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Clinical relevance of antiphospholipid antibodies in systemic sclerosis: A systematic review and meta-analysis☆

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ABSTRACT

Objective: To evaluate the clinical relevance of antiphospholipid antibodies (aPL) in systemic sclerosis (SSc).

Methods: A systematic search of EMBASE and PubMed databases from January 1983 to July 2016 was carried out according to PRISMA guidelines whereas Peto's odds ratio (OR) for rare events was used for the meta-analysis.

Results: The pooled prevalence of participants positive for IgG and IgM anticardiolipin (aCL) antibodies was higher in SSc than controls (12.8% vs 1.6% and 7.8% vs 0.6%; $p < 0.0001$ for both) as was that of IgG and IgM anti-beta-2-glycoprotein-I antibodies (aβ_2GPI) (6.1% vs 0.58%, $p < 0.0001$; 3.5% vs 0.3%, $p = 0.001$). The pooled prevalence of pulmonary arterial hypertension (PAH) was more common in SSc positive than negative patients for aCL (IgG/IgM combined) (26.5% vs 10.9%, $p < 0.0001$) whereas the pooled prevalence of renal disease (RD) was more common in IgG aCL positive than negative patients (36.3% vs 10.9%, $p = 0.02$). The pooled prevalence of thrombosis was higher in IgG aCL, IgM aCL, and IgM aβ_2GPI positive than negative SSc patients (12.6% vs 1.4%, $p < 0.0001$), (15.1% vs 2.7%, $p = 0.002$) and (15% vs 0.78%, $p = 0.009$), respectively. The pooled prevalence of digital infarction/ischemia (DI) was higher in IgG aCL and IgM positive than negative SSc (52.8% vs 39.8%, $p = 0.002$) and (68.1% vs 29%, $p = 0.07$).

Conclusions: A strong relationship exists between aCL and aβ_2GPI of IgG/IgM isotype and SSc; patients positive for these antibodies are more likely to suffer from PAH, RD, thrombosis, and DI. However, data expressed as frequency of aPL positive patients rather than average antibody titers preclude further insight into the relevance of these assumptions.

Introduction

Systemic sclerosis (SSc) is characterized by endothelial damage that over time develops into micro- and macro-vascular disease followed by the appearance of clinical symptoms involving the skin, lungs, kidneys, heart, and gastrointestinal tract. Digital infarction/ischemia (DI), acute and chronic renal disease (RD), and pulmonary arterial hypertension (PAH) are some typical manifestations of long standing endothelial damage [1]. The first reports of arterial [2,3] and venous occlusions [4] in patients with SSc appeared in the early 70s, occasionally associated with the presence of antiphospholipid antibodies (aPL) [5,6]. Ever since, several investigators addressed the potential role of aPL in SSc with regards to thrombosis and to other vascular manifestations of SSc. The purpose of this systematic review and meta-analysis is to assess the available evidence for a possible or definitive role of aPL in SSc.

Material and methods

Search strategy and selection criteria

A systematic review according to the PRISMA guidelines [7] was carried out by searching the electronic databases MEDLINE and EMBASE from January 1983 to July 2016. For the search strategy we used the terms ["systemic sclerosis" OR "scleroderma"] and ["anticardiolipin" OR "anti-beta 2-glycoprotein-I" OR "antiphospholipid syndrome," OR "lupus anticoagulant" OR "lupus inhibitor"]. The search yielded 1093 records that were processed according to Figure 1.

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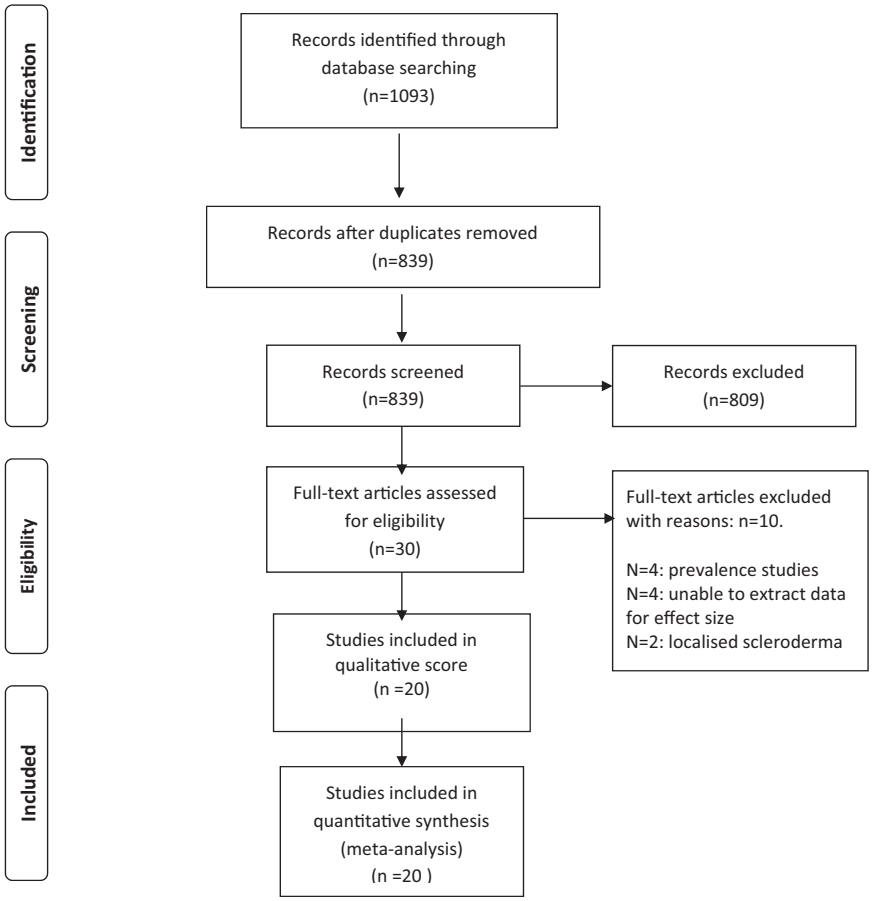


Fig. 1. Summary of literature search according to the Prisma flow-chart.

Criteria for selecting articles

Two investigators (M.M. and P.R.J.A.) screened all the retrieved articles for relevancy. Inclusion criteria were as follows: (1) observational studies (case–control, cross-sectional or cohort) investigating (a) the difference in aPL prevalence and titer between SSc and controls, (b) the difference in aPL prevalence and titer between different vascular manifestations of SSc, and (c) the difference in the prevalence of vascular manifestations between SSc patients positive and negative for aPL; (2) aPL measured by immune or clotting assays; and (3) articles written in English, French, Spanish, German, or Portuguese. If more than two studies investigated the same population, the latest or highest-quality study was chosen. Exclusion criteria were as follows: (1) prevalence studies only; (2) non-original research; (3) studies not reporting the relationship between aPL and SSc; and (4) articles not written in the languages indicated in the inclusion criteria. M.M. and P.R.J.A. applied the eligibility criteria to identify appropriate studies for inclusion and independently extracted data including date of publication, study design, populations, participant data, and results.

Evaluation of the quality of the studies

The quality of the studies identified was assessed by the Newcastle–Ottawa Quality Assessment Scale (NOQAS) for case–control studies specifically developed to assess quality of observational studies; the case–control studies included in the meta-analysis are simply comparing two different groups because they had no real exposure to qualify as true case–control and the same applies to the SSc cohorts with or without certain clinical manifestations or with or without aPL [8]. The scale covers three major domains (selection of cases and controls, comparability of selected groups, and ascertainment of either the exposure or outcome of interest) and the resulting score may range between 0 and 8, a higher score representing a better methodological quality. Data were independently extracted into a standard electronic form and averaged and any discrepancies were resolved by consensus.

Outcome measures

The primary outcomes were as follows: (1) the comparative pooled prevalence of participants positive for aPL in SSC and controls (with odd ratios and level of significance); (2) the standardized mean difference of aPL titers between SSc and controls; and (3) the comparative pooled prevalence of aPL in MS participants with and without several vascular manifestations of SSc, alternatively the pooled prevalence of several vascular manifestations in SSc patients with and without aPL. Secondary outcomes were as follows: (1) the pooled standardized mean differences of aPL titer measured in SSc patients and controls and (2) the pooled standardized mean differences of aPL titer measured in SSc patients with and without a defined clinical manifestation.

Statistical analysis

Statistical analysis was carried out using Comprehensive Meta-Analysis, Biostat, USA; Peto's method for pooled odds ratios was used to compare aPL in SSc and control groups because it is the appropriate statistical analytic method for rare

events [9]. Cohen's kappa assessed the inter-rater scoring agreement of two investigators.

Results

Number and quality of the studies

After completion of the screening and exclusion process (Fig. 1) we identified 9 case–control studies exploring the association between aPL and SSc (some of their case groups also allowed the investigation between aPL and some clinical manifestations of SSc) (Table 1) and 11 cohort studies exploring specifically the relationship between aPL and several clinical manifestations of SSc (Table 2). Serum aPL was measured only once in all but three studies in which it was measured serially [16,22,29].

A score of ≥ 7 on the NOQAS arbitrarily defined a good study and only three studies met our criteria; reasons for achieving lower scores were failure of showing the ages and sex of the patient and controls, poor documentation of inclusion/exclusion criteria, failure to report disease duration and/or disease activity, limited comparability, and failure to describe average levels of aPL. The inter-rater reliability agreement of the two investigators (M.M. and P.R.J.A.) for NOQAS was 0.47 (95%CI: 0.293–0.654) according to Cohen's kappa.

Clinical definitions

Pulmonary arterial hypertension

The definition of PAH varied among studies: three studies defined PAH as a systolic pulmonary arterial pressure (sPAP) >25 mmHg [26,27,29], three as sPAP >40 mmHg [15,17,29], one as a mean PAP >35 mmHg [11], and five studies did not define PAH [13,14,21,24,25]. Six studies clearly defined PAH as primary and not secondary to interstitial lung disease [11,15,22,26,27,29].

Renal disease

The definition of RD varied among studies: two defined it as proteinuria [10,16]; one as subnormal creatinine clearance [19], one as malignant hypertension and rapidly progressive renal failure [11], and one as renal crisis only [17]. One study reported separate data for proteinuria, renal crisis, and hypertension [23]. Two studies did not define RD [14,20].

Digital infarction/ischemia

There was no specific definition throughout all the studies for digital infarction or ischemia.

Antiphospholipid antibodies and systemic sclerosis

The relationship between different aPL and SSc was explored in nine case–control studies. The link between aCL of IgG/IgM isotype and SSc was addressed in eight studies [10–12,14–18] that comprised 725 controls and 484 SSc participants for the effect size of this outcome: the pooled prevalence of participants positive for IgG aCL and IgM was greater in SSc than in controls (12.8% vs 1.6% and 7.8% vs 0.6%, respectively, $p < 0.0001$ for both) with no heterogeneity (Fig. 2A and B). The relationship between IgG aβ_2GPI and SSc was addressed in five studies comprising 342 controls and 342 SSc participants [11–15,17] for the effect size of this outcome: the pooled prevalence of participants positive for IgG aβ_2GPI was greater in SSc than controls (6.1% vs 0.58%, $p < 0.0001$) (Fig. 2C). The relationship between IgM aβ_2GPI and SSc was addressed in five studies comprising 330 controls and 308 SSc participants [11–15,17] for the effect size of this outcome: the pooled prevalence of participants positive for IgM aβ_2GPI was greater in SSc

Table 1
Demographics of controls and systemic sclerosis participants from case–controls studies

	CTR No	Age	F/M	aCL IgG (%)	aCL IgM (%)	aβ2 GPI IgG (%)	aβ2 GPI IgM (%)	SSC No	Age	F/M	Subtype L/D	aCL IgG (%)	aCL IgM (%)	aβ2 GPI IgG (%)	aβ2 GPI IgM (%)	PAH (%)	RD (%)	THR (%)	DI (%)	NOS
Katayama et al. [10]	45	10–65	NR	6.6	6.6	NR	NR	40	NR	35/5	NR	32.5	NR	NR	NR	NR	27	NR	NR	3
Ihn et al. [11]	120	NR	NR	0	0	0	0	80	NR	NR	37/43	25	5	10	6.25	26	7	NR	NR	4
Shoenroth et al. [12]	21	NR	NR	4.7	0	NR	0	26	NR	21/5	10/16	3.8	7.6	NR	7.6	NR	NR	0	NR	6
Hasegawa et al. [13]	33	NR	29/4	NR	NR	0	NR	60	NR	NR	NR	NR	NR	7	NR	45	10	8	30	5
Sanna et al. [14]	100	NR	NR	3	2	2	1	25	50 (28–70)	NR	18/7	16	8	4	4	12	0	4	NR	5
Assous et al. [15]	20	45 ± 7	12/8	0	0	0	0	108	59 ± 13	NR	61/47	11	2.7	4.6	1.8	14	NR	4	31	7
Enzenauer et al. [16]	200	NR	NR	1	0	NR	NR	82	NR	71/11	25/49 8 overlap	12.1	3.6	NR	NR	UC	UC	UC	UC	6
Marie et al. [17]	69	58 (26–85)	60/9	2	NR	0	NR	69	58 (26–85)	60/9	43/26	14.4	10	4.3	1.44	6	NR	1	NR	7
Liberati et al. [18]	150	NR	NR	1.3	0	NR	NR	54	51 ± 11	49/5	33/12	9.25	7.4	NR	NR	NR	NR	15	0	6

Abbreviations: aCL, anticardiolipin; aβ2 GPI, anti-beta-2-glycoprotein-I; NOS, Newcastle–Ottawa Scoring; CTR, controls; F/M, female/male; SSC, systemic sclerosis; L/D, limited/diffuse; PAH, pulmonary arterial hypertension; RD, renal disease; THR, thrombosis; DI, digital infarction/ischemia; NR, not reported; UC, unclear.

Table 2
Demographics and clinical manifestations of systemic sclerosis patients from cohort studies

	SSc No	Age	Sex F/M	DD years	L/D No	aCL		aβ2GPI		LA (%)	PAH (%)	RD (%)	THR (%)	DI (%)	NOS
						IgG (%)	IgM (%)	IgG (%)	IgM (%)						
Pucillo et al. [19]	103	49 (19–75)	94/9	10 (1–44)	28/35/32	86	12	ND	ND	NR	73	100	7.6	NR	3
Parodi et al. [20]	90	NR	86/4	NR	NR	12	3	UC	UC	NR	NR	7	NR	NR	2
Antonioli et al. [21]	60	57	56/4	13 (1–42)	48/12	8	6	3	21	NR	25	NR	50	NR	3
Gupta et al. [22]	72	35	63/9	4.01	53/19	7	5	UC	UC	2.7	0	NR	NR	71	4
Wielosz et al. [23]	50	52 ± 13	41/9	6 ± 6	27/23	UC	UC	UC	UC	NR	NR	21	NR	NR	3
Touré et al. [24]	40	41 (18–68)	29/11	NR	NR	17	5	37	32	5	NR	NR	NR	NR	3
Mellal et al. [25]	147	45 ± 13	137/10	12 ± 9.3	106/41	3	8	NR	NR	NR	33	NR	33	NR	2
Morrisroe et al. [26]	869										21			55	3
Herrick et al. [28]	68	49 (19–79)	58/10	NR	NR	20	20	NR	NR	NR	NR	NR	NR	31	5
Boin et al. [29]	150	52 ± 13	122/28	10 ± 7	NR	6	15	0.5	25	NR	NR	NR	NR	75	8
Launay et al. [27]	53	53 (27–71)	44/9	12 (3–45	NR	aCL 23%	NR	NR	NR	11	NR	NR	NR	4	

Abbreviations: SSc, systemic sclerosis; DD, disease duration; LD, limited, diffuse SSc; aCL, anticardiolipin; aβ2GPI, anti-beta2-glicoproteina-I; aPL, antiphospholipid; LA, lupus anticoagulant; PAH, pulmonary arterial hypertension; DI, digital infarction; RD, renal disease; THR, thrombosis; NOS, Newcastle–Ottawa Score; No, number; NR, not reported; UC, unclear.

than in controls (3.5% vs 0.3%, $p = 0.001$) (Fig. 2D). The link between lupus anticoagulant (LA) and SSc was addressed in three studies [11–15,17] that comprised 209 controls and 257 SSc patients: the pooled prevalence of participants positive for LA was greater in SSc than controls (1.94% vs 0%, $p = 0.01$) (graph not shown). Analysis of aPL by scleroderma subset was unrevealing (data not shown).

Antiphospholipid antibodies and pulmonary arterial hypertension

Overall, 12 articles evaluated the relationship between different aPL and PAH. Eight studies [11,15,17,21,22,24–26] comprising 1286 aCL negative SSc patients and 209 aCL positive SSc patients addressed the effect size of PAH but only two studies addressed the effect size according to different aCL isotype [21,22] whereas the remaining six studies addressed the combined effect of both antibody isotypes [11,15,17,21,22,24–26].

The pooled prevalence of PAH was superior in aCL positive than negative patients (26.5% vs 10.9%, $p < 0.0001$) with elevated heterogeneity ($I^2 = 78.51\%$, $p < 0.0001$) (Fig. 3A) though all studies but one favoured the association. The wide heterogeneity was not affected by removal of the two studies that investigated IgG/IgM aCL separately [21,22]. Subgroup analysis according to primary PAH [11,15,22], to different sPAP values [11,15,17] or to PAH lacking definition [13,21,24,25] did not modify heterogeneity (data not shown).

Two studies [14,27] comprising 80 SSc patients without PAH and 14 SSc patients with PAH addressed the effect size of IgG aCL in PAH: the pooled prevalence of IgG aCL and IgM aCL was slightly higher in SSc patients with PAH (12.5% vs 14.9%, $p = 0.24$) with no heterogeneity (plot not shown). The pooled prevalence of IgM aCL was slightly higher in SSc patients with PAH (22.5% vs 25.4%, $p = 0.61$) with elevated heterogeneity ($I^2 = 78.35\%$, $p = 0.03$) (plot not shown). Two studies dealt with anti-phosphatydilserine/prothrombin [13,14]; however, the first explored the frequency of PAH in IgG anti-PS/PT positive and negative patients (56% vs 18%, $p = 0.01$) and the second explored the frequency of IgM anti-PS/PT positive patients in SSc with and without PAH (66% vs 4%, $p = 0.03$) precluding the possibility of meta-analysis.

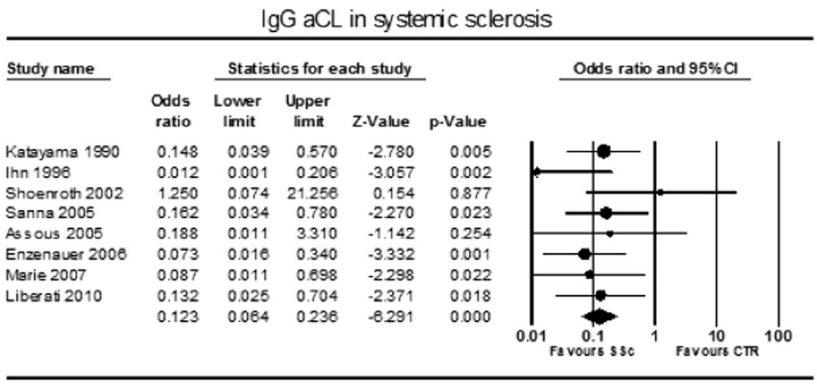
Four studies comprising 56 patients with PAH and 224 patients without PAH were pooled for the effect size of average IgG aCL titer. Random effect meta-analysis revealed no heterogeneity among the studies suggesting strong pooled estimates for average IgG aCL difference (Fig. 3B).

Antiphospholipid antibodies and renal disease

Nine studies contained data regarding aPL and RD [10,11,13,14,16,17,19,20,23]. Two studies did not discriminate between IgG/IgM isotypes and aPL specificity [10,23], and another dealt with anti-prothrombin and anti-phosphatidylserine antibodies: these were excluded from the meta-analysis [13]. A total of 66 SSc patients positive for IgG aCL and 365 negative for IgG aCL were available for the effect size of this outcome: the pooled prevalence of RD was greater in IgG aCL positive than negative patients (36.3% vs 10.9%, $p = 0.02$) with elevated heterogeneity ($I^2 = 87.06\%$, $p < 0.0001$) (Fig. 4). It was not possible to perform subgroup analysis as the definitions of RD varied across the studies: [11,16,17,19,20] or were not provided [14,20]. Five studies investigated RD in relation to IgM aCL [14,16,17,19,23] and three in relation to $a\beta_2$GPI [11,14,23] but their different definitions of RD precluded a meta-analysis.

Antiphospholipid antibodies and thrombosis

The occurrence of any thrombosis (either arterial or venous) was addressed in 11 studies [12–21,25]: two studies [10,25] did not



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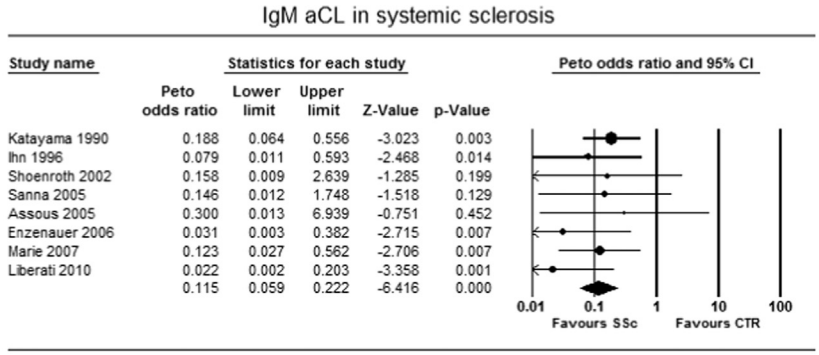

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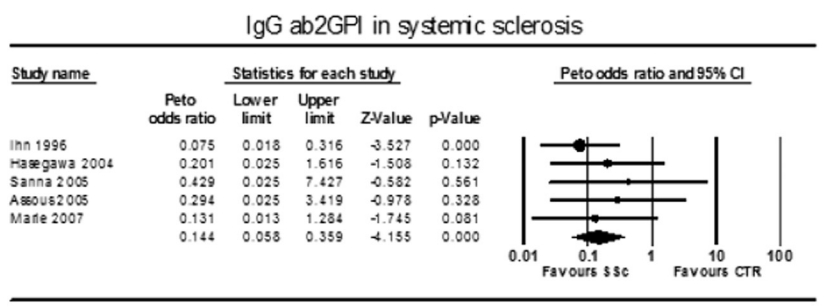

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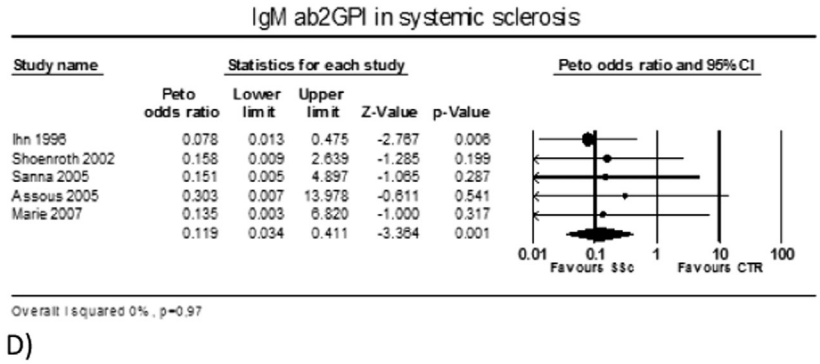
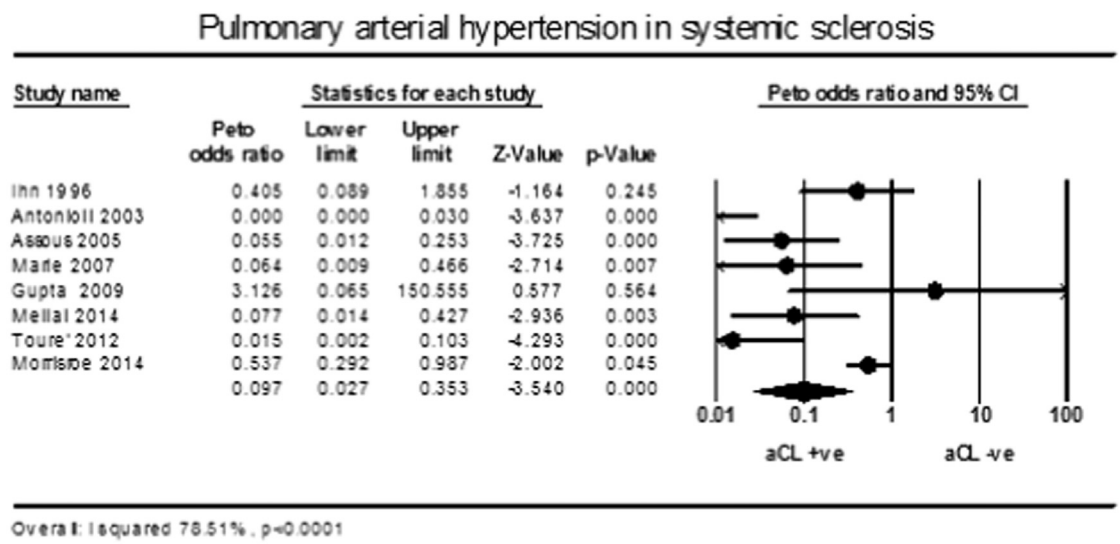


D)

Fig. 2. Forest plots of the effect size of different antiphospholipid antibodies in the populations under study: (A) effect size of IgG aCL; (B) effect size of IgM aCL; (C) effect size of IgG aβ_2GPI; and (D) effect size of IgM aβ_2GPI. Abbreviations: aCL, anticardiolipin; aβ_2GPI, anti-beta$_2$glycoprotein-I antibodies; SSc, systemic sclerosis; CTR, controls.



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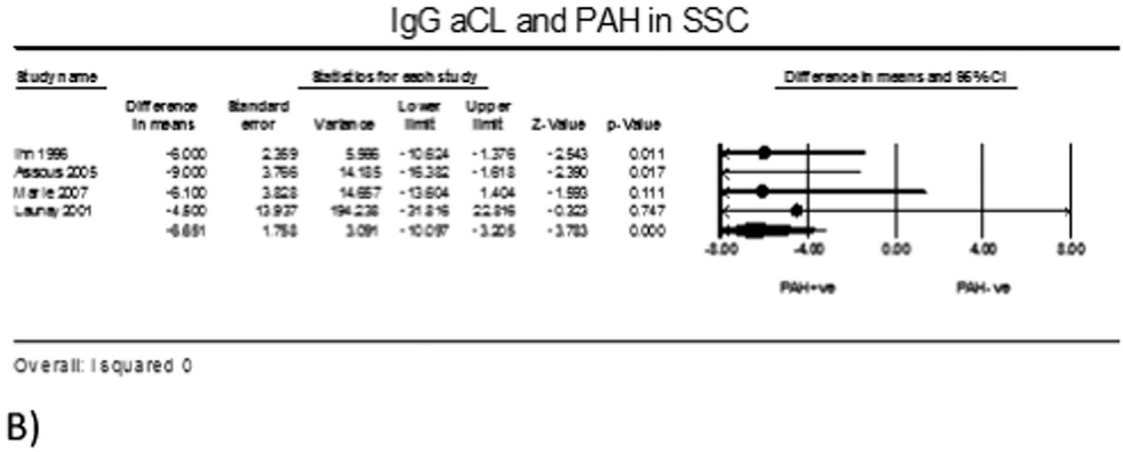


B)

Fig. 3. Forest plots of the effect size of different antiphospholipid antibodies and pulmonary arterial hypertension in systemic sclerosis: (A) effect size of combined IgG/IgM aCL and (B) effect size for average IgG aCL difference. Abbreviations: aCL, anticardiolipin; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis.

discriminate between IgM and IgG aCL antibodies and was excluded from the meta-analysis. A total of 542 IgG aCL negative and 87 IgG aCL positive SSc patients were available for the effect size of this outcome: the pooled prevalence of thrombosis was higher in IgG aCL positive than negative SSc patients (12.6% vs 1.4%, $p < 0.0001$) with no heterogeneity (Fig. 5A). With regards to IgM aCL and thrombosis one study was excluded [15] because unclear whether an IgM patient had thrombosis: a total of 474 IgM aCL negative and 33 IgM aCL positive SSc patients were available for the effect size of this outcome: the pooled prevalence of thrombosis was higher in IgM aCL positive than in IgM aCL negative SSc patients (15.1% vs 2.7%, $p = 0.002$) with no heterogeneity (Fig. 5B).

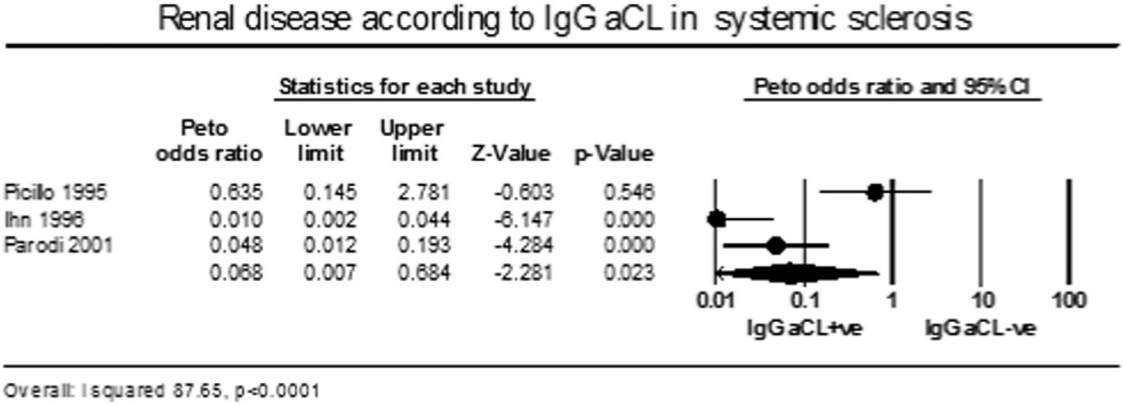


Fig. 4. Forest plots of the effect size of IgG anticardiolipin antibody and renal disease in systemic sclerosis. Abbreviation: aCL, anticardiolipin.

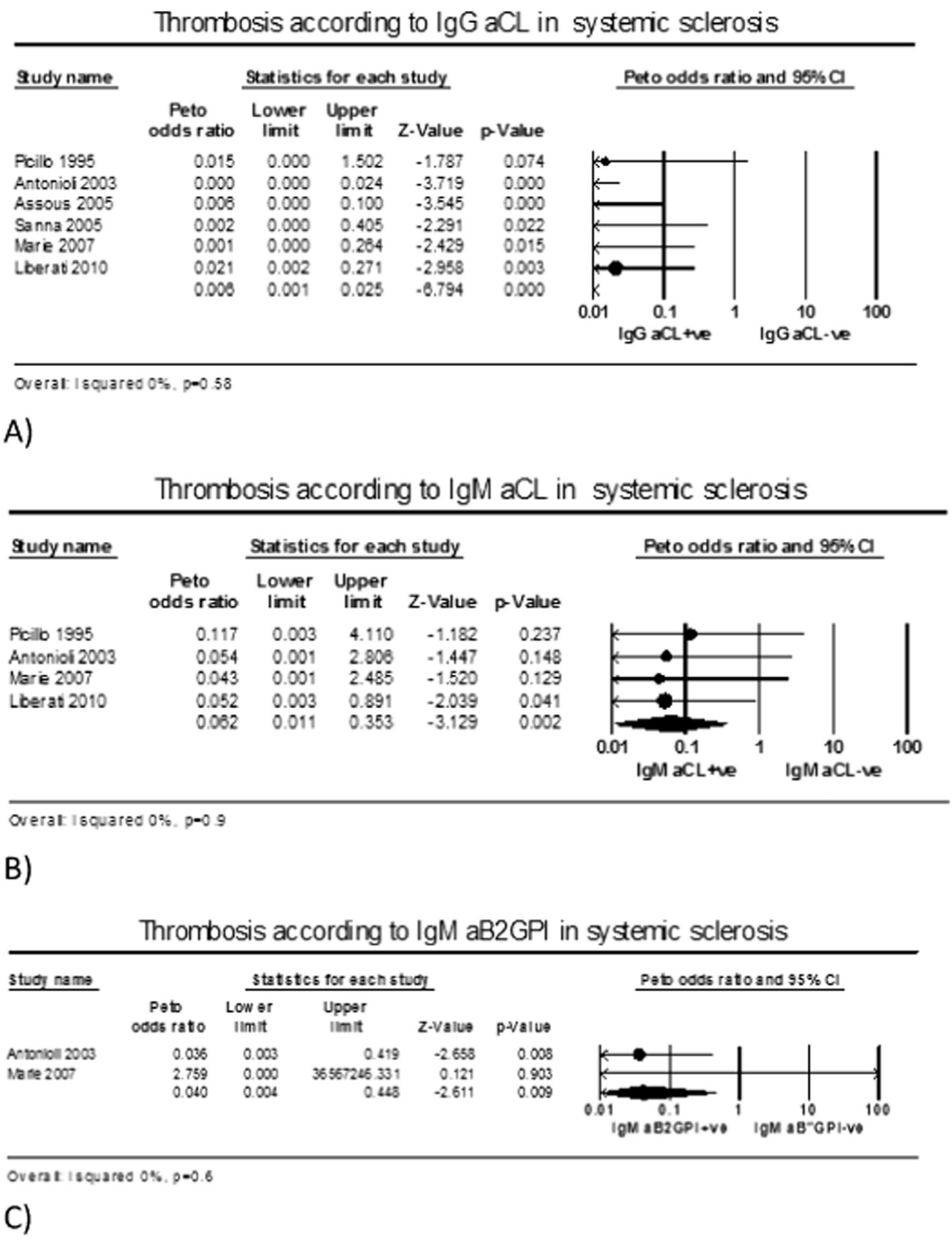
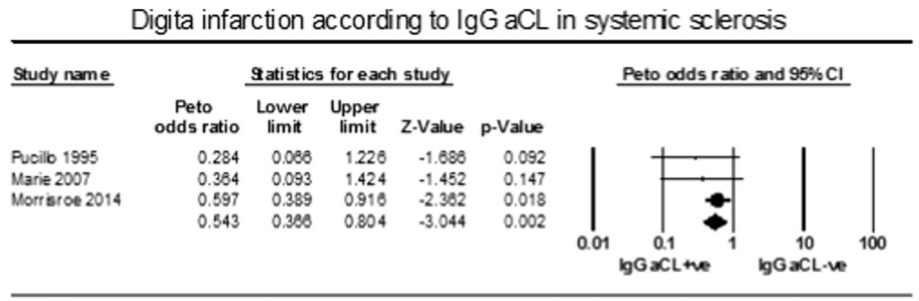


Fig. 5. Forest plots of the effect size of different antiphospholipid antibodies and thrombosis in systemic sclerosis: (A) effect size of IgG aCL; (B) effect size of IgM aCL; and (C) effect size of IgM aβ_2GPI. Abbreviations: aCL, anticardiolipin; aβ_2GPI, anti-beta2-glycoprotein-I.

Six studies addressed the association between IgG aβ_2GPI and thrombosis [12,14,15,17,20,21] but one did not separate thrombotic events by antibody isotype and was excluded [15]. A total of 266 IgG aβ_2GPI negative and 10 IgG aβ_2GPI positive patients were available for the effect size of this outcome: the prevalence of thrombosis was similar in both groups (2% vs 0%, $p = 0.690$) (plot not shown). Six studies addressed the association between IgM aβ_2GPI and thrombosis [12,14,15,17,20,21]: one did not separate thrombotic events by antibody isotype and was excluded [15]. A total of 256 IgM aβ_2GPI negative and 20 IgM aβ_2GPI positive patients were available for the effect size of this outcome: the prevalence of thrombosis was higher in the IgM aβ_2GPI positive than negative group (15% vs 0.78%, $p = 0.009$) (Fig. 5C).

Antiphospholipid antibodies and digital infarction/ischemia

The relationship between aPL and DI was explored in 12 studies. Five studies [15,17,19,22,26] investigated the prevalence of DI in IgG aCL positive patients but one did not discriminate DI by antibody isotypes and was excluded [22]; a total of 1024 IgG aCL



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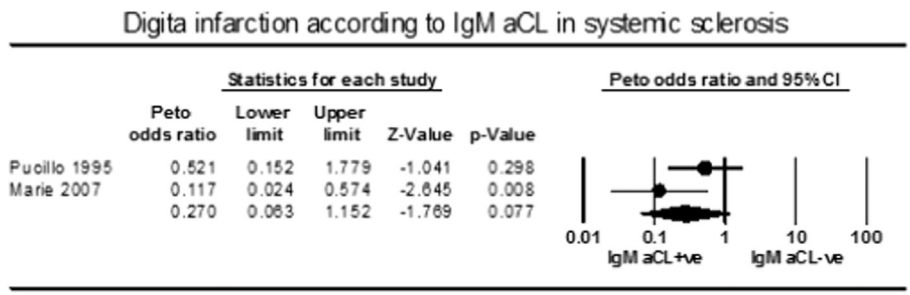

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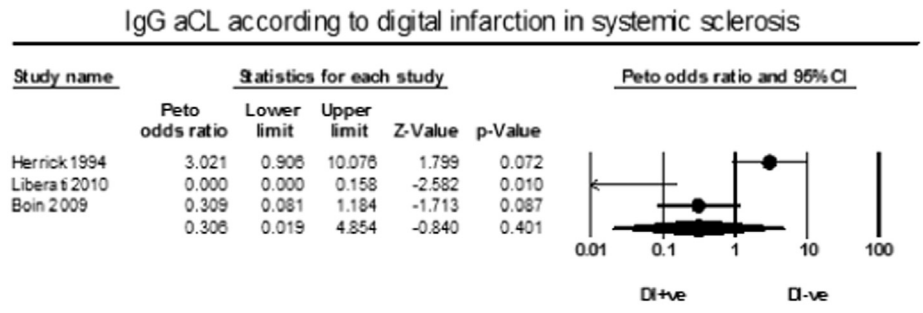

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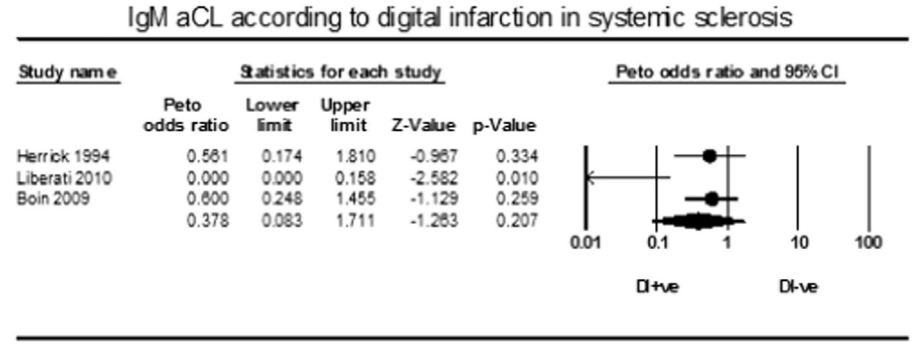

D)

Fig. 6. Forest plots of the effect size of different antiphospholipid antibodies and digital infarction in systemic sclerosis: (A) effect size of IgG aCL; (B) effect size of IgM aCL; (C) effect size of DI by IgG aβ_2GPI; and (D) effect size of DI by IgM aβ_2GPI. Abbreviations: aCL, anticardiolipin; DI, digital infarction.

negative and 125 IgG aCL positive patients addressed the effect size of DI. The pooled prevalence of DI was slightly higher in the IgG aCL positive group than in the IgG aCL negative group (52.8% vs 39.8%, $p = 0.002$)(Fig. 6A). Four studies [15,17,19,22] investigated the prevalence of DI in IgM aCL positive patients but one did not separate DI by antibody isotypes and was excluded [22]; a total of 258 IgM aCL negative and 22 IgM aCL positive patients addressed the effect size of DI: the pooled prevalence of DI was higher in the IgM aCL positive than in the negative group (68.1% vs 29%, $p = 0.07$) with high heterogeneity ($I^2 = 52\%$, $p < 0.1$) (Fig. 6B).

Eight studies [10,12,13,17,18,20,28,29] addressed the effect size of IgG and IgM aCL in SSc patients with and without DI but four studies did not discriminate among antibody subtypes [10,12,17,20] and were excluded from the meta-analysis that comprised 152 SSc without DI and 112 SSc with DI: the pooled prevalence of participants positive for IgG aCL was similar in the two groups (9.85% vs 7.8%, $p = 0.4$)(Fig. 4C). The pooled prevalence of participants positive for IgM aCL was greater in the group with DI than in the one without DI (21.5% vs 9.8%, $p = 0.2$) (Fig. 4D).

Discussion

This systematic review includes articles dealing with a possible relationship between aPL and SSc spanning almost 30 years. The initial surveys addressed the link between aPL and SSc with reference to a control group: they revealed a convincing strong association between aCL/aβ_2GPI of either isotype and SSc, but did not differentiate the effects of these aPL on the clinical manifestations of SSc that were explored in subsequent studies.

With regards to PAH our meta-analysis revealed a strong association between aCL and PAH both in terms of higher average aCL titer and greater PAH prevalence in aCL positive patients: unfortunately most of the studies included in this part of the meta-analysis evaluated the combined effect of IgG and IgM aCL isotypes eventually contributing to the wide heterogeneity. This was not explained by the different definitions of PAH, though all studies but one favoured the association. On the other hand, the four studies having a similar definition of PAH revealed strong pooled estimates between average IgG aCL titers and PAH with no heterogeneity, strengthening the link between aPL and PAH. With regards to RD the relationship with IgG aCL was offset by wide heterogeneity likely due to the varied definitions of RD adopted by the individual studies.

Nevertheless there is pathogenetic evidence to explain why PAH and RD are more prevalent in the presence of IgG aCL: vasoactive endotelin-1 and isoprostane relate to lung [30,31] and renal disease [31,32] in SSc but they are also elevated in primary APS [33] whereas the biologic activity of nitric oxide is impaired in both conditions and relate to aPL titers [34,35]. Conceivably the presence of IgG aCL in SSc may worsen these effects and contribute to more severe disease expression.

The meta-analysis also revealed a strong association between IgG/IgM aCL and thrombosis in SSc and a discreet association between IgG aCL and DI, expression of microvascular occlusion. These findings need interpretation: the guidelines for the diagnosis of antiphospholipid syndrome (APS) suggest that (1) persistence of aPL should be assessed at 12 weeks (previously 6 weeks) from initial testing and that (2) to associate a thrombotic event with aPL, a titer of least 40 GPL/MPL for aCL of either antibody isotype or greater than the 99th percentile of a control population should be detected [36]. Only three studies measured aCL at least twice [15–17] though one study did not report thrombotic events [16] and the average aCL titers [15–17] were below the thrombogenic cut-off: thus these SSc patients do not have APS according to accepted criteria [36]. Notwithstanding APS and SSc share several thrombogenic pathways such as endothelial dysfunction [37,38], thrombin generation [39,40], and platelet activation [41,42]: the presence of aPL in SSc may add to the previous pathways and lead to large and small vessel occlusions compared to SSc aPL negative patients. However, this finding would also suggest that even low titer aPL may have thrombogenic properties if present in disorders characterized by oxidative stress and pre-existing vascular damage.

Our meta-analysis suffers from some inherent limitations such as (1) the literature search applied to two major electronic databases without looking into gray literature (university thesis and conference proceedings); (2) heterogeneity, that was affected by (a) the inclusion criteria of our meta-analysis that were relatively loose to cater for a larger sample size eventually offset by wider heterogeneity; (b) the different definitions of the clinical manifestations under study; and (c) the lack of differentiation of the effect of IgM/IgG isotypes in several studies; (3) the data presented in individual articles did not allow adjustments by age, sex, and SSc subtypes; (4) aPL expressed as frequency of patients with a positive aPL test and seldom as average serum levels; (5) full aPL profiling addressed in few studies with LA data available in three studies only; (6) aPL measured only once (with the exception of three articles) hence they could have been transient and/or secondary to infection; and (7) the influence of medication on aPL not taken into account.

Given the shortcomings of point 4 above and in the absence of a serum antibody titer to comment upon it could be argued that IgM aCL and IgM aβ_2GPI, relating to PAH, thrombosis, and DI, are natural autoantibodies against oxidated lipid epitopes that appear as part of the oxidative stress occurring in SSc and as such may be devoid of pathogenic potential [43].

Conclusions

Despite its limitations our meta-analysis shows that aPL are clinically relevant in SSc to implement on their significance future cohorts should be of a prospective nature and include the assessment of the full aPL profile including LA, as the latter better associates with some clinical manifestations of APS than aPL [44,45]. In the presence of thrombosis aPL ought to be measured at least twice to fulfill diagnostic criteria for APS and at least yearly to evaluate persistence and effect on clinical features of SSc. Moreover the titers of the aPL should be clearly indicated as patients with higher aPL titers are more likely to have more severe non-criteria manifestations of APS than patients with low-moderate titers [46] and higher titers may impact more negatively and prematurely on some clinical manifestations of SSc [26,29].

References

[1] Asano Y, Sato S. Vasculopathy in scleroderma. Semin Immunopathol 2015;37:489–500.
[2] Furey NL, Schmid FR, Kwaan HC, Friederici HH. Arterial thrombosis in scleroderma. Br J Dermatol 1975;93:683–93.
[3] Nair CK, Goli-Bijanki R, Lyckholm L, Sketch MH. Inferior myocardial infarction complicated by mural thrombus and systemic embolization despite anticoagulation in progressive systemic sclerosis with normal coronary arteriograms. Am Heart J 1988;116:1357–9.
[4] Leak A, Patel KJ, Tuddenham EG, Pearson JD, Woo P. Axillary vein thrombosis in adolescent onset systemic sclerosis. Ann Rheum Dis 1990;49:557–9.
[5] Shapiro LS. Large vessel arterial thrombosis in systemic sclerosis associated with antiphospholipid antibodies. J Rheumatol 1990;17:685–8.
[6] Whittaker R, Barnett A, Ryan P. Antiphospholipid syndrome in scleroderma. J Rheumatol 1993;20:1598–600.
[7] Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;1514:65–94.

[8] Wells GA, Shea B, O'Connell D, et al. Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available from: ⟨www.ohri.ca/programs/clinical_epidemiology / oxford.htm⟩.
[9] Bradburn MJ, Deeks JJ, Berlin JA, Russell LA. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Statistics in Med 2007;26:53–77.
[10] Katayama I, Otoyama K, Kondo S, Nishioka K, Nishiyama S. Clinical manifestations in anticardiolipin antibody-positive patients with progressive systemic sclerosis. J Am Acad Dermatol 1990;23:198–201.
[11] Ihn H, Sato S, Fujimoto M, et al. Measurement of anticardiolipin antibodies by ELISA using β2-glycoprotein I (β2-GPI) in systemic sclerosis. Clin Exp Immunol 1996;105:475–9.
[12] Schoenroth L, Fritzler M, Lonzetti L, Senécal JL. Antibodies to beta2 glycoprotein I and cardiolipin in SSc. Ann Rheum Dis 2002;61:183–4.
[13] Hasegawa M, Sato S, Yanaba K, et al. Autoantibodies against phosphatidylserine-prothrombin complex in patients with systemic sclerosis. Ann Rheum Dis 2004;63:1514–7.
[14] Sanna G, Bertolaccini ML, Mameli A, et al. Antiphospholipid antibodies in patients with scleroderma: prevalence and clinical significance. Ann Rheum Dis 2005;64:1795–6.
[15] Assous N, Allanore Y, Batteux F, et al. Prevalence of antiphospholipid antibodies in systemic sclerosis and association with primitive pulmonary arterial hypertension and endothelial injury. Clin Exp Rheumatol 2005;23:199–204.
[16] Enzenauer RJ, Collier DH, Lopez LR. Anticardiolipin antibodies in scleroderma. J Clin Rheumatol 2006;12:324–6.
[17] Marie I, Jouen F, Hellot MF, Levesque H. Anticardiolipin and anti-β2 glycoprotein-I antibodies and lupus-like anticoagulant: prevalence and significance in systemic sclerosis. Br J Dermatol 2008;158:141–4.
[18] Liberati APT, Ribeiro CF, Skare T. Study about the association between anticardiolipin antibodies and peripheral vascular phenomena in patients suffering from systemic scleroderma. An Bras Dermatol 2010;85:403–5.
[19] Pucillo U, Migliaresi S, Marcialis MR, Ferruzzi AM, Tirri G. Clinical significance of anticardiolipin antibodies in patients with systemic sclerosis. Autoimmunity 1995;20:1–7.
[20] Parodi A, Drosera M, Barbieri L, Rebora A. Antiphospholipid antibody system in systemic sclerosis. Rheumatology 2001;40:111–12.
[21] Antonioli CM, Danieli E, Airò P, Cattaneo R, Tincani A. More on anticardiolipin and anti-β2 glycoprotein I in systemic sclerosis. Ann Rheum Dis 2003;62:589–90.
[22] Gupta R, Thabah MM, Gupta S, Shankar S, Kumar A. Clinical significance of antiphospholipid antibodies in Indian scleroderma patients. Rheumatol Int 2009;30:277–9.
[23] Wielosz E, Dryglewska M, Majdan M. Antiphospholipid antibodies and kidney involvement in patients with systemic sclerosis. Clin Rheumatol 2009;28:955–9.
[24] Touré AO, Ly F, Sall A, et al. Antiphospholipid antibodies and systemic scleroderma. Turk J Hematol 2013;30:32–6.
[25] Mellal YM, Djidjik R, Tahiat A, et al. Anticardiolipin antibodies are associated with pulmonary arterial hypertension in Algerian systemic scleroderma patients. Indian J Rheumatol 2014;9:48–9.
[26] Morrisroe KB, Stevens W, Nandurkar H, et al. The association of antiphospholipid antibodies with cardiopulmonary manifestations of systemic sclerosis. Clin Exp Rheumatol 2014;32(6 Suppl. 86):S133–7.
[27] Launay D, Hachulla E, Hatron PY, et al. Pulmonary hypertension screening in systemic sclerosis: Apropos 67 patients. Rev Med Intern 2001;22:819–29.
[28] Herrick AL, Heaney M, Hollis S, Jayson MIV. Anticardiolipin, anticentromere and anti-Scl-70 antibodies in patients with systemic sclerosis and severe digital ischaemia. Ann Rheum Dis 1994;53:540–2.
[29] Boin F, Franchini S, Colantuoni E, et al. Independent association of anti-β2-glycoprotein I antibodies with macrovascular disease and mortality in scleroderma patients. Arthritis Rheum 2009;60:2480–9.
[30] Silver RM. Endothelin and scleroderma lung disease. Rheumatology 2008;47 (Suppl. 5):v25–6.
[31] Volpe A, Biasi D, Caramaschi P, et al. Levels of F2 isoprostanes in systemic sclerosis: correlation with clinical features. Rheumatology 2006;45:314–20.
[32] Mouthon L, Mehrenberger M, Teixeira L, et al. Endothelin-1 expression in scleroderma renal crisis. Hum Pathol 2011;42:95–102.
[33] Atsumi T, Khamashta MA, Haworth RS, et al. Arterial disease and thrombosis in the antiphospholipid syndrome: a pathogenic role for endothelin 1. Arthritis Rheum 1998;41:800–7.
[34] Dooley A, Gao B, Bradley N, et al. Abnormal nitric oxide metabolism in systemic sclerosis: increased levels of nitrated proteins and asymmetric dimethylarginine. Rheumatology 2006;45:676–84.
[35] Ames PRJ, Batuca JR, Ciampa A, Delgado Alves J. Clinical relevance of nitric oxide metabolites and nitrative stress in thrombotic primary antiphospholipid syndrome. J Rheum 2010;37:2523–30.
[36] Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 2006;4:295–306.
[37] Altorok N, Wang Y, Kahaleh B. Endothelial dysfunction in systemic sclerosis. Curr Opin Rheumatol 2014;26:615–20.
[38] Cugno M, Borghi MO, Lonati LM, et al. Patients with antiphospholipid syndrome display endothelial perturbation. J Autoimmun 2010;34:105–10.
[39] Ames PRJ, Lupoli S, Alves J, et al. The coagulation/fibrinolytic balance in systemic sclerosis. Evidence for a haematological stress syndrome. Br J Rheumatol 1997;36:1045–50.
[40] Ames PRJ, Iannaccone L, Tommasino C, Brillante M, Brancaccio V. Coagulation activation and fibrinolytic imbalance in subjects with idiopathic antiphospholipid antibodies. A crucial role for acquired free protein S deficiency. Thromb Haemost 1996;76:190–4.
[41] Herrick AL, Illingworth K, Blann A, et al. Von Willebrand factor, thrombomodulin, thromboxane, beta-thromboglobulin and markers of fibrinolysis in primary Raynaud's phenomenon and systemic sclerosis. Ann Rheum Dis 1996;55:122–7.
[42] Ames PRJ, Tommasino C, Alves J, et al. Antioxidant susceptibility of pathogenic pathways in subjects with antiphospholipid antibodies. A pilot study. Lupus 2000;9:1–8.
[43] Tsiantoulas D, Perkmann T, Afonyushkin T, Mangold A, Prohaska TA, Papac-Milicevic N, et al. Circulating microparticles carry oxidation-specific epitopes and are recognized by natural IgM antibodies. J Lipid Res 2015;56:440–8.
[44] Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood 2003;101:1827–32.
[45] Lockshin MD, Kim M, Laskin CA, et al. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. Arthritis Rheum 2012;64:2311–8.
[46] Erkan D, Barbhaiya M, George D, Sammaritano L, Lockshin M. Moderate versus high-titer persistently anticardiolipin antibody positive patients: are they clinically different and does high-titer anti-beta 2-glycoprotein-I antibody positivity offer additional predictive information? Lupus 2010;19:613–9.