ORIGINAL PAPER

Available from: http://www.jgld.ro/wp/archive/y2015/n3/a7
DOI: http://dx.doi.org/10.15403/jgld.2014.1121.243.yao

Risk Factors for Hepatic Encephalopathy after Transjugular Intrahepatic Portosystemic Shunt in Patients with Hepatocellular Carcinoma and Portal Hypertension

Jiannan Yao[1], Li Zuo[2], Guangyu An[1], Zhendong Yue[3], Hongwei Zhao[3], Lei Wang[3], Fuquan Liu[3]

1) Department of Oncology, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020;
2) Department of Respiratory Medicine, NO. 731 Hospital of CASIC, Beijing 100074;
3) Department of Interventional Therapy, Beijing Shijitan Hospital, Capital Medical University, Beijing 100038;
China

Address for correspondence:
Fuquan Liu
Department of Interventional Therapy,
Beijing Shijitan Hospital,
Capital Medical University,
Beijing 100038; China
lfuquan@aliyun.com

Received: 15.02.2015
Accepted: 28.06.2015

ABSTRACT

Aims: This study aimed at assessing the risk factors for hepatic encephalopathy (HE) after transjugular intrahepatic portosystemic shunt (TIPS) in patients with hepatocellular carcinoma (HCC) and portal hypertension.

Method: Consecutive patients (n=279) with primary HCC who underwent TIPS between January 1997 and March 2012 at a single institution were retrospectively reviewed. Patients were followed up for 2 years. Pre-TIPS, peri-TIPS and post-TIPS clinical variables were reviewed using univariate and multivariate analyses to identify risk factors for HE after TIPS.

Results: The overall incidence of HE was 41% (114/279). Multivariate analysis showed an increased odds for HE in patients with: >3 treatments with transcatheter arterial chemoembolization (TACE) and/or trans-arterial embolization (TAE) (odds ratio [OR], 4.078; 95% confidence interval [95%CI], 1.748-9.515); hepatopetal portal flow (OR, 2.362; 95%CI, 1.032-5.404); high portosystemic pressure gradient (OR, 1.198; 95%CI, 1.073-1.336) and high pre-TIPS MELD score (OR, 1.693; 95%CI, 1.390-2.062). Odds for HE were increased 1.693 fold for each 1-point increase in the MELD score, and 1.198 fold for each 1-mmHg decrease in the post-TIPS portosystemic pressure gradient.

Conclusion: The identification of clinical variables associated with increased odds of HE may be useful for the selection of appropriate candidates for TIPS. Results suggest that an inappropriate decrease in the portosystemic pressure gradient might be associated with HE after TIPS. In addition, >3 treatments with TACE/TAE, hepatopetal portal flow, and high MELD score were also associated with increased odds of HE after TIPS.

Key words: hepatocellular carcinoma – portal hypertension – transjugular intrahepatic portosystemic stent shunt – hepatic encephalopathy.

Abbreviations: HE: hepatic encephalopathy; HCC: hepatocellular carcinoma; IVC: inferior vena cava; MELD: Model for End-stage Liver Disease; PSG: portosystemic pressure gradient; PVTT: portal vein tumor thrombosis; RFA: radiofrequency ablation; TIPS: transjugular intrahepatic portosystemic shunt; TACE: transcatheter arterial chemoembolization; TAE: trans-arterial embolization.

INTRODUCTION

A transjugular intrahepatic portosystemic shunt (TIPS) can effectively reduce portal pressure and relieve the clinical symptoms associated with various medical conditions. TIPS has found a wide range of applications including the treatment of portal hypertension due to cirrhosis, gastrointestinal bleeding, refractory ascites, hepatic hydrothorax, hepatorenal syndrome, Budd-Chiari syndrome, hepatopulmonary syndrome and portal thrombosis, and as a bridge to liver transplantation [1-7]. However, the procedure has two potential drawbacks that have long-term effects on the patients' post-TIPS quality of life: the occurrence of shunt stenosis and hepatic encephalopathy (HE). The use of covered stents has significantly decreased the occurrence of shunt stenosis [8-12]. In contrast, only slow progress has been made in the investigation and treatment of HE. Available literature indicates that post-TIPS HE occurs in approximately 31-47% of patients with portal hypertension, with a tendency toward a higher incidence in patients with hepatic tumors [13-16]. A retrospective review of 38 patients with cancer who underwent TIPS revealed that primary technical success was achieved

in 97% of patients without procedure-related complications, and that HE occurred in 44% of patients [17]. The occurrence of post-TIPS HE in patients with hepatocellular carcinoma (HCC) has a serious negative impact on life expectancy and quality of life. There is some evidence that the incidence of HE is lower for an 8-mm stent (5-10%) than for larger stents [11, 18]. However, there are few published reports concerning the risk factors for post-TIPS HE in patients with HCC.

The present study was a retrospective review of the clinical data of 279 consecutive patients with HCC and portal hypertension who underwent TIPS between January 1997 and March 2012 at a single institution. The aim of the study was to evaluate the relationship between the occurrence of HE and the clinical status of the patient pre-, peri- and post-TIPS, and to determine the risk factors for post-TIPS HE.

METHODS

Patients

Complete clinical data were collected retrospectively for 279 patients with primary HCC who underwent TIPS between January 1997 and March 2012 at the Department of Interventional Therapy, Beijing Shijitan Hospital, Capital Medical University (Beijing, China). The diagnosis was preferably confirmed by aspiration biopsy; for patients who refused biopsy, the diagnosis was made based on computed tomography (CT) and/or magnetic resonance imaging (MRI). All patients had HCC when they underwent TIPS. Central HCC is a contraindication to TIPS, and these patients were not included. The indications for TIPS included: 1) patients with HCC and esophageal and/or gastric variceal bleeding; 2) patients with HCC and refractory ascites; or 3) HCC combined with esophageal and/or gastric variceal bleeding and refractory ascites. In all cases, tumoral lesions had to be out of the puncture way.

Exclusion criteria were: 1) a definite diagnosis of HE prior to TIPS; 2) patients with advanced cancer and a life expectancy of less than 3 months; and 3) patients who had received transplantation or systematic therapies.

The diagnostic criteria for HE were as defined by the 11th World Congresses of Gastroenterology [19]. The 279 patients included in the study were grouped according to the presence of HE. Patients were followed up for 2 years. The post-TIPS occurrence of HE, or death were selected as the primary endpoints of the study.

The study was approved by the local Ethics Committee. The need for individual consent was waived by the Committee. This study was performed according to the guidelines of the Declaration of Helsinki.

Therapeutic procedure

A routine TIPS technique was used. The right internal jugular vein was punctured; a RUPS-100 (Cook Medical, Bloomington, IN, USA) was then advanced into the inferior vena cava (IVC) or the hepatic vein, and an appropriate position and angle were chosen to maneuver it into the left or right branch of the portal vein. After confirming that the RUPS-100 was in the portal vein using venography, an intrahepatic access set (Cook Medical, Bloomington, IN, USA) was inserted into the portal vein. Portography was performed with a pigtail catheter placed in the main portal vein, and the portosystemic pressure gradient (PSG) was measured. Catheters were placed into the right atrium and inferior vena cava through the internal jugular vein, followed by insertion into the hepatic veins to measure the free hepatic vein pressure. The catheter was then advanced to the end of the hepatic vein to measure its wedge pressure. The difference of the above hepatic vein pressures represented the portosystemic gradient. Varices were blocked using coils and/or gelatin sponges and/or absolute ethanol pre- or post-TIPS; the portal vein pressure was then re-measured. A balloon (8-mm or 6-mm) was advanced through the guide-wire to expand the shunt, and a stent (8-mm or 10-mm) was then implanted inside the shunt. The portal vein pressure was measured again, and portography was performed. Of the 279 patients included in the study, nitinol bare stents (Ev3; Cordis Corporation, USA) were used in 112, and covered stents (Fluency; Bard Inc., USA) in 167. A single stent was implanted in 201 patients, and two or more stents in 78. An 8-mm stent was used in 208 patients, while a 10-mm stent was used in 71. The shunt was created through the hepatic vein in 235 patients, and through the hepatic inferior vena cava in 44. The shunt was created in the right branch of the portal vein in 238 patients, and in the left branch in 41. TIPS combined with percutaneous transhepatic portal vein venography or gastric coronary vein embolization was performed de facto in 28 patients in whom portal puncture was evaluated pre-TIPS to be challenging or direct procedures were considered pre-TIPS to be high risk. Percutaneous transhepatic puncture of the portal vein was undertaken in the right rib area or subcostally, and a 4F catheter was then advanced inside the portal vein to perform portography and/or block varices (mainly emergency patients). The shunt was created with the catheter serving as an indicator of the location of the portal vein. A total of 253 patients had percutaneous transhepatic varices blocked or shunted.

All patients underwent 2-7 routine transcatheter arterial chemoembolization (TACE) and/or trans-arterial embolization (TAE) sessions before and/or after TIPS. One hundred and twenty-one patients underwent radiofrequency ablation (RFA). For TACE and TAE, a catheter was selectively or super-selectively inserted into the target tumor‘s blood-supplying artery, and appropriate amount of embolization reagent was administered at a suitable speed to close the artery and induce ischemic necrosis of tumor tissues. Each treatment was tailored to each specific patient. Embolization aimed to embolize completely the tumor‘s blood-supplying artery. No patient received transplantation or systemic therapies.

Follow-up

Patients were followed up for two years through observation of clinical symptoms and the use of investigations as necessary including routine blood tests, coagulation tests, hepatic function tests, blood ammonia levels, color ultrasound, barium meals, CT scans, and/or gastroscopy. Portography and measurement of portal venous pressure were undertaken if the color ultrasound suggested stenosis and/or gastrointestinal bleeding, or refractory ascites and/or hydrothorax occurred. Patients with normal blood flow but an increased portal venous pressure or stenosis/occlusion of the shunt required

balloon dilatation and/or stent reinsertion. A second TIPS was performed (n=195) if the initial shunt was difficult to re-open or had insufficient flow. Follow-up methods included telephone calls, outpatient reviews, and inpatient follow-up when medical events occurred. Patients requiring continuous treatment of their HCC were followed up every month for the first 3 months after the procedure, and then every 1 to 3 months, as appropriate. Patients not needing treatment of their HCC were followed up every 3 months. No patient was lost to follow-up.

Statistical analysis

All statistical analyses were conducted using SPSS 19.0 (IBM, Armonk, NY, USA). Continuous data were tested for normality using the Kolmogorov-Smirnov test and all were normally distributed; they are expressed as mean ± standard deviation (SD). Categorical data are expressed as ratios and percentages. Comparisons of pre-TIPS, peri-TIPS and post-TIPS clinical characteristics between the HE and non-HE groups were performed using the chi-square test or the Student's *t*-test, as appropriate. Variables with statistically significant associations with the primary endpoints were analyzed by multivariate logistic regression analysis to assess the risk factors related to the endpoints, and odds ratio (OR) values with 95% confidence intervals (95%CI) were calculated to perform risk analysis. A p value <0.05 was considered to be statistically significant.

RESULTS

Characteristics of the patients

A total of 279 patients (172 men and 107 women) with HCC were included in the study, having a mean age of 49.2±11.6 (range 25-78) years. The underlying etiologies were: hepatitis B (n=252), alcoholic cirrhosis (n=12), hepatitis C (n=11), hepatitis B and C (n=2), primary biliary cirrhosis (n=1), and autoimmune cirrhosis (n=1). In 78 patients, HCC was accompanied by portal vein tumor thrombosis (PVTT). Eight patients underwent splenectomy and azygoportal disconnection before TIPS, and 23 patients underwent pre-TIPS endoscopic varice ligation. Sixty patients had their tumor surgically removed before TIPS; eight patients underwent curative surgery, and no residual tumor was found in these patients. The numbers of patients with a single HCC lesion, double lesions, and three or more lesions were 206, 64, and 9, respectively. Esophagogastric variceal bleeding occurred in 226 patients, refractory ascites (and/or hydrothorax) in 36, and refractory ascites (and/or hydrothorax) accompanied by gastrointestinal bleeding in 17 (Table I). Three patients had intra-abdominal hemorrhage because of puncture into extrahepatic tissues, and they recovered after treatment. No tumor progression was found that could be related to tumor seeding.

Factors associated with hepatic encephalopathy

Hepatic encephalopathy occurred in 114 patients (41%) about 3 months after TIPS. In univariate analysis, the Model for End-stage Liver Disease (MELD) score determined just before TIPS and the number of TACEs/TAEs performed post-TIPS were the clinical characteristics associated with HE after TIPS (Table I). The peri-TIPS clinical characteristics associated with the occurrence of HE after TIPS placement were the mean decreased pressure differential and portal vein flow direction (hepatopetal vs. hepatofugal) (Table I). In the multivariate logistic regression analysis (Table II), patients who received >3 TACE/TAE treatments had much higher odds of HE compared with patients who received ≤ 3 TACE/TAE treatments (OR, 4.078; 95%CI, 1.748-9.515). The odds of HE after TIPS increased in patients with hepatopetal main portal vein flow compared with hepatofugal main portal vein flow (OR, 2.362; 95%CI, 1.032-5.404). The lowering of portal vein pressure by TIPS is central to the improvement of the symptoms of portal hypertension; however, the odds of HE increased by about 20% for each 1-mmHg decrease in post-TIPS PSG (OR, 1.198; 95%CI, 1.073-1.336), indicating that excessive reductions in portal vein pressure were associated with higher odds of HE. In addition, the odds of HE increased by about 70% for each 1-point increase in the MELD score (OR, 1.693; 95%CI, 1.390-2.062).

DISCUSSION

The main finding of the present study was that increased odds of post-TIPS HE were associated with >3 TACE/TAE treatments, hepatopetal main portal vein flow, an excessive decrease in the post-TIPS PSG, and higher MELD score. These data might provide guidance to clinicians for selecting patients with HCC and portal hypertension for TIPS. To the best of our knowledge, the present study is the first to examine the risk factors associated with HE in Chinese patients with HCC and portal hypertension.

TIPS is an effective procedure for treating the complications of portal hypertension in patients with cirrhosis caused by various etiologies [20] or HCC. Approximately 80% of patients with HCC and cirrhosis have symptoms associated with portal hypertension, and the main cause of death in some cases is not the tumor itself but related complications such as esophageal and gastric variceal bleeding, refractory ascites, and hepatic dysfunction due to PVTT or accompanying thrombosis. Although TIPS can effectively resolve the problems associated with portal hypertension, the high incidence of post-TIPS HE has significant implications in terms of the quality of life and the long-term success of the procedure. The incidence of post-TIPS HE observed in the present study (41%) was similar to that reported by previous studies (31-47%) [11, 13-16, 21]. To optimize the benefits of TIPS, it is important to screen patients carefully for any risk factor for HE, to select an appropriate treatment approach, and to take appropriate measures to maximize the prevention of HE. This, of course, necessitates the identification of factors associated with HE.

Numerous studies have evaluated the risk factors associated with post-TIPS HE in patients with portal hypertension due to cirrhosis, although these studies did not focus on patients with HCC. A review of 77 patients with cirrhosis treated using TIPS and followed up for one year suggested that non-alcoholic liver disease, female gender, and low albumin levels increased the risk of HE [22]. Riggio et al. [11] retrospectively reviewed 78 patients with cirrhosis treated with TIPS using a PTFE-

Table I. Comparison of the pre-, peri-, and post-TIPS characteristics of the patients from the HE group and the non-HE group.

Variable	HE group (n=114)	Non-HE group (n=165)	X^2 value	P value
Age (years), mean ± SD	49.8±10.9	48.3±12.7		0.306
Gender (male/female)			0.033	0.857
Male (n/%)	71 (62.3)	101 (61.2)		
Female (n/%)	43 (37.7)	64 (38.8)		
Surgery			0.542	0.462
Yes (n/%)	27 (23.7)	33 (20.0)		
No (n/%)	87 (76.3)	132 (80.0)		
MELD score	14.7±3.8	9.8±2.1		<0.001
History of cirrhosis			0.024	0.876
Viral cirrhosis (n/%)	108 (94.7)	157 (95.2)		
Alcoholic and other (n/%) cirrhosis	6 (5.3)	8 (4.8)		
Original no. of cancer lesions lesion			0.362	0.547
Single (n/%)	82 (71.9)	124 (75.2)		
Multiple (n/%)	32 (28.1)	41 (24.8)		
Blood supply of the cancer lesion			1.538	0.215
Rich (n/%)	84 (73.7)	132 (80.0)		
Insufficient (n/%)	30 (26.3)	33 (20.0)		
Total diameter of the tumor (cm)			2.073	0.355
≤3 (n/%)	26 (22.8)	43 (26.1)		
>3, ≤5 (n/%)	53 (46.5)	84 (50.9)		
>5 (n/%)	35 (30.7)	38 (23.0)		
Portal vein tumor thrombosis			0.152	0.696
Yes (n/%)	25 (21.9)	33 (20.0)		
No (n/%)	89 (78.1)	132 (80.0)		
Blood alpha-fetoprotein			0.122	0.727
Positive (n/%)	73 (64.0)	109 (66.1)		
Negative (n/%)	41 (36.0)	56 (33.9)		
Choice of stent			0.647	0.421
Bare stent (n/%)	49 (43.0)	63 (38.2)		
Covered stent (n/%)	65 (57.0)	102 (61.8)		
Number of stents implanted			0.094	0.759
1 (n/%)	81 (71.1)	120 (72.7)		
≥2 (n/%)	33 (28.9)	45 (27.3)		
Stent diameter			1.946	0.163
8 mm (n/%)	80 (70.2)	128 (77.6)		
10 mm (n/%)	34 (29.8)	37 (22.4)		
Varice occlusion (n/%) (yes/no)			0.463	0.496
Yes (n/%)	105 (92.1)	148 (89.7)		
No (n/%)	9 (7.9)	17 (10.3)		
Coronary trunk diameter			0.174	0.676
≥0.5 cm (n/%)	51 (44.7)	78 (47.3)		
<0.5 cm (n/%)	63 (55.3)	87 (52.7)		
Portal vein diameter			0.343	0.558
≥1.5 cm (n/%)	43 (37.7)	68 (41.2)		
<1.5 cm (n/%)	71 (62.3)	97 (58.8)		
TIPS method			0.117	0.733
HV-PV shunt (n/%)	95 (83.3)	140 (84.8)		
VC-PV shunt (n/%)	19 (16.7)	25 (15.2)		

Table I. (continued)				
Branch for TIPS creation			0.363	0.547
Right branch of portal vein (n/%)	99 (86.8)	139 (84.2)		
Left branch of portal vein (n/%)	15 (13.2)	26 (15.8)		
Portal vein flow pre-TIPS			4.360	0.037
Hepatofugal portal flow (n/%)	47 (41.2)	89 (53.9)		
Hepatopetal portal flow (n/%)	67 (58.8)	76 (46.1)		
Pressure differential pre- and post-TIPS			2.054	0.152
≥50% (n/%)	41 (36.0)	46 (27.9)		
<50% (n/%)	73 (64.0)	119 (72.1)		
Mean decreased pressure differential	18.6±5.1	12.8±3.0		<0.0011
Number of TACEs post-TIPS			4.640	0.031
≤3 times (n/%)	50 (43.9)	94 (57.0)		≤3 times
>3 times (n/%)	64 (56.1)	71 (43.0)		>3 times
TIPS creation and recreation			0.232	0.630
Initial creation (n/%)	54 (47.4)	83 (50.3)		
Interventional re-management (n/%)	60 (52.6)	82 (49.7)		
Refractory ascites			0.211	0.646
Yes (n/%)	13 (11.4)	16 (9.7)		
No (n/%)	101 (88.6)	149 (90.3)		
Recurrent gastrointestinal bleeding			2.602	0.107
Yes (n/%)	51 (44.7)	58 (35.2)		
No (n/%)	63 (55.3)	107 (64.8)		

HE: hepatic encephalopathy; HV: hepatic vein, PV: portal vein, VC: vena cava; TACE: transcatheter arterial chemoembolization; TAE: trans-arterial embolization; TIPS: transjugular intrahepatic portosystemic shunt; MELD: Model for End-stage Liver Disease.

Table II. Multivariate analysis of the risks of HE post-TIPS.

Independent variable	Odds ratio	95% confidence interval	P value
Number of TACEs/TAEs	4.078	1.748, 9.515	0.001
Portal vein flow pre-TIPS	2.362	1.032, 5.404	0.042
Portosystemic pressure gradient post-TIPS	1.198	1.073, 1.336	0.001
MELD score	1.693	1.390, 2.062	<0.001

HE: hepatic encephalopathy; TACE: transcatheter arterial chemoembolization; TAE: transarterial embolization; TIPS: transjugular intrahepatic portosystemic shunt; MELD: Model for End-stage Liver Disease.

covered stent, and the multivariate analysis revealed that high creatinine levels, low serum sodium, and low albumin levels were independent risk factors for HE. Low serum fibrinogen levels have also been correlated with an elevated risk of post-TIPS HE [23]. Several studies have suggested that older age is associated with an elevated risk of HE [11, 13, 21, 24], although this was not observed in the present study. This may reflect differences in the patient cohorts, including the fact that the patients of our study had HCC and that they may be with different ethnic background.

The hepatic functional status has been deemed to be directly associated with post-TIPS HE [25, 26]. Higher pre-TIPS Child-Pugh score has been reported to be associated with post-TIPS HE [23, 24]. TIPS can worsen liver dysfunction, and the Child-Pugh score has disadvantages when applied in such patients. In 2000, Malinchoc et al. adopted the MELD score for the first time to predict the mortality rate of patients with end-stage liver disease treated by TIPS [27]. A 15-year retrospective evaluation demonstrated a significantly poorer survival after TIPS in patients with a MELD score greater than 15 [28]. Consistent with this report, the results of the present study suggested that the odds of HE increased by about 70% for each 1-point increase in the MELD score.

The PSG has also been involved in the risk of post-TIPS HE. In the present study, the odds of HE were increased by about 20% for each 1-mmHg decrease in the post-TIPS PSG, suggesting that an inappropriately large reduction in portal vein pressure might increase the odds of HE. These results are consistent with those described previously by Chung et al. [29], i.e. that the critical lower threshold for post-TIPS PSG was 5 mmHg, such that a PSG >5 mmHg would lead to HE. In particular, patients with a Child-Pugh score >10 and a MELD score >14 tended to show a significant increase in the occurrence of refractory HE. Rossi et al. [15] showed that HE occurred in all patients with a PSG ≤12 mmHg, while Riggio et al. [21] reported that a portacaval gradient <10 mmHg was a predictor of HE. Interestingly, Zuckerman et al. [13] found that a low portal vein pressure correlated with post-TIPS HE. Although TIPS can successfully reduce portal pressure and relieve the symptoms of portal hypertension, an excessive reduction in portal pressure appears to be associated with higher odds of HE. Thus, there is evidence that portal pressure should not be reduced too aggressively in order to avoid the occurrence of HE.

In the present study, the use of pre-TIPS ultrasonography and peri-TIPS main portal vein venography revealed that hepatopetal portal flow was associated with greater odds of HE compared with hepatofugal portal flow. Moreover, multivariate analysis suggested that the odds of HE were 2.362 times higher in the hepatopetal group, compared with the hepatofugal group. Similar results have been reported by a previous study [30]. In patients with hepatofugal portal flow, the change in liver hemodynamics after TIPS would be small because the blood supply would depend mainly on the hepatic artery, which is a similar situation to the autologous portacaval shunt effect caused by the pre-TIPS hepatofugal portal flow. This would result in relatively lower odds of HE in this subset of patients. In contrast, liver hemodynamics in patients with hepatopetal main portal vein flow would be altered substantially by TIPS, with blood flow changing from a dual supply from the portal vein and hepatic artery to a supply predominant by the hepatic artery. This would create a large number of portacaval shunts in a short time, leading to a rapid increase in un-detoxified and pro-HE toxic substances, predisposing this subset of patients to HE.

A unique aspect of the present study was that all 279 patients had HCC and portal hypertension, and all had underwent at least one post-TIPS TACE or TAE treatment. The odds of HE in patients who underwent >3 TACE treatments were approximately 4 times higher than that in patients who underwent ≤3 treatments. Although TACE is beneficial to cancer therapy, repeated TACE may accelerate the development of cirrhosis. Hepatic peripheral arterial embolization causes hepatic tissues to produce free radicals that activate the lysosomal system, leading to ATPase dysfunction, cell membrane damage, and decreased tolerance to the toxicity of chemotherapeutic agents. Moreover, some embolization agents can induce ischemic injury in non-HCC tissues. The degree of liver damage is an independent risk factor for patients' survival [31]. Patients with a proper function of TIPS depend on hepatic arterial flow for liver perfusion, as the flow in the branch portal veins is usually reversed. Therefore, any kind of an arterial embolic procedure could be expected to lead to more hepatic ischemia in patients with TIPS compared with patients without TIPS who have hepatopetal flow in branch portal veins. Therefore, liver damage due to repeated TACE might accelerate the development of HE.

The present study has its limitations. This was a retrospective study, and some data were unavailable or incomplete for some patients (e.g. ascites and hydrothorax); in addition, no consideration was given to the timing of HE during follow-up, the severity of HE, the requirement for hospitalization, or the use of concomitant medications. Patients with a definite diagnosis of pre-TIPS HE were excluded from the study; however, we cannot exclude the possibility that some patients had subclinical HE prior to TIPS. Finally, the cohort did not include patients who underwent TIPS but who did not have HCC. These issues will be clarified in the next prospective study.

CONCLUSIONS

The occurrence of HE after TIPS in patients with portal hypertension due to HCC and cirrhosis has been associated with a complex interplay of various pre-, peri-, and post-TIPS factors including specific interactions between TIPS, HCC and portal hypertension, as well as other risk factors similar to those reported previously in patients without HCC. Obtaining detailed knowledge of the risk factors for HE is relevant to the screening of patients eligible for TIPS, selection of appropriate surgical methods, optimization of postoperative management, and prevention of HE. Although some of our results were consistent with previous studies, there were also novel findings that may help to reduce and prevent TIPS complications in patients with HCC and cirrhosis. Larger-scale studies are warranted to investigate this further.

Conflicts of interest: The authors declare that they have no competing interests.

Financial support: None.

Authors' contribution: J.Y., L.Z., G.A. and F.L. contributed to the conception and design; J.Y., L.Z., Z.Y., H.Z., L.W., G.A. and F.L. contributed to the acquisition of data, or analysis and interpretation of data; J.Y., L.Z., G.A. and F.L. were involved in drafting the manuscript or revising it critically for important intellectual content; all authors gave final approval of the version to be published.

REFERENCES

1. Dhanasekaran R, West JK, Gonzales PC, et al. Transjugular intrahepatic portosystemic shunt for symptomatic refractory hepatic hydrothorax in patients with cirrhosis. Am J Gastroenterol 2010; 105: 635-641. doi: 10.1038/ajg.2009.634
2. Qi X, Guo W, He C, et al. Transjugular intrahepatic portosystemic shunt for Budd-Chiari syndrome: techniques, indications and results on 51 Chinese patients from a single centre. Liver Int 2014; 34: 1164-1175. doi: 10.1111/liv.12355
3. Chevallier P, Novelli L, Motamedi JP, Hastier P, Brunner P, Bruneton JN. Hepatopulmonary syndrome successfully treated with transjugular intrahepatic portosystemic shunt: a three-year follow-up. J Vasc Interv Radiol 2004; 15: 647-648. doi: 10.1097/01.RVI.0000127885.68272.E9
4. Kikolski SG, Aryafar H, Rose SC, Roberts AC, Kinney TB. Transjugular intrahepatic portosystemic shunt for treatment of cirrhosis-related chylothorax and chylous ascites: single-institution retrospective experience. Cardiovasc Intervent Radiol 2013; 36: 992-997. doi: 10.1007/s00270-012-0530-x
5. Han G, Qi X, He C, et al. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with symptomatic portal hypertension in liver cirrhosis. J Hepatol 2011; 54: 78-88. doi: 10.1016/j.jhep.2010.06.029
6. Garcia-Pagan JC, Caca K, Bureau C, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. N Engl J Med 2010; 362: 2370-2379. doi: 10.1056/NEJMoa0910102
7. Bonnel AR, Bunchorntavakul C, Rajender Reddy K. Transjugular intrahepatic portosystemic shunts in liver transplant recipients. Liver Transpl 2014; 20: 130-139. doi: 10.1002/lt.23775
8. Yang Z, Han G, Wu Q, et al. Patency and clinical outcomes of transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stents versus bare stents: a meta-analysis. J Gastroenterol Hepatol 2010; 25: 1718-1725. doi: 10.1111/j.1440-1746.2010.06400.x
9. Vignali C, Bargellini I, Grosso M, et al. TIPS with expanded polytetrafluoroethylene-covered stent: results of an Italian multicenter

study. AJR Am J Roentgenol 2005; 185: 472-480. doi: 10.2214/ajr.185.2.01850472
10. Rossle M, Siegerstetter V, Euringer W, et al. The use of a polytetrafluoroethylene-covered stent graft for transjugular intrahepatic portosystemic shunt (TIPS): Long-term follow-up of 100 patients. Acta Radiol 2006; 47: 660-666. doi: 10.1080/02841850600806324
11. Riggio O, Angeloni S, Salvatori FM, et al. Incidence, natural history, and risk factors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stent grafts. Am J Gastroenterol 2008; 103: 2738-2746. doi: 10.1111/j.1572-0241.2008.02102.x
12. Bureau C, Pagan JC, Layrargues GP, et al. Patency of stents covered with polytetrafluoroethylene in patients treated by transjugular intrahepatic portosystemic shunts: long-term results of a randomized multicentre study. Liver Int 2007; 27: 742-747. doi: 10.1111/j.1478-3231.2007.01522.x
13. Zuckerman DA, Darcy MD, Bocchini TP, Hildebolt CF. Encephalopathy after transjugular intrahepatic portosystemic shunting: analysis of incidence and potential risk factors. AJR Am J Roentgenol 1997; 169: 1727-1731. doi: 10.2214/ajr.169.6.9393198
14. Hausegger KA, Karnel F, Georgieva B, et al. Transjugular intrahepatic portosystemic shunt creation with the Viatorr expanded polytetrafluoroethylene-covered stent-graft. J Vasc Interv Radiol 2004; 15: 239-248. doi: 10.1097/01.RVI.0000116194.44877.C1
15. Rossi P, Salvatori FM, Fanelli F, et al. Polytetrafluoroethylene-covered nitinol stent-graft for transjugular intrahepatic portosystemic shunt creation: 3-year experience. Radiology 2004; 231: 820-830. doi: 10.1148/radiol.2313030349
16. Masson S, Mardini HA, Rose JD, Record CO. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt insertion: a decade of experience. QJM 2008; 101: 493-501. doi: 10.1093/qjmed/hcn037
17. Wallace MJ, Madoff DC, Ahrar K, Warneke CL. Transjugular intrahepatic portosystemic shunts: experience in the oncology setting. Cancer 2004; 101: 337-345. doi: 10.1002/cncr.20367
18. Barrio J, Ripoll C, Banares R, et al. Comparison of transjugular intrahepatic portosystemic shunt dysfunction in PTFE-covered stent-grafts versus bare stents. Eur J Radiol 2005; 55: 120-124. doi: 10.1016/j.ejrad.2004.10.007
19. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy--definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology 2002; 35: 716-721. doi: 10.1053/jhep.2002.31250
20. Qin JP, Jiang MD, Tang W, et al. Clinical effects and complications of TIPS for portal hypertension due to cirrhosis: a single center. World J Gastroenterol 2013; 19: 8085-8092. doi: 10.3748/wjg.v19.i44.8085
21. Riggio O, Merlli M, Pedretti G, et al. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunt. Incidence and risk factors. Dig Dis Sci 1996; 41: 578-584. doi: 10.1007/BF02282344
22. Somberg KA, Riegler JL, LaBerge JM, et al. Hepatic encephalopathy after transjugular intrahepatic portosystemic shunts: incidence and risk factors. Am J Gastroenterol 1995; 90: 549-555.
23. Bai M, Han GH, Yuan SS, et al. Early hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: the risk factors and long-time survival. Zhonghua Gan Zang Bing Za Zhi 2011; 19: 498-501. doi: 10.3760/cma.j.issn.1007-3418.2011.07.008
24. Bai M, Qi X, Yang Z, et al. Predictors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt in cirrhotic patients: a systematic review. J Gastroenterol Hepatol 2011; 26: 943-951. doi: 10.1111/j.1440-1746.2011.06663.x
25. Haskal ZJ, Radhakrishnan J. Transjugular intrahepatic portosystemic shunts in hemodialysis-dependent patients and patients with advanced renal insufficiency: safety, caution, and encephalopathy. J Vasc Interv Radiol 2008; 19: 516-520. doi: 10.1016/j.jvir.2007.11.011
26. Deltenre P, Mathurin P, Dharancy S, et al. Transjugular intrahepatic portosystemic shunt in refractory ascites: a meta-analysis. Liver Int 2005; 25: 349-356. doi: 10.1111/j.1478-3231.2005.01095.x
27. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. Hepatology 2000; 31: 864-871. doi: 10.1053/he.2000.5852
28. Pan JJ, Chen C, Caridi JG, et al. Factors predicting survival after transjugular intrahepatic portosystemic shunt creation: 15 years' experience from a single tertiary medical center. J Vasc Interv Radiol 2008; 19: 1576-1581. doi: 10.1016/j.jvir.2008.07.021
29. Chung HH, Razavi MK, Sze DY, et al. Portosystemic pressure gradient during transjugular intrahepatic portosystemic shunt with Viatorr stent graft: what is the critical low threshold to avoid medically uncontrolled low pressure gradient related complications? J Gastroenterol Hepatol 2008; 23: 95-101. doi: 10.1111/j.1440-1746.2006.04697.x
30. Deng D, Liao MS, Qin JP, Li XA. Relationship between pre-TIPS hepatic hemodynamics and postoperative incidence of hepatic encephalopathy. Hepatobiliary Pancreat Dis Int 2006; 5: 232-236.
31. Takayasu K, Arii S, Ikai I, et al. Prospective cohort study of transarterial chemoembolization for unresectable hepatocellular carcinoma in 8510 patients. Gastroenterology 2006; 131: 461-469. doi: 10.1053/j.gastro.2006.05.021