

Platelet glycoprotein V autoantibodies and complement C3 are associated with thrombosis in systemic lupus erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is associated with an increased cardiovascular disease risk not fully explained by traditional factors. This retrospective study investigated the frequency and clinical relevance of platelet-specific glycoprotein (GP) autoantibodies and anti-phospholipid antibodies (aPL) in SLE. Serum from 89 patients with SLE (≥ 4 American College of Rheumatology 1982 criteria) was analyzed at higher (H) and lower (L) disease activity (median SLEDAI-2K: H=9.6 and L=2.1). Platelet GPIIb/IIIa-, GPV- and GPIb/IX-autoantibodies were detected using the indirect monoclonal antibody immobilization of platelet antigens assay, while immunoglobulin (Ig)M/IgG aPL, anti- $\beta 2$ glycoprotein 1 (a $\beta 2$ GP1), anti-cardiolipin (anti-CL), anti-phosphatidylserine/prothrombin complex (anti-PS/PT) and anti-annexin V (anti-AV) antibodies were measured by enzyme-linked immunosorbent assay. At high activity, 64% (57/89) of patients tested positive for at least one anti-GP antibody, compared to 42% (37/89) with low-disease activity. Anti-GPIIb/IIIa prevalence was stable ($\sim 30\%$), whereas anti-GPV and anti-GPIb/IX were more frequent during H (48% [43/89] vs. 24% [21/89] and 49% [44/89] vs. 27% [24/89], respectively). Anti-GPV levels correlated positively with SLEDAI-2K ($r=0.34$; $P=0.001$) and negatively with C3 and C4. Twenty-four patients developed unprovoked thromboembolic events during follow-up. In multivariate analysis, anti-GPV and C3 independently predicted thrombosis (hazard ratio [HR]=2.17; 95% confidence interval [CI]: 1.39-3.36; $P=0.001$; and HR=2.16; 95% CI: 1.32-3.54; $P=0.002$). Platelet counts remained within the normal range irrespective of disease activity, antibody status or thrombotic events. In summary, platelet-specific anti-GP antibodies are prevalent in SLE patients. Anti-GPV, previously not studied in this context and complement C3, independently predicted thrombotic events.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that primarily affects women, with peak incidence during reproductive age.¹ The clinical presentation is heterogenous, most commonly including arthritis, skin involvement, nephritis and hematologic manifestations.² Disease onset and development is dependent on an interplay between genetic predisposition and environmental factors and is characterized by aberrant innate as well as adaptive immune responses. Dysregulated apoptosis and

impaired clearance of apoptotic cells are central to SLE pathogenesis, through excessive exposure of nuclear epitopes and modified self-antigens, lowering the tolerance threshold, and subsequent generation of autoantibodies.³ Despite improvements in treatment and management of SLE, thrombotic events and cardiovascular disease remain a significant cause for morbidity and mortality.⁴⁻⁶ A major part of the driving mechanisms behind these complications are predicted to be disease specific, independent of traditional risk factors, and in need of better characterization. Thus, to meet this clinical need, a deeper understanding

of underlying pathogenetic mechanisms is needed and identification of relevant biomarkers. Platelets have increasingly been recognized for their non-hemostatic role^{7,8} in autoimmune diseases,⁹ including SLE,¹⁰ where they have an altered phenotype and protein profile enriched in complement proteins from both the classical and alternative pathways, immunoglobulins, and autoantigens.¹¹ Activated platelets are well-established mediators of thrombosis in anti-phospholipid syndrome (APS),¹² characterized by recurrent venous and/or arterial thrombosis and pregnancy morbidity in the presence of anti-phospholipid antibodies (aPL): anti-cardiolipin (anti-CL), anti- β 2 glycoprotein 1 (anti- β 2GPI), and lupus anticoagulant (LA). However, known aPL do neither fully explain ongoing platelet activation nor do they predict all APS-related clinical manifestations, whether primary or secondary to SLE.^{4,13} Consequently, several “non-criteria” aPL are under evaluation, including anti-phosphatidylserine/prothrombin (aPS/PT) and anti-annexin V (aAV).¹⁴

Autoantibodies directed against platelet glycoprotein GPIIb/IIIa and GPIb/IX are well established and anti-GPV is an emerging marker of the autoimmune disorder immune thrombocytopenia (ITP).^{15,16} Although these glycoproteins belong to two different receptor complexes (GPIIb/IIIa and GPIb-IX-V), their individual roles have been delineated, and studies of autoantibodies targeting different components of the same complex have demonstrated divergent functional effects.¹⁷ The clinical spectrum of ITP is dominated by bleeding and immune-mediated platelet destruction, but an increased rate of both arterial and venous thrombosis has been reported in ANA-positive patients.^{18–21} In SLE, anti-platelet antibodies are well documented in the context of thrombocytopenia, predominantly with anti-GPIIb/IIIa specificity. Pujol *et al.* (N=90) reported a significant association with ongoing thrombocytopenia and an independent association with disease activity using platelet suspension immunofluorescence.²² Several studies have confirmed this association with GPIIb/IIIa or corresponding B cells with minor contributions from GPIa/IIa and GPIb/IX).^{21,23} However, previous studies on anti-GP antibodies in SLE have been limited in scope, largely focused on thrombocytopenia, with no or very limited attention towards a wider array of clinical manifestations. To our knowledge, no studies have examined the role of anti-GP antibodies in SLE, leaving their potential clinical significance unexplored.

The aims of this study were to: (i) determine the frequency of anti-GP antibodies in patients with high- and low-disease activity; (ii) assess their association with thrombocytopenia ($<150 \times 10^9/L$); and (iii) explore their role in other clinical manifestations, including thrombotic events. We conducted a retrospective study in a well-characterized cohort of patients with SLE, based on paired samples obtained during periods of high- and low-disease activity, as defined by the SLEDAI-2K. We then analyzed anti-GP

as well as aPL profiles, linked them to clinical features, including thrombotic complications, during an average follow-up time of 20 years. Our findings reveal that platelet-specific anti-GP antibodies are prevalent in patients with SLE. Anti-GPV, previously not studied in SLE, is associated with decreased levels of complement C3 and C4, in addition to thrombotic complications, highlighting its potential as novel biomarker.

Methods

Patients

This retrospective study included 89 patients with SLE (≥ 4 American College of Rheumatology 1982 criteria). For each patient, two serum samples were collected: one during higher (H) and one during lower (L) activity, defined by the SLE Disease Activity Index 2000 (SLEDAI-2K). Samples were collected between January 1987 and May 2015 and stored in -80°C with one to two freeze-thaw cycles including the current study. Clinical data, including thrombotic events, platelet count, C-reactive protein (CRP) and complement protein C3/C4 were obtained from medical records. The study was approved by the Swedish Ethical Review Authority (DNR 2020-03515) and all patients provided informed consent.

Platelet glycoprotein and anti-phospholipid antibody assays

Antibodies against GPIIb/IIIa, GPV and GPIb/IX were measured in H and L samples, using indirect monoclonal antibody immobilization of platelet antigens assay (MAIPA) as previously described (cut-off, optical density 0.13).^{24,25} MAIPA testing was performed at Sanquin Diagnostic Services, Amsterdam, the national reference center for platelet autoantibody diagnostics in the Netherlands. Serum samples were stored at -80°C from collection until analysis, with storage durations ranging from approximately 1 to 25–30 years. An unknown subset of samples may have undergone a single freeze-thaw cycle prior to analysis. Presence of criteria aPL (IgG/IgM anti- β 2GPI and aCL) antibodies and non-criteria aPL (IgG/IgM anti-PS/PT and anti-AV), were analyzed using commercially available enzyme-linked immunosorbent assay (ELISA) (Aesku, Wendelsheim, Germany).

Thrombotic events

Medical records were reviewed for confirmed, unprovoked thrombotic events occurring after collection of the first serum sample; earlier events were excluded. Thrombotic events were defined according to the 2023 ACR/EULAR APS criteria; however, the retrospective design may still permit residual misclassification (*Online Supplementary Table S3*). Time to event was measured from the first sampling date. Events associated with malignancy, surgery or other provoking factors, were excluded from the analysis in agreement with attribution criteria.

Statistical analysis

Correlations between antibody levels (anti-GP, aPL) and total SLEDAI-2K were assessed by Spearman’s rank correlation and with individual SLEDAI-2K items using Pearson’s correlation (SPSS v29.0.0.0). Paired comparison between H and L were performed by Wilcoxon signed-rank test, GraphPad Prism software (version 10.6.1). Potential predictors of thrombosis were assessed using a multivariable Cox regression model. Predictors included normalized average antibody titers (mean of H and L) for anti-GP and aPL, clinical characteristics (age at diagnosis, sex, disease duration, prior nephritis), clinical variables (platelet count, CRP, C3, C4, SLEDAI-2K) and baseline treatment (antimalarial treatment or prednisolone treatment >10 mg/day). In sensitivity analyses, we also examined alternative aPL definitions, including persistent high-titer positivity (≥40 U/mL at ≥2 time points ≥12 weeks apart). Missing values in platelet count (5.6%), CRP (4.5%), C3 (3.9%) and C4 (3.9%) were imputed by fully conditional specification (SPSS v29.0.0.0). For Kaplan-Meier survival analyses, patients were stratified based on antibody levels and complement concentrations. Antibody levels measured by MAIPA (anti-GP) and ELISA (aPL) were first classified as detectable or non-detectable using assay-specific cut-offs (MAIPA optical density ≥0.13; ELISA >18 U/mL). Detectable values were then categorized as low or high using the median among detectable samples; non-detectable samples were classified as negative. For both MAIPA and ELISA, antibody levels were categorized as negative (below assay cutoff), low positive (detectable and below the median of detectable values), or high positive (detectable and above the median). Complement C3 and C4 levels were divided into tertiles (low, medium, high) based on their distribution. Graphs were generated using GraphPad Prism (version 10.6.1).

Results

Patient characteristics, high and low disease activity

The mean age at inclusion (H) was 43 years and at the second sampling (L) 48 years. The median disease duration at inclusion was 2 years, but a third (34%) of the patients were included during their first year. Seventy-one percent of patients had a history of positivity for double-stranded DNA antibodies, 47% a history of nephritis and 8% either had or received a diagnosis of APS during the course of the study. The average SLEDAI-2K was 9.6 during first and 2.1 during second sample (Table 1). Mean (± standard deviation [SD]) CRP levels were 6.6±11.1 mg/L at high disease activity and 3.7±6.9 mg/L at low. Corresponding C3 levels were 0.79±0.31 versus 0.93±0.27 g/L, and C4 levels 0.14±0.08 versus 0.16±0.07 g/L. Platelet counts were similar: 233.8±69.3 versus 246.3±68.3x10⁹/L (Figure 1). As expected, the median level of prednisolone administered was higher

during H, while L had higher usage of disease-modifying antirheumatic drugs (DMARD), including antimalarial drugs. Hydroxychloroquine (HCQ) or chloroquine (CQ) was used by 40 (45%) during inclusion and 59 (66%) at follow-up. For a detailed distribution of SLEDAI-2K items in H versus L, see *Online Supplementary Table S1*.

Anti-glycoprotein V correlated positively with disease activity and inversely with complement levels and platelet count

During active disease, 57 (64%) had at least one type of anti-GP antibody, compared with 37 (42%) in patients with less active disease. Detection of anti-GPIIb/IIIa had a similar presence in H and L (27% and 26%), while anti-GPV (48% vs. 24%) and anti-GPIb/IX (49% vs. 27%) both had higher percentages positive in H versus L (Figure 2A). The levels of anti-GPV and anti-GPIb/IX during high disease were significantly elevated compared with low (P=0.0001 and P<0.0001, respectively, Wilcoxon signed-rank test). Average

Table 1. Characteristics of systemic lupus erythematosus patients.

Characteristics	Values
N of patients	89
Female, N (%)	78 (88)
Caucasian, N (%)	81 (91)
Mean age at diagnosis, years (SD)	38 (15)
Mean age at sample 1, years	43.2
Mean age at sample 2, years	48.0
Nephritis, N (%)	42 (47)
Disease duration, years, median	2
APS diagnosis, N (%)	7 (8)
Autoantibodies, N (%)	
Anti-dsDNA	63 (71)
anti-Sm	11 (12)
ANA - ever	89 (100)
SLEDAI-2K score H, median (range)	9.6 (0-28)
SLEDAI-2K score L, median (range)	2.1 (0-14)
Treatment H/L, N/N	
HCQ/CQ	40/59
Cyc	4/0
Aza	8/22
Beli	0/4
Mtx	5/3
MMF	4/19
Rtx	1/4
Cic	3/1
GC - median dose, mg, H/L	10/5

SD: standard deviation; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; dsDNA: double-stranded DNA; APS: antiphospholipid syndrome; anti-Sm: anti-Smith; ANA: antinuclear antibodies; HCQ: hydroxychloroquine; CQ: chloroquine; Cyc: cyclophosphamide; Aza: azathioprine; Bel: belimumab, Mtx: methotrexate; MMF: mycophenolate mofetil; Rtx: rituximab; Cic: ciclosporin A; GC: glucocorticoids (prednisolone).

levels of anti-GPV were found to correlate positively with average SLEDAI-2K score ($r=0.34$; 95% confidence interval [CI]: 0.13-0.52; $P=0.0012$), negatively with average levels of complement protein C3 and C4 ($r=-0.28$; 95% CI: -0.47 to -0.070; $P=0.0079$ and $r=-0.40$; 95% CI: -0.57 to -0.21; $P<0.0001$) and negatively with average platelet count ($r=-0.24$; 95% CI: -0.43 to -0.027; $P=0.024$) (Table 2; *Online Supplementary Figure S1*).

Anti-phospholipid antibodies are correlated with disease activity

IgG and IgM antibodies targeting β 2 glycoprotein 1 (β 2GPI), cardiolipin (CL), phosphatidylserine/prothrombin (PS/PT), and annexin V (AV) were also detected in H and L samples using ELISA (Figure 2B, C). All IgG and IgM anti-PL antibodies were detected at higher levels at SLEDAI-2K H compared with L. Average levels of IgG type anti-cardiolipin (anti-CL), anti- β 2 glycoprotein 1 (anti- β 2GPI), anti-PS/PT and anti-AV also correlated significantly with SLEDAI-2K, but the correlation was less strong than anti-GPV (Figure S1; *Online Supplementary Table S2*).

Twenty-four thromboembolic events were recorded during extended follow-up

All patient records were reviewed for the occurrence of thromboembolic events. This extended follow-up time after the collection of the first serum sample was 20 years. Events occurring prior to this point were excluded. During the whole period, 24 patients experienced thromboembolic events, including eight deep vein thrombosis (DVT), seven myocardial infarction (MI), five cerebrovascular insult (CVI), two pulmonary embolism (PE), one branch retinal vein occlusion and one pathology confirmed case of kidney fibrin thrombus. The average time to the thrombotic event was 4 years. Three cases were excluded: the first had DVT as-

sociated with orthopedic surgery, the second had DVT and was later confirmed to have widespread ovarian malignancy and the third had pulmonary embolism associated with surgery and lymphoma. A detailed distribution of events and relative, average antibody titers is presented in *Online Supplementary Table S3*.

Anti-glycoprotein V, complement C3 and disease duration were identified as independent predictors of thrombosis

Potential predictors of thrombosis were assessed in a multivariable Cox-regression analysis. Evaluation of antibodies (IgG and IgM aPL, anti-GP), clinical variables (SLEDAI-2K, platelet count, CRP, C3, C4), clinical characteristics (sex, previous nephritis, age at diagnosis, disease duration), and baseline treatment (antimalarial use, prednisolone ≥ 10 mg/day) identified five predictors significantly associated with thrombotic outcomes (Figure 3). Anti-GPV (hazard ratio [HR]=2.17; 95% CI: 1.39-3.36; $P=0.001$) and C3 (HR=2.16; 95% CI: 1.32-3.54; $P=0.002$) showed the strongest predictive effect, each associated with an approximately 2.2-fold increased risk per SD increase. Disease duration (HR=1.07; 95% CI: 1.01-1.12; $P=0.01$) was also associated with an increased risk, equivalent to 7% per year. Ongoing prednisolone treatment (HR=2.5; 95% CI: 0.90-7.2; $P=0.08$) and IgM anti-PS/PT antibodies (HR=3.2; 95% CI: 0.97-10.9, $P=0.08$) showed a trend towards increased risk but did not reach statistical significance. In contrast, female sex (HR=0.25; 95% CI: 0.09-0.69; $P=0.008$) as well as antimalarial treatment at baseline (HR=0.40; 95% CI: 0.16-0.99; $P=0.046$), was associated with a protective effect of 75% and 60% respectively. Neither aPL, anti-GPIIb/IIIa, nor anti-GPIb/IX showed any independent association with increased risk of thrombotic outcome. Kaplan-Meier analyses of thrombosis-free survival showed largely overlapping curves across strata defined by autoantibody levels (anti-GP and aPL)

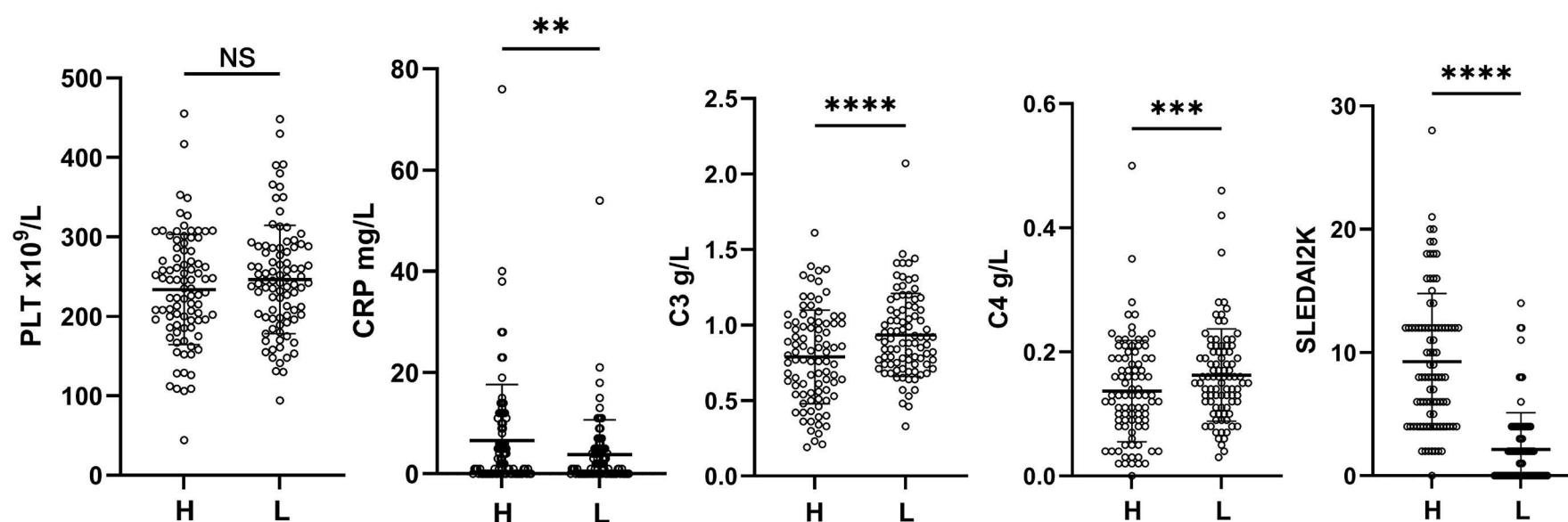


Figure 1. Clinical laboratory measurements and systemic lupus erythematosus disease activity index 2000. Patients had equal platelet counts (PLT) during high (H) and low (L) disease activity, but significantly higher C-reactive protein (CRP) and lower complement C3 and C4 levels at the first sample. The average systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) was 9.6 during H and 2.1 during L. * $P<0.05$; ** $P<0.01$; *** $P<0.001$; **** $P<0.0001$ by Wilcoxon signed-rank test. Mean $\pm$ standard deviation: CRP 6.6 ± 11.1 versus 3.7 ± 6.9 ; C3 0.79 ± 0.31 versus 0.93 ± 0.27 ; C4 0.14 ± 0.08 versus 0.16 ± 0.07 .

and across tertiles of complement levels (*Online Supplementary Figure S2*). Restricted mean thrombosis-free survival estimates are provided in *Online Supplementary Table S4A*. Consistent with this, global between-group comparisons using Mantel-Cox, Gehan-Breslow-Wilcoxon, and Tarone-Ware tests did not show statistically significant differences for anti-GPIIb/IIIa, anti-GPV, anti-GPIb/IX, or C3/C4 (*Online Supplementary Table S4B*). In contrast, aCL IgM showed significant differences across all three tests (all $P=0.03$). Given that persistent high aPL titers confer the

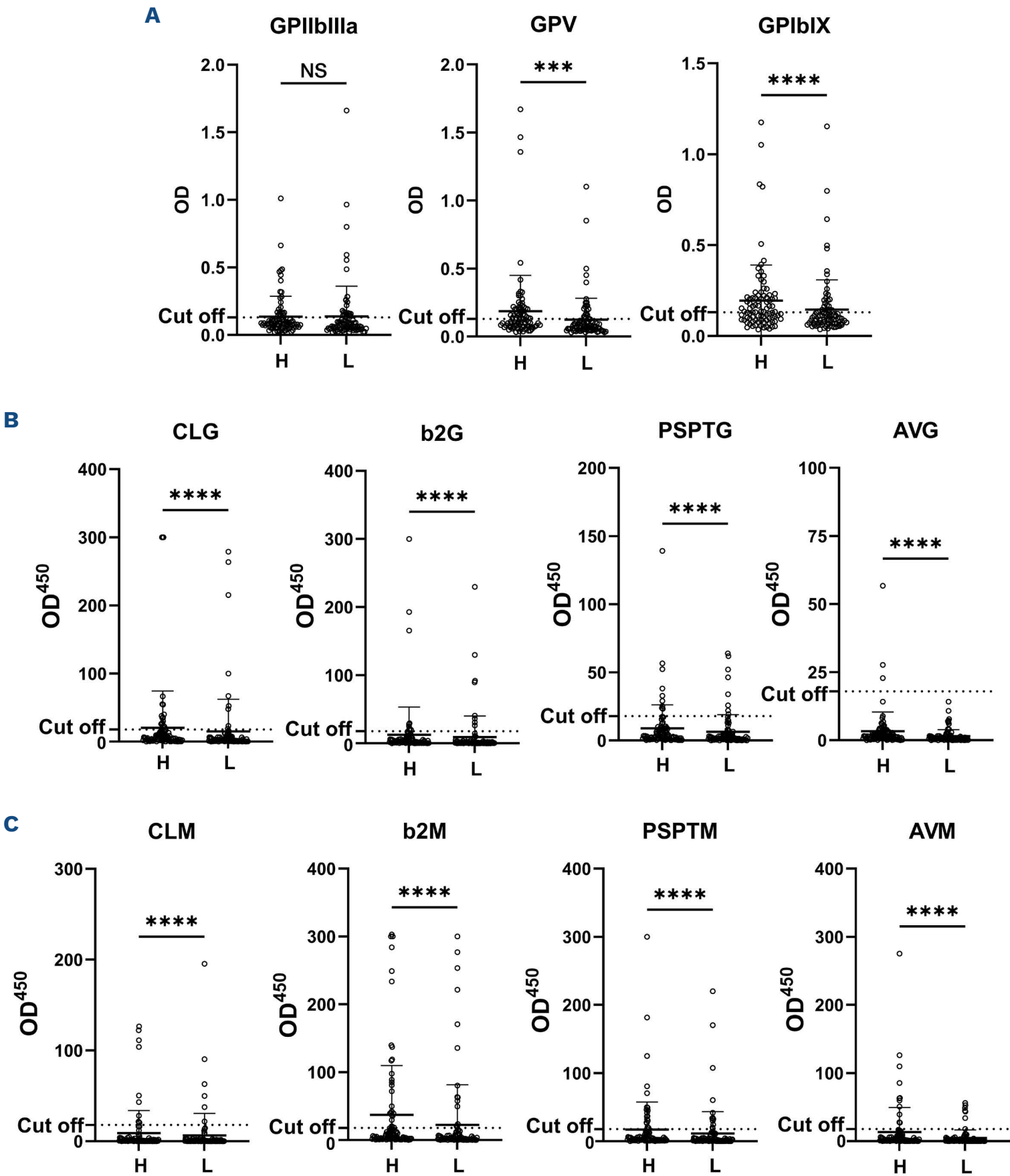


Figure 2. Anti-platelet glycoprotein and antiphospholipid antibodies in systemic lupus erythematosus at high- and low-disease activity. Antibodies targeting glycoprotein (GP)IIb/IIIa, GPV, and GPIb/IX were detected in serum from patients during high (H) and low (L) systemic lupus erythematosus disease activity index 2000 (SLEDAI-2K) (A), using the monoclonal antibody immobilization of platelet antigens (MAIPA) assay. Anti-GPIIb/IIIa antibodies showed similar prevalence at high and low activity (27% and 26%, respectively), whereas anti-GPV (48% vs. 24%) and anti-GPIb/IX (49% vs. 27%) were increased during high activity. (B, C) Immunoglobulin (Ig)G and IgM antibodies targeting β 2GPI, cardiolipin (CL), phosphatidylserine/prothrombin (PS/PT), and annexin V (AV) were measured by enzyme-linked immunosorbent assay. All aPL were detected at higher levels during high-disease activity. Assay cut-offs: MAIPA=0.13; ELISA=18. *** $P<0.001$; **** $P<0.0001$ by Wilcoxon signed-rank test. OD: optical density.

strongest thrombotic risk, we tested the predictive value of persistent high-titer aPL (≥ 40 U/mL at 2 time points). In this sensitivity analysis, we observed a strong association with outcome (HR=15.8; 95% CI: 4.38–57.11; $P=0.00002$), consistent with previous studies, though CI were wide due to the low number of positive patients. Lifestyle-related factors such as smoking, obesity, hypertension, and physical inactivity could not be reliably extracted from available clinical records.

Platelet count and thrombocytopenia

Median platelet count remained within the normal range in both high- and low-disease activity states and were similar across anti-GP antibody strata (Online Supplementary Table S5). Accordingly, thrombocytopenia was infrequent and did not show an apparent association with thrombotic events (Online Supplementary Table S6). Average anti-GPV levels showed a modest inverse Spearman correlation with average platelet counts ($r=-0.24$; 95% CI: -0.43 to -0.027; $P=0.024$).

Discussion

Platelets in SLE exhibit a chronically activated phenotype, with increased P-selectin expression, phosphatidylserine

exposure and activated GPIIb/IIIa, and an enhanced propensity to aggregate *ex vivo*.^{11,26–28} Thrombotic complications remain an incompletely understood clinical challenge, particularly among aPL-negative patients.⁴ In this study, anti-GPIIb/IIIa, anti-GPV and anti-GPIb/IX antibodies were common during active SLE, with anti-GPV and anti-GPIb/IX increasing with disease activity, whereas anti-GPIIb/IIIa remained stable. To our knowledge, anti-GPV has not been investigated in SLE prior to this study. Despite frequent anti-GP antibodies, platelet counts remained within the normal range during both disease states, although average anti-GPV levels showed a modest inverse correlation with platelet count, suggesting compensated platelet consumption. In multivariate models, average anti-GPV antibody levels, C3, and disease duration independently predicted thrombotic events, whereas antimalarial therapy and female sex were protective. No aPL isotypes remained independently associated with thrombosis. Notably, aCL IgM showed significant differences in unadjusted Kaplan-Meier analyses, but this signal did not persist in multivariable models, suggesting confounding or limited power. Kaplan-Meier and RMST analyses showed largely overlapping thrombosis-free survival curves across all antibody strata and complement tertiles, likely reflecting limited power and fluctuating an-

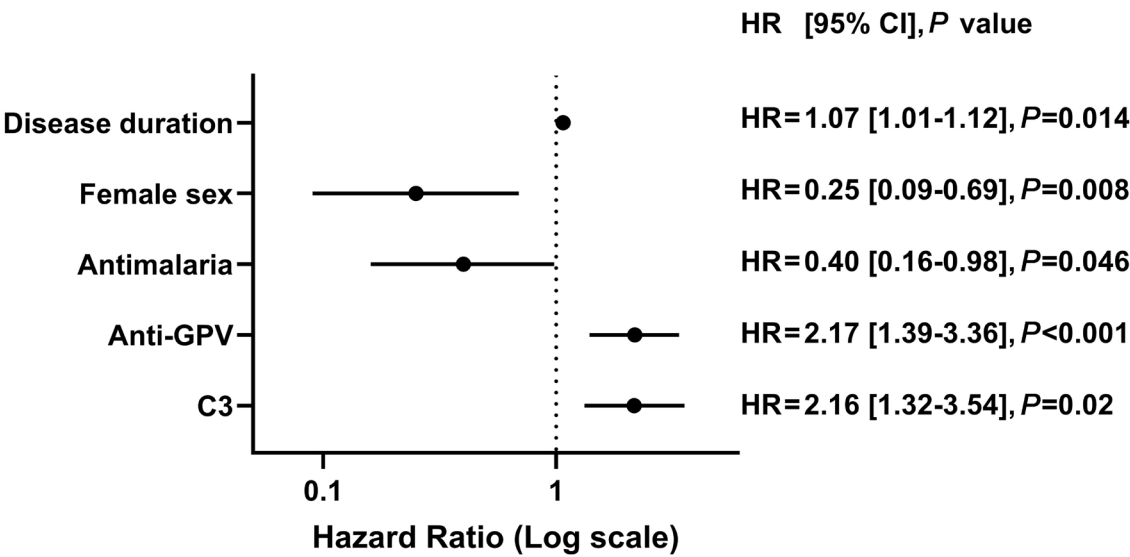


Figure 3. Predictors of thrombotic events in multivariate Cox regression analysis. Increased risk was observed for disease duration (hazard ratio [HR]=1.07; 95% confidence interval [CI]: 1.01-1.12; $P=0.014$), anti-GPV (HR=2.17; 95% CI: 1.39-3.36; $P=0.001$), and C3 (HR=2.16; 95% CI: 1.32-3.54; $P=0.002$), whereas female sex (HR=0.25; 95% CI: 0.09-0.69; $P=0.008$) and antimalarial treatment (HR=0.40; 95% CI: 0.16-0.99; $P=0.046$) were protective.

Table 2. Correlations between average anti-glycoprotein, platelet, C-reactive protein, complement C3, C4 and systemic lupus erythematosus disease activity index 2000.

Spearman	GP IIb/IIIa			GP V			GP Ib/IX		
	r	95% CI	P	r	95% CI	P	r	95% CI	P
PLT	-0.08	-0.29 to 0.13	0.44	-0.24	-0.43 to -0.027	0.024	-0.13	-0.34 to 0.083	0.21
CRP	0.06	-0.16 to 0.27	0.60	0.06	-0.16 to 0.27	0.60	0.12	-0.098 to 0.33	0.27
C3	-0.11	-0.32 to 0.10	0.29	-0.28	-0.47 to -0.070	0.0079	-0.11	-0.32 to 0.11	0.30
C4	-0.20	-0.39 to 0.020	0.07	-0.40	-0.57 to -0.21	<0.0001	-0.16	-0.36 to 0.054	0.13
SLEDAI-2K	0.16	-0.053 to 0.37	0.13	0.34	0.13-0.52	0.0012	0.14	-0.078 to 0.34	0.19

PLT: platelet count; GP: glycoprotein; C3: complement protein C3; C4: complement protein C4; CI: confidence interval; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000.

tibody expression. Our findings align with studies showing complement-platelet crosstalk in SLE and population-based data linking C3 levels to arterial and venous thrombosis.^{4,29,30} The anti-GPV associated thrombotic risk, reduced complement levels and minimal thrombocytopenia differ from the clinical pattern in primary ITP.³¹ Older ITP studies have described divergent functional effects of anti-GP antibodies, resulting in activating or inhibitory effects on platelets depending on epitope specificity; antibody cross-linking capacity; FcγRIIa engagement or the presence of local modulating factors.³² Activating factors include immune complexes that can engage FcγRIIa and activated complement, resembling the inflammatory environment found in the circulation of patients with active SLE.¹⁰ Although GPV belongs to the platelet GPIb-IX-V receptor complex, the subunits are distinct glycoproteins that may be differentially targeted by autoantibodies. Thus, anti-GPV and anti-GPIb/IX responses may occur independently despite belonging to the same receptor complex.^{17,33} Recent mechanistic work supports a role for GPV in thrombus regulation. GPV-deficient mice exhibit a pro-thrombotic phenotype, and soluble GPV (sGPV), released after thrombin cleavage, binds fibrin and locally inhibits thrombin activity, limiting thrombus propagation.^{34,35} Thus, if anti-GPV reduces availability or function of sGPV, it may shift the balance towards increased thrombin activity and fibrin formation. Such an effect may be amplified in SLE, where platelets are pre-activated and exposed to persistent complement activation and immune complexes. Strengths of this study include systematic MAIPA profiling, longitudinal design and adjustment for treatment. Limitations include incomplete data on conventional cardiovascular risk factors, lack of systematic LA testing and potential selection bias from early thrombosis or long-term anticoagulation. Validation in larger, prospective

cohorts is needed.

In conclusion, anti-GPV antibodies emerge as potential biomarkers of thrombotic risk in SLE, independent of aPL, and our findings highlight a potentially underrecognized pro-thrombotic role of complement C3. Integrating platelet-directed antibodies into risk assessment models may improve prediction of thrombotic complications in SLE.

Disclosures

No conflicts of interest to disclose.

Contributions

PL conceived the study, curated clinical data, conducted the statistical analyses and wrote the first draft of the manuscript. PL and AAB developed the study design and oversaw the project. RKap, LP and JWS provided expertise on platelet autoantibodies/MAIPA methodology and contributed to interpretation of the results. AJ, RKah and EG contributed to clinical interpretation and manuscript revision. All authors critically reviewed the manuscript, provided feedback, and approved the final version.

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Data-sharing statement

The data underlying this article are not publicly available due to privacy or ethical restrictions.

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