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## Characteristics of Patients With Antiphospholipid Antibody Positivity in the APS ACTION International Clinical Database and Repository

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## Abstract

**Objective**—To describe the baseline characteristics of patients with positivity for antiphospholipid antibodies (aPLs) who were enrolled in an international registry, the Antiphospholipid Syndrome (APS) Alliance for Clinical Trials and International Networking (APS ACTION) clinical database and repository, overall and by clinical and laboratory subtypes.

**Methods**—The APS ACTION registry includes adults who persistently had positivity for aPLs. We evaluated baseline sociodemographic and aPL-related (APS classification criteria and “non-criteria”) characteristics of patients overall and in subgroups (aPL-positive without APS, APS overall, thrombotic APS only, obstetric APS only, and both thrombotic APS/obstetric APS). We assessed baseline characteristics of patients tested for the presence of three aPLs (lupus anticoagulant [LAC] test, anticardiolipin antibody [aCL], and anti- $\beta$ 2-glycoprotein I [anti- $\beta$ 2GPI]) antibodies by aPL profiles (LAC only, single, double, and triple aPL positivity).

**Results**—The 804 aPL-positive patients assessed in the present study had a mean age of  $45 \pm 13$  years, were 74% female, and 68% White; additionally, 36% had other systemic autoimmune diseases. Of these 804 aPL-positive patients, 80% were classified as having APS (with 55% having thrombotic APS, 9% obstetric APS, and 15% thrombotic APS/obstetric APS). In the overall cohort, 71% had vascular thrombosis, 50% with a history of pregnancy had obstetric morbidity, and 56% had experienced at least one non-criteria manifestation. Among those with three aPLs tested ( $n = 660$ ), 42% were triple aPL-positive. While single-, double-, and triple aPL-positive subgroups had similar frequencies of vascular, obstetric, and non-criteria events, these events were lowest in the single aPL subgroup, which consisted of aCLs or anti- $\beta$ 2GPI only.

**Conclusion**—Our study demonstrates the heterogeneity of aPL-related clinical manifestations and laboratory profiles in a multicenter international cohort. Within single aPL positivity, LAC

may be a major contributor to clinical events. Future prospective analyses, using standardized core laboratory aPL tests, will help clarify aPL risk profiles and improve risk stratification.

## INTRODUCTION

Antiphospholipid syndrome (APS) is characterized as an autoimmune disease marked by thromboses and/or pregnancy morbidity with persistent positivity for antiphospholipid antibodies (aPLs), lupus anticoagulant (LAC) test, anticardiolipin antibodies (aCLs), and/or anti- $\beta_2$ -glycoprotein I (anti- $\beta_2$ GPI) antibodies, as defined by the revised Sapporo criteria for APS (1, 2). Other well-recognized “non-criteria” clinical manifestations may occur in aPL-positive patients, including thrombocytopenia, autoimmune hemolytic anemia, livedo reticularis, aPL-associated nephropathy, cardiac valve disease, cognitive dysfunction, and skin ulcers (1, 3). APS can occur in isolation (primary APS) or in association with other autoimmune diseases, most notably systemic lupus erythematosus (SLE) (4). Patients with positivity for aPLs can have heterogeneous clinical manifestations, including asymptomatic aPL positivity (no thrombosis or pregnancy morbidity), thrombotic APS (which is characterized by venous, arterial, or microvascular involvement), and obstetric APS (which is characterized by pregnancy complications such as fetal loss, recurrent early miscarriages, placental insufficiency, or preeclampsia). Furthermore, not every positive result for aPL testing is clinically significant, and transient low titer aPL positivity may occur in settings of infection or malignancy (5, 6). Despite accumulating data showing an important role for aPL laboratory profiles in APS assessment (7–9), the risk of aPL-related clinical events by aPL laboratory profile remains under investigation. Few large cohorts have estimated the prevalence of aPL-related clinical manifestations (10–12). Furthermore, the distribution of demographic and clinical factors by aPL-related clinical subtypes or laboratory profiles is not well-established.

The Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) is an international network established in 2010 to conduct large-scale multicenter studies and clinical trials in persistently aPL-positive patients (2). 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. See Appendix A for APS ACTION registry investigators and their locations. In the present study, our primary objective was to retrospectively evaluate the baseline demographic and clinical characteristics of aPL-positive patients enrolled in the APS ACTION registry since 2010, overall and by clinical subtype (aPL positive without APS classification, thrombotic APS, and obstetric APS). Secondly, we also assessed the clinical characteristics of aPL-positive patients who were tested at baseline for all three “criteria” aPLs (LAC, aCLs, and anti- $\beta_2$ GPI antibodies), categorized by aPL profile (LAC positivity only and single, double, and triple aPL positivity).

## PATIENTS AND METHODS

### APS ACTION registry and data collection

The inclusion criteria for the APS ACTION Registry were the following: individuals ages 18 to 60 years with persistent positivity for aPLs (at least 12 weeks apart) according to

the revised Sapporo criteria (1), within 12 months prior to screening. Patients referred to APS ACTION sites were referred from hospital or outpatient settings and had received aPL testing for a variety of reasons such as thrombosis, pregnancy morbidity, false-positive serologic test for syphilis, prolonged activated partial thromboplastin time, thrombocytopenia, or concomitant systemic autoimmune diseases. As part of the registry entry criteria, patients must have had persistent aPL positivity prior to registry entry. Positivity for aCLs and/or anti- $\beta_2$ GPI antibodies was defined as an individual having IgG, IgM, or IgA titers of  $\geq 40$  units/ml (medium-to-high titers). LAC activity was detected by coagulation assays according to the International Society on Thrombosis and Hemostasis guidelines for lupus anticoagulant detection (13).

An international web-based application, REDCap, was used to store and manage data on baseline sociodemographic information, aPL-related clinical events, pregnancy history, medications, and laboratory profile (14). Blood samples were also collected at registry entry for confirmation of aPL positivity. Patients were followed every  $12 \pm 3$  months with clinical data and blood collection, or at the time of a new aPL-related thrombosis and/or pregnancy morbidity.

### Study cohort

All participants who were persistently positive for aPLs and who were enrolled in the APS ACTION registry between May 2010 and March 2019 were included in the study cohort. We categorized patients into two groups by clinical subtype at baseline—1) patients who had positivity for aPLs without APS and who met laboratory criteria for APS classification, but not the clinical revised Sapporo criteria (1) and 2) patients with overall APS who met both laboratory and clinical criteria for definite APS. Patients with overall APS were further categorized into three mutually exclusive groups as follows: 1) patients with thrombotic APS, which is defined by a history of any vascular event (including any arterial thrombosis, venous thrombosis, or microvascular involvement, but excluding only superficial vascular thrombosis); 2) patients with obstetric APS, which is defined by a history of any pregnancy morbidity event (defined by the revised Sapporo classification criteria [1]); and 3) patients with thrombotic APS/obstetric APS, who were defined as individuals who have experienced any vascular thrombosis event and any pregnancy morbidity event (Table 1).

After categorizing patients into subgroups, we evaluated the baseline laboratory profiles of aPL-positive patients in the registry. We assessed the baseline clinical characteristics of aPL-positive patients with different laboratory profiles (single, double, and triple aPL positivity) among patients tested for all three aPLs (LAC, aCLs, and anti- $\beta_2$ GPI antibodies). We also subcategorized the subgroup with single aPL positivity by separately evaluating those with LAC only and those with single aPL positivity excluding LAC (Table 2). For the purposes of this study, positivity for aCL IgG, IgM, and IgA and anti- $\beta_2$ GPI IgG, IgM, and IgA was defined as a patient having a titer of  $\geq 40$  units, with the highest titer among all test results taken into consideration during analysis.

## Data collection for baseline characteristics

Demographic characteristics collected included mean age, race (White, Latin American Mestizo, Asian, Black, or “Other”), ethnicity (Non–Latin American or Latin American [for the US, Canada, and Europe], Afro-descendent, Mestizo, or Caucasian [for South America], Afro-descendent [for South Africa], or “Other”), and region of residence (Europe, North America [for the US and Canada], Latin America, and Asia-Pacific). Clinical manifestations were subgrouped into vascular events (arterial thrombosis, venous thrombosis, microvascular involvement), catastrophic APS (CAPS), pregnancy morbidity, and “other.” Other clinical manifestations included livedo reticularis/racemosa, persistent thrombocytopenia defined as a platelet count of <100,000 per microliter tested twice at least 12 weeks apart, autoimmune hemolytic anemia, echocardiography-proven cardiac valve disease, aPL-related nephropathy, skin ulcers, chorea, seizure disorder, radiographic white matter lesions (only identified in those patients who had magnetic resonance imaging performed), and neuropsychiatric test–proven cognitive dysfunction (Supplementary Table 1, available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.24468/abstract>). CAPS was defined as “definite” or “probable” based on the international consensus statement on classification criteria and treatment guidelines for CAPS (15). Past and current medications, including aspirin, warfarin, low molecular weight heparin, direct oral anticoagulants, glucocorticoids, hydroxychloroquine, intravenous immunoglobulin, rituximab, azathioprine, cyclophosphamide, cyclosporine, methotrexate, and mycophenolate mofetil, were collected at the time of registry entry.

## Study design and statistical analysis

Data from the APS ACTION registry were locked in March 2019. First, we evaluated the baseline demographic and clinical characteristics of aPL-positive patients overall, and by clinical subtype: aPLs without APS, APS (overall), obstetric APS, thrombotic APS, and thrombotic APS/obstetric APS. We also classified aPL-positive patients (overall and by aPL-related clinical subtypes) as having primary aPL/APS or aPL/APS with other systemic autoimmune disease, including SLE, rheumatoid arthritis, mixed connective tissue disease, Sjögren’s syndrome, systemic sclerosis, inflammatory muscle disease, and vasculitis.

Second, we assessed the clinical characteristics of aPL-positive patients with different baseline laboratory profiles (LAC positivity only, single aPL positivity, single aPL positivity after excluding LAC positivity, double aPL positivity, and triple aPL positivity), among patients tested for all three aPLs. Descriptive statistics were used to describe continuous variables (mean  $\pm$  SD, minimum, median, and maximum).

## RESULTS

### Baseline characteristics in overall cohort

As of March 2019, 804 patients who were persistently positive for aPLs were enrolled from 26 centers worldwide (mean age of  $45 \pm 13$  years at study entry, with 594 [74%] of patients being female, 546 [68%] being White, 87 [11%] being Latin American Mestizos, 387 [48%] from Europe, and 232 [29%] from North America). Table 1 shows the baseline demographic and clinical characteristics of aPL-positive patients at registry entry, both

overall and by clinical subtype. In the study cohort, 642 (80%) of patients met the clinical criteria for definite APS; among these patients, 74 (12%) had obstetric APS only, 446 (69%) had thrombotic APS only, and 122 (19%) had both obstetric APS and thrombotic APS. One-hundred sixty-two patients (20%) did not meet the clinical criteria for definite APS; among these patients who have aPL positivity without APS, 76 (47%) had one or more other (non-criteria) clinical manifestations associated with aPLs, and 86 (53%) were asymptomatic. Thirty-six percent of the overall cohort had at least one concomitant systemic autoimmune disease, with 30% having SLE, 2% having Sjögren's syndrome, 2% having mixed connective tissue disease, 1% having rheumatoid arthritis, 1% having vasculitis, 1% having systemic sclerosis, and 4% having other systemic autoimmune diseases. The frequency of systemic autoimmune diseases was slightly higher in the group that had aPL positivity without APS as compared to APS patients (45% and 33%, respectively).

Among the 804 registry participants, 568 (71%) experienced at least one vascular event (arterial thrombosis, venous thrombosis, or microvascular involvement), and 28% experienced recurrent vascular events. Venous thrombosis occurred more frequently than arterial thrombosis (43% versus 37%) in the overall cohort, with both types of thrombosis appearing in 11% of the cohort; 12% of the cohort had microvascular involvement, and 1% had CAPS. Among those with arterial thrombosis, strokes (21%) occurred much more frequently than cardiac events (4%); events in the lower extremities were the most common type of venous thrombosis (27%) recorded. Of the 393 women in the registry who had a history of pregnancy, 50% had experienced a pregnancy morbidity event, most commonly due to unexplained fetal death at 10 weeks of gestation (69%). Over half (56%) of the overall cohort had at least one non-criteria manifestation; among these, the most common were white matter lesions of the central nervous system and persistent thrombocytopenia.

In terms of medications that were being used at the time of registry entry, 62% of aPL-positive patients were receiving anticoagulation, with 54% receiving warfarin, 6% receiving low molecular weight heparin, and 3% receiving factor Xa inhibitor. Other commonly used medications were aspirin (46%), hydroxychloroquine (45%), and statins (24%).

### **Baseline characteristics by clinical subtype**

When comparing characteristics by aPL-related clinical subtypes (Table 1), the incidence of concomitant systemic autoimmune disease was highest in patients with aPL positivity without APS (45%) and lowest in patients with obstetric APS (26%). A similar pattern was reflected in aPL-positive patients with concomitant SLE specifically (37% in patients who had aPL positivity without APS versus 20% in patients with obstetric APS). The mean age was lowest among patients with obstetric APS ( $41.47 \pm 11$  years) and highest among patients with thrombotic APS ( $46.69 \pm 14$  years). The majority of patients in each clinical subtype were White, whereas there were very few Black patients in each clinical subtype; the highest percentage of Latin American Mestizo patients were in the thrombotic APS/obstetric APS group (Table 1). Approximately 50% of patients in each clinical subtype were recruited from Europe, except in individuals with thrombotic APS/obstetric APS, which occurred less frequently in European patients (37%). Approximately

30% of thrombotic APS/obstetric APS patients were recruited from Latin America, which was the most common clinical subtype observed in recruited patients from this region.

Within the thrombotic APS group compared to the thrombotic APS/obstetric APS groups, while we observed similar frequencies of arterial thrombotic events (54% and 50%, respectively) and venous thrombotic events (60% and 64%, respectively) within the these subgroups, lower extremity venous thrombosis events were slightly higher among patients with thrombotic APS only compared to patients with both thrombotic and obstetric APS (40% and 33%, respectively) (Table 1). Between the thrombotic APS group and the thrombotic APS/obstetric APS group, we also observed a similar rate of microvascular involvement (15% and 17%, respectively) and catastrophic APS (2% each). When comparing pregnancy morbidity in patients with obstetric APS to that in patients with thrombotic APS/obstetric APS, we found similar frequencies of unexplained death of the fetus at 10 weeks of gestation or later (69% versus 70%, respectively), premature birth occurring earlier than 34 weeks of gestation due to eclampsia, pre-eclampsia or placental insufficiency (34% versus 35%, respectively), and at least 3 unexplained spontaneous abortions occurring prior to 10 weeks of gestation (15% versus 19%, respectively).

Compared to the overall cohort, patients who had aPL positivity without APS had a slightly lower rate of other clinical manifestations (47% versus 58%). Other clinical manifestations were highest in the thrombotic APS/obstetric APS group (66%) and lowest in the obstetric APS group (41%). In particular, patients with thrombotic APS/obstetric APS had substantially higher rates of livedo reticularis/racemosa, persistent thrombocytopenia, cardiac valve disease, skin ulcer, and cognitive dysfunction compared to patients with other subtypes of APS and the overall study cohort (Table 1). Thrombotic APS patients also had a higher rate of other clinical manifestations (59%) compared to obstetric APS patients (41%).

Compared to APS patients at the time of registry entry, patients who had aPL positivity without APS had higher rates of current use of aspirin (67% versus 40%) and hydroxychloroquine (56% versus 43%) and lower rates of anticoagulation, statin, and antihypertensive use. Aspirin use was highest in patients with a history of obstetric APS (70%) compared to patients with thrombotic APS (38%) or those with both thrombotic and obstetric APS (31%). A majority of APS patients had been receiving anticoagulation therapy with warfarin (66%) at the time of registry entry. Current use of any anticoagulation therapy (warfarin, low molecular weight heparin, factor Xa inhibitor, thrombin inhibitor) at registry entry was highest among patients with thrombotic APS (83%) compared to patients with aPL positivity without APS (11%). A similar pattern of medication use was observed for “ever” use at the time of registry entry among the aPL-related clinical subgroups (Table 1).

### **Baseline characteristics by aPL profile**

Of the 804 aPL-positive patients, 660 (83%) were tested for all three aPLs (LAC, aCLs, and anti- $\beta_2$ GPI antibodies), and 42% had triple positivity for aPLs. We excluded eight patients who were tested for three aPLs but had low titers (20–39 units) of aPLs measured by enzyme-linked immunosorbent assay with negative LAC test. Approximately one-fifth (17%) of patients were missing at least one aPL test; in this group, the proportion with single positivity was similar to that with double positivity (50% and 46%, respectively).

Among those without testing for the three aPLs and with single positivity only (50%), LAC positivity was most common (37%); the combination of LAC plus aCL positivity was more common than aCL plus anti- $\beta_2$ GPI antibody positivity in those with double aPL positivity (Figure 1).

While similar frequencies of vascular thrombosis, pregnancy morbidity, and other clinical manifestations were observed across subgroups with single, double, and triple aPL positivity, the subgroup with single aPL positivity (excluding the patients with only LAC positivity) had substantially lower frequencies of all three event types (Table 2). Compared to the other aPL profile subgroups, triple aPL positivity had the highest proportion of patients with at least one preterm delivery before 34 weeks of gestation, persistent thrombocytopenia, aPL-related nephropathy, and cardiac valve disease. Within the group with single aPL positivity, LAC only positivity had the highest proportion of patients who experienced any vascular events, pregnancy morbidity, and other clinical manifestations (Table 2).

## DISCUSSION

Based on our multi-center international cohort of aPL-positive patients, 20% of patients who met the entry criteria did not fulfill classification criteria for clinical APS, 71% experienced vascular events, 50% of individuals with a history of pregnancy had aPL-related obstetric morbidity, and 56% had at least one non-criteria clinical aPL manifestation—most commonly thrombocytopenia and white matter lesions. Non-criteria clinical manifestations were highest in the thrombotic APS/obstetric APS group versus thrombotic APS or obstetric APS only. APS patients overall had higher rates of current anticoagulation therapy and statin use, but lower aspirin and hydroxychloroquine use than patients with aPL positivity without APS at registry entry. Compared to single-, double-, and triple-aPL-positive subgroups, the subgroup consisting of patients with single aPL positivity excluding LAC only had substantially lower frequencies of vascular events, pregnancy morbidity, and other clinical events; this suggests that LAC positivity appears to be a major contributor to aPL-related clinical features.

Our study adds to prior work demonstrating the clinical heterogeneity of aPLs, which can result in a broad spectrum of clinical manifestations. Although the current revised classification criteria for APS incorporates vascular events and pregnancy morbidity, various “non-criteria” manifestations, known to occur frequently in aPL-positive patients, were not included (16–18). Since then, various systematic reviews and meta-analyses in SLE patients have aimed to better characterize the role of aPL-related “non-criteria” manifestations, demonstrating an increased likelihood of cardiac valve disease, pulmonary hypertension, livedo reticularis, thrombocytopenia, hemolytic anemia, and renal impairment in aPL-positive SLE patients compared to aPL-negative SLE patients (11, 19). Other investigators have assessed these manifestations in APS patients in the absence or presence of concomitant systemic autoimmune disease and have demonstrated increased rates of cognitive dysfunction, white matter lesions, aPL-related nephropathy, thrombocytopenia, and livedo reticularis among these individuals (10, 20). The present study adds to this literature by demonstrating that non-criteria manifestations, most commonly white matter



lesions and thrombocytopenia, occurred in the majority (56%) of international aPL-positive patients and were more likely to occur in thrombotic APS/obstetric APS patients (66%), suggesting that non-criteria manifestations are prevalent in aPL-positive patients and potentially associated with more severe disease (20, 21). In fact, efforts are underway using cluster analysis methodology, a data-driven method that groups patients by combinations of aPL profiles and clinical features, to further identify clinical phenotypes and distinct “clusters” of patients enrolled in the APS ACTION registry (22, 23).

Assessment of clinical phenotypes, along with a better understanding of the role of aPL laboratory profiles, may play a critical role in risk stratification for aPL-positive patients (24). Although the definition of a “clinically significant” and “high-risk” aPL profile has not been clearly defined, different aPL profiles appear to confer different thrombosis risks (7, 25–27). Positive LAC test (compared to enzyme-linked immunosorbent testing for aCLs or anti- $\beta_2$ GPI antibodies), moderate-to-high (> 40 units) titers of aCLs or anti- $\beta_2$ GPI antibodies (compared to lower titers), IgG isotype (compared to IgM and IgA isotype), and triple positivity for aPLs (compared to single or double positivity for aPLs) have a stronger correlation with aPL-related clinical events (28–30). However, there is ongoing debate about the clinical significance of isolated LAC positivity and whether it is as important as triple aPL positivity. Additionally, one recent study demonstrated that aCL IgG, but not IgM, and LAC test positivity are associated with higher rates of thromboses in SLE patients (31). Our cross-sectional analysis, demonstrating a relatively similar frequency of aPL-related clinical events in single, double, and triple aPL positivity, and a substantially lower frequency in single aPL positivity patients without positive findings on LAC test, supports the association of clinical events with LAC positivity. Furthermore, while accumulating data show that LAC positivity may be a stronger risk factor for thrombosis and pregnancy morbidity compared to positivity for either aCLs or anti- $\beta_2$ GPI antibodies (1, 32), standardization of laboratory testing and cutoff thresholds are still needed (1). Prospective studies will determine the association between laboratory study levels and clinically relevant disease.

While anticoagulation is the mainstay in treatment of aPL-related clinical events in thrombotic APS (33), alternative treatments are needed in patients with refractory disease or microvascular APS (24, 34–39). Although the majority of APS patients overall received anticoagulation therapy, less than half received aspirin or immunosuppression treatment, and few received other treatments, such as intravenous immunoglobulin, plasma exchange, or rituximab. This finding may reflect an inherently low rate of refractory/microvascular APS or selection bias in our cohort. While data regarding treatment of obstetric APS are controversial in regard to the need for prophylactic low-dose aspirin versus the addition of unfractionated heparin to low-dose aspirin (40–44), the majority of patients in our cohort with obstetric APS only received aspirin (ever and at registry entry) and low molecular weight heparin (ever).

Furthermore, no clear consensus exists on primary prevention management of the symptoms of patients with persistent positivity for aPLs (45), including the use of aspirin, hydroxychloroquine, or anticoagulation therapy, although recent European Alliance of Associations for Rheumatology guidelines suggest that low-dose aspirin may be beneficial for various patients who were aPL-positive (46). Our registry data show that the majority

of patients who have aPL positivity without APS were treated with aspirin (67%) and hydroxychloroquine (56%), which may be driven by use of these medications for the prevention of thrombosis, underlying concomitant systemic autoimmune disease (45% of patients who have aPL positivity without APS), or other comorbid medical diseases, including cardiovascular risk factors. Patients who had positivity for aPLs without a diagnosis of APS had the highest percentage of concomitant SLE, which may have prompted aPL testing in this group.

Although we previously reported that LAC positivity, livedo reticularis, and cognitive dysfunction are more common in patients recruited from Brazil compared to those recruited from other parts of the world (47), the current study did not investigate specific clinical and laboratory differences by geographic region as a comprehensive regional analysis of the registry is already ongoing. Additionally, the low rate of Black patients (3–4%) in the registry may reflect selection bias (e.g., half of the patients were recruited from Europe) or disparities in access to care and would be worth investigation in future studies.

While the present study was limited in its retrospective, cross-sectional study design, we used data from a large, multi-center international patient cohort enriched with granular sociodemographic, clinical, laboratory, and medication information. Epidemiologic studies focusing on APS are limited; few large APS cohorts that are inclusive of different genders, races, and geographic regions are available to estimate the distribution of APS across clinical and laboratory subtypes. As data collection is ongoing in our registry, our data represents an interim assessment of baseline characteristics. Future analyses will use statistical testing and APS ACTION core laboratory aPL test results to evaluate significant differences between subgroups. Selection bias could be a factor in the low percentage of “other” clinical manifestations and systemic autoimmune disease in the obstetric APS group, as some patients in this group are recruited from obstetrics clinics. Our future prospective study will assess the risk of incident systemic autoimmune disease development after the diagnosis of primary obstetric APS.

Although selection and referral bias to APS “experts” should be considered in the interpretation of our registry data, our study demonstrated a low rate of CAPS or use of medications suggestive of refractory disease. Additionally, given that aPL profiles were not necessarily collected at the time of clinical events, our results should be confirmed in prospective studies. Moreover, while other “non-criteria” aPL tests such as those for anti-phosphatidylserine/prothrombin and anti-domain 1 antibodies, have increasingly shown to contribute to a diagnosis of APS and risk assessment for thrombosis (48, 49), our study did not evaluate these laboratory tests as they are not currently standardized or widely commercially available. Finally, although we did not stratify our cohort by those with or without an systemic autoimmune disease, in a previous analysis of APS ACTION registry patients, the frequencies of thrombosis and pregnancy morbidity were similar in aPL-positive patients in the absence or presence of concomitant SLE; however, SLE in patients with persistent aPL positivity was associated with increased frequency of thrombocytopenia, hemolytic anemia, low complement, and positive findings for IgA anti- $\beta_2$ GPI antibodies (50).

In conclusion, our study demonstrates the heterogeneity of aPL-related clinical manifestations and laboratory profiles in a multicenter, international cohort of aPL-positive patients. Identification of APS patients by different clinical phenotypes and aPL profiles may improve risk stratification and help physicians and researchers better characterize the disease and understand clinical outcomes. Future prospective analyses, using standardized core laboratory aPL tests, will help clarify the role of aPL risk profiles.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## APPENDIX A: THE APS ACTION INVESTIGATORS

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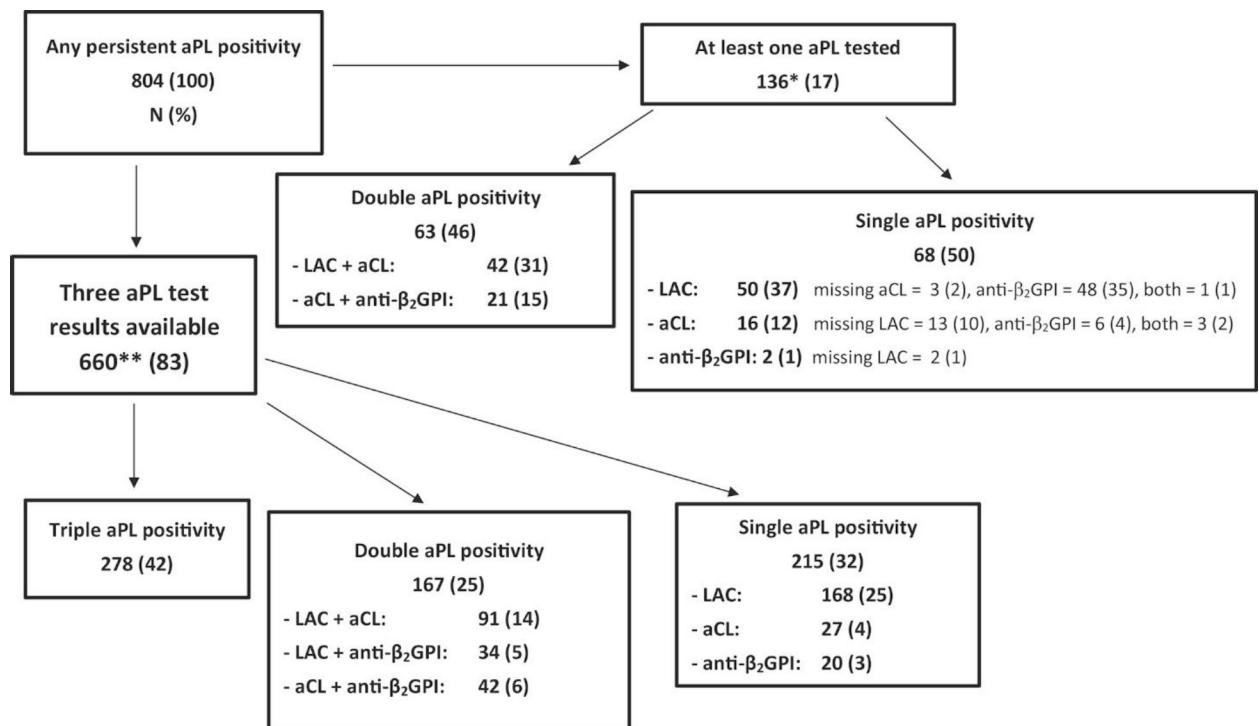
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### SIGNIFICANCE & INNOVATIONS

- Using the multicenter, international Antiphospholipid Syndrome (APS) Alliance for Clinical Trials and International Networking (ACTION) registry, we described baseline clinical and laboratory characteristics of patients with persistent positivity for antiphospholipid antibodies (aPLs), including 36% of patients with other systemic autoimmune disease included in this registry.
- One-fifth of the registry patients did not fulfill clinical classification criteria for clinical APS. Among the registry patients, 71% experienced vascular events, 25% had aPL-related obstetric morbidity, and 56% had at least one other non-criteria clinical aPL manifestation, most commonly thrombocytopenia and white matter lesions of the central nervous system.
- Although single-, double-, and triple-aPL-subgroups had similar frequencies of vascular, pregnancy, and non-criteria events, these events were less common in the single aPL subgroup after excluding LAC-positive patients, suggesting the importance of LAC positivity in APS.
- Future prospective analyses, using standardized core laboratory testing for aPLs, will help clarify risk profiles for individuals with aPL positivity.



**Figure 1 - Antiphospholipid antibody (aPL) profile at baseline in patients (n = 804) with persistent aPL positivity who were included in the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking Registry.**

\* = Of 804 patients, 136 (17%) had missing data for their aPL profiles, with 38 (5%) patients lacking test results for LAC, 3 (0.3%) lacking test results for aCLs, 100 (12%) lacking test results for anti- $\beta$ 2GPI antibodies. \*\* = An additional 8 patients (1%) were tested for 3 aPLs but were excluded from the study due to low titers (20–39 units) on an aPL enzyme-linked immunosorbent assay with negative LAC test. Anti- $\beta$ 2GPI = anti- $\beta$ 2-glycoprotein I; aCL = anticardiolipin antibody; LAC = lupus anticoagulant.



**Table 1.**

Baseline demographic and clinical characteristics of patients with positivity for aPLs between different groups of aPL-positive patients included in the APS ACTION registry according to aPL-related clinical phenotype (2010–2019)\*

	All patients, (N = 804)	Patients with aPL positivity without APS, 162 (20)	Patients with APS (overall), 642 (80)	Patients with OAPS only, 74 (9)	Patients with TAPS only, 446 (55)	Patients with TAPS + OAPS, 122 (15)
Primary aPL/APS	516 (64)	89 (55)	427 (67)	55 (74)	295 (66)	77 (63)
Concomitant systemic autoimmune disease <sup>†</sup>	288 (36)	73 (45)	215 (33)	19 (26)	151 (34)	45 (37)
SLE	242 (30)	60 (37)	182 (28)	15 (20)	129 (29)	38 (31)
Sociodemographic characteristics						
Age at registry entry, mean ± SD years						
45.12 ± 13	43.80 ± 13	45.45 ± 13	41.47 ± 11	46.69 ± 14	43.34 ± 12	
Female sex	594 (74)	127 (78)	467 (73)	74 (100)	271 (61)	122 (100)
Race <sup>‡</sup>						
White	546 (68)	118 (73)	428 (67)	52 (70)	305 (68)	71 (58)
Latin American Mestizos	87 (11)	6 (4)	81 (13)	6 (8)	47 (11)	28 (23)
Asian	56 (7)	17 (10)	39 (6)	8 (11)	24 (5)	7 (8)
Black	26 (3)	7 (4)	19 (3)	2 (3)	12 (3)	5 (4)
American Indian or Alaskan	2	1 (1)	1	0	1	0
Native American	0	0	0	0	0	0
Reported as “other” <sup>§</sup>	14 (2)	2 (1)	12 (2)	1 (1)	9 (2)	2 (2)
Ethnicity <sup>¶</sup>						
US, Canada, and Europe	377 (47)	92 (57)	285 (44)	43 (58)	201 (45)	41 (34)
Non-Hispanic	356 (44)	88 (54)	268 (42)	38 (51)	194 (43)	36 (30)
Hispanic	21 (3)	4 (2)	17 (3)	5 (7)	7 (2)	5 (4)
South America	137 (17)	8 (5)	129 (20)	8 (11)	82 (18)	39 (32)
Mestizos	72 (9)	2 (1)	70 (11)	4 (5)	42 (9)	24 (20)
Caucasian	47 (6)	4 (2)	43 (7)	2 (3)	31 (7)	10 (8)
African descent	18 (2)	2 (1)	16 (2)	2 (3)	9 (2)	5 (4)
Other <sup>#</sup>	135 (17)	35 (22)	100 (16)	16 (22)	65 (15)	19 (16)
Australia	4 (1)	0	4 (1)	0	2	2 (2)
Not Aboriginal	4 (1)	0	4 (1)	0	2	2 (2)
Aboriginal	0	0	0	0	0	0
Region of residence						
Europe	387 (48)	84 (52)	303 (47)	37 (50)	221 (50)	45 (37)
North America	232 (29)	60 (37)	172 (27)	23 (31)	117 (26)	32 (26)

	All patients, (N = 804)	Patients with aPL positivity without APS, 162 (20)	Patients with APS (overall), 642 (80)	Patients with OAPS only, 74 (9)	Patients with TAPS only, 446 (55)	Patients with TAPS + OAPS, 122 (15)
US	201 (25)	56 (35)	145 (23)	21 (28)	95 (21)	29 (24)
Canada	31 (4)	4 (2)	27 (4)	2 (3)	22 (5)	3 (4)
Latin America	131 (16)	6 (4)	125 (19)	7 (9)	83 (19)	35 (29)
Asia Pacific	54 (7)	12 (7)	42 (7)	7 (9)	25 (6)	10 (8)
Clinical manifestations						
Any vascular event	568 (71)	0	568 (71)	0	446 (100)	122 (100)
Any arterial thrombosis	300 (37)	0	300 (37)	0	239 (54)	61 (50)
Stroke	165 (21)	0	165 (26)	0	127 (28)	38 (31)
Transient ischemic attacks	69 (9)	0	69 (11)	0	50 (11)	19 (16)
Myocardial infarction	31 (4)	0	31 (5)	0	29 (7)	2 (2)
Intracardiac thrombus	3	0	3	0	2	1 (1)
Peripheral artery **	30 (4)	0	30 (5)	0	27 (6)	3 (3)
Visceral	10 (1)	0	10 (2)	0	9 (2)	1 (1)
Retinal	5 (1)	0	5 (1)	0	3 (1)	2 (2)
Any venous thrombosis	347 (43)	0	347 (54)	0	269 (60)	78 (64)
Central venous sinus	13 (2)	0	13 (2)	0	12 (3)	1 (1)
Pulmonary embolism	76 (9)	0	76 (12)	0	64 (14)	12 (10)
Upper extremity	7 (1)	0	7 (1)	0	7 (2)	0
Lower extremity	217 (27)	0	217 (34)	0	177 (40)	40 (33)
Visceral	8 (1)	0	8 (1)	0	4 (1)	4 (3)
Retinal	6 (1)	0	6 (1)	0	5 (1)	1
Any microvascular involvement	93 (12)	3 (2)	90 (14)	2 (3)	67 (15)	21 (17)
Biopsy-proven	32 (4)	0	32 (5)	0	26 (6)	6 (5)
Kidney	15 (2)	0	15 (2)	0	11 (2)	4 (3)
Skin	9 (1)	0	9 (1)	0	9 (2)	0
Pulmonary	3	0	3	0	3 (1)	0
Other	5 (1)	0	5 (1)	0	3 (1)	2 (2)
Clinical suspicion, no biopsy	61 (8)	3 (2)	58 (9)	2 (3)	41 (9)	15 (12)
Kidney	14 (2)	0	14 (2)	2 (3)	10 (2)	2 (2)
Skin	37 (5)	3 (2)	34 (5)	0	24 (5)	10 (8)
Pulmonary	2	0	2	0	2	0
Other	8 (1)	0	8 (1)	0	5 (1)	3 (2)
Both arterial and venous thrombosis	92 (11)	0	92 (14)	0	72 (16)	20 (16)
Recurrent vascular events (arterial and/or venous)						
225 (28)	0	225 (35)	0	173 (39)	52 (43)	

	All patients, (N = 804)	Patients with aPL positivity without APS, 162 (20)	Patients with APS (overall), 642 (80)	Patients with OAPS only, 74 (9)	Patients with TAPS only, 446 (55)	Patients with TAPS + OAPS, 122 (15)
Catastrophic APS <sup>††</sup>	9 (1)	0	9 (1)	0	7 (2)	2 (2)
History of pregnancy	393/594 (66)	70/127 (55)	323 (50)	74 (100)	127/271 (47)	122 (100)
Pregnancy morbidity	196/393 (50)	0	196/323 (61)	74 (100)	0	122 (100)
Unexplained fetal death at 10 weeks of gestation or later						
136/196 (69)	0	136/196 (69)	51/74 (69)	0	85/122 (70)	
Premature birth prior to 34 weeks of gestation due to eclampsia, preeclampsia, or placental insufficiency						
68/196 (35)	0	68/196 (35)	25/74 (34)	0	43/122 (35)	
3 unexplained spontaneous abortions prior to 10 weeks of gestation	34/196 (17)	0	34/196 (17)	11/74 (15)	0	23/122 (19)
3 consecutive unexplained spontaneous abortions prior to 10 weeks of gestation	29/196 (15)	0	29/196 (15)	9/74 (12)	0	20/122 (16)
Other clinical manifestations <sup>†††</sup>	451 (56)	76 (47)	375 (58)	30 (41)	264 (59)	81 (66)
Livedo reticularis/racemosa	100 (12)	10 (6)	90 (14)	8 (11)	56 (13)	26 (21)
Persistent thrombocytopenia (platelet count <100,000/μl)						
151 (19)	32 (20)	119 (19)	14 (19)	75 (17)	30 (25)	
Autoimmune hemolytic anemia	40 (5)	9 (6)	31 (5)	4 (5)	22 (5)	5 (4)
Cardiac valve disease	65/688 (9)	10/142 (7)	56/546 (10)	2/52 (4)	34/391 (9)	20/103 (19)
Skin ulcer	50 (5)	3 (2)	47 (6)	0	36 (6)	11 (7)
aPL-associated nephropathy	29/755 (4)	0/156 (0)	29/599 (5)	2/69 (3)	21/414 (5)	6/116 (5)
Neurologic presentations						
Cognitive dysfunction	85 (11)	11 (7)	74 (12)	3 (4)	53 (12)	18 (15)
MS-like disease	6 (1)	1 (1)	5 (1)	0	5 (1)	0
Chorea	13 (2)	2 (1)	11 (2)	0	7 (2)	4 (3)
Seizure disorder	67 (8)	8 (5)	59 (9)	3 (4)	42 (9)	14 (11)
White matter lesions						
136/549 (25)	17/103 (17)	119/446 (27)	6/35 (17)	90/326 (28)	23/85 (27)	
Medications (registry entry)						
Any anticoagulation therapy	497 (62)	18 (11)	479 (75)	9 (12)	372 (83)	98 (80)
Warfarin	434 (54)	13 (8)	421 (66)	4 (5)	328 (74)	89 (73)
LMWH	48 (6)	4 (2)	44 (7)	5 (7)	30 (7)	9 (7)
Factor Xa inhibitor	28 (3)	1 (1)	27 (4)	0	26 (6)	1 (1)

	All patients, (N = 804)	Patients with aPL positivity without APS, 162 (20)	Patients with APS (overall), 642 (80)	Patients with OAPS only, 74 (9)	Patients with TAPS only, 446 (55)	Patients with TAPS + OAPS, 122 (15)
Thrombin inhibitor	0	0	0	0	0	0
Acetylsalicylic acid (aspirin)	366 (46)	108 (67)	258 (40)	52 (70)	168 (38)	38 (31)
Clopidogrel	29 (4)	2 (1)	27 (4)	1 (1)	21 (5)	5 (4)
Hydroxychloroquine	364 (45)	90 (56)	274 (43)	31 (44)	189 (42)	54 (44)
Statins	191 (24)	16 (10)	175 (27)	9 (12)	143 (32)	23 (19)
ACE inhibitor/ARB	163 (20)	21 (13)	142 (22)	9 (12)	106 (24)	27 (22)
Intravenous immunoglobulin	5 (1)	0	5 (1)	0	5 (1)	0
Plasma exchange	1	0	1	0	0	1 (1)
Rituximab	16 (2)	3 (2)	13 (2)	0	12 (3)	1 (1)
Other immunosuppression <sup>§§</sup>	202 (25)	42 (26)	160 (25)	10 (14)	116 (26)	34 (28)
No medications	28 (3)	16 (10)	12 (2)	9 (12)	2	1 (1)
Medications (ever)						
Any anticoagulation therapy	763 (95)	37 (23)	566 (88)	43 (58)	407 (91)	116 (95)
Warfarin	526 (65)	20 (12)	506 (79)	10 (14)	388 (87)	108 (89)
LMWH	340 (42)	21 (13)	319 (50)	41 (55)	200 (45)	78 (64)
Factor Xa inhibitor	43 (5)	2 (1)	41 (6)	1 (1)	37 (8)	3 (3)
Thrombin inhibitor	4 (1)	0	0	0	4 (1)	0
Acetylsalicylic acid (aspirin)	516 (64)	121 (75)	395 (62)	63 (85)	250 (56)	82 (67)
Clopidogrel	50 (6)	3 (2)	47 (7)	1 (1)	38 (9)	8 (7)
Hydroxychloroquine	428 (53)	101 (62)	327 (51)	34 (46)	223 (50)	70 (57)
Statins	210 (26)	20 (12)	190 (30)	9 (12)	153 (34)	28 (23)
ACE inhibitor/ARB	192 (24)	23 (14)	169 (26)	11 (15)	121 (27)	37 (30)
Intravenous immunoglobulin	57 (7)	11 (7)	46 (7)	4 (5)	35 (8)	7 (6)
Plasma exchange	16 (2)	1 (1)	15 (2)	2 (3)	8 (2)	5 (4)
Rituximab	48 (6)	9 (6)	39 (6)	1(1)	34 (8)	4 (3)
Other immunosuppression <sup>§§</sup>	297 (37)	57 (35)	240 (37)	18 (24)	174 (39)	48 (39)
No medications	11 (1)	9 (6)	2	2	0	0

\* Except where indicated otherwise, values are the number (%) of patients. Missing data and other categories are not included. ACE = angiotensin-converting enzyme; aPLs = antiphospholipid antibodies; APS = antiphospholipid syndrome; APS ACTION = APS Alliance for Clinical Trials and International Networking; ARB = angiotensin receptor blocker; LMWH = low molecular weight heparin; MS = multiple sclerosis; OAPS = obstetric APS; SLE = systemic lupus erythematosus; TAPS = thrombotic APS.

<sup>†</sup> Systemic autoimmune diseases included SLE, rheumatoid arthritis, mixed connective tissue disease, Sjögren's syndrome, systemic sclerosis, inflammatory muscle disease, and vasculitis.

<sup>‡</sup> Races were collected in a total of 731 patients (162 patients with aPL positivity only, 69 patients with OAPS, 403 patients with TAPS, and 97 patients with both TAPS and OAPS). Latin American Mestizo refers to a person of combined European and Indigenous American descent.

<sup>§</sup> Includes American Indian or Alaskan, Native Hawaiian or Pacific Islander, and other unspecified races as indicated by the patient.

<sup>¶</sup> Ethnicities were collected in a total of 653 patients (146 patients with aPL positivity only, 65 patients with OAPS, 354 patients with TAPS, and 88 patients with both TAPS and OAPS).

<sup>#</sup> Other unspecified ethnicities as indicated by the patient.

<sup>\*\*</sup> Consists of the arteries not in the chest or abdomen (i.e., in the arms, hands, legs, and feet).

<sup>††</sup> Catastrophic APS was diagnosed as “probable” or “definite” based on the international consensus statement on classification criteria and treatment guidelines for catastrophic APS (15).

<sup>‡‡</sup> Livedo reticularis/racemosa, persistent thrombocytopenia, and autoimmune hemolytic anemia, which patients were considered as “ever” or “never” having had these conditions at the time of registry entry.

<sup>§§</sup> Other immunosuppression treatment included azathioprine, glucocorticoids, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil, and other therapies.

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**Table 2.**

Clinical characteristics of patients with aPL positivity in the APS ACTION registry (2010–2019) who were tested for 3 aPL, categorized according to aPL profile (N = 660)\*

	LAC only positivity, 168 (25)	Positivity for any single aPL (including LAC only) <sup>†</sup> , 215 (32)	Single aPL positivity (excluding LAC only), 47 (7)	Double aPL positivity <sup>‡</sup> , 167 (25)	Triple aPL positivity <sup>‡</sup> , 278 (42)
Any vascular events	127 (73)	148 (67)	21 (45)	118 (68)	195 (70)
Arterial thrombosis	61 (36)	73 (34)	12 (26)	68 (41)	96 (35)
Venous thrombosis	81 (48)	92 (43)	11 (23)	66 (40)	132 (47)
Microvascular thrombosis	10 (6)	12 (6)	2 (4)	9 (5)	16 (6)
Transient ischemic attacks	11 (7)	13 (6)	2 (4)	19 (11)	20 (7)
Any pregnancy morbidity	43/84 (51)	53/108 (49)	10/24 (42)	41/86 (48)	62/117 (53)
>1 fetal death at 10 weeks of gestation or later					
31 (51)	39 (52)	8 (57)	29 (53)	43 (56)	
>1 preterm delivery prior to 34 weeks of gestation					
12 (20)	13 (17)	1 (7)	14 (25)	29 (38)	
3 pre-embryonic/embryotic losses prior to 10 weeks of gestation					
9 (15)	14 (19)	5 (36)	6 (11)	6 (8)	
Any other clinical manifestation	93 (55)	107 (50)	14 (30)	104 (62)	158 (57)
Livedo reticularis/racemosa	27 (16)	28 (13)	1 (2)	24 (14)	32 (12)
Persistent thrombocytopenia <sup>†</sup>	26 (15)	30 (14)	4 (9)	29 (17)	70 (25)
Hemolytic anemia <sup>‡</sup>	9 (5)	10 (5)	1 (2)	7 (4)	16 (6)
Cardiac valve disease	11/146 (8)	12/188 (6)	1/42 (2)	12/142 (8)	32/234 (14)
Skin ulcers	6 (4)	7 (3)	1 (2)	7 (4)	10 (4)
aPL-associated nephropathy	4/157 (3)	4/201 (2)	0	5/160 (3)	11/256 (4)
Cognitive dysfunction	14 (8)	17 (8)	3 (6)	20 (12)	33 (12)
Multiple sclerosis–like disease	2 (1)	3 (1)	1 (2)	3 (2)	0
Chorea	2 (1)	2 (1)	0	4 (2)	6 (2)
Seizure	17 (10)	21 (10)	4 (9)	13 (8)	23 (8)
White matter lesions	33/120 (28)	40/155 (26)	7/35 (20)	33/116 (28)	45/190 (24)

\* Except where indicated otherwise, values are the number (%) of patients. Patients in this analysis were tested for three aPLs (LAC, aCL, and anti-β2GPI antibodies). An additional 8 patients were tested for these three aPLs but had low titers (20–39 units) on enzyme-linked immunosorbent assay with negative LAC test, and were thus excluded from the analysis. Single aPL positivity was defined as positivity on one of the three aPL tests for aPLs, double aPL positivity was defined as positivity on two of three tests, and triple aPL positivity was defined as positivity on all three tests. All groups except LAC only and single aPL positivity were mutually exclusive. Only 5 (0.8%) of 660 patients had isolated aCL/anti-β2GPI IgA positivity with negative results for LAC and aCL/anti-β2GPI IgG and IgM. In total, 6 patients had catastrophic APS, distributed between double aPL- and triple aPL-positive groups. aCL = anticardiolipin antibody; anti-β2GPI = anti-β2-glycoprotein I; aPL = antiphospholipid antibody; APS = antiphospholipid syndrome; APS ACTION = APS Alliance for Clinical Trials and International Networking; LAC = lupus anticoagulant.

<sup>†</sup>Cutoff value for aCL positivity and anti-β2GPI IgG, IgM, and IgA positivity was defined as a patient having a titer of at least 40 units upon antibody testing.

<sup>‡</sup>Defined as a platelet count of <100,000 per microliter tested twice at least 12 weeks apart.

<sup>§</sup>Defined as anemia in the presence of antibodies directed against red blood cells, evidenced by either direct or indirect Coombs' tests.

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