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

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AI statement

Artificial intelligence (AI), specifically ChatGPT, was used to improve syntax, grammar and clarity of the text. All scientific content, data interpretation, figures, tables, and references were generated and selected by the authors. The final manuscript was thoroughly reviewed and edited by the authors to ensure accuracy and integrity.

Data availability

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

Author contribution

P.L. conceived the study, curated clinical data, conducted the statistical analyses and wrote the first draft of the manuscript. P.L. and A.A.B. developed the study design and oversaw the project. R.Kap., L.P. and J.W.S. provided expertise on platelet autoantibodies/MAIPA methodology and contributed to interpretation of the results. A.J., R.Ka. and E.G. contributed to clinical interpretation and manuscript revision. All authors critically reviewed the manuscript, provided feedback, and approved the final version.

Disclosures

The authors declare that they have no conflicts of interest related to this work.

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 ACR 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 (MAIPA) assay, while IgM/IgG anti-phospholipid (anti-PL), anti-β2 Glycoprotein 1 (aβ2GP1), anti-cardiolipin (anti-CL), anti-phosphatidylserine/prothrombin complex (anti-PS/PT) and anti-annexin V (anti-AV) antibodies were measured by ELISA.

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 (~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 (HR 2.17, 95% 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 underlaying 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 antiphospholipid syndrome (APS)(12), characterized by recurrent venous and/or arterial thrombosis and pregnancy morbidity in the presence of anti-phospholipid antibodies (aPL): anticardiolipin (anti-CL), anti-β2 glycoprotein 1 (anti-β2GPI), and lupus anticoagulant (LA).

However, known aPL do not 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 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 its potential clinical significance unexplored.

The aims of this study were to: (1) determine the frequency of anti-GP antibodies in patients with high and low disease activity; (2) assess their association with thrombocytopenia (< $150x10^9$/L); and (3) 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, was 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 -80ºC 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.

Anti-GP and aPL

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-β2GPI and aCL) antibodies and non-criteria aPL (IgG/IgM anti-PS/PT and anti-AV), were analyzed using commercially available 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 (**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 cut-off), 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 sample (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 (± 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 vs. 0.93 ± 0.27 g/L, and C4 levels 0.14 ± 0.08 vs. 0.16 ± 0.07 g/L. Platelet counts were similar: 233.8 ± 69.3 vs. 246.3 ± 68.3 x 10^9/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 (DMARDs), 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 vs L, see Suppl. **Table S1**.

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

Antiphospholipid antibodies correlated with disease activity

IgG and IgM antibodies targeting beta 2 glycoprotein 1 (β_2GP1), 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-β2 glycoprotein 1 (anti-β2GPI), anti-PS/PT and anti-AV also correlated significantly with SLEDAI-2K, but the correlation was less strong than anti-GPV (**Figure S1** and **Table S2).**

Twenty-four thromboembolic events 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 four years. Three cases were excluded: the first had DVT associated 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 Supplementary **Table S3**.

Anti-GPV, C3 and disease duration 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 (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 standard deviation (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) and across tertiles of complement levels (**Figure S2**). Restricted mean thrombosis-free survival estimates are provided in **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 (**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 strongest thrombotic risk, we tested the predictive value of persistent high-titer aPL (≥40 U/ml at two 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 literature, though confidence intervals 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 (**Table S5**). Accordingly, thrombocytopenia was infrequent and did not show an apparent association with thrombotic events (**Table S6**). Average anti-GPV levels showed a modest inverse Spearman correlation with average platelet count (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 antibody 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.

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Table 1. Characteristics of SLE patients

Number, n	89
Female, n (%)	78 (88%)
Caucasian, n (%)	81 (91%)
Age at diagnosis, mean (+/- SD), years	38 (15)
Age, sample 1 (years) mean	43.2
Age, sample 2 (years) mean	48.0
Nephritis, n (%)	42 (47%)
Disease duration, median (years)	2
APS diagnosis, n (%)	7 (8%)
Autoantibodies	
Anti-dsDNA, n (%)	63 (71%)
anti-Sm, n (%)	11 (12%)
ANA (ever), n (%)	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)	
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 prednisolone, mg)	10/5

Abbreviations: HCQ = Hydroxychloroquine, CQ = Chloroquine, Cyc = Cyclophosphamide, Aza = Azathioprine, Bel = Belimumab, Mtx = Methotrexate, MMF = Mycophenolate mofetil, Rtx = Rituximab, Cic = Ciclosporin A, GC = Glucocorticoids (Prednisolone).

Table 2. Correlations between average anti-GP, PLT, CRP, complement C3, C4 and SLEDAI2K

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

Abbreviations: PLT=platelet count. C3 = complement protein C3. C4 = complement protein C4.

Figure 1. Clinical laboratory measurements and SLEDAI-2K.
Patients had equal platelet counts (PLT) during high (H) and low (L) disease activity, but significantly higher CRP and lower complement C3 and C4 levels at the first sample. The average 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 ± SD: CRP 6.6 ± 11.1 vs. 3.7 ± 6.9; C3 0.79 ± 0.31 vs. 0.93 ± 0.27; C4 0.14 ± 0.08 vs. 0.16 ± 0.07.

Figure 2. Anti-platelet glycoprotein and antiphospholipid antibodies in SLE at high and low disease activity.
Antibodies targeting GPIIb/IIIa, GPV, and GPIb/IX were detected in serum from patients during high (H) and low (L) SLEDAI-2K (A), using the 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) IgG and IgM antibodies targeting β2GPI, cardiolipin (CL), phosphatidylserine/prothrombin (PS/PT), and annexin V (AV) were measured by ELISA. 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.

Figure 3. Predictors of thrombotic events in multivariate Cox regression analysis.
Increased risk was observed for disease duration (HR 1.07, 95% 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.

Figure 1

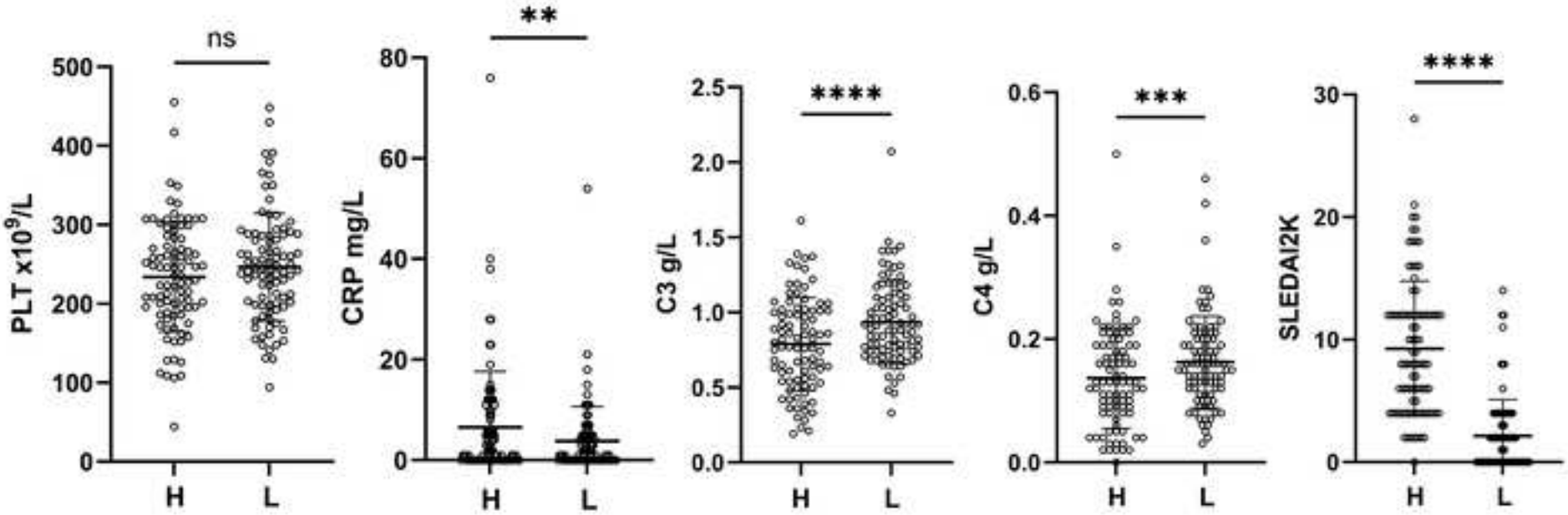


Figure 2

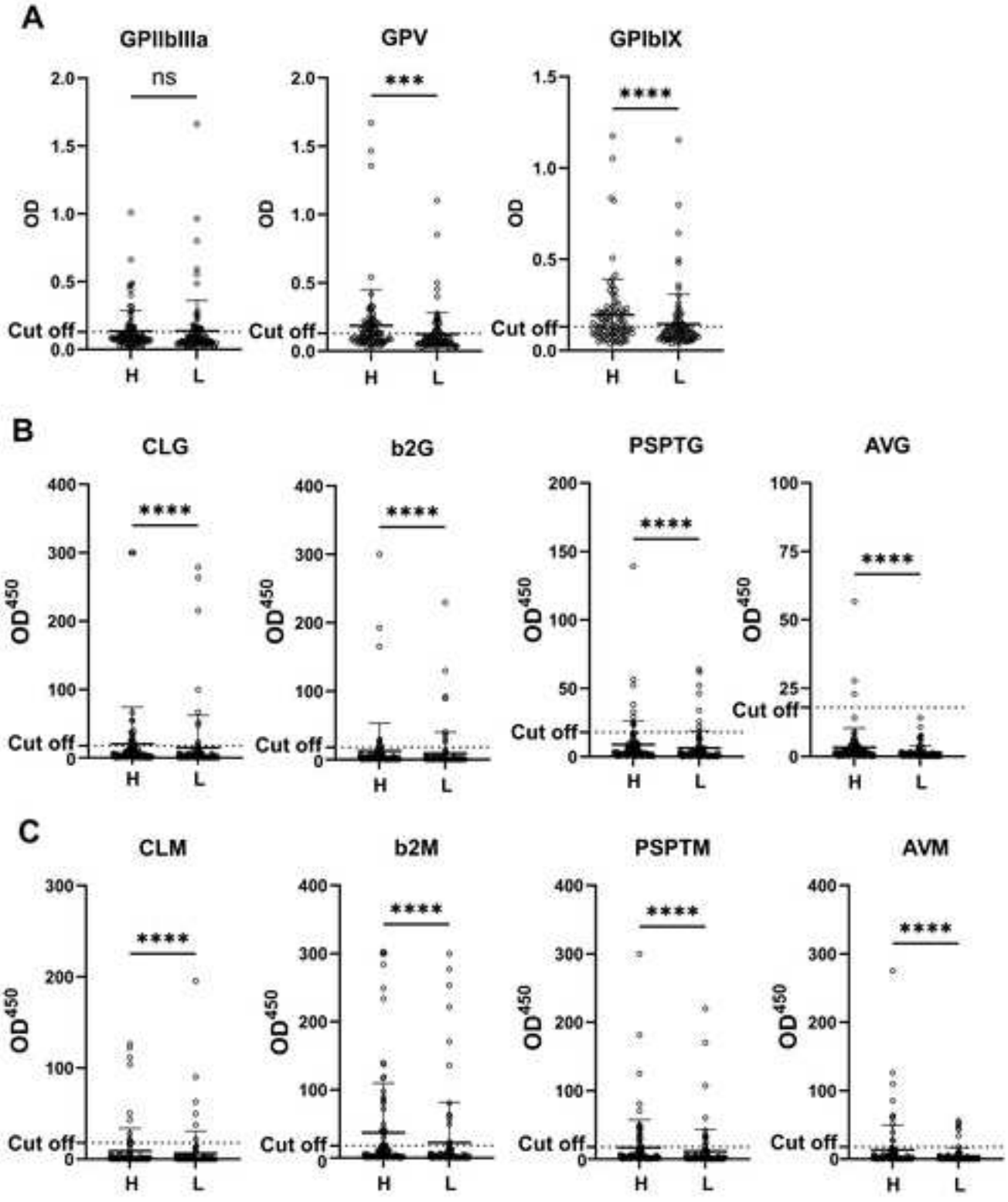
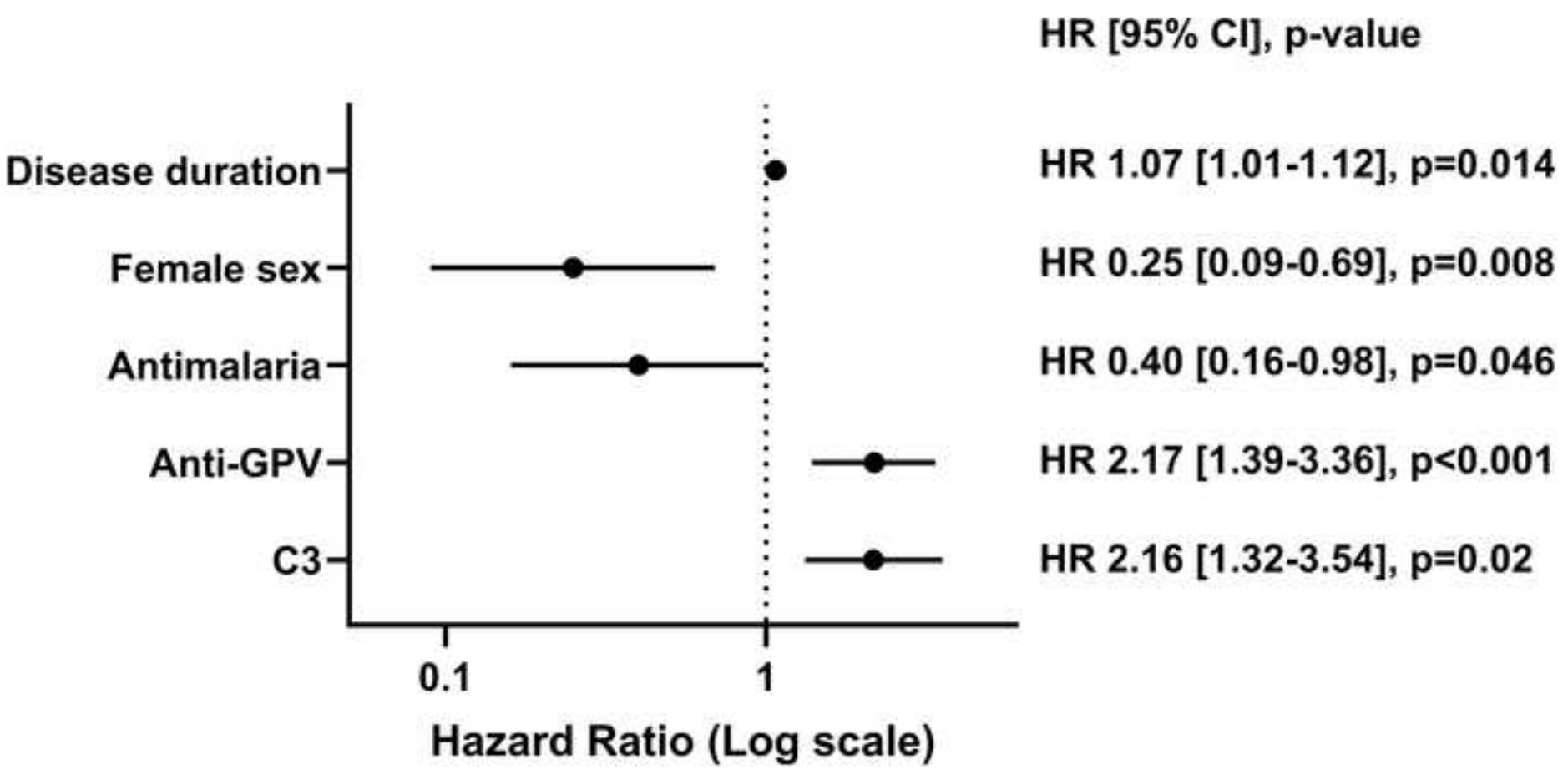

A
GPIIbIIIa
GPV
GPIbIX
ns
***
****
OD
Cut off
H
L
B
CLG
b2G
PSPTG
AVG
****
OD450
C
CLM
b2M
PSPTM
AVM

Figure 3


HR [95% CI], p-value
Disease duration
Female sex
Antimalaria
Anti-GPV
C3
HR 1.07 [1.01-1.12], p=0.014
HR 0.25 [0.09-0.69], p=0.008
HR 0.40 [0.16-0.98], p=0.046
HR 2.17 [1.39-3.36], p<0.001
HR 2.16 [1.32-3.54], p=0.02
0.1
1
Hazard Ratio (Log scale)

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

Supplementary Methods

Stability of indirect MAIPA and long-term sample storage

MAIPA analyses were performed on serum samples stored at -80 °C for up to approximately 25-30 years. Previous work has demonstrated a strong correlation between indirect and direct MAIPA optical density values for platelet autoantibodies, including anti-GPV (1). In preliminary observations using samples stored at -20 °C, up to two freeze-thaw cycles did not affect indirect MAIPA results (Porcelijn, Kapur et al., unpublished observations). Although long-term storage at -20 °C may reduce detectability of platelet autoantibodies, this has not been formally assessed for samples stored at -80 °C. Any storage-related effects in the present study would therefore be expected to bias results toward underestimation rather than false-positive detection.

Reference

1. Porcelijn L, Schmidt DE, Oldert G, et al. Evolution and Utility of Antiplatelet Autoantibody Testing in Patients with Immune Thrombocytopenia. Transfusion medicine reviews. 2020;34(4):258-69.

Supplemental tables

Supplemental table S1. Distribution of SLEDAI-2K items during high (H) and low (L) disease activity states

SLEDAI-2K (points)	H (n)	H %	L (n)	L %
Seizure (8)	0	0%	0	0%
Psychosis (8)	0	0%	0	0%
Organic brain syndrome (8)	0	0%	0	0%
Visual disturbance (8)	1	1%	0	0%
Cranial nerve disorder (8)	0	0%	0	0%
Lupus headache (8)	0	0%	0	0%
CVA (8)	0	0%	0	0%
Vasculitis (8)	1	1%	0	0%
Arthritis (4)	31	35%	4	4%
Myositis (4)	0	0%	0	0%
Urinary Casts (4)	17	19%	1	1%
Hematuria (4)	33	37%	3	3%
Proteinuria (4)	39	44%	4	4%
Pyuria (4)	3	3%	0	0%
Rash (2)	31	35%	8	9%
Alopecia (2)	6	7%	2	2%
Oral/Nasal ulcer (2)	13	15%	2	2%
Pleuritis (2)	1	1%	0	0%
Pericarditis (2)	0	0%	0	0%
Low complement (2)	53	60%	34	38%
Anti-DNAab (2)	45	51%	20	22%
Fever (1)	6	7%	1	1%
Thrombocytopenia (1)	1	1%	1	1%
Leukopenia (1)	8	9%	4	4%

Table S2. Correlation between average SLEDAI-2K and anti-phospholipid antibodies

		SLEDAI-2K		
Spearman		**r**	**CI (95%)**	**p**
CL	IgG	**0.32**	**0.11 - 0.50**	**0.0023**
	IgM	0.01	-0.21 - 0.22	0.96
β2GP1	IgG	**0.31**	**0.11 - 0.49**	**0.0029**
	IgM	0.08	-0.14 - 0.29	0.45
PS/PT	IgG	**0.33**	**0.12 - 0.51**	**0.0018**
	IgM	-0.07	-0.28 - 0.15	0.53
AV	IgG	**0.28**	**0.074 - 0.47**	**0.0072**
	IgM	0.00	-0.21 - 0.22	0.97

Table S3. Thrombotic events and corresponding average antibody titers (anti-GP and aPL) measured by MAIPA and ELISA

Thrombotic events include deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), cerebrovascular insult (CVI), venous thrombosis (VT) and microthrombosis (MT). Anti-GP antibodies: GP IIb/IIIa, GPV, GPIb/IX. Anti-PL antibodies: anti-cardiolipin (CL), anti-β2-glycoprotein I (b2), anti-phosphatidylserine/prothrombin complex (PSPT), anti-annexin V (AV). Diagnostic methods: US = Ultrasound, MRI = Magnetic Resonance Imaging, CT = Computed Tomography. For the purpose of visual comparison between MAIPA and ELISA antibody titers, min-max normalization was applied to each antibody titer value (anti-GP and aPL) for each assay. All normalized values range between 0 to 1, where 0 represents the minimum observed value and 1 represents the maximum observed value. Shades of red indicate relative levels of anti-GP and shades of green aPL. *normalized values were used for graphical representation in figures and were not used in any statistical analyses.

Patient	Sex	Event (type)	Time to event (years)	Age at diagnosis	Age at baseline	GP IIb/IIIa*	GPV*	GP Ib/IX*	CL (IgG)*	CL (IgM)*	b2 (IgG)*	b2 (IgM)*	PSPT (IgG)*	PSPT (IgM)*	AV (IgG)*	AV (IgM)*	SLEDAI-2K H	SLEDAI-2K L	Thrombosis type	Detection method
1	M	MT	7	39	52	0.17	0.17	0.20	0.14	0.12	0.06	0.70	0.15	0.55	0.02	0.21	6	2	VT: Left, branch retinal v occlusion	Ocular exam and OCT
2	F	DVT	5	49	60	0.05	0.07	0.09	0.07	0.00	0.02	0.03	0.01	0.01	0.00	0.00	4	0	PE: decr perf right lung and left lower lobe	Ventilation/perfusion (V/Q) scan
3	F	CVI	7	46	48	0.00	0.01	0.02	0.00	0.01	0.00	0.01	0.00	0.01	0.00	0.01	2	0	CVI: Multiple vascular lesions	MRI
4	F	MI	2	50	71	0.03	0.07	0.07	0.02	0.01	0.01	0.02	0.02	0.01	0.01	0.01	4	0	MI: Right dominant coronary artery	Coronary angiography
5	F	DVT	2	32	48	0.12	0.27	0.27	0.20	0.00	0.12	0.02	0.09	0.01	0.04	0.00	19	2	DVT: lower extremity	US
6	F	CVI	0	55	55	0.03	0.12	0.28	0.01	0.06	0.02	0.25	0.01	0.06	0.00	0.06	8	0	CVI	CT and MRI
7	F	MI	3	28	37	0.04	1.00	0.71	0.02	0.00	0.17	0.02	0.01	0.00	0.00	0.01	12	2	MI: Thrombosis in LAD	Coronary angiography
8	F	MI	4	67	67	0.04	0.04	0.10	0.02	0.01	0.01	0.06	0.01	0.10	0.01	0.02	4	0	MI	Coronary angiography
9	F	DVT	0	45	45	0.27	0.03	0.05	0.01	0.01	0.00	0.07	0.13	0.89	0.00	0.02	8	0	DVT	US
10	F	MT	1	31	31	0.49	0.60	0.56	0.01	0.00	0.01	0.01	0.03	0.00	0.00	0.00	19	11	MT: fibrin thrombus	Kidney biopsy, histology
11	F	DVT	9	25	25	0.41	0.55	0.53	0.05	0.10	0.04	0.57	0.05	0.26	0.02	0.52	12	2	DVT: left v. fibularis	US
12	F	MI	7	24	35	0.06	0.27	0.15	0.09	0.01	0.03	0.04	0.05	0.04	0.01	0.02	8	2	MI: LAD occulsion	Coronary angiography
13	M	DVT	0	26	26	0.06	0.13	0.07	0.01	0.00	0.01	0.01	0.01	0.00	0.00	0.00	12	0	DVT: right v. femoralis	US and CT
14	F	DVT	0	16	19	0.19	0.11	0.20	0.01	0.06	0.01	0.31	0.01	0.08	0.00	0.05	5	2	DVT: left v. poplitea	US
15	F	MI	9	59	59	0.02	0.04	0.02	0.01	0.00	0.00	0.00	0.00	0.01	0.00	0.01	4	0	MI: LAD occlusion	Coronary angio
16	F	DVT	0	37	67	0.03	0.05	0.09	0.01	0.00	0.00	0.01	0.00	0.00	0.00	0.00	12	2	DVT: right lower extr	US
17	F	CVI	7	62	70	0.04	0.13	0.35	0.00	0.07	0.01	0.28	0.00	0.09	0.00	0.07	12	4	CVI: ischemic lesion frontal right	CT
18	F	PE	3	20	34	0.17	0.07	0.08	0.16	0.00	0.06	0.03	0.02	0.00	0.01	0.01	14	0	PE: right lung, lower lobe and left basal	Ventilation/perfusion (V/Q) scan
19	F	DVT	12	40	52	0.06	0.20	0.15	0.02	0.00	0.00	0.02	0.01	0.01	0.01	0.01	5	2	DVT	US
20	M	MI	5	46	46	0.03	0.02	0.01	0.04	0.06	0.03	0.27	0.09	0.09	0.01	0.08	8	0	MI	Coronary angiography
21	F	PE	0	50	57	0.06	0.06	0.09	0.03	0.00	0.01	0.00	0.01	0.01	0.01	0.00	7	0	PE	Ventilation/perfusion (V/Q) scan
22	M	MI	2	54	56	0.05	0.11	0.11	0.00	0.00	0.00	0.00	0.00	0.01	0.00	0.00	2	0	MI: LAD occlusion	Cor Angiography
23	M	CVI	9	77	77	0.13	0.13	0.14	0.02	0.03	0.01	0.25	0.02	0.09	0.01	0.13	8	2	CVI	CT
24	F	CVI	12	47	49	0.14	0.20	0.28	0.97	0.27	1.00	0.98	0.10	0.19	0.06	0.24	11	4	CVI	CT

Table S4. Thrombosis-free survival analyses according to platelet autoantibodies, antiphospholipid antibodies, and complement levels in SLE.

(A) Restricted mean thrombosis-free survival time (RMST) with 95% confidence intervals for each group. Patients were stratified as negative, low positive (below median), or high positive (above median) for each antibody; complement C3 and C4 were categorized into tertiles (low/mid/high). Time is expressed in years; thrombotic events were coded as events and all others as censored. RMST was truncated at the largest observed follow-up time due to tail censoring.

(B) Global between-group comparisons (df=2) using three standard tests: logrank (Mantel–Cox), Gehan–Breslow–Wilcoxon, and Tarone–Ware (intermediate weighting). *NE indicates not estimable due to sparse group size (e.g., anti-annexin V IgG with only one positive sample), precluding meaningful stratified estimation.*

A) RMST (95% CI) per group

Group	GPIIbIIIa	GPV	GPIbIX		C3	C4		
Neg	25.13 (22.09-28.17)	26.28 (23.08-29.48)	20.19 (17.65-22.73)	Low	19.78 (16.75-22.80)	20.03 (17.24-22.82)		
Low	10.54 (6.22-14.86)	16.48 (12.01-20.94)	24.08 (18.26-29.89)	Mid	25.96 (21.63-30.30)	23.98 (19.20-28.75)		
High	18.97 (13.96-23.99)	15.08 (10.34-19.83)	14.81 (10.05-19.56)	High	16.24 (12.41-20.07)	17.55 (13.76-21.34)		
Group	**CLg**	**CLm**	**b2g**	**b2m**	**PSPTg**	**PSPTm**	**AVg**	**AVm**
Neg	24.75 (21.85-27.66)	25.22 (22.38-28.05)	24.26 (21.42-27.10)	19.58 (17.18-21.98)	24.76 (21.93-27.59)	25.63 (22.77-28.49)	NE	24.95 (22.10-27.81)
Low	16.20 (9.20-23.20)	9.67 (1.86-17.47)	11.25 (1.64-20.86)	27.42 (21.58-33.25)	15.17 (7.38-22.96)	13.00 (6.97-19.03)	NE	12.00 (4.75-19.25)
High	15.11 (7.95-22.27)	15.89 (11.39-20.40)	20.75 (16.93-24.57)	13.65 (8.66-18.64)	13.87 (4.40-23.33)	13.91 (8.54-19.27)	NE	14.94 (10.00-19.89)

B) Overall comparisons (df=2)

	GPIIbIIIa		GPV		GPIbIX		C3		C4	
Test (SPSS)*	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p
Logrank (Mantel-Cox)	5.32	0.07	4.26	0.12	3.69	0.16	4.02	0.13	1.25	0.54
Gehan-Breslow-Wilcoxon	4.10	0.13	2.41	0.30	2.88	0.24	3.24	0.20	2.09	0.35
Tarone-Ware	4.65	0.10	3.22	0.20	3.25	0.20	3.62	0.16	1.66	0.44

	CLg		CLm		b2g		b2m		PSPTg		PSPTm		AVg		AVm	
Test (SPSS)*	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p	χ^2	p
Logrank (Mantel-Cox)	1.59	0.45	7.04	0.030	1.90	0.39	4.82	0.09	2.31	0.32	5.61	0.06	0.36	0.55	3.53	0.17
Gehan-Breslow-Wilcoxon	1.34	0.51	7.05	0.029	2.66	0.27	3.71	0.16	2.03	0.36	4.04	0.13	0.34	0.56	1.51	0.47
Tarone-Ware	1.45	0.49	7.07	0.029	2.30	0.32	4.24	0.12	2.15	0.34	4.81	0.09	0.36	0.55	2.37	0.31

Table S5. Platelet counts and thrombocytopenia by anti-platelet glycoprotein antibody status across disease activity states

Platelet counts and frequencies of thrombocytopenia stratified by anti-platelet glycoprotein antibody status and disease activity state. Data are shown separately for (A) anti-GPIIb/IIIa, (B) anti-GPV, and (C) anti-GPIb/IX. Frequencies indicate the number of samples positive/negative for each antibody in the high- and low-disease activity states. Platelet counts are presented as median (interquartile range, IQR). Thrombocytopenia is summarized using two cut-offs (PLT <150×10⁹/L and PLT <100×10⁹/L), expressed as n/N (%) within each antibody stratum and disease activity state. *PLT = platelet count. High/Low denote the two disease activity states as defined in the main manuscript.*

A)

Antibody	GPIIb/IIIa+		GPIIb/IIIa-	
Disease activity	High	Low	High	Low
Frequency	24/89 (27%)	23/89 (26%)	65/89 (73%)	66/89 (74%)
PLT, median (IQR)	229 (201-262)	248 (234-290)	235 (186-286)	238 (190-279)
PLT <150×10⁹/L	2/24 (8%)	1/23 (4%)	6/65 (9%)	5/66 (8%)
PLT <100×10⁹/L	0/24 (0%)	0/23 (0%)	1/65 (2%)	1/66 (1%)

B)

Antibody	GPV+		GPV-	
Disease activity	High	Low	High	Low
Frequency	43/89 (48%)	21/89 (24%)	46/89 (52%)	68/89 (76%)
PLT, median (IQR)	213 (186-248)	248 (208-286)	259 (200-302)	242 (197-286)
PLT <150×10⁹/L	6/43 (14%)	2/21 (10%)	2/46 (4%)	4/68 (6%)
PLT <100×10⁹/L	1/43 (2%)	0/21 (0%)	0/46 (0%)	1/68 (1%)

C)

Antibody	GPIb/IX+		GPIb/IX-	
Disease activity	High	Low	High	Low
Frequency	48/89 (54%)	27/89 (30%)	41/89 (46%)	62/89 (70%)
PLT, median (IQR)	223 (193-262)	253 (210-286)	246 (195-299)	240 (190-285)
PLT <150×10⁹/L	4/48 (8%)	1/27 (4%)	4/41 (10%)	5/62 (8%)
PLT <100×10⁹/L	1/48 (1%)	0/27 (0%)	0/41 (0%)	1/62 (2%)

Table S6. Overall thrombocytopenia frequency by disease activity and platelet counts by thrombosis status

Overall frequency of thrombocytopenia by disease activity state and platelet counts by thrombosis status. (A) Thrombocytopenia prevalence in the high and low disease activity states using cut-offs PLT <150×10⁹/L and PLT <100×10⁹/L. (B) Platelet counts (median, IQR) in patients with and without thrombotic events during follow-up. PLT, platelet count; IQR, interquartile range. Thrombosis refers to incident thrombotic events during follow-up as defined in Methods.

A)

Thrombocytopenia	High	Low
PLT <150×10⁹/L	8 (9%)	6 (7%)
PLT <100×10⁹/L	1 (1%)	1 (1%)

B)

Thrombosis	Yes (n24)	No (n65)
PLT, median (IQR)	229 (177-266)	249 (202-277)

Figure S1. Correlation matrix for antibodies, clinical laboratory results and SLEDAI-2K

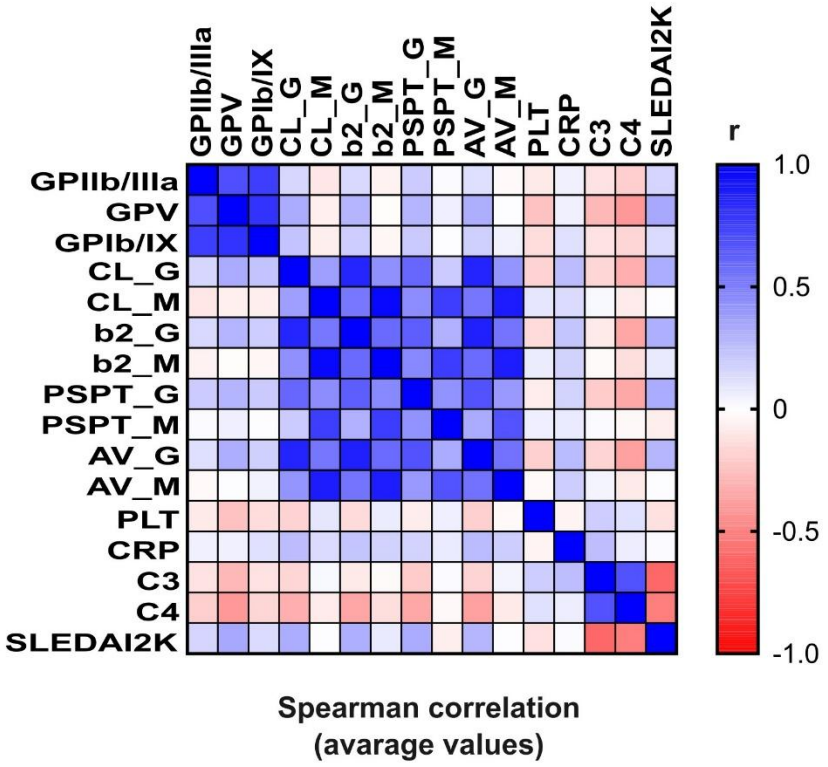
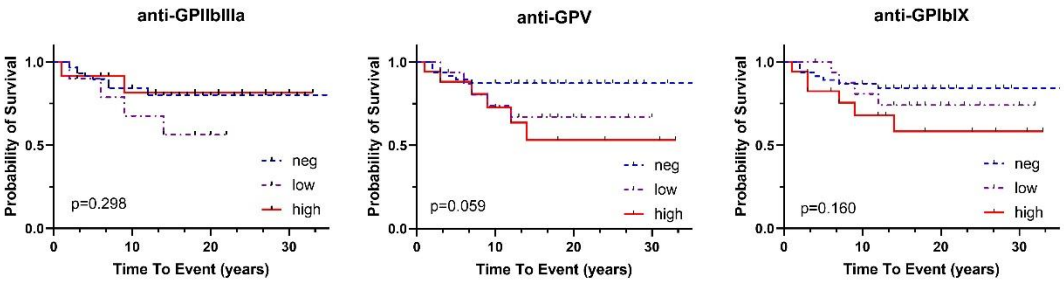


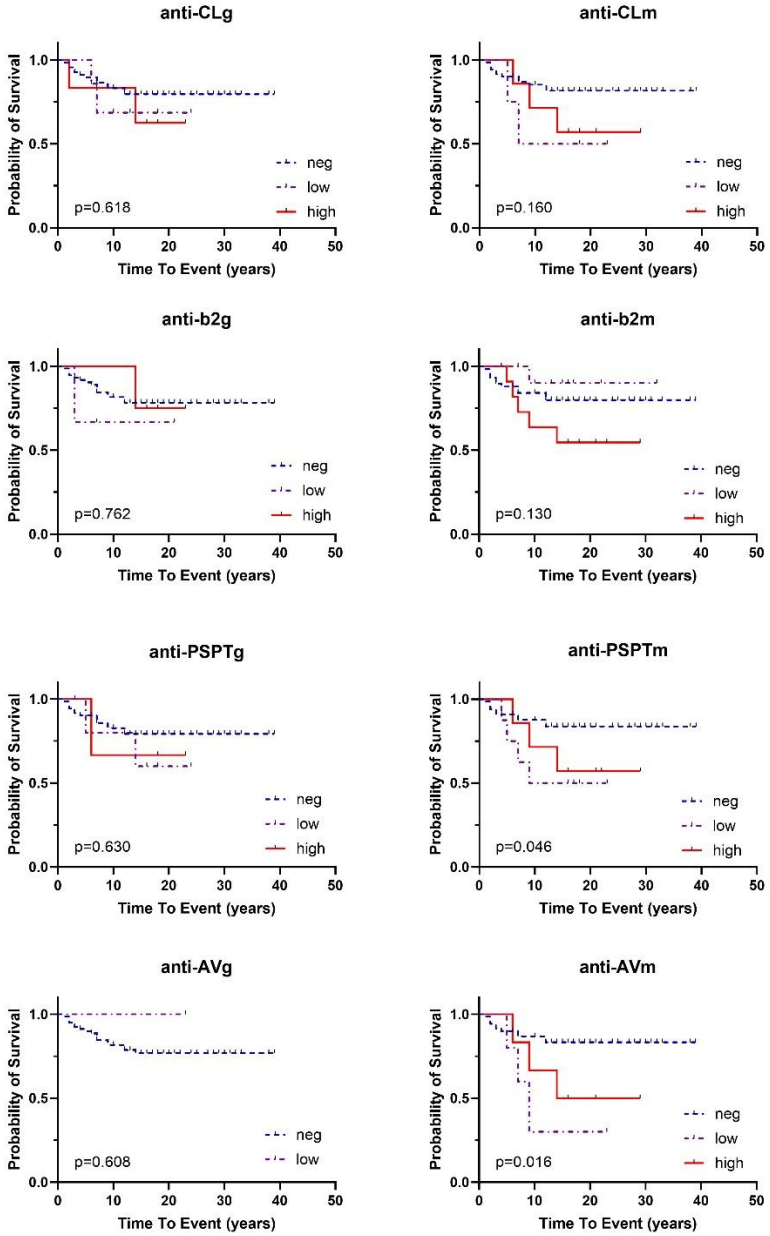
Figure S1. Correlation between average values from baseline sample (H) and follow up (L). Both anti-GP and aPL categories of antibodies showed a strong correlation within each group. A weaker, but significant correlation was detected between anti-GPV and IgG type aPL, and between anti-GPIb/IX and anti-CLG. Average levels of anti-GPV, IgG type anti-cardiolipin (CL_G), anti-β2 glycoprotein 1 (b2_G), anti-PS/PT (PSPT_G) and anti-AV (AV_G) correlated significantly with SLEDAI-2K. anti-GPV, CL_G, b2_G, PSPT_G and AV_G also correlated significantly with C4, but only GPV showed a significant correlation with C3.

Supplementary Figure S2

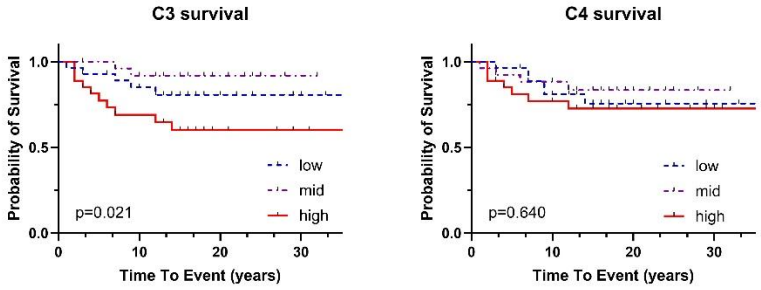
A



B



C



Kaplan–Meier curves were compared using the log-rank (Mantel–Cox) test. Log-rank p-values are displayed in (A) platelet-specific anti-GP antibodies, (B) antiphospholipid antibody (aPL) positivity, and (C) complement proteins. For antibodies, patients were stratified as negative, low positive (below median), or high positive (above median). For complement C3 and C4, levels were divided into tertiles: low, medium, and high. For anti-annexin V IgG (AVg), only one positive sample was available, precluding further stratification. Anti-CL = anticardiolipin; anti-b2 = anti-β2 glycoprotein I; anti-PSPT = anti-phosphatidylserine/prothrombin; anti-AV = anti-annexin V; g = IgG isotype; m = IgM isotype. Supplementary robustness analyses using the log-rank test for trend and the Gehan–Breslow–Wilcoxon test are shown in Supplementary Table S4. Anti-GPV showed a borderline separation by the log-rank test ($p = 0.059$), with a significant linear trend across groups ($p = 0.0187$). PS/PT IgM and anti–Annexin V IgM demonstrated significant separation by the log-rank test ($p = 0.0456$ and $p = 0.0156$), confirmed in Wilcoxon testing. High C3 levels were significantly associated with reduced thrombosis-free survival (log-rank $p = 0.0207$). No other antibody specificities showed significant differences by any of the three methods.
Median thrombosis-free survival time pending analysis. Hazard ratios are provided in Supplementary Table S4.