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Keymessage: Higher aGAPSSscores are associated with higher levels of pro-thrombotic circulating molecules in APS patients.

Sir,

Recently, the Global Antiphospholipid Syndrome Score (GAPSS) has been proposed as a scoring system to positively stratify patients with antiphospholipid antibodies (aPL) according to their risk of developing clinical features of antiphospholipid syndrome (APS)[1]. GAPSS is a combination of traditional cardiovascular risk factors, such as hyperlipidaemia and arterial hypertension, and the aPLprofile, including anticardiolipin, anti-β2-glycoprotein-I, antiphosphatidylserine/prothrombin (aPS/PT) antibodies and lupus anticoagulant. Additionally, a complementary version was also designed, identified asthe adjusted GAPSS (aGAPSS), which excludesaPS/PTand is not routinely available in the clinical setting[2]. Previousstudies have demonstrated the clinical utility of the GAPSS/aGAPSSto 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 andrecurrent thrombotic events and/or pregnancy morbidity) [4]. Similarly, patients with higher aGAPSSvalues had more extra-criteria manifestations of APS [5].

The recent improvements in the diagnostic accuracy forAPS 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.* have shown that APS patients have elevated plasma levels of tissue factor (TF), vascular endothelial growth factor A (VEGF-A), vascular endothelial growth factor receptor 1 (VEGF-R1 or FLT-1), monocyte chemoattractant protein-1 (MCP-1) and plasminogen activator inhibitor-1 (PAI-1)when compared to healthy donors. These

molecules were quantified using Procarta Plex multiplex immunoassay, following the manufacturer's recommendations (Affymetrixe Bioscience, Vienna, Austria). Plasma levels of TF weredeterminedby 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-thromboticrisk at the molecular level.

In this study,38thrombotic APS patients (mean age 52.2± 11.1 years, 12(31.6%)females) were included. Seventeen patients (44.7%) had a history of arterial thrombosis, 21 (55.2%) had a previous venous thrombotic event, and 7 patients (18.4%) have a history ofpregnancy morbidity. Regarding traditional cardiovascular risk factors, 9 patients (23.7%) had arterial hypertension and 17 (44.7%) had dyslipidaemia. The aGAPSS was calculated as previously reported [2]. Twenty healthy donorswere included as controls. APS patients and healthy donors were tested for TF,VEGF-A, VEGF-R1, MCP-1 and PAI-1, as previously described [6]. Positive correlations amongplasma 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 3 groups of relative risk determined by aGAPSS(low risk:aGAPSS<6; medium risk: aGAPSS 6-12; high risk: aGAPSS>12), aGAPSS values wereincreasingprogressively in the 3 groups (Figure 1).

These observations support the fact that higher GAPSS/aGAPSSvaluesfound in patients with higher pro-thrombotic profiles, assessed by a translationalapproach, are in line with the results by Pérez-Sánchez C. *et al,* who investigatedthe clinical role for the use of microRNAs ratiosto 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 comparedtopatients 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 on their pro-thrombotic risk profileinvestigated at the molecular level. The future challenge will be to translate this information into clinical practice, ideally tailoring therapeuticapproaches according to the individual risk of each patient.

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