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Clinical science

Vascular liver disorders in patients with antiphospholipid syndrome: a national retrospective multicentre study

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Abstract

Objective: Antiphospholipid syndrome (APS) is an acquired autoimmune prothrombotic condition. Vascular liver disorders (VLD), such as portal vein thrombosis (PVT), Budd–Chiari syndrome (BCS) and porto-sinusoidal vascular disorder (PSVD), are rare and related to an underlying hypercoagulable state in most cases. We aimed to describe the clinical and immunological features of APS patients with VLD.

Methods: The study is a national, multicentre, retrospective study of APS patients followed in four French tertiary university centres, including three national referral centres for rare autoimmune diseases. Clinical, serological and liver characteristics at diagnosis of APS patients with VLD were collected. New thrombotic events and major bleeding during follow-up were analysed.

Results: Forty-one VLD were reported in 34 APS patients (59% women; mean age 35+/−15 years; 65% of primary APS) including PVT ($n=26/41$, 63%), BCS ($n=12/41$, 29%) and PSVD ($n=3/41$, 7%). VLD was the first thrombotic event in 79% ($n=27/34$) of patients. Fifteen patients ($n=15/34$, 44%) had portal hypertension, including 10 ($n=10/34$, 29%) with esophageal varices at the time of VLD diagnosis. All patients were treated with oral anticoagulants including VKA in all but one case. Over a median of 9.5 (5; 14) years of follow-up, 62% ($n=21/34$) of patients displayed a new thrombotic event and 26% ($n=9/34$) suffered major bleeding.

Conclusion: Although rare, VLD may be the presenting manifestation of APS. APS patients with VLD are at high risk of both recurrent thrombotic events and major bleeding.

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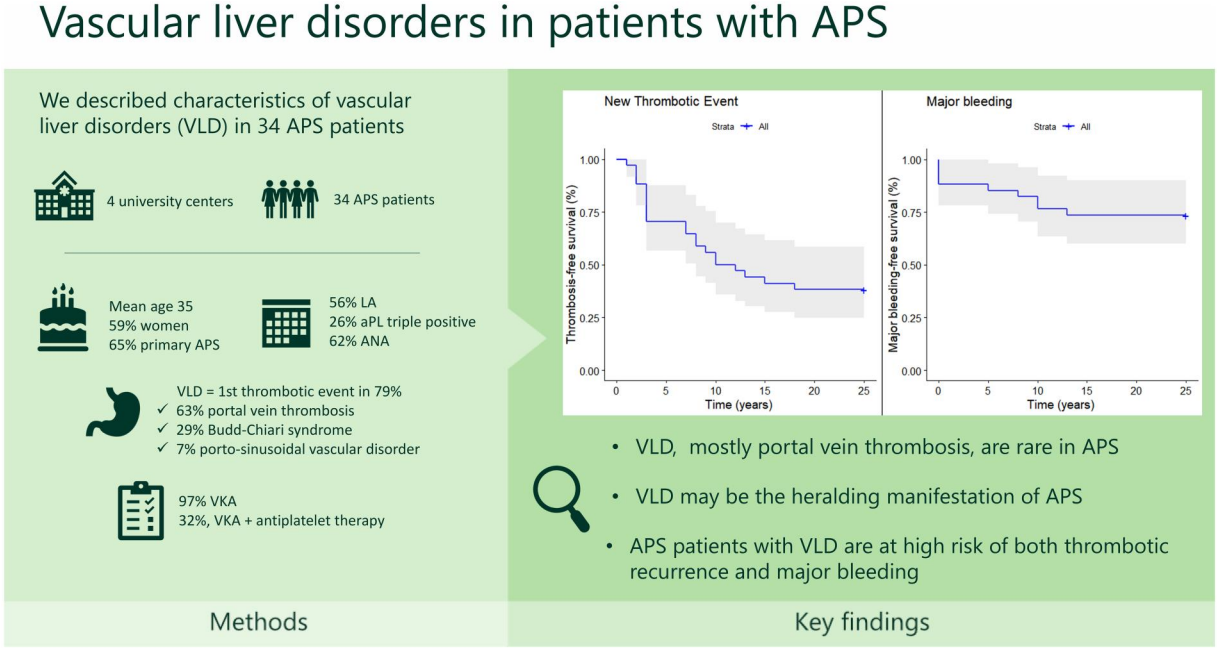
Graphical abstract



Keywords: antiphospholipid syndrome, portal vein thrombosis, Budd–Chiari syndrome, porto-sinusoidal vascular disorder, thrombotic recurrence, major bleeding, outcome

Rheumatology key messages

- Vascular liver disorders (VLD), mostly portal vein thrombosis, are rare in antiphospholipid syndrome (APS).
- VLD may be the heralding manifestation of APS.
- The risk of both thrombotic recurrence and major bleeding in APS patients with VLD is high.

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by venous, arterial or microvascular thromboses and/or pregnancy morbidity in patients with persistent antiphospholipid autoantibodies (aPL); namely, lupus anticoagulant (LA) and/or IgG or IgM anticardiolipin (aCL) and/or IgG and/or IgM anti-β2glycoprotein-1 (aβ2GPI) [1–4].

Vascular liver disorders (VLD) such as portal vein thrombosis (PVT), Budd–Chiari syndrome (BCS) and porto-sinusoidal vascular disorder (PSVD) are rare disorders characterized by the obstruction of blood vessels in and near the liver. Underlying thrombophilia, such as myeloproliferative neoplasia, can be found in around 50% of patients with non-cirrhotic VLD [5, 6]. Although VLD might be the initial presentation of APS [7–11], hepatic manifestations including BCS and small hepatic vein thrombosis were reported in <1% of APS patients in a large European cohort involving 1000 patients (the EuroPhospholipid cohort) [12]. No study has directly addressed the question of specific APS features in VLD. The objective of this study was to describe the clinical and immunological manifestations and outcomes of APS patients with VLD.

Methods

Patients

The study is a national, multicentre, retrospective study involving APS patients followed at four French tertiary university centres with large active APS files. Three national referral centres for lupus and APS (Centre National de Reference des Maladies Auto-Immunes Systemiques) and one national referral centre for vascular liver disorders (Centre National de Reference des Maladies Vasculaires du Foie) took part in the study. All APS patients with VLD were included. Demographic data, medical history, underlying autoimmune disease, clinical events at disease onset and during follow-up (including death), laboratory features at diagnosis and treatment data were retrieved from medical records. APS diagnosis

was based on a history of venous and/or arterial thromboses or recurrent miscarriages in the presence of aPL antibodies in accordance with 2006 APS published criteria [13]. Plasma LA was detected by coagulation assays on two or more occasions at least 12 weeks apart, according to the guidelines of the International Society on Thrombosis and Haemostasis [14]. The presence of aCL antibody of IgG and/or IgM isotype was measured in serum by a standardized ELISA. Results were considered positive if medium to high titre (that is, >40 GPL or MPL, or >99th percentile) was present on two or more occasions, at least 12 weeks apart. The presence of anti b2GPI of IgG and/or IgM isotype was measured in serum by a standardized ELISA. Results were considered positive if medium-to-high titre (in titre >99th percentile) were present on two or more occasions, at least 12 weeks apart. All these tests were performed in referral laboratories. Patients were considered to have catastrophic APS if they presented with acute multiple organ involvement, as previously defined [15]. Underlying autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), dermatomyositis, Sjögren's syndrome and systemic vasculitis were considered when the patient met the relevant classification criteria sets. Primary APS was defined in patients who did not fulfil criteria for any of the other conditions. Major bleeding in APS patients with VLD was defined as (i) fatal bleeding; and/or (ii) bleeding in a critical area or organ; and/or (3) bleeding causing a fall in haemoglobin level of 2 g/dl or more or leading to transfusion of whole blood or red cells.

Vascular liver disorders

Vascular liver disorders (VLD) included portal vein thrombosis, hepatic vein thrombosis – known as Budd–Chiari syndrome – and porto-sinusoidal vascular disorder. Portal vein thrombosis and Budd–Chiari syndrome were identified by vascular ultrasound and/or abdominal CT scan. Diagnosis of porto-sinusoidal vascular disorder was made in patients with signs of portal hypertension associated with suggestive liver lesions and the absence of cirrhosis at liver biopsy examination, according to VALDIG's criteria [6]. Liver characteristics at diagnosis of VLD, including abdominal pain, ascites, encephalopathy, splenomegaly, esophageal varices, liver blood tests and Model for End-Stage Liver Disease (MELD) score were collected.

Ethical statement

Our study is a retrospective human non-interventional study. According to the Public Health French Law (Méthodologie de Reference MR004 https://www.legifrance.gouv.fr/cnil/id/CNILTEXT000037202328? isSuggest=true), approval from institutional review board and written consent are not mandatory for human non-interventional studies. For ethical considerations, patients were, however, informed that data that were collected in medical records might be used for research study in accordance with the privacy rule. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Our study involves personal health data and has been authorized by the Commission nationale de l'informatique et des libertés (CNIL) (declaration number 2235448).

Statistical analysis

Data were expressed as median with quartiles (quartile 1; quartile 3) and/or mean with standard deviation (S.D.) and frequency (percentage) as appropriate. The Kaplan–Meier method was used to analyse the survival without new thrombotic event and the survival without major bleeding. The starting date for the survival analysis is the date of APS diagnosis, and the analysis is stopped after a new thrombotic event, major bleeding or loss to follow-up. Two-sided P values of <0.05 were considered to indicate statistical significance. Statistical analyses were performed with GraphPad Prism 10.2.3 software.

Results

General characteristics

Thirty-four APS patients with VLD were identified. Twenty patients ($n=20/34$, 59%) were women. The mean age at APS diagnosis was 35 ±15 [median (Q1; Q3): 35 (24.5; 42)] years. Of note, the 2023 ACR/EULAR APS classification criteria were satisfied in all but three cases with median clinical and laboratory scores per patient of 5 (5; 7.75) and 5 (4; 10), respectively (Supplementary Table S1, available at *Rheumatology* online) [1]. Most patients ($n=22/34$; 65%) had primary APS. LA, aCL and anti-B2GP1 were present in 19 ($n=19/34$, 56%), 25 ($n=25/34$, 71%) and 15 ($n=15/34$, 43%) patients, respectively. Nine patients ($n=9/34$, 26%) were aPL triple positive. Antinuclear antibodies were detected in 21 ($n=21/34$, 62%) patients (Table 1). Two patients had a JAK2V617F mutation with overt myeloproliferative disorder in one of them. Three patients had low impact inherited thrombophilia including partial protein C deficiency ($n=2$) and heterozygosity for factor V Leiden ($n=1$). One patient had a monoclonal gammopathy of undetermined significance and one had a history of Hodgkin lymphoma. One patient had a biopsy-proven cirrhosis.

Vascular liver disorders associated with APS

Forty-one VLD were reported in 34 APS patients including portal vein thrombosis ($n=26/41$, 63%), Budd–Chiari

Table 1. Characteristics of APS patients with VLD

	VLD $n=34$
Age, years	35 +/– 15
Female, %	20 (59)
Primary APS, *n* (%–)	22 (65)
Associated diseases, *n* (%)	
SLE	11 (32)
RA	0 0
Sjogren's syndrome	0 0
Systemic vasculitis	1 (3)
Dermatomyositis	0 0
aCL antibodies, *n* (%)	25 (71)
IgG and IgM	2 (6)
IgG alone	21 (62)
IgM alone	2 (6)
aβ2GPI, n (%)	15 (43)
IgG and IgM	0 0
IgG alone	11 (32)
IgM alone	4 (12)
LA, n (%)	19 (56)
Triple positive, *n* (%)	9 (26)
Antinuclear antibodies, *n* (%)	21 (62)

aβ2GPI: anti-β2glycoprotein-1; aCL: anticardiolipin; APS: antiphospholipid syndrome; LA: lupus anticoagulant; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; VLD: vascular liver disorders.

syndrome ($n = 12/41$, 29%) and porto-sinusoidal vascular disorder ($n = 3/41$, 7%). VLD was the first thrombotic event in 27 ($n = 27/34$, 79%) patients. In patients in whom VLD was the heralding manifestation of APS, APS diagnosis was made at VLD onset ($n = 18/27$, 67%) or a median of 6 years (3–7) afterwards, when a second thrombotic event occurred ($n = 9/27$, 33%).

At VLD diagnosis, abdominal pain, ascites and encephalopathy were reported in 18 ($n = 18/34$, 53%), 10 ($n = 10/34$, 29%) and 1 ($n = 1/34$, 3%) patients, respectively. Liver blood tests were abnormal in 18 ($n = 18/34$, 53%) with increased aminotransferase ($n = 18/18$) and/or alkaline phosphatase ($n = 6/18$) levels. Fifteen patients ($n = 15/34$, 44%) displayed portal hypertension including 10 ($n = 10/34$, 29%) with esophageal varices (details given Table 2). Liver biopsy was performed in five cases at VLD onset showing porto-sinusoidal vascular disorder ($n = 3$), liver fibrosis ($n = 1$) or hepatic congestion ($n = 1$).

APS manifestations at baseline in patients with VLD included thrombopenia <100G/l ($n = 13/34$, 38%), lower-limb deep-vein thrombosis ($n = 10/34$, 29%), pulmonary embolism ($n = 7/34$, 21%) and myocardial infarction ($n = 4/34$, 12%). VLD was the only thrombotic event in six patients ($n = 6/34$, 18%). Of note, VLD occurred in the setting of a CAPS in three cases ($n = 3/34$, 9%) (Table 3).

Treatment and follow-up

All APS patients with VLD have been treated by oral anticoagulants, including vitamin K antagonists (VKA) in all but one case ($n = 33/34$, 97%). Some patients ($n = 11/34$, 32%) also received antiplatelet therapy in addition to anticoagulants.

Over a median of 9.5 (5; 14) years of follow-up, 21 patients ($n = 21/34$, 62%) had a new thrombotic event while being under VKA in all but two ($n = 19/21$, 90%) cases. New thrombotic events included recurrent VLD ($n = 5/21$, 24%; PVT and BCS in two and three cases, respectively), lower-limb deep-vein thrombosis and/or pulmonary embolism ($n = 3/21$, 14%), stroke ($n = 4/21$, 19%), CAPS ($n = 3/21$, 14%) and myocardial infarction ($n = 3/21$, 14%) (Table 3). Although 90% of new thrombotic events occurred under VKA, the INR was in the optimal range in only 68% ($n = 13/19$) of patients. At 7 years, 57.3% (15 patients, 95% CI: 41.3–79.4) were free of recurrent thrombotic events (Fig. 1). We did not identify factors associated with a higher risk of new thrombotic event in APS patients with VLD (Table 4).

Major bleeding occurred in nine patients ($n = 9/34$, 26%) including gastrointestinal bleeding ($n = 5$), intramuscle bleeding ($n = 1$), retroperitoneal bleeding ($n = 1$), hemoptysis ($n = 1$) and metrorrhagia requiring blood transfusion ($n = 1$). At 8 years, 79.8% (19 patients, 95% CI: 66.2–96.1) were free of major bleeding (Fig. 1). Major bleeding tended to be associated with thrombopenia and esophageal varices (Table 5). Four patients died during follow-up.

Discussion

Antiphospholipid antibodies have been previously associated with the risk of BCS, non-cirrhotic PVT, nodular regenerative hyperplasia and even liver cirrhosis [16, 17]. In the EuroPhospholipid cohort of 1000 APS patients, VLD was reported in 0.7% of cases [12]. With only 34 APS patients with VLD identified in four tertiary university centres including three national referral centres for autoimmune diseases, our study confirms that VLD is rare in APS. On the other hand, VLD was the heralding manifestation of APS in almost 80% of cases. This finding supports the systematic screening of aPL in patients admitted for PVT, BCS or PSVD [8]. Compared with the 1000 patients enrolled in the EuroPhospholipid cohort [4, 12], APS patients with VLD were more likely to be male (Supplementary Table S2, available at *Rheumatology* online) and to experience both recurrent thrombotic events and major bleeding (Supplementary Table S3, available at *Rheumatology* online).

In our study, all patients had high levels and persistent antiphospholipid antibodies consistent with APS and all but three fulfilled the highly specific 2023 ACR/EULAR APS classification criteria [1, 13]. Additional thrombophilic risk factors (that is, JAK2V617F mutation, partial protein C deficiency, heterozygosity for factor V Leiden) were identified in almost 15% of APS patients with VLD. In APS, thrombotic events occur only occasionally suggesting that other factors ('second hits') trigger thrombosis. The presence of additional risk factors for thrombotic events might thus have increased the risk of VLD in patients with APS [18–20]. In APS, recurrent thrombotic events are efficiently prevented by long-term anticoagulation with VKA, aimed at an international normalized ratio (INR) between 2 and 3 [21, 22]. Despite oral anticoagulants, the frequency of thrombotic recurrence was extremely high (>60% over a median of 9.5 years of follow-up) in APS patients with VLD as compared with both APS patients without VLD and patients with non-cirrhotic portal vein thrombosis [4, 23, 24]. The fact that portal hypertension increases the risk of gastrointestinal bleeding may explain the rate of major bleeding, higher than usually reported in APS patients [4]. Because of the high risks of thrombotic events and severe bleeding, long-term anticoagulation is especially difficult to manage.

Our study has limitations. First, its retrospective design and sample size limit the statistical power and may impede the ability to generalize our findings. To our best knowledge, this is, however, the first and larger cohort study of APS patients that specifically focuses on VLD. Second, our restrictive inclusion criteria based on patients followed in national referral centres may confer a selection bias as suggested by the high frequency of CAPS in our cohort. However, APS patients with VLD displayed the general characteristics of APS patients such as a young age, a female predominance and a high frequency of SLE. Third, underlying myeloproliferative neoplasms are frequent in patients with VLD but no next-generation sequencing for detection of mutations involved in myeloid disorders was performed. Fourth, we did not record long-term liver outcomes such as thrombus recanalisation, cirrhosis or liver failure.

Our study has also some strengths. Data were extracted from electronic medical records using a standardized data collection form with detailed medical history. Follow-up was protracted. In this context, the high rate of both thrombotic recurrences and severe bleeding is clearly of clinical relevance.

In conclusion, VLD may occur in the setting of APS. APS patients with VLD have a high risk of both thrombotic recurrence and major bleeding. Specific trials are required to define optimal treatment in APS patients with VLD.

Table 2. Liver characteristics at diagnosis of VLD in APS patients

Age	Sex	VLD	Abdominal pain	Ascites	Encephalopathy	Splenomegaly	Esophageal varices	Bilirubin	ALAT	ASAT	Albumin	Platelet count	INR	Creatinine	MELD score
28	F	BCS	0	0	0	na	na	na	81	36	23	na	na	na	na
31	F	PVT	1	1	0	0	0	6	28	31	31	214	1.1	61	8
28	F	PVT	0	1	0	1	1	15	42	39	30	243	1.3	84	9
59	F	PVT	1	1	0	na	0	18	27	22	na	174	na	na	na
32	F	PVT	0	0	0	1	1	12	31	41	43	93	na	60	na
32	M	PVT	0	0	0	0	0	16	112	52	45	186	1.2	93	9
62	F	PSVD/PVT	1	0	0	1	1	na	na	na	na	69	2.1	194	na
27	M	PVT	1	1	0	1	0	5	10	24	28	63	na	HD	na
58	F	PVT	1	1	0	1	0	na	na	na	28	160	3.7	29	na
23	F	PVT	0	0	0	1	1	5	55	35	35	60	2.3	110	18
38	F	PVT	0	1	0	1	1	8	22	24	40	40	1.8	94	14
30	M	BCS	1	1	0	1	1	95	50	60	33	80	1.8	77	19
27	M	PVT	0	0	0	0	0	na	na	na	na	na	1.1	79	na
21	F	BCS	0	0	0	0	0	3	29	40	38	144	2.9	94	19
16	F	BCS	1	0	0	0	0	15	20	25	35	100	2.6	59	17
13	M	BCS	1	0	0	0	0	11	82	43	na	193	5.3	56	25
18	F	BCS	0	0	1	0	0	na	40	25	na	74	2.7	60	na
22	M	BCS	1	1	0	0	1	42	34	30	45	60	1.8	65	16
45	M	BCS	1	1	0	0	0	na	27	38	na	190	2.5	72	NA
25	M	BCS	1	0	0	1	na	3	20	43	na	170	1.5	52	11
58	F	PVT	0	0	0	0	0	18	15	44	37	28	2.5	94	17
26	F	PSVD/PVT	0	0	0	1	1	5	37	42	43	172	1.2	45	8
60	F	PVT	0	0	0	0	1	31	na	na	21	41	2.3	151	24
24	F	BCS	1	1	0	1	0	5	37	34	na	134	na	na	na
28	F	PVT	1	0	0	0	0	14	na	na	40	80	2.4	83	16
42	M	PVT	0	0	0	1	0	na	na	na	35	110	2.5	na	na
18	F	PVT	na	na	na	na	0	na	na	na	na	150	na	na	na
35	F	PVT	1	0	0	0	0	na	na	na	na	324	2.1	52	na
48	M	PVT	1	0	0	0	0	na	200	84	47	173	1.2	80	na
17	M	BCS	1	0	0	na	0	5	38	26	na	150	2.7	54	18
56	M	PVT	0	0	0	0	0	6	23	25	39	188	2.3	80	16
42	M	BCS	1	0	0	na	0	na	na	na	na	160	na	na	na
49	M	PVT	1	0	0	1	1	24	74	72	47	200	na	77	na
39	F	PSVD	0	0	0	1	0	4	36	23	43	10	2.0	65	14

ALAT: alanine aminotransferase; ASAT: aspartate aminotransferase; BCS: Budd–Chiari syndrome; F: female; HD: hemodialysis; M: male; MELD: model for end-stage liver disease; na: not available; PSVD: porto-sinusoidal vascular disorder; PVT: portal vein thrombosis; VLD: vascular liver disorders.
Serum total bilirubin, $N < 17$ μmol/L; ALAT, $N < 34$ U/L; ASAT, $N < 31$ U/L; serum albumin, g/L; platelet count, G/L; creatinine, μmol/L.

Table 3. Main APS clinical manifestations at baseline and during follow-up.

	At baseline[a] $n = 34$	During follow-up[b] $n = 34$
Deep vein thrombosis	10 (29)	4 (12)
Stroke	1 (3)	4 (12)
Pulmonary embolism	7 (21)	3 (9)
Myocardial infarction	4 (12)	3 (9)
Renal manifestations	0 0	2 (6)
Splenic infarction	2 (6)	2 (6)
Addison's syndrome	0 0	1 (3)
Cutaneous necrosis	1 (3)	—
Pre-eclampsia/eclampsia	0 0	2 (13)
Early pregnancy loss	0 0	2 (13)
Late pregnancy loss	1 (7)	1 (7)
Live birth with prematurity	0 0	2 (13)
Live birth with IGR	0 0	1 (7)
Thrombocytopenia	13 (38)	—
CAPS	3 (9)	3 (9)
Major bleeding	—	9 (26)
Death	0 0	4 (12)

CAPS, catastrophic antiphospholipid syndrome; IGR, intrauterine growth restriction; VLD, vascular liver disorders.
Obstetric manifestations are related to number of childbearing-age women.
Thrombocytopenia defined by a platelet count <100 G/L.
[a] Cumulative clinical manifestations at baseline.
[b] Over a median of 9.5 (5; 14) years of follow-up.

Table 4. Factors associated with recurrent thrombosis in APS patients with VLD

	New TE N = 21	No new TE N = 13	*P*
Age, years mean +/– SD	34 +/– 16	36 +/– 13	0.61
Female, *n* (%)	15 (71)	7 (54)	0.46
Primary APS, *n* (%)	16 (76)	6 (46)	0.14
SLE, *n* (%)	5 (24)	6 (46)	0.26
aCL antibodies, *n* (%)	16 (76)	9 (69)	0.70
aβ2GPI antibodies, *n* (%)	10 (48)	5 (38.5)	0.73
LA, *n* (%)	14 (67)	5 (38.5)	0.16
Triple aPL positive, *n* (%)	7 (33)	2 (15)	0.43
Antinuclear antibodies, *n* (%)	13 (62)	8 (61.5)	0.99
Additional thrombophilia, *n* (%)	5 (24)	0 0	0.13
JAK2V617F mutation	2 (9.5)	0 0	0.51
Partial protein C deficiency	2 (9.5)	0 0	0.51
Heterozygosity for factor V Leiden	1 (4.8)	0 0	0.99
VKA alone, *n* (%)	11 (52)	10 (77)	0.28
VKA and antiplatelet therapy, *n* (%)	8 (38)	2 (15)	0.25
Length of follow-up, years	12 (9–19)	4 (1–8)	<0.05
Death, *n* (%)	2 (9.5)	2 (15.4)	0.63

aβ2GPI: anti-β2glycoprotein-1; aCL: anticardiolipin; aPL: antiphospholipid; APS: antiphospholipid syndrome; LA: lupus anticoagulant; SLE: systemic lupus eruthematosus;TE: thrombotic event; VKA: vitamin K antagonists.

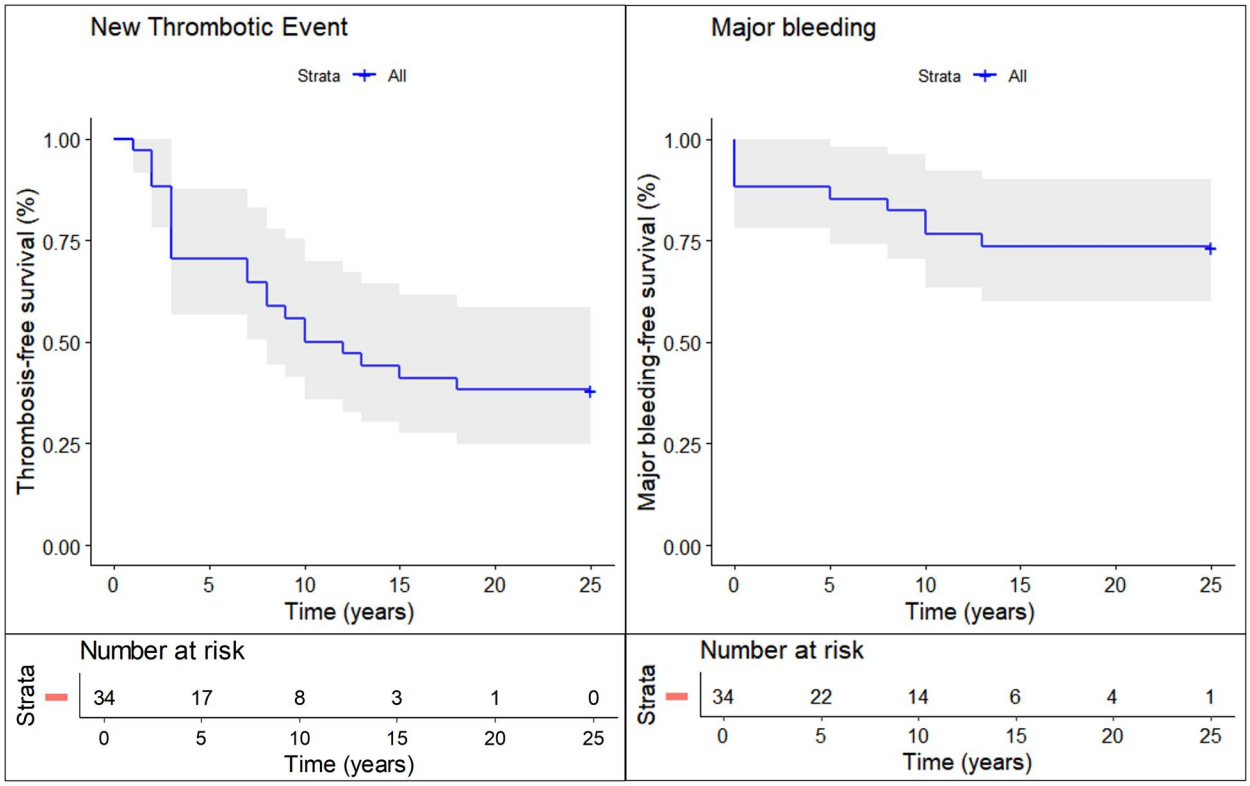


Figure 1. New thrombotic event and major bleeding free survival in APS patients with VLD. New thrombotic event (left)- and major bleeding (right)-free survival curves in 34 APS patients with VLD

Table 5. Factors associated with major bleeding in APS patients with VLD

	Major bleeding N = 9	No major bleeding N = 25	*P*
Age, years	38 +/− 16	33 +/− 14	0.45
Female, *n* (%)	7 (78)	15 (60)	0.44
Primary APS, *n* (%)	8 (89)	14 (56)	0.12
SLE, *n* (%)	1 (11)	10 (40)	0.21
Antinuclear antibodies, *n* (%)	6 (67)	15 (60)	0.99
Thrombopenia <100 G/L	6 (67)	7 (28)	0.06
Portal hypertension, *n* (%)	6 (67)	9 (36)	0.14
Esophageal varices, *n* (%)	5 (56)	5 (20)	0.08
VKA alone, *n* (%)	4 (44)	18 (72)	0.22
VKA and antiplatelet therapy, *n* (%)	4 (44)	7 (28)	0.43
Length of follow-up, years	12 (9–14)	8 (4–13)	0.39
Death, *n* (%)	1 (11)	3 (12)	0.99

APS: antiphospholipid syndrome; SLE: systemic lupus eruthematosus; VKA: vitamin K antagonists.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data described in the manuscript will be made available on request pending application and approval of the authors.

Contribution statement

K.S. directed the project. M.K., N.C.C., P.-E.R., L.D. and K. S. designed the study. M.K. conducted analysis. M.K. and K. S. wrote the manuscript. M.PdC., C.Y., A.C., M.P., Z.A., M. L., P.R.-N. and T.P. were involved in the selection of patients, the project development and edited the manuscript. All authors reviewed and approved of the final manuscript.

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