Title Page

Running head: Cluster Analysis in aPL-Positive Patients.

Full Title: Cluster Analysis for the Identification of Clinical Phenotypes Among Antiphospholipid Antibody-Positive Patients from the APS ACTION Registry.

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Abstract word count: 249

Number of tables and figures: 4

Number of references: 28

Abstract:

Objective: ~~Antiphospholipid Syndrome patients are heterogeneous with different clinical manifestations. Our primary objective was~~This study aimed to use cluster analysis (CA) to identify different clinical phenotypes among antiphospholipid antibodies (aPL)-positive patients.

Methods: ~~APS~~ The Alliance for Clinical Trials and InternatiOnal Working (APS ACTION) ~~Clinical Database and Repository (“~~Registry~~”)~~ ~~is a web-based data capture system used to store patients’ information. The inclusion criterion is~~includes persistently positive aPL ~~based on the Updated Sapporo APS classification criteria~~of any isotype based on the Sydney antiphospholipid syndrome (APS) classification criteria. We performed CA ~~, using Ward’s minimum-variance hierarchical method,~~ on the baseline characteristics ~~of the first 500 patients included in the registry~~collected retrospectively at the time of the registry entry of the first 500 patients included in the registry. A total of 30 ~~Thirty~~ clinical data points were included in the primary CA to cover the broad spectrum of aPL-positive patients. ~~Secondary CA was performed with a special focus on female patients with any pregnancy history.~~

Results: A total of 497 patients from ~~20~~ international centers were analyzed, resulting in three main exclusive clusters: a) female patients with no other autoimmune diseases, but with venous thromboembolism (VTE) and triple-aPL positivity; b) female patients with lupus, VTE, aPL-nephropathy, thrombocytopenia, hemolytic anemia, and positive lupus anticoagulant test; and c) older ~~patients~~ men with arterial thrombosis, heart valve disease, livedo, skin ulcer, neurological manifestations, and cardiovascular disease (CVD) risk factors.

Conclusions: Based on our hierarchical cluster analysis, we identified different clinical phenotypes of aPL-positive patients discriminated by aPL profile, lupus, or CVD risk factors. Our results, while supporting the heterogeneity of aPL-positive patients, also provide a foundation to understand disease mechanisms, create new approaches for APS classification, and ultimately to develop new management approaches.

Introduction:

Persistent antiphospholipid antibodies (aPL) are recognized risk factors for thrombosis or obstetrical morbidity leading to antiphospholipid syndrome (APS). Furthermore, aPL are associated with several non-thrombotic manifestations also known as “non-criteria” manifestations, e.g., thrombocytopenia, autoimmune hemolytic anemia, livedo, aPL-nephropathy, heart valve disease, and neurological manifestations (1). Antiphospholipid syndrome can be either associated with another autoimmune disease (mainly systemic lupus erythematosus [SLE]), or referred as “primary APS” when no other concomitant autoimmune disease exists. Thus, clinical presentations of aPL-positive patients represent a wide spectrum including asymptomatic carriers of aPL, arterial/venous/micro thrombosis, obstetrical morbidity, non-thrombotic manifestations, and the most severe form of the disease, catastrophic APS (2).

Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) is an international network created to design and conduct large-scale, multicenter studies and clinical trials in persistently aPL-positive patients (3). The APS ACTION clinical database and repository (“registry”) was created to study the natural course of persistently aPL-positive patients with or without autoimmune disorders over at least 10 years; the registry allows us to perform large-scale cross-sectional and prospective analyses, which will eventually help us better understand the clinical characteristics of APS patients.

Cluster analysis (CA) is a data driven method that can group patients in a way that patients in the same group (cluster) are more similar to each other than to those in other groups. Several studies have used CA to identify phenotypes in chronic diseases such as Parkinson's Disease, asthma, inflammatory bowel disease, or SLE (4). However, CA has not been used in aPL-positive patients to identify different clinical phenotypes.

Therefore, to improve our understanding of APS disease characteristics and facilitate potential targeted therapies, our primary objective was to use CA to identify different clinical phenotypes among aPL-positive patients. Secondary objective was to identify homogeneous groups of aPL-related clinical manifestations and cardiovascular disease (CVD) risk factors occurring in similar patients.

Material and Methods:

APS ACTION Registry:

An international web-based application, the REDCap (Research Electronic Data Capture) (5), captures data on patient demographics, aPL-related clinical and laboratory characteristics, and medications. The inclusion criteria are: a) age between 18 and 60 years; and b) persistent (at least 12 weeks apart) aPL-positivity within 12 months prior to screening; positivity is defined as anticardiolipin antibodies (aCL) IgG/M/A (> 40 GPL/MPL/APL, medium-to-high titer, and/or greater than the 99th percentile), anti-β_2-glycoprotein-I (aβ_2GPI) IgG/M/A (> 40 GPL/MPL/APL, medium-to-high titer, and/or greater than the 99th percentile), and/or positive lupus anticoagulant (LA) test based on International Society of Thrombosis and Hemostasis

guidelines (6). Patients are followed every 12 ± 3 months with clinical data and blood collection.

Study Cohort and Data Points:

The primary CA was performed on the first 500 persistently aPL-positive patients with or without other systemic autoimmune diseases included in the APS ACTION registry. We analyzed 30 baseline (collected retrospectively at the time of the registry entry) demographic and clinical data points representative of the whole clinical spectrum of aPL-positive patients: *gender* (male/female); *race* (white/non-white); *arterial thrombosis* (yes/no); *venous thromboembolism (VTE)* (yes/no); *biopsy-proven micro thrombosis* (pulmonary, skin, kidney, and "other") (yes/no); *fetal death after 10th week of gestation* (yes/no); *premature birth due to preeclampsia, eclampsia, or placental insufficiency before 34th week of gestation* (yes/no); *three or more consecutive ~~consecutive~~ pre-embryonic or embryonic losses before 10th week of gestation* (yes/no); *superficial vein thrombosis* (yes/no); *transient ischemic attack* (yes/no); *livedo reticularis/racemosa* (past/current/never); *persistent thrombocytopenia defined as platelets<100,000x10^{9} tested twice at least 12 weeks apart* (past/current/never), *autoimmune hemolytic anemia* (past/current/never); *echocardiography-proven heart valve disease* (yes/no/unknown); *biopsy-proven aPL-nephropathy* (yes/no/unknown), *neuropsychiatric test-proven cognitive impairment* (abnormal/normal/unknown), *chorea* (yes/no), *seizure* (yes/no); *skin ulcer* (yes/no); *brain white matter abnormalities* (yes/no/unknown); *body-mass index > 30* (yes/no); *hypertension requiring treatment* (yes/no), *diabetes mellitus requiring treatment* (yes/no), *hyperlipidemia requiring treatment* (yes/no); *smoking* (past/current/never); *positive LA test* (yes/no); *positive aCL IgG/IgM/IgA* (yes/no), *positive aβ$_2$GPI*

IgG/IgM/IgA (yes/no); *SLE based on the American College of Rheumatology Classification Criteria* (yes/no); and *other autoimmune disease*, e.g. rheumatoid arthritis, Sjogren, systemic sclerosis, inflammatory muscle disease, or vasculitis (yes/no). In a subgroup analysis, we limited our CA to female patients with a history of pregnancy; we only used 15 baseline demographic and clinical data points as *arterial thrombosis* (yes/no); *venous thromboembolism* (yes/no); *biopsy-proven micro thrombosis* (pulmonary, skin, kidney, and "other") (yes/no); *fetal death after 10th week of gestation* (yes/no); *premature birth due to preeclampsia, eclampsia, or placental insufficiency before 34th week of gestation* (yes/no); *three or more pre-embryonic or embryonic losses before 10th week of gestation* (yes/no); *body-mass index > 30* (yes/no); *hypertension requiring treatment* (yes/no); *diabetes mellitus requiring treatment* (yes/no); *hyperlipidemia requiring treatment* (yes/no); *smoking* (past/current/never); *positive LA test* (yes/no); *positive aCL IgG/IgM/IgA* (yes/no); *positive aβ_2GPI IgG/IgM/IgA* (yes/no); and *SLE* based on the American College of Rheumatology Classification Criteria (yes/no).

For the secondary CA, clinical criteria for definite APS according to Sydney criteria (*arterial thrombosis, venous thrombosis, small vessel thrombosis, more than 3 recurrent early fetal losses, late fetal death, premature birth due to preeclampsia/eclampsia*), "non-criteria" manifestations (*aPL-related nephropathy, livedo, superficial vein thrombosis, heart valve disease, hemolytic anemia, thrombocytopenia, transient ischemic attack, chorea, cognitive impairment*), as well as CVD risk factors (*hypertension, hyperlipidemia, diabetes, smoking, obesity*) were analyzed.

Statistical Analysis:

Characteristics of sample were described by percentage for categorical variables and mean, standard deviation, median, quartiles, and min/max values for continued variables. Pearson's χ^2 (or Fisher's Exact test when assumption of expected frequency is violated) and Student's t-test were applied to compare qualitative variables and quantitative variables, respectively.

To identify clinical phenotypes, the CA method we used was the hierarchical ascending classification method based on Ward's criterion considered as the most relevant. From a statistical point of view, the objective of Ward's method is to find at each stage those two clusters whose fusion gives the minimum increase in the total within-groups error sum of squares. This method optimizes the variance criterion (7).

Regarding the robustness of the primary CA analysis, the Cubic Clustering Criterion and the SPRSQ (Semiparial R^2) were used to identify the optimal number of patient clusters (κ coefficient). The results of this analysis were validated by the bootstrap method (1,000 iterations) (8). To identify differences between clusters, ANOVA, and χ^2 test of independence were used. Tests were adjusted for all pairwise comparisons within a row using the Bonferroni correction to identify predominant and discriminant variables. The variable with the highest percentage, which is significantly more common compared to one other cluster only is defined as "Predominant Variable", and to all other clusters as "Discriminant Variable". Alpha risk was fixed to 5% for all analysis. These statistical analyses were done with SPPS software, Version 22.0.

Results:

After excluding three patients with missing data, 497 persistently aPL-positive patients from 20 international centers were analyzed (female: 384 (77%), mean age: 44.5±12.9, primary aPL/APS: 324, and aPL/APS associated with other systemic autoimmune diseases: 173).

Primary Cluster Analysis - Clinical Phenotypes of Patients within the Entire Cohort:

Table 1 demonstrates the demographic, clinical, and laboratory characteristics of the patients, clustered in three main groups following a dendrogram analysis (Figure 1). The number of clusters was validated through the visual inspection of the dendrogram and confirmed by the computation of the κ coefficient, which indicated a robust classification (κ=0.716 [95% CI; 0.567–0.863]). The three clusters were: a) female patients with no other autoimmune diseases, but with venous VTE and triple-aPL positivity (Cluster 1); b) female patients with SLE, VTE, “non-criteria” manifestations (aPL-nephropathy, thrombocytopenia, and hemolytic anemia), positive LA test, and positive SLE serology (Cluster 2); and c) older patients with arterial thrombosis, heart valve disease, livedo, skin ulcer, neurological manifestations, and CVD risk factors (Cluster 3). Discriminant variables were triple aPL positivity (Cluster 1), SLE (Cluster 2), and older age, arterial thrombosis, heart valve disease, neurological manifestations, and CVD risk factors (except diabetes mellitus) (Cluster 3).

Primary Cluster Analysis Subgroup Analysis - Clinical Phenotypes of Female Patients with Pregnancy History:

Table 2 demonstrates the demographic, clinical, and laboratory characteristics of 290 female patients with pregnancy history clustered in four main groups: a) older female patients with arterial thrombosis, CVD risk factors, statin treatment (Cluster 1); b) female patients with pregnancy morbidity only (Cluster 2); c) asymptomatic aPL-positive female patients with aCL/aβ_2GPI treated with aspirin (Cluster 3); and d) female patients with VTE, obesity, SLE, positive LA test, and warfarin treatment (Cluster 4). Discriminant variables were fetal death (Cluster 2), asymptomatic aPL, particularly aβ_2GPI positivity (Cluster 3), and SLE, VTE, and obesity (Cluster 4).

Secondary Cluster Analysis - Clusters of Clinical Characteristics Occurring Together

Three main clusters with different combinations of manifestations were identified (Figure 2): a) obstetrical morbidity, “non-criteria” manifestations, and diabetes (Cluster 1); b) arterial thrombosis with CVD risk factors (hypertension, hyperlipidemia, and smoking) (Cluster 2); c) venous thrombosis and obesity (Cluster 3).

Discussion

According to our hierarchical primary and secondary CA, we confirmed the heterogeneity of clinical phenotypes of aPL-positive patients including aPL-positive female with a history of pregnancy; factors resulting in this heterogeneity were mainly aPL profile, SLE diagnosis, and CVD risk factors. Furthermore, we identified that *non-criteria* manifestations do not share the same cluster of clinical APS criteria.

Antiphospholipid antibody profile, especially triple aPL-positivity, is considered as the most clinically significant laboratory profile that expose patients to a higher risk for developing aPL-related clinical events (9-13). Furthermore, the additive impact of CVD risk factors on the development of thrombosis in aPL-positive patients is well determined (14); a similar effect of CVD risk factors (mainly smoking, hypertriglyceridemia, and obesity) on obstetrical outcomes are also identified in women with a history of pregnancy (15). In fact, CVD risk factors are now incorporated in thrombosis prediction models (17,18). Lastly, overlapping manifestations exist between SLE and APS; while aPL modify the clinical presentation of SLE patients (19–21), conversely, SLE could also modify the clinical presentation of aPL-positive patients. Thus, as supported by our findings, the identification of triple aPL positivity, CVD risk factors, and SLE in aPL-positive patients is critical for a precise clinical phenotyping allowing a better risk stratification in aPL-positive patients.

Since 2010's new data confirmed the significant association between some of the non-criteria manifestations and aPL (21). Indeed current classification criteria are suboptimal due to several factors: e.g. no representation of many heterogeneous manifestations of aPL. In parallel with an international collaborative effort to develop new APS classification criteria, our finding of the significant associations between non-criteria and classical criteria manifestations reinforce the need to take into account these manifestations in the global clinical assessment of aPL-positive patients.

From a pathogenic point of view, several non-criteria manifestations share the same underlying pathogenic process (24): a vascular wall involvement with proliferation and endothelium impairment has been demonstrated in the kidneys of APS patients with aPL-related nephropathy (intimal hyperplasia), in the brain of patients with cognitive decline, in the lungs of patients with pulmonary arterial hypertension (plexiform lesion), in placentas of women with placental-mediated complications (decidual vasculopathy), and in vessels of patients with arterial stenosis (coronary and renal artery). This “aPL-related vasculopathy” is not completely understood however activation of the AKT/mTORC pathway ~~was impaired~~ in endothelial cells was implicated in ~~of~~ APS patients presenting with aPL nephropathy (25) although its involvement in other organs is still to be demonstrated. We found that all non-criteria manifestations were gathered in one cluster suggesting that patients with these manifestations could share a common phenotype supporting the hypothesis of a common underlying pathologic mechanism.

Commented [BHM1]: In the NEJM activation of endothelial cells by IgG fraction of patients with PAPS and APSN was demonstrated in vitro using cultured MVEC not in vivo. In other words, no direct demonstration of actviation of this pathway involving patient’s endothelial cells.

The limitations of this study include a potential lack of generalizability to other patient populations. However, the APS ACTION “registry” represents the largest ongoing prospective collaborative clinical database and repository gathering a large number of aPL positive patients followed regularly. Confounding factors may impact the results; nevertheless, CA is an exploratory analysis that is used to identify subsets of cases if the grouping is not previously known. Therefore, it does not make any distinction between dependent and independent variables. The CA can identify groups of patients that present with similar symptoms/manifestations and simultaneously maximize the difference between the groups. Thus, even if potential confounding factors are not addressed in a classical fashion, e.g., multivariate

analysis, the identification of a clinical heterogeneity between aPL-positive patients could help understand different outcomes (28).

In conclusion, our results confirm the heterogeneity of aPL-positive patients and provide a foundation to identify different disease mechanisms, create new approaches for APS classification, and ultimately develop new tailored management approaches. Furthermore, our results have new research implications such as long-term follow-up of patients based on their initial clusters, or conducting randomized controlled studies based on different clusters.

Acknowledgments

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Figure Legends

Figure 1: Dendrogram. Using Wald's minimum-variance hierarchical clustering method, 497 subjects were clustered to a single final group. At each generation of clusters, samples were merged into larger clusters to minimize the within-cluster sum of squares or maximize between-cluster sum of squares. With successive clustering, three balanced groups became obvious.

Figure 2: Cluster Analysis of Antiphospholipid Antibody Related Clinical Manifestations and Cardiovascular Disease Risk Factors. Using Wald's minimum-variance hierarchical clustering method, three main clusters of manifestations were identified (arterial thrombosis and cardiovascular risk factors; venous thrombosis and obesity; non-criteria manifestations, diabetes and obstetrical morbidity).

Figure 1

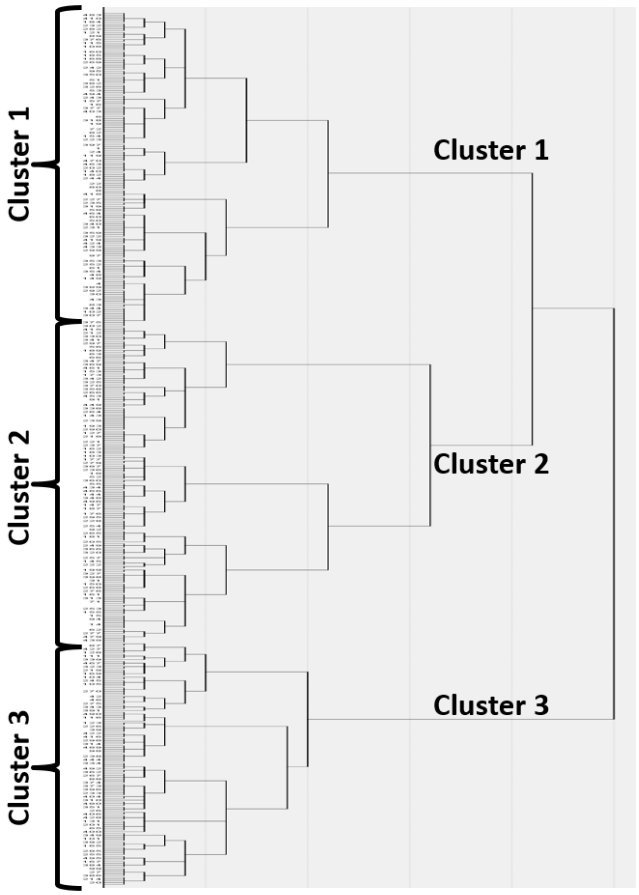
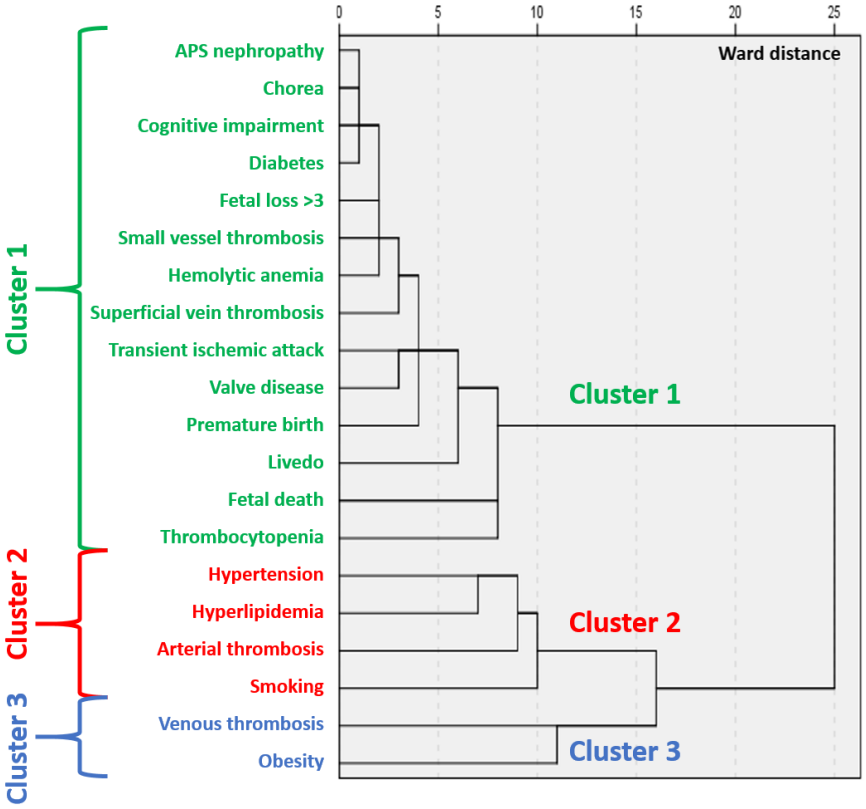


Figure 2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Diabetes
Fetal loss >3
Small vessel thrombosis
Hemolytic anemia
Superficial vein thrombosis
Transient ischemic attack
Valve disease
Premature birth
Livedo
Fetal death
Thrombocytopenia
Hypertension
Hyperlipidemia
Arterial thrombosis
Smoking
Venous thrombosis
Obesity
Cluster 1
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Cluster 2
Cluster 3

Table 1: Identification of Three Distinct Clusters of Patients among Those Included in the APS ACTION Registry

Variables, n (%)	Cluster 1 (n=179)	Cluster 2 (n=180)	Cluster 3 (n=138)
Demographics			
Mean Age, year±SD	41.9±11.6	42.3±12.5	**51.0±12.4**[a,b]
Female	**145 (81.0)**[c]	**145 (80.6)**[c]	92 (66.7)
Past Medical History			
Clinical Criteria			
Arterial Thrombosis	28 (15.6)	51 (28.3)[a]	**95 (68.8)**[a,b]
Venous Thrombosis	**84 (46.9)**[c]	**85 (47.2)**[c]	45 (32.6)
Small vessel thrombosis	9 (5.0)	11 (6.1)	10 (7.2)
Pregnancy morbidity	73 (40.8)	67 (37.2)	42 (30.4)
Non-Criteria Manifestations			
Heart Valve Disease	9 (5.0)	6 (3.3)	**23 (16.7)**[a,b]
Livedo	15 (8.4)	26 (14.4)	**30 (21.7)**[a]
Skin Ulcer	6 (3.4)	11 (6.1)	**14 (10.1)**[a]
Neurological Manifestations	22 (12.3)	26 (14.4)	**58 (42.0)**[a,b]
aPL Nephropathy	2 (1.1)	**10 (5.6)**[c]	0 (0)
Thrombocytopenia	22 (12.3)	**45 (25.0)**[a]	22 (15.9)

Other AutoImmune Diseases			
None	**114 (63.7)[b]**	86 (47.8)	79 (57.2)
SLE	25 (14.0)	**74 (41.1)[a,c]**	26 (18.8)
Cardiovascular Risk Factors			
Hypertension	14 (7.8)	33 (18.3)[a]	**99 (71.7)[a,b]**
Diabetes	4 (2.2)	5 (2.8)	**12 (8.7)[a]**
Hyperlipidemia	12 (6.7)	31 (17.2)[a]	**65 (47.1)[a,b]**
Obesity	31 (17.3)	49 (27.2)	**60 (43.5)[a,b]**
Smoking	44 (24.6)	61 (33.9)	**74 (53.6)[a,b]**
Laboratory Parameters			
Antiphospholipid Antibodies			
Lupus Anticoagulant	129 (72.1)	**152 (84.4)[a]**	105 (76.1)
Anticardiolipin Antibodies	**166 (92.7)[b,c]**	63 (35.0)	115 (83.3)[b]
Anti-β_2-GPI Antibodies	**138 (77.1)[b,c]**	25 (13.9)	73 (52.9)[b]
Triple aPL-positivity	**99 (55.3)[b,c]**	13 (7.2)	56 (40.6)[b]
Other Laboratory Parameters			
Hemolytic Anemia	2 (1.1)	**18 (10.0)[a]**	6 (4.3)
Antinuclear Antibodies	104 (58.4)	**117 (65.7)[c]**	72 (52.2)
dsDNA Antibodies	43 (24.0)	**61 (33.9)[c]**	23 (16.7)

Low C3	20 (29.9)	**39 (49.4)[a]**	18 (48.6)

[a,b,c]Significantly ($p<0.05$) more prevalent than Cluster 1, 2, and 3, respectively.

Anti-β_2-GPI: Anti-β_2-Glycoprotein I antibodies; aPL: antiphospholipid antibodies; SD: Standard Deviation; SLE: Systemic Lupus Erythematosus.

The variable with the highest percentage, which is significantly more common compared to one other cluster only is defined as "**Predominant Variable (bold)",** and to two other clusters as "**Discriminant Variable (bold & underlined)".**

Table 2: Identification of Four Distinct Clusters of Patients with a History of Pregnancy Among the APS ACTION Registry

Variables, n (%)	Cluster 1 (n=85)	Cluster 2 (n=69)	Cluster 3 (n=92)	Cluster 4 (n=44)
Demographics				
Mean Age, year±SD	**47.95 ± 9.63[b]**	38.94 ± 11.67	44.86 ± 11.74[b]	42.94 ± 11.30
White	52 (65.8)	35 (54.7)	53 (66.3)	22 (50.0)
Asian	3 (3.8)	**11 (17.2)[a]**	8 (10.0)	4 (9.1)
Latin American	22 (27.8)	16 (25.0)	12 (15.0)	12 (27.3)
Black	1 (1.3)	2 (3.1)	5 (6.3)	5 (11.4)
Past Medical History				
Clinical Criteria				
Arterial Thrombosis	**40 (47.1)[b,d]**	12 (17.4)	31 (33.7)	8 (18.2)
Venous Thrombosis	37[c] (43.5)	27[c] (39.1)	16 (17.4)	**34 (77.3)[a,b,c]**
Small Vessel Thrombosis	8 (9.4)	1 (1.4)	4 (4.3)	2 (4.5)
≥ 3 Fetal Losses	7 (8.2)	5 (7.2)	8 (8.7)	3 (6.8)
Fetal Death > 10th Week	30 (35.3)[c]	**58 (84.1)[a,c,d]**	3 (3.3)	11 (25.0)[c]
Premature Birth	12 (14.1)	**21 (30.4)[d]**	18 (19.6)[d]	1 (2.3)
Classification				
Asymptomatic aPL-carriers	11 (12.9)	3 (4.3)	**33 (35.9)[a,b,d]**	5 (11.4)

Obstetrical APS	7 (8.2)	**29 (42.0)[a,c,d]**	15 (16.3)	3 (6.8)
Thrombotic	30 (35.3)[c]	**25 (36.2)[c]**	13 (14.1)	12 (27.3)
& obstetrical APS				
Thrombotic APS	37 (43.5)[b]	12 (17.4)	31 (33.7)	**24 (54.5)[b]**
Other AutoImmune Disease				
SLE	21 (24.7)	11 (15.9)	20 (21.7)	**25 (56.8)[a,b,c]**
Lupus-Like Disease	7 (8.2)	4 (5.8)	15 (16.3)	0 (0.0)
Cardiovascular Risk Factors				
Hypertension	**42 (49.4)[b,c]**	12 (17.4)	17 (18.5)	13 (29.5)
Diabetes	4 (4.7)	3 (4.3)	5 (5.4)	2 (4.5)
Hyperlipidemia	**29 (34.1)[b,c]**	6 (8.7)	13 (14.1)	6 (13.6)
Obesity	21 (24.7)	10 (14.5)	21 (22.8)	**25 (56.8)[a,b,c]**
Smoking	14 (16.5)[b]	2 (2.9)	**16 (17.4)[b]**	5 (11.4)
Treatments				
Aspirin	32 (38.1)	32 (46.4)[d]	**57 (62.0)[a,d]**	9 (20.5)
Warfarin	56 (65.9)[c]	31 (44.9)	35 (38.0)	**33 (75.0)[b,c]**
LMWH	7 (8.2)	4 (5.8)	7 (7.6)	2 (4.5)
Statins	**29 (34.1)[b,d]**	5 (7.2)	16 (17.4)	5 (11.4)
Hydroxychloroquine	35 (41.7)	23 (33.3)	37 (40.2)	23 (52.3)

Laboratory Parameters				
Antiphospholipid Antibodies				
Lupus Anticoagulant	75 (88.2)[c]	55 (79.7)[c]	53 (57.6)	**39 (88.6)[c]**
Anticardiolipin Antibodies	63 (74.1)[d]	47 (68.1)[d]	**78 (84.8)[d]**	7 (15.9)
Anti-β_2-GPI Antibodies	37 (43.5)[d]	28 (40.6)[d]	**59 (64.1)[a,b,d]**	1 (2.3)
Other Parameters				
Anti-Ro	6 (7.1)	6 (8.7)	11 (12.0)	10 (22.7)
Anti-La	1 (1.2)	2 (2.9)	2 (2.2)	4 (9.1)

[a,b,c,d] Significantly ($p<0.05$) more prevalent than Cluster 1, 2, 3 and 4, respectively.

Anti-β_2-GPI: Anti-β_2-Glycoprotein I; LMWH: Low Molecular Weight Heparin; SLE: Systemic Lupus Erythematosus.

The variable with the highest percentage, which is significantly more common compared to one other cluster only is defined as "**Predominant Variable (bold)**", and to three other clusters as "**Discriminant Variable (bold & underline**