


Thrombocytopenia in a cohort of primary and secondary antiphospholipid syndrome patients: Relation to clinical, laboratory manifestations and damage index

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ABSTRACT

Objectives: This study aims to evaluate the prevalence of thrombocytopenia in a cohort of patients with primary and secondary antiphospholipid syndrome (APS) and to examine the relation of thrombocytopenia to the clinical, laboratory findings, and damage index for antiphospholipid syndrome (DIAPS).

Patients and methods: Between August 2018 and February 2019, a total of 168 patients (16 males, 152 females; mean age: 32.5±8.4 years; range, 18 to 59 years) who were followed in our clinic for APS were retrospectively analyzed. Medical records of the patients were screened and clinical data, laboratory investigations, and treatments applied were recorded. The DIAPS was calculated for all patients. The patients were divided into two groups according to the presence or absence of thrombocytopenia and both groups were compared regarding clinical, laboratory findings and DIAPS. Further subgroup analysis was done for patients with primary APS.

Results: The most common clinical manifestations in our patients were obstetric manifestations (77.4% in pregnant women), musculoskeletal manifestations (69%) and peripheral vascular thrombosis (54.8%). The prevalence of thrombocytopenia in our study was 42.3%, and it was significantly associated with musculoskeletal manifestations ($p=0.043$), vascular thrombosis ($p=0.043$), neurological manifestations ($p=0.030$), cutaneous manifestations ($p=0.006$), and use of immunosuppressives ($p=0.047$). The DIAPS was significantly higher in the thrombocytopenia group ($p=0.034$). Further subgroup analysis of patients with primary APS revealed that neurological manifestations ($p=0.010$) were significantly higher in the thrombocytopenia group, while the DIAPS was higher in the thrombocytopenia group, but it did not reach statistical significance ($p=0.082$).

Conclusion: Thrombocytopenia may be associated with a higher incidence of vascular thrombosis, neurological manifestations, musculoskeletal manifestations, use of immunosuppressive treatment, and DIAPS. In primary APS patients, thrombocytopenia may be a risk for neurological manifestations.

Keywords: Antiphospholipid syndrome, damage index, Egyptian patients, thrombocytopenia.

Antiphospholipid syndrome (APS) is an autoimmune-mediated acquired thrombophilia.^{1,2} It is defined as a syndrome of recurrent venous and/or arterial thromboses, pregnancy complication together with the presence of antiphospholipid antibodies (aPL), that are directed against phospholipid-binding plasma proteins.¹⁻³

Thrombocytopenia is one of the most common non-criteria findings in APS patients.⁴ The estimated prevalence of thrombocytopenia in patients with APS ranged from 20 to 53%, depending on the cut-off value used ($<100 \times 10^9/L$ or $<150 \times 10^9/L$),⁵ and the frequency of patients with primary APS (PAPS) and secondary APS

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(SAPS) in the studied cohort.⁶⁻⁸ Interestingly, the prevalence of thrombocytopenia may reach up to 65 to 100% in patients with catastrophic APS (CAPS).^{8,9} Thus, some authors have suggested that a progressive decrease in the platelet count in APS patients may be considered a sign for progressive disease and be a risk factor for developing CAPS in the future.^{1,10} Furthermore, Artim-Esen et al.⁴ reported coexistence of thrombocytopenia and neuropsychiatric manifestations, in association with lupus anticoagulant and high titers of anticardiolipin antibodies.

Although several studies have been conducted on thrombocytopenia in APS patients to date,^{6,11-13} there are important issues that still need to be addressed, such as relation of thrombocytopenia to clinical associations of APS, its effect on the disease outcomes, and finally the relation of thrombocytopenia to the APS damage index (DIAPS). In the present study, we aimed to evaluate the prevalence of thrombocytopenia in patients with APS and to examine the relation of thrombocytopenia to the clinical and laboratory findings, and DIAPS.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at Cairo University Hospital, Faculty of Medicine, Department of Rheumatology, between August 2018 and February 2019. A total of 168 patients (16 males, 152 females; mean age: 32.5±8.4 years; range, 18 to 59 years) who were followed in our clinic and fulfilled the update of Sapporo Classification Criteria for definite APS¹⁴ were included. The medical records were revised for demographic data, clinical features of the disease, immune profile, routine laboratory investigations, and treatments applied. In addition, the DIAPS¹⁵ was calculated for all patients. The patients were divided into two groups according to the presence or absence of thrombocytopenia and both groups were compared regarding demographic data, clinical, laboratory findings, treatments, and DIAPS. Patients less than 18 years old or with disease duration of less than two years were excluded from the study. Thrombocytopenia was considered a clinical feature of APS in our study, when the platelet count of less than 150×10⁹/L was found on a minimum of two occasions.¹¹

Further subgroup analysis was done for patients with PAPS according to the presence or absence of thrombocytopenia.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max) for quantitative variables and in number and frequency for qualitative variables. Comparison between the groups was conducted using the Student t-test for normally distributed data and Mann-Whitney U test for skewed data. The chi-square test was used analyze qualitative variables. A *p* value of <0.05 was considered statistically significant.

RESULTS

The mean disease duration was 9.3±6.1 years, and the mean age at onset was 23.3±7.6 years. Forty-five (26.8%) patients had PAPS, 116 (69%) patients had APS secondary to systemic lupus erythematosus (SLE), while seven (4.2%) patients had APS secondary to other diseases. The most commonly reported manifestations in our patients were obstetric manifestations (77.4% in pregnant women), musculoskeletal manifestations (69%), and peripheral vascular thrombosis (54.8%) (Table 1).

The laboratory features of our patients in the last visit, their treatment and DIAPS are shown in Table 2. Our patients were divided into two groups according to presence or absence of thrombocytopenia, the two groups were compared regarding demographic, clinical, laboratory, treatments, and DIAPS as shown in Table 3. Furthermore, we studied patients with PAPS to exclude any impact of associated disease, and we divided them into two groups according to the presence or absence of thrombocytopenia and both groups were compared regarding the previously mentioned items as shown in Table 4.

DISCUSSION

The estimated prevalence of thrombocytopenia in APS in the literature ranges between

Table 1. Demographic data, clinical manifestations, and immune profile of APS patients (n=168)

	n	%	Mean±SD	Range	Median	IQR
Age (year)			32.5±8.5	18-59	32	26-37
Sex						
Male	9.5	16				
Female	90.5	152				
Age at onset (year)			23.3±7.6	11-52	22	18-25
Disease duration (year)			9.3±6.1	1-41	8	4.5-13
Time till diagnosis (year)			3±3.8	0-25	2	0.3-4.5
Obstetric manifestations related to APS	103	77.4				
Musculoskeletal manifestations	116	69				
Hematological manifestations (anemia-leukopenia-thrombocytopenia)	81	48.2				
Hemolytic anemia	24	14.3				
Thrombocytopenia at onset	51	30.4				
Thrombocytopenia throughout disease	71	42.3				
Constitutional manifestations	86	51.2				
Peripheral vascular thrombosis	92	54.8				
Venous thrombosis	78	46.4				
Arterial thrombosis	24	14.3				
Neurological manifestations (Seizures, stroke, TIA, psychosis)	69	41.1				
Cardiovascular manifestations (valve disease, pericardial effusion, coronary vascular diseases)	68	40.5				
Cutaneous manifestations (Thrombophlebitis,digital gangrene, cutaneous ulcers, livido reticularis)	56	33.3				
Pulmonary manifestations (Pulmonary hypertension, embolism, insufficiency)	34	20.2				
Renal manifestations (Nephritis, thrombotic microangiopathy, renal failure, renal artery/vein thrombosis)	61	36.3				
Ophthalmological manifestations (Retinal vasculitis, retinal thrombosis)	11	6.5				
Hepatic and GI manifestations (Budd chiari and mesenteric thrombosis)	6	3.6				
Associated disease	56	33.3				
Hypertension	43	25.6				
Diabetes	11	6.5				
Others	11	6.5				
Antinuclear antibody	127	75.6				
Anti-double-stranded deoxyribonucleic acid	59	35.1				
Lupus anticoagulant	97	57.7				
ACL IgG	86	51.2				
ACL IgM	54	32.1				
Anti-B2 glycoprotein IgG	41	24.4				
Anti-B2 glycoprotein IgM	26	15.5				

APS: Antiphospholipid syndrome; SD: Standard deviation; IQR: Interquartile range; TIA: Transient ischemic attack; GI: Gastrointestinal; ACL: Anti-cardiolipin antibodies; Ig: Immunoglobulin.

Table 2. Laboratory features, treatment and DIAPS

	n	%	Mean±SD	Range	Median	IQR
Hemoglobin			11±1.8	6.7-18.6	11	10-12.1
Total leucocytic count			7.6±6.3	0.5-66	7	5-8.3
Erythrocyte sedimentation rate			41.2±35.5	2-337	32	20-54.5
Alanin aminotransferaz			25.4±35.4	3-380	19	14.5-27.5
Creatinine			0.9±0.9	0.3-8	0.7	0.5-0.9
Anticoagulation	119	70.8				
Antiplatelet	150	89.3				
Corticosteroids	141	83.9				
Antimalarial	139	82.7				
Immunosuppressive treatment	124	73.8				
DIAPS			2.2±2.1	0-9	2	0-4

DIAPS: Damage index for antiphospholipid syndrome; APS: Antiphospholipid syndrome; SD: Standard deviation; IQR: Interquartile range.

20 and 50%,^{4,6} which is consistent with our results (42.3%). The similarity in the frequency of thrombocytopenia between males and females in the current study (43.75% and 42.1%) is in accordance with that reported in previous studies.^{6,7}

Regarding obstetric manifestations, we could not detect significant associations between thrombocytopenia and obstetric morbidity in our patients. On the other hand, our results showed a high rate of overall neurological manifestations in thrombocytopenia group compared to non-thrombocytopenia group (50.7% vs. 34%) with a statistically significant difference ($p=0.03$). We also found a strong association between thrombocytopenia and musculoskeletal manifestations (77.5% vs. 62.9%) ($p=0.043$). Similarly, Krause et al.⁶ reported that obstetric complications were similar in patients with and without thrombocytopenia and that the presence of thrombocytopenia might be a risk factor for neurological and articular manifestations. Also, Artim-Esen et al.⁴ reported that thrombocytopenia represents a risk factor for thrombosis and neurological manifestations in aPL-positive patients.

Our results showed a high rate of venous thrombosis in thrombocytopenia group compared to non-thrombocytopenia group (50.7% vs. 43.3%); however, this was not statistically significant ($p=0.342$). A high rate of arterial thrombosis was also found in

thrombocytopenia group compared to the other, but also this was not statistically significant (18.3% vs. 11.3%) ($p=0.202$). Also, total peripheral vascular thrombosis was higher in the positive group compared to the negative group (63.4% vs. 48.5%), with a p value quite close to the significant value ($p=0.055$). Comparing the two groups regarding total thrombotic events (peripheral vascular and internal organs), thrombocytopenia group showed a higher incidence of total thrombosis (77.5% vs. 62.9%) with a significant p value of 0.043, although the rate of thrombosis in the study conducted by Krause et al.⁶ was slightly higher in the thrombocytopenia group; however, it did not reach statistical significance. On the other hand, Atsumi et al.¹⁶ reported that the presence of thrombocytopenia in patients with APS was not typically associated with hemorrhagic complications; rather, it could trigger thrombotic events. It was also found that the more severe the thrombocytopenia, the higher the possibility of future thrombosis. Also, Pontara et al.⁸ reported that a decrease in platelet count was associated with the development of the catastrophic form of the disease, a decrease in platelet count in high-risk APS patients should be evaluated cautiously for the disease progression to CAPs.

Furthermore, our results are in accordance with Demetrio Pablo et al.,¹⁷ as they reported that aPL-positive patients who developed thrombocytopenia had a potential risk of developing thrombosis. In addition,

Table 3. Comparison of all APS patients included in our cohort according to presence and absence of thrombocytopenia

	Thrombocytopenia throughout disease										p	
	+VE (n=71)					-VE (n=97)						
	n	%	Mean±SD	Range	Median	IQR	n	%	Mean±SD	Range	Median	IQR
Age (year)	7	9.9	31.7±9	18-59	30	24-38	9	9.3	33.1±8.1	18-55	32	28-37
Sex												
Male	64	90.1					88	90.7				
Female												
Age at onset (year)			23±7.9	12-45	21	18-25			23.4±7.3	11-52	22	19-26
Disease duration (year)			8.7±6.9	1-41	7	4-11			9.7±5.3	1-26	9	5-14
Time till diagnosis (year)			3.3±4.5	0-25	1	0.3-5			2.8±3.2	0-14	2	0.4-4
Obstetric manifestations	43	74.1					60	80				
Musculoskeletal manifestations	55	77.5					61	62.9				
Hemolytic anemia	14	19.7					10	10.3				
Systemic manifestations	40	56.3					46	47.4				
Vascular thrombosis (Peripheral and internal organs)	55	77.5					61	62.9				
Peripheral vascular thrombosis	45	63.4					47	48.5				
Venous thrombosis	36	50.7					42	43.3				
Arterial thrombosis	13	18.3					11	11.3				
Neurological manifestations	36	50.7					33	34				
Cardiovascular manifestations	33	46.5					35	36.1				
Cutaneous manifestations	32	45.1					24	24.7				
Pulmonary manifestations	14	19.7					20	20.6				
Renal manifestations	26	36.6					35	36.1				
Ophthalmological manifestations	7	9.9					4	4.1				
Hepatic and GIT manifestations	4	5.6					2	2.1				
Antinuclear antibody	56	78.9					71	73.2				
Anti-double-stranded deoxyribonucleic acid	22	31					37	38.1				
Lupus anticoagulant	43	60.6					54	55.7				
ACL IgG	37	52.1					49	50.5				
ACL IgM	25	35.2					29	29.9				
Anti- B2 glycoprotein IgG	16	22.5					25	25.8				
Anti- B2 glycoprotein IgM	11	15.5					15	15.5				
Hemoglobin			11±1.8	6.7-18.6	10.7	9.7-12			11.1±1.8	6.9-15.8	11.2	10-12.5
Total leucocytic count			6.8±2.6	2.4-15	6.9	5-8.4			8.2±7.9	0.5-66	7	5-8.2
Erythrocyte sedimentation rate			41±26.7	2-113	33	20-55			41.4±40.9	5-337	30	18-50
Anticoagulation	53	74.6					66	68				
Antiplatelet	65	91.5					85	87.6				
Corticosteroids	62	87.3					79	81.4				
Antimalarial	62	87.3					77	79.4				
Immunosuppressive treatment	58	81.7					66	68				
DJ/APS			2.6±2.3	0-9	2	1-4			1.9±1.9	0-8	1	0-3

APS: Antiphospholipid syndrome; SD: Standard deviation; IQR: Interquartile range; GIT: Gastrointestinal tract; ACL: Anti-cardiolipin antibodies; Ig: Immunoglobulin; DJ/APS: Damage index for antiphospholipid syndrome; * Chi square test; # Student t-test; † Mann-Whitney U test.

Table 4. Comparison of APS patients included in our cohort according to presence and absence of thrombocytopenia (n=45)

	Thrombocytopenia throughout disease										p	
	Yes (n=15)					No (n=30)						
	n	%	Mean±SD	Range	Median	IQR	n	%	Mean±SD	Range	Median	IQR
Age (year)	0	0	30.7±7.8	22-47	29	24-37	2	6.7	31.8±7	20-48	32.5	26-36
Sex	15	100					28	93.3				
Male							2					
Female							28					
Age at onset (year)			21.7±8.4	13-43	19	17-22			23±5.5	16-40	21.5	19-25
Disease duration (year)			8.9±7.5	1-24	6	3-16			8.8±5	2-18	8	4-12
Time till diagnosis (year)			3.6±3.7	0-12	3	0.3-5			3.7±3.1	0-14	3	2-5
Obstetric manifestations	12	80					24	88.9				
Musculoskeletal manifestation	9	60					9	30				
Hemolytic anemia	2	13.3					0	0				
Constitutional manifestations	6	40					4	13.3				
Vascular manifestations	9	60					12	40				
Venous thrombosis	5	33.3					9	30				
Arterial thrombosis	6	40					4	13.3				
Neurological manifestations	8	53.3					4	13.3				
Cardiovascular manifestations	3	20					6	20				
Cutaneous manifestations	6	40					5	16.7				
Pulmonary manifestations	1	6.7					6	20				
Renal manifestations	2	13.3					2	6.7				
Ophthalmological manifestations	1	6.7					1	3.3				
Hepatic and GIT manifestations	1	6.7					1	3.3				
Antinuclear antibody	3	20					6	20				
Anti-double-stranded deoxyribonucleic acid	0	0					0	0				
Lupus anticoagulant	12	80					23	76.7				
ACL IgG	8	53.3					13	43.3				
ACL IgM	7	46.7					7	23.3				
Anti- B2 glycoprotein IgG	3	20					6	20				
Anti- B2 glycoprotein IgM	3	20					1	3.3				
Hemoglobin			10.9±1.4	8.5-13	10.9	10-12			11±1.4	8-13	11.3	10-12
Total leucocytic count			7.8±1.7	5-11	7.8	7-9			10.6±13.3	4-66	7	5.5-9.1
Erythrocyte sedimentation rate			36.6±25.1	10-110	30	20-50			42.4±60.2	6-337	25	18-43
Anticoagulation	14	93.3					26	86.7				
Antiplatelet	14	93.3					27	90				
Corticosteroids	6	40					14	46.7				
Antimalarial	11	73.3					20	66.7				
Immunosuppressive treatment	4	26.7					5	16.7				
DJAPS			2.1±2.2	0-6	1	0-4			1.1±1.7	0-6	0	0-2

APS: Antiphospholipid syndrome; SD: Standard deviation; IQR: Interquartile range; GIT: Gastrointestinal tract; ACL: Anti-cardiolipin antibodies; Ig: Immunoglobulin; D/APs: Damage index for antiphospholipid syndrome; * Chi square test; † Mann-Whitney U test.

Abreu et al.¹⁸ showed that thrombocytopenia in APS was a consequence of consumption of platelets, as binding of aPL antibodies, particularly anti-beta-2 glycoprotein antibodies, to the surface of activated platelets promoted their aggregation and thrombus formation. Finally, Proulle et al.¹⁹ showed that, among aPL-positive patients, thrombosis might develop more frequently in patients with a low platelet count, compared to those without.

Although Krause et al.⁶ found significant associations between thrombocytopenia and cardiac valves thickening and dysfunction, our results showed no statistically significant difference between the two groups regarding overall cardiac manifestations.

Regarding cutaneous manifestations (cutaneous ulcers, digital gangrene, livedo, thrombophlebitis), our results showed an overall increase in the rate of cutaneous manifestations in the thrombocytopenia group compared to the other group (45.1% vs. 24.6%) with a statistically significant difference ($p=0.006$). Similarly, Krause et al.⁶ and Comellas-Kirkerup et al.²⁰ reported significant associations between thrombocytopenia and cutaneous manifestations including livedo reticularis and skin ulcerations. Furthermore, many reports have suggested that livedo reticularis may be associated with more severe disease, as it may be associated with thrombosis,²¹ and also it may be associated with stroke.²² In our study, both thrombosis and stroke were significantly higher in the thrombocytopenia group and this is in line with the findings of Artim-Esen et al.⁴ Moreover, the association of thrombocytopenia with neurological manifestations was also confirmed in our PAPS cohort.

The significantly higher usage of immunosuppressive in the thrombocytopenia group, in our study, was expected as thrombocytopenia, particularly if severe, may require treatment with high dose glucocorticoids, immunosuppressive drugs, and rituximab along with intravenous immunoglobulin and plasma exchange.²³⁻²⁵

Damage index for APS was significantly higher in thrombocytopenia group ($p=0.034$). This may be a sequence of the higher prevalence of neurological manifestations, thrombosis and cutaneous manifestations, all of which

may be associated with more damage. Also, thrombocytopenia itself may be a sign of more aggressive disease and may require treatment with immunosuppressors adding to the disease burden and may affect the disease outcome. To the best of our knowledge, no previous study has compared damage accrual in APS patients with and without thrombocytopenia; however, Ruiz-Irastorza et al.²⁶ concluded that APS associated with thrombosis might present more damage in SLE. Furthermore, Artim-Esen et al.⁴ reported that thrombocytopenia was a risk factor for thrombosis in aPL-positive patients. All the aforementioned data may give a reasonable explanation of the higher damage index in the thrombocytopenia group.

On analyzing PAPS patients and although DIAPS was higher in PAPS patients with thrombocytopenia (2.1 ± 2.2) compared to (1.1 ± 1.7) in those without, the difference did not reach statistical significance ($p=0.082$). Similarly, venous thrombosis, arterial thrombosis, and total peripheral vascular thrombosis were higher in thrombocytopenia group; however, the difference did not reach statistical significance ($p=0.062$). The lack of association of thrombocytopenia with DIAPS and arterial thrombosis, although p value quite close to significant in both situations, may be due to the small sample size of patients with PAPS in the current cohort. In our opinion, thrombocytopenia may represent more than an incidental laboratory finding in APS patients, and further studies may be needed to explore its role in APS pathogenesis and in damage occurrence in APS patients.

The small number of patients with PAPS included in the current study is the main limitation. We, therefore, recommend further studies on thrombocytopenia to be conducted on a large cohort of PAPS patients to avoid the impact of any associated disease as SLE on APS characteristics and DIAPs.

In conclusion, thrombocytopenia may be associated with a higher incidence of vascular thrombosis, neurological manifestations, musculoskeletal manifestations, use of immunosuppressive treatment, and DIAPS. In PAPS patients, thrombocytopenia may be a risk for neurological manifestations; however further large-scale studies are needed to confirm our findings.

Ethics Committee Approval: The study protocol was approved by the local department committee in June 2018 and by the faculty post graduate research committee in 15 August 2018. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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