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NAFLD and Diabetes are Associated with Post-TIPS Renal Dysfunction: An ALTA Group Study

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Abstract

Background and Aims: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective intervention for portal hypertensive complications, but its effect on renal function is not well-characterized. Here, we describe renal function and characteristics associated with renal dysfunction at 30-days post-TIPS.

Methods: Adults with cirrhosis who underwent TIPS at nine hospitals in the US 2010-2015 were included. We defined "post-TIPS renal dysfunction" as a change in estimated glomerular filtration rate (ΔeGFR) ≤ 15ml/min/1.73m^2 and eGFR ≤ 60ml/min/1.73m^2, or new renal replacement therapy (RRT) at day 30. We identified the characteristics associated with post-TIPS renal dysfunction by logistic regression and evaluated survival using adjusted competing risk regressions.

Results: Of 673 patients: median age 57 years, 38% female, 26% had diabetes, median MELDNa 17. Thirty days post-TIPS, 66 (10%) had renal dysfunction, of which 23 (35%) required new RRT. Patients with post-TIPS renal dysfunction, compared to those with stable renal function, were more likely to have NAFLD (33% versus 17%, p = 0.01) and comorbid diabetes (42% versus 24%, p < 0.01). Multivariate logistic regressions showed NAFLD (OR 2.04, 95%CI 1.00 to 4.17, p = 0.05), serum sodium (OR 1.06 per mEq/L, 95%CI 1.01 to 1.12, p = 0.03), and diabetes (OR 2.04, 95%CI 1.16 to 3.61, p = 0.01) were associated with post-TIPS renal dysfunction. Competing risk regressions showed those with post-TIPS renal dysfunction were at higher sub-hazard of death (sHR 1.74, 95%CI 1.18 to 2.56, p = 0.01).

Conclusions: In this large multi-center cohort, we found NAFLD, diabetes, and baseline serum sodium associated with post-TIPS renal dysfunction. This study suggests that patients with NAFLD and diabetes undergoing TIPS evaluation may require additional attention to cardiac and renal comorbidities prior to proceeding with the procedure.

Keywords

Portal Hypertension; Renal Function; TIPS; NAFLD; Diabetes

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is an effective intervention for certain complications of portal hypertension, such as refractory ascites and variceal bleeding.(1,2) In addition to its use in relieving these complications, TIPS is hypothesized to improve renal function in certain patients with cirrhosis through alleviating functional hypovolemia, derangements in renin-angiotensin-aldosterone and sympathetic nervous systems, and increasing natriuresis.(3-6) In a single-center study of 129 TIPS patients in the United States, those with baseline serum creatinine ≥ 2.0mg/dL appeared to have derived the greatest benefit from TIPS with an improvement in mean creatinine from 2.8 to 1.5mg/dL.(7)

While TIPS may improve renal function related to portal hypertension, such as in hepatorenal syndrome-chronic kidney disease (HRS-CKD, formerly described as HRS type 2),(8) this benefit has not been definitively shown in all those who undergo TIPS.(4) In addition, TIPS placement requires complex clinical decision-making as there are many competing factors associated with the procedure. In poorly selected patients, TIPS could be associated with contrast induced nephropathy and rapid volume shifts leading to precipitation of acute cardiac, renal, neurologic, and/or hepatic decompensations.(1,2,9) Previous evidence have suggested that TIPS placement may not be beneficial in patients with non-portal hypertensive parenchymal renal disease.(4,10) Moreover, prior studies on renal function after TIPS placement, have been limited by small sample sizes or have been conducted in a single-center setting.(4,7,10,11)

We hypothesize that there are vulnerable subpopulations of patients with cirrhosis whose renal function may worsen after TIPS. To evaluate for this, we are leveraging data from a large multi-center retrospective cohort based in the United States, for which the primary outcomes have already been presented.(12) Using this data, we conducted this secondary analysis to better understand renal outcomes after TIPS and clinical characteristics associated with post-TIPS renal dysfunction.

Methods

Participants

This retrospective study included adults ≥ 18 years with cirrhosis who underwent TIPS from January 1, 2010 through December 31, 2015 at nine academic medical centers in the United States participating in the Advancing Liver Therapeutic Approaches (ALTA) Study Group. All participants were followed until liver transplantation, death, or loss to follow up through December 31, 2016. Exclusion criteria for the primary study included prior liver transplantation and non-cirrhotic portal hypertension, such as acute Budd-Chiari syndrome, granulomatous liver diseases, nodular regenerative hyperplasia, and sarcoidosis. All data were gathered through a combination of electronic medical record queries via International Classification of Diseases-9/10 or Current Procedural Terminology codes and/or via manual chart review. Study data were managed using Research Electronic Data Capture (REDCap) hosted at the organizing center, Northwestern University.(13) This study was approved by the Institutional Review Boards at each of the nine participating sites.

Clinical Data

Etiologies of cirrhosis were categorized as: alcohol-associated (ALD), hepatitis C, non-alcoholic fatty liver disease (NAFLD), or other etiologies (hepatitis B, cholestatic diseases, autoimmune, and others). Primary indications for TIPS were abstracted from radiology procedure reports and categorized as: refractory ascites and/or hydrothorax; variceal bleeding; portal venous thrombosis and other indications, such as optimization prior to endoscopy/surgery; or multiple indications. Hepatic venous pressure gradients at the time of TIPS were calculated from the difference between wedged portal venous and hepatic venous pressures. Post-TIPS portal gradient pressures were calculated from the difference between direct portal and hepatic venous pressures. Demographic and clinic data, including comorbid conditions relevant medication, laboratory data, liver imaging (ultrasound or computed tomography), endoscopy reports, and echocardiograms were also abstracted from the medical chart. Baseline data were defined as those obtained within 2 to 28 days prior to TIPS and post-procedure data were obtained up to one year after TIPS with data designated at day 30, defined as any obtained between days 15 and 45.

Assessments of Renal Function

Renal function was assessed by serum creatinine and corresponding estimated glomerular filtration rate (eGFR), calculated by the Chronic Kidney Disease-Epidemiology (CKD-EPI) equation.(14) We chose this equation as blood urea nitrogen levels, which are necessary for the Modification of Diet in Renal Study (MDRD)-6 estimation, were not routinely drawn on all patients as it is not included in the Model for End-Stage Liver Disease-Sodium (MELDNa) score and that the CKD-EPI equation closely estimates GFR relative to GFR as measured by iothalamate clearance in patients with cirrhosis.(15-17) Chronic kidney disease (CKD) stages were defined based on guidelines issued by the National Kidney Foundation Kidney Disease Quality Outcome Initiative (K/DOQI).(18,19) Renal replacement therapy (RRT) 30 days post-TIPS were defined as at least two encounters for intermittent hemodialysis or continuous renal replacement therapy up to 30 days post-TIPS.

For this analysis, participants were divided into two groups based on renal function at day 30 post-TIPS: “post-TIPS renal dysfunction” and “stable/improved renal function:”

1. “Post-TIPS renal dysfunction,” defined as:
    a. eGFR ≤ 60ml/min/1.73m^2 at day 30 post-TIPS, AND one of the following two:
        i. eGFR change of greater than −15ml/min/1.73m^2 (ΔeGFR ≤ −15ml/min/1.73m^2) from baseline at day 30 post-TIPS, OR
        ii. New RRT defined as intermittent hemodialysis or continuous renal replacement therapy at day 30 post-TIPS.
2. “Stable/improved renal function,” encompassing all patients who did not meet the above criteria for “post-TIPS renal dysfunction”:
    a. eGFR >60 ml/min/1.73m^2 at day 30 post-TIPS, OR

b. eGFR change of less than −15ml/min/1.73m^2 (ΔeGFR > −15ml/min/1.73m^2) from baseline at day 30 post-TIPS.

We chose 30 days to evaluate the impact of TIPS on renal function due to previous data showing that the effects of TIPS on renal hemodynamics, neurohormonal activity, and sodium homeostasis begin to stabilize at 1 month.(3-6) With regards to decline in renal function triggering "post-TIPS renal dysfunction," we chose eGFR ≤60ml/min/1.73m^2 as a major criterion because eGFR that persists for ≥3 months at below this benchmark is accepted as the development of CKD in patients without cirrhosis and HRS-CKD in those with cirrhosis.(18-20) We used eGFR change of greater than −15ml/min/1.73m^2 (ΔeGFR ≤ −15ml/min/1.73m^2) as a minor criterion as this is the threshold that changes CKD staging – for example: a decline of 15ml/min/1.73m^2 from 40ml/min/1.73m^2 to 25ml/min/1.73m^2 would be trigger a change in CKD severity from G3b to G4.(18,21,22) Acute kidney injury (AKI) after TIPS was defined, based International Club of Ascites criteria, as a rise in serum creatinine by ≥0.3 mg/dL or >50% from baseline at any time prior to and including follow up at day 30.(23,24)

Study participants with terminal events (death or transplantation) prior to day 30, without follow up on or after day 30, lost to follow up, or without a serum creatinine recorded at day 30 post-TIPS were excluded from this secondary analysis as they did not sustain enough follow up for evaluation of the potential impact of TIPS on renal function. Patients undergoing RRT at baseline prior to TIPS, defined as at least two encounters in the 2 to 28 days prior to TIPS were also excluded from this secondary analysis as they could not achieve the endpoint of "post-TIPS renal dysfunction."

Statistical Analyses

Participants were grouped by post-TIPS renal dysfunction and stable/improved renal function as defined above. Demographic characteristics, clinical characteristics, and laboratory data were summarized by medians and interquartile ranges (IQR) for continuous variables or numbers and percentages (%) for categorical variables. Comparisons between groups were performed using chi-square and Kruskal-Wallis tests. Univariate logistic regression models were used to assess for clinical characteristics associated with post-TIPS renal dysfunction. A significance level of $\alpha = 0.25$ was utilized for inclusion into multivariate modeling with stepwise backwards selection of covariates. Covariates included into the multivariate logistic regression model included etiology of cirrhosis; serum INR, total bilirubin, and sodium at baseline; and comorbid diabetes.

Based on the renal function groups defined above, we then evaluated survival starting at 30 days after TIPS. We made comparisons between the post-TIPS renal dysfunction and stable/improved renal function groups using adjusted competing risk regression models of the Fine and Gray method to estimate the sub-hazard of death with transplantation as a competing event.(25) Covariates included in the adjusted competing risk model included renal function groups, serum sodium at baseline, and comorbid diabetes. Two-sided p-values < 0.05 were considered statistically significant in all analyses. Analyses were performed using STATA statistical software, version 16.1 (StataCorp, College Station, TX, USA)

Results

During the six-year study period between January 1, 2010 and December 31, 2015, there were 1,260 patients with cirrhosis who underwent TIPS placement at the nine participating centers, 92 of whom died < 30 days, 50 were transplanted < 30 days, and 71 who only accrued < 30 days of follow up time. Of the remaining 1,047, 673 (64%) had complete data for inclusion into this analysis, 119 (11%) were lost to follow up, 237 (23%) were missing data at day 30, and 18 (2%) were on RRT at baseline prior to TIPS (Figure 1).

Compared to the 673 participants included in the analysis, those who had died < 30 days (92 patients) or transplanted < 30 days (50 patients) were similar with regards to age, gender, race/ethnicity, and etiologies of cirrhosis at the time of TIPS. By TIPS indications, there was a greater proportion of patients who died < 30 days that underwent TIPS for variceal bleeding (52%) versus in the population included in the analysis (29%) and those transplanted < 30 days (22%, $p < 0.01$). Patients who died < 30 days or transplanted < 30 days had higher MELDNa scores with medians of 24 and 26, respectively, versus MELDNa scores with median of 17 in those included in this analysis ($p < 0.01$).

Baseline Characteristics

Baseline characteristics of all 673 participants included in this analysis, segmented by changes in renal function at 30 days defined above, are presented in Table 1. For the entire population, median age was 57 years (IQR 51 to 63), 38% were female, and 68% were non-Hispanic White. The most common etiologies of cirrhosis were alcohol-associated (34%), hepatitis C (30%), NAFLD (19%), and others (17%). The most common indications for TIPS were recurrent ascites/hydrothorax (58%), variceal bleeding (29%), portal venous thrombosis and other indications (7%), and multiple indications (5%). Median MELDNa at TIPS was 17 (IQR 13 to 21) for all participants. Median eGFR at baseline was 73ml/min/1.73m^2 (IQR 52 to 96ml/min/1.73m^2) with 66% of all participants having an eGFR > 60ml/min/1.73m^2 (CKD stages 1 and 2) and 34% with eGFR ≤ 60ml/min/1.73m^2 (CKD stage 3a+).

Renal Function at 30 Days Post-TIPS

The relevant day 30 post-TIPS data are presented in Table 2. In the 673 participants, TIPS was associated with a median change in eGFR of +5ml/min/1.73m^2 (IQR −6 to 15ml/min/1.73m^2) by day 30. Thirty days post-TIPS, 66 (10%) out of the 673 participants met our definition of post-TIPS renal dysfunction and 607 (90%) experienced stable/improved renal function. Those with stable/improved renal function had eGFR changes with a median of +6ml/min/1.73m^2 (IQR −2 to 17ml/min/1.73m^2) versus those with post-TIPS renal dysfunction had eGFR changes with a median of −34ml/min/1.73m^2 (IQR −55 to −23ml/min/1.73m^2). By day 30 post-TIPS, a total of 89 patients, representing 13% of the included study population, had AKI based on ICA-AKI guidelines. Of the 89 patients with AKI: 66% (59) had stage 1, 4% (4) had stage 2, and 29% (26) had stage 3 injuries.

The two groups, stable/improved renal function and post-TIPS renal dysfunction, were not significantly different in terms of ages (median 57 years versus 59 years), race/ethnicity

(69% versus 65% non-Hispanic White), TIPS indications (58% versus 58% ascites/hydrothorax), composite MELDNa scores at baseline (median 17 versus 17), and eGFR at baseline (median 74 versus 69ml/min/1.73m^2). Compared to the patients with stable/improved renal function, those with post-TIPS renal dysfunction, however, had higher serum sodium values at baseline (median 135 versus 137, p = 0.05). Participants with post-TIPS renal dysfunction were more likely to have NAFLD (17% versus 33%, p = 0.01) as the etiology of their liver disease and more likely to have diabetes (42% versus 24%, p < 0.01).

Clinical Characteristics Associated with Post-TIPS Renal Dysfunction

The following covariates were ultimately included in the multivariate logistic model for associates of post-TIPS renal dysfunction: etiology of liver disease, serum INR at baseline, serum total bilirubin at baseline, serum sodium at baseline, and diabetes (Table 3). The significantly associated clinical characteristics in the adjusted model included NAFLD (OR 2.04, 95%CI 1.00 to 4.17, p = 0.05), serum sodium (OR 1.06 per mEq/L, 95%CI 1.01 to 1.12, p = 0.03), and comorbid diabetes (OR 2.04, 95%CI 1.16 to 3.61, p = 0.01). Interaction testing between NAFLD and diabetes was not statistically significant (OR 0.43, 95% CI 0.10 to 1.86, p = 0.26) and thus this interaction term was not included in the final adjusted model.

Transplant Free Survival

In multivariate competing risk analyses (Table 4), we found that post-TIPS renal dysfunction had a significantly higher sub-hazard of death with transplantation being a competing event (sub-hazard ratio [sHR] 1.74, 95%CI 1.18 to 2.56, p = 0.01) after adjustment for serum sodium (sHR 0.97 per mEq/L, 95%CI 0.95-0.99, p = 0.02) and comorbid diabetes (sHR 1.96, 95%CI 1.46-2.60, p < 0.01). The Kaplan-Meier curve for survival with transplantation as a competing event in the two groups is shown in Figure 2.

Overall death rates were significantly lower for patients with stable/improved renal function compared to those with renal dysfunction at 32% versus 50%, p < 0.01. Transplantation rates between the two groups were similar at 22% for those with stable/improved renal function versus 22% for those with renal dysfunction, p = 0.80. The median transplant free survival across the entire study population was 361 days (IQR 53 to 841 days). Compared to patients with stable/improved renal function, those with renal dysfunction had significantly lower transplant free survival (median 167 versus 479 days, p < 0.01).

Discussion

In this large multi-center cohort of 673 patients with cirrhosis who underwent TIPS in the United States, we found that 10% of patients suffered renal dysfunction at day 30 post-TIPS with a median change in eGFR of −34ml/min/1.73m^2 (IQR −55 to −23ml/min/1.73m^2). Twenty-three (35%) of these 66 patients initiated new RRT by day 30. These patients who suffered renal dysfunction were more likely to have NAFLD at 2.04 odds versus ALD, or comorbid diabetes at 2.04 odds versus no diabetes. The presence of post-TIPS renal dysfunction was ultimately associated with 1.74 sub-hazard of death (with transplantation as a competing event) after adjustment for baseline serum sodium and diabetes.

In these previous studies, post-TIPS renal recovery was thought to be driven by correction of neurohormonal derangements and increasing natriuresis, thereby correcting portal hypertensive fluid overload states.(3-6,11) As such, patients with refractory ascites and hepatic hydrothorax were thought to be the best candidates for TIPS as they would derive the greatest benefits from TIPS.(11) The finding of NAFLD and diabetes, which are known to be associated with chronic renal and cardiac diseases,(26,27) to be associated with higher odds of renal dysfunction after TIPS in our population indicate that other factors may be at play in these specific patient populations. One hypothesis is that some patients with NAFLD and/or diabetes had concomitant non-portal hypertensive parenchymal renal disease and that their worsening renal function may be reflective of both a lack of response to TIPS plus propensity to peri-procedural AKI. This hypothesis is supported by earlier studies on the efficacy of TIPS, showing those patients with parenchymal renal diseases had little or no response to TIPS.(4,28,29)

A second hypothesis is that non-portal hypertensive systemic volume overload disorders become “uncovered” in some patients with NAFLD and/or diabetes – and that increased renal venous pressures after TIPS could be responsible for renal dysfunction seen. In our study, unfortunately, we did not have pre- and post-TIPS echocardiography for all patients. In the 61/673 (9%) patients with both pre- and post-TIPS echocardiography data by day 30, however, there were no changes in left ventricular ejection fraction in either of the two renal function group. Post-TIPS hepatic vein and inferior vena cava pressure measurements are more direct proxies for renal venous pressures and have been shown to be associated with renal dysfunction in patients with cirrhosis.(30-32) In the 50/673 (7%) patients with either inferior vena cava or free hepatic vein pressure measurements after TIPS, the 45 patients categorized as stable renal function had lower pressures (median 16 versus 20mmHg) versus the five patients categorized as decreased renal function. These differences, however, were not statistically significant – likely due to the small sample size in which these measurements were taken.

We acknowledge the several limitations to this study. First, the current report is a retrospective analysis: Its results and conclusions are limited by the availability of follow up data, which can introduce a selection bias. We defined renal outcomes at day 30 to better account for the impact of TIPS on renal hemodynamics, neurohormonal changes, and natriuresis changes – by doing so, we introduced immortal time bias as 142 patients were transplanted or had died by day 30. In addition, only 64% of the 1,047 participants in the ALTA Study Group who had follow up by day 30 had complete data for analysis. We speculate that the lack of follow up and missing data may be related to the nature of our study being conducted at tertiary academic referral centers as substantial proportions of participants were referred for TIPS and then followed locally post-procedure.

Second, our definition of renal outcomes was based on eGFR calculated by the four-variable creatinine-based CKD-EPI equation. While CKD-EPI equation most closely estimates measured GFR by iothalamate clearance in patients with cirrhosis, this equation underperforms more modern estimators inclusive of blood urea nitrogen and serum albumin, such as MDRD-6 or the Glomerular Filtration Rate Assessment in Liver Disease (GRAIL) model.(15-17,33) In addition, more recent studies have indicated that Cystatin C is a

superior biomarker for estimating GFR in the post-TIPS setting, especially in women, whose renal function are overestimated by serum creatinine based equations.(34,35) Our use of the CKD-EPI equation may have overestimated the true renal function of 258 (36%) women included in this analysis.

Third, not all patient comorbidities potentially impacting renal function, such as arterial hypertension and hyperlipidemia prior to the diagnosis of cirrhosis, were captured in the retrospective data acquisition. While the diagnoses of NAFLD and diabetes are often comorbid with renal disease, the lack of recorded diagnoses directly implicating renal disease in our results is a limitation and therefore limits causal inference on possible mechanisms for renal dysfunction. Fourth, our analysis does not include detailed information periprocedural management, such as contrast loads, treatment of infections, nephrotoxic drugs administered, management of blood pressure, and volume management (e.g. transfusions, paracenteses, and albumin loads). As such, we were unable to evaluate whether periprocedural events, such as contrast-induced nephropathy, could have contributed to post-TIPS renal dysfunction.

In conclusion, in this large multi-center study, we found that pre-TIPS diagnoses of NAFLD and diabetes, and a TIPS indication of variceal bleeding to be associated with post-TIPS renal dysfunction. Moreover, post-TIPS renal dysfunction at day 30 was shown to be associated with higher sub-hazards of death in follow up. Despite our finding of an association between NAFLD and diabetes with post-TIPS renal dysfunction, it is ultimately reassuring that most patients with NAFLD (83%) or diabetes (84%) who underwent TIPS had stable or improved renal function by day 30. Our findings indicate that patients with these at-risk clinical characteristics perhaps should have more thorough vetting for comorbid parenchymal renal and cardiac dysfunction as they are at higher risk of decreased renal function after TIPS. Further avenues for exploration include whether medical interventions for renal optimization, such as pre-procedure hydration, and decreased contrast loads, are warranted for candidates with NAFLD or diabetes prior to TIPS.

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Abbreviations

AKI	acute kidney injury
ALD	alcohol-associated liver disease

ALTA	Advancing Liver Therapeutic Approaches
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology
eGFR	estimated glomerular filtration rate
GRAIL	Glomerular Filtration Rate Assessment in Liver Disease
HE	hepatic encephalopathy
HPVG	hepatic portal venous gradient
HR	hazard ratio
HRS-CKD	hepatorenal syndrome-chronic kidney disease
ICA-AKI	International Club of Ascites – Acute Kidney Injury
IQR	interquartile ranges
K/DOQI	Kidney Disease Quality Outcome Initiative
MELDNa	Model for End-Stage Liver Disease-Sodium
MDRD	Modification of Diet in Renal Study
NAFLD	non-alcoholic fatty liver disease
OR	odds ratio
REDCap	Research Electronic Data Capture
RRT	renal replacement therapy
sHR	sub-hazard ratio
TIPS	Transjugular Intrahepatic Portosystemic Shunt

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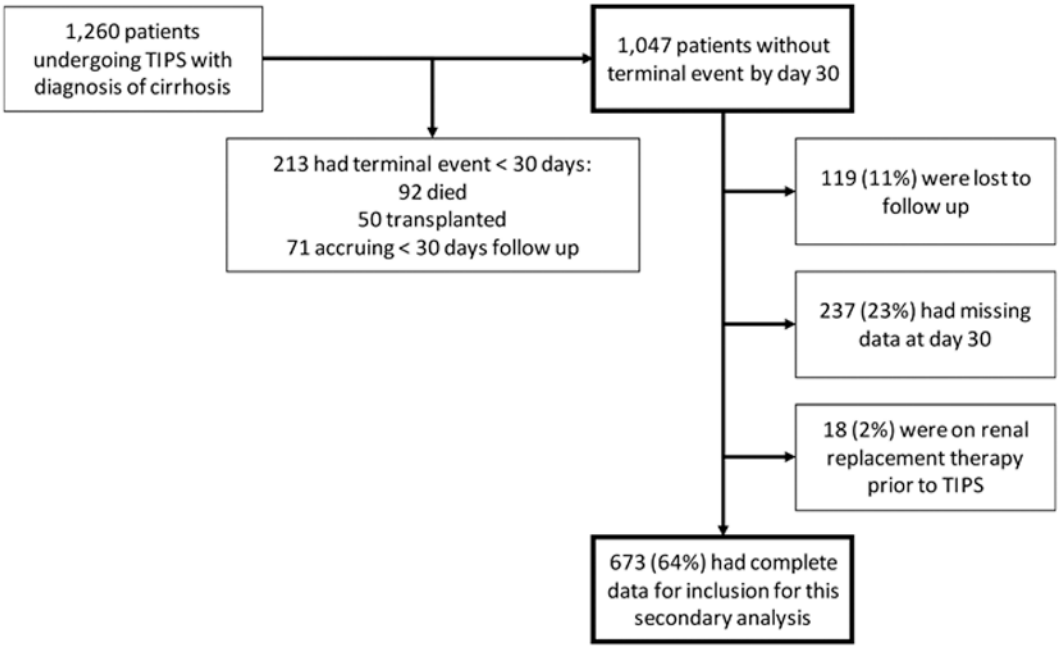
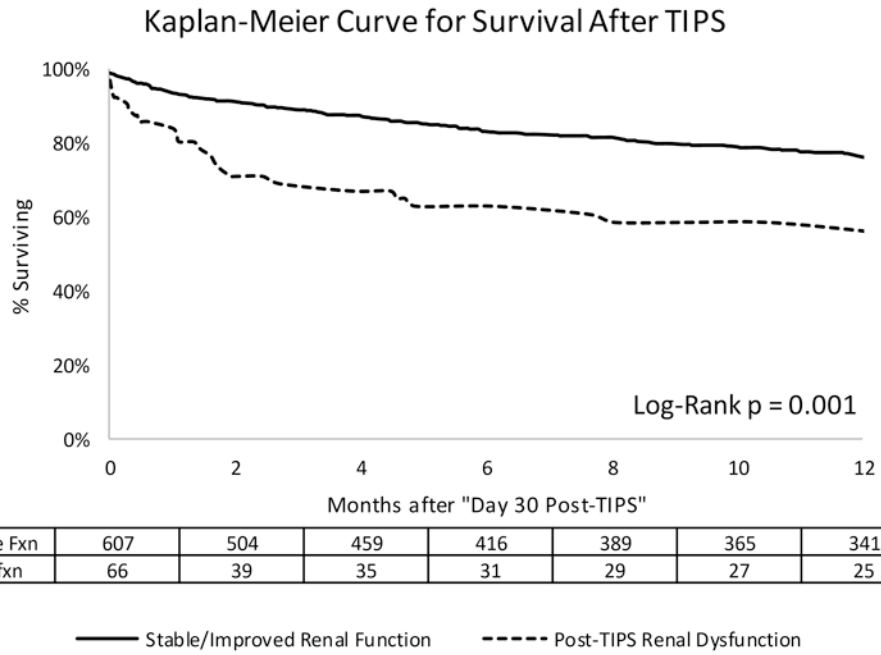


Figure 1.
Flowchart of Patients Included for Analysis



Stable Fxn	607	504	459	416	389	365	341
Dysfxn	66	39	35	31	29	27	25

Figure 2.
Kaplan-Meier Curve for Survival Starting at 30 Days Post-TIPS

Table 1 –

Baseline Characteristics of Study Population

	Total Population (N = 673)	Stable/Improved Renal Function (N = 607)	Post-TIPS Renal Dysfunction (N = 66)	P-Value
Age (years)	57 (51-63)	57 (50-63)	59 (52-65)	0.49
Female (%)	258 (38)	229 (38)	29 (44)	0.32
Race/Ethnicity (%)				0.47
White	461 (68)	418 (69)	43 (65)	
Black	26 (4)	22 (4)	4 (6)	
Hispanic	121 (18)	106 (17)	15 (23)	
Asian	12 (2)	12 (2)	0 (0)	
Other	53 (8)	49 (8)	4 (6)	
Etiology of Liver Disease (%)				0.01
Alcohol-associated	228 (34)	210 (35)	18 (27)	
Hepatitis C	202 (30)	183 (30)	19 (29)	
NAFLD	128 (19)	106 (17)	22 (33)	
Other etiologies	115 (17)	108 (18)	7 (11)	
TIPS Indication				0.92
Ascites/Hydrothorax	392 (58)	354 (58)	38 (58)	
Variceal Bleed	195 (29)	174 (29)	21 (32)	
PVT and Other Indications	50 (7)	46 (8)	4 (6)	
Multiple Indications	36 (5)	33 (5)	3 (5)	
MELDNa, median at baseline	17 (13 to 21)	17 (13-20)	17 (14-23)	0.31
INR	1.4 (1.2 to 1.6)	1.4 (1.2-1.5)	1.4 (1.2-1.7)	0.56
T. bili (mg/dL)	1.4 (1.0 to 2.3)	1.4 (1.0-2.2)	1.5 (1.0-2.7)	0.30
Cr (mg/dL)	1.0 (0.8 to 1.3)	1 (0.8-1.3)	1.1 (0.9-1.5)	0.15
Na (mEq/L)	136 (132 to 138)	135 (132-138)	137 (133-139)	0.05
Serum Albumin, median (g/L)	2.9 (2.5 to 3.4)	2.9 (2.5-3.5)	2.8 (2.3-3.3)	0.03
eGFR, median at baseline (ml/min/1.73m^2)	73 (52 to 96)	74 (53-97)	69 (50-85)	0.05
eGFR > 60 (ml/min/1.73m^2)	447 (66)	408 (67)	39 (59)	0.18
eGFR ≤ 60 (ml/min/1.73m^2)	226 (34)	199 (33)	27 (41)	
HVPG Pre-TIPS (mmHg)	16 (13 to 21)	17 (14-21)	15 (12-21)	0.24
Portal Pressure Gradient Post-TIPS (mmHg)	6 (4-8)	6 (4-8)	6 (5-9)	0.13
Portal Pressure Gradient Change (mmHg)	10 (7 to 14)	11 (8-14)	9 (7-12)	0.08
HE Pre-TIPS (%)	292 (43)	260 (43)	32 (48)	0.43
Lactulose Use (%)	268 (40)	237 (39)	31 (47)	0.23
Rifaximin Use (%)	160 (24)	143 (24)	17 (26)	0.68
Lactulose + Rifaximin Use (%)	124 (18)	109 (18)	15 (23)	0.34
Ascites Pre-TIPS	490 (73)	442 (73)	48 (73)	0.79
Diuretic Use (%)	458 (68)	410 (68)	48 (73)	0.33
Diabetes (%)	173 (26)	145 (24)	28 (42)	<0.01

Abbreviations: NAFLD, non-alcoholic fatty liver disease; MELDNa, Model for End-Stage Liver Disease-Sodium; INR, international normalized ratio; T. bili, serum total bilirubin; Cr, serum creatinine; Na, serum sodium; eGFR, estimated glomerular filtration rate; TIPS, Transjugular Intrahepatic Portosystemic Shunt; HPVG, hepatic portal venous gradient; HE, hepatic encephalopathy.

Continuous variables were summarized by medians and interquartile ranges (IQR). Categorical variables were summarized by numbers and percentages (%). Comparisons between groups were performed using chi-square and Kruskal-Wallis tests as appropriate for categorical variables and continuous variables, respectively.

Table 2 –

Post-TIPS Outcomes at Day 30

	Total Population (N = 673)	Stable/Improved Renal Function (N = 607)	Post-TIPS Renal Dysfunction (N = 66)	P-Value
MELDNa, median	18 (13 to 23)	17 (13 to 22)	26 (21 to 34)	<0.01
INR	1.5 (1.3 to 1.7)	1.4 (1.3 to 1.7)	1.6 (1.4 to 2.1)	<0.01
T. bili (mg/dL)	2.5 (1.5 to 4.3)	2.5 (1.5 to 4.1)	3.3 (1.7 to 8.6)	0.03
Cr (mg/dL)	1.0 (0.7 to 1.3)	0.9 (0.7 to 1.1)	2.2 (1.5 to 4.0)	<0.01
Na (mEq/L)	136 (133 to 139)	136 (133 to 139)	136 (133 to 139)	0.42
Serum Albumin, median (g/L)	2.8 (2.4 to 3.2)	2.8 (2.4 to 3.2)	2.9 (2.5 to 3.3)	0.40
eGFR, median (ml/min/1.73m^2)	81 (54 to 102)	86 (62 to 103)	27 (0 to 46)	<0.01
Change in eGFR, median (ml/min/1.73m^2)	5 (−5 to 15)	6 (−1 to 17)	−34 (−55 to −23)	<0.01
New renal replacement as of day 30 Post-TIPS (%)	23 (3)	0 (0)	23 (35)	<0.01
HE Post-TIPS (%)	460 (81)	404 (80)	56 (93)	0.01
Lactulose Use Post-TIPS (%)	527 (78)	473 (78)	54 (82)	0.31
Rifaximin Use Post-TIPS (%)	437 (65)	387 (64)	50 (76)	0.03
Lactulose + Rifaximin Use Post-TIPS (%)	411 (61)	363 (60)	48 (73)	0.04
Ascites Post-TIPS (%)	296 (57)	263 (56)	33 (63)	0.33
AKI Post-TIPS (ICA-AKI)				<0.01
Stage 1	59 (9)	27 (4)	32 (48)	
Stage 2	4 (1)	0 (0)	4 (6)	
Stage 3	26 (4)	0 (0)	26 (39)	

Abbreviations: MELDNa, Model for End-Stage Liver Disease-Sodium; INR, international normalized ratio; T. bili, serum total bilirubin; Cr, serum creatinine; Na, serum sodium; eGFR, estimated glomerular filtration rate; HE, hepatic encephalopathy; TIPS, Transjugular Intrahepatic Portosystemic Shunt; AKI, acute kidney injury; ICA-AKI, International Club of Ascites – AKI.

Continuous variables were summarized by medians and interquartile ranges (IQR). Categorical variables were summarized by numbers and percentages (%). Comparisons between groups were performed using chi-square and Kruskal-Wallis tests as appropriate for categorical variables and continuous variables, respectively.

Table 3 –

Logistic Regressions of Factors Associated with Post-TIPS Renal Dysfunction

	Univariable Logistic Regression			Multivariable Logistic Regression		
	OR	**95% CI**	**P-Value**	**OR**	**95% CI**	**P-Value**
Etiology of Liver Disease						
Alcohol-associated	Ref			Ref		
Hepatitis C	1.21	0.62 to 2.38	0.58	1.14	0.57 to 2.29	0.70
NAFLD	2.42	1.24 to 4.71	0.01	2.04	1.00 to 4.17	0.05
Other etiologies	0.76	0.31 to 1.87	0.54	0.67	0.27 to 1.71	0.41
NAFLD vs non-NAFLD						
Non-NAFLD	Ref					
NAFLD	2.36	1.36 to 4.11	<0.01			
TIPS Indication						
Ascites/ Hydrothorax	Ref					
Variceal Bleed	1.12	0.64 to 1.97	0.68			
Other Indications	0.81	0.28 to 2.37	0.70			
Multiple Indications	0.85	0.25 to 2.89	0.79			
MELDNa Components						
INR	1.68	0.83 to 3.39	0.15	1.70	0.76 to 3.79	0.19
T. bili (mg/dL)	1.09	0.98 to 1.21	0.12	1.11	0.98 to 1.26	0.09
Cr (mg/dL)	1.15	0.80 to 1.66	0.46			
Na (mEq/L)	1.06	1.00 to 1.12	0.04	1.06	1.01 to 1.12	0.03
Serum Albumin	1.00	1.00 to 1.00	0.81			
eGFR at TIPS						
eGFR > 60	Ref					
eGFR ≤ 60	1.41	0.84 to 2.39	0.19			
HVPG Pre-TIPS (mmHg)	0.97	0.92 to 1.03	0.29			
Portal Pressure Gradient Change (mmHg)	0.95	0.90 to 1.01	0.09			
Medications at TIPS						
Rifaximin Use	1.37	0.82 to 2.28	0.23			
Lactulose Use	1.13	0.63 to 2.03	0.68			
Diuretic Use	1.33	0.74 to 2.37	0.34			
Comorbidities at TIPS						
Diabetes	2.34	1.39 to 3.96	<0.01	2.04	1.16 to 3.61	0.01

Abbreviations: OR, odds ratio; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; TIPS, Transjugular Intrahepatic Portosystemic Shunt; MELDNa, Model for End-Stage Liver Disease-Sodium; INR, international normalized ratio; T. bili, serum total bilirubin; Cr, serum creatinine; Na, serum sodium; eGFR, estimated glomerular filtration rate; HPVG, hepatic portal venous gradient.

Univariate logistic regression model was used to assess for clinical characteristics associated with post-TIPS renal dysfunction. Significance level of $p < 0.25$ was utilized for inclusion into multivariate modeling with stepwise backwards selection of covariates. Covariates ultimately included into the multivariate model included etiology of cirrhosis, TIPS indication, MELDNa score, and diabetes.

Table 4 –

Competing Risk Regression of Sub-Hazard of Death with Transplantation as Competing Event

	Univariable Competing Risk Regression			Multivariable Competing Risk Regression		
	sHR	**95% CI**	**P-Value**	**sHR**	**95% CI**	**P-Value**
Change in Renal Function						
Stable or Improved	Ref			Ref		
Decease in Renal Function	1.94	1.32 to 2.85	<0.01	1.74	1.18 to 2.58	0.01
Etiology of Liver Disease						
Alcohol-associated	Ref					
Hepatitis C	1.16	0.84 to 1.61	0.37			
NAFLD	1.25	0.86 to 1.80	0.24			
Other etiologies	0.96	0.65 to 1.42	0.83			
NAFLD vs non-NAFLD						
Non-NAFLD	Ref					
NAFLD	1.19	0.86 to 1.63	0.29			
TIPS Indication						
Ascites/ Hydrothorax	Ref					
Variceal Bleed	0.64	0.41 to 0.86	<0.01			
Other Indications	0.88	0.55 to 1.41	0.59			
Multiple Indications	0.98	0.56 to 1.74	0.95			
MELDNa Components						
INR	1.00	0.91 to 1.09	0.95			
T. bili (mg/dL)	1.06	0.99 to 1.14	0.10			
Cr (mg/dL)	1.27	1.08 to 1.49	<0.01			
Na (mEq/L)	0.97	0.94 to 0.99	0.01	0.97	0.95 to 0.99	0.02
Serum Albumin	1.00	1.00 to 1.00	0.40			
eGFR at TIPS						
eGFR > 60	Ref					
eGFR ≤ 60	1.63	1.25 to 2.12	<0.01			
HVPG Pre-TIPS (mmHg)	0.98	0.96 to 1.01	0.21			
Portal Pressure Gradient Change (mmHg)	0.99	0.96 to 1.01	0.23			
Medications at TIPS						
Rifaximin Use	1.19	0.91 to 1.55	0.20			
Lactulose Use	0.95	0.39 to 1.31	0.77			
Diuretic Use	1.41	1.07 to 1.86	0.02			
Comorbidities at TIPS						
Diabetes	1.81	1.38 to 2.38	<0.01	1.96	1.48 to 2.60	<0.01

Abbreviations: sHR, sub-hazard ratio; CI, confidence interval; NAFLD, non-alcoholic fatty liver disease; TIPS, Transjugular Intrahepatic Portosystemic Shunt; MELDNa, Model for End-Stage Liver Disease-Sodium; INR, international normalized ratio; T. bili, serum total bilirubin; Cr, serum creatinine; Na, serum sodium; eGFR, estimated glomerular filtration rate; HPVG, hepatic portal venous gradient.

Univariate logistic regression model was used to assess for clinical characteristics associated with post-TIPS renal dysfunction. Significance level of $p < 0.25$ was utilized for inclusion into multivariate modeling with stepwise backwards selection of covariates. Covariates ultimately included into the multivariate model included etiology of cirrhosis, TIPS indication, MELDNa score, and diabetes.