Journal of Frailty, Sarcopenia and Falls

Original Article

Frailty as a risk-stratification tool in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS)

Aalam Sohal[1]*, Hunza Chaudhry[2]*, Isha Kohli[3], Kirti Arora[4], Jay Patel[5], Nimrat Dhillon[6], Ishandeep Singh[4], Dino Dukovic[7], Marina Roytman[8]

[1]Department of Hepatology, Liver Institute Northwest, Seattle, USA;
[2]Department of Internal Medicine, University of California, San Francisco, Fresno, USA;
[3]Department of Public Health, Icahn School of Medicine, Mount Sinai, New York, USA;
[4]Dayanand Medical College and Hospital, India;
[5]Department of Internal Medicine, Orange Park Medical Center, Orange Park, Florida, USA;
[6]Shri Guru Ram Das Medical College, India;
[7]Ross University School of Medicine, Barbados, USA;
[8]Department of Gastroenterology and Hepatology, University of California, San Francisco, Fresno, USA
** Equal contribution*

Abstract

Objectives: The concept of frailty has gained importance, especially in patients with liver disease. Our study systematically investigated the effect of frailty on post-procedural outcomes in patients undergoing transjugular intrahepatic portosystemic shunt (TIPS). **Methods:** We used National Inpatient Sample(NIS) 2016-2019 data to identify patients who underwent TIPS. Hospital frailty risk score (HFRS) was used to classify patients as frail (HFRS>=5) and non-frail (HFRS<5). The relationship between frailty and outcomes such as death, post-procedural shock, non-home discharge, length of stay (LOS), post-procedural LOS, and total hospitalization charges (THC) was assessed. **Results:** A total of 13,700 patients underwent TIPS during 2016-2019. Of them, 5,995 (43.76%) patients were frail, while 7,705 (56.24%) were non-frail. There were no significant differences between the two groups based on age, gender, race, insurance, and income. Frail patients had higher mortality (15.18% vs. 2.07%, p<0.001), a higher incidence of non-home discharge (53.38% vs. 19.08%, p<0.001), a longer overall LOS (12.5 days vs. 3.35,p<0.001), longer post-procedural stay (8.2 days vs. 3.4 days, p<0.001), and higher THC ($240,746.7 vs. $121,763.1, p<0.001) compared to the non-frail patients. On multivariate analysis, frail patients had a statistically significant higher risk of mortality (aOR-3.22, 95% CI-1.98- 5.00, p<0.001). **Conclusion:** Frailty assessment can be beneficial in risk stratification in patients undergoing TIPS.

Keywords: Cirrhosis, Emerging, Frailty, National Inpatient Sample, TIPS

Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) is a well-established modality for decreasing portal hypertension[1]. It is used in patients with refractory variceal bleeding, refractory ascites, refractory hydrothorax, Budd-Chiari syndrome, and hepatorenal syndrome[2]. Patients undergoing TIPS are at increased risk of in-hospital mortality, with one study reporting mortality as high as 10.1%[3]. It has also been reported that the risk of mortality differs by the indication of TIPS[4]. In carefully selected candidates, TIPS is associated with improved survival and quality of life,

The authors have no conflict of interest.

Corresponding author: *Aalam Sohal, MD, Liver Institute Northwest, 3216 NE 45th Pl, Suite 212, Seattle, WA98105*

E-mail: *asohal@liverinstitutenw.org*

Edited by: *George Lyritis*

Accepted *8 May 2023*

especially in patients with refractory ascites and variceal bleeding[5-6]. Due to the inherent risks and benefits associated with this procedure, proper patient selection is critical[7].

Multiple models have been developed to predict survival in patients undergoing TIPS. Model for the end-stage liver disease (MELD) and Child-Pugh classification has been shown to predict survival in patients undergoing TIPS[8-9]. These scores focus on several physiological parameters but fail to capture elements such as the physical conditioning of the patients. In recent years, frailty has gained importance, especially in patients with chronic liver disease. It has been reported that 17-49% of the patients with chronic liver disease are frail, defined using various scores, including LFI (liver frailty index), CFS (Clinical frailty scale), FFS (Fried Frailty Score), and SPPBT (short physical performance test)[10-15]. Some studies have reported that incorporating frailty into traditional risk assessment scores, such as MELD, can help predict worse outcomes[14].

Hospital Frailty risk score (HFRS) is another tool for frailty assessment developed by Gilbert et al. using electronic health hospital records[16]. This score was developed using ICD-10 codes of diseases overrepresented in frail patients. Each ICD-10 code was awarded one specific value proportional to how strongly they predicted frailty. This score has been studied in patients undergoing spinal surgery, acute pancreatitis, and endoscopy for gastrointestinal bleeding and has been shown to predict poor clinical outcomes[17-19]. This score has also been shown to predict worse outcomes in patients with chronic conditions such as inflammatory bowel disease and chronic pancreatitis[20-21].

Perioperative frailty is an important indicator of post-surgical outcomes[22]. A random-effect meta-analysis concluded that despite various definitions, frailty is associated with increased morbidity and mortality in patients undergoing surgeries[23]. Until now, no studies have implemented HFRS to assess frailty and its impact on patients undergoing TIPS. Our study aimed to systematically investigate the effect of frailty, defined using HFRS, on post-procedural outcomes in patients undergoing TIPS.

Materials and methods

Data source

The National Inpatient Sample (NIS) is maintained by the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. It is the largest openly-accessible database of inpatient hospital stays in the United States[24]. It collects data from a 20% stratified sample of United States hospitals from 37 states and has been reliably used to estimate disease burden and outcomes. NIS contains data on 7 million unweighted and 35 million weighted hospitalizations annually. Each hospitalization is de-identified and maintained in the NIS as a unique entry with one primary discharge diagnosis and up to 39 secondary diagnoses. Each entry carries patient demographics, including age, sex, race, insurance status, primary and secondary procedures (up to 25), hospitalization outcomes, total charges, and LOS. Since the data is de-identified and publicly available, this study did not require IRB approval.

Study population

Patients with a procedure code for TIPS were identified using the International Classification of Diseases, Clinical Modification-10th Revision (ICD-10-CM). We excluded patients who were missing data on demographics (n=830) and mortality(n=0) from the analysis and those less than 18 years of age (n=70). Patients were stratified into two groups - frail and non-frail, based on HFRS scores. The inclusion flow diagram is presented in Figure 1.

Definition of frailty

Gilbert et al. developed HFRS using 109 ICD-10 codes, which were noted to be overrepresented in frail patients. Each ICD-10 code was awarded a specific value proportional to how strongly it predicted frailty. In their analysis, HFRS >5 was used to classify patients as frail. Scores below five were classified as non-frail. We used the same approach to classify patients.

Study Variables

Data were collected on patient demographics (age, gender, race, insurance status, and income quartile), hospital characteristics (region, hospital size, the location of the hospital, and teaching status), and etiologies of liver diseases (alcohol-related liver disease, hepatitis B, hepatitis C, and non-alcoholic steatohepatitis (NASH). Data were also collected regarding the common indications of TIPS (ascites, hepatorenal syndrome, variceal bleeding, and Budd Chiari syndrome), Elixhauser comorbidities, and Elixhauser comorbidity index (ECI). ECI is a well-validated index based on ICD 10-CM codes meant to be used in large administrative data to predict mortality and hospital resource use[25]. Information regarding common interventions such as esophagogastroduodenoscopy (EGD) and blood transfusion was also collected.

Study outcomes

The primary outcome assessed was the impact of frailty on inpatient mortality in patients undergoing TIPS. Secondary outcomes included non-home discharge, length of stay (LOS), post-procedural length of stay, and total hospitalization charges (THC). Post-procedural length of stay was calculated by subtracting the time to the procedure from LOS. Hospital charges are defined as the dollar amount a hospital charges for services before negotiating discounts with insurance companies.

Statistical analysis

Hospital-level discharge weights provided by NIS were used to generate national estimates. Categorical variables

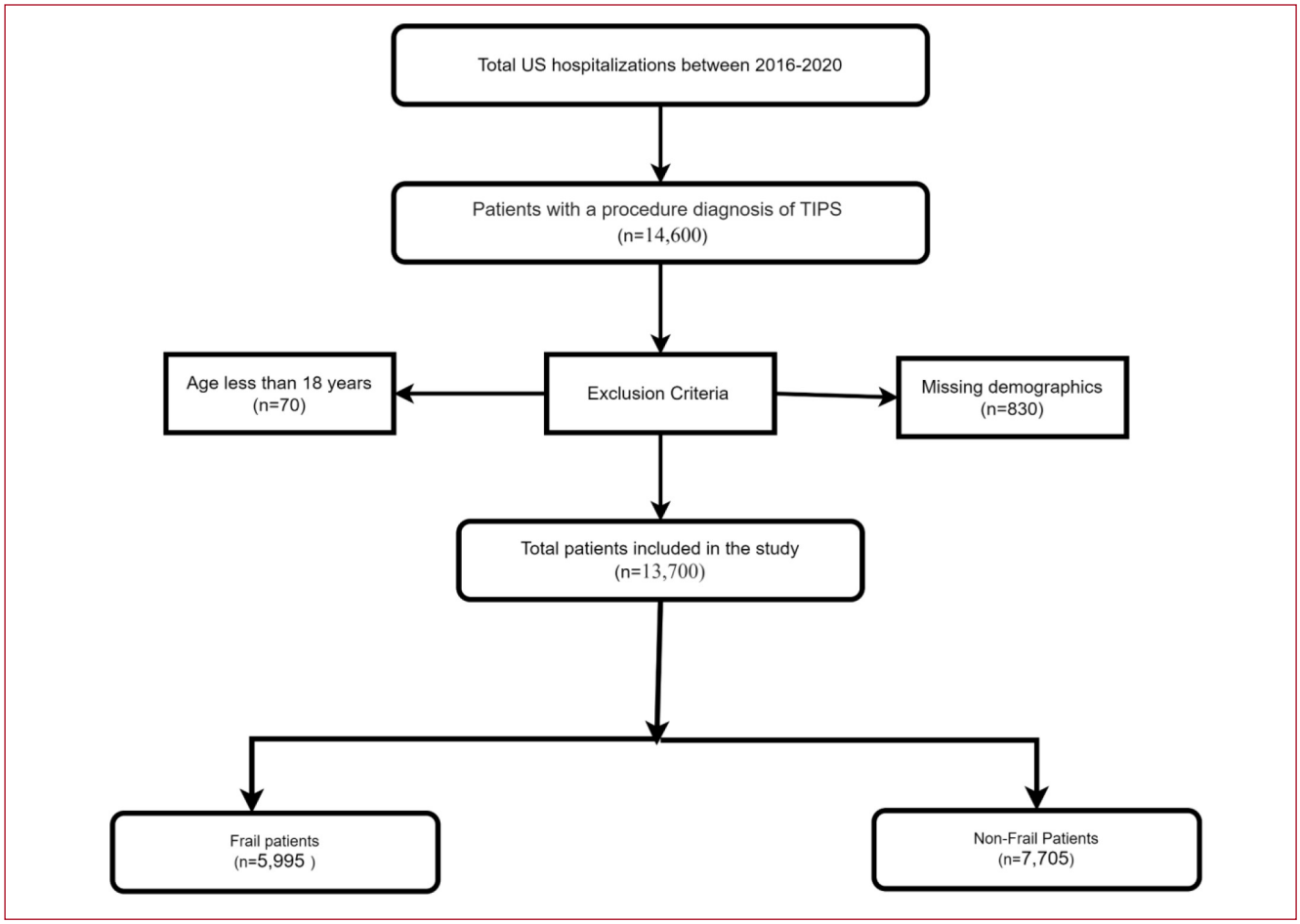

Figure 1. Inclusion flow diagram for the study population.

were compared using the chi-square, whereas an independent sample t-test was used for continuous variables. Logistic/ Linear regression analysis was used to identify the impact of frailty on outcomes in TIPS. Univariate logistic regression was done to identify the impact of variables on outcomes. A p-value of 0.1 was considered a cut-off to be included in the multivariate regression model. All the variables that met the criteria were included for multivariate logistic regression for categorical outcomes. Similarly, for continuous variables, univariate and multivariate linear regression was done. The unadjusted and adjusted odds ratio were calculated with a 95% confidence interval. A type I error of <0.05 was considered statistically significant. Data analysis was done using STATA 17.0 (Texas).

Results

A total of 13,700 patients were included in the analysis. Of those, 5,995 (43.76%) patients were frail, while 7,705 (56.24%) were non-frail.

Patient demographics

Majority of the patients in the frail group were aged between 45-64 years (57.3%), male (62.9%), White (71.5%), and had Medicare insurance (39.28%). There were no significant differences between the groups on gender, race, ace categories, insurance status, or income quartile. The results are presented in Table 1.

Etiology and complications of liver disease

The incidence of alcohol-related liver disease and NASH was higher in frail patients when compared to non-frail patients. Frail patients also had higher rates of ascites, variceal bleeding, spontaneous bacterial peritonitis (SBP), and hepatorenal syndrome than non-frail patients. A complete list of liver disease etiologies and decompensations of liver disease is present in Table 2.

Additional Comorbidities and interventions

Frail patients were noted to have a higher incidence of

Table 1. Patient characteristics, stratified by frailty.

	Low Frailty score n(%)	High Frailty Score n(%)	P-Value
Mean Age	57.2 (+/- 0.3)	57.9 (+/-0.35)	0.169
Age categories			0.31
18-45	1,100 (14.3)	765 (12.8)	
45-65	4,465 (58)	3,435 (57.3)	
>65	2,140 (27.8)	1,795 (30)	
Sex			0.78
Male	4,805 (62.4)	3,770 (62.9)	
Female	2,900 (37.6)	2,225 (37.1)	
Race			0.52
White	5,515 (71.6)	4,285 (71.5)	
African American	265 (3.4)	295 (4.9)	
Hispanic	1,400 (18.2)	1,010 (16.9)	
Asian/Pacific islander	155 (2.01)	125 (2.1)	
Native American	125 (1.62)	95 (1.6)	
Other	245 (3.1)	185 (3.1)	
Insurance			0.72
Medicare	2,950 (38.29%)	2,355 (39.28%)	
Medicaid	1,885 (24.46%)	1,555 (25.94%)	
Private	2,235 (29.01%)	1,585 (26.44%)	
Uninsured	370 (4.80%)	295 (4.92%)	
Income			0.19
Lowest quartile	2,435 (31.6)	2,115 (35.3)	
Second quartile	2,065 (26.8)	1,495 (24.9)	
Third quartile	1,855 (24.1)	1,335 (22.3)	
Highest quartile	1,350 (17.5)	1,050 (17.5)	
Region			0.83
Northeast	1,320 (17.1)	1,075 (17.9)	
Midwest	1,590 (20.6)	1,205 (20.1)	
South	3,075 (39.9)	2,455 (41)	
West	1,720 (22.3)	1,260 (21)	
Hospital Location			**0.02**
Rural	125 (1.6)	40 (0.67)	
Urban	7,580 (98.4)	5,955 (99.3)	
Teaching status			0.68
Non-Teaching	750 (9.7)	615 (10.3)	
Teaching	6,955 (90.3)	5,380 (89.7)	
Hospital bed size			**0.03**
Small	510 (6.6)	480 (8)	
Medium	1,485 (19.3)	1,360 (22.7)	
Large	5,710 (74.1)	4,155 (69.3)	
Elixhauser comorbidities			**<0.001**
0	15 (0.2%)	0	
1	325 (4.21%)	15 (0.25%)	
2	960 (12.46%)	80 (1.33%)	
3 or more	6,405 (83.13%)	5,900 (98.42%)	

Etiology of liver disease	Low Frailty score n(%)	High Frailty Score n(%)	P-Value
NASH	1,775 (13)	1,125 (18.8)	**0.01**
Alcohol-related liver disease	3,400 (44.1)	3,330 (55.6)	**<0.001**
Hepatitis B	165 (2.1)	110 (1.8)	0.55
Hepatitis C	650 (8.4)	500 (8.4)	0.92
Budd Chiari syndrome	125 (1.6)	65 (1.1)	0.24
Complications of liver disease			
Ascites	4,935 (64.1)	4,255 (71)	**<0.001**
Variceal bleeding	2,040 (26.48)	2,545 (42.5)	**<0.001**
Hepatorenal syndrome (HRS)	140 (1.8)	710 (11.8)	**<0.001**
Spontaneous bacterial peritonitis (SBP)	105 (1.4)	385 (6.4)	**<0.001**
Hepatic encephalopathy	230 (3)	775 (12.9)	**<0.001**

Table 2. Etiology and complications of liver disease, stratified by frailty.

cardiac arrhythmias (11.1% vs. 7.6%,p-0.002), congestive heart failure (19.9% vs. 10%,p-<0.001), paralysis (0.6% vs. 0.1%, p-0.04), other neurological disorders (19% vs. 4.9%, p<0.001), renal failure (23.9% vs. 11.2%, p<0.001), and coagulopathy (64.2% vs. 40.8%, p<0.001) than non-frail patients. More than 80% of frail patients had fluid and electrolyte disorders. There was no statistically significant difference between the two groups in the incidence of obesity or cancer. The results of additional comorbidities are presented in supplementary Table 2. There was a higher incidence of additional interventions in frail patients than in non-frail patients. Frail patients had a higher incidence of blood transfusion (33.3% vs. 20.3%, p<0.001) and esophagogastroduodenoscopy (44.3% vs. 27.06%, p<0.001).

Outcomes

1. **In-hospital mortality** - Total in-hospital mortality in the study population was 1,070 (7.8%). The mortality in non-frail patients was 160 (3.1%) compared to 910 (15.2%) in non-frail patients. There was a statistically significantly higher mortality risk than in non-frail patients (aOR-3.22, p<0.001). The results of the multivariate regression model are presented in Table 3.
2. **Shock following the procedure** - There were 200 (1.5%) patients who developed shock following the procedure. 155 (2.6%) frail patients and 45 (0.58%) non-frail patients developed shock following the procedure. Although no statistically significant association was noted, a trend towards a higher risk of shock in frail patients was noted (aOR-2.43, p-0.07).
3. **Non-routine discharge** - A total of 4,670 (34.1%) patients had non-routine discharge. 3,200 frail patients and 1,470 non-frail patients had a non-routine discharge. The data regarding their disposition is presented in supplementary Table 2. After adjusting for confounding factors, frail patients had higher odds of non-routine discharge (aOR- 2.37, p<0.001).
4. **Length of stay (LOS)** - The mean LOS in frail patients was 12.52 (+/-0.38) days compared to 5.36 (+/-0.17) in non-frail patients. Frail patients were noted to have statistically significant longer LOS after adjusting for confounding factors (adj. coefficient- 3.13 days, p<0.001).
5. **Post-procedural LOS** - The mean post-procedural LOS in frail patients was 8.23 (+/- 0.3) compared to 3.43 (+/-0.12) in non-frail patients. Frail patients were also noted to have statistically significant longer post-procedural LOS after adjusting for confounding factors (adj. coefficient-2.01 days, p<0.001).
6. **Total hospitalization charges** - The mean total hospitalization charge in frail patients was 240,746.7 (+/-7749.23) compared to121,763.1 (+/-3439.25) in non-frail patients. Frail patients were also noted to have statistically significant higher total hospitalization charges after adjusting for confounding factors (adj. coefficient- $ 51,458.15, p<0.001).

Discussion

Frailty has become an increasingly relevant topic and has been shown to predict clinical outcomes, especially in chronic liver disease[26,27]. Our study systematically investigated the impact of frailty using HFRS as a tool to predict outcomes in patients undergoing TIPS. Using nationally representative data from 13,700 patients undergoing TIPS, we found that HFRS is associated with higher in-hospital mortality and resource utilization.

Patients undergoing TIPS procedures are at an inherently higher risk of mortality, given the underlying conditions necessitating TIPS placement. Mortality in patients

Categorical outcomes	Adjusted Odds Ratio	P- value	95% Confidence Interval
In-hospital mortality	3.22	**<0.001**	2.03-5.10
Non-routine discharge	2.37	**<0.001**	1.90-2.96
Post-procedure shock	2.43	0.070	0.93-6.37
Continuous outcomes	**Adjusted Coefficient**	**p-value**	**95% Confidence Interval**
Length of stay	3.13	**<0.001**	2.38-3.89
Total charges	51,458.15	**<0.001**	38372.02-65439.1
Post-procedural LOS	2.07	**<0.001**	1.48-2.76

Table 3. Results of the multivariate regression model in outcomes in patients undergoing TIPS, stratified by frailty.

undergoing TIPS between 1995 and 2012 was 12.3%. The mortality decreased from 13.5% before 2005 to 11.5% in 2013[28]. In our study using nationally representative data between 2016-2020, there was a 7% overall in-hospital mortality, likely reflecting improved post-procedural care and patient selection compared to earlier years.

Mahmud et al., in their study of 804 patients with cirrhosis undergoing non-transplant major surgery, reported that frailty, defined by HFRS, was associated with poor postoperative survival compared to non-frail patients[26]. Klein et al. reported frailty criteria such as unintended weight loss and low hand grip strength as prognostic factors for survival after liver transplantation[27]. Lai et al. measured frailty using Liver Frailty Index (LFI), using three performance-based tests (grip, chair stands, and balance)[29]. They reported that combining LFI with the subjective clinician assessment was more likely to predict waitlist mortality than either score alone. Mahmoud et al. reported frailty (measured by psoas muscle density) to be associated with mortality in cirrhotic patients undergoing TIPS[30]. In their study, frailty was associated with increased mortality when the patients had a mean follow-up of 29.9 months (+/-34.1)[30]. Our study provides insight that not only the long-term mortality is increased, but immediate survival is also worse in frail patients. In our study, non-frail patients undergoing TIPS procedures had 2.1% in-hospital mortality compared to 15% in frail patients. After adjusting for confounding factors, frail patients, defined by high HFRS, were at a 3.22 times higher mortality risk than non-frail patients. Our findings, combined with the above-mentioned prior results, support the need to incorporate frailty as a risk-stratification tool in patients with chronic liver disease undergoing invasive interventions. HFRS was initially developed to evaluate outcomes in elderly patients, however recent studies have noted its utility in evaluating outcomes among younger patients[19].

Goh et al., in their study of 189 patients, reported frailty, as measured by short physical performance battery (SPPB), to be associated with longer postoperative intensive care (ICU) stay and higher 30-day complication rates[31]. Another study by Spoletini et al. reported that the pre-transplant CONUT score, calculated using serum albumin, cholesterol levels, and lymphocyte count, is an independent risk factor for a complicated post-LT course[32]. This score was developed to measure frailty in elderly patients and is beneficial in predicting the course after surgical procedures. In our study, the trend toward a higher risk of post-procedural shock was noted in frail patients, although these findings did not reach statistical significance (2.6% of frail patients versus 0.6% in non-frail patients, p=0.07). A higher post-procedural length of stay was also noted in the frail group compared to non-frail patients. Our findings support prior studies and emphasize that frailty predicts post-procedural adverse outcomes.

In our study, frail patients had $51,458 higher hospitalization charges and 3.13 days longer LOS than non-frail patients. This could be attributed to higher severity as evidenced by a higher incidence of decompensations and additional interventions, such as endoscopy and blood transfusion in frail patients. Furthermore, higher rates of post-procedural shock and care coordination required for a non-routine discharge in frail patients might also contribute to higher resource utilization. Our results align with the findings of a cross-sectional study in Germany, which concluded that the mean total 3-month cost of care of frail patients (€1616 - €3659) was more than non-frail patients (€642)[33]. An Italian 3-year observational cohort study established frailty, determined by CFS score, as an independent risk factor for not being discharged home[34]. They reported that patients in the "moderate-severe" frailty and "very severe" frailty groups had an increased likelihood of being discharged somewhere other than home by five-fold and six-fold, respectively. Our findings and previous studies emphasize that frailty is predictive of increased resource utilization without clear evidence of improved survival or other health outcomes.

We acknowledge that our study has several limitations. Our study relies on a large national database and is subject to observational data limitations. The NIS database does not include information required for physical assessment of frailty. Since the data only contains information on acute hospitalization episodes, we cannot follow patients

longitudinally and track readmissions; therefore, we cannot calculate 30-day and 90-day mortality. We did not stratify the patient based on their transplant or pregnancy status as the proportion of these patients was relatively lower. Additionally, the NIS database lacks variables needed to calculate prognostic scores, such as the MELD score or the Child-Pugh class. To account for this limitation, we used decompensations of liver disease as surrogate markers of severity. Since the data relies on ICD-10 codes, the possibility of miscoding errors could not be ruled out. To account for this limitation, we used ICD-10 codes that have been validated in prior studies[35-37]. The strengths of our study include the large patient size from across the country, which limits selection bias.

Conclusion

Our study reported a strong association between frailty and adverse outcomes such as higher in-hospital mortality and resource utilization in patients undergoing TIPS. Since HFRS is an administrative score that can be cumbersome to use in clinical practice, we recommend that physicians use other user-friendly scores, such as the liver frailty index, to risk-stratify patients. We believe there is an urgent need to incorporate frailty into the pre-procedural risk assessment in patients undergoing TIPS. The objective assessment of frailty may help physicians, patients and families to engage in joint decision-making prior to proceeding with TIPS or other potentially high risk procedures and patients with advanced liver disease.

Authors' contributions

Aalam Sohal, Hunza Chaudhry, Isha Kohli, Kirti Arora, Jay Patel, Nimrat Dhillon, Ishandeep Singh and Dino Dukovic planned the study, reviewed the literature, drafted the manuscript, revised it for important intellectual content, and were involved in the final approval of the version to be published. Marina Roytman revised the article for important intellectual content and was involved in the final approval of the version to be published. Aalam Sohal accepts responsibility for the integrity of data analysis.

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Supplementary Table 1. ICD-10 codes used in the study.

Complications of liver disease	
Bleeding Varices	I85.01, I85.11
Spotaneous Bacterial Peritonitis	K65.2
Ascites	R18, K71.51, K70.11, K70.31
Hepaticencephalopathy	K7211, K7291, G934
Hepatorenal Syndrome	K76.7
Liver Etiology	
Hepatitis C	B17.1, B18.2, B19.2
NASH	K75.81, K76.0
Hepatitis B	B19.1, B16 , B18.1,B18.0
Budd-Chiari Syndrome	I820
Procedures	
Endoscopy	0D917ZX,0D917ZX,0D918ZX,0D927ZX,0D928ZX,0D937ZX,0D938ZX,0D947ZX,0D948ZX, 0D957ZX,0D958ZX,0D967ZX,0D968ZX,0D977ZX,0D978ZX,0D987ZX,0D988ZX,0D997ZX, 0D938ZX,0D998ZX,0D9A7ZX,0D9A8ZX,0D9B7ZX,0D9B8ZX,0D9C4ZX,0D9C7ZX,0D9C8ZX», 0DB17ZX,0DB18ZX,0DB27ZX,0DB28ZX,0DB37ZX,0DB38ZX,0DB47ZX,0DB48ZX,0DB57ZX, 0DB58ZX,0DB67ZX,0DB68ZX,0DB77ZX,0DB78ZX,0DB97ZX,0DB98ZX,0DD18ZX,0DD28ZX, 0DD38ZX,0DD48ZX,0DD58ZX,0DD68ZX,0DD78ZX,0DD98ZX,0DDA8ZX,0DDB8ZX,0DDC8ZX, 0DJ08ZZ,0DJ68ZZ,06L34CZ,06L38CZ
TIPS	06183J4, 06184J4,06183JY,06183DY
Pressor	3E030XZ,3E033XZ,3E040XZ,3E043XZ,3E050XZ,3E053XZ,3E060XZ,3E063XZ
Mechanical Ventilation	5A1935Z, 5A1945Z, 5A1955Z
ICU	Pressor + Mechanical Ventilation
Co-morbidity	**ICD 10 code**
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, 142.5-I42.9, I43.x, I50.x, P29.0
Cardiac arrhythmias	I44.1-I44.3, I45.6, I45.9, I47.x-I49.x, R00.0, R00.1, R00.8, T82.1, Z45.0, Z95.0
Valvular disease	A52.0, I05.x-I08.x, I09.1, I09.8, I34.x-I39.x, Q23.0Q23.3, Z95.2, Z95.4
Pulmonary circulation Disorders	I26.x, I27.x, I28.0, I28.8, I28.9
Peripheral vascular disorders	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Hypertension, uncomplicated	I10.x
Hypertension, complicated	I11.x-I13.x, I15.x
Paralysis	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9
Other neurological disorders	G10.x-G 13.x, G20.xG22.x, G25.4, G25.5, G31.2, G31.8, G31.9, G32.x, G35.x-G37.x, G40.x, G41.x, G93.1, G93.4, R47.0, R56.x
Chronic pulmonary disease	I27.8, 127.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
Diabetes, uncomplicated	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9, E12.0, E12.1, E12.9, E13.0, E13.1, E13.9, E14.0, E14.1, E14.9
Diabetes, complicated	E10.2-E10.8, E11.2-E11.8, E12.2E12.8, E14.2-E14.8 E13.2-E13.8,
Hypothyroidism	E00.x-E03.x, E89.0
Renal failure	I12.0, I13.1, N18.x, NI9.x, N25.0, Z94.0,Z49.0-Z49.2,
Liver disease	B18.x, I85.x, I86.4, I98.2, K70.x, K71.1, K71.3K71.5, K71.7, K72.xK74.x, K76.0, K76.2K76.9. Z94.4
Peptic ulcer disease excluding bleeding	K25.7, K25.9, K26.7, K26.9, K27.7, K27.9, K28.7, K28.9
AIDS/HIV	B20.x-B22.x, B24.x
Lymphoma	C81.x-C85.x, C88.x, C96.x, C90.0, C90.2
Metastatic cancer	C77.x-C80.x
Solid tumor without metastasis	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C97.x

Supplementary Table 1. *(Cont. from previous page)*

Rheumatoid arthritis/ collagen vascular diseases	L94.0, L94.1, L94.3, M05.x, M06.x, M08.x, M12.0, M12.3, M30.x, M31.0-M31.3, M32.x-M35.x, M45.x, M46.1, M46.8, M46.9
Coagulopathy	D65-D68.x, D69.1, D69.3-D69.6
Obesity	E66.x
Weight loss	E40.x-E46.x, R63.4, R64
Fluid and electrolyte disorders	E22.2, E86.x, E87.x
Blood loss anemia	D50.0
Deficiency anemia	D50.8, D50.9, D51.x-D53.x
Alcohol abuse	F10, E52, G62.1, I42.6, K29.2, K70.0, K70.3, K70.9, T51.x, Z50.2, Z71.4, Z72.1
Drug abuse	F11.x-F16.x, F18.x, F19.x, Z71.5. Z72.2
Psychoses	F20.x, F22.x-F25.x, F28.x, F29.x, F30.2, F31.2, F31.5
Depression	F20.4, F31.3-F31.5, F32.x, F33.x, F34.1, F41.2, F43.2

Supplementary Table 2. Elixhauser comorbidities, stratified by frailty.

Comorbidities	Low Frailty score n(%)	High Frailty Score n(%)	p-value
Cardiac arrhythmias	770 (10)	1,190 (19.9)	**<0.001**
Congestive heart failure	585 (7.6)	665 (11.1)	**0.002**
Valvular disease	240 (3.1)	175 (2.9)	0.78
Pulmonary circulation disorder	260 (3.4)	245 (4.1)	0.31
Peripheral vascular disease	250 (3.2)	255 (4.3)	0.17
Hypertension, uncomplicated	2,685 (34.9)	1,705 (28.4)	**<0.001**
Paralysis	10 (0.1)	35 (0.6)	**0.04**
Other neurological disorders	380 (4.9)	1,140 (19)	**<0.001**
Chronic pulmonary disease	1,160 (15.1)	925 (15.4)	0.78
Diabetes, uncomplicated	1,580 (20.5)	805 (13.4)	**<0.001**
Diabetes, complicated	1,365 (17.7)	1,420 (23.7)	**<0.001**
Hypothyroidism	940 (12.2)	705 (11.8)	0.73
Renal failure	860 (11.2)	1,435 (23.9)	**<0.001**
Peptic ulcer disease, excluding bleeding	155 (2)	140 (2.3)	0.57
AIDS/HIV	30 (0.4)	30 (0.5)	0.66
Lymphoma	55 (0.7)	30 (0.5)	0.48
Metastatic cancer	100 (1.3)	65 (1.1)	0.59
Solid tumor (without metastasis)	485 (6.3)	365 (6.1)	0.82
Rheumatoid arthritis/collagen vascular disease	180 (2.3)	135 (2.3)	0.88
Coagulopathy	3,140 (40.8)	3,850 (64.2)	**<0.001**
Obesity	1,255 (16.3)	965 (16.1)	0.9
Malnutrition	870 (11.3)	1,625 (27.1)	**<0.001**
Fluid and electrocyte disorder	1,730 (22.5)	5,020 (83.7)	**<0.001**
Blood loss anemia	275 (3.6)	200 (3.3)	0.74
Deficiency anemia	500 (6.5)	400 (6.7)	0.85
Alcohol abuse	3,495 (45.4)	3,455 (57.6)	**<0.001**
Drug abuse	360 (4.7)	385 (6.4)	0.04
Psychoses	65 (0.8)	70 (1.2)	0.39
Depression	940 (1.2)	920 (15.4)	0.02
Hypertension, complicated	935 (12.1)	1,275 (21.3)	**<0.001**