Impact of SARS-CoV-2 vaccination in patients with vascular liver diseases: Observations from a VALDIG multicenter study
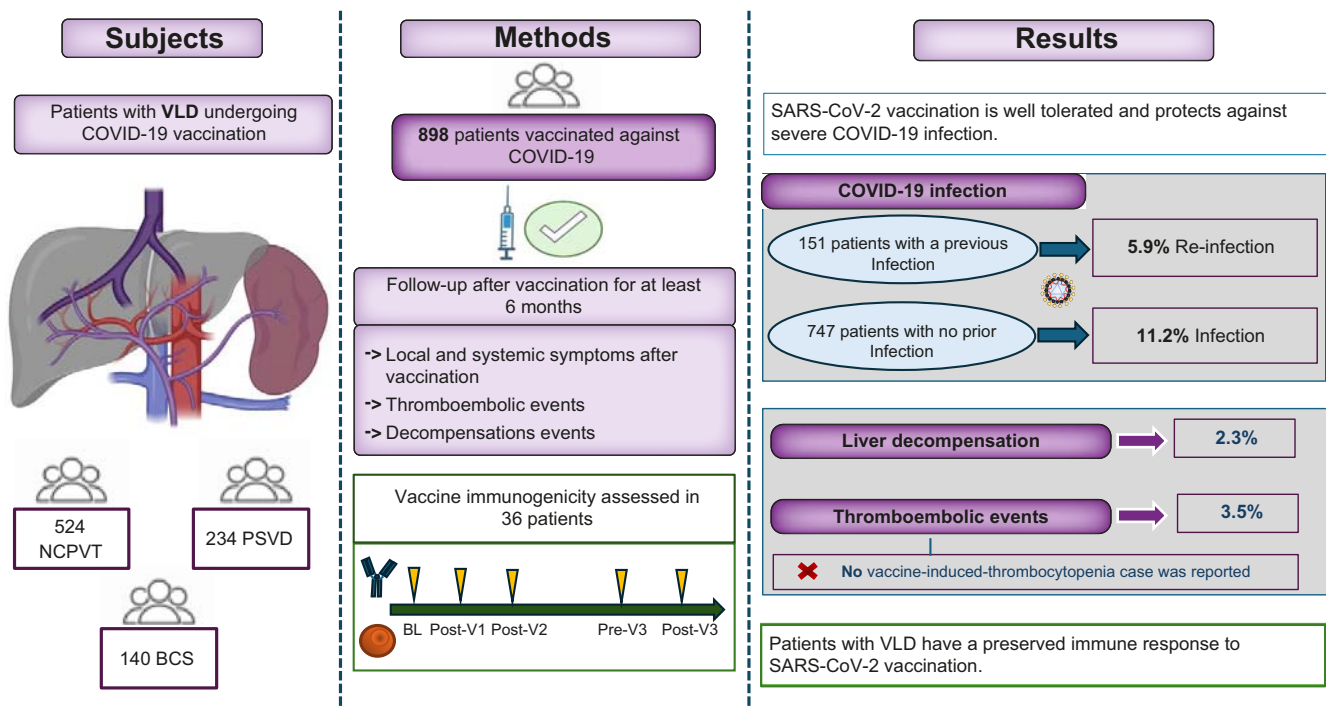
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Graphical abstract

Highlights:

- Patients with VLD have a preserved immune response to SARS-CoV-2 vaccination.

- SARS-CoV-2 vaccination is well tolerated and protects against severe COVID-19.

- There is a low risk of liver decompensation and thrombosis following vaccination.

- No vaccine-induced-thrombocytopenia case was reported in patients with VLD.

Impact and implications:

Patients with vascular liver disease (VLD) are at increased risk of both SARS-CoV-2 infection and severe COVID-19 disease. The potential risks associated with vaccination against this infection need thorough investigation. Our research enhances the understanding of the effects of COVID-19 vaccination in patients with VLD, highlighting its good tolerability. Moreover, patients with VLD appear to have a preserved immune response to SARS-CoV-2 vaccination, providing protection against severe COVID-19 infection. Our study cannot definitively establish a direct link between vaccination and thrombotic events, and no cases of vaccine-induced thrombocytopenia were reported.

Impact of SARS-CoV-2 vaccination in patients with vascular liver diseases: Observations from a VALDIG multicenter study[☆]

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Background & Aims: Patients with vascular liver diseases (VLD) are at higher risk of both severe courses of COVID-19 disease and thromboembolic events. The impact of SARS-CoV-2 vaccination in patients with VLD has not been described and represents the aim of our study.

Methods: International, multicenter, prospective observational study in patients with VLD analyzing the incidence of COVID-19 infection after vaccination, severity of side effects, occurrence of thromboembolic events and hepatic decompensation. In a subgroup of patients, the humoral and cellular responses to vaccination were also analyzed.

Results: A total of 898 patients from 14 European centers – part of the VALDIG network – were included, 872 (97.1%) patients received two vaccine doses (fully vaccinated), and 674 (75.1%) three doses. Of the total cohort, 151/898 had a COVID-19 infection prior to vaccination, of whom 9/151 (5.9%) were re-infected. Of the 747/898 patients who were not previously infected, 11.2% (84/747) were diagnosed with a COVID-19 infection during the study period. Two infected patients required intensive care unit admission and infection was fatal in two fully vaccinated patients. Adverse effects were reported in around 40% of patients, with local side effects being the most frequent. During the study period, 31 (3.5%) patients had thromboembolic events and 21 (2.3%) hepatic decompensations. No cases of vaccine-induced thrombocytopenia were reported. Vaccine immunogenicity was assessed in 36 patients; seroconversion reached 100% and IFNy T-cell responses significantly increased post two mRNA-1273 vaccine doses.

Conclusion: Patients with VLD seem to have a preserved immune response to SARS-CoV-2 vaccination, which appears to be safe and effective in preventing severe COVID-19 infection. Our study cannot definitively establish a direct link between vaccination and thrombotic events, though the contribution of vaccination as a cofactor in VLD remains to be elucidated.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused an unprecedented health crisis, leading to the rapid development and subsequent approval of COVID-19 vaccines. These vaccines have proven to be effective in preventing both symptomatic and severe infections. Patients with chronic liver disease have an increased risk of severe infection and, due to impairment in the immune response, the immediate and long-term protective response through immunization may be incomplete.[1,2] Vaccines have also been shown to be safe. However, concerns have arisen regarding a potential elevated risk of unusual-site thrombosis, including within the splanchnic territory, and vaccine-induced immune thrombotic thrombocytopenia following vaccination.[5,6]

Vascular liver diseases (VLD) collectively encompass several rare conditions that pose a significant global health concern.[3] Patients with VLD, specially with portosinusoidal vascular disorder (PSVD) and splanchnic vein thrombosis are at higher risk of both infection by SARS-CoV-2 and severe COVID-19 disease.[4] VLD are commonly associated with other systemic and inflammatory conditions, such as autoimmune disorders, that may potentially impair the immune response to vaccination.

Furthermore, individuals with VLD face an elevated risk of thromboembolic events, particularly within the splanchnic vasculature. It remains uncertain whether this risk could worsen after vaccination, a concern that remains pertinent, particularly considering the requirement for additional vaccine doses to address new waves of the pandemic.

Hence, the immunological response and thrombosis risk post-vaccination in patients with VLD remain uncertain. Our study aims to address these questions by examining a large cohort of patients with VLD who received the SARS-CoV-2 vaccine, with a specific emphasis on assessing effectiveness, tolerability, safety, and immune response.

Patients and methods

We conducted a prospective, international, multicenter study enrolling patients with VLD undergoing COVID-19 vaccination; we included all patients with VLD. Exclusion criteria comprised refusal to participate and a diagnosis of cirrhosis. Patients were followed up prospectively at least 6 months after vaccination and data on COVID-19 infection, tolerance and secondary events were recorded. We also evaluated the humoral and cellular responses in a subgroup of patients; antibodies against spike antigen and specific T-cell responses were quantified at baseline, after the first, and before and after the second and third doses of the vaccine.

All patients signed an informed consent to participate in the study, in accordance with the International Guideline for Ethical Review of Epidemiological studies and principles of the Declaration of Helsinki and was approved by the local ethics committees (Study register: HCB/2021/0477).

Study population

Fourteen European centers participated in the study, nine Spanish centers from the REHEVASC network and five European referral centers from the VALDIG network (Table S1).

The study period extended from May 2021 and March 2022. Enrolment initiated at the time of first SARS-CoV-2 vaccine dose. All patients had a minimum follow-up of 6 months. Patients were interviewed in the outpatient clinic or contacted by phone to get information on presence of secondary events after vaccination, liver-related decompensations and thromboembolic events, focusing on: 1) 1 week after the first dose and second dose, 2) at 3 months and 3) 6 months after the second dose. For patients receiving a third dose, any side effects following vaccination were also documented. We created an online registry including baseline characteristics such as age, gender, associated comorbidities, chronic medication, existence of portal hypertension, hepatic decompensations and history of thrombosis. We actively investigated if they had previous SARS-CoV-2 infections prior to vaccination.

Due to the widespread vaccination efforts among patients with VLD, who were considered a high-risk group, and the strong advocacy for vaccination by both VALDIG and ERN Rare Liver, a control group was not feasible. Instead, we conducted a comparative analysis of COVID-19 infection prevalence in our VLD patient cohort. We compared our findings with the cohort presented by Baiges et al.[4] of non-vaccinated patients with VLD and with the general population. To facilitate this comparison, we selected our largest cohorts from Spain and

France. We then compared the infection prevalence in our study with the data available on the official websites of the Spanish government (ine.es) and the French government (santepubliquefrance.fr) for the corresponding period of our study (Table S2).

Definitions

Complete vaccination schedule (fully vaccinated patients) was considered after receiving two doses with a mRNA vaccine (Pfizer/BioNTech® BNT162b2 mRNA or Moderna®-mRNA-1273), or of the adenoviral vector vaccines (two doses of AstraZeneca®/University of Oxford ChAdOx1-nCoV-19 or one dose of the Janssen Ad26.CoV2–S vaccine).

Primoinfection or breakthrough infection was defined as an infection reported more than 14 days after the administration of the last vaccine dose in fully vaccinated patients. Infections occurring after the third dose of vaccination are discussed separately.

Adverse events (AEs) were classified as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening or disabling (grade 4).

Secondary/adverse events after vaccination were defined as local at the injection site, systemic symptoms after vaccination and a thrombotic event or a decompensation event of the underlying liver disease after vaccination and during the follow-up period.

Immunological response

The serological response after vaccination was analyzed in a subgroup of 36 patients with VLD, from the Hospital Clinic Cohort. All patients were vaccinated with Moderna® mRNA-1273 vaccine. We evaluated immunogenicity to wild-type and omicron variants, using a Roche Elecsy® Anti-SARS-CoV-2 S ECLIA we quantified anti-RBD Ig response with a cut-off >0.8 U/m. IFNy T-cell responses to full SARS-CoV-2 spike protein were measured using an IFNy ELISpot assay. Blood samples were taken at baseline (before the first dose: pre-V1), 24 h after the first dose of vaccine (V1), 28 days after the first dose (V2), 1 month (V3) and 6 months (V4) after the second dose and 21-28 days after the third booster dose (V5). Data on this cohort has previously been reported alongside data on other chronic liver diseases,[7] focusing on antibody and cellular data; however, details on immune responses according to VLD subtype and breakthrough infection status have not previously been disclosed.

Analysis

To assess the normality of the distribution of the variables we used the Kolmogorov Smirnov test. Quantitative variables are reported as mean ± standard deviation, and ± interquartile range when applicable and compared using the t test, the Mann-Whitney U test or Kruskal-Wallis test when appropriate. Categorical variables are reported as absolute and relative frequencies, the Fisher exact test and Chi-square test were used for categorical variables when appropriate. Mann-Whitney U test or Wilcoxon matched-paired signed rank test were used. Thrombosis episodes were plotted using the Kaplan-Meier method with the log-order test. Statistical analyses were performed using SPSS 25.0 package (SPSS, Chicago, IL, USA).

Results

Patient characteristics

Nine hundred and nine patients with VLD received a COVID-19 vaccine. For geographical distribution see Table S1. Throughout the study, 11 patients were excluded from the analysis due to insufficient follow-up post-administration of the initial vaccine dose, resulting in a final cohort of 898 patients from the initial 909. None of the patients who completed the follow-up revoked consent for participation in the study. We finally analyzed: 524 patients with non-cirrhotic–non-malignant-splanchnic vein thrombosis (NCPVT), 234 with PSVD and 140 with Budd-Chiari syndrome (BCS). Mean age was 54.5 ± 14.7 years and 483 were men (53.8%). At the time of enrolment, 267 (29.7%) patients had decompensated liver disease and clinical signs of portal hypertension were present in 542 (60.4%) patients. In the PSVD group, 19.2% (45/234) had a history of previous splanchnic thrombosis. Baseline characteristics are described in Table 1.

A total of 872 patients (97.1%) received two vaccine doses and 674 (75.1%) had a third dose. mRNA vaccines were administered for the first, second and third vaccine doses in 87%, 90% and 98% of patients, respectively (Table S3).

Adverse events

Within 24-48 h after vaccine administration, at least one adverse event was reported in 42.6% of the patients; none of these events were classified as severe (grade 3). Local side effects at the injection site were reported in 26.9%, 22% and 17.4% of patients after the first, second and third vaccine doses, respectively. The most common systemic side effects were asthenia in 13.6%, 17% and 13% and fever in 6.9%, 12.7% and 8.5% with the first, second and third doses of vaccination, respectively. No hypersensitivity reactions were reported. Detailed information is provided in Table S4.

COVID-19 infection

Among 151 (16.8%) patients with previous COVID-19 infection, 9 (5.9%) had a re-infection post-vaccination: three after one dose, four after two doses, and two after the third dose. Two patients were asymptomatic, and seven patients presented a mild clinical presentation without the need for hospital admission.

Out of 747 without previous COVID-19 infection, 84 (11.2%) had a primary infection: 43 with NCPVT, 28 with PSVD, and 13 with BCS. Of these, 53 (7.1%) were fully vaccinated, 31 (4.1%) after a third vaccine dose (Fig. 1). Severity of infection in fully vaccinated patients was mostly mild: only four patients required hospitalization, and two patients were admitted to the ICU. Table S5 details infection characteristics by VLD subgroup.

After receiving a third dose, severity of primary infection remained mild: two patients were hospitalized, none were admitted to the ICU and no deaths were reported.

Table 1. Baseline characteristics before vaccination.

Baseline characteristics	Total cohort, N = 898	NCPVT n = 524	PSVD n = 234	BCS n = 140	p values
Sex (male)	483 (53.8%)	299 (57.1%)	136 (57.9%)	48 (34.3%)	<0.01
Age (years)	54.5 ± 14.7	56.1 (± 14.6)	54.5 (± 13.9)	48.3 (± 14.7)	1
Decompensated liver disease	267 (29.7%)	126 (24.0%)	71 (30.3%)	70 (50.0%)	<0.01
Portal hypertension					
Portal hypertension	542 (60.4%)	285 (54.4%)	165 (70.5%)	92 (65.7%)	<0.01
Ascites at inclusion	120 (13.4%)	40 (7.6%)	26 (11.1%)	54 (38.6%)	<0.01
Varices	125 (13.9%)	75 (14.3%)	33 (14.1%)	17 (12.1%)	0.811
Previous portal hypertensive bleeding	139 (15.5%)	80 (15.3%)	44 (18.8%)	15 (10.7%)	0.109
Hepatic encephalopathy at inclusion	18 (2.0%)	6 (1.1%)	7 (3.0%)	5 (3.6%)	0.086
Associated comorbidities					
No comorbidities	244 (27.2%)	168 (32.1%)	46 (19.7%)	30 (21.4%)	<0.01
Inflammatory bowel disease	39 (4.3%)	17 (3.2%)	20 (8.5%)	2 (1.4%)	0.001
Immune mediated diseases	59 (6.6%)	25 (4.8%)	20 (8.5%)	14 (10.0%)	0.001
Hematological disorders	249 (27.7%)	141 (26.9%)	33 (14.1%)	75 (53.6%)	<0.01
Cardiovascular diseases/cardiovascular risk-associated diseases	225 (25.1%)	150 (28.6%)	58 (24.8%)	17 (12.1%)	<0.01
Arterial hypertension	172 (19.2%)	119 (22.7%)	38 (16.2%)	15 (10.7%)	0.002
Diabetes mellitus	77 (8.6%)	51 (9.7%)	23 (9.8%)	3 (2.1%)	0.013
Obesity	80 (8.9%)	63 (12.0%)	12 (5.1%)	5 (3.6%)	0.001
Pulmonary diseases	60 (6.7%)	31 (5.9%)	20 (8.5%)	9 (6.4%)	0.42
HIV	28 (3.1%)	5 (1.0%)	22 (9.4%)	1 (0.7%)	<0.01
Chronic medication - non PHT					
Anticoagulation	559 (62.2%)	365 (69.7%)	71 (30.3%)	123 (87.9%)	<0.01
Antiplatelets	79 (8.8%)	36 (6.9%)	20 (8.5%)	23 (16.4%)	0.002
Immunomodulating drugs	68 (7.6%)	26 (5.0%)	26 (11.1%)	16 (11.4%)	0.002
Hydroxyurea	79 (8.8%)	40 (7.6%)	4 (1.7%)	35 (25.0%)	<0.01
Medication for PHT					
Diuretics	141 (15.7%)	62 (11.8%)	39 (16.7%)	40 (28.6%)	<0.01
Non-selective beta-blocker	310 (34.5%)	183 (34.9%)	99 (42.3%)	28 (20.0%)	<0.01
Lactulose	44 (4.9%)	14 (2.7%)	19 (8.1%)	11 (7.9%)	<0.01
TIPS	63 (7.0%)	8 (1.5%)	14 (6.0%)	41 (29.3%)	<0.01

BCS, Budd-Chiari syndrome; NCPVT, non-cirrhotic non-tumoral portal vein thrombosis; PHT, portal hypertension; PSVD, portal sinusoidal vascular disease; TIPS, transjugular intrahepatic portosystemic shunt. Quantitative variables expressed as mean ± SD; qualitative variables expressed as "n" and relative frequencies (percentage). The Kruskal-Wallis H test and Chi-square test used. Level of significance p <0.05.
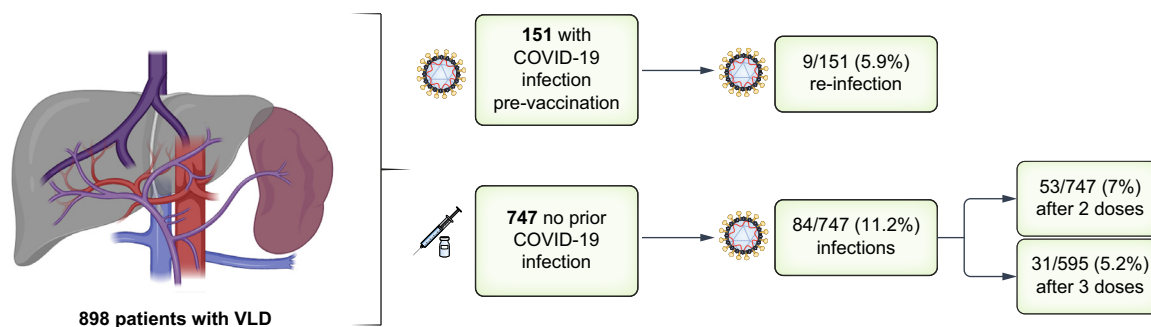
Fig. 1. COVID-19 infection in the total cohort. Created in BioRender. Hernandez-gea, V. (2024) BioRender.com/ o45q212.

We compared the prevalence of infection in our study with that of the general population. Our findings indicate that the prevalence of infection in both the Spanish and French cohorts (the two largest cohorts in our study), was significantly lower compared to their respective contemporary general populations. Specifically, the Spanish cohort (434 patients) and the French cohort (307 individuals) were compared with contemporary data available on the official websites of the Spanish government (ine.es) and the French government (santepubliquefrance.fr). In the Spanish cohort, the prevalence of infection was 8.4%, compared to 36% in the contemporary Spanish general population. In the French cohort, the prevalence was 6.2%, compared to 20% in the contemporary French general population.

We also reviewed the prevalence of infection from January 1, 2022, onwards, as most cases in both countries were likely secondary to the newly emergent Omicron variant. The incidence of infection in our Spanish cohort was 4.3%, compared to 7.3% in the general population. In the French cohort, the incidence was 1.3%, compared to 8.2% in the general population. Notably, these values decreased when comparing data from January 1, 2022, onwards, as most cases in both countries were likely secondary to the Omicron variant.

Mortality

A total of eight deaths were reported within the study period, among them two were attributed to a COVID-19 infection, while six were due to other causes in uninfected patients. The two deaths related to COVID-19 infection occurred within the group of 747 patients without a prior COVID-19 infection, resulting from primary infection events, which occurred in 84 individuals (11.2%). Consequently, the observed mortality rate in primary infected patients was 2.3%.

Both deaths occurred in fully vaccinated patients and occurred 29 and 31 weeks after the second dose, respectively. The first patient was an 85-year-old individual with NCPVT and refractory ascites and was admitted to the hospital with COVID-19 infection. The second patient was a 61-year-old patient with NCPVT and medullar aplasia, that required intensive care unit admission and died due to respiratory insufficiency.

Of the six remaining deaths unrelated to a COVID-19 infection that were reported, one was due to liver failure in a 90-year-old patient with PSVD who developed a progressive worsening of hepatic function 6 weeks after the first dose of vaccine. Five patients died due to non-liver-related causes,

three of them due to decompensation of a heart condition, and two due to a severe infection (pneumonia in a patient with an advanced oncologic disease and sepsis of unknown origin in a patient with medullar aplasia).

Liver decompensation

Twenty-one patients (2.3%) (11 with NCPVT, 5 with PSVD and 5 with BCS) developed hepatic decompensation after vaccination. Of these cases, 61.9% (13/21) had pre-existing decompensated liver disease before vaccination. Twelve of these events occurred within the first week after vaccination, and nine events during the follow-up period, with a mean of 23.2 ± 9.2 weeks (range 13 to 42 weeks) from vaccination.

Within the first week after vaccination, 12 decompensations were reported: two portal hypertensive bleedings (both in patients who had received previous non-selective β-blocker therapy), four episodes of ascites (3 worsening of ascites and 1 new-onset of ascites), and six hepatic encephalopathy events. Two of these events were associated with re-thrombosis. Patient characteristics and type of decompensation are detailed in Table 2.

Among the nine events reported during follow-up, all of them occurred in patients with pre-existing decompensated VLD. These events included one episode of hepatic encephalopathy, two new onsets of ascites, three worsening of ascites and three episodes of portal hypertensive bleeding, none were related to a concurrent thrombotic event.

Thrombotic event

The total thrombotic events reported in our cohort during the study period were 31/898 (3.5%), with 27/31 (87.1%) occurring in the splanchnic territory and 4/31 (12.3%) in the systemic territory. Mean time after vaccination was 11.2 ± 10.7 weeks (range 2-39 weeks). Of the total cohort of 898, 13 (1.4%) patients experienced a thrombotic event within 30 days after vaccination, comprising nine cases of splanchnic re-thrombosis, two cases of *de novo* thrombosis, and two cases of deep vein thrombosis. Among these patients, four cases were reported within the first 2 weeks: two cases of splanchnic re-thrombosis, one of *de novo* thrombosis, and one of deep vein thrombosis.

Among the non-anticoagulated patients, only 8 out of 339 (2.4%) developed a thrombotic event, while 23 out of 559 (4.1%) of those experiencing thrombosis were under chronic

Table 2. Decompensation event within the first week after vaccination.

Patient	Type of VLD	Type of decompensation	Previously decompensated	Previous decompensation	Splanchnic thrombosis related event	Required hospital admission
1	NCPVT	Worsening of ascites	Decompensated	Ascites, hepatic encephalopathy	No	No
2	NCPVT	Portal hypertensive bleeding	Compensated	None	No	Yes
3	NCPVT	Hepatic encephalopathy	Decompensated	Ascites	No	No
4	NCPVT	Portal hypertensive bleeding	Compensated	None	Re-thrombosis 4 weeks after decompensation	Yes
5	NCPVT	Worsening of ascites	Decompensated	Ascites	No	No
6	NCPVT	Worsening of ascites	Compensated	None	No	No
7	NCPVT	Hepatic encephalopathy	Compensated	None	No	Yes
8	NCPVT	Hepatic encephalopathy	Compensated	None	No	Yes
9	BCS	New onset ascites	Compensated	None	Re-thrombosis 4 weeks after decompensation	Yes
10	PSVD	Hepatic encephalopathy	Decompensated	Hepatic encephalopathy	No	No
11	PSVD	Hepatic encephalopathy	Decompensated	Hepatic encephalopathy	No	No
12	PSVD	Hepatic encephalopathy	Compensated	None	No	Yes

BCS, Budd-Chiari syndrome; NCPVT, non-cirrhotic non-tumoral portal vein thrombosis; PSVD, portal sinusoidal vascular disease; VLD, vascular liver disease.

anticoagulation. Among the anticoagulated patients, 7 (21.9%) had a decompensated liver disease at the time of enrolment.

No vaccine-induced thrombocytopenia (VITT) cases were reported in our cohort.

Out of the 31 patients diagnosed with thrombosis, 17 (54.8%) were identified through radiological findings during their routine clinic follow-up, whereas symptoms prompted diagnosis in the remaining 14 patients. Eleven patients required hospital admission, one of them complicated with portal hypertensive bleeding and one developed ascites. None of the admitted patients had mesenteric ischemia and no deaths were reported.

The splanchnic venous system was the most common location for thrombosis, occurring in 27 (87%) patients (re-thrombosis in 23 cases and *de novo* in 4 cases). Four patients (14.3%) had underlying hematological disorder and most of the events occurred in patients under anticoagulation, namely 4 (100%) of the *de novo* cases and 19 (82%) of the re-thrombosis cases. Data on the main VLD and thrombotic events are detailed in Table S6 and Fig. 2.

SARS-COV-2 vaccination immunogenicity

We evaluated immune responses to vaccination in a subgroup of 36 patients all vaccinated with the Moderna® (m-RNA-1273) vaccine: 11 patients with PSVD, 9 with BCS and 16 with NCPVT (Table 3). The serological and cellular response to SARS-CoV-2 spike antigen were assessed before and after one, two and three vaccine doses. Seroconversion was observed in 97% of patients following a single vaccine dose, reaching 100% after two doses and remained consistent after the third dose across all three VLD subgroups (Fig. 3A). There were incremental increases in anti-RBD titers following each vaccine dose in all patients across all three subgroups reaching the upper limit of detection post-V3 (Fig. 3A and Table S7).

IFNy T-cell responses to full SARS-CoV-2 spike protein were measured using an IFNy ELISpot assay. Before vaccination, low IFNy T-cell responses were observed in unexposed
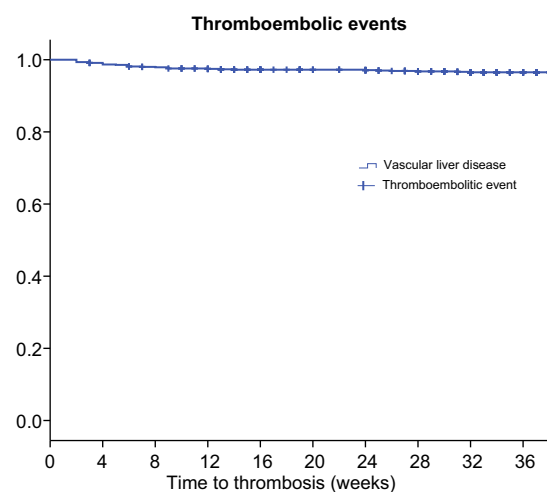

Fig. 2. Thromboembolic events after vaccination and during the follow-up period. Kaplan-Meier method. VLD, vascular liver disease.

Table 3. General characteristics before vaccination of the total cohort (n=36) and between vascular liver disease of the subgroup of patients with serological analyses.

Baseline characteristics	Total, n = 36	NCPVT, n = 16	PSVD, n = 11	BCS, n = 9
Sex (male)	21 (58.3%)	8 (50%)	3 827.3%)	4 (44.4%)
Decompensated liver disease	18 (50%)	6 (37.5%)	7 (63.6%)	5 (55.6%)
Previous decompensations				
Ascites	7 (19.4%)	1 (6.3%)	2 (18.2%)	4 (44.4%)
Portal hypertensive bleeding	11 (30.6%)	5 (31.3%)	5 (45.5%)	1 (11.1%)
Hepatic encephalopathy	2 (5.6%)	0	1 (9.1%)	1 (11.1%)
Associated comorbidities				
Autoimmune diseases	2 (5.6%)	0	1 (9.15)	1 (11.1%)
Hematological disorders	11 (30.6%)	4 (25%)	3 (37.3%)	4 (44.4%)
Cardiovascular diseases	10 (27.8%)	5 (31.3%)	2 (18.25)	3 (33.3%)
Chronic medication				
Anticoagulation	20 (55.6%)	9 (56.3%)	3 (27.35)	8 (88.9%)
Diuretics	3 (8.3%)	0	1 (9.1%)	2 (22.2%)
Non-selective beta-blocker	13 (36.15)	5 (31.3%)	5 (45.5%)	3 (33.3%)

Qualitative variables expressed as "n" and relative frequencies (percentage).
BCS, Budd-Chiari syndrome; NCPVT, non-cirrhotic non-tumoral portal vein thrombosis; PSVD, portal sinusoidal vascular disease.
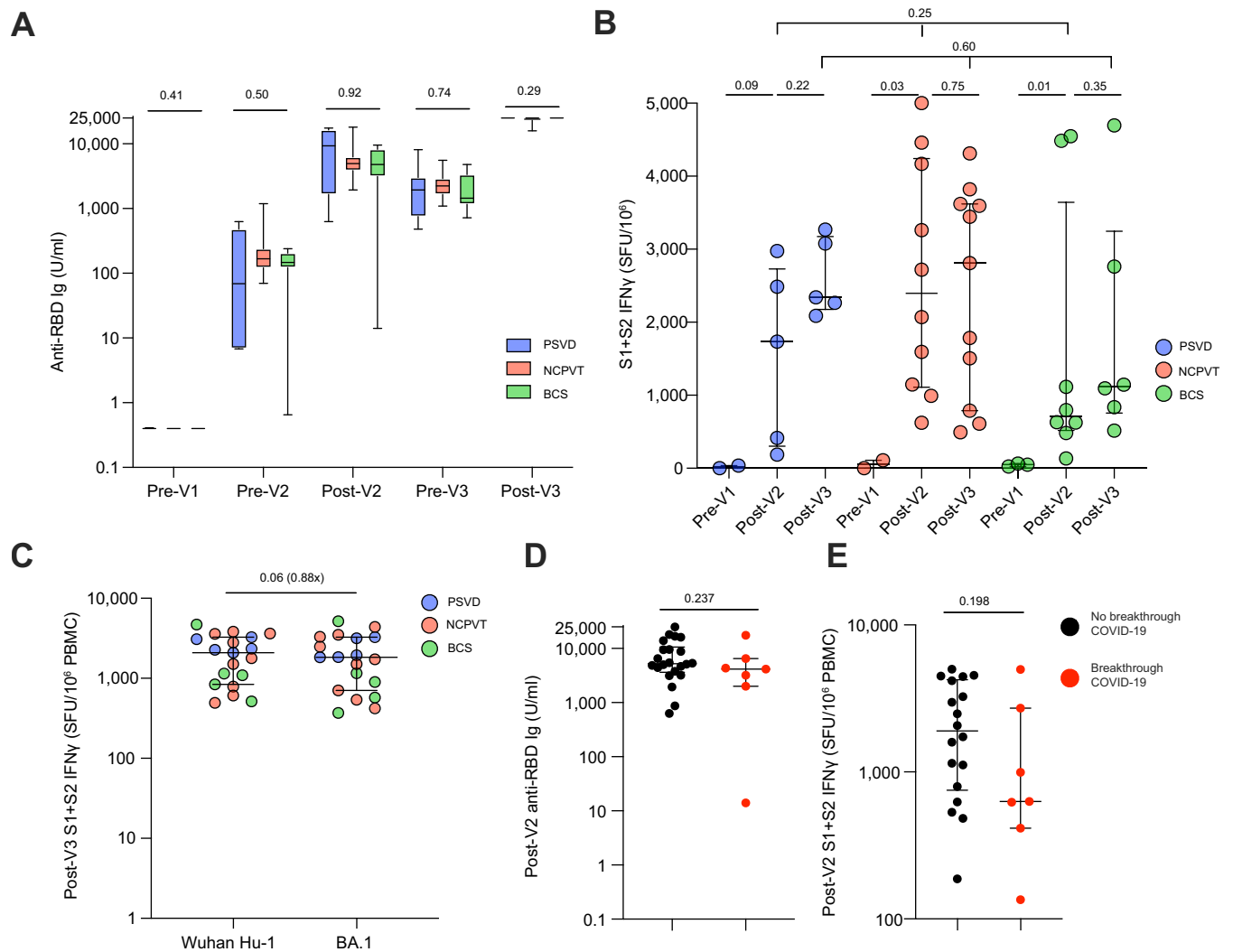
Fig. 3. Serological and cellular responses to mRNA-1273 in SARS-COV-2 infection naïve patients with VLD. (A) Antibody response to SARS-COV-2 spike protein RBD assessed before first dose (Pre-V1), before second dose (Pre-V2), 28-days following second dose (Post-V2), before third dose (Pre-V3) and 28-days following third dose (Post-V3) (n = 30). (B) IFNy T cell responses to overlapping peptide pools covering Wuhan Hu-1 SARS-CoV-2 spike (S1+S2) (n = 23) and (C) IFNy T cell responses to overlapping peptide pools covering Omicron BA.1 at the post-V3 timepoint (n = 19). (D, E) the magnitude of anti-RBD Ig (D) and IFNy T cell responses to Wuhan Hu-1 SARS-COV-2 spike (E) at the post-v2 timepoint in individuals that did or did not report breakthrough COVID-19 infection after two doses of COVID-19 vaccine. Median and IQR shown. (A) Bars and lines represent min, max, IQR and median. Mann-Whitney *U*, Wilcoxon matched-pairs signed rank test or Kruskal-Wallis test were used. BCS, Budd-Chiari syndrome; NCPVT, non-cirrhotic non-tumoral portal vein thrombosis; PSVD, portal sinusoidal vascular disease; RBD, receptor binding domain; VLD, vascular liver disease.

patients with VLD, similar to healthy individuals.[8] After two mRNA-1273 vaccine doses, responses significantly increased in all subgroups (Fig. 3B). T-cell responses persisted after a third dose, without significant additional increases (Fig. 3B). Comparing two and three vaccine doses to prior studies,[9,10] VLD subgroups had similar responses to healthy controls. Cross-reactivity of vaccine-induced responses was explored using Omicron (BA.1) spike peptides, showing modest reduction vs. Wuhan Hu-1 spike, mainly maintained in all VLD subgroups (Fig. 3C).

Out of 36 patients, 8 (22%) had breakthrough COVID-19 (3 NCPVT, 2 PSVD, 2 BCS), with mild symptoms and no hospitalization. Breakthrough cases occurred after two or a third vaccine dose. Immune responses in breakthrough cases showed minor declines in post-V2 antibody titers and IFNγ responses, but these changes were not significant (Fig. 3D,E). Notably, all breakthrough patients maintained detectable antibody and T-cell responses, likely contributing to their mild disease course and lack of need for hospitalization.

Discussion

The SARS-CoV-2 pandemic had a great impact on society, with the development of vaccines being one of the most crucial measures, manufactured in record time and with early implementation in society at the end of 2020. While their efficacy against infection has been well-established, two concerns relevant for patients with VLD have been raised, 1) the potential for incomplete protective responses through immunization in patients with altered liver function and 2) increased risk of thrombotic events in unusual sites (including the splanchnic territory) and development of VITT.

VLDs are frequently associated with diseases altering the immune system and with an increased risk of developing thrombosis in the splanchnic territory. However, data on the level of protection after vaccination, severity of post-vaccination infection and risk of thromboembolic events after vaccination are unknown in these patients.

The only available study evaluating, in a multicentric fashion, the impact of COVID-19 infection in patients with VLD was performed before the availability of vaccines. The prevalence of COVID-19 primoinfection in this non-vaccinated VLD cohort was higher than in our study[4] (14% vs. 11.1%), despite similar baseline characteristics (Table S8), as was the need for hospitalization due to infection (14% vs. 7.1%) and the severity of infection (ICU admission cases of 3.8% vs. 3%) and mortality (4% vs. 2%).

When comparing the prevalence of infection in our study with the general population, the prevalence of infection was significantly lower in patients with VLD.

Vaccination was very well tolerated, with mild and transient local and systemic side effects. Despite the absence of severe adverse events reported during follow-up, this alone does not definitively establish efficacy and safety. However, these findings suggest a favorable safety profile for vaccination in patients with VLD, underscoring the need for comprehensive studies to fully assess these aspects.

Regarding thrombosis, in the whole cohort, 31/898 (3.5%) patients experienced thrombosis after vaccination. Previous studies focusing on thrombosis at atypical sites, particularly VITT, have reported a time frame ranging from 14 to 34 days from vaccination to the onset of thrombosis.[5,6] Nine re-thrombosis events were reported in the first 30 days after vaccination (4 [0.6%] events within the first 2 weeks). We only reported 4/898 cases in the first 2 weeks, although this represents a low frequency of events, the role of vaccination as a potential prothrombotic factor in these patients cannot be ruled out.

Given the distinct risk of thrombosis between VLD, we interpreted the events separately.

In the NCPVT cohort, 21/524 patients experienced thrombosis, most of the events were re-thrombosis (18/21) and occurred at a mean time of 11 weeks after vaccination. Re-thrombosis in our not anticoagulated cohort was 3/524 (0.6%), a lower incidence compared to the 2.6% rate of re-thrombosis described in the literature in patients with NCPVT not receiving anticoagulation.[11]

In the PSVD group, 6/234 patients had a thrombosis, with a prevalence of 2.6%, all of them occurring in the splanchnic territory (3 re-thrombosis, 3 de novo thrombosis). Only one non-symptomatic de novo thrombosis arose within 15 days after vaccination, while the remaining five cases were reported during follow-up, three of them being non-symptomatic findings. Previous studies on the natural history of PSVD[12] have described an approximately 9% annual risk of splanchnic thrombosis. The most recent study on the natural history of PSVD[13] describes a 5.7% cumulative incidence of thrombosis in patients without a previous history of thrombosis.

In the BCS cohort, 4/104 (2.9%) thrombotic events were reported, three of them occurred in the splanchnic territory and two of them were re-thromboses in patients who had a transjugular intrahepatic portosystemic shunt (TIPS), both with a diagnosis of polycythemia vera as a pro-thrombotic disorder. While the precise expected rate of re-thrombosis in patients with BCS remains uncertain, much of the available data originates from long-term observational studies in patients with TIPS, which suggest that up to 40% of patients with BCS may experience TIPS dysfunction attributable to thrombosis during extended periods.[14] However, specific data concerning the exact rate at 1 year is unavailable. Preliminary data from the ongoing VALDIG study, including 139 patients with BCS so far and 69 with TIPS, reported an annual rate of TIPS thrombosis of 10%.[15] The lower thrombosis rate in our cohort suggests that the association with vaccination may not be direct but rather could be attributed to the natural progression of the disease. While we cannot definitively establish a direct link between vaccination and thrombotic events, the contribution of vaccination as a cofactor in fostering thrombotic events in VLD remains to be elucidated.

Liver related decompensation was reported in only 2.3% of our cohort.

Within the NCPVT group, 11 out of 524 (2%) individuals experienced a decompensation event, with over 60% having a history of prior decompensated liver disease. One of these events was linked to a re-thrombotic incident leading to ascites.

In patients with NCPVT, the annual rate of decompensation is also unknown and available information belongs to the most common decompensation in this population: variceal bleeding. The rate of variceal bleeding was 9% at 1-year follow-up in the study by Noronha et al.[16] compared to 2/524 (0.4%) bleeding events in our cohort.

In the PSVD cohort, only a few cases 5/234 (2.1%) of decompensation were reported, four of them had a decompensated liver disease before vaccination. Three patients developed a decompensation during the first week after vaccination and two patients developed decompensation during follow-up; all decompensation events were mild without need for hospitalization. This prevalence of decompensation is lower than the one described in the most recent study on the natural history of PSVD, with an incidence of first decompensation of around 13% at 1 year or further decompensation of around 20%.[13]

In the BCS cohort, 3.5% (5/140) patients developed decompensation. One case of new onset of ascites, later diagnosed as TIPS thrombosis, occurred 4 weeks post-vaccination. The rest of the cases emerged during follow-up, over 3 months after vaccination. As no comparable data are available in the literature, we provide context by analyzing preliminary data from the ongoing VALDIG long-term follow-up of patients with BCS,[15] in which 2.9% of patients had portal hypertensive bleeding and 15% worsening of ascites at 1-year follow-up. In the present study, 1/140 (0.7%) experienced gastrointestinal bleeding and 3/140 (2.1%) experienced worsening of ascites. This low risk of decompensation following immunization reinforces the safety of vaccination in patients with VLD.

We also evaluated the immune response in a subgroup of patients with VLD representative of the whole sample. Our analysis indicates that the subgroup of individuals analyzed display a robust immune response to SARS-CoV-2 vaccination, both humoral and cellular, which remains consistent and reinforced with subsequent doses. Furthermore, the clinical data available in the whole cohort, characterized by a limited infection rate and very few cases of severe disease, further strengthen the notion of a preserved immune response to SARS-CoV-2 vaccination among individuals with VLD. This immune response after vaccination was characterized by a preserved humoral and cellular immune response. Seroconversion and cellular response rates were comparable to those observed in the general population, and this response, particularly the humoral response, notably improved with successive vaccination doses. We acknowledge that the small sample size may have limited the generalizability of our findings, but the results reinforce the clinical observations seen in the entire cohort.

The main strength of our study is the inclusion of a large cohort of patients with VLD. This study stands out as the first to assess the tolerance and impact of COVID-19 vaccines specifically in this patient population. Additionally, the serological analysis, although performed on a subgroup of patients, provides valuable information that complements the clinical outcome data observed in the larger cohort, further supporting the conclusions of the study.

We acknowledge several limitations of the study such us its descriptive nature and the lack of a control group which could have provided a basis for comparison and helped assess the specific effects of vaccination in patients with VLD.

In conclusion, our study represents a large European cohort of patients with rare hepatic vascular diseases. Our results indicate that vaccination against COVID-19 infection is well tolerated with mild local and systemic reactogenicity. Furthermore, our study demonstrates that patients with VLD exhibit an adequate immune response to COVID-19 vaccines, which offers effective protection against severe COVID-19 infection.

Regarding concerns related to thromboembolic events, our study found a low prevalence, and was unable to establish a direct relationship with vaccination. Most cases of thrombosis occurred as re-thrombosis events in patients with NCPVT and, to a lesser extent, in patients with PSVD. It cannot be ruled out that these findings are part of the natural progression of the disease, potentially influenced by vaccination. Importantly, no cases of VITT were reported in our study.

Overall, our study contributes to the understanding of COVID-19 vaccine effects in patients with VLD, highlighting their safety in providing protection against severe COVID-19 infection.

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Abbreviations

BCS, Budd-Chiari syndrome; NCPVT, non-cirrhotic–non-malignant-splanchnic vein thrombosis; PSVD, portosinusoidal vascular disorder; TIPS, transjugular intrahepatic portosystemic shunt; VITT, vaccine-induced thrombocytopenia; VLD, vascular liver disease.

Conflict of interest

Authors' contributions

Data availability statement

Acknowledgement

Supplementary data

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