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The Adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) and the Risk of Recurrent Thrombosis: Results from the APS ACTION cohort

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Disclosure and conflict of interests

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Abstract

Objectives:

To assess whether patients with antiphospholipid syndrome (APS) and history of recurrent thrombosis have higher levels of adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) when compared to patients without recurrent thrombosis.

Methods:

In this cross-sectional study of antiphospholipid antibody (aPL)-positive patients, we identified APS patients with a history of documented thrombosis from the AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ("Registry"). Data on aPL-related medical history and cardiovascular risk factors were retrospectively collected. The aGAPSS was calculated at Registry entry by adding the points corresponding to the risk factors: three for hyperlipidemia, one for arterial hypertension, five for positive anticardiolipin antibodies, four for positive anti-β_2 glycoprotein-I antibodies and four for positive lupus anticoagulant test.

Results:

The analysis included 379 APS patients who presented with arterial and/or venous thrombosis. Overall, significantly higher aGAPSS were seen in patients with recurrent thrombosis (arterial or venous) compared to those without recurrence (7.8±3.3 vs. 6±3.9, $p<0.05$). When analyzed based on the site of the recurrence, patients with recurrent arterial, but not venous, thrombosis had higher aGAPSS (8.1 ±SD 2.9vs. 6±3.9; $p<0.05$).

Conclusions:

Based on analysis of our international large-scale Registry of aPL-positive patients, the aGAPSS might help risk stratifying patients based on the likelihood of developing recurrent thrombosis in APS.

Significance and Innovations

1- The aGAPSS is a risk score for predicting clinical manifestations of APS.

2- The APS ACTION is an international research network with a web-based Registry of aPL-positive patients.

3- In the APS ACTION cohort, high aGAPSS was found in patients with recurrent thrombosis.

1. Introduction:

The current Antiphospholipid Syndrome (APS) classification criteria [1] are useful in clinical research, however, identifying patients with antiphospholipid antibodies (aPL)who are at higher risk for thrombosis and/or pregnancy morbidity remains an unmet clinical need and a major challenge in clinical practice.

Recently, the global APS score (GAPSS),a risk score for clinical manifestations of APS, which incorporates independent cardiovascular disease risk factors and aPL profile, was developed. The Global APS Score, initially developed and validated in systemic lupus erythematosus (SLE), has been applied in a cohort of SLE patients followed prospectively, and then validated in APS patients without associated SLE[2–6]. Due to the relative low prevalence of APS in the general population, estimated as an incidence of five cases per 100,000 persons per year[7,8], APS clinical research requires international efforts and multicenter collaborations. The AntiPhospholipid Syndrome Alliance For Clinical Trials and InternatiOnal Networking (APS ACTION) is an international research network that has launched a web-based Registry of aPL-positive patients with or without systemic autoimmune diseases. With these resources, our objective was to assess the clinical utility of the aGAPSS to identify whether patients with thrombotic APS and history of recurrent thrombosis have higher levels of aGAPSS when compared to patients without recurrent thrombosis, using the data from the APS ACTION Registry.

2. Patients and methods:

2. 1 Patients:

APS ACTION Registry inclusion criteria have been extensively described elsewhere[9]. In brief, the inclusion criteria were: positive lupus anticoagulant (LA) test based on the International Society on Thrombosis and Haemostasis (ISTH) and British Committee for Standards in Haematology (BSH) recommendations [10–12] and/or medium-to-high titer anticardiolipin (aCL) and/or anti-β2 glycoprotein I (aβ_2GPI) antibodies (>=40 GPL/MPL), tested at least twice 12 weeks apart within one year prior to enrolment. A secure web-based data capture system (REDCap) was used to store patient information including demographics, clinical manifestations, and aPL data [13]. Patients are followed annually with clinical data and blood collection.

2.2 Study Design:

Computed variables were collected at entry visit in the APS ACTION Registry and demographic, clinical and laboratory data were retrospectively analyzed. Cardiovascular disease risk factors at Registry entry (hypertension, hyperlipidemia, diabetes, hormone replacement therapy, and smoking history) were retrieved from the clinical database. Thrombotic manifestations of APS were defined as “documented” if confirmed by appropriate imaging report at the registry entry.

The cumulative global APS score was calculated for each patient, as previously reported, by adding all points corresponding to the risk factorsbased on a linear transformation derived from the ß-regression coefficient (Table1S) [14]. Despite much data supporting the usefulness of antiphosphatidylserine/prothrombin (aPS/PT) antibodies as a diagnostic and prognostic biomarker, these antibodies are not included as a laboratory criterion for APS or used in the routine clinical setting, and therefore, were unavailable for this study[15]. For this reason, we performed our analysis using the previously validated adjusted GAPSS or aGAPSS, which excludes aPS/PT from the computation[3].

2.3 Statistical analysis:

Categorical variables are presented as number (%) and continuous variables are presented as mean ±SD. The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. Multivariate logistic regression analysis was used to identify any independent predictors of recurrence of thrombosis. A two-sided p-value <0.05 was considered as statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

3. Results:

Three hundred and seventy-nine patients with thrombotic APS [mean age at Registry entry: 47.3±11.4 y, female 70%, Primary APS: 259 (68%)] were included in the analysis. Of the total 379 patients, 154 (40%) had at least one episode of documented arterial thrombosis,199 (53%) had at least one episode of documented venous thrombosis, and 26 (7%) had at least one episode of both an arterial and a venous event. One hundred and eleven patients (29%) had a recurrence of thrombosis, either arterial or venous. Of them, 30 patients (27%) experienced recurrences of arterial thrombosis and 65 patients (58.6%) experienced recurrences of venous thrombosis, ranging from 2 to 5 documented events. Sixteen patients (14.4%) had a history of both recurrent arterial and venous events.

The demographic, clinical and laboratory characteristics of patients with or without documented recurrent thrombosis, are summarized in Table 1. In multivariate analysis, when we included each cardiovascular disease risk factor individually (i.e., dyslipidemia, arterial hypertension, age, and smoking) and aPL positivity (single, multiple, or triple), no significant differences were observed between APS patients with and without recurrent arterial and/or venous thrombosis).

Overall, aGAPSS was significantly higher in patients with recurrent thrombosis (arterial or venous), compared to those without recurrence (7.8±3.3 vs. 6 ±3.9, p<0.05). In subgroup analysis, patients with recurrent arterial thrombosis, but not venous, had higher aGAPSS (8.1 ±2.9 vs. 6 ±3.9; p<0.05) when

compared to those without recurrences (Figure 1). The calculated ORs [95%] and diagnostic accuracy for different cut-off values are provided as supplementary materials.

4. Discussion

Antiphospholipid syndrome remains a clinical challenge for the physicians, and accurate thrombotic risk assessment plays a crucial part in the management of APS patients[16]. When identifying patients at higher risk of developing clinical manifestations of APS, aPL profile represents the most accurate risk stratification tool. In this study, we demonstrated the utility of aGAPSS in stratifying subgroups of patients at different thrombotic risks, finding higher levels of aGAPSS in patients with recurrent thrombosis (arterial or venous), compared to those without recurrences, and in patients who developed recurrent arterial thrombotic manifestations. Among others, Pengo *et al.* found that triple aPL positivity was associated with a higher risk of thrombosis in APS (13). However, in the current study, we did not demonstrate differences between each aPL profile when comparing the rate for recurrence in patients with single/double/triple positivity. Similarly, no single cardiovascular disease risk factor seemed to be independently associated with the risk of developing recurrent thrombosis. It is important to clarify that this lack of association should not be considered as a rebuttal of previous data since all patients recruited to this study fulfill the criteria for APS and are strictly monitored in tertiary centers, potentially representing a sampling bias when compared to other observational cohorts. In addition, these findings are in line with the concept that aPL is a necessary but insufficient step in the development of thrombosis where a “second hit” probably pushes the haemostatic balance in favor of thrombosis by including added factors necessary for its development, such as uncontrolled traditional cardiovascular risk factors [18,19]. Among the various methods for risk stratifications, aGAPSS displays important advantages. First, scoring systems have been proven to be valid tools easily accessible for the treating clinician. Second, when considering the “second hit” theory, aGAPSS considers both the aPL profile (including both criteria and non-criteria aPL) and traditional cardiovascular risk factors. Although no single aPL positivity and traditional cardiovascular risk factor was found to be

independently associated with an increased risk of developing recurrence of thrombosis, when computed in a scoring system, both factors contribute to the risk assessment stratification as part of the variables included in the aGAPSS score.

It is important to acknowledge the limitations for our study. First, the use of a retrospective as well as the cross-sectional approach might influence the reproducibility of the results, as individual aGAPSS scores could fluctuate at different time points and a potential recall bias cannot be excluded. Second, APS ACTION Registry does not include clinical information on cardiovascular risk factors at the time of the recurrent event or on other potential thrombotic risk factors. However, one should consider the fact that APS is a low prevalence condition[20] and our study composed one of the largest thrombotic APS cohorts. Forth, details on different methods used in local laboratories to test aPL (e.g. type of ELISA Kit, home-made assay information) were not available. While a longitudinal study would be highly informative, a cross-sectional approach using international joint efforts represents a solid shared ground for further investigation. Finally, GAPSS/aGAPSS is meant to be an accessible and easy tool to help physicians when assessing the thrombotic risk of a patient with aPL and its use should be complementary to traditional cardiovascular risk factors management.

Having said that, from a pragmatic point of view, we observed that patients with recurrent events were more frequently observed in the group of patients with higher aGAPSS values, paving the way for future studies investigating if patients with higher GAPSS/aGAPSS values should receive tailored thrombo-prophylactic approaches.

In conclusion, analysis of our international large-scale Registry of aPL-positive patients, the aGAPSS might help to risk stratifying patients based on the history of recurrent thrombosis in APS.

Scoring systems are not meant to substitute the judgment of the treating physicians. The combination of accessible tools for risk stratification such as aGAPSS and the APS ACTION scientific networking collaborative efforts, could aid improved management of APS patients, as more accurate identification of those a higher risk for thrombotic events would provide a basis for tailored therapeutic approaches.

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Legend of Tables and Figures:

Table 1. *Demographic, clinical and laboratory characteristics of the cohort*

Figure 1. *Levels of aGAPSS among different study populations*

Table 1S*. The adjusted Global AntiPhospholipid Syndrome Score (aGAPSS)*

Table 1S. The Adjusted Global AntiPhospholipid Syndrome Score (aGAPSS)

Factor	Point Value
Anticardiolipin Antibody IgG/IgM	5
Anti-β_2-glycoprotein I IgG/IgM	4
Lupus anticoagulant	4
Hyperlipidemia	3
Arterial hypertension	1

Table 1. Demographic, Clinical and Laboratory Characteristics of the Cohort

	No Recurrent Thrombosis n=268 (%)	Recurrent Thrombosis n=111 (%)			
		Any n=111 (%)	Only Arterial n=30 (%)	Only Venous n=65 (%)	Arterial & Venous n=16 (%)
Female sex,	180 (67%)	73 (71%)	20 (67%)	45 (69%)	12 (75%)
Age, years, mean (±SD)	48 (±13)	50 (±12)	50 (±12)	48 (±13)	59 (±15)
Arterial hypertension,n=128	85 (32%)	43 (39%)	16 (53%)	19 (29%)	6 (38%)
Hyperlipedemia, n=103	70 (26%)	33 (30%)	7 (23%)	17 (26%)	5 (31%)
Diabetes, n=18	14 (5%)	4 (4%)	2 (4%)	3 (4%)	0 (0%)
Smoking [H*=(n= 101); C(n= 38]	H: 71(27%) C: 26 (9%)	H: 30 (26%) C: 12 (11%)	H: 9 (30%) C: 3 (9%)	H: 17 (26%) C: 6 (9%)	H: 4 (25%) C: 4 (25%)
LA, n=239	168 (62%)	71 (64%)	13 (43%)	46 (71%)	11 (69%)
aCLIgG/IgM, n=160	114 (42%)	46 (51%)	14 (47%)	34 (52%)	7 (43%)
aβ_2GPI IgG/IgM, n=103	71 (27%)	32 (29%)	12 (40%)	20 (31%)	4 (25%)
Triple positive, n= 57	38 (14%)	19 (17%)	5 (16%)	11 (17%)	3 (19%)

LA: Lupus anticoagulant; aCL: anticardiolipin antibodies; aß$_2$GPI:antiß2-glycoprotein 1 antibodies; aGAPSS: adjusted global antiphospholipid score

***H= history; C= current**

No statistical differences between groups was observed in the variables described in the Table

Figure 1. Levels of Adjusted Global AntiPhosholipid Syndrome Score Among Different Study Subgroups