Autoimmunity Reviews 18 (2019) 102395

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Antiphospholipid antibodies and the risk of thrombocytopenia in patients with systemic lupus erythematosus: A systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Antiphospholipid antibodies
Systemic lupus erythematosus
Thrombocytopenia
IgM

ABSTRACT

Background: According to criteria for the classification of Systemic Lupus Erythematosus (SLE), thrombocytopenia is one of the disease-defining hematologic disorders. Since the recognition of Antiphospholipid Syndrome (APS), thrombocytopenia was frequently reported but several studies yielded contradictory results on the association between aPL-positivity and thrombocytopenia.

Methods: We evaluated the role of antiphospholipid antibodies (aPL) and different aPL profiles on the risk of thrombocytopenia in SLE patients by conducting a systematic review and meta-analysis of available literature from 1987 to 2018. MEDLINE, EMBASE, Cochrane Library, congress abstracts, and reference lists of eligible studies were searched. Studies were selected if they included SLE patients with descriptions of the exposure to aPL and the outcomes (thrombocytopenia). Two reviewers extracted study characteristics and outcome data from published reports. Estimates were pooled using random effects models and sensitivity analyses. We followed the PRISMA guidelines for all stages of the meta-analysis. PROSPERO registration number: CRD42015027378.

Results: From 3278 articles identified, 53 studies met inclusion criteria amounting to 9019 SLE patients. Twenty-nine percent of aPL-positive SLE patients had thrombocytopenia compared to 15.1% in aPL-negative SLE patients. The overall pooled Odds Ratio (OR) for thrombocytopenia in aPL positive patients was 2.48 (95% CI; 2.10–2.93). Among aPL subtypes, the risk of thrombocytopenia was highest for lupus anticoagulant (OR = 3.56 [95% CI, 2.57–5.25]), IgM anti-β_2-GP1(OR = 2.87 [95% CI; 2.57–5.25]), IgG and IgM anticardiolipin antibodies (OR = 1.87 [95% CI; 1.52–2.31] and OR = 1.73 [95% CI; 1.36–2.19] respectively).

Conclusions: The occurrence of thrombocytopenia was strongly determined by various aPL profiles in SLE patients. While the association between IgM antibodies and other APS manifestations including thrombosis is debated, IgM isotypes are helpful in the risk stratification of thrombocytopenia in SLE.

1. Introduction

Antiphospholipid antibodies (aPL) form complexes with phospholipid-binding proteins such as β_2-glycoprotein-I, promoting thrombosis [1,2]. Revised Sapporo classification criteria [1] define Antiphospholipid Syndrome (APS) as the presence of aPL on two or more occasions at least twelve weeks apart and clinical manifestations (thrombosis or pregnancy morbidity). However, many studies have identified other clinical features highly associated with aPL [3,4]; some of these "non-criteria" clinical manifestations of APS include thrombocytopenia, nephropathy, and heart valve disease [5,6]. Thrombocytopenia is defined by low platelet counts below the 2.5th lower percentile of the normal platelet distribution. It can be classified as mild ($100–149 \times 10^9$ /L), moderate ($50–99 \times 10^9$/L), and severe ($< 50 \times 10^9$ /L) [7].

Antiphospholipid Syndrome may occur as an independent disease, known as primary APS, or in association with another autoimmune condition, such as Systemic Lupus Erythematosus (SLE).

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https://doi.org/10.1016/j.autrev.2019.102395
Received 7 May 2019; Accepted 12 May 2019
Available online 11 September 2019

Thrombocytopenia can be observed in both SLE and APS [8–10].

A previous study identified two different clinical profiles in patients with aPL, one was predominantly associated with hematologic manifestations only and one was associated with thrombosis and obstetrical manifestations together with hematologic manifestations. The type of aPL associated with these different clinical subgroups remains to be established [11,12].

Therefore, the purpose of the study was to investigate an association between aPL and thrombocytopenia in patients with SLE by conducting a systematic review and meta-analysis. In addition, we aimed to determine the risk of thrombocytopenia associated with different aPL profiles.

2. Methods

2.1. Meta-analysis protocol

Our study protocol was registered on PROSPERO (CRD42015027378). We refer to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines during the planning, implementation and reporting of this study.

2.2. Data sources and search strategy

Two reviewers (Y.P.C. and S.Z.) performed searches in databases Pubmed, Embase, and Cochrane Library for systematic review, we also hand-searched relevant articles. We reviewed congress abstracts and reference lists from relevant studies. We searched articles from 1986 to May 2018 and we did not restrict the search to study design, publication date or language. We used the following search terms: *Antibodies, Antiphospholipid; Antiphospholipid Syndrome; Lupus Coagulation Inhibitor; Antibodies, Anticardiolipin; beta2-Glycoprotein I; Systemic Lupus Erythematosus; Thrombocytopenia; Low platelet count.*

2.3. Study selection

We determined the selection criteria prior to data collection. The inclusion criteria we used for the selected studies was as follows: Studies must include SLE patients of any sex and age fulfilling four or more ACR classification criteria with reported laboratory values of thrombocytopenia [13]. Studies also must report their results on the association between aPL (exposure) and thrombocytopenia (outcome). Exposure to aPL was as defined by laboratory measurement in the included studies. The aPL described in the studies were either one or more of the following aPL: lupus anticoagulant (LA), anticardiolipin antibodies (aCL) IgG or M, anti-β_2-glycoprotein 1 antibodies (aβ_2-GP1) IgG or M. The definition of thrombocytopenia was reported by authors of each included study. We included cohort, case-control and cross-sectional studies. Studies were excluded if they recruited participants with other autoimmune condition apart from SLE, or specific SLE manifestations only (i.e lupus nephritis, cutaneous lupus). We restricted this analysis to English papers and we excluded unpublished abstracts as we were unable to extract data both quantitatively and qualitatively.

2.4. Search and data extraction

Two reviewers (Y.P.C. and S.Z.) independently screened all the studies from our search. We utilized a systematic review management software to screen and organize the studies (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Duplicate studies were detected by Covidence hence eliminated. Potential eligible studies (search) and data (extraction) were compared and any discrepancies were resolved via consensus between both reviewers.

2.5. Extraction of data and data synthesis

The primary outcome studied was thrombocytopenia, we analyzed the association between the main exposure (aPL) and outcome from each study. The reviewers (Y.P.C. and S.Z.) each independently extracted data into a Microsoft Excel spreadsheet using 2×2 contingency tables. We also performed secondary analyses by assessing the relationship of thrombocytopenia with different aPL subtypes (LA, aCL, aβ_2GP1), isotypes (aCL IgG, M and aβ_2GP1 IgG, M) and titers (low vs. high aCL titers according to authors of primary papers) to compare if thrombocytopenia was more frequently encountered with a specific subtype of aPL.

2.6. Sensitivity analyses

We conducted sensitivity analyses by evaluating the impact of the following on the risk estimates: a) Location of research (America, Africa, Europe, Asia), b) publication period (1980–1989, 1990–1999, 2000–2009, 2010–2018), c) study design (cohort, cross-sectional, case-control), d) inclusion of patients (consecutive vs. non-consecutive), e) platelet count laboratory value cutoff (100×10^9/L and 50×10^9/L).

2.7. Assessment of methodological quality

To control the quality of the observational studies included in the meta-analysis, we used the Newcastle-Ottawa Score (NOS) to achieve this [14]. Two reviewers (Y.P.C. and T.M.) evaluated all included studies independently. The NOS quality assessment encompassed 7 items with questions evaluating each study in the following categories: a) methods of selecting study participants, b) adequacy of the sample size to generate adequate power, c) appropriateness of statistical methods, d) appropriateness of measuring outcome variables. Each item is rated from 0 (high risk of bias) to 3 (low risk of bias) thus NOS ranges from 0 to 21. The higher the score reflects higher quality of the study.

For every one study, each reviewer independently provided a score for each category and a total score was obtained. Mean total scores obtained from two reviewers were used for analyses.

2.8. Assessment of heterogeneity

We assessed heterogeneity among studies with the use of the I^2 statistics (low = 25.0%; moderate = 50.0%; high = 75.0%) [15].

2.9. Publication bias

We examined the extent of publication bias through both a visual inspection of funnel plot asymmetry, and Begg and Mazumdar's rank correlation test and Egger's test. The presence of a publication bias was handled through the use of the Duval and Tweedie's trim and fill method which can adjust for missing studies by adding negative small studies to the main analysis and provide a better approximation of the point estimate of the overall effect size [16]. To test the robustness of our data we determined the classic fail-safe number using the Rosenthal's method which correspond to the number of non-significant unpublished or missing studies that would need to be added to our meta-analysis to reduce our overall statistically significant observed result to non-significance [17].

2.10. Cumulative meta-analyses

We performed cumulative meta-analyses according to a) ascending publication date to allow assessment of the changes in association between exposure to aPL and thrombocytopenia in SLE patients over time; b) increasing study size to reveal how many patients are needed until statistical significance is obtained; and c) increasing NOS to determine whether high quality studies impact the overall risk estimate.

Study (first author)	Year	Patients, n	Total patients, n
Macchi	1997	21	21
Gao	2013	22	43
Golstein	1993	24	67
Pauzner	1986	32	99
Averbuch	1987	36	135
Asherson	1993	37	172
Fanopoulos	1998	46	218
Stratta	1992	54	272
Padmakumar	1990	55	327
Rai	2015	55	382
Sahin	2007	59	441
Altintas	2008	62	503
Cronin	1988	64	567
Sebastiani	1991	64	631
Jouhikainen	1993	74	705
Michel	2002	64	769
Ishii	1990	68	837
Marschalko	1998	69	906
Falcao	2002	70	976
Mitic	2002	72	1048
Sturfelt	1987	75	1123
Shrivastava	2001	76	1199
Weinstein	1987	78	1277
Teixido	1997	79	1356
Amoroso	2003	87	1443
Intraugumtornchai	1993	91	1534
Lopez- Soto	1997	92	1626
Ninomiya	1992	97	1723
McHugh	1988	98	1821
Basiri	2013	100	1921
Picillo	1992	102	2023
Ghirardello	1994	105	2128
Derksen	1988	106	2234
Wang	1990	108	2342
Romero	1998	118	2460
McClain	2004	130	2590
Gulko	1993	139	2729
Kaburaki	1995	140	2869
Jallouli	2012	148	3017
Ziakias	2006	150	3167
Lockshin	2000	157	3324
Nojima	1999	180	3504
Deak	2014	224	3728
Cucurull	1999	238	3966
Sachsce	1995	353	4319
Scofield	2003	387	4706
Abu-Shakra	1995	390	5096
Skare	2015	443	5539
Deleze	1989	500	6039
Sebastiani	1999	574	6613
Fernandez	2007	616	7239
Cervera	1999	842	8071
Gonzalez-Naranjo	2016	948	9019

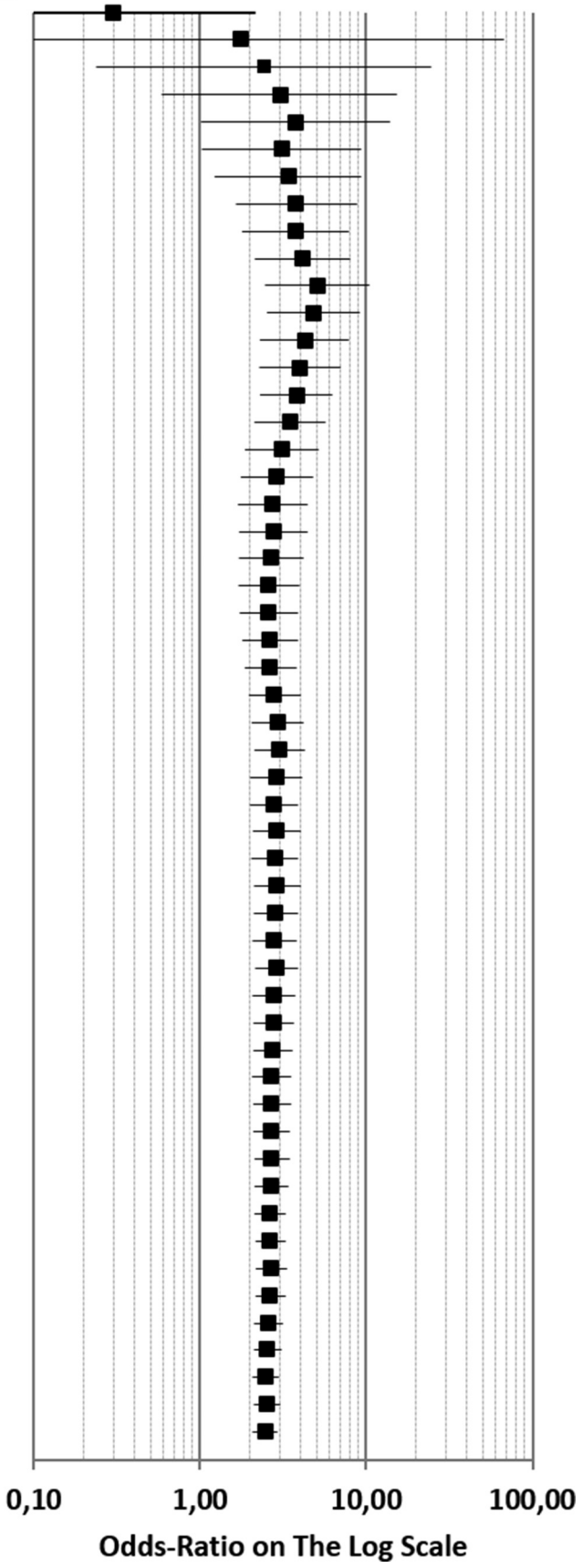

Fig. 1. Study flow chart.

Table 1
Characteristics of included studies.

First author[reference]	Year of publication	Country	SLE patients (included in the analysis/total), n	Female, n (%)	Mean or median age	Exposure to aPL	Thrombocytopenia threshold (/mm^3)
Cohort studies							
Abu-Shakra [36]	1995	Canada	390	343 (88)	30	aCL	NR
Averbuch [37]	1987	Israel	36	32 (89)	39.5–40.8	LA	100,000
Cucurull [38]	1999	Spain, Colombia	238/320	224 (70)	29.7–31.9	aCL IgG/M, aβ$_2$GP1 IgG/M	NR
Deak [39	2014	Hungary	224	204 (91)	49	Overall aPL	NR
Deleze [40]	1989	Mexico	500	NR	NR	aCL, aCL IgG/M	NR
Fernandez [41]	2007	United States of America	616	554 (90)	34.4	Overall aPL	100,000
Golstein [42]	1993	France	24	NR	33	Overall aPL	NR
Gonzalez-Naranjo [43]	2016	Mutiple locations in Central America	948/1437	853 (90)	28.7	Overall aPL (based on LA, aCL IgG/M, aβ$_2$GP1)	100,000
Gulko [44]	1993	United Kingdom	139	107 (77)	NR	aCL	NR
Jallouli [45]	2012	Tunisia	148/182	160 (88)	30.6	aCL IgG/M, APS, LA	100,000
Lockshin [46]	2000	United States of America	157/243	230 (95)	40.1	APS	100,000
Lopez-Soto [47]	1997	Spain	92	84 (91)	33	LA, aCL	NR
Macchi [48]	1997	France	21/68	56 (82)	46	Overall aPL (based on LA, aCL, aCL IgG/M)	NR
McHugh [49]	1988	United Kingdom	98	85 (87)	NR	aCL IgG	NR
Padmakumar [50]	1990	India	55	54 (98)	24.9	LA	NR
Picillo [51]	1992	Italy	102	90 (88)	24	aCL	NR
Romero [52]	1998	United Kingdom	118	114 (97)	40	aβ$_2$GP1 IgG	NR
Sachse [53]	1995	Germany	353/368	332 (90)	48	aCL IgG/M	NR
Sebastiani [54]	1991	Italy	64	55 (92)	35.1	aCL	100,000
Sebastiani [55]	1999	Italy	574	523 (91)	37.9	aCL IgG	100,000
Skare [56]	2015	Brazil	443	430 (97)	NR	APS, LA, aCL IgG/M	100,000
Stratta [57]	1992	Italy	54/ 124	NR	NR	LA	NR
Sturfelt [58]	1992	Sweden	75	61 (81)	50[a]	aCL	NR
Weinstein [59]	1987	Australia	78	73 (94)	38	aCL	NR
Cross-sectional studies							
Amoroso [60]	2003	Italy	87	77 (89)	41	aCL IgG/M, aβ$_2$GP1 IgG/M, aPA IgG/M, aPI IgG/M, aPS IgG/M,	NR
Asherson [61]	1993	UK, France	37	30 (81)	37	Overall aPL (based on LA, aCL)	NR
Basiri [62]	2013	Middle East	100	88 (88)	42	aCL	NR
Cervera [63]	1999	Belgium, Norway	842/1000	908 (91)	37	LA, aCL IgG	NR
Cronin [64]	1988	United States of America	64	NR	NR	aCL IgG/M	NR
Derksen [65]	1988	The Netherlands	106/111	96 (86)	31[a]	Overall aPL (based on LA)	NR
Ghiradello [66]	1994	Italy	105	97 (92)	37	Overall aPL (based on LA, aCL IgM/G)	NR
Ishii [67]	1990	Japan	68/155	145 (94)	34	aCL IgG	NR
Kaburaki [68]	1995	Japan	140	124 (89)	34.1	aβ$_2$GP1 IgG	NR
Ninomiya [69]	1992	Japan	97	NR	NR	LA, aCL	NR
Pauzner [70]	1986	Israel	32/66	57 (86)	30	LA	NR
Rai [71]	2015	India	55	NR	NR	Overall aPL (based on LA, aCL)	NR
Scofield [72]	2003	United States of America	387	NR	NR	Overall aPL	100,000
Case-control studies							
Altintas [73]	2008	Turkey	62	51 (82)	37	aCL IgG/M, aβ$_2$GP1 IgG	NR
Falcao [74]	2002	Brazil	70	67 (96)	33.5	Overall aPL, aCL IgG	NR
Fanopoulos [75]	1998	United States of America	46	30 (65)	NR	Overall aPL (based on aCL IgG/M/A, aβ$_2$GP1 IgG/M/A)	NR
Gao [76]	2013	China	22/26	23 (88)	30.8	Overall aPL (based on aCL, LA)	NR
Intragumtornchai [77]	1993	Thailand	91	89 (98)	30.6	LA	NR
Jouhikainen [78]	1993	Finland	74	NR	23	LA	NR
Marschalko [79]	1998	Hungary	69/289	NR	NR	aCL IgG	150,000
McClain [80]	2004	United States of America	130	84 (65)	30.4	aCL	NR
Michel [81]	2002	France	64	NR	34.5	aCL, aCL IgG/M	50,000
Mitic [82]	2002	Serbia	72	66 (92)	37.03	Overall aPL (based on LA, aCL)	NR
Nojima [83]	1999	Japan	180	164 (91)	40.6	LA, aCL	NR
Sahin [84]	2007	Turkey	59	53 (90)	35	APS	NR
Shrivastava [85]	2001	India	76	71 (93)	24	aCL, aβ$_2$GP1	100,000

(*continued on next page*)

Table 1 (*continued*)

First author[reference]	Year of publication	Country	SLE patients (included in the analysis/total), n	Female, n (%)	Mean or median age	Exposure to aPL	Thrombocytopenia threshold (/mm^3)
Teixido [86]	1997	Spain	79	72 (91)	41.3	Overall aPL, aβ$_2$GP1	NR
Wang [87]	1990	Australia	108/111	105 (95)	39.5	aCL, aCL IgG/M	NR
Ziakias [88]	2006	Greece	150	NR	27.4	APS, aCL, aCL IgG/M	100,000

Underlined: aPL exposure included in the main analysis.
Abbreviations: APS, antiphospholipid syndrome; aCL, anticardiolipin antibodies; aβ$_2$GP1, anti-β$_2$-glycoprotein 1 antibodies; aPA, antiphosphatidic acid; aPI, antiphosphoinositol; aPS, antiphosphatidylserine; LA, lupus anticoagulant; SLE, Systemic Lupus Erythematosus.
NR: not reported.
[a] Median.

2.11. Statistical tests

To perform the meta-analysis, we used the following softwares: Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014 and Comprehensive meta-analysis Version 2.2.064. We calculated the odds ratio for dichotomous outcomes. The extracted results were combined in the meta-analysis using the random-effects model. Two-sided *P* values were calculated with a P value < .05 considered significant for all tests.

3. Results

3.1. Literature flow chart and study characteristics

We identified 3278 articles with the use of MEDLINE, EMBASE, Cochrane Library, conference abstracts, and hand searching from 1987 to 2018. We included 53 studies in the quantitative and qualitative analysis (Fig. 1 and Table 1). Majority for the studies (n = 27) were published between years 1990 to 1999, 19 studies were published between years 2000 to 2018. All studies were in the English language. The designs of the studies were categorized into cohort (n = 24), cross-sectional (n = 13) and case-control (n = 16).

3.2. Patients characteristics

Total number of SLE participants was 9019, taking into account the studies that reported sex of participants, the total number of female participants was 5948 (65.9%). The mean age of participants ranged from 27.4 years to 49 years (Table 1) Thirty six studies reported the presence of aCL, eighteen studies assessed LA, eight studies evaluated aβ$_2$GP1 and one study did not specify aPL subtypes. Most studies (n = 41) did not precisely define laboratory values for 'thrombocytopenia'. Thrombocytopenia was defined as platelet count of 50 × 10^9/L or less in one study, equal to 100 × 10^9/L or less in ten studies and equal to 150 × 10^9/L or less in one study.

3.3. Risk of thrombocytopenia associated with antiphospholipid antibodies in systemic lupus erythematosus patients

Of the 53 studies including 9019 SLE patients, 943/3254 (29.0%) of aPL-positive patients had thrombocytopenia and 872/5765 (15.1%) cases of thrombocytopenia was observed in aPL-negative patients. The percentage of patients having thrombocytopenia in LA-positive vs LA-negative patients was 34.9% vs. 13.1%, IgG aCL 30.7% vs. 17.1%, IgM aCL 35.8% vs. 23.4%, IgG aβ$_2$GP1 26.3% vs. 17.3%, and IgM aβ$_2$GP1 37.8% vs. 17.7%. The OR for thrombocytopenia in aPL-positive patients compared to aPL-negative patients was 2.48 (95% CI; 2.10 to 2.93) (Fig. 2). The heterogeneity was moderate justifying the use of a random model (I^2 = 36%, p = .0006). The risk for thrombocytopenia was significantly increased in SLE patients with any aPL test except for IgG aβ$_2$GP1 (Table 2). The risk for developing thrombocytopenia in SLE patients with high aCL titers tended to be higher than with low aCL titers without reaching statistical significance.

3.4. Determinants of the risk estimates of thrombocytopenia associated with antiphospholipid antibodies in systemic lupus erythematosus patients

The magnitude of the risk of thrombocytopenia was similar (OR above 2) among studies performed in different regions of the world (Table 3); however based on one study only, the risk was non-significant in Africa. In studies performed in Asia and Middle East, the risk estimates was above 3. The risk of thrombocytopenia was quite stable across the publication periods. Of note the risk was lower but still significant in cohort studies in comparison with other studies (i.e. case-control or cross-sectional). Finally, the cut-off of 100 × 10^9/L was the only one significantly associated with aPL positivity while others did not reach statistical significance.

3.5. Quality assessment

The agreement between evaluators, measured by the ICC was very good (ICC = 0.96 [95% CI; 0.93–0.98]). The mean NOS for all primary studies being evaluated was 15.57 ± 3.46 (min = 4.5; max = 20.5). While correlation between mean NOS and publication year was not significant (R^2 = 0.001, P = .79), we found a negative correlation between mean NOS and log(OR) (R^2 = 0.39, P < .0001).

3.6. Assessment of statistical heterogeneity among primary studies

Primary studies reported either a statistically significant association between aPL and thrombocytopenia in SLE patients (n = 26) or no significant association (n = 27). Depending on aPL tests, a significant moderate heterogeneity among studies was identified and ranged from 14% to 57% (Table 2).

3.7. Cumulative meta-analyses

When ordered by increasing study size (Fig. 3), studies with large sample size were associated with lower risk estimates. The cumulative meta-analysis of studies arranged by ascending publication date (Fig. 4) demonstrated that the risk estimate of thrombocytopenia was highly variable between 1986 and 1999 and stable afterwards. Finally, when ordered by increasing NOS (Fig. 5), studies of high quality were associated with lower risk estimates.

3.8. Publication bias

The funnel plot generated for this meta-analysis revealed mild asymmetry with more positive studies published than negative studies (Fig. 6). The Begg and Mazumdar rank correlation test (P = .036) and the Egger's test (P = .005) confirmed a statistically significant publication bias. After adjustment using the Tweedie's trim and fill method, the risk of thrombocytopenia was still significantly increased:

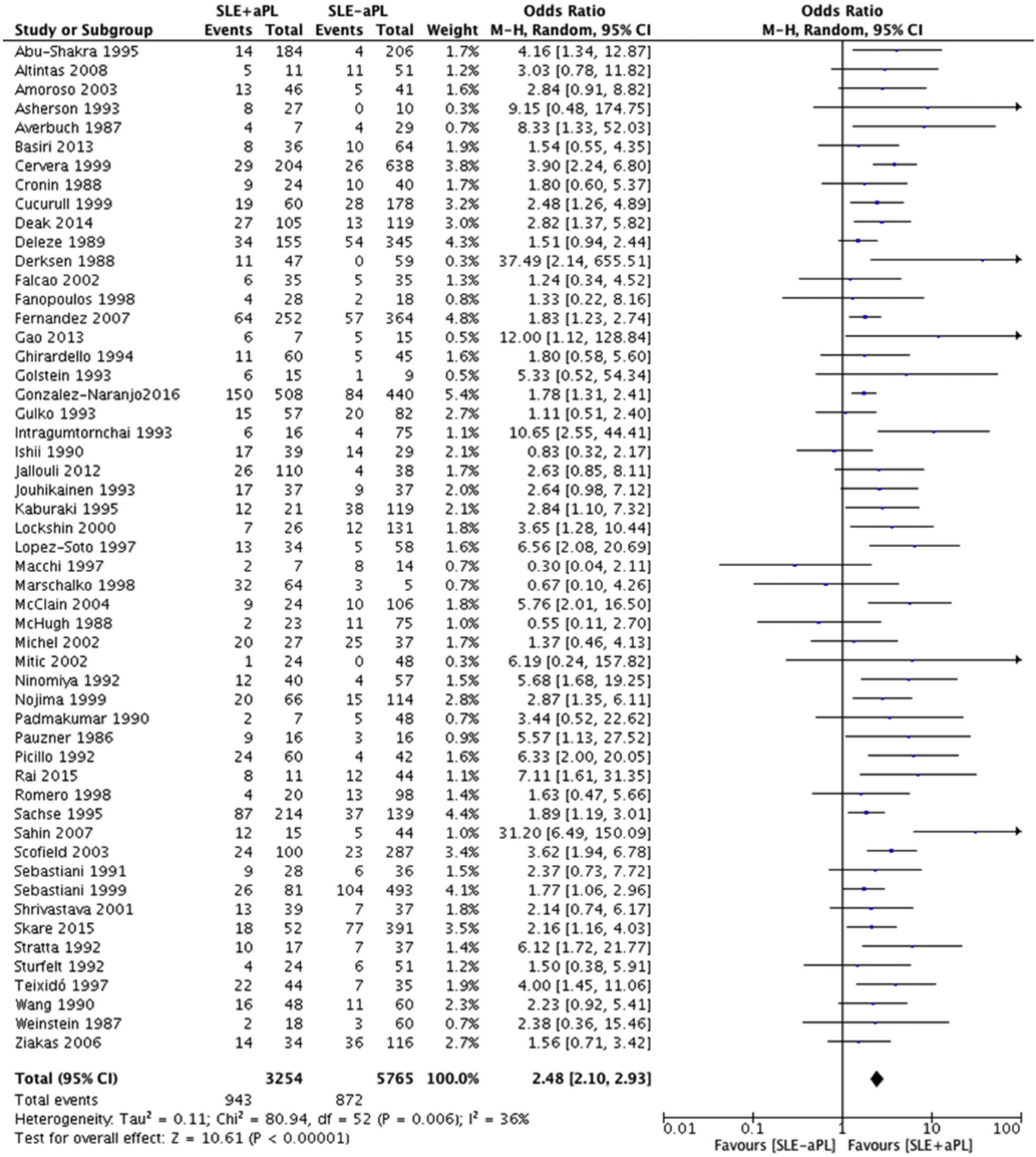

Fig. 2. Pooled data evaluating the risk of thrombocytopenia in SLE patients.

$OR_{adjusted}$ = 2.11 [95% CI; 1.88 to 2.36] (random effects). The classic fail-safe number, corresponding to the number of non-significant unpublished or missing studies that would need to be added to our meta-analysis to reduce our overall statistically significant observed result to non-significance, was 2471 i.e. 46 missing studies for every observed study (n = 53) would be needed to nullify the effect size.

4. Discussion

In this systematic review and meta-analysis including 53 studies and 9091 SLE patients, we demonstrated that aPL strongly determine the risk of thrombocytopenia. While overall aPL positivity was associated with a 2.5-fold increased risk of thrombocytopenia, specific aPL tests, i.e., LA, IgG and IgM aCL as well as IgM aβ_2GP1 profiles, were associated with a higher risk for thrombocytopenia.

Table 2
Risk of Thrombocytopenia According to Types of Antiphospholipid Antibodies.

Sensitivity Analysis	OR (95% CI)	Studies, n	Patients, n	Heterogeneity
Antiphospholipid Syndrome	3.51 (1.86 to 6.61)	7	266	I^2 = 57%, p = .03
Overall aPL	2.48 (2.10 to 2.93)	53	9019	I^2 = 36%, p = .006
Type of aPL test				
Lupus Anticoagulant	3.56 (2.57 to 5.25)	16	2177	I^2 = 30%, p = .12
Anticardiolipin antibodies	2.14 (1.76 to 2.60)	23	5723	I^2 = 26%, p = .09
IgG	1.87 (1.52 to 2.31)	19	3991	I^2 = 14%, p = .28
IgM	1.73 (1.36 to 2.19)	16	2315	I^2 = 0%, p = .95
High titre	6.71 (0.94 to 48.03)	2	127	I^2 = 79%, p = .03
Low titre	0.56 (0.12 to 2.64)	2	82	I^2 = 0%, p = .78
Anti-β_2GP1 antibodies	2.06 (1.35 to 3.13)	7	192	I^2 = 0%, p = .43
IgG	1.74 (0.97 to 3.11)	4	94	I^2 = 0%, p = .78
IgM	2.87 (1.37 to 6.00)	2	54	I^2 = 0%, p = .33

aPL, Antiphospholipid Antibodies; Anti-β_2-GP1, Anti-β_2-Glycoprotein 1.

Table 3
Risk of thrombocytopenia according to studies characteristics and methodology.

Sensitivity analysis	OR (95% CI)	Studies, n	Patients, n	Heterogeneity
Study characteristics				
Location				
Africa	2.63 (0.85 to 8.11)	1	148	Not applicable
America	2.06 (1.66 to 2.55)	13	4128	I^2 = 7%, p = .37
Asia	3.27 (1.92 to 5.56)	9	784	I^2 = 43%, p = .08
Australasia	2.25 (1.01 to 5.03)	2	186	I^2 = 0%, p = .95
Europe	2.63 (1.96 to 3.53)	25	3605	I^2 = 44%, p = .01
Middle East	3.38 (1.15 to 9.96)	3	253	I^2 = 40%, p = .19
Period of publication				
2010–2018	2.17 (1.61 to 2.91)	7	1940	I^2 = 14%, p = .33
2000–2009	2.75 (1.86 to 4.05)	12	1930	I^2 = 47%, p = .04
1990–1999	2.51 (1.98 to 3.20)	27	4235	I^2 = 33%, p = .05
1980–1989	2.43 (1.17 to 5.03)	7	914	I^2 = 50%, p = .06
Study design				
Cohort	2.10 (1.74 to 2.54)	24	5547	I^2 = 23%, p = .15
Case- control	2.89 (1.95 to 4.28)	13	2120	I^2 = 40%, p = .05
Cross- sectional	2.93 (2.03 to 4.22)	16	1352	I^2 = 33%, p = .12
Study methodology				
Inclusion of patients				
Consecutive patients	2.58 (1.92 to 3.45)	15	3537	I^2 = 36%, p = .08
Non-consecutive or NR	2.45 (1.98 to 3.03)	38	5482	I^2 = 37%, p = .01
Thrombocytopenia definition (/mm^3)				
150,000	0.67 (0.10 to 4.26)	1	69	Not applicable
100,000	1.99 (1.66 to 2.93)	10	3442	I^2 = 0%, p = .58
50,000	1.37 (0.46 to 4.13)	1	64	Not applicable
NR	2.59 (2.22 to 3.02)	41	6497	I^2 = 40%, p = .005

NR, Not reported.

The association between thrombocytopenia and aPL in SLE patients is widely accepted but the degree of association and its statistical significance were poorly documented. By summarizing the literature, we confirmed a clear and substantially increased risk of thrombocytopenia associated with aPL in SLE patients. This formal meta-analysis enabled us to examine these associations in greater details with enhanced statistical power, and to calculate the magnitude of the associations and to identify their significance.

Thrombocytopenia was associated with LA positivity and IgG aCL (Table 2). This is in line with previously demonstrated associations between aPL and clinical manifestations of APS, whether included in classification criteria (in particular thrombosis [2]) or not (such as heart valve disease [3] or pulmonary hypertension [4]). Recent data show that IgM aPL isotypes were less likely to be associated with thrombosis that IgG and their diagnostic value in this setting is being questioned. Interestingly we show the opposite for thrombocytopenia, i.e. that IgM aCL and aβ_2GP1 antibodies are significantly associated with thrombocytopenia in the setting of SLE [18,19]. Thus, for some clinical manifestations such as thrombocytopenia, IgM may have an unexpected diagnostic value. Preliminary data suggest that this may also be the case for autoimmune hemolytic anemia [20].

Qualitative analysis was performed with a very good agreement between raters. In most studies, thrombocytopenia threshold was not reported and no confounders that may influence the risk of thrombocytopenia were investigated. Finally, further analyses demonstrated that low quality studies (cross-sectional or case-control vs. cohort, or low quality score) tended to overestimate the risk estimate but with a low impact on overall results.

4.1. Clinical importance

The clinical importance of thrombocytopenia in SLE is confirmed by a dramatic increased mortality rate in lupus patients without a complete remission of their thrombocytopenia vs. those with a complete remission [21]. Besides mortality, lupus patients with thrombocytopenia are exposed to a higher risk of bleeding depending on its severity: from 25% when platelets are between 21 to 50 $\times$ 10^9/L to 76% when platelets drop below 20 $\times$ 10^9/L. [22–24] In aPL-positive patients, management of bleeding due to severe thrombocytopenia is challenging due to the baseline increased thrombotic risk [11,25]. In patients with

Study (first author)	Year	Patients, n	Total patients, n
Macchi	1997	21	21
Gao	2013	22	43
Golstein	1993	24	67
Pauzner	1986	32	99
Averbuch	1987	36	135
Asherson	1993	37	172
Fanopoulos	1998	46	218
Stratta	1992	54	272
Padmakumar	1990	55	327
Rai	2015	55	382
Sahin	2007	59	441
Altintas	2008	62	503
Cronin	1988	64	567
Sebastiani	1991	64	631
Jouhikainen	1993	74	705
Michel	2002	64	769
Ishii	1990	68	837
Marschalko	1998	69	906
Falcao	2002	70	976
Mitic	2002	72	1048
Sturfelt	1987	75	1123
Shrivastava	2001	76	1199
Weinstein	1987	78	1277
Teixido	1997	79	1356
Amoroso	2003	87	1443
Intraugumtornchai	1993	91	1534
Lopez- Soto	1997	92	1626
Ninomiya	1992	97	1723
McHugh	1988	98	1821
Basiri	2013	100	1921
Picillo	1992	102	2023
Ghirardello	1994	105	2128
Derksen	1988	106	2234
Wang	1990	108	2342
Romero	1998	118	2460
McClain	2004	130	2590
Gulko	1993	139	2729
Kaburaki	1995	140	2869
Jallouli	2012	148	3017
Ziakias	2006	150	3167
Lockshin	2000	157	3324
Nojima	1999	180	3504
Deak	2014	224	3728
Cucurull	1999	238	3966
Sachsce	1995	353	4319
Scofield	2003	387	4706
Abu-Shakra	1995	390	5096
Skare	2015	443	5539
Deleze	1989	500	6039
Sebastiani	1999	574	6613
Fernandez	2007	616	7239
Cervera	1999	842	8071
Gonzalez-Naranjo	2016	948	9019

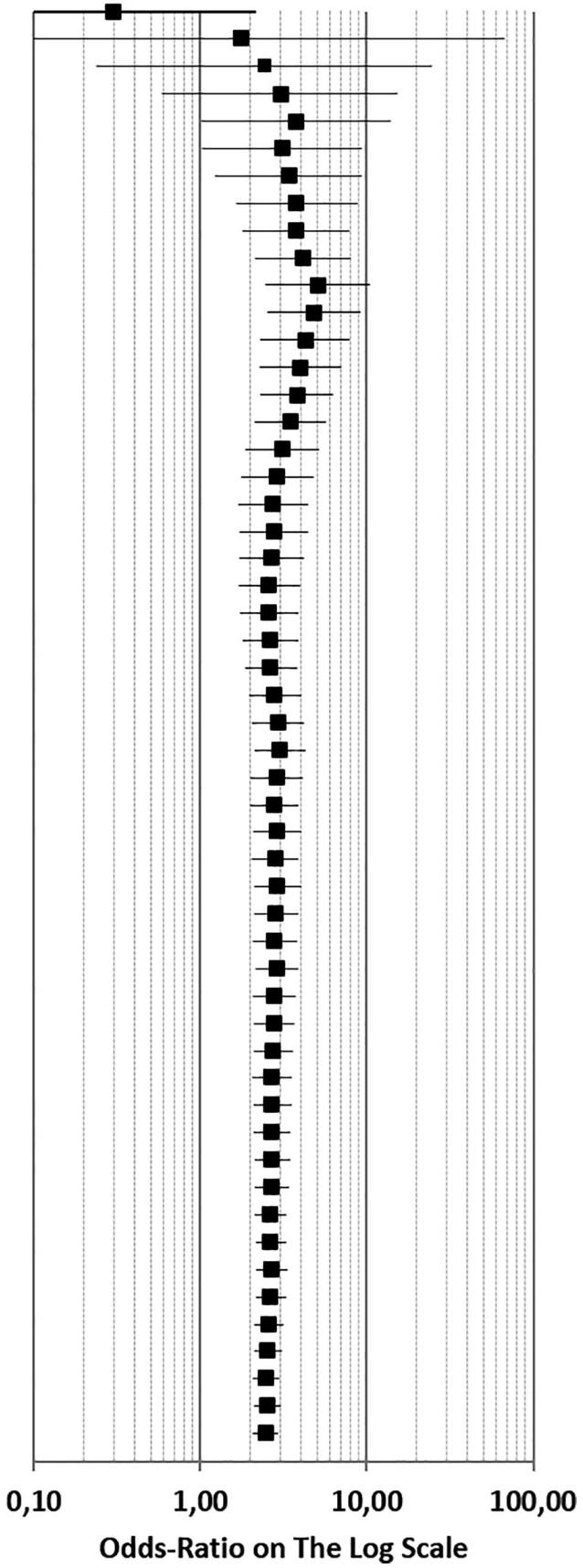

Fig. 3. Cumulative meta-analyses according to increasing study size.

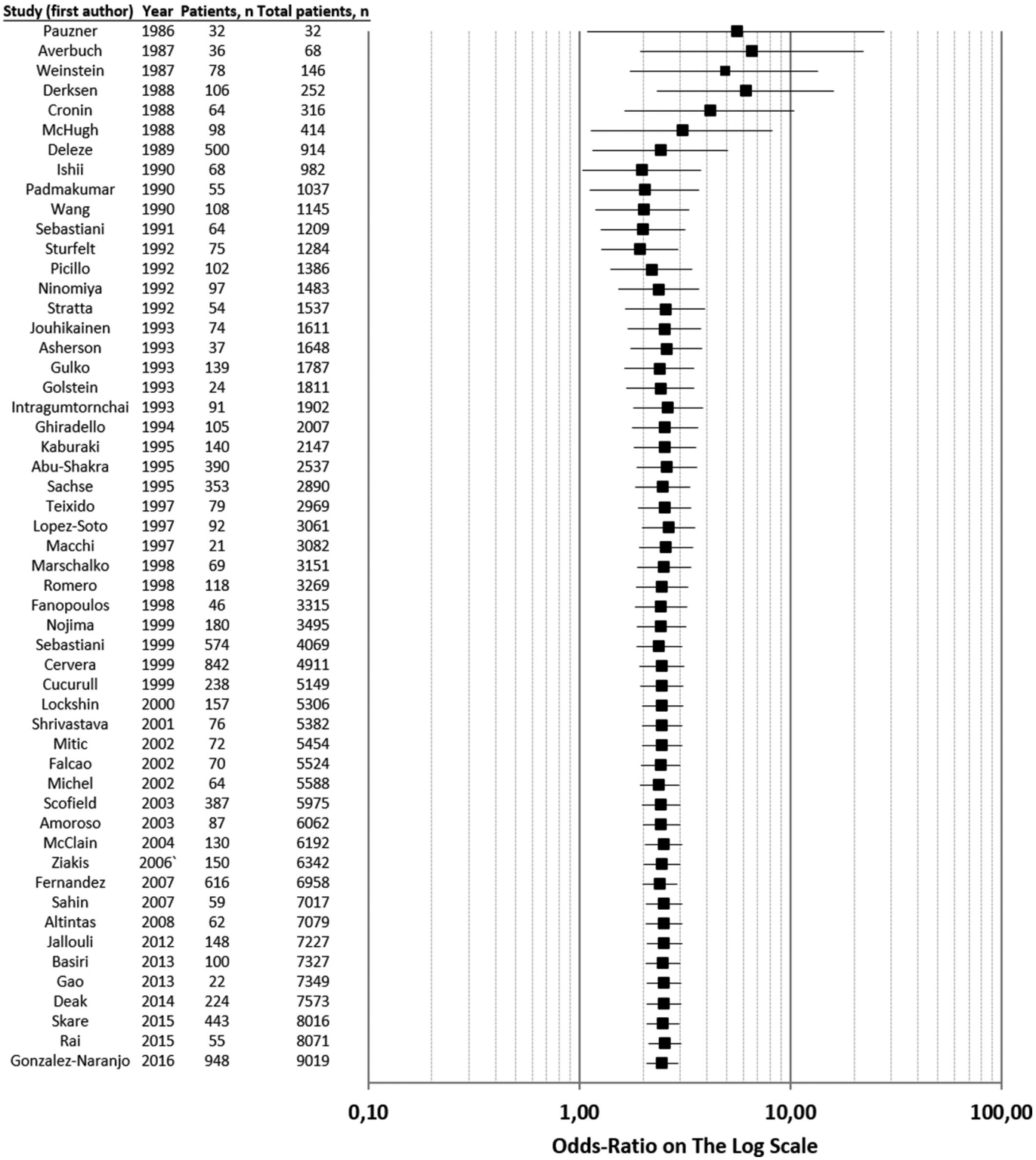

Fig. 4. Cumulative meta-analyses according to increasing publication date.

moderate thrombocytopenia, persistence of a high thrombotic risk profile and thrombosis usually requires continuation of anticoagulant therapy [26,27].

4.2. Plausibility

The results from our study are plausible based on known pathophysiology and pathogenesis of aPL. Autoantibodies toward glycoproteins on platelet surfaces are present in patients with aPLs resulting in platelet destruction [28,29]. Patients with thrombocytopenia and aPL include several subsets of patients: some develop classical thrombotic and/or obstetric APS whereas others will mainly have hematologic manifestations [11]. Platelet-associated immunoglobulins include IgM and IgG isotypes in immune thrombocytopenia [30]. Recent data indicate that sole IgM positivity is not associated with a higher thrombotic risk in APS [19]. Thus the difference in clinical

Study (first author)	Year	Patients, n	Total patients, n
Intragumtornchai	1993	91	91
Stratta	1992	54	145
Rai	2015	55	200
Teixido	1997	79	279
Basiri	2013	100	379
Pauzner	1986	32	411
Averbuch	1987	36	447
Weinstein	1987	78	525
Macchi	1997	21	546
Skare	2015	443	989
Asherson	1993	37	1026
Gao	2013	22	1048
McHugh	1988	98	1146
Wang	1990	108	1254
Golstein	1993	24	1278
Mitic	2002	72	1350
Marschalko	2005	69	1419
Sahin	2007	59	1478
Sebastiani	1991	64	1542
Ghiradello	1994	105	1647
Lopez-Soto	1997	92	1739
Falcao	2002	70	1809
Shrivastava	2001	76	1885
Padmakumar	1990	55	1940
Picillo	1992	102	2042
Jouhikainen	1993	74	2116
Sachse	1995	353	2469
Michel	2002	64	2533
Altintas	2008	62	2595
Amoroso	2003	87	2682
Deleze	1989	500	3182
Cronin	1988	64	3246
Abu- Shakra	1995	390	3636
Ziakis	2006	150	3786
Romero	1998	118	3904
Fanopoulos	1998	46	3950
Derksen	1988	106	4056
Gonzalez-Naranjo	2016	948	5004
Nojima	1999	180	5184
Ishii	1990	68	5252
Ninomiya	1992	97	5349
Sebastiani	1999	574	5923
Gulko	1993	139	6062
Kaburaki	1995	140	6202
Sturfelt	1992	75	6277
Cucurull	1999	238	6515
Jallouli	2012	148	6663
McClain	2004	130	6793
Lockshin	2000	157	6950
Deak	2014	224	7174
Cervera	1999	842	8016
Scofield	2003	387	8403
Fernandez	2005	616	9019

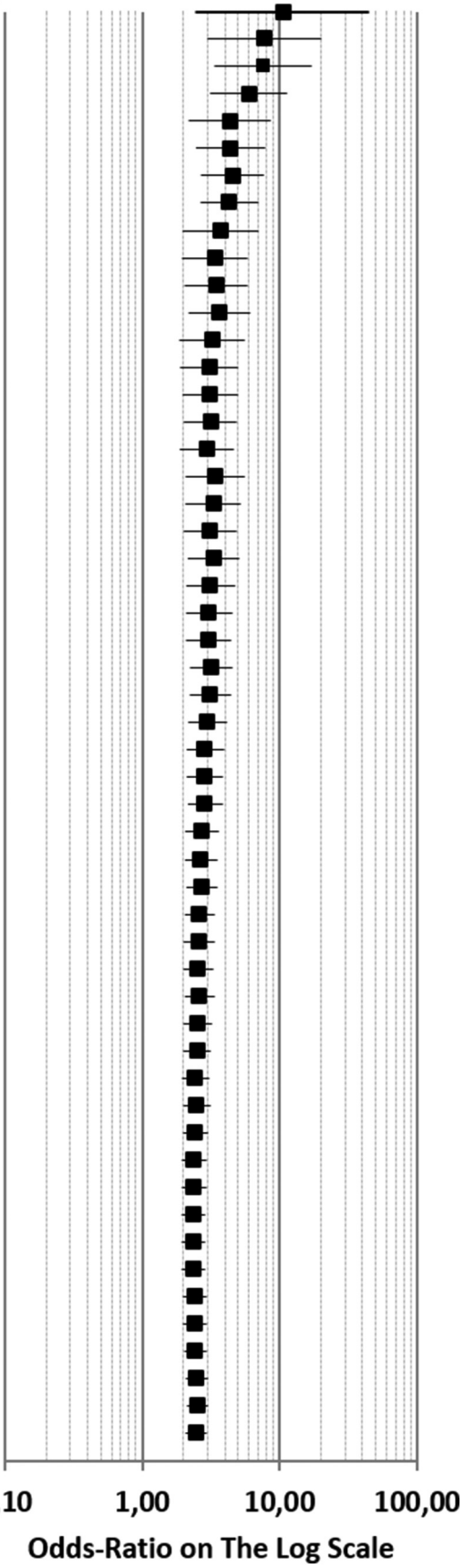

Fig. 5. Cumulative meta-analyses according to increasing NOS.

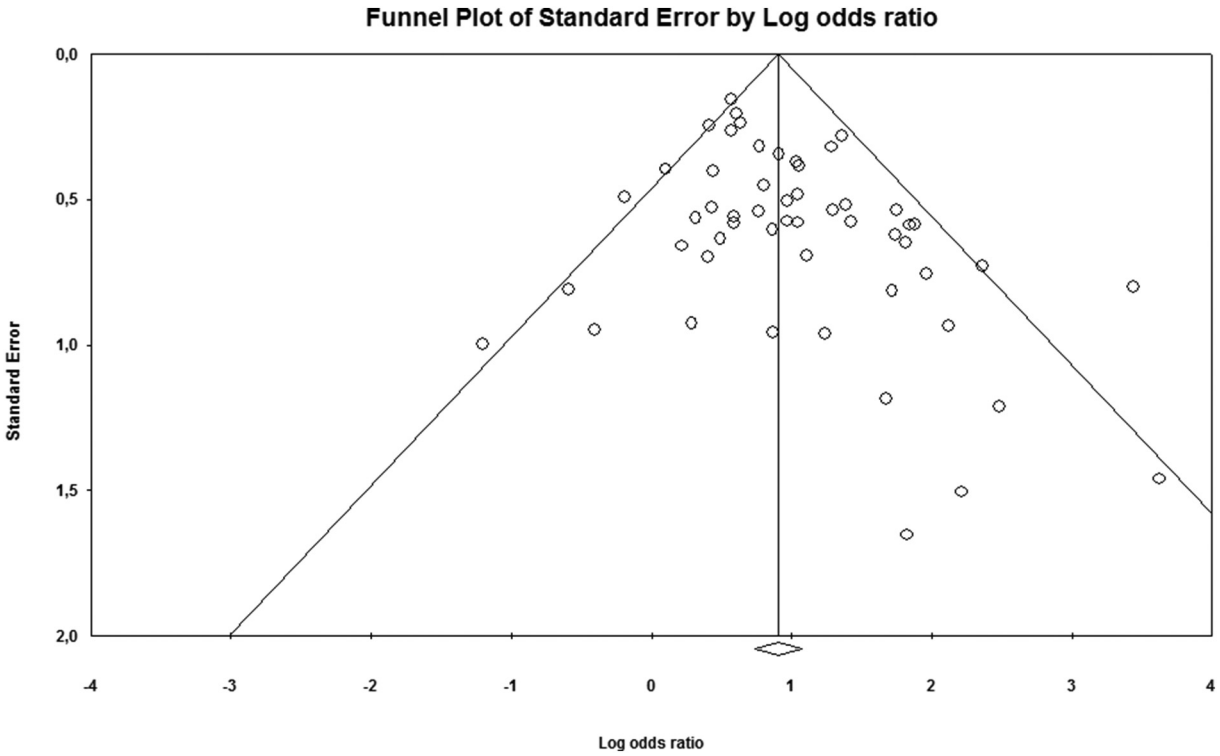

Fig. 6. Funnel plot of the risk of thrombocytopenia associated with antiphospholipid antibodies in systemic lupus erythematosus patients.

presentations in APS with thrombocytopenia could be explained by aPL profiles. In patients with immune thrombocytopenia, endothelial cell activation is observed only in patients with IgG aPL. Furthermore IgG from patients with LA have enhanced platelet and endothelial cells activation. Patients with immune thrombocytopenia and such aPL profiles are at risk of thrombosis when correction of thrombocytopenia is obtained [31]. In the same line it has been demonstrated that IgG aPL activate the mTORC pathway of vascular endothelial cells. Whether the inhibition of the mTORC pathway could decrease platelet activation and thus thrombus formation in APS remains a challenging research question [32,33]. Finally, the overall plausibility of our meta-analysis results are supported by the computation of the fail-safe number indicating that > 2400 studies would be required to reduce our overall statistically significant observed result to non-significance. This large number relative to the 53 primary studies included in our meta-analysis strongly sustains our results and allows us to be confident in our conclusions.

For thrombocytopenia management, our results may help risk stratification: while patients with LA and aCL IgG are at high risk of thrombosis [31] in particular in association with aβ_2GPI antibodies, this is not the case for IgM aCL and aβ_2GP1. Regarding the use of thrombopoietin-receptor agonists, several thrombotic recurrences including catastrophic APS occurred during follow-up of patients with aPL. Thus, it has been recommended that aPL should be systematically screened before the initiation of thrombopoietin-receptor agonists in SLE patients [34]. Our results suggest the use of thrombopoietin-receptor agonists for SLE aPL-positive patients should be avoided in patients with LA or IgG aPL but could be considered in patients with isolated IgM aCL or aβ_2GP1.

4.3. Limitations

Some methodological issues warrant consideration. First, most studies included in the review and meta-analysis did not stipulate the laboratory cut-off value used to define thrombocytopenia. However in our sensitivity analyses, we were able to identify that a value of 100×10^9/L as the definition of thrombocytopenia was the only statistically significant threshold. This significant cutoff identified through our meta-analysis is in line with the one chosen empirically in the revised Sapporo criteria [6]. Moreover we could recommend that future studies should report the cut-off used for the definition of thrombocytopenia. Second, there was a moderate statistical heterogeneity in the main analysis, measured by the chi-squared I^2. This can be explained by the high power of the test in detecting small heterogeneity within the studies which is relatively negligible when there is a high number of studies included in the main analysis [35]. Third, a publication bias was identified, since negative studies are less prone to be published, however the Tweedie's trim and fill method allows taking into account this bias and the risk estimates was comparable and still significantly increased. Finally we selected a SLE population, which may limit the spectrum of patients, but allowed to compare patients with a similar underlying disease for aPL-positive (exposed) vs. aPL-negative (unexposed) SLE patients.

5. Conclusion

Our findings from this systematic review and meta-analysis pooling together a large number of studies, indicate that there is substantial evidence that aPL are strongly associated with a 2.5-fold increased risk of thrombocytopenia in SLE patients. We have identified aPL profiles – and especially LA and IgM isotypes – as biomarkers for the risk-stratification of thrombocytopenia in SLE patients. Finally, for everyday practice, in aPL-positive patients with SLE, platelet count monitoring should be performed. In SLE patients with thrombocytopenia and aPL, risk stratification according to different aPL profiles may guide clinical management.

Authorship contributions

Y.P.C., S.Z. and D.W. conceived and designed the study and statistical analyses.

Y.P.C., T.M., V.D., D.E., D.W. and S.Z. contributed to acquisition of

data, quality assessment, and data analysis.

Y.P.C. and S.Z. interpreted the data and wrote the first draft of the report.

Y.P.C., T.M., V.D., D.E., D.W. and S.Z. contributed to critical revision of the report for important intellectual content and approval of the final version to be published.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

Y.P.C., T.M., V.D., D.E., D.W. and S.Z. have no conflict of interest to disclose.

Acknowledgments

We would like to thank the Kim Barrett Memorial Library team (Mrs. Indira Garcia, Bridget Jivanelli, Rie Smethurst) at the Hospital for Special Surgery, New York, NY, USA for their invaluable help in retrieving studies.

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