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Laboratory and Clinical Correlates of Lupus Anticoagulant Positivity in an Albanian Cohort

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Abstract

Background: Antiphospholipid syndrome (APS) is an autoimmune disease in which immune-mediated mechanisms promote a chronic prothrombotic state, leading to an increased risk for thrombotic events and obstetric complications. Particularly during their reproductive ages, females are disproportionately affected, making APS a major clinical concern in female populations. Lupus anticoagulant (LAC) is recognized as the strongest laboratory predictor for thrombosis and adverse pregnancy outcomes, among antiphospholipid antibodies. However, the clinical and laboratory correlates of LAC in women, including thrombosis, homocysteine metabolism, genetic thrombophilia, and reproductive complications, remain poorly understood.
Methods and Results: This observational study included 522 individuals with a thrombotic event or pregnancy morbidity, suspected of having APS. They were tested for LAC, homocysteine (HCY), and antiphospholipid antibodies. Subsequent analyses were conducted exclusively among female participants to provide a more clinically meaningful and statistically reliable evaluation. Association between LAC levels and APS classification, thrombotic events, homocysteine levels, the *MTHFR* gene mutations (C677T and A1298C), and other conditions of pregnancy losses were evaluated using chi-square tests, Welch two-sample t-test, and Pearson correlation as appropriate. Statistical analyses were performed using R software.
Among female participants (n=452), LAC positivity was observed in 35.2%, elevated homocysteine levels in 18.8%, and APS in 11.3%. Lupus anticoagulant levels were highly significant in participants with thrombotic events and APS classified. No significant linear correlation was observed between LAC and homocysteine levels. In contrast, significant differences in LAC levels were observed according to the *MTHFR* mutation status and history of other pregnancy losses.
Conclusion: This study highlights the central role of lupus anticoagulant as a key laboratory marker associated with thrombotic events and APS-related manifestations in women. The lack of association with homocysteine further supports the concept of independent pathogenic pathways. These findings underscore the importance of LAC assessment in the clinical evaluation and risk stratification of patients with suspected antiphospholipid syndrome.(**International Journal of Biomedicine. 2026;16(2):223-226.**)

Keywords: antiphospholipid syndrome • lupus anticoagulant • homocysteine • *MTHFR* gene

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Abbreviations

APS, antiphospholipid syndrome; **aCL**, anticardiolipin; **ß2-GPI**, ß2-glycoprotein I; **HCY**, homocysteine; **LAC**, lupus anticoagulant; **MTHFR**, methylenetetrahydrofolate reductase.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease in which immune-mediated mechanisms promote a chronic prothrombotic state, leading to an increased risk for thrombotic events and obstetric complications.[1] Antiphospholipid syndrome represents one of the leading causes of arterial and venous thrombosis, as well known for its contribution to pregnancy morbidity, including recurrent pregnancy loss, placental insufficiency, and preeclampsia.

The diagnosis and risk stratification rely on the detection of antiphospholipid antibodies, including lupus anticoagulant (LAC), anti-cardiolipin (aCL), and anti-ß2-glycoprotein I (anti-ß2GPI), in combination with clinical criteria.[2] Among antiphospholipid antibodies, LAC has been shown to be the strongest laboratory predictor of thrombotic events and pregnancy morbidity.[3] Despite LAC being established as a criterion for APS diagnosis, its contribution to the broader clinical and laboratory spectrum of APS remains poorly understood. Elevated levels of homocysteine represent an independent risk factor for endothelial dysfunction and thrombosis and have been associated with adverse pregnancy outcomes. Similarly, the *MTHFR* gene mutations may alter homocysteine levels, contributing to thrombotic manifestations and pregnancy complications.[4]

However, data that integrates LAC levels with homocysteine metabolism, genetic thrombophilia, thrombotic manifestations, and pregnancy morbidity in female cohorts remains limited. Given the clinical impact of APS in women and the central role of LAC in APS-pathology, a focused evaluation of LAC-associated clinical and laboratory features in female populations is warranted.

The aim of the present study was to investigate the laboratory and clinical correlates of lupus anticoagulant in a female cohort evaluated for APS, with emphasis on thrombotic events, homocysteine levels, *MTHFR* mutations, other causes of pregnancy loss, and antiphospholipid antibodies (aCL, anti-β2GPI).

Materials and Methods

This retrospective, observational study was based on data obtained from Intermedica Laboratory in Tirana, Albania, collected between 2017 and 2025. All laboratory tests included in the analyses were performed during routine clinical care and are requested by treating clinicians. All data are analyzed in anonymized form, with no access to identify personal information. In this study, a total of 522 individuals/patients were initially included with a thrombotic event or pregnancy morbidity. Demographic characteristics, including age and sex, were recorded. Age was analyzed as a continuous variable. Because of the clinical relevance of APS in females and unequal gender distribution, analyses were restricted only to females (n = 452). All female participants were classified according to clinical history and laboratory data. They were stratified into four clinical groups: females with thrombotic events, females with pregnancy losses associated with *MTHFR* positivity, females with pregnancy losses related to APS, and females with pregnancy losses for other conditions. Thrombotic events were recorded as a binary variable (presence/absence) based on clinical history. Detailed classification into venous or arterial thrombosis was not available. The *MTHFR* mutation status was assessed as part of routine thrombophilia screening and was analyzed as a dichotomous variable (positive/negative), without distinction between polymorphism type (C677T or A1298C) or zygosity. APS status in this study reflects antiphospholipid antibody positivity rather than a confirmed APS diagnosis based on repeat testing after 12 weeks. Lupus anticoagulant was measured using the dilute Russell's viper venom time (dRVVT) assay, according to standard laboratory procedures, and expressed as ratio values. Positivity was defined according to laboratory-specific cut-off values. Anticardiolipin antibodies and anti-β2GPI (IgM/IgG) were measured using a standardized enzyme-linked immunosorbent assay (ELISA). Homocysteine levels were determined using a standardized chemiluminescent immunoassay (CLIA).

For comparative analyses, participants were grouped according to a binary classification (negative vs. positive) for each variable of interest. Statistical analyses were performed using Pearson's chi-square test for categorical variables and the Welch two-sample t-test for continuous variables. Pearson correlation analysis was applied to assess linear relationships between continuous variables. All analyses were conducted using R software (version 4.5.1).

Results

A total of 522 participants were included in the analysis (86.6% female, 13.4% male). The mean age of the study population was 36.45±11.45 years. Among female participants, the mean age was 36.15±10.73 years, ranging from 3 to 74 years. A small number of pediatric cases were included, as testing for thrombophilia and antiphospholipid antibodies was performed as part of routine clinical evaluation.

The overall prevalence of LAC, HCY, and APS positivity was 37.4%, 19.2%, and 10.7 %, respectively. LAC values showed a wide distribution within the study population (up to 111.1 dRVVT ratio), with significantly higher mean values observed among participants with thrombotic events and those classified as APS-positive. A statistically significant association was observed between gender and LAC status (P=0.0089). LAC positivity was more frequent in males than females (51.4% vs 35.2%). Male participants had nearly twofold higher odds of LAC positivity compared with females (OR=1.96, 95% CI: 1.18-3.25) (Table 1). In contrast, no statistically significant association was found between gender and HCY status (P=0.62). The prevalence of HCY positivity was comparable between males and females (21.4% vs. 18.8%). Similarly, gender was not significantly associated with APS status (P=0.30). APS positivity was observed in 11.3% of females and 7.1 % of males.

Table 1.

Overall prevalence of LAC, HCY, and APS.

Variable	Gender	Negative n (%)	Positive (%)	*P*-value	*OR (95% CI)
LAC	Female (n=452)	293 (64.8)	159 (35.2)	0.0089	1.96 (1.18-3.25)
	Male (n=70)	34 (48.6)	36 (51.4)		
HCY	Female (n=452)	367 (81.2)	85 (18.8)	0.62	1.18 (0.63-2.22)
	Male (n=70)	55 (78.6)	15 (21.4)		
APS	Female (n=452)	401(88.7)	51 (11.3)	0.30	0.77 (0.29-2.02)
	Male (n=70)	65 (92.9)	5 (7.1)		

**ORs represent the odds of positivity in males compared with females (reference category: female)*

Table 2.

Comparison of LAC levels according to clinical and laboratory characteristics in female participants (n = 452).

Variable	Negative (Mean LAC)	Positive (Mean LAC)	t (df)	*P*-value	95% CI
Thrombosis	41.11	48.92	−6.31 (99.01)	<0.001	−10.26 to −5.35
APS status	40.85	46.85	−6.93 (186.36)	<0.001	−7.71 to −4.29
MTHFR mutation	43.04	40.32	2.71 (81.41)	0.008	0.72 to 4.72
Other pregnancy losses	43.52	41.19	3.55 (444.93)	<0.001	1.04 to 3.62
aCL IgM	42.92	49.59	−1.46 (14.16)	0.166	–
aCL IgG	42.92	62.56	−1.46 (4.00)	0.219	–
Anti-β2GPI IgM	42.96	44.60	−0.85 (49.06)	0.400	–
Anti-β2GPI IgG	43.04	61.15	−1.70 (1.00)	0.338	–

Pearson correlation analysis showed no significant linear association between LAC and HCY levels (r = 0.05, *P* = 0.25). No significant correlation was observed between LAC and antiphospholipid antibodies aCL and anti-β2GPI (IgM/IgG). Given the predominance of female participants in the cohort (86.6%) and the clinical relevance of thrombotic and obstetric manifestations in women, subsequent analyses were restricted to female patients. Comparisons of LAC levels according to clinical and laboratory variables are presented in Table 2. LAC levels were higher in women who were *MTHFR* negative and in those without abortions attributable to other causes, whereas APS-positive individuals demonstrated significantly elevated LAC values. This pattern suggests a potential independent role of LAC in thrombosis and pregnancy morbidity.

Discussion

In this retrospective cross-sectional study of 522 participants, we investigated the prevalence and laboratory – clinical associations of lupus anticoagulant within an Albanian cohort, with particular emphasis on female patients. Our findings demonstrate that LAC levels are associated with thrombotic events and APS classification, while no meaningful correlation was observed with homocysteine levels. A key finding of this study is the strong association between elevated LAC levels and thrombotic events. Women with thrombosis had significantly higher mean LAC values than those without thrombosis. This observation is consistent with previous studies that have identified LAC as the strongest laboratory predictor of thrombotic risk among antiphospholipid antibodies.[2,5] Clinical and experimental evidence suggests that LAC contributes to thrombosis through endothelial activation, interference with anticoagulant pathways, and complement -mediated mechanisms.[6,7] The association observed in our cohort reinforces the clinical importance of LAC in risk stratification. Similarly, LAC levels were significantly higher in participants classified as APS- positive. This finding aligns with the established role of LAC as a laboratory criterion for APS classification. However, the magnitude of difference observed in our study suggests that LAC may reflect not only diagnostic classification but also disease activity or thrombotic burden. Importantly, APS classification in this study reflects antiphospholipid antibody positivity rather than a confirmed APS diagnosis based on repeat testing after 12 weeks, as required by classification criteria.[8] In contrast, no significant linear correlation was identified between LAC and homocysteine levels. This suggests that these factors may contribute to thrombosis through distinct and potentially independent mechanisms. Hyperhomocysteinemia is recognized as a risk factor for endothelial dysfunction and thrombosis;[9] its lack of association with LAC in our cohort indicates that it does not directly modulate the autoimmune prothrombotic state driven by antiphospholipid antibodies. This supports the concept of parallel rather than overlapping pathogenic pathways. Interestingly, LAC levels differed significantly by *MTHFR* status and a history of pregnancy losses attributed to other causes. Higher LAC levels were observed in *MTHFR*- negative individuals and in women without pregnancy losses due to other etiologies. These findings may suggest that LAC-related pathology represents a distinct autoimmune mechanism rather than a secondary effect of inherited thrombophilia. However, these observations should be interpreted cautiously, as the role of *MTHFR* polymorphisms in thrombosis and pregnancy complications remains controversial.[10,11] No statistically significant differences in LAC levels were observed according to aCL and β2GPI antibody status. This may reflect limited subgroup sizes or the known heterogeneity of antiphospholipid antibody profiles. It is well established that LAC, aCL, and anti-β2GPI antibodies may not always coexist and may exhibit different clinical associations.[12] Among these, LAC is considered the most strongly associated with thrombotic events, supporting its role as a functionally relevant marker of thrombogenic potential.[3] Notably, LAC positivity was more frequent in males compared to females, despite the predominance of females in the cohort. Although APS is more commonly reported in women, particularly with obstetric manifestations, this finding may reflect differences in referral patterns or underlying risk profiles within the studied population.

Taken together, these findings support the hypothesis that LAC may act as a primary autoimmune driver of

thrombosis and pregnancy morbidity, rather than merely reflecting secondary interactions with other risk factors such as homocysteine metabolism or inherited thrombophilia.

This study has several strengths, including a relatively large sample size, the use of both continuous and categorical analyses, and the focused evaluation of a clinically relevant female cohort. The integration of laboratory markers with clinical outcomes provides a comprehensive assessment of LAC-associated risk profiles.

Several limitations should be acknowledged. First, the APS classification in this study was based on single-time antibody positivity and did not include confirmatory testing after 12 weeks, as required by the classification criteria. Secondly, a retrospective design may lead to selection bias and limit causal inference. Third, thrombotic events were recorded as a binary variable without detailed classification into arterial and venous subtypes. Finally, subgroup analyses for certain variables were limited by small sample sizes.

In conclusion, this study highlights the central role of lupus anticoagulant as a key laboratory marker associated with thrombotic events and APS-related manifestations in women. The lack of association with homocysteine further supports the concept of independent pathogenic pathways. These findings underscore the importance of LAC assessment in the clinical evaluation and risk stratification of patients with suspected antiphospholipid syndrome.

Ethical Considerations

This retrospective observational study was conducted in accordance with the ethical principles of the World Medical Association Declaration of Helsinki (1964, revised 2013). All study data were fully anonymized prior to access and analysis, and no identifiable personal information was available to the researchers at any stage of the study. Given the retrospective design and the use of fully anonymized data, formal ethical approval and individual informed consent were not required, in accordance with applicable institutional policies and standard research practices. Institutional permission to use data was obtained from Intermedica Laboratory. An official institutional statement confirming these conditions has been provided with the manuscript submission.

Author Contributions

Ina Toska: Conceptualization, Investigation, Data curation, Writing – original draft.
Ervin Rapushi: Conceptualization, Investigation, Methodology, Writing – review and editing.
Anila Mitre: Investigation, data curation, Writing – review and editing.
Ervin Toci: Data curation, Formal analysis, Writing – original draft.
Rexhep Shkurti: Supervision, Conceptualization, Writing – review and editing.
All authors have approved the final article.

Conflict of Interest

The authors have declared no conflict of interest.

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