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Prevalence of Clinically Meaningful Antiphospholipid Antibodies in Patients with Systemic Lupus Erythematosus Varies by Race and Ethnicity

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The presence of antiphospholipid antibodies (aPLs), highly pathogenic autoantibodies that may trigger thrombosis and serious pregnancy complications, can influence the course of

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SLE and contribute to organ damage (1,2). Reports of the frequency of aPLs in SLE patients are highly variable, ranging from 11 to 86% of patients, but generally quoted as 25–40% (3,4). Determination of the prevalence of aPLs is challenged by lack of standardization of assays to measure lupus anticoagulant (LAC) and lack of standardization of cut-off values in reports of aPL positivity for anti-cardiolipin (aCL) and anti-β_2 glycoprotein I antibody (aβ_2GPI) assays. Some reports include any positive aPL test (values >95th percentile), whereas others include only clinically meaningful aPL results (moderate-to-high titers) defined by international guidelines and considered strongly associated with clinical manifestations (4). Criteria for classification of antiphospholipid syndrome (APS) consider only moderate-to-high titer aPL antibodies (≥40 GPL/MPL units) and/or the presence of LAC (4,5). Moderate-to-high titers of antibodies alone provide a strong basis for risk stratification (4,5), whereas low titers do not. Race and ethnicity influence prevalence, manifestations, disease activity, and severity of SLE and have been associated with some autoantibodies (6). Yet, accurate assessment of the prevalence of clinically meaningful aPL antibodies in diverse SLE populations is lacking.

We used multiple prospectively collected longitudinal SLE cohorts (described in legend for Table 1) to examine overall prevalence of aPLs as well as their presence by race. All patients met ACR criteria for SLE. Participant race and ethnicity were provided by self-report. APL assays were performed following international guidelines in local laboratories (4). Clinically meaningful aPLs were defined as presence of LAC, and/or moderate-to-high titers of aCL IgG/IgM and/or moderate-to-high titers of aβ_2GPI IgG/IgM (≥40 GPL/MPL units), according to revised Sapporo criteria (4). Data are expressed as number of patients with positive tests/total number tested (% of total). Chi-square test and Cochran-Mantel-Haenszel test based on combined data were used to compare aPL prevalence across race and ethnicity.

Our key discovery is the remarkably low frequency of moderate-to-high titers of aPLs (overall totals 3–7%) in patients from many SLE cohorts that include over 2,500 racially, ethnically, and geographically diverse patients (Table 1). LAC positivity was higher (7–24%), but LAC assays are not standardized and have high rates of false positives due to anticoagulant agents, interference by acute phase reactants, and poor sample handling. International efforts are ongoing to standardize LAC assays and to determine whether other autoantibodies, such as anti-domain 1-β2GPI or anti-phosphatidyl-serine/prothrombin antibodies, are associated with clinical APS, highly correlate with LAC, and provide comparable risk for clinical events.

Our second important finding is that prevalence of clinically meaningful levels of conventional aPLs differed significantly by race and ethnicity groups in stratified analyses of combined cohort data (aCL IgG $p<0.0001$; aβ_2GPI IgG $p<0.0002$; LAC $p=0.12$), lowest in Black patients. Trends were consistent across the various longitudinal cohorts as detailed in Table 1.

The strengths of our study include the large number of prospectively enrolled SLE diverse patients and the use of a strict definition for aPL positivity. The main limitation is absence of multiple positive tests in some cohorts as required for classification criteria (4) which may result in over reporting aPL positivity. Other limitations include missing data on aPL

determinations (similar across races), use of local rather than core labs, and absence of clinical correlates for aPLs.

Our findings provide the impetus to discover the basis for skewed racial distribution of aPLs. Evidence that aPLs are distributed differently among different races and ethnicities should catalyze studies to better understand the genetic and environmental factors contributing to this variability and the subphenotypes of SLE patients. Furthermore, our findings can also influence clinical trials and management of Black SLE patients. Trials with new agents for SLE and APS must enroll patients that reflect real world racial and ethnic distribution of disease to assess potential differential treatment responses and assure equity in access. To design trials to prevent aPL-mediated adverse outcomes in SLE patients and assess feasibility of enrolling under-represented groups, it is necessary to know the prevalence of clinically meaningful aPL levels in diverse populations.

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Table 1.

Clinically meaningful aPL positivity by ethnicity/race in SLE patients

	Overall	Black*	Asian	Hispanic	White	p-value
aCL IgG						
CLUES	25/273 (9)	0/29 (0)	7/100 (7)	10/63 (16)	8/81 (10)	0.07#
HSS	42/688 (6)	2/150 (1)	3/60 (5)	8/119 (7)	29/359 (8)	0.04
EMORY	3/140 (2)	3/119 (3)	0/2 (0)	0/5 (0)	0/14 (0)	1
AECOM	22/238 (9)	11/156 (7)	0/10 (0)	2/30 (7)	9/42 (21)	0.05
MUSC	29/462 (6)	17/357 (5)	1/5 (20)	2/12 (17)	9/88 (10)	0.03
PROMISSE+	25/392 (6)	0/79 (0)	3/47 (6)	1/35 (3)	21/231 (9)	0.01
GR2+	21/350 (6)	0/59 (0)	0/21 (0)	NA	21/270 (8)	0.03
OVERALL TOTAL	**167/2543 (7)**	**33/949 (3)**	**14/245 (6)**	**23/264 (9)**	**97/1085 (9)**	**<0.0001** §
aCL IgM						
CLUES	23/273 (8)	1/29 (3)	4/100 (4)	10/63 (16)	8/81 (10)	0.04
HSS	31/688 (5)	4/150 (3)	2/60 (3)	1/119 (1)	24/359 (7)	0.03
EMORY	4/138 (3)	2/117 (2)	0/2 (0)	0/5 (0)	2/14 (14)	0.15
AECOM	4/239 (2)	2/155 (1)	0/10 (0)	1/32 (3)	1/42 (2)	0.49
MUSC	12/526 (2)	10/423 (2)	1/5 (20)	0/12 (0)	1/86 (1)	0.15
PROMISSE	7/392 (2)	0/79 (0)	0/47 (0)	0/35 (0)	7/231 (3)	0.33
GR2	5/350 (1)	1/59 (2)	0/21 (0)	NA	4/270 (1)	1
OVERALL TOTAL	**86/2606 (3)**	**20/1012 (2)**	**7/245 (3)**	**12/266 (5)**	**47/1083 (4)**	**0.01**
Ab2GPI IgG						
CLUES	18/271 (7)	1/29 (3)	7/99 (7)	4/63 (6)	6/80 (8)	0.97
HSS	31/664 (5)	3/144 (2)	2/58 (3)	3/119 (3)	23/343 (7)	0.08
EMORY	8/131 (6)	7/111 (6)	0/2 (0)	0/4 (0)	1/14 (7)	1
AECOM	22/214 (10)	10/136 (7)	0/8 (0)	3/31 (10)	9/39 (23)	0.05
MUSC	18/301 (6)	9/204 (4)	1/6 (17)	2/11 (18)	6/80 (8)	0.09
PROMISSE	12/391 (3)	0/79 (0)	1/47 (2)	2/35 (6)	9/230 (4)	0.18
GR2	19/349 (5)	0/59 (0)	0/21 (0)	NA	19/269 (7)	0.04
OVERALL TOTAL	**128/2321 (6)**	**30/762 (4)**	**11/241 (5)**	**14/263 (5)**	**73/1055 (7)**	**0.0002**
Ab2GPI IgM						
CLUES	10/272 (4)	1/29 (3)	2/99 (2)	4/63 (6)	3/81 (4)	0.52
HSS	35/664 (5)	2/144 (1)	1/58 (2)	3/119 (3)	29/343 (8)	0.002
EMORY	2/132 (2)	2/112 (2)	0/2 (0)	0/4 (0)	0/14 (0)	1
AECOM	6/232 (3)	3/149 (2)	0/10 (0)	1/32 (3)	2/41 (5)	0.58
MUSC	9/302 (3)	7/205 (3)	1/6 (17)	0/11 (0)	1/80 (1)	0.19
PROMISSE	10/389 (3)	0/78 (0)	0/47 (0)	0/35 (0)	10/229 (4)	0.1
GR2	6/72 (8)	2/12 (17)	0/3 (0)	NA	4/57 (7)	0.44
OVERALL TOTAL	**78/2063 (4)**	**17/729 (2)**	**4/225 (2)**	**8/264 (3)**	**49/845 (6)**	**0.01**
LAC						
CLUES	15/79 (19)	1/6 (17)	4/30 (13)	8/20 (40)	2/23 (9)	0.06

	Overall	Black*	Asian	Hispanic	White	p-value
HSS	111/486 (23)	16/104 (15)	12/48 (25)	21/95 (22)	62/239 (26)	0.19
EMORY	25/126 (20)	23/108 (21)	0/2 (0)	1/5 (20)	1/11 (9)	0.85
AECOM	46/228 (20)	24/149 (16)	1/9 (11)	7/30 (23)	14/40 (35)	0.05
MUSC	61/333 (18)	47/237 (20)	0/5 (0)	1/10 (10)	13/81 (16)	0.72
PROMISSE	27/390 (7)	3/79 (4)	2/46 (4)	3/34 (9)	19/231 (8)	0.51
GR2	84/350 (24)	12/59 (20)	4/21 (19)	NA	68/270 (25)	0.63
OVERALL TOTAL	**369/1992 (18)**	**126/742 (17)**	**23/161 (14)**	**41/194 (21)**	**179/895 (20)**	**0.12**

All patients met ACR revised classification criteria for SLE. Laboratory data were obtained within the past 10 years.

Race and ethnicity were provided by self-report.

*For GR2, only geographical origin was collected: Black = sub-Saharan African ancestry and White = European ancestry

SLE Patient cohorts (n for the current work):

CLUES = California Lupus Epidemiology Study, longitudinal cohort of individuals from San Francisco, CA with physician-confirmed SLE (n=278)

AECOM= longitudinal cohort of SLE patients followed in the Lupus Clinics of Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY (n=263)

EMORY= longitudinal cohort of SLE patients cared for at Emory University or Grady Lupus Clinic in Atlanta, GA (n=144)

HSS= longitudinal cohort of SLE patients cared for at Hospital for Special Surgery and enrolled in the HSS Lupus Registry, New York, NY (n=700)

MUSC = longitudinal cohort of patients with SLE followed at the Medical University of South Carolina as part of the ongoing research registry and biorepository (n=663)

+**Pregnant SLE Patient cohorts** (n for the current work; aPLs positive if present in first trimester and at another time point)

GR2 = Groupe de Recherche sur la Grossesse au cours des maladies Rares (GR2) study, a French multicentre, prospective, observational study of pregnancies in women with rheumatic diseases (n=350 SLE patients).

PROMISSE = Predictors of pRegnancy Outcome: bioMarkers In antiphospholipid antibody Syndrome and Systemic lupus Erythematosus study, a North American multi-center observational study of pregnancies in SLE and/or aPL patients (n=358 SLE patients)

Clinically meaningful aPLs were defined by the presence of LAC and/or moderate-to-high titers of aCL IgG/IgM (≥40 units) and/or moderate-to-high titers of aβ2GPI IgG/IgM (≥40 units) (4,5) at least once. In GR2 and PROMISSE, two positive tests were required.

Data are expressed as number of patients with positive tests/total number tested (% of the total).

#Chi-square test;

§Cochran-Mantel-Haenszel test based on combined data. A two-sided $p<0.05$ was considered statistically significant.

Abbreviations: aCL= anticardiolipin antibodies, aβ2GPI = anti-β2Glycoprotein I antibodies, LAC = lupus anticoagulant, NA= not available