Research article

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Link between persistent, unexplained gamma-glutamyltransferase elevation and porto-sinusoidal vascular disorder

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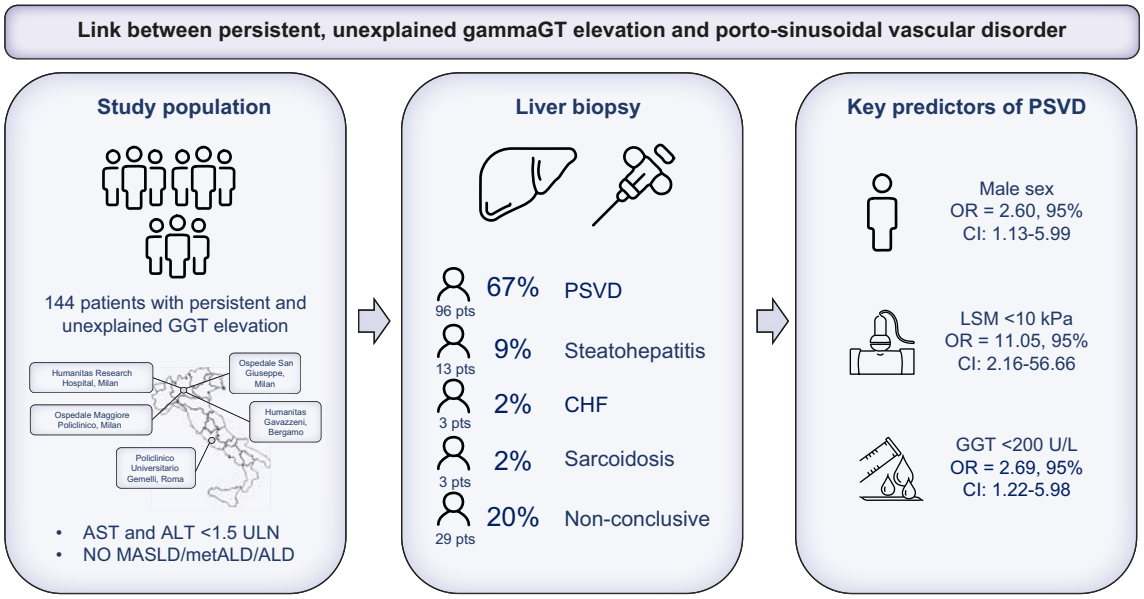
Graphical abstract



Highlights:

- PSVD is common in individuals with persistent and unexplained GGT elevation.
- Male sex, LSM <10 kPa and GGT <200 U/L are predictors of PSVD.
- The diagnosis of PSVD in patients without signs of PH is challenging.

Impact and implications:

In outpatient settings, it is common to encounter individuals with persistent and unexplained gamma-glutamyltransferase elevations. This study reveals, for the first time, a non-negligible prevalence of porto-sinusoidal vascular disorder among these individuals when they undergo liver biopsy. Male sex, liver stiffness measurement <10 kPa, and gamma-glutamyltransferase <200 IU/L predict this histological finding. These results may raise awareness of clinically relevant conditions that may be present in patients with persistent liver enzyme changes, even in the absence of signs of advanced chronic liver disease or portal hypertension. Additionally, the data may encourage further studies in the field of porto-sinusoidal vascular disorder, particularly to define its clinical evolution in patients without signs of portal hypertension at diagnosis.

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Research article

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Link between persistent, unexplained gamma-glutamyltransferase elevation and porto-sinusoidal vascular disorder

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Background & Aims: Porto-sinusoidal vascular disorder (PSVD) is a group of vascular disorders characterized by lesions involving portal venules and sinusoids, irrespective of the presence of portal hypertension. Liver biopsy is essential for diagnosis. In a single-center study, we demonstrated high rates of PSVD in patients with persistently elevated gamma-glutamyltransferase (GGT). This multicenter study aims to establish PSVD prevalence in a larger dataset of individuals with persistent and unexplained GGT elevation, and to identify associated risk factors.

Methods: The study included all patients who underwent liver biopsy for persistent and unexplained GGT elevation in five Italian hepatology units between March 2015 and December 2021.

Results: A total of 144 patients met the inclusion criteria. The majority were males (76/144, 52.8%) and mean age was 51.9 years (range 19-74). Only 12 (8.3%) had liver stiffness measurements (LSM) >10 kPa, while 7 (4.8%) had ultrasound evidence of portal hypertension. Histological findings were consistent with PSVD in 96 patients (67%). Alternative diagnoses were steatohepatitis in 13 (9%), sarcoidosis in 3 (2%) and congenital hepatic fibrosis in 3 (2%) patients. Histological findings were non-specific in 29 (20%) patients. PSVD was associated with male sex (odds ratio [OR] 2.60, 95% CI 1.13-5.99), LSM <10 kPa (OR 11.05, 95% CI 2.16-56.66) and GGT <200 U/L (OR 2.69, 95% CI 1.22-5.98).

Conclusions: PSVD was the main cause of persistent and unexplained elevation of GGT3. Male sex, LSM <10 kPa and GGT <200 U/L were associated with PSVD. These findings highlight the role of liver biopsy in elucidating the underlying pathology and aiding in the diagnosis of patients with persistent and unexplained GGT elevation.

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Introduction

Porto-sinusoidal vascular disorder (PSVD) is a term introduced to describe a group of hepatic vascular disorders characterized by lesions in the portal venules and sinusoids, irrespective of the presence of portal hypertension (PH).[1,2] This terminology addresses the diagnostic challenge of patients with histological lesions suggestive of vascular disorder even in the absence of PH, who were previously excluded from the definition of idiopathic non-cirrhotic PH.[3] The diagnosis of PSVD necessitates a liver biopsy to exclude cirrhosis and to identify specific diagnostic features, which can be subtle and require expert examination.[1,2] Three histological elements that are diagnostic of PSVD, even in the absence of PH, are nodular regenerative hyperplasia (NRH), portal vein stenosis and incomplete septal cirrhosis.[1,2] The presence of other causes of liver damage does not exclude the coexistence of PSVD, as long as the liver biopsy findings support the diagnosis.[1,2,4]

PSVD has been associated with a variety of conditions, including hematological, autoimmune, or genetic disorders, infections, or the use of certain medications.[5–9] However, the etiology of PSVD remains uncertain in 14-53% of cases, although most of the data are derived from studies including only patients with PH.[1,4,9–11] PSVD is typically suspected when there are radiological or endoscopic signs of PH, despite the absence of clear evidence of advanced chronic liver disease (ACLD). It can also occur in patients with persistent and unexplained abnormalities in liver enzymes.[9,12] In a previous study, we reviewed liver biopsies from 29 patients with persistently elevated serum gamma-glutamyltransferase (GGT) levels greater than twice the upper limit of normal (ULN).[12] Surprisingly, liver histology was diagnostic for PSVD in 13 patients (45%). However, these findings were derived from a small retrospective monocenter cohort, which precluded the identification of clinical or biochemical variables associated with PSVD.[12]

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Therefore, a multicenter study was designed to enroll patients with persistent and unexplained GGT elevations who consecutively underwent liver biopsy to assess the prevalence of PSVD and to identify variables independently associated with PSVD in this subgroup of patients.

Patients and methods

Patient selection and data collection

The study was conducted in five highly specialized Italian hepatology units: IRCCS Humanitas Research Hospital in Rozzano (Milan), San Giuseppe IRCCS MultiMedica Hospital in Milan, Humanitas Gavazzeni in Bergamo, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico in Milan and Fondazione Policlinico Universitario Gemelli IRCCS in Rome. All consecutive patients who underwent percutaneous needle liver biopsy between March 2015 and December 2021 for persistent and unexplained elevation of GGT levels, defined as at least twice above the ULN on three tests within a 12-month period, were included in the study. Patients from the previous monocentric study by Pugliese *et al.* were also included.[12]

Patients with concomitant elevations of alanine aminotransferase, aspartate aminotransferase and/or alkaline phosphatase (ALP) greater than 1.5x ULN at the time of liver biopsy were excluded, as were patients taking medications known to cause GGT elevation. Also excluded were patients with a self-reported alcohol consumption exceeding 30 g per day for men and 20 g per day for women, patients with metabolic dysfunction-associated steatotic liver disease or with concomitant infectious, autoimmune or genetic liver disease.[13] Patients with evidence of biliary tree abnormalities on magnetic resonance cholangiopancreatography, which was required in all individuals with concomitant ALP elevation, were also excluded.

Patients who met the inclusion criteria underwent a comprehensive medical history. This included their past medical history, comorbidities, smoking habits, and alcohol consumption. The medical history was reviewed with particular attention to any comorbidities associated with PSVD and any personal history of thrombotic events.[1,2,7]

Each enrolled patient underwent a thorough review of their current and past medication history, with particular attention paid to medications known to be associated with PSVD. These drugs include azathioprine, tioguanine, oxaliplatin, cytarabine, cyclophosphamide, chlorambucil and didanosine.[1,2,7]

Weight and height were measured, and BMI was calculated. Biochemical parameters were recorded within 15 days of the liver biopsy and included serum levels of aspartate aminotransferase, alanine aminotransferase, ALP, platelet count, total and direct bilirubin, international normalized ratio (INR), creatinine, and screening for serum autoantibodies. HIV testing was performed in all patients within 12 months of histological evidence of PSVD.

The Fibrosis 4 (FIB-4) index was used to assess the severity of liver disease. Cut-off values of less than 1.30 and greater than 3.25 were chosen to rule out and rule in advanced fibrosis, respectively.[14]

All enrolled patients underwent an abdominal ultrasound examination to look for signs of PH. Signs of PH, according to the VALDIG criteria, were identified as a spleen size of 13 cm or greater in the largest axis, the presence of porto-systemic collaterals or ascites.[1,2] All patients were also assessed for patency of the spleno-portal axis.

All patients underwent vibration-controlled transient elastography using the Echosens Fibroscan device. Transient elastography was performed according to the manufacturer's guidelines by eight experienced physicians (NP, FRP, FS, CB, MM, LV, MV and AA). Reliable and accurate measurements were ensured with a success rate of over 70% in all patients included in the study. The choice of probe was determined by the patient's BMI. The M probe was used to assess patients with a BMI below 30 kg/m^2, while the XL probe was used for patients with a BMI above 30 kg/m^2 To identify patients with suspected compensated ACLD, a cut-off of 10 kPa was chosen for liver stiffness measurement (LSM) based on the Baveno criteria and previous studies. This cut-off is known to be helpful in distinguishing PSVD from cirrhosis.[10,15]

Finally, all patients diagnosed with PSVD underwent upper gastrointestinal endoscopy within 12 months of histological diagnosis. According to the VALDIG criteria, signs of PH, such as esophageal or gastric varices, were considered.[1,2]

Histological analysis and diagnosis of PSVD

Liver tissue samples obtained by percutaneous liver biopsy were processed using standard techniques, including formalin fixation paraffin embedding, and staining to assess various aspects of liver pathology. The stains used included H&E, reticulin, Gomori, Sirius red, periodic acid-Schiff, Perls and orcein. Four experienced hepato-pathologists (L.D.T. and L.T. for Humanitas Research Hospital and Humanitas Gavazzeni, M.M. for Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano and San Giuseppe IRCCS MultiMedica Hospital, and M.C.G for Fondazione Policlinico Universitario Gemelli IRCCS) initially evaluated all liver biopsy specimens. Histological specimens were re-evaluated in digital form by L.T. and L.D.T., in case of disagreement the cases were discussed among all hepato-pathologists. Liver specimen quality was assessed based on biopsy length, number of portal tracts, and specimen fragmentation.

The diagnosis of PSVD was defined by the VALDIG criteria, meaning exclusion of histological features of cirrhosis and histological evidence of portal vein stenosis (thickening and fibrosis of the portal vein walls leading to luminal narrowing, obliteration and eventual loss of intrahepatic portal vein branches), NRH or incomplete septal cirrhosis (delicate fibrous septa originating from a portal tract and terminating blindly within a hepatic lobule without clear connection to central veins or other portal tracts) as specific signs of PSVD.[1,2] NRH was defined on the basis of the following specific histopathological features, assessed by both H&E and reticulin staining: the presence of hepatocellular nodules <3 mm, consisting of a central part of enlarged hepatocytes and/or thickened hepatic cell plates with a rim of smaller hepatocytes and/or thinner hepatic cell plates with compression of the sinuses in the periphery, where perisinusoidal but not septal fibrosis may occur.[16,17] According to the Wanless scoring system, the diagnosis of NRH was defined only in the presence of a distinct micronodularity of the liver parenchyma, visible in most areas on H&E and highlighted by Gomori staining (grade 3).[18]

Non-specific histological signs of PSVD include portal tract abnormalities, architectural disturbances, non-zonal sinusoidal

dilatation, and mild perisinusoidal fibrosis. These signs in combination with non-specific signs of PH (splenomegaly, presence of ascites, thrombocytopenia) enable the diagnosis of PSVD according to the VALDIG criteria.[1,2]

Statistical analysis

Continuous variables with normal and non-normal distributions were presented, respectively as means ± standard deviations and medians with interquartile ranges, respectively; categorical data were presented as absolute frequencies and percentages. The association of individual demographic, laboratory, metabolic and clinical factors with the histological evidence of PSVD was assessed using logistic regression models, estimating the odds ratio (OR) with the corresponding 95% CIs. We first performed unadjusted modeling for each of the factors considered. We then fitted a multivariable logistic regression model, simultaneously including as independent variables those significantly associated with the outcome in the unadjusted analyses and study center. Patient age and arterial hypertension were also included in the multivariable model to address their potential confounding effects on the outcome variable. A logistic regression model adjusted for age and sex was used to estimate the OR of PSVD according to the number of factors associated with the condition as identified in the multivariable analysis.

Ethical approval

This study included only retrospective and fully anonymized data from standard of care investigations and assessments. As such, ethical approval was not required according to the policies of the participating centers.

Results

Patient characteristics

During the study period, a total of 2,570 patients underwent liver biopsy in the five participating Italian hepatology units. Of these, 144 patients (5.6%) met the inclusion criteria and were included in the study (Fig. 1). Their characteristics are shown in Table 1. Most patients were males (52.8%, 76/144), the mean age was 51.9 years (19-74 years), with 85 patients (59%) aged 50 years or older. The mean BMI was 23.6 ± 3 kg/m^2. Fifteen patients (10.4%) reported smoking, but none reported significant alcohol consumption, as required by the study design.

Autoimmune diseases were reported in 16 of 144 (11.2%) patients. Specifically, 11 patients had autoimmune hypothyroidism, three had inflammatory bowel disease (all with Crohn's disease, without previous surgery), and two had psoriasis. In addition, five (3.5%) patients had type 2 diabetes mellitus, and 17 (11.8%) patients had a history of solid malignant neoplasm, although they had been disease-free and untreated for at least 5 years prior to liver biopsy. Five (3.5%) patients reported past or current immunosuppressive therapy, with only one patient receiving azathioprine. In addition, 15 (10.4%) patients reported past or current hormone therapy. Only one patient had received oxaliplatin for colorectal cancer. No patients reported current or previous therapy with tioguanine, cytarabine, cyclophosphamide, chlorambucil or didanosine.

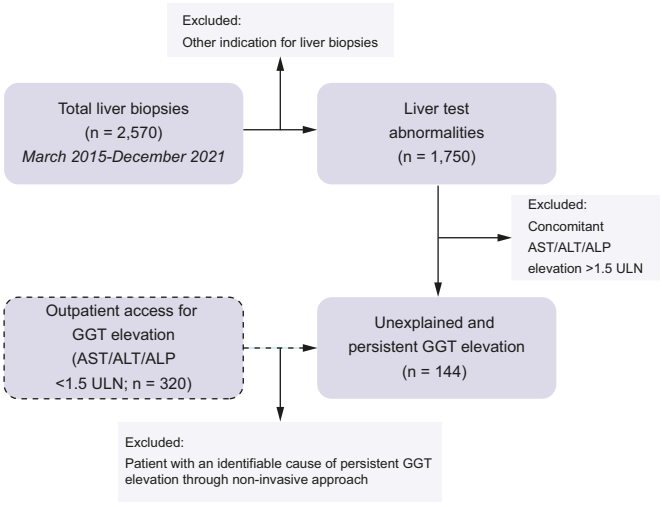

Fig. 1. Flowchart of the patient enrolment process. ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; ULN, upper limit of normal.

None of the patients had a history of thrombosis or any form of diagnosed thrombophilic disorder. All patients were HIV negative.

The median platelet count among the patients was 237,000/μl and only two patients had a FIB-4 index >3.25. However, 12 (8.3%) patients had LSM values consistent with cACLD (>10 kPa).

Fifty-two (36.9%) patients were positive for anti-nuclear autoantibodies and 10 (7.6%) patients for anti-smooth muscle antibodies. None of the patients showed positivity for liver kidney microsomal autoantibodies.

Only seven (4.8%) patients had ultrasound evidence of PH, in particular all had splenomegaly. None had porto-systemic collaterals or ascites. No patient had thrombosis of the spleno-portal axis. In these patients, the presence of PH was confirmed by a CT scan.

The median GGT level was 174 (127-242 U/L). The median time from the first detection of GGT elevation to liver biopsy was 48 months (range 12-108 months).

Histological findings

All liver biopsies were adequate in terms of size, with a mean length of 24.7 mm (range 20-46 mm) and more than 10 portal tracts in each sample. There were no cases of fragmentation that prevented proper evaluation of the histological specimen.

Histological findings showed that 96 of 144 (67%) patients had liver disease consistent with PSVD (Table 1): all of these patients had histological features diagnostic of NRH (grade 3 according to the Wanless scoring system).[17]

Thirteen patients (9%) had liver histology consistent with steatohepatitis, although they did not meet the diagnostic criteria for metabolic dysfunction-associated steatotic liver disease/steatohepatitis. In addition, three (2%) patients had liver histology consistent with hepatic sarcoidosis and three (2%) other patients had congenital hepatic fibrosis. Histological examination could not provide a definitive diagnosis in 29 (20%) patients.

Sub-analysis of the 27 patients in the cohort with persistent and unexplained elevated GGT but completely normal

Table 1. Patient characteristics, overall and stratified by presence of PSVD.

	All patients* (n = 144)	PSVD* (n = 96)	No PSVD* (n = 48)
Age, mean (SD)	51.9 (11.4)	50.8 (11.0)	54.1 (12.0)
Age ≥50, n (%)	85 (59.0)	53 (55.2)	32 (66.7)
Men, n (%)	76 (52.8)	57 (59.4)	19 (39.6)
Current smoking, n (%)	15 (10.4)	12 (12.5)	3 (6.3)
BMI (kg/m^2), mean (SD)	23.6 (3.0)	23.3 (2.7)	24.1 (3.5)
Hypertension, n (%)	22 (15.3)	16 (16.7)	6 (12.5)
Diabetes, n (%)	5 (3.5)	0 (0)	5 (10.4)
Neoplasm, n (%)	17 (11.8)	11 (11.5)	6 (12.5)
Autoimmune disease, n (%)	16 (11.2)	10 (10.5)	6 (12.5)
GGT (IU/L), median (IQR)	174 (127-242)	173 (129-225)	200 (121-286)
ALT (IU/L), median (IQR)	53 (35-72)	52 (35-80)	56 (37-70)
AST (IU/L), median (IQR)	36 (29-48)	36 (29-50)	36 (31-42)
ALP (IU/L), median (IQR)	119 (85-185)	119 (85-167)	130 (86-240)
Total bilirubin (mg/dl), median (IQR)	0.8 (0.6-1.0)	0.8 (0.6-1.0)	0.8 (0.6-1.1)
INR, median (IQR)	1.00 (0.95-1.04)	1.00 (0.95-1.03)	1.00 (0.97-1.06)
Platelets, median (IQR)	237 (195-284)	240 (195-302)	229 (197-263)
Albumin (g/dl), median (IQR)	4.4 (4.1-4.5)	4.4 (4.1-4.5)	4.3 (4.1-4.5)
ANA positivity, n (%)	52 (36.9)	36 (37.9)	16 (34.8)
AMA positivity, n (%)	1 (0.7)	0 (0)	1 (2.2)
ASMA positivity, n (%)	10 (7.6)	8 (9.1)	2 (4.7)
LKM positivity, n (%)	0 (0)	0 (0)	0 (0)
FIB-4, median (IQR)	1.12 (0.82-1.72)	1.08 (0.77-1.64)	1.28 (0.92-1.73)
FIB-4 >3.25, n (%)	2 (1.4)	1 (1.0)	1 (2.1)
LSM (kPa), median (IQR)	4.9 (4.2-6.3)	4.8 (4.2-5.9)	5.9 (4.2-7.5)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibodies; AST, aspartate aminotransferase; FIB-4, fibrosis-4; GGT, gamma-glutamyltransferase; INR, international normalized ratio; LKM, liver kidney microsomal antibodies; LSM, liver stiffness measurement; PSVD, porto-sinusoidal vascular disorder.

*Data were missing for some individuals: one for diabetes, one for history of autoimmune disease, three for BMI, one for ALP, two for total bilirubin, three for albumin, three for ANA positivity, three for AMA positivity, 13 for ASMA.

aminotransferases and ALP showed diagnostic histology for PSVD in 17 (63%) individuals, for steatohepatitis and congenital hepatic fibrosis in two (7%) patients each, and inconclusive histology in the remaining six patients.

PSVD group

The PSVD group consisted of 57 (59%) men, with a mean age of 50.8 years (range 19-73 years) (Table 2). The mean BMI was 23.3 ± 2.7 kg/m^2. Twelve of the patients were active smokers.

Ten patients had systemic autoimmune diseases. Seven of these patients had autoimmune hypothyroidism and were receiving hormone therapy. Two patients had chronic inflammatory bowel disease, both with ileo-colonic Crohn's disease, and had not undergone surgery. One patient was not receiving any therapy at the time of PSVD diagnosis, while the other had received infliximab for 12 months. The second patient had been treated with azathioprine, which was stopped 24 months before the liver biopsy. In addition, one patient with psoriasis who had been taking secukinumab for 6 months at the time of PSVD diagnosis was identified. The patient had previously only received topical treatment.

Nine patients had a history of solid malignancies, including three with breast cancer, two with lung cancer, one with renal cancer, one with plasmacytoma, one with colorectal cancer, and one with prostate cancer. None of the patients were receiving oncological treatment at the time of the liver biopsy. Only one patient had received oxaliplatin for colorectal cancer, which was discontinued 30 months before the biopsy. None of the other patients had been treated with drugs known to be potentially associated with PSVD.

No patient tested positive for HIV within 12 months of the histological diagnosis, had a history of thrombosis, or a diagnosed thrombophilic disorder. Additionally, no patients were known to have been diagnosed with congenital immunodeficiencies.

Three patients had a LSM indicating advanced liver fibrosis (>10 kPa). Only one patient had a FIB-4 >3.25. Nine patients had a platelet count below 150,000/μl. Of the patients with histological evidence of PSVD, seven had ultrasound evidence of PH, including four with LSM <10 kPa.

Table 2 presents the association between selected demographic and clinical patient characteristics and the presence of PSVD. In the multivariate analysis, male sex (OR 2.60, 95% CI 1.13-5.99), LSM <10 kPa (OR 11.05, 95% CI 2.16-56.66) and GGT <200 IU/L (OR 2.69, 95% CI 1.22-5.98) were significant predictors of histological findings of PVSD. No significant association was found with neoplasia or autoimmune diseases and FIB-4 <1.3.

A sub-analysis of the cohort was performed excluding patients with persistent and unexplained elevated GGT and associated clinical features potentially suggestive of PSVD.[1,2] Specifically, patients with immune disorders (n = 16) or previous exposure to drugs potentially associated with PSVD (n = 2) were excluded. In addition, patients with LSM <10 kPa and ultrasound evidence of PH (n = 4) were also excluded. Analysis of the remaining 122 patients revealed that 78 (64%) had histological evidence of PSVD. Furthermore, the factors identified as statistically associated with PSVD in the multivariate

Table 2. Association of selected demographic and clinical patients' characteristics with PSVD.

	PSVD n (%)	No PSVD n (%)	Unadjusted OR (95%CI)	Adjusted OR¶ (95% CI)
Age				
<50	43 (44.8)	16 (33.3)	Ref	Ref
≥50	53 (55.2)	32 (66.7)	0.62 (0.30-1.27)	0.71 (0.29-1.70)
Gender				
Female	39 (40.6)	20 (60.4)	Ref	Ref
Male	57 (59.4)	19 (39.6)	2.23 (1.10-4.53)	2.60 (1.13-5.99)
BMI (kg/m^2)*				
≥25	27 (28.4)	16 (34.8)	Ref	
<25	68 (71.6)	30 (65.2)	1.34 (0.63-2.85)	
Arterial hypertension				
No	80 (83.3)	42 (87.5)	Ref	Ref
Yes	16 (16.7)	6 (12.5)	1.40 (0.51-3.84)	2.64 (0.74-9.38)
Diabetes*				
No	95 (100)	43 (89.6)		
Yes	0 (0)	5 (10.4)	n.e.	
Neoplasm				
No	85 (88.5)	42 (87.5)	Ref	
Yes	11 (11.5)	6 (12.5)	0.91 (0.31-2.62)	–
Autoimmune disease*				
No	85 (89.5)	42 (87.5)	Ref	
Yes	10 (10.5)	6 (12.5)	0.82 (0.28-2.42)	–
GGT (IU/L)				
≥200	31 (32.3)	24 (50.5)	Ref	Ref
<200	65 (67.7)	24 (50.0)	2.10 (1.03-4.26)	2.69 (1.22-5.98)
LSM (kPa)				
≥10	3 (3.1)	9 (18.8)	Ref	Ref
<10	93 (96.9)	39 (81.3)	7.15 (1.84-27.85)	11.05 (2.16-56.66)
FIB-4				
≥1.3	37 (38.5)	22 (45.8)	Ref	
<1.3	59 (61.5)	26 (54.2)	1.35 (0.67-2.72)	–
ANA positivity*				
No	59 (62.1)	30 (65.2)	Ref	
Yes	36 (37.9)	16 (34.8)	1.14 (0.55-2.39)	–
AMA positivity*				
No	95 (100)	45 (97.8)		
Yes	0 (0)	1 (2.2)	n.e.	–
ASMA positivity*				
No	80 (90.9)	41 (95.4)	Ref	
Yes	8 (9.1)	2 (4.7)	2.05 (0.42-10.10)	–

AMA, anti-mitochondrial antibodies; ANA, anti-nuclear antibodies; ASMA, anti-smooth muscle antibodies; FIB-4, fibrosis-4; GGT, gamma-glutamyltransferase; LSM, liver stiffness measurement; n.e., not estimable; OR, odds ratio; PSVD, porto-sinusoidal vascular disorder.

¶ORs derived from a logistic regression model including terms for age, sex, center of patients' recruitment, arterial hypertension, GGT, LSM.

*The sum does not add up to the total because of some missing values.

analysis of the whole cohort were confirmed when this subgroup was considered.

Discussion

This multicenter study provides compelling results regarding the clinical significance of liver biopsies in Italian patients with persistent and unexplained GGT elevation, with a diagnosis established in 80% of cases. Consistent with previous findings from our group, the study shows that 67% of patients with persistent and unexplained GGT elevation had PSVD.[12] Furthermore, liver biopsies also led to the identification of other rare liver diseases in a significant proportion of individuals. These findings highlight the role of liver biopsy in elucidating the underlying pathology and aiding in the diagnosis of patients with persistent and unexplained GGT elevation.

The interpretation of increased GGT levels in patients with PSVD is complex and requires further scientific investigation. One hypothesis is that the elevation of GGT levels may be linked to endothelial dysfunction resulting from oxidative stress, a phenomenon observed in vascular liver disorders such as PH-PSVD.[19–21] Moreover, recent research by Hernandez Gea *et al.* utilized transcriptomics to compare patients with PH-PSVD, cirrhosis, and healthy controls.[22] The findings revealed a distinct genetic profile in patients with PSVD, particularly enriched in pathways related to oxidative phosphorylation.[22] While this evidence sheds light on the molecular mechanisms underlying PSVD, it remains to be determined whether similar pathways contribute to the persistent and unexplained elevation of GGT values observed in patients without PH, as seen in our cohort.

Our study identified several predictive factors associated with histological evidence of PSVD in patients with persistent and unexplained GGT elevation. These factors include male sex, GGT levels and evidence of LSM <10 kPa. These findings contribute to a better understanding of PSVD and provide valuable insights for the pre-identification of patients who may

be at higher risk. The results of our study are consistent with those of another multicenter study that aimed to evaluate the accuracy of LSM in differentiating PSVD from compensated biopsy-proven cirrhosis in patients with evidence of PH. In that study, the 77 patients with PSVD exhibited a significantly lower median LSM (7.9 kPa) compared to patients with alcohol-, HCV- or NAFLD-associated cirrhosis (33.8, 18.2 and 33.6 kPa, respectively; p <0.001).[14] In particular, a cut-off value of 10 kPa demonstrated a specificity of 97% and a positive predictive value of 85% for the diagnosis of PSVD, distinguishing it from cirrhosis.[10] Regarding the association between male gender and histological findings of PSVD, epidemiological data on PSVD are limited. While some studies from Asia and India have indicated a higher prevalence of PSVD in women, albeit with a decreasing female-to-male ratio compared to previous findings, other studies from Europe and North America, including our own, have suggested a higher incidence of PSVD in men.[23] Further research is needed to confirm the generalizability of these findings across broader demographic groups.

The overall prevalence of PSVD is likely to be higher than reported. This could be due to under-diagnosis, as a result of the frequent absence of signs of PH or elevations in blood tests. Our study may overestimate the prevalence of histological evidence of PSVD because many patients with persistent and unexplained GGT elevation do not routinely undergo liver biopsy. Another limitation of this study is the lack of follow-up. In particular, the lack of information on individuals with a histological diagnosis of PSVD but without evidence of PH at the time of diagnosis hinders our understanding of the natural history of the disease. There is a paucity of evidence on the progression and outcomes of PSVD. It remains unclear whether there is a risk of developing PH and, if so, whether there are baseline factors that can predict its occurrence. It is also uncertain whether PSVD without PH represents an early stage of PSVD with PH or whether they are distinct entities with their own characteristics. Ongoing studies are addressing these questions in order to provide valuable insights into the appropriate management and follow-up of these patients. Currently, there is no distinction between the groups according to the recent Baveno guidelines.[15] In particular, they may shed light on the clinical relevance of histological identification in individuals without evidence of PH.

Our study also has several strengths. Firstly, the multicentric design of the study permitted the inclusion of a large sample size, thereby enhancing the generalizability of our findings and providing statistical power. Furthermore, the expertise of the pathologists who evaluated the liver biopsies ensured accurate and reliable histological diagnoses of PSVD.

With regard to the exclusive finding of NRH in our study, though unexpected, this is strongly supported by our rigorous methodology, including central re-evaluation of liver histology by pathologists specializing in vascular liver disease. While we acknowledge the challenge of providing a precise explanation for this finding and the absence of other diagnostic histological features of PSVD in our cohort, we offer potential insights. Previous studies have indicated a potential association between unexplained liver enzyme changes and NRH, which lends credibility to our findings.[24] Additionally, the slow progression of NRH not associated with PH to clinically significant liver disease may have influenced patient inclusion, potentially excluding those with other specific histological signs of PVSD. While these hypotheses provide valuable insights, further research is needed to elucidate the underlying mechanisms and implications of our findings. At present, we can only offer hypotheses rather than definitive explanations. Nevertheless, we are committed to advancing our understanding through continued investigation.

In conclusion, our study highlights the importance of recognizing PSVD as a possible underlying condition in patients with persistent and unexplained GGT elevation, irrespective of the presence of PH. It is crucial to conduct further research to accurately determine the true prevalence of PSVD in a broader population and to investigate prognostic factors and long-term outcomes specifically in individuals diagnosed with PSVD in the absence of PH. This will provide valuable information to optimize patient management and improve our understanding of the clinical implications of PSVD. In particular, the factors we have identified as predictive of PSVD in patients with persistent and unexplained elevations in GGT could be used to avoid biopsies that are only useful for identifying NRH, if prospective data over a long period of time demonstrate the absence of progression from PSVD without PH to PSVD with PH.

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Abbreviations

ACLD, advanced chronic liver disease; ALP, alkaline phosphatase; FIB-4, fibrosis-4; GGT, gamma-glutamyltransferase; LSM, liver stiffness measurement; NRH, nodular regenerative hyperplasia; PH, portal hypertension; PSVD, porto-sinusoidal vascular disorder.

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Conflict of interest

The authors who have taken part in this study declare they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Conceptualization: NP, FRP, MV, AA. Methodology: NP, MV, AA, FT, CLV. Investigation: NP, FC, FRP, MV, CM, FS, LDT, LT, MM, MAM, MCG, CB, LV. Formal analysis: NP, FT, CLV. Project administration: AA, MV. Supervision: AA, MV. Writing original draft: NP, FT.

Data availability statement

The raw/processed data required to reproduce the above findings may be shared upon appropriate request.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2024.101150.

References

[1] De Gottardi A, Sempoux C, Berzigotti A. Porto-sinusoidal vascular disorder. J Hepatol 2022;77(4):1124–1135. https://doi.org/10.1016/j.jhep.2022.05.033.

[2] De Gottardi A, Rautou PE, Schouten 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.

[3] Wöran K, Semmler G, Jachs M, et al. Clinical course of porto-sinusoidal vascular disease is distinct from idiopathic noncirrhotic portal hypertension. Clin Gastroenterol Hepatol 2022;20(2):e251–e266. https://doi.org/10.1016/j.cgh.2020.11.039.

[4] Olivas P, Perez-Campuzano V, Orts L, et al. Porto-sinusoidal vascular disorder in chronic HBV: a significant coexistence not to be overlooked. JHEP Rep 2023:100996. https://doi.org/10.1016/j.jhepr.2023.100996. ISSN 2589-5559.

[5] Gioia S, Nardelli S, Ridola L, et al. Causes and management of non-cirrhotic portal hypertension. Curr Gastroenterol Rep 2020;22(12):56. https://doi.org/10.1007/s11894-020-00792-0. Published 2020 Sep 17.

[6] Pugliese N, Giuli L, Mastrorocco E, et al. Exploring the link: porto-sinusoidal vascular disorder and inflammatory bowel disease - a comprehensive narrative review. Dig Liver Dis 2023. https://doi.org/10.1016/j.dld.2023.11.021. Published online December 2.

[7] Gioia S, Riggio O, Nardelli S, et al. Identifying patients at high risk of developing non-cirrhotic portal hypertension. Hepat Med 2021;13:105–111. https://doi.org/10.2147/HMER.S282674. Published 2021 Nov 3.

[8] Dajti E, Ravaioli F, Paiola G, et al. The non-invasive evaluation of liver involvement in patients with cystic fibrosis: a prospective study [published online ahead of print, 2023 Sep 19]. Liver Int 2023. https://doi.org/10.1111/liv.15748. 10.1111/liv.15748.

[9] Guido M, Sarcognato S, Sonzogni A, et al. Obliterative portal venopathy without portal hypertension: an underestimated condition. Liver Int 2016;36(3):454–460. https://doi.org/10.1111/liv.12936.

[10] Elkrief L, Lazareth M, Chevret S, et al. Liver stiffness by transient elastography to detect porto-sinusoidal vascular liver disease with portal hypertension. Hepatology 2021;74(1):364–378. https://doi.org/10.1002/hep.31688.

[11] Cazals-Hatem D, Hillaire S, Rudler M, et al. Obliterative portal venopathy: portal hypertension is not always present at diagnosis. J Hepatol 2011;54(3):455–461. https://doi.org/10.1016/j.jhep.2010.07.038.

[12] Pugliese N, di Tommaso L, Lleo A, et al. High prevalence of porto-sinusoidal vascular disease in patients with constantly elevated gamma-glutamyl transferase levels. Liver Int 2022;42(7):1692–1695. https://doi.org/10.1111/liv.15257.

[13] Rinella ME, Lazarus JV, Ratziu V, et al. A multisociety Delphi consensus statement on new fatty liver disease nomenclature. J Hepatol 2023;79(6):1542–1556. https://doi.org/10.1016/j.jhep.2023.06.003.

[14] European Association for the Study of the Liver. EASL Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis - 2021 update. J Hepatol 2021;75(3):659–689. https://doi.org/10.1016/j.jhep.2021.05.025.

[15] de Franchis R, Bosch J, Garcia-Tsao G, et al. Baveno VII - renewing consensus in portal hypertension [published correction appears in J Hepatol. 2022 Apr 14;:]. J Hepatol 2022;76(4):959–974. https://doi.org/10.1016/j.jhep.2021.12.022.

[16] Guido M, Sarcognato S, Sacchi D, et al. Pathology of idiopathic non-cirrhotic portal hypertension. Virchows Arch 2018;473(1):23–31. https://doi.org/10.1007/s00428-018-2355-8.

[17] Jharap B, van Asseldonk DP, de Boer NK, et al. Diagnosing nodular regenerative hyperplasia of the liver is thwarted by low interobserver Agreement. PLoS One 2015;10(6):e0120299. https://doi.org/10.1371/journal.pone.0120299. Published 2015 Jun 8.

[18] Wanless IR. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 1990;11(5):787–797. https://doi.org/10.1002/hep.1840110512.

[19] Brennan PN, Dillon JF, Tapper EB. Gamma-Glutamyl Transferase (γ-GT) - an old dog with new tricks? Liver Int 2022;42(1):9–15. https://doi.org/10.1111/liv.15099.

[20] Lee DH, Blomhoff R, Jacobs Jr DR. Is serum gamma glutamyltransferase a marker of oxidative stress? Free Radic Res 2004;38(6):535–539. https://doi.org/10.1080/10715760410001694026.

[21] Muti LA, Pârvu AE, Crăciun AM, et al. Nitro-oxidative stress, VEGF and MMP-9 in patients with cirrhotic and non-cirrhotic portal hypertension. Clujul Med 2015;88(2):140–145. https://doi.org/10.15386/cjmed-458.

[22] Hernández-Gea V, Campreciós G, Betancourt F, et al. Co-expression gene network analysis reveals novel regulatory pathways involved in porto-sinusoidal vascular disease. J Hepatol 2021;75(4):924–934. https://doi.org/10.1016/j.jhep.2021.05.014.

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

[24] Ward C, Lucas M, Piris J, et al. Abnormal liver function in common variable immunodeficiency disorders due to nodular regenerative hyperplasia. Clin Exp Immunol 2008;153(3):331–337. https://doi.org/10.1111/j.1365-2249.2008.03711.x.

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