GE – Portuguese Journal of Gastroenterology

Clinical Case Study

GE Port J Gastroenterol 2025;32:54–60
DOI: 10.1159/000539092

Received: December 18, 2023
Accepted: February 12, 2024
Published online: June 14, 2024

Porto-Sinusoidal Vascular Disease and Downhill Varices: Separate Clinical Entities?

Inês Pestana[a] Carlos Noronha Ferreira[b] Rita Luís[c, d] Rui Sousa[a]
Eduardo Abrantes Pereira[a] António Banhudo[a]

[a]Department of Gastroenterology, Hospital Amato Lusitano ULSCB, Castelo Branco, Portugal; [b]Department of Gastroenterology, Hospital de Santa Maria CHULN, Lisbon, Portugal; [c]Department of Anatomic Pathology, Hospital São José CHULC, Lisbon, Portugal; [d]Department of Anatomic Pathology, Hospital de Santa Maria CHULN, Lisbon, Portugal

Keywords
Porto-sinusoidal vascular disease · Downhill varices · Pulmonary arterial hypertension · Liver hemodynamic study · Transjugular liver biopsy

Abstract

Introduction: Porto-sinusoidal vascular disease (PSVD) is an entity characterized by the absence of histologic liver cirrhosis and the detection of specific or non-specific histological findings, irrespective of the presence of portal hypertension (PHT). The pathogenesis remains poorly understood. Pulmonary arterial hypertension (PAH), independently of the presence of PHT, can be associated with an increase in central venous pressure, which can rarely lead to the development of downhill varices in the proximal esophagus. ***Case Presentation:*** A 53-year-old woman, with an unremarkable medical and pharmacological history, presented with a 3-day history of melena, epigastric pain and hematemesis. Physical examination revealed bilateral peripheral edema of the legs. Laboratory findings included severe anemia, normal hepatic enzymology, and NT-proBNP 1,748 pg/mL. Endoscopy showed large proximal esophageal varices and mild hypertensive gastropathy. A complete liver disease etiology panel was negative. Ultrasound showed an irregular liver surface, splenomegaly, and dilated supra-hepatic veins and inferior vena cava. Echocardiogram revealed significant cardiac valve and cavity abnormalities, especially on the right side, as well as moderate to severe PAH. Diuretics therapy was started with clinical improvement. Beta-blockers were suspended due to intolerance. There were no images suggestive of portosystemic collateralization on angiography. Re-evaluation endoscopy showed large but reduced esophageal varices, without red spots. Cardiopulmonary hemodynamic assessment revealed moderate PAH (40 mm Hg). Liver hemodynamic study revealed non-clinically significant sinusoidal PHT. Transjugular liver biopsy revealed nodular regenerative hyperplasia suggestive of PSVD. ***Discussion/Conclusion:*** The case was complex and presented diagnostic challenges, illustrating the uncommonly reported association between PSVD and porto-pulmonary hypertension and the importance of the transjugular liver biopsy and pressure measurements to confirm both diagnoses.

karger@karger.com
www.karger.com/pjg

Karger
OPEN ACCESS

Correspondence to:
Inês Pestana, ines_pestana15@hotmail.com

Doença vascular porto-sinusoidal e varizes downhill: entidades clínicas distintas?

Palavras Chave
Doença vascular porto-sinusoidal · Varizes downhill · Hipertensão arterial pulmonar · Estudo hemodinâmico hepático · Biópsia hepática transjugular

Resumo
Introdução: A doença vascular porto-sinusoidal (PSVD) é uma entidade caracterizada pela ausência histológica de cirrose hepática e pela detecção de achados histológicos específicos ou inespecíficos, independentemente da presença de hipertensão portal (PHT). A sua fisiopatologia permanece pouco compreendida. A hipertensão arterial pulmonar (PAH), independentemente da presença de PHT, pode estar associada ao aumento da pressão venosa central, o que, raramente, pode levar ao desenvolvimento de varizes *downhill* no esófago proximal. ***Caso clínico:*** Mulher de 53 anos, sem antecedentes pessoais e farmacológicos de relevo, com quadro de melenas, epigastralgia e hematemeses com 3 dias de evolução. O exame físico revelou edema periférico bilateral dos membros inferiores. Os achados laboratoriais revelaram anemia grave, enzimologia hepática normal e NT-proBNP 1748 pg/mL. A endoscopia mostrou varizes esofágicas proximais grandes e gastropatia hipertensiva ligeira. Foi realizado um painel completo de etiologia de doença hepática, que não revelou alterações. A ultrassonografia mostrou uma superfície hepática irregular, esplenomegália e veias supra-hepáticas e veia cava inferior dilatadas. O ecocardiograma revelou alterações significativas nas válvulas e cavidades cardíacas, especialmente no lado direito, bem como PAH moderada a grave. A doente iniciou terapêutica diurética com melhoria clínica. A terapêutica com beta-bloqueantes foi suspensa por intolerância. Não se verificaram imagens sugestivas de colateralização portossistémica na angiografia. A endoscopia de reavaliação mostrou varizes esofágicas grandes, mas reduzidas em relação ao exame anterior, sem *red spots*. A avaliação hemodinâmica cardiopulmonar revelou PAH moderada (40 mm Hg). O estudo hemodinâmico hepático revelou PHT sinusoidal não clinicamente significativa. A biópsia hepática transjugular revelou hiperplasia regenerativa nodular sugestiva de PSVD. ***Discussão/Conclusão:*** Este caso apresentou elevada complexidade e múltiplos desafios diagnósticos, ilustrando a associação incomumente relatada entre PSVD e hipertensão porto-pulmonar e a importância da biópsia hepática transjugular e medições de pressão para confirmar ambos os diagnósticos.

Introduction

Portal hypertension (PHT) is the main clinical manifestation of advanced chronic liver disease. Clinically significant PHT (hepatic venous pressure gradient – HVPG ≥10 mm Hg) [1] predicts complications like variceal bleeding, ascites, jaundice, and encephalopathy [2–4]. These can occur in the absence of cirrhosis (Table 1) [4, 5].

Porto-sinusoidal vascular disease (PSVD) is a rare cause of PHT and is characterized by absence of liver cirrhosis and detection of specific or non-specific histological findings, irrespective of PHT [4, 7]. The presence of other causes of liver disease does not rule it out [4]. The pathogenesis remains poorly understood. Drugs, hematologic and infectious diseases, prothrombotic and immune disorders, and genetic factors have been associated [4, 8]. Imaging and non-invasive tests like liver (LSM) and spleen stiffness measurements (SSM) have a diagnostic role, but hemodynamic study with transjugular liver biopsy (TJLB) is crucial to assess HVPG and obtain liver tissue for histopathology [4].

Pulmonary arterial hypertension (PAH), characterized by elevated mean pulmonary artery pressure (PAP) (>25 mm Hg), is most commonly idiopathic, but may be associated with PHT (porto-pulmonary hypertension-PoPH). PAH and PoPH are histologically indistinguishable [9–11].

PAH can be associated with increased central venous pressure [12], which can rarely lead to downhill varices in the proximal esophagus [13]. Blood flows from the superior vena cava to the esophageal venous plexus [14]. It is a rare etiology for hematemesis (0.1%) [13], due to their localization in the proximal esophageal submucosa [14]. Treatment should be directed at the vascular obstruction's underlying cause [15, 16].

Case Report

A 53-year-old-woman presented with a 3-day history of melena, epigastric pain and hematemesis. Medical history included obesity (BMI 34 kg/m^2) and peripheral vascular

Table 1. Causes of noncirrhotic portal hypertension [6]

Prehepatic
Portal vein thrombosis
Splenic vein thrombosis
Splanchnic arteriovenous fistula
Splenomegaly (e.g., from lymphoma, Gaucher's disease*)
Intrahepatic
Presinusoidal
Schistosomiasis*
Idiopathic noncirrhotic portal hypertension (including nodular regenerative hyperplasia)
Primary biliary cholangitis
Sarcoidosis*
Congenital hepatic fibrosis
Primary sclerosing cholangitis
Hepatic arteriopetal fistula
Adult polycystic liver disease
Arteriovenous fistulas
Autoimmune cholangiopathy
Vinyl chloride toxicity*
Neoplastic occlusion of the intrahepatic portal vein
Mineral oil granuloma*
Sinusoidal
Arsenic poisoning
Vinyl chloride toxicity*
Drugs (e.g., amiodarone, methotrexate)
Alcoholic liver disease*
Nonalcoholic fatty liver disease
Gaucher's disease*
Zellweger syndrome
Viral hepatitis
Chronic Q fever
Schistosomiasis*
Amyloid or light-chain deposition in the space of Disse
Acute hepatic injury
Mastocytosis
Agnogenic myeloid metaplasia
Acute fatty liver of pregnancy
Postsinusoidal
Sinusoidal obstruction syndrome (venoocclusive disease)
Budd-chiari syndrome*
Alcoholic liver disease*
Chronic radiation injury
Vitamin A toxicity
Epithelioid hemangioendothelioma
Angiosarcoma
Sarcoidosis*
Mycobacterium avium or *M. intracellulare* infection
Mineral oil granuloma*
Posthepatic
IVC obstruction (e.g., Budd-Chiari syndrome*)
Cardiac disease (constrictive pericarditis, restrictive cardiomyopathy)

IVC, inferior vena cava. *May cause noncirrhotic portal hypertension via several mechanisms.

disease treated with bioflavonoids. She denied fever, jaundice, choluria, alcohol consumption, and liver disease. She also denied taking nonsteroidal anti-inflammatory drugs, anti-platelets, or anticoagulants.

Physical examination was unremarkable except for bilateral peripheral edema of the legs. Laboratory findings included severe iron deficiency anemia (hemoglobin 4.1 g/dL), platelet count 188 × 10^9/L, INR 1.13, albumin 4.6 g/dL, normal hepatic enzymes, and raised NT-proBNP (1,748 pg/mL).

Endoscopy showed large proximal esophageal varices, without red spots, and mild portal hypertensive gastropathy (shown in Fig. 1). Abdominal ultrasound revealed slight hepatomegaly with irregular liver surface; no focal lesions; marked echogenicity of the fibrovascular axes and hilum; ectasia of the inferior vena cava (IVC) and hepatic veins; no portal vein abnormalities; mild splenomegaly (14 cm). A comprehensive chronic liver disease etiology panel was negative.

Echocardiograms revealed good systolic function; dilated right heart cavities; mild aortic and mitral insufficiency; moderate tricuspid and pulmonary insufficiency; severe PAH. Furosemide and spironolactone were instituted, with clinical improvement. Perindopril and carvedilol were introduced but the latter was suspended due to intolerance (symptomatic hypotension, lipothmia, platypneia).

Coronary angiography ruled out coronary disease. Thoracoabdominal computed tomography angiography showed enlargement of the pulmonary artery with no evidence of thrombus, as well as absence of porto-systemic collateralizaion, portal vein thrombosis, and structural lung disease. A re-evaluation endoscopy showed large but reduced esophageal varices, without red spots (shown in Fig. 2).

Cardiopulmonary and hepatic hemodynamic (HH) study revealed moderate PAH (mean PAP 40 mm Hg, pulmonary capillary wedge pressure 5 mm Hg) and HVPG of 6 mm Hg, which was suggestive of non-clinically significant sinusoidal PHT (shown in Fig. 3). There were no hepatic vein-to-vein communicants detected during the HH study.

The biopsy fragments obtained with TJLB measured 48 mm in length. Histopathological evaluation revealed nodular regenerative hyperplasia (NRH) and obliterated portal veins, without fibrosis, suggesting PSVD (shown in Fig. 4).

She was discharged on diuretics, with improvement of peripheral edema. Additionally, she was medicated with macitentan and tadalafil. She underwent variceal bleeding prophylaxis with endoscopic band ligation.

Discussion

As previously stated, diagnosis of PSVD requires histological confirmation and exclusion of liver cirrhosis [4, 17]. HH study with TJLB is often performed due to thrombocytopenia, and was key in the diagnostic process [18]. In PSVD, HVPG is normal/slightly elevated and often <10 mm Hg, due to pre-sinusoidal PHT [4, 17, 19] and presence of vena-vena communications [4, 19]. Hence, HVPG is often not correlated with events like variceal bleeding/ascites [17].

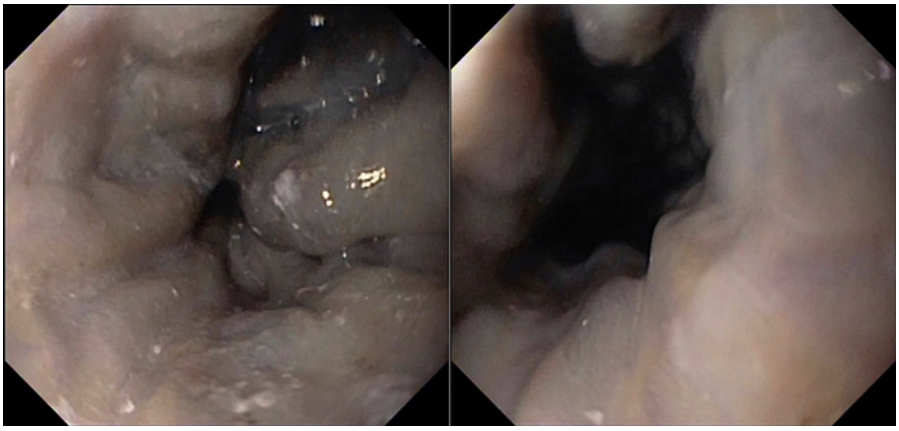

Fig. 1. Large proximal esophageal varices without red spots.

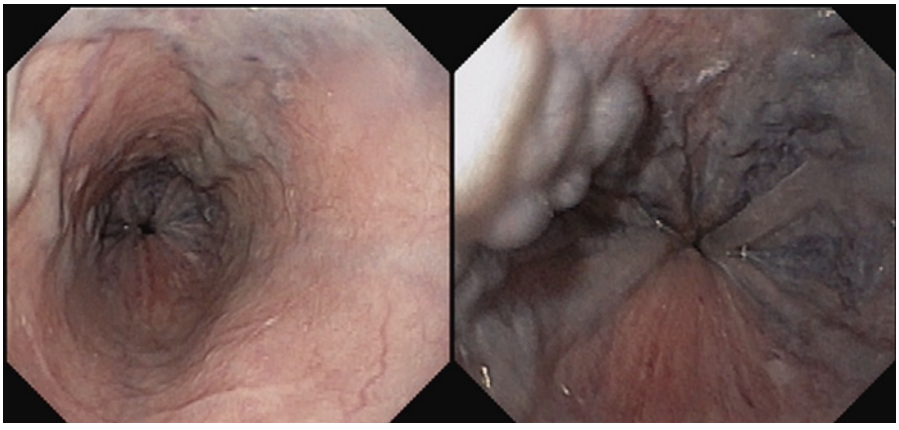

Fig. 2. Large esophageal varices, reduced in size in comparison to the previous evaluation, without red spots.

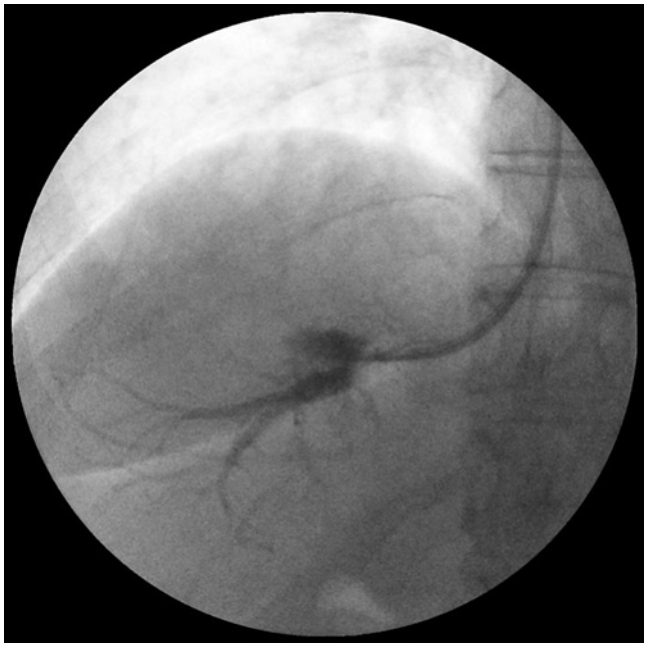

Fig. 3. Wedged supra-hepatic vein pressure measurement with Fogharty balloon catheter.

Specific histologic features include obliterative portal venopathy, NRH (present in this case) and incomplete septal cirrhosis/fibrosis [4, 17]. NRH is a nodular parenchymal transformation with hyperplastic hepatocytes surrounded by atrophic hepatocytes without fibrosis [20].

Abdominal ultrasound features of PSVD include normal/inhomogeneous liver with irregular surface; right hepatic lobe atrophy/hypotrophy; caudate lobe hypertrophy; marginal atrophy; compensatory central hypertrophy; features of PHT (splenomegaly, portosystemic collaterals, portal venous dilation); portal vein abnormalities (portal atypical thickening, hyperechoic walls, and portal vein thrombosis [PVT]) [4, 19], some of which were identified in the abdominal ultrasound performed, as is stated above.

LSM are usually normal/slightly elevated, and SSM are increased [4, 19]. LSM <10 kPa as a cut-off value has good diagnostic performance and low LSM values should prompt a biopsy [21]. A higher spleen-to-liver stiffness may be suggestive of PSVD and should indicate a HH study and TJLB to rule it out [4, 19].

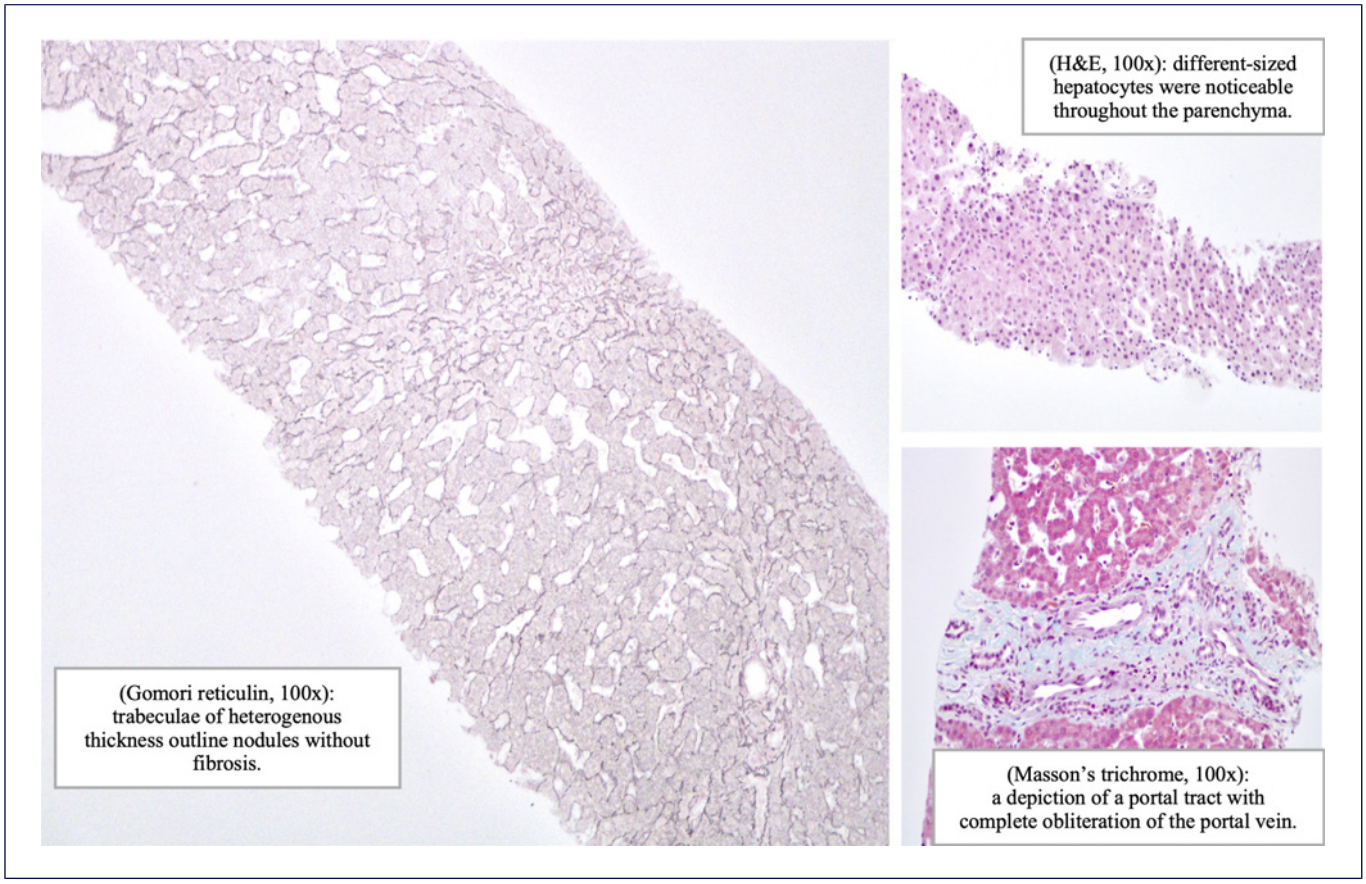

Fig. 4. Liver histological features suggesting PSVD.

Patients with PSVD and PHT are usually asymptomatic until they develop complications. Thrombocytopenia is common and transaminases, alkaline phosphatase and gamma-glutamyltransferase are normal/slightly elevated, but hepatocellular function is relatively preserved (normal serum albumin and bilirubin) [4, 19].

Gastrointestinal bleeding secondary to ruptured varices is a presenting symptom in 20–40% [4, 5, 19]. Esophageal varices are frequently large and gastric varices are more common than in cirrhosis [18]. In our patient, the varices were in the proximal esophagus, a vascular territory less influenced by PHT, raising the possibility of downhill varices. Although the ultrasound showed an irregular liver surface, hyperechoic walls of the fibrovascular axes and splenomegaly (compatible with PSVD), the IVC, and hepatic veins ectasia suggested a cardiovascular disorder. Furthermore, the patient had peripheral leg edema without ascites and the echocardiogram revealed significant cardiac valve and cavity abnormalities and severe PAH. In this case, the cardiopulmonary and HH study and TJLB were essential in confirming both PSVD and PAH.

The risk factors linking PSVD and PoPH are unknown [4], and few cases have been reported. PoPH has a multifactorial pathogenesis (genetic predisposition; pulmonary vascular wall shear stress; dysregulation of vasoactive, proliferative, angiogenic, and inflammatory mediators) [10, 11]. Patients may be asymptomatic but often present with exertional dyspnoea and may have clinical signs of right heart failure when moderate to severe disease develops [22]. In this case, the patient presented with peripheral edema. It is unclear if the level of portal hypertension is correlated with the severity of PoPH [23]. The treatment includes general measures, such as diuretics, which can reduce volume overload, and specific treatment for PAH, such as endothelin receptor antagonists (caution is advised due to hepatic impairment), phosphodiesterase subtype-5 inhibitors, and prostacyclin analogues [22, 23]. Our patient was intolerant to beta-blockers, but even if this was not the case, withdrawal of beta-blocker therapy (in the context of

esophageal varices) may help to increase cardiac output and thereby help exertional dyspnoea [22, 23]. Cohort studies have demonstrated that patients with PoPH have a worse prognosis compared with patients with idiopathic PH [23].

The initial management of PSVD includes treatment of underlying conditions. Complications of PHT should be treated according to cirrhosis recommendations. Patients should be screened regularly for varices and adequate prophylaxis of variceal bleeding with endoscopic band ligation/beta-blockers should be implemented. The indications for transjugular intrahepatic portosystemic shunts and transplantation are the same as for cirrhosis [5, 7].

PVT, a frequent complication (13–45%) during follow-up [7] (increased incidence if history of bleeding and HIV infection) [4], is an indicator of worse prognosis [5]. Anticoagulation is reserved for prothrombotic disorders or PVT [4, 5, 7].

Long-term outcome in PSVD is better than in cirrhosis, given the relatively preserved hepatocellular function [4, 7]. Despite higher frequency of variceal bleeding, mortality is lower than in cirrhosis [4]. In conclusion, this case illustrates the uncommonly reported association between PSVD and PoPH and the importance cardiopulmonary and HH study with TJLB to confirm both.

Acknowledgment

There were no sources of funding or financial disclosures for this manuscript.

Statement of Ethics

The authors declare that all ethical procedures and standards were followed. The patient gave consent to the publication of the case report and accompanying images. Ethical approval was not needed according to local laws.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors do not have any financial disclosures to report.

Author Contributions

All authors fulfilled criteria of ICMJE for authorship: acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

References

1 Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 2007;133(2):481–8. https://doi.org/10.1053/j.gastro.2007.05.024

2 Bosch J, Iwakiri Y. The portal hypertension syndrome: etiology, classification, relevance, and animal models. HepatolInt. 2018; 12(Suppl 1):1–10. https://doi.org/10.1007/s12072-017-9827-9

3 Al-Busafi SA, McNabb-Baltar J, Farag A, Hilzenrat N. Clinical manifestations of portal hypertension. Int J Hepatol. 2012;2012: 203794. https://doi.org/10.1155/2012/203794

4 De Gottardi A, Sempoux C, Berzigotti A. Porto-sinusoidal vascular disorder. J Hepatol. 2022;77(4):1124–35. https://doi.org/10.1016/j.jhep.2022.05.033

5 Kmeid M, Liu X, Ballentine S, Lee H. Idiopathic non-cirrhotic portal hypertension and porto-sinusoidal vascular disease: review of current data. GastroenterologyRes. 2021; 14(2):49–65. https://doi.org/10.14740/gr1376

6 Schouten JN, Garcia-Pagan JC, Valla DC, Janssen HL. Idiopathic noncirrhotic portal hypertension. Hepatology. 2011;54(3): 1071–81. https://doi.org/10.1002/hep.24422.

7 De Gottardi A, Rautou PE, Schouten J, Rubbia-Brandt L, Leebeek F, Trebicka J, et al. Porto-sinusoidal vascular disease: proposal and description of a novel entity. Lancet Gastroenterol Hepatol. 2019;4(5):399–411. https://doi.org/10.1016/S2468-1253(19)30047-0

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):959–74. https://doi.org/10.1016/j.jhep.2021.12.022

9 Mazzola M, Madonna R, Badagliacca R, Caterina R. Porto-pulmonary arterial hypertension: translation of pathophysiological concepts to the bedside. Vascul Pharmacol. 2022;145:107022. https://doi.org/10.1016/j.vph.2022.107022

10 Liberal R, Grant CR, Baptista R, Macedo G. Porto-pulmonaryhypertension: a comprehensivereview. Clin Res Hepatol Gastroenterol. 2015;39(2):157–67. https://doi.org/10.1016/j.clinre.2014.12.011

11 Raevens S, Geerts A, Van Steenkiste C, Verhelst X, Van Vlierberghe H, Colle I. Hepatopulmonary syndrome and portopulmonary hypertension: recent knowledge in pathogenesis and overview of clinical assessment. Liver Int. 2015;35(6):1646–60. https://doi.org/10.1111/liv.12791

12 Li DK, Mao JY, Long Y, Liu DW, Wang XT. Pulmonary hypertension with adult respiratory distress syndrome: prevalence, clinical impact, and association with central venous pressure. Pulm Circ. 2020;10(3):2045894020933087. https://doi.org/10.1177/2045894020933087

13 Loudin M, Anderson S, Schlansky B. Bleeding "downhill" esophageal varices associated with benign superior vena cava obstruction: case report and literature review. BMC Gastroenterol. 2016;16(1):134. https://doi.org/10.1186/s12876-016-0548-7
14 Ayvaz MA, Rakici H, Allescher HD. Are downhill varices an overlooked entity of upper gastrointestinal bleedings? Gastroenterol Res Pract. 2018;2018:7638496. https://doi.org/10.1155/2018/7638496
15 Chakinala RC, Kumar A, BarsaMehta JED, Mehta D, Haq KF, Solanki S, et al. Downhill esophageal varices: a therapeutic dilemma. Ann Transl Med. 2018;6(23):463. https://doi.org/10.21037/atm.2018.11.13
16 Areia M, Romãozinho JM, Ferreira M, Amaro P, Freitas D. "Downhill" varices: a rare cause of esophageal hemorrhage. Rev Esp Enferm Dig. 2006;98(5):359–61. https://doi.org/10.4321/S1130-01082006000500006
17 Gioia S, Nardelli S, Ridola L, Riggio O. Causes and management of non-cirrhotic portal hypertension. Curr Gastroenterol Rep. 2020;22(12):56. https://doi.org/10.1007/s11894-020-00792-0
18 Nicoară-Farcău O, Rusu I, Stefănescu H, Tanțău M, Badea RI, Procopeț B. Diagnostic challenges in non-cirrhotic portal hypertension: porto sinusoidal vascular disease. World J Gastroenterol. 2020;26(22):3000–11. https://doi.org/10.3748/wjg.v26.i22.3000
19 Jin SJ, Choi WM. Porto-sinusoidal vascular disease: a concise updated summary of epidemiology, pathophysiology, imaging, clinical features, and treatments. Korean J Radiol. 2023;24(1):31–8. https://doi.org/10.3348/kjr.2022.0668
20 Zimmermann A. Nodular regenerative hyperplasia and other noncirrhotic nodular hyperplastic lesions of the liver. In: Tumors and tumor-like lesions of the hepatobiliary tract; 2016; p. 1–26. https://doi.org/10.1007/978-3-319-26587-2_118-1
21 Ferreira-Silva J, Gaspar R, Liberal R, Cardoso H, Macedo G. Splenic-hepatic elastography index is useful in differentiating between porto-sinusoidal vascular disease and cirrhosis in patients with portal hypertension. Dig Liver Dis. 2023;55(1):75–80. https://doi.org/10.1016/j.dld.2022.09.018
22 European Association for the Study of the Liver Electronic address easloffice@easloffi-ceeuEuropean Association for the Study of the Liver. Corrigendum to "EASL clinical practice guidelines for the management of patients with decompensated cirrhosis" [J hepatol 69 (2018) 406-460. J Hepatol. 2018;69(5):1207. https://doi.org/10.1016/j.jhep.2018.08.009
23 Jasso-Baltazar EA, Peña-Arellano GA, Aguirre-Valadez J, Ruiz I, Papacristofilou-Riebeling B, Jimenez JV, et al. Portopulmonary hypertension: an updated review. Transplant Direct. 2023;9(8):e1517. https://doi.org/10.1097/TXD.0000000000001517