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Predictors and interrelationship of patient-reported outcomes in antiphospholipid syndrome: a cross-sectional study

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ABSTRACT

Objective: This study assessed patient-reported outcomes (**PROs**) in individuals with persistently positive antiphospholipid antibodies (**aPL**) to better understand how living with aPL may affect their quality of life.

Methods: Patients completed PROMIS® Physical Function (**PF**) and Cognitive Function (**CF**) Short Forms, as well as pain intensity rating (**PI**, scale 1-10). Patients were characterized for demographics, clinical manifestations of antiphospholipid syndrome (**APS)**, cardiovascular risk factors, laboratory results, and medication usage. Multivariate modeling was done via linear regression.

Results: Of 139 patients, 89 had primary APS, 21 secondary APS, and 29 persistent aPL without meeting clinical criteria for APS. The average T-scores (± SD) for PF and CF were 45.4 ± 9.2 and 48.6 ± 11.6, respectively; the average for PI was 3.0 ± 2.6. Approximately half of the patients (47%) endorsed at least mild impairment in PF (T-score <45). Mean PF, CF, and PI did not differ between diagnostic groups. Individuals who endorsed more impairment on one measure also tended to endorse more impairment on another (Pearson r=0.43-0.59). In the multivariate models, age, smoking, pain medications, and serotonergic medications were associated with impairment in at least one PRO domain. The Damage Index for APS (DIAPS) was significantly correlated with both PF and CF.

Conclusion: Individuals living with APS endorsed more impairment in PF (and potentially CF) than expected for the general population. The relationship between certain medications and PROs warrants further study, as does the longitudinal trajectory of these and other PROs.

INTRODUCTION

Antiphospholipid syndrome (**APS**) is a thrombo-inflammatory autoimmune disease characterized by persistently positive antiphospholipid antibodies (**aPL**) as defined by testing for anticardiolipin antibodies (**aCL**), anti-beta-2-glycoprotein I antibodies (**aβ_2GPI**), and/or lupus anticoagulant (**LA**, a functional assay that detects various types of aPL) (1). Approximately 1% of the population will be positive for at least one aPL test, with this frequency rising as high as 14% and 20% in those with thrombosis and pregnancy loss, respectively (2). Individuals can be diagnosed with *(i)* primary APS (persistently positive aPL along with a history of thrombosis or pregnancy morbidity), *(ii)* secondary APS (APS in the presence of systemic lupus erythematosus/**SLE**), or *(iii)* persistent aPL with a history of neither thrombosis nor obstetric morbidity (1, 3, 4). Patients with aPL are also at risk for certain "non-criteria" manifestations, including livedo reticularis and racemosa, cognitive dysfunction, heart valve damage, nephropathy, thrombocytopenia, and others (5).

The long-term obligation to take medications such as vitamin K antagonists, as well as the burden of non-criteria manifestations like joint pain and brain fog, may disrupt the physical and emotional quality of life of patients living with APS. Meanwhile, patients with APS are sometimes afflicted with irreversible damage to the heart, lungs, kidneys, and other organs resulting from progressive dysfunction and occlusion of the microvasculature. Therefore, it is not surprising that more than 60% of patients with primary APS reported severe fatigue in a recent study (6). Despite the burdens that come with a diagnosis of APS, patient-reported outcomes (**PROs**) have not been routinely incorporated into clinical care or research protocols.

The PRO research performed to date in APS has focused mainly on traditional quality-of-life measures. For example, Georgopoulou and colleagues administered a cross-sectional survey known as the SF-36 to 270 individuals living with APS. Major issues identified included pain and fatigue, lack of health care professional/public awareness, and medication unpredictability (7). Furthermore, health-related quality of life for primary APS appeared to be generally better than SLE and secondary APS in physical domains, but poorer in mental domains (7). In a different study of 66 patients with primary APS, health-related quality of life by SF-36 was below that of the general Brazilian population and was associated with female sex and the presence of cardiovascular risk factors (8). An Italian study focused on 92 relatively young patients with primary APS (ages 18 to 45) and found lower quality of life in physical and mental domains

compared to the general Italian population (9). Both components were significantly lower in women and in patients with fatigue (9). Meanwhile, at least two recent studies have demonstrated an association between damage accrual as measured by the Damage Index for APS (DIAPS) (10, 11) and quality of life (12, 13). Although not systematically characterized from the patient perspective, there is also a high prevalence of cognitive dysfunction (40-82%) in individuals with APS (14). The wide variance in the prevalence of cognitive dysfunction may be due to the limited number of studies objectively measuring cognitive dysfunction in APS, and the lack of a gold standard assessment tool.

The collection of PROs may contribute to more accurate tracking of disease activity while also serving as a platform by which patients and providers can engage in shared decision-making. PROMIS® (Patient-Reported Outcomes Measurement Information System) is a series of questionnaires used for tracking PROs (15). Supported by the National Institutes of Health, all English and some Spanish PROMIS measures are publicly available for use in research protocols, clinical practice, educational assessments, or other applications without licensing or royalty fees. An advantage of this system is that all results can be converted into a common T-score and compared to legacy measures obtained with a different metric (16). This allows for cross-comparisons between diseases for a variety of specific domains. PROMIS® has been evaluated in over 200,000 individuals across the United States, with the average (± standard deviation) T-score being 50 ± 10 (17). In this exploratory study, our objective was to characterize PROs associated with physical and cognitive function in patients with persistently positive aPL seen in the APS clinic of an academic medical center. We sought to determine the extent to which these parameters tracked together, as well as demographic and clinical features that might predict individuals more likely to endorse impaired function.

PATIENTS AND METHODS

Patients and PROs. Between 2019 and 2022, University of Michigan patients (n=139) with persistent aPL documented at least 12 weeks apart completed PROMIS® PF Short Form 10A v2.0 and CF Short Form 8A as part of their routine clinical care during a visit to the APS clinic. For reference, T-scores for PF can be categorized as mild impairment (<45), moderate impairment (30-40), or severe impairment (<30), as has been described (18, 19). Patients also rated self-perceived pain intensity (**PI**) on a scale of 0-10, with 10 representing the most pain. The PROMIS® questionnaires and PI rating were integrated into the electronic medical record and were administered as part of standard clinical care to all patients seen in the clinic. The patients completed the questionnaires via a web-based patient portal or via a handheld device before the clinic appointment. The 139 patients included in this analysis are part of a prospective longitudinal antiphospholipid cohort at the University of Michigan; 96% of individuals approached for this research cohort have agreed to participate. All signed an informed consent form approved by the University of Michigan IRB (HUM00122519), which allows their demographics and clinical details to be used for research studies such as this. Of the 139 patients, 89 had primary APS, 21 had secondary APS, and 29 had persistent aPL without meeting clinical thrombotic or obstetric criteria for APS ("aPL alone").

Data collection and variables. Data regarding lab testing and clinical manifestations associated with APS were captured via chart review. Some clinical information was abstracted using EMERSE, an automated electronic health record search tool, followed by manual review of clinic notes (20). Thrombotic events and obstetric morbidity were defined according to the 2006 updated Sapporo criteria (1); heart valve damage was also defined according to these criteria (1). Thrombocytopenia was defined as a history of platelet count persistently below 100,000/μl but was not necessarily present at the time of this study. Sedentary lifestyle was defined as less than 30 minutes of physical activity per day according to the patient's report. The cumulative risk score known as the adjusted Global APS Score (**aGAPSS**) takes into account aCL IgG/IgM (5 points), aβ_2GPI IgG/IgM (4 points), LA (4 points), hypertension (1 point), and hyperlipidemia (3 points) (21); the maximum score is 17 and a score greater than or equal to 10 is typically consider "high risk" (21). The aGAPSS was designed to help clinicians not intimately familiar with aPL testing to integrate the different tests into a single clinically relevant score. DIAPS (which includes 10 systems and 37 items) was calculated as previously described (10, 11); the maximum score is 37. DIAPS includes 22 items taken from the Systemic

Lupus International Collaborating Clinics Damage Index (SDI) (22), but also includes 15 APS-specific items covering issues such as ischemic leg ulcers, heart valve damage, sensorineural hearing loss, chorea, renal thrombotic microangiopathy, avascular necrosis of bone, and adrenal insufficiency. In addition, pain medications (narcotics and gabapentinoids), serotonergic medications (selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors), anticoagulants (vitamin K antagonists, low-molecular weight heparin, and direct oral anticoagulants), antimalarials (hydroxychloroquine), antiplatelet agents (aspirin, clopidogrel, and dipyridamole), and anticonvulsant medications (any medication prescribed for seizure disorder) were recorded. It should be noted that many of these medications were prescribed by providers outside of the tertiary care center, and, as such, the medications were not linked to diagnosis codes. They were grouped here to improve statistical power, but it should not be assumed that they were definitively prescribed for pain, mental health, etc.

Statistical analysis. Age, PF, CF, and PI were compared between diagnostic groups (primary APS, secondary APS, aPL alone) using one-way ANOVA. Categorical variables (such as sex) were compared using Chi-squared testing, except for variables with a cell count <5; in those cases, Fisher's exact test was used. Bivariate associations between covariates and outcome measures (PF, CF, and PI) were assessed using simple linear regression. Multivariate associations were assessed using multivariate linear regression and were composed of all variables with p-values <0.2 in bivariate analysis. Statistical significance was measured via Wald test. R (version 4.1.1) was used for all statistical analyses.

RESULTS

Key clinical characteristics of the patient cohort are described in **Table 1**. Across all 139 patients, the mean PROMIS® PF and CF Short Form scores were 45.4 ± 9.2 and 48.6 ± 11.6, respectively; the mean PI rating was 3.0 ± 2.6 (**Table 2**). There were significant correlations between the scores, with those who endorsed more impairment in one domain also likely to endorse more impairment in another (**Figures 1A-C**). The strongest correlation was found between PF and PI (**Figure 1B**).

The mean age of the patients studied here was 46.1 years; 65.5% were female and 93.5% White (**Table 2**). There were no statistically significant differences between the mean scores for PF, CF, and PI across the different diagnostic groups: primary APS, secondary APS, and aPL-alone (**Table 2**). Notably, 26% of primary APS patients, 29% of secondary APS patients, and 21% of aPL-alone patients endorsed moderate to severe impairment in PF (T-score <40). Regarding CF, 26% (primary APS), 16% (secondary APS), and 15% (aPL alone) of patients had scores less than 40. There were some expected differences in age, sex, race, and anticoagulant use between diagnostic groups (**Table 2**); for example, patients with secondary APS were more likely to be female and non-White and to be taking antimalarial medications, while patients meeting criteria for APS (whether primary or secondary) were more likely to be taking anticoagulant medications.

For each of PF, CF, and PI, we performed bivariate analyses for 29 variables including demographics; the presence of APS and/or SLE; time since first positive aPL test (a surrogate for disease duration); clinical features associated with APS; aPL lab testing including aGAPSS (21); and medications. Hypertension and hyperlipidemia were not individually included in the analysis as they are already incorporated into the aGAPSS. After bivariate analyses by simple linear regression, multivariate linear regression was undertaken for all variables with p-values <0.2.

For PF, history of venous thrombosis, obesity, smoking (both past and current), sedentary lifestyle, higher aGAPSS, pain medication use, serotonergic medication use, and anticoagulant medication use were all associated with lower PF scores based on bivariate analysis ($p<0.05$) (**Table 3**). After adjusting for covariates, older age, current smoking, pain medication use, and serotonergic medication use all demonstrated significant associations with decreasing PF in the

multivariate model (**Table 3**). The parameter estimate in the table describes the expected change on the PF scale when the variable is present.

For CF, seizure disorder, obesity, past smoking, higher aGAPSS, serotonergic medication use, and anticoagulant medication use were associated with lower CF scores (**Table 4**). After adjustment for covariates, only serotonergic medication use was significantly associated with lower CF score in the multivariate model (**Table 4**).

For PI, obesity, smoking (both past and current), pain medication use, and serotonergic medication use were all associated with higher pain intensity ($p<0.05$). After adjustment for covariates, variables associated with more pain included pain medication use and serotonergic medication use (**Table 5**).

Finally, we asked the extent to which the 37-item DIAPS instrument (10, 11) might associate with PF, CF, and PI. For the entire 139-patient cohort, the mean (± SD) DIAPS was 2.1 ± 2.1. The median was 2.0, and the maximum DIAPS for the cohort was 10. DIAPS was significantly associated with PF (Pearson r=-0.28, p=0.0008) and CF (Pearson r=-0.21, p=0.01), but not PI (Pearson r=0.12, p=0.15).

DISCUSSION

This study assessed PROs in individuals with persistently positive aPL (64% with primary APS) to better understand how living with aPL may affect their quality of life. One notable finding is that 47% of individuals with persistent aPL had PROMIS® PF scores below 45, suggesting at least mild self-perceived impairment (17). For reference, assuming a normal distribution with a mean PROMIS® score of 50 and SD of 10, a T-score of 45 or lower should occur in approximately 31% of the population. In contrast to PF, the CF score distribution was relatively similar to the general population (APS mean=48.6), although 26% of patients with primary APS did have T scores <40, which is suggestive of at least moderate impairment. PROMIS® has previously been administered to cohorts of patients with various autoimmune diseases, including rheumatoid arthritis (**RA**), SLE, systemic sclerosis (**SSc**), and multiple sclerosis (**MS**) (23). Patient-reported physical function (**PF**) was reduced in all four groups as compared with the general population (RA=42.0 ± 9.1; SLE=43.9 ± 9.7; severe SSc=40.6 ± 7.3; and MS=42.5 ± 9.7) (23-25). Patient-reported cognitive function (**CF**) has been reported as impaired in patients with MS (19.65 ± 9.19) (26) and SLE (39.0 ± 11.2) (27). To our knowledge, this is the first usage of PROMIS® in a cohort of individuals with APS and/or persistently positive aPL.

Across all measures (PF, CF, and PI), patients who reported impairment in one domain were more likely to report impairment in another. One possibility is that these findings could be impacted by factors such as lower socioeconomic status (28-30) or psychiatric conditions such as depression (31, 32), which we were not able to control for in our study. The prevalence of depression appears to be higher among individuals with APS. One study suggested that approximately 10% of individuals with APS have depression (33), while a different analysis found that patients with APS are 1.57 to 1.64 times more likely to develop depression and anxiety than the general population (34). While the number of individuals in our cohort who are clinically diagnosed with depression is not known, it should be noted that 30.2% (n=42) of the subjects in this study were taking serotonergic medications, often (although not always) prescribed for mental health conditions. Research in the context of total joint arthroplasty replacement found that individuals with diagnosed depression had significantly lower pre-operative and post-operative PF scores compared to individuals in the cohort without depression (35). However, data from a separate orthopedic cohort suggest that improved PF and PI scores do not correlate with improved PROMIS® depressive symptom scores (36).

Analysis of PROMIS® score means revealed no significant difference in scores between individuals with primary APS, secondary APS, or aPL alone (**Table 2**). This is perhaps not what would have been predicted, as SLE is a risk factor for morbid clinical manifestations beyond what would be expected for primary APS (37, 38). An important future direction will be to increase the number of patients with SLE included in this and similar studies. It should be noted that, for the most part, individuals with SLE followed in the APS clinic (and therefore studied here) have SLE that is under good control, with APS as the more active medical issue.

While the dose and duration of pain medication were not accounted for in our analysis, patients taking medications for pain endorsed more impairment in PROs. Out of the 139 individuals in our cohort, 18.7% (n=26) of subjects were prescribed pain medications, defined here as narcotics and/or gabapentinoids (**Table 2**). There was a significant difference in the PF scores for individuals prescribed pain medications (p=0.0007) as compared with those not prescribed pain medications (**Table 3**); the same was true for PI (p=0.004) (**Table 5**). These findings are similar to those derived from a cohort of individuals taking pain medication for fibromyalgia, where subjects taking long-term medications were more likely to endorse severe pain (≥7) (39). While there is mixed evidence that gabapentinoids impact cognition (40-42), there are more consistent findings revealing that narcotics may negatively impact cognition (42).

Subjects taking serotonergic medications, often used for mental health diagnoses, also tended to endorse impairment across all PRO domains (**Tables 3-5**). In terms of the self-reported CF studied here, some literature suggests that serotonergic medications may be associated with decreased cognition (43-45), while other studies suggest that adherence to these medications improves cognitive performance on certain tasks (46-48). As discussed above, the higher frequency of depression that has been reported in the APS patient population may also contribute to the association between these medications and impairment in PROs (34, 43, 47-49). Going forward, concurrently administering a depression screen such as PHQ-9 or a PROMIS® depression short-form questionnaire with the PROMIS® domain short forms may help clarify these findings. It will also be interesting to compare self-reported CF to objective testing of cognitive functioning, which was available for only a minority (n=5) of patients here. In this potential future direction, data on serologies, MRI, and other radiographic imaging could also be analyzed. In the literature, a few studies suggest an association between self-reported and objective cognitive dysfunction (44, 45); however, most often, there is a limited relationship between these outcomes (50-53). Additionally, there may be a psychosocial component that

mediates self-reported CF (43, 54-58). Thus, there is an unmet need to evaluate the relationship between subjective and objective CF in APS patient populations, which often have a high prevalence of depression compared to the general population (33, 34). This may provide insight on how to improve clinical care for APS patients with symptoms of depression and cognitive dysfunction.

In summary, while clinical features of APS did not appear to be dominant drivers of PRO results, the aGAPSS, which uses both laboratory and clinical criteria, was associated with PRO impairment for PF and CF in the univariate analysis. Our study does have limitations, including data being cross-sectional and from a primarily White cohort and a limitation on the number of PROs that could practically be captured during routine clinic visits (depression, fatigue, sleep, and many others would have also been interesting). However, this study does offer potentially valuable data on an understudied patient population and reveals a correlation between PF and CF. Longitudinal data analysis will be needed to develop guidelines for PF and CF scores that are most clinically meaningful for individuals living with APS. Furthermore, concurrent evaluation of domains such as depression and sleep disturbance may help identify factors influencing cognitive function. While an APS-specific PRO tool is not yet available, PROMIS® holds promise as a clinically relevant instrument that may enhance our understanding of issues pertinent to APS patients, allowing us to address their priorities and health concerns more effectively.

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CONTRIBUTIONS

JKW, TS, CKH, CS, JAM, AA, AT, NP, CP, and KG collected and interpreted data. JKW, TS, and JSK analyzed data. JKW, YZ, EMB, VN, and JSK conceived the study. All authors contributing to writing and/or revising the manuscript and approved the final version for submission.

Table 1: Clinical manifestations and laboratory results for 139 patients with persistently positive antiphospholipid antibodies (aPL)

	Total (n=139)	
Diagnoses		
Antiphospholipid Syndrome (n, %)	110	79.1%
Systemic Lupus Erythematosus (n, %)	28	20.1%
Timeline		
Years Since First aPL (mean, SD)	9.37	2.29
aPL-associated		
Venous Thrombosis (n, %)	68	48.9%
Arterial Thrombosis (n, %)	46	33.1%
Small Vein Thrombosis (n, %)	18	13.0%
Transient ischemic attack (n, %)	13	9.4%
Obstetric Morbidity (n, %)	20	14.4%
Thrombocytopenia (n, %)	43	30.9%
Heart Valve Damage (n, %)	16	11.5%
Seizure Disorder (n, %)	11	7.9%
Livedo Reticularis or Racemosa (n, %)	41	29.5%
Cardiovascular Risk Factors		
Hypertension (n, %)	47	33.8%
Hyperlipidemia (n, %)	22	15.8%
Obesity (n, %)	75	54.0%
Smoking (Past) (n, %)	39	28.1%
Smoking (Current) (n, %)	18	13.0%
Sedentary Lifestyle (n, %)	73	52.5%
Laboratory		
Any aCL Positive (n, %)	125	89.9%
Any aβ_2GPI Positive (n, %)	125	89.9%
Lupus anticoagulant (n, %)	83	59.7%
aGAPSS (mean, SD)	11.29	3.20

Except for adjusted global APS score (aGAPSS), which was calculated, all variables were captured via chart review.

Table 2: Demographics and patient-reported outcomes for 139 patients with persistently positive antiphospholipid antibodies (aPL)

	Total (n=139)	**Primary APS** (n=89)	**Secondary APS** (n=21)	**aPL alone** (n=29)	**p-value**
Age (mean, SD)	46.1 15.0	48.0 15.6	39.2 11.9	45.2 14.0	**0.0458**
Sex					**0.0232**
Female	91 65.5%	51 57.3%	16 76.2%	24 82.8%	
Male	48 34.5%	38 42.7%	5 23.8%	5 17.2%	
Race					**0.0279**
White	130 93.5%	86 96.6%	17 81.0%	27 93.1%	
Non-White	9 6.5%	3 3.4%	4 19.1%	2 6.9%	
Medications					
Pain	26 18.7%	18 20.2%	5 23.8%	3 10.3%	0.3947
Serotonergic	42 30.2%	28 31.5%	8 38.1%	6 20.7%	0.3806
Anticoagulant	99 71.2%	78 87.6%	17 81.0%	4 13.8%	**<0.0001**
Antimalarial	82 59.0%	46 51.7%	20 95.2%	16 55.2%	**<0.0001**
Antiplatelet	60 43.2%	36 40.5%	7 33.3%	17 58.6%	**0.0012**
Anticonvulsant	17 12.2%	15 16.9%	0 0.0%	2 6.9%	0.1410
PROs (mean, SD)					
Physical Function	45.4 9.2	45.5 9.0	42.3 9.4	47.7 9.6	0.1280
Cognitive Function*	48.6 11.6	47.3 11.7	49.4 11.0	52.1 11.0	0.1630
Pain	3.0 2.6	2.8 2.6	3.5 2.6	3.0 2.4	0.5860

Physical function and cognitive function were assessed using PROMIS® PF Short Form 10A v2.0 and CF Short Form 8A, respectively. Pain intensity was measured by asking patients to rate their pain on a scale from 0-10, with 10 being the most pain.

Continuous variables are reported as mean (SD); differences between groups were assessed using one-way ANOVA test. Categorical variables are reported as n (%); differences between groups were assessed using Chi-squared test (or Fisher's exact test when n<5).

PROs=patient-reported outcomes
*n=130 for the Cognitive Function Short Form and n=139 for the other PROs

Table 3: Model estimates for the association of demographic and clinical features with physical function scores in patients with persistently positive antiphospholipid antibodies (aPL)

	Physical Function (n=139)			
	Bivariate Associations		Final Model	
	Parameter	p-value	Parameter	p-value
Age	-0.0796	0.1300	-0.1026	**0.0438**
Sex (ref = Male)	0.7830	0.6360	-	-
Race (ref = White)	-0.5934	0.8530	-	-
Diagnoses				
Antiphospholipid Syndrome	-2.7940	0.1480	2.1623	0.3453
Systemic Lupus Erythematosus	-1.7410	0.3740	-	-
Timeline				
Years Since First aPL	0.0176	0.9060	-	-
aPL-associated				
Venous Thrombosis	-4.0130	**0.0099**	-2.1388	0.2351
Arterial Thrombosis	-1.0920	0.5130	-	-
Small Vein Thrombosis	1.5387	0.5110	-	-
Transient ischemic attack	-0.5151	0.8490	-	-
Obstetric Morbidity	-0.2615	0.9070	-	-
Thrombocytopenia	-0.7067	0.6780	-	-
Heart Valve Damage	-1.3068	0.5960	-	-
Seizure Disorder	-2.0813	0.4750	-	-
Livedo Reticularis or Racemosa	-1.6916	0.3260	-	-
Cardiovascular Risk Factors				
Obesity	-4.8180	**0.0019**	-2.0060	0.2025
Smoking (Past)	-5.0707	**0.0038**	-2.5899	0.1218
Smoking (Current)	-6.9818	**0.0029**	-5.2015	**0.0191**
Sedentary Lifestyle	-4.0050	**0.0101**	-1.2908	0.3861
Laboratory				
Any aCL Positive	-1.4920	0.5680	-	-
Any $a\beta_2$GPI Positive	0.9463	0.7170	-	-
Lupus Anticoagulant	-2.5220	0.1140	-2.2038	0.1797
aGAPSS	-0.4956	**0.0428**	-0.1910	0.4580
Medications				
Pain Medication	-8.1300	**<0.0001**	-6.3144	**0.0007**
Serotonergic Medication	-3.8430	**0.0236**	-3.6877	**0.0205**
Anticoagulant Medication	-3.6380	**0.0349**	-2.8521	0.1951
Antimalarial Medication	-0.7048	0.6600	-	-
Antiplatelet Medication	1.2390	0.4350	-	-
Anticonvulsant Medication	-2.1544	0.3690	-	-

Bivariate associations were assessed using simple linear regression. Multivariate associations were assessed using multivariate linear regression and were composed of all variables with p-values <0.2 in bivariate analysis. Statistical significance was measured via Wald test.

Table 4: Model estimates for the association of demographic and clinical features with cognitive function scores in patients with persistently positive antiphospholipid antibodies (aPL)

	Cognitive Function (n=130)			
	Bivariate Associations		Final Model	
	Parameter	p-value	Parameter	p-value
Age	0.0520	0.4380	-	-
Sex (ref = Male)	-0.2121	0.9210	-	-
Race (ref = White)	3.9030	0.3870	-	-
Diagnoses				
Antiphospholipid Syndrome	-4.4060	0.0776	0.5867	0.8430
Systemic Lupus Erythematosus	3.7520	0.1390	2.3799	0.3630
Timeline				
Years Since First aPL	-0.0188	0.9240	-	-
aPL-associated				
Venous Thrombosis	-2.4280	0.2320	-	-
Arterial Thrombosis	-2.6270	0.2270	-	-
Small Vein Thrombosis	3.3300	0.2580	-	-
Transient ischemic attack	-1.1350	0.7380	-	-
Obstetric Morbidity	-2.4880	0.3880	-	-
Thrombocytopenia	-1.7610	0.4280	-	-
Heart Valve Damage	-5.2850	0.0866	-2.6455	0.3880
Seizure Disorder	-7.5880	**0.0455**	-4.7902	0.1880
Livedo Reticularis or Racemosa	-4.2970	0.0552	-2.4764	0.2640
Cardiovascular Risk Factors				
Obesity	-4.4320	**0.0284**	-0.2432	0.9050
Smoking (Past)	-5.6010	**0.0151**	-3.7045	0.1180
Smoking (Current)	-1.8920	0.5459	-1.1373	0.7170
Sedentary Lifestyle	-2.4370	0.2310	-	-
Laboratory				
Any aCL Positive	-5.3290	0.1150	0.3460	0.9490
Any aβ_2GPI Positive	-4.8600	0.1830	-2.8621	0.5720
Lupus Anticoagulant	-1.6880	0.4180	-	-
aGAPSS	-0.7259	**0.0215**	-0.3563	0.4220
Medications				
Pain Medication	-4.6800	0.0832	-2.6339	0.3050
Serotonergic Medication	-8.9220	**<0.0001**	-8.9503	**<0.0001**
Anticoagulant Medication	-4.7110	**0.0339**	-3.9861	0.1360
Antimalarial Medication	3.0020	0.1470	2.0484	0.3510
Antiplatelet Medication	2.4160	0.2390	-	-
Anticonvulsant Medication	-3.7950	0.2200	-	-

Bivariate associations were assessed using simple linear regression. Multivariate associations were assessed using multivariate linear regression and were composed of all variables with p-values <0.2 in bivariate analysis. Statistical significance was measured via Wald test.

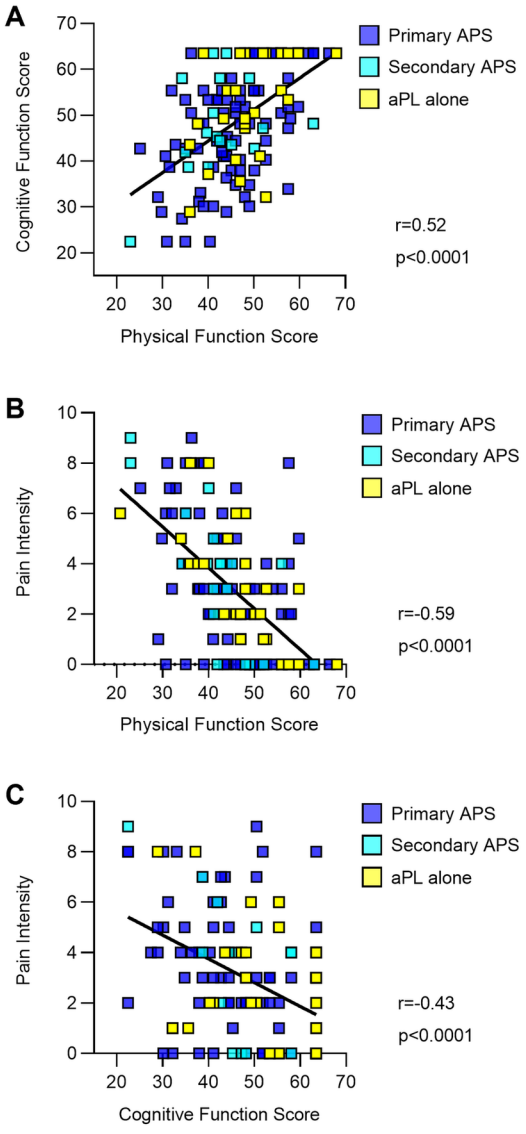
Table 5: Model estimates for the association of demographic and clinical features with pain intensity scores in patients with persistently positive antiphospholipid antibodies (aPL)

	Pain Intensity (n=139)			
	Bivariate Associations		Final Model	
	Parameter	p-value	Parameter	p-value
Age	-0.0011	0.9390	-	-
Sex (ref = Male)	0.3478	0.4480	-	-
Race (ref = White)	0.6402	0.4690	-	-
Diagnoses				
Antiphospholipid Syndrome	-0.0110	0.9840	-	-
Systemic Lupus Erythematosus	0.3671	0.4990	-	-
Timeline				
Years Since First aPL	-0.0146	0.7240	-	-
aPL-associated				
Venous Thrombosis	0.7179	0.0980	0.6317	0.1232
Arterial Thrombosis	-0.4554	0.3250	-	-
Small Vein Thrombosis	-0.5886	0.3640	-	-
Transient ischemic attack	-0.5464	0.4650	-	-
Obstetric Morbidity	0.1672	0.7880	-	-
Thrombocytopenia	-0.0722	0.8780	-	-
Heart Valve Damage	0.5432	0.4260	-	-
Seizure Disorder	0.5405	0.5030	-	-
Livedo Reticularis or Racemosa	0.6493	0.1730	0.4351	0.3294
Cardiovascular Risk Factors				
Obesity	1.0204	**0.0184**	0.4143	0.3272
Smoking (Past)	1.1751	**0.0164**	0.8464	0.0726
Smoking (Current)	1.6409	**0.0123**	1.0845	0.0889
Sedentary Lifestyle	0.5237	0.2290	-	-
Laboratory				
Any aCL Positive	-0.5246	0.4690	-	-
Any aβ_2GPI Positive	-0.6040	0.4040	-	-
Lupus Anticoagulant	0.5258	0.2360	-	-
aGAPSS	0.0111	0.8705	-	-
Medications				
Pain Medication	2.0402	**0.0002**	1.5575	**0.0040**
Serotonergic Medication	1.1878	**0.0114**	1.0493	**0.0213**
Anticoagulant Medication	0.1500	0.7550	-	-
Antimalarial Medication	0.0161	0.9710	-	-
Antiplatelet Medication	-0.3932	0.3710	-	-
Anticonvulsant Medication	0.5853	0.3780	-	-

Bivariate associations were assessed using simple linear regression. Multivariate associations were assessed using multivariate linear regression and were composed of all variables with p-values <0.2 in bivariate analysis. Statistical significance was measured via Wald test.

FIGURE LEGENDS

Figure 1: Associations between patient-reported outcomes for physical function, cognitive function, and pain intensity (n=130 for A and C; n=139 for B). Pearson r and associated p-values are indicated.



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