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Within-patient temporal variance in MELD score and impact on survival prediction after TIPS creation

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ABSTRACT

Background. To assess within-patient temporal variability in Model for End Stage Liver Disease (MELD) scores and impact on outcome prognostication after transjugular intrahepatic portosystemic shunt (TIPS) creation. **Material and methods.** In this single institution retrospective study, MELD score was calculated in 68 patients (M:F = 42:26, mean age 55 years) at 4 pre-procedure time points (1, 2-6, 7-14, and 15-35 days) before TIPS creation. Medical record review was used to identify 30- and 90-day clinical outcomes. Within-patient variability in pre-procedure MELD scores was assessed using repeated measures analysis of variance, and the ability of MELD scores at different time points to predict post-TIPS mortality was evaluated by comparing area under receiver operating characteristic (AUROC) curves. **Results.** TIPS were successfully created for ascites (n = 30), variceal hemorrhage (n = 29), hepatic hydrothorax (n = 8), and portal vein thrombosis (n = 1). Pre-TIPS MELD scores showed significant (P = 0.032) within-subject variance that approached ± 18.5%. Higher MELD scores demonstrated greater variability in sequential scores as compared to lower MELD scores. Overall 30- and 90-day patient mortality was 22% (15/67) and 38% (24/64). AUROC curves showed that most recent MELD scores performed on the day of TIPS had superior predictive capacity for 30- (0.876, P = 0.037) and 90-day (0.805 P = 0.020) mortality compared to MELD scores performed 2-6 or 7-14 days prior. **Conclusions.** In conclusion, MELD scores show within-patient variability over time, and scores calculated on the day of TIPS most accurately predict risk and should be used for patient selection and counseling.

Key words. Transjugular intrahepatic portosystemic shunt (TIPS). Model for End Stage Liver Disease (MELD).

INTRODUCTION

The utility of the Model for End Stage Liver Disease (MELD) score in predicting clinical outcomes after transjugular intrahepatic portosystemic shunt (TIPS) creation has been established.[1-5] MELD scores performed at the time of TIPS creation are associated with high predictive capacity for early patient mortality, with area under receiver operating characteristic (AUROC) curves or c-statistics ranging from 0.8-0.9 at 1- and 3-months post-procedure.[5] Although the MELD score represents an objective, statistically founded, and liver specific metric, it is nonetheless subject to potential variation based on transient influences, such as patient nutritional status and medication use, which may result in minor deviation in lab values.[6,7] As TIPS risk stratification varies significantly based on MELD value,[5] dynamic fluctuation in the calculated MELD score may theoretically alter patient-specific outcome prognostication, and thus has potential to affect patient selection and risk counseling for TIPS. With this in mind, the cur rent study was undertaken with the intent of measuring the degree of within-patient temporal variation in MELD score prior to TIPS and quantifying its impact on prediction of early survival outcomes after TIPS creation.

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MATERIALS AND METHODS

The study protocol conformed to the ethical guide lines of the 1975 Declaration of Helsinki, and was granted approval with waiver of consent for inclusion in this retrospective analysis by the institutional review board at our hospital. All patients provided written informed consent for TIPS procedures, which were created within medical standard of care for various indications.

Clinical setting and study design

Between November 1999 and July 2011, consecutive patients with liver cirrhosis who underwent successful TIPS creation at a single tertiary care, academic university affiliated hospital situated in a large metropolitan area were identified through review of our hospital's Picture Archiving and Communication System (PACS), and were selected for retrospective study.

Patients, liver disease, and MELD scores

Two hundred twenty nine patients who underwent technically successful TIPS creation were identified for potential inclusion. Of these, 161 patients were excluded due to missing lab data precluding calculation of MELD score at designated pre-procedure time points. Sixty-eight patients were included in the final study cohort. The formula for calculation of the MELD score has been previously described.[1] MELD score was calculated at 3-4 time points before TIPS using pre-procedure lab values:

- Within 24 h of ("immediately" before) TIPS.
- 2-6 days prior to TIPS.
- 7-14 days prior to TIPS, and, when available.
- 15-35 days prior to TIPS (n = 41).

Patient demographics, liver disease characteristics, clinical presentation data, and pre-procedure MELD scores of the study cohort are summarized in table 1.

Table 1. Patient demographics, liver disease characteristics, and clinical presentation.

Measure	All TIPS (mean ± standard deviation)
Patients	68
Age (years)	54.7 ± 8.6
Gender	
Male	42 (62%)
Female	26 (38%)
Liver disease etiology	
Alcohol	21 (31%)
HBV or HCV	18 (26%)
Alcohol and HBV or HCV	14 (21%)
Other*	15 (22%)
Procedure indication	
Intractable ascites	30 (44%)
Variceal hemorrhage	29 (43%)
Refractory hepatic hydrothorax	8 (12%)
Portal vein thrombosis	1 (1%)
Procedure urgency	
Emergent	19 (28%)
Non-emergent	49 (72%)
Prior liver transplant	5 (7%)
Pre-procedure MELD score †	
Immediate	20.1 ± 9.8
2-6 (mean 3.3 ± 1.6) days	19.6 ± 9.0
7-14 (mean 11.5 ± 2.4) days	19.2 ± 7.6
15-35 (mean 27.9 ± 6.4) days	18.1 ± 6.3

HBV: hepatitis B virus. HCV: hepatitis C virus. *Includes non-alcoholic steatohepatitis (NASH), primary biliary cirrhosis, cryptogenic liver disease, autoimmune liver disease, alpha-one antitrypsin deficiency, congenital hepatic fibrosis, idiopathic adult ductopenia, and unknown causes of cirrhosis. †No statistically significant difference in baseline MELD score across time points (P = 0.692).

TIPS procedures, post-procedure care, and clinical follow-up

The technique for TIPS creation has been previously described.[8] Procedures were performed in the Interventional Radiology (IR) suite using general anesthesia. Jugular venous access was gained with dilation to a 10 French sheath. A 5 French catheter was used to engage the right hepatic vein. Hepatic venography, pressure measurement, and wedged hepatic venography were performed. Next, a Rösch-Uchida transjugular liver access set (Cook Medical Co., Bloomington IN) was used to access the portal vein. Portal vein catheterization and pressure measurement, balloon dilation of the hepatic parenchymal tract, and direct portography were performed. Subsequently, 10 or 12 mm Wallstent bare metal stents (Boston Scientific, Natick MA) (used from 1999-2003) or 10 mm Viatorr covered stent-grafts (W. L. Gore & Associates; Flagstaff AZ) (used from 2004-2011) were deployed, followed by 7-10 mm

balloon dilation. After measurement of final portal and right atrial pressures, shunt venography was performed. Gastroesophageal variceal embolization was performed in select cases of variceal hemorrhage. Catheterization of the coronary vein or gastroesophageal varix using a 5 French catheter or microcatheter was followed by embolization with 0.035 inch or 0.018 inch metallic coils. After TIPS procedures, patients were monitored in an intensive care unit. Early clinical follow-up was performed while patients remained hospitalized following TIPS. Subsequent clinical follow-up was in the outpatient Hepatology clinic.

Measured outcomes and statistical analysis

The primary outcome measures of this study were overall and within-patient variance in MELD score, 30- and 90-day overall mortality, and AUROC curves or c-statistics generated using MELD scores at each pre-procedure time point and mortality outcomes. Patients receiving liver transplants within 90 days of TIPS were censored from survival analysis. TIPS hemodynamic success, defined as portosystemic pressure gradient (PSG) reduction to an absolute value less than 12 mmHg, and procedure-related complications, classified according to the Society of Interventional Radiology Standards of Practice Committee classification of complications,[9] were secondary outcome measures.

Descriptive statistics were used to characterize demographic features of the study population. Between patient variance in MELD score was compared using one-way analysis of variance (ANOVA). Within-patient variance in MELD score was assessed using repeated measures ANOVA, with *post-hoc* comparison of MELD scores across different time points using the paired samples t-test. AUROC curves were compared using the method of De Long, *et al.*[10] Statistical analysis was performed utilizing commercially available software packages (SPSS version 18; SPSS Inc., Chicago IL and MedCalc; MedCalc Software, Belgium). P-values ≤ 0.05 were considered statistically significant.

RESULTS

TIPS procedures and procedure-related complications

TIPS procedure results are summarized in Table 2. 51/68 (75%) patients underwent Viatorr TIPS, while 17/68 (25%) patients underwent Wallstent TIPS. Variceal embolization was performed in 11/68 (16%) bleeding patients. 30-day procedure-related adverse events included hepatic encephalopathy in 26/68 (38%) patients and liver insufficiency in 2/68 (3%) patients.

Within-patient MELD score variation

Overall and risk stratified within-patient temporal changes in MELD score are shown in table 3. Statistically significant within-subject variance was identified between MELD scores at different time points (P = 0.032), with significant differences between immediate and 15-35 day MELD score (P = 0.014), 2-6 day and 15-35 day MELD

Table 2. TIPS results.

Outcome	Result (mean ± standard deviation)
Hemodynamic success	64/68 (94%)
Pre-TIPS PSG (mm Hg)	21 ± 6
Post-TIPS PSG (mm Hg)	7 ± 3
PSG reduction (mm Hg)	14 ± 6

TIPS: transjugular intrahepatic portosystemic shunt. PSG: portosystemic gradient.

Table 3. Overall and risk stratified within-patient MELD score variance.

Score	Score 1-2 difference	Score 1-3 difference	Score 1-4 difference
MELD (entire cohort)	± 2.6 (11.1%)	± 3.9 (18.5%)	± 3.8 (16.0%)
MELD (≤ 18) *	± 1.3 (8.7%)	± 2.6 (19.2%)	± 2.1 (15.0%)
MELD (19-25) †	± 2.6 (12.3%)	± 2.9 (13.4%)	± 2.0 (9.3%)
MELD (≥ 26) ‡	± 6.0 (16.0%)	± 7.9 (21.3%)	± 9.3 (24.4%)
P-value	< 0.001	< 0.001	< 0.001

MELD = Model for End Stage Liver Disease. *Associated with 13% 90-day mortality after TIPS creation (5). †Associated with 33% 90-day mortality after TIPS creation (5). ‡Associated with 80% 90-day mortality after TIPS creation (5).

score (P = 0.037), and 7-14 day and 15-35 day MELD score (P = 0.033). Among risk stratified MELD scores, higher risk categories showed significantly greater variability in sequential MELD scores as compared to lower risk categories (Table 3). Using a three-tier risk assessment system (low risk = MELD ≤ 18, intermediate risk = MELD 19-25, high risk = MELD ≥ 26), use of more remote MELD scores for TIPS patient selection affected accuracy of risk appraisal. For example, if 2-6 day MELD scores were used instead of immediate pre-procedure MELD scores, 18/68 (27%) patients would have been upstaged or down staged to a higher or lower risk category. Similarly, if 7-14 day or 15-35 day MELD scores were used instead of immediate pre-procedure MELD scores, 23/68 (34%) and 11/41 (27%) patients would have been upstaged or down staged, respectively.

Table 4. Temporal AUROC variance.*

Time	30-day AUROC	90-day AUROC
MELD within 24 hours	0.876	0.805
MELD 2-6 days prior	0.854	0.754
MELD 7-14 days prior	0.796	0.697

AUROC: area under receiver operating characteristic (AUROC) curve. MELD: Model for End Stage Liver Disease. *Incomplete data set precluded calculation of c-statistics based on 15-35 day pre-procedure MELD scores.

Patient survival and AUROC analysis

68/68 (100%) patients achieved 30- and 90-day clinical follow-up. However, 1/68 (1%) and 4/68 (6%) patients were censored from 30- and 90-day analysis due to liver transplantation performed within 90 days after TIPS. Overall 30- and 90-day patient mortality was 22% (15/67) and 38% (24/64).

30- and 90-day AUROC values for MELD scores at various pre-procedure time points are shown in table 4. When MELD scores were analyzed across dif ferent time points, 30-day AUROC for immediate pre-procedure MELD score showed statistically superior predictive capacity for mortality as compared to 7-14 day pre-procedure MELD score (0.876 *vs.* 0.796, P = 0.037). For 90-day AUROCs, a statistical ly superior prognostic capability was identified for immediate pre-procedure MELD score *vs.* 7-14 day pre-procedure MELD score (0.805 *vs.* 0.697, P = 0.020). Interestingly, among the entire cohort,

Table 5. Temporal AUROC variance subset analysis.*

Score	MELD within 24 h	MELD 2-6 days prior	MELD 7-14 days prior
Emergent			
30-day AUROC	0.981	0.974	0.890
90-day AUROC	0.963	0.926	0.809
Non-emergent			
30-day AUROC	0.784	0.755	0.721
90-day AUROC	0.710	0.656	0.629
VH			
30-day AUROC	0.975	0.969	0.910
90-day AUROC	0.908	0.873	0.802
Ascites			
30-day AUROC	0.708	0.659	0.620
90-day AUROC	0.680	0.614	0.596
Covered			
30-day AUROC	0.797	0.817	0.696
90-day AUROC	0.664	0.631	0.581
Bare metal			
30-day AUROC	0.910	0.917	0.889
90-day AUROC	0.986	0.957	0.879

AUROC: area under receiver operating characteristic (AUROC) curve. MELD: Model for End Stage Liver Disease. VH: variceal hemorrhage. Ascites: ascites TIPS. Covered: covered stent TIPS. Bare metal: bare metal stent TIPS. *Incomplete data set precluded calculation of c-statistic s based on 15-35 day pre-procedure MELD scores.

MELD scores for patients with Child-Pugh C liver disease (n = 41) showed improved prognostic capacity for prediction of 30- (0.893 *vs.* 0.710) and 90-day (0.779 *vs.* 0.667) mortality as compared to MELD scores for patients with Child-Pugh A or B liver disease (n = 27); this indicates enhanced accuracy of MELD scores for predicting survival in the setting of more advanced liver disease.

To account for the heterogeneous nature of the study population, analysis of 30- and 90-day AUROC values for MELD scores at various pre-procedure time points was performed for emergent *vs.* non-emergent, variceal hemorrhage versus ascites, and covered stent *vs.* bare metal stent TIPS patient subsets. This revealed that the predictive capacity of MELD generally worsened with use of more remote scores in the different subset cohorts (Table 5), a finding consistent with that of the overall population.

DISCUSSION

In recent years, TIPS creation has emerged as an established treatment for various complications of portal hypertension;[11] traditional indications include treatment of uncontrollable gastroesophageal variceal hemorrhage[8] and medically refractory ascites,[12] while emerging indications include early use in variceal bleeding patients[13] and treatment of portal vein thrombosis.[14] Because TIPS can precipitate hepatic decompensation and contribute to mortality in patients with advanced liver disease, concrete patient selection criteria are necessary to identify optimal procedure candidates and recognize individuals expected to have poor clinical outcomes. The MELD score, which was developed in 2001 and incorporates serum creatinine, total bilirubin level, and patient international normalized ratio into a quantitative score,[15] has been validated as an accurate predictor of early survival after TIPS creation.[5] Nonetheless, MELD score is subject to intrinsic variability based on its derivation from laboratory values, and an understanding of the degree and impact of potential MELD score variation is necessary for accurate outcome prediction.

In the current study, we investigated the within-patient temporal variance in MELD score prior to TIPS creation. In examining the MELD at four pre-procedure time points prior to TIPS creation, we found that scores showed statistically significant variation over time, differing by approximately 11% as early as 2-6 days prior to TIPS, and by about 16% 15-35 days before TIPS. We further found that higher MELD scores showed a greater degree of fluctuation than lower MELD scores, highlighting the capricious nature of liver function in decompensated patients. Our results herein confirm the susceptibility of MELD score to within-patient variability despite its basis in objective lab measures, and further expand on the findings of Fitzgerald, *et al.,* who reported significant variance in MELD scores performed within 72 hours of TIPS.[6]

In exploring the impact of MELD score variance on TIPS survival outcomes, we found that immediate pre-procedure MELD scores were most accurate for prediction of both 30- and 90-day mortality, and had statistically superior performance compared to scores at more remote time points. The better predictive capacity of more recent MELD scores in forecasting TIPS survival outcomes is corroborated by similar findings in the transplant literature, where more current MELD scores have shown better predictive value for death while on the wait list compared to MELD scores calculated at the time of transplant listing.[7] The practical implication of our results is clearly reflected in the non-trivial percentage of patients who would have had TIPS risk either upstaged or down staged through use of older MELD scores for patient selection and outcome counseling; such inaccuracy affected up to one-third of cases in this investigation and may have significant day-to-day clinical bearing. Based on the findings herein, we suggest that TIPS risk be assessed using most current lab value measures and <pMELD scores, obtained even as recent as a few days prior, be avoided for such use due to reduced accuracy.

There are several limitations to this investigation. First, this study was retrospective and non-randomized in nature, and is subject to the inherent weaknesses of non-prospective studies. Second, our investigation represents the experience of a single institution and had a relatively smaller patient sample size that represented only 30% of our TIPS population during the study period, which may lead to sampling bias. Third, because patients in this study were accrued over a ten-year period, minor technical differences in TIPS placement and improvements in medical care during the study period could have contributed to differences in clinical outcomes over time. Fourth, our study was focused on the relation ship between liver disease score and clinical outcome, and did not take into account factors such as patient clinical stability or emergent procedure circumstances when assessing survival outcomes of the whole population. However, our analysis confirmed similar findings of worse predictive capacity of more

remote MELD scores for post-TIPS outcomes upon analysis of the different patient subsets, including emergent TIPS.

In summary, MELD scores show significant within-patient variation, and most updated MELD scores have the best accuracy for prediction of early survival outcomes after TIPS. Our findings suggest that hepatology physicians and IR operators should strongly consider use of MELD scores performed on the day of potential TIPS creation for most accurate stratification of patient risk, optimization of patient selection for TIPS, and counseling of patients on expected post-procedure outcomes.

ABBREVIATIONS

- **ANOVA:** analysis of variance.
- **AUROC:** area under receiver operating characteristic curves.
- **IR:** Interventional Radiology.
- **MELD:** Model for End Stage Liver Disease.
- **PACS:** Picture Archiving and Communication System.
- **PSG:** portosystemic pressure gradient.
- **TIPS:** transjugular intrahepatic portosystemic shunt.

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