Journal of Clinical and Translational Hepatology **2024**
DOI: 10.14218/JCTH.2023.00554

Research Letter

Transjugular Intrahepatic Portosystemic Shunt Linked to Increased Risk of Hepatocellular Carcinoma: A VA Matched Cohort Study

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Received: 14 December 2023 | **Revised:** 1 February 2024 | **Accepted:** 9 February 2024 | **Published online:** 8 April, 2024

Citation of this article: Bansal S, Taddei T, Wells R, Serper M, Bittermann T, Mahmud N, *et al*. Transjugular Intrahepatic Portosystemic Shunt Linked to Increased Risk of Hepatocellular Carcinoma: A VA Matched Cohort Study. J Clin Transl Hepatol 2024. doi: 10.14218/JCTH.2023.00554.

Hepatocellular carcinoma (HCC) is the most common primary tumor of the liver and often evolves from regenerating nodules in liver cirrhosis. While there have been significant advances in the treatment of HCC, the overall prognosis in patients with a large tumor burden, vascular invasion, or extrahepatic spread remains poor.[1] The magnitude of liver stiffness in cirrhosis has been consistently associated with an increased risk of development of HCC.[2] While liver stiffness partially results from highly cross-linked collagen,[3] increased vascular pressure within the intrahepatic sinusoids due to portal hypertension appears to be the more dominant driver of stiffness *in vivo*.[4] In animal models, transjugular intrahepatic portosystemic shunt (TIPS) creation, by diverting portal vein inflow from sinusoids and reducing intra-acinar pressure, rapidly decreases liver stiffness.[5] Therefore, if stiffness were a primary driver of carcinogenesis, TIPS might be expected to reduce the risk of HCC. In contrast, animal models with spontaneous portosystemic shunts are associated with an increased risk of HCC mediated by increased bacterial translocation, systemic bile acids, and Cox activation.[6] Few existing human studies have explored the clinical impact of TIPS on the risk of HCC. The objective of this study was to further explore the association between TIPS and HCC risk in a large, well-characterized cirrhosis cohort.

This was a retrospective Institutional Review Board-approved (Approval #01399) cohort study of patients with cirrhosis who underwent TIPS in the Veterans Outcomes and Cost Associated with Liver Disease (VOCAL) cohort between 2008 and 2021. The VOCAL cohort includes representative data from 49 of the 50 states and territories and has been used in numerous studies relating to chronic liver disease as well as healthcare utilization.

Patients with TIPS were propensity matched by a Mahalanobis distance of 1:4 with non-TIPS controls using the following demographics: clinical and biological data, including age, sex, etiology of liver disease, indication for TIPS placement, FIB-4 score, number of large-volume paracenteses (LVP) in the prior 6 months, selective and nonselective beta-blocker use, statin use, aspirin use, platelet count, time since hepatitis C virus cure, hazardous alcohol use, model for end-stage liver disease-sodium score, and Child-Turcotte-Pugh class (Table 1). For the TIPS patients, follow-up began at the time of their procedure. For the non-TIPS patients, follow-up began at the time of optimal risk-set matching to TIPS cases.

Kaplan-Meier analysis and Cox proportional hazards regression with death treated as a competing risk were performed to determine the association between TIPS and incident of HCC diagnosis. Observations were right-censored at death, transplant, or maximum follow-up. Those with a history of HCC prior to TIPS were excluded from the study.

To account for the potential ascertainment bias of HCC due to differential surveillance rates, we compared the percentage of days up-to-date with this screening (referred to herein as PTUDS)[7] across cases and controls using Wilcoxon rank sum test.

A total of 1,482 patients who underwent TIPS were matched with 5,928 non-TIPS controls. Excellent matching was achieved, as demonstrated by an absolute standardized mean difference of <0.1 for each covariate (Fig. 1). The cohort had a median age 61.6 years and 97.5% were men with an average of 0.47 LVPs in the 6 months prior to the index date. TIPS was primarily performed for variceal hemorrhage.

Of the patients who underwent TIPS, 167 (11.3%) developed HCC compared to 297 (5.0%) controls through 5 years of maximum follow-up, with a median follow-up time of 708 (239, 1,439) days in the patients who underwent TIPS and 854 (381, 1,695) days in the controls. In Cox regression

Abbreviations: FIB4, Fibrosis-4 Index for Liver Fibrosis; HCC, hepatocellular carcinoma; LVP, large volume paracentesis; TIPS, transjugular intrahepatic portosystemic shunt; VOCAL, Veterans Outcomes and Cost Associated with Liver Disease; PTUDS, percentage time up-to-date with liver cancer surveillance.

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Table 1. Demographic Information for TIPS and non-TIPS Patients

Variables	TIPS, *n*=1,482	Non-TIPS, *n*=5,928	*p*-value	SMD
Age in years, mean [SD]	61.4 [56.0, 66.2]	61.8 [56.9, 66.4]	0.007	0.11
Male sex, *n* (%)	1,442 (97.3)	5,778 (97.5)	0.78	0.01
Race, *n* (%)			0.89	0.03
White	1,111 (75.0)	4,467 (75.4)		
Black	85 (5.7)	371 (6.3)		
Hispanic	119 (8.0)	449 (7.6)		
Asian	12 (0.8)	44 (0.7)		
Other	155 (10.5)	597 (10.3)		
Etiology, *n* (%)			1.00	0.01
EtOH	711 (48.0)	2,855 (48.2)		
EtOH + HCV	356 (24.0)	1,435 (24.2)		
HCV	110 (7.4)	436 (7.4)		
HBV	14 (0.9)	56 (0.9)		
MAFLD/MASH	248 (16.7)	977 (16.5)		
Cryptogenic	19 (1.3)	76 (1.3)		
Other	24 (1.6)	93 (1.6)		
BMI, median [IQR]	27.9 [24.7, 32.4]	27.8 [24.1, 31.6]	0.27	0.07
AUDIT-C, mean [SD]	0.16 [0.37]	0.16 [0.37]	1.00	<0.001
Ascites-CTP subscore, *n* (%)			0.99	0.004
None	741 (50.0)	2,954 (49.8)		
Mild	515 (34.8)	2,071 (34.9)		
Severe	226 (15.2)	903 (15.2)		
HE - CTP subscore, *n* (%)			0.98	0.006
None	1,306 (88.1)	5,235 (88.3)		
Mild	155 (10.5)	610 (10.3)		
Severe	21 (1.4)	83 (1.4)		
Prior SBP=yes, *n* (%)	127 (8.6)	509 (8.6)	1.00	0.001
Large-volume paracentesis within prior 6 months, *n* (%)			0.99	0.11
0	1,393 (94.0)	5,593 (94.3)		
1–5	40 (2.7)	140 (2.5)		
6–10	27 (1.9)	39 (0.6)		
11–15	10 (0.8)	39 (0.6)		
16–20	5 (0.3)	21 (0.3)		
21–25	5 (0.4)	20 (0.4)		
26–30	1 (0.1)	4 (0.1)		
>31	1 (0.1)	4 (0.0)		
MELD-Na score, median [IQR]	13 [9, 19]	12 [9, 18]	<0.001	0.11
Total bilirubin, median [IQR]	1.4 [0.9, 2.1]	1.3 [0.8, 2.0]	0.001	0.06
Serum albumin, median [IQR]	3.0 [2.6, 3.4]		< 0.001	0.03
INR, median [IQR]	1.3 [1.2, 1.5]	1.37 (0.7)	< 0.001	0.05
Creatinine in mg/dL, median [IQR]	1.0 [0.8, 1.4]	3.69 (10.5)	0.007	0.03
Platelets, median [IQR]	108 [76, 155]	124 (63.2)	0.16	0.008

(continued)

Table 1. *(continued)*

Variables	TIPS, *n*=1,482	Non-TIPS, *n*=5,928	*p*-value	SMD
Active HCV infection (yes), *n* (%)	296 (20.0)	1,173 (19.8)	0.90	0.005
Treated HCV infection (yes), *n* (%)	21 (1.4)	82 (1.4)	0.07	0.06
Medication days within prior 6 months, *n* (median days [IQR])				
Ascites – distal diuretics	79 [0, 137]	72 [0, 131]	0.003	0.09
Ascites – loop diuretics	89.5 [0, 148]	87 [0, 142]	0.003	0.09
HBV direct acting antivirals	0 [0, 0]	0 [0, 0]	0.90	0.002
HCV direct acting antivirals	0 [0, 0]	0 [0, 0]	0.90	0.003
Dyslipidemia - statin	0 [0, 0]	0 [0, 0]	0.02	0.07
DM - insulin	0 [0, 0]	0 [0, 0]	0.001	0.09
DM - metformin	0 [0, 0]	0 [0, 0]	0.004	0.08
HE - lactulose	1 [0, 55]	0 [0, 48]	0.01	0.07
HE - rifaximin	0 [0, 0]	0 [0, 0]	0.11	0.05
HTN - ARB inhibitors	0 [0, 0]	0 [0, 0]	0.16	0.04
HTN - ACE inhibitors	0 [0, 0]	0 [0, 0]	0.04	0.06
HTN - nonselective beta blockers, *n* (%)	0 [0, 106]	0 [0, 90]	<0.001	0.11
PTUDS with HCC screening, median % [IQR]	16 [0, 85]	0 [0, 57]	<0.001	0.26

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; AUDIT-C, Alcohol Use Disorders Identification Test - Consumption; BMI, body mass index; CTP, Child-Turcotte Pugh; DM, diabetes mellitus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HE, hepatic encephalopathy; HTN, hypertension; INR, international normalized ratio; IQR, interquartile range; MASLD, metabolic dysfunction-associated steatotic liver disease; MASH, metabolic dysfunction-associated steatohepatitis; MELD-Na, model for end-stage liver disease-sodium; SBP, spontaneous bacterial peritonitis, SD, standard deviation; SMD, standardized mean difference.

models, TIPS was associated with a 26% increased hazard of HCC development [hazard ratio 1.26, (95% confidence interval: 1.06–1.50), p=0.007; Fig. 2]. There was modestly higher PTUDS in TIPS cases (16% vs. 0%, p<0.0001), a bias unlikely to account for the observed increased hazard rate.

In this large cohort of Veterans with cirrhosis matched for key potential confounders, placement of TIPS was associated with a statistically significant increased risk of HCC development. These data stand in contradiction to a previous smaller study[8] and a meta-analysis[9] that did not show an increased risk of HCC post-TIPS. For example, in the 2014 retrospective case-control study[8] that followed patients who received TIPS vs. those who did not, there was no association between TIPS and the development of HCC. Our findings also contradict the results of a 2023 study of liver transplant patients that found no difference in HCC incidence in a pretransplant TIPS population.[10] However, the median duration of follow-up in that study was less than 1 year, whereas we found the median time to HCC was 708 days (1.94 years). It is possible that the negative findings from that study could have resulted from the shorter observation time following TIPS. In a 2015 retrospective study of histopathological data comparing 68 explants from patients who underwent TIPS compared with 146 non-TIPS explants, an increased frequency of liver dysplasia was associated with the presence of TIPS but not HCC.[11] It is important to note that all prior studies have been limited by relatively small sample sizes, short follow-up periods, or the inability to control for complex confounders. Our study, which includes the largest cohort of patients studied thus far, excellent cohort matching, and long-term follow-up sheds new light on this potential and concerning association.

These findings have several important clinical implications. Although the vast majority of patients received TIPS for variceal hemorrhage, which is often needed on an emergency basis as opposed to TIPS for the management of refractory ascites, counseling for the potentially increased risk of HCC may still need to be included in these discussions and perhaps consideration given to enhanced HCC. Lastly, better subset analyses and longer-term follow-up may provide greater insight into additional risk factors associated with HCC development after TIPS.

While the results of this study have significant clinical implications, there are several important limitations. First, the majority of patients were men, making the applicability for women less clear. This is inherent to the study population at the United States Veterans Administration hospitals. While a majority of these patients were also of White race, the representation of Black and Hispanic patients is higher than present in most liver disease datasets. Future studies could utilize matching methods and apply it to populations that include more women and other races. Second, TIPS was overwhelmingly performed for variceal bleeding; thus, its applicability to those receiving TIPS for refractory ascites is not certain. However, based on biological plausibility, similar results would be expected for diverse indications of TIPS. Third, despite extensive matching for the severity of liver disease, baseline liver stiffness via Fibroscan, histological grading, and duration of time with cirrhosis were not available. Many of the patients in this cohort were included in the VOCAL database before widespread use of Fibroscan in the USA, and few were biopsied to confirm a diagnosis of cirrhosis. Therefore, those who required TIPS may have had more advanced disease or other confounding factors that could not be accounted for in the matching process. From a mechanistic perspective, hemodynamic changes after TIPS, including increased hepatic arterial blood flow, may have led to increased oxidative stress and increased oxygen delivery, promoting carcinogenesis.[12]

In conclusion, in this large study of veterans with cirrhosis,

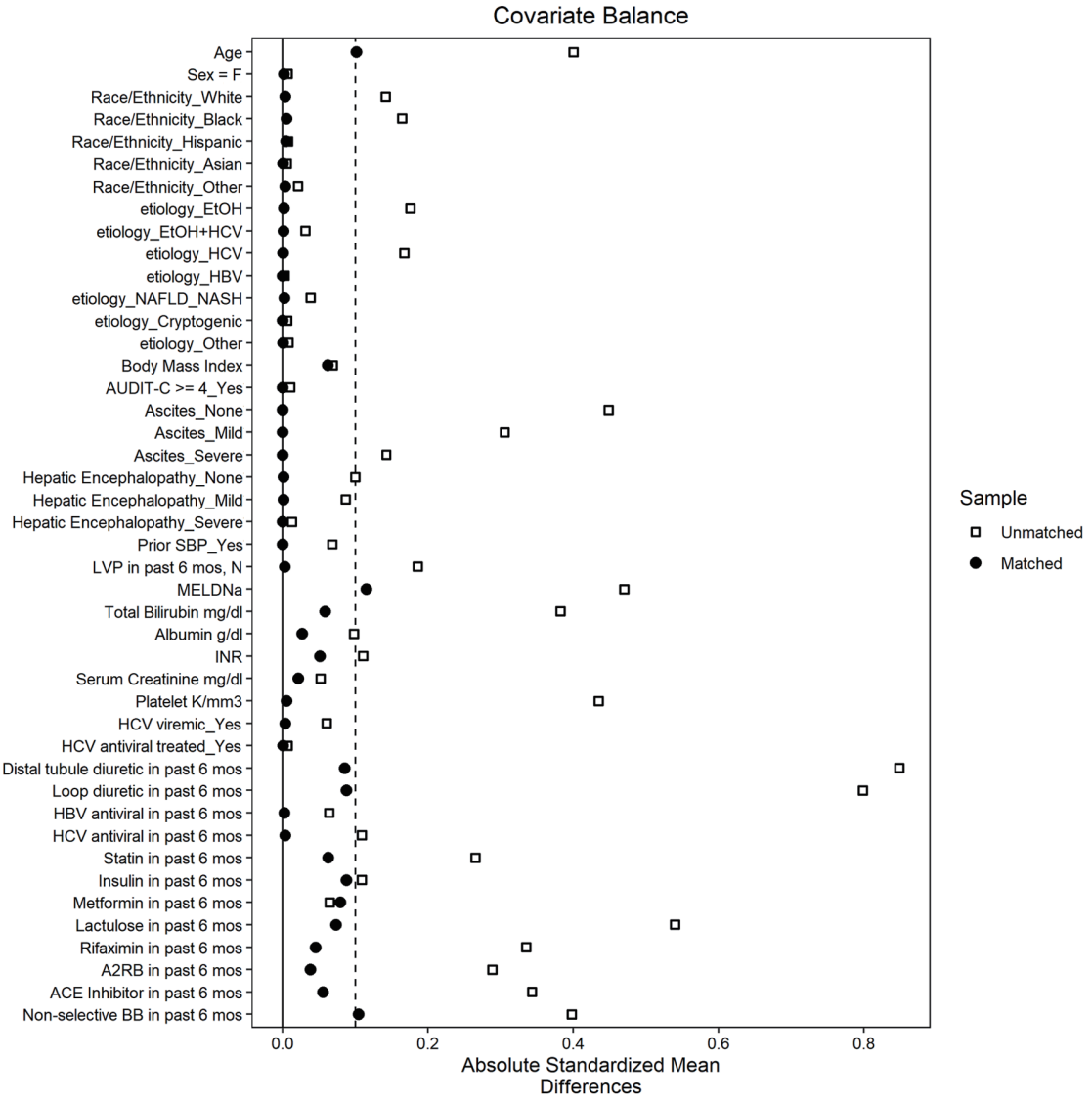

Fig. 1. Propensity Matching of TIPS and non-TIPS Patients. Standardized mean differences (SMD) comparing TIPS and non-TIPS patients before and after 1:4 propensity matching. Pre-matching differences are indicated by the circle while post-matching differences are indicated by the black square. The dotted line represents SMD<0.1. ACE, angiotensin-converting enzyme; HBV, hepatitis B virus; HCV, hepatitis C virus; LVP, large volume paracentesis; INR, international normalized ratio.

we found a significantly increased hazard of incidence of HCC in patients who received TIPS. Future studies should identify additional modifying risk factors for post-TIPS HCC and seek to clarify the underlying pathophysiology.

Funding

None to declare.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (DEK, SB, RW, TB, MS, TT, NM), acquisition of data (SB, DEK, TT), analysis and interpretation of data (DEK, SB, RW, TB, MS, TT, NM), drafting of the manuscript (SB, DEK), critical revision of the manuscript for important intellectual content (DEK, SB, RW, TB, MS, TT, NM), administrative, technical, or material support (TT, DEK), and study supervision (DEK). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

This study was carried out in accordance with the Helsinki Declaration as revised in 2013. The protocol was approved by the Institutional Review Board (Approval #01399). The individual consent for this retrospective analysis was waived.

Data sharing statement

No additional data are available.

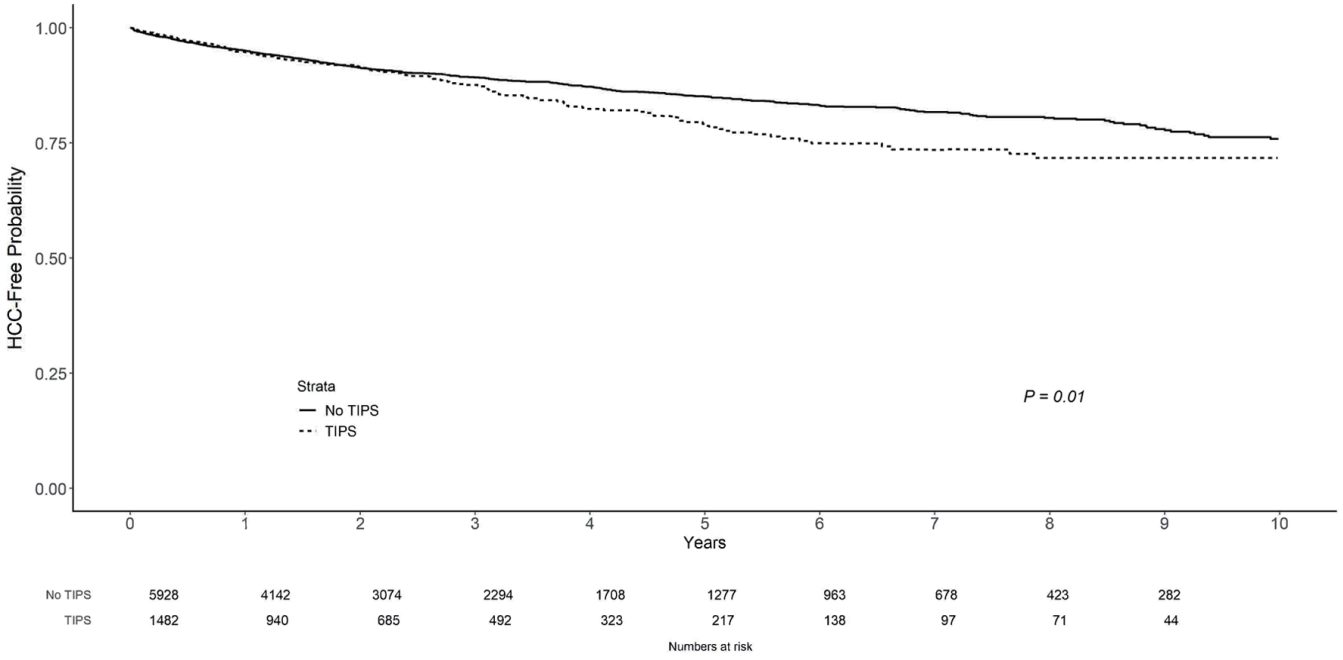

Fig. 2. Kaplan Meier Curve for HCC Incidence in TIPS vs. non-TIPS Patients. Kaplan-Meier curve showing HCC-free survival in patients who received TIPS (solid line) compared to those that did not receive TIPS (dotted line) over 10 years. HCC, hepatocellular carcinoma; TIPS, transjugular intrahepatic portosystemic shunt.

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