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Clinical utility of the Global Antiphospholipid Syndrome Score (GAPSS) for risk stratification: a pooled analysis

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This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation
Abstract

Background/Purpose:
Recently, our group conceived a risk score for clinical manifestations of APS [the global APS score or GAPSS] that takes into account the combination of independent cardiovascular risk factors and the aPL positivity profile. These include hyperlipidemia, arterial hypertension, aCL, anti-β2GPI, aPS/PT and the LA. A complementary version, the adjusted GAPSS or aGAPSS, which excludes aPS/PT, was also designed.

Methods:
We pooled data from available cohort studies, including a total of 10 studies, counting for a total of 2273 patients in which the GAPSS score has been applied. A search strategy was developed a priori to identify available cohort that reported findings that investigated the clinical utility of GAPSS or aGAPSS score.

Results:
Seven studies used the GAPSS in their cohort, whether three studies used the aGAPSS. In brief, we found a statistically significant difference in the cumulative GAPSS and aGAPSS scores between patients that experienced arterial and/or venous thrombotic event (Cumulative GAPSS 10.6±4.74 and aGAPSS 7.6±3.95), patients without any thrombotic manifestation (Cumulative GAPSS 7.01±5.46 and aGAPSS 4.9±4.33) and patients with pregnancy morbidity (Cumulative GAPSS 8.79±2.59 and aGAPSS 6.7±2.8).
The highest levels of GAPSS were found in patients that experienced arterial thrombosis (mean GAPSS 12.2±5.2) and patients that experienced any recurrences of clinical manifestations of APS (mean GAPSS 13.7±3.1).

**Conclusion:**

GAPSS may represent a useful tool to assess the thrombosis or pregnancy loss risk in aPL positive patient, switching from the concept of aPL as a sole diagnostic antibody to aPL as risk factors for clinical events.
**Key Messages**

- GAPSS is a risk score for clinical manifestations of APS.

- In a pooled analysis, high GAPSS was found in patients with clinical manifestations of APS.
A risk assessment, using tools as GAPSS, could identify APS patients at a higher risk of recurrences. **1.1 Introduction**

Antiphospholipid syndrome (APS) is the most common acquired thrombophilia, an autoimmune disorder characterized by arterial and/or venous thrombosis and/or pregnancy morbidity in the presence of persistent positivity for antiphospholipid antibodies (aPL)[1]. The current classification criteria for APS include three laboratory tests: lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2 glycoprotein-I (β2GPI). To prevent the detection of transient antibodies, tests must be positive on more than 2 occasions, at least 12 weeks apart [1].

Identifying patients with aPL who are at higher risk for developing any clinical manifestations of APS (thrombotic and/or pregnancy morbidity) is still an unmet clinical need and remains a major challenge -in routine clinical practice. Recently, our group conceived a risk score for clinical manifestations of APS [the global APS score or GAPSS] that takes into account the combination of independent cardiovascular risk factors and the aPL positivity profile. These include hyperlipidemia, arterial hypertension, aCL, anti-β2GPI, aPS/PT and the LA[2]. Despite the staggering amount of data supporting the usefulness of aPS/PT as a diagnostic and prognostic biomarker, these antibodies are not included as a laboratory criteria for APS and therefore, although being available, are still not routinely used in the clinical setting [3]. For this reason, a complementary version, the adjusted GAPSS or aGAPSS, which excludes aPS/PT, was also designed. The aim of our study was to systematically review the literature to assess the clinical utility of the GAPSS and adjusted GAPSS (aGAPSS) score for risk stratification of any APS clinical manifestation.
2.1 Material and Methods

2.2 Literature search

A detailed literature search has been developed a priori to identify articles that reported findings from clinical and laboratory studies that demonstrated the clinical utility of GAPSS or aGAPSS score. Key words and subject terms included: ("GAPSS"[MeSH Terms] OR global APS score [MeSH Terms] OR global APS score [All Fields] OR "GAPSS "[All Fields] OR "GAPSS"[All Fields]) AND aGAPSS [All Fields]. The search strategy was applied to Ovid MEDLINE, In-Process and Other Non-Indexed Citation and Ovid Medline 1986 to present. Abstracts from European League Against Rheumatism (EULAR), International Society on Thrombosis and Haemostasis (ISTH) and American College of Rheumatology (ACR) and the Association for Rheumatology Health Professionals (ARHP) Annual Meetings (2011-2016) were screened and included in the analysis when meeting the inclusion criteria and not replicating studies published elsewhere.

Studies that met the criteria to evaluate the clinical utility of GAPSS or aGAPSS and their association with clinical manifestations of APS in patients and control populations were systematically analyzed by two independent reviewers (MR and IC). Disagreements were resolved by consensus; if consensus could not be achieved, a third party (SS) would provide an assessment of eligibility. As the data on eligibility were dichotomous (eligible: yes / no), inter-rater agreement at both the title and abstract review and the full article review stages was determined by calculation of Cohen’s kappa coefficient (k=0.93).
We included in our analysis only studies reporting: a) clinical data referring to aPL-related manifestations; b) laboratory data including aCL, LA, anti-β2GPI and/or anti-phosphatidylserine/prothrombin antibodies testing; c) Studies reporting the GAPSS and/or aGAPSS in the different populations reported in the analysis. All published series including 10 or more patients meeting the above inclusion criteria were recorded. Methods of enrollment were also analyzed. The present study has been performed according to PRISMA guidelines [4].

2.3 Statistical Analysis

Cumulative GAPSS score was calculated as weighted average when means and standard deviations were provided from the included studies for each study group.

The significance of baseline differences between groups was determined by the unpaired t-test. A two-sided P-value <0.05 was statistically significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY, USA).

3.1 Results:

A total of 10 studies [2,5-13], including a total of 2273 patients, met the inclusion criteria. Studies characteristics and patients enrolled are summarized in Table 1. In brief, we retrieved one cross-sectional study (including 105 patients), seven retrospective analyses (1980 patients) and two prospective studies (188 patients).

Seven studies [2,5-10] used the GAPSS in their cohort, whether three studies[11-13] used the aGAPSS. For the studies that used the GAPSS score, six
studies [2,5–8,10] including a total 1187 patients were found to be eligible to calculate a cumulative GAPSS score for different clinical manifestation of APS.

In brief, we found a statistically significant difference in the cumulative GAPSS scores between patients that experienced arterial and/or venous thrombotic event (Cumulative GAPSS score 10.6±4.74), patients without any thrombotic manifestation (Cumulative GAPSS score 7.01±5.46) and patients with pregnancy morbidity (Cumulative GAPSS score 8.79±2.59). Data comparing the GAPSS and aGAPSS scores in the different cohort of patients are summarized in Graph 1 and Table S1.

The highest levels of GAPSS were found in patients that experienced arterial thrombosis (mean GAPSS 12.2±5.2) and patients that experienced any recurrences of clinical manifestations of APS, including thrombosis and/or pregnancy morbidity (mean GAPSS 13.7±3.1).

When analyzing the studies that assessed the risk of clinical manifestations of APS using the aGAPSS, all three studies were found eligible for calculating the cumulative aGAPSS between cohorts. Similarly to the study that used the GAPSS, we found a statistically significant difference between patients that experienced arterial and/or venous thrombotic event (Cumulative aGAPSS score 7.6±3.95), patients without any thrombotic manifestation (Cumulative aGAPSS score 4.9±4.33) and patients with pregnancy morbidity (Cumulative aGAPSS score 6.7±2.8).

4.1 Discussion:

Risk stratification is one of the fundamentals of current medical research, aiming to identify individuals who have a high risk of developing an adverse
outcome over a specific time period, so that they can be targeted for early preventative strategies and possible treatments. Prediction models have been widely developed for cardiovascular diseases [14,15], with most of them focusing on cardiac or cerebrovascular events.

Recently, three score systems have been formulated to quantify the risk of thrombosis/obstetric events in subjects with aPL, with or without clinical evidence of confirmed APS, in an attempt to help physicians to stratify patients according to risk [2,16,17]. The first two scores[16,17] focus on aPL profile, while the most recently developed one, the Global APS Score or GAPSS [2] also includes cardiovascular risk factors when computing the risk.

In this systematic review, we aimed at collecting available evidence on the clinical relevance of the GAPSS. When analyzing together data from 2273 patients, we found that the GAPSS is a valid tool to stratify patients with aPL according to their thrombotic risk, being the highest levels of GAPSS found in patients who experienced thrombosis, especially arterial thrombosis. Interestingly, the GAPSS has also been proven to identify patients at higher likelihood of developing further events, as patients who suffered from any recurrences of clinical manifestations of APS showed higher value of GAPSS when compared to those who did not.

The presence of aPS/PT has been associated with thrombosis in APS [18] and testing for these antibodies has been shown to improve the diagnostic accuracy when APS is suspected [19]. Although aPS/PT testing is now more widely available [20], this test is still not included among the criteria aPL and not all laboratories routinely test for aPS/PT.
For this reason, a complementary version, the adjusted GAPSS or aGAPSS, which excludes aPS/PT, was also designed. Similar results to those found with the GAPSS were seen when applying the aGAPSS.

We acknowledge that our study has some limitations. First, despite the systematic nature of this review, combining heterogeneous studies (i.e. heterogeneous enrolled populations) might lead to shortcomings in the interpretation of the results. Including only studies from unselected patients (regardless of the underlying autoimmune status) would provide conclusions that are more generalizable. However, to the best of our knowledge, such studies are not available and therefore, this combination of studies from both patients with and without underlying autoimmune diseases provided us with larger number of patients, for meaningfully calculating the estimates.

Secondly, the information that could potentially increase the accuracy of the risk estimation, including adjustments for clinical or historical factors, treatments, physical examination findings, the timing of the GAPSS computation when referred to the clinical manifestation onset, and other diagnostic test results, was rarely reported in the analyzed studies.

In contrast, the strength of GAPSS, when compared with the previously proposed scores, lies in the inclusion of conventional cardiovascular risk factors into the computation.

In summary, this study, while owning limitations, contains some important clinical messages: GAPSS may represent a useful tool to assess the thrombosis or pregnancy loss risk in aPL positive patient, switching from the concept of aPL as a sole diagnostic antibody to aPL as risk factors for clinical events. A risk assessment, using appropriate tools as GAPSS, should be implemented to
identify and monitor those patients at a higher risk of recurrences and those needing a strict control of all modifiable risk factors for cardiovascular events; in agreement with the above, in the future the management of APS should also modulate according to the GAPSS values.
5.1 References


[19] Sciascia S, Murru V, Sanna G, Roccatello D, Khamashta MA, Bertolaccini

Legend of Tables and Figures:

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

**Table S1.** GAPSS and aGAPSS between groups

**Graph 1.** Cumulative GAPSS values between groups

GAPSS – Global Antiphospholipid Syndrome Score; aGAPSS – Adjusted Global Antiphospholipid Syndrome Score; PM – Pregnant morbidity;
Authors Contribution

SS and MR designed the study, performed data analysis and drafted the manuscript. GS, IC, DR and MLB gave a substantial contribution to concept and study design and participated in the interpretation of data. DR and MLB critical revised the intellectual content. All the Authors gave the final approval of the version to be published.