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Letter to the Editor (Other)

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Translational validation of the Global Antiphospholipid Syndrome Score in patients with thrombotic APS

Rheumatology key message

- Higher adjusted-Global Antiphospholipid Syndrome Scores are associated with higher levels of pro-thrombotic molecules in APS.

SIR, Recently, the Global Antiphospholipid Syndrome Score (GAPSS) has been proposed as a scoring system to positively stratify patients with aPL according to their risk of developing clinical features of APS [1]. GAPSS is a combination of traditional cardiovascular risk factors, such as hyperlipidaemia and arterial hypertension, and the aPL profile, including anticardiolipin, anti-β2-glycoprotein-I, aPS/PT antibodies and lupus anticoagulant. Additionally, a complementary version was also designed, identified as the adjusted GAPSS (aGAPSS), which excludes aPS/PT and is not routinely available in the clinical setting [2].

Previous studies have demonstrated the clinical utility of the GAPSS/aGAPSS to assess the risk of both thrombosis and pregnancy morbidity in aPL-positive patients [3]. In 2018, the clinical utility of GAPSS/aGAPSS in a pooled analysis of 2273 patients reported higher values of GAPSS in patients with clinical manifestations of APS. Moreover, the highest values of GAPSS were associated with the most severe clinical manifestations of the disease (arterial thrombosis and recurrent thrombotic events and/or pregnancy morbidity) [4]. Similarly, patients with higher aGAPSS values had more extra-criteria manifestations of APS [5].

The recent improvements in the diagnostic accuracy for APS have been paralleled by a better understanding of the mechanisms underlying the clinical manifestations of the syndrome. APS pathogenesis is linked to the altered levels of several proteins directly involved in the development of thrombotic events. In this sense, among others, Pérez-Sánchez C. *et al.* [6] have shown that APS patients have elevated plasma levels of tissue factor (TF), VEGF-A, VEGF receptor 1 (VEGF-R1 or FLT-1), monocyte chemoattractant protein-1 and plasminogen activator inhibitor-1 when compared with healthy donors. These molecules were quantified using Procarta Plex multiplex immunoassay, following the manufacturer's recommendations (Affymetrixe Bioscience, Vienna, Austria). Plasma levels of TF were determined by ELISA [Human Tissue factor (CD142) ELISA Abcam, Cambridge, MA, US].

In addition, they demonstrated the direct effect of IgG-aPL antibodies in the production of these molecules in monocytes isolated from healthy donors and human umbilical vein endothelial cells [6].

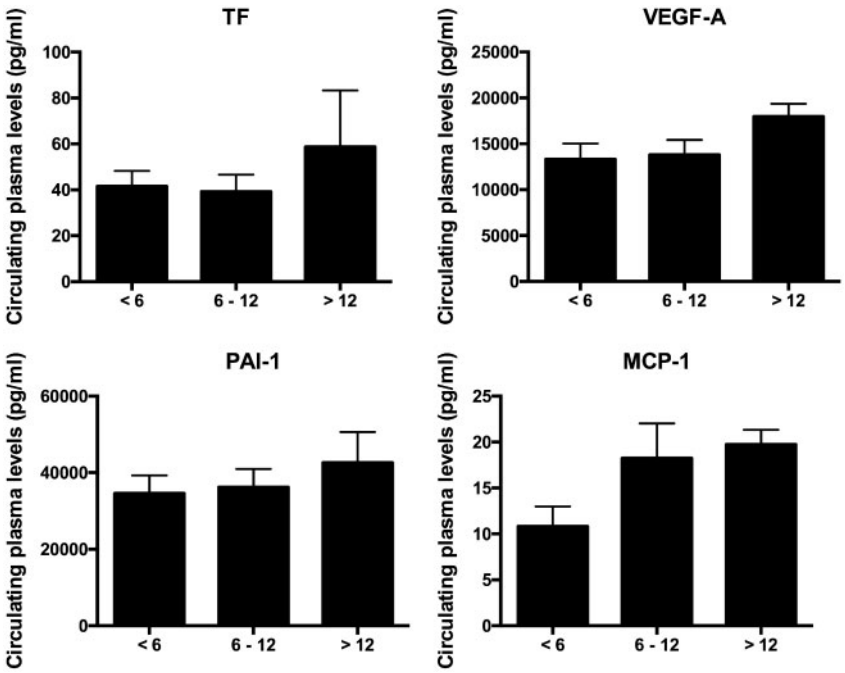
Taking all the above together, in this study we aimed to perform a translational validation study to investigate the relevance of aGAPSS in assessing the pro-thrombotic risk at the molecular level.

In this study, 38 thrombotic APS patients [mean age 52.2 (11.1) years, 12 (31.6%) females] were included after obtaining approval from the ethics committee of the Reina Sofia Hospital in Cordoba (Spain). Patients provided written informed consent. Seventeen patients (44.7%) had a history of arterial thrombosis, 21 (55.2%) had a previous venous thrombotic event, and seven patients (18.4%) have a history of pregnancy morbidity. Regarding traditional cardiovascular risk factors, nine patients (23.7%) had arterial hypertension and 17 (44.7%) had dyslipidaemia. The aGAPSS was calculated as previously reported [2]. Twenty healthy donors were included as controls. APS patients and healthy donors were tested for TF, VEGF-A, VEGF-R1, monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 (PAI-1), as previously described [6]. Positive correlations among plasma levels of TF ($r = 0.268$, $P = 0.08$), VEGF-A ($r = 0.486$, $P < 0.01$), FLT-1 ($r = 0.286$, $P = 0.09$), MCP-1 ($r = 0.332$, $P = 0.01$), PAI-1 ($r = 0.506$, $P < 0.01$) and aGAPSS values were observed. This demonstrated that aGAPSS might stratify patients depending on the levels of these relevant molecules related to pro-thrombotic status and cardiovascular disease. Moreover, after stratifying APS patients in three groups of relative risk determined by aGAPSS (low risk: aGAPSS < 6; medium risk: aGAPSS 6–12; high risk: aGAPSS > 12), aGAPSS values were increasing progressively in the three groups (Fig. 1).

These observations support the fact that higher GAPSS/aGAPSS values found in patients with higher pro-thrombotic profiles, assessed by a translational approach, are in line with the results by Pérez-Sánchez C. *et al.* [6] who investigated the clinical role for the use of microRNAs ratios to stratify patients according to their thrombotic risk. They performed a cluster analysis in this APS cohort, demonstrating that patients with a high rate of multiple aPL positivity, arterial thrombosis and lower rate of cardiovascular risk factors showed higher aGAPSS compared with patients with a high rate of multiple aPL positivity, venous thrombosis and lower prevalence of cardiovascular risk factors [4]. Similarly, the higher aGAPSS scores significantly correlated with serum levels of B cell stimulating factor in a cohort of primary APS patients ($r = 0.40$, $P = 0.03$) [7].

Taken together, these results confirm for the first time that aGAPSS might be able to classify APS patients based

Fig. 1 Pro-thrombotic plasma molecules levels in APS patients based on the relative risk determined by aGAPSS



TF: Tissue factor; VEGF-A: vascular endothelial growth factor A; PAI-1: plasminogen activator inhibitor-1; MCP1: monocyte chemoattractant protein-1.

on their pro-thrombotic risk profile investigated at the molecular level. The future challenge will be to translate this information into clinical practice, ideally tailoring therapeutic approaches according to the individual risk of each patient.

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