Journal of Clinical and Translational Hepatology **2026**
DOI: 10.14218/JCTH.2026.00077

Original Article

Clinicopathological Evolution of Pyrrolizidine Alkaloid-induced Liver Injury: Transition From SOS to PSVD?

Si Zhao[1#], Feng Zhang[1#], Yao Liu[2], Shuyan Zeng[1], Han Zhang[1], Jingjing Tu[1], Hui Xu[1], Qin Yin[1], Wei Zhang[1], Bing Xu[1], Jiangqiang Xiao[1], Lei Wang[1], Juan Carlos García-Pagán[3], Jun Chen[2*] and Yuzheng Zhuge[1*]

[1]Department of Gastroenterology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China; [2]Department of Pathology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, Nanjing, Jiangsu, China; [3]Hepatic Hemodynamic Unit, Hospital Clínic, Clínic Barcelona, ERN-RareLiver (Health Care Provider of the European Reference Network on Rare Liver Disorders), CSUR Centro de referencia del Sistema Nacional de Salud en Enfermedad Hepática Vascular Compleja en adultos. Barcelona, Spain. Liver disease and the vascular system group (LiVas), FRCB-IDIBAPS (Fundació de Recerca Clínic Barcelona-Institut d'Investigacions Biomèdiques August Pi i Sunyer), Barcelona, Spain. CIBEREHD (Centro de Investigación Biomédica en Red Enfermedades Hepáticas y Digestivas), Madrid, Spain

Received: January 27, 2026 | **Revised:** June 07, 2026 | **Accepted:** August 07, 2026 | **Published online:** September 17, 2026

Abstract

Background and Aims: Hepatic sinusoidal obstruction syndrome (SOS) is characterized by hepatic sinusoidal endothelial cell injury and detachment, hepatic sinusoidal congestion, and hepatic cell necrosis. Currently, limited data exist concerning changes during the recovery period, especially histopathological changes. The purpose of this study was to investigate the evolution of pathology in patients with pyrrolizidine alkaloid (PA)-induced SOS and in a monocrotaline-induced SOS rat model. ***Methods:*** Patients diagnosed with PA-induced SOS who underwent liver biopsy after achieving clinical remission were consecutively enrolled in this retrospective study. To compare the clinical and pathological differences between patients with acute and convalescent SOS, a 2:1 matched analysis was performed based on age, sex, treatment regimen, and baseline Drum Tower Severity Scoring (DTSS) during the acute phase. Additionally, an animal model of PA-induced SOS was established through the administration of monocrotaline. ***Results:*** Fourteen consecutive patients with SOS who had adequate liver biopsy specimens obtained during recovery were identified. During convalescence, most laboratory and imaging findings, such as the map-like enhancement observed on computed tomography, also disappeared. However, histopathological analysis revealed a distinct shift from hepatic sinusoidal endothelial cell injury in the acute phase to portal tract abnormalities, primarily characterized by portal vein stricture, in the recovery phase. These pathological changes were corroborated in our animal model. ***Conclusions:*** Our study suggests that both patients with PA-induced SOS and rats in the convalescent stage may exhibit porto-sinusoidal vascular disease-like changes. Regular follow-up and dynamic pathological assessment are therefore recommended to facilitate the early detection of potential signs of portal hypertension.

Citation of this article: Zhao S, Zhang F, Liu Y, Zeng S, Zhang H, Tu J, *et al*. Clinicopathological Evolution of Pyrrolizidine Alkaloid-induced Liver Injury: Transition From SOS to PSVD? J Clin Transl Hepatol 2026. doi: 10.14218/JCTH.2026.00077.

Introduction

Sinusoidal obstruction syndrome (SOS), also known as veno-occlusive disease, is a hepatic vascular disease characterized by liver dysfunction, intrahepatic congestion, and sinusoidal portal hypertension.[1] SOS is typically observed in Western countries after hematopoietic stem cell transplantation, whereas the ingestion of products containing pyrrolizidine alkaloids (PAs), such as *Gynura segetum*, is a leading cause of SOS in China. Untreated PA-SOS is associated with high mortality.[2] However, since the implementation of anticoagulation-transjugular intrahepatic portosystemic shunt (TIPS) stepwise therapy, mortality has markedly decreased to approximately 10%, resulting in the survival of most patients.[3] Although several studies have extensively evaluated the pathophysiology, diagnosis, liver histology, and natural history of patients with PA-SOS,[4–6] the long-term outcomes of surviving patients remain poorly understood.

In recent years, we have identified a substantial number of patients who survived the acute phase of PA-SOS. In some of these patients, a second liver biopsy was performed while they were completely asymptomatic. This cohort of patients who survived PA-SOS offers a unique opportunity to assess the long-term consequences of the disease, which is the aim

Keywords: Pyrrolizidine alkaloids-induced liver injury; Sinusoidal obstruction syndrome; Pathology; Obliterative portal venopathy; Porto-sinusoidal vascular disease.

[#]Contributed equally to this work.

[*]**Correspondence to:** Yuzheng Zhuge, Department of Gastroenterology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, 321 Zhongshan Road, Nanjing, Jiangsu 210008, China. ORCID: https://orcid.org/0000-0002-3829-5831. Tel: +86-15996289206, E-mail: yuzheng9111963@aliyun.com; Jun Chen, Department of Pathology, Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University, 321 Zhongshan Road, Nanjing, Jiangsu 210008, China. ORCID: https://orcid.org/0000-0003-3905-4615. Tel: +86-13813889190, E-mail: ichenjun@qq.com.

of our study. In addition, we aimed to evaluate findings observed in liver biopsies performed during complete or partial recovery from PA-SOS.

Methods

Study population

The Department of Gastroenterology, Drum Tower Hospital affiliated with Nanjing University Medical School, has maintained a prospective registry of patients diagnosed with PA-SOS since January 2017. These patients were followed up regularly until the end of follow-up for this study, which was April 20, 2025. Long-term follow-up was based on outpatient clinic visits and telephone interviews.

PA-SOS is diagnosed according to the Nanjing criteria (a combination of a definitive history of exposure to plants containing PAs before the appearance of symptoms, typical radiological findings, abnormal laboratory indicators, and clinical manifestations),[3] which have been confirmed to have a diagnostic accuracy close to 100% compared with pathological diagnosis.[7] Patients must be older than 18 years and must not have any of the following exclusion criteria: (1) the presence of two or more additional etiologies of liver injury, such as HBV positivity, HCV positivity, alcohol abuse, or autoimmune liver disease; (2) other serious diseases (cardiopulmonary failure, serious cardiovascular or cerebrovascular diseases, or malignant tumors); or (3) a large amount of incomplete clinical data. To ensure a comprehensive study and fully informed consent, our protocol stipulated that only patients under regular outpatient follow-up would be considered for convalescent liver biopsy. As such, most patients were not asked about liver biopsy because their follow-up was conducted via telephone or through data uploaded from local hospitals. Finally, 14 patients who were willing to undergo liver biopsy during the clinical recovery period and had good-quality biopsy specimens (greater than 1.5 cm in length or otherwise considered adequate for interpretation by an expert pathologist)[8] were identified. The clinical recovery period was defined as beginning at least 3 months after the initiation of anticoagulation or TIPS treatment if the following additional conditions were met: (1) significant improvement in abdominal distention and upper abdominal pain; (2) a decrease in serum alanine aminotransferase levels to 50% of the baseline value or within the normal range (9–40 U/L); (3) disappearance of ascites confirmed by abdominal ultrasound; and (4) a Drum Tower Severity Scoring (DTSS) of 4–6 points, reflecting at most mild disease severity.[9]

As previously mentioned, a liver biopsy is not mandatory for the diagnosis of PA-SOS. Consequently, only 3 of the 14 patients also had liver biopsy results available at the time of diagnosis of PA-SOS. To compare diagnostic and recovery biopsy findings, we selected patients from our registered PA-SOS cohort who had undergone a diagnostic liver biopsy. For each of the 14 patients with a recovery liver biopsy, two PA-SOS patients with a diagnostic liver biopsy were matched on the basis of age, sex, treatment method, and baseline DTSS score.

This study protocol was reviewed and approved by the Ethics Committee of Nanjing Drum Tower Hospital (2022-486-02). The flow diagram is shown in Figure 1.

Data collection

Clinical data of the 14 included patients were retrospectively extracted from the clinical records of the patients using a case report form specifically predesigned for the study. Demographic, clinical, biochemical, and imaging (ultrasound and/or computed tomography [CT] scan) data were collected at baseline and at 1, 3, 6, 12, 24, and 48 months or longer whenever possible for a comprehensive assessment of baseline clinical characteristics and follow-up changes. Liver histology data were obtained from 28 diagnostic liver biopsies (3/14 in our study and another 25 PA-SOS cases) and 14 recovery liver biopsies.

Histopathologic assessment

Liver biopsy specimens that had been fixed in 10% buffered formaldehyde were processed for paraffin embedding according to standard procedures. Subsequently, 5 μm sections were cut from the paraffin-embedded samples and stained with hematoxylin and eosin (H&E), Sirius red, and immunohistochemistry (IHC) in accordance with a previously described protocol. Antibodies against CD34 (Proteintech, 14486-1-AP) and CD34 (Servicebio, GB15013) were used for human and rat IHC, respectively. Normal CD34 staining was defined as strong cytoplasmic expression confined to the endothelial cells of the portal tract and central vein. Cases were scored from 0 (normal) to 3+ (markedly aberrant, defined as strong centrilobular sinusoidal expression).[10]

Histopathological evaluation was jointly performed by two experienced hepatic pathologists (JC and YL) who were blinded to the clinical data and biopsy time points. They reviewed the slides together, resolved discrepancies through on-site discussion, and finalized unified semiquantitative and quantitative results. The primary observational features of specific and nonspecific histologic findings in porto-sinusoidal vascular disease (PSVD) were as follows: specific findings included obliterative portal venopathy (OPV), incomplete septal fibrosis, and nodular regenerative hyperplasia; nonspecific findings included portal vein herniation, an increased number of portal vessels, nonzonal sinusoidal dilation, perisinusoidal fibrosis, collagen fiber hyperplasia, and portal tract remnants. Moreover, other histological signs, such as bile ductular proliferation, sinusoidal hemorrhage, steatosis, portal inflammation, and lobular inflammation, were also recorded. In addition, the Scheuer scoring system was used for grading inflammation (G0–G4) and staging fibrosis (S0–S4) for overall evaluation. The expression was evaluated throughout the entire area of each sample, both quantitatively and qualitatively. Detailed definitions of the indices mentioned above are presented in Supplementary Table 1 according to a literature review and group consensus.[10,11]

Animal models of PA-induced liver injury

Male Sprague-Dawley rats were purchased from Beijing Vital River Laboratory Animal Technology Co. Ltd. (Beijing, China). They were kept in a 12-h dark/light cycle at a temperature of 23 °C and a humidity of 65%. Rats were gavaged with monocrotaline (MCT) (Sigma-Aldrich, St. Louis, MO, USA) to establish a model of PA-induced liver injury, which is a well-established and reproducible model of SOS. The MCT solution was prepared according to previously reported methods. We established a rat model of acute resolving liver injury as described in a previous study.[12] Briefly, the rats were intragastrically administered a single dose of MCT (130 mg/kg) on Day 0. Equal volumes of vehicle were used as controls. After 2 days, 1 week, 2 weeks, or 4 weeks, the rats were euthanized for blood collection. These time points, covering the recognized acute and early chronic stages of MCT-induced SOS as well as recovery phases, were chosen based on our preliminary experiments and a published study.[12] Afterwards, the livers were collected for H&E staining, Sirius red staining, IHC, Western blotting, and quantitative real-time polymerase chain reaction (PCR).[13]

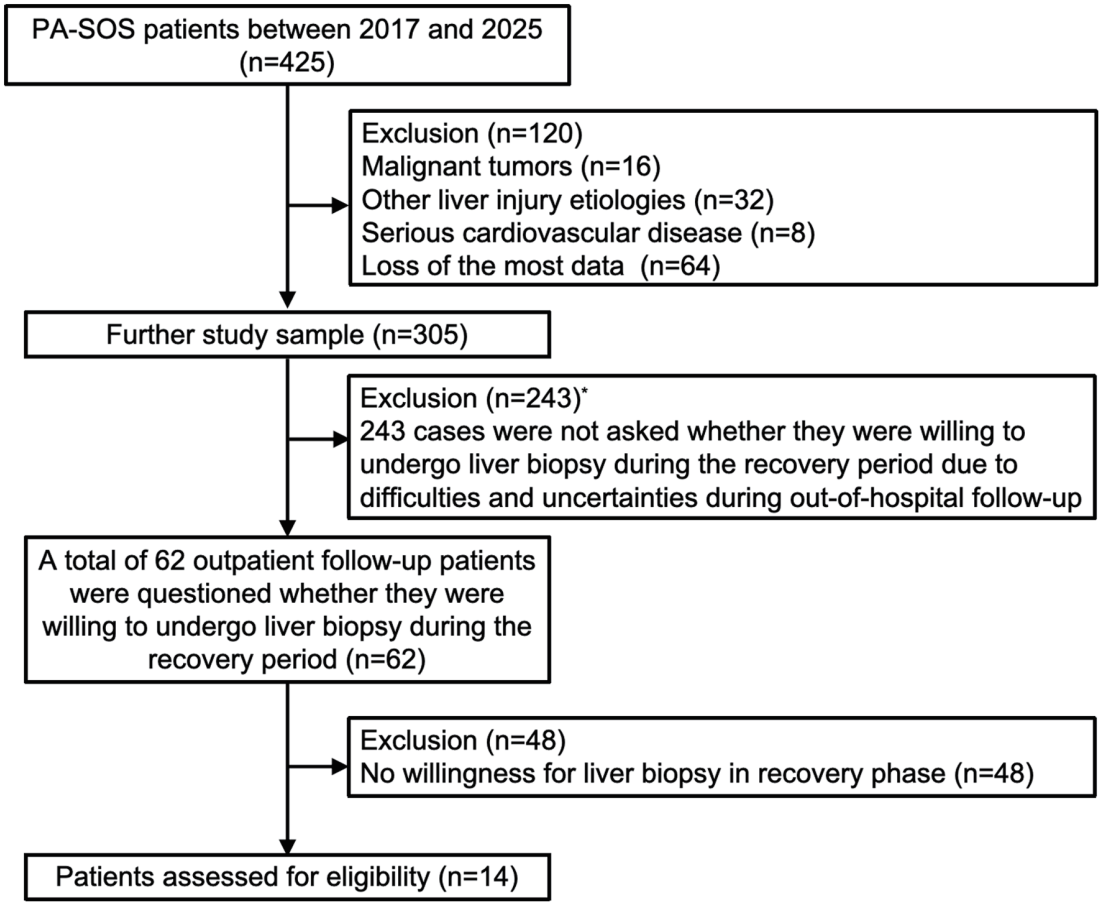

Fig. 1. Flowchart for establishing a cohort of 14 consecutive patients who underwent liver biopsy during the clinical recovery period of PA-SOS. *To ensure comprehensive study introduction and fully informed consent, our protocol stipulated that only patients under regular outpatient follow-up would be considered for convalescent liver biopsy. As such, the 243 patients were not asked about liver biopsy because their follow-up was conducted via telephone or through data uploaded from local hospitals. PA-SOS, pyrrolizidine alkaloid-induced sinusoidal obstruction syndrome.

Western blotting

Liver tissues were lysed with RIPA lysis buffer (Beyotime, Shanghai, China) containing a protease inhibitor cocktail and phosphatase inhibitor. Total protein was quantified using the BCA Protein Assay Kit (Thermo Fisher Scientific, MA, USA). Equal amounts of protein were added to SDS-PAGE gels for electrophoresis, blocked with 5% nonfat milk, and incubated with a suitable concentration of primary antibody overnight at 4 °C. The antibodies used were CD34 (1:800, Servicebio, GB15013) and β-actin (1:3,000, Proteintech, 81115-1-RR). After incubation with the corresponding secondary antibodies, the protein was visualized with UltraSignal hypersensitive ECL chemiluminescence substrate (4A Biotech, Beijing, China).[14]

RNA extraction and quantitative reverse-transcriptase (qRT)-PCR

Total RNA from tissues and cells was extracted using the Takara MiniBEST Universal RNA Extraction Kit, and cDNA was synthesized using the Takara PrimeScript RT Reagent Kit (Takara, Kyoto, Japan) as described previously.[14,15] Then, qRT-PCR assays were performed using SYBR Green qPCR MasterMix (abm, Vancouver, Canada) according to the manufacturer's instructions. The primer sequences used were as follows: CD34 (Rat), forward, 5′-GCCTGCCGTCTG TCAATG-3′, reverse, 5′-TCCTCACAACTAGATGCTTCACTT-3′; β-actin (Rat), forward, 5′-CGTTGACATCCGTAAAGACCTC-3′, reverse, 5′-TAGGAGCCAGGGCAGTAATCT-3′.

Statistical analysis

Normally distributed continuous variables are expressed as means and standard deviations (means ± standard deviations), whereas medians and interquartile ranges were calculated for variables that did not meet the assumption of normality. Continuous variables were compared using paired-sample *t* tests or Wilcoxon signed-rank tests for paired data, and Student's *t* tests or Mann–Whitney *U* tests for unpaired data, as appropriate. Categorical data were presented as frequencies and percentages and compared using the chi-square or Fisher's exact test, as appropriate. Propensity score matching was conducted using the MatchIt package for R software. All statistical analyses were conducted using SPSS 23.0 or GraphPad Prism 8 (GraphPad Software). *P*-values < 0.05 were considered statistically significant.

Results

Histological findings at recovery liver biopsy

Fourteen PA-SOS patients, with a mean age of 67 ± 8 years and a male-to-female ratio of 1.8:1, were included in the

study. As summarized in Supplementary Table 2, among the 14 patients included, 11 patients (78.6%) received TIPS after 2 weeks of ineffective anticoagulation treatment, while 3 patients (21.4%) were in the control group and received anticoagulation alone. The indications for TIPS were defined as (1) either total bilirubin ≥ 5 mg/dL or peak portal vein velocity < 10 cm/s or (2) any two of the following four criteria being met during 2 weeks of anticoagulation therapy: no improvement in total bilirubin (<5 mg/dL), an increase of less than 10% in the peak portal vein velocity from baseline, no significant improvement in ascites, or concurrent renal or coagulation deterioration.[16] The median time from symptom onset to TIPS intervention was 38 days (range, 11–95 days). The changes in serological and imaging indicators at different stages can be found in Supplementary Tables 3 and 4. All the above clinical, biochemical, and imaging alterations gradually improved until they disappeared after a median of 3 months (range, 1.5–6 months) following TIPS or after a median of 2.5 months of anticoagulation therapy (range, 2–3 months) (Supplementary Figs. 1–3). Given that most patients declined liver biopsy, we also compared patients who underwent biopsy with those who did not, using the available data, to rule out potential selection bias, and no significant differences were detected (Supplementary Table 5).

In the 14 patients who underwent liver biopsy at recovery, the mean time from the first manifestation to liver biopsy was 20.5 months (range, 3–61 months), and the time from recovery to biopsy was 17.5 months (range, 0–58 months). As previously mentioned, only 3 patients underwent liver biopsy at the time of PA-SOS diagnosis, allowing direct comparison of pathological changes before and after recovery. For this reason, and to better characterize the acute lesions of PA-SOS, we selected a group of 25 additional PA-SOS patients from our prospective registry who, although they did not undergo liver biopsy at recovery, had a liver biopsy during the acute phase. The characteristics of the two groups are shown in Supplementary Table 6, indicating that both groups were well matched at the time of acute PA-SOS diagnosis.

Overall, compared with the findings of PA-SOS in diagnostic liver biopsies, there was a high prevalence of specific and nonspecific histological signs described in PSVD in liver biopsies performed at recovery. Eight patients (57%) showed at least 1 of the 3 histological features designated by the Vascular Liver Disease Group as "specific for the diagnosis of PSVD," i.e., enabling a diagnosis of PSVD irrespective of clinical findings (Table 1). Fifty percent of the patients exhibited OPV, and 1 patient had incomplete septal fibrosis; representative images are shown in Figure 2. However, the duration of follow-up might have been too short to detect any changes in nodular regenerative hyperplasia. Among the 6 remaining cases, 3 met the alternative criteria for a PSVD diagnosis, i.e., the joint presence of 1 less-specific clinical sign of portal hypertension. Specifically, one patient had a platelet count of 85×10^9/L accompanied by portal vein herniation and perisinusoidal fibrosis; the second had a platelet count of 65×10^9/L with portal vein herniation alone; and the third had a platelet count of 106×10^9/L, with both portal vein herniation and an increased number of portal vessels. With the inclusion of these 3 cases, a total of 11 cases (79%) exhibited histological PSVD-like changes on liver biopsy. In particular, all patients had collagen fiber hyperplasia, while 43% of them had increased portal vessel counts, 50% had portal vein herniation, 86% had portal tract remnants, and 79% had perisinusoidal fibrosis. Furthermore, nonzonal sinusoidal dilation was present in 64% of the patients. Representative histopathological images with matched pathology from the same patient at diagnostic and recovery liver biopsy are also shown in Figure 3. Overall, patients manifested hepatic sinusoidal dilation and congestion in the acute phase. CD34 expression was absent or minimal, with scores ranging from 0 to 1, and no prominent portal vein abnormalities were observed. In contrast, most cases presented with portal vein abnormalities, such as herniation, stenosis, or occlusion, during the recovery phase, and CD34 scores rose to 2–3.

Interestingly, hepatic steatosis was detected in 6 of 14 patients (43%), comprising 4 cases of microvesicular steatosis and 2 cases of mixed-type steatosis, involving approximately 5%–8% of hepatocytes. Among the 13 evaluable recovery biopsies, 46% of patients had aberrant expression of CD34 in centrilobular sinusoids (score of 1+), 46% had a score of 2+, and 8% had a score of 3+ (Supplementary Figs. 4 and 5).

In addition, we conducted a further analysis of the characteristics of pathological alterations at different time points of liver biopsy when the patients achieved recovery (from a clinical and biochemical point of view). Detailed pathological information for the 14 patients is provided in Supplementary Table 7. The interval between initial clinical recovery and liver biopsy at recovery ranged from 0 to 58 months. After stratification by time period, we found 3 cases within 3 months, 3 cases between 3 and 12 months, 4 cases between 12 and 24 months, and 4 cases beyond 24 months. As shown in Supplementary Figure 6, within 3 months, patients experienced portal vein stenosis, accompanied by incomplete repair of sinusoidal hemorrhage. After the initial 3-month period, patients developed obvious OPV, increased portal vessel counts, and proliferation of collagen fibers in the portal tract, with the disappearance of sinusoidal hemorrhage; however, in some cases, sinusoidal dilation could occur. On the basis of clinical recovery and liver biopsy time, we also conducted a correlation analysis and found that, with prolongation of the time from first manifestation to clinical recovery, collagen fiber proliferation tended to increase, but no significant correlation was found between this proliferation and the time from recovery to liver biopsy (Fig. 4). In addition, the data also suggested a consistent trend toward longer recovery times among patients with concomitant OPV or portal vein herniation, although the difference was not significant.

Follow-up

The mean duration from disease initiation to the last follow-up was 50.9 months (range, 3–81 months). All 14 patients recovered well and achieved symptom improvement. Only one patient in our study group who underwent TIPS developed splenomegaly and persistent thrombocytopenia during the 23-month follow-up period after the initial visit. Notably, none of the three patients in the anticoagulation therapy group developed clinically evident portal hypertension-related symptoms during the follow-up period.

Animal model analysis

To further confirm these findings, an animal model of PA-induced SOS was created through the administration of MCT following the flowchart shown in Figure 5A. The serum levels of alanine aminotransferase and aspartate aminotransferase gradually decreased as the recovery period progressed and returned to baseline at 2 weeks (Fig. 5B). Surprisingly, in contrast to the serological results, both the H&E and Sirius Red staining results revealed significant histopathological abnormalities at the second week (Fig. 5C and D). Unlike the pathological features on the second day of modeling, rats showed no significant hepatic sinusoidal dilation or conges-

Table 1. Evaluation of pathological characteristics in patients with PA-induced liver injury between liver biopsies at diagnosis and recovery.

Variable	Levels	Liver biopsy at diagnosis (n = 28)	Liver biopsy at recovery (n = 14)	*P*-value
Specific histological signs				
Obliterative portal venopathy	No	26 (93%)	7 (50%)	0.003
	Yes	2 (7%)	7 (50%)	
Incomplete septal fibrosis	No	28 (100%)	13 (93%)	0.406
	Yes	0 (0%)	1 (7%)	
Nodular regenerative hyperplasia	No	28 (100%)	14 (100%)	0.999
	Yes	0 (0%)	0 (0%)	
Nonspecific histological signs				
Portal vein herniation	No	26 (93%)	7 (50%)	0.003
	Yes	2 (7%)	7 (50%)	
Increased number of portal vessels	No	26 (93%)	8 (57%)	0.011
	Yes	2 (7%)	6 (43%)	
Non-zonal sinusoidal dilation	0 point	1 (4%)	5 (36%)	<0.001
	1 point	13 (46%)	8 (57%)	
	2 points	14 (50%)	1 (7%)	
Perisinusoidal fibrosis*	0 point	4 (40%)	3 (21%)	0.146
	1 point	5 (50%)	5 (36%)	
	2 points	1 (10%)	5 (36%)	
	3 points	0 (0%)	1 (7%)	
Collagen fiber hyperplasia	0 point	14 (50%)	0 (0%)	<0.001
	1 point	11 (39%)	2 (14%)	
	2 points	3 (11%)	8 (57%)	
	3 points	0 (0%)	4 (29%)	
Portal tract remnant	No	18 (64%)	2 (14%)	0.003
	Yes	10 (36%)	12 (86%)	
Other histological signs				
CD34-aberrant centrilobular sinusoidal staining*	0 point	12 (60%)	0 (0%)	<0.001
	1 point	7 (35%)	6 (46%)	
	2 points	1 (5%)	6 (46%)	
	3 points	0 (0%)	1 (8%)	
Bile ductular proliferation	No	24 (86%)	4 (29%)	<0.001
	Yes	4 (14%)	10 (71%)	
Sinusoidal hemorrhage	%	37.14 ± 24.09	0.71 ± 2.67	<0.001
Steatosis	No	26 (93%)	8 (57%)	0.011
	Yes	2 (7%)	6 (43%)	
Portal inflammation	0 point	25 (89%)	0 (0%)	<0.001
	1 point	3 (11%)	14 (100%)	
Lobular inflammation	0 point	24 (86%)	9 (64%)	0.092
	1 point	4 (14%)	4 (29%)	
	2 points	0 (0%)	0 (0%)	
	3 points	0 (0%)	1 (7%)	
Grading of inflammation	0 point	21 (75%)	0 (0%)	<0.001
	1 point	7 (25%)	12 (86%)	
	2 points	0 (0%)	1 (7%)	
	3 points	0 (0%)	1 (7%)	
Staging of liver fibrosis	0 point	15 (54%)	1 (7%)	<0.001
	1 point	13 (46%)	9 (64%)	
	2 points	0 (0%)	3 (21%)	
	3 points	0 (0%)	1 (7%)	

*Only specimens with complete tissue sections and available staining were evaluated for perisinusoidal fibrosis and CD34 staining.

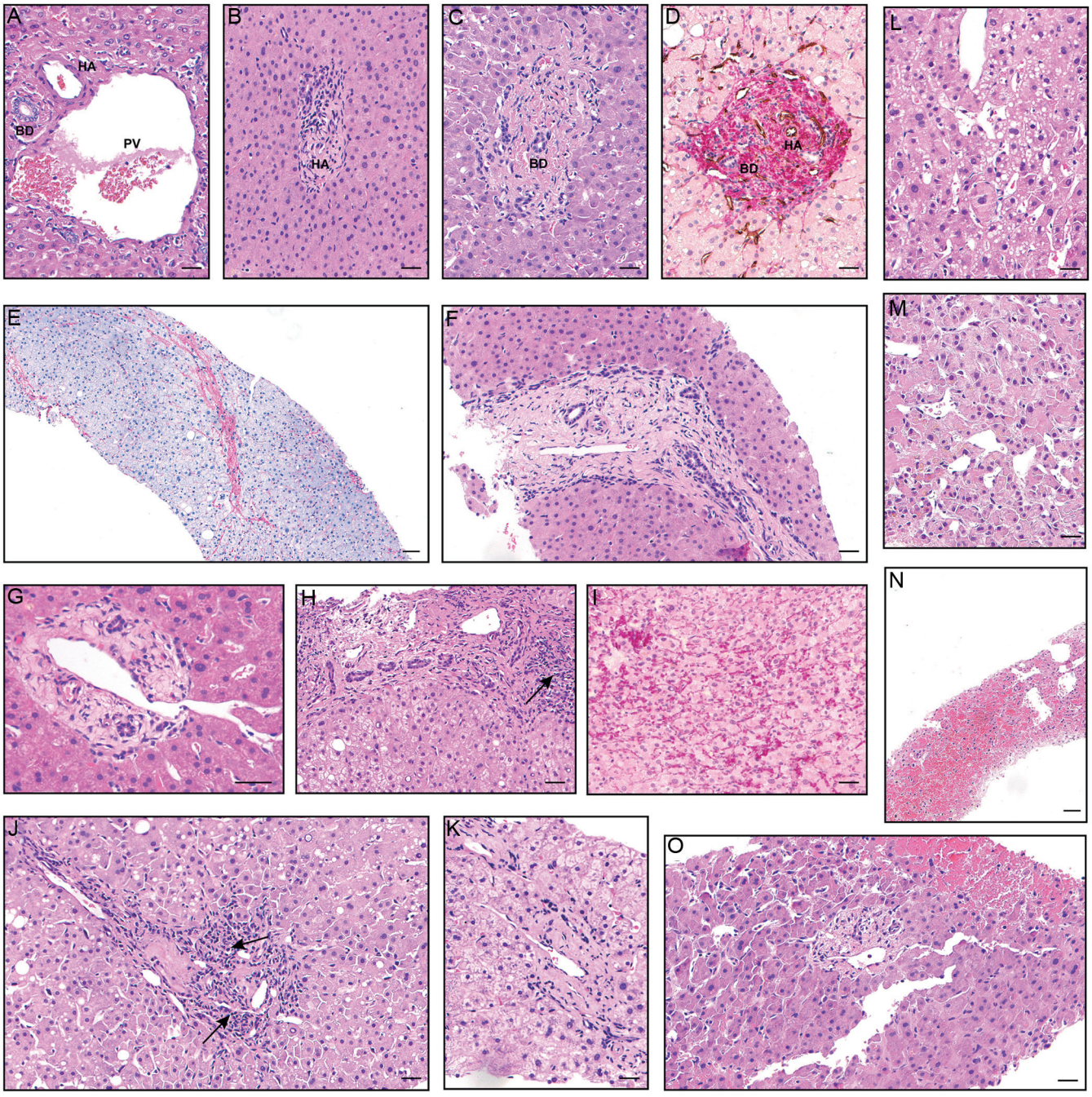

Fig. 2. Representative histopathological images during PA-induced liver injury. (B–L) Images of PA-SOS patients in the recovery phase; (M–O) images of PA-SOS patients in the acute phase. (A) Normal portal tract with a triad; (B–C) obliterative portal venopathy; (D) obliterative portal venopathy (Sirius red); (E) incomplete septal fibrosis (Sirius red); (F) massive collagen fiber hyperplasia in the portal tract; (G) portal vein herniation; (H) bile ductular proliferation; (I) perisinusoidal fibrosis (Sirius red); (J) increased number of portal vessels; (K) portal vein stricture; (L) microvesicular steatosis; (M) sinusoidal dilatation; (N) hemorrhagic necrosis within the hepatic lobules; (O) representative portal tract with a triad in the acute phase. Scale bars are 50 μm. Black arrows indicate inflammatory cell infiltration. PV, portal vein; BD, bile duct; HA, hepatic interlobular artery; PA-SOS, pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome.

tion after 2 weeks of treatment. Instead, they exhibited obvious fibrous septa formation and portal vein stenosis (Supplementary Table 8), which were similar to the pathological evolution observed in PA-induced SOS patients. In addition, the percentage of CD34-positive cells and the RNA and protein expression levels of CD34 significantly increased at 2 or 4 weeks (Fig. 5E and Supplementary Figs. 7 and 8). The main histological alterations observed in the MCT-induced SOS animal models are summarized in Figure 6.

Discussion

Studies of the pathological features of both hematopoietic stem cell transplantation- and PA-related SOS have focused

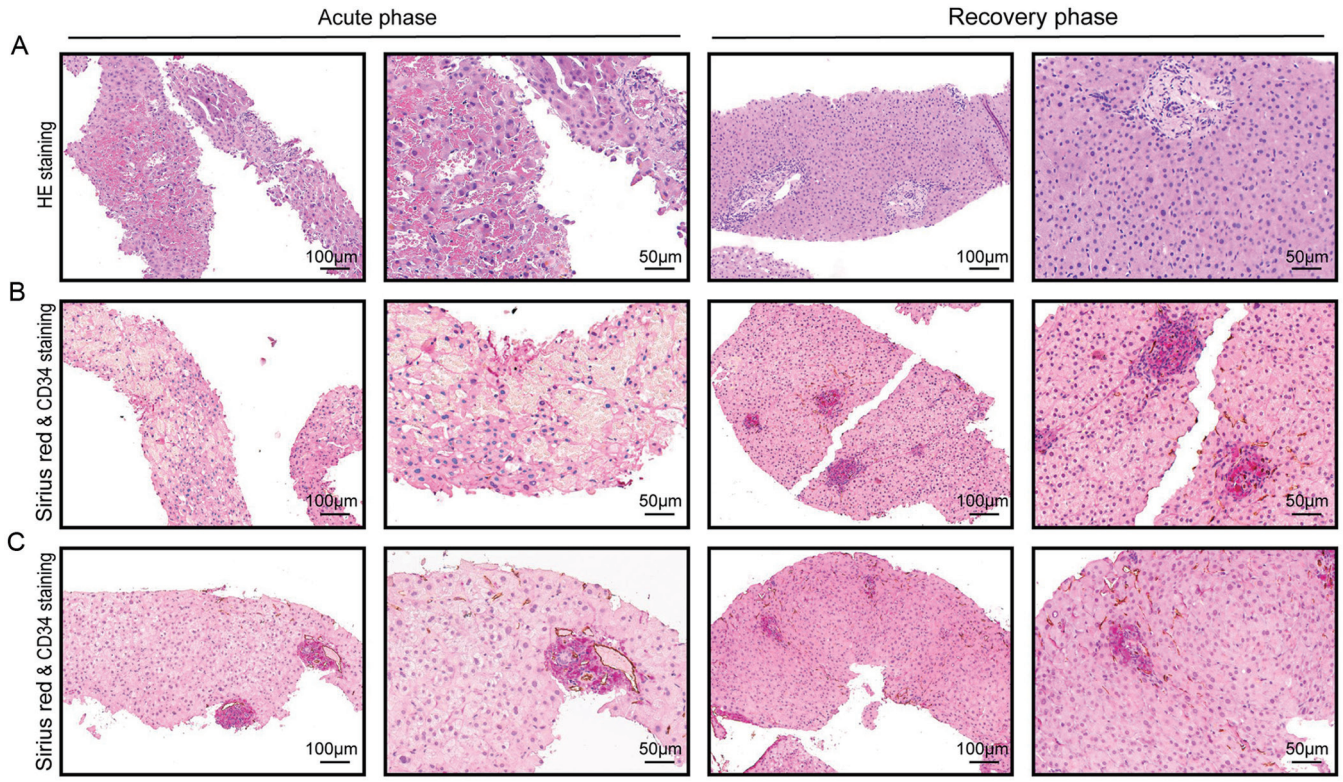

Fig. 3. Representative histopathological images of patients with matched pathology in diagnostic liver biopsy and recovery liver biopsy. (A–C) Paired diagnostic and recovery liver biopsy specimens from three patients. The left and right panels show the acute and recovery phases, respectively. HE, hematoxylin and eosin.

on the initial stages of the disease. Understanding of the natural history of SOS remains limited, especially regarding the histopathological features of the liver during the clinical recovery period or even after clinical cure. In this study, we first reported that PSVD-specific changes, predominantly OPV, were observed in more than half of the patients at recovery. Additional nonspecific alterations, including portal vein herniation, an increased number of portal vessels, and hyperplasia of collagen fibers, were also identified among the 14 consecutive patients. Our animal experiments also revealed this phenomenon.

We found that the vast majority of serological markers returned to normal, with no map-like enhancement on CT. Furthermore, during the month after the initiation of treatment, the results of most liver function tests returned to within normal limits, accompanied by regression of ascites, which is consistent with the findings of other studies.[17] Only a small number of patients had mild biochemical abnormalities at the time of liver biopsy, which may potentially confound the pathological findings. With respect to the imaging findings during the follow-up of patients with SOS, anticoagulation therapy or TIPS not only improved blood flow velocity in the portal vein system but also reduced the degree of patchy and map-like enhancement. Similar results were previously reported by Huang *et al*., who reported that liver parenchymal enhancement tended to become homogeneous again, with disappearance of ascites 1 month after TIPS.[18] In particular, although liver biopsy provides clear evidence for the diagnosis of SOS, only a small number of patients underwent percutaneous liver biopsy because of coagulopathy and the high risk associated with excessive ascites. In addition, considering its invasive nature, high cost, and technical requirements, the application of transjugular liver biopsy was also limited, and patients in the recovery stage were often reluctant to undergo liver biopsy.[19]

We delineated the pathological features of different phases of PA-induced liver injury for the first time. The evolution from hepatocellular and hepatic sinusoidal injury in the acute stage to hepatic fibrosis, portal vein stenosis, and even atresia and herniation in the recovery stage raises a series of questions: 1. The pathological changes in PA-related SOS during the convalescent period are obviously similar to the specific pathological features of PSVD. Does this mean that SOS and PSVD are essentially two stages of the same disease? 2. This alteration in PA-related liver pathology during the convalescent phase is rarely observed in the convalescent phase in patients treated with acetaminophen or in most other cases of drug-related acute liver injury[20,21]; therefore, what are the mechanisms responsible for this difference?

With the advent of specific histopathological and clinical diagnostic criteria, PSVD, a spectrum of diseases that encompasses a multiplicity of subtle abnormalities of the hepatic portal tract, sinusoids, and parenchymal architecture,[22,23] is no longer solely a diagnosis of exclusion. This realization provides a new perspective in which PSVD and other diseases can coexist.[24,25] To date, the evolution of the pathological features of PA-SOS has not been reported. The most intuitive and common alteration was that all patients had portal vein stenosis to varying degrees, with more than half of them showing strong OPV, which was a typical histologic finding of PSVD. Additionally, CD34 staining, proposed in the literature to indicate abnormal vascular marker expression in livers

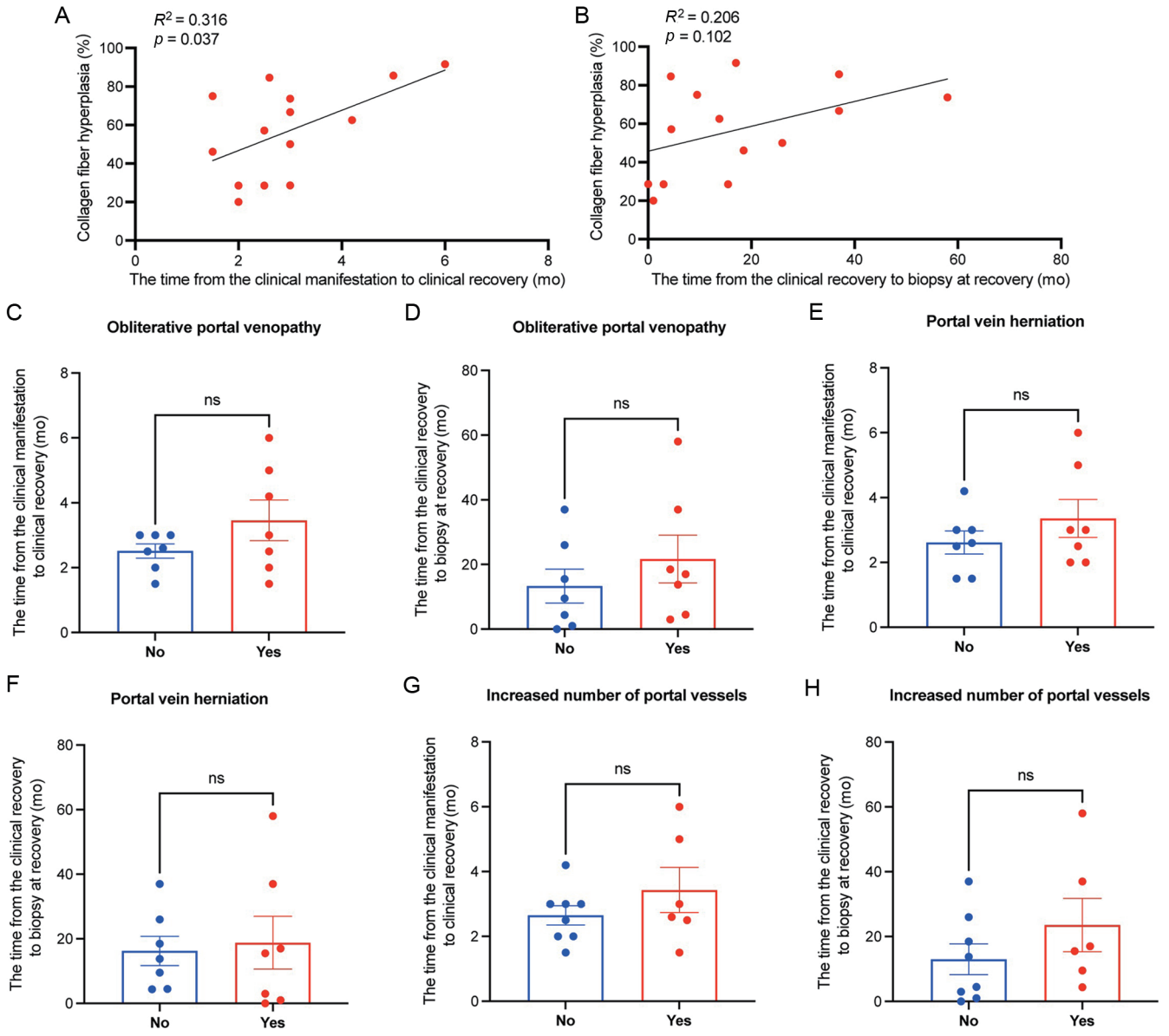

Fig. 4. Comparison of histological features at the time of recovery from the first manifestation or recovery liver biopsy. The evaluated pathological features included collagen fiber hyperplasia (A–B), obliterative portal venopathy (C–D), portal vein herniation (E–F), and increased number portal vessels (G–H). The two time intervals were from first clinical manifestation to clinical recovery (the left panels) and from clinical recovery to recovery liver biopsy (the right panels). ns, not significant; mo, month.

with PSVD-type alterations,[26,27] was at least mildly aberrant (1+) in patients during the recovery period, revealing capillarization of the sinusoids, which was associated with the development of PSVD.[28–30] Similarly, a study by Jafari *et al*. suggested that abnormal CD34 expression may be a valuable adjunct in the workup of PSVD.[10] Although CD34 is not specific for PSVD, its increased expression in our cohort may also be associated with PSVD-like changes. Moreover, hepatic steatosis was observed in a subset of patients and may represent a potential confounding factor, as mild steatosis may contribute to perisinusoidal fibrosis. However, it is unlikely to fully explain the portal tract abnormalities observed in our cohort.

Furthermore, three cases were diagnosed using alternative nonspecific clinical and histological criteria in our cohort, which may overestimate the true prevalence of PSVD. Larger cohorts with longer follow-up are required for further validation. In addition, no specific signs of portal hypertension that could be clearly attributed to these pathological changes were observed during the follow-up period in our cohort. The reasons might include the following two aspects. On the one hand, 79% of patients underwent TIPS at disease initiation, during which stent implantation in the portal vein can establish a shunt pathway and significantly reduce portal vein pressure. On the other hand, as indicated by Zhang *et al*.,[31] PSVD patients without portal hypertension experienced slow progression and did not exhibit any new signs of portal hypertension during follow-up; moreover, only a small number

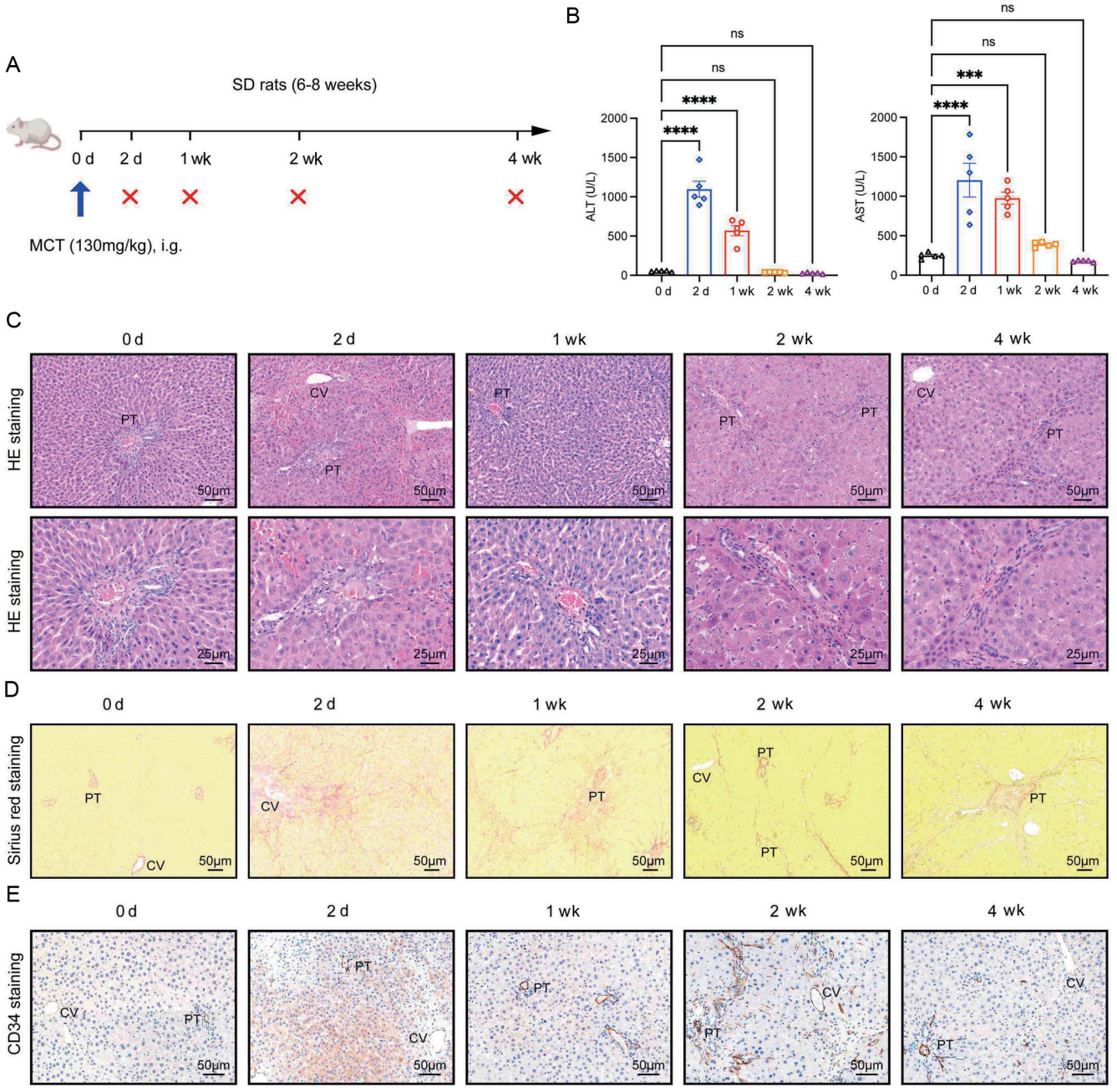

Fig. 5. Rat model of PA-induced SOS. (A) Flowchart of the construction of the PA-induced SOS model. (B) Serum ALT and AST levels in the five groups. (C) H&E histopathological sections of representative livers from the five groups. (D) Sirius red histopathological sections of representative livers from the five groups. (E) CD34 histopathological sections of representative livers from the five groups. n = 5/group. ns, not significant; ***$P < 0.001$; ****$P < 0.0001$. PA, pyrrolizidine alkaloid; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, portal tract; CV, central vein; SOS, sinusoidal obstruction syndrome. HE, hematoxylin and eosin.

of patients were diagnosed after a median follow-up of 8.6 years in a study in France.[32] To address this issue, a multicenter study with a larger sample size and longer duration of follow-up is needed.

Nonetheless, an unresolved question remains: why do certain patients experience this transition in PA-induced liver injury? Previous studies have shown that PA metabolites primarily have direct toxic effects on sinusoidal endothelial cells, which can persist in the blood for 2–4 months.[33] This indicates that even during the clinical recovery phase, toxic metabolites of PAs may persist in the circulation and possibly remain in liver tissues for an extended period, thereby continuing to cause injury. Nevertheless, PSVD-like pathological changes have been observed in patients even several years after the recovery phase, suggesting that other factors may play important roles in this pathological transition process. Our recent study revealed that the gut microbiota and intestinal barrier play vital roles in maintaining SOS homeostasis.[34] Similarly, PSVD patients exhibit altered intestinal permeability, and in particular, gut-derived endotoxins are

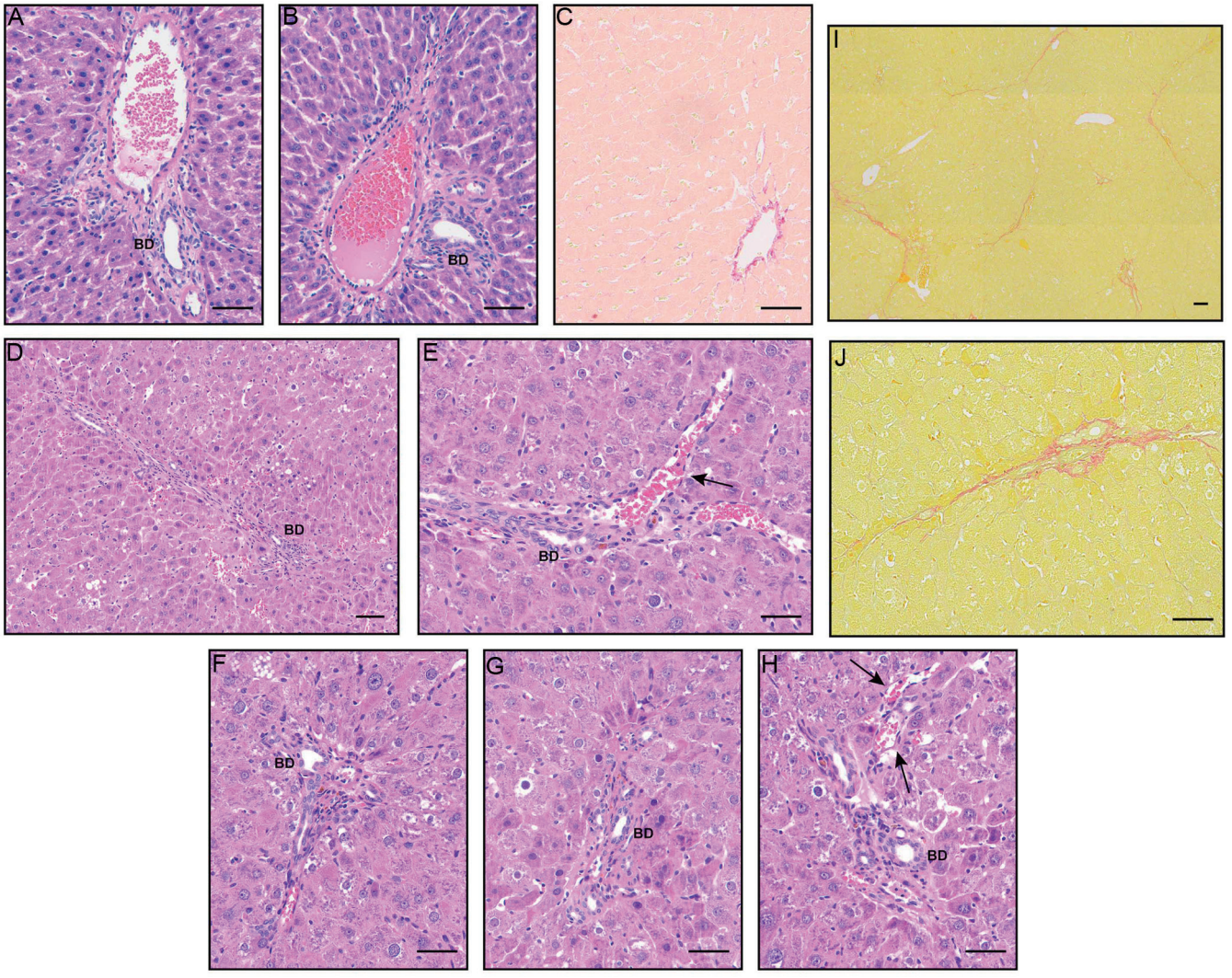

Fig. 6. Main histological alterations observed in MCT-induced SOS animal models. (A–C) Control rat liver; (D–J) MCT-induced SOS rat liver at 2 weeks. (A–B) Normal portal tract with a triad; (C) Sirius red staining in control rat liver; (D) narrowing of the portal tract area and obliterative portal venopathy, accompanied by steatosis at low magnification; (E) portal vein herniation. Black arrows indicate these veins herniating from the portal tract into the lobules; (F–G) portal vein stricture; (H) portal vein branch abnormality. Black arrows indicate an increased number of portal vessels; (I–J) Sirius red staining displaying some degree of incomplete septal fibrosis. Scale bars are 50 μm. BD, bile duct; MCT, monocrotaline; SOS, sinusoidal obstruction syndrome.

of paramount importance in this process.[35–37] Recent studies have proposed that gut microbiota dysbiosis may contribute to hepatic microvascular abnormalities and PSVD development, while experimental and clinical evidence also supports a regulatory role of the gut microbiota in endothelial and microvascular homeostasis.[38–40] With this background, it is possible to speculate that gut microbiota dysbiosis in patients with SOS might not be fully restored during the clinical recovery period, during which bacterial translocation and their metabolites through the enterohepatic axis cause repeated insults to the liver blood vessels, culminating in portal fibrosis and obliteration of the portal vein. Of course, this is just speculation, and specifically designed studies are needed to shed light on these aspects. Given the available data, we first present evidence for the possible existence of PSVD in PA-induced liver injury, reflecting the natural course of the disease.

Considering that alterations in liver pathology in PA-SOS patients may be influenced by confounding factors such as treatment methods and specific diseases, we constructed an animal model to simulate the natural evolution of MCT-induced SOS in rats without any intervention. A similar phenomenon was reported in a previous study.[12] They reported typical pathological features of SOS, such as sinusoidal dilation and endothelial cell damage on Day 2 and obvious liver fibrosis at 1–2 weeks if there was no further PA exposure. Moreover, PSVD-like changes in MCT-induced rats at 2–4 weeks were also identified, showing histopathological parallels with those in established PSVD models.[41] Although assessments of portal vein pressure and splenomegaly were not conducted in our study, experiments are currently underway in our laboratory to develop a more convenient and stable animal model that could comprehensively mimic key clinicopathological dimensions of PSVD.

However, several limitations of the present study need to be acknowledged, primarily attributable to its insufficient

sample size and retrospective design. Given the relative rarity of PA-induced liver injury and the lack of access to pathological specimens due to the noninvasive criteria for SOS, the availability of samples was limited, especially matched pathology specimens, which may consequently decrease the statistical power. Notably, the observation of the above phenomenon in 14 consecutively collected cases highlights certain issues. In addition, compared with that of PSVD, the follow-up period was not long enough. Hence, a high-quality prospective study with a larger sample size and longer follow-up duration is needed to confirm our findings. Another noteworthy limitation is that most included patients had relatively severe PA-SOS and thus received TIPS intervention.

Given that TIPS stents markedly alter portal hemodynamics, this may interfere with the observation of natural portal hypertension progression. Accordingly, our findings are less generalizable to patients without TIPS intervention. Studies enrolling a larger sample of patients receiving anticoagulation therapy are needed, although we also performed further experimental validation.

Conclusions

We are the first to systematically compare the clinical and hepatic pathological features of SOS induced by PAs during the acute and recovery stages, filling a gap in this area. Notably, histological changes shifted from sinusoidal congestion to portal venopathy, raising the possibility of PSVD-related pathological alterations during the disease course. From this perspective, clinicians should be aware of these alterations, as they may suggest the potential occurrence of PSVD during the recovery stage of PA-induced liver injury. Regular long-term follow-up and dynamic pathological assessment are recommended to monitor disease progression. However, further large-sample studies are needed to validate our findings and establish standardized follow-up strategies.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/JCTH.2026.00077.

Acknowledgments

The authors would like to thank all the study participants for their voluntary participation and the Affiliated Drum Tower Hospital, Medical School of Nanjing University, for funding this study.

Funding

This work was supported by funding from the Clinical Trials program of the Affiliated Drum Tower Hospital, Medical School of Nanjing University (2022-LCYJ-MS-17), the Clinical Trials program of the Affiliated Drum Tower Hospital, Medical School of Nanjing University (2024-LCYJ-PY-01), and the Youth Development Project of Nanjing Drum Tower Hospital (2025-JCYJ-QP-49).

Conflict of interest

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

Author contributions

Drafted the manuscript (SZ, FZ), conducted the experiments and analyzed the data (SZ, FZ, YL, SyZ, HZ), participated in the research design (HX, QY, WZ, BX, JX, LW, JCGP, JT), and revised the manuscript (SZ, JC, YZ). All authors discussed the results and contributed to the final manuscript.

Ethical statement

The study complied with the Declaration of Helsinki (as revised in 2024) and was approved by the Ethics Committee of Nanjing Drum Tower Hospital (Approval No. 2022-486-02). All animal experiments were conducted in accordance with the guidelines approved by the Committee on the Ethics of Animal Experiments of Drum Tower Hospital Medical School of Nanjing University (Approval No. 2021AE01088), in compliance with the ARRIVE guidelines. Written informed consent was obtained from all patients in this study. All animals received humane care.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

[1] Fan CQ, Crawford JM. Sinusoidal obstruction syndrome (hepatic veno-occlusive disease). J Clin Exp Hepatol 2014;4(4):332–346. doi:10.1016/j.jceh.2014.10.002, PMID:25755580.
[2] Yu Z, Li W, Tian C, Cao Y, Zhang C. Drug-induced hepatic sinusoidal obstruction syndrome: current advances and future perspectives. Arch Toxicol 2025;99(3):835–850. doi:10.1007/s00204-024-03950-9, PMID:39718593.
[3] Zhuge Y, Liu Y, Xie W, Zou X, Xu J, Wang J, *et al*. Expert consensus on the clinical management of pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome. J Gastroenterol Hepatol 2019;34(4):634–642. doi:10.1111/jgh.14612, PMID:30669184.
[4] Zhu L, Zhang CY, Li DP, Chen HB, Ma J, Gao H, *et al*. Tu-San-Qi (Gynura japonica): the culprit behind pyrrolizidine alkaloid-induced liver injury in China. Acta Pharmacol Sin 2021;42(8):1212–1222. doi:10.1038/s41401-020-00553-9, PMID:33154553.
[5] Jiang X, Ma X, Tian S, Peng L. Efficacy and safety of transjugular intrahepatic portosystemic shunt in hepatic sinusoidal obstruction syndrome: systematic review and meta-analysis. Front Med (Lausanne) 2025;12:1625825. doi:10.3389/fmed.2025.1625825, PMID:40880758.
[6] Dai F, Qiao W, Kang Z, Chen Y, Li K, Shen W, *et al*. Clinical Features and CT Imaging Analysis of Hepatic Sinuscase-Syndrome and Budd-Chiari Syndrome. Int J Gen Med 2022;15:2389–2396. doi:10.2147/IJGM.S348176, PMID:35264876.
[7] Zhang W, Liu L, Zhang M, Zhang F, Peng C, Zhang B, *et al*. Validation of the Nanjing Criteria for Diagnosing Pyrrolizidine Alkaloids-induced Hepatic Sinusoidal Obstruction Syndrome. J Clin Transl Hepatol 2021;9(3):345–352. doi:10.14218/JCTH.2020.00124, PMID:34221920.
[8] de Franchis R, Bosch J, Garcia-Tsao G, Reiberger T, Ripoll C, Baveno VII Faculty. Baveno VII - Renewing consensus in portal hypertension. J Hepatol 2022;76(4):959–974. doi:10.1016/j.jhep.2021.12.022, PMID:35120736.
[9] Wang X, Zhang W, Zhang M, Zhang F, Xiao J, Yin Q, *et al*. Development of a Drum Tower Severity Scoring (DTSS) system for pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome. Hepatol Int 2022;16(3):669–679. doi:10.1007/s12072-021-10293-5, PMID:35023026.
[10] Jafari P, Evaristo G, Du XA, Sharma AE, Marcus V, Liu X, *et al*. Portosinusoidal Vascular Disorder: A Heretofore Unrecognized Manifestation of Sickle Cell Disease? Mod Pathol 2024;37(1):100351. doi:10.1016/j.modpat.2023.100351, PMID:37820763.
[11] El Jabbour T, McHugh KE, Patil DT, Zuo C, Koo BH, Kim S, *et al*. Histologic Lesions of Porto-Sinusoidal Vascular Disease Following Phlebotomy in Hemochromatosis. Gastroenterology Res 2020;13(1):32–39. doi:10.14740/gr1236, PMID:32095171.
[12] Chen X, Ma J, He Y, Xue J, Song Z, Xu Q, *et al*. Characterization of liver injury induced by a pyrrolizidine alkaloid in rats. Phytomedicine 2021;89:153595. doi:10.1016/j.phymed.2021.153595, PMID:34153877.
[13] Hu Z, Lu Y, Cao J, Lin L, Chen X, Zhou Z, *et al*. N-acetyltransferase NAT10 controls cell fates via connecting mRNA cytidine acetylation to chromatin signaling. Sci Adv 2024;10(2):eadh9871. doi:10.1126/sciadv.adh9871, PMID:38215194.
[14] Li G, Lin J, Zhang C, Gao H, Lu H, Gao X, *et al*. Microbiota metabolite butyrate constrains neutrophil functions and ameliorates mucosal inflammation in inflammatory bowel disease. Gut Microbes 2021;13(1):1968257. doi:10.1080/19490976.2021.1968257, PMID:34494943.
[15] Jiang LP, Fan SQ, Xiong QX, Zhou YC, Yang ZZ, Li GF, *et al*. GRK5 functions as an oncogenic factor in non-small-cell lung cancer. Cell Death Dis 2018;9(3):295. doi:10.1038/s41419-018-0299-1, PMID:29463786.
[16] Xiao J, Tu J, Zhang H, Zhang F, Zhang W, Xu H, *et al*. Risk factors of poor

prognosis in patients with pyrrolidine alkaloid-induced hepatic sinusoidal obstruction syndrome after transjugular intrahepatic portosystemic shunt. Hepatol Int 2021;15(3):720–729. doi:10.1007/s12072-020-10126-x, PMID:33507485.
[17] Huang T, Zhang X, Yan K, Lou D, He Y, Dai S, *et al*. Transjugular intrahepatic portosystemic shunt for pyrrolidine alkaloids-induced hepatic sinusoidal obstruction syndrome: a retrospective cohort study. Eur J Gastroenterol Hepatol 2023;35(9):1004–1011. doi:10.1097/MEG.0000000000002591, PMID:37395216.
[18] Huang Q, Zhang Q, Xu H, Zu M, Xiao J, Shen B. Mid- to long-term outcomes of initial transjugular intrahepatic portosystemic shunt versus anticoagulation for pyrrolizidine alkaloid-induced hepatic sinusoidal obstruction syndrome. Eur J Gastroenterol Hepatol 2023;35(4):445–452. doi:10.1097/MEG.0000000000002509, PMID:36719828.
[19] Liu F, Rong X, Guo H, Xu D, Liu C, Meng L, *et al*. Clinical characteristics, CT signs, and pathological findings of Pyrrolizidine alkaloids-induced sinusoidal obstructive syndrome: a retrospective study. BMC Gastroenterol 2020;20(1):30. doi:10.1186/s12876-020-1180-0, PMID:32019495.
[20] Technology Committee on DILI Prevention and Management, Chinese Medical Biotechnology Association; Study Group of Drug-Induced Liver Disease, Chinese Medical Association for the Study of Liver Diseases. [Chinese guideline for diagnosis and management of drug-induced liver injury (2023 version)]. Zhonghua Gan Zang Bing Za Zhi 2023;31(4):355–384. doi:10.3760/cma.j.cn501113-20230419-00176-1, PMID:37248976.
[21] Siu JT, Nguyen T, Turgeon RD. N-acetylcysteine for non-paracetamol (acetaminophen)-related acute liver failure. Cochrane Database Syst Rev 2020;12(12):CD012123. doi:10.1002/14651858.CD012123.pub2, PMID:33294991.
[22] De Gottardi A, Sempoux C, Berzigotti A. Porto-sinusoidal vascular disorder. J Hepatol 2022;77(4):1124–1135. doi:10.1016/j.jhep.2022.05.033, PMID:35690264.
[23] Premkumar M, Anand AC. Porto-sinusoidal Vascular Disease: Classification and Clinical Relevance. J Clin Exp Hepatol 2024;14(5):101396. doi:10.1016/j.jceh.2024.101396, PMID:38601747.
[24] Sarin SK, Lohse AW, Kamath PS. Poor long-term outcome in patients with porto-sinusoidal vascular disease (PSVD): fact or disease misclassification? J Hepatol 2025;82(1):4–6. doi:10.1016/j.jhep.2024.09.015, PMID:39306284.
[25] Olivas P, Perez-Campuzano V, Orts L, Montironi C, Magaz M, Ruiz P, *et al*. Porto-sinusoidal vascular disorder in chronic HBV: A significant coexistence not to be overlooked. JHEP Rep 2024;6(3):100996. doi:10.1016/j.jhepr.2023.100996, PMID:38384671.
[26] Guido M, Sarcognato S, Sonzogni A, Lucà MG, Senzolo M, Fagiuoli S, *et al*. Obliterative portal venopathy without portal hypertension: an underestimated condition. Liver Int 2016;36(3):454–460. doi:10.1111/liv.12936, PMID:26264219.
[27] Zhang X, Thomas C, Schiano TD, Thung SN, Ward SC, Fiel MI. Aberrant von Willebrand factor expression of sinusoidal endothelial cells and quiescence of hepatic stellate cells in nodular regenerative hyperplasia and obliterative portal venopathy. Histopathology 2020;76(7):959–967. doi:10.1111/his.14083, PMID:31994248.
[28] Declercq M, Treps L, Geldhof V, Conchinha NV, de Rooij LPMH, Subramanian A, *et al*. Single-cell RNA sequencing of cystic fibrosis liver disease explants reveals endothelial complement activation. Liver Int 2024;44(9):2382–2395. doi:10.1111/liv.15963, PMID:38847551.
[29] Cerda Reyes E, González-Navarro EA, Magaz M, Muñoz-Sánchez G, Diaz A, Silva-Junior G, *et al*. Autoimmune biomarkers in porto-sinusoidal vascular disease: Potential role in its diagnosis and pathophysiology. Liver Int 2021;41(9):2171–2178. doi:10.1111/liv.14997, PMID:34173316.
[30] Hernández-Gea V, Campreciós G, Betancourt F, Pérez-Campuzano V, Seijo S, Díaz A, *et al*. Co-expression gene network analysis reveals novel regulatory pathways involved in porto-sinusoidal vascular disease. J Hepatol 2021;75(4):924–934. doi:10.1016/j.jhep.2021.05.014, PMID:34052252.
[31] Zhang Y, Xiong Q, Zhong Y, Liu D, Liu H, Wang L, *et al*. Clinical characteristics and natural history of porto-sinusoidal vascular disease: A cohort study of 234 patients in China. Liver Int 2024;44(9):2329–2340. doi:10.1111/liv.16002, PMID:38828515.
[32] Cazals-Hatem D, Hillaire S, Rudler M, Plessier A, Paradis V, Condat B, *et al*. Obliterative portal venopathy: portal hypertension is not always present at diagnosis. J Hepatol 2011;54(3):455–461. doi:10.1016/j.jhep.2010.07.038, PMID:21087805.
[33] Ma J, Zhang W, He Y, Zhu L, Zhang C, Liu J, *et al*. Clinical application of pyrrole-hemoglobin adducts as a biomarker of pyrrolizidine alkaloid exposure in humans. Arch Toxicol 2021;95(2):759–765. doi:10.1007/s00204-020-02947-4, PMID:33210216.
[34] Zhao S, Zhang H, Zhu H, Zhao T, Tu J, Yin X, *et al*. Gut microbiota promotes macrophage M1 polarization in hepatic sinusoidal obstruction syndrome via regulating intestinal barrier function mediated by butyrate. Gut Microbes 2024;16(1):2377567. doi:10.1080/19490976.2024.2377567, PMID:39012957.
[35] Gioia S, Carnevale R, Tavano D, Overi D, Ridola L, Nardelli S, *et al*. Association between gut-derived endotoxins and porto-sinusoidal vascular disorder with portal hypertension. Aliment Pharmacol Ther 2023;58(11-12):1205–1216. doi:10.1111/apt.17727, PMID:37728001.
[36] Pugliese N, Giuli L, Mastrorocco E, Santopaolo F, Marcozzi G, Bezzio C, *et al*. Exploring the link: Porto-sinusoidal vascular disorder and inflammatory bowel disease - A comprehensive narrative review. Dig Liver Dis 2024;56(6):964–970. doi:10.1016/j.dld.2023.11.021, PMID:38044225.
[37] Overi D, Pugliese N, Carnevale R, Nardelli S, Tavano D, Ridola L, *et al*. Role of Gut-Derived Endotoxins in Porto-Sinusoidal Vascular Disorder: Comparison Between patients with and without portal hypertension. Liver Int 2025;45(9):e70277. doi:10.1111/liv.70277, PMID:40781803.
[38] Li Y, Lyu L, Ding H. The potential roles of gut microbiome in porto-sinusoidal vascular disease: an under-researched crossroad. Front Microbiol 2025;16:1556667. doi:10.3389/fmicb.2025.1556667, PMID:40099185.
[39] Kiouptsi K, Pontarollo G, Reinhardt C. Gut Microbiota and the Microvasculature. Cold Spring Harb Perspect Med 2023;13(8):a041179. doi:10.1101/cshperspect.a041179, PMID:37460157.
[40] Formes H, Bernardes JP, Mann A, Bayer F, Pontarollo G, Kiouptsi K, *et al*. The gut microbiota instructs the hepatic endothelial cell transcriptome. iScience 2021;24(10):103092. doi:10.1016/j.isci.2021.103092, PMID:34622147.
[41] Campreciós G, Vilaseca M, Tripathi DM, Montironi C, Díaz A, Aguilar D, *et al*. Interspecies transcriptomic comparison identifies a potential porto-sinusoidal vascular disorder rat model suitable for in vivo drug testing. Liver Int 2024;44(1):180–190. doi:10.1111/liv.15765, PMID:37872644.