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Clinical Interpretation of Platelet Activation Marker sCLEC-2 in Antiphospholipid Syndrome

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ABSTRACT

Background: Soluble C-type lectin-like receptor 2 (sCLEC-2) has emerged as a biomarker of platelet activation and thrombus formation. Antiphospholipid syndrome (APS) is characterized by arterial and venous thrombosis and pregnancy complications, driven in part by platelet activation. However, the clinical utility of sCLEC-2 and the sCLEC-2/D-dimer ratio in APS remains unclear.

Methods: Plasma samples from 19 patients with primary APS, 30 with SLE-associated APS, 10 with SLE without APS, 40 with other collagen diseases, and 40 healthy controls ($n = 139$) were analyzed. Plasma sCLEC-2 levels and D-dimer levels were quantified by immunoassay. Antiphospholipid antibodies (anti-cardiolipin antibodies and anti-β_2-glycoprotein I antibodies IgG/IgM) were measured by ELISA kits. Group comparisons and correlations were evaluated.

Results: Using the upper limit of the 95% CI of healthy controls as a cutoff, sCLEC-2 positivity was observed in 100% of non-APS autoimmune disease patients, and 98.0% of APS patients. sCLEC-2, D-dimer, and the sCLEC-2/D-dimer ratio were significantly higher in non-APS and APS groups compared with controls ($p < 0.001$). A slight but significant difference in the sCLEC-2 and the ratio was observed between the non-APS and APS groups. However, no significant differences were found among APS subgroups stratified by thrombosis type. sCLEC-2 showed no correlation with any of four major antiphospholipid antibody titers.

Conclusion: Although we observed raised sCLEC-2 and sCLEC-2/D-dimer ratio among APS and non-APS groups and modest differences between the two groups, clinical interpretation of the findings requires a prospective study evaluating dynamic changes of sCLEC-2 in the clinical course.

1 | Introduction

Detecting platelet activation in vivo is useful for predicting the risk of thrombotic complications. However, platelet activation markers covered by the Japanese national health insurance—platelet factor 4 (PF4) and β-thromboglobulin (β-TG)—are easily released upon minimal stimulation, requiring careful attention during sample collection and handling [1].

In contrast, the recently established assay for C-type lectin-like receptor 2 (CLEC-2), a receptor expressed on the platelet membrane, shows no significant fluctuation in measured values even when blood is collected using a standard vacuum tube holder. The endogenous ligand for CLEC-2 is podoplanin (PDPN), a membrane protein, and accumulating evidence suggests that CLEC-2 may contribute to platelet aggregation and thrombus formation through its interaction with PDPN [2].

Abbreviations: β-TG, β-thromboglobulin; aCL, anti-cardiolipin antibodies; APS, antiphospholipid syndrome; AUC, area under the curve; aβ_2GPI, anti-β_2-glycoprotein I antibodies; CLEIA, chemiluminescent enzyme immunoassay; COVID-19, coronavirus disease 2019; IRAK, interleukin-1 receptor-associated kinase; MW test, Mann–Whitney test; NF-κB, phosphorylation and nuclear factor kappa B; PDPN, podoplanin; PF4, platelet factor 4; ROC, receiver operating characteristic; r_S, Spearman's rank correlation coefficient; sCLEC-2, soluble form of C-type lectin-like receptor 2; TF, tissue factor.

The soluble form of CLEC-2 (sCLEC-2) is released into plasma as both a shed receptor and a microvesicle-associated form in response to platelet activation [3].

Reports on CLEC-2 and its soluble form (sCLEC-2) have been published in various diseases, including acute cerebral infarction [4], acute ischemic stroke [5], disseminated intravascular coagulation (DIC) [6], acute coronary syndrome [7], and coronavirus disease 2019 (COVID-19) [8], indicating potential associations with thrombus formation. Notably, in a study of patients with acute cerebral infarction, sCLEC-2 levels were significantly higher in atherothrombotic infarction than in cardioembolic infarction [4], suggesting a particular relevance to arterial thrombogenesis, in which platelet-rich thrombi predominate. These findings highlight sCLEC-2 as a promising novel biomarker in diseases complicated by arterial thrombosis.

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies in the circulation, leading to a variety of clinical manifestations such as arterial and venous thrombosis, pregnancy complications, and thrombocytopenia [9]. In Japan, APS patients are notable for exhibiting a higher frequency of recurrent cerebral infarction compared with those in Western countries, and this has been attributed to the enhancing effect of antiphospholipid antibodies on platelet activation [10].

In this study, we evaluated sCLEC-2, D-dimer, and their ratio in patients with APS and compared the results with those obtained from patients with other autoimmune diseases (non-APS patients) and from healthy individuals. In addition, we analyzed the associations among the markers and their correlations with antiphospholipid antibody titers.

2 | Materials and Methods

2.1 | Subjects

We utilized archival specimens from well-defined clinical cases of APS and non-APS, as we did in the preceding study that evaluated five major antiphospholipid antibody assays in distinquishing the two groups [11]. Plasma samples were obtained at the time of diagnosis using sodium citrate as an anticoagulant. They comprised, as APS group, 19 patients with primary APS (PAPS) (mean age, 47.0 years [range, 14–70 years]; sex ratio = 2:17), 30 patients with SLE-associated APS (SLE/APS) (mean age, 44.3 years [15–67 years]; sex ratio = 6:24), and, as non-APS group, 10 patients with SLE without APS (mean age, 33.7 years [16–56 years]; all female), and 40 patients with connective tissue diseases other than APS or SLE (mean age, 59.3 years [18–86 years]; sex ratio = 17:23).

As a control group, 40 healthy volunteers were newly recruited. The inclusion criteria were as follows: no abnormality in major health screening tests; no regular hospital visits due to chronic diseases; no hospitalization for acute illness or surgery within the past month; no medication use within the past 3 days; and no subjective symptoms at the time of blood collection. Plasma sampling was performed under fasting conditions. They had a mean age of 28.7 years [19–60]; sex ratio of 11:29.

Plasma concentrations of sCLEC-2 and D-dimer were measured in all samples.

APS was diagnosed according to the 2006 revised international classification criteria (Sydney revised Sapporo criteria) [12], and SLE was diagnosed based on the 1997 revised classification criteria of the American College of Rheumatology (ACR) [13]. Plasma samples from the 10 SLE patients and 40 connective tissue disease patients were collected from individuals who did not exhibit APS-related clinical manifestations (thrombosis or pregnancy morbidity) at the time of sampling.

This study was reviewed and approved by the medical research ethics committee of Yamaguchi University Graduate School of Medicine, Faculty of Health Sciences (approval no. 783), and informed consent was obtained from all patients.

2.2 | Methods

2.2.1 | Measurement of sCLEC-2 Concentrations

Plasma sCLEC-2 concentrations were measured on the STACIA automated analyzer (PHC Corporation, Tokyo, Japan), which is a general-purpose instrument capable of multiple analytical principles such as chemiluminescent enzyme immunoassay (CLEIA), latex agglutination, and absorbance-based methods. For sCLEC-2 measurement in this study, a CLEIA-based assay [1] was employed. In this assay, patient plasma was first incubated with magnetic particles coated with an anti-sCLEC-2 antibody (11D5), followed by incubation with an alkaline phosphatase-labeled secondary antibody (11E6). CDP-Star (Applied Biosystems, MA, USA) was then added as the chemiluminescent substrate, and the emitted light generated by the enzymatic reaction was quantified using the analyzer's luminometric detection system.

2.2.2 | Measurement of D-Dimer Concentrations

Plasma D-dimer concentrations were also measured on the STACIA automated analyzer. For the D-dimer assay, a latex agglutination-based reagent was employed. Plasma samples were reacted with latex particles sensitized with the mouse monoclonal anti-human D-dimer antibody (MIF-220), and the resulting agglutination was optically quantified. The reagent used in this study was LPIA-GENESIS D-dimer (PHC Corporation) [14].

2.2.3 | Measurement of Antiphospholipid Antibody Titers

Four antiphospholipid antibodies included in the international APS classification criteria (anti-cardiolipin antibodies (aCL) IgG/IgM and anti-β_2-glycoprotein I antibodies (aβ_2GPI) IgG/IgM) were measured using QUANTA Lite ACA IgG/IgM III and QUANTA Lite β2GPI IgG/IgM III kits (INOVA Diagnostics, USA).

The kit uses purified cardiolipin or β_2GPI antigens immobilized onto microplate wells. IgG and IgM classes of aCL and aβ_2GPI in patient samples bind to the immobilized antigens. An enzyme-labeled anti-human IgG or IgM conjugate is then added, which binds to the patient antibodies. Enzyme activity is measured by adding a chromogenic substrate, and the resulting color intensity is detected using a Multiskan FC microplate reader (Thermo Fisher Scientific Inc., USA) [11].

2.2.4 | Statistical Analysis

Between-group differences in continuous numerical parameters were evaluated using the Mann–Whitney (MW) test and Dunn's test in need for considering multiplicity of the testing, receiver operating characteristic (ROC) curve analysis with its effect size expressed in area under the curve (AUC), and correlations between those parameters were assessed using Spearman's rank correlation coefficient (r_S). All statistical analyses were performed using StatFlex software (version 7; Artec Co. Ltd., Osaka, Japan).

3 | Results

3.1 | Positivity Rate of sCLEC-2

The 95% confidence interval (95% CI) of sCLEC-2 values measured by the CLEIA method in healthy individuals has been reported to range from 63.4 to 156.0 pg/mL [1]. Using the upper limit of this 95% CI as the cutoff value, the positivity rate of sCLEC-2 was evaluated. As a result, sCLEC-2 positivity was observed in 2.5% (1/40) of healthy controls, 100% (50/50) of the non-APS group (40 connective tissue disease cases + 10 SLE cases), and 98.0% (48/49) of the APS group (19 PAPS cases + 30 SLE/APS cases).

3.2 | Comparison of sCLEC-2, D-Dimer, and the sCLEC-2/D-Dimer Ratio Among the Three Groups

sCLEC-2 levels, D-dimer levels, and the sCLEC-2/D-dimer ratio were compared among the three groups—healthy controls, non-APS patients, and APS patients. Between-group differences were evaluated by MW test and calculation of AUC (Figure 1).

Compared with healthy controls, sCLEC-2 levels were significantly higher in both the non-APS and APS groups (MW test, both $p < 0.001$; AUC = 1.00 and 0.98, respectively). Furthermore, APS patients showed significantly higher sCLEC-2 levels than the non-APS group ($p < 0.05$; AUC = 0.62).

D-dimer level was significantly higher in both non-APS and APS groups compared with healthy controls (both $p < 0.001$; respective AUC = 0.93, 0.92). However, no significant difference was observed in D-dimer levels between the non-APS and APS groups (NS; AUC = 0.55).

As for the sCLEC-2/D-dimer ratio, the levels were significantly higher in both the non-APS and APS groups compared with healthy controls (both $p < 0.001$; respective AUC = 0.74, 0.79). In addition, a slight but significant difference in the ratio was observed between the non-APS group and APS groups ($p < 0.05$; AUC = 0.61).

3.3 | Comparison of sCLEC-2, D-Dimer, and the sCLEC-2/D-Dimer Ratio Within the APS Group

The APS group was subdivided into four categories: no thrombosis ($n = 12$), venous thrombosis ($n = 11$), arterial thrombosis ($n = 19$),

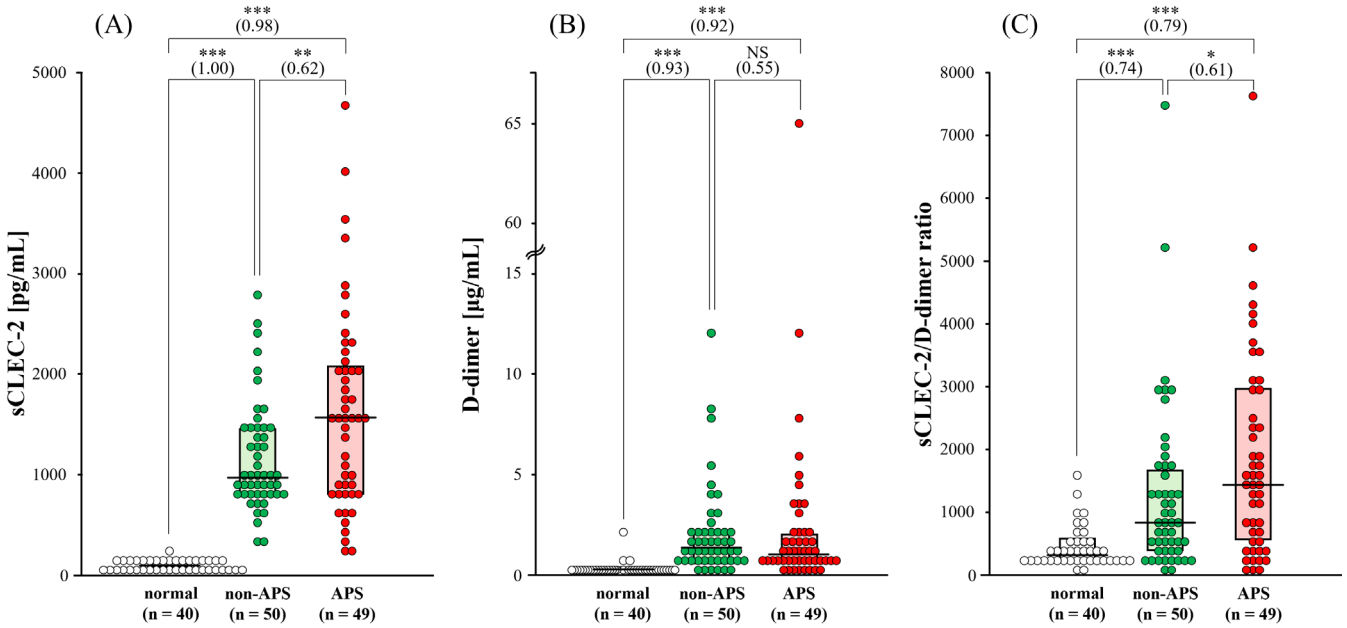

FIGURE 1 | Comparison of sCLEC-2 [A], D-dimer [B], and the sCLEC-2/D-dimer ratio [C]. MW test: ***$p < 0.001$, **$p = 0.02$, *$p = 0.04$. Values in parenthesis represent AUC in distinguishing the two groups. APS, antiphospholipid syndrome; AUC, area under the ROC curve; sCLEC-2, soluble C-type lectin-like receptor 2.

and combined arterial and venous thrombosis ($n=8$). sCLEC-2 levels, D-dimer levels, and the sCLEC-2/D-dimer ratio were compared among these subgroups (Figure 2). No significant differences were observed in sCLEC-2 levels, D-dimer levels, or the sCLEC-2/D-dimer ratio among the four groups (Dunn's test, NS).

3.4 | Correlation Between sCLEC-2 and Antiphospholipid Antibody Titers

The correlations between sCLEC-2 and four antiphospholipid antibodies (aCL IgG, aCL IgM, aβ_2GPI IgG, and aβ_2GPI IgM) were analyzed in the non-APS and APS groups (Figure 3). Spearman's rank correlation coefficients (r_s) of sCLEC-2 were 0.06 with aCL IgG, −0.19 with aCL IgM, −0.11 with aβ_2GPI IgG, and −0.01 with aβ_2GPI IgM. None of the r_S between sCLEC-2 levels and the antiphospholipid antibody titers were significant.

4 | Discussion

The 95% confidence interval (95% CI) of sCLEC-2 levels in healthy individuals measured using the CLEIA method has been reported to range from 63.4 to 156.0 pg/mL [1]. In the present study, 37 of 40 healthy subjects (92.5%) fell within this CI, which was largely consistent with previous findings. Using the upper limit of this CI as the cutoff value, we determined sCLEC-2 positivity as 100% in the non-APS group and 98.0% in the APS group. Moreover, a slight but significant difference in the ratio was observed between the non-APS and APS groups. In contrast, no significant differences were observed among subgroups stratified by arterial or venous thrombosis. These mixed findings suggest that sCLEC-2 may be of some interest in understanding the pathophysiology of APS, but it is of no clinical use in predicting the type of APS complications.

sCLEC-2 has gained attention as a novel marker of platelet activation and reflects the multifaceted roles of platelets not only in hemostasis but also in inflammation and immune responses. The stability of sCLEC-2 and its ease of sampling is also a beneficial property of the marker, unlike PF-4 or β-TG that require strict sampling/storage conditions. In rheumatoid arthritis, chronic immune activation leads to platelet activation and increased levels of procoagulant factors such as P-selectin and PF4. These increases correlate with disease activity [15], suggesting a similar mechanism may operate in APS. Indeed, APS patients with a history of thrombotic events exhibit marked elevations in platelet-derived microparticles and high levels of platelet-derived bioactive substances including PF4 [16, 17]. Nevertheless, sCLEC-2 is considered to primarily reflect acute platelet activation, and its interpretation may be limited in chronic disease states or in patients receiving therapeutic interventions, particularly antiplatelet therapy. Given that coagulation abnormalities are also frequently observed in APS, elevated sCLEC-2 may reflect both immune activation and hypercoagulability, although disentangling these contributions remains challenging in the present study population with lack of detailed information on clinical stages of each patient.

The sCLEC-2/D-dimer ratio, which integrates platelet activation (sCLEC-2) and coagulation activation (D-dimer), has emerged as a potential biomarker for distinguishing thrombotic mechanisms. Previous studies have suggested that this ratio may differentiate atherothrombotic stroke (arterial thrombosis) from cardioembolic stroke (venous thrombosis) [4]. Although APS can cause both arterial and venous thrombosis, no significant differences in the sCLEC-2/D-dimer ratio were observed between APS patients with and without thrombosis in the present study. In contrast, a modest but statistically significant difference in the sCLEC-2/D-dimer ratio was observed between the non-APS and APS groups. ROC curve analysis further demonstrated that

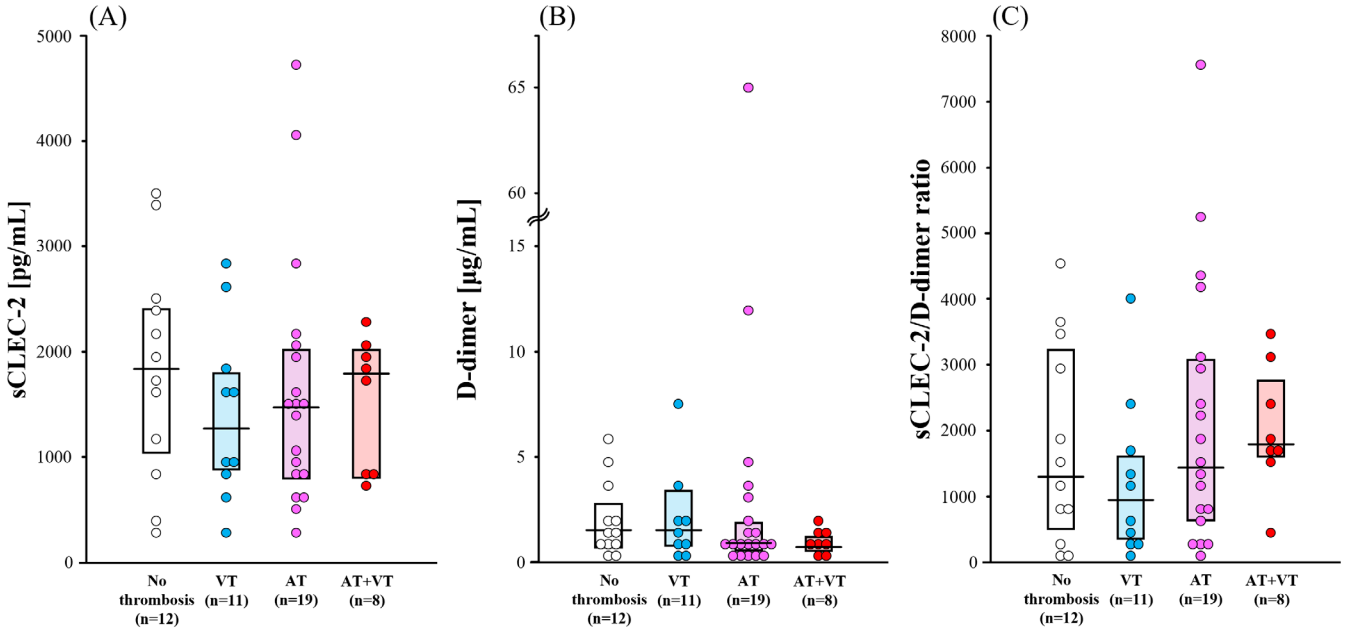

FIGURE 2 | Comparison of sCLEC-2 [A], D-dimer [B], and the sCLEC-2/D-dimer ratio [C] in relation to thrombosis subtypes. Dunn's test: $p=$ NS for all pairwise comparisons vs. the control group (NT). NT, no thrombosis; AT, arterial thrombosis; sCLEC-2, soluble C-type lectin-like receptor 2; VT, venous thrombosis.

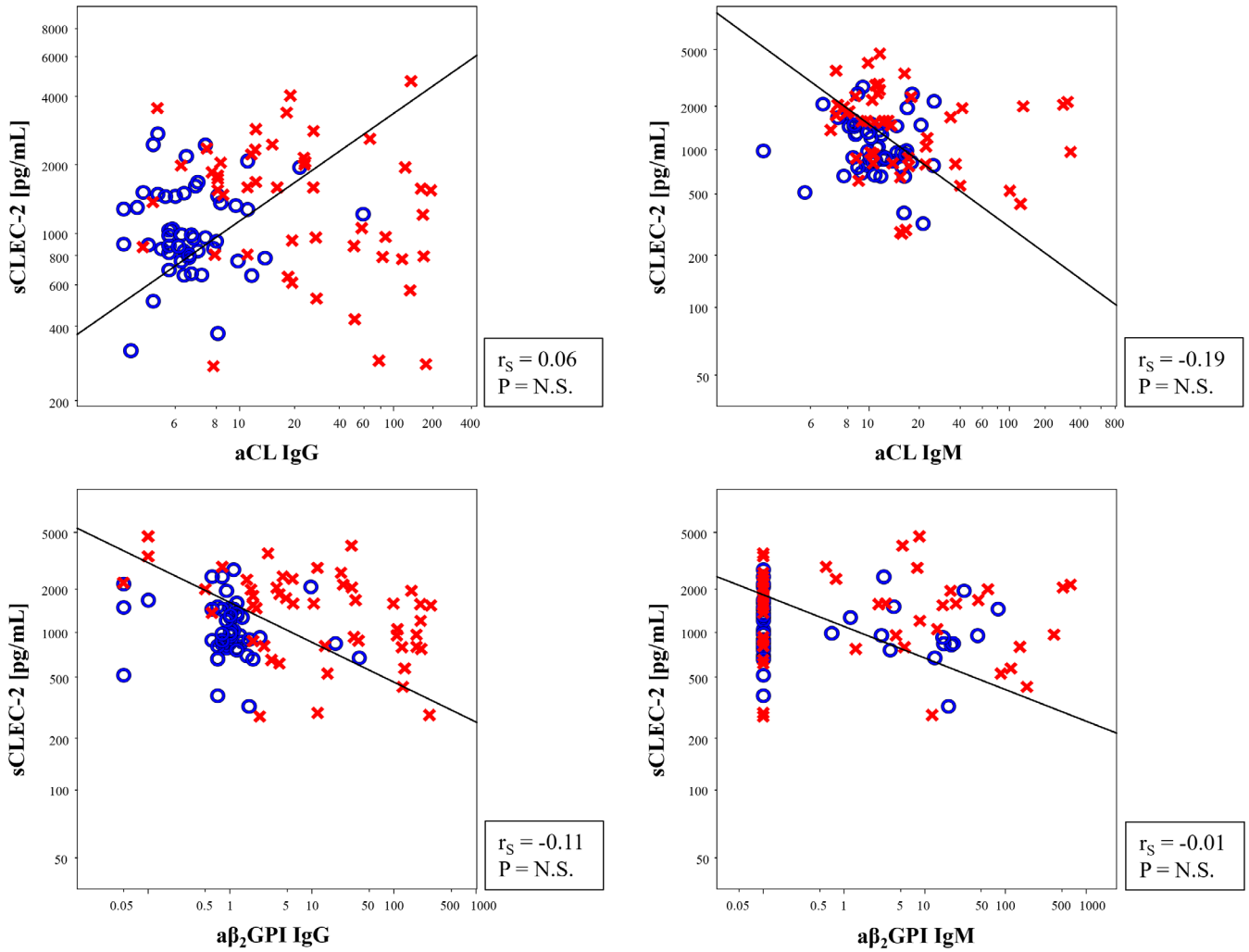

FIGURE 3 | Correlation between sCLEC-2 and antiphospholipid antibodies. The blue open circles in the graph represent data points from 50 non-APS cases, and 49 APS cases are shown as red cross symbols. r_S ranged from −0.19 to 0.06 (p = NS). aCL, anti-cardiolipin antibodies; aβ_2GPI, anti-β_2-glycoprotein I antibodies; r_S, Spearman's rank correlation coefficient; sCLEC-2, soluble C-type lectin-like receptor 2.

the sCLEC-2 and sCLEC-2/D-dimer ratio exhibited a modest but discernible discriminative ability for distinguishing patients with APS from non-APS, with AUC values of 0.62 and 0.61, respectively. Although the diagnostic performances were limited and insufficient for use as a standalone diagnostic marker, these findings support the notion that the sCLEC-2/D-dimer ratio may have clinical relevance as supplemental markers reflecting pathophysiology and disease-related alterations in the platelet–coagulation balance in APS, even in the absence of overt thrombotic events. The lack of clear discrimination according to thrombotic phenotype may be attributable to the fact that most patients were in the chronic phase and were receiving anticoagulant and/or antiplatelet therapy, conditions under which the original pathophysiological characteristics of the biomarker are likely attenuated. Therefore, the sCLEC-2/D-dimer ratio may be most informative in untreated patients and in samples obtained during the acute phase prior to therapeutic intervention, and clinical interpretation of the ratio should consider treatment status.

The significant elevation of sCLEC-2 in autoimmune diseases observed in this study supports the notion that platelet activation contributes to disease pathogenesis, including in APS. CLEC-2 is expressed on platelets and modulates inflammation and coagulation through interactions with immune and endothelial cells. In autoimmune disorders, chronic inflammatory conditions may activate platelets, leading to the release of sCLEC-2 into the circulation via disease-related pathophysiological mechanisms.

Although double- and triple-positivity are generally considered high-risk antiphospholipid antibody profiles [18, 19], we did not observe a trend of stepwise increase in sCLEC-2 levels, D-dimer levels, or the sCLEC-2/D-dimer ratio with increasing antibody positivity in this cohort. This finding suggests that sCLEC-2-related marker elevation is not simply proportional to cumulative antibody burden.

At the same time, the absence of a clear association between sCLEC-2 levels and thrombotic phenotype suggests that elevated sCLEC-2 does not necessarily indicate ongoing thrombosis in this clinical context.

No correlations were identified between sCLEC-2 and aCL IgG, aCL IgM, aβ_2GPI IgG, or aβ_2GPI IgM. This finding suggests that

sCLEC-2 may serve as a thrombosis-related marker independent of antiphospholipid antibody titers. However, given the heterogeneity of clinical backgrounds and limited availability of detailed information in the non-APS group, caution is warranted when interpreting these results.

Furthermore, our findings indicate that in APS—where both arterial and venous thrombosis may occur—elevated sCLEC-2 does not necessarily reflect thrombus formation directly but may instead represent underlying systemic inflammation and immune activation, particularly in chronic or treated populations.

Platelets play a central role in the thromboinflammatory pathophysiology of APS through their interaction with aβ_2GPI via membrane receptors including Toll-like receptors (TLRs), LRP8/ApoER2, and GPIbα [20, 21]. These interactions occur within lipid raft microdomains and trigger downstream signaling pathways involving interleukin-1 receptor-associated kinase (IRAK) phosphorylation and nuclear factor kappa B (NF-κB) activation, ultimately inducing tissue factor (TF) overexpression, a key contributor to the hypercoagulable state in APS [20, 21]. In endothelial cells, activation of the LRP8/ApoER2 pathway reduces endothelial nitric oxide synthase phosphorylation, leading to decreased nitric oxide production and further promoting prothrombotic conditions [22]. Moreover, heparanase has been implicated in this process, as inhibition of heparanase attenuates aβ_2GPI–induced IRAK/NF-κB signaling and TF expression [23]. Collectively, these findings indicate that platelet activation in APS is mediated by complex raft-dependent signaling networks rather than simple platelet stimulation. Accordingly, the elevated sCLEC-2 observed in our cohort may reflect broader thromboinflammatory processes rather than direct thrombotic activity, particularly in chronically treated patients.

The interaction between CLEC-2 and its ligand PDPN has recently attracted attention as a potential therapeutic target in cancer and thrombotic diseases. Loss of CLEC-2 function does not impair physiological hemostasis but suppresses pathological thrombosis, and efforts are underway to develop CLEC-2 inhibitors and anti-PDPN antibodies as therapeutic agents [24]. Taken together, the present findings highlight the limitations of interpreting sCLEC-2 levels in chronic, treated autoimmune populations and underscore the importance of carefully defining target populations and sampling timing. Future studies should investigate the clinical significance of sCLEC-2 through prospective analyses that account for treatment status, disease activity, and timing of thrombotic events, while also considering potential therapeutic applications targeting the CLEC-2/PDPN axis.

5 | Limitation

This study has several limitations that should be acknowledged. First, a small fraction of patients with APS were receiving anticoagulant therapy. The differences in treatment type, duration, and dosage may have influenced sCLEC-2 and D-dimer levels. In addition, due to the retrospective nature of this study, employing archived plasma samples, detailed information regarding disease activity and the precise timing of blood sampling relative to thrombotic events was not available. Proper clinical interpretation of our findings requires a prospective study evaluating dynamic pathophysiological changes in hemostasis. Second, although differences in sCLEC-2 and the sCLEC-2/D-dimer ratio were clearly observed between healthy individuals and disease groups, the differences between non-APS and APS groups were modest and discrimination of the thrombotic phenotype was not possible, presumably reflecting the combined effects of chronic inflammation, coagulation activation, and therapeutic intervention. Third, correlations between sCLEC-2 and disease activity were not assessed, hence, the clinical utility of sCLEC-2 regarding disease activity assessment or thrombotic risk stratification remains to be determined.

Author Contributions

R.K. conceived and designed the study. R.K. and Y.M. analyzed the data and drafted the original manuscript. K.I. and J.N. provided professional advice, including support for manuscript preparation. All authors reviewed the draft and approved the final version for submission.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

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