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Antiphospholipid Antibodies in Patients Hospitalized With Acute Coronary Syndrome at a Cardiovascular Center in Puerto Rico

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Abstract

Background: Antiphospholipid (aPL) antibodies have been associated with coronary artery disease, but their prevalence and clinical significance in acute coronary syndromes (ACS) vary across ethnic populations and remain understudied.

Objective: This study aims to evaluate the frequency of single-time-point aPL positivity and its clinical associations in hospitalized patients with ACS in Puerto Rico.

Methodology: A retrospective cross-sectional study of adults admitted with ACS to a tertiary cardiovascular center in Puerto Rico was conducted. ACS was defined as the presence of myocardial infarction or unstable angina. aPL testing included lupus anticoagulant (LA) and anticardiolipin (aCL) and anti-β2-glycoprotein I (anti-β2GPI) antibodies. Demographic characteristics, comorbidities, and in-hospital outcomes were compared between patients with positive and negative aPL testing using univariable and multivariable analyses.

Results: Among 100 patients with ACS (mean age: 65.3 years; 55.0% male), 31% had at least one positive aPL test. LA was the most common positive test (26.0%), whereas aCL and anti-β2GPI antibodies were infrequent (≤3.0% for any isotype). Although aPL positivity was associated with longer hospitalization and more infections in univariable analyses, these associations were not retained after adjustment for age and sex. No differences were found in demographics, lifestyle behaviors, cardiovascular risk factors, comorbidities, or mortality.

Conclusions: In this group of patients with ACS, aPL positivity was common, occurring in nearly one-third of patients, with LA accounting for the majority of positive results. The prevalence of aPL positivity in this ACS cohort exceeds that reported in prior studies and supports the need for confirmatory testing at ⩾12 weeks to distinguish persistent from transient positivity and to further elucidate its prognostic significance.

Categories: Cardiology, Rheumatology
Keywords: acute coronary syndrome, antiphospholipid antibodies, myocardial infarction, puerto rico, unstable angina

Introduction

Antiphospholipid syndrome (APS) is an autoimmune hypercoagulable disorder characterized by venous and arterial thrombosis in the presence of antiphospholipid antibodies (aPL), including lupus anticoagulant (LA) test, and anticardiolipin (aCL) and anti-β2-glycoprotein I (anti-β2GPI) antibodies [1-2]. Venous thrombosis, most commonly involving the lower extremities, occurs more frequently than arterial thrombosis; however, arterial events are often associated with greater morbidity and mortality [1]. Among arterial manifestations, ischemic stroke and transient ischemic attack are the most common, while coronary artery thrombosis, though less frequent, represents a clinically significant subset [3].

Myocardial infarction (MI) may be an early manifestation of APS, particularly in younger individuals, and can occur with either nonobstructive (MINOCA) or obstructive coronary artery disease (MICAD) [4]. A case-control study found higher aPL IgG antibody levels in patients with both MINOCA and MICAD than in healthy controls [5]. Previous studies have reported aPL positivity in approximately 11% of patients with MI and up to 23% of younger patients (<55 years) with acute coronary syndromes (ACS) [6-7]. However, prevalence estimates have varied across studies because of differences in patient populations and testing strategies [1]. Despite the recognized association between APS and coronary artery thrombosis, patients presenting with ACS are not routinely screened for aPL. Moreover, data regarding the prevalence, patterns, and clinical significance of aPL positivity in ACS populations remain limited. Therefore, we sought to determine the prevalence and patterns of aPL positivity and to evaluate their clinical correlates among

patients admitted with ACS to a tertiary cardiovascular referral center in Puerto Rico. This study aimed to estimate the background frequency of aPL seropositivity based on single-time-point and acute-phase testing in a consecutive, real-world group of patients with ACS and to characterize the clinical phenotype of seropositive patients. However, it was not designed to determine the prevalence of APS, which requires persistent aPL positivity on two occasions at least 12 weeks apart to distinguish persistent antibodies from transient or false-positive results [1].

Materials And Methods

Study design and population

We conducted a retrospective cross-sectional study of adults admitted with ACS to the Cardiovascular Center of Puerto Rico and the Caribbean from November 2024 to November 2025. ACS encompassed three major clinical entities: ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina. The 2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients with Acute Coronary Syndromes was used to define each ACS category [8]. During the study period, consecutive ACS patients admitted to the Cardiology Division of the University of Puerto Rico on Mondays were tested for aPL. Blood samples were collected at the beginning of the week to ensure adequate sample processing, handling, and timely shipment to the reference laboratory. Testing was not ordered based on clinical suspicion of autoimmune or thrombophilic pathology. The study was approved by the Institutional Review Board of the University of Puerto Rico Medical Sciences Campus (protocol number: 2290034526). Written informed consent was waived because the study involved no more than minimal risk to participants and no procedures for which written consent would normally be required. All information collected was obtained during hospitalization as part of clinical care for patients with ACS.

Antiphospholipid antibody testing

The aPL panel included LA testing and aCL and anti-β2GPI antibodies (IgG, IgM, and IgA isotypes). LA was assessed using the dilute Russell viper venom time (dRVVT) and the hexagonal phase II phospholipid neutralization assay. Blood samples for aPL testing were collected in tubes containing 3.2% sodium citrate. Samples were centrifuged at 1,500 × g for 15 minutes within 60 minutes of collection. Plasma was carefully removed without disturbing the leukocyte/platelet buffy coat and transferred to a plastic vial. Plasma was then centrifuged a second time and transferred to a new plastic vial to obtain platelet-poor plasma, with a target residual platelet count of less than 10,000/μL. Plasma samples were immediately frozen and shipped to the reference laboratory for analysis. aCL and anti-β2GPI antibodies were measured using immunoassays. Positivity for either antibody was defined as a titer of >20 units, whereas high-titer positivity was defined as ⩾65 units. LA positivity by dRVVT was defined as a dRVVT screen-to-confirm ratio (dRVVT with phospholipid confirmation) of >1.2. For the hexagonal phase II phospholipid neutralization assay, the activated partial thromboplastin time (aPTT) was measured in plasma aliquots incubated with and without added phospholipid; a difference of >8 seconds between the two measurements was considered diagnostic of LA. A positive aPL result was defined as at least one positive finding among all aPL assays performed during the index hospitalization. Cutoff values for aPL positivity were established according to International Society on Thrombosis and Haemostasis (ISTH) guidelines [9-10]. All assays were conducted at the same reference laboratory, Quest Diagnostics of Puerto Rico, Inc., to ensure consistency in testing procedures and interpretation of results. Blood samples were collected during the index hospitalization and, in most cases, after enoxaparin had been initiated. Given the potential effects of anticoagulant therapy and acute-phase conditions on coagulation-based assays, LA results were interpreted in the clinical context [9,10].

Data collection

The following variables were collected: demographic characteristics (age and sex); lifestyle behaviors (tobacco, cannabis, alcohol, and cocaine use); pre-existing comorbidities (severe obstructive coronary artery disease, heart failure with reduced ejection fraction, atrial fibrillation, type 2 diabetes mellitus, arterial hypertension, dyslipidemia, cerebrovascular accident, ischemic stroke, transient ischemic attack, deep vein thrombosis, pulmonary embolism, chronic obstructive pulmonary disease, chronic kidney disease, systemic lupus erythematosus, fibromyalgia, gout, osteoarthritis, hyperuricemia, hypothyroidism, malignancy, and major depressive disorder); and clinical characteristics during hospitalization, including COVID-19, obstructive coronary artery disease on coronary angiography, and anticoagulation use. In-hospital outcomes included complications, categorized as cardiovascular, renal, metabolic, infectious, neurologic, respiratory, gastrointestinal, noncardiac thrombotic, or hemorrhagic; length of hospital stay; and in-hospital mortality. Severe coronary artery stenosis was defined as ⩾70% diameter stenosis in a non-left main epicardial coronary artery or ⩾50% stenosis in the left main coronary artery, based on visual angiographic assessment. In the database, three-vessel disease and left main coronary artery disease were grouped into a single category.

Statistical analysis

Patients were compared according to aPL positivity status. Continuous variables are presented as mean (standard deviation (SD)) and were compared using the Student's *t* test or Mann-Whitney U test, as appropriate. Categorical variables are presented as frequencies (percentages) and were compared using the

Chi-square test or Fisher's exact test, as appropriate.

An exploratory multivariable binary logistic regression model was used to examine associations between aPL positivity and selected clinical characteristics. The dependent variable was aPL positivity (yes = 1; no = 0). Infectious complications (yes/no) and length of hospitalization (continuous, in days) were included as independent variables based on univariable associations, while age and sex were retained as clinically relevant adjustment variables regardless of statistical significance. All predictors were entered simultaneously. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Multicollinearity was assessed using variance inflation factors (VIFs). The regression analysis was considered exploratory.

Variables that were significant in univariable analyses were entered into a logistic regression model adjusted for age and sex. Statistical significance was defined as p-value < 0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 31 (Released 2025; IBM Corp., Armonk, New York, United States).

Results

A total of 100 patients admitted with ACS were included in the study. The mean (SD) age was 65.3 (14.7) years, and 55% were male. The distribution of ACS categories was as follows: 29% STEMI, 50% NSTEMI, and 21% unstable angina. Eighty-seven patients received anticoagulation (85 with enoxaparin and two with intravenous heparin). In all patients who received anticoagulation, treatment was initiated before aPL sample collection, but the exact interval between the last anticoagulant dose and sample collection was not documented.

Complete aPL serologic testing, including LA, aCL, and anti-β2GPI antibodies, was performed in all patients. At least one aPL test was positive in 31% of patients (Table *1*). LA was the most frequently positive aPL test, identified in 26% of patients. In contrast, aCL and anti-β2GPI antibodies were uncommon, with positivity rates of ⩽3% for any isotype. High-titer aCL and anti-β2GPI antibodies were rare (⩽1% for each reported isotype), and no patient exhibited triple aPL positivity.

aPL test	n (%)
aPL testing (presence of at least one)	31 (31.0)
Lupus anticoagulant	26 (26.0)
Anticardiolipin IgM	
Any titer	3 (3.0)
High titer	1 (1.0)
Anticardiolipin IgG	
Any titer	1 (1.0)
High titer	1 (1.0)
Anticardiolipin IgA	
Any titer	3 (3.0)
High titer	1 (1.0)
Anti-β2-glycoprotein I antibody IgM	
Any titer	1 (1.0)
High titer	1 (1.0)
Anti- β2-glycoprotein I antibody IgG	
Any titer	0 (0.0)
High titer	0 (0.0)
Anti- β2-glycoprotein I antibody IgA	
Any titer	1 (1.0)
High titer	1 (1.0)

TABLE 1: Prevalence and patterns of aPL antibody positivity among patients hospitalized with acute coronary syndromes (n = 100)

aPL: antiphospholipid

The demographic and clinical characteristics of the study population are presented in Table 2. The most prevalent comorbidities were arterial hypertension (82%), dyslipidemia (56%), type 2 diabetes mellitus (54%), heart failure with reduced ejection fraction (46%), and chronic kidney disease (38%). Current smoking was reported by 31% of patients. Systemic lupus erythematosus was present in only 2% of patients, and neither of these individuals had positive aPL testing. During hospitalization, 87% of patients received therapeutic anticoagulation. Obstructive coronary artery disease, defined as >70% luminal stenosis in at least one epicardial coronary artery, was identified in 93.8% of patients. Three-vessel involvement was the most common pattern (60.5%), followed by one-vessel (19.7%) and two-vessel disease (13.6%). Nonobstructive coronary artery disease was observed in 6.2% of patients. Overall, in-hospital complications occurred in 57% of patients, most commonly cardiovascular (27%), renal (17%), and infectious (12%) complications. The mean (SD) length of hospitalization stay was 8.9 (8.6) days, and the in-hospital mortality rate was 3%.

Characteristics	All patients (n = 100)	aPL positive (n = 31)	aPL negative (n = 69)	p-value	Statistical test
Age, mean (SD)	65.3 (14.7)	66.4 (15.0)	64.8 (14.7)	0.604	t(98) = -0.521; Cohen's d = -0.113
Male sex, n (%)	55 (55.0)	20 (64.5)	35 (50.7)	0.200	$\chi^2(1) = 1.644$; φ = 0.128
Current lifestyle behaviors, n (%)					

Tobacco use	31 (31.0)	6 (19.4)	25 (36.2)	0.091	$\chi^2(1) = 2.848$; $\varphi = 0.169$
Cannabis use	7 (7.0)	1 (3.2)	6 (8.7)	0.431	FET
Alcohol use	24 (24.0)	5 (16.1)	19 (27.5)	0.217	$\chi^2(1) = 1.526$; $\varphi = 0.124$
Cocaine use	3 (3.0)	0 (0.0)	3 (4.3)	0.550	FET
Pre-existing comorbidities, n (%)					
Severe obstructive coronary artery disease	18 (18.0)	6 (19.4)	12 (17.4)	0.813	$\chi^2(1) = 0.056$; $\varphi = 0.024$
Heart failure with reduced ejection fraction	46 (46.0)	17 (54.8)	29 (42.0)	0.235	$\chi^2(1) = 1.413$; $\varphi = 0.119$
Atrial fibrillation	13 (13.0)	6 (19.4)	7 (10.1)	0.205	$\chi^2(1) = 1.604$; $\varphi = 0.127$
Type II diabetes mellitus	54 (54.0)	16 (51.6)	38 (55.1)	0.748	$\chi^2(1) = 0.103$; $\varphi = 0.032$
Arterial hypertension	82 (82.0)	26 (83.9)	56 (81.2)	0.744	$\chi^2(1) = 0.107$; $\varphi = 0.033$
Dyslipidemia	56 (56.0)	20 (64.5)	36 (52.2)	0.250	$\chi^2(1) = 1.322$; $\varphi = 0.115$
Cerebrovascular accident	8 (8.0)	2 (6.5)	6 (8.7)	>0.999	FET
Ischemic stroke	7 (7.0)	1 (3.2)	6 (8.7)	0.431	FET
Transient ischemic attack	3 (3.0)	1 (3.2)	2 (2.9)	>0.999	FET
Deep venous thrombosis	1 (1.0)	1 (3.2)	0 (0.0)	0.310	FET
Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Chronic obstructive pulmonary disease	6 (6.0)	4 (12.9)	2 (2.9)	0.072	FET
Chronic kidney disease	38 (38.0)	16 (51.6)	22 (31.9)	0.060	$\chi^2(1) = 3.534$; $\varphi = 0.188$
Systemic lupus erythematosus	2 (2.0)	0 (0.0)	2 (2.9)	>0.999	FET
Fibromyalgia	2 (2.0)	1 (3.2)	1 (1.4)	0.526	FET
Gout	2 (2.0)	1 (3.2)	1 (1.4)	0.526	FET
Osteoarthritis	8 (8.0)	2 (6.5)	6 (8.7)	>0.999	FET
Hyperuricemia	30 (30.0)	13 (41.9)	17 (24.6)	0.174	$\chi^2(1) = 1.851$; $\varphi = 0.136$
Hypothyroidism	24 (24.0)	4 (12.9)	20 (29.0)	0.082	$\chi^2(1) = 3.033$; $\varphi = 0.174$
Malignancy (any)	11 (11.0)	2 (6.5)	9 (13.0)	0.495	FET
Major depressive disorder	8 (8.0)	2 (6.5)	6 (8.7)	>0.999	FET
Clinical features during hospitalization, n (%)					
Current COVID-19	2 (2.0)	0 (0.0)	2 (2.9)	>0.999	FET
Coronary angiography, n/N (%)					
Nonobstructive	5/81 (6.2)	0 (0.0)	5/54 (9.2)	0.317	FET
1-vessel disease	16/81 (19.7)	5/27 (18.5)	11/54 (20.4)	>0.999	FET
2-vessel disease	11/81 (13.6)	4/27 (14.8)	7/54 (13.0)	0.726	FET
3-vessel disease	49/81 (60.5)	18/27 (66.7)	31/54 (57.4)	0.109	$\chi^2(1) = 2.567$; $\varphi = 0.164$
Use of anticoagulation during hospitalization	87 (87.0)	28 (90.3)	59 (85.5)	0.749	FET
Complications during hospitalization, n (%)	57 (57.0)	21 (67.7)	36 (52.2)	0.146	$\chi^2(1) = 2.115$; $\varphi = 0.145$
Cardiovascular	27 (27.0)	10 (32.3)	17 (24.6)	0.427	$\chi^2(1) = 0.630$; $\varphi = 0.079$

Renal	17 (17.0)	6 (19.4)	11 (15.9)	0.674	$\chi^2(1) = 0.177$; $\varphi = 0.042$
Metabolic	4 (4.0)	1 (3.2)	3 (4.3)	>0.999	FET
Infectious	12 (12.0)	7 (22.6)	5 (7.2)	0.044	FET
Respiratory	3 (3.0)	2 (6.5)	1 (1.4)	0.226	FET
Thromboembolism	2 (2.0)	1 (3.2)	1 (1.4)	0.557	FET
Gastrointestinal	2 (2.0)	0 (0.0)	2 (2.9)	>0.999	FET
Liver	1 (1.0)	0 (0.0)	1 (1.4)	>0.999	FET
Hemorrhagic	4 (4.0)	2 (6.5)	2 (2.9)	0.586	FET
Length of hospitalization stay, mean (SD) days	8.9 (8.6)	12.0 (11.9)	7.5 (6.2)	0.011	MWU = 1410.5; r = 0.255
Mortality, n (%)	3 (3.0)	1 (3.2)	2 (2.9)	>0.999	FET

TABLE 2: Comparison of demographic and clinical characteristics according to aPL antibody status in patients hospitalized with acute coronary syndromes (n = 100)

aPL: antiphospholipid; SD: standard deviation; t: Student's t-test; Cohen's d: standardized mean difference; χ^2: Chi-square test; φ: Phi coefficient; FET: Fisher's exact test; MWU: Mann-Whitney U; r: rank-based effect size for the Mann-Whitney U test

Comparison of demographic and clinical characteristics according to aPL status in patients hospitalized with ACS is shown in Table 2. Patients with positive aPL antibody testing had a significantly longer hospital stay compared with aPL-negative patients (median: 7 vs. 5 days, respectively; Mann-Whitney U = 1410.5; p = 0.011). The Hodges-Lehmann estimated difference was 2.0 days (95% CI: 1.0-4.0). Additionally, infectious complications were more frequent among aPL-positive patients (22.6% vs. 7.2%; Fisher's exact test; p = 0.044), with an unadjusted odds ratio of 3.73 (95% CI: 1.08-12.90). In contrast, demographic characteristics, lifestyle behaviors, comorbidities (including cardiovascular risk factors), prior history of thrombosis, coronary anatomy, and other in-hospital complications did not differ significantly between groups.

In the exploratory multivariable logistic regression analysis adjusted for age and sex, neither infectious complications (adjusted OR: 1.97; 95% CI: 0.35-11.02; p = 0.440) nor length of hospitalization (adjusted OR: 1.06 per additional day; 95% CI: 0.98-1.14; p = 0.134) was significantly associated with aPL positivity. Collinearity diagnostics demonstrated VIFs ranging from 1.039 to 1.804, without evidence of severe multicollinearity (Table 3).

Characteristic	OR (95% CI)	p-value	Statistical test
Infectious complication	1.97 (0.35-11.02)	0.440	Multivariable binary logistic regression; Wald $\chi^2(1) = 0.596$
Length of hospitalization	1.06 (0.98-1.14)	0.134	Multivariable binary logistic regression; Wald $\chi^2(1) = 2.244$

TABLE 3: Exploratory multivariable binary logistic regression analysis of associations between antiphospholipid antibody positivity and in-hospital clinical characteristics.

OR: odds ratio; CI: confidence interval; Wald χ^2: Wald chi-square statistic

The dependent variable was aPL positivity (aPL-negative = 0; aPL-positive = 1). The reference group was patients without aPL positivity (aPL-negative). The multivariable binary logistic regression model included infectious complications and length of hospitalization, adjusted for age and sex. Length of hospitalization was modeled as a continuous variable (per additional day). Variables with $p < 0.05$ in univariable analyses were included in the model. This analysis was exploratory and was intended to evaluate statistical associations rather than establish causal or predictive relationships

Discussion

In this retrospective study of hospitalized patients with ACS, nearly one-third had positive aPL testing. Positivity was predominantly driven by LA, whereas aCL and anti-β2GPI antibodies detected by immunoassay were uncommon. High-titer antibodies were rare, and no cases of triple positivity were observed, suggesting that the overall signal was largely driven by clot-based LA assays rather than a high-burden immunoassay-defined aPL profile.

The overall frequency of aPL positivity in this study exceeds the approximately 11% reported in pooled estimates of patients with MI, a difference likely attributable to the inclusion of LA testing, the broader ACS case definition, and the inpatient testing context [7]. Our results differ from prior studies because study populations, timing of sampling, and the components of aPL testing were not the same. Chezel et al. studied 37 French adults younger than 40 years with acute MI and focused on identifying APS (13.5%) in a high pre-test probability setting, which differs from our hospitalized ACS population (older, broader case definition) and from our objective of describing inpatient aPL test results rather than confirming APS [11]. Greco et al. reported a US hospital series of 232 patients evaluated for coronary artery disease/ACS and found that 37% had at least one positive aPL-related test. However, their immunoassay-based panel included additional antibody specificities, such as antiphosphatidylserine, antiprothrombin, and anti-oxidized LDL/β2-glycoprotein I antibodies, while LA testing was not performed [12]. This difference in antibody profiling limits direct comparison with studies employing a conventional APS laboratory assessment that includes LA testing. In Scandinavia, Svenungsson et al. enrolled 98 patients with MINOCA, 99 with myocardial infarction due to obstructive coronary disease, and 100 controls, measuring aCL and anti-β2GPI antibodies using a multiplex platform [6]. They found higher frequencies of IgG antibody tests in MI groups than in controls, but LA testing was not performed, and sampling occurred later after the event, which differs from inpatient testing. Bayartaikishigtai et al. analyzed 777 Chinese patients with acute MI and included LA testing plus aCL and anti-β2GPI IgG/IgM antibody tests [4]. They reported a lower overall frequency of positive aPL testing than in our hospitalized ACS patients, and they assessed outcomes after discharge over a mean follow-up of 18.8 months, which differs from an in-hospital cross-sectional assessment. More recently, Villalobos-Sánchez et al. prospectively studied 52 ACS patients under 55 years of age in Spain and found aPL positivity in 23%, with only three patients meeting the Sydney criteria for APS and none meeting the 2023 ACR/EULAR criteria [8]. This further illustrates that transient or single-time-point aPL positivity is common in ACS populations.

Despite these differences, several findings are consistent across studies. In the RATIO population-based case-control study of 1006 predominantly Dutch women (203 MI, 175 ischemic stroke, 628 controls), Urbanus et al. showed that a positive LA test was strongly associated with first MI, increasing the odds more than fivefold, and the odds of ischemic stroke more than 40-fold [13]. The association was much stronger in smokers and oral contraceptive users, which supports a "second hit" effect in arterial thrombosis. In a Chinese retrospective study of 239 patients with APS, Gan et al. reported that acute MI occurred in 12.1% of patients and often occurred before APS was confirmed or at the time of diagnosis, demonstrating that coronary events can precede formal recognition of APS [14]. The American Heart Association has recognized APS as an acquired hypercoagulable cause of MINOCA and recommends comprehensive aPL testing, including LA, in the diagnostic evaluation of these patients [15]. Overall, these studies support that myocardial infarction may be an early thrombotic presentation in APS and that a positive LA test is a high-risk finding, especially in premature or atypical myocardial infarction.

Although our study evaluated single-time-point aPL seropositivity rather than the prevalence of APS or its clinical correlates in patients with ACS, our findings may have clinical implications for understanding the potential role of aPL in coronary artery disease. APS is increasingly understood as a thrombo-inflammatory condition in which aPL contribute directly to immunothrombosis [16-17]. A "two-hit" model has been proposed, in which aPL prime the vasculature through endothelial activation and tissue factor expression (the "first hit"), with thrombosis triggered by a secondary stimulus such as infection, surgery, or traditional cardiovascular risk factors. This priming is amplified through platelet and myeloid cell activation, complement-mediated injury, and neutrophil extracellular trap (NET) formation [18]. This framework provides biologic plausibility for coronary thrombosis in ACS, including presentations with limited obstructive disease and potential microvascular ischemia. In experimental work linked to acute MI, Bayartaikishigtai et al. demonstrated that APS IgG-stimulated human coronary artery endothelial cells upregulated neutrophil-related chemokines, and an APS mouse model exhibited accelerated disease progression with increased neutrophil infiltration and NET formation [4]. APS is also associated with accelerated subclinical atherosclerosis; in a prospective 7-year follow-up study, patients with thrombotic APS had a three-fold higher risk of new atherosclerotic plaque formation compared with healthy controls (OR: 3.07; $p = 0.007$), and this risk exceeded that observed in patients with diabetes mellitus (OR: 2.25; $p = 0.047$) [19].

This study has several limitations. First, because aPL testing was performed only once, we could not establish the temporal relationship between aPL positivity and the occurrence of ACS. Second, the study was performed at a single tertiary center with a modest sample size, which may limit generalizability. Third, the exploratory regression analysis was limited by the relatively small number of aPL-positive patients and the selection of candidate predictors based on univariable statistical significance, potentially resulting in unstable estimates. Although age and sex were included as adjustment variables, residual confounding by baseline disease severity and other unmeasured factors cannot be excluded. Additionally, infectious complications and length of hospitalization represent in-hospital characteristics rather than established antecedent exposures; therefore, the observed associations should not be interpreted as causal. Fourth, aPL testing was obtained during hospitalization and after initiation of enoxaparin for most patients. LA positivity (26%) was disproportionately higher than solid-phase antibody positivity, highlighting the plausible role of concurrent anticoagulation or acute-phase reactant interference. However, the ISTH Scientific and Standardization Committee has noted that LA assays are much less affected by low molecular

weight heparins than by other anticoagulants [9-10]. Likewise, a large retrospective analysis evaluated the risk of a single-positive LA test and found that anticoagulation was associated with an approximately fourfold greater likelihood of single-positive results, but this association was driven primarily by rivaroxaban, warfarin, heparin, and apixaban, whereas enoxaparin was not significantly associated with single positivity [20]. Nonetheless, results should be interpreted in clinical context, and the possibility of false-positive LA results during anticoagulation cannot be excluded. Finally, APS classification frameworks, including the 2023 ACR/EULAR criteria, are intended for research definitions and include specific laboratory requirements, such as persistent aPL positivity on two occasions at least 12 weeks apart together with appropriate clinical criteria (thrombosis and/or specific pregnancy morbidity) [21]. This study evaluated inpatient aPL testing results rather than confirming APS classification status, and the frequency of confirmed APS in this population would be expected to be substantially lower than the frequency of single-time-point aPL positivity.

Conclusions

In summary, this study, together with prior reports, suggests that single-time-point aPL positivity is not uncommon in ACS. In our study, aPL positivity was frequent, with LA being the most commonly detected test, whereas aCL and anti-β2GPI antibodies were uncommon. Overall, these findings support a more targeted clinical suspicion for APS/aPL in selected coronary presentations, particularly in cases of atypical myocardial infarction, including MINOCA, recurrent events, or when systemic autoimmune features raise concern for an immune-mediated thrombotic phenotype. On the other hand, both anticoagulant therapy and the acute-phase state can interfere with the coagulation-based assays used for LA detection, potentially resulting in transient or false-positive results. Therefore, prospective studies incorporating confirmatory aPL testing at 12 weeks and longitudinal outcome assessment are needed to determine whether inpatient aPL positivity in ACS identifies a distinct subgroup of patients who may benefit from tailored antithrombotic strategies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Luis M. Vilá, Edwin Plaza-Lamoli, Marcel Mesa-Pabón

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. University of Puerto Rico Medical Sciences Campus IRB issued approval 2290034526. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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Data are available upon reasonable request. The data are stored as de-identified participant data and are available on request to luis.vila2@upr.edu.

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