DANISH MEDICAL JOURNAL

Original Article

Prevalence of misclassification and remission of antiphospholipid syndrome

Sherin Gnanapragasam[1] & Jørn Dalsgaard Nielsen[2]

1) Department of Clinical Biochemistry, Copenhagen University Hospital – Næstved Hospital, 2) Center of Excellence for Anticoagulant Treatment, Department of Cardiology, Copenhagen University Hospital – Bispebjerg and Frederiksberg Hospital, Denmark

Dan Med J 2026;73(7):A11250969. doi: 10.61409/A11250969

ABSTRACT

INTRODUCTION. Antiphospholipid syndrome (APS) is an acquired autoimmune disorder mediated by antiphospholipid antibodies (aPLs) and accompanied by clinical symptoms in the form of arterial and/or venous thromboses or pregnancy complications. APS is a severe form of acquired thrombophilia that often requires lifelong anticoagulant treatment. As the diagnostic criteria for APS are complex, the correct diagnosis of APS is challenging. The purpose of this retrospective study was to investigate the proportion of patients diagnosed with APS that met the formal criteria for APS.

METHODS. The study included patients > 18 years of age in the Capital Region and Region Zealand in Denmark with an International Classification of Diseases, Tenth Revision (ICD-10) code for APS (D68.61) in the medical record management system EPIC during the period 2016 to 2023.

RESULTS. Among 175 included patients, 46 (26%) did not meet the formal APS criteria. Among 53 patients < 50 years, APS occurred more frequently in women than in men (41 versus 12; $p < 0.0001$) but not in patients ≥ 50 years (38 versus 38). The reasons for misclassified APS were mostly incorrect interpretation of laboratory results. In ten cases, the clinical criteria were not met. In 15 patients, aPLs became negative after several months or years.

CONCLUSIONS. The formal APS criteria were not met in 26% of our patients. This raises the question whether better diagnostic performance can be achieved through further education, or whether the diagnosis of APS should be regarded as a specialist task.

FUNDING. None.

TRIAL REGISTRATION. Approved by the health authorities in Denmark, project number R-23014587.

Antiphospholipid syndrome (APS) is an acquired autoimmune disorder mediated by a heterogeneous group of antiphospholipid antibodies (aPLs), which can cause thrombosis in the venous, arterial and microvascular circulation and predispose to pregnancy complications [1]. The three commonly used tests to detect aPLs are lupus anticoagulant (LA) functional coagulation assay, anticardiolipin (aCL), IgG- and IgM antibodies and anti-β2-glycoprotein I (aB2GPI) IgG and IgM antibodies. To further standardisation of clinical studies in APS, international consensus criteria have been developed. The diagnostic criteria have changed over time. In 1999, the Sapporo preliminary classification criteria were presented [2]. These were revised in 2006 after a workshop in Sydney [3]. Most recently, the 2023 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria have been published [4].

APS is a rare disorder with approximately two new cases per 100,000 persons/year [5]. As with other rare

diseases, establishing the right diagnosis can be challenging, particularly because APS requires meeting multiple biochemical and clinical criteria, and because the diagnostic criteria have changed over time.

From 2006 to 2023, the APS criteria remained unchanged. During this period, the criteria were detection of at least one type of positive aPL tested twice, combined with the presence of clinical criteria. The clinical criteria were objectively validated cases of arterial, venous or small-vessel thrombosis within the past five years or pregnancy morbidity in the form of a) one or more unexplained deaths of a morphologically normal foetus at or beyond the tenth week of gestation; b) one or more premature births of a morphologically normal neonate before the 34th week of gestation due to eclampsia or placental insufficiency; or c) three or more unexplained consecutive spontaneous abortions before the tenth week of gestation. The laboratory criteria called for at least one of the aPL assays (LA, aCL and aB2GPI) to be positive when tested twice with at least a 12-week interval. The criterion for positive aCL and aB2GPI was > 40 GPL or MPL, or > 99th percentile, measured with standardised enzyme-linked immunosorbent assay (ELISA) [3].

The requirement that positive aPLs be detectable for at least 12 weeks is warranted by the potential presence of infections and other conditions with acute-phase reactions that can cause transient increases in aPLs [6]. In these cases, aPLs usually normalise within 12 weeks. It was therefore expected that after 12 weeks, aPLs would be present permanently.

Given the complexity of APS diagnosis, we investigated how often APS is diagnosed on an incomplete basis and how frequently aPLs disappear after having been present for at least 12 weeks.

Methods

This was a retrospective cohort study conducted at public hospitals in the Capital Region and Region Zealand, Denmark. The included hospitals started using the EPIC medical record management system in 2016. Patients older than 18 years with an International Classification of Diseases, Tenth Revision (ICD-10) code for APS (D68.61) before the publication of the 2023 ACR/EULAR APS Classification criteria were searched in the system from 2016 to 2023. We extracted data on patient demographics, aPLs laboratory results, diagnoses, imaging codes and use of antithrombotic drugs with dates and times specified. Manual chart reviews were performed to evaluate the diagnostic criteria for each included patient. Deep venous thrombosis was detected by duplex ultrasound scan; pulmonary embolism and extracardiac arterial thromboses, by CT or magnetic resonance imaging (MRI). Myocardial infarction was diagnosed by electrocardiogram (ECG) and elevated cardiac biomarkers. In one patient with catastrophic APS, microvascular thrombosis was considered the cause of multiorgan failure. Patients were considered appropriately classified with APS if they met the Sydney criteria [3]. Testing for LA was performed using a dilute Russell's viper venom time (RVV) assay and a sensitive activated partial thromboplastin time (aPTT). Positive test for LA was reported by the laboratory as “lupus anticoagulant detected”. Testing for aCL and aB2GPI IgG and IgM antibodies was performed using commercially available methods. Results were considered positive if they were > 40 GPL or MPL, or > 99th percentile, as specified by the laboratory or the assay manufacturer.

Trial registration: The project was approved as a quality assurance and development project by the health authorities in Denmark, project number R-23014587.

Results

A total of 175 patients were identified with APS based on the ICD-10 code D68.61. Among these, APS was confirmed in 129 (74%), whereas 46 (26%) did not meet the formal criteria for APS. Patient demographics are

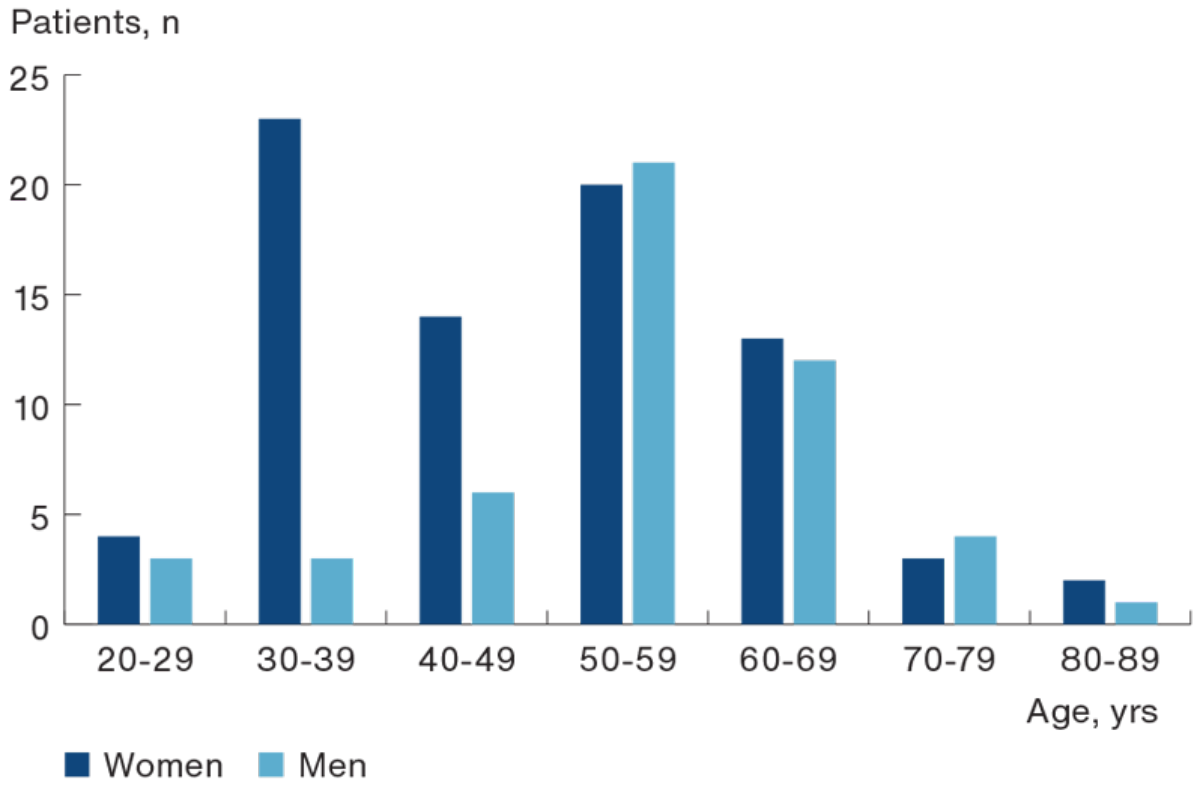
shown in **Table 1**. Among the 53 patients under 50 years of age, APS was significantly more common in women than in men (41 versus 12; Mann-Whitney test $p < 0.0001$) (**Figure 1**). 59% of patients with APS were ≥ 50 years of age. This group showed no gender-dependent differences in the prevalence of APS.

TABLE 1 Patient demographics (N = 175).

Women	
n (% of N)	110 (63)
Age, median (range), yrs	49 (20-81)
APS, n (% of women):	
Confirmed	79 (72)
Misclassified	31 (28)
Men	
n (% of N)	65 (37)
Age, median (range), yrs	57 (22-83)
APS, n (% of men):	
Confirmed	50 (77)
Misclassified	15 (23)
Presence of criteria for APS, n (% of N)	
Clinical and biochemical criteria met	129 (74)
Neither clinical nor biochemical criteria met	4 (2)
Solely clinical criteria not met	6 (3)
Solely biochemical criteria not met	36 (21)
Clinical criteria in patients with confirmed APS, n (% of 129)	
Venous thromboembolism	50 (39)
Ischaemic stroke	42 (33)
Other arterial thrombosis	15 (12)
Venous and arterial thrombosis	12 (9)
Obstetric criteria	9 (7)
Small vessel thrombosis	1 (1)
aPL positivity in patients with confirmed APS, n (% of 129)	
Single positive	75 (58)
Double positive	32 (25)
Triple positive	22 (17)

aPL = antiphospholipid antibodies; APS = antiphospholipid syndrome.

FIGURE 1 Distribution of age in women and men with confirmed antiphospholipid syndrome.



The most common clinical criteria for APS were arterial thromboembolism (45%), venous thromboembolism (39%) or arterial and venous thromboembolism (9%). Among 15 patients with obstetric criteria, six (40%) did not meet the formal criteria for APS.

In most cases, the reasons for misclassified APS were incorrect interpretation of laboratory results (**Table 2**). In ten cases, APS was based solely on elevated aPLs, and the clinical criteria therefore were not met. The most common laboratory reason for misclassification was that patients with negative LA were considered single-positive with aCL or aB2GPI, even though the results were below the threshold for APS diagnosis. Other common reasons were falsely positive LA due to failure to pause anticoagulant therapy and lack of follow-up of positive tests after ≥ 12 weeks.

TABLE 2 Causes of antiphospholipid syndrome misclassification.

aCL and aB2GPI below threshold, LA-negative, n (% of N)	15 (27)
Falsely positive LA, n (% of N)	11 (20)
Clinical criteria not met, n (% of N)	10 (18)
All aPLs negative and no previous evidence of APS, n (% of N)	8 (14)
aPL-positive but only measured 1 × and no previous evidence of APS, n (% of N)	6 (11)
aPL-positive but turned negative within 12 wks, n (% of N)	4 (7)
aPL-positive twice but only measured within 12 wks, n (% of N)	2 (4)
Total, N	56[a]

aB2GPI = anti-β2-glycoprotein I; aCL = anticardiolipin; aPL = antiphospholipid antibodies; APS = antiphospholipid syndrome; LA = lupus anticoagulant.
a) Among the 46 patients with misclassified APS, 10 patients had 2 causes of misclassification.

The group of patients with confirmed APS included 15 patients (six single positive and nine double positive) in whom LA, aCL and aB2GPI became negative after several months or years. Twelve of these patients were still on antithrombotic treatment, of whom nine were on warfarin and three on aspirin.

Discussion

APS is a diagnosis with serious consequences, partly because it is one of the most severe forms of acquired thrombophilia and partly because it is most often considered a lifelong condition. Furthermore, the diagnosis poses treatment challenges, as direct oral anticoagulants (DOACs) do not confer the same protection against arterial thrombosis as warfarin in these patients [7]. Therefore, it is recommended that patients be treated with warfarin rather than DOACs, especially if they are triple positive or have positive LA. However, warfarin treatment can also be challenging, as some patients with APS form antibodies that interfere with the international normalised ratio (INR) analysis, causing the INR to be falsely elevated [8]. For these reasons, it is important to always carefully consider whether a patient meets the criteria for APS or may be affected by a condition with a less serious risk of future thrombosis or obstetric complications.

In 2014, guidance from the Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies of the International Society on Thrombosis and Haemostasis recommended that testing for aPL focus on individuals < 50 years of age to prevent incidental findings in older patients [9]. However, the Sidney criteria found no reason to have a fixed age limit for the diagnosis of APS [3]. Elderly patients typically have more risk factors for thromboembolic disease than younger patients, but the presence of aPLs represents a significant addition to the total number of risk factors. Some studies have shown that positivity of aPLs is seen as frequently in the elderly as in younger people [5, 10]. The present study confirms this, as 59% of the patients we considered to have APS were > 50 years of age. Furthermore, we found that APS had a later onset in men than in women (Figure 1). A recent study showed that this is also the case in systemic lupus erythematosus [11].

It has previously been described that many patients are diagnosed with APS even though they do not meet the formal criteria for the diagnosis. In 2005, Dunn et al. found that only 10% of patients followed for APS in an anticoagulation clinic met the criteria for APS [12]. In a later study, Ballif et al. found that only a third of patients with presumed APS met the classification criteria [13]. The patients in the present study were diagnosed when the Sidney criteria had been in effect for at least 10 years, and it was therefore expected that the diagnostic requirements were well known. We found fewer patients with misclassified APS than in previous studies.

However, it remains a problem that one quarter of patients were misclassified and thus possibly exposed to unnecessary lifelong antithrombotic therapy.

Our study shows that in 26% of patients, evidence to make a diagnosis of APS was insufficient. Common reasons for this were misinterpretation of test results and failure to pause anticoagulant treatment when checking LA. Laboratory charts usually show reference ranges only for aCL and aB2GPI among normal, healthy individuals, but might also show threshold values &;&;for APS. This would avoid many misdiagnoses. If it is discovered that LA is falsely elevated due to anticoagulant treatment, this should be noted in the medical record and corrected in the laboratory chart, because the false result may otherwise be perceived as true upon later admission.

APS is usually considered to have a lifelong course. However, examples of aPLs negativisation have been recorded even after being present for > 12 weeks. In a retrospective study of patients with APS who were followed for APS, Ballul et al. reported that aPL disappeared in 21 of 81 patients (25.9%) a median of 6.4 years after APS diagnosis [14]. Kovacs et al. followed 73 patients with aPS for 2-19 years and found that LA and aCL became negative (aB2GPI was not tested) in 36/73 (49.3%) [15]. We found that aPLs became negative in 15/129 (11.6%) APS patients after 0.5-7 years.

Since only a few studies have investigated the disappearance of aPLs, the consequences of late negativisation of aPLs remain unclear [16, 17]. In our study, 12/15 (80%) of the patients continued antithrombotic treatment, of whom 9/15 (60%) were on warfarin. Warfarin is the most commonly recommended form of thrombotic prophylaxis in APS. However, a recent meta-analysis has shown that low-dose aspirin may also be effective for long-term prophylaxis [18].

For years, antithrombotic treatment of patients with obstetric APS without thrombotic events has been recommended only during pregnancy and in the post-partum period. However, a recent study of such patients showed that 24/67 (36%) suffered from thrombotic events during a ten-year follow up even though most of the patients were receiving antithrombotic treatment [19]. The presence of heart valve disease and seropositive antinuclear antibodies (ANA) were related to thrombosis following obstetric APS.

Our study has limitations inherent to a retrospective design. First, the lack of planned clinical follow-up limited the ability to understand the real-world consequences of misclassification. Second, follow-up was very short for some patients. It is therefore possible that patients with aPL negativity would subsequently fluctuate between negative and positive. Third, we were unable to provide a meaningful overview of confounding factors, such as cardiovascular risk factors (smoking, hypertension, diabetes mellitus and dyslipidemia) and hereditary thrombophilia, as decisions to investigate for these factors were highly variable and left to the individual departments. Fourth, this study used data collected before the publication of the ACR/EULAR classification criteria for APS. This was, however, intentional because we wanted to investigate whether unchanged criteria over a long period had led to few cases of misdiagnosis. Future research incorporating these updated criteria will be essential to expand upon our findings.

A strength of our study is that the electronic search was supplemented with a manual review of the medical records. This allowed us to examine in detail whether all clinical and laboratory criteria for APS were present.

Another strength of the study is that we observed most patients over several years, during which we found that a significant proportion of patients with APS had negativisation of aPLs after several months or years.

Finally, since we had no upper age limit, we could show that aPLs as a risk factor for thrombosis in patients ≥ 50 years of age occurs as frequently in men as in women.

Conclusions

Diagnosis of APS is a complicated process because it requires that multiple clinical and laboratory criteria be met. Our study shows that even with an unchanged classification system for over ten years, problems with making a correct diagnosis were frequent. The 2023 ACR/EULAR classification criteria introduce new specific requirements for the diagnosis of APS, which hopefully will lead to a more detailed characterisation of the disease. However, the criteria also present new challenges. As APS is rare and associated with a high risk of both arterial and venous thrombosis and pregnancy complications, this real-world study suggests that the final diagnosis should be made by specialists to reduce the risk that many patients will be misclassified and unnecessarily placed on lifelong antithrombotic treatment. In some patients with APS, aPLs negativisation is seen after several months or years. As aPLs may reappear later, follow-up of patients and caution when discontinuing thromboprophylaxis are recommended.

Correspondence *Jørn Dalsgaard Nielsen*. E-mail: jdn@dadlnet.dk

Accepted 18 May 2026

Published 23 June 2026

Conflicts of interest none. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. These are available together with the article at ugeskriftet.dk/dmj

References can be found with the article at ugeskriftet.dk/dmj

Cite this as Dan Med J 2026;73(7):A11250969

doi 10.61409/A11250969

REFERENCES

1. Arachchillage DRJ, Pericleous C. Evolution of antiphospholipid syndrome. Semin Thromb Hemost. 2023;49(3):295-304. https://doi.org/10.1055/s-0042-1760333
2. Wilson WA, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: report of an international workshop. Arthritis Rheum. 1999;42(7):1309-1311. https://doi.org/10.1002/1529-0131(199907)42:7<1309::AID-ANR1>3.0.CO;2-F
3. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4(2):295-306. https://doi.org/10.1111/j.1538-7836.2006.01753.x
4. Barbhaiya M, Zuily S, Naden R, et al. The 2023 ACR/EULAR antiphospholipid syndrome classification criteria. Arthritis Rheumatol. 2023;75(10):1687-1702. https://doi.org/10.1002/art.42624
5. Duarte-García A, Pham MM, Crowson CS, et al. The epidemiology of antiphospholipid syndrome: a population-based study. Arthritis Rheumatol. 2019;71(9):1545-1552. https://doi.org/10.1002/art.40901
6. Amiral J, Peyrafitte M, Dunois C, et al. Anti-phospholipid syndrome: current opinion on mechanisms involved, laboratory characterization and diagnostic aspects. Transfus Apher Sci. 2017;56(4):612-625. https://doi.org/10.1016/j.transci.2017.07.014
7. Celia AI, Vescovo GM, Sarto G, et al. Direct oral anticoagulants versus vitamin K antagonists in antiphospholipid syndrome: a systematic review and meta-analysis. Semin Arthritis Rheum. 2025;73:152741. https://doi.org/10.1016/j.semarthrit.2025.152741
8. Nielsen JD, Hermann TS, Dimopoulos K, Nørskov AS. Control of warfarin treatment in patients with antiphospholipid syndrome and falsely high INR at point-of-care-testing. Thromb Res. 2025;252:109361. https://doi.org/10.1016/j.thromres.2025.109361

9. Devreese KMJ, Pierangeli SS, de Laat B, et al. Testing for antiphospholipid antibodies with solid phase assays: guidance from the SSC of the ISTH. J Thromb Haemost. 2014;12(5):792-795. https://doi.org/10.1111/jth.12537
10. Grimaud F, Yelnik C, de Chambrun MP, et al. Clinical and immunological features of antiphospholipid syndrome in the elderly: a retrospective national multicentre study. Rheumatology (Oxford). 2019;58(6):1006-1010. https://doi.org/10.1093/rheumatology/key437
11. Albrecht K, Troll W, Callhoff J, et al. Sex- and gender-related differences in systemic lupus erythematosus: a scoping review. Rheumatol Int. 2025;45(7):160. https://doi.org/10.1007/s00296-025-05910-7
12. Dunn AS, Kaboli P, Halfdanarson T, et al. Do patients followed in anticoagulation clinics for antiphospholipid syndrome meet criteria for the disorder? Thromb Haemost. 2005;94(3):548-554. https://doi.org/10.1160/TH04-11-0756
13. Ballif M, Vazquez SR, Saunders J, Witt DM. Prevalence of antiphospholipid antibody syndrome misclassification in an academic health system. Thromb Res. 2023;232:163-167. https://doi.org/10.1016/j.thromres.2022.11.011
14. Ballul T, Mageau A, Nicaise PR, et al. Recurrent thrombotic events after disappearance of antiphospholipid autoantibodies: a long-term longitudinal study in patients with antiphospholipid syndrome. Thromb Res. 2023;224:1-3. https://doi.org/10.1016/j.thromres.2023.02.005
15. Kovacs MR, Lazo-Langner A, Kovacs MJ. Long term monitoring of patients with positive lupus anticoagulant and antiphospholipid antibodies. Are all cases persistently positive? Thromb Res. 2020;194:119-120. https://doi.org/10.1016/j.thromres.2020.06.031
16. Chighizola CB, Willis R, Maioli G, et al. Deciphering the clinical significance of longitudinal antiphospholipid antibody titers. Autoimmun Rev. 2024;23(3):103510. https://doi.org/10.1016/j.autrev.2023.103510
17. Cuadrado MJ, Tincani A, Merayo EE, et al. Can anticoagulation be withdrawn in APS patients after aPL negativization? Autoimmun Rev. 2024;23(1):103427. https://doi.org/10.1016/j.autrev.2023.103427
18. De Pascali F, Filippova YA, Donadini MP, et al. Efficacy and safety of low-dose acetylsalicylic acid for the prevention of thromboembolic events in individuals positive for antiphospholipid antibodies: a systematic review and meta-analysis. Thromb Res. 2025;245:109225. https://doi.org/10.1016/j.thromres.2024.109225
19. Niznik S, Rapoport MJ, Avnery O, et al. Long term follow up of patients with primary obstetric antiphospholipid syndrome. Front Pharmacol. 2022;13:824775. https://doi.org/10.3389/fphar.2022.824775

