

# Clinical and Serological Findings of Patients with Antiphospholipid Syndrome in Mashhad, Iran, from 2008 to 2018: A Retrospective, Descriptive, Cross-sectional Study

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## Abstract

**Objective:** Antiphospholipid syndrome (APS) is among the autoimmune disorders caused by anti-phospholipid antibodies, which provoke blood clots (thrombosis) in arteries and veins. It can also cause such complications as severe preeclampsia, miscarriage, premature birth, and stillbirth in pregnant women. We investigated the clinical and serological characteristics of antiphospholipid syndrome patients.

**Methods:** This retrospective cross-sectional study was performed on those with persistently positive antiphospholipid syndrome. Data were extracted from medical records from the hospital information system (HIS) of rheumatology, neurology, cardiology, gynecology, general, and hematology wards of Ghaem Hospital and private rheumatology clinics of Mashhad, which were surveyed for 10 years (2008-2018).

**Results:** Of the 284 patients, 85.6% were female. The most common adverse outcome of pregnancy was miscarriage (68.1%). Non-criteria manifestations, including arthralgia and arthritis, were observed in 37.7% and 33.1% of the patients, respectively. Moreover, deep vein thrombosis (DVT) and cerebrovascular accident (CVA) (13%), organ gangrene (7.4%), and pulmonary thromboendarterectomy (PTE) and transient ischemic attack (TIA) (4.6%) were the most common thrombotic events in antiphospholipid syndrome patients. Deep vein thrombosis was seen in 70.3% of females ( $P = .005$ ), and subclavian thrombosis was seen in 66.7% of males ( $P < .001$ ). The risk of DVT in the presence of anti-cardiolipin Ab IgG positive was increased 2.7 times (CI: 95%, 1.2-5.7;  $P = .007$ ), and it was increased 2.4 times in the presence of anti- $\beta$ -2 glycoprotein 1 Ab IgG positive (CI: 95%, 1-5.8;  $P = .033$ ) and 4.2 times in the presence of lupus anticoagulant Ab positive (CI: 95%, 1.9-9.1;  $P < .001$ ). In patients with anti- $\beta$ -2 glycoprotein 1 Ab IgG positive, the risk of placental dysfunction increased 4.3 times (CI: 95%, 0.9-20.3;  $P = .04$ ).

**Conclusion:** This study's results found that this APS syndrome is mainly seen in women with a mean age of 38, and the most common symptoms associated with it are DVT, CVA, and abortion. Anti- $\beta$ -2 Glycoprotein 1 Ab IgM and Anti-Cardiolipin Ab IgM were the most common positive antibodies in the patients.

**Keywords:** Abortion, antiphospholipid syndrome, stroke, thrombosis

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## Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by several clinical manifestations resulting from a hypercoagulable state involving venous and arterial vasculatures. It is determined by vascular thrombosis and pregnancy loss or morbidity in connection with the constant positivity of auto-antibodies called antiphospholipid antibodies (aPL).<sup>1</sup> Miakis et al (2006) classified the criteria for definite antiphospholipid syndrome into 2 main categories: laboratory (anticardiolipin (aCL) antibody (IgG and IgM), lupus anticoagulant (LAC) present in plasma, and anti-b2 glycoprotein-I antibody) and clinical (vascular thrombosis and pregnancy morbidity). If one of these categories has been identified, antiphospholipid antibody syndrome (APS) is present.<sup>2</sup> However, these criteria have recently been updated. The 2023 American College of Rheumatology (ACR)/European League Against Rheumatism (ACR/EULAR) APS categorization criteria involve a positive antiphospholipid antibody (aPL) test within 3 years of identifying a clinical criterion related to aPL. Additional criteria are then used, with each of the parameters assigned a score

ranging from 1 to 7 points. The classification is organized into 6 clinical domains: macrovascular venous thromboembolism, macrovascular arterial thrombosis, microvascular, obstetric, cardiac valve, and hematologic. Additionally, there are 2 laboratory domains: lupus anticoagulant functional coagulation assays and solid-phase enzyme-linked immunosorbent assays for IgG/IgM anticardiolipin and/or IgG/IgM anti- $\beta$ 2-glycoprotein I ( $\beta$ 2GPI) antibodies of IgG and/or IgM. Patients who score at least 3 points in both the clinical and laboratory areas are categorized as having APS.<sup>3</sup>

The average age at which APS is diagnosed, as indicated by current population-based research, is approximately 50 years.<sup>4,7</sup> In different research, the age at which the incidence of APS peaks varies. For instance, the UK Clinical Practice Research Datalink (CPRD) study found that incidence peaked at 55-59 years for males and 35-39 years for women.<sup>8</sup> The Korean nationwide population-based study found that APS incidence increased with age only in men, peaking at 70-79. Female incidence peaked at 30-39 and 70-79.<sup>6</sup> Meanwhile, the US study found that males peaked at 55-64 and women at 75+.<sup>4</sup> It should be noted that reports on the prevalence of APS in men and women are different.<sup>9</sup>

To diagnose APS, a positive aPL and persistent clinical symptoms are required.<sup>10</sup> The clinical spectrum of APS includes obstetrical (recurrent pregnancy loss), hematological (thrombocytopenia, venous thrombosis), cardiovascular (cardiac valve disease), neurological (stroke, transient ischemic attack, chorea, migraine, cognitive dysfunction, seizures, transverse myelitis, multiple sclerosis), renal (glomerulonephritis, renal thrombotic microangiopathy), dermatological (livedo reticularis and racemosa, skin ulceration and necrosis), and orthopedic (avascular necrosis of bones, non-traumatic fractures) manifestations, etc.<sup>1</sup> The pathogenic mechanisms involved in thrombotic events and pregnancy morbidity in APS are not fully understood, and several mechanisms might be responsible.<sup>1</sup>

In this regard, several studies suggested that the activation of monocytes, endothelial cells, platelets, complement, induction of a prothrombotic state, and interference with the process of coagulation proteins can play a role here.<sup>10,11</sup> When aPL binds to  $\beta$ 2GPI on cellular surfaces, it activates complement and endothelial, monocyte, and platelet cells, resulting in prothrombotic and proinflammatory phenotypes. This ultimately causes thrombosis and may

interfere with trophoblast and decidual cells. Recent studies also suggest that neutrophils may contribute to aPL-related vasculopathy by expressing tissue factor (TF), releasing neutrophil extracellular traps (NETosis), and upregulating the mTOR complex on endothelial cells.<sup>12</sup> Many APS-associated autoantibodies, including the LAC, immunoglobulin (Ig)G, and IgM anticardiolipin antibodies (aCL) and anti- $\beta$ 2GPI antibodies, are directed against some plasma proteins and proteins expressed on or bound to the surface of vascular endothelial cells or platelets.<sup>11</sup> In addition, mechanisms through which aPL can contribute to thrombotic events in APS patients include its involvement in clinically significant procoagulant and anticoagulant reactions and its influence on specific cells, altering their expression and secretion of numerous molecules.<sup>13,14</sup> However, because APS also has a high number of non-thrombotic symptoms, it is critical to diagnose this disease.

Moreover, it is essential to take the necessary, appropriate, and well-timed treatment measures to prevent these complications. Despite the severe risks of antiphospholipid syndrome and its impact on different parts of the patients' lives, there is no comprehensive study investigating the various aspects of the disease. Most previous studies in Iran have focused on the frequency of antiphospholipid antibodies in specific patient populations<sup>15,16</sup> or were provided in the form of case reports of unique symptoms.<sup>17</sup>

## Material and Methods

This was a cross-sectional retrospective study conducted on patients with APS who were referred to Ghaem Hospital and private rheumatology clinics of the collaborating authors in Mashhad over 10 years.

### Inclusion and Exclusion Criteria

Only patients with APS were included in the study, and patients with other autoimmune syndromes were excluded. Moreover, we excluded patients with incomplete information files.

### Study Design and Sampling

We gathered information on patients with APS by referring to medical records from the HIS system of "Ghaem Hospital" in rheumatology, neurology, cardiology, hematology, gynecology, general wards, and rheumatology clinics of the collaborating authors in Mashhad during 10 years (2008-2018).

According to the retrospective approach of this study, the patient's clinical information

was collected based on the information in the medical record. Therefore, it was possible that not all symptoms were available. Incomplete information files were excluded from the study (out of 314 evaluated files, 30 were deleted). Therefore, data were gathered from 284 medical records. In the case of incomplete information, we tried to collect necessary data by referring to the main file of the patient in the archive, the relevant laboratory, the file of the attending physician in the office, or by calling the patient.

We categorized and extracted the cases in which antiphospholipid syndrome was reported based on demographic and clinical information, laboratory criteria, and drug treatments. The information was classified according to the following:

1. Demographic information such as age, gender, reason for referral to the medical training center, patient death or discharge from the hospital, cause of death, complications over time, disease duration, hospitalization department, concurrent rheumatic diseases including Sjögren's syndrome (SS), progressive systemic sclerosis (PSS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), dermatomyositis/poly myositis (DM/PM), and mixed connective tissue disease (MCTD), underlying disease history such as certain medical conditions, diabetes, hypertension, dyslipidemia, and malignancy, and smoking history.
2. Clinical information (criteria and non-criteria) gathered from diagnosis to follow-up, such as vascular thrombosis and pregnancy complications, included one or more morphologically normal embryonic deaths after 10 weeks confirmed by ultrasonography or direct fetal examination; one or more premature births morphologically before 34 weeks of gestation (due to preeclampsia); and more than 3 consecutive abortions under 10 weeks of pregnancy (by rejecting anatomical or hormonal problems in mothers and genetic reasons in mothers and fetuses). Cases with missing data were omitted from the study.
3. Other clinical criteria manifestations observed in the patients at the onset of diagnosis or during follow-up include superficial thrombophlebitis, thrombocytopenia, hemolytic anemia, Ounce syndrome, non-traumatic fracture, heart disease (such as increased valve thickness, endocarditis, Liebmann-Sachs, and cardiomyopathy), alveolar hemorrhage,

leg ulcer, vascular necrosis, livedo reticularis, splinter hemorrhage, migraine, chorea, seizure, epilepsy, cerebellar ataxia, Guillain-Barré, cognitive impairment, sensorineural hearing loss, arthritis, arthralgia, transverse myelitis, optic neuritis, thrombotic thrombocytopenic purpura (TTP), APS nephropathy, glomerulonephritis, and MS-like syndrome.

4. Criteria utilized in the laboratory to assess the entire antiphospholipid panel: The following tests are included: anticardiolipin antibody (IgG/IgM), beta2 glycoprotein (IgG/IgM), lupus anticoagulant, complete blood cell count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA) profile (anti-double-stranded DNA, anti-Smith, anti-U1RNP, anti-Ro/SSA, anti-La/SSB), anti-C3, anti-C4, CH50, LDH, urinalysis, 24-hour urine protein analysis, and factor 5 Leiden hereditary thrombophilia panel (PrC-PrS-ATIII, mutant prothrombin, hyperhomocysteinemia), as well as direct and indirect Coombs.

The following details are included (1) LAC present in plasma, two or more cases discovered during 12 weeks using the International Society of Thrombosis and Hemostasis recommendations (LAC phospholipid antibody). (2) aCL antibody of IgG or IgM isotype in serum or plasma with medium or high titer in 2 or more cases assessed by a conventional ELISA during 12 weeks. 3- Anti-β2GPI antibody or IgM in serum or plasma (with a titer of 99%) in 2 or more instances determined by ELISA over a 12-week period (within which interval they had not been positive for more than 5 years), and additional cases were collected.

#### Statistical Analysis

The analysis was performed using descriptive and analytical statistical methods. The data were analyzed using SPSS software (version 24). Descriptive data, including quantitative and qualitative data, were expressed as percentages and mean ± SD, respectively. The Chi-square test was used to compare quantitative variables. For all calculations, the statistically significant level was set at  $P \leq 0.05$ .

#### Ethical Considerations

This study was extracted from a thesis to obtain a doctorate in rheumatology (Thesis Code: 971799). Ethical approval was obtained from Mashhad University of Medical Sciences' research ethics committee (Ethics Code: IR.MU.MS.MEDICAL.REC.1398.257). Informed written consent was obtained from all patients.

To ensure confidentiality, all records were coded before being added to the researcher's checklist.

#### Results

Of the 284 patients included in the present study, 85.6% were female (n=243). The mean age of the patients at diagnosis was  $38.08 \pm$

12.1 years. Most of the patients (84.5%) had been referred to a rheumatology clinic.

Only 1% of patients (n=3) had a history of malignancy, and mortality was reported in 1.8% of patients (n=5). The primary and secondary antiphospholipid syndromes were observed in 47.2% (n=134) and 52.8%

**Table 1. Demographic Data of Participants**

Variable	No. (%)
Age	Mean ± SD= 38.08 ± 12.1
Sex	
Female	243 (85.6)
Male	41 (14.4)
Consequence of disease	
Alive	279 (98.2)
Dead	5 (1.8)
History of Malignancy*	3 (1)
Department	
Rheumatology clinic and office	240 (84.5)
Neurology	10 (3.5)
Hematology	1 (0.4)
Gynecology and obstetrics	4 (1.4)
Rheumatology	20 (7)
General	3 (1.1)
Cardiology	2 (0.7)
Intensive care unit	3 (1.1)
Pediatric	1 (0.4)
<b>Thrombotic Events in Antiphospholipid Syndrome Patients</b>	
Deep vein thrombosis	37 (13)
pulmonary thromboembolism	13 (4.6)
Multi-infarction dementia	6 (2.1)
Transient ischemic attack	13 (4.6)
Cerebrovascular accident	37 (13)
Myocardial infarction	7 (2.5)
Amaurosis fugax	7 (2.5)
Central retinal vein occlusion	5 (1.8)
Central retinal artery occlusion	1 (0.4)
Cerebral venous thrombosis	17 (6)
Gangrene of the lower extremity	21 (7.4)
Subclavian vein thrombosis	6 (2.1)
Jugular vein thrombosis	1 (0.4)
Budd-Chiari syndrome	3 (1.1)
Mesenteric ischemia	1 (0.4)
Adrenal infarction	0
Splenic infarction	1 (0.4)
Pancreatic infarction	1 (0.4)
Peripheral vein thrombosis	6 (2.1)

\*Papillary thyroid carcinoma (n = 1), lymphoma (n = 1), multiple myeloma (n = 1)

(n=150), respectively. The prevalent thrombotic events in APS patients were deep vein thrombosis (DVT) (13%), cerebrovascular accident (CVA) (13%), limb gangrene (7.4%), pulmonary thromboendarterectomy (PTE) (4.6%), and transient ischemic attack (TIA) (4.6%). The most frequent adverse pregnancy outcomes in the APS patients were abortion under ten weeks (68.1%), pre-eclampsia (10.2%), stillbirth (8.5%), preterm delivery (4.6%), uteroplacental (2.5%), and eclampsia (1.1%).

Non-criteria manifestations of APS were found in 19.7% (56 cases) of patients. The most prevalent non-criteria manifestations of APS were arthralgia (37.7%), arthritis (33.1%), thrombocytopenia (17.6%), convulsions (10.9%), and hemolytic anemia (8.1%).

Examining the paraclinical findings showed that Anti-Cardiolipin Ab IgM, Anti-Cardiolipin Ab IgG, Anti anti-2GPI Ab IgM, Anti anti-2GPI Ab IgG, and LAC Ab were positive in 37.3%, 30%, 59.2%, 15%, and 18.3% of patients, respectively. Moreover, positive ANA (51.8%) and positive Anti-dsDNA Ab (46.5%) were the most frequent among the investigated antibodies in the ANA profile. The assessment of the relationship between gender and the outcome of the APS showed that DVT was seen in 70.3% of females ( $P=.005$ ), and subclavian thrombosis was seen in 66.7% of males ( $P < .001$ ). There was no significant relationship between gender and other consequences of APS. Table 2 presents the relationship between triple positive and double positive profiles with APS outcomes, which showed

no significant relationship between the triple positive profile and APS consequences. However, as can be seen in Table 1, in examining the relationship between the double positive profile and the consequences of APS, there was a positive and significant relationship between different variables between the double positive profile and the presence of DVT ( $P=.002$ ).

The risk of DVT in the presence of anti-cardiolipin Ab IgG positive (CI: 95%, 1.2-5.7) is 2.7 times higher ( $P=.007$ ) (Table 3B), in the presence of Anti-2GPI Ab IgG positive (CI: 95%, 1-5.8) is 2.4 times ( $P=.033$ ) (Table 4A) and also in the presence of lupus anticoagulant Ab positive (CI: 95%, 1.9-9.1) is 4.2 times ( $P < .001$ ) (Table 4B).

**Table 2.** Relationship Between Triple Positive Profile and Double Positive Profile with Antiphospholipid Syndrome Outcomes

Variables		Triple Positive Profile		P	Double Positive Profile		P
		N (%)	Positive N (%)		N (%)	Positive N (%)	
Deep vein thrombosis	Yes	93.9 (31)	6.1 (2)	.28	72.7 (24)	27.3 (9)	.002*
	No	97.4 (222)	2.6 (6)		91.2 (208)	8.8 (20)	
Pulmonary thromboembolism	Yes	92.3 (12)	7.7 (1)	.23	92.3 (12)	7.7 (1)	.68
	No	97.2 (241)	2.8 (7)		88.7 (220)	11.3 (28)	
Multi-infarction dementia	Yes	83.3 (5)	16.7 (1)	.06	66.7 (4)	33.3 (2)	.08
	No	97.3 (248)	2.7 (7)		89.4 (228)	10.6 (27)	
Transient ischemic attack	Yes	91.7 (11)	8.3 (1)	.27	88.3 (10)	16.7 (2)	.53
	No	97.2 (242)	2.8 (7)		89.2 (222)	10.8 (27)	
Cerebrovascular accident	Yes	96.8 (30)	3.2 (1)	.95	83.9 (26)	16.1 (5)	.33
	No	97 (223)	3 (7)		89.6 (206)	10.4 (24)	
Myocardial infarction	Yes	100 (5)	0 (0)	.68	100 (5)	0 (0)	.42
	No	96.9 (248)	3.1 (8)		88.7 (227)	11.3 (29)	
Amaurosis fugax	Yes	100 (7)	0 (0)	.63	71.4 (5)	28.6 (2)	.13
	No	96.9 (246)	3.1 (8)		89.4 (227)	10.6 (27)	
Central retinal vein occlusion	Yes	100 (5)	0 (0)	.68	100 (5)	0 (0)	.42
	No	96.9 (248)	3.1 (8)		88.7 (227)	11.3 (29)	
Cerebral venous thrombosis	Yes	100 (12)	0 (0)	.52	91.7 (11)	8.3 (1)	.75
	No	96.8 (241)	3.2 (8)		88.8 (221)	11.2 (28)	
Gangrene of the lower extremity	Yes	94.4 (17)	5.6 (1)	.52	94.4 (17)	5.6 (1)	.72
	No	97.1 (236)	2.9 (7)		88.5 (215)	11.5 (28)	
Subclavian vein thrombosis	Yes	100 (5)	0 (0)	.66	80 (4)	20 (1)	.52
	No	96.9 (248)	3.1 (8)		89.1 (228)	10.9 (29)	
Thrombophlebitis	Yes	100 (5)	0 (0)	.68	100 (5)	0 (0)	.42
	No	96.9 (248)	3.1 (8)		88.7 (227)	11.3 (29)	
Non-criterion symptoms	Yes	98.1 (53)	1.9 (1)	.63	85.2 (46)	14.8 (8)	.28
	No	96.6 (200)	3.4 (7)		89.9 (186)	10.1 (21)	

\*p-value: <0.05

**Table 3.** Relationship Between Anti-Cardiolipin Ab IgM (A), Anti-Cardiolipin Ab IgG (B), and Anti-β-2 Glycoprotein 1 Ab IgM (C) Antiphospholipid Syndrome Outcomes

Variables		Anti-Cardiolipin Ab IgM (A)			Anti-Cardiolipin Ab IgG (B)			Anti-β-2 Glycoprotein 1 Ab IgM (C)		
		+ % (fχ)	- % (fχ)	P	+ % (fχ)	- % (fχ)	Pe	+ % (fχ)	- % (fχ)	P
Deep vein thrombosis	Yes	31.3 (10)	68.7 (22)	.33	53.1 (17)	46.9 (15)	.007	46.9 (15)	53.1 (17)	.06
	No	41.7 (95)	58.3 (133)		29.4 (67)	70.6 (161)		64.9 (148)	35.1 (80)	
Pulmonary thromboendarterectomy	Yes	23.1 (3)	76.9 (10)	.19	38.5 (5)	61.5 (8)	.62	69.2 (9)	30.8 (4)	.61
	No	41.3 (102)	58.7 (145)		32 (79)	68 (168)		62.3 (154)	37.7 (93)	
Multi-infarction dementia	Yes	66.7 (4)	33.3 (2)	.18	50 (3)	50 (3)	.34	66.7 (4)	33.3 (2)	.83
	No	39.8 (101)	60.2 (153)		31.9 (81)	68.1 (173)		62.6 (159)	37.4 (95)	
Transient ischemic attack	Yes	33.3 (4)	66.7 (8)	.61	41.7 (5)	58.3 (7)	.47	91.7 (11)	8.3 (1)	.03*
	No	40.7 (101)	59.3 (147)		31.9 (79)	68.1 (169)		61.3 (19)	38.7 (12)	
Cerebrovascular accident	Yes	35.5 (11)	64.5 (20)	.55	45.2 (14)	54.8 (17)	.1	61.3 (19)	38.7 (12)	.86
	No	41 (94)	59 (135)		30.6 (70)	69.4 (159)		62.9 (144)	37.1 (85)	
Myocardial infarction	Yes	60 (3)	40 (2)	.36	20 (1)	80 (4)	.52	20 (1)	80 (4)	.06
	No	40 (102)	60 (153)		32.5 (83)	67.5 (172)		63.5 (162)	36.5 (93)	
Amaurosis fugax	Yes	28.6 (2)	71.4 (5)	.51	28.6 (2)	71.4 (5)	.83	57.1 (4)	42.9 (3)	.75
	No	40.7 (103)	59.3 (150)		32.4 (82)	67.6 (171)		62.8 (159)	37.2 (94)	
Central retinal vein occlusion	Yes	0 (0)	100 (5)	.06	20 (1)	80 (4)	.55	80 (4)	20 (1)	.41
	No	41.2 (105)	58.8 (150)		32.5 (83)	67.5 (172)		62.4 (159)	37.6 (96)	
Cerebral venous thrombosis	Yes	33.3 (4)	66.7 (8)	.61	25 (3)	75 (9)	.57	50 (6)	50 (6)	.35
	No	40.7 (101)	59.3 (147)		32.7 (81)	67.3 (167)		63.3 (157)	36.7 (91)	
Gangrene of the lower extremity	Yes	33.3 (6)	66.7 (12)	.52	22.2 (4)	77.8 (14)	.34	77.8 (14)	22.2 (4)	.17
	No	40.9 (99)	59.1 (143)		33.1 (80)	66.9 (162)		61.6 (149)	38.4 (93)	
Subclavian vein thrombosis	Yes	60 (3)	40 (2)	.36	40 (2)	60 (3)	.71	60 (3)	40 (2)	.9
	No	40 (102)	60 (153)		32.2 (82)	67.8 (173)		62.7 (160)	37.3 (95)	
Thrombophlebitis	Yes	60 (3)	40 (2)	.36	20 (1)	80 (4)	.55	60 (3)	40 (2)	.9
	No	40 (102)	60 (153)		32.5 (83)	67.5 (172)		62.7 (160)	37.3 (95)	
Non-criterion symptoms	Yes	46.3 (25)	53.7 (29)	.43	31.5 (17)	68.5 (37)	.68	59.3 (32)	40.7 (22)	.73
	No	39.6 (76)	60.4 (116)		31.8 (61)	68.2 (131)		64.1 (123)	35.9 (69)	

\*p-value: ≤ 0.05

The presence of Anti-2GPI Ab IgG positive increased 12.11 times the risk of multifactorial dementia (CI: 95%, 2.1-68.5) (Table 3A). The risk of TIA in the presence of anti-2GPI Ab IgM positive was increased 6.94 times (CI: 95%, 0.88-54.6) (Table 3C). No significant link was noticed between the presence of antibodies and other consequences of antiphospholipid syndrome (Tables 3-6).

## Discussion

Antiphospholipid syndrome is a group of autoimmune diseases characterized by the presence of antibodies against anionic phospholipids. The incidence of this disease was studied by focusing on the patient's clinical and serological characteristics. The highly

prevalent thrombotic events included DVT, CVA, limb gangrene, PE, and TIA. In summary, the present study showed a higher rate of DVT in females than in males, while the frequency of subclavian thrombosis was higher in males. Moreover, no relationship was observed between gender and other consequences of antiphospholipid syndrome. The negative consequences of pregnancy in the context of antiphospholipid syndrome were investigated in the next phase of our study, with abortion being one of the most important and significant cases. Furthermore, we evaluated the relationship between triple and double positive status and the consequences of antiphospholipid syndrome in patients. Another of our objectives was to look into and observe

Anti-Cardiolipin Ab IgM, Anti-Cardiolipin Ab IgG, Anti-β-2 Glycoprotein 1 Ab IgM, Anti-β-2GPI Ab IgG, and lupus anticoagulant Ab in patients. Positive ANA and positive Anti-dsDNA Ab were the most common antibodies found in patients.

For the first time, Jara compared male and female PAPS (primary APS) patients on the basis of their clinical manifestations. In their study, male and female PAPS patients had different clinical manifestations. The differences were mainly based on organ involvement. Females experienced stroke/TIA more often, and males were more likely to experience mesenteric thrombosis as well as Budd-Chiari syndrome. Male and female patients had similar

**Table 4.** Relationship between Anti- $\beta$ -2 Glycoprotein 1 Ab IgG (A), Lupus anticoagulant Ab (B) and antiphospholipid syndrome outcomes

Variables		Anti- $\beta$ -2 Glycoprotein 1 Ab IgG (A)			Lupus Anticoagulant Ab (B)		
		+ % (f $\chi$ )	- % (f $\chi$ )	P	+ % (f $\chi$ )	- % (f $\chi$ )	P
Deep vein thrombosis	Yes	28.1 (9)	71.9 (23)	.03*	42.4 (14)	57.6 (19)	< .001*
	No	13.6 (31)	86.4 (197)		14.9 (34)	85.1 (194)	
Pulmonary thromboendarterectomy	Yes	23.1 (3)	76.9 (10)	.43	30.8 (4)	69.2 (9)	.23
	No	15 (37)	85 (210)		17.7 (44)	82.3 (204)	
Multi-infarction dementia	Yes	66.7 (4)	33.3 (2)	< .001*	33.3 (2)	66.7 (4)	.33
	No	14.2 (36)	85.8 (218)		18 (46)	82 (209)	
Transient ischemic attack	Yes	25 (3)	75 (9)	.34	16.7 (2)	83.3 (10)	.87
	No	14.9 (37)	85.1 (21)		18.5 (46)	81.5 (203)	
Cerebrovascular accident	Yes	22.6 (7)	77.4 (24)	.23	16.1 (5)	83.9 (26)	.72
	No	14.4 (33)	85.6 (196)		18.7 (43)	81.3 (187)	
Myocardial infarction	Yes	0 (0)	100 (5)	.36	20 (1)	80 (4)	.92
	No	15.7 (40)	84.3 (215)		18.4 (47)	81.6 (209)	
Amaurosis fugax	Yes	14.3 (1)	85.7 (6)	.93	28.6 (2)	71.4 (5)	.48
	No	15.4 (39)	84.6 (214)		18.1 (46)	81.9 (208)	
Central retinal vein occlusion	Yes	0 (0)	100 (5)	.33	0 (0)	100 (5)	.28
	No	15.7 (40)	84.3 (215)		18.8 (48)	81.2 (208)	
Cerebral venous thrombosis	Yes	16.7 (2)	83.3 (10)	.9	25 (3)	75 (9)	.54
	No	15.3 (38)	84.7 (210)		18.1 (4)	81.9 (204)	
Gangrene of lower extremity	Yes	11.1 (2)	88.9 (16)	.6	33.3 (6)	66.7 (12)	.09
	No	15.7 (38)	84.3 (204)		17.3 (42)	82.7 (201)	
Subclavian vein thrombosis	Yes	0 (0)	100 (5)	.6	20 (1)	80 (4)	.92
	No	15.7 (40)	84.3 (215)		18.4 (47)	81.6 (209)	
Thrombophlebitis	Yes	20 (1)	80 (4)	.77	0 (0)	100 (5)	.28
	No	15.3 (39)	84.7 (216)		18.8 (48)	81.3 (208)	
Non-criterion symptoms	Yes	18.5 (10)	81.5 (44)	.22	14.8 (8)	85.2 (46)	.35
	No	15.6 (30)	84.4 (162)		20.2 (39)	79.8 (154)	

\*p-value:  $\leq 0.05$ 

rates of thrombocytopenia and cardiac, renal, and skin manifestations. In addition, in both men and women, peripheral vascular thrombosis and pulmonary embolism continued to be the most prevalent manifestations.<sup>18</sup> In Iran, Emadifar et al<sup>19</sup> reported similar results. Moreover, 56 patients had only non-criteria manifestations without other diagnostic manifestations, of which arthralgia (37.7%) and arthritis (33.1%) were the most common symptoms.

Previous studies have mentioned that PAPS is characterized by thrombotic events occurring in both the veins and the arteries, with a high recurrence rate.<sup>20</sup> Based on the obtained results, DVT and CVA are the most common symptoms among patients with antiphospholipid syndrome.

According to Shen's study, young females were more prone to cerebral venous sinus thrombosis (CVST). They found that 52 percent of their APS patients with CVST developed the condition chronically, and only one patient had it acutely.<sup>21</sup> Nevertheless, the pathogenesis of APS-related CVST is not known and may have caused a different onset pattern from those with other causes.<sup>22</sup>

Some studies have reported other cases of pathological and unpleasant conditions resulting from antiphospholipid syndrome and subsequent clinical criteria. The most common of these are fetal morbidities such as miscarriage, fetal death, delayed intrauterine growth, or preterm delivery. For example, it was found that early and late fetal loss (35.4% and 16.9% of pregnancies, respectively),

early birth (10.6% of live births), and fetal loss were the most prevalent fetal complications in the Cervera study, where 71.9% of the women had at least one pregnancy. Moreover, preeclampsia (9.5% of pregnant women), eclampsia (4.4%), and abruptio placentae were the most common obstetric complications.<sup>23</sup> We observed miscarriage in 68.1% of PAS patients, which is very high and may be related to the lack of care before and during pregnancy in Iran or the demographic characteristics of Iranian society.<sup>24</sup> In the study of Sciascia, APS was found in 81 patients, and 73 of them had a history of arterial (n=48) and venous thrombosis (n=41). There were 41 miscarriages and 34 fetal deaths among the 144 women who had ever been pregnant. Compared to patients without clinical events, those experiencing thrombosis or pregnancy

**Table 5.** Relationship Between Anti-Cardiolipin Ab IgG (A), Anti-β-2 Glycoprotein 1 Ab IgM (B), Anti-β-2 Glycoprotein 1 Ab IgG (C), Lupus Anticoagulant Ab (D) and Consequences of Pregnancy

Variables		Anti-Cardiolipin Ab IgG (A)		Pe	Anti-β-2 Glycoprotein 1 Ab IgM (B)		P	Anti-β-2 Glycoprotein 1 Ab IgG (C)		Pe	Lupus Anticoagulant Ab (D)		P
		+ % (fχ)	- % (fχ)		+ % (fχ)	- % (fχ)		+ % (fχ)	- % (fχ)		+ % (fχ)	- % (fχ)	
Abortion	Less than 3 items	32.9 (24)	67.1 (49)	.44	69.9 (51)	30.1 (22)	.66	17.8 (13)	82.2 (60)	.2	15.1 (11)	84.9 (62)	.3
	3 items and more	25.7 (9)	74.3 (26)		65.7 (23)	34.3 (12)		8.6 (3)	91.4 (32)		22.9 (8)	77.1 (27)	
Stillbirth	Yes	38.1 (8)	61.9 (13)	.55	66.7 (14)	33.3 (7)	.69	19 (4)	81 (17)	.62	19 (4)	81 (17)	.93
	No	31.8 (76)	68.2 (163)		62.3 (149)	37.7 (90)		15.1 (36)	84.9 (203)		18.3 (44)	81.7 (196)	
Preeclampsia	Yes	37.5 (9)	62.5 (15)	.56	70.8 (17)	29.2 (7)	.38	29.2 (7)	70.8 (17)	.05*	29.2 (7)	70.8 (17)	.15
	No	31.8 (75)	68.2 (161)		61.9 (146)	38.1 (90)		14 (33)	86 (203)		17.3 (41)	82.7 (196)	
Eclampsia	Yes	33.3 (1)	66.7 (2)	.97	66.7 (2)	33.3 (1)	.88	0 (0)	100 (3)	.45	33.3 (1)	66.7 (2)	.5
	No	32.3 (83)	67.7 (174)		62.6 (161)	37.4 (96)		15.6 (40)	84.4 (217)		18.2 (47)	81.8 (211)	
Preterm delivery	Yes	18.2 (2)	81.8 (9)	.3	72.7 (8)	27.3 (3)	.48	9.1 (1)	90.9 (10)	.55	18.2 (2)	81.8 (9)	.98
	No	32.9 (82)	67.1 (167)		62.2 (155)	37.8 (94)		15.7 (39)	84.3 (210)		18.4 (46)	81.6 (204)	
Placental dysfunction	Yes	28.6 (2)	71.4 (5)	.83	57.1 (4)	42.9 (3)	.75	42.9 (3)	57.1 (4)	.04	28.6 (2)	71.4 (5)	.48
	No	32.4 (82)	67.6 (171)		62.8 (159)	37.2 (94)		14.6 (37)	85.4 (216)		18.1 (46)	81.9 (208)	

\*p-value: ≤ 0.05

loss showed higher aPL-S.<sup>24</sup> In a study by Sahebari et al, the relationship between simultaneous neuroimmune manifestations and positive antiphospholipid antibodies was examined in 100 patients. The results showed that 89% of patients with persistent antiphospholipid antibodies were persistent (respectively, anti-phospholipid antibodies), lupus coagulation, IgG anticardiolipin, IgM anticardiolipin, IgG beta two glycoprotein

1, and IgM β2-GP1 (in 16%, 41%, 42%, 17%, and 15% of patients, respectively). In addition, cerebrovascular events (33%), arterial/venous occlusion (21%), and seizures (20%) were the most common neurological manifestations among patients.<sup>25</sup> These results are also confirmed in Sarabi et al<sup>26</sup>'s study on the relationship between stable positive antiphospholipid antibodies and systemic lupus erythematosus activity performed on

59 patients in Mashhad.<sup>26</sup> According to studies and evidence obtained, unraveling the mechanisms that lead to these pathological conditions is critical in developing therapeutic strategies for controlling vascular thrombi and pregnancy loss in APS patients. In the *in vivo* finding of Agostinis et al, MBB2 imitated the activities of aPL antibodies, resulting in blood clots and pregnancy failure. Based on these results, the DI domain is the main target of

**Table 6.** Relationship Between Triple Positive Profile (A), Double Positive Profile (B), Anti-Cardiolipin Ab IgM (C), and Consequences of Pregnancy

Variables		Triple Positive Profile (A)		P	Double Positive Profile (B)		P	Anti-Cardiolipin Ab IgM (C)		P
		- % (fχ)	+ % (fχ)		- % (fχ)	+ % (fχ)		+ % (fχ)	- % (fχ)	
Abortion	Less than 3 items	95.9 (70)	4.1 (3)	.74	90.4 (66)	9.6 (7)	.49	34.2 (25)	65.8 (48)	.76
	3 items and more	97.1 (34)	2.9 (1)		94.3 (33)	5.7 (2)		37.1 (13)	62.9 (22)	
Stillbirth	Yes	95.2 (20)	4.8 (1)	.63	85.7 (18)	14.3 (3)	.62	38.1 (8)	61.9 (13)	.82
	No	97.1 (233)	2.9 (7)		89.2 (214)	10.8 (142)		40.6 (97)	59.4 (142)	
Preeclampsia	Yes	91.7 (22)	8.3 (2)	.11	79.2 (19)	20.8 (5)	.11	33.3 (8)	66.7 (16)	.46
	No	97.5 (231)	2.5 (6)		89.9 (213)	10.1 (24)		41.1 (97)	58.9 (139)	
Eclampsia	Yes	100 (3)	0 (0)	.75	66.7 (2)	33.3 (1)	.21	33.3 (1)	66.7 (2)	.8
	No	96.9 (250)	3.1 (8)		89.1 (230)	10.9 (28)		40.5 (104)	59.5 (153)	
Preterm delivery	Yes	100 (11)	0 (0)	.54	100 (11)	0 (0)	.23	18.2 (2)	81.8 (9)	.12
	No	96.8 (242)	3.2 (8)		88.4 (221)	11.6 (29)		41.4 (103)	58.6 (146)	
Placental dysfunction	Yes	85.7 (6)	14.3 (1)	.08	85.7 (6)	14.3 (1)	.78	71.4 (5)	28.6 (2)	.09
	No	97.2 (247)	2.8 (7)		89 (226)	11 (28)		39.5 (100)	60.5 (153)	

\*p-value: ≤ 0.05

pathogenic antibodies.<sup>15</sup> The findings support recent insights from clinical research, indicating that antibodies to DI, which are found in APS cases, are often more associated with a thrombosis history than antibodies to other domains of the molecule.<sup>28,29</sup> In mice, Ioannou and colleagues discovered that soluble DI inhibited the rise in thrombus size mediated by the antibody.<sup>30</sup> Contrary to popular belief, even though thrombosis and fetal death have unique histological and clinical symptoms, an antibody specific for  $\beta$ 2GPI's DI domain kick-starts these pathological events, while other antibodies with various specificities may also play a role. The main distinction between the onsets of these 2 disorders is that proinflammatory stimuli are necessary to trigger the creation of thrombi but are antibody-mediated, while fetal loss does not require prior stimulation.<sup>15</sup> Moreover, researchers discovered that using a mutant antibody lacking the CH2 domain necessary for C1q binding and complement activation, MBB2's procoagulant and pro-abortive activities were lost.<sup>31</sup> Murthy and colleagues demonstrated that, especially when other antiphospholipid antibodies are absent, IgA anti- $\beta$ 2GPI antibodies are linked with clinically significant thrombosis. They also confirmed the pathogenicity of pure IgA anti- $\beta$ 2GPI antibodies with binding activities for domains I and IV/V in a mouse model.<sup>32</sup>

#### Advantages and Limitations

One advantage of our study is the appropriate sample size with a long follow-up period for APS patients. Examining clinical and serological signs in this study has become a unique example in the country. Of course, one of the limitations and weaknesses of this study is its retrospective approach, which includes the risk of missing or not performing the same tests among patients. In addition, the evaluation of symptoms in terms of the occurrence of symptoms and the reason for referring patients makes it impossible to identify the true prevalence of symptoms. Finally, the study findings cannot equip the scientific community with information about the effectiveness of treatments and the recurrence rate of thrombotic events.

#### Conclusion

We examined the clinical and serological profile of APS patients for the first time in Iran. According to the obtained results, this syndrome occurs mainly in females with a mean age of 38, and the most common symptoms associated with this syndrome are DVT, CVA, and abortion. The most common positive antibodies in the patients were Anti- $\beta$ -2 Glycoprotein

1 Ab IgM and then Anti-Cardiolipin Ab IgM. Also, the presence of antibodies studied in this study was associated with different outcomes and symptoms of antiphospholipid syndrome.

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (Approval no: IR.MUMS.MEDICAL.REC.1398.257, Date: 2019-06-18)

**Informed Consent:** Written informed consent was obtained from the patients who agreed to take part in the study.

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