

# Differences in clinical features observed between childhood-onset versus adult-onset systemic lupus erythematosus

# A systematic review and meta-analysis

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#### Abstract

**Background:** Systemic lupus erythematosus (SLE) affects people in childhood (childhood onset) or in adulthood (adult onset). Observational studies that have previously compared childhood-onset versus adult-onset SLE were often restricted to 1 ethnic group, or to a particular area, with a small sample size of patients. We aimed to systematically compare childhood-onset versus adult-onset SLE through a meta-analysis.

**Methods:** Electronic databases were searched for relevant publications comparing childhood-onset with adult-onset SLE. Adverse clinical features were considered as the endpoints. The Newcastle Ottawa Scale (NOS) was used to assess the methodological quality of the studies and RevMan software (version 5.3) was used to carry out this analysis whereby risk ratios (RRs) and 95% confidence intervals (95% Cls) were used as the statistical parameters.

**Results:** A total number of 10,261 participants (1560 participants with childhood-onset SLE and 8701 participants with adult-onset SLE) were enrolled. Results of this analysis showed that compared with childhood-onset SLE, pulmonary involvement was significantly higher with adult-onset SLE (RR: 1.51, 95% CI: 1.18–1.93; P=.001), whereas renal involvement was significantly higher with childhood-onset SLE (RR: 0.65, 95% CI: 0.55–0.77; P=.00001). Raynaud phenomenon and photosensitivity were significantly higher in adult-onset SLE (RR: 1.29, 95% CI: 1.04–1.60; P=.02) and (RR: 1.08, 95% CI: 1.01–1.17; P=.03), respectively. Malar rash significantly favored adult-onset SLE (RR: 0.84, 95% CI: 0.75–0.94; P=.002). Childhood-onset SLE was associated with significantly higher hemolytic anemia, thrombocytopenia, leukocytopenia, and lymphopenia. Seizure and ocular manifestations were significantly higher with childhood-onset SLE (RR: 0.57, 95% CI: 0.47–0.70; P=.00001) and (RR: 0.34, 95% CI: 0.21–0.55; P=.00001), respectively, whereas pleuritis was significantly higher with adult-onset SLE (RR: 0.51, 95% CI: 0.36–0.74; P=.0004) and (RR: 0.78, 95% CI: 0.68–0.89; P=.0002) respectively.

**Conclusion:** Significant differences were observed between childhood-onset versus adult-onset SLE, showing the former to be more aggressive.

Abbreviations: CI = confidence intervals, RR = risk ratios, SLE = systemic lupus erythematosus.

Keywords: adult-onset, childhood-onset, clinical features, hematological manifestations, renal diseases, seizures, systemic lupus erythematosus

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## 1. Introduction

Autoimmune diseases have not well been studied through randomized controlled trials. However, even if small prospective, retrospective, and case–control studies were commonly used to study those diseases, they have gradually been able to show the impact of autoimmune diseases on the population.

Systemic lupus erythematosus (SLE) is one among the common autoimmune disorders affecting a large number of female patients.<sup>[1]</sup> Even if it is often misdiagnosed or remains undiagnosed by physicians, several important classifications have been proposed according to recent guidelines.<sup>[2]</sup> The diagnosis of SLE is based on 17 important criteria, whereby a diagnosis of SLE could be made based on 4 of the criteria, including at least 1 of the 11 clinical criteria and 1 of the 6 immunological criteria or by a biopsy-proven nephritis compatible with SLE in the presence of antinuclear antibodies (ANAs) or anti-double stranded DNA antibodies (ds-DNA).<sup>[3]</sup>

SLE affects people in childhood (childhood-onset) or in adulthood (adult-onset). However, observational studies that have previously compared childhood-onset versus adult-onset SLE were often restricted to 1 ethnic group,<sup>[4]</sup> or to a particular area,<sup>[5]</sup> with a small sample size of patients.<sup>[6]</sup> Childhood-onset versus adult-onset SLE were not compared on an International or most probably on a worldwide basis (including patients from different parts of the world) to know whether the differences could be applied throughout any population. Therefore, we aimed to systematically compare childhood-onset versus adult-onset SLE using a large number of patients that were extracted from studies based on different regions, with different ethnic groups, in order to obtain a generalized outcome.

# 2. Methods

#### 2.1. Data sources and searched strategies

Data sources included

- (1) MEDLINE/PubMed database of medical research articles;
- (2) EMBASE database;
- (3) Cochrane library;
- (4) www.ClinicalTrials.gov;
- (5) Reference lists of suitable publications;
- (6) Google scholar;
- (7) Official websites of several journals of rheumatology.

#### 2.2. Searched strategies

The following terms were used in the search process:

- (1) "systemic lupus erythematosus," "childhood," and "adult";
- (2) "systemic lupus erythematosus" and "childhood";
- (3) "systemic lupus erythematosus" and "adult-onset";
- (4) "childhood-onset systemic lupus erythematosus";
- (5) "adult-onset systemic lupus erythematosus";
- (6) "childhood onset systemic lupus erythematosus" and "adult onset systemic lupus erythematosus."

The abbreviation "SLE" was also used in this search process to replace its full-form.

Only English publications were searched.

# 2.3. Inclusion and exclusion criteria

Studies that satisfied the inclusion criteria were

- (1) Studies that compared childhood-onset versus adult-onset SLE;
- (2) Studies that reported clinical outcomes which were observed between childhood-onset versus adult-onset SLE;
- (3) Studies that reported their data in the form of dichotomous data (number of events), which could be used in this analysis.

Studies were excluded based on the fact that

- (1) They did not compare childhood-onset with adult-onset SLE;
- (2) They did not report adverse clinical outcomes as their endpoints;
- (3) They reported data in a form that could not be used in this meta-analysis;
- (4) They were duplicate studies or replicated themselves through different searched databases.

#### 2.4. Types of participants, outcomes, and definitions

This analysis involved participants with childhood-onset and adult-onset SLE, respectively. Onset of SLE before the age of 17 years was classified as childhood-onset, whereas SLE onset after the age of 17 years, but before the age of 50 years, was considered as adult-onset SLE in this analysis. Late-onset participants who acquired SLE after the age of 50 years were not included.

Endpoints that were assessed were first of all based on systemic involvement such as

- (1) Pulmonary involvement;
- (2) Gastrointestinal involvement;
- (3) Dermatological involvement;
- (4) Neurological involvement;
- (5) Musculoskeletal involvement;
- (6) Neuropsychiatric involvement;
- (7) Renal involvement;
- (8) Cardiovascular involvement;
- (9) Hematological involvement;
- (10) In addition, detailed clinical manifestations were also assessed.

#### 2.5. Rheumatological and connective tissue manifestations

- (1) Raynaud phenomenon
- (2) Photosensitivity
- (3) Alopecia
- (4) Serositis
- (5) Myositis
- (6) Oral ulcers
- (7) Arthritis
- (8) Malar rash
- (9) Discoid rash

#### 2.6. Hematological manifestations

- (1) Hemolytic anemia
- (2) Thrombocytopenia
- (3) Leukocytopenia
- (4) Lymphopenia

#### 2.7. Central nervous system manifestations

- (1) Seizure
- (2) Psychosis

#### 2.8. Other clinical manifestations

- (1) Pericarditis
- (2) Ocular manifestations
- (3) Pleuritis
- (4) Vasculitis
- (5) Fever.

The clinical features that were reported in each study have been summarized in Table 1.<sup>[7–29]</sup>

#### 2.9. Data extraction and review

Data were extracted by 2 independent reviewers (PKB and AK). All the relevant information to be used in this analysis was collected. The clinical features that were reported, the age of disease onset, the types of participants, the total number of participants that were extracted from each study, the total number of events that were reported, were all recorded. As baseline features of the participants were seldom reported, we could not include these data in our analysis.

During this data extraction and data collection process, if ever any disagreement occurred, it was discussed between the 2 reviewers. However, if a final decision could not be made, the third reviewer (FH) was called to discuss and solve the issue.

As all the studies which were included in this analysis were observational studies, the Newcastle Ottawa Scale (NOS) was used to assess the methodological quality of the studies. NOS has been refined on the basis of expertise and experience whereby it was used in several projects.<sup>[30]</sup>

NOS assessment involved a minimum number of zero star to a maximum number of 9 stars depending on the quality of the study being assessed. The region where these studies were conducted and the number of stars allotted following the NOS assessment have been listed in Table 2.

#### 2.10. Statistical analysis

The latest version of the RevMan software (version 5.3) was used to carry out this analysis whereby risk ratios (RRs) and 95% confidence intervals (95% CIs) were used as the statistical parameters. However, a short coming that often affects metaanalyses is the presence of inconsistency across studies during subgroup analysis.<sup>[31]</sup> Hence, the Q statistic test and the I<sup>2</sup> statistic test were used to assess heterogeneity.

Statistically significant value was less or equal to 0.05.

Significance of  $I^2$ : A low percentage of  $I^2$  denoted a low level of heterogeneity.

Fixed effects model: used if  $I^2$  was less than 50%.

Random effects model: used if  $I^2$  was greater than 50%.

Ethical approval was not necessary for this analysis.

Publication bias was visually assessed by observing funnel plots.

#### 3. Results

#### 3.1. Searched outcomes

The PRISMA study guideline was used.<sup>[32]</sup> A total number of 1432 publications were obtained. A first elimination was directly carried out based upon assessment of the titles and abstracts whereby 1345 articles were rejected. Further eliminations were based on

- (1) the study was a meta-analysis (1);
- (2) the studies did not include any comparative group (14);
- (3) the studies involved late-onset SLE participants (13);
- (4) the studies were duplicates (36).

Finally, only 23 articles<sup>[7–29]</sup> were selected for this analysis (Fig. 1).

#### 3.2. Main features of the studies which were included

The types of study that were reported, the number of participants who were classified in the childhood-onset and the adult-onset SLE groups, respectively, and the time period of patients' enrollment have all been listed in Table 3.

A total number of 10,261 participants (1560 participants with childhood-onset SLE and 8701 participants with adult-onset SLE) who were enrolled from the year 1980 to 2013 were included in this analysis.

#### 3.3. System involvement

Results of this current analysis showed that compared with childhood-onset SLE, pulmonary involvement was significantly higher with adult-onset SLE with RR: 1.51, 95% CI: 1.18 to 1.93; P = .001,  $I^2 = 0\%$  (Fig. 2). Gastrointestinal involvement, dermatological involvement, musculoskeletal involvement, and neuropsychiatric involvement as a whole were not significantly different between childhood-onset and adult-onset SLE with RR: 1.18, 95% CI: 0.76 to 1.86; P = .46,  $I^2 = 2\%$ , RR: 0.69, 95% CI: 0.37 to 1.29; P = .24,  $I^2 = 0\%$ , RR: 0.84, 95% CI: 0.51 to 1.39; P = .50,  $I^2 = 0\%$  and RR: 0.94, 95% CI: 0.67 to 1.31; P = .70,  $I^2 = 48\%$ , respectively, as shown in Fig. 2. However, neurological involvement was significantly higher in childhood-onset SLE with RR: 0.60, 95% CI: 0.44 to 0.80; P = .0006,  $I^2 = 0\%$  (Fig. 2). A fixed effects model was used to assess these outcomes.

A random effects model was used to assess several other outcomes. This analysis showed renal involvement to be significantly higher with childhood-onset SLE with RR: 0.65, 95% CI: 0.55 to 0.77; P = .00001,  $I^2 = 76\%$  as shown in Fig. 3. However, cardiovascular and hematological involvement as a whole were not significantly different with childhood-onset or adult-onset SLE with RR: 1.02, 95% CI: 0.59–1.77; P = .93,  $I^2 = 50\%$  and RR: 0.93, 95% CI: 0.74 to 1.17; P = .54,  $I^2 = 68\%$ , respectively (Fig. 3).

#### 3.4. Rheumatological and connective tissue involvement

Raynaud phenomenon and photosensitivity were significantly higher in adult-onset SLE with RR: 1.29, 95% CI: 1.04 to 1.60; P=.02,  $I^2=29\%$  and RR: 1.08, 95% CI: 1.01 to 1.17; P=.03,  $I^2=46\%$ , respectively (Fig. 4). On the contrary, oral ulcers were significantly higher with childhood-onset SLE with RR: 0.85, 95% CI: 0.77 to 0.94; P=.001,  $I^2=0\%$  (Fig. 4). However, alopecia, serositis, and myositis were not significantly different with RR: 0.97, 95% CI: 0.69 to 1.36; P=.86,  $I^2=35\%$ , RR: 1.03, 95% CI: 0.86 to 1.22; P=.77,  $I^2=0\%$ , and RR: 0.46, 95% CI: 0.11 to 1.91; P=.28,  $I^2=51\%$ , respectively (Fig. 4).

This current result also showed malar rash to significantly favored adult-onset SLE and affected patients with childhood-onset SLE to a higher extent with RR: 0.84, 95% CI: 0.75 to 0.94; P = .002,  $I^2 = 70\%$  (Fig. 5). However, arthritis and discoid rash were similarly manifested between childhood-onset and adult-onset SLE with RR: 1.04, 95% CI: 0.98 to 1.11; P = .21,  $I^2 = 69\%$  and RR: 1.04, 95% CI: 0.72 to 1.50; P = .83,  $I^2 = 63\%$ , respectively (Fig. 5).

Table 1

Types of participants, ou	tcomes, and follow-up.	
Studies	Reported outcomes	Follow-up periods
Brunner et al <sup>[7]</sup>	Ocular damage, neuropsychiatric damage, renal damage, pulmonary damage, cardiovascular damage, peripheral vascular damage, gastrointestinal damage, skin damage, diabetes damage, patients with any renal involvement, WHO classification of the first renal biopsy: class I–V	Following disease
Carreño et al <sup>18]</sup>	Arthritis, arthralgia, malar rash, fever, Raynaud, pleuritis, vasculitis, articular manifestation, discoid rash, photosensitivity, oral ulcers, cutaneous vasculitis, pericarditis, renal disorder, neurologic disorder, hematologic disorder, hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia	At the onset and following disease
Fatemi et al <sup>[9]</sup>	Arthritis, malar rash, oral ulcer, seizure, psychosis, peripheral neuropathy, valvular heart disease, myocarditis, pericarditis, pleurisy, nephritis, hemolytic anemia, thrombocytopenia, leukopenia	Following disease
Feng et al <sup>[10]</sup>	Arthritis, renal involvement, fever, malar rash, alopecia, photosensitivity, oral ulcers, serositis, pleuritis, pericarditis, vasculitis, CNS involvement, discoid rash, myositis, thrombocytopenia, leukopenia	Following disease
Font et al <sup>[11]</sup>	Malar rash, discoid lesion, subacute cutaneous lesion, photosensitivity, oral ulcers, arthritis, serositis, nephropathy, neurological involvement, thrombocytopenia, hemolytic anemia, fever, Raynaud phenomenon, livedo reticularis, thrombosis, myositis, lung involvement, chorea, sicca syndrome, lymphadenopathy	At the onset and following disease
Gómez et al <sup>[12]</sup>	Malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, pleuritis, pericarditis, renal involvement, neurologic disorder, thrombocytopenia, leukopenia, hemolytic anemia, Raynaud phenomenon, alopecia, fever, lymphadenopathy, sicca syndrome, thrombosis	At diagnosis/onset
Ramírez Gómez et al <sup>[13]</sup>	Fever, myalgia, xerophthalmia, sicca syndrome, oral ulcers, chorea, TIA, CVA, cranial nerve lesion, hemolytic anemia, malar rash, thrombocytopenia, arthritis, photosensitivity, discoid rash, pleuritis, psychosis, seizure, leukopenia, lymphopenia	Following disease
Gormezano et al <sup>[14]</sup>	Monoarthritis, oligoarthritis, polyarthritis, myositis, fever, adenomegaly, hepatomegaly, splenomegaly, malar rash, discoid rash, photosensitivity, mucosal ulcers, alopecia, Raynaud phenomenon, pleuritis, pericarditis, neuropsychiatric involvement, CNS involvement, renal involvement	Following disease
Gormezano et al <sup>(15)</sup>	Fever, adenomegaly, hepatomegaly, splenomegaly, malar rash, discoid rash, photosensitivity, mucosal ulcers, alopecia, cutaneous vasculitis, arthritis, myositis, serositis, neuropsychiatric involvement, nephritis, multiple hemorrhagic manifestations, leukopenia, lymphopenia, thrombocytopenia	At diagnosis/onset
Hersh et $al^{[16]}$	Renal involvement, pulmonary involvement, seizures, myocardial infarction	At diagnosis
Hersh et al <sup>[17]</sup> Hoffman et al <sup>[18]</sup>	Mortality Malar rash, photosensitivity, alopecia, oral ulcers, discoid rash, xerostomia, xerophthalmia, fatigue, Raynaud phenomenon, fever, arthralgia, arthritis, myalgia, pleuritis, pericarditis, glomerulonephritis, headache, depression, encephalopathy, seizures, cerebrovascular accidents, psychosis, leukopenia, lymphopenia, thrombocytopenia, hemolytic anemia, thrombosis.	Following disease Following disease
Janwityanujit et al <sup>[19]</sup>	Fever, malar rash, photosensitivity, oral ulcer, discoid rash, vasculitis, Raynaud phenomenon, musculoarthritis, pleuropericarditis, adenopathy, neuropsychiatric, renal involvement, hematologic involvement, pulmonary involvement, gastrointestinal involvement, cardiac involvement, anemia, leukopenia, thrombocytopenia	At onset
Joo et al <sup>[20]</sup> das Chagas Medeiros et al <sup>[21]</sup>	Seizure, arthritis, musculoskeletal involvement Dermatological manifestations, photosensitivity, arthritis, nephritis, lymphopenia, hemolytic anemia, thrombocytopenia, serositis, seizure, psychosis, cutaneous vasculitis, cardiovascular diseases, death	Following disease Following disease
Mok et al <sup>[22]</sup>	Arthritis, alopecia, Raynaud phenomenon, malar rash, photosensitivity, discoid lesions, oral ulcers, leukopenia, lymphopenia, thrombocytopenia, hemolytic anemia, lymphadenopathy, serositis, psychosis, seizure, neuropsychiatric, renal involvement, cutaneous vasculitis, ocular involvement, neuropsychiatric involvement, renal involvement, pulmonary involvement, cardiovascular involvement, gastrointestinal involvement, musculoskeletal involvement, dermatological involvement	At onset and following disease
Pande et al <sup>[23]</sup>	Joint involvement, fever, photosensitivity, malar rash, alopecia, hepatomegaly, splenomegaly, lymphadenopathy, renal disease, cardiac involvement, seizures, psychosis, pulmonary involvement, gastrointestinal involvement, Raynaud phenomenon, vasculitis, thrombosis, anemia, leukopenia, lymphopenia, thrombocytopenia	Following disease
Rood et al <sup>[24]</sup>	Fever, lymphadenopathy, hepatosplenomegaly, arthritis, malar rash, alopecia, oral ulcers, photosensitivity, Raynaud phenomenon, vasculitis, discoid lesions, renal disorders, pleuritis, pericarditis, headache, seizure, psychosis, anemia, thrombocytopenia, leukocytopenia, lymphocytopenia	Following disease
Sassi et al <sup>[25]</sup>	Malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, nephritis, neurologic disorders, hematologic disorders, hemolytic anemia, leuko/lymphopenia, thrombocytopenia	At onset
Sousa et al <sup>[26]</sup>	Malar rash, discoid rash, photosensitivity, oral ulcers, arthritis, serositis, renal involvement, neurologic disorders, hematologic disorders	Following disease
Tu et al <sup>[27]</sup>	Neurological involvement, seizure, stroke, psychological symptoms, anemia, leukopenia, thrombocytopenia	Following disease
Tucker et al <sup>[29]</sup> Tucker et al <sup>[29]</sup>	Myositis, mortality, rash, arthritis, renal involvement, CNS involvement, hematologic involvement. Ocular manifestation, neuropsychiatric, renal involvement, pulmonary involvement, cardiovascular involvement, gastrointestinal involvement, musculoskeletal involvement	Following disease At diagnosis

A=adult; C=childhood; CNS=central nervous system; CVA=cerebrovascular accident; SLE=systemic lupus erythematosus; TIA=transient ischemic attack; WHO=World Health Organization.

involvement, gastrointestinal involvement, musculoskeletal involvement

4

# Table 2

Study assessment using the Newcastle Ottawa Scale.

		Stars allotted following
Studies	Location/region	NOS assessment
Brunner et al <sup>[7]</sup>	Toronto	*****
Carreño et al <sup>[8]</sup>	Spain	*****
Fatemi et al <sup>[9]</sup>	Iran	*****
Feng et al <sup>[10]</sup>	China	*****
Font et al <sup>[11]</sup>	Spain	*****
Gómez et al <sup>[12]</sup>	Spain	*****
Ramírez Gómez et al <sup>[13]</sup>	Latin-America	*****
Gormezano et al <sup>[14]</sup>	Brazil	*****
Gormezano et al <sup>[15]</sup>	Brazil	*****
Hersh et al <sup>[16]</sup>	United States	*****
Hersh et al <sup>[17]</sup>	San Francisco	*****
Hoffman et al <sup>[18]</sup>	Belgium	*****
Janwityanujit et al <sup>[19]</sup>	Thailand	*****
Joo et al <sup><math>[20]</math></sup>	Korea	******
das Chagas Medeiros et al <sup>[21]</sup>	Brazil	*****
Mok et al <sup>[22]</sup>	China	******
Pande et al <sup>[23]</sup>	India	*****
Rood et al <sup>[24]</sup>	Netherland	*****
Sassi et al <sup>[25]</sup>	Brazil	*****
Sousa et al <sup>[26]</sup>	Portugal	*****
Tu et al $[27]$	Taiwan	*****
Tucker et al <sup>[28]</sup>	United Kingdom	*****
Tucker et al <sup>[29]</sup>	United States	******



### 3.5. Hematological manifestations

When hematological involvement was further subdivided, childhood-onset SLE was associated with significantly higher hemolytic anemia, thrombocytopenia, leukocytopenia, and lymphopenia with RR: 0.69, 95% CI: 0.58 to 0.81; P=.00001,  $I^2$ =39%, RR: 0.85, 95% CI: 0.76 to 0.96; P=.006,  $I^2$ =10%, RR: 0.83, 95% CI: 0.76 to 0.90; P=.0001,  $I^2$ =49%, and RR:

## Table 3

NOS = Newcastle Ottawa scale.

Studies	Type of study	Period of patients' enrollment, y	No. of patients with childhood-onset SLE (n)	No. of patients with adult-onset SLE (n)
Brunner et al <sup>[7]</sup>	Prospective	1990–1998	67	131
Carreño et al <sup>[8]</sup>	Prospective	_	49	130
Fatemi et al <sup>[9]</sup>	Retrospective	1992–2013	180	394
Feng et al <sup>[10]</sup>	Observational	_	108	1551
Font et al <sup>[11]</sup>	Prospective	1980–1995	34	396
Gómez et al <sup>[12]</sup>	Report	2003	13	259
Ramírez Gómez et al <sup>[13]</sup>	Cohort	>1996	230	984
Gormezano et al <sup>[14]</sup>	Observational	1983–2014	8	69
Gormezano et al <sup>[15]</sup>	Retrospective	_	49	49
Hersh et al <sup>[16]</sup>	Longitudinal	2004–2006	90	795
Hersh et al <sup>[17]</sup>	Longitudinal	2002–2003	98	859
Hoffman et al <sup>[18]</sup>	Observational	—	55	188
Janwityanujit et al <sup>[19]</sup>	Observational	1990–1992	51	308
Joo et al <sup>[20]</sup>	Prospective	1998–2012	133	979
das Chagas Medeiros et al <sup>[21]</sup>	Observational	2010-2012	60	338
Mok et al <sup>[22]</sup>	Prospective	1991–2003	50	213
Pande et al <sup>[23]</sup>	Retrospective		83	187
Rood et al <sup>[24]</sup>	Observational	1986–1995	31	135
Sassi et al <sup>[25]</sup>	Cross-sectional	2003–2015	89	419
Sousa et al <sup>[26]</sup>	Cross-sectional		89	89
Tu et al <sup>[27]</sup>	Retrospective	1999–2008	12	15
Tucker et al <sup>[28]</sup>	Prospective	_	39	165
Tucker et al <sup>[29]</sup>	Case-control		31	48
Total no. of patients (n)			1560	8701

SLE = systemic lupus erythematosus.

	Adult Onse	I OLE	Childhood Ons	et SLE		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
I.1.1 Pulmonary invol	vement						
Brunner2008	3	131	2	66	0.9%	0.76 [0.13, 4.41]	
Font1998	15	396	2	34	1.2%	0.64 [0.15, 2.70]	
Hersh2009	344	795	21	90	12.1%	1.85 [1.26, 2.72]	
lanwityanujit1995	68	308	8	51	4.4%	1.41 [0.72, 2.75]	
Mok2005	6	213	0	50	0.3%	3.10 [0.18, 54.11]	
Pande1993	68	187	24	83	10.7%	1.26 [0.85, 1.85]	+
Fucker2008	3	48	1	31	0.4%	1.94 [0.21, 17.80]	
Subtotal (95% CI)		2078		405	29.9%	1.51 [1.18, 1.93]	◆
Total events	507		58				
Heterogeneity: Chi² = 4 Fest for overall effect: Z			<sup>2</sup> = 0%				
I.1.2 Gastrointestinal	involvement	t					
Brunner2008	3	131	2	66	0.9%	0.76 [0.13, 4.41]	
Janwityanujit1995	31	308	7	51	3.9%	0.73 [0.34, 1.58]	
Mok2005	0	213	0	50		Not estimable	
Pande1993	36	187	11	83	4.9%	1.45 [0.78, 2.71]	+
Fucker2008	5	48	1	31	0.4%	3.23 [0.40, 26.34]	<u> </u>
Subtotal (95% CI)	-	887		281	10.0%	1.18 [0.76, 1.86]	<b>*</b>
Total events	75		21			-	
Heterogeneity: Chi <sup>2</sup> = 3 Fest for overall effect: Z	.05, df = 3 (P						
1.1.3 Dermatological i	nvolvement						
Brunner2008	9	131	6	66	2.6%	0.76 [0.28, 2.03]	
Mok2005	19	213	7	50	2.0 % 3.6%	0.64 [0.28, 1.43]	<del></del>
Subtotal (95% CI)	10	344	,	116	6.2%	0.69 [0.37, 1.29]	
Fotal events	28		13		/ 0		-
Heterogeneity: Chi <sup>2</sup> = 0 Test for overall effect: Z	.07, df = 1 (P						
1.1.4 Neurological inv	olvement						
Carreno1999	26	130	18	49	8.4%	0.54 [0.33, 0.90]	
Font1998	63	396	9	34	5.3%	0.60 [0.33, 1.10]	
Gomez2006	21	259	9	13	0.6%	1.05 [0.15, 7.24]	
Sassi2017	47	239 419	15	89	0.0 <i>%</i> 7.9%	0.67 [0.39, 1.14]	<b>_</b> _
Sousa2016	47 5	419 89	10	89 89	3.2%	0.50 [0.18, 1.40]	
Fu2011	2	89 15	4	69 15	3.2% 1.3%	0.50 [0.18, 1.40]	
Subtotal (95% CI)	2	1308	4	289	<b>26.8%</b>	0.60 [0.44, 0.80]	▲
Fotal events	164		57	200	20.070	0.00 [0.77, 0.00]	▼
Heterogeneity: Chi <sup>2</sup> = 0 Fest for overall effect: Z	.79, df = 5 (P						
I.1.5 Musculoskeletal	involvemen	t					
/lok2005	41	213	11	50	5.7%	0.87 [0.49, 1.58]	— <del>-</del>
Fucker2008	7	48	6	31	2.3%	0.75 [0.28, 2.03]	
Subtotal (95% CI)		261		81	8.1%	0.84 [0.51, 1.39]	<b></b>
Fotal events	48		17				
Heterogeneity: Chi² = 0 Fest for overall effect: Z							
1.1.6 Neuropsychiatric	: involveme	nt					
Brunner2008	13	131	8	66	3.4%	0.82 [0.36, 1.88]	
Gormezano2015	0	69	1	8	0.9%	0.04 [0.00, 0.97]	<
Gormezano2016	10	49	16	49	5.1%	0.63 [0.32, 1.24]	+
lanwityanujit1995	49	308	9	51	5.0%	0.90 [0.47, 1.72]	— <del>—</del> —
Mok2005	60	213	9	50	4.7%	1.56 [0.83, 2.94]	<del></del>
Subtotal (95% CI)		770		224	19.1%	0.94 [0.67, 1.31]	<b>+</b>
Fotal events Heterogeneity: Chi² = 7 Fest for overall effect: Z			43 ² = 48%				
Fotal (95% CI)		5648		1396	100.0%	1.02 [0.88, 1.17]	
otal events	954		209				
		(P = 0.03)					· · · · · · · · · · · · · · · · · · ·
leterogeneity: Chi <sup>2</sup> = 4		. 0.00	,,				0.01 0.1 1 10 1
leterogeneity: Chi <sup>2</sup> = 4 est for overall effect: Z		0.81)					Favours [Adult onset] Favours [Childhood onset]

0.91, 95% CI: 0.84 to 0.98; P=.01,  $I^2=50\%$ , respectively (Fig. 6).

# no significant difference was observed with psychosis, with RR: 0.88, 95% CI: 0.64 to 1.20; P=.40, $I^2=0\%$ (Fig. 7).

# 3.6. Nervous system manifestations

Seizure was significantly higher with childhood-onset SLE with RR: 0.57, 95% CI: 0.47 to 0.70; P = .00001,  $I^2 = 31\%$ . However,

# 3.7. Other clinical manifestations

Ocular manifestation was significantly higher with childhoodonset SLE, with RR: 0.34, 95% CI: 0.21 to 0.55; P = .00001,  $I^2 =$ 

	Adult Onse		Childhood One			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 Renal involven	nent						
Brunner2008	68	131	52	67	7.8%	0.67 [0.54, 0.82]	-
Carreno1999	63	130	33	49	7.1%	0.72 [0.55, 0.94]	
Gomez2006	80	259	10	13	6.0%	0.40 [0.28, 0.57]	
Gormezano2015	2	69	3	8	0.7%	0.08 [0.02, 0.40]	
Hersh2009	295	795	51	90	7.9%	0.65 [0.54, 0.80]	-
Janwityanujit1995	206	308	42	51	8.5%	0.81 [0.70, 0.94]	-
Mok2005	107	213	28	50	6.9%	0.90 [0.68, 1.19]	
Pande1993	123	187	65	83	8.5%	0.84 [0.72, 0.98]	-
Sousa2016	28	89	52	80	6.0%	0.48 [0.34, 0.68]	
Tucker2008	8	48	14	31	2.6%	0.37 [0.18, 0.78]	
Subtotal (95% CI)		2229		522	62.0%	0.65 [0.55, 0.77]	◆
Total events	980		350				
Heterogeneity: Tau <sup>2</sup> =	= 0.05; Chi <sup>2</sup> = 3	37.15, df	= 9 (P < 0.0001);	l² = 76%			
Test for overall effect:	: Z = 4.93 (P <	0.00001	)				
1.1.2 Cardiovascula	r involvement	t					
Brunner2008	6	131	1	66	0.4%	3.02 [0.37, 24.59]	
Janwityanujit1995	46	308	5	51	2.0%	1.52 [0.64, 3.65]	
Medeiros2015	44	322	3	58	1.3%	2.64 [0.85, 8.22]	
Mok2005	27	213	9	50	2.9%	0.70 [0.35, 1.40]	
Pande1993	33	187	24	83	4.7%	0.61 [0.39, 0.96]	
Tucker2008	2	48	2	31	0.5%	0.65 [0.10, 4.35]	
Subtotal (95% CI)		1209		339	11.9%	1.02 [0.59, 1.77]	<b>•</b>
Total events	158		44				
Heterogeneity: Tau <sup>2</sup> =			5 (P = 0.08); I <sup>2</sup> =	50%			
Test for overall effect	: Z = 0.09 (P =	0.93)					
1.1.3 Hematological	involvement						
Janwityanujit1995	188	308	24	51	6.5%	1.30 [0.96, 1.76]	
Sassi2017	306	419	67	89	8.7%	0.97 [0.85, 1.11]	*
Sousa2016	53	89	68	89	7.9%	0.78 [0.63, 0.96]	
Tucker1995	12	50	11	28	3.0%	0.61 [0.31, 1.20]	
Subtotal (95% CI)		866		257	26.1%	0.93 [0.74, 1.17]	•
Total events	559		170				
Heterogeneity: Tau <sup>2</sup> =			3 (P = 0.03); I <sup>2</sup> =	68%			
Test for overall effect:	: Z = 0.61 (P =	0.54)					
		4304		1118	100.0%	0.74 [0.64, 0.85]	♦
Total (95% CI)	1007		564				
Total (95% CI) Total events	1697						
Total events Heterogeneity: Tau² =	= 0.05; Chi² = 7		= 19 (P < 0.0000	1); l² = 73	%		
Total events	= 0.05; Chi² = 7		= 19 (P < 0.0000	1); l² = 73	%		0.01 0.1 1 1 0 10 Favours [Adult onset] Favours [Childhood onset]

0%, whereas pleuritis was significantly higher with adult-onset SLE with RR: 1.45, 95% CI: 1.17 to 1.79; P=.0008,  $I^2=0\%$ . However, pericarditis was similarly manifested with RR: 0.84, 95% CI: 0.63 to 1.11; P=.23,  $I^2=40\%$ .

Vasculitis and fever were significantly higher with childhoodonset SLE, with RR: 0.51, 95% CI: 0.36 to 0.74; P = .0004,  $I^2 = 53\%$  and RR: 0.78, 95% CI: 0.68 to 0.89; P = .0002,  $I^2 = 66\%$ , respectively.

Significant and un-significant outcomes are listed in Table 4.

#### 3.8. Publication bias

A visual assessment of the 3 funnel plots, which were obtained from RevMan, showed a low to moderate risk of publication bias across the studies that assessed the relevant clinical endpoints. The funnel plots have been represented in Figs. 8 to 10.

# 4. Discussion

In this analysis, we aimed to compare the clinical features that were associated with childhood-onset versus adult-onset SLE using a large number of participants, which was obtained from several corners around the world. The current results showed significantly more adverse features to be associated with childhood-onset SLE when compared with adult-onset SLE. Neurological and renal involvement were more significant with childhood-onset SLE. Even fever significantly favored adult-onset SLE compared with childhood-onset SLE. When hematological manifestation was further analyzed, hemolytic anemia, thrombocytopenia, leukopenia, and lymphopenia were significantly higher with childhood-onset SLE. However, pulmonary involvement, Raynaud phenomenon, and photosensitivity were significantly higher with adult-onset SLE.

A recent meta-analysis comparing the differences in autoantibody profiles and disease activity and damage score associated with childhood-onset versus adult-onset SLE showed increased anti-ds DNA and anticardiolipin antibodies to be significantly associated with childhood-onset SLE.<sup>[33]</sup> The authors also suggested more disease activity in this category of SLE patients than adult-onset SLE. This current analysis has further supported their conclusion proving that more adverse clinical manifestations were present with childhood-onset SLE. Another metaanalysis comparing cutaneous manifestations between earlyonset versus late onset SLE showed the latter to be associated with less severe outcomes.<sup>[34]</sup> However, this current analysis did not involve patients with late-onset (elderly) SLE.

A review article based on the recent updates on the differences between childhood-onset and adult-onset SLE showed the latter to be 10 times more common than the former in United States. However, the authors mentioned that childhood-onset SLE was more severe.<sup>[35]</sup> Another review article based on the similarities and differences between childhood-onset versus adult-onset SLE

	Adult Ons	et SLE	Childhood Ons	set SLE		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	
1.2.1 Raynaud pheno			10		4 70/		
Carreno1999 Font1998	45 100	130 396	18 7	49 34	1.7% 0.8%	0.94 [0.61, 1.46] 1.23 [0.62, 2.42]	<u> </u>
Gormezano2015	19	69	1	8	0.1%	2.20 [0.34, 14.33]	
Hoffman2008	77	188	22	55	2.2%	1.02 [0.71, 1.48]	+
Janwityanujit1995	48	308	1	51	0.1%	7.95 [1.12, 56.31]	
Mok2005 Pande1993	39 69	213 187	4 24	50 83	0.4% 2.2%	2.29 [0.86, 6.11] 1.28 [0.87, 1.88]	
Subtotal (95% CI)	00	1491	24	330	7.6%	1.29 [1.04, 1.60]	◆
Total events	397		77				
Heterogeneity: Chi <sup>2</sup> = 8			l² = 29%				
Test for overall effect:	Z = 2.35 (P =	= 0.02)					
1.2.2 Photosensitivity	/						
Carreno1999	66	130	20	49	1.9%	1.24 [0.85, 1.81]	+ <del>-</del>
Feng2010	227	1551	15	108	1.8%	1.05 [0.65, 1.71]	
Font1998 Gomez2006	140 90	396 259	15 4	34 13	1.8% 0.5%	0.80 [0.54, 1.20]	
Gomez2008 Gomez2008	90 559	259 984	122	230	12.9%	1.13 [0.49, 2.60] 1.07 [0.94, 1.22]	+
Gormezano2016	30	49	21	49	1.4%	1.43 [0.96, 2.12]	
Hoffman2008	100	188	25	55	2.5%	1.17 [0.85, 1.61]	+
Janwityanujit1995	129	308	8	51	0.9%	2.67 [1.39, 5.11]	
Medeiros2015 Mok2005	179 45	338 213	34 10	60 50	3.8% 1.1%	0.93 [0.73, 1.19] 1.06 [0.57, 1.95]	
Pande1993	115	187	61	83	5.5%	0.84 [0.70, 0.99]	
Rood1999	58	135	12	31	1.3%	1.11 [0.68, 1.80]	
Sassi2017	308	419	63	89	6.8%	1.04 [0.90, 1.20]	ť_
Sousa2016 Subtotal (95% CI)	53	89 5246	41	89 991	2.7% 44.6%	1.29 [0.97, 1.71] 1.08 [1.01, 1.17]	
Total events	2099		451				ľ
Heterogeneity: Chi <sup>2</sup> = 2		3 (P = 0.0					
Test for overall effect: 2	Z = 2.19 (P =	= 0.03)					
1.2.3 Alopecia							
Feng2010	285	1551	22	108	2.7%	0.90 [0.61, 1.33]	<u> </u>
Gomez2006	71	259	0	13	0.1%	7.70 [0.50, 117.95]	<b>.</b>
Gomez2008	0	984	0	230		Not estimable	
Gormezano2016 Subtotal (95% CI)	10	49 2843	14	49 400	0.9% 3.6%	0.71 [0.35, 1.45]	
Total events	366	2043	36	400	3.0%	0.97 [0.69, 1.36]	Ŧ
Heterogeneity: Chi <sup>2</sup> = 3		P = 0.22);					
Test for overall effect:							
1.2.4 Sevenitie							
1.2.4 Serositis Feng2010	313	1551	13	108	1.6%	1.68 [1.00, 2.82]	
Font1998	109	396	13	34	1.3%	0.85 [0.51, 1.42]	<del></del>
Gomez2006	68	259	3	13	0.4%	1.14 [0.41, 3.13]	
Gormezano2016	20	49	20	49	1.3%	1.00 [0.62, 1.61]	
Medeiros2015	125 27	338 213	24 5	60 50	2.7% 0.5%	0.92 [0.66, 1.30]	<u> </u>
Mok2005 Sassi2017	111	419	25	89	2.7%	1.27 [0.51, 3.13] 0.94 [0.65, 1.36]	
Sousa2016	17	89	23	89	1.5%	0.74 [0.42, 1.29]	-+
Subtotal (95% CI)		3314		492	11.9%	1.03 [0.86, 1.22]	•
Total events	790 240 - # - 7 (	D - 0 50).	124				
Heterogeneity: Chi <sup>2</sup> = 6 Test for overall effect: 2			1- = 0%				
	L 0.00 ()	0.11)					
1.2.5 Myositis							
Gormezano2016 Tucker1995	0	49 165	4	49 39	0.3% 0.1%	0.11 [0.01, 2.01] 1.42 [0.18, 11.44]	
Subtotal (95% CI)	6	214	1	39	0.1%	0.46 [0.11, 1.91]	
Total events	6		5				
Heterogeneity: Chi <sup>2</sup> = 2			l² = 51%				
Test for overall effect:	Z = 1.07 (P =	= 0.28)					
1.2.6 Oral ulcers							
Carreno1999	49	130	20	49	1.9%	0.92 [0.62, 1.38]	-+
Fatemi2016	42	394	18	180	1.6%	1.07 [0.63, 1.80]	+
Feng2010 Font1998	164 100	1551 396	12 13	108 34	1.5% 1.6%	0.95 [0.55, 1.65]	
Gomez2006	100	396 259	13 12	34	1.6%	0.66 [0.42, 1.05] 0.79 [0.66, 0.94]	-
Gomez2008	393	984	113	230	11.9%	0.81 [0.70, 0.95]	+
Hoffman2008	44	188	16	55	1.6%	0.80 [0.49, 1.31]	-+
Janwityanujit1995	89	308	18	51	2.0%	0.82 [0.54, 1.23]	
Mok2005 Rood1999	24 57	213 135	9 15	50 31	0.9% 1.6%	0.63 [0.31, 1.26] 0.87 [0.58, 1.32]	·
Sassi2017	151	419	36	89	3.9%	0.89 [0.67, 1.18]	+
Sousa2016	31	89	29	89	1.9%	1.07 [0.71, 1.61]	+
Subtotal (95% CI)	4000	5066		979	31.8%	0.85 [0.77, 0.94]	•
Total events Heterogeneity: Chi <sup>2</sup> = 5	1332 5.47 df = 11	(P = 0.04	311 ): l <sup>2</sup> = 0%				
Test for overall effect: 2			j, i = ∪ /o				
Total (95% CI)		18174		3280	100.0%	1.01 [0.96, 1.07]	1
Total events Heterogeneity: Chi <sup>2</sup> = 6	4990 89.70 df - 4	5 (D - 0 0	1004				
Test for overall effect: 2			17,135%				0.01 0.1 1 10 100
Test for subgroup diffe			df = 5 (P = 0.000	7), I² = 76.	7%		Favours [Adult onset] Favours [Childhood onset]
	Figure	1 04	oumotoloo	ical c	nd oor	noctive ties "	a manifestations (part 1)
	rigure	<b>4.</b> D	เธินเทลเบเบตู	ગળવા લા	iu col	INSCLIVE LISSUE	e manifestations (part 1).

showed higher prevalence of renal involvement (nephritis) and central nervous system involvement in children than in adults, further supporting the results of this current analysis.<sup>[36]</sup> The authors also suggested that additional steroid use and more aggressive treatment strategy should be considered in childhood-onset SLE. Moreover, data from the 2002 to 2010 cycles of the Lupus Outcomes Study showed childhood-onset SLE to significantly increase the risk of not working in adulthood, despite of full control of the disease.<sup>[37]</sup>

This current analysis showed childhood-onset SLE to be more aggressive; therefore, specific therapy with better management should be reserved to this particular subgroup. A few studies showed hematuria to significantly increase the mortality rate in participants with childhood-onset SLE that might have been due to complications associated with the renal organ.<sup>[38]</sup> However, other studies have concluded that patients with childhood-onset and adult-onset SLE with renal involvement should both be carefully monitored to prevent unwanted outcomes.

	Adult Onse	et SLE	Childhood On	set SLE		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
.2.1 Arthritis							
Carreno1999	51	130	11	49	1.0%	1.75 [1.00, 3.07]	
Fatemi2016	232	394	91	180	3.5%	1.16 [0.99, 1.38]	-
Feng2010	960	1551	61	108	3.5%	1.10 [0.92, 1.30]	
Font1998	320	396	30	34	3.9%	0.92 [0.80, 1.04]	-
Gomez2006	188	259	12	13	3.4%	0.79 [0.66, 0.94]	-
Gomez2008	807	984	191	230	4.5%	0.99 [0.93, 1.05]	+
Gormezano2015	69	69	8	8	3.6%	1.00 [0.85, 1.17]	+
Gormezano2016	34	49	27	49	2.2%	1.26 [0.92, 1.72]	
Hoffman2008	126	188	33	55	2.8%	1.12 [0.88, 1.42]	
Janwityanujit1995	185	308	26	51	2.4%	1.18 [0.89, 1.57]	+
Vedeiros2015	287	338	51	60	4.1%	1.00 [0.89, 1.12]	+
Mok2005	144	213	34	50	3.1%	0.99 [0.80, 1.23]	+
Rood1999	127	135	31	31	4.5%	0.95 [0.90, 1.01]	
Sassi2017	329	419	65	89	3.8%	1.08 [0.94, 1.23]	-
Sousa2016	79	89	62	89	3.6%	1.27 [1.09, 1.49]	-
Fucker1995	162	165	35	39	4.1%	1.09 [0.98, 1.22]	-
Subtotal (95% CI)	102	5687	55	1135	54.0%	1.04 [0.98, 1.11]	
Fotal events	4100	0001	768	1100	04.070	1.04 [0.00, 1.11]	
Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.01; Chi² = 4			); I² = 69%			
1.2.2 Malar rash							
Carreno1999	77	130	29	49	2.5%	1.00 [0.76, 1.31]	+
atemi2016	190	394	88	180	3.4%	0.99 [0.82, 1.18]	+
Feng2010	728	1551	40	108	2.7%	1.27 [0.99, 1.63]	
-ont1998	203	396	27	34	3.2%	0.65 [0.53, 0.79]	-
Gomez2006	49	259	0	13	0.1%	5.33 [0.35, 82.01]	
Gomez2008	582	984	162	230	4.2%	0.84 [0.76, 0.93]	-
Gormezano2015	8	69	2	8	0.2%	0.46 [0.12, 1.82]	
Gormezano2016	30	49	26	49	1.9%	1.15 [0.82, 1.63]	
Hoffman2008	110	188	38	55	3.0%	0.85 [0.68, 1.05]	
Janwityanujit1995	191	308	30	51	2.7%	1.05 [0.82, 1.35]	+-
Mok2005	106	213	33	50	2.8%	0.75 [0.59, 0.96]	
Pande1993	123	187	69	83	3.8%	0.79 [0.69, 0.91]	<del></del>
Rood1999	54	135	22	31	2.2%	0.56 [0.42, 0.77]	
Sassi2017	234	419	64	89	3.6%	0.78 [0.66, 0.91]	-
Sousa2016	32	89	55	89	2.1%	0.58 [0.42, 0.80]	
Subtotal (95% CI)	02	5371	00	1119	38.4%	0.84 [0.75, 0.94]	•
Fotal events	2717		685				, i i i i i i i i i i i i i i i i i i i
Heterogeneity: Tau² = Fest for overall effect:	0.03; Chi² = 4			); I² = 70%			
1.2.3 Discoid rash	40	400	40	40	0.00/	0 50 10 00 0 001	
Carreno1999	18	130	13	49	0.8%	0.52 [0.28, 0.98]	
Feng2010	131	1551	16	108	1.2%	0.57 [0.35, 0.92]	
Font1998	17	396	5	34	0.4%	0.29 [0.11, 0.74]	
Gomez2006	130	259	5	13	0.7%	1.31 [0.65, 2.62]	
Gomez2008	114	984	29	230	1.7%	0.92 [0.63, 1.35]	
Gormezano2016	4	49	3	49	0.2%	1.33 [0.31, 5.65]	
Hoffman2008	54	188	10	55	0.9%	1.58 [0.86, 2.89]	T
Janwityanujit1995	59	308	2	51	0.2%	4.88 [1.23, 19.37]	
Mok2005	12	213	3	50	0.2%	0.94 [0.28, 3.20]	
Rood1999	36	135	3	31	0.3%	2.76 [0.91, 8.37]	<u> </u>
Sassi2017	52	419	9	89	0.7%	1.23 [0.63, 2.40]	_ <del></del>
Sousa2016	6	89	3	89	0.2%	2.00 [0.52, 7.75]	
Subtotal (95% CI)		4721		848	7.6%	1.04 [0.72, 1.50]	<b>•</b>
Fotal events	633		101				
Heterogeneity: Tau <sup>2</sup> = Fest for overall effect:			= 11 (P = 0.002);	l² = 63%			
Гotal (95% СІ)		15779		3102	100.0%	0.96 [0.90, 1.02]	•
	7450		1554			· -	
lotal events							
otal events leterogeneity: Tau² =		149.49, di	f = 42 (P < 0.000	01); l² = 7	2%	H 0.01	0.1 1 10 1

This analysis satisfied all the criteria which are relevant for a good systematic review and meta-analysis. The methodological quality of the studies which were included were assessed. Robust results which match with the clinical literature were obtained. In addition, the current results have been generalized, and not limited to a specific ethnic group or region.

# 4.1. Novelty

This analysis is new because of several reasons:

- It is the first meta-analysis comparing clinical manifestations that were observed between childhood-onset versus adultonset SLE; in contrast, a previously published meta-analysis only compared the laboratory features.
- (2) This analysis includes a very large number of participants from different regions, thus, representing a generalized result that is not affected by a particular region or ethnic group.
- (3) This idea is important in clinical medicine; the word SLE has often been heard, but, childhood-onset and adult-onset SLE,

Study or Subgroup	Adult Onse Events	Total	Childhood Ons Events		Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% Cl
1.3.1 Hemolytic anemi		iotai	-venta	iotai	maight		
Carreno1999		130	10	49	0.00/	0 40 10 22 4 041	
	13				0.8%	0.49 [0.23, 1.04]	
atemi2016	36	394	22	180	1.7%	0.75 [0.45, 1.23]	
ont1998	26	396	5	34	0.5%	0.45 [0.18, 1.09]	
Gomez2006	57	259	3	13	0.3%	0.95 [0.34, 2.64]	
Gomez2008	106	984	37	230	3.3%	0.67 [0.47, 0.95]	
loffman2008	24	188	21	55	1.8%	0.33 [0.20, 0.55]	
Medeiros2015	59	338	13	60	1.2%	0.81 [0.47, 1.37]	
/lok2005	42	213	16	50	1.4%	0.62 [0.38, 1.00]	
Pande1993	19	187	11	83	0.8%	0.77 [0.38, 1.54]	<del></del>
Sassi2017	103	419	21	89	1.9%	1.04 [0.69, 1.57]	
Subtotal (95% CI)	100	3508	2.	843	13.7%	0.69 [0.58, 0.81]	
	485		159	0.0		0.00 [0.00, 0.0.1]	•
Γotal events Heterogeneity: Chi² = 1 Γest for overall effect: Ζ	4.68, df = 9 (		; I² = 39%				
		0.00001)					
1.3.2 Thrombocytoper	nia						
Carreno1999	50	130	15	49	1.2%	1.26 [0.78, 2.02]	+
atemi2016	61	394	27	180	2.0%	1.03 [0.68, 1.57]	- <b>-</b>
Feng2010	597	1551	47	108	4.8%	0.88 [0.71, 1.11]	-+
Font1998	91	396	9	34	0.9%	0.87 [0.48, 1.56]	<del></del>
Gomez2006	35	259	2	13	0.3%		
						0.88 [0.24, 3.26]	
Gomez2008	175	984	58	230	5.2%	0.71 [0.54, 0.91]	
Gormezano2016	10	49	3	49	0.2%	3.33 [0.98, 11.38]	
loffman2008	47	188	17	55	1.4%	0.81 [0.51, 1.29]	<u>+</u>
Janwityanujit1995	25	308	5	51	0.5%	0.83 [0.33, 2.06]	
Medeiros2015	72	338	20	60	1.9%	0.64 [0.42, 0.97]	
Mok2005	54	213	18	50	1.6%	0.70 [0.46, 1.09]	
Pande1993	30	187	11	83	0.8%	1.21 [0.64, 2.30]	_ <del></del>
Rood1999	49	135	15	31	1.3%	0.75 [0.49, 1.15]	<del></del>
Sassi2017	80	419	21	89	1.9%	0.81 [0.53, 1.23]	
Subtotal (95% CI)	00	5551	21	1082	23.9%	0.85 [0.76, 0.96]	•
Total events	1076	0001	269	1002	2010 /0	0.00 [0.10, 0.00]	•
	1376		268				
0 ,		0.006)					
Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z 1.3.3 Leukocytopenia	Z = 2.73 (P =	,					
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999	Z = 2.73 (P = 74	130	27	49	2.1%	1.03 [0.77, 1.39]	+
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016	Z = 2.73 (P = 74 34	130 394	20	180	1.5%	0.78 [0.46, 1.31]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999	Z = 2.73 (P = 74 34 576	130 394 1551	20 60				
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010	Z = 2.73 (P = 74 34	130 394	20	180	1.5%	0.78 [0.46, 1.31]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006	Z = 2.73 (P = 74 34 576	130 394 1551	20 60	180 108	1.5% 6.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gomez2008	Z = 2.73 (P = 74 34 576 125	130 394 1551 259	20 60 4	180 108 13	1.5% 6.1% 0.4%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gormez2008 Gormezano2016	Z = 2.73 (P = 74 34 576 125 408 16	130 394 1551 259 984 49	20 60 4 106 15	180 108 13 230 49	1.5% 6.1% 0.4% 9.4% 0.8%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gormez2008 Gormezano2016 Hoffman2008	z = 2.73 (P = 74 34 576 125 408 16 107	130 394 1551 259 984 49 188	20 60 4 106 15 35	180 108 13 230 49 55	1.5% 6.1% 0.4% 9.4%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995	z = 2.73 (P = 74 34 576 125 408 16 107 79	130 394 1551 259 984 49 188 308	20 60 4 106 15 35 61	180 108 13 230 49 55 51	1.5% 6.1% 0.4% 9.4% 0.8% 3.0%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gomez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005	z = 2.73 (P = 74 34 576 125 408 16 107 79 91	130 394 1551 259 984 49 188 308 213	20 60 4 106 15 35 61 25	180 108 13 230 49 55 51 51 50	1.5% 6.1% 0.4% 9.4% 0.8% 3.0%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17]	
Test for overall effect: 2 <b>1.3.3 Leukocytopenia</b> Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Wok2005 Pande1993	z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24	130 394 1551 259 984 49 188 308 213 187	20 60 4 106 15 35 61 25 21	180 108 13 230 49 55 51 50 83	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86]	
Fest for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Rood1999	z = 2.73 (P = 74 34 576 125 408 16 107 79 91	130 394 1551 259 984 49 188 308 213 187 135	20 60 4 106 15 35 61 25	180 108 13 230 49 55 51 50 83 31	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Rood1999	z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24	130 394 1551 259 984 49 188 308 213 187	20 60 4 106 15 35 61 25 21	180 108 13 230 49 55 51 50 83	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86]	
Fest for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Subtotal (95% Cl) Fotal events	z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24 68 1602	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b>	20 60 4 106 15 35 61 25 21 23 397	180 108 13 230 49 55 51 50 83 31	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89]	
Test for overall effect: 2 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gormez2008 Gormezano2016 Hoffman2008 Janwityanuji1995 Wok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1	z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 (	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04)	20 60 4 106 15 35 61 25 21 23 397	180 108 13 230 49 55 51 50 83 31	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89]	
Fest for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Sormez2008 Sormezano2016 Hoffman2008 lanwityanujit1995 Mok2005 Pande1993 Rood1999 Subtotal (95% Cl) Fotal events Heterogeneity: Chi <sup>2</sup> = 1 Fest for overall effect: Z	z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 (	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04)	20 60 4 106 15 35 61 25 21 23 397	180 108 13 230 49 55 51 50 83 31	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z 1.3.4 Lymphopenia	Z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P <	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001)	20 60 4 106 15 35 61 25 21 23 397 ;   <sup>2</sup> = 49%	180 108 13 230 49 55 51 50 83 31 <b>899</b>	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1% <b>29.3%</b>	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] <b>0.83 [0.76, 0.90]</b>	
Fest for overall effect: 2 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gormez2008 Gormezano2016 Hoffman2008 Janwityanuji1995 Wok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Fest for overall effect: 2 1.3.4 Lymphopenia Carreno1999	z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( z = 4.18 (P < 28	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001)	20 60 4 106 15 35 61 25 21 23 397 ; I <sup>2</sup> = 49%	180 108 13 230 49 55 51 50 83 31 <b>899</b>	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 29.3%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90]	
Test for overall effect: 2 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 1.3.4 Lymphopenia Carreno1999 Gomez2006	z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( z = 4.18 (P < 28 125	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001)	20 60 4 106 15 35 61 25 21 23 397 ;   <sup>2</sup> = 49%	180 108 13 230 49 55 51 50 83 31 <b>899</b> 49 13	1.5% 6.1% 0.4% 9.4% 3.0% 2.2% 1.6% 2.1% <b>29.3%</b>	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90]	
Fest for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Rood1999 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1 Fest for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gomez2008	z = 2.73 (P = 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( z = 4.18 (P < 28 125 581	130 394 1551 259 984 49 188 308 213 185 4398 P = 0.04) 0.0001) 130 259 984	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 49 13 230	1.5% 6.1% 0.4% 0.8% 3.0% 2.2% 1.6% 2.1% <b>29.3</b> %	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90]	
Fest for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Subtotal (95% Cl) Fotal events Heterogeneity: Chi <sup>2</sup> = 1 Fest for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gomez2008 Gormezano2016	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001) 130 259 984 49	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139 27	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 13 230 49	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1% <b>29.3%</b> 1.2% 0.4% 12.3% 1.5%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90] 0.83 [0.76, 0.90]	
Test for overall effect: 2 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanuji1995 Wok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gormez2008 Gormez2016 Hoffman2008	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22 121	130 394 1551 259 984 49 188 308 213 187 135 4398 P = 0.04) 0.0001) 130 259 984 49 188	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139 27 37	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 49 13 230 49 55	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 29.3% 1.2% 0.4% 1.2% 0.4% 1.5% 3.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90] 0.83 [0.76, 0.90]	
Test for overall effect: 2 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanuji1995 Wok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gormez2008 Gormez2016 Hoffman2008	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001) 130 259 984 49	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139 27	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 13 230 49	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1% <b>29.3%</b> 1.2% 0.4% 12.3% 1.5%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90] 0.83 [0.76, 0.90]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Wok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gomez2008 Gormez2016 Hoffman2008 Wedeiros2015	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22 121	130 394 1551 259 984 49 188 308 213 187 135 4398 P = 0.04) 0.0001) 130 259 984 49 188	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139 27 37	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 49 13 230 49 55	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 29.3% 1.2% 0.4% 1.2% 0.4% 1.5% 3.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30]	
Fest for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2006 Gomez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Subtotal (95% Cl) Fotal events Heterogeneity: Chi <sup>2</sup> = 1 Fest for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gomez2008 Gomez2008 Gormezano2016 Hoffman2008 Medeiros2015 Mok2005	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28)) 125 581 22 121 148	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001) 130 259 984 49 188 338	20 60 4 106 15 35 61 25 21 23 397 $  ^2 = 49\%$ 15 4 139 27 37 37	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 49 13 230 49 55 560	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 29.3% 1.2% 0.4% 12.3% 1.2% 3.1% 3.4%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 <b>[0.76, 0.90]</b> 0.70 [0.41, 1.20] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90]	
Test for overall effect: 2 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Rood1999 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gormez2008 Gormezano2016 Hoffman2008 Medeiros2015 Mok2005 Pande1993	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 74) 28 125 581 22 121 148 165	130 394 1551 259 984 49 188 308 213 185 4398 P = 0.04) 0.0001) 130 259 984 49 188 338 213	20 60 4 106 15 35 61 25 21 23 397 $  ^2 = 49\%$ 15 4 139 27 37 37 36	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 13 230 49 55 60 0 50	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 2.2% 1.6% 2.1% 29.3% 1.2% 0.4% 12.3% 1.5% 3.4% 3.2%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30]	
Test for overall effect: 2 <b>1.3.3 Leukocytopenia</b> Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Wok2005 Pande1993 Rood1999 <b>Subtotal (95% CI)</b> Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 <b>1.3.4 Lymphopenia</b> Carreno1999 Gomez2006 Gormez2008 Gormez2008 Gormez2015 Mok2005 Pande1993 Rood1999	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22 121 148 165 37 35	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001) 130 259 984 49 188 338 213 187 135	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139 27 37 37 36 30 9	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 49 13 230 49 55 60 55 60 50 83 31	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 29.3% 1.2% 0.4% 1.5% 3.1% 3.4% 3.2% 0.8%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 <b>[0.76, 0.90]</b> 0.83 <b>[0.76, 0.90]</b> 0.83 <b>[0.77, 1.18]</b> 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66]	
Test for overall effect: 2 <b>1.3.3 Leukocytopenia</b> Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: 2 <b>1.3.4 Lymphopenia</b> Carreno1999 Gomez2006 Gomez2008 Gormez2008 Gormez2016 Hoffman2008 Medeiros2015 Mok2005 Pande1993 Rood1999 Sassi2017	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 74) 28 125 581 22 121 148 165 37	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001) 130 259 984 49 188 338 213 187	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139 27 37 36 30	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 49 13 230 49 55 60 50 83 31 89	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 2.1% 29.3% 1.2% 0.4% 12.3% 1.2% 0.4% 3.1% 3.2% 2.3% 0.8% 0.8%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90] 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66] 0.93 [0.76, 1.12]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2008 Gomez2008 Gomez2008 Gomez2008 Gomez2008 Gomez2008 Gomez2008 Rodel993 Rood1999 Sassi2017 Subtotal (95% CI)	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 74) 28 125 581 22 121 148 165 37 35 231	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04; 0.0001) 130 259 984 49 188 338 213 187 135 419	20 60 4 106 15 35 61 25 21 23 397 $;  ^2 = 49\%$ 15 4 139 27 37 37 36 30 9 53	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 49 13 230 49 55 60 55 60 50 83 31	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 29.3% 1.2% 0.4% 1.5% 3.1% 3.4% 3.2% 0.8%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 <b>[0.76, 0.90]</b> 0.83 <b>[0.76, 0.90]</b> 0.83 <b>[0.77, 1.18]</b> 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66]	
Fest for overall effect: 2   1.3.3 Leukocytopenia   Carreno1999   Fatemi2016   Feng2010   Gomez2006   Gomez2008   Gormezano2016   Hoffman2008   Janwityanujit1995   Wok2005   Pande1993   Rood1999   Subtotal (95% CI)   Total events   Heterogeneity: Chi² = 1   Carreno1999   Gomez2006   Gormezano2016   Hoffman2008   Gomez2006   Gormezano2016   Gormezano2016   Gormezano2016   Gormezano2016   Sormezano2016   Sormezano2016   Hoffman2008   Wedeiros2015   Mok2005   Pande1993   Rood1999   Sassi2017   Subtotal (95% CI)   Total events   Heterogeneity: Chi² = 1	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22 121 148 165 37 35 231 1493 8.00, df = 9 (	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001) 130 259 984 49 188 338 213 187 135 419 <b>2902</b> P = 0.04)	20 60 4 106 15 35 61 25 21 23 397 $;  ^2 = 49\%$ 15 4 139 27 37 37 36 30 9 53 387	180 108 13 2300 49 55 51 50 83 31 <b>899</b> 49 13 230 49 55 60 50 83 31 89	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 2.1% 29.3% 1.2% 0.4% 12.3% 1.2% 0.4% 3.1% 3.2% 2.3% 0.8% 0.8%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90] 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66] 0.93 [0.76, 1.12]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Mok2005 Pande1993 Rood1999 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Medeiros2015 Mok2005 Pande1993 Rood1999 Sassi2017 Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22 121 148 165 37 35 231 1493 8.00, df = 9 (	130 394 1551 259 984 49 188 308 213 135 4398 P = 0.04) 0.0001) 130 259 984 49 188 338 213 187 135 439 2902 P = 0.04) 0.01)	20 60 4 106 15 35 61 25 21 23 397 $;  ^2 = 49\%$ 15 4 139 27 37 37 36 30 9 53 387	180 108 13 230 49 55 51 1 50 83 31 <b>899</b> 49 13 230 49 55 60 50 83 31 89 <b>709</b>	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1% 29.3% 1.2% 0.4% 12.3% 1.5% 3.1% 3.2% 2.3% 0.8% 4.8% 33.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] <b>0.83 [0.76, 0.90]</b> 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66] 0.93 [0.76, 1.12] <b>0.91 [0.84, 0.98]</b>	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Wok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2008 Gormez2008 Gormez2008 Gormez2008 Gormez2008 Gormez2008 Gormez2008 Sormez2008 Sormez2008 Sormez2008 Sormez2008 Sormez2008 Sormez2008 Sormez2008 Sormez2008 Hedeiros2015 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z Total (95% CI)	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22 121 148 165 37 35 231 1493 8.00, df = 9 ( Z = 2.53 (P = 2))	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001) 130 259 984 49 188 338 213 187 135 419 <b>2902</b> P = 0.04)	20 60 4 106 15 35 61 25 21 23 397 $  ^2 = 49\%$ 15 4 139 27 37 36 30 9 53 387 $  ^2 = 50\%$	180 108 13 230 49 55 51 1 50 83 31 <b>899</b> 49 13 230 49 55 60 50 83 31 89 <b>709</b>	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 2.1% 29.3% 1.2% 0.4% 12.3% 1.2% 0.4% 3.1% 3.2% 2.3% 0.8% 0.8%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] 0.83 [0.76, 0.90] 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66] 0.93 [0.76, 1.12]	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Wok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gomez2008 Gormez2008 Gormez2008 Gormez2015 Mok2005 Pande1993 Rood1999 Sassi2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z Total events	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22 121 148 165 37 35 231 1493 8.00, df = 9 ( Z = 2.53 (P = 2))	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04) 0.0001) 130 259 984 49 188 338 213 187 135 419 <b>2902</b> P = 0.04) 0.01) <b>16359</b>	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139 27 37 37 36 30 9 53 387 ; $ ^2 = 50\%$	180 108 13 230 49 55 51 1 50 83 31 <b>899</b> 49 13 230 49 55 60 50 83 31 89 <b>709</b>	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1% 29.3% 1.2% 0.4% 12.3% 1.5% 3.1% 3.2% 2.3% 0.8% 4.8% 33.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] <b>0.83 [0.76, 0.90]</b> 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66] 0.93 [0.76, 1.12] <b>0.91 [0.84, 0.98]</b>	
Test for overall effect: Z 1.3.3 Leukocytopenia Carreno1999 Fatemi2016 Feng2010 Gomez2008 Gormez2008 Gormezano2016 Hoffman2008 Janwityanujit1995 Wok2005 Pande1993 Rood1999 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z 1.3.4 Lymphopenia Carreno1999 Gomez2006 Gomez2008 Gormez2008 Gormez2008 Gormez2008 Gormez2008 Gormez2016 Hoffman2008 Wedeiros2015 Wok2005 Pande1993 Rood1999 Sassi2017 Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = 1 Test for overall effect: Z Total events Heterogeneity: Chi <sup>2</sup> = 7 Total events Heterogeneity: Chi <sup>2</sup> = 7	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28)) 125 581 22 121 148 165 37 35 231 1493 8.00, df = 9 ( Z = 2.53 (P = 9)) 24 68 125 581 22 121 148 165 37 35 231 1493 8.00, df = 9 ( Z = 2.53 (P = 9)) 24 1493 8.00, df = 9 ( Z = 2.53 (P = 9)) 1495 1605 1495 1495 1495 1605 1605 1605 1605 1605 1605 1605 1605 1605 1605 1605 1605 1605 1605 1495 145 1495 1455	130 394 1551 259 984 49 188 308 213 187 135 <b>4398</b> P = 0.04; 0.0001) 130 259 984 49 188 338 213 187 135 419 <b>2902</b> P = 0.04; 0.01) <b>16359</b> (P = 0.00;	20 60 4 106 15 35 61 25 21 23 397 ; $ ^2 = 49\%$ 15 4 139 27 37 37 36 30 9 53 387 ; $ ^2 = 50\%$	180 108 13 230 49 55 51 1 50 83 31 <b>899</b> 49 13 230 49 55 60 50 83 31 89 <b>709</b>	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1% 29.3% 1.2% 0.4% 12.3% 1.5% 3.1% 3.2% 2.3% 0.8% 4.8% 33.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] <b>0.83 [0.76, 0.90]</b> 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66] 0.93 [0.76, 1.12] <b>0.91 [0.84, 0.98]</b>	
Fest for overall effect: Z   1.3.3 Leukocytopenia   Carreno1999   Fatemi2016   Feng2010   Gomez2006   Gomez2008   Gormezano2016   Hoffman2008   Janwityanujit1995   Wok2005   Pande1993   Rood1999   Subtotal (95% CI)   Total events   Heterogeneity: Chi² = 1   Carreno1999   Gomez2006   Gormezano2016   Hoffman2008   Gorrezano2016   Gormezano2016   Gormezano2016   Gormezano2016   Gormezano2016   Jormezano2016   Sormez2008   Gormez2008   Gormez2015   Mok2005   Pande1993   Rood1999   Sassi2017   Subtotal (95% CI)   Total events   Heterogeneity: Chi² = 1   Test for overall effect: Z   Fotal (95% CI)   Total events	Z = 2.73 (P = 74) 74 34 576 125 408 16 107 79 91 24 68 1602 7.63, df = 9 ( Z = 4.18 (P < 28) 125 581 22 121 148 165 37 35 231 1493 8.00, df = 9 ( Z = 2.53 (P = 43) Z = 6.79 (P < 20)	$\begin{array}{c} 130\\ 394\\ 1551\\ 259\\ 984\\ 49\\ 188\\ 308\\ 213\\ 135\\ 4398\\ P=0.04)\\ 0.0001)\\ 130\\ 259\\ 984\\ 49\\ 188\\ 213\\ 187\\ 135\\ 419\\ 2902\\ P=0.04)\\ 0.01)\\ 16359\\ (P=0.00\\ 0.00001)\\ \end{array}$	20 60 4 106 15 35 61 25 21 23 397 ; $l^2 = 49\%$ 15 4 139 27 37 36 30 9 53 387 ; $l^2 = 50\%$ 1211 008); $l^2 = 45\%$	180 108 13 230 49 55 51 150 83 31 <b>899</b> 49 13 230 49 55 60 50 83 31 899 <b>709</b> <b>3533</b>	1.5% 6.1% 0.4% 9.4% 0.8% 3.0% 2.2% 1.6% 2.1% 29.3% 1.2% 0.4% 12.3% 1.5% 3.1% 3.2% 2.3% 0.8% 4.8% 33.1%	0.78 [0.46, 1.31] 0.67 [0.56, 0.80] 1.57 [0.69, 3.58] 0.90 [0.77, 1.05] 1.07 [0.60, 1.91] 0.89 [0.71, 1.13] Not estimable 0.85 [0.62, 1.17] 0.51 [0.30, 0.86] 0.68 [0.52, 0.89] <b>0.83 [0.76, 0.90]</b> 0.83 [0.76, 0.90] 1.57 [0.69, 3.58] 0.98 [0.87, 1.10] 0.81 [0.55, 1.22] 0.96 [0.77, 1.18] 0.71 [0.56, 0.90] 1.08 [0.89, 1.30] 0.55 [0.36, 0.82] 0.89 [0.48, 1.66] 0.93 [0.76, 1.12] <b>0.91 [0.84, 0.98]</b>	0.01 0.1 Line Favours [Childhood onset]

and their influence on clinical features might show something new to the readers.

# 4.2. Limitations

This analysis also has several limitations:

- (4) This analysis is very informative, showing a lot of data and results that are related to the differences between these 2 onset-periods of SLE, representing a new feature.
- (1) In those patients to whom clinical features were not reported following the course of the disease, clinical

Study or Subara	Adult Onse Events	Total	Childhood On Events		Woight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
Study or Subgroup 1.4.1 Seizure	Events	Total	Events	Total	weight	MI-H, FIXED, 95% CI	MI-H, FIXed, 95% CI
Fatemi2016	33	394	21	180	10.7%	0.72 [0.43, 1.21]	
Gomez2008	73	984	26	230	15.6%	0.66 [0.43, 1.00]	
Hersh2009	134	795	21	90	14.0%	0.72 [0.48, 1.08]	
Hoffman2008	13	188	8	55	4.6%	0.48 [0.21, 1.09]	
Joo2016	19	979	9	133	5.9%	0.29 [0.13, 0.62]	
Medeiros2015	31	338	7	60	4.4%	0.79 [0.36, 1.70]	
Mok2005	17	213	7	50	4.2%	0.57 [0.25, 1.30]	
Pande1993	7	187	16	83	8.2%	0.19 [0.08, 0.45]	
Rood1999	19	135	8	31	4.8%	0.55 [0.26, 1.13]	
Tu2011	1	15	3	12	1.2%	0.27 [0.03, 2.25]	
Subtotal (95% CI)		4228		924	73.8%	0.57 [0.47, 0.70]	◆
Total events	347		126				
Heterogeneity: Chi <sup>2</sup> =	13.04, df = 9 (	(P = 0.16)	); I² = 31%				
Test for overall effect:	: Z = 5.52 (P <	0.00001)	)				
1.4.2 Psychosis							
Fatemi2016	1	394	0	180	0.3%	1.37 [0.06, 33.58]	
Gomez2008	38	984	11	230	6.6%	0.81 [0.42, 1.56]	
Hoffman2008	11	188	5	55	2.9%	0.64 [0.23, 1.77]	
Medeiros2015	16	338	2	60	1.3%	1.42 [0.34, 6.02]	
Mok2005	15	213	3	50	1.8%	1.17 [0.35, 3.90]	
Pande1993	42	187	21	83	10.8%	0.89 [0.56, 1.40]	
Rood1999	8	135	4	31	2.4%	0.46 [0.15, 1.43]	<del></del>
Tu2011	2	15	0	12	0.2%	4.06 [0.21, 77.37]	
Subtotal (95% CI)		2454		701	26.2%	0.88 [0.64, 1.20]	◆
Total events	133		46				
Heterogeneity: Chi <sup>2</sup> =	3.44, df = 7 (F	P = 0.84):	l <sup>2</sup> = 0%				
Test for overall effect:	, ,						
Total (95% CI)		6682		1625	100.0%	0.65 [0.55, 0.77]	♦
Total events	480		172				
Heterogeneity: Chi <sup>2</sup> =		(P = 0.2)				F	
						0	
		0.0001	/				Favours [Adult onset] Favours [Childhood onset]
Test for overall effect: Test for subgroup diff	· ·	= 5 05 df	f = 1 (P = 0.02)	$^{2} = 80.2\%$			r aroaro (riaar onood) ir aroaro (onnanood onood)

Results of this analysis.	
Table 4	

	RR with 95% CI	Р	<i>ľ</i> ² (%)
Significant outcomes			
Pulmonary involvement	1.51 [1.18–1.93]	.001	0
Neurological involvement	0.60 0.44-0.80	.0006	0
Renal involvement	0.65 0.55-0.77	.00001	75
Renaud phenomenon	1.29 [1.04–1.60]	.02	29
Photosensitivity	1.08 [1.01-1.17]	.03	46
Oral ulcers	0.85 0.77-0.94	.001	0
Malar rash	0.84 [0.75-0.94]	.02	70
Hemolytic anemia	0.69 0.58-0.81	.00001	39
Thrombocytopenia	0.85 0.76-0.96	.006	10
Leukocytopenia	0.83 0.76-0.90	.0001	49
Lymphopenia	0.91 [0.84–0.98]	.01	50
Seizure	0.57 [0.47-0.70]	.00001	31
Ocular manifestation	0.34 0.21-0.55	.00001	0
Pleuritis	1.45 [1.17–1.79]	.0008	0
Vasculitis	0.51 0.36-0.74	.0004	53
Fever	0.78 0.68–0.89	.0002	66
Un-significant outcomes			
Gastrointestinal involvement	1.18 [0.76-1.86]	.46	2
Dermatological involvement	0.69 [0.37-1.29]	.24	0
Musculoskeletal involvement	0.84 0.51-1.39	.50	0
Neuropsychiatric involvement	0.94 [0.67–1.31]	.70	48
Cardiovascular involvement	1.02 [0.59–1.77]	.93	50
Hematological involvement	0.93 0.74-1.17	.54	68
Alopecia	0.97 [0.69–1.36]	.86	35
Serositis	1.03 0.86-1.22	.77	0
Myositis	0.46 [0.11-1.91]	.28	51
Arthritis	1.04 [0.98–1.11]	.21	69
Discoid rash	1.04 [0.72-1.50]	.83	63
Psychosis	0.88 [0.64-1.20]	.40	0
Pericarditis	0.84 [0.63-1.11]	.23	40

CI = confidence interval; RR = risk ratio.





Figure 9. Funnel plot showing publication bias.



Figure 10. Funnel plot showing publication bias.

features at onset of the disease were considered relevant.

- (2) All the data which were extracted were obtained from observational studies, which could be another limitation.
- (3) Moderate to less severe heterogeneity was reported in several of the subgroups assessing the clinical features.

#### 5. Conclusion

Significant differences were observed between childhood-onset and adult-onset SLE. Childhood-onset SLE was associated with significantly higher adverse clinical features whereby neurological involvement, renal involvement, oral ulcers, malar rash, vasculitis, fever, ocular, and hematological manifestations were significantly higher, whereas pulmonary involvement, Raynaud phenomenon, and photosensitivity were significantly higher with adult-onset SLE. However, no significant difference was observed in gastrointestinal involvement, cardiovascular involvement, discoid rash, psychosis, alopecia, serositis, and arthritis.

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