

Transjugular Intrahepatic Portosystemic Shunt Does Not Independently Increase Risk of Death in High Model for End Stage Liver Disease Patients

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Physicians often exclude patients with a model for end-stage liver disease (MELD) score ≥ 18 from a transjugular intrahepatic portosystemic shunt (TIPS) procedure due to the concern for higher risk of death. We aimed to determine if TIPS increased the risk of death in these patients. We analyzed the interaction between TIPS and MELD in 106 patients with TIPS and 79 with intractable ascites without TIPS. We performed Cox proportional hazard regression, including both TIPS and MELD as time-dependent covariates together with their interaction, to calculate the impact of TIPS on the risk of death associated with a high MELD score. We found a negative interaction between a high MELD score and a history of TIPS, with potentially important effect sizes. Patients with MELD scores ≥ 18 had a 51% lower incremental risk of death (lower risk than would be expected from the combined independent risks of MELD and needing/receiving TIPS) associated with TIPS than patients with MELD scores < 18 (hazard ratio for TIPS, 0.49; 95% confidence interval, 0.10-2.45) in the first 6 months following TIPS. There was an 80% lower incremental risk of death among patients with a MELD score ≥ 18 (hazard ratio for TIPS, 0.20; 95% confidence interval, 0.03-1.23) 6 months after the TIPS procedure. *Conclusion:* Risk of death is associated with underlying disease severity as shown by the MELD score and the need for TIPS, and both history of TIPS and high MELD score independently increased the risk of mortality. However, the risk of death after TIPS was progressively lower than expected as the MELD score increased. (*Hepatology Communications* 2017;1:460-468)

Introduction

Patients with high model for end-stage liver disease (MELD) scores who undergo a transjugular intrahepatic portosystemic shunt (TIPS) procedure are at a high risk of dying after the procedure.⁽¹⁻⁷⁾ This high death rate could be because patients with high MELD scores have a higher risk of death than those with low MELD scores,⁽⁸⁻¹¹⁾ or because they have a life-threatening complication, such as intractable ascites⁽¹²⁻¹⁴⁾ or variceal bleeding,⁽¹⁵⁻²⁰⁾ which increases their risk of dying, or because the TIPS procedure itself increases the risk of death.⁽²¹⁻²³⁾ It is impossible in retrospective studies to separate the risk of death due to the condition that is the indication for the TIPS (such as intractable ascites, hepatic

hydrothorax, or variceal hemorrhage) and death caused by the TIPS procedure as the two are confounded. However, the TIPS procedure is sometimes blamed for the increased risk of death in patients with high MELD scores.⁽¹⁻⁷⁾

We hypothesized that the increased mortality risk after TIPS in patients with high MELD scores is due to the intrinsic risks of having both a high MELD score and a complication necessitating a TIPS, the *confounding by indication* effect.^(24,25) The most important consequence of this is that patients with high MELD scores could be denied a potentially lifesaving procedure if the TIPS did not add to the risk over and above that accounted for by these two preexisting risk factors.

To definitively answer this question, a controlled study is needed in which patients with a high MELD

Abbreviations: AH, alcoholic hepatitis; CI, confidence interval; GI, gastrointestinal; HR, hazard ratio; MELD, model for end-stage liver disease; TIPS, transjugular intrahepatic portosystemic shunt.

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score and an indication for TIPS were randomized to receive a TIPS procedure or to be managed without TIPS. As no such randomized studies exist, we used Cox proportional hazards modeling to determine the risk attributable to needing/receiving TIPS and separately the risk attributable to a high MELD score. By comparing the mortality to be expected from combining these independent factors with the actual mortality observed in our patients, we determined the statistical *interaction effect* or *effect modification*.⁽²⁶⁾ If mortality was higher than expected from the combination of the separate independent risks of MELD and of needing/receiving a TIPS procedure, the interaction effect would be positive.

Patients and Methods

PATIENTS

This single-center retrospective study was approved by the University of Iowa Institutional Review Board. The study included all patients who had received a TIPS procedure at our institution between 1999 and 2011. We also included patients who were seen during this period with refractory ascites, as defined by the International Ascites Club criteria,⁽²⁷⁾ but had not received a TIPS. We collected data from each patient's first encounter at our institution and every 6 months thereafter. In some cases, the first encounter was years before the TIPS procedure. We excluded patients who did not have cirrhosis and patients

with prior liver transplants, end-stage renal disease on dialysis, and hepatocellular or other forms of cancer.

The data collected included sex, age, etiology of liver disease, indication for TIPS, date of death or liver transplant, diagnosis of alcoholic hepatitis (AH), date of the TIPS procedure, and year diagnosed with cirrhosis. Laboratory data included serum sodium, albumin, bilirubin, creatinine, and international normalized ratio. MELD scores were calculated based on data obtained at the time of study inclusion and every 6 months thereafter, including the latest set obtained prior to the procedure and prior to death or transplantation.

STATISTICAL ANALYSIS

Descriptive statistics (mean, median, frequency, and percentage) for demographic, clinical, and laboratory variables were computed and compared between patients that did or did not undergo a TIPS procedure. We compared TIPS and non-TIPS groups using Pearson's chi-square test for categorical variables and two-sample *t* tests or Wilcoxon rank-sum tests for continuous variables. We analyzed each patient's highest and lowest value for variables measured at multiple times (i.e., creatinine, MELD).

We used Cox proportional hazard regression to analyze the risk of death. TIPS and MELD were included as time-dependent variables, and the TIPS-MELD interaction was determined in a time-dependent manner. Because more people die in the first 6 months after a TIPS procedure than thereafter, we fitted separate coefficients for TIPS for the time period ≤ 6

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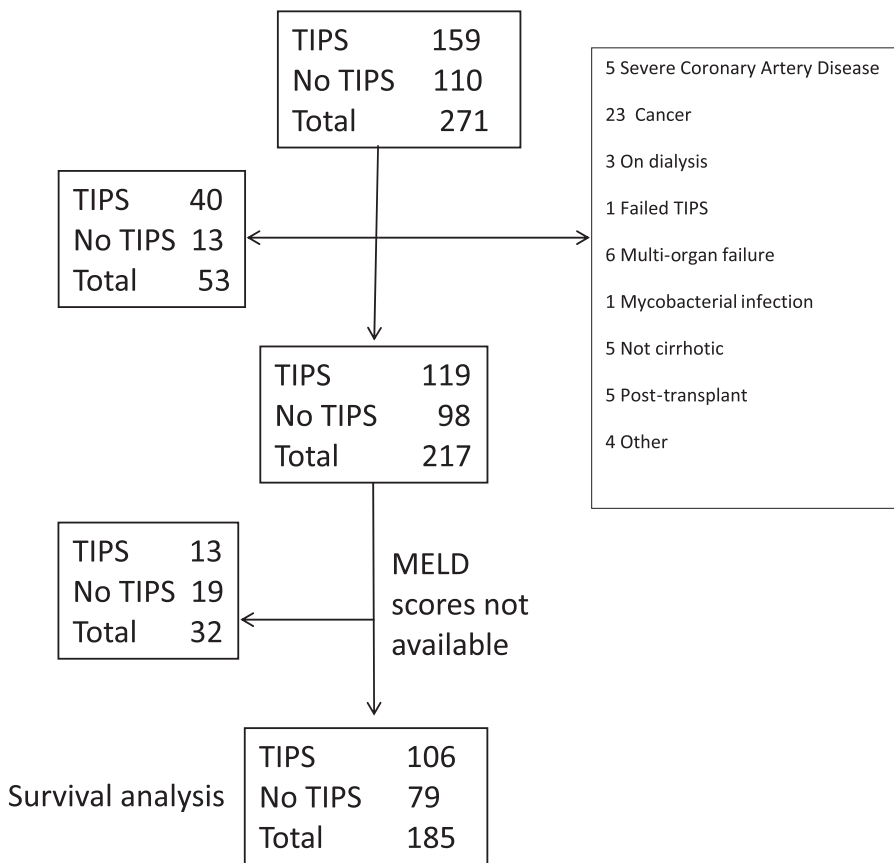


FIG. 1. Flow diagram of patients entered into the study.

months and >6 months after the TIPS procedure. Our model included MELD scores that had been updated at 6-month intervals, liver disease etiology (alcoholic versus all other), and age as a linear factor. We followed patients until death or censored them at transplant, date of last clinical contact, or study completion.

The primary outcome was the effect of the TIPS–MELD interaction on death in the time intervals ≤6 months and >6 months after the TIPS procedure. Because prior studies had suggested that a MELD score ≥18 was a cutoff for increasing mortality due to TIPS, we did a sensitivity analysis in which we dichotomized the MELD score to <18 and ≥18 and determined the impact of the TIPS–MELD interaction on the risk of death at the two specified time intervals.

Results

We identified 159 patients with TIPS and 110 patients with intractable ascites or hydrothorax who

did not have a TIPS procedure (total 271). We excluded 53 patients, leaving 217 (119 TIPS and 98 non-TIPS). The reasons for excluding patients from the study are given in Fig. 1; the majority were patients who had competing causes for death: 5 patients (9.4%) had severe coronary artery disease, 23 (43.4%) had cancer, 3 (5.7%) were on dialysis, 7 (13.2%) had an infection or multiorgan failure, 5 (9.4%) were not cirrhotic, 5 (9.4%) had the TIPS placed posttransplant, and other exclusions were present in 4 (7.5%).

The indication for TIPS was ascites and recurrent variceal bleeds in 8 (6.7%) patients, ascites and/or hepatic hydrothorax in 61 (51.3%), emergent variceal bleeding in 11 (9.2%), and recurrent variceal bleeding in 39 (32.8%). In the patients that did not receive a TIPS procedure, 38 had a history of gastrointestinal (GI) bleeding (38.8%), 3 had a history of multiple GI bleeds (3.1%), and 21 (21.4%) had hepatic hydrothorax.

Cox regression analysis included 185 of these 217 patients because MELD scores were not available on 32 patients. Among the 185 patients with adequate data, there were 49 deaths. The characteristics of the

TABLE 1. BASELINE CHARACTERISTICS OF TIPS AND NON-TIPS PATIENTS

Variable	With TIPS (n = 106)	No TIPS (n = 79)	P value
Sex (male)	66 (62%)	51 (65%)	0.75
Age, mean (SD)	54.1 (11.7)	49.0 (9.2)	0.001
Etiology of liver disease			<0.0001
Alcoholic liver disease	57 (54%)	57 (72%)	
AAT/Other	12 (11%)	0 (0%)	
Crypto/NASH	21 (20%)	1 (1%)	
Hepatitis C	16 (15%)	21 (27%)	
Follow-up in months, median [IQR]	27.93 [12.89–64.67]	22.75 [7.10–51.19]	0.13
Varices	(n = 92) 82 (89%)	(n = 63) 46 (73%)	0.009
History of GI bleed	69 (65%)	35 (44%)	0.005
Alcoholic hepatitis	16 (15%)	27 (34%)	0.002
Hepatic hydrothorax	38 (36%)	18 (23%)	0.06
Lowest MELD score	8.43 [6.00–11.99]	11.37 [6.30–15.17]	0.02
Highest MELD score	15.58 [11.80–21.07]	17.67 [10.01–24.36]	0.57
Highest MELD score ≥ 18	37 (35%)	38 (48%)	0.07
Lowest INR	1.2 [1.1–1.3]	1.3 [1.1–1.4]	0.09
Highest INR	1.4 [1.2–1.7]	1.5 [1.3–1.9]	0.42
Lowest creatinine	0.8 [0.7–1.1]	0.9 [0.8–1.1]	0.12
Highest creatinine	1.3 [0.9–1.7]	1.1 [0.9–1.6]	0.22
Lowest bilirubin	1.1 [0.8–2.1]	1.5 [0.8–3.5]	0.12
Highest bilirubin	2.9 [1.7–6.7]	3.7 [1.1–10.5]	0.76
Transplant recipients	14 (13%)	14 (17%)	0.40
Died	28 (26%)	21 (27%)	See Tables 2-4

Abbreviations: AAT, α -1 antitrypsin deficiency; Crypto/NASH, cryptogenic nonalcoholic steatohepatitis; INR, international normalized ratio; IQR, interquartile (25%–75%) range.

patients in the TIPS and non-TIPS groups are given in Table 1. The most common etiologies of liver disease were hepatitis C and alcoholic liver disease. As expected, there were fewer patients in the TIPS group ($P = 0.07$) with MELD score ≥ 18 . There was no significant difference in the number of patients that underwent transplantation ($P = 0.40$). Patients with TIPS were more likely to have GI bleeding, esophageal varices, and hepatic hydrothorax.

MORTALITY RISK ATTRIBUTABLE TO THE MELD SCORE

The risk of death increased for every 5-point increment in the MELD score, with a hazard ratio (HR) of 2.03 (95% confidence interval [CI], 1.65–2.50; $P = 0.0001$).

MORTALITY RISK ATTRIBUTABLE TO NEEDING AND RECEIVING A TIPS (HISTORY OF TIPS)

After adjustment for MELD score, age, and cause of liver disease, the HR for death was 6.58 (95% CI, 3.07–14.08; $P < 0.0001$) in the first 6 months after the

TIPS procedure and 1.05 (95% CI, 0.38–2.93; $P = 0.92$) after 6 months (Table 2).

The expected risk of death in patients receiving a TIPS is the sum of the HR of 2.03 for each 5-point increase in the MELD score combined with the HR of 6.58 from needing and receiving a TIPS at < 6 months after the TIPS procedure. For the period after 6 months, the expected total HR was the sum of 1.05 for TIPS plus 2.03 for each 5-point increment in the MELD score.

INTERACTION OF TIPS AND MELD ON THE RISK OF DEATH

The impact of a history of TIPS includes both the risk associated with the condition serving as the indication for TIPS and the risk associated with the TIPS itself. These two factors are confounded and cannot be separated in a retrospective study. However, if a high MELD score has a disproportionately negative impact on either the risk of the underlying indication for TIPS or of the TIPS itself, this should be apparent as a positive interaction between the history of TIPS and the MELD score. That is, the risk associated with TIPS in patients with a high MELD score should be increased beyond that associated simply with the presence of these two factors separately. Therefore, our

TABLE 2. COX MODEL OF THE IMPACTS OF MELD AND TIPS ON PATIENT SURVIVAL, MAIN EFFECTS ONLY (EXCLUDING THE MELD × TIPS INTERACTION)

Parameter	Estimate ± SE	HR	95% CI	P value
Age (per 10 years)	0.20 ± 0.18	1.22	0.86-1.74	0.27
Etiology of liver disease (alcohol vs. other)	0.12 ± 0.42	1.13	0.49-2.57	0.08
MELD (per 5 MELD units)	0.71 ± 0.11	2.03	1.65-2.50	<0.0001
TIPS (≤6 months)	1.88 ± 0.39	6.58	3.07-14.09	<0.0001
TIPS (>6 months)	0.52 ± 0.52	1.05	0.38-3.53	0.92

analysis focused on the size and sign of this interaction. The interaction effect for the period <6 months after TIPS was -0.25 ± 0.19 for every 5-point increase in the MELD score. The ratio of the HR for death divided by the HR predicted by the sum of the HR for TIPS and the HR for MELD was 0.78 (95% CI, 0.53-1.13; $P=0.18$). The *negative* interaction indicates a potential lower than expected risk associated with the history of TIPS of 22% for every 5-point increase in the MELD score in the first 6-month period after the TIPS procedure (Table 3). In other words, although the absolute risk of death increases after the TIPS procedure as the MELD score increases, the risk is lower than would be expected for needing/having a TIPS together with having the higher MELD score. The incremental risk of death in the first 6 months following TIPS is progressively lower than predicted as the MELD score increases.

In the period >6 months after TIPS, the interaction effect was -0.25 ± 0.23 (HR, 0.78; 95% CI, 0.49-1.23; $P=0.28$) for every 5-point increase in the MELD score (Table 3). The negative interaction effect once again indicates that for each 5-point increment in the MELD score, the actual risk of death after TIPS was 22% lower than expected. This again illustrates the strikingly lower incremental risk of death than would have been expected if the risks attributable to the higher MELD score and the risk attributable to the TIPS were treated separately and summed.

An alternative way to view this interaction is that the adverse impact of a high MELD score is *lower* in patients who have undergone a TIPS procedure. The net incremental risk of death associated with a history of TIPS as a function of the patient's MELD score is shown in Fig. 2, which illustrates the striking reduction in this incremental risk of a history of TIPS as the MELD score increases, especially in the first 6 months following TIPS.

Given that a MELD score of ≥ 18 has often been used as a value at or above which a TIPS should not be pursued, a sensitivity analysis was performed with the data dichotomized to a MELD score <18 and MELD score ≥ 18 . The results (Table 4) were similar to those from the model with the MELD score as a linear value. The effect of the TIPS × MELD interaction in the first 6 months after TIPS for a MELD score ≥ 18 was -0.71 ± 0.82 (HR, 0.49; 95% CI, 0.10-2.45; $P=0.39$) and for the period >6 months was -1.60 ± 0.92 (HR, 0.20; 95% CI, 0.03-1.23; $P=0.09$). In the first 6 months following TIPS, patients with MELD scores ≥ 18 were estimated to have a 51% lower than expected incremental risk of death associated with TIPS than patients with MELD scores <18 (HR for TIPS, 0.49; 95% CI, 0.10-2.45). After 6 months, the incremental risk of death associated with a history of TIPS was 80% lower than expected among patients with a MELD score ≥ 18 (HR for TIPS, 0.20; 95% CI, 0.03-1.23, Table 4).

TABLE 3. COX MODEL OF THE IMPACTS OF MELD AND TIPS ON PATIENT SURVIVAL, INCLUDING THE MELD × TIPS INTERACTION TERM (MELD ENTERED AS A CONTINUOUS VARIABLE)

Parameter	Estimate ± SE	Ratio of HR*	95% CI	P value
Age (per 10 years)	0.22 ± 0.18	1.24	0.87-1.76	0.23
Etiology of liver disease (alcohol vs. other)	0.17 ± 0.43	1.18	0.51-2.73	0.69
MELD (per 5 MELD units)	0.83 ± 0.13	2.30	1.77-2.99	<0.0001
TIPS (≤6 months) (at MELD 15)	2.11 ± 0.43	8.28	3.56-19.26	<0.0001
†TIPS (≤6 months) × 5 MELD points	-0.25 ± 0.19	0.78*	0.53-1.13	0.18
TIPS (>6 months) (at MELD 15)	0.21 ± 0.53	1.24*	0.43-3.53	0.69
†TIPS (>6 months) × 5 MELD points	-0.25 ± 0.23	0.78	0.49-1.23	0.28

*Ratio of HR represents the ratio of actual hazard ratio for death divided by the sum of hazard ratio due to TIPS combined with the hazard ratio due to each 5 point increment of MELD.

†The sign of the parameter estimate for the interaction terms is negative and the HR is less than 1, implying lower incremental relative risk of TIPS at MELD values ≥ 18 .

TABLE 4. COX MODEL OF THE IMPACTS OF MELD AND TIPS ON PATIENT SURVIVAL, INCLUDING THE MELD \times TIPS INTERACTION TERM, WITH MELD DICHOTOMIZED AS <18 OR ≥ 18

Parameter	Estimate \pm SE	HR	95% CI	P value
Age (per 10 years)	0.21 \pm 0.18	1.23	0.87-1.75	0.24
Etiology of liver disease (alcohol vs. other)	0.41 \pm 0.42	1.51	0.66-3.45	0.33
MELD ≥ 18	2.870 \pm 0.573	17.65	5.74-54.28	<0.0001
TIPS (≤ 6 months) (with MELD < 18)	2.63 \pm 0.58	13.90	4.49-42.98	<0.0001
[†] TIPS (≤ 6 months) \times MELD ≥ 18	-0.71 \pm 0.82	0.49*	0.10-2.45	0.39
TIPS (> 6 months) (with MELD < 18)	0.87 \pm 0.66	2.39	0.66-8.68	0.18
[†] TIPS (> 6 months) \times MELD ≥ 18	-1.60 \pm 0.92	0.20*	0.03-1.23	0.09

*HR represents the ratio of the incremental risk of TIPS with a MELD score ≥ 18 to that of a TIPS with a MELD score < 18 .

[†]The sign of the parameter estimate for the interaction terms is negative and the HR is less than 1, implying lower incremental relative risk of TIPS at MELD values ≥ 18 .

The estimated interactions for both time intervals were not only negative but also had potentially important effect sizes. The widely held belief that a TIPS indication/procedure increases the risk of death more than expected from the combined risks of MELD and needing/receiving a TIPS would have to give a *significant positive* interaction effect. Our data showed the opposite.

Discussion

Elective TIPS has been shown to improve quality of life and may decrease morbidity and mortality in patients with refractory ascites,⁽²⁸⁻³²⁾ variceal hemorrhage,⁽³³⁻³⁵⁾ and hepatic hydrothorax.⁽³⁶⁻³⁸⁾ However, it is an invasive procedure performed in an inherently high-risk population that has a higher mortality than the general population with cirrhosis due to their complications of intractable ascites, esophageal varices, and GI bleeding. Many physicians exclude patients with high MELD scores (≥ 18) from receiving TIPS because of concerns that patients with higher MELD scores have a disproportionately higher risk of death from the procedure.⁽¹⁻⁷⁾

In our study, we confirmed that patients who undergo a TIPS procedure have an increased mortality risk compared to patients who did not have TIPS for all MELD scores (Table 2). This is expected and likely reflects that the patients who needed TIPS were inherently sicker. The need for TIPS confounds the outcome (death); this confounding by indication^(24,25) cannot be overcome in nonrandomized studies. The higher rates of prior esophageal varices, GI hemorrhage, and hepatic hydrothorax in this group in our study support the hypothesis that patients with TIPS were inherently sicker. Alternatively, injury to the liver, altered blood flow, or anesthesia effects associated with the procedure may increase the procedure's mortality risk.^(21,39,40) It is

not possible in this retrospective study to separate the mortality risk associated with the indications for TIPS from the risk of the procedure itself. This does not, however, affect our ability to assess the interaction of a high MELD score and TIPS and whether this combination is disproportionately risky.

Our data showed that, as expected, a higher MELD score is associated with increased mortality risk. Because a history of TIPS and higher MELD scores both independently predict a higher risk of death, we expected that patients with both high MELD scores and TIPS would have a higher risk of death than patients with lower MELD scores who undergo a TIPS procedure. Our study and multiple others show this.

The key finding of our study was that mortality went up considerably less than expected when a TIPS

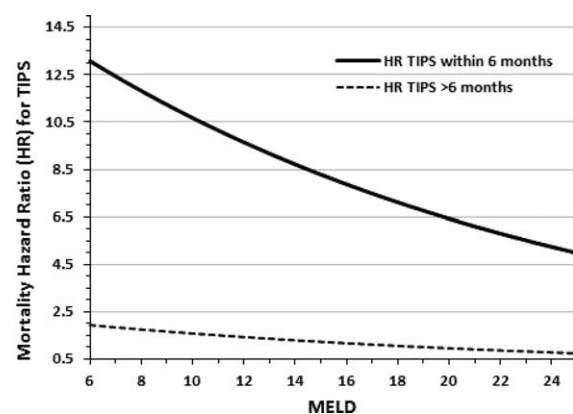


FIG. 2. Net incremental mortality hazard of TIPS at varying MELD levels at the time of a TIPS procedure. Mortality risk after TIPS consists of the two independent confounding factors, MELD score and needing/receiving TIPS (history of TIPS). The estimated incremental risk (contribution to the total risk of death) of a history of TIPS is markedly lower at higher MELD scores, especially within the first 6 months following transplant.

procedure was performed in patients with higher MELD scores. The interaction effect of MELD and a history of TIPS on mortality was negative, i.e., the mortality associated with a history of TIPS and a high MELD score was lower than what would be expected from combining the risk of these two factors independently. This indicates an important potential decrease in expected mortality associated with TIPS in patients with higher MELD scores, as evidenced by a negative interaction sign. Although this interaction term is not statistically significant, the effect size was relatively large. Patients with high MELD scores (≥ 18) who need/receive a TIPS would be expected to have a higher mortality risk than patients with low MELD scores (< 18) who need a TIPS. However, when comparing the mortality of the patients with high MELD (≥ 18) and low MELD (< 18) scores, the mortality risk was 51% lower than expected during the first 6 months following TIPS for patients having a high MELD score (≥ 18) after taking into account the risk of needing/receiving a TIPS. In patients who survived more than 6 months following a TIPS procedure, there was an 80% lower risk of death in patients with high MELD scores (≥ 18) than would be expected if the risks of high MELD and needing/having a TIPS were combined. This is contrary to the current perception that patients with higher MELD scores have disproportionately worse outcomes after the TIPS procedure.

Our data should not be dismissed because the P value for the interaction effect was not significant. A recent statement by the American Statistical Society points out that statistical significance and P values are frequently misinterpreted and specifically state “A p -value, or statistical significance, does not measure the size of an effect or the importance of a result”⁽⁴¹⁾ and urges journals to stop using statistical significance to accept an article; many high-ranking medical journals have recently highlighted this in editorials. In our study, the HR for death divided by the HR that was predicted by the sum of the HR for TIPS and the HR for MELD was 0.78 (95% CI, 0.53-1.13; $P = 0.18$). The *negative* interaction indicates a potential *reduction* of risk associated with the history of TIPS of 22% for every increment in a MELD score of 5 points. The 95% CI shows the risk is potentially 47% lower than the predicted risk for every 5-point increase in MELD, but the maximum possible increase over the expected risk is only 13%. The negative interaction sign is the opposite of what we would expect if the TIPS itself were associated with a disproportionate risk of death in patients with high MELD scores.

The primary limitation of this study is that it is a relatively small, retrospective, single-center study. Our patients mostly had cirrhosis from alcoholic liver disease or hepatitis C, which may not reflect the demographics of all centers. There were fewer patients with a history of AH in the TIPS group (15% versus 34%; $P = 0.002$), which likely reflects the expectation that TIPS would not be necessary as patients with AH may recover. Patients with AH may have better survival as AH is reversible with abstinence; the Cox model adjusted for the difference in diagnosis and would mitigate the effect. However, survival could have been confounded by the higher proportion of AH in non-TIPS patients. Only a prospective randomized study could truly avoid a confounding factor such as AH.

Despite its limitations, our data suggest that the current practice of excluding patients with high MELD scores (≥ 18) from having a TIPS procedure should be reexamined. The only way to determine accurately whether patients with an indication for TIPS and with high MELD scores could benefit or be harmed by undergoing a TIPS procedure is with a prospective randomized control trial. We believe such a trial is urgently needed.

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