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Original Article

ORIGINAL ARTICLE

Antiphospholipid antibody positivity is associated with maturation failure and thrombosis of native arteriovenous fistula: a retrospective study in HD patients

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ABSTRACT

Background and hypothesis. The prevalence of antiphospholipid antibody (aPL) is high among hemodialysis (HD) patients compared to the general population and is inconsistently associated with arteriovenous fistula (AVF) thrombosis or stenosis. The association with maturation failure has never been investigated. This study aims to evaluate native AVF complications (thrombosis, stenosis, and maturation failure) and primary patency in aPL positive HD patients.
Methods. We retrospectively identified 116 HD patients with native AVF. We collected the aPL profiles, the clinical and biological data potentially involved in AVF maturation failure, thrombosis, and stenosis, and investigated the association of these complications and aPL positivity. Kaplan–Meier survival analysis was performed.
Results. In our cohort, the prevalence of aPL persistent positivity was 32.7% and this was strongly associated with AVF maturation failure defined by ultrasound. aPL persistent positivity was a strong predictor in multivariate analysis and this association was independent of AVF stenosis or thrombosis during maturation process. There was no association with primary and functional primary patency, and stenosis. However, aPL persistent positivity according to ACR/EULAR classification criteria was associated with thrombosis when compared to strictly negative aPL patients.
Conclusions. In our cohort, aPL persistent positivity was significantly associated with AVF maturation failure and thrombosis but not with AVF stenosis. To our knowledge, we report for the first time, a statistically significant association between aPL positivity and delay or absence of native AVF maturation.

Keywords: antiphospholipid antibodies, arteriovenous fistula, hemodialysis, maturation, stenosis, thrombosis

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KEY LEARNING POINTS

What was known:

- The prevalence of antiphospholipid antibody (aPL) persistent positivity is higher among hemodialysis patients (HD) compared to the general population.
- aPL persistent positivity is a known risk factor for thrombosis in the general population, however, it is inconsistently associated with AVF thrombosis.
- Data are lacking regarding the association between aPL persistent positivity and AVF stenosis and maturation failure.

This study adds:

- We demonstrate a significant association between aPL persistent positivity and native AVF delay or absence of maturation. In binary logistic regression, aPL persistent positivity has a significant effect on the occurrence of AVF delay or absence of maturation.
- We report a higher prevalence of thrombosis in aPL persistently positive patients; however, we did not find any association between aPL persistent positivity and AVF stenosis.
- When comparing patients with only one aPL positive assay and a negative follow-up test to strictly negative patients, AVF survival without thrombosis is significantly lower.

Potential impact:

- aPL persistent positivity may be used as a risk factor for AVF maturation failure and thrombosis.
- Only one aPL positive assay may be a risk factor for AVF thrombosis and maturation failure.
- Further studies may focus on the pathophysiology of maturation failure as a non-thrombotic manifestation of aPL in HD patients.

INTRODUCTION

Chronic hemodialysis (HD) is the most frequent treatment option for end-stage kidney disease. It requires the creation of a patent vascular access such as native arteriovenous fistula (AVF), arteriovenous graft (AVG) or the placement of a HD central venous catheter (CVC). Compared to CVC and AVG, AVF is associated with lower morbidity and mortality, and is therefore considered the gold standard vascular access for HD [1–3].

AVF creation consists of performing a surgical or endovascular anastomosis of an artery to an adjacent vein [1]. This outflow vein will experience a complex vascular remodeling process called "maturation" [4], usually taking place in ∼6 weeks to 3 months [5]. This process is characterized by an increase in the efferent vein diameter, thickness, and blood flow, which are crucial changes for routine puncture [6, 7]. Assessment of AVF maturation is performed by ultrasonography (US) [8], combined to clinical examination [9]. An absence or a delay in maturation is frequently seen after AVF creation. Indeed, AVF have a high rate of primary maturation failure with up to 60% not suitable for HD by 5 months after creation, and can lead to significant morbidity and mortality [1, 10–12]. Other complications may occur such as AVF thrombosis, stenosis, infection, aneurysm, pseudoaneurysm, and hemorrhage. Stenosis and thrombosis are the most frequent complications, often requiring angioplasty, thrombolysis, or thrombectomy [13].

Antiphospholipid syndrome (APS) is an autoimmune disease, characterized by the persistent positivity of at least one antiphospholipid antibody (aPL). It is the most frequent acquired thrombophilia affecting both the arterial and the venous vasculature. APS is also associated with non-thrombotic vasculopathy as well as other features newly incorporated in the 2023 ACR/EULAR classification criteria based on a scoring system [14]. Patients can be classified as APS for research purposes if they combine at least three points from clinical domains and at least three points from laboratory domains [14]. In the absence of clinical criteria, aPL persistent positivity alone does not allow the diagnosis of APS. However, it is associated with an increased thrombotic risk in the general population and in lupus patients [15, 16] Among HD patients, up to 37% have aPL persistent positivity [17, 18]. The reason for the higher prevalence of aPL positivity in HD patients in not well known. Several hypotheses have been proposed, such as molecular mimicry, as responses to the exposure to microorganisms, to endotoxins, to HD membranes (e.g. cuprophane membranes), etc. Some authors suggest that aPL positivity in end-stage kidney disease may simply reflect a response to oxidation (i.e. cross-reactive immunoglobulins against epitopes of oxidized lipids) [18]. aPL positivity has been inconsistently associated with AVF complications such as thrombosis and stenosis [17–20]. To our knowledge, there are no published data reporting the maturation process in persistently positive aPL patients. The aim of the present study is to evaluate major AVF outcomes in aPL positive patients.

MATERIALS AND METHODS

Study design

This is a monocentric retrospective observational study. Institutional Review Board authorization was obtained from our local ethics committee (Ethics Committee of Brugmann University Hospital—reference number CE2022/279) in accordance with the Declaration of Helsinki. The requirement for informed consent was waived by the Ethics Committee of Brugmann University Hospital because of the retrospective nature of the study.

We have identified all HD patients treated in our hospital between 1 January 2019 and 31 December 2023, who have had a native AVF surgical creation, whether used or not. Exclusion criteria were: (i) the absence of available aPL assay or uninterpretable assays (concomitant anticoagulant therapy, i.e. vitamin K antagonists, low molecular weight heparins, fondaparinux, and oral anticoagulants), inflammatory state, or acute thrombosis), and (ii) the presence of innate or acquired thrombophilia other than APS.

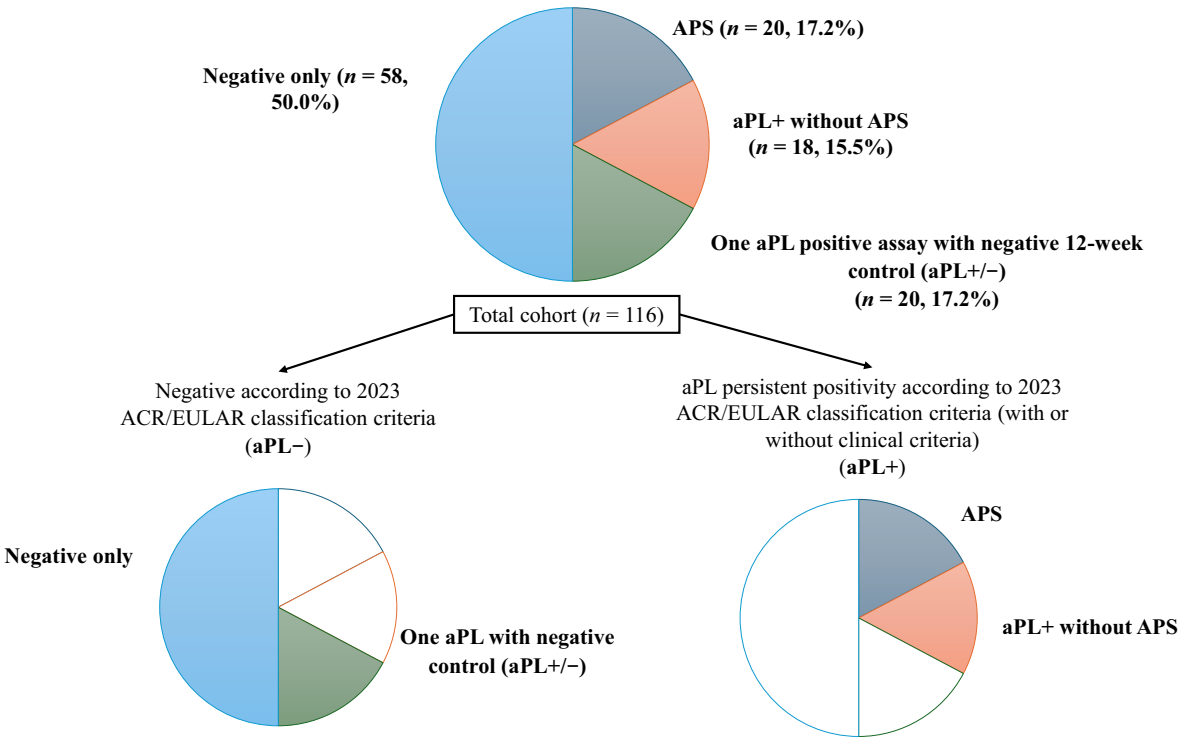

Figure 1: Antiphospholipid antibody distribution in the total cohort (*n* = 116). The lower left diagram shows the negative group (aPL−), and the lower right diagram shows persistently positive aPL patients either "APS" or "aPL without APS" according to the 2023 ACR/EULAR classification criteria (aPL+).

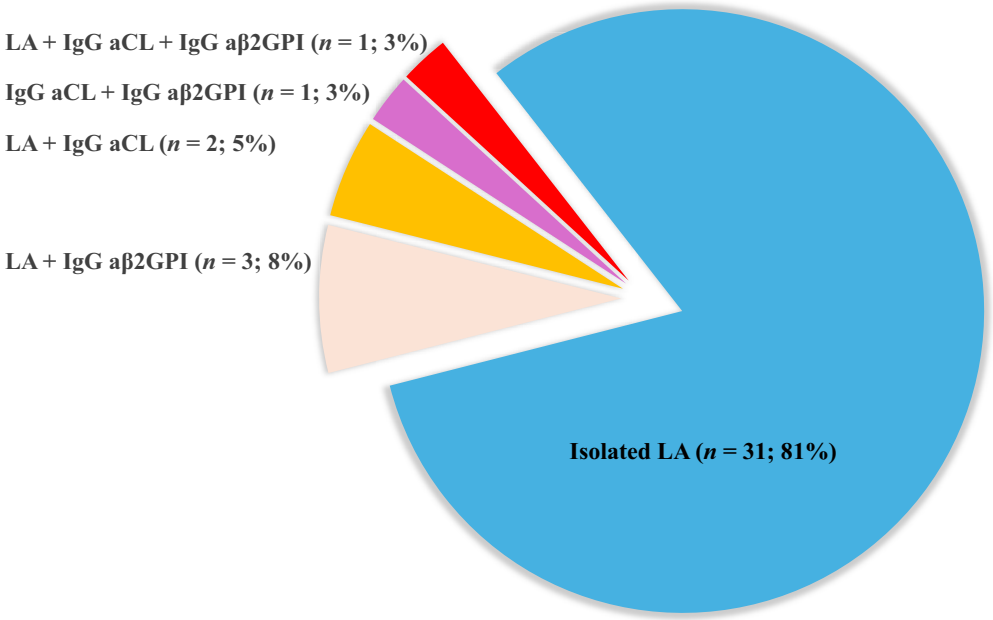

Figure 2: Distribution of antiphospholipid antibody isotypes in the aPL+ group.

Study groups

We classified patients according to the new 2023 ACR/EULAR classification criteria for APS by scoring each patient by using the weighted criteria clustered into six clinical domains (macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic) and two laboratory domains [14]. The patients were divided into the following two groups:

(i) aPL+, gathering all patients with aPL persistent positivity:

- APS: patients with at least three points in both clinical and laboratory criteria according to the 2023 ACR/EULAR classification criteria for APS.

Table 1: Baseline clinical, demographic, and arteriovenous fistula characteristics of the patients included in the study.

	Total cohort ($n = 116$)	aPL+ ($n = 38$)	aP− ($n = 78$)	P
Demographics				
Age, mean (SD)	54.1 (15.0)	50.1 (15.6)	56.3 (14.9)	.042
Sex (n, %)				
Male	80 (69.0)	28 (73.7)	52 (66.7)	.448
Female	36 (31.0)	10 (26.3)	26 (33.3)	
Ethnicity (n, %)				
European	43 (37.1)	11 (28.9)	32 (41.0)	.199
African	39 (31.0)	15 (39.5)	24 (30.8)	.356
North African	31 (26.7)	11 (28.9)	20 (25.6)	.709
Other	3 (2.6)	1 (2.6)	2 (2.6)	.983
BMI (kg/m², mean (SD))	27.8 (6.4)	26.7 (6.5)	28.2 (6.6)	.245
AVF characteristics				
AVF type (n, %)				
Radiocephalic	85 (74.8)	30 (78.9)	55 (70.5)	.257
Brachiocephalic	18 (15.5)	5 (13.2)	13 (16.7)	.628
Radiobasilic	7 (6.0)	3 (7.9)	4 (5.1)	.561
Brachiobasilic	6 (5.2)	0 (0)	6 (7.7)	.045
General anesthesia (n, %)	42 (36.2)	15 (44.1)	27 (40.9)	.761
Side-to-end AVF (n, %)	81 (94.2)	28 (96.6)	53 (93.0)	.509
Anastomosis diameter (mm, mean (SD))	7.9 (2.3)	8.14 (2.4)	7.8 (2.4)	.628
Perioperative complications (n, %)	25 (24.5)	12 (36.4)	13 (18.8)	.078
Edema	7 (6.0)	6 (15.8)	1 (1.3)	.023
Hypotension	18 (17.6°)	6 (18.2)	12 (17.4)	.461
Hematoma	4 (3.9)	1 (3.0)	3 (4.3)	.376
Catheter use before AVF creation (n, %)	81 (73.6)	29 (80.6)	52 (70.3)	.233
Past medical history				
Smoker (n, %)	31 (26.7)	12 (31.6)	19 (24.4)	.414
Hypertension (n, %)	107 (92.2)	33 (86.8)	74 (94.9)	.097
Stroke or TIA (n, %)	22 (19.0)	6 (15.8)	16 (20.5)	.547
Ischemic heart disease	25 (21.6)	10 (26.3)	15 (19.2)	.194
Peripheral vascular disease (n, %)	15 (12.9)	5 (13.2)	10 (12.8)	.480
Total cardiovascular disease (n, %)	41 (35.3)	14 (36.8)	27 (34.6)	.408
Diabetes mellitus (n, %)	57 (49.1)	15 (39.5)	42 (52.8)	.149
HFrEF (LVEF < 50%) (n, %)	23 (20.7)	9 (23.7)	14 (19.2)	.582
Deep vein thrombosis (n, %)	18 (15.5)	14 (36.8)	4 (5.1)	<.001
Renal disease characteristics				
Etiology unknown (n, %)	80 (68.9)	25 (65.9)	55 (70.5)	.582
Urine output >500 ml (n, %)	98 (84.5)	30 (78.9)	68 (87.2)	.290

BMI, body mass index; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricle ejection fraction; TIA, transient ischemic attack.

- aPL carriers without APS: patients with at least three points in laboratory criteria but fewer than three points in clinical criteria

(ii) aPL−, gathering patients with one (or more) negative aPL assay, or patients with an initial positive assay but showing a negative assay at 12-week follow up.

To further assess the significance of isolated aPL positivity even with negative follow-up test, we separately analyzed a subgroup of patients with one positive aPL assay and a negative 12-week follow-up test (aPL+/−). This subgroup was included in the negative group in the main analysis according to ACR/EULAR classification criteria (Fig. 1).

aPL assays

In our laboratory, lupus anticoagulant detection is assessed by using a three-step diagnostic procedure: screening, mix and confirmation procedures using diluted-Russell-viper venom (dRVVT-Siemens®) and Silica Clotting time (SCT-Werfen®). Lupus anticoagulant is confirmed if one of the two functional coagulation assays (dRVVT or SCT) is positive in terms of screening to confirmation ratio, using a citrated plasma sample (3.2%) in accordance with current pre-analytical and analytical recommendations [21, 22]. Screening to confirmation ratio was considered positive if superior to 11.4% for SCT and superior to 9.9% for dRVVT. The determination of anti-cardiolipin antibodies (aCL) and anti-β2 Glycoprotein I (aβ2GPI) is performed by a chemiluminescence immunoassay (HemosIL Acustar aCL IgM/IgG Kit and aβ2GPI IgM/IgG kit, Werfen®). According to the standards of our laboratory the results are interpreted as positive (>99th percentile) or negative when the IgG or IgM titers are >20 or ≤20 U/ml, respectively.

Data collection and definitions

We collected demographic and clinical data potentially associated with AVF complications, including patients' medications and cardiovascular comorbidities as well as laboratory findings. Data regarding vascular access were collected as well:

Table 2: Baseline treatment and laboratory findings of the patients included in the study.

	Total cohort ($n = 116$)	aPL+ ($n = 38$)	aPL− ($n = 78$)	P
Treatment				
Statins (n, %)	46 (41.4)	14 (37.9)	32 (43.2)	.590
Antiplatelet therapy (n, %)	47 (42.3)	13 (35.1)	34 (45.9)	.277
ACE/ARBs (n, %)	67 (60.4)	22 (59.5)	45 (60.1)	.892
β blockers (n, %)	52 (49.1)	19 (55.9)	33 (45.8)	.339
Erythropoietin (n, %)	76 (68.5)	26 (70.3)	50 (67.6)	.775
Laboratory findings				
Hemoglobin (g/dl, mean (SD))	10.4 (1.4)	10.1	10.6	.337
Platelet count ($\times 10^3$ cells/μl, mean (SD))	221.2 (59.3)	213.4 (64.2)	225 (57.0)	.346
Ferritin (μg/l, mean (SD))	330.8 (205.7)	398,0 (268.8)	298.3 (205.6)	.359
CRP (mg/l, mean (SD))	5.3 (8.3)	7.1 (11.5)	4.5 (5.4)	.203
aPTT (second, mean (SD))	31.4 (6.1)	33.9 (8.1)	30.2 (4.4)	.011
Antiphospholipid antibody isotypes				
LA (n, %)	31(26.7)	31 (81.6)		
LA and IgG aCL (n, %)	2 (1.7)	2 (5.3)		
LA and Ig G aβ2GP1 (n, %)	3 (2.6)	3 (7.9)		
LA and IgG aCL and IgG aβ2GP1 (n, %)	1 (0.9)	1 (2.6)		
IgG aCL and IgG aβ2GPI (n, %)	1 (0.9)	1 (2.6)		
IgG aCL titer[a] (mean, SD)	6.9 (14.4)	11.9 (21.4)	3.5 (3.2)	<.001
IgG aCL min/max (U/ml)		1.3/94.0	1.2/17.0	
IgG aβ2GPI[a] (mean, SD)	10.5 (38.4)	19.0 (59.8)	4.8 (5.1)	.014
		0.5/417.8	1.1/13.6	
LA SCT ratio[a] (mean in %, SD)		36.8 (19.2)		
LA dRVVT ratio[a] (mean in %, SD)		23.2 (12.3)		

aβ2GP1, anti- β2GP1 antibody, ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; CRP, c-reactive protein.
[a]Expressed as mean value of the first assay and the follow-up assay at 12 weeks.

Table 3: AVF maturation outcomes in the total cohort and in the two groups.

	Total cohort ($n = 116$)	aPL+($n = 38$)	aPL−($n = 78$)	P
AVF maturation				
Delay or absence of maturation (n, %)	71 (68.3)	28 (84.8)	43 (60.6)	.006
Delay	20 (37.7)	10 (66.7)	10 (26.3)	.006
Absence	51 (60.7)	18 (78.3)	33 (54.1)	.031
AVF blood flow, mean (SD)	611.9 (435.4)	526.4 (406.4)	650.5 (473.7)	.279
Efferent vein diameter, mean (SD)	5.92 (3.5)	6.22 (7.70)	5.89 (2.49)	.626
Clinical maturation (n, %)	56 (50.9)	16 (47.1)	40 (52.6)	.593
Thrombosis during maturation process (n, %)	27 (24.3)	7 (20.6)	20 (26.0)	.546
Stenosis during maturation process (n, %)	32 (28.8)	11 (32.4)	21 (27.3)	.590
Assisted maturation (n, %)	12 (16.2)	5 (16.7)	7 (14.9)	.598
Time before cannulation (months, mean (SD))	5.54 (6.26)	5.43 (6.46)	5.61 (6.60)	.908
Primary patency (months, mean (SD))				
Time from AVF creation to first intervention	15.86 (21.76)	32.0 (30.76)	29.9 (39.78)	.725
Functional primary patency (months, mean (SD))				
Time from AVF cannulation to first intervention	11.27 (13.15)	30.4 (27.8)	25.4 (31.8)	.535
Intervention (primary patency)				
Angioplasty	43 (88.0)	13 (76.5)	30 (90.9)	.232
Thrombolysis or thrombectomy	7 (14.0)	4 (23.5)	3 (9.1)	.080

CVC use before AVF creation, AVF type, and surgical procedure information [type of anesthesia, anastomosis diameter, vein diameter, perioperative complications (i.e. edema, hypotension, hematoma)].

We collected the information regarding the following AVF complications:

- AVF maturation failure. AVF maturation was defined either clinically or by using Doppler US. Doppler US maturation criteria were the following: AVF flow >600 ml/min, outflow vein diameter >6 mm, 6 weeks after AVF creation [8, 23, 24]. Clinical criteria for AVF maturation were the following: two-needle cannulation, for 75% of HD sessions over a continuous 4-week period, including either a mean HD machine blood pump speed superior to 300 ml/min over four consecutive sessions or a measured urea $K_t/V > 1.4$ or a urea reduction ratio >70% [9].

Table 4: Factors associated with AVF absence or delay of maturation in multivariable linear regression.

	Final model			
Independent variables	B	OR	95% CI	P
aPL+	2.20	9.01	1.37–59.24	.022
Diabetes mellitus	2.25	9.50	1.46–61.68	.018
Distal AVF	1.71	5.53	0.93–32.98	.061
aPTT	0.286	1.33	1.01–1.75	.040
Catheter use before AVF creation	1.15	3.15	0.47–21.14	.492

- We recorded assisted maturations, with procedures (balloon assisted maturations) and we recorded the success rate (clinically usable AVF).
- Primary patency rate: defined as the time from AVF creation to first intervention to maintain AVF patency.
- Functional primary patency rate: defined as the time from AVF first cannulation to intervention to maintain AVF patency [24]. Information regarding secondary patency was not collected.
- Thrombosis or stenosis during follow up, as well as the time period to first thrombosis and stenosis were also collected, with clinical and iconographic details. Criteria for thrombosis or stenosis were the followings: any acute or chronic change in AVF physical examination of blood flow associated with a confirmation by using either US or angiography.

Baseline characteristics were collected at AVF surgical creation. AVF complications were collected until loss of AVF, or loss of follow up (death, transplantation, transfer to another center).

Statistical analyses

Data were expressed as mean ± standard deviation (SD) for variables with a normal distribution. Student's *t*-test was used to compare the means of the quantitative variables following a normal distribution by group. The Mann–Whitney Wilcoxon test was used to study the variation between two groups of variables following an asymmetric distribution. The significance level of the tests was 0.05 with odds ratios and 95% confidence intervals of odds ratio. Multivariate models were proposed through logistic regression for variables showing statistically significant differences between groups. We employed Kaplan–Meier survival analysis to estimate the probability of AVF survival (without stenosis, thrombosis, or intervention to maintain patency) over time, accounting for censoring and to compare survival curves between groups. All statistical analyses were performed using SPSS software.

RESULTS

From 348 reviewed patient medical records, a total of 116 HD patients with native AVF fulfilled the inclusion criteria. Thirty-eight (32.7%) patients had persistently positive aPL (aPL+), of which 20 (17.2%) were APS and 18 (15.5%) had persistently positive aPL+ without APS. Out of 38 aPL+ patients, three had secondary APS (two systemic lupus erythematosus, one rheumatoid arthritis). The distribution of aPL profiles is represented in Fig. 1 and the distribution of aPL isotypes in the aPL+ group is represented in Fig. 2 and Table 2.

About two-thirds of the cohort had a CVC for HD before AVF creation, with most being heterolateral to the AVF in 93.6%. All the AVF were native AVF, surgically created, mostly radiocephalic in 74.8% (Table 1), and almost exclusively on the left arm in 94.8%. Most patients (71.6%) were on HD before the AVF creation with a mean HD vintage of 12.0 ± 2.3 months without statistical difference between the two groups ($P = .613$).

The absence or delay of maturation was significantly more prevalent in aPL+ patients ($P < .001$), but AVF blood flow and efferent vein diameter were not different. The prevalence of clinical maturation was 66.7% and 78% in the aPL+ and the aPL− groups, respectively ($P = .254$). There was no difference between groups in terms of assisted maturation and thrombosis or stenosis during the maturation process (Table 3).

In univariate analysis, risk factors for AVF maturation failure were aPL+, distal AVF (radiocephalic and radiobasilic) ($P = .05$), the use of CVC before AVF creation ($P = .023$), diabetes mellitus ($P = .017$), activated partial thromboplastin time (aPTT) ($P = .003$), and deep venous thrombosis ($P = .044$). Thrombosis during maturation process tended to significance ($P = .08$).

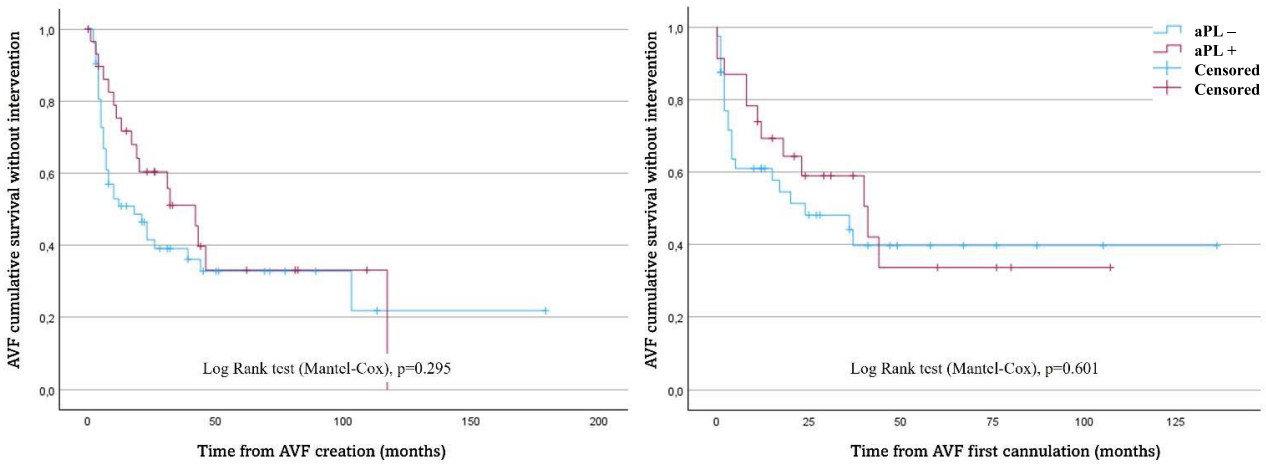

Figure 3: Kaplan–Meier analysis showing the probability of native AVF primary patency (left curve) and functional primary patency (right curve) in aPL+ and aPL− patients.

Table 5: AVF thrombosis and stenosis outcomes in the total cohort and in the two groups.

	Total cohort ($n = 127$)	aPL+ ($n = 38$)	aPL− ($n = 78$)	P
Thrombosis and stenosis				
Mean follow-up period (months, mean (SD))	42.9 (49.1)	51.8 (69.2)	39.3 (36.7)	.214
Thrombosis				
Prevalence of thrombosis during follow up (*n*, %)	46 (37.7)	16 (43.2)	26 (34.7)	.038
Time to first thrombosis (months, mean (SD))				
From AVF creation	33.3 (38.3)	39.5 (42.1)	31.2 (36.4)	.291
From AVF first cannulation	38.2 (36.5)	42.8 (41.8)	37.0 (32.6)	.516
Stenosis				
Prevalence of stenosis during follow up (*n*, %)	71 (58.2)	24 (64.9)	40 (53.3)	.250
Time to first stenosis (months, mean (SD))				
From AVF creation	21.0 (30.6)	20.1 (23.7)	21.8 (32.7)	.780
From AVF first cannulation	26.3 (30.5)	21.6 (20.1)	27.9 (32.4)	.419

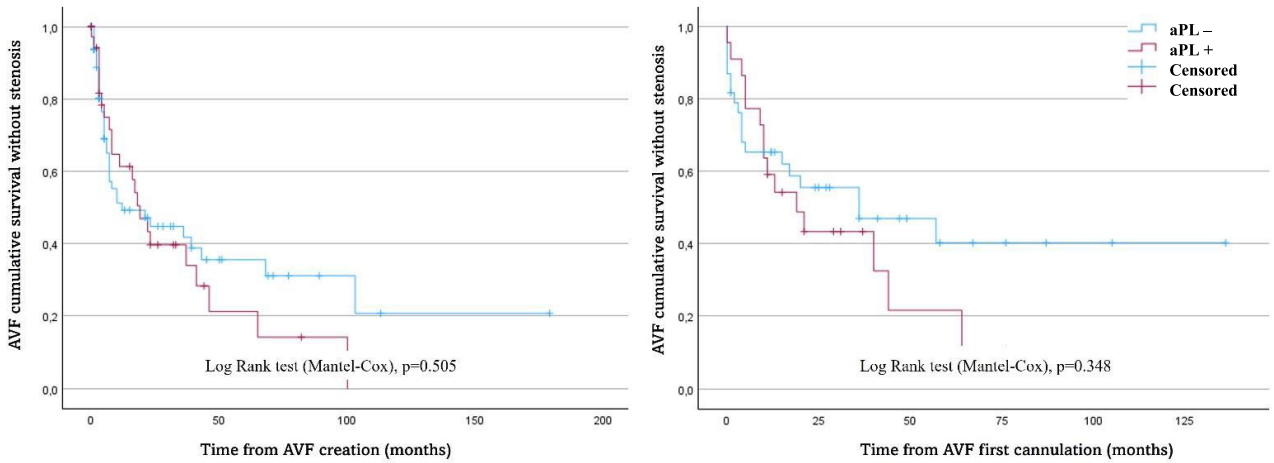

Figure 4: Kaplan–Meier survival curve showing the probability of native AVF survival without stenosis in aPL+ and aPL− patients.

Binary logistic regression models using a forward regression model demonstrated that the absence or delay of maturation was associated with aPL+ ($P = .022$) (Table 4). Out of five tested variables, aPL+, diabetes mellitus, and aPTT were significantly associated with AVF absence or delay of maturation.

With respect to primary patency and functional primary patency, no difference was observed between groups. Kaplan–Meier survival analysis showed similar time to first intervention both from AVF creation (primary patency) and from AVF first cannulation (functional primary patency) (Fig. 3). Interventions were mostly angioplasty with ballon in 84.2% whereas thrombolysis or thrombectomy were performed in 15.8%. Thrombolysis and thrombectomy tend to be significantly more prevalent in the aPL+ group compared to aPL− (23.5% and 9.1%, respectively, $P = .08$) (Table 3).

AVF thrombosis during the follow up was significantly more prevalent in aPL+ patients (42.3% and 34.7%, respectively, $P = .038$). There was no difference between groups with respect to stenosis outcomes (Table 5).

Kaplan–Meier analysis showed similar probability of AVF survival without stenosis (Fig. 4) and without thrombosis (Fig. 5a). Subgroup analyses were performed, comparing patients with only one positive aPL assay with a negative control at follow up (aPL+/−), to strictly negative patients (Fig. 5b). The probability of AVF survival without thrombosis from AVF first cannulation was significantly lower in the aPL strictly negative compared to the aPL+/− group (Fig. 5b).

DISCUSSION

Although rare in the general population, aPL persistent positivity is a frequent finding in HD patients. In our study, its prevalence was 32.7%, which is high but consistent with the literature [18].

Besides the usually described complications such as stenosis and thrombosis, AVF delay or absence of maturation is a frequent complication encountered in HD patients [25]. To our knowledge, we describe for the first time an association between aPL persistent positivity and AVF maturation failure defined as the delay or absence of maturation by US evaluation. This association was confirmed by binary logistic regression (odds ratio, 9.01; 95% CI, 1.37 to 59.24; $P = .022$), suggesting

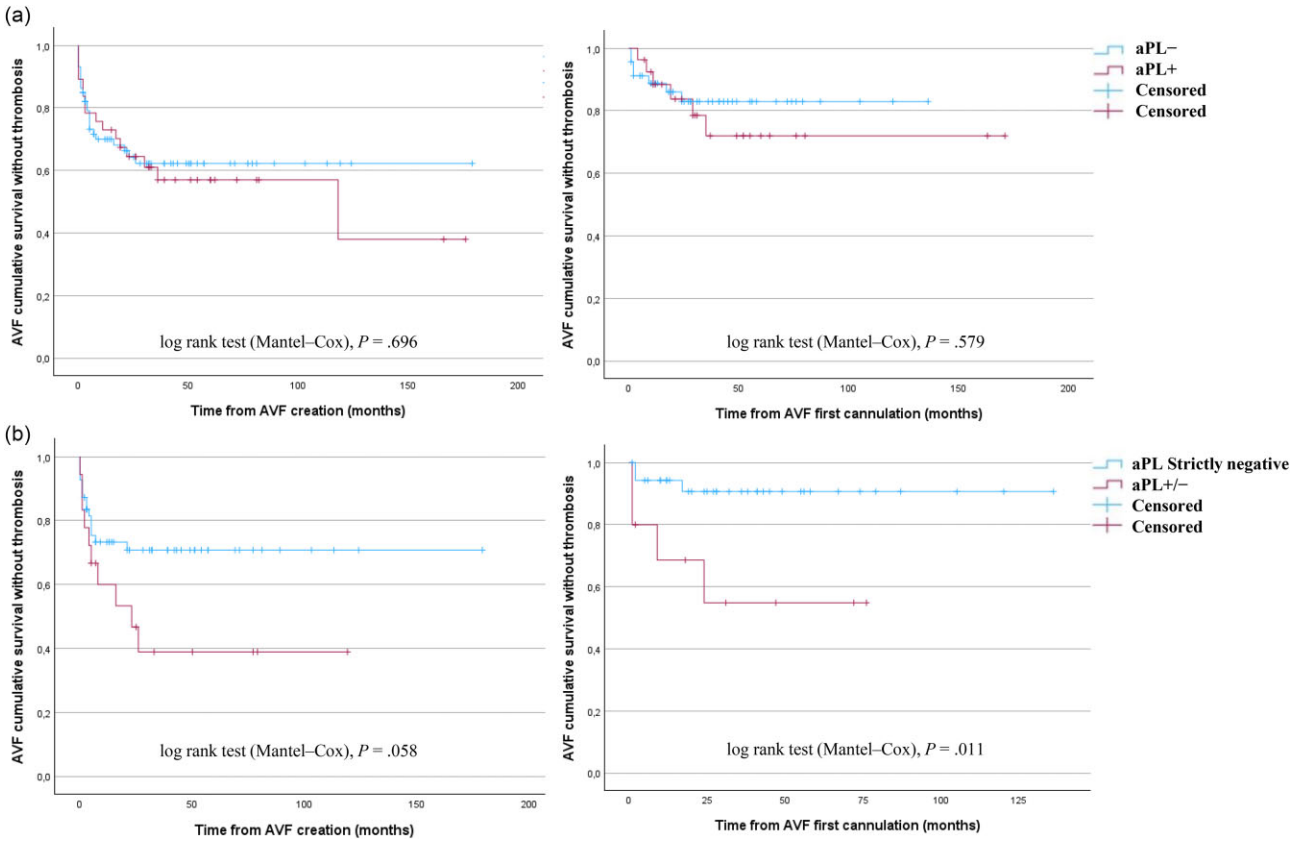

Figure 5: Kaplan–Meier analysis of native AVF survival without thrombosis from AVF creation (left column) and from AVF first cannulation (right column). (**a**) The cumulative AVF survival without thrombosis in aPL+ and aPL− patients according to 2023 ACR/EULAR classification criteria. (**b**) The cumulative AVF survival without thrombosis in the subgroup aPL+/− compared to strictly negative patients.

that aPL persistent positivity has a significant impact on the occurrence of AVF delay or absence of maturation (Table 4). AVF maturation failure was mainly due to delayed maturation, rather than absence of maturation. However, both were statistically significant. Indeed, we did not find any difference with respect to clinical maturation and ability to cannulate the AVF, and with assisted maturation rate, suggesting that the maturation process required a longer period of time in this group.

Thrombosis and stenosis both may influence AVF maturation, but they cannot always be distinguished [25]. In our cohort, neither thrombosis nor stenosis during maturation process were different between groups (Table 3). These findings suggest that aPL+ was associated with maturation failure, independently of thrombosis or stenosis. Most research studies on the pathophysiology of AVF maturation failure focus on intimal hyperplasia, stenosis, and thrombosis occurring during AVF maturation. However, vascular efferent vein remodeling process is not well known. We hypothesize that endothelial dysfunction could explain AVF maturation failure in the absence of stenosis and thrombosis. Indeed, endothelial dysfunction is considered to play a crucial role in the pathophysiology of AVF maturation and failure [26, 27]. Nitric oxide (NO), which is generated by endothelial NO synthase, has a vasodilatation effect, as well as anti-inflammatory and antiplatelet properties and has been shown to be involved in AVF maturation [28, 29]. Endothelial NO synthase may contribute to AVF maturation and vein wall remodeling both through its anti-inflammatory and antithrombotic properties as well as through its anti-proliferative properties [10]. In the HD population, the role of uremic toxins in endothelial dysfunction has been pointed out by several authors [30, 31]. Endothelial dysfunction has also been reported in APS patients, and impaired NO release could play a major role in APS [32, 33]. Actually, the possible additional role of aPL over uremia in the pathophysiology of endothelial dysfunction has never been investigated. We hypothesize that aPL persistent positivity could result in insufficient vascular remodeling process of the outflow vein by enhancing endothelial dysfunction, preventing the efferent vein from vasodilatation and remodeling, independently of the occurrence of any thrombosis or stenosis.

Also, the initial phase of AVF remodeling process implies the increase of metalloproteinases (MMPs) such as MMP-2 and MMP-9, and the ratio of MMP-2 and tissue inhibitor of metalloproteinase-1 (TIMP-1) is a predictor of AVF maturation [10]. MMPs, as well as other elastases, are upregulated in the AVF, suggesting that elastin degradation is crucial to enhance the efferent vein remodeling, by degrading the internal elastic lamina and basement membrane [34, 35]. Although patients with ESRD frequently present with systemic inflammation and oxidative stress, the latter can be modulated by several factor and can contribute to MMPs expression. Indeed, MMPs can be stimulated by many factors in the setting of AVF creation, such as blood flow, stretch, mechanical injury, inflammation, and

oxidative stress [10, 25]. Interestingly, oxidative stress has been well described in the setting of aPL positivity [32], and the decrease in MMP-2 and MMP-9 expression has also been described in those patients, suggesting that MMPs can be a putative mechanism of AVF maturation failure in the setting of aPL positivity [36]. We then hypothesize that aPL positivity may have an additive impact on uremia and other factors, in terms of oxidative stresses and endothelial dysfunction, leading to AVF maturation failure.

We did not find any difference between groups, in terms of primary patency and functional primary patency (Table 3 and Fig. 3). Salmela *et al*. performed a prospective observational study, following 219 patients with underlying thrombophilia and assessing primary and functional primary patency. aPL positivity was present in 11% but was not associated with patency failure [37]. However, despite similar patency rates found in our study, thrombolysis and thrombectomy interventions performed to maintain patency tend to be significantly more prevalent in the aPL+ group than in the aPL− group (23.5% and 9.1%, respectively, $P = .08$).

In our cohort, we did not find any association between aPL persistent positivity and AVF survival probability without thrombosis in Kaplan–Meier analysis (Table 5 and Fig. 5a). However, we found an association with the overall prevalence of thrombosis during the follow up (Table 5). In the literature, aPL persistent positivity has been inconsistently associated with AVF thrombosis [18]. One metanalysis published in 2020 reported an association between LA and IgG aCL and AVF thrombosis. However, studies included in this meta-analysis mostly did not mention aPL confirmation [18, 20].

In a day-to-day practice, the assessment of aPL positivity can be cumbersome. Indeed, real-life data from the literature, show that <10% of patients have a follow-up aPL test [38]. Moreover, aPL negativation or fluctuation have been described in ∼10% of APS patients with uncertain clinical impact [39, 40]. For these reasons, we decided to separately analyze patients with only one aPL positive assay with a negative follow-up test (aPL+/−), to a strictly aPL negative group. Interestingly, the Kaplan–Meier analysis showed significant differences between these groups (Fig. 5b) in terms of thrombosis-free survival. It is important to acknowledge, that 2023 ACR/EULAR classification criteria are made for research purposes and are highly specific but lack sensitivity [14]. Our results highlight the importance of a single aPL positive assay even with a negative 12-week-follow-up test, in terms of thrombosis, as suggested by other studies [18].

In our cohort, we did not find any association between aPL+ and AVF stenosis. In Kaplan–Meier analysis, the results were not statistically significant, however, curves diverge, showing a trend toward lower survival without stenosis in aPL+ patients. One of the most common complications associated with native AVF is the stenosis of the outflow vein [41]. A common cause of stenosis is intimal hyperplasia (IH) [25, 42], usually occurring at the anastomotic level and involving endothelial cell activation [10]. Indeed, NO seems to play a role in preventing AVF intimal hyperplasia and therefore increasing AVF patency [43]. Intimal hyperplasia has also been reported in aPL-associated disorders such as aPL-associated nephropathy and is a non-thrombotic manifestation of APS [44]. Its pathophysiology involves the activation of the mammalian target of rapamycin pathway [45]. There are few studies evaluating AVF stenosis in the setting of aPL positivity. In a combined retrospective and prospective cohort study of a single outpatient dialysis unit, the presence of IgM aCL was associated with AVF stenosis [46]. Whether this phenomenon is mediated by the mammalian target of rapamycin pathway has not yet been explored.

Furthermore, aPL has been associated with accelerated atherosclerosis, arterial vascular disease such as cardiovascular disease and peripheral artery disease [47, 48]. Thus, an atherogenic hypothesis has been proposed by some authors and may explain the link between aPL and fistula occlusion [20, 49]. Endothelial dysfunction is also associated with increased oxidative stress and inflammation, factors recognized to be involved in the pathogenesis and the progression of atherosclerosis in the early stages [28, 43, 48]. Also, atherosclerosis with thickened vessels, and vascular calcification could also lead to an impaired remodeling process, to stenosis and/or thrombosis and therefore to AVF maturation failure [50]. We did not find any association between the aPL persistent positivity and cardiovascular disease, or associated treatment. However, the younger age in the aPL+ group can be a confounding factor.

The present study has limitations. It is a single-center retrospective study with a limited number of patients. Because of the retrospective design of this study some clinical criteria could be missed during the evaluation of classification criteria for APS. Also, the exclusion of patients with anticoagulation treatment might have influenced the results in terms of thrombosis risk.

CONCLUSIONS

We report for the first time a statistically significant association between aPL persistent positivity and native AVF maturation failure in HD patients. This association was independent of the onset of stenosis or thrombosis during this maturation process. We hypothesize that endothelial dysfunction—through impaired NO release and/or decreased levels of MMPs or elastases—could be responsible for the inability of the efferent vein vasodilatation and remodeling leading to AVF maturation failure. We also describe an association between aPL persistent positivity and AVF thrombosis, but we did not find any association with AVF stenosis. Interestingly, patients who had only one aPL positive assay were also at risk of AVF thrombosis and maturation failure. We suggest that aPL could be a useful biomarker candidate for the clinicians in identifying patients at risk of AVF maturation failure and thrombosis.

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AUTHORS' CONTRIBUTIONS

All the authors were involved in the conception and design of the study. M.T. and A.J. did the data collection. M.T. wrote the first draft of the manuscript. A.J., L.J., M.D.C.F.M., M.L., Y.D., C.D., A.P., A.D., F.C., and J.N. revised the manuscript. All authors were involved in the analysis and the interpretation of data and participated in the writing. F.C. and J.N. supervised the writing of the manuscript. All authors approved the version to be published.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are not open access.

CONFLICT OF INTEREST STATEMENT

None declared.

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