Review:

The assessment of patients with the antiphospholipid antibody syndrome – where are we now?

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Key messages:

- DIAPS is a new and promising damage score system for thrombotic APS.
- Generic HRQoL scoring systems do not cover the full impact of this disease.
- APS disease activity index is an unmet need that must be addressed.

Abstract

The antiphospholipid antibody syndrome (APS), a chronic autoimmune thrombophilia with an increased mortality and morbidity, has been recognised for more than three decades. Unlike other autoimmune rheumatic conditions such as systemic lupus erythematosus, myositis and Sjögren's syndrome relatively few attempts have been made to develop activity, damage or disease-specific quality of life indices for APS.

In this review of the literature, we consider those attempts that have been made to develop assessment tools for patients with APS, but also reflect upon the nature of the condition, to discuss, in particular, whether an activity index is appropriate for this disease.

Introduction

Significant advances have been made in how we assess patients with a variety of autoimmune rheumatic diseases. Arguably, to capture the full consequences of one of these diseases, it is necessary to have assessment tools which distinguish disease activity (with potentially reversible change usually due to ongoing inflammation) from damage (implying permanent change) and to obtain the patients' own view of their condition. In this regard the British Isles Lupus Assessment Group (BILAG) (1) and Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) (2) are disease activity tools that have been successfully developed for patients with systemic lupus erythematosus (SLE). They have been validated, shown to be reliable and sensitive to change (reviewed in 3). They are widely used in clinical practice and in lupus clinical trials.

The Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) damage index (4) (SDI) has also been used for over 20 years and has also found widespread application in clinical practice and clinical trials. The generic SF-36 (5) and a lupus-specific health assessment tools e.g. the Lupus Quality of Life (QoL) index (6) have also

been used in many clinical studies. Similarly activity, damage and health assessment tools have been developed, tried and tested in patients with myositis (7, 8) and Sjögren's syndrome (9).

The antiphospholipid antibody syndrome (APS) is an acquired autoimmune thrombophilia characterised clinically by recurrent miscarriages or other obstetric morbidity and venous and/or arterial or microvascular thromboses in the presence of various types of antiphospholipid antibodies (aPL). The non-criteria clinical features may vary from thrombocytopenia, often mild but occasionally severe, to troublesome leg ulcers (10). Over time, patients can progress to organ damage that carries increased morbidity and mortality (11).

Assessing Organ Damage

APS causes irreversible organ damage

Recurrent thrombosis is the hallmark of thrombotic APS and is usually the clue to the diagnosis. In thrombotic APS, venous thrombosis is the most common manifestation followed by arterial thrombosis (12). According to the Euro-Phospholipid Project Group (13) 9.3% of APS patients died with a mean age of 59±14 years. The main causes of death were severe thrombotic events (myocardial infarction, stroke and pulmonary embolism) followed by infections and haemorrhagic complications. Erkan *et. al* (14) reported that one-fifth of patients would be functionally impaired due to cognitive dysfunction, cardiovascular disease or aphasia. Later, Grika *et. al* (11) studied, retrospectively, a cohort of 135 APS patients (89 primary APS; 46 secondary APS) over a 10 years follow-up period and found that up to one-third of the patients progressed to organ damage. Similar findings have also been reported by others (15). The highest morbidity was related to neurological involvement that was significantly more frequent in patients whose first clinical manifestation was an arterial thrombosis rather than a venous thrombosis (35.4/1000 vs 8.97/1000 person-years, p=0.01, respectively) (11). Obstetric morbidity is also a well-known, and sometimes the sole, manifestation of the disease. The risks of venous thromboembolism and of cerebrovascular manifestations are higher in women with

purely obstetric APS than in women without APS (16). Nevertheless, this subsets of patients show lesser organ damage compared with those with thrombosis at presentation (11).

In patients treated with vitamin K antagonists (VKA), the pattern of initial clinical manifestations seems to be preserved with regard to the second event. Thus, venous thrombosis is usually followed by venous thrombosis, arterial thrombosis by arterial thrombosis and pregnancy morbidity by pregnancy morbidity (11, 17). It is noted that despite adequate treatment with anticoagulation and/or antiplatelet therapy, the initial clinical features show an increasing cumulative prevalence as the disease progresses over time (11, 13). As an example, the prevalence of cerebral ischaemic events (both stroke and transient ischaemic attacks) increased from approximately 8% to 34% and pulmonary emboli from 5.2% to almost 12% during a follow-up period of 10 years (10). Taking the current data into account, APS has significant impact in long-term prognosis and survival that are largely influenced by the risk of recurrent thrombosis and consequent organ damage (11, 13, 14, 17). This reflects the chronic and recurrent nature of the disease and reinforces the need for risk stratification and damage assessment tools.

Thrombotic APS is a major predictor of irreversible organ damage and death in SLE patients (14, 18, 19). Moreover, the presence, type and titre of aPL influences the risk for clinical APS and confer a higher hazard for major organ involvement in SLE patients (20). Through the years, some authors (11, 21) have analysed the usefulness of the SLICC Damage Index (SDI) developed for SLE in APS patients (both in primary and secondary). However the SDI misses some key features of APS and therefore could underestimate little aPL-related damage (21) for example the SDI does not capture well-known manifestations of APS notably chronic thromboembolic pulmonary hypertension, renal thrombotic microangiopathy, adrenal insufficiency and some neurological features that can be very debilitating causing for example movement disorders. These deficiencies highlight the need for an improved APS-specific damage score.

Which tools do we have?

Since the late 1990s, Amigo *et. al* (22) have developed a system to assess aPL-related organ damage in patients with APS. After years of international expert debates and initial validation attempts, they finally proposed a damage index for patients with APS (DIAPS) (23). The DIAPS is a 38-item score that was designed to include thrombotic APS-specific features not considered in SDI and believed to reflect damage in APS patients. Even though the DIAPS was not developed to assign the impact of pregnancy morbidity, infertility was included. The authors have applied the DIAPS to 156 patients with thrombotic APS (23) and demonstrated content, criterion and construct validity as well as a significant correlation with health-related quality of life measured by EuroQoL. The DIAPS is shown in Table 1 (**Appendix**). A long-term retrospective cohort study composed by 38 patients (57.9% primary APS) showed an increasing DIAPS score (3±2 vs. 5±3, p <0.0001) during a follow-up time up to 18 years (24). Accrual damage was also recently showed in a Brazilian study that analysed 100 APS patients (50% primary APS) during 10 years (25). During the observational period, the authors showed a 35% increment damage in primary APS patients whereas secondary APS reached 139% (0.43±0.30 vs. 1.22±1.24, p <0.001) (25). The only published prospective study showed low DIAPS scores (median of 2) in a cohort of 29 patients followed up for one year (26). Arterial thrombosis was one of the variables associated with higher scores, but did not reach statistical significance (26). SDI and DIAPS were compared in 60 secondary APS patients and, although both indices showed a significant correlation in terms of mean value (4.15±2.58 vs 4.08±3.41; R=0.826, p <0.000), they diverged when comparison was done for each organ system affected. Notably, DIAPS value correlated significantly to neurological (p=0.002) and pulmonary damage (p=0.004), whereas SDI showed no difference (27) which is in line with previous statements (21).

The DIAPS has limitations. Potentially severe non-thrombotic non-criteria manifestations such as multiple sclerosis-like disease or diffuse pulmonary haemorrhage are not included (23). Unlike the SDI, the DIAPS does not take into account the consequences of drug treatment. The standard treatment of APS is anticoagulation (28). Dall'Ara et al. (15) reported severe

haemorrhagic complications in 8% (N=3) of a cohort of 35 primary APS patients. Sixty-one major haemorrhages occurred during the 10-year follow-up period of the Euro-Phospholipid Project and were the main cause of death in 10.7% (N=10) of patients (13). The authors were aware of this limitation and stated that, even though the DIAPS showed good content validity on initial validation, additional clinical manifestations of APS should be evaluated to determine the possible contribution to irreversible damage (23). Moreover, to the best of our knowledge, the vast majority of DIAPS studies were done in Latin Americans (22-26). Thus, future assessments will need to review its utility and validation in populations with different genetic/ethnic backgrounds. Finally, DIAPS items are binary, which means that every item counts in a similar manner. It is arguable that pulmonary hypertension secondary to chronic thromboembolic events carries a worse prognosis than, for instance, adrenal insufficiency which is easily treated with steroid replacement therapy and thus should probably score more highly.

Further long-term follow-up, preferable prospective, studies are needed and should address the aforementioned issues but also focus on DIAPS's sensitivity, specificity, sensitivity to change, clinimetric validation and impact on mortality.

Assessing Quality of Life (QoL)

How can we asses QoL?

Health-related quality of life (HRQoL) is an important consideration when assessing a disease especially when it has a chronic relapsing character and carries a long-term burden which is clearly true of APS. APS affects predominantly young patients (mean age of onset = 42 years) (13) and its effects and consequences are highly variable, ranging from mild thrombocytopenia or to recurrent miscarriage to the sudden onset of permanent disability following a stroke with hemiplegia. HRQoL can be assessed using generic scores, such as the Short Form-36 (SF-36) (5) and the Euro Quality of Life 5 dimensions (EQ-5D) (29). The SF-36 Health Survey is a generic, reliable and valid measure for assessing HRQoL. It is a questionnaire made up of eight domains

scored from 0 (worse) to 100 (better). The domains consist of: body pain, general health, physical function, role physical, mental health, role emotional, socio function and vitality. The EQ-5D measures five domains - mobility, self-care, usual activities, pain/discomfort and anxiety/depression - scored in three levels (no; some; extreme problem). Both questionnaires are self-administered, easy to complete and have validated translations. These scores can be applied in healthy populations and have been applied in various rheumatic (e.g. fibromyalgia (30), SLE (31)) and non-rheumatic diseases (e.g. deep vein thrombosis (32)), thus allowing us to estimate the health impact that the disease has on patients´ quality of life.

APS impairs QoL

Georgopoulou *et. al* (33) used the SF-36 to analyse the HRQoL in a cohort of 270 primary and secondary APS patients from the Hughes Syndrome Foundation. They showed that both primary and secondary APS patients had significantly lower SF-36 scores than the age- and sex-matched normal population. Primary APS appears to be generally better than secondary APS in physical domains, but poorer in most mental health domains. In contrast, secondary APS patients experienced a more adverse impact on HRQoL with seven out of eight domains being affected compared to primary APS. Accordingly, Zuily et al (34) reported that SLE-associated APS patients had the worst HRQoL scores in comparison with SLE or aPL-positive patients alone. Compared to the general population, patients from 45 to 54 years old had the highest HRQoL impairment and men were the most affected (affected domains male = 8 vs. female = 5). Amigo *et. al* (23) showed anxiety/depression, impaired mobility, inability to perform daily living activities, pain and self-care difficulties in 50.6%, 35.2%, 33.9%, 30.4% and 11.5% of patients respectively. Overall, the global DIAPSscore correlated significantly with impairment in HRQoL assessed by EQ-5D (23).

Patients with thrombotic APS or SLE with thromboembolic event have poorer HRQoL scores than aPL-positive SLE patients without thrombosis (35). In particular, a history of arterial thrombosis

significantly impaired HRQoL in both physical and mental health domains in APS patients. While myocardial infarction affects mainly the physical health, peripheral arterial thrombosis and, to a lesser extent, ischaemic neurological events, seems to affect predominantly the mental health domain (34). Deep vein thrombosis (DVT) is commonly the most frequent vascular event reported in thrombotic APS (10, 11, 34). Post-thrombotic syndrome is a frequent complication of DVT and has significant impact on HRQoL (32). Curiously, HRQoL was not impaired in a French cohort of APS patients with a history of venous thrombosis, possibly because the mean age of the population included in the study (mean age 42.7±14.1 years), and the short period of follow-up (three years) (34). Overall, the impact of the type of thrombotic event on HRQoL has been poorly studied in APS patients and further studies are needed.

Pain and fatigue, lack of education of clinicians and public awareness, and medication unpredictability related to possible haemorrhagic side effects are the three major issues related to impaired QoL in APS patients (33). A recent study showed a relationship between social support and HRQoL (36). The social support was divided in three categories (emotional, instrumental and informational) and patients were asked to indicate, through a multiple choice questionnaire, the support they felt they were receiving (perceived) and the support they would like to receive (ideal). The discrepancy between perceived and ideal support was far greater in informational support than in the other two categories (36). Lack of information (healthcare professional and general public) was perceived by patients to be a contributory factor to a delay in receiving a diagnosis and general disbelief in the existence and severity of the disease (33). Anticoagulation with warfarin or another vitamin K antagonist remains the cornerstone of APS treatment (28). Hernández-Molina et al (37) showed for the first time that patients with APS on oral anticoagulation reported lower HRQoL especially with regard to their physical functioning, intimate relationships, burden to others and pain domains. The RAPS trial (38) showed a small difference in the visual analogue health score in the rivaroxaban group (mean difference 6.5,

95% CI 1.4 – 11.5, p=0.013), although the EQ-5D did not differ between groups (mean difference 0.04, 95% CI 0.02 – 0.09, p=0.19).

Is a generic questionnaire enough?

It is clear that both the disease burden/damage, the anticoagulant therapy as well as the lack of social support contributes to the impaired HRQoL in APS patients that have been measured by the SF-36 and EQ-5D (23, 33, 34, 36, 37). Although their generic nature allow us to compare QoL in various diseases as well as with healthy populations, they may miss some APS-specific characteristics and, therefore, lack sensitivity. In SLE, sleep disorder, body image, fatigue, inability to plan/disease unpredictability and social relations are important themes to take into account and that are not addressed in the generic HRQoL questionnaires (39). LupusQoL is a disease-specific questionnaire that is more sensitive and shows a greater responsiveness to change than the generic SF-36 (40). Likewise, post-thrombotic syndrome shows a significant impact on disease-specific QoL score that was not captured by SF-36 (32). To date, no data are available indicating how HRQoL changes during the lives of APS patients with regard to the accrual damage and treatment effect/complications. Future studies must explore this topic in order to improve this unmet need in the assessment of APS patients.

Can we assess Activity?

The nature of many of the thrombotic consequences of APS results in permanent effects. Thus, a patient who suffers a cerebrovascular accident resulting in a hemiplegia will often remain damaged for the rest of their life. It is thus challenging to think of the effects of APS in the kind of “activity” mode seen in patients with lupus, myositis and even Sjögren’s where the fundamentally inflammatory nature of their disease can be substantially, if not fully corrected. However, certain vascular events such as transient ischaemic attacks, or the development of thrombocytopenia, which are amenable to treatment do lend themselves more readily to

consideration an 'activity' features. Furthermore the immunopathology of APS [reviewed in detail elsewhere 41] is now thought to include abnormal intracellular signalling in diverse cells [eg endothelial cells, monocytes, neutrophils and platelets] through mitogen-activated protein kinases utilizing a key transcription regulator, nuclear factors kappa B. Increasing evidence supports the idea that the complement system is also involved in the development of APS. Thus it seems feasible that a genuine inflammatory process is central to the clinical presentations associated with APS, which may thus be considered as activity features. The strong association between APS and SLE does however complicate matters in determining causation. The time is surely right for a group of international experts to consider developing and testing a disease activity index.

Laboratory testing for APS diagnosis

The diagnosis of APS, based on the international consensus (Sapporo/Sydney) classification criteria requires demonstration of persistently positive aPL, i.e. lupus anticoagulant (LA) and/or IgG or IgM anticardiolipin antibodies (aCL) present in medium or high titre (i.e. >40 GPL or MPL or >99th percentile), and/or aβ2GPI (IgG and/or IgM) >99th percentile, present on two or more occasions at least 12 weeks apart (42). Accurate diagnosis of APS is essential to guide appropriate management and omission of any of the components of the full complement of aPL may result in a missed diagnosis (43, 44). Although testing for LA can be challenging (45), LA is thought to carry the highest risk for thrombosis among all aPL (46) and is associated with increased mortality (47). Triple aPL positivity is the aPL phenotype associated with the highest risk of thrombosis (48). Triple aPL positive APS patients are also at high risk of developing recurrent thrombosis despite anticoagulation (49) and it is important to identify these patients as they are therefore at highest risk of damage.

Conclusion

APS is chronic acquired autoimmune thrombophilia that can course with recurrent thromboembolic events despite the optimal treatment. A significant proportion of patients are left with organ damage that influences the long-term prognosis and QoL negatively. DIAPS has been developed and validated for ascertain APS-related damage. Although promising and, to the best of our knowledge, the sole score system to do so, further studies are needed as it has some limitations that deserve to be addressed. Generic HRQoL scoring systems are probably not enough to cover the full impact of this disease in patients' life and development of more effective and patient-tailored interventions should be kept in mind. APS disease activity is undoubtedly an unmet need in the assessment of this condition.

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PG, HC and DI drafted and revised the manuscript and contributed to the literature review. All authors approved the final version.

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REFERENCES

1. Yee CS, Farewell V, Isenberg DA, Rahman A, Teh LS, Griffiths B et al. British Isles Lupus Assessment Group 2004 index is valid for assessment of disease activity in systemic lupus erythematosus. Arthritis Rheum 2007; 56: 4113-9.

2. Gladman DD, Ibanez D, Urowitz M. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002; 29: 288-91.

3. Feld J, Isenberg DA. Why and how should we measure disease activity and damage in lupus? Presse Med 2014; 43: 151-6.

4. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M et al. The development and validation of the Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology Damage Index for systemic lupus erythematosus. Arthritis Rheum 1996; 39: 363-9.

5. Thumboo J, Fong KY, Leong KH, Feng PH, Thio S, Boey ML. Validation of the MOS SF-36 for quality of life assessment of patients with systemic lupus erythematosus in Singapore. J Rheumatol 1999; 26: 97-102.

6. McElhone K, Castelino M, Abott J, Bruce I, Ahmad Y, Shelmerdine J et al. the Lupus QoL and association with demographic and clinical measurements in patients with systemic lupus erythematosus. J Rheumatol 2010; 73: 2273-9.

7. Sultan S, Allan E, Oddis CV, Kiely P, Cooper R, Lundberg I et al. Reliability and validity of a myositis activity assessment tool. Arthritis Rheum 2008; 58: 3593-8.

8. Sultan S, Allan E, Cooper R, Agarawal S, Kiely P, Oddis CV et al. inter-rater reliability and aspects of validity of the myositis damage index. Ann Rheum Dis 2011; 70: 1272-6.

9. Camper A, Isenberg DA. Primary Sjögren's syndrome activity and damage indices comparison. Eur J Clin Invest 2010; 40: 636-44.

10. Cervera R, Boffa MC, Khamashta MA, Hughes GRl. The Euro-Phospholipid project: epidemiology of the antiphospholipid syndrome in Europe. Lupus 2009; 18: 889-93.

11. Grika EP, Ziakas PD, Zintzaras E, Moutsopoulos HM, Vlachoyiannopoulos PG. Morbidity, mortality, and organ damage in patients with antiphospholipid syndrome. J Rheumatol. 2012; 39: 516–23.

12. Cervera R, Piette JC, Font J, Khamasha MA, Shoenfeld Y, Camps MT et al. Antiphospholipid syndrome: Clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum 2002; 46: 1019–1027.

13. Cervera R, Serrano R, Pons-Estel GJ, Ceberio-Hualde L, Shoenfeld Y, de Ramón E et al. Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: A multicentre prospective study of 1000 patients. Ann Rheum Dis 2015; 74: 1011-8

14. Erkan D, Yazici Y, Sobel R, Lockshin MD. Primary antiphospholipid syndrome: Functional outcome after 10 years. J Rheumatol. 2000; 27: 2817–21.

15. Dall'Ara F, Reggia R, Taraborelli M, Andreoli L, Taglietti M, Frassi M et al. Patients with longstanding primary antiphospholipid syndrome: retrospective analysis of organ damage and mortality. Lupus 2014; 23: 1255–8.

16. Gris JC, Bouvier S, Molinari N, Galanaud JP, Cochery-Nouvellon E, Mercier E et al. Comparative incidence of a first thrombotic event in purely obstetric antiphospholipid syndrome with pregnancy loss: the NOH-APS observational study. Blood 2012; 119: 2624–32.

17. Tektonidou MG, Ioannidis JP, Boki KA, Vlachoyiannopoulos PG, Moutsopoulos HM. Prognostic factors and clustering of serious clinical outcomes in antiphospholipid syndrome. QJM 2000; 93: 523–30.

18. Ruiz-Irastorza G, Egurbide MV, Ugalde J, Aguirre C. High impact of antiphospholipid syndrome on irreversible organ damage and survival of patients with systemic lupus erythematosus. Arch Intern Med 2004; 164: 77–82.

19. Zarrabeitia LR, Taboada VM, Figueroa IR, Alonso FS, Izquierdo MG, Ovalles J et al. Antiphospholipid Syndrome (APS) In Systemic Lupus Erythematosus (SLE) Leads To A More Severe Disease. Ann rheum Dis 2019 published on 27 June 2019. Doi: 10.1136/annrheumdis-2019-eular.2475 (abstract).

20. Zarrabeitia LR, Taboada VM, Figueroa IR, Alonso FS, Izquierdo MG, Ovalles J et al. Do All Antiphospholipid Antibodies Confer the Same Risk For Major Organ Involvement in SLE Patients?. Ann rheum Dis 2019 published on 27 June 2019. Doi: 10.1136/annrheumdis-2019-eular.2485 (abstract).

21. Barbhaiya M, Erkan D, Rodriguez-Almaraz E, Ramon G, Vega J, Lockshin MD. Utility of the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index for Antiphospholipid Antibody (aPL) Positive Patients. Arthritis Rheumatol. 2010; 63:S3. (abstract).

22. Amigo MC, Khamashta MA, Cardiel M, et al. Development and validation of an antiphospholipid damage index: A multicenter, binational project. Lupus 1998; 7 (suppl 1): 68.

23. Amigo MC, Goycochea-Robles MV, Espinosa-Cuervo G, Medina G, Barragán-Grafias JA, Vargas A et al. Development and initial validation of a damage index (DIAPS) in patients with thrombotic antiphospholipid syndrome (APS). Lupus 2015; 24: 927–34.

24. Martinez-Martinez LA, Chacon-Perez MJMN, M.C. Amigo MC. Damage Index in Patients With Thrombotic Antiphospholipid Syndrome: Retrospective Cohort Study. Ann Rheum Dis 2016. Doi: 10.1136/annrheumdis-2016-eular.4290. (abstract).

25. Acrabstracts.org [Internet]. Torricelli AK, Ugolini-Lopes MR, Bonfa E, Andrade D. Antiphospholipid Syndrome Damage Index (DIAPS): Distinct Long-term Kinetic in Primary Antiphospholipid Syndrome and APS related to SLE. Arthritis Rheumatol. 2019; 71 (suppl 10). [Accessed 2019 Dec 4]. Available from: https://acrabstracts.org/abstract/antiphospholipid-syndrome-damage-index-diaps-distinct-long-term-kinetic-in-primary-antiphospholipid-syndrome-and-aps-related-to-sle/.

26. Bermúdez BPE, Rodríguez AS, Carriles AT, Amigo MC. Evaluación del daño crónico en pacientes con síndrome antifosfolípidos con el instrumento DIAPS. An Med (Mex) 2016; 61: 177-181

27. Potarniche D, Mazilu D, Saulescu I, Borangiu A, Groseanu L, Constantinescu C et al. Damage indexes in patients with systemic lupus erythematosus and secondary antiphospholipid syndrome: diaps vs slicc/acr damage index. Ann Rheum Dis 2017; 76: 304. (abstract).

28. Tektonidou MG, Andreoli L, Limper M, Amoura Z, Cervera R, Costedoat-Chalumeau N et al. EULAR recommendations for the management of antiphospholipid syndrome in adults. Ann Rheum Dis. 2019; 78: 1296-1304.

29. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy Amst Neth. 1990; 16: 199–208.

30. Campos RP, Vázquez Rodríguez MI. Health-related quality of life in women with fibromyalgia: Clinical and psychological factors associated. Clin Rheumatol 2012; 31: 347–55.

31. Wang S-l, Wu B, Zhu L-a, Leng L, Bucala R, Lu L-j. Construct and criterion validity of the euro Qol-5D in patients with systemic lupus erythematosus. PLoS One 2014; 9: e98883. Published online 3 June 2014. doi: 10.1371/journal. pone.0098883.

32. Kahn SR, Hirsch A, Shrier I. Effect of postthrombotic syndrome on health-related quality of life after deep venous thrombosis. Arch Intern Med 2002; 162: 1144–8.

33. Georgopoulou S, Efraimidou S, MacLennan SJ, Ibrahim F, Cox T. Antiphospholipid (Hughes) syndrome: Description of population and health-related quality of life (HRQoL) using the SF-36. Lupus 2015; 24: 174–9.

34. Zuily S, Rat AC, Reganult V, Kaminsky P, Mismetti P, Ninet J et al. Impairment of quality of life in patients with antiphospholipid syndrome. Lupus 2015; 24: 1161-8.

35. Balitsky AK, Peeva V, Su J, Aghdassi E, Yeo E, Gladman DG et al. Thrombovascular events affect quality of life in patients with systemic lupus erythematosus. J Rheumatol 2011; 38: 1017–19.

36. Georgopoulou S, Efraimidou S, MacLennan SJ, Ibrahim F, Cox T. The relationship between social support and health-related quality of life in patients with antiphospholipid (hughes) syndrome. Modern Rheumatology 2018; 28: 147-55.

37. Hernandez-Molina G., González-Pérez I, Pacheco-Molina C, Cabral AR. Quality of life in patients with antiphospholipid syndrome is related to disease burden and anticoagulant therapy. Int J Rheum Dis 2017; 20: 755-9.

38. Cohen H, Hunt BJ, Efthymiou M, Arachchillage DR, Mackie IJ, Clawson S et al. Rivaroxaban versus warfarin to treat patients with thrombotic antiphospholipid syndrome, with or without systemic lupus erythematosus (RAPS): a randomised, controlled, open-label, phase 2/3, non-inferiority trial. Lancet Haematol 2016; 3: e426–e436. doi: 10.1016/s2352-3026(16)30079-5

39. McElhone K, Abbott J, Gray J, Williams A, Teh LS. Patient perspective of systemic lupus erythematosus in relation to health-related quality of life concepts: a qualitative study. Lupus 2010; 19: 1640–47.

40. Nantes SG, Strand V, Su J, Touma Z. Comparison of the Sensitivity to Change of the 36-Item Short Form Health Survey and the Lupus Quality of Life Measure Using Various Definitions of Minimum Clinically Important Differences in Patients With Active Systemic Lupus Erythematosus. Arthritis Care Res 2018; 70: 125–33.

41. Giles I, Cohen H, Ioannou Y. Pathogenesis of anti-phospholipid antibody syndrome. In: Dubois Lupus Erythematosus and related sydnromes. 9th edn Elsevier 2019 pp 324-37.

42. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4: 295–306.

43. Nash MJ, Camilleri RS, Kunka S, Mackie IJ, Machin SJ, Cohen H. The anticardiolipin assay is required for sensitive screening for antiphospholipid antibodies. J Thromb Haemost 2004; 2: 1077–81.

44. Gardiner C, Hills J, Machin SJ, Cohen H. Diagnosis of antiphospholipid syndrome in routine clinical practice. Lupus 2013; 22: 18-25.

45. Cohen H, Mackie IJ, Devreese KMJ, International Society for Thrombosis and Haemostasis Scientific and Standardization Committee for Lupus Anticoagulant/Antiphospholopid Antibodies. Clinical and laboratory practice for lupus anticoagulant testing: an International Society of Thrombosis and Haemostasis Scientific Standardization Committee survey. J of Thromb Haemost 2019; 17: 1715-32.

46. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003; 101: 1827-32.

47. Gebhart J, Posch F, Koder S, Perkmann T, Quehenberger P, Zoghlami C et al. Increased mortality in patients with the lupus anticoagulant: the Vienna Lupus Anticoagulant and Thrombosis Study (LATS). Blood 2015; 125: 3477-83.

48. Pengo V, Ruffatti A, Legnani C, Testa S, Fierro T, Marongiu F et al. Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood 2011; 118: 4714-8

49. Pengo V, Ruffatti A, Legnani C, Gresele P, Barcellona D, Erba N et al. Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost 2010; 8: 237– 42.

Appendix

Table 1 - Damage Index for Antiphospholipid Syndrome (DIAPS) adapted from Amigo et al (23)

Item	*Definition*
Peripheral vascular	
Deep vein thrombosis	Blood clot inside the lumen of a deep vein
Intermittent Claudication	Fatigue, cramps, pain and weakness of the legs secondary to peripheral arterial disease which begins with walking and improves with rest
Tissue loss (minor)	Absence of tissue secondary to necrosis of the affected area. Minor (pulp)
Tissue loss (major)	Absence of tissue secondary to necrosis of the affected area. Major (digit or limb)
Vascular venous Insufficiency	Morphological or functional abnormalities (venous valvular incompetence) of long duration, have to be categorized and treated accordingly with CEAP Classification[a]
Pulmonary	
Pulmonary infarction	X-Ray or CAT demonstration of pulmonary opacity or wedged-shaped density as a consequence of pulmonary vessel thromboembolic occlusion
Pulmonary arterial hypertension	Pulmonary artery pressure>25mmHg at rest or >30mmHg on exercise. Mild 30 - 49mmHg, Moderate 50- 69mmHg; Severe>70mm Hg.
Chronic thromboembolic pulmonary hypertension	Obstructive lesions, in the lobar, segmental, or the main branches of the pulmonary artery secondary to chronic thromboembolism
Respiratory insufficiency	Secondary to multiple infarctions
Cardiovascular	
Coronary artery bypass	Surgical treatment of occlusive disease of the coronary arteries that provides better blood flow in the epicardial coronary arteries leading to a decrease angina symptoms, complications of myocardial infarction and mortality.
Myocardial infarction	Clinical syndrome characterized by damage of the myocardial tissue caused by imbalance between oxygen myocardial input and oxygen demand
Cardiomyopathy	Alterations in myocardial perfusion obstruction microvasculature in the presence of normal coronary arteries
APL associated valve hearth disease: (asymptomatic, symptomatic)	ECHO detection of valve lesions and /or regurgitation and/or stenosis of mitral and/or aortic valve (Valve Lesions according to Miyakis S et al[b]**)**
APL associated valve hearth disease requiring valve replacement	Progressive, symptomatic (NYHA[b] functional class III-IV) moderate or severe valve disease
Neuropsychiatric	
Cognitive impairment	Memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level, documented on clinical examination or by formal neurocognitive testing.
Seizures	Paroxysmal electrical discharge occurring in the brain and producing characteristics physical changes including tonic and clinical movements and certain behavioural disorders.
Ischemic stroke with hemiparesia	Cerebrovascular thrombotic event resulting in focal finding as paresis
Ischemic stroke with hemiplegia	Cerebrovascular thrombotic event resulting in focal finding such as hemiplegia or aphasia
Multinfarct dementia	Cognitive impairment caused by, or associated with, vascular factors confirmed by neuroimaging (MRI/CAT)

Cranial Neurophaty	Damage to a cranial nerve resulting in either motor or sensory dysfunction
Sudden sensorineural hearing loss	Acute unexplained hearing loss nearly always unilateral that occurs over less than 72 hour period (demonstrated by evoked potentials)
Transverse myelitis	Lower-extremity weakness or sensory loss with loss of rectal and urinary bladder sphincter control
Optic Neuropathy	Inflammatory or ischemic condition documented by MRI of the brain and orbits that causes acute visual loss
Peripheral neuropathy	Damage to a peripheral nerve resulting in either motor or sensory dysfunction
Abnormal movements	
– Dystonia	Movement disorder characterized by involuntary sustained muscle contraction that result in twisting and repetitive movements or abnormal postures
– Chorea	Movement disorder characterized by involuntary brief, random and irregular movements of the limbs and face, emotional or abnormal postures
– Parkinsonism	Bradykinesia, tremor, rigidity without a good response to dopaminergic therapy
Ophthalmologic	
Retinal vaso-occlusive disease	Occlusion caused by arterial or venous thrombosis, conditioning severe loss of visual acuity
Blindness	Total visual loss caused by any of the above ocular manifestations
Renal	
Chronic renal failure	Estimated or measured by a GFT less than 60ml/min/1.73m2. Regardless of dialysis or transplantation
Proteinuria	Proteinuria >3.5g/24hrs
Renal thrombotic microangiopathy	Demonstrated by kidney biopsy
Musculoskeletal	
Avascular necrosis	Pathologic process characterized by compromise of the bone vasculature leading to the death of bone and marrow cells, demonstrated by imaging techniques
Cutaneous	
Chronic cutaneous ulcers	Skin ulceration secondary to thrombotic microangiopathy
G**astrointestinal**	
Mesenteric thrombosis	Thrombosis of the mesenteric arteries or veins, leading to ischemia and eventually necrosis of any intestinal segment, spleen, liver or gall bladder.
Budd Chiari syndrome	Clinic-pathological entity caused by thrombotic obstruction of hepatic venous blood flow either at the level of the hepatic veins or the inferior vena cava.
Cirrhosis of the liver	Chronic liver disease characterized by progressive fibrosis leading to loss of liver function
Endocrine	
Suprarenal Insufficiency	Deficit in the production of suprarenal steroid hormones due to a thrombosis or haemorrhagic infarct of the suprarenal glands
Hypopituitarism	Pituitary gland Insufficiency caused by of thrombosis/ischemia
Infertility	Failure to conceive after 12 months of frequent intercourse without use of contraception in women under age 35 and after six months in women over age 35

Legend

[a] Eklöf B, Rutherford RB, Bergan JJ, Carpentier PH, Gloviczki P, Kristner RL et al. Revision of the CEAP classification for chronic venous disorders: consensus statement. J vasc Surg 2004; 40: 1248–52.

[b] Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006; 4: 295–306.

[c] The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed Little, Brown & Co; Boston, Mass: 1994. pp. 253–256.

Abreviations: CAT: computerized axial tomography; CEAP: Clinical Etiologic Anatomical and Pathophysiological; ECHO: echocardiogram; GFR: glomerular filtration rate; NYHA: New York Heart Association; MRI: magnetic resonance imaging