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Clinical and genetic factors involved in Porto-sinusoidal vascular disorder after oxaliplatin exposure

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ABSTRACT

Background and aims: Oxaliplatin (OX) has been described as a potential etiologic agent for porto-sinusoidal vascular disorder (PSVD). Our aim was to describe the natural history of PSVD due to OX in colon cancer (CRC) and identify risk factors for its development.
Methods: We made a multicenter retrospective case-control (ratio 1:3) study with patients diagnosed of PSVD-OX. Baseline data, end of treatment, years of follow-up and diagnosis of PSVD were collected and compared to controls (without PSVD). Besides, 16 different SNPs were selected from bibliography and analyzed by genotyping in the case group to identify potential genetic risk factors.
Results: 41 cases were identified, with a median time to PSVD diagnosis after the end of OX of 34 months. Spleen diameter was the strongest predictor of PSVD during treatment (OR 43.94 (14.48–133.336); $p < 0.0001$). Additionally, thrombocytopenia (<150 × 10^9) at one year was a significant disease risk marker (OR 9.35; 95% CI: 3.71–23.58; $p = 0.001$). We could not establish any significant association between the selected SNPs and PSVD diagnosis.
Conclusion: The increase of spleen diameter is the strongest predictor of PSVD in patients treated with OX for CRC. These patients could be candidates for a specific follow-up of portal hypertension-related complications.

Introduction

Porto-sinusoidal vascular disorder (PSVD), previously known as idiopathic portal hypertension (IPH), encompasses a group of rare vascular liver diseases of unknown etiology that can lead to portal hypertension (PHT) complications [1,2]. The prevalence of PSVD among patients with portal hypertension is approximately 3% to 7% in Western countries. The epidemiology of PSVD remains unclear, with several implicated factors including immunological disorders, infections, human immunodeficiency virus, certain medications (azathioprine, oxaliplatin), toxins, genetic predisposition, and thrombophilia [2–5]. Previously, PSVD was often diagnosed in advanced stages due to PHT-related complications. However, recent

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advances now allow for earlier-stage diagnoses, even when PHT signs and symptoms are absent [6,7].

Oxaliplatin (OX), a third-generation derivative of platinum [8], forms the cornerstone of the current treatment strategy for gastrointestinal tumors, primarily colon cancer (CRC), in the context of neoadjuvant/ adjuvant and palliative chemotherapy. In stages III and IV CRC, it is commonly used in combination with 5-fluorouracil (5-FU) (FOLFOX®) or capecitabine (XELOX®) [8]. The most frequently encountered side effects associated with OX include peripheral neuropathy, isolated alterations of liver tests, and acute splenomegaly and thrombocytopenia, which typically resolve following the completion of treatment [9,10]. Indeed, some degree of sinusoidal obstruction syndrome (SOS) is almost universally observed when specifically sought via systematic liver biopsy, possibly explaining, at least in part, these alterations [10,11]. In addition to the potential effect on platelet count (PLT) and spleen size secondary to the acute increase in portal pressure prompted by SOS, myelosuppression and immune mechanisms have also been implicated in contributing to splenomegaly and thrombocytopenia during OX treatment [12]. These alterations typically reverse at the end of treatment, whereas the long-term persistence of a low platelet count (PLT) and of splenomegaly.

Although histological SOS is quite common following OX treatment, the development of PSVD is relatively infrequent [2]. The literature regarding OX-related PSVD (PSVD-OX) is sparse and primarily consists of a small series of cases with no clear definition of PSVD [12,15,16]. Moreover, the risk factors for developing PSVD in patients treated with OX remain unknown, and a genetic component for PSVD has not yet been identified and validated beyond case reports [17–21]. This lack of clarity accounts, at least in part, for the delay in diagnosing and appropriately treating portal hypertension-related complications [2]. Consequently, this study aims to outline the natural history of PSVD-OX and identify risk factors for its development in patients receiving OX treatment

Materials and methods

Patients

Cases

Between February 2019 and June 2019, Spanish centers participating in the Spanish Registry of Hepatic Vascular Diseases (REHEVASC) were contacted to retrospectively identify PSVD patients who had been exposed to OX in the context of CRC treatment.

Data were analyzed (based on local databases) for patients diagnosed with PSVD-OX and a history of CRC who were included in the REHEVASC registry from 2004 to 2018 across eight Spanish tertiary University Hospitals. Due to the retrospective nature of the study, the diagnosis of PSVD was made according to the criteria for idiopathic portal hypertension (Supplementary, Table 1) (cases prior to 2018–19) [22] or the new criteria proposed by the VALDIG group for PSVD (Supplementary Table 2) (cases post-2019) [2]. The histological diagnosis of PSVD was confirmed by liver pathologists. At the time of inclusion in the registry, blood samples were collected.

Controls

The PSVD-OX cohort was compared to a control cohort of patients with CRC and no prior liver disease from the Oncology Department of Marqués de Valdecilla University Hospital (spanning from 2004 to 2019), who were also exposed to OX as part of neoadjuvant or adjuvant chemotherapy but did not develop PSVD. Patients were deemed not to have developed portal hypertension if no signs of portal hypertension surfaced during a follow-up period of at least 2 years

Methods

Cases and controls were matched based on age, date of tumor diagnosis, sex, body mass index, tumor staging, cumulative dose of OX, and follow-up duration. A 1:3 case-control ratio was selected. The inclusion and exclusion criteria, definitions, and data collection process are detailed in the Supplementary text and Tables 1–2.

We established several time points for analysis in cases and controls: baseline data before initiating OX treatment (B-OX), fifty percent of the final OX dose (50%-OX), at the conclusion of OX treatment (END-OX), yearly following the end of OX treatment (year-OX), and finally at the end of the follow-up period for controls, or at time of PSVD diagnosis for cases (F-PSVD). The time of PVSD diagnosis was calculated from the date of the last OX dose to the date of PSVD diagnosis. The follow-up was extended until June 2019, in order to assess survival and development of portal hypertension-related complications (Supplementary Figure 1).

The supplementary text provides details on the methodologies used to study a set of polymorphisms (SNPs) in genes related to drug metabolism, coagulation, and immunity that may increase the risk of EVPS [23]. Briefly, we selected a group of 16 SNPs from the literature (Supplementary Table 3) and divided them into three groups: those related to OX toxicity (GSTP1 rs1695) [24]; those associated with the development of splenomegaly (MMP-9, VEGF, NOS3…) [25]; and those associated with regenerative nodular hyperplasia in common variable immunodeficiency (GNG12-AS1, rs1926283) [26].

The study was approved by our institutional review board (APS-OXA-2019–01 and InVAL21/27), and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Statistical analysis

Continuous variables for the groups were compared using either the unpaired Student's *t*-test, U-Mann-Whitney test, or the Friedman test as appropriate. For categorical data, the Chi-square/Fisher's exact tests were utilized. Qualitative variables were expressed as proportions and quantitative variables as mean ± standard deviation (SD) or median (interquartile range) as applicable. The log-likelihood ratio (LLR) was employed to test the potential association between genotypes and the disease. Logistic regression analyses were conducted to identify factors associated with the development of PSVD. Variables that were related ($p < 0.05$) in the univariate analysis or deemed clinically significant, irrespective of the P value, were introduced into a multivariate analysis. The strength of the association of each variable was estimated by the odds ratio (OR) along with its 95% confidence interval (CI). Statistical analyses were performed using the Statistical Package for Social Sciences (version 24.0; SPSS, Chicago, IL), and GraphPad Prism software (Version 7.0, GraphPad Software Inc., San Diego, CA, USA) was used for the graphical section

Results

Patients' characteristics at baseline

We identified 41 patients with PSVD-OX (in 25 cases liver biopsy was available). Although a specific epidemiological study was not conducted, at the Marqués de Valdecilla University Hospital we have reviewed over 1200 patients treated with OX for CRC since 2005, of whom only 6 developed the disease (a prevalence of 0.5%). Their baseline characteristics are presented in Supplementary Table 4. The majority of patients were treated with adjuvant chemotherapy ($n = 32$; 78%). Six patients (14.6%) received treatment with antiangiogenic drugs (of the bevacizumab type). None of the patients showed signs of liver disease or portal hypertension

Table 1
Clinical features of porto-sinusoidal vascular disorder associated to oxaliplatin.

Median time of follow up until diagnosis (months)	33.7 ± 27
Non-invasive diagnosis	
Liver Elastography (kPa) by Fibroscan® *n* = 32	7.6 ± 0.04
Platelet count <150 × 10^9 *n* = 40	*n* = 37 (90.25%)
Splenomegaly (>13 cm) *n* = 35	*n* = 28 (80.5%)
Invasive diagnosis	
HVPG mmHg *n* = 13	7.9 mmHg± 4.9 mmHg
Liver Biopsy *n* = 25	(60.9%)
Clinical features	
Asymptomatic (radiological, analytical or endoscopy features) at diagnosis.	*n* = 28 (68.3%)
Portal hypertension related complications during follow up	82.9% (*n* = 34)
Varices	*n* = 34 (82.9%) - Esophagueal varices *n* = 31 (75.6%) - Stomal varices *n* = 3 (7.3%)
Variceal bleeding	*n* = 15 (37.5%) Drugs *n* = 3 (20%) Drugs plus variceal ligation *n* = 10 (66.7%) Embolization *n* = 1 (6.7%) TIPS+ embolization *n* = 1 (6.7%)
Ascites	*n* = 14 (34.1%) Grade I *n* = 10 (71.4%) Grade II *n* = 4 (28.6%) Grade III *n* = 0
Encephalopathy	*n* = 2 (4.8%)
Portal thrombosis	*n* = 9 (22%) - Cavernoma *n* = 1 (2.4%) - Main portal trunck/portal branches *n* = 5 (12.2%) - Splenoportal confluent *n* = 1 (2.4%) - Complete *n* = 2 (4.9%)
Management of portal thrombosis	- Observation *n* = 3 (7.3%) - Anticoagulation *n* = 4 (9.8%) - TIPS *n* = 2 (4.9%)

at baseline, and in no case was the spleen diameter (SLD) above the upper limit of normal (>13 cm).

Control cohort

One hundred and twenty-three patients with CRC who had been treated with OX were included as controls. As expected, there were no significant differences in baseline matching characteristics between cases and controls, as shown in Supplementary Table 4 excluding SLD, which was marginally higher in the case group but remained under 13 cm.

Patient characteristics at diagnosis of PSVD

The diagnosis of PSVD was established after a mean of 34 months from END-OX. Table 1 details the characteristics of the patients at the time of PSVD diagnosis. In 25 of the 41 patients (61%), the diagnosis was based on all accepted criteria (PSVD-OX-confirmed) including a compatible liver biopsy (percutaneous in 12 patients and transjugular in 13 patients; the latter involving hepatic venous pressure measurements). In the remaining 16 patients, the PSVD diagnosis was considered highly likely despite the absence of a liver biopsy, based on non-invasive criteria such as liver stiffness, imaging studies, and the exclusion of any other potential causes of portal hypertension via a comprehensive etiological study in the context of patients with a previously normal liver receiving OX treatment (PSVD-OX-assumed). No differences in clinical parameters were found between the two groups (Supplementary Table 5).

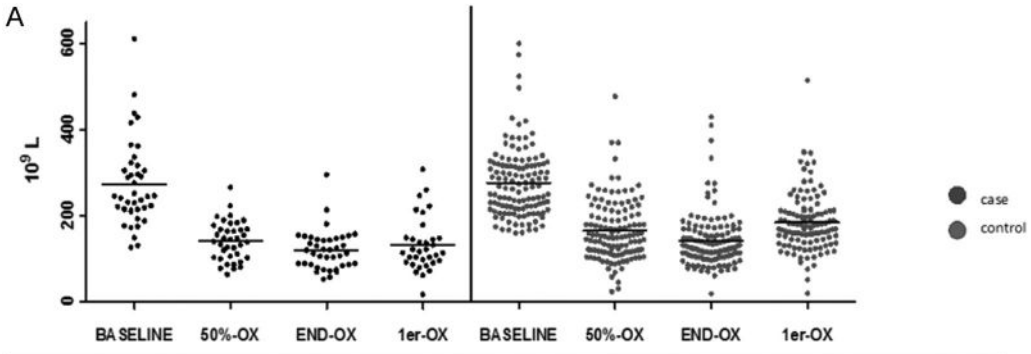
After a mean follow-up of 44.9 ± 31.6 months since OX treatment, 36 of the 41 patients with PSVD (88%) had developed at least one complication of portal hypertension, with variceal bleeding being the most frequent (*n* = 15, 37.5%, Table 1). Nine patients (22%) developed portal vein thrombosis, which was treated with anticoagulation in 4 patients and TIPS in 2.

At the end of the follow-up period (June 2019), 6 patients had passed away (14.6%): 5 due to progression of the oncological condition and one due to a liver-related complication (sepsis and liver encephalopathy). A similar number of controls (*n* = 17, 13.8%) died during the follow-up period.

Laboratory and spleen size changes during and after ox treatment in cases and controls

The duration of treatment was similar in cases and controls (median 5 months, range [2–34] months vs 5 [2-125] months, $p = 0.678$, respectively). Baseline platelet levels (PLT) prior to OX treatment were similar and decreased significantly at 50%-OX and at END-OX in both cases and controls (Table 1). However, at 50%-OX and END-OX, PLT in cases was significantly lower than in controls (Fig. 1A). Median average decrease of PLT (10^9/L) either at 50%-OX (Δ −133, range 34 to −447, vs Δ 97, range −120 to −381, mean difference 27.2 95%CI [−7.8 to 62.2], $p < 0.186$) or END-OX (Δ −132, range −34 to 480, vs Δ −123, range 145 to 430, mean difference 21.5 95% [−12.1 to 51.1], $p < 0.0001$) was higher in cases than controls. Likewise, a PLT count less than 150 × 10^9/L was detected more frequently in cases than in controls at 50%-OX and END-OX, but this difference was not statistically significant (Fig. 1B).

As previously noted, the SLD was slightly but significantly higher in cases than in controls, and only one patient in the control group had a spleen diameter of 13 cm. More notably, in cases, the SLD significantly increased at 50%-OX, and a further increase was observed at END-OX (Fig. 2A). However, in the control group, no significant changes in the SLD were observed either at 50%-OX or END-OX (Table 2). The median average increase of SLD at 50%-OX and at END-OX was Δ1.1 ± 1.4 cm vs −0.02±0.6 cm and Δ2.1 ± 2.1 cm vs 0.09±1.1 cm with $p < 0.0001$ in cases and controls, respectively. As shown in Fig. 2B, a significant percentage of cases presented an SLD >13 cm during follow-up. At END-OX,



PLT (x10^9/L)	CASES (median/range)	CONTROLS (median/range)	Mean difference 95%CI	P
BASELINE	246 [150- 661]	264 [30-600]	-3.2 (-38.5 to 32.1)	0.765
50%-OX	147 [64- 266]	153 [24- 477]	-18.9 (-0.8 to 38.7)	**0.017**
END OF TREATMENT	120 [53- 295]	126 [19—430]	-21.3 (2.7 to 39.9)	**0.047**
1er-OX	114 [17- 308]	174 [20- 514]	-51.6 (26.4 to 77.3)	**<0.001**

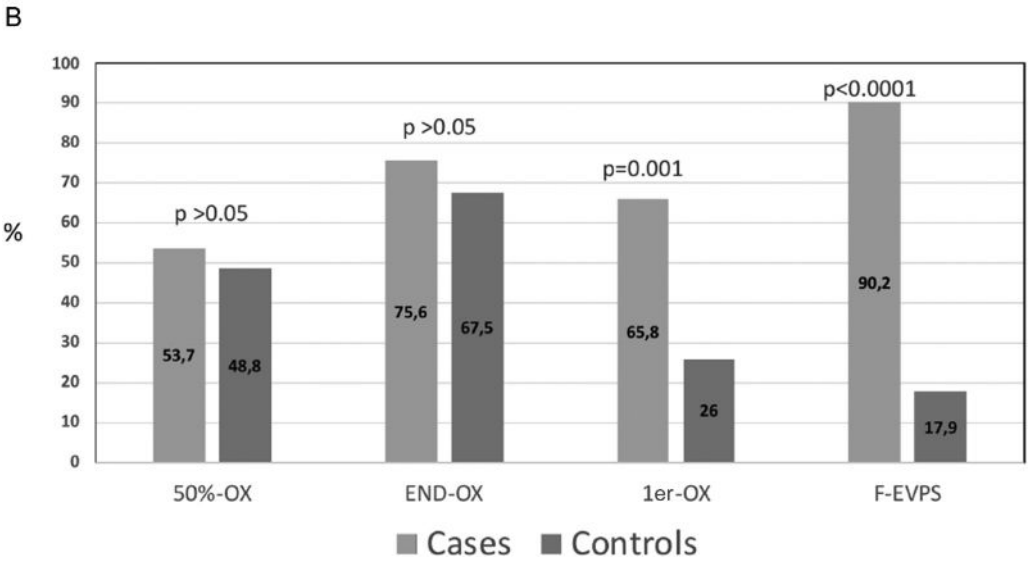


Fig. 1. A. Significant differences between cases and controls in platelet count at different points during treatment and first year of follow up., B. Percentage of patients with a platelet count <150 × 10^9/L. Differences between cases and controls. Caption: significant differences in each points of follow up ($p < 0.05$).

more than half of the cases showed SLD >13 cm, while only 2.6% of controls did.

Risk factors for psvd development

In an attempt to identify factors that can early predict the development of PSVD, we analyzed several variables gathered at different time points.

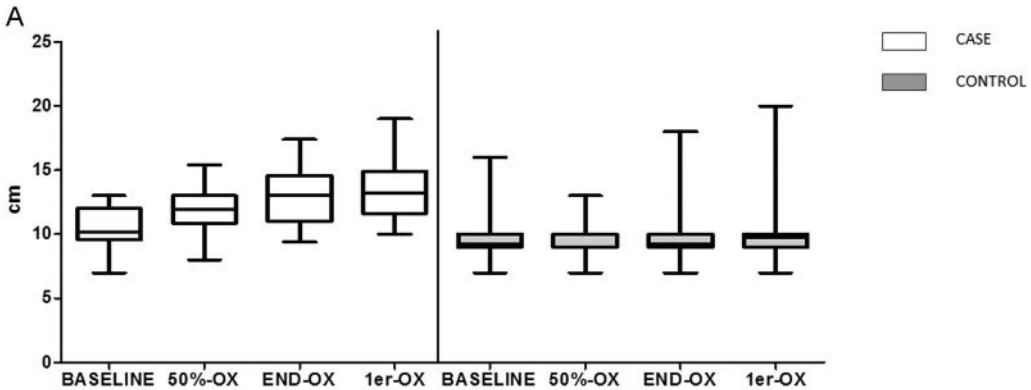
At baseline, we found that AST, ALP, and SLD were associated with PSVD development, but only SLD was confirmed as a significant factor in the multivariate analysis (Table 3).

At 50%-OX, the absolute value of SLD, splenomegaly (SLD>13 cm), bilirubin levels and platelet count (PLT) were associated with PSVD development at the univariate analysis level. Interestingly, a platelet count below 150, 100 or 50 × 10^9/L were not predictors of PSVD development. In the multivariate analysis, which didn't include variables showing collinearity, either the absolute value of SLD or SLD>13 cm were shown as the only independent predictors of PSVD development (Table 3).

Upon analysis of the data at the END-OX and first year-OX, either SLD or SLD>13 cm emerged as the only independent predictors of future PSVD development (Table 3).

Subsequent univariate and multivariate analyses of qualitative and quantitative variables were conducted. Categorical variables such as sex, alcohol use, diabetes, and hypertension did not show any significant association. Likewise, the administration of bevacizumab was not found to be a protective factor against the development of PSVD (OR 0.78 (0.29–2.08); $p = 0.618$), and neither the cumulative dose of OX nor the occurrence of neuropathy emerged as risk factors for PSVD development.

We additionally conducted both univariate and multivariate regression analyses (as shown in Supplementary Table 6) using delta variables, defined as the change from baseline to the end of the oxaliplatin-based regimen (END-OX), for PLT, s SLD, and liver function tests. Consequently, patients exhibiting an enlargement in SLD during the therapeutic regimen, with a continued increase at one year post-treatment, manifested a markedly elevated risk for PSVD [OR 43.94; 95% confidence interval [CI], 14.48–133.336; $p < 0.0001$). Comparative analysis of cases with biopsy-confirmed



cm	CASE (mean ±SD)	CONTROL (mean ±SD)	P
BASELINE	10.5 ± 1.6	9.5 ±1.3	0.001
50% TREATMENT	11.7 ±1,6	9.4 ±1.2	<0.001
END-OX	12.9 ±2.3	9.5± 1.5	<0.001
1er-OX	13.5±2.4	9.7±1.8	<0.001

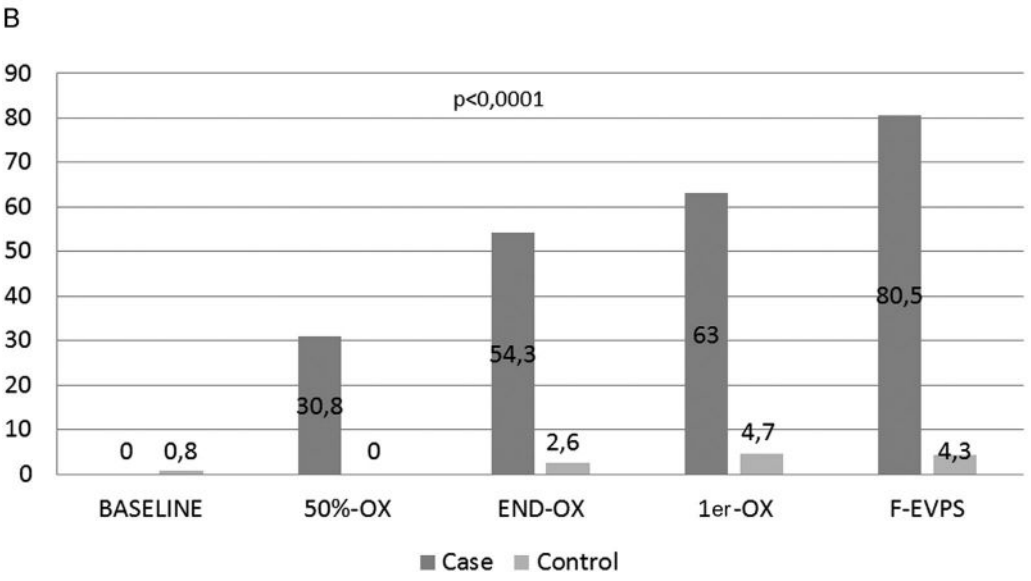


Fig. 2. A: Significant differences between cases and controls in spleen diameter at different points during treatment and first year of follow up. B: Percentage of patients with a spleen diameter >13 cm. Differences between cases and controls. Caption: significant differences in every time point of follow up ($p < 0.0001$).

PSVD and those without biopsy-proven PSVD yielded congruent outcomes (refer to Supplementary Tables 5, 7 and 8).

To establish a cutoff point that could act as an early indicator of disease progression, we first analyzed the increase in SLD between baseline and 50% of treatment, as well as the completion of oxaliplatin therapy (END-OX). We found that an SLD increase of >1.05 cm from baseline to 50%-OX had an AUROC of 0.772, while an increase of >3.05 cm from baseline to END-OX had an AUROC of 0.826 ($p < 0.001$). We plotted a ROC curve with SLD and PLT at 50%-OX, END-OX, and the first-year follow-up (Fig. 3A and B). We identified the optimal cutoff point with the highest sensitivity and lowest 1 – specificity for each category. The SLD proved to be the most reliable risk indicator for the disease at all stages. As expected, neither the PLT cutoff at 50%-OX nor at END-OX exhibited sufficient sensitivity for diagnosis. The strongest early marker of the disease emerged in the first year following treatment. A combination of SLD >11.75 cm and PLT $<149 \times 10^9$ /L offered a positive predictive value (PPV) of 76% and a negative predictive value (NPV) of 91% for PVSD diagnosis.

Genetic study

We evaluated the genotype of an assortment of 16 Single Nucleotide Polymorphisms (SNPs) within the case group, and contrasted their frequency with the established frequencies found within the Iberian population (refer to Supplementary Table 3). Utilizing the Log-Likelihood Ratio (LLR) test, we were unable to ascertain any notable association between the alleles and the manifestation of PSVD-OX (refer to Supplementary Tables 9 and 10), save for the Methylenetetrahydrofolate Reductase (MTHFR) SNP rs1801133 (p.Asn324Ser).

This particular variant has previously been linked to the occurrence of homocystinuria, according to data available at ClinVar [27] and has been connected with early onset portal vein thrombo-

Table 2
Case and control features at different time points compared with baseline.

	BASELINE	50 %–0X	P	END-OX	P	1er-OX	P
Haemoglobin (g/dl)							
Case	12.9 ± 1.9	12.7 ± 1.6	***0.84***	14.8 ± 1.2	***0.347***	13.6 ± 2.0	***0.220***
Control	13.5 ± 1.8	13.52±9.8	***0.986***	12.5 ± 2	***0.0001***	13.9 ± 1.34	***0.55***
Platelet count (10^9 /L)							
Case	277.4 ± 99.8	142.1 ± 45.6	***0.001***	119.8 ± 45.8	***0.0001***	132.3 ± 62.9	***0.0001***
Control	274.3 ± 83.9	165.6 ± 70.5	***0.0001***	141.9 ± 6.8	***0.0001***	184±68.2	***0.001***
Leukocytes count (10^9 /L)							
Case	8.1 ± 2.30	5.1 ± 2.1	***0.001***	5.2 ± 3.4	***0.0001***	5.8 ± 2.4	***0.0001***
Control	7.4 ± 2.1	5.2 ± 2.2	***0.0001***	4.7 ± 2.1	***0.0001***	7.2 ± 6.5	***0.848***
Bilirubin (mg/dl)							
Case	0.5 ± 0.4	0.7 ± 0.5	***0.030***	0.9 ± 0.8	***0.002***	0.5 ± 3.5	***0.001***
Control	0.5 ± 0.2	0.5 ± 0.3	***0.327***	0.7 ± 0.3	***0.358***	0.8 ± 1.2	***0.043***
AST (UI/L)							
Case	27.9 ± 20.1	41.6 ± 18.4	***0.006***	44.2 ± 14.4	***0.002***	43.4 ± 21.8	***0.003***
Control	21 ± 7.8	40.3 ± 28.7	***0.0001***	21±7.8	***0.0001***	29.8 ± 12.7	***0.000***
ALT (UI/L)							
Case	26.7 ± 20.1	43.7 ± 42.7	***0.045***	36.2 ± 17.4	***0.031***	42.7 ± 26.8	***0.018***
Control	21.7 ± 10.3	42.7 ± 41.9	***0.0001***	35.5 ± 19.8	***0.0001***	30.5 ± 16.7	***0.000***
Albumin (mg/dl)							
Case	4.2 ± 0.6	4.07±0.29	***0.092***	3.9 ± 0.2	***0.0001***	4.1 ± 0.8	***0.374***
Control	4.1 ± 0.6	4.1 ± 0.27	***0.554***	4.1 ± 0.2	***0.069***	4.2 ± 0.7	***0.577***
Spleen diameter (cm)							
Case	10.5 ± 1.6	11.5 ± 1.5	***0.001***	12.8 ± 2.3	***0.0001***	13.06±2.2	***0.0001***
Control	9.4 ± 1.4	9.3 ± 1.2	***0.637***	9.5 ± 1.33	***0.326***	9.67±1.7	***0.168***
FIB-4 score							
Case	1.2 ± 0.6	3.1 ± 1.2	***0.001***	4.2 ± 1.9	***0.001***	4.4 ± 4.5	***0.002***
Control	1.1 ± 0.5	2.7 ± 1.8	***0.001***	3.4 ± 2.2	***0.001***	2.1 ± 1.5	***0.001***

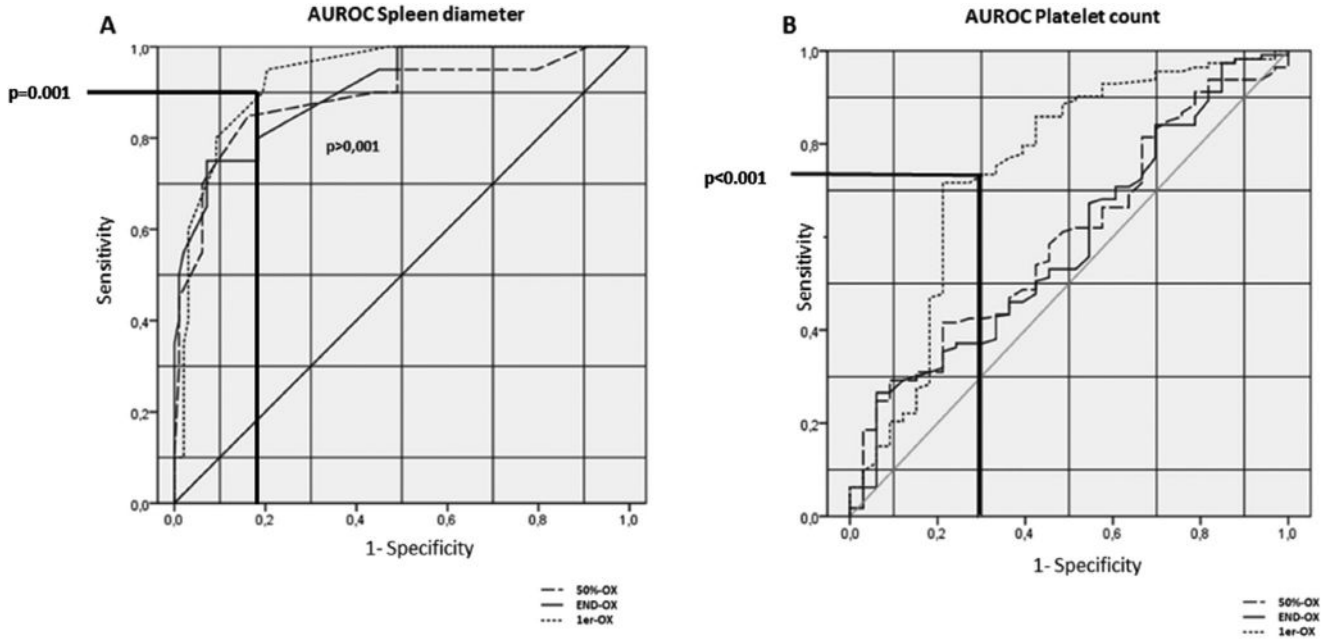


Fig. 3. ROC curve for spleen diameter as marker of exclusion of the disease (A) and low platelet count for risk factor of PSVD (B). Caption: A) Patients with a spleen diameter >11.1 cm at 50%-OX (big dashed line) with AUROC 0.885 (IC 95% 0.791–0.980), Sensitivity 0.7 and 1 - Specificity 0.086, $p < 0.001$; at END-OX (continuous line) a SLD>11.7 cm has an AUROC 0.75 (IC 95% 0.835–0.985), Sensitivity 0.70 and 1-Specificity 0.071, $p < 0.001$; and AUROC 0.933 (IC 95% 0.884–0.981) for a SLD>11.75 cm at first year after treatment (small dashed line) with a Sensitivity 0.90, 1-Specificity 0.192, $p = 0.001$. B) Platelet count at 50%-OX (big dashed line) with AUROC 0.599 (IC 95% 0.494–0.704), $p = 0.054$; END-OX (continuous line) AUROC 0.584 (IC 95% 0.474–0.693), $p = 0.056$; patients with PLT<149.5 × 10^9/L at 1st year after treatment (small dashed line) has an AUROC for diagnosis of the disease of 0.745 (IC 95% 0.638–0.853), Sensitivity 0.717, and 1-Specificity 0.212, $p = 0.0001$.

sis in patients suffering from cirrhosis [28] and our patient with a homozygosis AA allele had developed portal vein thrombosis. However, within our patient cohort, the A allele, which has been associated with disease manifestation as cited above, was underrepresented when cross-referenced with its frequency within the Iberian population. Also, we have identified a homozygosis allele GG related with common variable immunodeficiency and a heterozygosis allele G, in two patients with PSVD-OX, also we coudnt́ confirm an incidence higher than general population.

Discussion

This study focused on the description of the natural history of PSVD-OX. It is a uncommon entity, underdiagnosed outside liver specialist setting [10–12]. Our cohort only included patients treated with OX in the context of CCR, with the aim of avoiding confounding factors such as the type of surgery or the probability of survival with other gastrointestinal tumors like gastric or pancreatic cancer. Unlike other OX-related liver diseases such as SOS, the progression

Table 3
Univariate and multivariate logistic regression analysis evaluating factors at baseline, 50% of treatment, end of treatment and first year after treatment associated with the development of PSVD.

	BASELINE				50 % TREATMENT				END OF TREATMENT				1er-OX			
	UNIVARIATE		MULTIVARIATE		UNIVARIATE		MULTIVARIATE		UNIVARIATE		MULTIVARIATE		UNIVARIATE		MULTIVARIATE	
	OR	P	OR	p	OR	p	OR	p	OR	p	OR	p	OR	P	OR	P
Platelets	0.999 (0.995 - 1.003)	0.758	–	–	0.99 (0.98 - 1.00)	0.05	1.00 (0.98–1.01)	0.949	0.99 (0.98–1.00)	0.051	1.01 (0.99–1.01)	0.385	0.98 (0.97 - 0.99)	**<0.001**	0.99 (0.98–1.01)	0.777
AST	1.049 (1.008 - 1.092)	**0.019**	0.995 (0.918–1.079)	1.049 (1.008 - 1.092)	1.002 (0.988 - 1.017)	0.760			1.013 (0.99–1.03)	0.216			1.04 (1.02 - 1.07)	**0.001**	1.08 (0.98–1.19)	0.096
ALT	1.026 (0.999 - 1.053)	0.057	1.017 (0.959–1.079)	1.026 (0.999 - 1.053)	1.00 (0.992 – 1.009)	0.913			1.00 (0.98–1.02)	0.911			1.02 (1.00 - 1.05)	**0.009**	0.99 (0.92–1.06)	0.850
δGT	1.005 (1.000 - 1.011)	0.051	1.001 (0.993–1.009)	1.005 (1.000 - 1.011)	1.00 (0.99 – 1.01)	0.614			1.00 (0.99–1.01)	0.212			1.01 (1.00 - 1.01)	**0.027**	1.00 (0.992–1.00)	0.907
Bilirubin	0.974 (0.767 - 1.237)	0.832		0.974 (0.767 - 1.237)	2.80 (1.22 – 6.43)	**0.015**	1.57 (0.36–6.74)	0.542	2.84 (1.41–5.69)	**0.003**	2.21 (0.67–7.26)	0.188	0.95 (0.74 - 1.22)	0.714		
Albumin	1.261 (0.527 - 3.019)	0.602		1.261 (0.527 - 3.019)	0.26 (0.04 – 1.40)	0.118	1.83 (0.11–28.89)	0.667	0.14 (0.02–0.97)	**0.048**	0.24 (0.023–2.64)	0.250	0.73 (0.37 - 1.45)	0.377		
SLD	1.679 (1.266 - 2.226)	**< 0.001**	1.821 (1.201–2.760)	1.679 (1.266 - 2.226)	3.39 (2.153 – 5.347)	**<0.001**	3.46 (1.86–6.43)	**<0.001**	2.39 (1.766–3.250)	**<0.001**	2.04 (1.440–3.014)	**<0.001**	1.980 (1.523 - 2.583)	**<0.001**	2.15 (1.49–3.11)	**<0.001**
PLT<150*	–	–	–	–	1.49 (0.715–3.11)	0.286	1.62 (0.56–4.64)	0.365	2.10 (0.856–5.188)	0.105	1.32 (0.427–4.084)	0.630	9.351 (3.708–23.579)	**<0.001**	48.33 (1.31–17.78)	**0.018**
PLT<100*	–	–	–	–	1.78 (0.69–4.56)	0.228	0.69 (0.14–3.27)	0.647	1.78 (0.696–4.567)	0.228	0.15 (0.019–1.256)	0.080	11.782 (3.770–36.823)	**<0.001**	0.99 (0.16–5.83)	0.994
PLT<50*	–	–	–	–	–	–	–	–	–		–	–	3.394 (0.207–55.749	0.392		
SLD >13 cm	–	–	–	–	48.88 (5.76–414.59)	**<0.001**	53.36 (6.16–462.13)	<0.001	44.72 (11.88–168.35	**<0.001**	137.07 (15.66–1199.44)	**<0.001**	34.34 (10.45–112.89)	**<0.001**	23.84 (6.03–94.19)	**< 0.001**

Caption: Data expressed as OR (odds ratio) and confidence interval IC 95%.
ALT: alanine transaminase; AST: aspartate transaminase; γGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase; INR: international normalized ratio.
* 10^9 platelet count.

to PSVD is slow, with the average time to diagnosis in our cohort being 33.8 ± 27 months. Most cases were asymptomatic at diagnosis (68.3%), but with obvious signs of portal hypertension (73.2%, esophageal varices; 22% portal thrombosis and 24% ascites grade I). Although this liver disease is only responsible for one death in our cohort against 5 due to progression of the oncological disease, PSVD resulted in several hospital admissions related to portal hypertension complications ($n = 15$ variceal bleeding, 9 portal thrombosis, 14 ascites and 2 episodes of hepatic encephalopathy). The management of these complications is complex and may include procedures (e.g. ligation of esophageal varices, TIPS insertion; or stomal varices embolization), which require the expertise of highly qualified liver units.

Therefore, one of the key objectives of our research was to identify early markers that could be employed for the prediction of liver disease during chemotherapy treatment or in the initial months following it. Our data demonstrated that both the decline in PLT and the enlargement of the spleen are significantly more pronounced in cases as compared to controls during and at the conclusion of the chemotherapeutic regimen. Furthermore, these parameters are not stationary but continue to evolve throughout the follow-up period until manifestations of portal hypertension ultimately emerge (see Figs. 1A and 2A).

As previously demonstrated, a PLT count below 150×10^9/L and SLD exceeding 13 cm at the first-year post-treatment serve as the most potent predictive indicators of the disease (with OR of 48.33, $p < 0.018$, and 23.848, $p < 0.0001$, respectively). Although a PLT count less than 100×10^9/L at the first year following treatment is significantly more prevalent in cases than in controls, the amplified risk in multivariate analysis is not confirmed. The mechanisms underlying OX-induced thrombocytopenia are twofold. The first mechanism involves direct myelosuppression, which results in PLT counts of $<75 \times 10^9$/L in approximately 77% to 79% of treated patients. The second mechanism implicates immune responses that induce a rapid decline in platelet count [13,14].

We tried to find the earliest marker that can be used by a non hepatologist physician, and without doubt it is the increase of spleen size. A slight increase of >1.05 cm at the middle of oxaliplatin (OX) treatment, that progress until the end of treatment, should be regarded as a strong indication of the disease. In fact, our results are in line with recently published data that the >30% increase after 6 months of treatment was a significant predictive marker for collateral vessel development [29] and a higher FIB-4 value at any time of treatment are related with PSVD-OX [30] and a higher FIB-4 index at any treatment phase is associated with PSVD-OX [31].

The fact that the increase in the SLD is the factor more strongly associated with PSVD risk can be explained by the toxic effect of OX on liver endothelial cells. OX causes sinusoidal wall fenestration, with subsequent obstruction to sinusoidal blood flow, increase of intrahepatic resistance, development of portal hypertension and secondary damage of spleen vessels [31,32]. In fact, although remaining within normal values, the cases presented a slightly larger SLD at the start of the OX treatment than the controls (10.5 ± 1.6 vs 9.5 ± 1.3, $p = 0.001$). None of our patients presented data of chronic liver disease or portal hypertension prior to inclusion in the study. Similarly, reversible splenomegaly has been described [12].

Nonetheless, an unresolved question remains: why do certain patients develop the disease while others do not? We have not discovered any correlation with the cumulative dose of oxaliplatin, gender, age, or the potential protective effect of Bevacizumab. It is likely, as postulated previously, that the reason could be attributed to the presence of genetic polymorphisms. The concurrent presence of these polymorphisms and a precipitating toxin such as OX would trigger the onset of the disease. However, we were unable to identify any significant association between the 16 selected SNPs and the development of PSVD-OX.

We acknowledge several limitations inherent to this study, primarily due to its retrospective design and sample size. The availability of DNA samples was limited to 35 cases, which consequently reduced the statistical power of the genetic association study, particularly with respect to less frequent SNPs. Therefore, we cannot rule out a possible association between the studied polymorphisms and PSVD-OX. To address this issue, larger, multicenter, and international collaborative studies are required. Furthermore, applying whole exome sequencing in such studies would favor the identification of genetic causes of PSVD-OX. Another potential limitation of this study is that a histological examination was conducted only on 25 out of the 41 cases included in the study. Although the remaining patients cannot be definitively diagnosed as PSVD, they met the non-invasive criteria for PSVD, providing strong support for the diagnosis. Recent evidence also supports the non-invasive diagnosis of PSVD as all patients with PSVD-OX exhibited an elastography reading of less than 13.4Kpa [33,34]. Significantly, as demonstrated in Supplementary Tables 5, 7 and 8, the results in the subgroup of patients with a histological diagnosis were similar to those described in the entire cohort, indicating that the results are sufficiently robust to confirm our hypothesis.

Our study has also considerable strengths. To the best of our knowledge, this is the largest study showing the natural history of PSVD-OX, in a perfectly characterized cohort of patients. Likewise, we confirmed that patients with both thrombocytopenia and an increase in SLD during and after OX treatment, especially those who do not improve during the first year after the end of chemotherapy, are at risk of developing PSVD.

In conclusion, our research findings further suggest that certain patients, who exhibit risk markers such as persistent thrombocytopenia and splenomegaly following treatment with oxaliplatin, are potential candidates for the development of PSVD. These patients should be targeted for specific follow-up within specialized liver units.

Conflicts of Interest

None.

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Authors’ contributions

AP, JIF, JCGP and JC contributed to the study concept and design. All authors contributed to the acquisition of data. AP, JIF, JCGP and JC contributed to the analysis and interpretation of data and drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors approved the final manuscript prior to submission.

Disclosures

A. Albillos has served as advisor/lecturer for AbbVie, Gilead Sciences, Gore, Griffols, Intercept Pharmaceuticals, and Merck & Co. and has received research/educational grants from Gilead Sciences. R. Bañares has received consultant fees from Abbvie and speaker fees from Gilead, Abbvie and Janssen. JC. Garcia-Pagan received consultant fees from Shionogi, Gore and research grants from Novartis, Theravance, and Exalenz. A. Giráldez received speaker fees from Gore. M. Alonso-Peña received a grant from Roche. The remaining authors have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.04.010.

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