

Original article

GAPSS: the Global Anti-Phospholipid Syndrome Score

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Abstract

Objective. To develop and validate a risk score [global APS score (GAPSS)] derived from the combination of independent risk for thrombosis and pregnancy loss (PL), taking into account the aPL profile, conventional cardiovascular risk factors and the autoimmune antibody profile.

Methods. This cross-sectional study included 211 consecutive SLE patients. Data on clinical manifestations, conventional cardiovascular risk factors, aPL profile, ANAs, ENA and anti-dsDNA were collected. Long-term low-dose aspirin, oral anticoagulant and HCQ treatment were also included in the analysis. Patients were randomly divided into two sets by a computer-generated randomized list. We developed GAPSS in the first set of patients ($n=106$), assigning the risk factors identified by multivariate analysis weighted points proportional to the β -regression coefficient values. GAPSS was validated in the second set of patients ($n=105$). The relationship between GAPSS and thrombosis and/or PL was analysed.

Results. In the first set, higher values of GAPSS were seen in patients who experienced thrombosis and/or PL compared with those without clinical events [GAPSS 9.3 (4.8) (range 1–19) and 5.3 (4) (range 0–16), $P<0.001$]. Also taken separately, patients who experienced thrombosis or PL showed higher GAPSS compared with those without clinical events [GAPSS 9.6 (4.8) (range 1–19) vs 4.9 (5) (range 0–14), $P=0.027$ for thrombosis; 7.3 (5) vs 3.9 (5.1) (range 0–16), $P=0.024$ for PL, respectively]. In the second set, the results were similar, with statistically higher values of GAPSS in patients with a clinical history of thrombosis and/or PL compared with those without events [GAPSS 9.5 (5.6) (range 0–20) and 3.9 (4.1) (range 0–17), $P<0.001$]. Higher values were also seen when subclassifying the patients according to the clinical manifestation, thrombosis or PL [GAPSS 9.5 (5.6) (range 0–20) vs 4.8 (5.4) (range 0–17), $P=0.036$ for thrombosis; 7.9 (3.3) vs 3.8 (5.4) (range 0–16), $P=0.037$ for PL, respectively].

Conclusion. These data propose a substantial improvement in risk prediction of thrombosis or PL in SLE based on assessment of the GAPSS, a quantitative scoring system.

Key words: antiphospholipid antibodies, pregnancy loss, thrombosis, Hughes syndrome, prothrombin.

Introduction

APS is defined by the persistent presence of moderate to high serum levels of aPLs in association with thrombotic events, pregnancy loss (PL) or both [1].

Several studies have investigated predictors for APS, but it is difficult to draw conclusions owing to the substantial differences in study design, patient selection criteria, aPL profiles and the risk factors included in the analysis [2–4].

Recently Otomo *et al.* [5] developed the aPL score (aPL-S) in an attempt to quantify the probability of APS. By testing multiple aPLs, they successfully evaluated its efficacy for the diagnosis of APS and its predictive value for thrombosis. Later on, our group independently validated the aPL-S [6]. Although this score is a useful quantitative index for diagnosing APS, it does not take into account associated conventional risk factors for thrombosis in addition to the aPL profile or evaluate the risk for PL, a common feature of APS.

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We conducted a cross-sectional study in a large cohort of well-characterized SLE patients. Our main objective was to develop a risk score [global APS score (GAPSS)] derived from the combination of independent risk for thrombosis and PL, taking into account the aPL profile (including criteria and non-criteria aPL), the conventional cardiovascular risk factors and the autoimmune antibody profile. The validity of this risk score was then tested in a separate cohort of patients.

Patients and methods

Patients

This study included 211 consecutive patients who attended the Louise Coote Lupus Unit at St Thomas' Hospital, London. All the patients fulfilled the 1982 criteria for SLE [7]. Data on clinical manifestations, conventional cardiovascular risk factors (smoking, hyperlipidaemia, arterial hypertension, oral contraceptive, HRT and diabetes), aPL profile, ANA, ENA (including Ro, LA, Sm, RNP) and anti-dsDNA were collected. Long-term low-dose aspirin (100 mg), oral anticoagulant and HCC treatment were also included in the analysis.

The aPL profile included aCLs, lupus anticoagulant (LA), anti β 2-glycoprotein I antibody (anti- β 2GPI), antibodies to solid-phase prothrombin (aPT) and to phosphatidylserine-prothrombin complex (aPS/PT), antibodies to phosphatidylethanolamine (aPE) and antibodies directed against protein S (anti-ProtS). aPL testing was considered positive only if confirmed at least 12 weeks apart.

PL was defined according to current APS classification criteria [1]. Ethical approval was obtained from the Guy's and St Thomas' Ethics Committee and all patients involved in this study gave their written consent. Demographic, clinical and laboratory characteristics are summarized in Table 1.

Data were collected on a database and patients were randomly divided into two sets. A computer-generated randomized list of patients filtered by the criterion of the diagnosis in order to equally distribute the disease prevalence (SLE/APS, SLE/aPL or SLE alone) was generated. To confirm the efficacy of randomization, the prevalence of the variables in the two sets was computed and no statistical difference was found. The same clinical and laboratory data were available for analysis in both cohorts. These two groups of patients are referred to as the development and validation cohort, respectively.

Assessment of cardiovascular risk factors

Cardiovascular risk factors were assessed following NICE guidelines [8]. In detail, enrolled patients underwent a physical examination, blood pressure determination and phlebotomy for vascular risk factors. Arterial hypertension was defined as high blood pressure on at least two occasions or use of oral hypertensive medication. Serum total and HDL cholesterol levels were determined with standardized enzymatic methods and interpreted according to current cut-off values. Cigarette smoking status was

ascertained by self-report. Diabetes was defined as fasting glucose \geq 126 mg/dl on at least two occasions or use of insulin or oral hypoglycaemic medication.

Detection of autoantibodies

aCL and anti- β 2GPI were detected by ELISA as described previously [9, 10]. Plasma samples were tested for the presence of LA according to the recommended criteria of the ISTH Subcommittee on Lupus Anticoagulant/Antiphospholipid-dependent antibodies [11].

Antibodies to prothrombin were tested by the aPT and aPS-PT as previously reported [12, 13]. aPE and anti-ProtS were tested as described elsewhere [14, 15].

ANA was measured by IIF on rodent liver cells, anti-dsDNA antibodies by RIA (Farr assay) and antibodies to ENA by CIE using bovine spleen and rabbit thymus extracts.

Statistical analysis

Categorical variables are presented as numbers and percentages, and continuous variables are presented as means (s.d.). The significance of baseline differences was determined by the chi-square test, Fisher's exact test or the unpaired *t*-test, as appropriate. A two-sided $P < 0.05$ was considered statistically significant.

Univariate and multivariate logistic regression analyses were used to determine the contribution of the variables in the first cohort of SLE patients, referred to as the development cohort. A step-wise forward conditional procedure was used for the multivariate logistic regression analysis, including all the significant risk factors obtained by the univariate analysis.

To develop the GAPSS, we assigned the risk factors identified by multivariate analysis weighted points proportional to the β -regression coefficient values (rounded to the nearest integer). In detail, assignment of points to risk factors was based on a linear transformation of the corresponding β -regression coefficient. The coefficient of each variable was divided by 0.54 (the lowest β -value, corresponding in our cohort to arterial hypertension) and rounded to the nearest integer. The formula used can be summarized as follows: GAPSS point = $[\beta_x/\beta_{\min}]$, where β_x is the β -regression coefficient for the variable *x* taken into account and β_{\min} is the lowest β -value among the significant variables after multivariate analysis. For example, in our cohort, the GAPSS score for hyperlipidaemia is 3, as the GAPSS point = $[\beta_{\text{hyperlipidaemia}}/\beta_{\text{arterial hypertension}}] = [1.73/0.54] = [3.20] = 3$, rounded to the nearest integer. A risk score was then calculated for each patient in both development and validation cohorts.

Sensitivity, specificity and positive and negative predictive values (PPV and NPV, respectively) were calculated to compare the accuracy between the different possible cut-off values for GAPSS. Areas under the receiver operating characteristic curve (AUC) of different cut-off values were computed. All statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL, USA).

TABLE 1 Demographic and clinical characteristics of the development and validation cohorts

	All (n = 211) n (%)	Development (n = 106) n (%)	Validation (n = 105) n (%)
Female sex	207 (98.1)	104 (98.1)	103 (98.1)
Age, mean (s.d.), year		42.6 (12.1)	42.8 (12.0)
Disease duration, mean (s.d.), year		13.4 (8.8)	11.4 (9.1)
Caucasian	163 (77.2)	86 (81.1)	77 (73.3)
APS	89 (42.2)	44 (41.5)	45 (42.9)
Thrombosis	73 (34.6)	36 (34.0)	37 (35.2)
Arterial thrombosis	48 (22.7)	23 (21.7)	25 (23.8)
Venous thrombosis	41 (19.4)	23 (21.7)	18 (17.1)
PL	41 (19.4)	19 (25.3)	22 (31.9)
Miscarriages ≥ 1	41 (19.4)	23 (30.7)	18 (26.1)
Miscarriages ≥ 3	10 (4.7)	6 (8.0)	4 (5.8)
Fetal deaths	34 (16.1)	16 (15.2)	18 (17.1)
Conventional risk factor (≥ 1)	124 (58.8)	65 (61.3)	59 (56.2)
Smoking	61 (28.9)	33 (31.1)	28 (26.7)
Oral contraceptive pill	20 (9.5)	13 (12.3)	7 (6.7)
Hyperlipidaemia	58 (27.5)	31 (29.2)	27 (25.7)
Arterial hypertension	60 (28.4)	32 (30.2)	28 (26.7)
Diabetes	5 (2.4)	2 (1.9)	3 (2.9)
HRT	17 (8.1)	7 (6.6)	10 (9.5)
dsDNA	60 (28.4)	29 (27.4)	31 (29.5)
ENA	106 (50.2)	57 (53.8)	49 (46.7)
RO	58 (27.5)	30 (28.3)	28 (26.7)
LA	24 (11.4)	14 (13.2)	10 (9.5)
RNP	19 (9.0)	9 (8.5)	10 (9.5)
Sm	19 (9.0)	11 (10.4)	8 (7.6)
aCL IgG/IgM	117 (55.4)	59 (55.7)	58 (55.4)
IgG	103 (48.8)	52 (49.1)	51 (48.6)
IgM	45 (21.3)	20 (18.9)	25 (23.8)
A β_2 GPI IgG/IgM	44 (20.8)	22 (20.7)	22 (20.9)
IgG	35 (16.6)	16 (15.1)	19 (18.1)
IgM	13 (6.2)	8 (7.5)	5 (4.8)
aPT IgG/IgM	49 (23.2)	21 (19.8)	28 (26.7)
IgG	35 (16.6)	16 (15.1)	19 (18.1)
IgM	15 (7.1)	8 (7.5)	7 (6.7)
aPS/PT IgG/IgM	68 (32.2)	37 (34.9)	31 (29.5)
IgG	52 (24.6)	30 (28.3)	22 (20.9)
IgM	32 (15.2)	16 (15.1)	16 (15.2)
aProtS IgG	60 (28.4)	35 (33.0)	25 (23.8)
aPE IgG/IgM	85 (40.3)	46 (43.4)	39 (37.1)
IgG	79 (37.4)	43 (40.6)	36 (34.3)
IgM	22 (10.4)	9 (8.5)	13 (12.4)
LA	58 (27.5)	30 (28.3)	28 (26.7)
LDA	74 (35.0)	34 (32.0)	40 (38.0)
HQC	84 (39.8)	44 (41.5)	40 (38.0)
OA	57 (27.0)	26 (24.5)	31 (29.5)

LDA: low-dose aspirin; OA: oral anti-coagulation.

Results

Development cohort

The development cohort comprised 106 SLE patients with a mean (s.d.) age of 42.6 (12.1) years and mean disease duration of 13.4 (8.8) years. Overall, 44 patients fulfilled the criteria for APS [1] and 36 patients had a history of thrombosis (23 arterial, 23 venous thrombosis). Out of 75 women who had ever been pregnant, 23 had a

history of miscarriages and 16 a history of fetal death. Demographics are summarized in Table 1.

Validation cohort

The validation cohort comprised 105 SLE patients with a mean (s.d.) age of 42.8 (12.0) years and mean disease duration of 11.4 (9.1) years. Of them, 37 patients had a history of thrombosis (25 arterial, 18 venous thrombosis). Out of 69 women who had ever been pregnant, 18 had a

TABLE 2 Univariate logistic regression analysis for the development cohort

	OR (95% CI)	P
Conventional risk factors (≥ 1)	1.84 (0.782, 4.253)	0.19
Smoking	0.823 (0.353, 1.920)	0.08
Oral contraceptive pill	0.558 (0.160, 1.950)	0.21
Hyperlipidaemia	2.492 (1.28, 5.918)	0.036
Arterial hypertension	1.831 (1.099, 8.280)	0.035
Diabetes	1.831 (0.81, 21.938)	0.6
HRT	3.55 (0.655, 13.23)	0.15
Anti-dsDNA	1.63 (0.738, 3.59)	0.53
ENA	1.304 (1.127, 2.780)	0.039
Anti-RO/SSA	0.471 (0.188, 9.178)	0.31
Anti-LA/SSB	1.885 (0.315, 7.482)	0.27
Anti-RNP	1.324 (1.116, 6.09)	0.047
Anti-Sm	0.369 (0.124, 2.0979)	0.61
aCL IgG/IgM	3.998 (1.987, 10.448)	0.023
Anti- β 2GPI IgG/IgM	3.98 (1.462, 10.892)	0.049
aPT IgG/IgM	2.778 (1.037, 7.47)	0.034
aPS/PT IgG/IgM	2.133 (1.368, 7.128)	0.006
aProtS IgG	1.424 (0.177, 8.22)	0.19
aPE IgG/IgM	1.997 (0.457, 2.193)	0.22
LA	1.885 (1.116, 8.507)	0.031
LDA	0.379 (0.141, 3.193)	0.47
HCCQ	0.63 (0.438, 3.98)	0.32
OA	0.55 (0.122, 1.71)	0.67

LDA: low-dose aspirin; OA: oral anti-coagulation; NS: non-significant.

history of miscarriage and 18 had a history of fetal death. Demographics are summarized in Table 1.

Analysis of risk factors for thrombosis and PL

Univariate and multivariate models analysed all clinical and laboratory characteristics in the development cohort, including thrombosis risk factors, as indicated in Tables 2 and 3. Odds ratio analysis reported that among conventional cardiovascular risk factors, arterial hypertension and hyperlipidaemia had an association with thrombosis and/or PL ($P=0.035$ and $P=0.036$, respectively). Anti-ENA and anti-RNP positivity were associated with thrombosis and/or PL ($P=0.039$ and $P=0.047$, respectively). For aPL, LA, aCL IgG and/or IgM, anti- β 2GPI IgG and/or IgM, aPT IgG and/or IgM, and aPS/PT IgG and/or IgM showed an association with thrombosis and/or PL ($P=0.031$, $P=0.023$, $P=0.049$, $P=0.034$ and $P=0.006$, respectively).

Multivariate logistic regression analysis showed that only arterial hypertension, hyperlipidaemia, LA, aCL IgG and/or IgM, anti- β 2GPI IgG and/or IgM and aPS/PT IgG and/or IgM were independent risk factors for thrombosis and/or PL (Table 3).

Development and validation of GAPSS

To calculate GAPSS, we assigned each of the six variables identified in the development cohort as independent risk factors for thrombosis and/or PL, a number of points that was proportional to its regression coefficient, as previously described. A score was calculated for each

TABLE 3 Multivariate logistic regression analysis for the development cohort and scoring system

	β -coefficient	GAPSS ^a
Hyperlipidaemia	1.73	3
Arterial hypertension	0.54	1
aCL IgG/IgM	2.63	5
Anti- β 2GPI IgG/IgM	2.02	4
aPS/PT IgG/IgM	1.78	3
LA	2.35	4

^aAssignment of points to risk factors was based on a linear transformation of the corresponding β -regression coefficient by using the formula $GAPSS = [\beta_x / \beta_{min}]$, where β_x is the β -regression coefficient for the variable x and β_{min} is the lowest β -value among the significant variables in the whole population after multivariate analysis. For example, in this cohort, the GAPSS for hyperlipidaemia is 3, as $GAPSS = [\beta_{hyperlipidaemia} / \beta_{arterial hypertension}] = [1.73 / 0.54] = 3.20 = 3$, when rounded to the nearest integer.

patient by adding together the points corresponding to the risk factors.

In the development cohort, higher values of GAPSS were seen in patients who experienced thrombosis and/or PL compared with those without clinical events [GAPSS 9.3 (4.8) (range 1–19) and 5.3 (4) (range 0–16), $P < 0.001$]. Also taken separately, patients who experienced thrombosis or PL showed higher GAPSS compared with those without clinical events [GAPSS 9.6 (4.8) (range 1–19) and 4.9 (5.0) (range 0–14), $P=0.027$ for thrombosis; 7.3 (5) and 3.9 (5.1) (range 0–16), $P=0.024$ for PL, respectively].

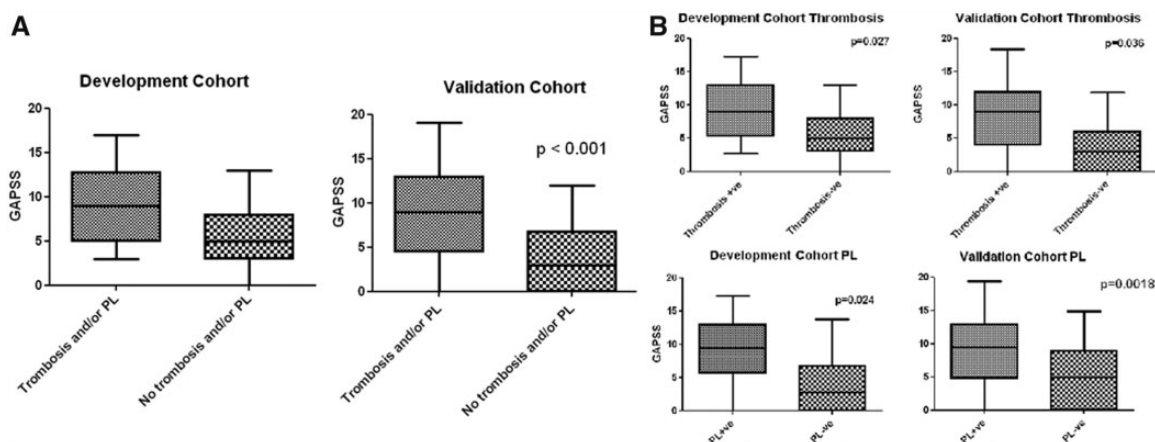
In the validation cohort the results were similar, with statistically higher values of GAPSS in patients with a clinical history of thrombosis and/or PL compared with those without events [GAPSS 9.5 (5.6) (range 0–20) and 3.9 (4.1) (range 0–17), $P < 0.001$] (Fig. 1A). Higher values were also seen when subclassifying the patients according to the clinical manifestation, thrombosis or PL [GAPSS 9.5 (5.6) (range 0–20) and 4.8 (5.4) (range 0–17), $P=0.036$ for thrombosis; 7.9 (3.3) and 3.8 (5.4) (range 0–16), $P=0.037$ for PL, respectively] (Fig. 1B).

The diagnostic accuracy for different cut-off values was also assessed. Sensitivity, specificity, PPV and NPV are shown in Table 4. The computed AUC demonstrated that GAPSS values ≥ 10 had the best diagnostic accuracy compared with the different thresholds (Fig. 2).

Discussion

APS is a heterogeneous entity with wide variation in clinical course and laboratory profile. In this study, six variables including arterial hypertension, hyperlipidaemia, aCL, LA, anti- β 2GPI and aPS/PT were shown to be independent risk factors for thrombosis and PL after multivariate analysis. A score derived by combining points for each of these six features was set up in a development cohort

Fig. 1 GAPSS in development and validation cohorts.

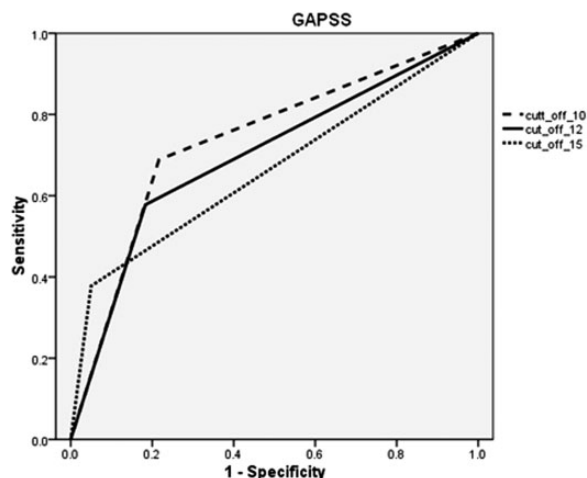


(A) Distribution of GAPSS in SLE in the development and validation cohorts. Data are shown as box plots, where each box represents the 25th–75th percentiles: lines inside the box represent the median. The whiskers represent the 95% CI. Higher values of GAPSS were seen in patients who experienced thrombosis and/or PL when compared with those without clinical events in both development and validation cohorts. (B) Distribution of GAPSS in SLE in the development and validation cohorts, analysing separately patients who experienced thrombosis or PL. Data are shown as box plots, where each box represents the 25th–75th percentiles: lines inside the box represent the median. The whiskers represent the 95% CI. Higher values of GAPSS were seen in patients who experienced thrombosis or PL when compared with those without clinical events in both development and validation cohorts.

TABLE 4 Diagnostic accuracy including sensitivity, specificity, PPV and NPV for different cut-off values of GAPSS

	AUC	Sensitivity	Specificity	NPV	PPV	P-value
GAPSS cut off = 10	0.736	0.709	0.793	0.7705	0.7045	0.000
GAPSS cut off = 12	0.697	0.578	0.817	0.7206	0.7027	0.001
GAPSS cut off = 15	0.664	0.378	0.950	0.6706	0.8500	0.004

Fig. 2 Receiver operating characteristic curves computed using different GAPSS thresholds.



The AUC was calculated according to the presence of a history of thrombosis and/or PL.

and validated in a separate cohort of patients. In this pilot study, we report that higher levels of GAPSS correlate with the major features of APS in a large cohort of SLE patients, suggesting that this score could be used as a potential quantitative marker for APS.

In 2011 we set up a preliminary risk model taking into account the issue of aPL profiles in the assessment of the risk for clinical events in APS [16]. More recently, Otomo *et al.* [5] elaborated an aPL-S with the purpose of quantifying the risk based on the aPL profile. An algorithm was created based on multiple aPL assays, with each assay being assigned a different score weighted on the relative risk of having clinical manifestations of APS as calculated in a cohort of patients affected by systemic autoimmune diseases.

The strength of our GAPSS, when compared with the previous proposed score, includes several points, one of the most relevant being the inclusion of conventional cardiovascular risk factors in the setting up of our model. Many observational studies have demonstrated the role of concomitant vascular risk factors such as hypertension, hypercholesterolaemia, smoking or oestrogen

therapy in the development of thrombosis. Our data support the multifactorial nature of thrombosis and PL, as a higher incidence of arterial hypertension and hyperlipidaemia was found in patients with higher GAPSS score [17].

Moreover, our study included a very homogeneous cohort of 211 patients from a single centre, all classified as having SLE by strict fulfilment of criteria. In addition to the ongoing debate about the value of multiple aPL positivity [18], our study evaluated the aPL profile of patients taking into account criteria and non-criteria aPL [19, 20]. To the best of our knowledge, this is the first score evaluating a panel of seven different aPLs, all shown to be relevant in APS [21–24]. In the current study, patients with higher GAPSS had a higher prevalence of multiple aPL positivity, whereas single or dual positivity was seen in patients with lower GAPSS. Our data support the notion that a combination of aPL tests should be considered when discussing the risk of thrombosis and/or pregnancy morbidity.

It is also true that our model has some limitations. First, a limitation of our analysis is the use of a history of thrombosis and/or PL rather than actual events as outcome. This use of a proxy outcome measure (inevitable in a cross-sectional study) may lead to misclassification in either direction, although the efficacy of this approach for cardiovascular risk factor evaluation has been demonstrated in diverse populations [25–27].

We also used dichotomized variables. Although this strategy simplified the creation of the risk score, making it more widely adoptable, the use of continuous variables would have the potential to provide more refined information. This is work in progress. In addition, we acknowledge that no consensual standardized method exists for the detection of non-criteria aPL, currently limiting the clinical application of these tests in routine practice. In this study we could not assess the effect of therapy because treatment was not controlled, but varied according to the clinical manifestations. Furthermore, these findings should also be validated in a prospective fashion, including not only primary APS but also aPL-positive patients without clinical symptoms suggestive of APS or other autoimmune disease.

In summary, we developed the GAPSS as a score model based on six clinical factors that has been proved to represent the probability or likelihood of having thrombosis or PL in SLE. This score was validated in a statistically independent sample of patients. The use of GAPSS may provide important information regarding thrombosis or PL risk for each SLE patient, switching from the concept of aPL as diagnostic antibodies to aPL as risk factors for clinical events.

These data propose a substantial improvement in risk prediction of thrombosis or PL in SLE based on assessment of the GAPSS, a quantitative scoring system. In turn, such an approach on the categorization of SLE patients based upon different combinations of positive aPL tests and conventional cardiovascular risk factors may, in future, influence not only prognostic judgement but also, more critically, pharmacological treatment.

In conclusion, we demonstrated that the risk profile in APS can be successfully assessed by GAPSS, suggesting that GAPSS can be a potential quantitative marker of APS. Clearly these observations need to be validated in prospective studies.

Rheumatology key messages

- GAPSS is based upon combinations of positive aPL tests and conventional cardiovascular risk factors.
- A combination of aPL tests should be considered when assessing the risk of thrombosis/PL in SLE.
- GAPSS represents an improvement in assessment of the risk of thrombosis/PL in SLE patients.

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