Thrombocytopenia and Autoimmune Hemolytic Anemia in Antiphospholipid Antibody-positive Patients: Descriptive Analysis of the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ("Registry")

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Abstract:

Background/Purpose: The APS ACTION Registry was created to study the natural course of antiphospholipid syndrome (APS) over 10 years in persistently antiphospholipid antibody (aPL) positive patients with or without systemic autoimmune disease (SAIDx). Our primary objective was to compare the clinical characteristics of aPL-positive patients with or without thrombocytopenia (TP) and/or autoimmune hemolytic anemia (AIHA). Secondly, we analyzed the immunosuppressive medications used in aPL-positive patients with TP and/or AIHA.

Methods: The registry inclusion criteria are positive aPL based on the laboratory section of the Revised Sapporo APS Classification Criteria, tested at least twice within one year prior to enrollment. For the primary comparison, patients, based on registry recruitment data, we divided patients into two groups (TP/AIHA ever and never). Thrombocytopenia was defined as a platelet count of <100,000 per microliter tested twice at least 12 weeks apart, and AIHA was defined as anemia with hemolysis and with a positive direct antiglobulin test (DAT). For the secondary analysis, the immunosuppressive use was compared between patients with primary aPL/APS versus those with systemic lupus erythematosus (SLE). Data on demographics, clinical, serologic, and treatment characteristics were compared by Fisher's exact test.

Results: As of April 2022, of 1,039 patients (primary aPL/APS: 618 [59%]; SLE classification: 334 [31%]) included in the registry, 228 (22%) had baseline (historical or current) TP and/or AIHA (TP only: 176 [17%]; AIHA only: 35 [3%], and both: 17 [2%]. Thrombocytopenia and/or AIHA was significantly associated with Asian race, SLE classification, cardiac valve disease, catastrophic APS, microvascular disease (diffuse alveolar hemorrhage, aPL-nephropathy, and livedoid vasculopathy related skin ulcers), lupus anticoagulant (LA) and triple aPL (LA, anticardiolipin antibody, and anti-β_2-glycoprotein-I antibody) positivity. When 101/618 (16%) primary aPL/APS patients and 101/334 [34%] SLE patients with TP and/or AIHA were compared, azathioprine, mycophenolate mofetil, and methotrexate use were more commonly reported in lupus patients, however corticosteroid, hydroxychloroquine, intravenous immunoglobulin, and rituximab use were similar between groups.

Conclusion: In our large multi-center international cohort of persistently aPL-positive patients, approximately one-fifth had active or historical TP and/or AIHA at the registry entry; half of these patients had additional lupus classification. Microvascular disease, cardiac valve disease, LA, and triple aPL-positivity were associated with TP and/or AIHA, suggesting a more severe APS clinical phenotype in aPL-patients with TP and/or AIHA.

Background:

Antiphospholipid syndrome (APS) is characterized by thrombosis and/or pregnancy morbidity in association with antiphospholipid antibodies (aPL); lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β_2 glycoprotein-I antibodies (aβ_2GPI)[1]. Antiphospholipid syndrome may exist in its primary form when it occurs in patients without concomitant systemic autoimmune diseases (SAIDx), or in association with other autoimmune disorders, particularly systemic lupus erythematosus (SLE)[2].

The Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) was created in 2010 specifically to conduct large-scale multi-center clinical studies and trials in persistently aPL-positive patients. The goal of the APS ACTION Clinical Database and Repository (‘‘Registry’’) is to study the natural course of persistently aPL-positive patients with or without other SAIDx over at least 10 years[3].

Thrombocytopenia (TP) and autoimmune hemolytic anemia (AIHA) can occur in aPL-positive patients; however, there is a limited number of studies on hematological manifestations of aPL, including the impact of these manifestations on APS presentation. Thus, our primary objective was to retrospectively compare the baseline demographics, clinical, serological characteristics of aPL-positive patients with or without TP and/or AIHA. Secondly, we analyzed immunosuppressive medications used in persistently aPL-positive TP and/or AIHA patients with or without SLE classification.

Methods:

The inclusion criteria for the APS ACTION registry are positive aPL based on the Revised Sapporo Classification Criteria at least twice within one year prior to enrollment. Demographics, aPL-specific medical history (including macrovascular, microvascular, or non-thrombotic aPL-related manifestations), historical aPL results and baseline platelet counts, historical and active aPL-related medications (including anticoagulant/antiplatelet medications and immunosuppressive agents), and blood samples (for aPL-positivity confirmation) are collected at registry entry. For the purposes of registry data collection, TP is defined as a platelet count of

<100 x 10^9/L tested twice at least 12 weeks apart, and AIHA as anemia with hemolysis and a positive direct antiglobulin test (DAT) . Patients are followed every 12 ± 3 months with additional clinical data and blood collection. The registry data are managed using REDCap electronic data capture tool, a secure, web-based system designed to support research studies[4].

For the primary analysis of this descriptive retrospective study, we identified all patients who ever developed TP and/or AIHA, and compared their baseline demographics, clinical, and serological characteristics to those who never had TP or AIHA. For the secondary analysis, following a comparison of the characteristics of TP and/or AIHA patients with or without SLE classification (based on the 1997 American College of Rheumatology SLE classification criteria), we compared the immunosuppressive medications ever received by these patients.

Data were summarized in a descriptive fashion; mean ± standard deviation (SD) was used for continuous variables. Statistical comparisons were performed using the chi-square test and Fisher's exact test for categorical variables, and the Mann–Whitney U-test and Student's t-test for continuous variables, as appropriate.

Results:

As of April 2022, of 1,039 persistently aPL-positive patients (primary aPL with or without APS classification [aPL/APS]: 618 [59%]; aPL/APS with SLE classification: 334 [31%]; and aPL/APS with non-SLE systemic autoimmune disease: 87 [10%]), 228 (22%) were reported to have TP and/or AIHA ever (TP only: 176 [17%] [52 with current TP and 124 historical]; AIHA only: 35 [3%] [9 active and 26 historical], and both TP and AIHA: 17 [2%] [7 active and 10 historical]). Of 59/193 patients with active TP at baseline, the mean baseline platelet count was 78 $\pm$ 26.5 x 10^9/L (range: 3-99 x 10^9/L) (there were 30 (3%) patients with baseline platelet count of 100-130 x 10^9/L, and 20 (2%) with 131-150 x 10^9/L, which were not included in the analysis given the lack of historical platelet counts).

Of 228 with TP and/or AIHA ever, 101 (44%) had primary aPL/APS and 101 (44%) had aPL/APS with SLE classification; patients with TP only were more likely to have primary aPL/APS (p= 0.02), whereas those with AIHA with/without TP were more likely to have SLE classification (p: 0.005) (Table 1).

Based on the primary analysis, TP and/or AIHA was significantly associated with Asian race (14% of those with TP/AIHA vs 7% without TP/AIHA), SLE classification (45% vs 29%), cardiac valve disease (14% vs 9%), catastrophic APS (3% vs 1%), and microvascular disease (diffuse alveolar hemorrhage, aPL-nephropathy, and/or livedoid vasculopathy related-skin ulcers) (33% vs 23%), Furthermore, triple-aPL (LA, aCL, and aβ_2GPI) positivity (49% vs 37%) as well as positive SLE serologies (anti-nuclear antibody [ANA] [71% vs 60%], anti-double-strand DNA antibody [anti-dsDNA] [43% vs 28%], anti-Smith antibody [anti-Sm] [8% vs 4%], and low complement C3 [52% vs 30%] and C4 [46% vs 32%] levels) were significantly more common in patients with TP and/or AIHA ever (Table 2).

Thrombocytopenia (with/without AIHA) or AIHA (with/without TP) were reported in 15% and 2% of primary aPL/APS patients, respectively, compared to 24% and 10% of aPL-positive patients with SLE classification ($p<0.05$ for both). Patients with SLE classification, compared to those without SLE classification, were more likely to have ANA and dsDNA positivity, and low C3 levels; however demographic, clinical, and other serologic characteristics were similar (Supplement Table 1).

In a subgroup analysis of 101 of 618 (16%) primary aPL/APS and 101/334 (34%) SLE patients with TP and/or AIHA, azathioprine (AZT), mycophenolate mofetil (MMF), and methotrexate (MTX) use were more commonly reported in SLE patients, however corticosteroid, hydroxychloroquine (HCQ), intravenous immunoglobulin, or rituximab (RTX), were similar between two groups (Table 3). When we compared the demographic and clinical characteristics of active *versus* historical TP and/or AIHA patients at baseline, there was no difference in medications except that HCQ was more common in patients with historical hematologic involvement (50% vs 73%, $p<0.001$) (full data not shown).

Discussion:

Based on our large multi-center international cohort of persistently aPL-positive patients, approximately one-fifth of our patients had active or historical TP (19%) and/or AIHA (5%) at the registry entry, half of these patients had additional SLE classification, and TP and/or AIHA was more common in patient of Asian descent. Cardiac valve disease, catastrophic APS, and microvascular disease were more commonly associated with TP and/or AIHA, suggesting a more severe APS clinical phenotype in aPL-positive patients with hematological manifestations.

Approximately 20% of aPL-positive patients with or without other systemic autoimmune diseases develop mild-to-moderate TP[5] and 5-10% AIHA[6,7]. Previous APS ACTION registry analysis based on 623 patients demonstrated that aPL-positive patients with SLE, compared to those with no other systemic autoimmune diseases, have an increased frequency of TP and AIHA[8]. Our current analysis with a larger number of patients supports our previous findings, and clearly demonstrates that hematological manifestations (TP and/or AIHA) are more common in aPL-positive patients with SLE classification (24% and 10%, respectively), compared to those without SLE (15% and 2% respectively). Furthermore, in our prior descriptive registry analysis 19% of registry patients had TP (with 7% being of Asian descent)[5], while a study conducted in China reported a higher prevalence of TP (33%) in their registry[9]. Our study reaffirms these previous findings, showing increased prevalence of TP and/or AIHA in Asian patients.

Although TP is an independent predictor of recurrent thrombotic and obstetric events[10], studies disagree if the clinical and serologic characteristics of aPL-positive patients with or without TP differ[11],[12]; these studies have a relatively small sample size and generally focus only on TP with the exclusion of AIHA. Our study adds to prior studies as we approached hematological manifestations from an integrative perspective demonstrating that history of TP and/or AIHA are associated with more severe disease phenotype, i.e., microvascular disease and cardiac valve disease. This finding is important and timely given that 2023 ACR/EULAR APS classification criteria[13] include well-defined microvascular, cardiac valve, and hematologic (TP) domains.

Assessment of the laboratory profile along with clinical phenotype plays an important role in assessing disease severity in aPL-positive patients. In a 38-year follow-up study, persistent TP

was commonly associated with LA positivity and more than one aPL test positivity[14.] Our analysis supports and expands these findings, demonstrating that LA and triple-aPL positivity were significantly more common in patients with TP and/or AIHA ever.

Thrombocytopenia usually does not require any treatment in aPL-positive patients because the degree of TP is generally above 30-50 × 109 L [15] and patients are not at significantly increased risk for bleeding [16]. For severe TP, corticosteroids and/or IVIG are first line treatment, with second-line therapy including [17], thrombopoietin receptor agonists (TPO-RA), rituximab, and other immunosuppressants [18,19, 18,19]. Although commonly used in ITP, TPO-RA have not been extensively studied in patients with APS and should be used in caution in patients with active thrombosis. Treatment of aPL-positive patients who develop DAT-positive warm AIHA includes corticosteroids with rituximab, other immunosuppressants, e.g., AZT, MMF, and splenectomy for refractory or relapsed disease [20,21,22]. When primary aPL/APS and SLE patients who were reported to have TP and/or AIHA were compared, AZT, MMF, and MTX use were more common in SLE patients, however CS, HCQ, IVIG, or rituximab use was similar between groups.

Thrombocytopenia can develop in aPL-positive patients due to aPL-mediated platelet activation and consumption, or life threatening systemic thrombotic microangiopathy.[23] Similarly, AIHA can develop due to autoantibodies directed at the red blood cell surface, specifically membrane-bound glycoproteins, causing decreased red blood cell survival. [24]Although our study cannot differentiate between warm AIHA and cold agglutinin disease, it provides valuable insights into the association between AIHA and APS.

While our study is retrospective in design, it drew upon data from a large, multi-center patient cohort. Although registry patients are followed prospectively, platelet counts during the follow-up visits are not collected, precluding our ability to assess improvements in platelet counts, as well as commentary on the efficacy of immunosuppressive medications. The indication for immunosuppression use was also unspecified, which could additionally constrain our study. Nonetheless, the incorporation of patients from diverse international centers enriches our registry and minimizes potential biases inherent in single-center studies. Future prospective APS

ACTION registry analysis will be instrumental in refining our understanding of hematological manifestations in APS.

In conclusion, our analysis of retrospective data from a substantial, multi-center international cohort of persistently aPL-positive patients revealed that one-fifth of the patients exhibited active or historical TP and/or AIHA upon registry entry, notably, half of these patients also met criteria for SLE classification. Furthermore, our findings indicated associations between TP and/or AIHA and various manifestations, including microvascular disease, cardiac valve disease, LA, and triple aPL-positivity. Overall, our study highlights a more severe APS clinical phenotype in aPL-positive patients with TP and/or AIHA.

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Table 1: Baseline Demographic, Clinical, and Laboratory Characteristics of Antiphospholipid antibody (aPL)-positive Patients Based on Thrombocytopenia and/or Autoimmune Hemolytic Anemia History

# of patients: 228	**TP without AIHA N: 176 (17%)**	**AIHA without TP N: 35 (3%)**	**TP and AIHA N: 17 (2%)**	**P-value**
Mean Age at Registry Entry	45±13	44±13	40±15	0.32
Gender				
-Female	132 (75%)	29 (83%)	9 (53%)	0.07
Race				
-White	111 (65%)	19 (56%)	12 (75%)	0.06
-Black	6 (4%)	1 (3%)	0	N/A
-Asian	22 (13%)	8 (34%)	3 (19%)	0.25
Primary APL/APS *	88 (51%)	9 (26%)	3 (19%)	**0.002**
SLE Classification**	67 (39%)	23 (68%)	12 (75%)	**0.0005**
TAPS only	84 (49%)	18 (53%)	10 (63%)	**0.005**
OAPS only	17/132(13%)	3/29 (10%)	1/9 (11%)	0.92
TAPS+OAPS	28 /132 (21%)	3/29 (10%)	2/9 (22%)	0.39
No APS Classification	42 (25%)	10 (29%)	3 (19%)	0.44
Cardiac Valve Disease	22/155 (14%)	4/30 (13%)	3/16 (19%)	0.87
Catastrophic APS	5 (3%)	1 (3%)	1 (14%)	0.78
Microvascular APS **	49 (29%)	6 (18%)	5 (31%)	0.38

Triple aPL positive	74/150 (49%)	12/28 (43%)	9/17 (53%)	0.76
LA positive only	33/170 (19%)	10/33 (30%)	1/17 (6%)	0.11
aCL and/or aβ$_2$GPI positive (excluding LA)	24/175 (14%)	3/29 (10%)	3/17 (18%)	0.77
Immunosuppressive Medication Use				
-Corticosteroids	44 (25%)	17 (49%)	4 (24%)	**0.01**
-IVIG	34 (19%)	9 (26%)	7 (41%)	0.10
-Plasma Exchange	11 (6%)	1 (3%)	3 (18%)	0.12
-Rituximab	22 (13%)	4 (11%)	8 (47%)	**0.0005**
-Azathioprine	16 (9%)	8 (23%)	4 (24%)	**0.02**
-Cyclophosphamide	4 (2%)	2 (6%)	0	N/A
-Cyclosporine	3 (2%)	0	0	N/A
-Mycophenolate Mofetil	25 (14%)	10 (29%)	4 (24%)	0.09
-Methotrexate	5 (3%)	2 (6%)	0	N/A

TAPS: Thrombotic APS; **OAPS:** Obstetric APS; **LA:** Lupus anticoagulant; **ANA:** antinuclear antibody. * p 0.009 for TP without AIHA vs AIHA without TP; p 0.01 for TP without AIHA vs TP and AIHA; and p 0.72 for AIHA without TP vs TP and AIHA; ** p 0.004 for TP without AIHA vs AIHA without TP; p 0.01 for TP without AIHA vs TP and AIHA; and p 1.0 for AIHA without TP vs TP and AIHA; *** Microvascular APS defined as DAH, aPL nephropathy, and/or livedoid vasculopathy

Table 2: Baseline Demographic, Clinical, and Laboratory Characteristics of Antiphospholipid antibody (aPL)-positive Patients, By Thrombocytopenia (TP) and Autoimmune Hemolytic Anemia (AIHA) History

# of patients: 1,039	**TP and/or AIHA Ever 228 (22%)**	**TP and/or AIHA Never 804 (77%)**	**P Value**
Mean Age (Registry Entry)	50±13	52±13	**0.04**
Gender			1.0
-Female	170 (75%)	598 (74%)	
Race			
-White	142 (62%)	555 (69%)	0.10
-Black	7 (3%)	26 (3%)	1.00
-Asian	33 (14%)	53 (7%)	**<0.01**
Primary APL/APS	101 (44%)	519 (65%)	**<0.01**
SLE Classification	102 (45%)	232 (29%)	**<0.01**
TAPS only	118 (52%)	438 (54%)	0.50
OAPS only	21/170 (12%)	70/598 (12%)	0.80
TAPS+OAPS	34/170 (20%)	92/598 (15%)	0.15
No APS Classification	55 (24%)	204 (25%)	0.70
Cardiac Valve Disease	29/201 (14%)	59/679 (9%)	**0.02**
Catastrophic APS	7 (3%)	5 (1%)	**<0.01**
Microvascular APS*	75 (33%)	187 (23%)	**<0.01**
Triple aPL-positive	96/195 (49%)	249/682 (37%)	**<0.01**
LA positive only	44/220 (20%)	217/762 (28%)	**0.01**

aCL and/or aB2GPI positive (excluding LA)	24/226 (11%)	142/802 (18%)	**0.01**
ANA positive **Anti-dsDNA positive** **Anti-SM positive**	160/226 (71%) 96/225 (43%) 19/225 (8%)	478/795 (60%) 220/797 (28%) 34/797 (4%)	**<0.01** **<0.01** **0.02**
Low C3 **Low C4**	50/97(52%) 45/97 (46%)	84/279 (30%) 88/279 (32%)	**0.0002** **0.001**

TAPS: Thrombotic APS; **OAPS:** Obstetric APS; **LA:** Lupus anticoagulant test; **ANA:** antinuclear antibody; **dsDNA:** Double stranded DNA; **Anti-SM:** Anti-smith antibody; **C3/C4:** Complement C3/C4. * Microvascular APS defined as DAH, aPL nephropathy, and/or livedoid vasculopathy

Table 3: Immunosuppressive Medication Use Reported (Ever) in Patients with History of Thrombocytopenia (TP) and/or Autoimmune Hemolytic Anemia (AIHA)*, By Systemic Lupus Erythematosus (SLE) Classification

# of patients: 202	**Primary aPL/APS N:101**	**aPL/APS with SLE Classification N: 101**	**P value**
Corticosteroids	23 (23%)	32 (32%)	0.20
-TP Only	19 (19%)	18 (18%)	1.0
-AIHA Only	3 (3%)	12 (12%)	**0.02**
-TP and AIHA**	1 (1%)	2 (2%)	1.0
IVIG	23 (23%)	21 (21%)	0.86
-TP Only	18 (18%)	11 (11%)	0.23
-AIHA Only	4 (4%)	5 (5%)	1.0
-TP and AIHA**	1 (1%)	5 (5%)	0.21
Plasma Exchange	6 (6%)	6 (6%)	1.0
-TP Only	6 (6%)	4 (4%)	0.74
-AIHA Only	0	1 (1%)	N/A
-TP and AIHA	0	1 (1%)	N/A
Rituximab	11 (11%)	18 (18%)	0.11
-TP Only	9 (9%)	10 (10%)	1.0
-AIHA Only	0	4 (4%)	N/A
-TP and AIHA**	2 (2%)	4 (4%%)	0.68
Azathioprine	8 (8%)	20 (20%)	**0.02**
-TP Only	6 (6%)	8 (8%)	0.79
-AIHA Only	2 (2%)	6 (6%)	0.28
-TP and AIHA**	0	4 (4%)	N/A
Cyclophosphamide	0	6 (6%)	**N/A**
-TP Only	0	4 (4%)	**N/A**

-AIHA Only	0	2 (2%)	**N/A**
-TP and AIHA**	0	0	N/A
Cyclosporine	2 (2%)	1 (1%)	1.0
-TP Only	2 (2%)	1 (1%)	1.0
-AIHA Only	0	0	N/A
-TP and AIHA**	0	0	N/A
Mycophenolate Mofetil	3 (3%)	32 (32%)	**0.0001**
-TP Only	3 (3%)	20 (20%)	**0.0002**
-AIHA Only	0	9 (9%)	**N/A**
-TP and AIHA**	0	3 (3%)	**N/A**
Methotrexate	0	7 (7%)	**N/A**
-TP Only	0	5 (5%)	**N/A**
-AIHA Only	0	2 (2%)	**N/A**
-TP and AIHA**	0	0	**N/A**

IVIG: intravenous immunoglobulin

*:TP only (n:176), AIHA only (n:35), and TP+AIHA (n:17)

** When we compared the medication use in patients with TP and AIHA *versus* TP only or AIHA only, only rituximab use was significantly more common in patients with TP and AIHA (p: xx)

Supplement Table 1: Baseline Demographic, Clinical, and Laboratory Characteristics of Antiphospholipid antibody (aPL)-positive Patients with Thrombocytopenia (TP) and/or Autoimmune Hemolytic Anemia (AIHA), By Systemic Lupus Eryhtematosus (SLE) Classification Based on the 1997 American College of Rheumatology Criteria

# of patients: 228*	**Primary aPL/APS 101 (44%)**	**aPL/APS with SLE Classification 101 (44%)**	**P Value**
Mean Age (Registry Entry)	44±13	43±13	0.58
Gender **-Female**	72 (71%)	82 (81%)	0.13
Race			
-White	63 (62%)	63 (62%)	1.0
-Black	2 (2%)	5 (5%)	0.44
-Asian	9 (9%)	19 (19%)	0.06
TAPS only	57 (56%)	46 (46%)	0.15
OAPS only	11/72 (15%)	9/82 (11%)	0.47
TAPS+OAPS	12/72 (17%)	18/82 (22%)	0.42
No APS Classification	20 (20%)	28 (28%)	0.24
Cardiac Valve Disease	10/87 (11%)	15/91 (16%)	0.39
Catastrophic APS	3 (3%)	4 (4%)	1.0
Microvascular APS**	12 (12%)	7 (7%)	0.33
Triple aPL-positive	47/85 (55%)	35/87 (40%)	0.06
LA positive only	15/96 (16%)	23/98 (23%)	0.20
aCL and/or B2 positive only	9/89 (10%)	12 /89 (13%)	0.64
ANA positive	47/100 (47%)	98/101 (97%)	**<0.01**
Anti-dsDNA positive	19/100 (19%)	73/100 (73%)	**<0.01**

Anti-SM positive	0	19/100 (19%)	N/A
Low C3	11/34 (32%)	31/53 (58%)	**0.02**
Low C4	12/34 (35%)	27/53 (51%)	0.18

TAPS: Thrombotic APS; **OAPS:** Obstetric APS; **LA:** Lupus anticoagulant; **ANA:** antinuclear antibody; **dsDNA:** Double stranded DNA; **Anti-SM:** Anti-smith antibody; **C3/C4:** Complement C3/C4. *:26 patients with autoimmune disease other than SLE (including Sjogren's, systemic sclerosis, inflammatory muscle disease, vasculitis, other) were excluded from the analysis. **: Microvascular APS defined as DAH, aPL nephropathy, and/or livedoid vasculopathy

References

[1]Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295–306.

[2] Cervera R, Piette JC, Font J, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002; 46: 1019-1027.

[3] Erkan D, Lockshin MD, for the APS ACTION members. APS ACTION: AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking. Lupu*s* 2012; 21: 695–698.

[4] Harris P, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42: 377–381.

[5] Sevim E, Zisa D, Andrade D, et al. Characteristics of Patients with Antiphospholipid Antibody Positivity in the APS ACTION International Clinical Database and Repository. Arthritis Care Res (Hoboken) 2022; 74: 324-335.

[6] Uthman I, Godeau B, Taher A, Khamashta M. The hematologic manifestations of the antiphospholipid syndrome. Blood Rev. 2008 Jul;22(4):187-94. doi: 10.1016/j.blre.2008.03.005. Epub 2008 Apr 15. PMID: 18417261.

[7] Cervera R, Piette JC, Font J, Khamashta MA, Shoenfeld Y, et al. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 2002 Apr;46(4):1019-27. doi: 10.1002/art.10187. PMID: 11953980.

[8] Unlu O, Erkan D, Barbhaiya M, Andrade D, Nascimento I, et al. The Impact of Systemic Lupus Erythematosus on the Clinical Phenotype of Antiphospholipid Antibody-Positive Patients: Results From the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Clinical Database and

Repository. Arthritis Care Res (Hoboken). 2019 Jan;71(1):134-141. doi: 10.1002/acr.23584. PMID: 29669399; PMCID: PMC6484425.

[9] Shi Y, Zhao J, Jiang H, Huang C, Qi W, et al. Thrombocytopenia in primary antiphospholipid syndrome: association with prognosis and clinical implications. Rheumatology (Oxford). 2022 Dec 23;62(1):256-263. doi: 10.1093/rheumatology/keac264. PMID: 35536236.

[10] Shi Y, Zhao J, Jiang H, Huang C, Qi W, Song Y, Wang Q, Li M, Tian X, Zhao Y, Zeng X. Thrombocytopenia in primary antiphospholipid syndrome: association with prognosis and clinical implications. Rheumatology (Oxford). 2022 Dec 23;62(1):256-263.

[11] Gamal S, Mohamed S, Moghazy A. Thrombocytopenia in a cohort of primary and secondary antiphospholipid syndrome patients: Relation to clinical, laboratory manifestations and damage index. Arch Rheumatol. 2022 Jan 23;37(2):252-260.

[12] Cuadrado MJ, Mujic F, Muñoz E, Khamashta MA, Hughes GR. Thrombocytopenia in the antiphospholipid syndrome. Ann Rheum Dis. 1997 Mar;56(3):194-6.

13 Barbhaiya M, Zuily S, Erkan D et al; ACR/EULAR APS Classification Criteria Collaborators. The 2023 ACR/EULAR Antiphospholipid Syndrome Classification Criteria. Arthritis Rheumatol. 2023 Oct;75(10):1687-1702. doi: 10.1002/art.42624. Epub 2023 Aug 28. PMID: 37635643.

[14] Pardos-Gea J, Marques-Soares JR, Buján S, Ordi-Ros J, Alijotas-Reig J. Persistent thrombocytopenia predicts poor long-term survival in patients with antiphospholipid syndrome: a 38-year follow-up study. Rheumatology (Oxford). 2022 Mar 2;61(3):1053-1061. doi: 10.1093/rheumatology/keab475. PMID: 34115832.

[15] Gkrouzman E, Erkan D. Antiphospholipid Syndrome. In: Stone JH (eds) Current Diagnosis & Treatment: Rheumatology. 4th ed. McGraw Hill, 2021, pp. 230-235.

[16] Neunert C, Terrell DR, Arnold DM, Buchanan G, Cines DB, Et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019 Dec 10;3(23):3829-3866. doi: 10.1182/bloodadvances.2019000966. Erratum in: Blood Adv. 2020 Jan 28;4(2):252. PMID: 31794604.

[17] Cervera R. Antiphospholipid syndrome. Throm Res 2017; 151 Suppl 1: S43–S47.

[18] Ruiz-Irastorza G, Cuadrado MJ, Ruiz-Arruza I, et al. Evidence-based recommendations for the prevention and long-term management of thrombosis in antiphospholipid antibody-positive patients: Report of a Task Force at the 13th International Congress on Antiphospholipid Antibodies. Lupus 2011; 20: 206–218.

[19] Garcia D, Erkan D. Diagnosis and management of the antiphospholipid syndrome. N Engl J Med 2018; 378: 2010-2021

[20] Erdozain JG, Ruiz-Irastorza G, Egurbide MV, Aguirre C. Sustained response to rituximab of autoimmune hemolytic anemia associated with antiphospholipid syndrome. Haematologica 2004; 89: 34.

[21] Jäger U, Barcellini W, Broome CM, Gertz MA, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020 May;41:100648. doi: 10.1016/j.blre.2019.100648. Epub 2019 Dec 5. PMID: 31839434.

[22] Barcellini W, Fattizzo B. How I treat warm autoimmune hemolytic anemia. Blood. 2021 Mar 11;137(10):1283-1294. doi: 10.1182/blood.2019003808. Erratum in: Blood. 2023 Jan 26;141(4):438-439. PMID: 33512406.

[23] Bertolaccini M, Amengual O, Artim-Eser B, et al. Clinical and Prognostic Significance of Non-criteria antiphospholipid antibody tests. In: Antiphospholipid Syndrome – Current Research Highlights and Clinical Insights. Eds (Erkan D, Lockshin MD). Springer, Switzerland, 2017 (ISBN978-3-319-55440-2), p. 171-188

[24] Jäger U, Barcellini W, Broome CM, Gertz MA, Hill A, et al. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020 May;41:100648. doi: 10.1016/j.blre.2019.100648. Epub 2019 Dec 5. PMID: 31839434.