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BRIEF ARTICLE

Clinical outcome and predictors of survival after TIPS insertion in patients with liver cirrhosis

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Abstract

AIM: To determine the clinical outcome and predictors of survival after transjugular intrahepatic portosystemic stent shunt (TIPS) implantation in cirrhotic patients.

METHODS: Eighty-one patients with liver cirrhosis and consequential portal hypertension had TIPS implantation (bare metal) for either refractory ascites (RA) (*n* = 27) or variceal bleeding (VB) (*n* = 54). Endpoints for the study were: technical success, stent occlusion and stent stenosis, rebleeding, RA and mortality. Clinical records of patients were collected and analysed. Baseline characteristics [e.g., age, sex, CHILD score and the model for end-stage liver disease score (MELD score), underlying disease] were retrieved. The Kaplan-Meier method was employed to calculate survival from the time of TIPS implantation and comparisons were made by log rank test. A multivariate analysis of factors influencing survival was carried out using the Cox proportional hazards regression model. Results were expressed as medians and ranges. Comparisons between groups were performed by using the Mann-Whitney *U*-test and the χ^2 test as appropriate.

RESULTS: No difference could be seen in terms of age, sex, underlying disease or degree of portal pressure gradient (PPG) reduction between the ascites and the bleeding group. The PPG significantly decreased from 23.4 ± 5.3 mmHg (VB) *vs* 22.1 ± 5.5 mmHg (RA) before TIPS to 11.8 ± 4.0 *vs* 11.7 ± 4.2 after TIPS implantation (P = 0.001 within each group). There was a tendency towards more patients with stage CHILD A in the bleeding group compared to the ascites group (24 *vs* 6, P = 0.052). The median survival for the ascites group was 29 mo compared to > 60 mo for the bleeding group (P = 0.009). The number of radiological controls for stent patency was 6.3 for bleeders and 3.8 for ascites patients (P = 0.029). Kaplan-Meier calculation indicated that stent occlusion at first control (P = 0.027), ascites prior to TIPS implantation (P = 0.009), CHILD stage (P = 0.013), MELD score (P = 0.001) and those patients not having undergone liver transplantation (P = 0.024) were significant predictors of survival. In the Cox regression model, stent occlusion (P = 0.022), RA (P = 0.043), CHILD stage (P = 0.015) and MELD score (P = 0.004) turned out to be independent prognostic factors of survival. The anticoagulation management (P = 0.097), the porto-systemic pressure gradient (P

= 0.460) and rebleeding episodes (P = 0.765) had no significant effect on the overall survival.

CONCLUSION: RA, stent occlusion, initial CHILD stage and MELD score are independent predictors of survival in patients with TIPS, speaking for a close follow-up in these circumstances.

Key words: Transjugular intrahepatic portosystemic stent shunt; Liver cirrhosis; Ascites; Gastrointestinal hemorrhage; Treatment outcome

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INTRODUCTION

Portal hypertension is a common problem in gastroenterology and the treatment of its complications is still a challenging task. Major complications of liver cirrhosis and portal hypertension include variceal bleeding (VB) and refractory ascites (RA)[1]. Despite a wide range of therapeutic modalities, including medical and surgical treatments, there is ongoing debate about the most effective treatment algorithm for the complications of portal hypertension[2-5].

At the end of the 1980's a new nonsurgical procedure was developed to enable decompression of the portal circulation *via* expandable metal stents between hepatic veins and the intrahepatic portal vein system - the transjugular intrahepatic portosystemic shunt (TIPS)[6-8]. Since then, the method has been established and improved systematically, culminating in the actual guidelines of the American Association for the Study of Liver Diseases (AASLD)[9].

Most clinicians agree that TIPS has an excellent hemostatic effect in VB (95%), with low rebleeding rates (< 20%)[10]. When endoscopic hemostasis of esophageal varices fails, TIPS becomes the first-line treatment of choice, with an estimated technical success rate in the range of 93%-100%[11-13]. Due to the circulatory effects on portal hypertension, TIPS is also an interesting approach in cases of RA[14-18] and hepatorenal syndrome[19]. However, following TIPS higher rates of hepatic encephalopathy are observed in patients with cirrhosis and RA[11]. Additionally, TIPS insertion has been reported to be successful in patients with portal vein thrombosis[20,21], Budd-Chiari syndrome[22] and portal cavernoma[23].

The use of bare metal stents has been the gold standard in TIPS procedure[24], but the higher occlusion rate with consecutive bleeding complications has recently led to the development of covered metal stents with significantly lower occlusion rates after TIPS implantation[25-28].

In a retrospective single centre study, we evaluated the efficacy and safety of TIPS in the treatment of portal hypertension using a self-expanding bare metal mesh-wire stent. The major objectives of the present study were to observe stenosis and occlusion rates, occurrence of rebleeding and predictors of survival.

MATERIALS AND METHODS

Patients

This retrospective single center study was conducted at the tertiary referral center of Muenster University Hospital (Department of Medicine B). One hundred and one patients were initially scheduled for TIPS implantation. Eventually 81 patients with complications of portal hypertension were enrolled from 1998 until 2008. Twenty patients were excluded because TIPS insertion was technically not feasible. The indication for TIPS treatment included acute or recurrent VB and RA.

Objectives of the study

Endpoints for the study analysis were: technical success (completed TIPS insertion, lowering of the portosystemic pressure gradient), rates of stent occlusion and stent stenosis, rebleeding, RA and mortality. Clinical records of patients were collected and carefully analysed. Baseline characteristics (e.g., age, sex) were retrieved as shown in Table 1.

Definitions

According to Bureau *et al*[29], the following definitions were used:

Stent dysfunction: > 50% reduction of the lumen of the stent at angiography with an increase of the portosystemic pressure gradient of more than 50% of the initial post-interventional value.

Recurrent VB: Recurrent VB that did not respond to the usual pharmacological and endoscopic therapy[30].

RA: Ascites that did not respond to conservative (low-salt diet) and pharmacological (diuretics) treatment or lack of treatment options because of treatment-induced complications[31].

Transjugular intrahepatic portosystemic stent procedure

All TIPS procedures were conducted in strong collaboration with an interventional radiologist and gastroenterologist at our hospital using standard techniques[32]. Through a transjugular venous approach, the right hepatic vein was catheterized. An intrahepatic branch of the portal vein was punctured. Before dilation of the liver parenchyma

Table 1 Baseline characteristics

Variables	Bleeding	Ascites	*P* value
Patients	54	27	
Age (yr)			0.497
mean ± SD	61.7 ± 10.4	63.3 ± 10.8	
Range	38-79	46-84	
Sex (male/female)	33/21	15/12	0.634
CHILD score			
A	24	6	0.052
B	28	18	NS
C	2	3	NS
MELD score	9.4 ± 4.9	13.7 ± 5.2	< 0.001
Underlying disease			
Chronic viral hepatitis B/C	7/1	2/1	0.949
Alcohol abuse	38	21	NS
Autoimmune hepatitis	2	0	NC
PSC/PBC	3	0	NC
Cryptogen	3	3	NS
Re-bleeding after TIPS	13	0	NC
PPG before TIPS (mmHg)	23.4 ± 5.3	22.1 ± 5.5	0.765
PPG after TIPS (mmHg)	11.8 ± 4.0	11.7 ± 4.2	0.883
Stent diameter[1] (mm)			
< 12/≥ 12	6/44	4/23	0.728
Anticoagulation after TIPS	31	9	0.042
LTX after TIPS	7	1	0.131
Median survival time (mo)	> 60	29	0.009
Number of radiological controls until evaluation	6.3 ± 4.8	3.8 ± 3.1	0.029
Time interval until first radiological control	9.3 ± 10.6	4.5 ± 5.6	0.133

[1]In four patients data acquisition of stent diameter not available. NS: Not significant; NC: Not calculated; LTX: Liver transplantation; TIPS: Transjugular intrahepatic portosystemic stent; PPG: Portal pressure gradient; MELD: Model for end-stage liver disease; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis.

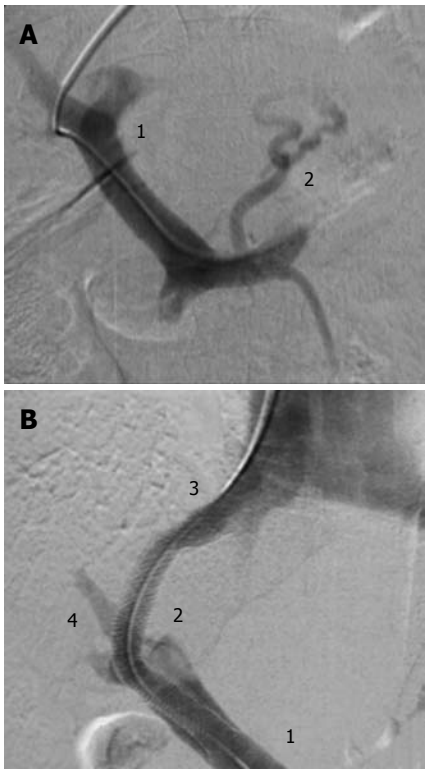

Figure 1 Fluoroscopic images showing transjugular intrahepatic portosystemic shunt placement procedure. A: Portogram after catheterisation of the portal vein, showing perfusion of the portal vein system (1) and oesophageal varices (2); B: Portogram after transjugular intrahepatic portosystemic stent placement. Contrast can be seen in the portal vein (1), through the shunt (2) flowing into the hepatic vein and inferior vena cava (3). Decompression of the portosystemic pressure can be seen in reduced contrast in the portal branch (4). The varices can no longer be identified in the fluoroscopic image.

both the portal pressure and the blood pressure of the right atrium were measured. Then the optimal stent length was defined using a special catheter with opaque markers. After the deployment of the bare metal stent the pressures of the portal vein and the right atrium were measured again. Pressures were measured using an Exadyn transducer set (Braun, Melsungen, Germany). The portal pressure gradient (PPG) resulted as the difference of the portal pressure minus the right atrium pressure (Figure 1). Postinterventional Doppler ultrasonography was carried out the day after TIPS insertion assessing stent patency. As presented by Sahagun *et al*[33] in 1997 shunt stenosis of bare metal stents can effectively be treated by interventional techniques to maintain patency. Stent stenosis due to endothelial growth usually occurs after 3 mo. It was therefore the policy of our institution to reevaluate each patient regularly with Doppler ultrasonography every 3 mo. Interventional angiography was performed every 12 mo or earlier when there was sonographic evidence of stenosis (fall of the initial increase of the portal blood velocity after stenting by > 50% according to Biecker *et al*[34]) or clinical features of recurrent portal hypertension (e.g., hepatic encephalopathy, worsening ascites, presence of high-risk varices at endoscopy or re-bleeding). A TIPS reintervention was performed, when a restenosis or occlusion was affirmed during the angiographic follow-up examination.

Model for end-stage liver disease score

To judge the clinical status of each cirrhotic patient, the model for end-stage liver disease score (MELD score) was calculated based on creatinine, bilirubin and clotting time.

The MELD score for each patient was computed according to the modified method of Wiesner *et al*[35]. This approach differs from the method originally published method by Malinchoc *et al*[36] in two ways: firstly, to avoid negative scores, laboratory serum creatinine levels that were less than 1 mg/dL were rounded off to 1. Preliminary studies in cohorts of non-transplantation candidates have implied that inclusion of the liver disease diagnosis variable does not increase the predictive value of the MELD score; secondly, as previously described by Wiesner *et al*[37,38], 6.43 points as a constant for liver disease aetiology was added to each patient's score to make the results comparable to the originally published studies. The following MELD equation was applied to calculate the severity score: 3.78 [Ln serum bilirubin (mg/dL)] + 11.20 (Ln international normalized ratio) + 9.57 [Ln serum creatinine (mg/dL)] + 6.43.

Table 2 Median survival times depending on various parameters

Parameter	Survival (mo)	95% CI (mo)	Tests	*P* value
Stent open	> 60	NC	Stent occluded *vs* open	0.027
Stent occluded at first control	50	36.6-63.4		
Ascites prior to TIPS	29	1.36-56.64	Ascites *vs* bleeding	0.009
Bleeding prior to TIPS	> 60	NC		
LTX after TIPS	> 60	NC	LTX *vs* no LTX	0.024
Stent diameter < 12 mm or ⩾ 12 mm	> 60	NC	Stent diameter < 12 mm *vs* ⩾ 12 mm	0.486
Anticoagulation	50	14.8–85.2	Anticoag *vs* no anticoag	0.060
No anticoagulation	> 60	NC		
PPG < 12 mmHg or ⩾ 12 mmHg after TIPS	> 60	NC	PPG < 12 mmHg *vs* ⩾ 12 mmHg	0.507
Age (yr)				
⩾ 65	51	33.4-68.6	Age < 65 yr *vs* ⩾ 65 yr	0.053
< 65	> 60	NC		
CHILD score				
A	48.9	40.6-57.2	CHILD A *vs* B	0.013
B	40.0	32.7-47.4		
C	15.0	1.4-28.6		
MELD score				
⩽ 10	52.2	46.3-58.0	MELD score ⩽ 10 *vs* > 10	0.001
> 10	35.3	26.9-43.6		

LTX: Liver transplantation; TIPS: Transjugular intrahepatic portosystemic stent; PPG: Portal pressure gradient; MELD: Model for end-stage liver disease; 95% CI: 95% confidence interval; NC: Not calculable.

Statistical analysis

Data were analyzed using SPSS 17.0 (Chicago, IL, United States). Results are expressed as medians and ranges. Comparisons between groups were performed by using the Mann-Whitney *U*-test and the χ^2 test as appropriate. $P < 0.05$ was considered statistically significant.

For screening of risk factors, univariate analysis was performed. The Kaplan-Meier method was employed to calculate survival from the time of TIPS implantation and comparisons were made by log rank test. A multivariate analysis of factors influencing survival was carried out using the Cox proportional hazards regression model.

RESULTS

Patient characteristics

In the study period (1998-2008), a total of 81 patients were admitted to the study with a mean age of 62.2 ± 10.5 years (range: 38-84 years). According to the indication for TIPS implantation, the patient cohort was subdivided into two groups: VB (group A) and RA (group B). The baseline characteristics of the study population are given in Table 1.

The aetiology of cirrhosis was related to chronic viral hepatitis B or C, alcohol abuse, autoimmune hepatitis and primary sclerosing cholangitis/primary biliary cirrhosis. The mean age in the VB and the RA group showed no statistical difference (61.7 years *vs* 63.3 years, $P = 0.497$). Likewise, the male/female ratio in both groups was comparable, with a slight trend to male patients. The severity of liver disease was calculated according to the CHILD scoring system[39]. Overall, 37% of patients with CHILD A, 57% with B and 6% with CHILD C were enrolled in this study. The MELD score in the RA group was significantly higher compared to the VB group (13.7 ± 5.2 *vs* 9.4 ± 4.9, $P = 0.001$).

TIPS shunt function and patient survival

The PPG significantly decreased from 23.4 ± 5.3 mmHg (VB) *vs* 22.1 ± 5.5 mmHg (RA) before TIPS to 11.8 ± 4.0 mmHg *vs* 11.7 ± 4.2 mmHg after TIPS implantation ($P = 0.001$ within each group). On the other hand, gradient reduction in the VB group did not statistically differ from that in the RA group. Referring to stent diameters there were no relevant differences between both groups. Anticoagulation therapy with enoxaparin at weight-calculated dose was applied for 12 wk after TIPS implantation in 50% of the patients. Thirty-one out of 54 patients in the bleeding group received subcutaneous anticoagulation therapy after TIPS, while only 9 out of 27 patients with RA were anticoagulated post-procedurally ($P = 0.042$). Neither the stent occlusion rate nor the rebleeding rate depended on the anticoagulation state ($P = 0.7$ and $P = 0.47$, respectively). In our patient cohort, the median patency rate of the TIPS shunt was 10 mo. The median survival time was > 60 mo in the VB group *vs* 29 mo in the RA group, showing a significant difference ($P = 0.009$). The number of radiological controls for stent patency was 6.3 ± 4.8 (VB) *vs* 3.8 ± 3.1 (RA) ($P = 0.029$). The mean time interval until the first radiological control was 9.3 ± 10.6 mo (VB) *vs* 4.5 ± 5.6 mo (RA) ($P = 0.133$).

Kaplan-Meier calculation indicated that the stent function (open *vs* occluded) at first control was a significant predictor of survival ($P = 0.027$) (Table 2 and Figure 2B). Furthermore, the median survival time was longer in patients with TIPS due to VB compared to that in patients with RA ($P = 0.009$) (Table 2 and Figure 2A). Seven patients in the VB group and one patient in the RA group underwent liver transplantation. As expected, in univariate analysis survival rates were significantly higher after liver transplantation ($P = 0.024$). The PPG after TIPS had no significant influence on median survival times in both groups (Table 2). Mortality was not significantly increased in patients aged > 65 years (Table

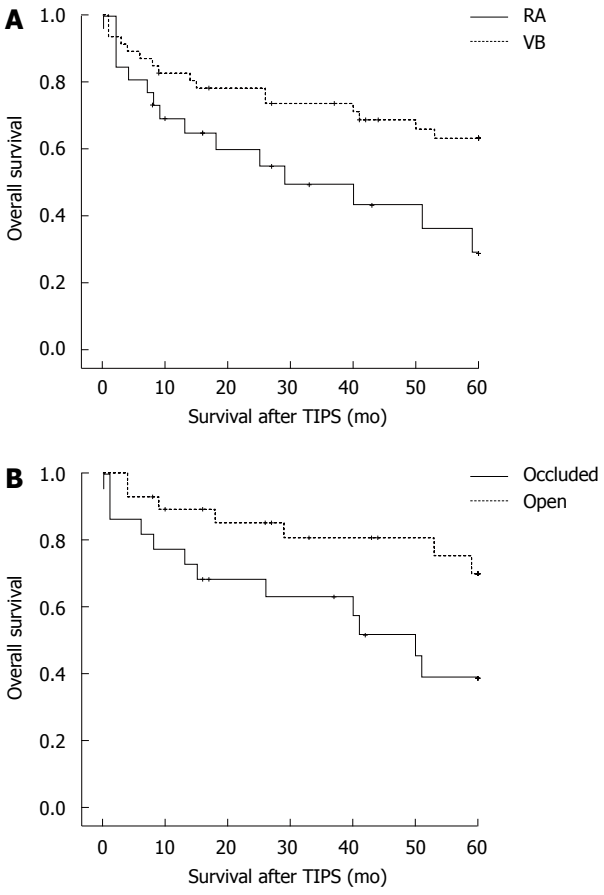

Figure 2 Kaplan-Meier survival analysis of patients after transjugular intrahepatic portosystemic shunt placement. A: In patients with initial ascites as indication for transjugular intrahepatic portosystemic stent (TIPS), survival is significantly shorter than that in patients with variceal bleeding [refractory ascites (RA) *vs* variceal bleeding (VB), log rank test $P = 0.009$]; B: In patients with occluded stent at first fluorographic control, survival is significantly shorter than that in patients with open stent (occluded *vs* open, log rank test $P = 0.027$).

2). For those patients having a MELD score greater than 10, the median survival was significantly shorter than for those with a MELD score less than or equal to 10 (35.3 mo *vs* 52.2 mo, $P = 0.001$).

In the Cox regression model, only stent occlusion at first control ($P = 0.022$), ascites prior to TIPS ($P = 0.043$), CHILD stage ($P = 0.015$) and MELD score ($P = 0.004$) were independent prognostic factors of survival. In contrast, anticoagulation management ($P = 0.097$), the porto-systemic pressure gradient ($P = 0.460$) and rebleeding episodes ($P = 0.765$) had no significant effect on the overall survival.

We further performed a subgroup analysis using the Kaplan-Meier method in terms of survival of the two groups considering the independent risk factors by Cox regression model analysis such as age, stent patency at first control, CHILD and MELD scores.

When survival was analyzed based on MELD scores (Figure 3A and B) we found that patients with VB had a statistically improved survival over those with RA (MELD score < 10 *vs* $\geqslant 10$, log rank $P = 0.001$).

Stratification by CHILD stages B and C or age > 65 years demonstrated that patients in the VB group had a significantly improved long-term survival compared with those in the RA group (log rank test $P = 0.021$ each) (Figure 3C and D).

Due to limited patient numbers the overall survival in patients with stent occlusion at first control did not differ significantly in both groups (Figure 3E, log rank test $P = 0.289$).

DISCUSSION

Since its introduction in the 1980s, the TIPS procedure has played a major role in the management of portal hypertension[9,24,40-43]. In the present study, shunt insertion was completed successfully in 81 patients (80% of patients scheduled). The baseline characteristics show the heterogeneous patient population at our hospital, the distribution of underlying diseases is typical for western countries[44,45] (Table 1).

Until recently, bare metal stents were the treatment of choice for establishing the TIPS tract. In contrast to the actual AASLD guidelines[9], in the United States[46] about 20% of all TIPS procedures still use uncovered TIPS stents.

Even though covered TIPS stents require fewer reinterventions, after a 12-mo-follow-up, the total procedure-related expenses were higher with covered TIPS stents due to their higher initial cost[43]. Further, a study by Bureau *et al*[25] in 2007 could not detect any survival benefit of covered *vs* uncovered stents. For these reasons we used non-coated TIPS stents during the study period of 1998 until 2008. Since this study was initiated at our institution, polytetrafluoroethylene-covered stents are now widely used, with the recent literature showing a significant improvement of primary patency up to 90% within 12 mo of application[25,28,47].

In agreement with Membreno *et al*[48], we show that in patients with TIPS due to VB, the overall long-term survival is significantly better than that in patients with TIPS due to RA (> 60 mo *vs* 29 mo, $P = 0.009$) (Figure 2A).

In the VB and RA groups of our study, the degree of reduction of the PPG following TIPS implantation was almost identical and there was no significant correlation with stent diameters. According to the literature, an adequate decompression of portosystemic hypertension can be achieved by 50% reduction of the initial pressure[49]. Other series describe a 20% reduction as sufficient and the PPG should be decreased and maintained under 12 mmHg[50]. In our study, the PPG was lowered post-procedurally at a recommended threshold of approximately 12 mmHg[24] (VB 11.8 ± 4.0 mmHg *vs* RA 11.7 ± 4.2 mmHg). Biecker *et al*[34] demonstrated in their study with 118 cirrhotic patients, that the initial decrease in the PPG after TIPS is a predictor of the rebleeding risk, but not of survival. Our study was not able, however, to confirm these findings.

In our patient cohort, the Cox multivariate regression analysis identified stent occlusion at first control as an

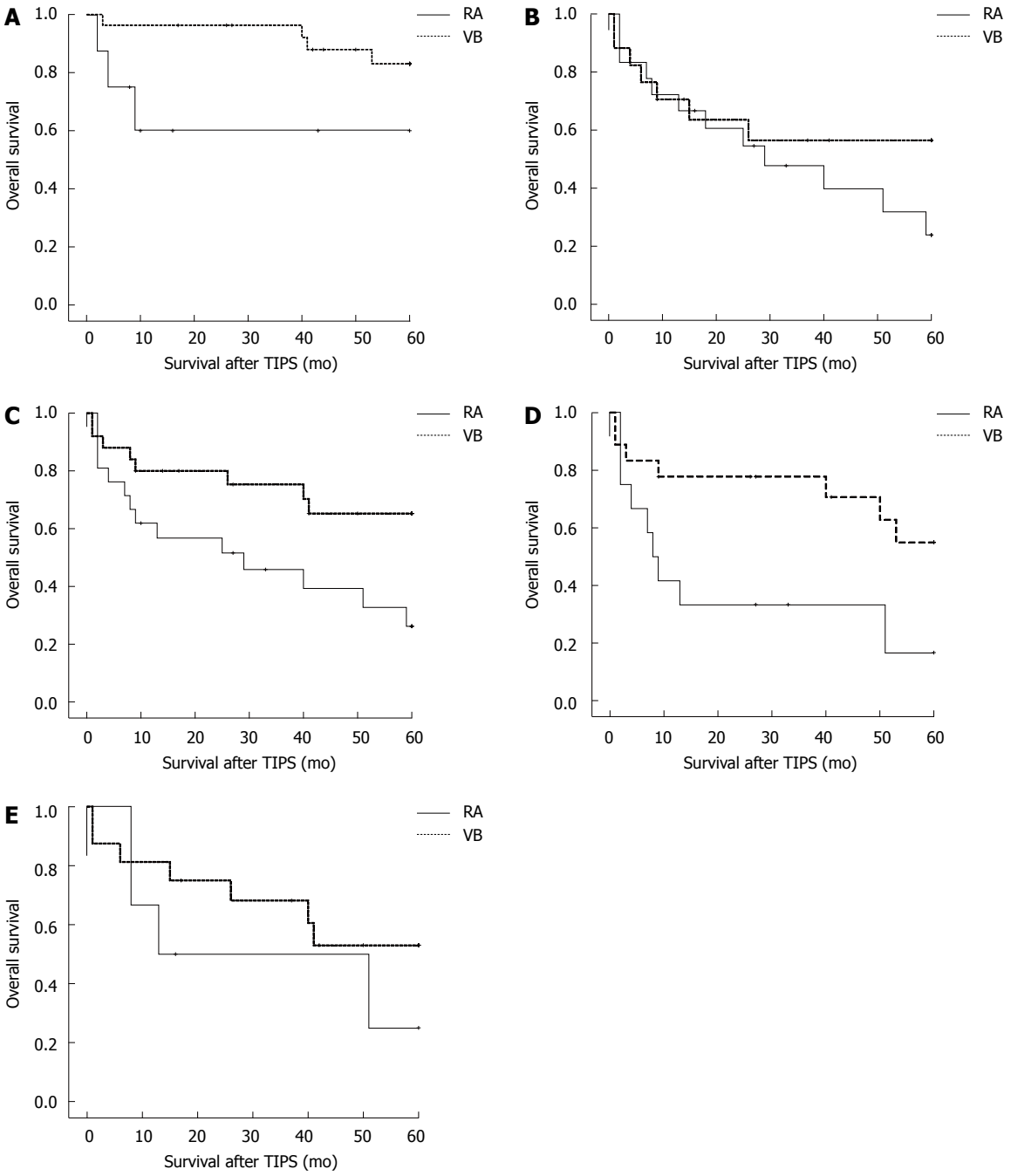

Figure 3 Kaplan-Meier survival analysis of patients after transjugular intrahepatic portosystemic shunt placement. A: Subgroup analysis with patients having a model for end-stage liver disease score (MELD) < 10: Significant difference in overall survival relating to indication [refractory ascites (RA) *vs* variceal bleeding (VB) group, log rank test $P = 0.031$]; B: Subgroup analysis with patients having a MELD score > 10: No significant difference in overall survival relating to indication (RA *vs* VB group, log rank test $P = 0.274$); C: Subgroup analysis with patients with CHILD B or C cirrhosis: Significant difference in overall survival relating to indication (RA *vs* VB group, log rank test $P = 0.021$); D: Subgroup analysis with patients age > 65 years: Significant difference in overall survival relating to indication (RA *vs* VB group, log rank test $P = 0.021$); E: Subgroup analysis with stent occlusion at first control: No significant difference in overall survival relating to indication (RA *vs* VB group, log rank test $P = 0.289$).

independent predictor of survival regardless of the indication for TIPS (Figure 2B and Figure 3E). Therefore, regular monitoring of the TIPS patients is highly recommended to provide early intervention when stenosis occurs[51]. In our institution, after successful TIPS insertion the first controls are conducted within 3 mo. Based on the results of the first interventional control (angiography), the following examinations are scheduled. Routinely colour Doppler ultrasound is used as a non-invasive device for monitoring the TIPS function.

Unsurprisingly, CHILD stage was an independent prognostic factor of survival ($P = 0.015$), probably due to the fact that the CHILD scoring system is a validated tool for assessing prognosis[39,52]. When survival was analyzed based on CHILD B or C, we found that patients with VB had a statistically improved survival over those

with RA (Figure 3C). Similar findings could be observed for patients being older than 65 years or having a MELD score < 10 leading to a significant overall survival relating to the indication for TIPS as displayed in Figure 3A, B and D.

These observations are consistent with those by Membreno *et al*[48]. The retrospective design and the use of uncovered stents as well as the relatively small sample size may introduce a certain bias. Nevertheless, our retrospective study emphasises several clinical aspects of portal hypertension in liver cirrhosis to be considered in conjunction with TIPS treatment.

In conclusion, TIPS is an established and safe nonsurgical method to decompress portal hypertension and to avoid its sequelae. RA prior to TIPS and stent occlusion at first control are independent predictors of survival in patients with bare metal TIPS shunts. This observation militates in favour of close follow-ups for patients with TIPS due to RA.

COMMENTS

Background

Liver cirrhosis is a common problem in gastroenterology. Various medical and interventional treatment options have been developed to manage the complications of portal hypertension. Minimal invasive placement of a transjugular intrahepatic portosystemic shunt (TIPS) is now widely used to lower the portosystemic pressure gradient.

Research frontiers

The authors undertook a retrospective study to work out the clinical outcome and predictors of survival after TIPS insertion with bare metal stents.

Innovations and breakthroughs

Refractory ascites (RA), stent occlusion at first control, initial CHILD stage and model for end-stage liver disease score were identified as independent predictors of survival in cirrhotic patients after TIPS implantation.

Applications

By understanding, which risk factors can influence survival in cirrhotic patients scheduled for TIPS insertion, the authors contribute to a better knowledge of this common clinical scenario. This may lead to a better risk stratification for the indication of TIPS insertion.

Terminology

The TIPS procedure decompresses the portosystemic pressure by establishing a "short cut" between the portal vein and the caval venous system.

Peer review

This is a retrospective study with the major objective to observe the role of stenosis and occlusion rates of uncovered stents on the survival of cirrhotic patients with TIPS inserted for variceal bleeding or RA.

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