Title: Hospital volume and mortality after trans-jugular intrahepatic portosystemic shunt creation in the United States

Short Title: Effect of hospital TIPS volume on mortality

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Abbreviations:

AHRQ: Agency for Healthcare Research and Quality

ANOVA: Analysis of Variance

APR-DRGs: All Patient Refined Diagnosis Related Groups

EVAR: Endovascular Aortic Repair

HCUP: Healthcare Cost and Utilization Project

HE: hepatic encephalopathy

HRS: hepatorenal syndrome

ICD-9: International Classification of Diseases version 9

ICU: Intensive Care Unit

MELD: Model of End-stage Liver Disease

NAFLD: non-alcoholic fatty liver disease

NIS: Nationwide Inpatient Sample

NRD: Nationwide Readmission Database

SBP: Spontaneous bacterial peritonitis

SID: State Inpatient Database

TIPS: Transjugular intrahepatic portosystemic shunt placement

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ABSTRACT

The link between higher procedure volume and better outcomes for surgical procedures is well established. We aimed to determine if procedure volume affected inpatient mortality in patients undergoing transjugular intra-hepatic portosystemic shunt (TIPS). An epidemiological analysis of an all-payer database recording hospitalizations during 2013 in the United States (Nationwide Readmissions Database) was performed. All patients' ≥18 years old undergoing TIPS during a hospital admission (n=5529) without concurrent or prior liver transplantation were selected. All-cause inpatient mortality was assessed. Risk-adjusted mortality was assessed for hospitals categorized into quintiles based on annual TIPS volume; very low (1-4/year), low (5-9/year), medium (10-19/year), high (20-29/year), and very high (≥30/year). TIPS were placed in 5529 patients (57±10.9 years; 37.5% female). Mortality decreased with rising annual TIPS volume (13% for very low to 6% for very high volume hospitals; p<0.01). Elective admissions were more common in hospitals with higher annual TIPS volume (20.3% for very low to 30.8% for very high; p<0.01). On multivariate analysis, compared to hospitals performing ≥30 TIPS per year, only hospitals performing 1-4/year (aOR: 1.9, 95%CI:1.21-3.01; p=0.01), 5-9/year (aOR: 2.0, 95%CI:1.25-3.17; p<0.01), and 10-19/year (aOR: 1.9, 95%CI:1.17-3.00; p=0.01) had higher inpatient mortality (20-29/year [aOR: 1.4, 95%CI:0.84-2.84; p=0.19]). The absolute difference between risk-adjusted mortality rate for very low volume and very high volume hospitals was 6.1% (13.9% vs. 7.8%). TIPS volume of ≤20 TIPS/year, variceal bleeding, and nosocomial infections were independent risk factors for inpatient mortality in patients with both elective and emergent admissions. **Conclusions:** The risk of inpatient mortality is lower in hospitals performing ≥20 TIPS per year. Future research exploring preventable factors for higher mortality and benefits of patient transfer to higher volume centers is warranted.

The association between hospitals with higher annual procedure volume and improved survival has been demonstrated for most major surgical procedures.(1–4) Better patient outcomes at higher volume centers have also been reported for percutaneous cardiovascular interventions, such as coronary and valvular procedures, peripheral arterial interventions, and endovascular abdominal aortic aneurysm repair (EVAR).(5–10) Building on these findings, several studies have shown that increasing referral of elective EVAR cases to high-volume centers by a process known as regionalization leads to improved patient outcomes.(11–14) However, such study has not yet been expanded to percutaneous procedures in non-cardiovascular patients, where interventional procedures can be complex, associated with an operator learning curve, and are performed in critically-ill patients.

Transjugular intrahepatic portosystemic shunt (TIPS) placement for treating sequalae of portal hypertension requires a high degree of technical and clinical experience to achieve optimal patient outcomes.(15,16) A recent study of the Nationwide Inpatient Sample (NIS) reported a reduction in inpatient mortality during admissions with TIPS placement from 12.5% in 2003 to 10.6% in 2012.(17) Studies have demonstrated that variation in inpatient mortality for patients with cirrhosis can be a result of hospital-level factors.(18) The annual hospital volume of admissions for patients with cirrhosis or esophageal variceal bleeding alone does not account for variations observed in inpatient mortality, although patients at high volume hospitals with these conditions were more likely to undergo TIPS placement, suggesting that additional study on the influence of TIPS volume on inpatient outcomes is likely warranted.(18,19)

Given the known variations in mortality for patients with cirrhosis and relationship between annual procedure volume and inpatient mortality for image-guided procedures, we sought to identify pre-procedure patient, hospital and volume characteristics that may explain variations in mortality after TIPS procedures.

METHODS

Data Source: The National Readmission Database (NRD) is a database developed by the Healthcare Cost and Utilization Project (HCUP) that includes all hospitalizations during 2013 in 21 geographically diverse states.(20) This all payer (insured and uninsured) database contains data from approximately 14 million discharges, representing 49.1% of all US hospitalizations. It records de-identified patient and hospital demographics, discharge diagnoses, inpatient procedures, length of stay, and discharge status. In addition, it includes 29 Elixhauser co-morbidity measures that are assigned using the Agency for Healthcare Research and Quality (AHRQ) comorbidity software.(21) These measures identify co-existing medical conditions not directly related to the principal diagnosis and likely to have originated prior to the hospital stay. It also includes All Patient Refined Diagnosis Related Groups (APR-DRGs) severity measures assigned using software developed by 3M Health Information Systems to adjust for case-mix severity. The APR-DRG risk of mortality score has been validated as the most discriminative and predictive mortality risk score for cirrhotic patients in the NIS, a smaller HCUP database (20% sample, 7.8 million annual discharges).(22) In contrast to the NIS, the NRD links all hospitalizations for each patient allowing analysis at a patient rather than discharge level and providing the ability to control for multiple hospitalizations with a TIPS procedure code for the same patient. To ensure generalizability, discharge weights were developed in the NRD to produce national estimates after the data were stratified, by patient and hospital characteristics. National estimates were calculated by applying discharge weights prior to analysis.

The study was reviewed by the institutional review board as appropriate for exemption from institutional review board oversight because no protected health information was available in the data.

Study population: Procedure diagnosis codes for all hospitalizations in the database were searched for TIPS procedures. Inclusion criteria were International Classification of Diseases 9th version (ICD-9) procedure code 39.1 (Intra-abdominal venous shunt), and age ≥18 years. Since placement of multiple TIPS in a single patient is rare, patients with multiple ICD-9 codes of 39.1 (n=58) were excluded. Liver transplantation changes outcomes for cirrhotic patients, therefore patients with ICD-9 procedure code 50.5* (liver transplantation)

(n=87) or ICD-9 diagnosis code 996.82 (complications of liver transplantation) (n=39) in either the index or prior hospitalizations were excluded.

Patients were categorized by age, gender, insurance status, and etiology of liver disease (alcoholic liver disease, viral liver disease, non-alcoholic fatty liver disease [NAFLD], other). Severity of liver disease is an important predictor of mortality after TIPS, but the absence of laboratory data precluded assessment of validated instruments such as Child-Pugh or Model for End-Stage Liver Disease (MELD) scores. Therefore, features of hepatic decompensation were controlled by using the presence or absence of ICD-9-CM diagnosis and procedure codes for ascites or hydrothorax, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis, and variceal bleeding (Appendix Table 1). Co-morbidities were assessed by the presence of 28 AHRQ co-morbidity measures (comorbidity measure for liver disease was excluded from analysis) and APR-DRG risk of mortality (likelihood of dying: minor, moderate, major, extreme).

Index hospitalizations were categorized by mode of admission (elective vs. emergent), length of stay and presence or absence of intensive care unit (ICU) admission. ICU admission was assessed using ICD-9 diagnosis codes of circulatory shock and a previously described classification of ICD-9 procedure codes typically found in cirrhotic ICU patients (Appendix Table 1).(23) Hospitalizations were further characterized by the presence of medical diagnoses that can cause (or result from) prolonged or complicated hospitalizations (acute renal failure, infection, diabetes, coagulopathy, respiratory failure, electrolyte imbalance [hyponatremia, hypokalemia, acidosis], and substance abuse) (Appendix Table 1).

Hospitals co-variates included ownership (government, non-federal; private, non-profit; private, investor-owned), bed size (small, medium, large), teaching status (metropolitan teaching, metropolitan non-teaching, non-metropolitan), and location by metropolitan size (metropolitan area with >1 million residents, metropolitan area with <1 million residents and micropolitan areas). Patients with ICD-9 procedure code 50.* (liver transplantation) during hospitalizations in the entire database were used to identify transplant hospitals.

The exposure of interest was annual TIPS procedural volume for each hospital. Patients were divided into categories of annual hospital TIPS volume with similar number of procedures in each category (assessed by visual estimation); very low (1-4/year; n=589), low (5-9/year; n=606), medium (10-19/year; n=502), high (20-29/year; n=394) and very high (≥30/year; n=497). The primary outcome of interest was inpatient mortality.

Statistical analysis: Descriptive statistics were obtained using Pearson's chi-square for dichotomous or categorical variables and ANOVA for continuous variables. Multivariate analysis was performed using generalized linear mixed model for logistic regression in order to correct the within-hospital correlations. Based on clinical and statistical significance, factors associated with higher inpatient mortality were selected for multivariate analysis. Age was included despite non-significant p-values based upon conceptual hypotheses that it may have an impact on mortality when controlling for other predictors. Variceal bleeding, alcoholic vs. non-alcoholic etiology of liver disease, infection, and diabetes were included given significant p-values as well as prior studies showing an effect on mortality with inclusion of these variables. Hospital-level predictors were non-significant across bivariate and multivariate analyses and thus were excluded from the final multivariable regression. Pearson correlation test was used for testing multicollinearity between any of the two co-variates in the multivariate model, and co-variates with an *r* above 0.6 were considered to have high interactions. Transplant hospital status was highly correlated with hospital TIPS procedure volume (Pearson correlation *r*=0.788), so only procedure volume was included in the final model. Adjusted mortality rates were calculated using average patient characteristics by back-transforming predicted mortality from the final model.

Due to significant differences in observed mortality rate between patients with elective and emergent admissions, two separate generalized linear mixed models were fit to these sub-cohorts. Considering the sample size of the two sub-cohorts, volume of TIPS was regrouped into two groups (1-19 TIPS/year and ≥20 TIPS/year), and patient income quartile by zip code was excluded from the models. Discrimination and goodness-of-fit statistics were calculated for each model. For our full model, there were 16 total variables (including dummy variables) with a c-statistic of 0.776; the models for elective admissions and emergent admissions have 9 variables, and c-statistics of 0.895 and 0.732, respectively. Our c-statistic was within the range reported for models investigating volume-outcome relationships for surgical procedures.(24,25) All

statistical tests were 2-tailed, and a p-value of 0.05 was considered statistically significant. Data management and analyses were performed using SAS (Version 9.4 of the SAS System for Windows. Copyright © 2016 SAS Institute Inc.), and SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) software.

RESULTS

Overall, 5529 adult patients underwent TIPS without prior or concurrent liver transplantation during the index admission. Inpatient mortality for this cohort was 10.5% (583/5529). There were 278/443 (63%) hospitals with 1-4 TIPS/year, 95/443 (21%) hospitals with 5-9 TIPS/year, 39/443 (9%) hospitals with 10-19 TIPS/year, 18/443 (4%) hospitals with 20-29 TIPS/year, and 13/443 (3%) hospitals with ≥30 TIPS/year. Inpatient mortality, characteristics of patients, hospitalizations, and hospitals for each quintile are reported in Table 1. Hospitals with ≥20 TIPS/year (7% of hospitals) and the lowest inpatient mortality were exclusively metropolitan teaching hospitals.

In univariate analysis, lower TIPS volume, increased patient age, non-elective admission, primary payer of Medicaid or self-pay, alcoholic etiology of liver disease (vs non-alcoholic, viral, other), median household income quartiles for patient's ZIP code, variceal bleeding, diabetes, and infection were associated with inpatient mortality (Appendix table 2).

Multivariate analysis revealed that increasing age, variceal bleeding, and/or infection during the admission, chronic conditions of coagulopathy and renal failure, higher income quartiles for patient ZIP code, and three lower annual hospital procedure volume groups were independently associated with higher odds of mortality (Table 2). Compared to hospitals performing ≥30 TIPS per year, only hospitals performing 1-4/year (aOR: 1.9, 95%CI:1.21-3.01; p=0.01), 5-9/year (aOR: 2.0, 95%CI:1.25-3.17; p<0.01) and 10-19/year (aOR: 1.9, 95%CI:1.17-3.00; p=0.01) had higher odds of inpatient mortality (20-29/year [aOR: 1.4, 95%CI:0.84-2.84; p=0.19]). Similarly, the adjusted mortality rate of the lowest quintile hospitals was nearly twice the adjusted mortality rate for the highest quintile (13.9% vs. 7.8%; Figure 1).

Mode of admission: Differentiating patients with an elective vs. emergent mode of admission, the unadjusted inpatient mortality rate decreased with increasing annual TIPS volume for both types of admissions. For elective admissions, the unadjusted mortality rate for the lowest quintile of annual TIPS volume (1-4 TIPS/year;

7.9%) was 2.7 times the mortality rate for the highest quintile of TIPS volume (≥30 TIPS/year; 3.1) (Figure 2). For emergent admissions, the unadjusted mortality rate for the lowest quintile (14.2%) was 1.9 times the mortality rate for the highest quintile (7.5%) (Figure 3). No significant interaction was noted between annual TIPS volume and mode of admission (Tier 1*mode, p=0.379; Tier 2*mode, p=0.774; Tier 3*mode, p=0.498; tier 4*mode, p=0.181).

A multivariate model to analyze patients with elective admissions found that variceal bleeding and infection during the index admission and coagulopathy were independently associated with higher odds of inpatient mortality (Appendix Table 3). Adjusted odds for mortality in hospitals with 1-19 TIPS per year was significantly higher than those for ≥20 TIPS per year (aOR 2.5, p=0.04). Similarly multivariate analysis of patients with emergent admissions found increase in age, variceal bleeding and infection during the index admission, and coagulopathy and renal failure as co-morbidities were independently associated with higher odds of inpatient mortality (Appendix Table 4). Adjusted odds for mortality in hospitals with 1-19 TIPS per year was also significantly higher than those for ≥20 TIPS per year (aOR 1.5, p=0.01).

DISCUSSION

In this national study of TIPS procedures, higher-volume hospitals had fewer deaths during the index admission. The absolute difference in adjusted mortality rates between very low and very high volume hospitals was large (6.1%), compared to similar results for open surgical procedures (0.2%-12.5%).(1) Specifically, 20 TIPS/year represented an annual threshold beyond which inpatient mortality was better for both emergent and elective procedures. Hospitals with ≥20 TIPS/year were exclusively metropolitan teaching hospitals but accounted for only 38% of all TIPS procedures. Finally, in addition to annual TIPS volume, inpatient mortality was higher for patients with variceal bleeding, nosocomial infections, and coagulopathy, independent of other factors.

Two main hypotheses seek to explain the volume-outcome relationship for procedures.(26) The practice-makes-perfect hypothesis posits that physicians and hospital personnel, who see more patients, develop better skills resulting in better outcomes. The selective-referral hypothesis states that hospitals and/or physicians with better outcomes attract more patients. In addition, studies in the surgical literature have identified several procedure-specific causes for the volume-outcome relationship. These include annual operator volume (e.g. in percutaneous cardiovascular procedures), complication rates and failure to rescue from complications.(24)

The selective-referral hypothesis appears to explain some of the findings in this study. Hospitals performing ≥20 TIPS/year were exclusively metropolitan teaching hospitals and more than 80% of hospitals in the top two quintiles performed liver transplantation. Therefore, it is plausible that patients benefitting from better outcomes at high-volume hospitals had end-stage liver disease requiring referral to these liver transplantation centers for management. Patients undergoing liver transplantation during the index admission were excluded from analysis, therefore the lower inpatient mortality was likely related to a combination of better patient selection, more experienced operators, and improved peri- and post-procedural care rather than liver transplantation performed to rescue patients with poor outcomes after TIPS. This is also supported by the lack of statistical significance of APR-DRG risk of mortality, the most discriminative and predictive mortality risk score in cirrhotic patients, for inclusion in our multivariate model. Of the significant risk factors revealed by the multivariate

model, variceal bleeding and coagulopathy are inherent to this population due to portal hypertension and liver dysfunction. However, the presence of nosocomial infections (e.g. pneumonia, clostridium difficile, urinary tract infection) as an independent risk factor for mortality may represent a modifiable risk factor for improving outcomes in these patients, distinct from annual TIPS volume.

The practice-makes-perfect hypothesis can also potentially apply to the TIPS procedure. Traditional fluoroscopic techniques for TIPS creation rely on blind trans-hepatic portal vein punctures guided by anatomic knowledge and operator experience. A small study revealed significant differences in procedure times between experience and inexperienced physicians.(27) Similarly, a study evaluating the use of intra-vascular ultrasound for TIPS creation found that direct visualization of the TIPS needle during trans-hepatic punctures reduced procedural time and intra-procedural complications, however this effect was limited to inexperienced operators (<20 TIPS placed).(28) These findings may support the practice-makes-perfect hypothesis as it relates to technical success. However, specific details for TIPS procedures, such as operator identity and procedure time, were not available in the NRD therefore whether more operator experience results in better outcomes after TIPS is unknown.

Based on our results, it appears the selective-referral hypothesis best explains our results. It appears that inpatient mortality was primarily driven by the decision making of multidisciplinary teams (likely including hepatologists, surgeons, interventional radiologists, and intensivists) regarding patient selection, peri-procedural care, and recognizing or rescuing from complications of care. These factors, as well as factors such as endoscopist skill and effective balloon tamponade, likely contribute to improved outcomes. Future work either investigating the interplay between these factors or standardizing and disseminating best care practices will likely lead to improvement in the care for these patients.

The volume-outcome relationship that was observed in this study with a 20 TIPS/year threshold and risk factors for inpatient mortality persisted in a sub-analysis looking at elective and emergent admissions. Emergent admissions (which typically occur for variceal bleeding) were more common than elective admissions (which typically occur for ascites) across hospital quintiles but hospitals in lower volume quintiles

had a higher percentage of emergent admissions. Regionalization of elective TIPS procedures to higher volume centers has the potential to improve patient outcomes, similar to how this process has improved outcomes for elective EVAR.(13,14)

However, the benefit of transfers to higher volume TIPS centers for patients requiring emergent admissions is less clear. First, most patients with emergent admissions likely represent patients with variceal bleeding, for whom medical and endoscopic management represent first-line treatment.(29) Second, a volume-outcome analysis of all patients with esophageal variceal bleeding in the NIS between 1998-2005 did not show a survival benefit for treatment at a high-volume hospital.(19) Third, inpatient mortality (75%) and 6-week mortality (35%) for uncovered TIPS in the salvage setting is high and despite the lack of robust data for covered TIPS, it may be unsafe to transfer the majority of these acutely sick patients.(30) However, recent guidelines have recommended the use of early covered TIPS placement (<72 hours after index variceal bleeding) in selected patients after successful endoscopic therapy.(31,32) Given the high adjusted odds ratio of variceal bleeding as an indication for TIPS placement in patients with both elective and emergent admissions (Appendix Table 3 and 4), these patients represent a sub-set of patients currently undergoing TIPS at low-volume hospitals who may derive benefit from a regionalization strategy, regardless of mode of admission as long as safe transfer can be arranged.

Several limitations are inherent to our study design. First, the use of an administrative database subjects our findings to coding error and reduced specificity compared to clinical assessments with discriminative properties in TIPS patients e.g. MELD score. Although the c-statistic for the predictive models developed in this analysis demonstrate good discriminative ability, it is still possible that unmeasured confounders (e.g. clinical or laboratory assessments) may affect the model. Second, although definitions for conditions such as variceal bleeding, infection, and ICU stays were derived from prior studies in similar cohorts, no validation studies comparing the accuracy of these definitions with medical record level data exist. Third, specific patient level data is not available nor accurately obtainable using ICD-9 codes e.g. covered vs. uncovered stent use, indication of TIPS (e.g. ascites, variceal bleeding, Budd-Chiari sydrome), total procedure time, post-TIPS clinical course. Finally, outcomes in this study were limited to in-patient mortality rather than post-discharge

mortality. However, similar studies on other procedures have previously shown good correlation between inpatient and 30-day mortality and no difference in the volume-outcome relationship when either of these outcomes is used.(1,33)

In conclusion, hospitals performing more than 20 TIPS per year have lower inpatient mortality compared to hospitals with lower annual TIPS volume. Standardizing patient selection, peri-procedural care, and a regionalization strategy for patients requiring elective TIPS may lead to improvement of outcomes at low-volume hospitals.

FIGURE LEGENDS:

Figure 1: Adjusted inpatient mortality for rate patients undergoing TIPS in 2013 according to quintile of annual hospital TIPS volume. Mortality rate was adjusted for: age, presence of alcoholic liver disease, emergent admission, variceal bleeding, infection, diabetes, quintiles of annual procedure volume, AHRQ comorbidity measures for congestive heart failure, coagulopathy and renal failure, and income quartile per patient zip code.

Figure 2: Observed mortality rate and indication for TIPS placement by quintiles of annual hospital TIPS volume for elective admissions.

Figure 3: Observed mortality rate and indication for TIPS placement by quintiles of annual hospital TIPS volume for non-elective admissions.

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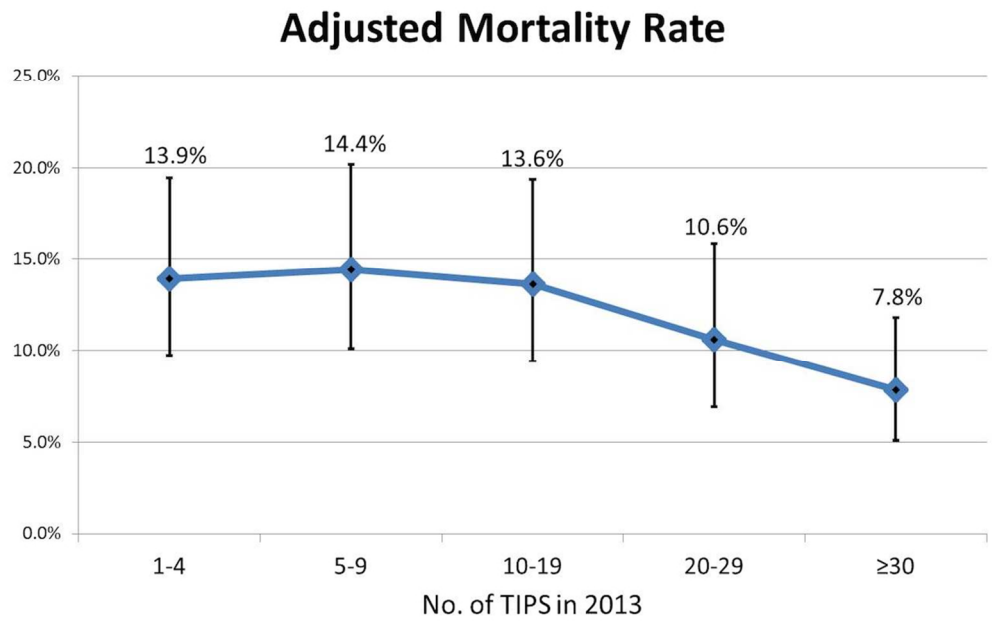
	Full cohort		1-4		5-9		10-19		20-29		≥30		p value
N of admissions	n=5529		n=1202 (22%)		n=1102 (20%)		n=1076 (19%)		n=982 (18%)		n=1167 (21%)		
	n	%	n	%	n	%	n	%	n	%	n	%	
Inpatient mortality	583	10.5	155	12.9	146	13.2	125	11.6	88	8.9	70	6.0	<0.01
Patient Demographics													
Age (year)	57±10.9		58±11.3		57±11.7		57±11.1		56±10.7		57±9.9		0.02
Female	2071	37.5	443	36.9	397	36.0	360	33.5	423	43.1	448	38.4	<0.01
Etiology of liver disease													<0.01
Alcoholic	2498	45.2	622	51.7	533	48.4	523	48.6	362	36.9	458	39.3	
NAFLD	1343	24.3	278	23.1	260	23.6	260	24.1	244	24.8	301	25.8	
Viral	1049	19.0	199	16.5	207	18.8	204	18.9	161	16.4	278	23.8	
Other	640	11.6	104	8.6	102	9.3	90	8.4	215	21.9	129	11.1	
Insurance status													<0.01
Medicare	2132	38.7	437	36.6	428	38.9	426	39.7	344	35.0	497	42.6	
Medicaid	1137	20.6	277	23.2	257	23.4	200	18.7	207	21.1	196	16.8	
Private	1442	26.1	293	24.5	235	21.4	241	22.5	326	33.2	347	29.7	
Self-pay	426	7.7	105	8.8	106	9.6	101	9.4	28	2.8	86	7.4	
No-charge	379	6.9	83	6.9	73	6.6	104	9.7	78	7.9	41	3.5	
Income by quartile													<0.01
$1-37,999	1566	28.3	296	24.6	335	30.4	322	29.9	222	22.6	391	33.5	
$38,000-47,999	1596	28.9	345	28.7	314	28.5	353	32.8	260	26.5	324	27.8	
$48,000-63,999	1445	26.1	286	23.8	318	28.9	263	24.4	307	31.3	271	23.2	
$64,000 or more	922	16.7	275	22.9	135	12.3	138	12.8	193	19.7	181	15.5	
Alcohol use	2186	39.5	550	45.8	483	43.8	444	41.3	291	29.6	418	35.8	
Substance abuse (non-alcohol)	348	6.3	99	8.2	77	7.0	54	5.0	44	4.5	74	6.3	<0.01
Diabetes	1735	31.4	365	30.4	350	31.8	349	32.4	249	25.4	422	36.2	<0.01
Hospitalization Characteristics													
Median length of stay (days)	7 (3-13)		8 (4-13)		8 (4-14)		7 (3-12)		7 (3-13)		7 (3-12)		<0.01
ICU stay	1889	34.2	406	33.8	454	41.2	379	35.2	373	38.0	277	23.7	<0.01
Emergent admission	4128	74.7	958	79.7	904	82.0	799	74.3	683	69.6	784	67.2	<0.01
Weekend admission	994	18.0	243	20.2	211	19.1	213	19.8	164	16.7	163	14.0	<0.01
Complications of Cirrhosis													
Bleeding	2885	52.2	707	58.8	668	60.6	599	55.7	445	45.3	466	39.9	<0.01
Ascites or hydrothorax	3803	68.8	778	64.7	695	63.0	727	67.6	675	68.7	928	79.5	<0.01
SBP	228	4.1	47	3.9	45	4.1	47	4.4	54	5.5	35	3.0	0.07
HE	1319	23.9	313	26.0	294	26.7	253	23.5	199	20.2	260	22.3	<0.01
HRS	332	6.0	60	5.0	53	4.8	71	6.6	77	7.8	71	6.1	0.02
HCC	167	3.0	23	1.9	22	2.0	33	3.1	45	4.6	44	3.8	<0.01
Complications of Inpatient Hospitalizations													
Infection	1280	23.2	278	23.1	253	23.0	237	22.0	255	26.0	257	22.0	0.20
Acute Renal Failure	1466	26.5	300	25.0	291	26.4	270	25.1	238	24.2	367	31.4	<0.01
Electrolyte imbalance	2225	40.2	512	42.6	467	42.3	489	45.5	313	31.9	444	38.0	<0.01
Comorbidities and Risk of Mortality													
AHRQ CM-CHF	308	5.6	73	6.1	74	6.7	60	5.6	40	4.1	61	5.2	0.10
AHRQ CM-Coag.	2593	46.9	584	48.6	562	51.0	515	47.9	442	45.0	490	42.0	<0.01
AHRQ CM-CRF	811	14.7	155	12.9	157	14.2	157	14.6	121	12.3	221	18.9	<0.01
APR-DRG Risk of Mortality													<0.01
No class specified	13	0.2	0	0.0	2	0.2	0	0.0	11	1.1	0	0.0	
Minor likelihood of dying	200	3.6	52	4.3	40	3.6	38	3.5	21	2.1	49	4.2	
Moderate likelihood of dying	1355	24.5	278	23.1	223	20.2	277	25.8	247	25.1	330	28.3	
Major likelihood of dying	2159	39.1	493	41.0	410	37.2	378	35.2	403	41.0	475	40.7	
Extreme likelihood of dying	1801	32.6	378	31.5	427	38.7	382	35.5	301	30.6	313	26.8	
Characteristics of Hospitals													
N of hospitals	443		278		95		39		18		13		
Hospital bed-size													<0.01
Small	32	7.2%	29	10.4%	2	2.1%	1	2.6%	0	0.0%	0	0.0%	
Medium	123	27.8%	97	34.9%	19	20.0%	4	10.3%	1	5.6%	2	15.4%	
Large	288	65.0%	152	54.7%	74	77.9%	34	87.2%	17	97.7%	11	84.6%	
Hospital ownership													0.03
Government	59	13.3%	30	10.8%	15	15.8%	7	17.9%	6	33.3%	1	7.7%	
Private nonprofit	311	70.2%	192	69.1%	67	70.5%	29	74.4%	11	61.1%	12	92.3%	
Private proprietary	73	16.5%	56	20.1%	13	13.7%	3	7.7%	1	5.6%	0	0.0%	
Hospital teaching status													<0.01
Metropolitan non-teaching	206	46.5%	154	55.4%	43	45.3%	9	23.1%	0	0.0%	0	0.0%	
Metropolitan teaching	222	50.1%	110	39.6%	51	53.7%	30	76.9%	18	100.0%	13	100.0%	
Non-metropolitan	15	3.4%	14	5.0%	1	1.1%	0	0.0%	0	0.0%	0	0.0%	

Hospital urban-rural location													0.07
Large metropolitan >1 million residents	263	59.4%	163	58.6%	59	62.1%	20	51.3%	9	50.0%	12	92.3%	
Small metropolitan <1 million residents	165	37.2%	101	36.3%	35	36.8%	19	48.7%	9	50.0%	1	7.7%	
Micropolitan	15	3.4%	14	5.0%	1	1.1%	0	0.0%	0	0.0%	0	0.0%	
Liver transplant hospital	49	11.1%	1	0.4%	5	5.3%	15	38.5%	15	83.3%	13	100.0%	<0.01

Table 1: Inpatient mortality, characteristics of patients, hospitalizations and hospitals for each quintile of annual procedure volume. NAFLD: Non-alcoholic fatty liver disease, ICU: Intensive care unit, SBP: Spontaneous bacterial peritonitis, HE: hepatic encephalopathy, HRS: hepatorenal syndrome, HCC: hepatocellular carcinoma, AHRQ CM: Agency for Healthcare Research and Quality Co-morbidity Measures, APR-DRG: All Patient Refined Diagnosis Related Groups.

All Patients	aOR	95% CI	p value	c-statistic
Annual procedure volume				
1-4 TIPS/year	1.9	1.21-3.01	0.01	
5-9 TIPS/year	2.0	1.25-3.17	<0.01	
10-19 TIPS/year	1.9	1.17-3.00	0.01	
20-29 TIPS/year	1.4	0.84-2.34	0.19	
≥30 TIPS/year	Reference			
AHRQ comorbidity measures				
Congestive heart failure	1.4	0.85-2.31	0.18	
Coagulopathy	2.0	1.46-2.62	<0.01	
Renal failure	1.5	1.06-2.21	0.03	
Income quartile for patient zip code				**0.776**
$1-37,999	0.9	0.60-1.29	0.51	
$38,000-47,999	0.5	0.36-0.82	<0.01	
$48,000-63,999	0.6	0.38-0.90	0.01	
$64,000 or more	Reference			
Other risk factors				
Age (per 1 year increase)	1.0	1.01-1.04	<0.01	
Alcoholic liver disease	1.0	0.78-1.40	0.76	
Emergent admission	1.4	0.88-1.04	0.16	
Variceal Bleeding	2.3	1.65-3.21	<0.01	
Infection	3.9	3.00-5.18	<0.01	
Diabetes	0.8	0.55-1.04	0.08	

Table 2: Multivariate model for inpatient mortality after TIPS hospitalization.



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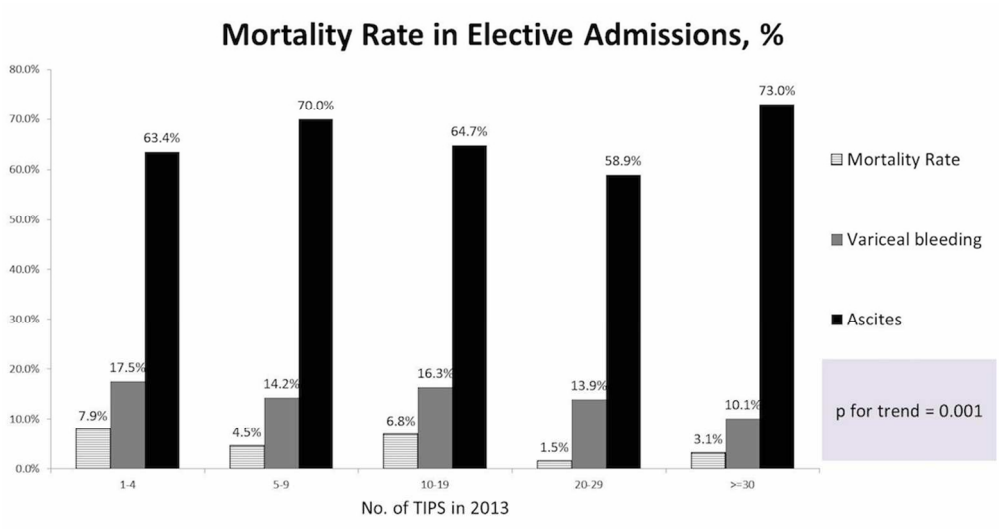

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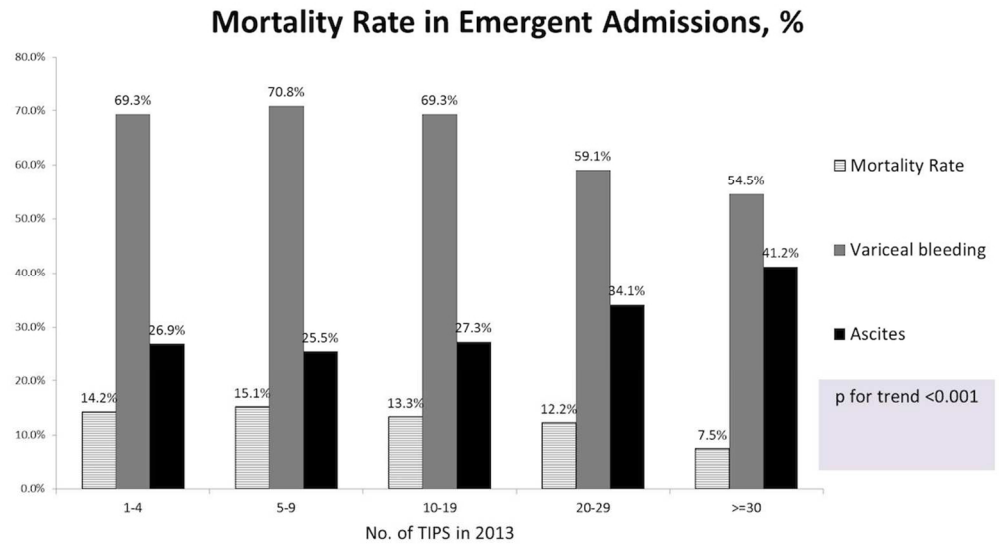

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APPENDIX TABLES

Code	Description
Liver Transplant	
Procedure	
50.51	AUXILIARY LIVER TRANSPLANT
50.59	OTHER TRANSPLANT OF LIVER
Diagnosis	
996.82	COMPLICATIONS OF TRANSPLANTED LIVER
Etiology of Liver Disease	
Alcoholic Liver Disease	
571.0	ALCOHOLIC FATTY LIVER
571.1	ACUTE ALCOHOLIC HEPATITIS
571.2	ALCOHOLIC CIRRHOSIS OF LIVER
571.3	UNSPECIFIED ALCOHOLIC LIVER DAMAGE
Non-Alcoholic Fatty Liver Disease	
571.5	CIRRHOSIS OF LIVER WITHOUT MENTION OF ALCOHOL
571.8	OTHER CHRONIC NON-ALCOHOLIC LIVER DISEASE
Viral Disease	
Hepatitis B	
070.20	VIRAL HEP B W/HEP COMA ACUTE/UNSPECIFIED W/O HEP DELTA
070.22	VIRAL HEP B W/HEP COMA CHRN W/O MENTION HEP DELTA
070.23	HEPATITIS B, CHRONIC, W HEPATIC COMA, W HEPATITIS DELTA
070.30	VIRAL HEP B W/O HEP COMA ACUT/UNS W/O HEP DELTA
070.32	VIRAL HEP B W/O HEP COMA CHRN W/O HEP DELTA
070.33	VIRAL HEP B W/O MENTION HEP COMA CHRN W/HEP DELTA
Hepatitis C	
070.41	ACUTE HEPATITIS C WITH HEPATIC COMA
070.44	CHRONIC HEPATITIS C WITH HEPATIC COMA
070.51	ACUTE HEPATITIS C WITHOUT MENTION HEPATIC COMA
070.54	CHRONIC HEPATITIS C WITHOUT MENTION HEPATIC COMA
070.70	UNSPECIFIED VIRAL HEPATITIS C W/O HEPATIC COMA
070.71	UNSPECIFIED VIRAL HEPATITIS C WITH HEPATIC COMA
070.59	OTHER SPECIFIED VIRAL HEPATITIS WITHOUT MENTION HEP COMA
Other Liver Diseases	
Non-Specific or Other Specified Hepatitis	
571.40	UNSPECIFIED CHRONIC HEPATITIS
571.49	OTHER CHRONIC HEPATITIS
571.9	UNSPEC CHRONIC LIVER DISEASE W/O MENTION OF ALCOHOL
078.5	CYTOMEGALIC INCLUSION VIRUS HEPATITIS
Autoimmune Hepatitis	
571.42	AUTOIMMUNE HEPATITIS
Wilson's Disease	
275.1	DISORDERS OF COPPER METABOLISM
Alpha-1-Antitrypsin Deficiency	
273.4	ALPHA 1 ANTITRYPSIN DEFICIENCY
Non-Specific Cirrhosis	
571.6	PRIMARY BILIARY CIRRHOSIS
Other Chronic Liver Disease	
573.0	CHRONIC PASSIVE CONGESTION OF LIVER
573.4	HEPATIC INFARCTION
573.9	UNSPECIFIED DISORDER OF LIVER
Alcohol use	
291.0	ALCOHOL WITHDRAWAL DELIRIUM
291.1	ALCOHOL-INDUCED PERSISTING AMNESTIC DISORDER
291.2	ALCOHOL-INDUCED PERSISTING DEMENTIA
291.3	ALCOHOL-INDUCED PSYCHOTIC DISORDER WITH HALLUCINATIONS
291.4	IDIOSYNCRATIC ALCOHOL INTOXICATION
291.5	ALCOHOL-INDUCED PSYCHOTIC DISORDER WITH DELUSIONS
291.8	OTHER SPECIFIED ALCOHOL-INDUCED MENTAL DISORDERS
291.81	ALCOHOL WITHDRAWAL
291.82	ALCOHOL-INDUCED SLEEP DISORDERS
291.89	OTHER ALCOHOL-INDUCED DISORDERS
291.9	UNSPECIFIED ALCOHOL-INDUCED MENTAL DISORDERS
303.00-03	ACUTE ALCOHOL INTOXICATION
303.90-93	OTHER AND UNSPECIFIED ALCOHOL DEPENDENCE

305.00-03	ALCOHOL ABUSE
357.5	ALCOHOLIC POLYNEUROPATHY
425.5	ALCOHOLIC CARDIOMYOPATHY
535.30-31	ALCOHOLIC GASTRITIS
Substance use (other than alcohol)	
292.0	DRUG WITHDRAWAL
292.11	DRUG-INDUCED PSYCHOTIC DISORDER WITH DELUSIONS
292.12	DRUG-INDUCED PSYCHOTIC DISORDER WITH HALLUCINATIONS
292.2	PATHOLOGICAL DRUG INTOXICATION
292.81	DRUG-INDUCED DELIRIUM
292.82	DRUG-INDUCED PERSISTING DEMENTIA
292.83	DRUG-INDUCED PERSISTING AMNESTIC DISORDER
292.84	DRUG-INDUCED MOOD DISORDER
292.85	DRUG INDUCED SLEEP DISORDERS
292.89	OTHER SPECIFIED DRUG-INDUCED MENTAL DISORDERS
292.9	UNSPECIFIED DRUG-INDUCED MENTAL DISORDER
304.00-03	OPIOID TYPE DEPENDENCE
304.10-13	SEDATIVE, HYPNOTIC OR ANXIOLYTIC DEPENDENCE
304.20-23	COCAINE DEPENDENCE
304.30-33	CANNABIS DEPENDENCE
304.40-43	AMPHETAMINE AND OTHER PSYCHOSTIMULANT DEPENDENCE
304.50-53	HALLUCINOGEN DEPENDENCE
304.60-63	OTHER SPECIFIED DRUG DEPENDENCE
304.70-73	COMBINATIONS OF OPIOID TYPE DRUG WITH ANY OTHER DRUG DEPENDENCE
304.80-83	COMBINATIONS OF DRUG DEPENDENCE EXCLUDING OPIOID TYPE DRUG
304.90-93	UNSPECIFIED DRUG DEPENDENCE
305.20-23	CANNABIS ABUSE
305.30-33	HALLUCINOGEN ABUSE
305.40-43	SEDATIVE, HYPNOTIC OR ANXIOLYTIC ABUSE
305.50-53	OPIOID ABUSE
305.60-63	COCAINE ABUSE
305.70-73	AMPHETAMINE OR RELATED ACTING SYMPATHOMIMETIC ABUSE
305.90-93	OTHER, MIXED, OR UNSPECIFIED DRUG ABUSE
648.30-34	DRUG DEPENDENCE COMPLICATING PREGNANCY, CHILDBIRTH, OR THE PUERPERIUM
965.00	POISONING BY OPIUM (ALKALOIDS), UNSPECIFIED
965.01	POISONING BY HEROIN
965.02	POISONING BY METHADONE
965.09	POISONING BY OTHER OPIATES AND RELATED NARCOTICS
969.6	POISONING BY PSYCHODYSLEPTICS (HALLUCINOGENS)
970.81	POISONING BY COCAINE
V654.2	COUNSELING, SUBSTANCE USE
Diabetes	
250.00-03	DIABETES MELLITUS WITHOUT MENTION OF COMPLICATION
250.10-13	DIABETES WITH KETOACIDOSIS
250.20-23	DIABETES WITH HYPEROSMOLARITY
250.40-43	DIABETES WITH RENAL MANIFESTATIONS
250.50-53	DIABETES WITH OPHTHALMIC MANIFESTATIONS
250.60-63	DIABETES WITH NEUROLOGICAL MANIFESTATIONS
250.70-73	DIABETES WITH PERIPHERAL CIRCULATORY DISORDERS
250.80-83	DIABETES WITH OTHER SPECIFIED MANIFESTATIONS
250.90-93	DIABETES WITH UNSPECIFIED COMPLICATION
Variceal Bleeding	
Diagnosis	
456.0	ESOPHAGEAL VARICES WITH BLEEDING
456.20	ESOPHAGEAL VARICES IN DISEASES CLASSIFIED ELSEWHERE, WITH BLEEDING
530.82	ESOPHAGEAL HEMORRHAGE
569.3	HEMORRHAGE OF RECTUM AND ANUS
578.0	HEMATEMESIS
578.1	BLOOD IN STOOL
578.9	HEMORRHAGE OF GASTROINTESTINAL TRACT, UNSPECIFIED
Procedure (endoscopy)	
42.33	ENDOSCOPIC EXCISION OR DESTRUCTION OF LESION OR TISSUE OF ESOPHAGUS
43.41	ENDOSCOPIC EXCISION OR DESTRUCTION OF LESION OR TISSUE OF STOMACH
44.43	ENDOSCOPIC CONTROL OF GASTRIC OR DUODENAL BLEEDING
45.13	OTHER ENDOSCOPY OF SMALL INTESTINE
45.16	ESOPHAGOGASTRODUODENOSCOPY [EGD] WITH CLOSED BIOPSY

45.23	COLONOSCOPY
Ascites and hydrothorax	
Diagnosis	
511.89	OTHER SPECIFIED FORMS OF EFFUSION, EXCEPT TUBERCULOUS
789.59	OTHER ASCITES
276.69	OTHER FLUID OVERLOAD
511.9	UNSPECIFIED PLEURAL EFFUSION
Procedure (percutaneous drainage)	
54.91	PERCUTANEOUS ABDOMINAL DRAINAGE
34.91	THORACENTESIS
Hepatic encephalopathy	
572.2	HEPATIC ENCEPHALOPATHY
348.39	OTHER ENCEPHALOPATHY
Other complications	
567.23	SPONTANEOUS BACTERIAL PERITONITIS
572.4	HEPATORENAL SYNDROME
155.0	MALIGNANT NEOPLASM OF LIVER, PRIMARY
584.5-9	ACUTE RENAL FAILURE
Electrolyte imbalance	
276.1	HYPOSMOLALITY AND/OR HYPONATREMIA
276.2	ACIDOSIS
276.8	HYPOPOTASSEMIA
Infection	
481-486	PNEUMONIA
682.2-9	CELLULITIS
790.7	BACTEREMIA
576.1	CHOLANGITIS
008.45	INTESTINAL INFECTION DUE TO CLOSTRIDIUM DIFFICILE
Sepsis	
995.91-92	SEPSIS
785.52	SEPTIC SHOCK
038.0-9	SEPTICEMIA
Urinary tract infection	
599.0	URINARY TRACT INFECTION, SITE NOT SPECIFIED
590.80	PYELONEPHRITIS, UNSPECIFIED
ICU stay	
785.50,51,59	SHOCK (Diagnosis)
Procedure	
00.17	INFUSION OF VASOPRESSOR AGENT
31.1	TEMPORARY TRACHEOSTOMY
37.61,62,68	IMPLANT OF HEART & CIRCULATORY ASSIST SYSTEM
37.78	INSERTION OF TEMPORARY TRANSVENOUS PACEMAKER SYSTEM
38.91	ARTERIAL CATHETERIZATION
39.65	EXTRACORPOREAL MEMBRANE OXYGENATION [ECMO]
39.95	HEMODIALYSIS
54.98	PERITONEAL DIALYSIS
89.60	CONTINUOUS INTRA-ARTERIAL BLOOD GAS MONITORING
89.62	CENTRAL VENOUS PRESSURE MONITORING
89.64	PULMONARY ARTERY WEDGE MONITORING
89.67	MONITORING OF CARDIAC OUTPUT BY OXYGEN CONSUMPTION TECHNIQUE
89.68	MONITORING OF CARDIAC OUTPUT BY OTHER TECHNIQUE
93.90,91,99	RESPIRATORY THERAPY
96.6	ENTERAL INFUSION OF CONCENTRATED NUTRITIONAL SUBSTANCES
99.15	PARENTERAL INFUSION OF CONCENTRATED NUTRITIONAL SUBSTANCES
96.70-72	OTHER INVASIVE MECHANICAL VENTILATION
97.23	REPLACEMENT OF TRACHEOSTOMY TUBE
97.37	REMOVAL OF TRACHEOSTOMY TUBE
99.60-63	CARDIOPULMONARY RESUSCITATION
99.78	AQUAPHERESIS
99.81	HYPOTHERMIA (CENTRAL) (LOCAL)

Appendix Table 1 List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes

Univariate analysis				
Patient		OR	95% CI	p
Age	1 year increase	1.0	1.00-1.02	<0.01
Gender	Female vs male	0.8	0.63-0.91	<0.01
Primary insurance payer				<0.01
	Medicaid vs Medicare	1.1	0.88-1.38	
	Private vs Medicare	0.8	0.64-1.01	
	Self-pay vs Medicare	1.5	1.12-2.03	
	No-charge vs Medicare	0.9	0.63-1.31	
Etiology of liver disease				<0.01
	NAFLD vs alcoholic	0.6	0.48-0.76	
	Viral vs alcoholic	0.7	0.55-0.89	
	Other vs alcoholic	1.1	0.81-1.37	
Income range for the zip code				<0.01
	$1-37,999 vs $64,000 or more	1.1	0.84-1.36	
	$38,000-47,999 vs $64,000 or more	0.6	0.49-0.83	
	$48,000-63,999 vs $64,000 or more	0.6	0.47-0.81	
Substance abuse (non-alcohol)	Yes vs no	0.8	0.55-1.17	0.25
Diabetes	Yes vs no	0.7	0.59-0.88	<0.01
Hospitalization Characteristics				
Length of stay	1 day increase	1.0	1.01-1.03	<0.01
Elective admission	Emergent vs elective	3.1	2.34-4.00	<0.01
Admission day	Weekend vs weekday	1.8	1.45-2.15	<0.01
ICU stay	Yes vs no	16.0	12.57-20.45	<0.01
Hospital				
Annual procedure volume				<0.01
	1-4 TIPS/year vs ≥30 TIPS/year	2.3	1.72-3.11	
	5-9 TIPS/year vs ≥30 TIPS/year	2.4	1.77-3.20	
	10-19 TIPS/year vs ≥30 TIPS/year	2.1	1.51-2.78	
	20-29 TIPS/year vs ≥30 TIPS/year	1.5	1.11-2.12	
Hospital bed-size				0.63
	Small vs large	1.1	0.67-1.88	
	Medium vs large	1.1	0.89-1.39	
Hospital ownership				0.50
	Government vs private proprietary	1.2	0.86-1.78	
	Private nonprofit vs private proprietary	1.1	0.81-1.47	
Hospital teaching status				0.19
	Metropolitan non-teaching vs non-metropolitan	2.2	0.81-5.78	
	Metropolitan teaching vs non-metropolitan	2.0	0.74-5.20	
Hospital urban-rural location				0.28
	large metropolitan >1 million residents vs micropolitan	2.0	0.75-5.27	
	small metropolitan <1 million residents vs micropolitan	2.0	0.77-5.42	
Liver transplant status	Transplant hospital vs non-transplant hospital	0.7	0.55-0.79	<0.01
Complication of cirrhosis				
Variceal bleeding	Yes vs no	3.0	2.47-3.65	<0.01
SBP	Yes vs no	1.4	0.97-2.08	0.07
HE	Yes vs no	2.3	1.90-2.71	<0.01
HRS	Yes vs no	5.4	4.24-6.91	<0.01
Ascites or hydrothorax	Yes vs no	1.1	0.95-1.39	0.15
Complications of Inpatient Hospitalizations				
Infection	Yes vs no	4.4	3.73-5.31	<0.01
Acute Renal Failure	Yes vs no	7.8	6.46-9.38	<0.01
Electrolyte imbalance	Yes vs no	3.9	3.20-4.64	<0.01

Appendix Table 2 Crude Odds Ratios for Inpatient Mortality

Elective admissions only	OR	95% CI	p value	c-statistics
Annual Procedure volume				
1-19 vs. ≥20 TIPS/year	2.7	1.10-6.41	0.03	
AHRQ Comorbidity measures				
Congestive heart failure	0.9	0.15-5.26	0.91	
Coagulopathy	4.2	1.89-9.52	<0.01	
Renal failure	0.4	0.10-1.35	0.13	
Income quartile for patient zip code				
$1-37,999	0.7	0.23-2.07	0.50	
$38,000-47,999	0.6	0.21-1.95	0.43	**0.895**
$48,000-63,999	1.1	0.35-3.13	0.93	
$64,000 or more	Reference			
Other Risk Factors				
Age (per 1 year increase)	1.0	0.94-1.01	0.13	
Alcoholic liver disease	0.7	0.30-1.78	0.50	
Variceal Bleeding	4.5	2.00-10.10	<0.01	
Infection	7.8	3.50-17.54	<0.01	
Diabetes	0.6	0.23-1.41	0.22	

Appendix Table 3: Multivariate model for inpatient mortality after elective admissions for TIPS.

Emergent admissions only	OR	95% CI	p value	c-statistics
Annual Procedure Volume				
1-19 vs. ≥20 TIPS/year	1.5	1.11-2.15	0.01	
Comorbidity measures				
Congestive heart failure	1.5	0.89-2.59	0.13	
Coagulopathy	1.8	1.29-2.45	<0.01	
Renal failure	1.8	1.19-2.64	0.01	
Income quartile for patient zip code				
$1-37,999	0.9	0.59-1.35	0.60	
$38,000-47,999	0.5	0.33-0.80	<0.01	**0.738**
$48,000-63,999	0.6	0.35-0.88	0.01	
$64,000 or more	Reference			
Other Risk Factors				
Age (per 1 year increase)	1.0	1.00-1.03	0.02	
Alcoholic liver disease	1.1	0.80-1.51	0.55	
Variceal Bleeding	2.1	1.44-2.97	<0.01	
Infection	3.5	2.63-4.77	<0.01	
Diabetes	0.8	0.54-1.08	0.13	

Appendix Table 4: Multivariate model for inpatient mortality after emergent admissions for TIPS.