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A Systematic Review and Meta-Analysis of Cutaneous Manifestations in Late Versus Early-Onset Systemic Lupus Erythematosus

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Abstract

Objectives—Although systemic lupus erythematosus (SLE) most commonly occurs in reproductive-age women, some are diagnosed after age 50. Recognizing that greater than one third of SLE criteria are cutaneous, we undertook a systematic review and meta-analysis to evaluate differences in cutaneous manifestations in early and late-onset SLE patients.

Methods—We searched the literature using PubMed, CINAHL, Web of Science and Cochrane Library. We excluded studies that did not include ACR SLE classification criteria, early-onset controls, that defined late-onset SLE as <50 years of age, or were not written in English. Two authors rated study quality using the Newcastle Ottawa Quality Scale. We used Forest plots to compare odds ratios (95% confidence intervals) of cutaneous manifestations by age. Study heterogeneity was assessed using I^2 .

Results—Thirty five studies, representing 11,189 early-onset and 1,727 late-onset patients with SLE, met eligibility criteria. The female: male ratio was lower in the late-onset group (5:1 versus 8:1). Most cutaneous manifestations were less prevalent in the late-onset group. In particular, malar rash (OR 0.43 (0.35, 0.52)), photosensitivity (OR 0.72 (0.59, 0.88)) and livedo reticularis (OR 0.33 (0.17, 0.64)) were less common in late-onset patients. In contrast, sicca symptoms were

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more common (OR 2.45 (1.91, 3.14)). The mean Newcastle Ottawa Quality Scale score was 6.3 \pm 0.5 (scale 0–9) with high inter-rater reliability for the score (0.96).

Conclusions—Overall, cutaneous manifestations are less common in late-onset SLE patients, except sicca symptoms. Future studies should investigate etiologies for this phenomenon including roles of immune senescence, environment, gender and immunogenetics.

Keywords

Systemic Lupus Erythematosus; Cutaneous; Late-Onset; Sicca; Malar Rash; Photosensitivity; Alopecia; Raynaud

Introduction

Systemic lupus erythematosus (SLE) most often occurs in women of reproductive age. SLE onset in adults \geq 50 years old is referred to as “late-onset SLE.” Previous studies report that late-onset SLE patients are more likely to include men and have a more insidious onset of disease [1–7]. Over one third of the ACR SLE classification criteria reflect cutaneous manifestations so it is not surprising that arthritis and cutaneous findings remain the most common presenting symptoms in both late-onset and early-onset SLE. Yet, previous literature suggested that these are less common in late-onset disease [3, 8–12]. Overall, the proportion of late-onset SLE among all SLE cases is relatively low, ranging from 4% to 20% [1, 3, 4, 8, 10, 13, 14]. However, due to a higher life expectancy and increasing awareness of the disease, the prevalence of late-onset SLE is expected to rise. Therefore, identifying the unique characteristics of this patient population is important. Conclusions drawn from previous studies including a 1989 meta-analysis of nine studies with 170 late-onset SLE patients [15] were limited by small sizes and heterogeneity of patient groups. To gain additional insight into the cutaneous manifestations of late-onset SLE, we conducted a systematic review and meta-analysis of published literature. We compared cutaneous manifestations in patients with early and late-onset SLE.

Methods

We performed a systematic review of the literature to identify articles comparing the cutaneous manifestations of patients with late versus early-onset lupus. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) consensus was followed in the completion of this systematic review and meta-analysis [16]. With assistance from a professional medical librarian we electronically searched the literature in PubMed, CINAHL, Web of Science and Cochrane Library with MESH and keyword subject headings “systemic lupus erythematosus,” “cutaneous lupus erythematosus,” “SLE,” or “late-onset SLE,” AND “age factors,” “age of onset,” “late-onset,” “older-onset,” “over 50,” “older adults,” and “geriatrics,” for entries published from databases’ inception through August 2013. Potential articles were reviewed first by title and abstract only, next by full text, and lastly by analyzing eligible studies in detail. A second reviewer scrutinized a random 10% of all potential titles and abstracts. The reviewers demonstrated 100% agreement in articles included and excluded. Bibliographies of all included articles were reviewed to identify additional citations.

Studies with the following criteria were included: (A) confirmed SLE using American College of Rheumatology (ACR) criteria [17] and (B) data on cutaneous findings of late-onset SLE defined as ≥ 50 years of age. We excluded studies that did not require SLE patients to meet ACR classification criteria, did not include early-onset controls, defined late-onset SLE as <50 years of age, or were written in a language other than English (Figure 1).

Methodological quality of eligible studies and risk of bias were evaluated using the Newcastle Ottawa Quality Assessment Scale for cohort and case control studies [18]. The scale assesses cohort selection and comparisons between groups (cases and controls), outcomes, and adequacy of follow-up. Two reviewers rated each study, assigning a score out of 9 possible points. Discrepancies in scores were resolved by consensus with a third MD reviewer. Inter-rater reliability of two reviewers was calculated.

Data was extracted by two authors including date of publication, study location (country and population vs hospital or clinic based), study type (cohort vs case study), follow-up period, late-onset age definition, and clinical manifestations. The numbers of late-onset patients who exhibited SLE cutaneous manifestations including malar rash, discoid rash, photosensitivity, mucosal ulceration, alopecia, sicca symptoms, Raynaud's phenomenon, cutaneous vasculitis, livedo reticularis, and subacute cutaneous lupus (SCLE) were recorded and compared to numbers of these manifestations in early-onset patients.

Statistical Analysis

We created Forest plots to summarize composite data, generating odds ratios and corresponding 95% confidence intervals for each cutaneous manifestation. Heterogeneity between studies was evaluated using the I^2 statistic with 25%, 50% and 75% indicating low, moderate, and high heterogeneity, respectively. Funnel plots were reviewed to detect publication bias. We performed additional sub-group analyses for Forest plots demonstrating $>30\%$ heterogeneity, excluding case-control studies and determining the relative risk of the cutaneous manifestation. All analyses were performed using R software version 3.1.2 and the package "meta."

Results

Literature searches yielded 1,549 potential articles. After screening titles and abstracts, 95 full articles were retrieved for full-text evaluation. After application of exclusion criteria, 35 articles met criteria for final inclusion and level 3 review (Figure 1), including 31 cohort studies and 4 case control studies [1–14, 19–39].

The 35 studies included in the systematic review and meta-analysis are summarized in Table 1. Studies reflected a geographically and ethnically diverse population. Overall, 27 studies used the classic inclusion of age ≥ 50 years old, while the remaining eight had definitions ranging from >50 to >65 years old. Of note, 24 of the 35 studies also included individuals < 18 years of age in the control group. The mean \pm standard deviation Newcastle Ottawa Quality Scale score of the 35 included articles was 6.3 ± 0.45 with a maximum possible score of 9 points. Inter-rater reliability for these quality scores was $k=0.96$ with two independent MD reviewers.

Our pooled cohorts included 1,727 patients with late-onset SLE and 11,189 early-onset controls. Female predominance was greater in the early-onset group compared to the late-onset group (89% vs. 83%, $p < 0.001$).

Meta-analysis Results

Random effects models were performed for each cutaneous manifestations to compare prevalence in late versus early-onset SLE (Table 2). First, we examined results of Forest plots for the manifestations included as ACR classification criteria as shown in Figure 2. In the random effects model, malar rash was significantly less common in late-onset, compared to early-onset, SLE patients (OR 0.43 (0.35, 0.52)). Due to study heterogeneity (I^2 64%, $p < 0.0001$), we performed sensitivity analysis by omitting the case-control studies. The subsequent relative risk of malar rash was similar (RR 0.65 (0.57, 0.73)).

Photosensitivity was also significantly less common in late-onset SLE patients (Figure 2, OR 0.72 (0.59, 0.88)). Again, due to observed heterogeneity (I^2 53.5%, $p < 0.0002$), sensitivity analysis was performed and when excluding case control studies, the relative risk of photosensitivity was nearly identical to the OR derived from inclusion of all studies (RR 0.85 (0.75, 0.96)). Odds of mucosal ulceration was similar in young and late-onset SLE (OR 0.88 (0.74, 1.04)) with low heterogeneity between studies (I^2 22.2%, $p = 0.14$). The composite OR for discoid rash was similar in early and late-onset SLE patients (OR 1.11 (0.91, 1.34)) with low study heterogeneity (I^2 9.2%, $p = 0.33$).

We next compared the age-related prevalence of cutaneous manifestations that are not part of the ACR diagnostic criteria for SLE. The composite OR for sicca symptoms was significantly higher in late-onset SLE patients (OR 2.45 (1.91, 3.14)) with low heterogeneity (I^2 13.1%, $p = 0.31$) (Figure 3). Raynaud's phenomenon and alopecia were significantly less likely in late-onset SLE patients (OR 0.84 (0.71, 0.99) and OR 0.63 (0.48, 0.82)) respectively (Figure 3) both with low heterogeneity. The odds ratios for cutaneous vasculitis, livedo reticularis and SCLÉ were similar in early and late onset patients (Figure 3).

Discussion

Our systematic review and meta-analysis of cutaneous manifestations in late onset-SLE shows that while cutaneous findings are still common, most cutaneous manifestations are less common in late compared to early-onset SLE (Table 2). In our pooled analysis of 1,727 patients with late-onset SLE, malar rash, photosensitivity, alopecia, and Raynaud phenomenon occurred less frequently in late than in early-onset SLE patients. In more conservative random effects models for the meta-analysis of ACR classification cutaneous manifestations, findings showed significantly lower odds of malar rash and photosensitivity. Our findings agree with several individual cohort studies, reporting fewer cutaneous disease in older adults [3, 8–10, 24, 25]. In our pooled analysis and the meta-analysis, sicca symptoms were more common in late versus early onset lupus patients, consistent with prior reports on this subject [9, 10, 15, 19, 21, 33, 40].

Late-onset lupus patients might have fewer cutaneous manifestations due to immune senescence and gender. Senescence of the immune system with aging is felt to contribute to

the differences in disease manifestations and the generally milder disease course observed in late-onset SLE patients [4, 9]. Several age-related changes in the immune system contribute to decreased cutaneous immune responsiveness including decreased production of keratinocyte immune cytokines, decreased density of Langerhans cells, and decreased T cell production resulting in less B cell activation [41]. Some studies also found that men experience fewer cutaneous manifestations including malar rash, mucosal ulceration, and alopecia [24, 30]. Such observations might contribute to lower odds of cutaneous manifestations in our study, since men were more often represented in the late-onset SLE group as reported by others [31].

The association between sicca symptoms and late-onset SLE was also reported in a 2012 meta-analysis comparing patients with lone SLE to those with SLE-Sjogren's overlap syndrome [40]. Those authors postulated that patients with late-onset SLE and sicca symptoms may have a lupus-SS overlap disease with its own defining characteristics and milder SLE [40]. This idea is supported by the similar immunogenic profiles and enlargement of salivary glands in patients with primary Sjogren's syndrome and late-onset SLE with sicca features, in direct contrast to rheumatoid arthritis with secondary SS [42]. In that study patients with primary SS and those with SLE and sicca symptoms both demonstrated increased frequency of HLA DRB1*0301, whereas those with SLE without sicca symptoms had increased frequency of DRB1*1501 and DQB1*0602. Other studies likewise report an increased prevalence of HLA DR3 in late-onset SLE patients with sicca symptoms [28, 43, 44]. It is notable that sicca symptoms are more common in older adults, so perhaps the higher prevalence is also age or medication-related rather than a SLE specific manifestation, as in one study that found 27% of older subjects had sicca symptoms [45].

Our systematic review and meta-analysis overall reveals less prevalence of cutaneous manifestations in late-onset SLE patients compared to their early-onset SLE peers, with the exception of sicca symptoms. We analyzed 35 studies encompassing 1727 late onset patients to update the last meta-analysis of nine studies (n=170 late-onset patients) that evaluated clinical manifestations, including cutaneous features, in late versus early-onset SLE patients [15]. Clinicians must be able to recognize and diagnose SLE in older patients and understanding the phenotype of fewer external cutaneous manifestations and more sicca symptoms for instance may be helpful. Our study highlights sicca as a potential clue to SLE requiring vigilance beyond Sjogren's diagnosis, particularly when additional SLE features are present such as arthritis, serositis, and lymphadenopathy.

Strengths of this study are the inclusion of a large-pooled multinational cohort and use of rigorous meta-analysis methods. The quality of studies was good, with a mean rating of 6.2 ± 0.45 using the Newcastle Ottawa Scale. As with any study, one must also consider limitations, including those related to the methodological qualities of the primary studies. First, a majority of the cohort studies were retrospective, which might under-report mild features such as cutaneous manifestations or features that are not included as lupus classification criteria such as sicca, vasculitis, livedo, and SCLE. In addition, the relatively small sample size of those evaluated for SCLE limits our ability to draw firm conclusions on the comparative prevalence of this manifestation between early and late onset SLE. Information bias is also possible; shorter lengths of follow-up in one SLE group might

reduce the observed frequency of a cutaneous manifestation [15]. Competing medical problems or explanations in older adults might also impact lower disease manifestation rates if alopecia for instance were deemed age versus disease related in older SLE patients. Likewise, a recent Olmstead County cohort showed increased incidence of isolated cutaneous lupus in older males [46] although such patients would have been excluded from this analysis restricted to those meeting full lupus criteria. As with all meta-analyses, there is always potential for publication bias as well as uncontrolled confounding variables. Finally since non-English studies were excluded, language bias is possible.

Conclusion

Our pooled analysis demonstrates that when SLE is diagnosed in older adults, most cutaneous manifestations are significantly less common. By contrast, sicca was significantly more prevalent in late-onset individuals. Future studies should examine differences in SLE manifestations in older versus younger-onset disease including investigating the roles of immune senescence in the skin and impact of gender and gene-environment interactions.

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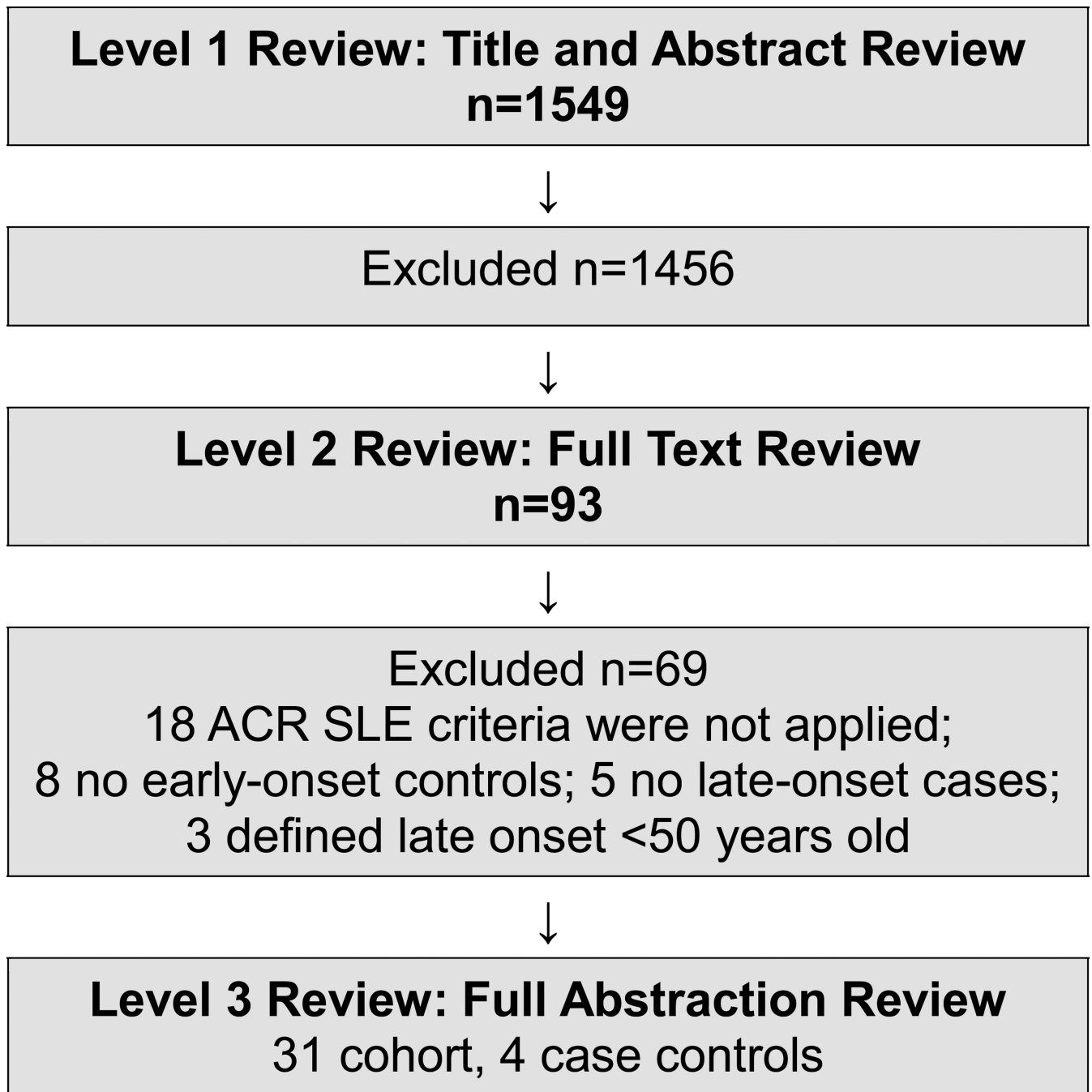


Figure 1.

Study selection process with description of study inclusion and exclusions during the three level review for the systematic review and meta-analysis.

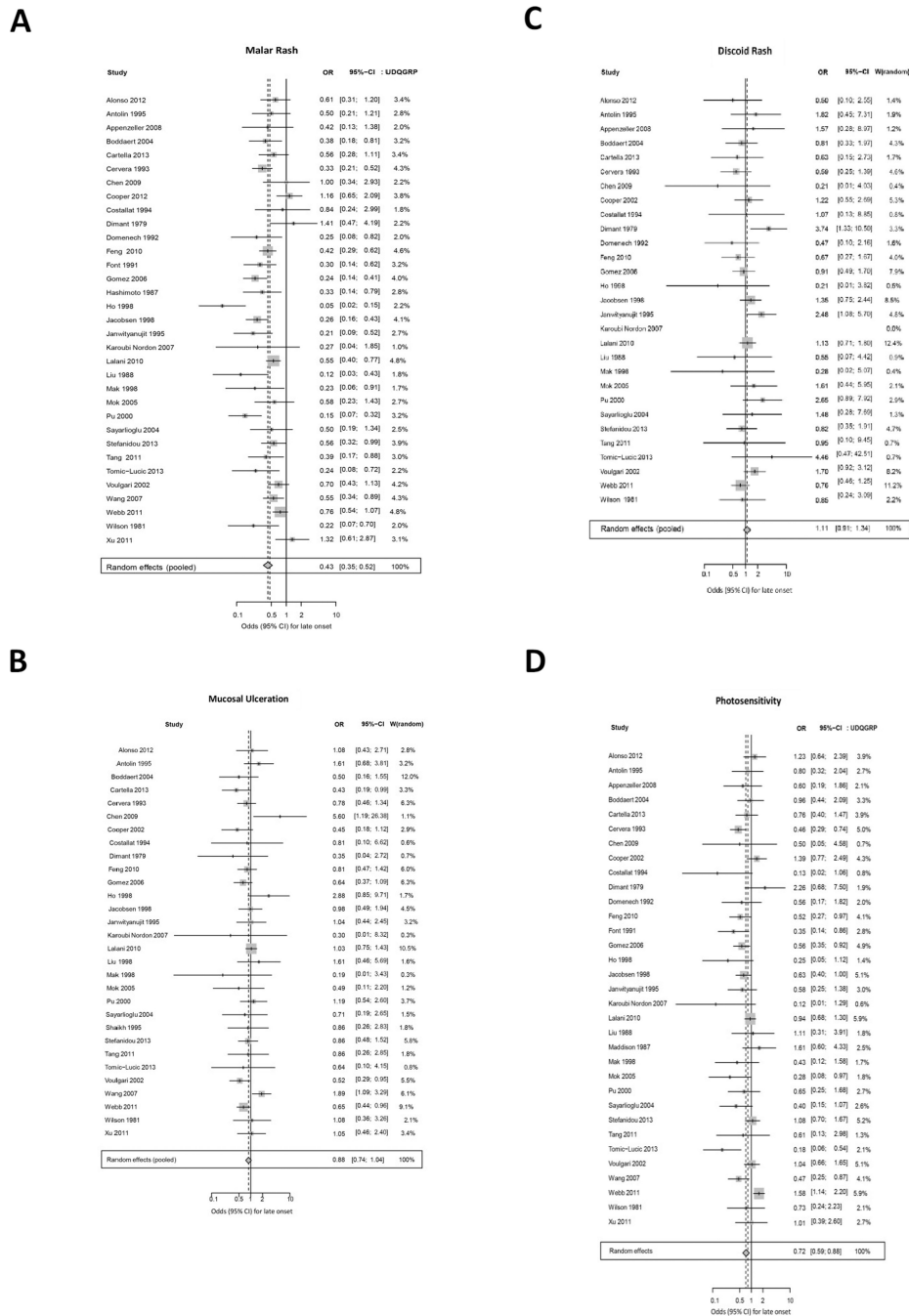
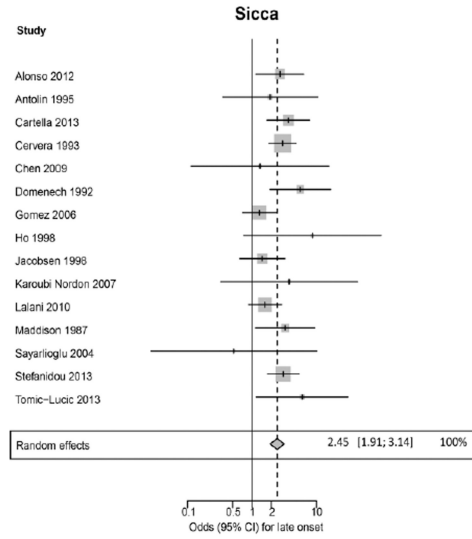
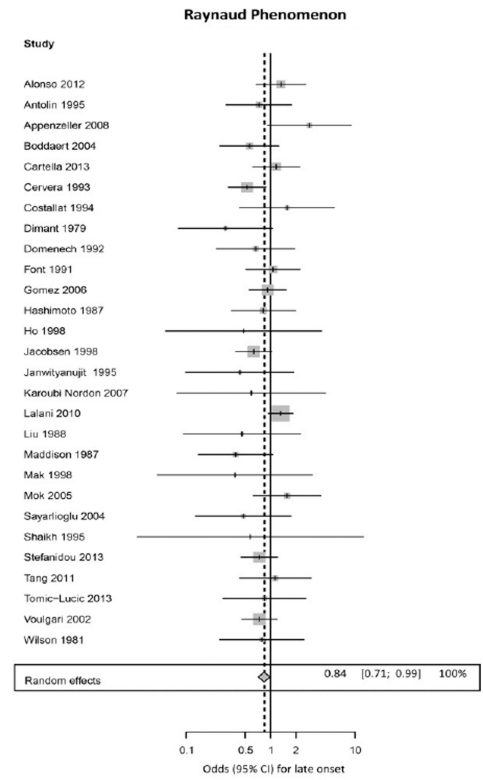


Figure 2. Meta-analysis results of weighted forest plots comparing prevalence of ACR cutaneous manifestations in late-onset versus early-onset SLE patients using random effects models ORs.

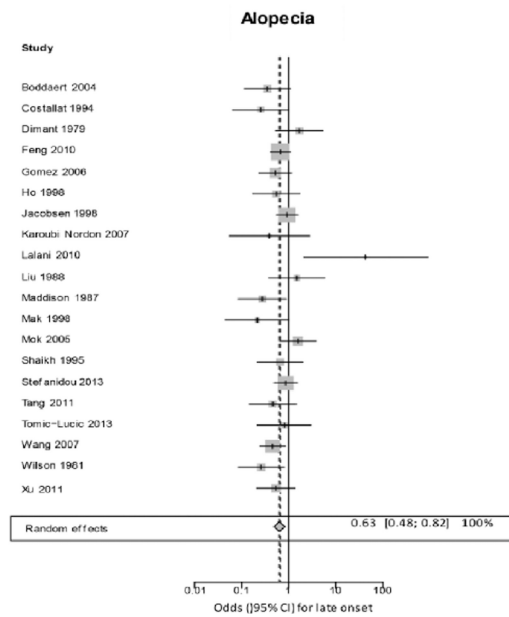
A



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B



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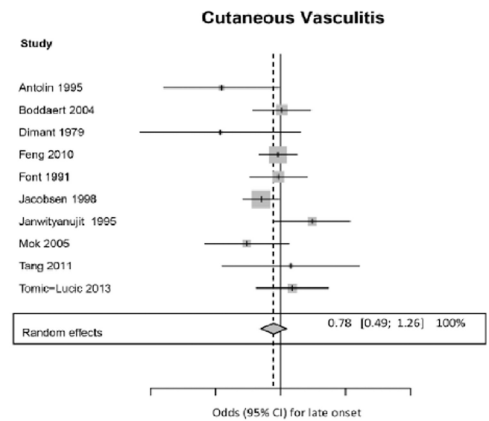


Figure 3. Meta-analysis results of weighted forest plots comparing prevalence of non-ACR cutaneous manifestations in late-onset versus early-onset SLE patients using random effects model ORs.

Table 1

Descriptions of studies included in meta-analysis of Late vs. Early-Onset SLE

Author and Publication Year	Setting (O)outpatient (P)opulation	Study type	Years	Early onset SLE (n)	Late onset SLE (n)	Late onset Age Def.	Newcastle Ottawa Score
Alonso 2012 ¹⁹	Spain; I	cohort	1987–2006	91	59	50*	6
Antolin 1995 ⁸	Spain; I	cohort	1980–1992	134	29	>50	7
Appenzeller 2008 ²⁰	Brazil; I	c-c	1974–2005	60	16	50*	7
Boddaert 2004 ¹	France; O	cohort	1980–2000	114	47	50*	6
Cartella 2013 ²¹	Italy; O	cohort	1976–2008	495	40	50	6
Cervera 1993 ⁹	Europe; P	cohort	1980–1990	910	90	>50*	6
Chen 2009 ²²	Taiwan; I/O	cohort	1998–2008	50	19	60*	6
Cooper 2002 ²³	USA; P	c-c	1997–1999	195	61	50	6
Costallat 1994 ¹³	Brazil; O	cohort	1973–1992	223	10	50*	6
Dimant 1979 ²	USA; I/O	cohort	1966–1976	218	16	>50*	6
Domenech 1992 ¹⁰	England; I/O	cohort	1985–1991	232	15	50*	6
Feng 2010 ²⁴	China; I	cohort	unknown	1550	131	50*	5
Font 1991 ³	Spain; I/O	cohort	1980–1988	210	40	50*	6
Gomez 2006 ²⁵	Spain; P	cohort	1992-?	259	91	50*	6
Hashimoto 1987 ⁴	Japan; O	cohort	1955–1985	501	21	50*	6
Ho 1998 ¹¹	China; O	cohort	1971–1997	100	25	>50*	7
Jacobsen 1998 ¹⁴	Denmark; P	cohort	1975–1995	354	103	50	6
Janwityanujit 1995 ¹²	Thailand; I	cohort	1990–1992	308	27	50*	7
Karoubi Nordon 2007 ⁵	France; O	c-c	1995–2003	11	11	50	8
Lalani 2010 ²⁶	Canada; P	cohort	2005-?	1367	161	50*	6
Liu 1988 ²⁷	Taiwan; I/O	cohort	1977–1986	207	11	50*	7
Maddison 1987 ²⁸	England; O	cohort	unknown	93	19	>60*	6
Mak 1998 ²⁹	China; I	cohort	1985–1995	89	13	>50*	6

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Author and Publication Year	Setting (I) Inpatient (O) Outpatient (P) Population	Study type	Years	Early onset SLE (n)	Late onset SLE (n)	Late onset Age Def.	Newcastle Ottawa Score
Mok 2005 ³⁰	China; I/O	cohort	1991–2003	213	22	>50*	8
Pu 2000 ³¹	Taiwan; I	cohort	1988–1998	152	42	50	6
Sayarlioglu 2004 ³²	Turkey; O	cohort	1978–2001	100	20	50*	6
Shaikh 1995 ⁶	Malaysia; O	cohort	1976–1992	52	17	>50	6
Stefanidou 2013 ³³	Greece; P	cohort	1989–2007	430	121	50*	6
Tang 2011 ³⁴	China; O	cohort	1986–2008	100	35	50	6
Tomic-Lucic 2013 ³⁵	Serbia; O	c-c	unknown	30	30	50	7
Voulgari 2002 ³⁶	Greece; O	cohort	1981–2000	398	90	55*	7
Wang 2007 ⁷	China; I/O	cohort	1999–2005	615	80	50*	6
Webb 2011 ³⁷	USA; P	cohort	unknown	1038	168	50	5
Wilson 1981 ³⁸	USA; O	cohort	1970–1978	49	17	50*	7
Xu 2011 ³⁹	China; I	cohort	2000–2008	241	30	50	6
TOTAL				11189	1727		

Abbreviations: c-c=case control;

* indicates SLE patients < 18 years old included in analysis.

Table 2

Meta-analysis summary statistics for cutaneous manifestations in Late vs Early-onset SLE

Cutaneous Manifestation	Total Cases n= 12,916	Late-onset n= 1,727	Early-onset n= 11,189	OR (95% CI)	Heterogeneity I^2 (%), p
Malar rash	12,731	1,691	11,040	0.43 (0.35, 0.52)	64, <0.001
Mucosal ulcerations	11,697	1,616	10,081	0.88 (0.74, 1.04)	22, 0.14
Discoid	10,997	1,520	9,477	1.11 (0.91, 1.34)	9, 0.33
Photosensitivity	12,318	1,698	10,620	0.72 (0.59, 0.88)	54, <0.001
Sicca	5,489	833	4,656	2.45 (1.91, 3.14)	13, 0.31
Raynaud	8,515	1,194	7,321	0.84 (0.71, 0.99)	14, 0.26
Alopecia	7,290	992	6,298	0.63 (0.48, 0.82)	36, 0.06
Cutaneous vasculitis	3,711	480	3,231	0.78 (0.49, 1.26)	37, 0.11
Livedo reticularis	1,619	197	1,422	0.63 (0.17, 2.31)	62, 0.03
Subacute cutaneous lupus	1,060	120	940	0.92 (0.43, 1.98)	0, 0.80

I^2 interpretation: low heterogeneity 25%, moderate 50%, and high >75%