortality in Asian countries.

Since Malinchoc et al. [26] developed a model of end-stage liver disease (MELD) to predict the 3-month survival rate after TIPS placement, several recent studies indicated that early mortality after elective TIPS placement could be accurately predicted using the MELD score [27–29]. Originally, the MELD score included the cause of liver cirrhosis as an individual component because the outcomes of patients with cholestatic or alcoholic liver cirrhosis were better than for those with viral hepatitis. It has been suggested that viral hepatitis has a more rapidly progressive course, or that patients with viral hepatitis have more impaired hepatocellular function and are less tolerant to portosystemic shunting [26]. However, recently several authors reported that the cause of liver disease has little effect on patient survival and deleted cause of liver disease in the modification of the MELD score [8, 9, 29]. Those studies divided patients into subgroups of those with alcoholic and those with nonalcoholic liver disease; nonalcoholic liver disease included hepatitis B viral, hepatitis C vi-

ral, cholestatic, and cryptogenic liver disease [8, 9, 29]. Therefore, the number of patients with viral liver disease, especially hepatitis B, was relatively small and accounted for 4.2–7.2% of the total population of the studies [8, 9]. In a recent investigation from an area in which hepatitis B virus is endemic, which included similar numbers of patients with alcoholic and viral liver disease, the patients with viral liver disease experienced more severe deterioration of liver function after TIPS placement [30]. Therefore, we think that the application of previously published data to patients with viral liver cirrhosis, especially in hepatitis endemic areas, is inappropriate. Further investigation comparing the prognosis after TIPS placement between patients with viral liver cirrhosis and those with alcoholic liver cirrhosis is needed.

In our group of patients with viral liver cirrhosis complicated by acute variceal bleeding, hyperbilirubinemia and an elevated creatinine level were associated with an increased risk of early mortality after TIPS placement.

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