RISK FACTORS FOR HEPATIC ENCEPHALOPATHY AFTER TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT PLACEMENT IN CIRRHOTIC PATIENTS

By

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ABSTRACT

Introduction: Hepatic encephalopathy (HE) is a frequent consequence of transjugular intrahepatic portosystemic shunt (TIPS) placement and a major cause of morbidity, mortality and healthcare utilization in cirrhotic patients. The prevention of post-TIPS HE is mainly achieved by a careful selection of patients before the procedure. A relationship between the occurrence of HE and a low post-TIPS hepatic venous pressure gradient (HVPG) has been shown, suggesting that a large diversion of the blood from the liver poses as a risk factor for this complication. However, no studies have investigated the association between degree of HVPG reduction and development of post-TIPS HE. This study proposes to address a void for predicting post-TIPS HE. We hypothesize that there exists a relative magnitude in the reduction of HVPG after TIPS placement in cirrhotic patients with complications of portal hypertension that is associated with increased risk of post-TIPS HE. The aim of the present study is to determine (1) the prevalence of post-TIPS HE among patients who have undergone TIPS procedure at Oregon Health & Science University (OHSU) from 2002-2012, (2) the degree of HPVG reduction post-TIPS that is associated with an increased risk of HE, and (3) other factors associated with post-TIPS HE.

Methods: This is a retrospective cohort study, and data are obtained through chart reviews of the electronic medical record, EPIC. Subjects are drawn from a group of cirrhotic patients who underwent TIPS procedure at OHSU as documented by Department of Interventional Radiology between June 2003 and October 2012. The outcome of interest is the frequency of clinically evident HE within 30 days after TIPS placement. Demographic, clinical, biochemical and hepatic hemodynamic characteristics of all subjects were analyzed. The effect measure for degree of HVPG reduction on post-TIPS HE was calculated using multivariable logistic regression analysis, adjusting

for potential confounding variables and effect modifiers. Critical threshold for the percent reduction of HVPG was determined by generating ROC curve with the largest AUC and goodness-of-fit test.

Results: The prevalence of post-TIPS HE was 31% in the study population. Percentage of HVPG reduction adjusted for age, sex, indication, etiology of liver disease, history of pre-TIPS HE, pre-TIPS serum albumin and MELD score was found to be a significant predictor for development of post-TIPS HE ($p = 0.01$) in multivariate analysis. Other independent predictors of post-TIPS HE include sex, history of pre-TIPS HE, serum albumin and INR. The OR for development of post-TIPS HE was 6.58 when HVPG was decreased by at least 50% ($p < 0.01$, 95% CI: 1.63 - 26.6). The ROC curve generated to predict the percent of reduction in HVPG leading to HE demonstrated an AUC of 0.77. The absolute value of the post-TIPS HVPG was not found to be a significant predictor of post-TIPS HE in the multivariate analysis. Subjects who underwent TIPS for the indications of recurrent variceal bleed and refractory ascites were found to demonstrate significant differences in their MELD (12.7 vs. 14.1; $p = 0.03$) and Child-Pugh (7.78 vs. 9.05; $p < 0.01$) scores, creatinine (0.83 vs. 1.51; $p < 0.01$) and bilirubin (2.06 vs. 1.39; $p < 0.01$).

Conclusions: The percent of reduction in HVPG is a significant predictor for development of post-TIPS HE and a superior predictor compared to post-TIPS HVPG. Specifically, we noted that at least 50% reduction in HVPG identifies patients at highest risk for post-TIPS HE. Our results agree with prior studies and identified additional variables that demonstrated a significant association for development of post-TIPS HE in multivariate analysis, including lowered albumin and history of pre-TIPS HE. Our findings suggest that cirrhotic patients who have >50% reduction in HVPG post-TIPS should be monitored closely for post-TIPS HE and may benefit from medication prophylaxis for development of HE.

INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) placement has been used for more than 20 years to manage complications of portal hypertension in patients with liver cirrhosis. It has been recommended by the American Association for the Study of Liver Disease (AASLD) in the 2009 guideline as an effective therapeutic approach for preventing recurrent variceal bleed and treating refractory ascites, two major complications of portal hypertension, a manifestation of cirrhosis of the liver (Boyer, 2010). However, one of the major problems after TIPS is the development of hepatic encephalopathy (HE), which occurs most frequently during the first months after the procedure (Riggio, 2005). The incidence of new or worsening HE after TIPS is approximately 30% (Somberg, 1995). While episodes of HE are typically mild, some patients my require hospitalization. Data from the Healthcare Cost and Utilization Project suggest that HE-related hospitalizations are associated with burdensome costs, not only to the patients, but their families and the healthcare system (Poordad, 2007). A relationship between the occurrence of HE and a low post-TIPS HVPG has been shown, suggesting that a large diversion of the blood from the liver poses as a risk factor for this complication (Casado, 1998). However, to date, the degree of HVPG reduction may be more predictive of post-TIPS HE, since the relative reduction in the pressure gradient takes into account the pre-TIPS pressure. To date, no studies have examined the degree of HVPG reduction as an independent risk factor for precipitating post-TIPS HE. The aim of this study is to elucidate the association between degree of HVPG reduction and development of post-TIPS HE to better identify patients who are at risk for this complication.

Pathogenesis and Clinical Implications of Portal Hypertension, Ascites and Variceal Bleeding

Portal hypertension, or high blood pressure in the portal vein system, which is composed of the portal vein, and its branches and tributaries, is a sequelae of chronic liver disease. It is defined as an elevation of hepatic venous pressure gradient to > 5 mmHg. The most common cause is liver cirrhosis that leads to an increased intrahepatic vascular resistance and portal-splanchnic blood flow (Toubia, 2008). Two commonly seen complications as a result of chronic portal hypertension and end-stage liver disease are development of ascites and variceal bleeding.

Ascites is defined as the pathologic accumulation of fluid in the peritoneum as a result of sinusoidal hypertension and sodium retention that is secondary to a decreased effective arterial blood volume, the most common complication of liver cirrhosis (Garcia-Tsao, 2006). Refractory ascites occurs in 5-10% of cirrhotic patients with ascites and signifies a poor prognosis. TIPS placement is indicated in cirrhotic patients with refractory ascites who require large-volume paracentesis more than two or three times per month through the process of improving effective arterial blood volume (Cesario, 2010).

Varices are dilated submucosal veins most commonly found in the distal esophagus or proximal stomach, but they can occur along all parts of the gastrointestinal tract. Variceal bleeding is likely to occur when hepatic venous portal gradient is > 12 mmHg. Variceal bleeding is also the most lethal complication of cirrhosis and found in approximately 50% of cirrhotic patients (Cesario, 2010). TIPS placement is recommended to control acute bleeding from varices

refractory to medical therapy and is effective in the prevention of rebleeding from gastric and ectopic varices (Boyer, 2010).

Pathophysiology, Diagnosis and Treatment of HE

HE is the occurrence of a wide array of transient and reversible neurologic and psychiatric manifestations that is commonly seen in patients with chronic liver disease and portal hypertension. These symptoms manifest as confusion, altered level of consciousness, and coma and may lead to death (Munoz, 2008). HE develops in 50 to 70% of patients with cirrhosis, and its occurrence is a poor prognostic indicator without liver transplantation, with projected one- and three-year survival rates of 42% and 23%, respectively (Nevah, 2010). One theory is that HE is typically triggered by an inciting event that results in a rise in the serum ammonia level, which is produced by the enterocytes residing in the colon. Under normal conditions, ammonia enters the portal circulation and is cleared by hepatocytes. In cirrhosis and portal hypertension, reduced hepatocyte function and portosystemic shunting leads to increased circulating ammonia, which can cross the blood-brain barrier and causes neurological symptoms (Nevah, 2010). There is a wide spectrum of events that can trigger HE in patients with end-stage liver disease, including gastrointestinal bleeding, electrolyte abnormalities, infections, medications, dehydration, and notably for the proposed study, undergoing a TIPS procedure (Cesario, 2010).

No specific laboratory findings indicate the presence of HE definitively, although blood ammonia level may be elevated with presence of HE. The diagnosis and evaluation of the severity of HE are based on the West Haven criteria of altered mental status proposed by Conn and Lieberthal in 1979 (Appendix A). A common finding on physical examination is asterixis,

which is a flapping tremor of hands when wrists are held in a flexion position with parallel and outstretched arms (Sundaram, 2009). However, there is currently no standardized method in the diagnosis of HE in the clinical setting, and the evaluations are primarily based on clinical judgment.

The mainstay of therapy is elimination of excess ammonia and the precipitating event, such as opioids and benzodiazepines, two medications commonly taken by cirrhotic patients, infection and TIPS shunt occlusion, where TIPS revision would then be warranted. Removal of excess ammonia is achieved by suppressing the production of the toxic substances in the intestine (Nevah, 2010). Pharmacological treatment is most commonly done with the poorly absorbed disaccharides such as lactulose or with non-absorbable antibiotics such as rifaximin (Munoz, 2008).

TIPS Placement (Appendix, Figure A)

A TIPS is a small-diameter portocaval shunt that can be regarded as a nonsurgical alternative to the side-to-side surgical portocaval shunt. It has several perceived advantages over surgical shunts. First, it does not distort the hepatic vascular anatomy important for subsequent liver transplantation that some patients may require. Second, it does not require general anesthesia. Finally, surgical complications such as wound infections are avoided, while achieving the desired hemodynamic goals in more than 90% of the cases (Haskal, 2003). Therefore, TIPS is potentially a safer and more efficacious method in decompressing portal hypertension (Somberg, 1995).

TIPS creation is a percutaneous method of reducing portal vein pressure wherein a decompressive channel is established between the outflow hepatic vein and the inflow intrahepatic branch of the portal vein (usually the right branch). It is created by an interventional radiologist using an image-guided endovascular approach, with the jugular vein as the entry site. A needle catheter is passed transjugularly into the hepatic vein and wedged there. The tract is made patent by placing an expandable metal stent across it, allowing blood to return to the systemic circulation (Haskal, 2003) (Appendix B). TIPS placement alleviates portal hypertension by decompressing the portal vein by decreasing the effective vascular resistance of the liver. Consequently, there is a reduced pressure drop over the liver, resulting in a decreased portal venous pressure. The pressure on the blood vessels in the intestinal walls is reduced so that future bleeding episodes is less likely to occur. Additionally, the reduced pressure also resolves ascites, although this benefit may take weeks to months to occur.

Complications Associated with TIPS Placement

According to the 2001 guidelines by the Society of Interventional Radiology for creation of a TIPS, a technically successful outcome is defined by creation of the shunt and a decrease in HVPG to less than 12mmHg (Haskal, 2003). Previous longitudinal studies also suggest that the HVPG or its equivalent, the hepatic venous pressure gradient, must be decreased to below the 12 mm Hg threshold, in order to decrease the risk of variceal bleeding (Groszmann, 1990 and Feu, 1995). However, this is at the cost of an increased incidence of HE, and further studies are needed to determine if lesser reductions have acceptable efficacy with a lower incidence of HE. Additionally, an optimal decrease in HVPG to control refractory ascites remains controversial.

Currently, a selection value of HVPG < 8mm Hg is based on limited data, and it has been suggested that a lower gradient may exacerbate HE (Sanyal, 2003).

It is now well-established that HE is a common and potentially fatal complication in patients having undergone the TIPS procedure. Although in recent meta-analyses, a covered-stent has been shown to reduce shunt dysfunction when compared to bare stent (Yang, 2010 and Bureau, 2004), up to 31% of patients who undergo a TIPS procedure with a covered stent still develop a new episode or worsening of pre-existing HE after the procedure (Boyer, 2010). Therefore, HE is considered to be a major complication in limiting the effectiveness of TIPS. Additionally, a meta-analysis of 30 studies demonstrated that age, sex, Child-Pugh score, etiology of liver disease (specifically, non-alcoholic steatohepatitis, or NASH) and previous history of HE are the most significant predictors for new or exacerbation of existing HE in post-TIPS placement (Bai, 2011). Other predictors for decompensation or mortality post-TIPS include bilirbuin > 3.0 - 4.0 mg/dL (Chalasani, 2000) and MELD score > 15-18 (Boyer, 2010). These predictors are non-modifiable biological, medical or lifestyle factors and therefore, no intervention measures could can be done to alter their effect. Potentially modifiable risk factors the post-TIPS HE have yet to be identified.

Currently, there are only a few existing studies evaluating HVPG as a risk factor for post-TIPS HE (Bureau, 2007 and Chung, 2008). In this study, Bivariate analysis was performed, demonstrating an increased risk of HE with a low HVPG at initiation of procedure. However, to date, no study has been done to investigate and determine whether a relative or absolute reduction in HVPG would precipitate *de novo* or worsen prior HE.

Several Bivariate and multivariate analyses of potential predictors of post-TIPS HE have been performed in the last two decades, although the qualities and results of these studies have shown to be highly variable. Most notably, there has been no consensus amongst previous studies showing that by inappropriately decreasing HVPG, defined as a reduction of greater than 5 mm Hg during TIPS, can lead to fatal complications such as HE (Chung, 2008 and Mullen, 2005). Furthermore, the relative reduction of venous pressure gradient as an independent risk factor in post-TIPS HE has not been examined. This study investigates the potential risk of HE post-TIPS placement by comparing the relative and absolute hepatic venous pressure reduction in subjects at OHSU between 2001 and 2012.

Significance

The estimated prevalence of chronic liver disease and cirrhosis in the United States is approximately 5.5 million cases and increasing, while the estimated associated mortality is 38,000 in 2009 (Kim, 2002). The toll of liver disease and its associated major complications such as HE on the United States population is extensive. The management of patients hospitalized with decompensated liver disease is known to have a substantial economic impact. National administrative data from the early 2000s estimated that the total economic burden of decompensated cirrhosis was reported to be between 1 and 2 billion dollars annually with an increasing trend (Poordad, 2007). Specifically, total national charges related to HE has increased from $4.68 billion in 2005 to $7.24 billion in 2009, a 55% increase in cost (Stepanova, 2011). In 2003, there were over 40,000 hospitalizations in the United States for the primary diagnosis of hepatic encephalopathy, leading to a total charge of approximately $932 million (Poordad, 2007).

HE is a condition associated with waxing and waning mental status and can be difficult to manage, as it can result in persistent cognitive deficits and disable patients from employment, driving, and self-care, and require involvement of family or household members in the care of affected patients (Poordad, 2007). Lactulose and rifaximin are the two mainstay medications in the treatment of HE. However, lactulose is difficult to take because of its potent laxative effects, while rifaximin is costly. Currently, prophylactic use of lactulose and rifaximin is not a recommended therapeutic approach by AASLD in preventing HE in those patients with end-stage liver disease without previous history of HE. HE is common post-TIPS. It is important to optimize clinical management of these patients by identifying the most significant risk factors in determining the risk of post-TIPS HE to reduce the morbidity and mortality of this group of severely ill patients.

The likelihood of developing complications after TIPS placement needs to be weighed on an individual basies. While a number of predictors for post-TIPS HE have been proposed in previous studies, to date,

no study has been done to investigate and determine whether an absolute reduction in HVPG would precipitate *de novo* or worsen prior HE. Understanding this relationship can help providers better identify patients who are at risk for developing post-TIPS HE.

Research Questions

Question 1: Does an increased percentage of reduction in HVPG after receiving TIPS placement in cirrhotic patients with complications of portal hypertension precipitate *de novo* HE or worsen pre-TIPS HE?

Question 2: What are the additional predisposing factors in the development of post-TIPS HE?

Question 3: Is there a specific percent reduction in HVPG that best predicts the development of post-TIPS HE?

METHODS

Study Population: Decompensated Cirrhotic Subjects

All subjects were individuals over the age of 18 who underwent TIPS procedure at OHSU as documented by the Department of Interventional Radiology between June 2012 and February 2014. Data were obtained through chart reviews of the electronic medical record, EPIC. Subjects were excluded for the following reasons: age < 18 years, non-cirrhotic or lack of portal hypertension, no follow-up visit documenting presence of HE within 30 days post-TIPS procedure, death within 30 days post-TIPS placement secondary to complications other than HE, intubation on admission, altered mental status from all competing etiologies other than HE, initiation of prophylactic lactulose and/or rifaximin therapy post-TIPS placement and starting antibiotics for infection, incomplete data, TIPS revision or Direct Intrahepatic Portosystemic Shunt (Figure 1). Demographic and clinical characteristics such as age, gender and MELD score were compared between patients included and excluded. Of note, subjects with baseline HE and documented use of lactulose and/or rifaximin during pre-TIPS placement with continuation of these medications post-TIPS placement were included, while subjects who initiated prophylactic medical treatment for HE post-TIPS placement but were not previously on the medication regimen were excluded. This is because prophylactic medical treatment post-TIPS placement was determined to be a confounding factor and would likely skew the outcome association towards the null. Demographic data, including sex, age and ethnicity, were collected.

Human Subjects Protections

This study was approved by the OHSU Institutional Review Board (IRB), which has a high standard for data protection and management. Since no direct subject contact was conducted, consent forms were not obtained from participants, nor was compensation provided to participants. The original subject list provided by OHSU Interventional Radiology Department and documentation linking participant identities to study identification number are stored in the password-protected file on the C drive of the OHSU archive only accessible to the research team. The working de-identified dataset was compiled as Microsoft Excel spreadsheet and was also stored on a password-protected file on the C drive of OHSU archive only accessible to the research team. The password was renewed every four months to ensure security.

Primary Predictor: Percent of HVPG Reduction (Table 1)

Primary predictor is relative HVPG reduction, defined by the percentage of HVPG reduction = [(post-TIPS HVPG - pre-TIPS HVPG) / pre-TIPS HVPG] x 100. Pre- and post-TIPS placement HVPG is determined by the pressure gradient between the portal vein and the inferior vena cava, or the difference between the wedged and the free hepatic venous pressure: HVPG = wedged hepatic portal venous pressure - right atrial pressure (Bosch, 2013). Measurements of pre- and post-TIPS placement were obtained and documented by Interventional Radiology attending physicians who performed the procedures.

Other Covariates (Table 1)

A number of covariates will be considered to adjust for confounding or evaluate their modifying effects (Table 1). Co-variates included age, sex, etiology of liver disease, indication for the procedure, presence of pre-TIPS HE, presence and severity of pre-TIPS ascites, pre-TIPS serum albumin, pre-TIPS serum bilirubin, pre-TIPS serum creatinine, pre-TIPS serum INR, Child-Pugh score, MELD score and procedure operator. Previous studies have suggested that age > 60, female sex, presence of pre-TIPS HE, Child-Pugh class C and hypoalbuminemia are risk factors for post-TIPS HE (Riggio, 1996).

Indication for the procedure is categorized into urgent and non-urgent. Urgent status is determined by if the patient was receiving TIPS for acute variceal bleeding at the time of admission or being transferred from another hospital for this reason. Presence of pre-TIPS HE is defined by documented physical exam findings of HE (based on West Haven criteria) or documented use of lactulose and/or rifaximin as part of active outpatient medication list.

West-Haven Criteria (Appendix, Figure C)

An acute episode of HE commonly manifests as a combination of impaired mental status and neuromuscular dysfunction over a period of hours to days. The evaluation of the severity of HE is measured by the West Haven Criteria of altered mental status , which is composed of five factors: the level of impairment of autonomy, changes in consciousness, intellectual function, behavior, and the dependence on therapy. The criteria is divided into 5 grades, ranging from 0 to

4, with 0 being normal, and 4 being in the state of coma, unresponsive to verbal or noxious stimuli. This has been the major grading system used for the past three decades that focuses on mental status and is most commonly utilized in the clinical setting.

Child-Turcotte-Pugh Scoring System (Appendix, Figure D)

A classification system was developed in the 1960's by Child and Turcotte to assess the likelihood of mortality in cirrhotic patients who were undergoing hepatovenous shunt surgery to prevent further variceal bleeds. This classification system was later modified by Pugh in the 1970s to produce the Child-Pugh scoring system (Pugh, 1973). The composite score employs five clinical measures and assigns the patient a Child's grading (of A, B or C) to stratify the risk of death due to the procedure. Child's grade A patients have the best prognosis, with 1-year survival rate of 84%, Child's grade B patients have a worse prognosis, with 1-year survival rate of 62%, Child's grade C patients have the worst prognosis, with 1-year survival rate of 42%.

Each measure has a score range 1 to 3, with 3 indicating the most severe derangement. Parameters consist of serum bilirubin (mg/dl: <2, 2-3, and >3), albumin (g/l: >35, 28-35, and <28), prothrombin (international normalized ratio, or INR: <1.7, 1.71-2.30, and >2.30), severity of ascites (none, mild, and moderate to severe) and severity of encephalopathy (none, grade I-II or suppressed with medication, and grade III-IV or refractory) (Pugh, 1973). Cirrhotic patients are classified into Child-Pugh class A to C by using the composite score.

Severity of ascites is measured with a score range 1 to 3, 1 being absent, 2 being moderate (medically controlled), and 3 being moderate to severe (medically uncontrolled). Subjects assigned a score of 2 have documented diuretics as part of their medications list but did not receive TIPS placement for the indication of refractory ascites. All subjects who underwent TIPS placement for the indication of refractory ascites are assigned a score of 3.

Similarly, severity of HE is measured with the same scoring range and rationale as severity of ascites. Subjects assigned a score of 2 have documented lactulose/rifaximin as part of their medications but did not demonstrate signs and symptoms of HE at the time of the visit or phone call.

Model for End-Stage Liver Disease (MELD) score

MELD is a scoring system for assessing the severity of chronic liver disease. It was initially developed to predict death within three months of surgery in patients who had undergone a TIPS procedure (Malinchoc, 2000), and was later found to be useful in determining prognosis and prioritizing for receipt of a liver transplant (UNOS, 2009). The MELD score calculation uses the following formula, with several adjustments. For subjects on dialysis defined as having 2 or more dialysis treatments within the prior week, their serum creatinine value is corrected to 4.0 mg/dl. For all other laboratory values < 1.0, they are corrected to 1.0.

MELD score = [0.957 x [ln serum creatinine (mg/dL)]

+ 0.378 x [ln serum bilirubin (mg/dL)]

+ 1.120 x [ln INR]

+ 0.643] x 10

Dependent variable: Post-TIPS HE (Table 1)

Primary outcome variable is post-TIPS HE, defined by documentation in the clinic note with physical exam findings suggestive of HE, including words such as "confusion," "altered mental status," and "presence of asterixis," within 30 days after the procedure. This definition is derived from the West Haven criteria discussed above. The choice of 30 days post-TIPS to specify the outcome is appropriate because portosystemic encephalopathy usually becomes clinically apparent two to three weeks after TIPS placement (Sanyal, 1994 and Riggio, 1996). Considering the retrospective nature of the study, no standardized psychometric tests or rapid bedside mental status assessments were available. Changes in medications for treatment of HE without documentation of physical exam findings or subjective symptomatic reporting through phone calls are not adequate to define a positive event, as the medications could have been initiated as a prophylactic rather than a therapeutic measure.

Statistical Analysis

For our descriptive analyses we included all subjects who underwent TIPS at OHSU during June 2002 and February 2014 and did not meet the exclusion criteria (n = 112). Statistical procedures were performed with a statistical analysis program package, STATA 12.0 (College Station,

Texas 1984-2012). A detailed evaluation of demographic characteristic to better define the population of subjects included in the study.

Demographic, clinical biochemical and hepatic hemodynamic characteristics

The prevalence of and mean values for risk factors that have been associated with increased risk of post-TIPS HE among patients who have undergone TIPS placement were reported by giving the raw number (n), percentage, and 95% confidence interval, stratified by occurrence of post-TIPS HE and indication, respectively. Results were expressed as means +/- SD. Statistical significance was established at $p < 0.05$. A one-sample test for proportion waas used to test the difference in prevalence between subjects in the variceal bleed group and subjects in the refractory ascites group.

Regression analysis

Two-sampled T-test and contingency tables via the use of Chi-Squared test were used in bivariate analysis to investigate the association between each predictor variable and the outcome variable. Simple logistic regression analysis was performed to further examine the association between each independent variable and post-TIPS HE. Histograms were constructed to demonstrate distributions and identify potential outliers. Covariates with likelihood ratio test (LRT), p-values < 0.10 were considered for multiple regression analysis. Wald-test statistics and deviance tests were performed to measure the significance among covariates for the multiple

regression analysis. Categorization and transformation of covariates were considered in an attempt to improve model prediction.

Confounding and interaction evaluation

Effects of confounding and interaction were examined. Confounding effect was defined as an approximate 10% change when comparing adjusted model odds ratio to the crude model odds ratio. Significant interaction was defined as having a significant Wald's test statistic when the variable was included in the model. When neither confounding nor interaction was detected, confirming that the particular variable did not significantly contribute to the model prediction, the variable was then eliminated. Final association model was constructed based on association power, parsimony and biological plausibility. Finally, the overall fit of the model was assessed using the Hosmer and Lemeshow method. Significance level was set at 0.05 to determine the significance of all variables, while significance level of 0.10 was used to determine the significance of interaction variables as a conservative approach.

Threshold determination for percent of HVPG reduction

To assess the optimal percent of HVPG reduction threshold, Receiver Operating Characteristics (ROC) curves for percent of HVPG reduction between 20% and 80% are generated for two models: the crude (percent of HVPG reduction and MELD score) and, and the final multivariate models. The crude model includes two variables in order to generate a test value for the Hosmer and Lemeshow Goodness-of-Fit test (H-L GOF). MELD score was chosen as it is considered the

most clinically valid variable for determining decompensation or mortality for patients with end-stage liver disease. Optimal threshold was determined by the value with the smallest p-value for the predictor, the largest AUC and the largest p-value for the Hosmer and Lemeshow Goodness-of-Fit test.

RESULTS

Demographic, clinical, biochemical and hepatic hemodynamic characteristics of subjects with versus. without post-TIPS HE

Numbers presented in Table 2 are representative of the total included study subjects who underwent TIPS procedure at OHSU between June 2002 and February 2014, stratified by occurrence of post-TIPS HE. The average ages for subjects who developed post-TIPS HE versus those who did not were similar (54.3 and 55.4), and approximately equal number of males and females among the subjects who developed post-TIPS HE (17 and 18).

Of note, a significantly greater proportion of subjects without history of pre-TIPS HE developed post-TIPS HE comparing to subjects with history of pre-TIPS HE did not develop post-TIPS HE (82.9% vs. 36.4%) ($p = 0.03$). There is also a significant difference in the percent of HVPG reduction (60.7 and 53.1, $p = 0.02$), pre-TIPS INR (1.28 and 1.40, $p < 0.01$) and absolute HVPG reduction (10.9 and 9.33, $p = 0.02$) between subjects who developed post-TIPS HE and those who did not.

There were no significant differences between the two groups for subjects having alcohol as etiology of cirrhosis, indication, urgency, pre-TIPS serum creatinine, bilirubin, serum albumin, Child-Pugh and MELD scores. Additionally, when albumin was dichotomized at 3.5 mg/dL, with hypoalbuminemia defined as < 3.5 mg/dL, there remained no significant differences between the two groups.

Table 4 shows that demographic and clinical characteristics such as age, gender and MELD score were similar between patients included and excluded (Tables 2 and 4).

Demographic, clinical, biochemical and hepatic hemodynamic characteristics of subjects with recurrent variceal bleed vs. refractory ascites

Numbers presented in Table 3 are representative of the total included study subjects who underwent TIPS procedure at OHSU between June 2002 and February 2014, stratified by indications for TIPS. The average ages for subjects who underwent TIPS for the indications of recurrent variceal bleed versus refractory ascites were similar (56.3 and 53.9, $p = 0.22$), and no difference in the distribution of males and females among the two groups ($p = 0.10$).

Of note, a significantly greater proportions of subjects underwent TIPS procedure for the indication of refractory ascites were elective (67.1%), while a significantly greater proportions of subjects underwent TIPS procedure for the indication of recurrent variceal bleed were urgent (92.6%) ($p < 0.001$).

There are no significant differences between the two groups for subjects who developed post-TIPS HE or not (51.6% and 48.1%, $p = 0.14$), having alcohol as etiology of cirrhosis (51.1% and 48.5%, $p = 0.14$) and pre-TIPS serum albumin (2.76 and 2.67, $p = 0.37$). Additionally, when albumin was dichotomized at 3.5 mg/dL, with hypoalbuminemia defined as < 3.5 mg/dL, there remained no significant differences for the two groups (46% vs. 54%, $p = 0.42$).

Bivariate analysis of risk factors associated with post-TIPS HE

Numbers presented in Table 6 reflect the odds ratios, 95% CI's and p-values associated with the primary predictor, percent of HVPG reduction, and sixteen covariates to be considered for the final model selection. In the Bivariate regression models, percent of HVPG reduction as a continuous variable (OR = 31.2, p = 0.02, 95% CI: 1.74 - 560), sex (OR 2.08, 95% CI 0.92 - 4.69, p = 0.08), history of pre-TIPS HE (OR = 0.36, 95% CI: 0.13 - 0.98, p = 0.05), pre-TIPS serum albumin (OR = 1.88, 95% CI: 0.92 - 3.80, p= 0.08), pre-TIPS INR (OR = 0.29, 95% CI: 0.002 - 0.39, $p < 0.01$) were independently and significantly associated with post-TIPS HE. P-values were considered statistically significant using p-values with $\alpha = 0.10$.

Confounding and interaction evaluation

Numbers presented in Table 5 demonstrates evaluation of potential confounding effects of the covariates. Sex (27.8%), indication for TIPS (61.8%) , alcohol as etiology of liver disease (10.6%), post-TIPS HVPG (115%), albumin (16.2%) and pre-TIPS INR (40.7%) showed a greater than 10% change when comparing adjusted model odds ratio to the crude model odds ratio (OR = 31.2).

Potential interaction between indication for TIPS and MELD score was assessed as shown in Table 7, and there was no significant interaction that improved the overall multivariate model. When percent of HVPG reduction was treated as a continuous variable, the interaction term was

not significant (OR = 1.01, 95% CI: 0.76 - 1.37, p = 0.94), and did not improved the overall multivariate model when it was not included (p = 0.008 vs. p = 0.005).

Multivariate analysis of risk factors associated with post-TIPS HE

Numbers presented in Table 7 reflect the odds ratios, 95% CI's and p-values associated with the primary predictor, percent of HVPG reduction, and seven covariates that were considered to be either clinically relevant, have demonstrated statistically significant Bivariate associations with post-TIPS HE, or displayed significant confounding effects. In the final multivariate regression model, percent of HVPG reduction (OR = 60.1, 95% CI: 2.34 - 1505, p = 0.13), indication (OR = 2.92, 95% CI: 1.10 - 7.77, p = 0.03) and pre-TIPS serum albumin (OR = 2.56, 95% CI: 0.95 - 1.04, p = 0.03) were significantly associated with post-TIPS HE, when percent of HVPG reduction is treated as a continuous variable (p < 0.01). The odds of developing post-TIPS HE for those with the indication of refractory ascites were 2.92 times as those with the indication of recurrent variceal bleed (p = 0.031, 95% CI: 1.10 - 7.78). The odds for those with lower pre-TIPS serum albumin is 2.55 times for those with the higher pre-TIPS serum albumin. Other adjusted covariates that were not found to be significant in the final multivariate model included age (OR = 0.91, 95% CI: 0.95 - 1.04, p = 0.67) , sex (OR = 1.70, 95% CI: 0.67 - 4.34, p = 0.27) , alcohol as etiology of cirrhosis (OR = 0.49, 95% CI: 0.13 - 1.83, p = 0.29), history of pre-TIPS HE (OR = 0.34, 95% CI: 0.10 = 1.08, p = 0.07), and MELD score (OR = 1.02, 95% I: 0.89 - 1.17, p = 0.81). P-values were considered statistically significant using p-values with $\alpha = 0.05$.

Optimal threshold for percent of HVPG reduction

In assessing the optimal percent of HVPG reduction threshold, ROC curves (Table 11) for percent of HVPG reduction between 20% and 80% generated for the crude model identified an optimal threshold at 60% HVPG reduction (p-value = 0.001, OR = 4.46, 95% CI: 1.90 - 10.5, AUC = 0.69, H-L GOF = 0.92). A threshold of 50% HVPG reduction also showed similar results, although slightly less optimal (p-value = 0.016, OR = 04.85, 95% CI: 1.35 - 17.4, AUC = 0.62, H-L GOF = 0.93). Similarly, ROC curves for percent of HVPG reduction between 20% and 80% generated for the final multivariate model identified an optimal threshold at 60% HVPG reduction (p-value = <0.001, OR 5.46, 95% CI: 2.01 - 14.8, AUC = 0.80, H-L GOF = 0.93). Likewise, a threshold of 50% HVPG reduction also showed similar results, although slightly less optimal (p-value = 0.008, OR 6.58, 95% CI: 1.63 - 26.6, AUC = 0.77, H-L GOF = 0.61). Comparisons between the crude and final multivariate model showed that a 50-60% in HVPG reduction most significantly associates with the development of post-TIPS HE.

DISCUSSION

Using chart review data from June 2002 - February 2014 at OHSU, we descrbied the demographic, clinical, biochemical and hepatic hemodynamic characteristics and the prevalence of these non-modifiable risk factors associated with post-TIPS HE, and compared the same set of characteristics among subjects who underwent TIPS procedure for the indications of recurrent variceal bleed versus refractory ascites.

Demographic, clinical, biochemical and hepatic hemodynamic characteristics of subjects with vs. without post-TIPS HE (Tables 2 and 4 and Figures 2, 3, 4 and 5)

Because previous studies have suggested that hypoalbuminemia as a risk factor for post-TIPS HE (Somberg, 1995), categorization of albumin was explored. When albumin was dichotomized at 3.5 mg/dL, with hypoalbuminemia defined as < 3.5 mg/dL, there remained no significant differences between the two groups. This is likely because out of our 112 study subjects, only a total of 9 subjects did not qualify as having hypoalbuminemia, with 6 that did not develop post-TIIPS HE and 3 that did. Due to the inadequate sample size for subjects in the category defined as having hypoabluminemia, albumin was left untransformed and as a continuous variable in our study.

Demographic and biochemical characteristics including age (54.9 vs. 54.3), sex (60.7% vs. 60.0% male) and MELD score (13.4 vs. 15.3) score were similar between patients included and excluded, respective (Tables 2 and 4). While excluded subjects appear to have slightly higher

MELD score than included subjects, the 3-month mortality in hospitalized patients are similar, 6.0%, for those with MELD scores of 10-19 (Wiesner, 2003).

Demographic, clinical, biochemical and hepatic hemodynamic characteristics of subjects with recurrent variceal bleed vs. refractory ascites (Table 3)

These values are consistent with previous studies, where patients who underwent TIPS procedure for the indication of refractory ascites were more ill than those for the indication of recurrent variceal bleed (Boyer, 2010). Majority of the urgent TIPS were performed in subjects for recurrent variceal bleed (92.6%), while majority of the elective TIPS were performed in subjects for refractory ascites (67.1%).

Effects of confounding and interaction evaluation (Tables 5 and 8)

Although the post-TIPS HVPG demonstrated an overwhelming confounding effect with a 115% change in odds ratio from the crude model, it was ultimately excluded from the final multivariate model. This is because post-TIPS HVPG did not contribute to improvement of the overall significance of the multivariate model ($p = 0.0045$ vs. $p = 0.0067$). For the reasons of power association and parsimony in variable selection, post-TIPS HVPG was excluded. Similarly, while pre-TIPS INR demonstrated both Bivariate significance at p-values, $\alpha = 0.05$ (OR = 0.29, 95% CI: <0.01 - 0.39, $p < 0.01$), it was ultimately excluded from the final multivariate model. For the same reasons of power association and parsimony.

The rationale for assessing potential interaction effect between indication for TIPS and MELD score is because as subjects who underwent TIPS for the indication of recurrent variceal bleed versus refractory ascites had demonstrated significant differences in several of the biochemical parameters, including MELD (12.7 and 14.2, $p = 0.03$)and Child-Pugh (7.77 and 9.05, $p < 0.001$) scores, pre-TIPS serum creatinine (0.83 and 1.51, $p < 0.001$) and bilirubin (2.06 and 1.39, $p < 0.01$). This suggested that perhaps the impact of indication depends on the level of MELD score.

Additionally, urgency between the two indications were also significantly different between the two groups (92.6% and 7.41%, $p < 0.001$), as the majority of the subjects undergoing TIPS procedure for recurrent variceal bleed was of urgent status, while the majority of the subjects undergoing TIPS procedure for refractory ascites was of elective status. This further supports the rationale that the conditions of the subjects in the recurrent variceal group versus the refractory ascites group at the time that they underwent TIPS procedure potentially were very different.

However, adding interaction term of indication*MELD score to the multivariate model did not contribute to improving significance of the overall model ($p = 0.0038$ vs. $p = 0.0039$, nor did it strengthen the association between indication and post-TIPS HE ($p = 0.013$ vs. $p = 0.013$). Finally, after being included in the multivariate model, indication*MELD score did not show a significant association with post-TIPS HE (OR = 1.01, 95% CI: 0.76 - 1.37, $p = 0.94$), when setting significance at p-values, $\alpha = 0.10$. Therefore, indication*MELD score was excluded from the final multivariate model for the reasons of power association and parsimony.

Risk factors associated with post-TIPS HE (Tables 6, 7, 9 and 10)

Although both Child-Pugh and MELD scores were initially considered as a potential surrogate marker for severity of liver disease, a risk factor for post-TIPS HE, MELD score was ultimately selected over Child-Pugh score. Only one of the two scores was used due to overlapping parameters, serum bilirubin and INR. While both previously validated tools are a composite score from multiple biochemical and/or clinical parameters, the MELD score consists of only serum biochemical parameters that are determined by a single laboratory. On the other hand, in addition to serum biochemical parameters, Child-Pugh score employs two clinical measures, severity of ascites and encephalopathy, that are based on clinical evaluations and unavoidably, resulting in significant inter-observer variability. Therefore, MELD score is thought to be a more robust surrogate marker to represent the severity of liver disease of the subjects prior to undergoing the TIPS procedure. Current AASLD guideline also employs MELD score as a predictor of 3-month mortality in patients after undergoing a TIPS procedure (Boyer, 2010).

While MELD score was not shown to have a significant association with post-TIPS HE in Bivariate analysis (OR = 0.967, 95% CI: 0.864 - 1.081, p 0.552), it was included in the final multivariate analysis for its clinical significance. Furthermore, while INR, one of the three components of MELD score, was found to be independently associated with development of post-TIPS HE and was found to have significant confounding effect (40.7% from the crude model), including INR in addition to MELD score did not improve the overall significance of the model. Therefore, INR was excluded from the multivariate analysis for the reason of parsimony.

Albumin was found to be associated with post-TIPS HE in both Bivariate and multivariate analyses whether or not percent reduction of HVPG was treated either as a continuous (OR = 2.555, 95% CI: 1.104 - 5.912, p = 0.028) or dichotomized variable (OR = 2.540, 95% CI: 1.076 - 5.994, p = 0.033) in multivariate analysis. This is consistent with previous findings (Boyer, 2010). Similarly, alcoholic liver disease has been described in prior liver studies to not be predictive of the development of post-TIPS HE (Somberg, 1995). The findings of our study in Bivariate analysis was again consistent with the literature (OR = 0.588, 95% CI: 0.198 - 1748, p = 0.340).

It is notable that history of pre-TIPS HE (OR = 0.362, 95% CI: 0.134 - 0.978, p = 0.045) was inversely associated with the development of post-TIPS HE in Bivariate analysis. This is likely because a majority of the subjects with history of pre-TIPS HE have been on treatment with lactulose/rifaximin for HE at the time of undergoing TIPS procedure. Therefore, they were less likely to develop post-TIPS HE than if they had not been on treatment. Furthermore, while previous studies have demonstrated an association between post-TIPS HVPG and post-TIPS HE (Boyer, 2010), our findings suggest otherwise (OR = 0.931, 95% CI: 0.819 - 1.059, p = 0.275). This is because that the interventional radiologists at OHSU are selective in not reducing pre-TIPS HVPG to a very low post-TIPS HVPG of 5mmg Hg or less, based on previous evidence that a post-TIPS gradient of < 5mmg Hg increases the risk for HE. This is reflected in the overall average post-TIPS HVPG of 7.28 mmHg.

Comparisons between subjects based on indications for TIPS revealed that there was a statistically significant difference in the MELD scores (p = 0.03) between subjects who

underwent TIPS secondary to recurrent variceal bleed (mean = 12.7 +/- 2.96) and those for refractory ascites (14.2 +/- 4.14), suggesting that subjects undergoing TIPS procedure for refractory ascites were clinically more ill than subjects undergoing TIPS procedure for recurrent variceal bleed. This is consistent with previous findings (Boyer, 2010). Therefore, although indication did not demonstrate a significant association with post-TIPS HE in Bivariate analysis, it was included in the multivariate analysis. Potential interaction between indication for TIPS and MELD score was further assessed, and we did not identify significant interaction that improved the overall significance of the model to warrant inclusion of this interaction term.

The final multivaraite model with percent reduction of HVPG as the primary predictor, was adjusted for age, sex, alcohol as etiology of cirrhosis, indication, history of pre-TIPS HE, serum albumin and MELD score, with development of post-TIPS HE at 30-days as the outcome.

Optimal threshold for percent of HVPG reduction (Table 11)

To determine the optimal percent of HVPG reduction threshold, ROC curves for percent of HVPG reduction between 20% and 80% generated for both the crude and final multivariate models. This was done as a measure to ensure that our final multivariate model was indeed the optimal model. We identified a greater than 60% in HVPG reduction as the optimal threshold for predicting post-TIPS HE. However, the 50-60% range remained significantly predictive as well, based on the dichotomized final multivariate model that generated the smallest p-value for the predictor, the largest AUC from ROC curves and the largest p-value for the Hosmer and Lemeshow Goodness-of-Fit test. From a clinical standpoint, a greater than 50% in HVPG

reduction casts a wider net and captures the majority of those who are at high risk for developing post-TIPS HE.

Strengths and Limitations

Limitations. We acknowledge several imitations of our study. We recognize that data were derived from retrospectively with its accompanied intrinsic limitations. First, there is no specific laboratory finding to definitively diagnose HE. While the West Haven criteria is the most widely used diagnostic tool in clinical practice to detect and grade the severity of HE, this scoring system is insensitive and inferior to standardized psychometric tests and rapid bedside mental status assessments (Nevah, 2011). To date, an objective, specific and sensitive method to diagnose and assess the severity of HE has not yet been devised. Since the latter two aforementioned methodologies were not employed in the proposed study, the specificity of both of our outcome variable, 30-day post-TIPS HE, and of our covariate, presence of pre-TIPS HE, may be lowered.

Similarly, since the study is performed retrospectively, the lack of standardized assessment may result in some difficulties in evaluating other subjective parameters such as the degree of ascites. Additionally, pre-TIPS placement labs were not collected at a standardized time prior to the procedure, and they were collected ranging from few hours to two weeks prior to the procedure. This variability likely reflect less accurate Child-Pugh and MELD scores in our subjects.

Secondly, we excluded subjects who were on narcotics and/or benzodiazepines both pre-TIPS and post-TIPS if they had developed altered mental status for all competing etiologies other than post-TIPS HE. It is possible that we have excluded subjects who were taking narcotics and/or benzodiazepines and developed post-TIPS HE, or true positives. However, sedation and altered mental status are common side effects of narcotics and/or benzodiazepine use (Tietze and Fuchs, 2014), as well as many other clinical conditions observed in our subjects post-TIPS, including infection, spontaneous bacterial peritonitis, dehydration and alcohol withdrawal. Therefore, the decision to minimize confounding effects secondary to clinical diagnosis dilemma outweighs the disadvantage of decreased true positives in our final cohort for analysis.

Thirdly, a number of subjects from the original sample pool was excluded either due to lost to follow up (23%, 71 out of 320) or because of factors that could potentially disturb the uniformity of the study, such as of TIPS, prophylactic use of lactulose/rifaximin post-procedure without documentation for development of HE, and concomitant use of narcotics/benzodiazepines. While the subject may not actually have been taking lactulose/rifaximin and/or narcotics/benzodiazepines as these medications frequently were prescribed as either prophylaxis or taken on as-needed basis, verification of use during the study period is not feasible. The reduced sample size likely decreases the precision of our study findings, and potentially introduces systematic bias. With 23% of subjects lost to follow up, the final sample is potentially but less likely systematically different from the original study population with regard to exposure and outcome status, suggesting potential spurious associations, as greater than 20 percent is more likely to suggest this likelihood.

Strengths. Despite several limitations, this study proposes to address a void in the literature for predicting post-TIPS HE. To date, no studies have investigated the association between the degree of HVPG reduction and development of post-TIPS HE. Furthermore, although our sample size appears small, in comparison to previous studies, our sample size is one of the largest, with more than 100 subjects. The single study that examined the lower threshold of HVPG as the primary risk factor for precipitating post-TIPS HE only included 66 subjects (Chung, 2008). Finally, multiple studies have concluded the benefit of covered stent in reducing the risk of post-TIPS HE (Yang, 2010 and Bureau, 2004). All of our subjects had received covered stents of the same type (Gore Viatorr) and therefore, eliminates stent type as a confounding variable from our study.

Generalizability/Comparison with Prior Studies

This study is generalizable to cirrhotic patients receiving TIPS for the indications of recurrent variceal bleed and refractory ascites at large academic hospitals in the United States. Patients that are under-represented in this study include those patients referred or transferred for care from rural settings or cities outside of Portland, or those who do not receive medical attention for their liver diseases. This is mostly due to lack of follow up documentation at OHSU as these patients either followed up with their local hepatologists or were those with financial, geographic or social barriers that limited their access to follow up care.

The potential subjects who do not access medical services likely experienced an increased incidence of post-TIPS HE, as they were likely sicker patients with more progressed cirrhosis

with previously unmanaged complications secondary to their end-stage liver diseases and thus, more likely to decompensate post-TIPS. Overall, our sample is comparable to sample described in previous literature with regard to age, sex, (Somberg 1995; Deng 2006; Masson 2007).

SUMMARY AND CONCLUSIONS

A number of risk factors predisposing decompensated cirrhotic patients to post-TIPS HE have been identified and validated in previous studies. To date, no studies have examined the degree of HVPG reduction as an independent risk factor for precipitating post-TIPS HE. The purpose of this study was to investigate the association between the percent reduction of HVPG and development of post-TIPS HE to better identify patients who are at risk for this complication.

The percent HVPG reduction is a significant predictor for development of post-TIPS HE and a superior predictor compared to post-TIPS HVPG. Specifically, we noted that at least 50% reduction in HVPG identifies patients at highest risk for post-TIPS HE. Our results agree with prior studies and identified additional variables that demonstrated a significant association for development of post-TIPS HE in multivariate analysis, including lowered albumin and history of pre-TIPS HE. Additionally, our study subjects demonstrated similar characteristics as previous studies, where those with refractory ascites were sicker patients than those with recurrent variceal bleed.

The results from this study provides strong evidence for larger prospective cohort studies to validate our findings and to further investigate a potential differential threshold of percent HVPG reduction for these two groups of patients. Prior to future prospective cohort studies, a similar retrospective study may be conducted at an additional medical institution that potentially may capture more subjects in the post-TIPS follow up period, such as the Portland Veterans

Affairs Medical Center, where many of the veterans receive both primary and specialty care. Findings from this additional study will serve as a comparison to our pilot study.

Our findings suggest that cirrhotic patients who have >50% reduction in HVG post-TIPS should be monitored closely for post-TIPS HE and may benefit from medication prophylaxis for development of HE. The percent reduction of HVPG serves as a novel modifiable risk factor for clinicians to potentially reduce the associated morbidity and mortality secondary to HE in this group of medically vulnerable patients.

FIGURE 1. Subject selection flowchart of cirrhotic patients undergoing TIPS procedure, OHSU 2002-2014

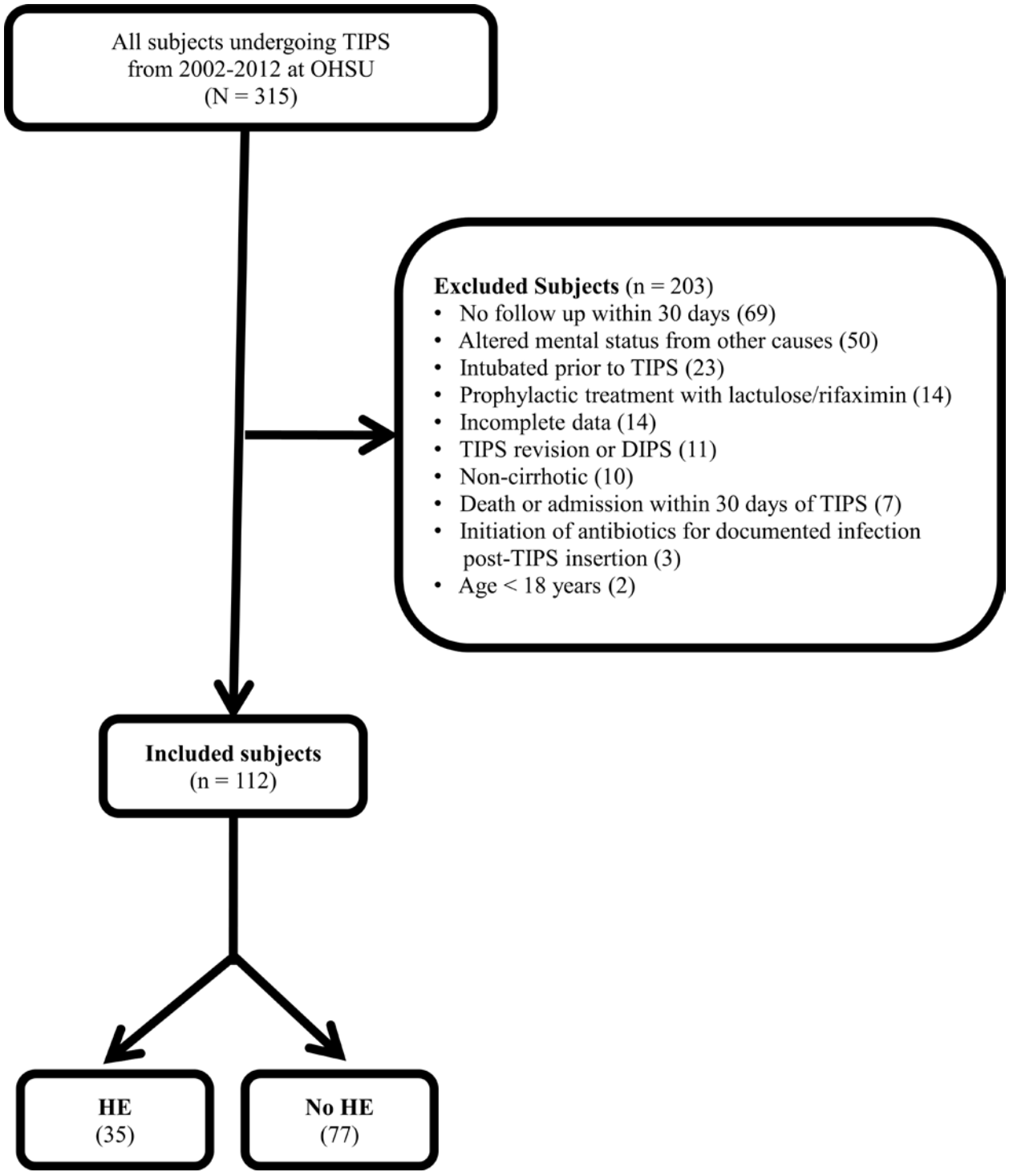


TABLE 1. Definitions of Primary Predictor, Covariates and Outcome Variables in Study of Cirrhotic Subject Undergoing TIPS procedure, OHSU 2002-2014

Variable	Unit	Description
PRIMARY PREDICTOR VARIABLE		
Percentage reduction of hepatic venous pressure gradient (HVPG)	mm Hg	Percentage reduction of HVPG = [(post-TIPS[a] HVPG - pre-TIPS HVPG) / pre-TIPS HVPG] x 100
COVARITES		
Sex		
Male		
Female		
Etiology		Cause of liver cirrhosis
All other etiologies		Including hepatitis B and/or C, automimmune heptitis, Non-alcoholic steatohepatitis (NASH - hepatitis with concurrent fat accumulation in liver), Budd-Chiari syndrome, primary biliary cirrhosis, azathioprine-induced portal hypertension, and alpha-1 antitrypsin deficiency
Alcoholic hepatitis		Hepatitis due to chronic alcohol use
Indication		Reason for TIPS placement
Recurrent variceal bleed		Two or more episode(s) of bleeding from dilated blood vessels in the esophagus or stomach
Refractory ascites		Accumulation of fluid in the peritoneal cavity not adequately managed with medical therapy, including therapeutic paracentesis and oral diuretics
Urgency		How urgently was the TIPS placement performed based on subject's conditions upon hospitalization
Urgent		TIPS placement performed due to uncontrolled variceal bleed upon hospitalization
Non-urgent		TIPS placement performed due to refractory ascites or non-active variceal bleed upon hospitalization

Child-Pugh Class/Score		One tool for classifying the severity of liver disease and assessing the prognosis of cirrhosis, according to degree of ascites, plasma concentrations of bilirubin and albumin, prothrombin time, and degree of encephalopathy
A/5-6		Well-compensated disease
B/7-9		Significant functional compromise
C/10-15		Decompensated disease
New narcotic and/or benzodiazepine use		Newly prescribed narcotic (oxycodone, oxycontin, methadone) and/or benzodiazepine (alprazolam, clonazepam, diazepam) after TIPS placement, including an increase in previous dosage
Yes		
No		
Presence of pre-TIPS HE[b]		Determined by clinic notes documented by gastroenterologist(s), physician's assistant, nursing phone calls based on symptoms delineated by West Haven criteria
Yes		
No		
Presence of pre-TIPS ascites		Determined by clinic notes documented by gastroenterologist(s) based on ultrasound, CT scan or physical examination
Yes		
No		
Stent type		
Covered		Gore-Viatorr
Uncovered		Bare metal
Age	years	Age of the patient at the time of TIPS placement
MELD score	1-40	Model for End-Stage Liver Disease (MELD), a scoring system for assessing the severity of chronic liver disease as a prognostic tool for mortality prediction within 3 months of TIPS placement and determining priority for a liver transplant recipient
Pre-TIPS serum albumin	mg/dl	A globular protein produced by the liver and

		reduced in quantity with end-stage liver disease
Pre-TIPS serum bilirubin	gm/dl	A product of hemoglobin metabolism processed in the liver and elevated in chronic liver disease
Pre-TIPS creatinine	gm/dl	A compound produced by metabolism of creatine and excreted in the urine and serves as a measurement of renal function
Pre-TIPS INR	ratio	International normalized ratio, a calculation made to standardize prothrombin time, which is a test to learn how fast the blood clots in patients receiving oral anticoagulant medication, typically warfarin.
OUTCOME VARIABLE		
HE		Clinician diagnosis within 30 days post-TIPS placement based on symptoms delineated by West Haven criteria
Yes		
No		

[a] TIPS = transjugular intrahepatic portosystemic shunt
[b] HE = hepatic encephalopathy

TABLE 2. Demographic, Clinical, Biochemical and Hepatic Hemodynamic Characteristics of Cirrhotic Subjects Undergoing TIPS procedure, Stratified by Occurrence of Post-TIPS HE, OHSU 2002-2014

Characteristic	No Post-TIPS HE (n = 77) Mean +/-SD or No. (%)	Post TIPS HE (n = 35) Mean +/-SD or No. (%)	p-value
DEMOGRAPHIC			
Age (years)	55.4 (+/-9.27)	54.3 (+/-12.37)	0.62
Sex			0.08
Male	51 (66.3)	17 (48.6)	
Female	26 (33.8)	18 (51.4)	
Alcoholic as etiology of cirrhosis			0.33
All other etiologies	60 (77.9)	30 (85.7)	
Alcohol only	17 (22.1)	5 (14.3)	
CLINICAL			
Indication			0.14
Recurrent variceal bleed	40 (52.0)	30 (85.7)	
Refractory ascites	17 (22.1)	5 (14.3)	
History of pre-TIPS HE			0.03^{++}
No	49 (63.6)	29 (82.9)	
Yes	29 (36.4)	6 (17.1)	
Urgency			0.49
No	57 (74.0)	28 (80)	
Yes	20 (26.0)	7 (20)	
BIOCHEMICAL			
Albumin (gm/dL)	2.65 (+/- 0.56)	2.65 (+/- 0.56)	0.08
Hypoalbuminemia			0.89
No	6 (66.7)	3 (33.3)	
Yes	71 (68.0)	32 (31.1)	
Creatinine (mg/dL)	1.15 (+/- 0.71)	1.27 (+/- 0.64)	0.39
Bilirubin (mg/dL)	1.74 (+/- 1.10)	1.65 (+/- 1.30)	0.70
INR (mean +/- SD)	1.40 (+/- 1.64)	1.28 (+/- 0.17)	$< 0.01^{++}$
Child-Pugh score	8.51 (+/- 1.64)	8.31 (+/- 1.37)	0.55
MELD score	13.6 (+/- 3.96)	13.2 (+/- 3.07)	0.56
HEPATIC HEMODYNAMIC			
% reduction of HVPG (continuous)	53.1 (+/- 15.8)	60.7 (+/- 14.4)	0.02^{++}
% reduction of HVPG			$< 0.01^{++}$
< 50%	24 (88.9)	3 (11.1)	
$\geq$ 50%	53 (62.4)	35 (31.3)	
Absolute HVPG reduction (mm Hg)	9.33 (+/-5.16)	10.9 (+/-4.54)	0.02^{++}
Pre-TIPS HVPG (mm Hg)	16.8 (+/-6.32	17.8 (+/-5.50)	0.41
Post-TIPS HVPG (mm Hg)	7.65 (+/-3.28)	6.91 (+/-3.32)	0.28

$^{++}$Values that are statistically significant using p-values, $\alpha = 0.05$

TABLE 3. Demographic, Clinical, Biochemical and Hepatic Hemodynamic Characteristics of Cirrhotic Subjects Undergoing TIPS Procedure, Stratified by Indications for TIPS, OHSU 2002-2014

Characteristic	Recurrent variceal bleed (n = 53) Mean +/-SD or No. (%)	Refractory ascites (n = 59) Mean +/-SD or No. (%)	p-value
DEMOGRAPHIC			
Age (years)	56.3 (10)	53.9 (10.5)	0.22
Sex			0.10
Male	35 (51.5)	33 (48.5)	
Female	18 (40.9)	26 (59.1)	
Alcoholic as etiology of cirrhosis			0.14
All other etiologies	46 (51.1)	44 (48.9)	
Alcohol only	7 (31.8)	15 (68.2)	
CLINICAL			
Post-TIPS HE			0.14
No	40 (51.6)	37 (48.1)	
Yes	13 (37.1)	22 (62.9)	
History of pre-TIPS HE			0.91
No	40 (51.3)	38 (48.7)	
Yes	13 (38.2)	21 (61.8)	
Urgency			$< 0.001^{++}$
No	28 (32.9)	57 (67.1)	
Yes	25 (92.6)	2 (7.41)	
BIOCHEMICAL			
Albumin (gm/dL)	2.76 (+/-0.62)	2.67 (+/-0.54)	0.37
Hypoalbuminemia			0.42
No	7 (58.3)	5 (41.7)	
Yes	46 (46)	54 (54)	
Creatinine (mg/dL)	0.83 (+/-0.28)	1.51 (+/-0.78)	$< 0.001^{++}$
Bilirubin (mg/dL)	2.06 (+/-1.39)	1.39 (+/-0.76)	$< 0.01^{++}$
INR (mean +/- SD)	1.39 (+/-0.20)	1.34 (+/-0.22)	0.16
Child-Pugh score	7.77 (+/-1.67)	9.05 (+/-1.17)	$< 0.001^{++}$
MELD score	12.7 (+/-2.96)	14.2 (+/-4.14)	0.03^{++}
HEPATIC HEMODYNAMIC			
% reduction of HVPG (continuous)	57.1 (+/-17.1)	54 (+/-14.4)	0.30
% reduction of HVPG			0.33
< 50%	15 (55.6)	12 (44.4)	
$\geq$ 50%	38 (44.7)	47 (55.3)	
Absolute HVPG reduction (mm Hg)	10.2 (+/-5.66)	9.44 (+/-4.35)	0.42
Pre-TIPS HVPG (mm Hg)	17.2 (+-6.71)	17.0 (+/-5.48)	0.82
Post-TIPS HVPG (mm Hg)	7.13 (+/-3.40)	7.68 (+/-3.21)	0.38

$^{++}$Values that are statistically significant using p-values, $\alpha = 0.05$

TABLE 4. Demographic and Biochemical Characteristics of Cirrhotic Subjects Undergoing TIPS Procedure, Excluded from the Study, OHSU 2002-2014

Characteristic	Excluded Subjects (n = 203) Mean +/-SD or No. (%)	p-value
DEMOGRAPHIC		
Age (years)	54.3 (+/-11.7)	--
Sex		--
Male	122 (60)	
Female	81 (40)	
BIOCHEMICAL		
MELD score	(n = 113) 15.3 (+/-6.50)	--

[++]Values that are statistically significant using p-values, $\alpha = 0.05$

TABLE 5. Statistical Confounding Analysis for Multivariate Model[b]

Model	% reduction of HVPG OR	% reduction of HVPG p-value	"Confounder" OR	"Confounder" p-value	Model p-value	% Change[a]
% reduction alone (continuous) (crude model)	31.16	0.02	-	-	0.014	-
% reduction + age	31.29	0.989	1.0	0.989	0.048	0.4%
% reduction + sex	22.51	0.037	1.789	0.175	0.019	27.8%[+++]
% reduction + indication	50.44	0.012	2.203	0.074	0.009	61.8%[+++]
% reduction + alcohol cirrhosis	34.48	0.017	0.536	0.273	0.025	10.6%[+++]
% reduction + pre-TIPS HE	30.89	0.017	0.346	0.039	0.005	0.87%
% reduction + pre-TIPS HVPG	28.81	0.025	1.012	0.720	0.045	7.54%
% reduction + post-TIPS HVPG	67.16	0.029	1.056	0.525	0.039	115%[+++]
% reduction + albumin	36.20	0.016	1.990	0.067	0.009	16.2%[+++]
% reduction + bilirubin	30.82	0.020	0.945	0.771	0.046	1.11%
% reduction + INR	18.48	0.052	0.038	0.015	0.0013	40.7%[+++]
% reduction + MELD score	29.40	0.022	0.976	0.692	0.045	5.67%
% reduction + Child-Pugh score	29.24	0.023	0.961	0.774	0.046	6.16%

[a] Magnitude of confounding = $(OR_{adjusted} - OR_{crude}) / OR_{crude}$

[b] Multivariate model using percent reduction of HVPG as continuous variable

[+++]Variables are considered confounding variables for an OR change of at least 10% from the crude OR

TABLE 6. Bivariate and Multivariate[a] Assessments of Risk Factors Associated with Post-TIPS HE Among Cirrhotic Subjects Undergoing TIPS Procedure at OHSU, 2002-2014

	Bivariate			Multivariate (HVPG continuous)[a]		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
DEMOGRAPHIC						
Age (years)	0.990	0.953 - 1.029	0.620	0.906	0.946 - 1.036	0.668
Sex (male vs. female)	2.077^{+}	0.920 - 4.687	0.078	1.700	0.667 - 4.335	0.266
Alcohol as etiology of cirrhosis	0.588	0.198 - 1.748	0.340	0.490	0.131 - 1.830	0.288
CLINICAL						
Indication (recurrent variceal bleed vs. refractory ascites)	1.830	0.807 - 4.148	0.148	2.924^{++}	1.100 - 7.771	0.031
History of pre-TIPS HE	0.362^{+}	0.134 - 0.978	0.045	0.336	0.104 - 1.080	0.067
Urgency	0.7125	0.269 - 1.884	0.494	--	--	--
BIOCHEMICAL						
Albumin (gm/dL)	1.870^{+}	0.921 - 3.796	0.083	2.555^{++}	1.104 - 5.912	0.028
Hypoalbuminemia	1.11	0.312 - 3.974	0.869	--	--	--
Creatinine (mg/dL)	1.278	0.730 - 2.238	0.391	--	--	--
Bilirubin (mg/dL)	0.930	0.648 - 1.340	0.698	--	--	--
INR (mean +/- SD)	0.292^{+}	0.002 - 0.385	0.007	--	--	--
Child-Pugh score	0.922	0.710 - 1.197	0.543	--	--	--
MELD score	0.967	0.864 - 1.081	0.552	1.017	0.885 - 1.170	0.810
HEPATIC HEMODYNAMIC						
% reduction of HVPG (continuous)	31.16^{+}	1.736 - 559.5	0.020	60.10^{++}	2.340- 1505	0.013
Absolute HVPG reduction (mm Hg)	1.062	0.981 - 1.149	0.139	--	--	--
Pre-TIPS HVPG (mm Hg)	1.027	0.963 - 1.096	0.411	--	--	--
Post-TIPS HVPG (mm Hg)	0.931	0.819 - 1.059	0.275	--	--	--

$^{+}$Values that are statistically significant using p-values, $\alpha = 0.10$

$^{++}$Values that are statistically significant using p-values, $\alpha = 0.05$

[a] Multivariate model using percent reduction of HVPG as continuous variable, p-value = 0.0045

TABLE 7. Multivariate Assessments of Risk Factors Associated with Post-TIPS HE, Comparing Percent Reduction of HVPG as Continuous Variable vs. Dichotomized Variable at 50%, Among Cirrhotic Subjects Undergoing TIPS Procedure at OHSU, 2002-2014

	Multivariate (HVPG continuous)[a]			Multivariate (HVPG dichotomized)[b]		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
DEMOGRAPHIC						
Age (years)	0.906	0.946 - 1.036	0.668	0.988	0.945 - 1.033	0.596
Sex (male v. female)	1.700	0.667 - 4.335	0.266	2.050	0.795 - 5.281	0.137
Alcohol as etiology of cirrhosis	0.490	0.131 - 1.830	0.288	0.540	0.143 - 2.042	0.364
CLINICAL						
Indication (recurrent variceal bleed vs. refractory ascites)	2.924^{++}	1.100 - 7.771	0.031	2.283	0.878 - 5.940	0.091
History of pre-TIPS HE	0.336	0.104 - 1.080	0.067	0.264^{++}	0.080 - 0.877	0.030
BIOCHEMICAL						
Albumin (gm/dL)	2.555^{++}	1.104 - 5.912	0.028	2.540^{++}	1.076 - 5.994	0.033
MELD score	1.017	0.885 - 1.170	0.810	1.022	0.888 - 1.176	0.760
HEPATIC HEMODYNAMIC						
% reduction of HVPG (continuous)	60.10^{++}	2.340- 1505	0.013	--	--	--
$\geq$ 50%% reduction of HVPG	--	--	--	6.584^{++}	1.627 - 26.64	0.008

$^{++}$Values that are statistically significant using p-values, $\alpha = 0.05$

[a] HVPG as continuous variable model p-value = 0.0045

[b] HVPG as dichotomized variable at 50% model p-value = 0.0021

TABLE 8. Multivariate Assessments of Risk Factors Associated with Post-TIPS HE, Comparing Percent Reduction of HVPG as Continuous Variable vs. Dichotomized Variable at 50%, Both Adjusted for Indication*MELD, Among Cirrhotic Subjects Undergoing TIPS Procedure at OHSU, 2002-2014

	Multivariate (HVPG continuous, adjusted for Indication*MELD)[a]			Multivariate (HVPG dichotomized, adjusted for Indication*MELD)[b]		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
DEMOGRAPHIC						
Age (years)	0.990	0.945 - 1.036	0.664	0.988	0.944 - 1.033	0.593
Sex (male v. female)	1.697	0.664 - 4.332	0.269	2.041^{++}	0.788 - 5.285	0.034
Alcohol as etiology of cirrhosis	0.487	0.130 - 1.831	0.287	0.537	0.141 - 2.043	0.362
CLINICAL						
Indication (recurrent variceal bleed vs. refractory ascites)	2.504	0.047 - 132.6	0.951	1.946	0.038 - 100.6	0.741
History of pre-TIPS HE	0.337	0.104 - 1.086	0.067	0.264^{++}	0.795 - 0.880	0.030
BIOCHEMICAL						
Albumin (gm/dL)	2.553^{++}	1.103 - 5.910	0.029	2.538^{++}	1.075 - 5.993	0.034
MELD score	1.008	0.775 - 1.312	0.951	1.013	0.777 - 1.320	0.926
HEPATIC HEMODYNAMIC						
% reduction of HVPG (continuous)	59.77^{++}	2.387 - 1496	0.013	--	--	--
$\geq$ 50%% reduction of HVPG	--	--	--	6.577^{++}	1.626 - 26.61	0.008
INTERACTION						
Indication * MELD score	1.012	0.759 - 1.367	0.937	1.013	0.000 - 2.359	0.097

$^{++}$Values that are statistically significant using p-values, $\alpha = 0.05$

[a] HVPG as continuous variable, adjusted for Indication*MELD score model p-value = 0.0081

[b] HVPG as dichotomized variable at 50% model p-value = 0.0039

TABLE 9. Multivariate Assessments of Risk Factors Associated with Post-TIPS HE, Comparing Percent Reduction of HVPG as Continuous Variable With Post-TIPS HVPG vs. Dichotomized Variable at 50% With Post-TIPS HVPG, Among Cirrhotic Subjects Undergoing TIPS Procedure at OHSU, 2002-2014

	Multivariate (HVPG continuous with post-TIPS HVPG)[a]			Multivariate (HVPG dichotomized with post-TIPS HVPG)[b]		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
DEMOGRAPHIC						
Age (years)	0.993	0.948 - 1.040	0.459	0.993	0.946 - 1.035	0.762
Sex (male v. female)	1.783	0.692 - 1.166	0.232	2.237	0.831 - 6.022	0.111
Alcohol as etiology of cirrhosis	0.478	0.128 - 1.793	0.274	0.544	0.144 - 2.059	0.370
CLINICAL						
Indication (recurrent variceal bleed vs. refractory ascites)	2.939	1.104 - 7.825	0.274	2.183	0.830 - 5.739	0.113
History of pre-TIPS HE	0.342	0.106 - 1.106	0.073	0.255	0.144 - 2.059	0.370
BIOCHEMICAL						
Albumin (gm/dL)	2.528^{++}	0.886 - 1.306	0.031	2.249^{++}	1.048 - 5.928	0.039
MELD score	1.011	0.876 - 1.166	0.881	1.011	0.884 - 1.175	0.797
HEPATIC HEMODYNAMIC						
% reduction of HVPG (continuous)	171.2^{++}	2.224 - 13184	0.020	--	--	--
$\geq$ 50%% reduction of HVPG	--	--	--	8.711^{++}	1.677 - 45.26	0.010
Post-TIPS HVPG (mm Hg)	1.076	0.886 - 1.306	0.459	1.061	0.890 - 1.264	0.509

$^{++}$Values that are statistically significant using p-values, $\alpha = 0.05$

[a] HVPG as continuous variable (with post-TIPS HVPG) model p-value = 0.0067

[b] HVPG as dichotomized variable at 50% (with post-TIPS HVPG) model p-value = 0.0033

TABLE 10. Multivariate Assessments of Risk Factors Associated with Post-TIPS HE, Comparing Percent Reduction of HVPG as Continuous Variable With INR vs. Dichotomized Variable at 50% With INR, Among Cirrhotic Subjects Undergoing TIPS Procedure at OHSU, 2002-2014

	Multivariate (HVPG continuous with INR)[a]			Multivariate (HVPG dichotomized with INR)[b]		
Variable	OR	95% CI	p-value	OR	95% CI	p-value
DEMOGRAPHIC						
Age (years)	0.985	0.940 - 1.032	0.516	0.983	0.939 - 1.030	0.474
Sex (male v. female)	1.516	0.582 - 3.950	0.395	1.747	0.660 - 4.623	0.261
Alcohol as etiology of cirrhosis	0.467	0.125 - 1.753	0.259	0.495	0.130 - 1.889	0.304
CLINICAL						
Indication (recurrent variceal bleed vs. refractory ascites)	2.109	0.735 - 6.040	0.165	1.731	0.661 - 4.633	0.261
History of pre-TIPS HE	0.343	0.104 - 1.123	0.077	0.279^{++}	0.083 - 0.938	0.039
BIOCHEMICAL						
Albumin (gm/dL)	2.254	0.953 - 5.333	0.064	2.294	0.939 - 1.030	0.065
INR (mean +/- SD)	0.045	0.002 - 1.262	0.068	0.037	0.001 - 1.060	0.054
MELD score	1.102	0.935 - 1.300	0.247	1.110	0.941 - 1.410	0.215
HEPATIC HEMODYNAMIC						
% reduction of HVPG (continuous)	33.28^{++}	1.212 - 913.5	0.038	--	--	--
$\geq$ 50%% reduction of HVPG	--	--	--	5.667^{++}	1.376 - 23.35	0.016

$^{++}$Values that are statistically significant using p-values, $\alpha = 0.05$

[a] HVPG as continuous variable (with INR) model p-value = 0.0022

[b] HVPG as dichotomized variable at 50% (with INR) model p-value = 0.0008

Table 11. Diagnostic Procedures, Receiver Operating Characteristic (ROC) curves and Hosmer and Lemeshow Goodness-of-Fit for Study Models, OHSU 2002-2014[a]

% HVPG Reduction	p-value (% HVPG reduction)	OR	95% CI	AUC	Hosmer and Lemeshow Goodness-of-Fit Test
Crude[b]					
continuous	0.022	29.40[++]	1.636 - 528.2	0.678	0.105
20	0.846	1.259	0.123 - 12.89	0.511	0.626
30	0.870	0.886	0.207 - 3.789	0.524	0.927
40	0.188	2.432	0.647 - 3.789	0.524	0.927
50	0.016	4.845[++]	1.347 - 17.42	0.618	0.929
60	0.001	4.460[++]	1.901 - 10.46	0.690	0.924
70	0.296	1.725	0.621 - 4.794	0.567	0.896
Multivariate[c]					
continuous	0.013	60.10[++]	2.400 - 1505	0.755	0.389
20	0.328	2.564	0.938 - 1.022	0.739	0.291
30	0.748	1.291	0.272 - 6.134	0.736	0.402
40	0.113	3.181	0.759 - 13.33	0.741	0.879
50	0.008	6.584[++]	1.627 - 26.64	0.768	0.614
60	<0.001	5.459[++]	2.007 - 14.847	0.795	0.926
70	0.467	1.919	0.512 - 6.328	0.727	0.154

[a] Diagnostic procedures were performed to assess goodness-of-fit and model discriminatory capacity by generating ROC curves. The area under the ROC curve (AUC) per specific model is reported.
[b] % Crude model assesses the association between percent of HVPG reduction adjusted for MELD score
[c] % Multivariate model assesses the association between percent of HVPG reduction adjusted for age, sex, indication, albumin, MELD score, alcoholic cirrhosis and history of pre-TIPS HE
[++]Values that are statistically significant using p-values, $\alpha = 0.05$

FIGURE 2. Distribution of Percent Reduction of HVPG
Average percent reduction of HVPG for 112 total subjects.

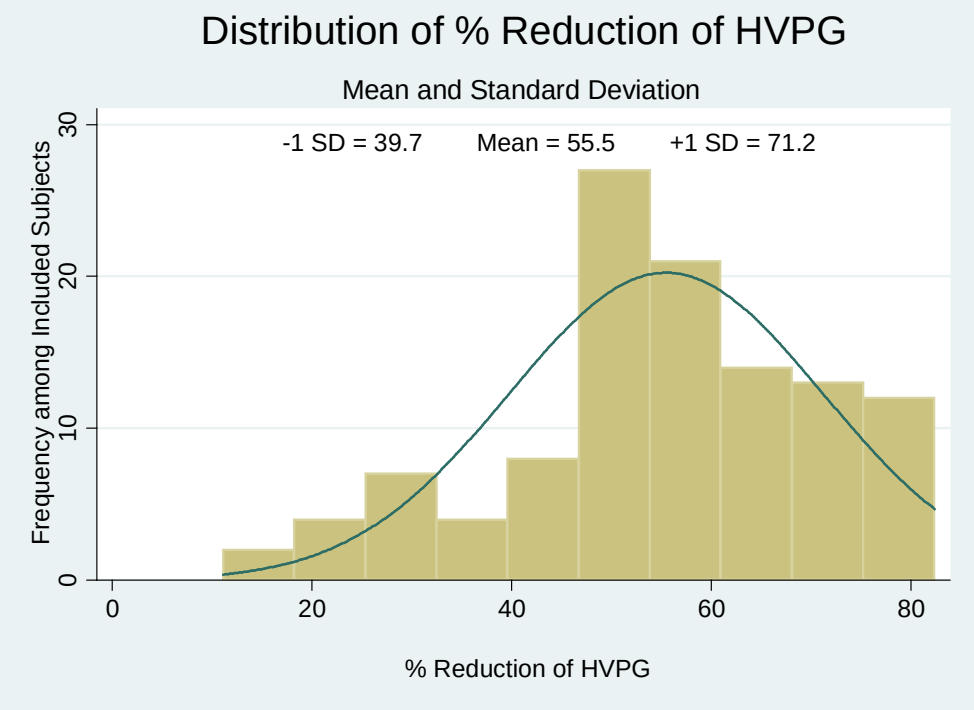


FIGURE 3. Distribution of Percent Reduction of HVPG, by Occurrence of Post-TIPS HE
Average percent reduction of HVPG for 112 total subjects, 35 with post-TIPS HE, 77 without.

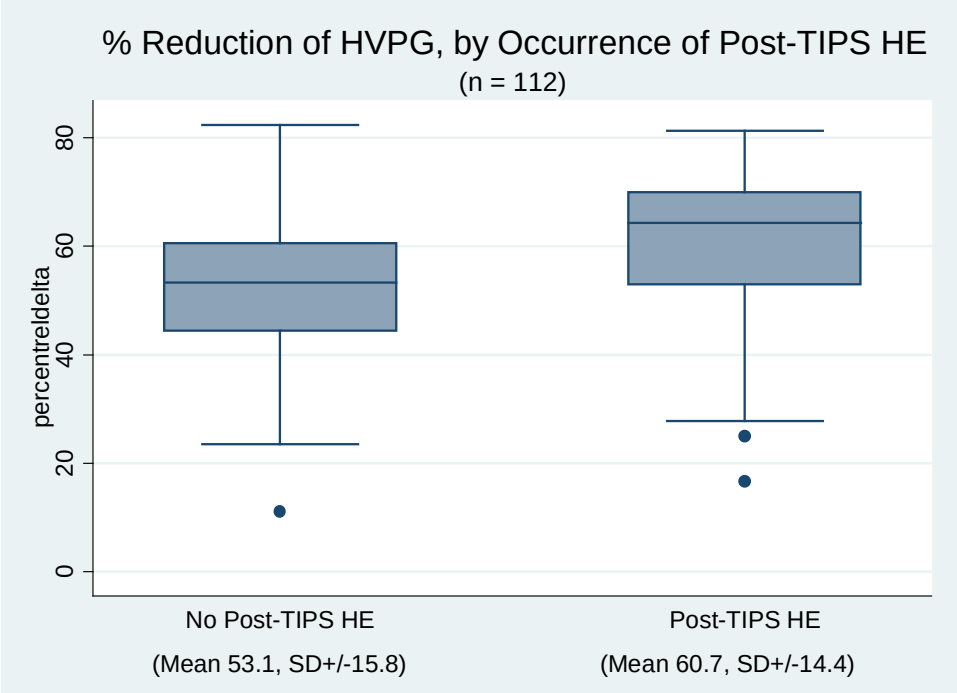


FIGURE 4. Distribution of MELD Score

Average MELD score for 112 total subjects.

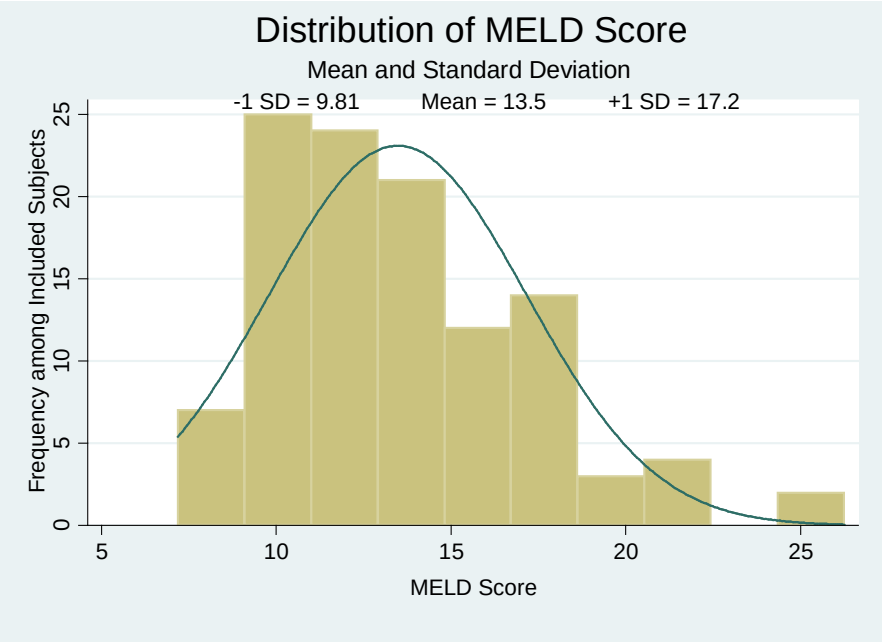
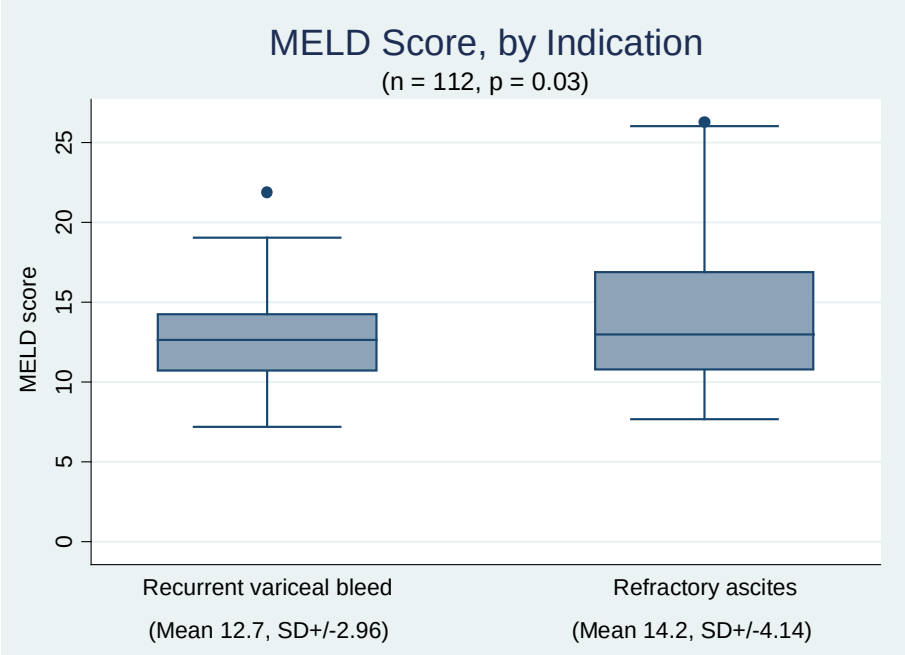
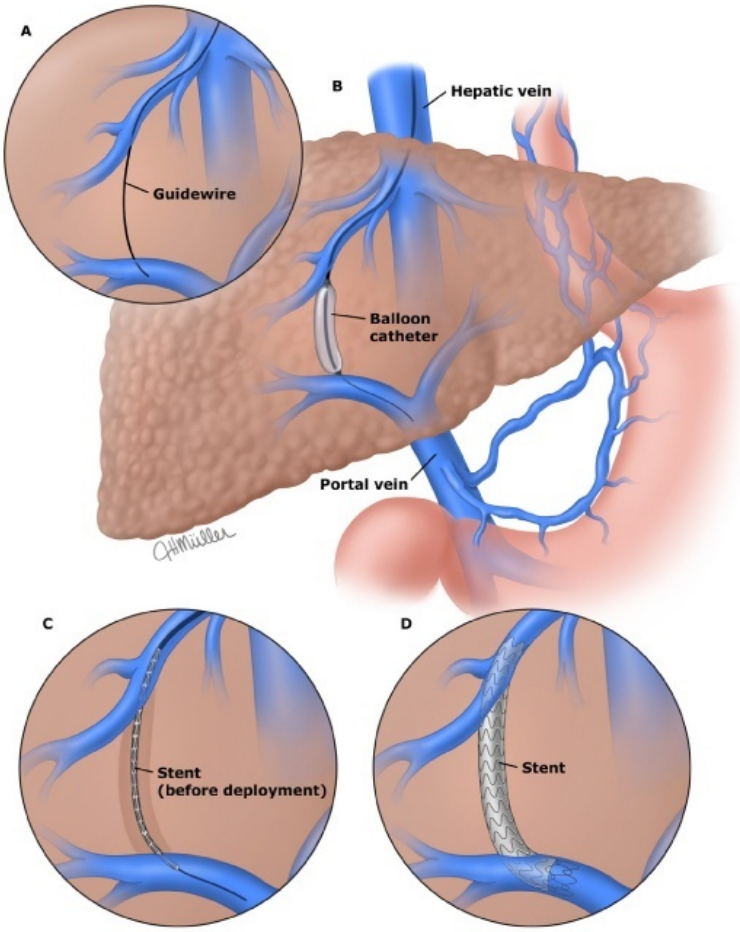


FIGURE 5. Distribution of MELD Score, by Indication
Average MELD score for 112 total subjects, 53 with recurrent variceal bleed, 59 with refractory ascites.



APPENDIX

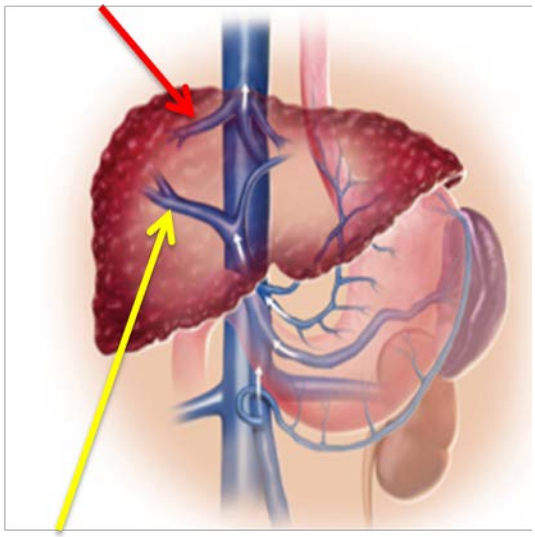
Figure A. Creation of transjugular intrahepatic portosystemic shunt (TIPS) (Haskal, 2003)



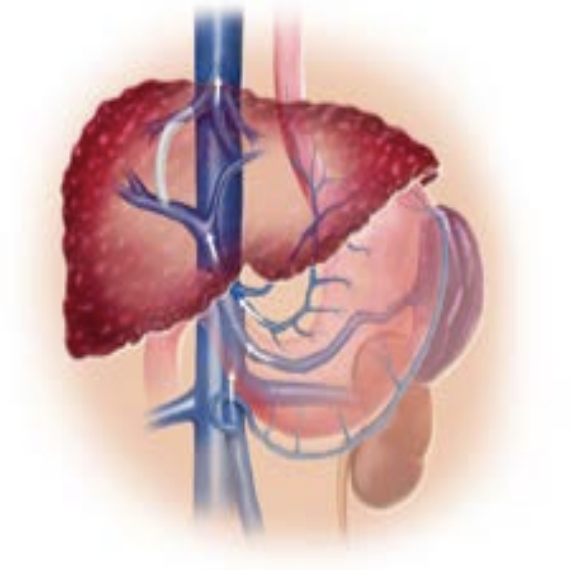
A transjugular intrahepatic portosystemic shunt (TIPS) is created by passing a needle catheter via the transjugular route into the hepatic vein and wedging it there. The needle is then extruded and advanced through the liver parenchyma to the intrahepatic portion of the portal vein and a stent is placed between the portal and hepatic veins. A TIPS functions like side-to-side surgical portocaval shunt, but does not require general anesthesia or major surgery for placement. (A) Passage of a guide wire between the hepatic vein and the portal vein. (B) Inflation of a balloon catheter within the liver to dilate the tract between the hepatic vein and the portal vein. (C) Deployment of the stent. (D) Stent in its final position.

Figure B. Measuring hepatovenous pressure gradient (HVPG) (W.L. Gore & Associates, Inc., 2000)

[free hepatic vein pressure]



[wedge hepatic venous pressure]



$HVPG_{pre}$ $HVPG_{post}$

$$\Delta HVPG = HVPG_{pre} - HVPG_{post}$$

$$\%\ \text{reduction HVPG} = (\Delta HVPG / HVPG_{pre}) \times 100$$

Figure C. West Haven Criteria of Altered Mental Status in Hepatic Encephalopathy (Conn *et al*, 1979)

Stage	Consciousness	Intellect and Behavior	Neurologic Findings
0	Normal	Normal	Normal examination. Impaired psychomotor testing
1	Mild lack of awareness	Shortened attention span Impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	Disoriented Inappropriate behavior	Obvious asterixis Slurred speech
3	Somnolent but arousable	Gross disorientation Bizarre behavior	Muscular rigidity and clonus Hyperreflexia
4	Coma	Coma	Decerebrate posturing

Figure D. Child-Turcotte-Pugh Scoring System (Pugh *et al*, 1973)

Measure	**1 point**	**2 points**	**3 points**
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/dl	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

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