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Predictors and Interrelationship of Patient-Reported Outcomes in Antiphospholipid Syndrome: A Cross-Sectional Study

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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 Patient-Reported Outcomes Measurement Information System Physical Function (PF) and Cognitive Function (CF) Short Forms as well as the pain intensity (PI) rating (scale of 1-10). Patients were characterized for demographics, clinical manifestations of antiphospholipid syndrome (APS), cardiovascular risk factors, laboratory test results, and medication usage. Multivariate modeling was done via linear regression.

Results. Of 139 patients, 89 had primary APS, 21 had secondary APS, and 29 had 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 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–β_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 1) primary APS (persistently positive aPL along with a history of thrombosis or pregnancy morbidity), 2) secondary APS (APS in the presence of systemic lupus erythematosus [SLE]), or 3) persistent aPL with a history of neither thrombosis nor obstetric morbidity (1,3,4). Patients with aPL are also at risk for certain "noncriteria" manifestations, including livedo reticularis and livedo 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 noncriteria manifestations, such as joint pain and brain fog, may disrupt the physical

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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 (7) administered a cross-sectional survey known as the 36-Item Short Form Health Survey (SF-36) to 270 individuals living with APS. Major issues identified included pain and fatigue, lack of health care professional and/or public awareness, and medication unpredictability. Furthermore, health-related quality of life for individuals with primary APS appeared to be generally better than that for those with 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 (aged 18-45) 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.

The Patient-Reported Outcomes Measurement Information System (PROMIS) 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, and 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 more than 200,000 individuals across the United States, with the average (±SD) T score being 50 ± 10 (17). In this exploratory study, our objective was to characterize PROs associated with physical function (PF) and cognitive function (CF) 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 the 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 (T score < 45), moderate impairment (T scores 30-40), or severe impairment (T score < 30), as has been described (18,19). Patients also rated self-perceived pain intensity (PI) on a scale of 0 to 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 Institutional Review Board (HUM00122519) that 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 laboratory testing and clinical manifestations associated with APS were captured via chart review. Some clinical information was abstracted using Electronic Medical Record Search Engine (EMERSE), 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 a 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 immunoglobulin G and immunoglobulin M (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

Table 1. Clinical manifestations and laboratory results for 139 patients with persistently positive aPL

	Total (n = 139)
Diagnoses, n (%)	
Antiphospholipid syndrome	110 (79.1%)
Systemic lupus erythematosus	28 (20.1%)
Timeline	
Years since first aPL, mean (SD)	9.37 (2.29)
aPL associated, n (%)	
Venous thrombosis	68 (48.9%)
Arterial thrombosis	46 (33.1%)
Small vein thrombosis	18 (13.0%)
Transient ischemic attack	13 (9.4%)
Obstetric morbidity	20 (14.4%)
Thrombocytopenia	43 (30.9%)
Heart valve damage	16 (11.5%)
Seizure disorder	11 (7.9%)
Livedo reticularis or livedo racemosa	41 (29.5%)
Cardiovascular risk factors, n (%)	
Hypertension	47 (33.8%)
Hyperlipidemia	22 (15.8%)
Obesity	75 (54.0%)
Smoking (past)	39 (28.1%)
Smoking (current)	18 (13.0%)
Sedentary lifestyle	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)

Note: Except for aGAPSS, which was calculated, all variables were captured via chart review.
Abbreviations: aβ_2GPI, anti–β_2-glycoprotein I antibodies; aCL, anticardiolipin antibodies; aGAPSS, global antiphospholipid syndrome score; aPL, antiphospholipid antibodies.

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 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 (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 and 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 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, and

Table 2. Demographics and patient-reported outcomes for 139 patients with persistently positive aPL

	Total (n = 139)	Primary APS (n = 89)	Secondary APS (n = 21)	aPL alone (n = 29)	*P*
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%)	
Other	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[a]	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

Note: Physical function and cognitive function were assessed using the Patient-Reported Outcomes Measurement Information System Physical Function Short Form 10A v2.0 and Cognitive Function Short Form 8A, respectively. Pain intensity was measured by asking patients to rate their pain on a scale from 0 to 10, with 10 being the most pain. Continuous variables are reported as mean (SD); differences between groups were assessed using the one-way analysis of variance test. Categorical variables are reported as n (%); differences between groups were assessed using the chi-square test (or Fisher's exact test when n < 5).
Abbreviations: aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; PROs, patient-reported outcomes.
[a]n = 130 for the Cognitive Function Short Form, and n = 139 for the other PROs.

aPL alone) using one-way analysis of variance. Categorical variables (such as sex) were compared using chi-squared testing, except for variables with a cell count less than 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 less than 0.2 in bivariate analyses. Statistical significance was measured via the 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 (Figure 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% were 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 patients with primary APS, 29% of patients with secondary APS, and 21% of patients with aPL alone 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 more likely to be taking antimalarial medications, whereas patients meeting criteria for APS (whether primary or secondary) were more likely to be taking anticoagulant medications.

For PF, CF, and PI, we performed bivariate analyses for 29 variables, including demographics, the presence of APS and/or SLE, time since the first positive aPL test result (a surrogate for disease duration), clinical features associated with APS, aPL laboratory testing (including aGAPSS) (21), and medications. Hypertension and hyperlipidemia were not individually included in the analysis because 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 less than 0.2.

For PF, history of venous thrombosis, obesity, smoking status (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 on the basis of bivariate analysis ($P < 0.05$) (Table 3). After adjustment 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

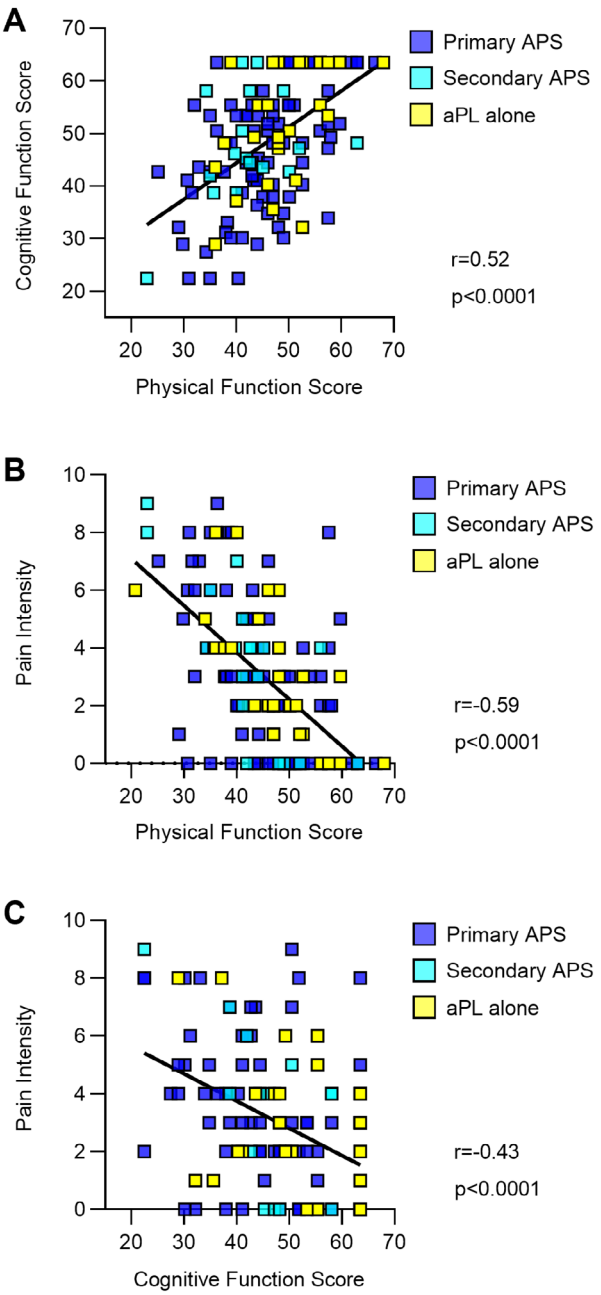

Figure 1. Associations between patient-reported outcomes for physical function, cognitive function, and pain intensity (n = 130 for **A** and **C**; n = 139 for **B**). Pearson *r* and associated *P* values are indicated. aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome.

Table 3. Model estimates for the association of demographic and clinical features with physical function scores in patients with persistently positive aPL

	Physical function (N = 139)			
	Bivariate associations		Final model	
	Parameter	*P*	Parameter	*P*
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 livedo 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 aβ_2GPI 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	-	-

Note: 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 the Wald test.
Abbreviations: aβ_2GPI, anti–β_2-glycoprotein I antibodies; aCL, anticardiolipin antibodies; aGAPSS, global antiphospholipid syndrome score; aPL, antiphospholipid antibodies.

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 status (both past and current), pain medication use, and serotonergic medication use were all associated with higher PI ($P < 0.05$). After adjustment for covariates, variables associated with more pain included pain medication use and serotonergic medication use (Table 5).

Finally, we analyzed the extent to which the 37-item DIAPS instrument (10,11) might be associated with PF, CF, and PI. For the entire 139-patient cohort, the mean (±SD) DIAPS score was 2.1 ± 2.1. The median score was 2.0, and the maximum DIAPS score for the cohort was 10. The 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

Table 4. Model estimates for the association of demographic and clinical features with cognitive function scores in patients with persistently positive aPL

	Cognitive function (n = 130)			
	Bivariate associations		Final model	
	Parameter	*P*	Parameter	*P*
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 livedo 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	-	-

Note: Bivariate associations were assessed using simple linear regression. Multivariate associations were assessed using multivariate linear regression and were composed of all variables with $P < 0.2$ in bivariate analysis. Statistical significance was measured via the Wald test.
Abbreviations: aβ_2GPI, anti–β_2-glycoprotein I antibodies; aCL, anticardiolipin antibodies; aGAPSS, global antiphospholipid syndrome score; aPL, antiphospholipid antibodies.

to PF, the CF score distribution was relatively similar to that in the general population (APS mean = 48.6), although 26% of patients with primary APS did have T scores less than 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 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 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), whereas 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). Although 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 participants in this study

Table 5. Model estimates for the association of demographic and clinical features with pain intensity scores in patients with persistently positive aPL

	Pain intensity (n = 139)			
	Bivariate associations		Final model	
	Parameter	*P*	Parameter	*P*
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 livedo 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	-	-

Note: Bivariate associations were assessed using simple linear regression. Multivariate associations were assessed using multivariate linear regression and were composed of all variables with $P < 0.2$ in bivariate analysis. Statistical significance was measured via the Wald test.
Abbreviations: aβ_2GPI, anti–β_2-glycoprotein I antibodies; aCL, anticardiolipin antibodies; aGAPSS, global antiphospholipid syndrome score; aPL, antiphospholipid antibodies.

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 preoperative and postoperative 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 differences in scores between individuals with primary APS, secondary APS, and aPL alone (Table 2). This is perhaps not what would have been predicted because 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 observed in the APS clinic (and therefore studied here) have SLE that is under good control, with APS as the more active medical issue.

Although the dose and duration of pain medication were not accounted for in our analysis, patients taking medications for pain endorsed more impairment in PROs. Of the 139 individuals in our cohort, 18.7% (n = 26) of participants 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, in which participants taking long-term medications were more likely to endorse severe pain (≥7) (39). Although there is mixed evidence that gabapentinoids impact cognition (40–42), there are more consistent findings revealing that narcotics may negatively impact cognition (42).

Participants 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), whereas 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 Patient Health Questionnaire-9 (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 serologic findings, magnetic resonance imaging, 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 patients with APS with symptoms of depression and cognitive dysfunction.

In summary, although 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 CF. Although 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 patients with APS, allowing us to address their priorities and health concerns more effectively.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Knight had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Weiner, Zuo, Briceño, Nagaraja, Knight.

Acquisition of data. Weiner, Smith, Hoy, Sarosh, Madison, Ambati, Tambralli, Peters, Packel, Gockman.

Analysis and interpretation of data. Weiner, Smith, Hoy, Sarosh, Madison, Ambati, Tambralli, Peters, Packel, Gockman, Knight.

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