History of Hepatic Encephalopathy Is Not a Contraindication to Transjugular Intrahepatic Portosystemic Shunt Placement for Refractory Ascites

Sammy Saab, MD, MPH[1,2], Matthew Zhao, BS[1], Ishan Asokan, MD, MSc[1], Jung Jun Yum, BA[2] and Edward Wolfgang Lee, MD, PhD[2,3]

INTRODUCTION: **The outcomes of transjugular intrahepatic portosystemic shunt (TIPS) placement in patients with hepatic encephalopathy (HE) are controversial. We studied the relationship of pre-TIPS HE in patients undergoing TIPS for refractory ascites on all-cause mortality and development of post-TIPS HE.**

METHODS: **A single-center retrospective comparison study was performed for patients undergoing TIPS for refractory ascites. Survival by history of pre-TIPS HE was demonstrated with Kaplan-Meier curves. Univariate and multivariate logistic regression analyses were performed to identify the predictors of post-TIPS clinical outcomes for patients with and without pre-TIPS HE.**

RESULTS: **We identified 202 TIPS recipients (61% male, mean ± SD; age 59.1 ± 10.2 years; mean model for end-stage liver disease score 17.3 ± 6.9). Pre-TIPS HE did not predispose patients for increased all-cause mortality, increased risk of experiencing HE within 60 days, or increased risk of hospital admission for HE within 6 months. A multivariate analysis demonstrated that total bilirubin (odds ratio [OR] 1.03; $P = 0.016$) and blood urea nitrogen (OR 1.15; $P = 0.002$) were predictors for all-cause mortality within 6 months post-TIPS. Age ≥65 years (OR 3.92; $P = 0.004$), creatinine (OR 2.22; $P = 0.014$), and Child-Pugh score (OR 1.53; $P = 0.006$) were predictors for HE within 60 days post-TIPS. Predictors of intensive care admission for HE within 6 months post-TIPS included age ≥65 years (OR 8.84; $P = 0.018$), history of any admission for HE within 6 months pre-TIPS (OR 8.42; $P = 0.017$), and creatinine (OR 2.22; $P = 0.015$).**

DISCUSSION: **If controlled, pre-TIPS HE does not adversely impact patient survival or clinical outcomes, such as development of HE within 60 days of TIPS or hospital admission for HE within 6 months. Patients may be able to undergo TIPS for refractory ascites despite a history of HE.**

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INTRODUCTION

Refractory ascites refers to accumulation of free fluid in the peritoneum that cannot be effectively mobilized by diuretics or where effective doses of diuretics cannot be used because of associated adverse effects (1). Treatment options for refractory ascites include repeat paracentesis, transjugular intrahepatic portosystemic shunt (TIPS), and liver transplantation (2). Compared with repeated large volume paracentesis, TIPS is associated with improved survival, improved quality of life, and less healthcare utilization, but potential increased risk of hepatic encephalopathy (HE) (3). Indeed, the development of post-TIPS HE increases mortality risk, hospitalization duration, and healthcare costs (4).

Limited studies have shown that pre-TIPS HE may contribute to post-TIPS HE and poor clinical outcomes (5–7). However, these were all noncomparison retrospective studies. Other factors that contribute to post-TIPS HE include patient sex and laboratory test results such as serum bilirubin, creatinine, and sodium levels (8). Timing of the development of HE also remains variable because it can take place months later (9). With these limited evidence, underlying pre-TIPS HE has served as a relative contraindication to TIPS placement (3,10). Existing literature posits that TIPS may worsen or precipitate encephalopathy, with thorough emphasis currently placed on pre-TIPS screening (11).

In patients with a diagnosis of HE, the current treatment recommendation is to address the HE precipitant and

[1]Division of Hepatology, Department of Medicine, UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California, USA; [2]Division of Liver and Pancreas Transplantation, Department of Surgery, UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, Los Angeles, California, USA; [3]Division of Interventional Radiology, Department of Radiology, UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California, USA.
Correspondence: Edward Wolfgang Lee, MD, PhD. E-mail: EdwardLee@mednet.ucla.edu.
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pharmacologic intervention such as lactulose. The addition of rifaximin has been found to significantly reduce breakthrough HE relative to patients treated with lactulose alone (12). These medical treatments are successful in both pre-TIPS HE and post-TIPS HE (4,13). Given the efficacy of pharmacologic intervention, the hypothesis of our study is that medically controlled pre-TIPS HE should not be considered a contraindication for TIPS. Here, we investigated a comparison study to suggest that utilization of TIPS in HE patients with refractory ascites is no longer a contraindication.

METHODS

The institutional review board approved this single-center retrospective study (IRB #10-000464). Data collection was performed for all adult TIPS (n = 337) recipients within our healthcare system from 2007 to 2019. Study data were stored using Research Electronic Data Capture in our institution. Patient demographic information, relevant clinical history, and post-TIPS outcomes were collected. Patients were excluded from analysis if they did not receive their TIPS for the primary indication of refractory ascites, had a history of portal vein thrombosis, received orthotopic liver transplant before TIPS placement, or if they were lost to follow-up. Subjects were then grouped by history of preprocedural HE. We used an operational definition of pre-TIPS HE, which included patients with documented history of HE before TIPS placement, as well as patients who received medical management with lactulose or rifaximin before their TIPS. All TIPS patients were referred by hepatologists at our institution, where lactulose is not routinely used for primary prophylaxis of HE. Standardized pre-TIPS West Haven Criteria were not available for grading the severity of pre-TIPS HE. All mortality calculations are excluding patients who received liver transplants at any time after TIPS placement. Baseline characteristics for all patients included in the study are detailed in Table 1.

Technique

The standard TIPS technique was used (14,15). In brief, through the right internal jugular venous access, the Rosch-Uchida transjugular access set (Cook Medical, Bloomington, IN) was used to access the hepatic vein, and subsequently, the portal vein was accessed intrahepatically through the parenchyma. Once the portal vein access was confirmed, the portal pressure and systemic pressure in the right atrium were measured to calculate the portosystemic pressure gradient (PSPG). Next, a portovenogram was performed to evaluate the anatomy and flow dynamics. Then, the GORE VIATORR endoprosthesis stent-graft (Gore Medical, Flagstaff, AZ) was placed through the sheath, connecting the portal vein to the hepatic vein/inferior vena cava confluent. Then, an appropriately sized balloon (6–10 mm) was used to dilate the stent-graft. Once the TIPS stent-graft was placed in an appropriate position, a post-TIPS PSPG was measured and a final portovenogram was obtained.

Statistical methods

Univariate logistic regression models were used to assess a history of pre-TIPS HE as an independent predictor for clinical outcomes including all-cause mortality within 6 months, development of post-TIPS HE within 60 days, and post-TIPS intensive care unit (ICU) admissions for HE within 6 months. Kaplan-Meier curves were generated for post-TIPS survival by history of pre-TIPS HE, with liver transplant recipients censored at date of transplant. Nineteen potential predictors were analyzed using a logistic regression analysis against primary clinical outcomes of mortality, post-TIPS HE, and post-TIPS ICU admission because of HE. Analyses were independently performed for patients with and without a history of pre-TIPS HE. Predictors trending toward significance ($P < 0.1$) on univariate analysis were examined with multivariate regression analyses for each clinical outcome. Change in PSPG after TIPS placement was separately examined by logistic regression analysis against our primary outcomes. P values <0.05 were considered statistically significant. All analyses were performed using Stata/IC 16.1 statistical software.

RESULTS

Our chart review of electronic medical records revealed 337 TIPS recipients at our institution from 2007 to 2019. Among these patients, 135 met at least 1 of our exclusion criteria, including having a primary indication other than refractory ascites (n = 119), having a history of portal vein thrombosis (n = 20), having received orthotopic liver transplant before their TIPS (n = 10), and being lost to follow-up (n = 8). After exclusion, a total of 202 patients (mean ± SD age 59.1 ± 10.2 years, mean ± SD model for end-stage liver disease score 17.3 [6.9]) were included in the study for analysis.

Among the 202 adult TIPS recipients who met the full inclusion criteria, 126 (62.4%) had a history of pre-TIPS HE and 76 (37.6%) had no history of pre-TIPS HE. Medical management of HE after TIPS placement with lactulose and rifaximin was high among both groups. In patients with pre-TIPS HE, 125 (99.2%) received post-TIPS medical management for HE, with 109 (86.5%) on both lactulose and rifaximin, 16 (12.7%) on lactulose alone, and none on rifaximin alone. Among patients without pre-TIPS HE, 67 (88.2%) received post-TIPS medical management for HE, with 53 (69.7%) on both lactulose and rifaximin, 13 (17.1%) on lactulose alone, and 1 (1.3%) on rifaximin alone. Of all 202 patients, 21 (10.4%) underwent at least 1 hospital admission for HE within 6 months before TIPS placement. Of the total study population, all 202 patients had a primary indication of refractory ascites. Some in the study population (20.3%) had a history of additional complications of portal hypertension including esophageal varices, gastric varices, or hepatic hydrothorax. The most common comorbidities were diabetes mellitus (44.1%), hypertension (41.1%), and hepatitis C (35.1%).

Among the total study population, 36 (17.8%) suffered all-cause mortality within 6 months post-TIPS, 101 (50.0%) experienced HE within 60 days post-TIPS, and 13 (6.4%) underwent ICU admission for their HE within 6 months post-TIPS. Among those patients who experienced HE within 60 days post-TIPS, 100% received post-TIPS medical management for HE, with both lactulose and rifaximin titrated to proper clinical responses. Of the 13 patients admitted to the ICU, 9 patients required TIPS reduction of which 89% (8/9) of patients had a resolution of HE.

Logistic regression analysis was used to examine the role of pre-TIPS HE as a potential predictor for clinically relevant outcomes (Table 2). Pre-TIPS HE was not a statistically significant risk factor for 3 primary outcomes of all-cause mortality within 6 months (odds ratio [OR] 0.89; 95% confidence interval [CI] 0.42–1.87; $P = 0.750$), development of post-TIPS HE within 60 days (OR 0.86; 95% CI 0.48–1.52; $P = 0.598$), or post-TIPS ICU admission for HE within 6 months (OR 0.96; 95% CI 0.30–3.06; $P = 0.949$). Figure 1a,b demonstrates 5-year post-TIPS survival and

Table 1. Baseline characteristics for recipients of TIPS placement for refractory ascites (n = 202)

Characteristic	Pre-TIPS HE (n = 126) Percent	Pre-TIPS HE (n = 126) Mean (SD)	No pre-TIPS HE (n = 76) Percent	No pre-TIPS HE (n = 76) Mean (SD)	*P*
Age, yr		58.3 (10.0)		60.5 (10.5)	0.137
Male	60.3		63.2		0.688
Race					
White (non-Hispanic)	49.2		59.2		0.168
Black	0.0		2.6		0.067
Hispanic (any race)	38.9		21.1		0.009
Asian	5.6		6.6		0.766
Other	6.3		10.5		0.287
TIPS indication					
Ascites only	73.0		90.8		0.002
Ascites and varices	8.7		5.3		0.363
Ascites and hydrothorax	17.5		3.9		0.005
Ascites, varices, and hydrothorax	0.8		0		0.436
MELD score at time of TIPS		17.6 (7.2)		16.7 (6.5)	0.365
MELD-Na score at time of TIPS		21.3 (7.1)		20.2 (6.8)	0.268
Child-Pugh score at time of TIPS		9.1 (1.4)		8.3 (0.8)	<0.001
Comorbidities					
Diabetes	42.9		46.1		0.658
Hypertension	33.3		53.9		0.004
Hepatitis C	38.1		30.3		0.259
Hepatitis B	4.0		9.2		0.127
Hepatocellular carcinoma	5.6		1.3		0.134
Congestive heart failure	0.8		5.3		0.048
History of pre-TIPS admission for HE within 6 mo	16.7		0.0		<0.001
TIPS endoprosthesis type					
Without controlled expansion	70.6		80.3		0.129
Controlled expansion	29.4		19.7		0.129
Pre-TIPS pressure measurements					
PV pressure		27.5 (6.1)		23.9 (5.4)	<0.001
RA pressure		10.0 (4.8)		9.4 (4.6)	0.384
Portosystemic gradient		17.8 (5.3)		15.2 (4.8)	<0.001

HE, hepatic encephalopathy; ICU, intensive care unit; MELD, model for end-stage liver disease; PV, portal vein; RA, right atrium; TIPS, transjugular intrahepatic portosystemic shunt.

hospital admission for HE by history of pre-TIPS HE, respectively. There was no significant difference in post-TIPS survival or post-TIPS admission for HE among patients with and without a history of pre-TIPS HE.

Other outcomes examined by history of pre-TIPS were post-TIPS admission for HE within 6 months not limited to ICU admissions (OR 0.87; 95% CI 0.46–1.64; $P = 0.670$), post-TIPS ascites within 60 days post-TIPS (OR 1.65; 95% CI 0.92–2.94; $P = 0.091$), receipt of orthotopic liver transplant within 12 months post-TIPS (OR 2.21; 95% CI 0.78–6.27; $P = 0.134$), and any TIPS revision (OR 1.74; 95% CI 0.90–3.40; $P = 0.102$). A total of 56 (27.7%) patients underwent TIPS revision at any time after initial TIPS placement. Reasons for TIPS revision included refractory ascites, encephalopathy, varices or variceal bleeding, hydrothorax, shunt stenosis, TIPS occlusion, and TIPS malfunction.

Univariate logistic regression analysis was performed among patients with and without history of pre-TIPS HE (Tables 3–5). The examined outcomes after TIPS placement were all-cause mortality within 6 months post-TIPS, development of HE within 60 days post-TIPS, and ICU admission for HE within 6 months post-TIPS. Subsequent multivariate logistic regression analysis identified risk factors for these outcomes in patients with pre-TIPS HE (Figure 2). Among potential risk factors identified from the initial univariate logistic regression screening, multivariate

Table 2. Post-TIPS outcomes by history of pre-TIPS HE

Outcomes	OR	*P*	95% CI
All-cause mortality within 6 mo[a]	0.89	0.750	0.42–1.87
HE after TIPS within 60 d	0.86	0.598	0.48–1.52
≥1 HE admission (ICU) within 6 mo	0.96	0.949	0.30–3.06
≥1 HE admission (all) within 6 mo	0.87	0.670	0.46–1.64
Post-TIPS ascites within 60 d	1.65	0.091	0.92–2.94
OLT within 12 mo	2.21	0.134	0.78–6.27
TIPS revision (any)	1.74	0.102	0.90–3.40

CI, confidence interval; HE, hepatic encephalopathy; ICU, intensive care unit; OLT, orthotopic liver transplant; OR, odds ratio; TIPS, transjugular intrahepatic portosystemic shunt.
[a]Excluding postorthotopic liver transplant mortality.

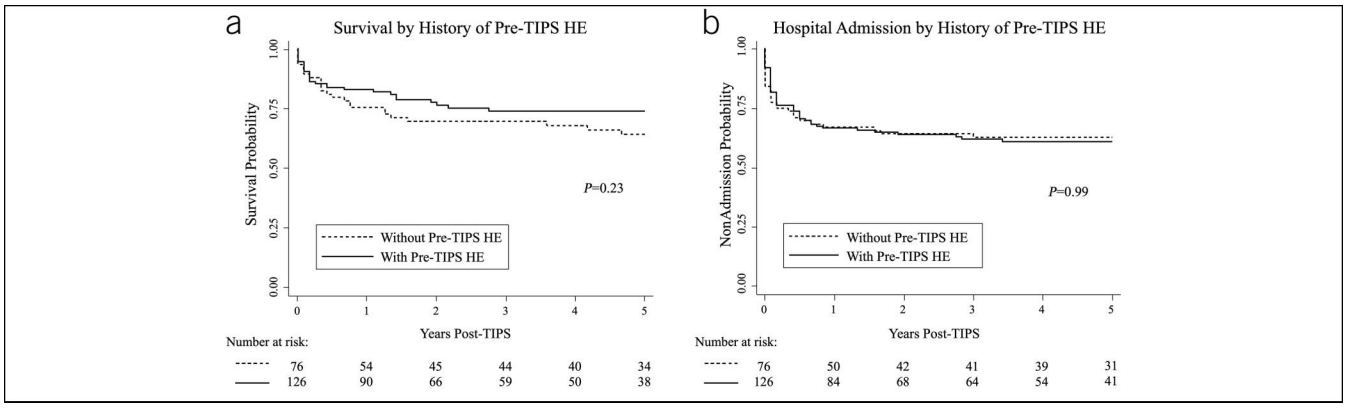

Figure 1. (**a**) Five-year survival after TIPS placement in patients with and without pre-TIPS HE. (**b**) Five-year hospital admission for hepatic encephalopathy after TIPS placement in patients with and without pre-TIPS HE. This curve is for any hospital admission for HE (ICU or otherwise). Note that the outcome we used on logistic regression analysis was specifically ICU admission. Patients not censored at transplant. HE, hepatic encephalopathy; ICU, intensive care unit; TIPS, transjugular intrahepatic portosystemic shunt.

analysis revealed pre-TIPS total bilirubin (OR 1.03; 95% CI 1.01–1.06; $P = 0.016$) and pre-TIPS blood urea nitrogen (OR 1.15; 95% CI 1.05–1.25; $P = 0.002$) to be predictors for the outcome of all-cause mortality within 6 months post-TIPS. Risk factors for post-TIPS HE within 60 days were age ≥65 years (OR 3.92; 95% CI 1.54–9.98; $P = 0.004$), pre-TIPS creatinine (OR 2.22; 95% CI 1.18–4.19; $P = 0.014$), and Child-Pugh score (OR 1.53; 95% CI 1.13–2.08; $P = 0.006$). Risk factors for ICU admission for HE within 6 months post-TIPS were age ≥65 years (OR 8.84; 95% CI 1.45–53.8; $P = 0.018$), history of any admission for HE within

Table 3. Univariate logistic regression analysis for post-TIPS mortality within 6 months

	History of pre-TIPS HE				No history of pre-TIPS HE			
Predictors for mortality within 6 mo[a]	n	OR	*P*	95% CI	n	OR	*P*	95% CI
Age ≥65 yr	126	1.78	0.266	0.64–4.94	76	1.46	0.527	0.45–4.77
Male vs female	126	0.54	0.197	0.21–1.38	76	1.06	0.923	0.32–3.55
Stent type: traditional vs controlled expansion	126	1.95	0.262	0.61–6.24	76	0.88	0.860	0.21–3.65
MELD score	125	1.12	0.001	1.05–1.21	75	1.04	0.411	0.95–1.14
MELD-Na score	125	1.13	0.002	1.05–1.21	75	1.04	0.323	0.96–1.14
Child-Pugh score	125	1.56	0.010	1.11–2.16	74	1.99	0.080	0.92–4.32
≥1 admission for HE within 6 mo pre-TIPS	126	2.40	0.117	0.80–7.16	0	—	—	—
≥1 ICU admission for HE within 6 mo pre-TIPS	126	1.74	0.518	0.33–9.26	0	—	—	—
PV pressure	121	0.99	0.725	0.91–1.07	75	1.02	0.790	0.91–1.14
RA pressure	120	0.98	0.699	0.88–1.09	74	1.04	0.525	0.92–1.18
PSPG	124	0.99	0.812	0.90–1.08	75	0.94	0.371	0.83–1.07
AST	126	0.99	0.628	0.97–1.02	75	1.00	0.295	1.00–1.01
ALT	126	1.00	0.8876	0.97–1.03	75	1.01	0.262	1.00–1.02
Sodium	126	0.96	0.389	0.87–1.06	76	0.96	0.534	0.86–1.08
Albumin	126	1.44	0.275	0.75–2.76	73	0.59	0.313	0.21–1.64
Bilirubin (total)	126	1.12	0.008	1.03–1.23	75	1.11	0.735	0.60–2.08
Creatinine	126	1.18	0.481	0.75–1.86	76	1.29	0.254	0.83–2.01
Blood urea nitrogen	122	1.02	0.052	1.00–1.05	74	1.02	0.348	0.98–1.05
Body weight	121	0.99	0.054	0.98–1.00	75	0.99	0.277	0.98–1.01
INR	124	5.17	0.011	1.45–18.4	76	1.45	0.840	0.04–53.1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HE, hepatic encephalopathy; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease; OR, odds ratio; PSPG, portosystemic pressure gradient; PV, portal vein; RA, right atrium; TIPS, transjugular intrahepatic portosystemic shunt.
[a]Excluding postorthotopic liver transplant mortality.

Table 4. Univariate logistic regression analysis for post-TIPS mortality within 60 days

	History of pre-TIPS HE				No history of pre-TIPS HE			
Predictors for development of HE within 60 d	n	OR	*P*	95% CI	n	OR	*P*	95% CI
Age ≥65 yr	125	2.63	0.027	1.11–6.23	76	2.45	0.072	0.92–6.53
Male vs female	125	1.05	0.884	0.52–2.16	76	0.94	0.900	0.37–2.40
Stent type: traditional vs controlled expansion	125	1.61	0.233	0.74–3.50	76	0.69	0.525	0.22–2.17
MELD score	124	1.04	0.109	0.99–1.10	75	1.01	0.748	0.94–1.09
MELD-Na score	124	1.02	0.472	0.97–1.07	75	1.01	0.716	0.95–1.08
Child-Pugh score	124	1.49	0.007	1.12–1.99	74	0.77	0.398	0.42–1.41
≥1 admission for HE within 6 mo pre-TIPS	125	1.90	0.192	0.72–4.96	0	—	—	—
≥1 ICU admission for HE within 6 mo pre-TIPS	125	1.82	0.429	0.41–7.95	0	—	—	—
PV pressure	120	1.05	0.151	0.98–1.11	75	1.05	0.233	0.97–1.15
RA pressure	119	1.03	0.410	0.96–1.11	74	0.95	0.308	0.85–1.05
PSPG	123	1.04	0.240	0.97–1.12	75	1.05	0.321	0.95–1.16
AST	125	0.99	0.395	0.98–1.01	75	1.00	0.465	0.99–1.00
ALT	125	1.01	0.421	0.99–1.03	75	1.00	0.514	0.99–1.01
Sodium	125	1.07	0.090	0.99–1.15	76	1.00	0.929	0.91–1.09
Albumin	125	1.08	0.766	0.64–1.82	73	1.08	0.854	0.49–2.36
Bilirubin (total)	125	1.06	0.160	0.98–1.15	75	0.56	0.049	0.31–1.00
Creatinine	125	1.95	0.020	1.11–3.42	76	1.21	0.390	0.78–1.88
Blood urea nitrogen	121	1.01	0.365	0.99–1.03	74	1.02	0.127	0.99–1.06
Body weight	120	0.99	0.231	0.99–1.00	75	0.99	0.061	0.98–1.00
INR	123	1.63	0.383	0.55–4.85	76	0.65	0.767	0.04–11.1

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HE, hepatic encephalopathy; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease; OR, odds ratio; PSPG, portosystemic pressure gradient; PV, portal vein; RA, right atrium; TIPS, transjugular intrahepatic portosystemic shunt.

6 months pre-TIPS (OR 8.42; 95% CI 1.46–48.7; $P = 0.017$), and pre-TIPS creatinine (OR 2.22; 95% CI 1.17–4.21; $P = 0.015$).

The role of the change in PSPG after TIPS placement was separately examined with a logistic regression analysis for our 3 primary outcomes (Table 6). Among patients with a history of pre-TIPS HE, a greater decrease in PSPG was found to be a significant negative predictor for ICU admission for HE within 6 months post-TIPS (OR 0.87; 95% CI 0.77–0.99; $P = 0.033$). Decrease in PSPG was not a significant predictor for any of the 3 primary outcomes among patients with no history of pre-TIPS HE, and was not a significant predictor for all-cause mortality within 6 months (OR 1.01; 95% CI 0.93–1.10; $P = 0.803$), or for the development of HE within 60 days (OR 0.1.06; 95% CI 0.99–1.14; $P = 0.094$) among patients with a history of pre-TIPS HE.

DISCUSSION

The results of our study indicate the pre-TIPS HE should not be regarded as an absolute contraindication to TIPS placement. In select patients with medically controlled HE, TIPS is an important option for managing refractory ascites. Increased incidence of HE after TIPS placement is well documented, and existing research has evaluated risk factors for post-TIPS HE. A systematic review examining predictors for post-TIPS HE showed that although pre-existing HE was a commonly cited risk factor for post-TIPS HE, approximately one-third of studies examining pre-TIPS HE failed to demonstrate that it was a significant predictor (9). It should be noted that the study population of all studies describing pre-TIPS HE as a significant predictor for post-TIPS HE included variceal bleeding as the primary TIPS indication, with most studies exclusively examining outcomes after TIPS for variceal bleeding. To date, there has not been a comparison study specifically examining outcomes after TIPS for refractory ascites among patients with and without pre-TIPS HE. Our investigation demonstrates that not only is risk of post-TIPS HE not increased after the procedure but also overall survival is not adversely affected based on the clinical findings of our study.

The American Association for the Study of Liver Diseases (AASLD) updated practice guideline lists HE as neither an absolute nor a relative contraindication for TIPS placement (16). However, the American College of Radiology practice parameters for TIPS creation and the Society of Interventional Radiology quality improvement guidelines for TIPS include clinically significant refractory HE and severe or uncontrolled HE as relative contraindications, respectively (17,18). These guidelines describe HE as a relative contraindication, despite limited evidence of severe negative clinical outcomes and despite being more contemporary than the updated AASLD practice guidelines. These

Table 5. Univariate logistic regression analysis for post-TIPS intensive care admission for HE within 6 months

	History of pre-TIPS HE				No history of pre-TIPS HE			
Predictors for ICU admission for HE within 6 mo	n	OR	*P*	95% CI	n	OR	*P*	95% CI
Age ≥65 yr	126	3.54	0.088	0.83–15.1	76	2.94	0.255	0.46–18.8
Male vs female	126	2.06	0.389	0.40–10.6	76	0.87	0.880	0.14–5.53
Stent type: traditional vs controlled expansion	126	1.27	0.780	0.24–6.58	76	0.34	0.258	0.05–2.22
MELD score	125	1.06	0.211	0.97–1.16	75	1.08	0.278	0.94–1.25
MELD-Na score	125	1.07	0.213	0.96–1.18	75	1.14	0.092	0.98–1.32
Child-Pugh score	125	1.22	0.425	0.75–1.99	74	1.66	0.389	0.52–5.24
≥1 admission for HE within 6 mo pre-TIPS	126	5.94	0.018	1.36–26.1	0	—	—	—
≥1 ICU admission for HE within 6 mo pre-TIPS	126	2.27	0.472	0.24–21.1	0	—	—	—
PV pressure	121	0.94	0.357	0.84–1.07	75	1.06	0.532	0.88–1.28
RA pressure	120	0.99	0.923	0.84–1.17	74	0.98	0.832	0.79–1.20
PSPG	124	0.91	0.244	0.78–1.07	75	1.06	0.572	0.87–1.28
AST	126	1.00	0.787	0.98–1.03	75	1.00	0.803	0.96–1.03
ALT	126	1.02	0.342	0.98–1.06	75	1.00	0.940	0.99–1.01
Sodium	126	0.97	0.641	0.84–1.12	76	0.78	0.015	0.64–0.95
Albumin	126	0.57	0.372	0.17–1.95	73	0.44	0.323	0.09–2.23
Bilirubin (total)	126	0.82	0.560	0.41–1.61	75	0.75	0.637	0.22–2.51
Creatinine	126	1.87	0.015	1.13–3.09	76	0.90	0.825	0.35–2.32
Blood urea nitrogen	122	1.01	0.328	0.99–1.04	74	1.01	0.703	0.96–1.06
Body weight	121	1.00	0.880	0.98–1.02	75	1.00	0.970	0.98–1.02
INR	124	0.30	0.487	0.01–9.02	76	0.32	0.715	0.00–139

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HE, hepatic encephalopathy; ICU, intensive care unit; INR, international normalized ratio; MELD, model for end-stage liver disease; OR, odds ratio; PSPG, portosystemic pressure gradient; PV, portal vein; RA, right atrium; TIPS, transjugular intrahepatic portosystemic shunt.

guidelines are contrary to our findings because medically managed and controlled HE, which is not clinically significant, should not be considered as a contraindication for TIPS. Only significant refractory or severe/uncontrolled HE should be considered as a relative contraindication of TIPS. These specific patient populations should be examined in future studies to identify the true relationship of uncontrolled HE and TIPS. Based on our findings, we are proposing that an updated recommendation be established as a large number of ascites patients can benefit from undergoing TIPS without fear of post-TIPS HE.

In addition to pre-TIPS HE being not a significant risk factor for post-TIPS clinical outcomes, we found several other notable pre-TIPS risk factors that influenced our patients post-TIPS clinical outcomes. Of significance, total bilirubin level has been noted to be one of the risk factors for all-cause mortality within 6 months. This is not unexpected because total bilirubin level (>4.0 mg/dL) has been closely associated with poor post-TIPS clinical outcomes, including 30-day mortalities stated on AASLD guidelines (16). Interestingly, the age >65 years has been associated with both increased risk of HE and increased risk of ICU admission because of HE. This was previously suggested by Riggio et al. in 2008 (13) and Routhu et al. in 2017 (19), and although the development of HE or HE-related admission was not evaluated, Suraweera et al. (20) showed that the age >65 years is associated with more hospitalization. Finally, elevated serum creatinine level has been described as a risk factor for post-TIPS HE in previous studies (13,19,21). Similarly, our results have shown that elevated pre-TIPS creatinine level is strongly associated with increased risk of post-TIPS HE and risk of ICU admission for HE within 6 months post-TIPS.

Although HE is a concern post-TIPS, shunt placement may improve systemic hemodynamics (lower mean arterial pressure), hyponatremia, renal function, nutritional status, and sarcopenia (22). Indeed, sarcopenia has been long considered a predictor of HE in patients with cirrhosis, with associated fat loss contributing to poor outcomes in cirrhotic patients (23,24). With correction of portal hypertension, sarcopenia is delayed or controlled, which may mitigate the long-term risks of HE after TIPS. As recently as 2013, increases in fat-free mass, body mass index, and ascites-free weight were documented at 3 months after TIPS (25). In patients with referenced HE, nutritional compromise is a grave concern and influences capacity to be considered for transplantation (22). Our study did not specifically examine fat-free mass or body mass index after TIPS, but HE no longer serving as a contraindication to treatment optimizes transplantation bridging and candidacy. Although pre-TIPS body weight alone is likely a poor surrogate for fat-free mass, it should be noted that body weight was not a significant predictor for any of our 3 main clinical outcomes. Correlative content to consider in future studies on HE includes evaluating incidence of recurrent HE in patients who had a

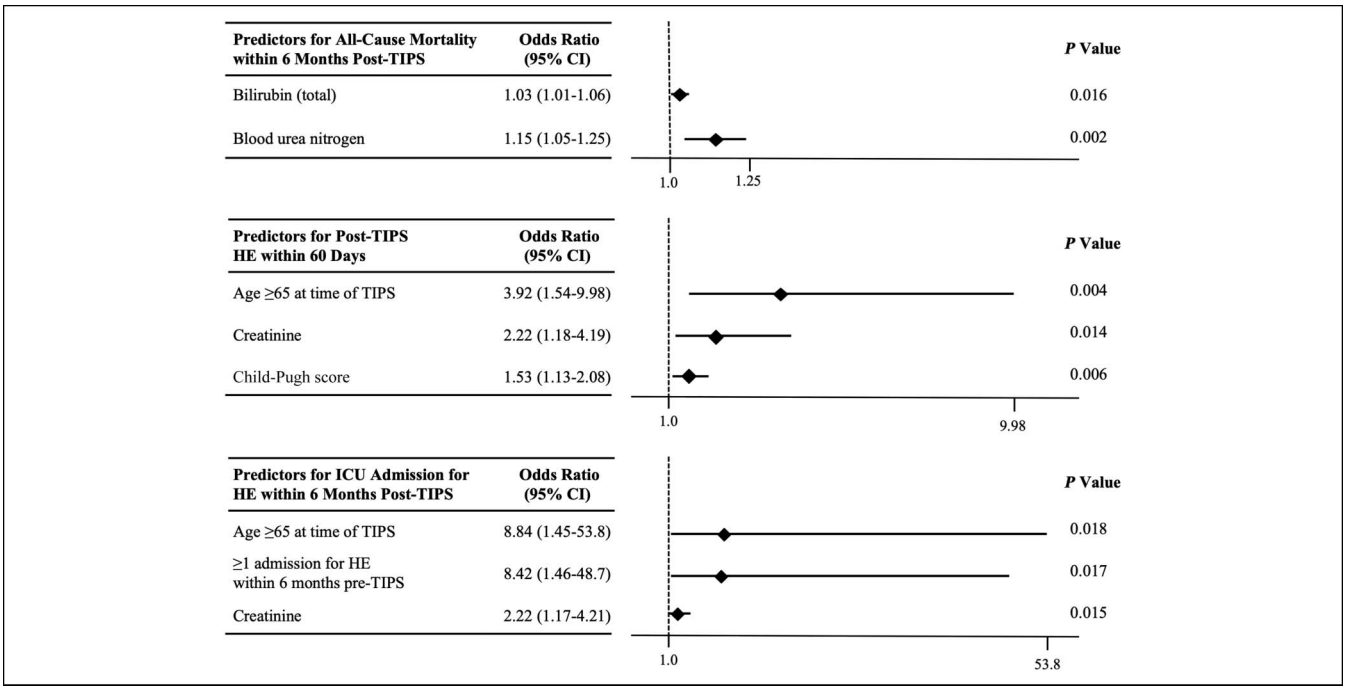

Figure 2. Multivariate logistic regression analysis among patients with pre-TIPS HE (n = 126). Mortality calculations exclude postorthotopic liver transplant mortality. HE, hepatic encephalopathy; ICU, intensive care unit; TIPS, transjugular intrahepatic portosystemic shunt.

positive increase in muscle area. It has further been documented that an increase in muscle area is associated with improved survival, with increase in total psoas muscle area often referenced (25).

Our analysis did not find the change in PSPG after TIPS to be significantly correlated with post-TIPS HE within 60 days or all-cause mortality within 6 months. However, our analysis found that among patients with a history of pre-TIPS HE, the decrease in PSPG after TIPS placement was negatively correlated with post-TIPS ICU admission for HE within 6 months after TIPS. This finding suggests that patients with a known history of pre-TIPS HE who are found to have minimally decreased or potentially increased PSPG after TIPS placement should be closely monitored for new or worsening HE because these patients may be at increased risk of decompensation requiring ICU admission.

Although not specifically studied in our analysis, the effects of TIPS shunt diameter and target PSPG have previously been shown to influence the occurrence of HE (26). Previous studies have demonstrated lower rates of HE with small 8-mm covered stents compared with the conventionally accepted 10-mm stents. Encephalopathy rates are reported to be 18% in 8-mm and 35% in 10-mm stents, indicating that smaller stents are preferable (9). In addition, a documented postprocedural PSPG of 10–12 mm Hg and decrease in shunt diameter (less than 6 mm) improve gradient hydrodynamics and reduce incidence of postoperative HE (27). Other studies have further examined the nature of the stent—bare vs covered (28)—and have noted reduced HE incidence in patients who received covered stents because of intimal hyperplasia (29). Given previous acceptability of shunt diameter influencing HE, we intentionally sought to not further stratify risk of HE recurrence in patients with pre-existing disease.

Although TIPS has been viewed historically as a bridge for liver transplantation, it is increasingly being seen as a treatment of its own for refractory ascites. Casadaban et al. (4) echoed the concerns reflected in our study regarding the incidence of post-TIPS HE, with their cohort specifically showcasing mild

Table 6. Decrease in portosystemic pressure gradient and post-TIPS outcomes by history of pre-TIPS HE

	Decrease in PSPG among patients with pre-TIPS HE				Decrease in PSPG among patients without pre-TIPS HE			
Outcomes	**n**	**OR**	***P***	**95% CI**	**n**	**OR**	***P***	**95% CI**
All-cause mortality within 6 mo	125	1.01	0.803	0.93–1.10	76	1.00	0.975	0.89–1.13
HE after TIPS within 60 d	124	1.06	0.094	0.99–1.14	76	1.09	0.087	0.99–1.21
≥1 HE admission (ICU) within 6 mo	125	0.87	0.033	0.77–0.99	76	1.11	0.271	0.92–1.35

CI, confidence interval; HE, hepatic encephalopathy; ICU, intensive care unit; OR, odds ratio; PSPG, portosystemic pressure gradient; TIPS, transjugular intrahepatic portosystemic shunt.

symptoms of HE 2–3 weeks after deployment. At this time, TIPS is particularly attractive for patients with refractory ascites and low model for end-stage liver disease scores who are unlikely to receive transplantation in the near future. Although liver transplantation remains the most successful method of handling end-stage liver disease, receiving transplantation remains a luxury because of limitations in listing and access. Indeed, the results of our study showed overall survival was not adversely affected by pre-TIPS HE, with quality-of-life postprocedure now weighing significantly.

There are several important limitations to our study. The retrospective nature prevents adequate control of variables that may be associated with the development post-TIPS HE. Future investigations may benefit from implementing a prospective cohort study design that specifically examines baseline risk of HE or severity of existing HE among patients with known liver disease who are not yet indicated for TIPS placement. These patients may be stratified by their risk of HE or severity of HE and would be prospectively followed and assessed for the development of new or worsening HE among patients who subsequently undergo TIPS placement. It should be noted that a formal assessment before TIPS for covert or overt HE was not performed in this patient population. Moreover, there is the potential for selection bias in that any patients deemed unfit for TIPS would not be captured within our study. Although it is uncommon at our institution for patients to be denied TIPS because of pre-existing HE, it remains unknown whether a subset of patients with recurrent ascites were never referred for TIPS evaluation at all because of severe HE. A better understanding of the role of pre-TIPS HE severity on post-TIPS outcomes would be of value, and future studies may consider determining whether there is a threshold for pre-TIPS HE severity that may significantly predispose TIPS recipients to poorer outcomes. Nevertheless, many of these predictors such as pre-TIPS creatinine and patient age were studied in our analysis, and the results were consistent with previous observations. Another limitation was the extended duration of review which spanned over a decade of data. Indeed, during the wide study time interview, there are likely variation of stents used, procedural techniques, and patient selection. However, we believe that the potential bias of time is mitigated by the large number of patients in our study. Several factors involving TIPS technique among our patient population may have contributed to post-TIPS clinical outcomes. These include having multiple interventional radiologists perform TIPS over the duration of the study, the systematic use of controlled-expansion stent types only after 2016, and the lack of clinical staging of pre-TIPS HE.

In conclusion, patients with refractory ascites and controlled HE can undergo TIPS without increasing their morbidity or mortality. TIPS is particularly attractive for patients who are symptomatic with ascites and whose wait time for liver transplant is prolonged. These findings can be incorporated into evidence-based risk stratification of patients with advanced liver disease and the timing of TIPS placement.

CONFLICTS OF INTEREST

Guarantor of the article: Edward Wolfgang Lee, MD, PhD.

Specific author contributions: Sammy Saab, MD, MPH, and Matthew Zhao, BS, are cofirst authors. S.S. and E.W.L.: study concept and design. M.Z., I.A., and J.J.Y.: acquisition of data. All authors: analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. M.Z.: statistical analysis. S.S. and E.W.L.: administrative, technical, or material support and study supervision.

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Study Highlights:

WHAT IS KNOWN

- ✓ Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment method for refractory ascites and often serves as a bridge to liver transplantation.
- ✓ TIPS placement carries the risk for precipitating post-procedural hepatic encephalopathy (HE).

WHAT IS NEW HERE

- ✓ A history of HE does not adversely impact all-cause mortality post-TIPS. Pre-TIPS HE does not adversely affect the development of HE within 60 days of TIPS or hospital admission for HE within six months post-TIPS.
- ✓ Patients may be able to undergo TIPS for refractory ascites despite a history of HE.

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