Heliyon 10 (2024) e23455

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Transjugular intrahepatic portosystemic shunt for the treatment of hepatic sinusoidal obstruction syndrome caused by pyrrolizidine alkaloids: A multicenter retrospective study

Chaoyang Wang [a,b,1], Yingliang Wang [a,b,1], Jianbo Zhao [c,1], Chongtu Yang [a,b,1], Xiaoli Zhu [d], Huanzhang Niu [e], Junhui Sun [f], Bin Xiong [a,b,g,*]

[a] Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 430022, China
[b] Hubei Province Key Laboratory of Molecular Imaging, Wuhan, 430022, China
[c] Department of Vascular and Interventional Radiology, Nanfang Hospital, Southern Medical University, Guangzhou, 510000, China
[d] Department of Interventional Radiology, The First Affiliated Hospital of Soochow University, Suzhou, 215000, China
[e] Department of Interventional Radiology, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, 471000, China
[f] Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhejiang University, Hangzhou, 310000, China
[g] Department of Interventional Radiology, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, 510000, China

ARTICLE INFO

Keywords:
Transjugular intrahepatic portosystemic shunt
Hepatic sinusoidal obstruction syndrome
Pyrrolizidine alkaloids
Multicenter

ABSTRACT

Purpose: To assess the impact of transjugular intrahepatic portosystemic shunt (TIPS) on clinical outcomes and liver histology in patients with hepatic sinusoidal obstruction syndrome (HSOS) caused by pyrrolizidine alkaloids (PA), and compare these results with those of patients who received supportive treatment alone.

Materials and methods: From June 2015 to August 2022, 164 patients diagnosed with PA-HSOS in six tertiary care centers were retrospectively included in this study and divided into TIPS group (n = 69) and supportive treatment (ST) group (n = 95). The main endpoint was to determine whether TIPS placement could improve survival in PA-HSOS patients. The clinical symptoms associated with portal hypertension were also evaluated in this study. Additionally, a small TIPS-subgroup of 7 patients received liver biopsies before and after TIPS for histological analysis.

Results: The incidence of death was markedly lower in the TIPS group than in the ST group (log-rank p = 0.026). Multivariate Cox model revealed that group assignment (hazard ratio (HR) 5.146; 95 % confidence interval (CI) 1.587–16.687; p = 0.006), total bilirubin (HR 1.029; 95 % CI 1.020–1.038; p < 0.001), and INR (HR 13.291; 95 % CI 3.637–48.566; p < 0.001) were independent predictors for mortality. In addition, TIPS placement reduced the risk of complications associated with portal hypertension but did not increase the rate of overt hepatic encephalopathy (log-rank p = 0.731). Furthermore, six of 7 TIPS patients receiving liver biopsies improved after TIPS placement, and one patient developed fibrosis.

* Corresponding author. Department of Radiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Jiefang Avenue #1277, Wuhan 430022, China. And Department of Interventional Radiology, The First Affiliated Hospital of Guangzhou Medical University, Jiangxi Avenue #151, Guangzhou, 510000, China.

E-mail addresses: jrkwzy@163.com (C. Wang), 18345197920@163.com (Y. Wang), zhaojianbohgl@163.com (J. Zhao), henrys1011@163.com (C. Yang), zhuxiaoli@163.com (X. Zhu), niuhuanzhangsci@sina.com (H. Niu), 1307005@zju.edu.cn (J. Sun), herr_xiong@126.com (B. Xiong).

[1] These authors contributed equally to this paper.

https://doi.org/10.1016/j.heliyon.2023.e23455
Received 12 May 2023; Received in revised form 4 December 2023; Accepted 4 December 2023
Available online 8 December 2023

Conclusions: TIPS placement decreased the mortality and risk of complications associated with portal hypertension. Histological evaluation in a few patients showed a potential improvement by TIPS.

1. Introduction

Hepatic sinusoidal obstruction syndrome (HSOS) is characterized by the injury of liver sinusoidal endothelial cells (LSECs), which detach from the vessel wall and block the outflow tract [1,2]. Subsequently, portal hypertension and hepatocyte apoptosis occur due to sinusoidal congestion. In Western countries, the primary cause of HSOS is hematopoietic stem cell transplantation (HSCT) [3–5]. While in China, HSOS is mostly caused by the ingestion of herbs containing pyrrolidine alkaloids (PA) [6–8]. And impaired liver function and refractory ascites are the main symptoms of PA-HSOS, but the clinical presentation may range from asymptomatic to liver failure [9, 10].

Anticoagulation, paracenteses, and albumin infusion are the major treatment for PA-HSOS. However, the mortality ranges from 22.2 % to 38.6 % with supportive treatment alone [11–13]. Previous studies have demonstrated that transjugular intrahepatic portosystemic shunt (TIPS) ameliorates portal hypertension and refractory ascites in PA-HSOS patients [14–16], but the long-term results and impact on survival remain unclear. And changes in the liver at the histological level have not been reported so far. As more and more such patients receive TIPS placement, a further investigation of these issues is necessary.

In this study, we aimed to assess the impact of TIPS on clinical outcomes and liver histology in PA-HSOS patients and compared these results with those of patients who received supportive treatment alone.

2. Materials and methods

2.1. Patients

Data from 199 patients diagnosed with HSOS between June 2015 and August 2022 in six tertiary care centers (Supplementary Table 1) were retrospectively collected. HSOS was diagnosed by medical history, clinical symptoms, laboratory tests, and imaging findings (Fig. 1A–D) according to EASL Clinical Practice Guidelines [1]. HSCT-induced HSOS was not included in this study. After excluding the patients with HBV/HCV infection (n = 12), malignant tumors (n = 6), severe active infection (n = 2), multiple organ failure (n = 4), and incomplete medical records (n = 9), 164 patients were enrolled for clinical analysis. And these patients were divided into TIPS group (n = 69) and supportive treatment (ST) group (n = 95) according to whether the patients underwent TIPS placement (Fig. 2).

This study was conducted according to the Declaration of Helsinki ethical principles and was approved by the ethics committee of Wuhan Union hospital (No. 20220264). Informed consent was obtained from the patients or their family for the publication of the

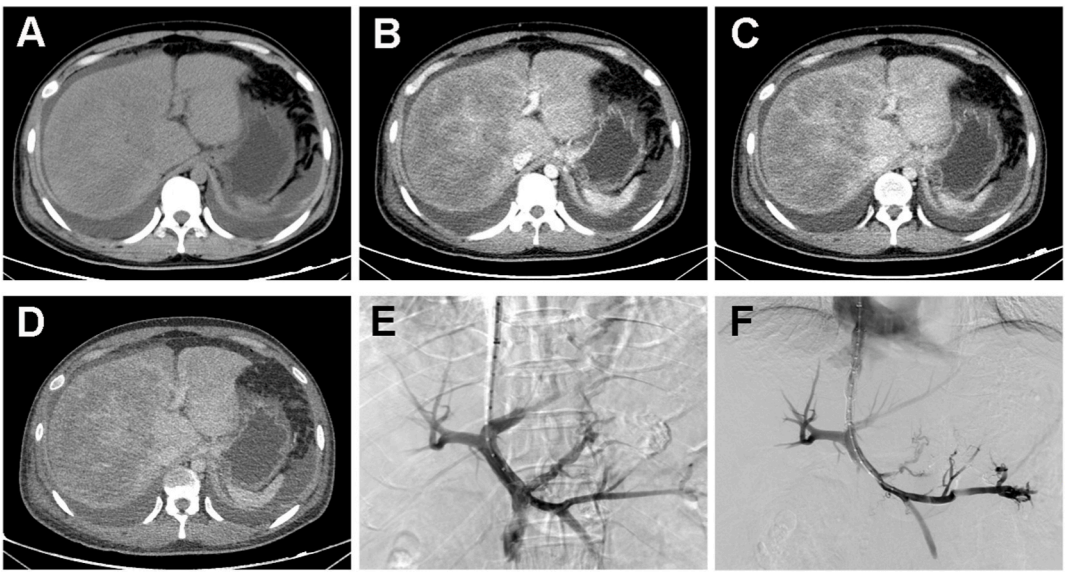

Fig. 1. A 55-year-old man diagnosed with HSOS with a history of ingestion of herbs containing PA. **A-D** Abdominal CT showed ascites, hepatomegaly, and heterogeneous enhancement. **A** Plain scan; **B** Arterial phase; **C** Portal phase; **D** Venous phase; **E** Portography before shunt creation; **F** Portography after shunt creation.

pictures associated with imaging and histology.

2.2. Treatment

For all patients, discontinuation of PA is the cornerstone of treatment. In the ST group, anticoagulation was started once the contraindications were ruled out. Paracentesis and albumin infusion were conducted if necessary.

The indication for TIPS placement was ascites that required repeated paracenteses with or without variceal bleeding. TIPS placement was performed as follows: a RUPS-100 (COOK Medical) was used to access the branch of portal vein from the hepatic vein under fluoroscopic guidance. A balloon catheter was introduced to dilate the intrahepatic channel. Then, an 8 mm TIPS stent (Viatorr, Gore) or an 8 mm uncovered (E-lumine, Bard) combined with a covered stent (Viabahn, Gore; or Fluency, Bard), was placed in the channel (Fig. 1E and F). The portal pressure gradient (PPG) was determined before and after shunt creation.

2.3. Liver tissue acquisition and histological analysis

We first collected the paraffin blocks containing liver tissues from PA-HSOS patients before treatment. Percutaneous transhepatic liver biopsies were performed on the patients who agreed to the procedures. After being fixed with 10 % formalin solution, embedded using paraffin, and cut into slices, the liver tissues were stained with hematoxylin-eosin (HE) and Sirius red. Terminal-deoxynucleoitidyl Transferase Mediated Nick End Labeling (TUNEL) assays were carried out by commercial kits (Wuhan Service-bio, China). The antibody CD68 (Wuhan Servicebio) was used for immunohistochemistry (IHC) to evaluate liver inflammation. The results were analyzed by at least two experienced pathologists.

2.4. Follow-up and endpoints

The follow-up data, including laboratory tests and imaging findings, were extracted from inpatient and outpatient electronic medical records (ECM). The clinical symptoms were recorded by ECM and telephone interview. The main endpoint was to assess the impact of TIPS on survival in PA-HSOS patients. In addition, the clinical symptoms associated with portal hypertension, liver function, and liver histology were also evaluated in this study.

2.5. Statistical analysis

Qualitative variates were shown as n (%) and compared by chi-squared or Fisher exact test. Quantitative variates were shown as mean $\pm$ SD, and compared by *t*-test or one-way ANOVA analysis. The cumulative incidence of shunt dysfunction, survival, and overt hepatic encephalopathy was evaluated by the Kaplan-Meier analysis, and the differences between the two groups were compared by log-rank test. The predictors for mortality were evaluated by univariate and multivariate Cox models, in which the variates with $p \leq 0.1$ were used for the multivariate analysis. The hazard ratio (HR) and 95 % confidence interval (CI) were calculated. Data analyses were conducted by SPSS 23.0 (IBM, Chicago, USA). $P < 0.05$ was considered as statistical significance.

3. Results

3.1. Baseline characteristics

164 patients were enrolled for clinical analysis, including 69 in the TIPS group and 95 in the ST group. The interval time between

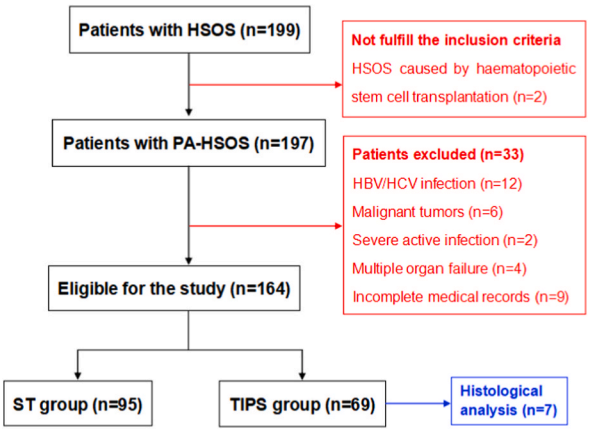

Fig. 2. Flowchart of patient selection.

the onset of HSOS (occurrence of clinical symptoms, such as ascites and impaired liver function) and receiving treatment was 23.52 ± 8.98 days (range, 12–51 days) in the TIPS group and 21.05 ± 10.36 days (range, 7–45 days) in the ST group (p = 0.114). The baseline characteristics of enrolled patients are presented in Table 1. All the parameters showed no significant difference between the TIPS and ST groups. The median follow-up time was 38.5 months (interquartile range, 21.2–58.9 months).

3.2. Outcomes associated with TIPS

TIPS placement was successfully performed on the first try in 66 patients. 3 patients had a secondary success after the first failure. The PPG dropped from 27.14 ± 6.04 mmHg to 11.40 ± 3.23 mmHg after shunt creation. Perioperative complications were observed in 4 patients, including pericardial tamponade (n = 1) and biliary hemorrhage (n = 3). These patients recovered uneventfully after being treated with percutaneous drainage and supportive treatment. 10 (14.5 %) patients developed shunt dysfunction. The cumulative incidence of shunt dysfunction at 1.5, 3, and 12 months were 0, 1.4 %, and 10.1 % (Fig. 3A). Angioplasty or stent placement was again performed in 4 patients, and the other six did not receive any special treatment for shunt dysfunction. However, the ten patients, with or without reintervention, did not have recurrent complications associated with portal hypertension.

3.3. Survival analysis

During the follow-up, none of the patients received transplantation. 7 (10.1 %) patients died in the TIPS group (5 died of liver failure, 1 of spontaneous bacterial peritonitis (SBP), and 1 of hepatorenal syndrome (HRS)), and 23 (24.2 %) in the ST group (16 died of liver failure, 3 of SBP, 1 of HRS, 2 of variceal bleeding, and 1 of stroke) (p = 0.021). The cumulative incidence of death at 1.5, 3, and 12 months was 2.9 %, 5.8 %, and 8.7 % in the TIPS group, and 6.3 %, 14.7 %, and 20.0 % in the ST group (log-rank p = 0.026) (Fig. 3B). In addition, multivariate Cox model revealed that group assignment (hazard ratio (HR) 5.146; 95 % confidence interval (CI) 1.587–16.687; p = 0.006), total bilirubin (HR 1.029; 95 % CI 1.020–1.038; p < 0.001), and INR (HR 13.291; 95 % CI 3.637–48.566; p < 0.001) were independent predictors for mortality (Table 2).

3.4. Complications related to portal hypertension

Overt hepatic encephalopathy occurred in 11 (15.9 %) patients in the TIPS group, and 13 (13.7 %) in the ST group. The cumulative incidence of overt hepatic encephalopathy at 1.5, 3, and 12 months was 8.7 %, 11.6 %, and 14.5 % in the TIPS group, and 3.2 %, 10.5 %, and 13.7 % in the ST group (log-rank p = 0.731) (Fig. 3C). No patients suffered variceal bleeding in the TIPS group, but 6 in the ST group (0 vs 6.3 %, p = 0.040). As for ascites, the numbers of paracenteses (2.25 ± 1.43 vs 8.45 ± 3.42, p < 0.001) markedly reduced in the TIPS group with less albumin infusion (19.06 ± 9.01 vs 47.74 ± 24.29, p < 0.001). In addition, the incidence of SBP (2.9 % vs 14.7 %, p = 0.012) and HRS (1.4 % vs 9.5 %, p = 0.034) significantly decreased by TIPS creation (Table 3).

Table 1
Baseline characteristics of the enrolled patients.

	TIPS group (n = 69)	ST group (n = 95)	P value
Sex (male/female)	39/30	61/34	0.319
Age (years)	52.25 ± 10.10	54.75 ± 11.57	0.152
Clinical symptoms			
Ascites	69 (100)	95 (100)	1.000
Variceal bleeding	2 (2.90)	2 (2.11)	0.745
Hepatic encephalopathy	1 (1.45)	1 (1.05)	0.819
Abdominal pain	19 (27.54)	24 (25.26)	0.744
Lower extremity swelling	17 (24.64)	33 (34.74)	0.165
Laboratory test			
Total bilirubin (μmol/L)	28.79 ± 11.40	26.31 ± 9.73	0.136
Albumin (g/L)	29.62 ± 3.86	30.44 ± 3.52	0.156
ALT (U/L)	51.94 ± 22.36	50.97 ± 20.41	0.772
AST (U/L)	64.91 ± 24.37	60.47 ± 24.37	0.259
INR	1.39 ± 0.25	1.35 ± 0.23	0.292
Creatinine (μmol/L)	70.77 ± 22.49	68.08 ± 20.45	0.428
Serum sodium (mmol/L)	138.19 ± 6.18	139.53 ± 4.23	0.102
Platelet count ($*10^9$/L)	127.29 ± 88.84	123.28 ± 66.77	0.742
Child-Pugh score	8.09 ± 1.34	7.92 ± 1.26	0.404
Child-Pugh class			0.920
A	8 (11.6)	12 (12.6)	
B	54 (78.3)	75 (78.9)	
C	7 (10.1)	8 (8.5)	
MELD score	12.49 ± 3.23	12.11 ± 3.06	0.435

TIPS, transjugular intrahepatic portosystemic shunt; ST, supportive treatment; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease.

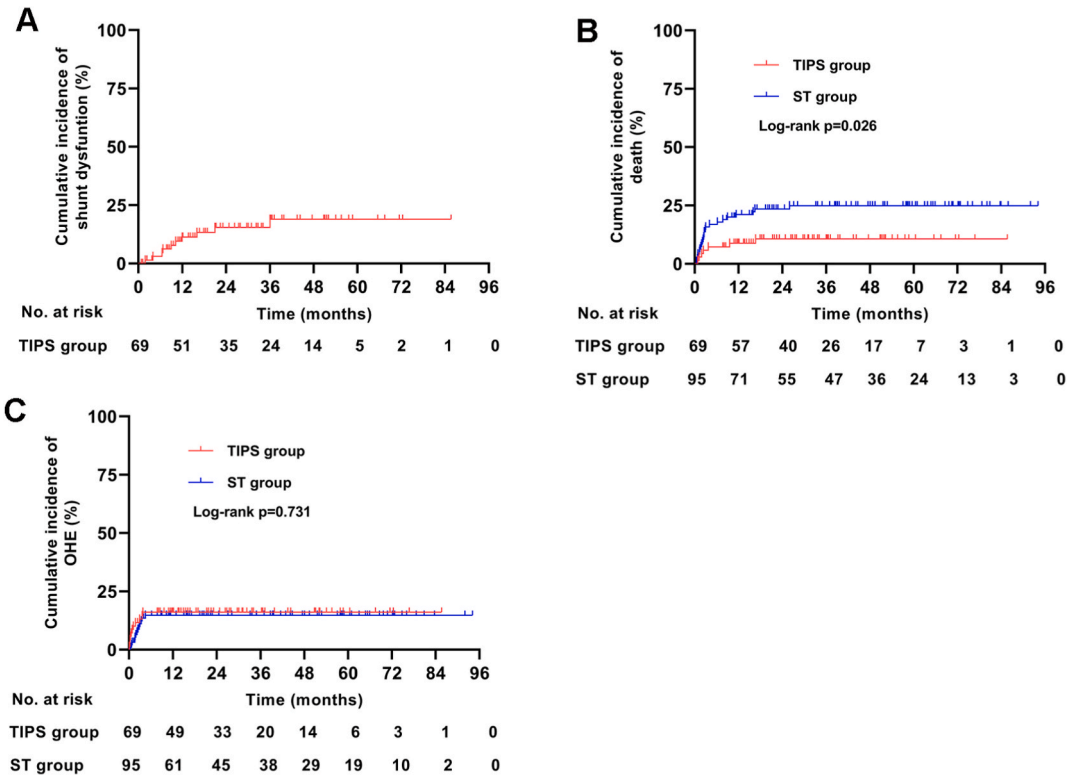

Fig. 3. Kaplan-Meier analysis for clinical outcomes. **A** Cumulative incidence of shunt dysfunction in the TIPS group. **B** Cumulative incidence of death in the TIPS and ST groups. **C** Cumulative incidence of overt hepatic encephalopathy.

Table 2
Prognostic factors associated with survival in univariate and multivariate analysis.

Variables	Univariate analysis		Multivariate analysis	
	HR (95 % CI)	P value	HR (95 % CI)	P value
Group (TIPS vs ST)	2.937 (1.025–8.418)	0.045	5.146 (1.587–16.687)	0.006
Sex (male vs female)	1.019 (0.495–2.099)	0.958		
Age	0.996 (0.960–1.033)	0.832		
Total bilirubin (μmol/L)	1.032 (1.024–1.040)	<0.001	1.029 (1.020–1.038)	<0.001
Albumin (g/L)	0.954 (0.874–1.041)	0.291		
ALT (U/L)	1.001 (0.996–1.005)	0.722		
AST (U/L)	1.000 (0.995–1.005)	0.970		
INR	15.131 (4.182–54.749)	<0.001	13.291 (3.637–48.566)	<0.001
Creatinine (μmol/L)	1.003 (0.988–1.017)	0.728		
Serum sodium (mmol/L)	1.012 (0.928–1.104)	0.784		
Platelet count (*10^9/L)	0.988 (0.979–0.988)	0.022	0.994 (0.985–1.004)	0.225

TIPS, transjugular intrahepatic portosystemic shunt; ST, supportive treatment; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio. HR, hazard ratio; CI, confidence interval.

3.5. *Liver function*

In the ST group, the level of total bilirubin and albumin showed no improvement at 2–3 months after treatment, but a marked reduction was found at 6–12 months (total bilirubin: 26.30 ± 9.73 μmol/L, 28.14 ± 12.06 μmol/L, and 22.03 ± 10.02 μmol/L; albumin: 30.44 ± 3.52 g/L, 30.73 ± 3.51 g/L, and 33.63 ± 3.29 g/L) (Fig. 4A and B). The levels of ALT (50.97 ± 20.41 U/L, 43.06 ± 23.35 U/L, and 34.97 ± 13.56 U/L) and AST (60.47 ± 24.37 U/L, 50.10 ± 25.05 U/L, and 42.54 ± 14.16 U/L) were significantly reduced at 2–3 months and 6–12 months after treatment (Fig. 4C and D). While in the TIPS group, all the parameters showed continuous improvement at 2–3 months and 6–12 months (total bilirubin: 28.79 ± 11.40 μmol/L, 24.43 ± 12.16 μmol/L, and 17.96 ± 5.88 μmol/L; albumin: 29.62 ± 3.86 g/L, 33.18 ± 2.95 g/L, and 35.65 ± 2.11 g/L; ALT: 51.94 ± 22.36 U/L, 37.34 ± 18.91 U/L, and 29.34 ± 12.27 U/L; AST: 64.91 ± 24.37 U/L, 45.95 ± 17.72 U/L, and 36.18 ± 16.88 U/L), and were superior to those in the ST group (Fig. 4A–D).

Table 3
Clinical outcomes in the TIPS and ST groups.

Outcome	TIPS group (n = 69)	ST group (n = 95)	P value
Death	7 (10.1)	23 (24.2)	0.021
OHE	11 (15.9)	13 (13.7)	0.686
Variceal bleeding	0 (0)	6 (6.3)	0.040
Numbers of paracenteses	2.25 ± 1.43	8.45 ± 3.42	<0.001
Albumin infusion (g)	19.06 ± 9.01	47.74 ± 24.29	<0.001
SBP	2 (2.9)	14 (14.7)	0.012
HRS	1 (1.4)	9 (9.5)	0.034

TIPS, transjugular intrahepatic portosystemic shunt; ST, supportive treatment; OHE, overt hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; HRS, hepatorenal syndrome.

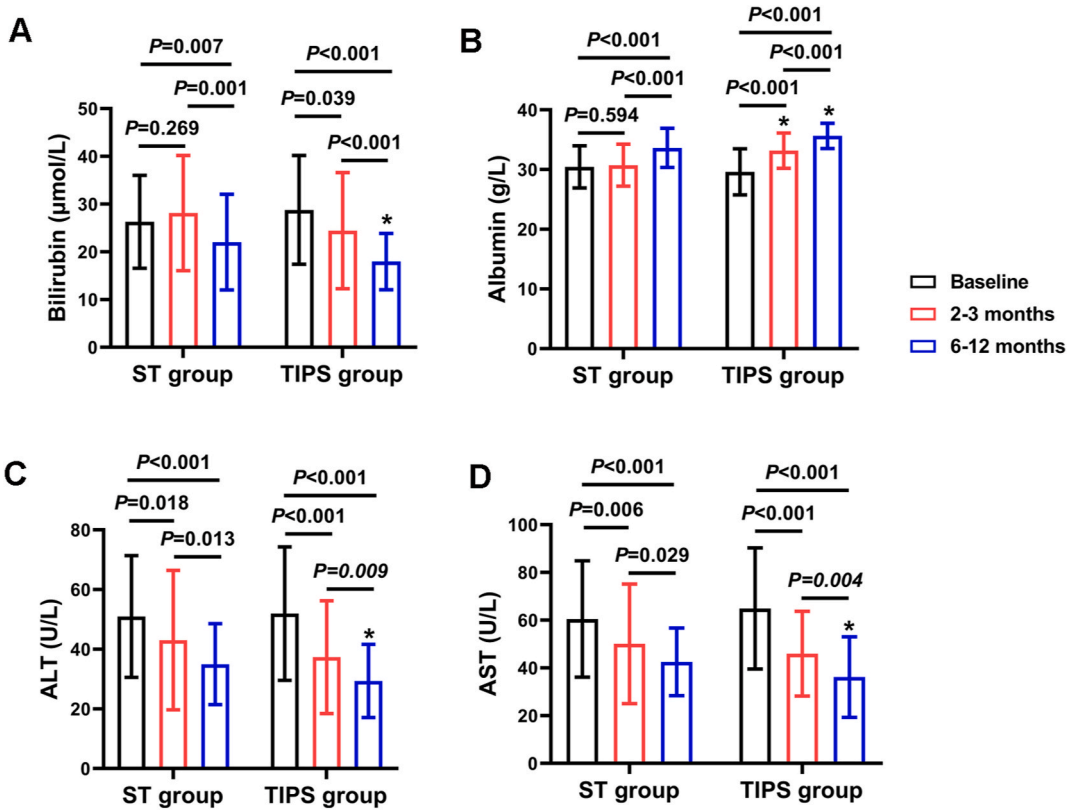

Fig. 4. Column chart showed liver function at baseline, 2–3 months, and 6–12 months. **A** Total bilirubin; **B** Albumin; **C** ALT; **D** AST.

3.6. Histological analysis

Transjugular liver biopsies were performed on 11 patients during TIPS procedures, among whom seven patients agreed to percutaneous transhepatic liver biopsies at 14, 23, 28, 37, 48, 55, and 69 months after TIPS placement. HE staining showed sinusoid congestion, hepatocyte swelling, mesenchymal cell proliferation, and disorder architecture in the liver from HSOS patients. Furthermore, increased hepatocyte apoptosis and hepatic inflammation were observed by TUNEL assay and macrophage infiltration ($CD68^{+}$ cells). It is exciting to note that these abnormalities were significantly improved after TIPS placement, and the damaged liver almost reversed to the normal level (Fig. 5A). However, we observed that 1 patient developed liver fibrosis after 55 months, as shown by HE staining (Fig. 5B) and Sirius red staining (Fig. 5C). The liver stiffness was 11.2 kPa by transient elastography (Fig. 5D). However, the patient had no clinical symptoms related to portal hypertension with normal liver function.

4. Discussion

Our study revealed that the PA-HSOS patients treated with TIPS had a better prognosis than those who only received supportive treatment, with improved survival rate and liver function. Also, treatment with TIPS reduced the risk of complications associated with

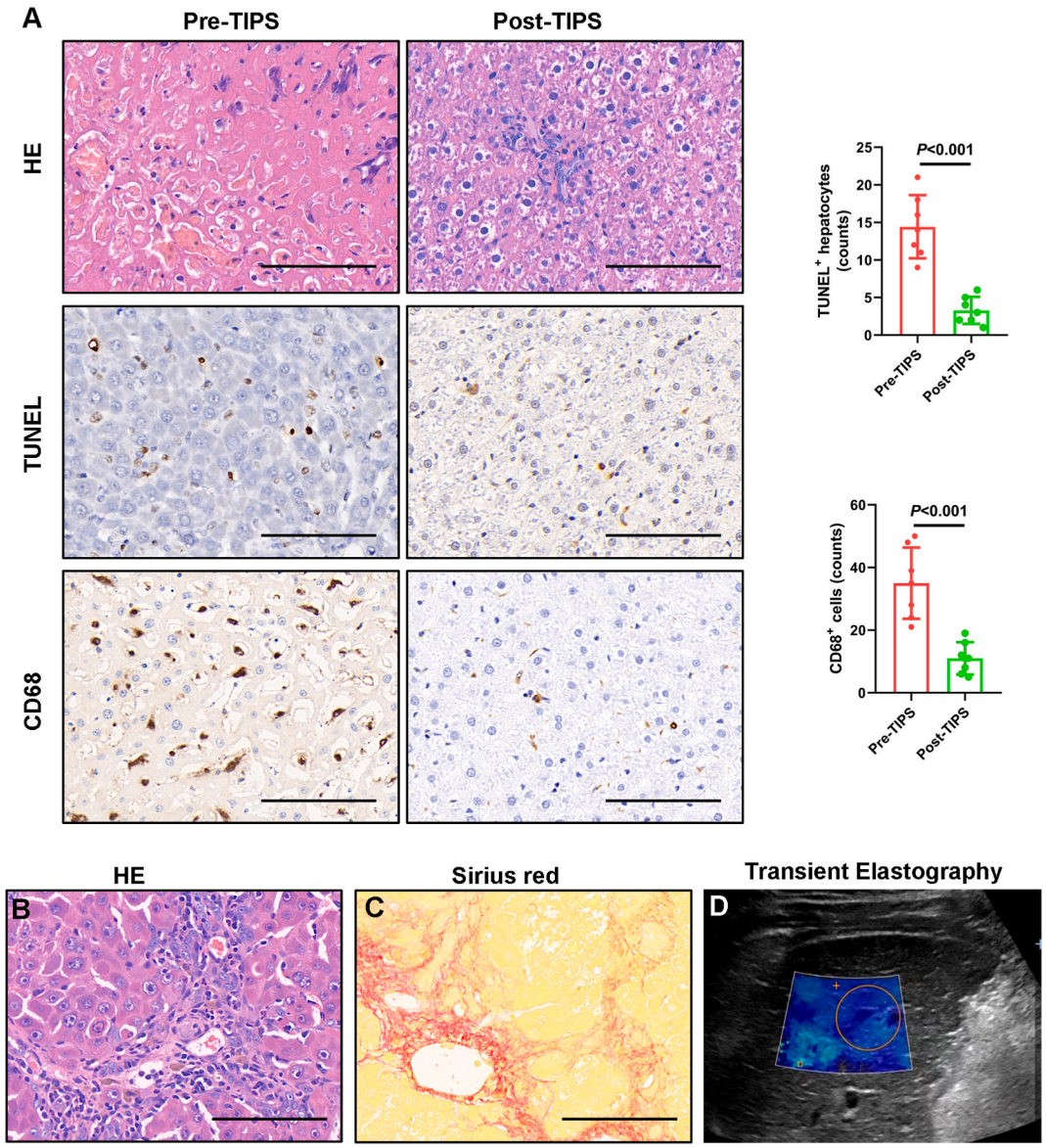

Fig. 5. Changes in liver histology. **A** The same patient in Fig. 1, the changes in liver histology 48 months after TIPS placement, including HE staining, TUNEL assay, and CD68 IHC. **B-D** A 61-year-old man underwent TIPS placement due to PA-HSOS and developed into liver fibrosis 55 months later, evidenced by HE staining (**B**), Sirius red staining (**C**), and transient elastography (**D**). Scale bar = 100 μm.

portal hypertension, including ascites, SBP, and HRS. Furthermore, these beneficial effects were consistent with the improvement of histological changes, though liver biopsies were taken in only seven patients, which limits the findings.

Several case-series studies reported that TIPS placement ameliorates portal hypertension and refractory ascites in PA-HSOS patients in the short term [14–16], but the impact on survival and long-term results remains unclear. Our study has the largest sample size with a long follow-up time. The results showed that the patients who received TIPS treatment had a higher survival rate. And group assignment was an independent predictor for mortality. In addition, increased INR and total bilirubin were also risk factors for poor prognosis, which was consistent with what Xiao et al. [14] reported.

Consistent with previous studies [14–16], TIPS placement alleviated the refractory ascites in PA-HSOS patients, evidenced by the reduced numbers of paracenteses and less albumin infusion. Meanwhile, the incidence of SBP and HRS markedly decreased in the TIPS group, which also contributed to the survival benefits. Moreover, TIPS placement did not increase the risk of overt hepatic encephalopathy, with an incidence of 15.9 %, which was lower than that in the cirrhotic patients treated with TIPS [17–20]. We speculated the reasons as follows: the damage to LSECs causes sinusoid congestion, which subsequently leads to hepatocyte apoptosis and portal hypertension. Portal hypertension, in turn, aggravates the damage to hepatocytes and LSECs [1,21]. After TIPS placement, the sinusoid congestion is alleviated, which promotes the recovery of hepatocytes and LSECs. And the improved liver function reduces the

incidence of overt hepatic encephalopathy and mortality.

Finally, we evaluated the histological changes in the liver after TIPS placement. The results revealed an amelioration in hepatocyte apoptosis and hepatic inflammation, which was consistent with the clinical outcomes. And the liver architecture almost recovered to the normal level, which explains why the patients had no symptoms associated with portal hypertension after shunt dysfunction. In addition, we found that PA-HSOS may develop into liver fibrosis, which may be due to the activation of hepatic stellate cells with excessive extracellular matrix production [22,23]. Further study is still required to investigate the underlying mechanism.

However, we have to admit the limitations of this study. Firstly, this study was retrospectively designed with a risk of selection bias. Secondly, bare combined with covered stents was used for TIPS placement in some patients, as a lack of Viatorr stent in 3 centers, but previous studies had demonstrated similar clinical outcomes between combined and Viatorr stents [24,25]. Finally, 7 TIPS patients received a liver biopsy at the intervention and thereafter. The results suggest improvement. However, the small number of biopsies and the lack of biopsies in non-TIPS patients limit the relevance of this finding.

In conclusion, we provided evidence that TIPS placement improves survival and reduces the risk of complications related to portal hypertension in PA-HSOS. Furthermore, these beneficial effects were consistent with liver recovery at the histological level. Therefore, it should be recommended in such patients to achieve a better prognosis.

Financial support

National Natural Science Foundation of China (81873917).

Ethics statement

This study was conducted according to the Declaration of Helsinki ethical principles and was approved by the ethics committee of Wuhan Union hospital (No. 20220264). Informed consent was obtained from the patients or their family for the publication of the pictures associated with imaging and histology.

Data availability statement

All the data in this study are available through the corresponding author (Bin Xiong).

CRediT authorship contribution statement

Chaoyang Wang: Writing - review & editing, Writing - original draft, Data curation, Conceptualization. **Yingliang Wang:** Software, Methodology, Investigation. **Jianbo Zhao:** Software, Project administration, Methodology, Investigation. **Chongtu Yang:** Software, Resources, Formal analysis. **Xiaoli Zhu:** Formal analysis, Conceptualization. **Huanzhang Niu:** Formal analysis, Data curation, Conceptualization. **Junhui Sun:** Software, Resources, Project administration, Methodology. **Bin Xiong:** Writing - review & editing, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23455.

References

[1] EASL Clinical Practice Guidelines, Vascular diseases of the liver, J. Hepatol. 64 (2016) 179–202.
[2] K.M. Mahadeo, R. Bajwa, H. Abdel-Azim, L.E. Lehmann, C. Duncan, N. Zantek, J. Vittorio, et al., Diagnosis, grading, and treatment recommendations for children, adolescents, and young adults with sinusoidal obstructive syndrome: an international expert position statement, Lancet Haematol 7 (2020) e61–e72.
[3] M. Stanulla, E. Schaeffeler, A. Moricke, S. Buchmann, M. Zimmermann, S. Igel, K. Schmiegelow, et al., Hepatic sinusoidal obstruction syndrome and short-term application of 6-thioguanine in pediatric acute lymphoblastic leukemia, Leukemia 35 (2021) 2650–2657.
[4] S. Corbacioglu, E.J. Jabbour, M. Mohty, Risk factors for development of and progression of hepatic veno-occlusive disease/sinusoidal obstruction syndrome, Biol. Blood Marrow Transplant. 25 (2019) 1271–1280.
[5] N.A. Kernan, S. Grupp, A.R. Smith, S. Arai, B. Triplett, J.H. Antin, L. Lehmann, et al., Final results from a defibrotide treatment-IND study for patients with hepatic veno-occlusive disease/sinusoidal obstruction syndrome, Br. J. Haematol. 181 (2018) 816–827.
[6] Y. Zhuge, Y. Liu, W. Xie, X. Zou, J. Xu, J. Wang, Expert consensus on the clinical management of pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome, J. Gastroenterol. Hepatol. 34 (2019) 634–642.
[7] G. Lin, J.Y. Wang, N. Li, M. Li, H. Gao, Y. Ji, F. Zhang, et al., Hepatic sinusoidal obstruction syndrome associated with consumption of Gynura segetum, J. Hepatol. 54 (2011) 666–673.

[8] F. Zhang, Y. Zhou, X. Yang, A.Z. Xiong, Z.T. Wang, L. Yang, Gynura Rhizoma containing pyrrolizidine alkaloids induces the hepatic sinusoidal obstruction syndrome in mice via upregulating fibrosis-related factors, Acta Pharmacol. Sin. 40 (2019) 781–789.
[9] W. Zhang, L. Liu, M. Zhang, F. Zhang, C. Peng, B. Zhang, J. Chen, et al., Validation of the nanjing criteria for diagnosing pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome, J Clin Transl Hepatol 9 (2021) 345–352.
[10] X.Q. Yang, J. Ye, X. Li, Q. Li, Y.H. Song, Pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome: pathogenesis, clinical manifestations, diagnosis, treatment, and outcomes, World J. Gastroenterol. 25 (2019) 3753–3763.
[11] X. Wang, W. Zhang, M. Zhang, F. Zhang, J. Xiao, Q. Yin, H. Han, et al., Development of a Drum Tower Severity Scoring (DTSS) system for pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome, Hepatol Int 16 (2022) 669–679.
[12] H. Tu, M. Li, Z. Chen, J. Zhao, H. Wang, J. Qian, C. Wei, et al., Plateletcrit for predicting prognosis in patients with hepatic sinusoidal obstruction syndrome caused by pyrrolizidine alkaloid, J. Clin. Lab. Anal. 36 (2022), e24240.
[13] H. Xiang, C. Liu, Z. Xiao, L. Du, N. Wei, F. Liu, Y. Song, Enoxaparin attenuates pyrrolizidine alkaloids-induced hepatic sinusoidal obstruction syndrome by inhibiting oncostatin M expression, Liver Int 43 (2022) 626–638.
[14] J. Xiao, J. Tu, H. Zhang, F. Zhang, W. Zhang, H. Xu, Q. Yin, et al., Risk factors of poor prognosis in patients with pyrrolidine alkaloid-induced hepatic sinusoidal obstruction syndrome after transjugular intrahepatic portosystemic shunt, Hepatol Int 15 (2021) 720–729.
[15] Y. Wang, D. Qiao, Y. Li, F. Xu, Risk factors for hepatic veno-occlusive disease caused by Gynura segetum: a retrospective study, BMC Gastroenterol. 18 (2018) 156.
[16] Y.Z. Zhuge, Y. Wang, F. Zhang, C.K. Zhu, W. Zhang, M. Zhang, Q. He, et al., Clinical characteristics and treatment of pyrrolizidine alkaloid-related hepatic vein occlusive disease, Liver Int. 38 (2018) 1867–1874.
[17] B. Xiong, C. Yang, C. Zhou, X. Wu, S. Huang, TIPS placement as the first-line therapy to prevent variceal rebleeding in patients with cirrhosis and sarcopenia, Eur. J. Radiol. 158 (2023), 110630.
[18] B. Xiong, C. Yang, X. Zhu, C. Zhou, S. Chen, Z. Zhang, X. Wu, et al., The added value of sarcopenia on existing risk scores to predict mortality after TIPS placement: a multicenter study, Acad. Radiol. 30 (Suppl 1) (2023) S246–S256.
[19] Y. Lv, Z. Yang, L. Liu, K. Li, C. He, Z. Wang, W. Bai, et al., Early TIPS with covered stents versus standard treatment for acute variceal bleeding in patients with advanced cirrhosis: a randomised controlled trial, Lancet Gastroenterol Hepatol 4 (2019) 587–598.
[20] J.C. Garcia-Pagan, K. Caca, C. Bureau, W. Laleman, B. Appenrodt, A. Luca, J.G. Abraldes, et al., Early use of TIPS in patients with cirrhosis and variceal bleeding, N. Engl. J. Med. 362 (2010) 2370–2379.
[21] J. Gracia-Sancho, E. Caparros, A. Fernandez-Iglesias, R. Frances, Role of liver sinusoidal endothelial cells in liver diseases, Nat. Rev. Gastroenterol. Hepatol. 18 (2021) 411–431.
[22] T. Kisseleva, D. Brenner, Molecular and cellular mechanisms of liver fibrosis and its regression, Nat. Rev. Gastroenterol. Hepatol. 18 (2021) 151–166.
[23] T. Higashi, S.L. Friedman, Y. Hoshida, Hepatic stellate cells as key target in liver fibrosis, Adv. Drug Deliv. Rev. 121 (2017) 27–42.
[24] J. Liu, J. Ma, C. Yang, M. Chen, Q. Shi, C. Zhou, S. Huang, et al., Sarcopenia in patients with cirrhosis after transjugular intrahepatic portosystemic shunt placement, Radiology 303 (2022) 711–719.
[25] W.E. Saad, W.M. Darwish, M.G. Davies, D.L. Waldman, Stent-grafts for transjugular intrahepatic portosystemic shunt creation: specialized TIPS stent-graft versus generic stent-graft/bare stent combination, J. Vasc. Intervent. Radiol. 21 (2010) 1512–1520.