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Author(s)	Hisada, R.; Kato, M.; Sugawara, E.; Fujieda, Y.; Oku, K.; Bohgaki, T.; Amengual, O.; Yasuda, S.; Atsumi, T.
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Thrombotic risk stratification by platelet count in patients with antiphospholipid antibodies: a longitudinal study

Ryo Hisada[1], Masaru Kato[1], Eri Sugawara[1], Yuichiro Fujieda[1], Kenji Oku[1], Toshiyuki Bohgaki[1], Olga Amengual[1], Shinsuke Yasuda[1] and Tatsuya Atsumi[1]

[1]Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Correspondence to:

Dr. Masaru Kato

N15W7, Kita-Ku, 060-8638 Sapporo, Japan

Tel: +81-11-706-5915 Fax: +81-11-706-7710

ktmasaru@med.hokudai.ac.jp

Running head: Platelet count and thrombosis in aPL carriers

Essentials

- Thrombotic risk stratification is currently on unmet needs in antiphospholipid antibody carriers.

- Platelet count and antiphospholipid score (aPL-S) were combined to predict thrombotic events.

- Patients with high aPL-S are at high thrombotic risk regardless of platelet count.

- If platelet count is low, patients with low aPL-S are also on high thrombotic risk.

Abstract. *Background:* Thrombocytopenia is a non-criteria clinical manifestation of antiphospholipid syndrome (APS). However, it remains to be elucidated whether thrombocytopenia increases thrombotic risk in antiphospholipid antibody (aPL) carriers. *Objectives:* To investigate the impact of platelet count in terms of predicting thrombotic events in aPL carriers and to stratify the thrombotic risk by combining platelet count and antiphospholipid score (aPL-S), which represents a quantification of aPL varieties and titres. *Patients/Methods:* A single centre retrospective, longitudinal study comprising 953 consecutive patients who were suspected to have autoimmune disease between January 2002 and December 2006. Low platelet count was defined as below 150×10^3 /μL at the time of aPL testing. *Results:* A negative correlation was observed

between aPL-S and platelet count (r = -0.2477). Among aPL-positive patients, patients with low platelet count developed thrombosis more frequently compared to those without (HR = 2.95, 95%CI 1.11 to 7.88). Among aPL-negative patients, no difference was found in the predictive value of thrombosis regardless of platelet count. Patients with aPL were further divided into two subgroups according to the levels of aPL-S. In low aPL-S patients' group, patients with low platelet count developed thrombosis more frequently compared to those without (HR = 3.44, 95%CI 1.05 to 11.2). In contrast, patients with high aPL-S developed thrombosis frequently regardless of platelet count.

Conclusions: aPL carriers with low platelet count are at high risk of developing thrombosis. In particular, "low aPL-S carriers" may be stratified by platelet count in terms of predicting future thrombotic events.

Key words: antiphospholipid syndrome; antiphospholipid antibodies; platelet count; thrombosis; thrombocytopenia

Introduction

Antiphospholipid syndrome (APS) is characterised by the occurrence of thrombosis and/or pregnancy morbidity associated with the persistent presence of antiphospholipid antibodies (aPL). Thrombocytopenia is one of the non-criteria manifestations of APS [1]. The prevalence of thrombocytopenia in APS has been reported to be between 20 and 53% [2], higher than that in other autoimmune diseases. In addition, a multicentre prospective study consisted of 1000 APS patients from 13 European countries reported that 8.7% of the patients newly developed thrombocytopenia during a 10-year-follow-up period [3]. Thrombocytopenia in APS patients is, however, mostly mild, above 50×10^3 /μL, and does not require therapeutic interventions to prevent bleeding events. The pathological mechanism underlying these unique clinical characteristics remains unclear [4-6].

In patients with idiopathic/immune thrombocytopenia (ITP), aPL increased the risk of thrombotic events with 5-year-thrombosis-free survival of only 39%, which is significantly lower than that of 97.7% in aPL-negative patients [7]. However, it remains to be elucidated whether thrombocytopenia "paradoxically" increases such risk of thrombosis in aPL carriers [8].

In this study, we evaluated the impact of platelet count in terms of predicting

thrombotic events in both aPL-positive and -negative patients. Furthermore, we stratified the risk of thrombosis in aPL-positive patients by combining platelet count and antiphospholipid score (aPL-S), which represents a quantification of aPL varieties and titres [9].

Methods

Study population

This is a single centre retrospective, longitudinal study comprising 953 consecutive patients who were suspected to have autoimmune disease at Hokkaido University Hospital between January 2002 and December 2006. Among these 953 patients, 262 had been followed-up less than two years, due to both completion and loss of follow-up, and were excluded from the analysis. The median follow-up period for the 691 eligible patients was 128 months. In patients with thrombosis, follow-up for the study was completed at the time of first vascular event. The historical profiles, clinical manifestations and diagnoses were carefully obtained by review of the medical records or by interviewing the patients. Low platelet count was defined as below $150\times10^3/\mu L$, the 2.5th lower percentile of the normal platelet count distribution [10], at the time of aPL testing. Arterial thrombotic events comprised stroke, myocardial infarction, iliac

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artery occlusion and mesenteric artery thrombosis as confirmed by computed tomography scanning, magnetic resonance imaging or conventional angiography. Venous thrombotic events comprised deep vein thrombosis and pulmonary thromboembolism confirmed by computed tomography scanning, angiography or scintigraphy.

Determination of aPL and aPL-S

Anticardiolipin antibodies (aCL, IgG and M) were assayed according to the standard enzyme linked immunosorbent assay (ELISA) [11]. Anti-β2 glycoprotein I antibodies (anti-β2GPI, IgG and M) were determined by in-house ELISA, as previously reported [12]. Phosphatidylserine dependent antiprothrombin antibodies (aPS/PT, IgG and M) were evaluated by in-house ELISA using the phosphatidylserine/prothrombin complex as antigen [13]. For the detection of lupus anticoagulant (LA), the guidelines recommended by the Subcommittee for Standardization of the International Society of Thrombosis and Haemostasis were followed [14]. aPL-S was calculated from 0 to 86 as previously described [9].

Statistical analysis

Categorical variables are expressed as percentages, and continuous variables are expressed as mean ± standard deviation (SD) for those normally distributed or otherwise

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as medians and interquartile ranges (IQR). Statistical analysis was performed by Mann-Whitney U test, Fisher's exact test or Dunnett's test, as appropriate. Correlation coefficients were assessed by the Spearman rank method. The Kaplan–Meier survival estimates were stratified by the optimal cut-off values and compared with log-rank tests. P values less than 0.05 were considered significant. All statistical analyses were performed using GraphPad Prism 7 (Graphpad Software, San Diegoa, CA, USA).

Results and discussion

First, we investigated the relationship between aPL and platelet count by a cross-sectional analysis. Of 691 patients enrolled in this study, 238 had systemic lupus erythematosus (SLE), 110 rheumatoid arthritis, 38 primary APS, 33 vasculitis syndrome and 26 polymyositis/dermatomyositis. At least one aPL was found positive in 42.1% [291/691] of patients at the time of enrolment. The prevalence of low platelet count was higher in aPL-positive compared to -negative patients (14.1% [43/291] vs 9.5% [38/400], p = 0.041). Among the 219 aPL-positive patients, LA and aPS/PT were significantly more prevalent in patients with low platelet count compared to those without (Table 1). Furthermore, aPL-S was significantly higher in patients with low platelet count compared to those without. We also evaluated the correlation between

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aPL-S and platelet count by the Spearman rank method and a negative correlation was observed with statistical significance (Fig. 1). Among the 400 aPL-negative patients, the presence of low platelet count was more frequently observed in SLE patients (Table 1).

Next, we evaluated the impact of low platelet count on the development of thrombotic events by a longitudinal follow-up in both aPL-positive and -negative patients. Included were any thrombotic events that had developed since the day of aPL testing until the last day of follow-up. During the follow-up period, median and IQR of 128 [76-148] months, thrombosis developed in 53 out of 691 patients (32 arterial and 21 venous thrombotic events). Among aPL-positive patients, patients with low platelet count developed thrombosis more frequently compared to those without (2.34 vs. 0.96 per 100 person-years, p = 0.021). Among aPL-negative patients, contrarily, there was no difference in the rate of thrombosis development between patients with and without low platelet count (0.89 vs. 0.54 per 100 person-years, p = 0.423) (Fig. 2A). Since 34% [238/691] of the enrolled patients had SLE, we performed a subgroup analysis in SLE and non-SLE patients. Regardless of having SLE, observed was the high risk of developing thrombosis in patients who had both aPL and low platelet count (Fig. 2B). Furthermore, subgroup analysis for other thrombotic risk factors including age, smoking, hypertension, dyslipidemia, diabetes mellitus and past history of thrombosis showed

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similar results (data not shown). The Kaplan–Meier estimates also showed the relationship between platelet count and thrombosis in aPL-positive but not in -negative patients (Fig. 3A, B).

Finally, to further assess the platelet count-thrombosis relationship in aPL-positive patients, we divided aPL-positive patients into two subgroups according to the levels of aPL-S. Among 242 patients with low aPL-S (0<aPL-S<30), patients with low platelet count developed thrombosis more frequently compared to those without. In contrast, 48 patients with high aPL-S (aPL-S≥30) developed thrombosis frequently regardless of the platelet count (Fig. 3C, D). These findings indicate the potential to stratify the risk of developing thrombosis in aPL carries by combining platelet count and aPL-S. These results were similar even if low platelet count was defined as below $100 \times 10^3 / \mu L$, which criteria was used for diagnosis of ITP [15] (data not shown).

Although previous cohorts have shown a high prevalence of thrombocytopenia in patients with APS compared to other autoimmune diseases [2], the underlying pathological mechanism remains to be elucidated. In ITP patients, the presence of aPL has been shown to be a thrombotic risk by a prospective cohort study [7] and, more recently, by a systematic review [16]. Our data vice versa indicate low platelet count as a risk of developing thrombosis in aPL carriers. Conversely, a retrospective study

performed by Krause, et al. showed a similar prevalence of thrombotic episodes in APS patients with and without thrombocytopenia [17]. One of the possible reasons for the discrepancy is that our study enrolled patients with various autoimmune diseases including APS and non-APS whereas the study by Krause, et al. enrolled APS patients only. Another reason may be the inclusion of aPL-S in our study. Kaplan–Meier estimates in our study showed a similar risk of developing thrombosis in aPL-S high (aPL-S≥30) patients with and without low platelet count.

To date, four different mechanisms has been suggested to be underlying thrombocytopenia with aPL; platelet activation with subsequent destruction, decreased platelet production, increased platelet pooling and pseudothrombocytopenia [5]. Of these potential mechanisms, platelet activation by aPL and destruction of platelets by antibodies directed against their membrane glycoproteins (GP) may particularly be linked to the risk of developing thrombosis. Some studies have shown that aPL induce the expression of platelet membrane GP, especially GP IIb/IIIa [18]. Platelet activation occurs after the binding of anti-β2GPI/dimerized β2GPI complex to platelet surface membrane GP in vitro [19]. Previous report showed thrombocytopenia in patients with aPL were associated with high titers of antibodies against platelet GP Ib/IX and IIb/IIIa [20]. Of particular importance, platelet count increases following the administration of

antiplatelet agents in some APS patients [21], presumably by decreasing the expression of GP and subsequently inhibiting the binding of anti-β2GPI/dimerized β2GPI complex on platelet surface.

Given the lack of evidence to recommend or unrecommend primary prophylaxis against thrombosis in aPL carriers [22], precise risk stratification of thrombosis is currently on unmet needs in such individuals. Our previous study has already shown high aPL-S (aPL-S≥30) as an independent risk for thrombosis [9]. Conversely, low aPL-S (0<aPL-S<30) was not identified as a thrombotic risk and was even similar with the absence of aPL in terms of predicting future thrombotic events [9]. The current data, by combining platelet count and aPL-S, are successful to extract individuals on high thrombotic risk from those "low aPL-S carriers".

The results of this study are subjected to some limitations. First, this is a single-centre retrospective study comprising only Japanese patients. With such design, antithrombotic agents would be selected according to physicians' decision, leading to a grouping bias. Second, aPL testing, one of the patient inclusion criteria in this study, was performed according to physicians' decision, suggesting a selective bias.

In summary, our data provide the first evidence of thrombotic risk stratification by platelet count in patients with aPL. Low platelet count is associated with aPL,

particularly with aPL-S, in autoimmune disease patients and the presence of low platelet

count or high aPL-S is a risk of developing thrombosis in aPL carriers. These findings

would give new insights to the management of APS, aPL carriers and ITP and also to

the understanding of the pathophysiology of APS.

Conflict of interest statement

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Table 1 Patients' baseline characteristics

	aPL (+)				aPL (-)			
	Low platelet count(+)	Low platelet count(-)	p	RR (95% CI)	Low platelet count(+)	Low platelet count(-)	p	RR (95% CI)
Patient number, n	43	248			38	362		
Age (years)	49.3±14.7	49.4±14.6	0.967		49.4±10.9	48.9±15.5	0.846	
Female, n (%)	34 (79.1)	206 (83.1)	0.518	0.952 (0.808 - 1.121)	32 (84.2)	279 (77.1)	0.413	1.093 (0.942 - 1.268)
SLE, n (%)	23 (53.6)	98 (39.5)	0.096	1.354 (0.984 - 1.861)	**19 (50.0)**	**101 (27.9)**	**0.008***	**1.792 (1.252 - 2.565)**
Smoking, n (%)	9 (20.9)	41 (16.5)	0.512	1.266 (0.664 - 2.412)	5 (13.1)	50 (13.8)	1.000	0.953 (0.405 - 2.243)
Hypertension, n (%)	14 (32.6)	53 (21.4)	0.118	1.523 (0.931 - 2.492)	11 (28.9)	77 (21.3)	0.304	1.361 (0.796 - 2.326)
Dyslipidemia, n (%)	13 (30.2)	53 (21.4)	0.236	1.415 (0.847 - 2.363)	7 (18.4)	78 (21.5)	0.835	0.855 (0.426 – 1.717)

Diabetes mellitus, n (%)	3 (7.0)	23 (9.3)	0.778	0.752 (0.236 - 2.397)	5 (13.1)	45 (12.4)	0.801	1.058 (0.447 - 2.505)
Past history of thrombosis, n (%)	16 (37.2)	63 (25.4)	0.136	1.465 (0.941 - 2.281)	3 (7.9)	48 (13.3)	0.450	0.595 (0.195 – 1.820)
aPL profile								
LA, n (%)	**35 (81.4)**	**161 (64.9)**	**0.035***	**1.254 (1.058 - 1.486)**				
aCL, n (%)	26 (60.5)	142 (57.3)	0.740	1.056 (0.811 - 1.376)				
aβ2GPI, n (%)	16 (37.2)	62 (25.0)	0.134	1.488 (0.955 - 2.321)				
aPS/PT, n (%)	**23 (53.5)**	**90 (38.3)**	**0.041***	**1.474 (1.066 - 2.038)**				
aPL score	**15.0 [7.5-34]**	**8.5 [2-21]**	**0.003***					
Medication								
Glucocorticoid, n (%)	28 (65.1)	129 (52.0)	0.136	1.252 (0.976 - 1.606)	**22 (57.9)**	**119 (32.9)**	**0.004***	**1.761 (1.294 – 2.398)**

Antiplatelet therapy, n (%)	18 (41.9)	69 (27.8)	0.072	1.505 (0.992 - 2.256)	3 (7.9)	36 (9.9)	1.000	0.794 (0.257 – 2.456)
Anticoagulant therapy, n (%)	8 (18.6)	28 (11.3)	0.208	1.648 (0.805 – 3.372)	3 (7.9)	24 (6.6)	0.733	1.191 (0.376 – 3.771)

SLE, systemic lupus erythematosus; aPL, antiphospholipid antibodies; LA, lupus anticoagulant; aCL, anticardiolipin antibodies IgG

and/or M; aβ2GPI, anti-β2-glycoprotein I antibodies IgG and/or M; aPS/PT, phosphatidylserine-dependent antiprothrombin antibodies

IgG and/or M; aPL score, antiphospholipid score. *p<0.05, using Fisher's exact test or Mann–Whitney U test. RR, relative risk; CI,

confidence interval.

Figure legends

Fig. 1. Spearman's rank correlation coefficients among antiphospholipid score (aPL-S) and platelet counts in aPL-positive patients.

Fig. 2. Annualized rate of thrombosis in each group divided according to the presence or absence of aPL and low platelet count (**A**) and of SLE, aPL and low platelet count (**B**), with 95% confidence intervals. n, number of patients; n.s., no statistical significance. *$p<0.05$, using Dunnett's test.

Fig. 3. Comparisons of cumulative rate of thrombosis in the presence or absence of low platelet count in aPL-positive patients (**A**), -negative patients (**B**), aPL-S-low (0<aPL-S<30) patients (**C**), and -high (aPL-S≥30) patients (**D**). LPC, low platelet count; HR, hazard ratio; CI, confidence interval.
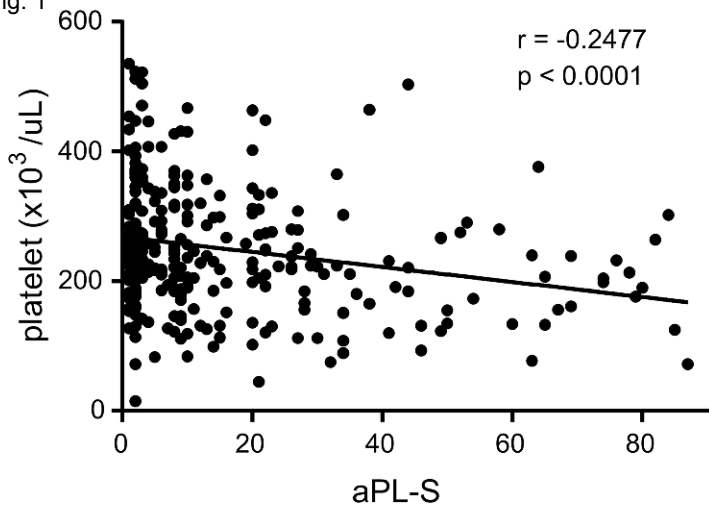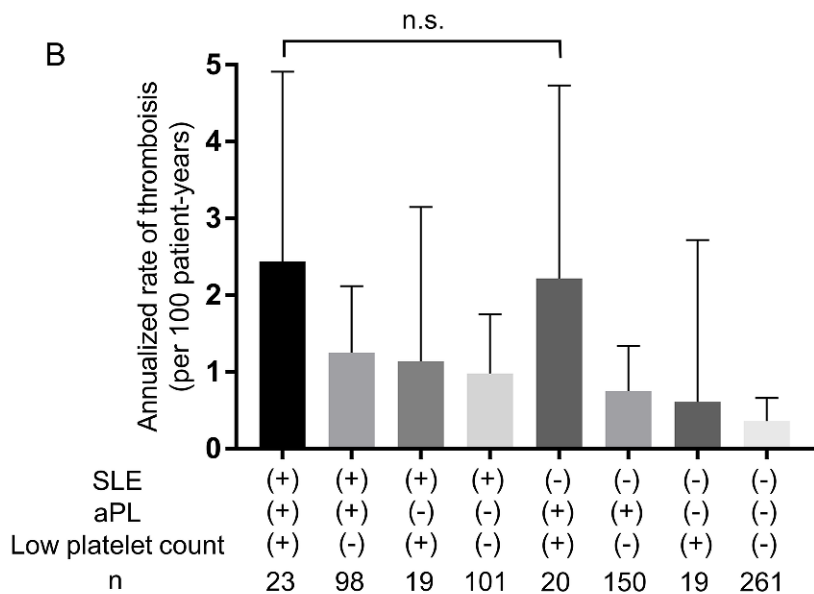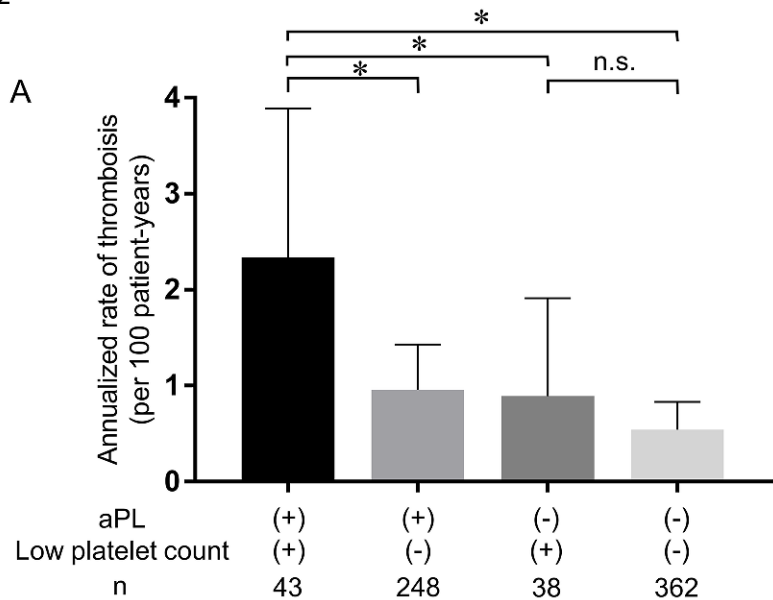
Fig. 1

Fig. 2

Fig. 3

A — aPL(+)

Cumulative rate of thrombosis(%)

Log rank p=0.031
HR=2.95,
95%CI 1.11 to 7.88

— LPC(+)
-- LPC(-)

Follow-up(Months)

Number at risk

LPC(+)	43	40	35	30	29	26
LPC(-)	248	238	210	190	167	137

B — aPL(-)

Cumulative rate of thrombosis(%)

Log rank p=0.880
HR=1.13,
95%CI 0.24 to 5.19

— LPC(+)
-- LPC(-)

Follow-up(Months)

Number at risk

LPC(+)	38	38	32	27	19	18
LPC(-)	362	356	322	292	257	202

C — 0 < aPL-S < 30

Cumulative rate of thrombosis(%)

Log rank p=0.040
HR=3.44,
95%CI 1.05 to 11.2

— LPC(+)
-- LPC(-)

Follow-up(Months)

Number at risk

LPC(+)	29	27	24	21	17	14
LPC(-)	213	197	181	164	144	105

D — aPL-S ≥ 30

Cumulative rate of thrombosis(%)

Log rank p=0.634
HR=0.75,
95%CI 0.23 to 2.44

— LPC(+)
-- LPC(-)

Follow-up(Months)

Number at risk

LPC(+)	13	13	11	10	10	8
LPC(-)	35	32	29	25	24	22