The global anti-phospholipid syndrome score in primary APS.

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Abstract

Objective. The aim of this study was to evaluate the clinical relevance of the global APS score (GAPSS) in a cohort of primary APS patients.

Methods. This study included 62 consecutive patients with primary APS. Data on clinical manifestations, conventional cardiovascular risk factors and aPL profile were collected. The GAPSS was calculated for each patient by adding together the points corresponding to the risk factors, based on a linear transformation derived from the β regression coefficient as follows: 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for aCL IgG/IgM, 4 for anti-β2 glycoprotein I IgG/IgM, 3 for aPS-PT IgG/IgM and 4 for LA.

Results. Higher GAPSS values were seen in patients who experienced thrombosis alone when compared with those with pregnancy loss alone [11.5 (S.D. 4.6) and 8.7 (S.D. 3.2), P = 0.04]. Patients with both thrombosis and pregnancy loss showed higher GAPSS than those with pregnancy loss alone [12.5 (S.D. 4.6) vs 8.7 (S.D. 3.2), P = 0.02]. Higher GAPSS values were also shown after subgrouping for the site of thrombosis when compared with pregnancy loss alone [12.2 (S.D. 5.2) for arterial thrombosis, 12.0 (S.D. 4.0) for venous vs 8.7 (S.D. 3.2), P = 0.02 and P = 0.04, respectively]. Patients with thrombotic recurrences showed higher GAPSS values when compared with those without recurrence [13.7 (S.D. 3.1) vs 9.4 (S.D. 3.9), P = 0.02]. This was also seen when comparing recurrences vs no recurrences independently of the site of the thrombotic event [13.9 (S.D. 3.6) vs 11.0 (S.D. 4.3), P = 0.01 for arterial and 13.6 (S.D. 2.18) vs 8.91 (S.D. 3.6), P < 0.01 for venous thrombosis]. GAPSS values ≥11 were strongly associated with a higher risk of recurrence [odds ratio (OR) 18.27 (95% CI 3.74, 114.5) for a cut-off of 11, OR 20.64 (95% CI 3.92, 185.92) for a cut-off of 12 and 21.64 (95% CI 3.89, 189.56) for a cut-off of 15]. GAPSS values ≥11 seemed to have the best risk accuracy in terms of sensitivity and specificity.

Conclusion. The GAPSS is demonstrated to be a valid tool for a substantial improvement in risk stratification for thrombosis in primary APS.

Key words: anti-phospholipid antibodies pregnancy loss thrombosis Hughes syndrome prothrombin

Introduction

APS is defined by the persistent presence of moderate to high serum levels of aPL in association with thrombotic events, pregnancy loss or both [1]. Recently we conducted a cross-sectional study in a large cohort of well-characterized SLE patients applying a risk score for APS clinical manifestations [the global APS score (GAPSS)]. This score derived from the combination of independent risk factors for thrombosis and pregnancy loss, taking into account the aPL profile (criteria and non-criteria aPL), the conventional cardiovascular risk factors and the autoimmune antibody profile [2]. We demonstrated that the risk profile in APS can be successfully assessed, suggesting that GAPSS can be a potential quantitative marker of APS-related clinical manifestations. In this study we aimed to evaluate the clinical relevance of the GAPSS in a cohort of primary APS patients.

Patients and methods

Patients

This study included 62 consecutive patients who attended the Louise Coote Lupus Unit at St Thomas' Hospital, London, UK. All the patients fulfilled the current APS classification criteria [1]. Thirty-nine patients (62.9%) had a history of previous thrombosis with (n = 20) or without (n = 19) pregnancy loss (thrombosis group). Fifteen patients (24.2 %) had arterial thrombosis, 18 (29.0%) had venous thrombosis and 6 (9.7%) had both arterial and venous events. Twenty-three patients (37.0%) had a history of pregnancy loss in the absence of thrombosis. Demographic, clinical and laboratory characteristics are summarized in Table 1. Ethics approval was obtained from the Guy's and St Thomas' ethics committee and all patients involved in this study gave their written informed consent.

Assessment of cardiovascular risk factors

Cardiovascular risk factors were assessed following the National Institute for Health and Care Excellence (NICE) guidelines [3]. In detail, enrolled patients underwent a physical examination, blood pressure determination and phlebotomy for vascular risk factors. Arterial hypertension was defined as an appropriately sized cut-off [3], high blood pressure on at least two occasions or use of oral antihypertensive medications. Serum total and high-density lipoprotein (HDL) cholesterol levels were determined with standardized enzymic methods and interpreted according to current cut-off values [3].

Autoantibody detection

The aPL profile included aCL, LA, anti-β2 glycoprotein I (anti-β2GPI) antibody and aPS-PT. The aCL and anti-β2GPI were detected by ELISA as described previously [4, 5]. Plasma samples were tested for the presence of LA according to the recommended criteria from the International Society on Thrombosis and Haemostasis (ISTH) Subcommittee on Lupus Anticoagulant/Phospholipid-Dependent Antibodies [6, 7]. aPS-PT were detected as previously reported [8, 9]. ANA was measured by indirect immunofluorescence on rodent liver cells and anti-dsDNA antibodies by RIA (Farr assay).

GAPSS calculation

The GAPSS was calculated for each patient as previously reported, by adding together the points corresponding to the risk factors [2]. In brief, the GAPSS was developed and validated in 211 consecutive SLE patients who were randomly divided into two sets by a computer-generated randomized list. Data on clinical manifestations, conventional cardiovascular risk factors, aPL profile, ANA, ENA and anti-dsDNA were collected and included in the analysis. We developed the 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. Assigned points to risk factors based on this linear transformation of the corresponding β regression coefficient were 3 for hyperlipidaemia, 1 for arterial hypertension, 5 for aCL IgG/IgM, 4 for anti-β2GPI IgG/IgM, 3 for aPS-PT IgG/IgM and 4 for LA. The GAPSS was then validated in the second set of patients (n = 105) [2]. A complementary analysis applying an adjusted version of the score, which excluded aPS-PT, was also performed. Data are presented as adjusted GAPSS (aGAPSS).

Statistical analysis

Categorical variables are presented as number (%) and continuous variables are presented as mean (S.D.). The significance of baseline differences was determined by the chi-squared test, Fisher's exact test or the unpaired t-test, as appropriate. A two-sided P-value <0.05 was statistically significant. The sensitivity and specificity for different cut-off values were also assessed for recurrences. Areas under the receiver operating characteristic (ROC) curve of different cut-off values were computed. Comparisons between different cut-off values for the risk of recurrence were expressed as the odds ratio (OR) with its 95% CI, where a lower limit >1.0 was considered significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

Results

Patients with APS showed a baseline GAPSS of 11.08 (S.D. 4.32, range 4–20) [aGAPSS 9.8 (S.D. 3.79, range 4–17)]. Higher GAPSS values were seen in patients who experienced thrombosis when compared with those with pregnancy loss alone [11.5 (S.D. 4.6, range 4–20) vs 8.7 (S.D. 3.2, range 4–16), P = 0.04; aGAPSS 10.7 (S.D. 5.7, range 4–17) vs 7.1 (S.D. 4.2, range 4–14), P = 0.04] (Fig. 1A). Patients who experienced both thrombosis and pregnancy loss showed higher GAPSS when compared with those with pregnancy loss alone [12.5 (S.D. 4.6, range 4–20) vs 8.7 (S.D. 3.2, range 4–16), P = 0.02; aGAPSS 10.8 (S.D. 5.1, range 4–17) vs 7.1 (S.D. 4.2, range 4–14), P = 0.04]. Higher GAPSS values were also seen when subgrouping the patients according to the site of thrombosis when compared with pregnancy loss alone [12.2 (S.D. 5.2, range 4–20, P = 0.04) for arterial and 12.0 (S.D. 4.0, range 4–20, P = 0.01) for venous thrombosis vs 8.7 (S.D. 3.2, range 4–16); aGAPSS 11.1 (S.D. 3.5, range 4–17, P = 0.04) for arterial and 10.4 (S.D. 5.3, range 4–17, P = 0.05) for venous thrombosis vs 7.1 (S.D. 4.2, range 4–14)] (Fig. 1B). Within the thrombosis group, no differences were observed when comparing GAPSS values obtained in the arterial vs venous thrombosis subgroups [12.2 (S.D. 5.2) vs 12.0 (S.D. 4.0), P = 0.32; aGAPSS 11.1 (S.D. 3.5) vs 10.4 (S.D. 5.3), P = 0.44].

Patients who experienced thrombotic recurrence showed higher GAPSS values when compared with those without recurrence [13.7 (S.D. 3.1, range 9–20) vs 9.4 (S.D. 3.9, range 4–17), P = 0.02 (Fig. 1C); aGAPSS 12.1 (S.D. 2.8, range 6–17) vs 7.8 (S.D. 3.1, range 4–17), P = 0.01] (Fig. 1D).

Higher GAPSS values were also seen when subdividing the patients according to the site of the thrombotic recurrence. Patients with arterial recurrences showed a GAPSS of 13.9 (S.D. 3.6, range 9–20) vs 11.0 (S.D. 4.3, range 4–17) in those without recurrent arterial events (P = 0.01). Patients with venous recurrences showed a GAPSS of 13.6 (S.D. 2.18, range 9–17) vs 8.91 (S.D. 3.6, range 5–17) in those with no recurrences (P < 0.01) (Fig. 1C). When excluding aPS-PT from the computation, patients with arterial recurrences showed an aGAPSS of 12.3 (S.D. 5.1, range 6–17) vs 9.8 (S.D. 4.8, range 4–17) in those without recurrent arterial events (P = 0.03). Accordingly, patients with venous recurrences showed an aGAPSS of 11.9 (S.D. 3.9, range 6–17) vs 8.52 (S.D. 4.6, range 5–17) in those with no recurrences (P = 0.04).

No statistically significant difference was found in patients with and without thrombotic recurrences when adjusting for disease duration [9.8 (S.D. 7.8) and 10.4 (S.D. 6.9), P = 0.65, respectively]. As higher values of GAPSS were shown to be associated with a higher risk of thrombotic recurrence, we attempted to establish a practical cut-off for the risk by using the ROC curve (see supplementary Table S1, available at Rheumatology Online). GAPSS values ≥11 were strongly associated with a higher risk of recurrence [OR 18.27 (95% CI 3.74, 114.5)], showing the best accuracy in terms of sensitivity and specificity (see supplementary Table S1, available at Rheumatology Online).

Discussion

This study was aimed at evaluating the clinical relevance of the GAPSS in a cohort of 62 primary APS patients from a single centre, all classified by strict fulfilment of the current criteria [1]. Recently we developed the GAPSS as a score model based on six clinical factors that were proved to represent the probability or likelihood of having thrombosis or pregnancy loss in SLE. This was also validated in a statistically independent sample of patients. The GAPSS was shown to provide important information regarding thrombosis and/or pregnancy loss risk in SLE patients, supporting the notion that aPL should not only be considered as a diagnostic marker, but also as a risk factor for clinical events [2].

In this study we showed that higher GAPSS values are seen in APS patients who experienced thrombosis when compared with those with pregnancy loss alone. In addition, we reported that APS patients who experienced recurrent thrombotic events showed higher GAPSS values when compared with those without recurrences. It has been shown that patients with APS and triple positivity for aPL are at high risk of developing future thromboembolic events [10]. Our data support these findings and indicate that the

combination of aPL tests should be considered when assessing the risk of thrombosis and/or its recurrence in primary APS. In this context the GAPSS represents a substantial improvement in quantifying the risk for thrombosis and thrombotic recurrence.

Recently Otomo et al. [11] developed the aPL score (aPL-S), with the purpose of quantifying the risk based on the aPL profile. That study included 32 patients with primary APS, the data were evaluated as a whole and no specific analysis was performed to quantify the risk in this subgroup of patients. Thus, to the best of our knowledge, our study represents the first attempt to quantify the risk of aPL-related clinical manifestations in a cohort of primary APS using a scoring system.

As aPS-PT is not routinely tested for in most clinical laboratories, its inclusion as part of the score might be of concern to many. Our data, in an adjusted model of the score, suggest that even when aPS-PT is not computed, the score is able to stratify patients for their rate of events, making it widely applicable.

We accept that this approach has some limitations. First, as discussed previously [2, 12–14], the use of a cross-sectional approach is a weak point that needs to be acknowledged. Most importantly, the effect of therapy, a significant variable when evaluating risk, could not be assessed, as treatment was not controlled in this cohort, but varied according to the clinical manifestations and clinician judgement.

In summary, in this study we confirmed that the GAPSS is a valid tool for thrombotic risk quantification in primary APS. Such an approach to the categorization of APS patients based upon a quantitative score may, in the future, influence pharmacological treatment, especially in patients with a higher rate of recurrence.

Supplementary data

Rheumatology key messages

- The global APS score is based on combinations of positive aPL tests and conventional cardiovascular risk factors.
- The global APS score was demonstrated to be a valid tool for risk stratification for thrombosis in SLE.
- The global APS score represents an improvement in assessment of the risk of thrombosis in primary APS patients.

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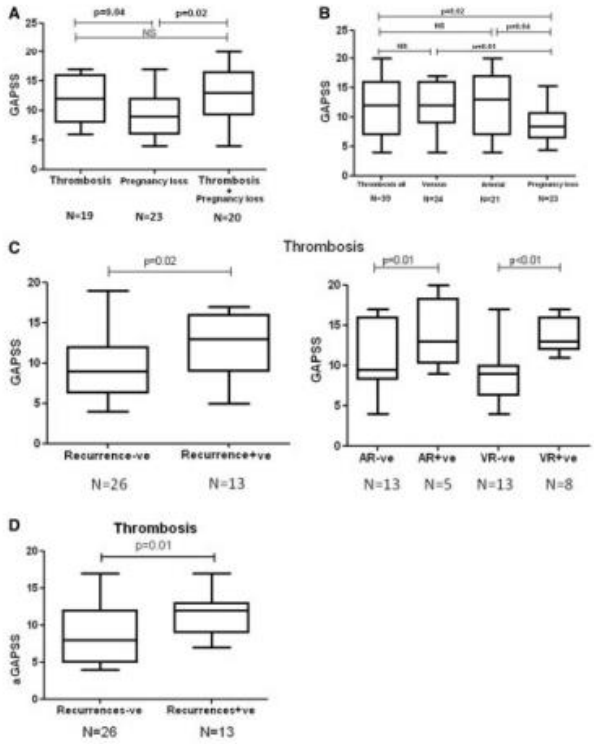
Characteristics	All (n = 62)	%
Female sex	57	92.0
Age, mean (S.D.), years	47.1 (11.5)	
Disease duration, mean (S.D.), years	10.2 (8.2)	
Caucasian, *n*	55	87.7
Thrombosis[a], *n*	39	62.9
Arterial thrombosis	21	33.8
Venous thrombosis	24	38.7
Recurrent thrombosis[b], *n*	13	21.0
Arterial thrombosis	8	12.9
Venous thrombosis	5	8.1
Time free from thrombosis, mean (S.D.), months[c]	37 (12.5)	
Pregnancy loss, *n*	44	84.6
Miscarriages ⩾3	11	21.1
Fetal death	37	71.1
Conventional risk factor, *n*		
Hyperlipidaemia	33	53.2
Arterial hypertension	20	32.3
dsDNA, *n*	0	0
ANA, *n*	13	21
aCL IgG/IgM, *n*	30	48.4
IgG	24	38.7
IgM	13	21.0
Anti-β2GPI IgG/IgM, *n*	29	46.8
IgG	20	32.3
IgM	17	27.4
aPS-PT IgG/IgM, *n*	32	51.6
IgG	22	35.5
IgM	23	37.0
LA, *n*	38	61.3
Low-dose aspirin, *n*	26	41.9
HCQ, *n*	22	35.5
Oral anticoagulation, *n*	28	45.1

a Six patients experienced both arterial and venous thrombosis. b Eleven patients were on oral anticoagulation at the time of recurrence. The remaining two cases were treated with low-dose aspirin (one patient with recurrent deep vein thrombosis and one with stroke). c Time free from thrombosis was only computed for those patients who had recurrences. All pregnancy data percentages were calculated over the total number of females who had ever been pregnant (n = 52).

FIG. 1 Distribution of GAPSS in primary APS



(A) Distribution of GAPSS in primary APS according to clinical manifestations. Data are shown as box plots, where each box represents the 25th75th 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 alone or associated with pregnancy loss when compared with those with pregnancy loss alone. (B) Distribution of GAPSS in primary APS analysing separately patients who experienced arterial or venous thrombosis, pregnancy loss or both. Data are shown as box plots, where each box represents the 25th75th percentiles: lines inside the box represent the median. The whiskers represent the 95% CI. (C) Distribution of GAPSS in primary APS analysing separately patients who experienced thrombotic recurrence, also taking into account the site of the event. Data are shown as box plots, where each box represents the 25th75th percentiles: lines inside the box represent the median. The whiskers represent the 95% CI. Higher values of GAPSS were seen in patients who experienced thrombotic recurrences when compared with those without. This was also seen when subdividing the cohort between those with arterial or venous thrombosis. Of note, six patients experienced both arterial and venous events. (D) Distribution of GAPSS in primary APS analysing separately patients who experienced thrombotic recurrence applying the adjusted version not including aPS-PT. Data are shown as box plots, where each box represents the 25th75th percentiles: lines inside the box represent the median. The whiskers represent the 95% CI. GAPSS: global APS score.