Quality of life in patients with antiphospholipid antibodies differs according to antiphospholipid syndrome damage index (DIAPS)

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Radin Massimo MD[1], Foddai Silvia Grazietta MD[1], Cecchi Irene MD[1], Roccatello Dario MD[1], Sciascia Savino MD-PhD[1]

[1]Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences, and SCDU Nephrology and Dialysis, S. Giovanni Bosco Hospital and University of Turin, Turin, Italy.

Corresponding Author: Massimo Radin

Center of Research of Immunopathology and Rare Diseases- Coordinating Center of Piemonte and Valle d'Aosta Network for Rare Diseases, Department of Clinical and Biological Sciences University of Turin and SCDU Nephrology and Dialysis, S. Giovanni Bosco Hospital, Piazza del Donatore di Sangue 3, 10154, Turin, Italy.

Email: massimo.radin@unito.it Tel +390112402056 Fax +390112402052

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Short Title: DIAPS predicts the QoL in aPL positive patients

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Antiphospholipid syndrome (APS) is the most common form of acquiredthrombophilia and its main clinical manifestations comprehend thrombosis (venous and/or arterial)and recurrent pregnancy morbidity, in the presence of confirmed antiphospholipid antibodies (aPL) positivity[1].

The thrombotic events can occur at any level of the vascular bed causing a wide variety of clinical manifestations, some of which associated with poor outcome and a negative impact on the quality of life (QoL) [2].

Because of the flourishing and sudden clinical presentations of APS, we still lack an activity score able to assess changes inpatients disease course during the follow up. Amigo and colleagues[3] conceived the APS damage index (DIAPS), derived from the Systemic Lupus International Collaborating Clinics Damage Index (SDI) score[4], to evaluate the permanent functional or structural impairment of a specific organ/system. Compared to SDI, the DIAPS gather 37-item score, including extra-criteria APS specific features, which haveemerged over the last years asimportant causes of morbidity.

The mainaim of our study was to validate the DIAPS, in the setting of an external proof, in our retrospectivecohort of persistent aPLpositive patients, investigating their overall QoL.

This retrospectivecross-sectionalstudy included consecutive persistent aPL positivepatients [1]who attended the San Giovanni Bosco Hospital(Turin, Italy), from January 2020 to December 2020. Inclusion criteria included: 1) at least a 3 year follow-up history in our center 2) regular six month follow-up visits 3)persistent aPL positive [1]. Demographic, clinical and laboratorycharacteristics, were retrieved from electronic medical records and are summarized in Table S1(supplementary materials). Current treatment at the time of data collection is summarized in Graph S1(supplementary materials).

DIAPS and Global APS score were calculated, as previously reported, by adding together all points corresponding to the clinical manifestations of the patients[3,5].

A self-administered questionnaire was appositely designed to enquire the 12-Item Short Form Health Survey (SF-12) score, which is usedto assess the impact of health on individuals[6]. The SF-12 is a validated, easy to dispense and widely used tool composed by twelve subscales that measure physical (PCS, physical component score) and psychological (MCS, mental component score) aspects of life: physical function, physical functioning, bodily pain, emotional role functioning, general health perception, vitality, social functioning, and mental health[6]. Questionnaires were filled out anonymously by the patients via Google Forms, right after study enrollment.

A total of 84 patients were included in the study. Of those, 67 patients fulfilled the classification criteria for APS [1] (39 PAPS; 28 SAPS,while 17 patients were aPL positive, but not fulfilling the clinical classification criteria for APS.

When analyzing DIAPS levels, APS patients had significantly higher scores of DIAPS when compared to aPL carriers (mean DIAPS 2.6±1.8 vs. 1.5±1.9, respectively; p=0.042). SAPS patients had significantly higher levels of DIAPS when compared to PAPS patients (mean DIAPS 3.1±1.9 vs. 2.2±1.7, respectively; p=0.029). When analyzing DIAPS domains in the entire cohort, the most frequently detected was the neuropsychiatric one, followed by peripheral vascular, renal,cardiovascular and pulmonary domains. When considering the three sub-cohort separately (PAPS, SAPS, aPL positive) we found that PAPS a higher rate of neuropsychiatric and cardiovascular domains.Figure 1 showsthe organ involvement divided by domains according to DIAPS in the three groups.

When considering GAPSS score, APS patients had significantly higher GAPSS levels when compared to aPL asymptomatic patients (mean GAPSS 12.5±5 vs. 9.6±5.4, respectively; p=0.037, while PAPS and SAPS patients had comparable GAPSS levels (mean GAPSS 12.7±5.1

vs. 12.3±.5.1, respectively).When investigating the relationship between GAPSS and DIAPSS levels in all the patients included in the study, we found a significantly positive correlation between the two scores (mean GAPSS 11.9±5.2 and mean DIAPS 2.4±1.9; Pearson 0.241; $p<0.05$). Thirty-three patients filled out the anonymous questionnaire via Google Forms. When applying the SF-12 score to our population [6], the mean PCS and MCS were lower than the average population (39.3±11.3 and 42.3±8, respectively). While no statistical significance was observed with the DIAPS score, we observed a negative correlation trend between both PCS and MCS (Pearson -0.133 and -0.183).

The majority of patients (67%) believed that their disease required special needs and attention from their treating clinician and 82% of them agreed that the National Health System should protect APS patients with special policies.

Furthermore, when asked, the preponderance of patients (42%) never received psychological counseling, but would like to know more about it, 24% were already receiving psychological counseling, 12% were considering it for the near future and 21% did not feel the need for this support. Similarly, when considering support groups consisted of APS patients, 42% were considering it for the near future, 30% were not considering it, but would like to know more about it, 1 patient was already enrolled in a support group and 24% did not feel the need for this support.

While in recent yearsa growing body of evidence has moved forward our understanding on APS, some clinical aspects, which can have a significant impact of patients' QoL, still require further investigation. In fact, clinical and laboratory parameters used in the currentcriteria [1] do not encompass all theheterogeneous spectrum of presentation of patients with APS. Critically, patients with same clinical presentation (e.g. ischemic stroke and confirmed aPL positive testing) might look similar in terms of meeting the classification criteria, yet being clinically very different, depending on the extensionand recovery of the affected tissue,

treatment, residual damage. While these patients are routinely managed in the clinical practice, to date we still lack validated tools to compare those subjects, negatively impacting on our ability of designingclinical studies to differentiate patients according to their characteristics in order to change the natural history of the disease. While those considerations might sound logical from a clinical point of view, they need to be translated into measurable validated tool and eventuallybrought back to clinic to improve patients' care.

Which evidence do we have to guide us in assessing theaPL-related organ damage? A limited number of studies have investigated the impact of organ damage in terms of morbidity, mortality of patients with APS. The long-term outcomes have been evaluated in two studies including PAPS and SAPS patients[2,7].The results from the studies highlighted the factors associated with poor outcomes as arterial thrombotic eventsand the concomitant diagnosis of SLE[2].

Our external validation of DIAPS proved the ability of the score to peculiarly correlate with APS spectrum of damage. Indeed, we found a statistically significant difference on DIAPS values when comparing our cohort of aPL positive subjects with the APS one ($p= 0.042$). When approaching DIAPS level of our PAPS and SAPS patients, we found that the latter had a significant higher score. This result can be explained by the time of the data collection and score evaluation, considering that we tested cumulative accrual damage. As suggested by Torricelli et al [8], PAPS suffer of a diagnostic delay and manifest a quick increase of the score, while SAPS, probably due to both referred follow-up visit and drug interference, increase their DIAPS value over-time.

Why assessing the health-relatedQoLalso in APS patients with or without SLE is important?First, APS might cause damage accrual independently related to the co-existing connective tissue disease. Second, APS clinical manifestations are diverse, and in many cases aPL can directly damage vital tissues and organs, leading to permanent impairment and

disability, with clear negative effect on QoL [9,10]. Nevertheless, there are multiple reasons to believe that, directly or indirectly, QoL may be adversely affected in patients with APS.

Some limitations should be acknowledged. First the retrospective nature of the study and the use of questionnairesto assess QoL could potentially affect the reproducibility of the results. Second, since this study is single-center, an intrinsic recruitment bias could not be excluded.

In conclusion, this study highlights the need for appropriate tools for evaluating activity, damage and QoL in APS patients, both for every-day clinical practice and for their application in clinical trials.

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Legend of Tables and Figures:

Figure 1. Relative involvement of the organ domains included in the DIAPS. Results are presented at the time of study inclusion

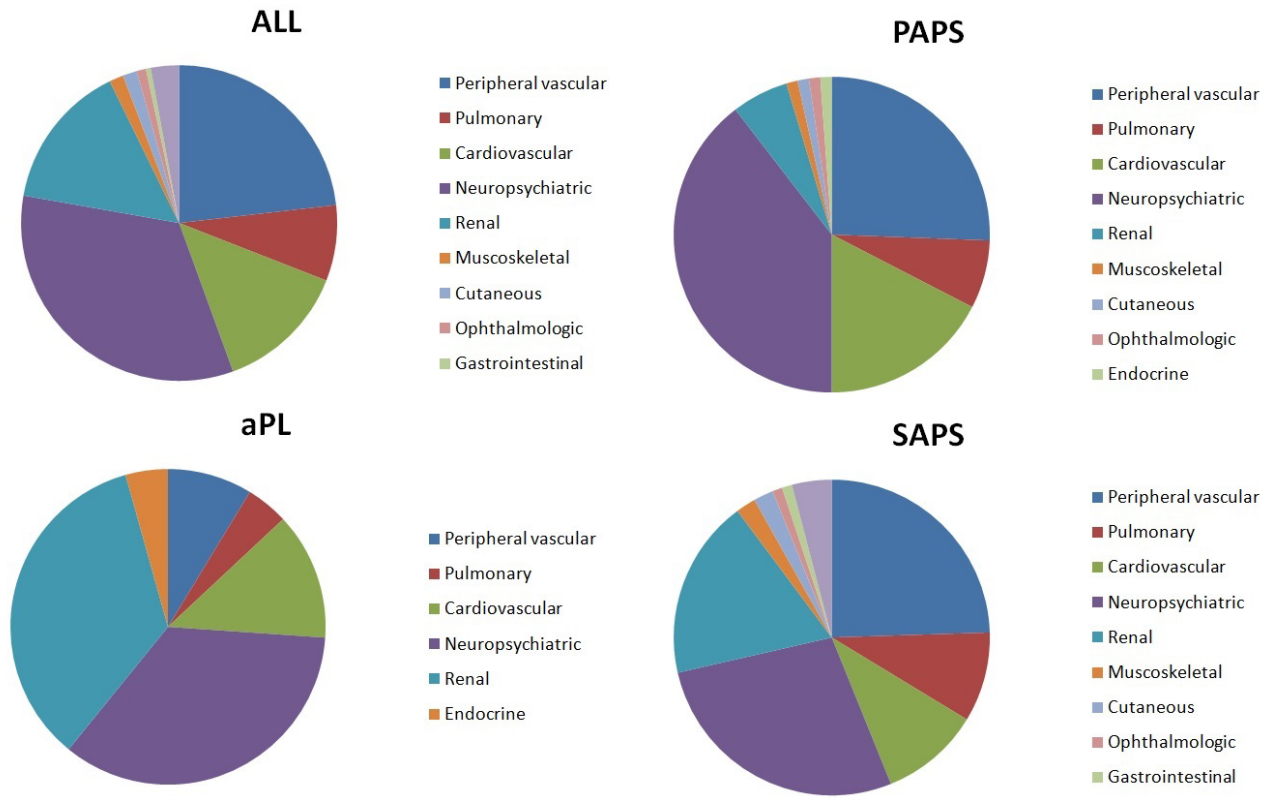

Figure 1.Relative involvement of the organ domains included in the DIAPS. Results are presented at the time of study inclusion

APS – Antiphospholipid Syndrome; PAPS- Primary APS; SAPS – Secondary APS; aPL – Antiphospholipid Antibodies