BMJ Open

Prevalence of dry eye in patients with systemic lupus erythematosus: a meta-analysis

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To cite: Wang L, Xie Y, Deng Y. Prevalence of dry eye in patients with systemic lupus erythematosus: a meta-analysis. *BMJ Open* 2021;**11**:e047081. doi:10.1136/bmjopen-2020-047081

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-047081).

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Received 18 November 2020
Accepted 13 September 2021

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ABSTRACT

Objectives To investigate dry eye disease (DED) in patients affected by systemic lupus erythematosus (SLE).

Methods We conducted a systematic search of the literature on PubMed, EMBASE and the Cochrane Library databases from conception to 30 April 2020 for studies related to dry eye, secondary Sjögren's syndrome (sSS) and SLE. Original full-text articles with the number of patients diagnosed with SLE of over 15 were included. The risk of bias was evaluated with a validated critical appraisal tool which assessed study quality based on confounding factors, selection bias, bias related to measurement and bias related to data analysis. Data were extracted and pooled to evaluate the overall prevalence of DED with the random-effect model and sSS with the fixed effect model.

Results A total of 29 studies were included and 18 273 participants were involved. The pooled data showed that the overall prevalence of DED was 16% (95% CI 10% to 21%, p<0.001) in patients of SLE. Dry eye symptoms and abnormal Schirmer's test were found in 26% (95% CI 20% to 32%, p<0.001) and 24% (95% CI 14% to 34%, p<0.001) of patients with SLE, respectively. 12% (95% CI 9% to 15%, p<0.001) of patients also met the criteria of sSS. The OR of DED in patients with SLE was 4.26 (95% CI 3.47 to 5.05, p<0.001) compared with healthy controls. The meta-regression analysis showed that the sample size (p=0.004) and study location (p=0.022) could be the source of heterogeneity.

Conclusions DED and sSS are both common in patients with SLE.

Strengths and limitations of this study

- The major strength of this study is that this is the first meta-analysis addressing the high prevalence of dry eye disease (DED) and Secondary Sjögren's syndrome (sSS) in patients with systemic lupus erythematosus (SLE), with subgroup analysis to demonstrate the impact of disease activity and disease duration.
- The study comprehensively summarises the literature about the association of DED, sSS and SLE. The findings suggest the need to more closely follow up patients with SLE in ophthalmology clinics.
- The high heterogeneity of the prevalence reported in individual studies, presumably and partly due to different diagnostic methods of DED and the race of the participants, may affect the overall reliability of the results.
- As some important factors, including the race and recruitment time of most individual studies, are not provided, we did not conduct the subgroup analysis based on these aspects.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can involve a great variety of organs and tissues, including skin, kidney, heart, blood, nervous system and so on.[1] In patients of SLE, various ocular manifestations have been reported and nearly every structure of the eye from the eyelid in the front to the optic nerve at the back can be involved.[2] Dry eye disease (DED) is thought to be one of the most common ocular manifestations in patients of SLE, and a portion of patients also meet the criteria of secondary Sjögren's syndrome (sSS), which is also an autoimmune disease and can lead to self-attack of lacrimal and salivary glands secondary to SLE.[3] In previous studies, a wide range of the prevalence of DED in patients with SLE from 0% to 32% has been reported.[4–31] This may result from the different ages, locations, gender and racial groups of participants as well as different disease duration, severity, activity and therapy of patients with SLE in different studies. Although a great quantity of studies addressing the association of SLE and DED has been published, currently, there is no meta-analysis to summarise the prevalence of DED in patients with SLE. Besides, there are controversial results on whether the disease duration, age groups or disease activity of SLE may influence the prevalence of DED.[11 15 20 29] Thus, we conducted a systematic search of literature and meta-analysis to evaluate the prevalence of DED in patients of SLE and to investigate possible factors which may be associated with the risk of DED in patients with SLE.

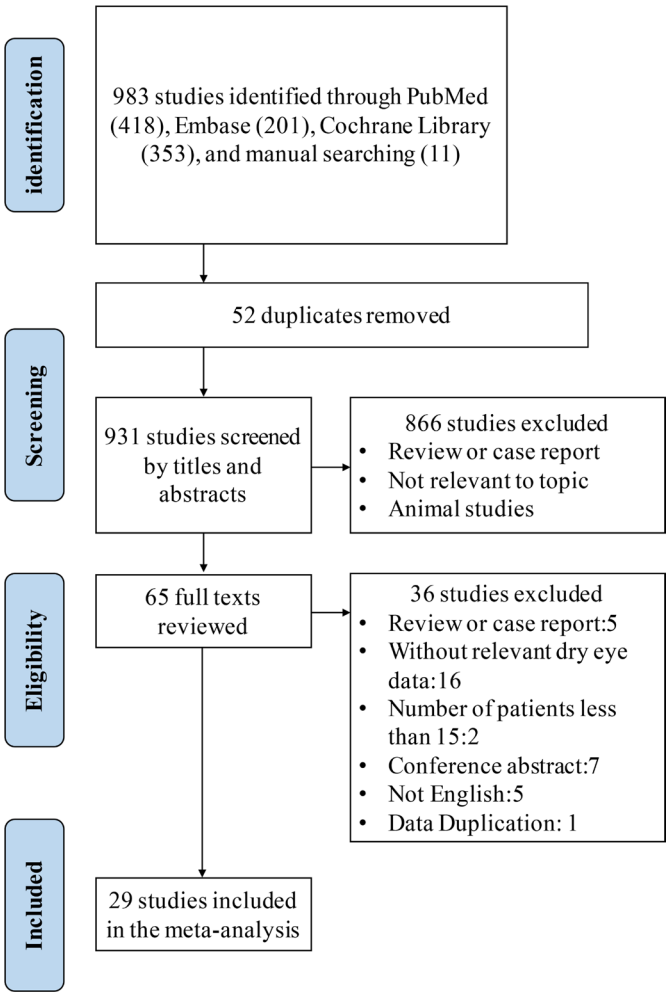

Figure 1 Flow chart of the study selection process.

METHODS

Search strategy

Following guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses and the Meta-analysis of Observational Studies in Epidemiology,[32] a comprehensive search of PubMed, EMBASE and the Cochrane Library databases was performed from conception of databases to 30 April 2020. Two investigators (YX and LW) independently searched the databases using varying combinations of the related search terms. Details of the search strategy are reported in online supplemental material. The electronic search was supplemented by a manual review of article reference lists. Abstract and unpublished studies were not included. The detailed steps of the search strategy were shown in figure 1.

Study selection

Studies included in our meta-analysis should fulfil the following criteria: (1) The study should be an original article. Reviews, commentaries, conference abstracts, books and meta-analyses should be excluded; (2) The study should be reported in full-text publication; (3) The diagnosis of SLE should be based on established criteria, including the 1971, 1982 or 1997 American College of Rheumatology classification criteria or the 2012 Systemic Lupus International Collaborating Clinics classification criteria.[33–36] Relevant data can be extracted from the study to evaluate the prevalence of dry eye in patients with SLE or the association between dry eye and SLE; (4) Studies should be written in English and (5) Number of reported patients with SLE should be over 15. Studies would be excluded if: (1) The number of reported patients with SLE was less than 15; (2) The reported cohort overlapped with other eligible studies and (3) Patients with SLE were selected for the study of a specific therapy. This selection process was finished by two reviewers (YX and LW) independently. If there was disagreement, a discussion would be carried out to reach a consensus.

Data extraction

The following data were extracted from the included studies: first author, year of publication, country, number of patients with SLE, mean age, sex ratio, duration of disease, disease activity (assessed by SLE Disease Activity Index (SLEDAI) score),[37] number of patients with dry eye symptoms, abnormal dry eye tests and DED. For each study, two reviewers (YX and LW) independently finished the data extraction process.

Patients with sSS were diagnosed according to the criteria proposed by the American-European Consensus Group in 2002, which was based on the simultaneous presentation of ocular symptoms (eye dryness, foreign body sensation or gravel sensation) or oral symptoms (oral dryness, frequent swallowing of saliva, frequent drinking of liquid to aid swallowing) plus at least two positive tests of the following: objective signs of dry eye, objective signs of dry mouth and inflammatory cell infiltration of minor salivary glands on biopsy.[38]

Definition of patients with DED: (1) Dry eye symptoms were defined as patients presented with any of the following symptoms: dryness, foreign body sensation, burning sensation or scratchiness; (2) Abnormal tear function was defined as abnormal findings in any of the following tests: Schirmer's test ≤5 mm, tear break-up time ≤10 s or other related tear tests; (3) Ocular surface damage was defined as positive vital staining with any dye: corneal fluorescein staining score ≥1, rose Bengal staining score ≥3.[39] DED (including probable and definite) was defined as the presence of at least two abnormal findings in dry eye symptoms, abnormal tear function and ocular surface damage according to the diagnostic criteria proposed by the Japan Dry Eye Society (JDES) in 1995.[40] In studies that no detailed diagnostic tests for DED was described, if there was a clear statement in the article that DED was clinically and officially diagnosed by ophthalmologists, we still considered the diagnosis to be appropriate and included the data in the meta-analysis.

Assessment of study quality

We used the risk of bias tool developed by Munn *et al* to access the quality of included studies.[41] This tool assesses the risk of bias and the methodological practices that may

impact the quality of a study. Each article was judged by 10 questions, including confounding factors, selection bias, bias related to measurement and bias related to data analysis. For each question, an answer of 'yes' would be scored as 1. A total score between 0 and 3 was considered as high risk, 4 and 6 as moderate risk, and 7 and 10 as low risk. YX and LW independently made the assessment. Discrepancies would be solved by a discussion.

Statistical analysis

All statistical analyses were finished by Stata (V.15.0) software. A p<0.05 was considered to be statistically significant. We calculated the prevalence estimates and 95% CIs for all included studies. The statistical heterogeneity was assessed by using Cochran's Q test. When p<0.05, the heterogeneity was considered to be present. I^2 statistic was also used to access the degree of heterogeneity. I^2 greater than 50% was defined as the presence of substantial heterogeneity. The selection of fixed and random effect models would be decided by the level of heterogeneity. Subgroup analysis was used to explain the identified heterogeneity, based on the number of patients, methodological quality, duration of disease, age groups and disease activity. Besides, univariate meta-regression analysis, based on a restricted maximum of likelihood, was also used to explore the origin of heterogeneity. Sensitivity analysis was conducted to test the robustness of the results and further explain the source of heterogeneity. Each study in the meta-analysis was omitted sequentially to investigate the influence of an individual study on the pooled estimates. Publication bias was accessed by using Bgee-Mazumdar's and Egger's tests. The association of the publication year and the prevalence of DED was analysed with maximal information coefficient (MIC), which was calculated on Python software according to the method described by Reshef *et al*.[42] MIC >0.20 was considered to indicate a significantly strong association.

The prevalence estimate of each study was used as the effect estimate, and the corresponding 95% CI for each study was calculated. Considering the small sample size and low prevalence of dry eye (<30%) in most included studies, we used Freeman-Tukey double arcsine transformation to get new transformed 95% CIs.

Patient and public involvement

This article was based on previously conducted studies and no patient was involved.

RESULTS

Search results and study characteristics

For this meta-analysis, we identified 972 articles by searching electronic databases and 11 articles by searching reference lists of the selected articles (figure 1). After removing duplicates and articles not related to our topic, we identified 65 studies for full-text review. After viewing the full text, 29 studies[4–31 43] were included in this meta-analysis (figure 1), which all provided cross-sectional data regarding the prevalence of DED in patients with SLE. Of these included studies, 23 studies had a low risk of bias, while the rest 6 studies had a moderate risk of bias. The major sources of bias came from the small sample size, lack of confounding adjustment and lack of objective criteria for the diagnosis of DED. Detailed characteristics of 29 studies were presented in table 1 and online supplemental table 1.

Dry eye and SLE: prevalence and association

A total of 18 included studies[4–11 14 16 18 19 23 25 27–30] revealed that DED was present in 0%–32% of patients with SLE. Forest plot analysis of pooled data showed that the overall prevalence of DED in patients with SLE was 16% (95% CI 10% to 21%, p<0.001) with a high level of heterogeneity (p<0.001, I^2=94.0%) in the random-effect model (figure 2). When considering the symptoms (online supplemental figure 1) or abnormal dry eye test (online supplemental figure 2) alone, the overall prevalence of dry eye symptoms or abnormal Schirmer's tests were found in 26% (95% CI 20% to 32%, p<0.001) and 24% (95% CI 14% to 34%, p<0.001) of patients with SLE, respectively, and both were higher than the prevalence of DED in SLE.

Two studies[30 43] provided data that enabled us to calculate the OR of DED in patients with SLE. The combined OR was 4.26 (95% CI 3.47 to 5.05; p<0.001; I^2=0, $P_{heterogenity}$=0.567), which demonstrated a significant association between DED and SLE (online supplemental figure 3).

The prevalence of sSS in patients with SLE

A total of five studies[3 8 9 17 22] provided information regarding the prevalence of sSS in patients with SLE and were included in the meta-analysis (figure 3). The fixed-effect model showed that the overall prevalence of sSS in patients of SLE was 12% (95% CI 9% to 15%, p<0.001). A low level of heterogeneity was found in these five studies (I^2=0.0, $P_{heterogenity}$=0.493).

Subgroup analysis and regression analysis

As the overall heterogeneity was high, subgroup analysis was carried out to explore the source of heterogeneity. The results were presented in table 2. As the results showed, we failed to explain the high level of heterogeneity through the difference of the number of patients (<50 vs 50–100 vs >100), disease activity (low disease activity *vs* high disease activity), duration of disease (<5 years vs 5–10 years vs >10 years) or study quality (low risk of bias *vs* moderate risk of bias).

We also conducted a meta-regression analysis to further explore the origin of heterogeneity. The results (online supplemental table 2) showed that mean age, disease duration, disease activity and publication year were not the main source of heterogeneity. However, sample size (p=0.004) and study location (p=0.022) could be the source of heterogeneity. And the meta-regression analysis

Table 1 Basic characteristics of patients with SLE from studies assessing the prevalence of dry eye in SLE

Author, year	Country	Total patients with SLE	Classification criteria of SLE	Age (mean year ±SD or range)	Sex (female/male)	Duration of disease (mean year ±SD or range)	SLEDAI (mean±SD or range)	Quality score
Grennan, 1977[4]	New Zealand	22	1971ACR	NA	NA	NA	NA	6
Moutsopoulos, 1980[5]	America	24	1971ACR	38(15-66)	23/1	7.6 (1–23)	NA	5
Yap, 1998[6]	Singapore	70	1982ACR	32.9 (9–67)	66/4	NA	NA	7
Frith, 1990[7]	England	18	1982ACR	46.5 (27–69)	16/2	11.6 (0.75–31)	NA	5
Jensen, 1999[8]	Norway	20	1982ACR	47(18-78)	19/1	5.5 (0.5–28.0)	5 (2–20)	8
Gilboe, 2001[9]	Norway	81	1982ACR	44(20-70)	72/9	7.8 (2–27)	6.67 (0–24)	8
Ausayakhun, 2002[10]	Thailand	74	1982 and 1997ACR	NA	NA	NA	NA	4
Wangkaew, 2006[11]	Thailand	50	1982 and 1997ACR	39.1±9.6	50/0	6.1±5.9	5.8±4.4	9
Guobis, 2008[12]	Lithuania	82	1997ACR	43.2±1.1	75/7	NA	NA	7
Vera-Recabarren, 2010[13]	Spain	56	1997ACR	NA	NA	NA	NA	7
Xu, 2010[14]	China	255	1982 and 1997ACR	33.6±33.0	225/30	4.7±3.8	9.8±9.7	8
Sitaula, 2011[15]	Nepal	91	1982ACR	26.6±10.1	84/5	1.8±0.8	NA	5
Cartella, 2013[16]	Italy	535	1997ACR	47±14.0	492/43	NA	NA	7
Hernández-Molina, 2013[17]	Canada	103	1997ACR	30.9±9.1	93/10	0.5±0.3	6.6±5.7	9
Pamuk, 2013[18]	Turkey	428	1982 and 1997ACR	40.3±12.4	399/29	5.9±4.5	3.8±2.9	9
El-Shereef, 2013[19]	Egypt	52	1997ACR	29.05±8.7	50/2	6.8±4.5	20.3±13.5	8
Catoggio, 2014[20]	Multi-national	1480	1982ACR	28.5±9.5	1330/150	6.1±4.8	7.5±6.2	9
Fredi, 2014[21]	Italy	540	1997ACR and 2012SLICC	34.0±12.8	498/42	NA	NA	9
Choi, 2015[22]	Korea	201	1982 and 1997ACR	34.1±12.7	184/17	1.0±2.1	11.0±2.2	8
Husseina, 2017[23]	Egypt	100	2012SLICC	31.3±12.2	86/14	4.8±4.7	9.7±5.2	10
Gawdat,2017[24]	Egypt	40	1997ACR	13 (5.7–18)	32/8	NA	4.3 (0–16)	8
Khan, 2017[25]	Pakistan	663	1997ACR	33.1±13.3	606/57	NA	NA	8
Dammacco, 2018[26]	Italy	98	1982 and 1997ACR, 2012SLICC,	33±10	90/8	3.8±1.7	9.1±4.7	5
Mosca, 2018[27]	Multinational	389	1997ACR, 2012SLICC	31.4±12.3	345/44	NA	NA	9
Ong Tone,2019[28]	Canada	34	1997ACR	15.4±2.1	30/4	NA	NA	8
Wang, 2019[29]	China	78	2012SLICC	37±11	76/2	5.6±4.3	6.6±7.0	7
Hsu, 2020[30]	China	521	1997ACR	41.2±15.8	462/59	NA	NA	9
Dias-Santos, 2020[31]	Portugal	161	1997ACR	47.6±13.4	145/16	11.5±5.1	NA	9
Wang, 2012[43]	China	NA	1997 ACR	52.4±17.5	35264/12764	NA	NA	8

.ACR, American College of Rheumatology; NA, not available; SLE, systemic lupus erythematosus; SLEDAI, systemic lupus erythematosus disease activity index; SLICC, Systemic Lupus International Collaborating Clinics.

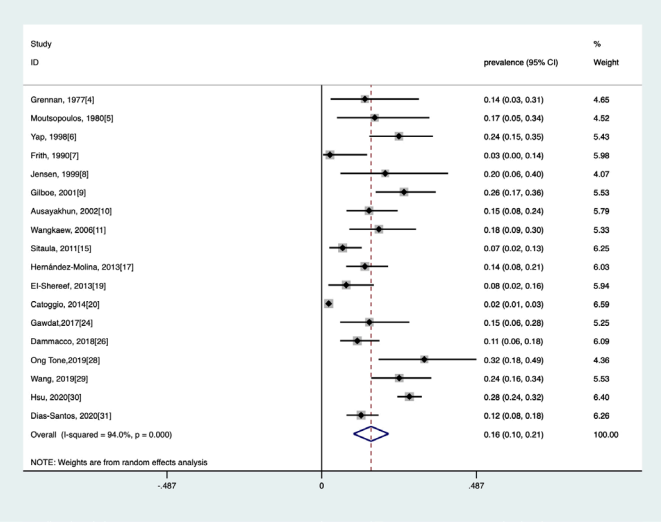

Figure 2 The prevalence of DED in patients with SLE. DED, dry eye disease; SLE, systemic lupus erythematosus.

based on the study location revealed that some source of heterogeneity came from the multi-national study conducted by Catoggio *et al*[20] (p=0.007, online supplemental table 2). The MIC for the association of the publication year and prevalence of DED was 0.121, suggesting no significantly strong linear or non-linear association. The bubble plot was demonstrated in online supplemental figure 4.

Sensitivity analysis

To analyse if the result of our meta-analysis was stable and not significantly influenced by a single study, we conducted sensitivity analysis. The sensitivity analysis was performed by removing one study at a time and the results remained significant when any study was excluded, thus indicating that the results of this meta-analysis were stable (online supplemental table 3 and online supplemental figure 5). After excluding two studies conducted by Catoggio *et al*,[20] and Hsu *et al*,[30] the heterogeneity reduced to a great extent (p=0.000, I^2=65.1%, online supplemental figure 6). Thus, these two studies were deemed to some sources of heterogeneity. When excluding these two studies, the combined prevalence of the remaining studies was 15% (95% CI 11% to 19%, p<0.001).

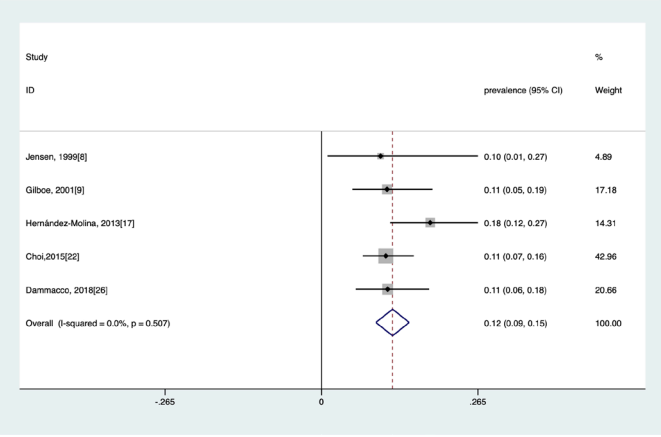

Figure 3 The prevalence of sSS in patients with SLE. SLE, systemic lupus erythematosus; sSS, Sjögren's syndrome.

Publication bias

Begg's test and Egger's test were performed to access publication bias. Both Begg's test (z=1.36, Pr>|z|=0.173) and Egger's test (t=−1.67, p=0.115) did not reveal any evidence of publication bias.

DISCUSSION

Our meta-analysis included 29 studies published from the conception of databases to 2020 and 18 273 patients diagnosed with SLE in total. We demonstrated that 26% (95% CI 20% to 32%) and 24% (95% CI 10% to 20%) of patients with SLE had dry eye symptoms or abnormal Schirmer's test, respectively. DED was present in 16% (95% CI 10% to 21%) of patients diagnosed with SLE in the random-effect model and 12% (95% CI 9% to 15%) of patients with SLE also met the criteria of sSS. Besides, the overall OR of DED in patients with SLE was 4.26 (95% CI 3.47 to 5.05), indicating that patients with SLE were four times more likely to get DED than healthy controls. Subgroup analysis demonstrated that there was no significant difference in the prevalence of DED in subgroups of different ages, disease duration and disease activity (evaluated with SLEDAI score) of patients with SLE. Our meta-analysis demonstrated a strong association of DED and SLE and showed that both DED and sSS were very common in patients suffering from SLE. Previous epidemiology studies of the general population demonstrated that the prevalence of DED was estimated to be 4.5%–7.8% in female populations of USA.[44–46] As the majority of patients with SLE were female, the data in our meta-analysis indicated an increased prevalence of DED in patients with SLE. As far as we know, this is the first meta-analysis addressing the issue of dry eye in patients with SLE. The findings suggest the need for regular ophthalmology referral and follow-up of patients with SLE and clinicians need to pay special attention to the diagnosis of sSS among patients with dry eye symptoms.

Quality of evidence and limitations

This meta-analysis includes studies published in different regions of the world which span five decades. The major limitation comes from the high heterogeneity in the study design and methodology. The potential source of heterogeneity in the study design include: (1) no consensus on the diagnostic methods of DED; (2) different subgroups and severity of patients with SLE; (3) racial difference which may affect the prevalence of DED and (4) time trends which may affect the prevalence of DED and prognosis of SLE.

Table 2 Prevalence estimates for DED stratified by number of patients with SLE, methodological quality, duration of disease and disease activity

	DED and SLE					
Factors stratified	No of involved data sets	Prevalence	95% CI	P value*	P value†	I^2
All studies	18[4–11 14 16 18 19 23 25 27–30]	0.15	0.10 to 0.20	<0.001	<0.001	94.2%
No of patients with SLE						
<50	6[4 5 7 8 23 27]	0.15	0.07 to 0.24	0.001	0.009	67.2%
50–100	8[6 9–11 14 16 18 25 28]	0.16	0.10 to 0.21	<0.001	<0.001	74.2%
>100	4[16 19 29 30]	0.14	0.00 to 0.28	0.047	<0.001	98.4%
Methodological quality						
Low risk	12[6 8 9 11 16 18 19 23 27–30]	0.18	0.10 to 0.26	<0.001	<0.001	95.9%
Moderate risk	6[4 5 7 10 14 25]	0.09	0.05 to 0.14	<0.001	0.149	38.6%
Disease activity						
Low disease activity	7[8 9 11 16 19 23 28]	0.17	0.07 to 0.26	0.001	<0.001	91.7%
High disease activity	2[18 25]	0.10	0.05 to 0.14	<0.001	0.469	0%
Duration of disease						
<5 years	3[14 16 25]	0.10	0.06 to 0.14	<0.001	0.225	32.9%
5–10 years	7[5 8 9 11 18 19 28]	0.16	0.07 to 0.25	0.001	<0.001	90.4%
>10 years	1[30]	0.12	0.07 to 0.17	<0.001	NA	NA

*P values from the test for overall effect.
†P values from the test of heterogeneity between strata.
DED, dry eye disease; NA, not available; SLE, systemic lupus erythematosus.

First of all, in the included studies, various methods to evaluate DED and sSS were used, including dry eye questionnaire, medical history of dry eye symptoms, tear secretion test, tear meniscus height, tear osmolarity, tear stability test, corneal staining and biopsy. Besides, the diagnostic criteria and definitions of DED were also different in selected studies. This may lead to heterogeneity in study designs when we directly combined the data in the meta-analysis. As the majority of studies assessed the state of dry eye with dry eye-related symptoms and 1–2 diagnostic tests, thus we made the diagnostic criteria of DED based on the criteria proposed by the JDES in 1995.[40] In our study, diagnosis of DED could be made when at least two positive findings were present in either subjective symptoms, tear function test or vital staining test. We calculated the number of patients who met the diagnostic criteria of DED based on the available information in the studies. However, two included studies only provided the number of patients diagnosed with DED but did not provide enough details about the way they made the diagnosis and the criteria they used.[20 30] As it was clearly stated in the articles that the patients were clinically diagnosed with DED by ophthalmologists based on clinical findings, we still included these two studies in our meta-analysis.

In the meta-analysis, we first pooled the data of all patients with SLE and calculated the overall prevalence of DED in patients with SLE to be 16% (95% CI 10% to 21%). However, the patients with SLE also consisted of a broad spectrum of disease activities and subtypes, and some previous reports demonstrated that factors such as disease activity and age may be associated with the risk of DED in patients with SLE.[11 15 20 29] Thus, we conducted further subgroup analysis. Our subgroup analysis showed that there was no difference in the prevalence of DED in subgroups of different ages, disease duration and SLEDAI scores. Thus, we thought the pooled prevalence of DED in patients with SLE would be a validated estimate to show the increased prevalence of dry eye associated with this rheumatic disease. However, even in different subgroups, high heterogeneity still existed and was further analysed with a meta-regression analysis.

The sensitivity analysis showed that the results of the meta-analysis was stable. No publication bias was found according to the Begg's test and Egger's test. However, two studies by Catoggio *et al*[20] and Hsu *et al*[30] were suspected to account for the heterogeneity of studies because the overall heterogeneity greatly reduced after excluding these two studies. The study by Catoggio *et al* demonstrated a relatively low prevalence of DED in patients with SLE. This study recruited patients from Latin America within 2 years of disease onset and reported the prevalence of DED in patients with SLE of <50 years old and ≥50 years old to be 2% and 6%, respectively. The rates were even significantly lower than healthy controls in many other included studies and particularly a low prevalence was found in African-Latin Americans, suggesting that racial

difference may be a factor to explain the low prevalence. As no detailed diagnostic criteria or diagnostic tests of DED was stated in the study, it was not clear whether the diagnostic criteria should account for the low prevalence of DED. The study by Hsu *et al* reported a high prevalence of DED to be 27.6% in Taiwan. However, the study population was patients with SLE who had ophthalmology problems and went to ophthalmology clinics. Thus, it was more likely to overestimate the prevalence of DED. In addition, as with the study by Catoggio *et al*,[20] this study also stated no clear criteria for the diagnosis of DED. After excluding these two studies, the prevalence of DED in patients with SLE was estimated to be 15% (95% CI 11% to 19%), and was very close to the original estimate.

In addition to the heterogeneity from the methodology of included studies, this meta-analysis includes studies published from 1977 to 2020, thus, there is a potential time trend that may affect the prevalence due to changes in treatment, diagnostic methods and coverage of the health system. Results from the bubble plot, meta-regression analysis, and association study with MIC demonstrate that there is no significant linear or non-linear association of the prevalence of DED with the publication time. Thus, the results of this meta-analysis don't show time trend and tend to be stable over different publication time.

Overall, our study demonstrated a higher prevalence of DED in patients with SLE compared with the general population. However, the reported prevalence from individual studies varies widely, and the subgroup analysis showed that the high level of heterogeneity could not be explained by disease duration, disease activity or study quality. This is consistent with the epidemiology studies of DED in the general population, as a wide variation of prevalence was noted.[47 48] The race is a well-studied factor that is associated with the predisposition to dry eye. DED is more prevalent in Asian and Hispanic women, compared with Caucasian women.[44] The meta-regression analysis suggested that the study location may be one source of heterogeneity. However, as most of the included studies in our meta-analysis lacked racial information, we did not conduct subgroup analysis based on the race of patients. In addition, although some diagnostic criteria and guidelines for DED are available, the diagnosis of dry eye is also largely subjective. There is no consensus on the combination of diagnostic tests in the diagnosis of dry eye.[49] No single diagnostic tool is adequately reliable and most of the clinical examinations, such as Schirmer's test, phenol red thread test, tear breakup time, tear meniscus height, *etc*, have limited repeatability and correlation with subjective symptoms.[50] Thus, the different diagnostic tools chosen in different studies may account for the wide variation of the prevalence of DED among studies.

The relationship between DED, sSS and SLE

Our meta-analysis demonstrated that nearly a quarter of patients with SLE had dry eye symptoms or abnormal findings of Schirmer's test. Some previous studies showed that dry eye was one of the most common ocular complications associated with rheumatic diseases, including SLE, but sSS was diagnosed in only a minority of patients.[3 29] However, our meta-analysis showed that sSS was present in 12% (95% CI 9% to 15%) of patients with SLE, which was just a little bit lower than the prevalence of DED, indicating that sSS was also common morbidity in these patients. Currently, few classification criteria addressing the diagnosis of sSS were available. The American-European Consensus Group proposed the classification criteria of sSS based on the simultaneous presentation of ocular symptoms (eye dryness, foreign body sensation or gravel sensation) or oral symptoms (oral dryness, frequent swallowing of saliva, frequent drinking of liquid to aid swallowing) plus at least two positive tests of the following: objective signs of dry eye, objective signs of dry mouth and inflammatory cell infiltration of minor salivary glands on biopsy.[38] As reported in a study group derived from the European population, this criteria showed a sensitivity of 97.2% and a specificity of 90.2% in the diagnosis of sSS, which was superior to the diagnosis based on clinical tests alone.[38] The important serum makers of primary sSS such as anti-Ro (Sjögren's syndrome-related antigen A, SSA) or anti-La (Sjögren's syndrome-related antigen B, SSB) were not included in the classification criteria of sSS, as these markers were also found to be elevated in patients of other rheumatic diseases.[51 52] As demonstrated in previous studies, anti-Ro52 was present in 53% of patients with subacute cutaneous lupus erythematosus, 19% of patients with systemic sclerosis and 35% of patients with myositis.[53] Thus, it is generally accepted that anti-Ro and anti-La are non-specific for sSS and cannot serve as diagnostic markers to distinguish the patients with sSS from comorbidities of other systemic connective tissue diseases.[54] Recently, some novel serum antibodies to salivary gland protein 1, carbonic anhydrase 6 and parotid secretory protein have demonstrated some value in the diagnosis of sSS, which are found to develop earlier than anti-Ro and anti-La. However, the diagnostic efficiency of these markers in combination with the previous diagnostic criteria needs further validation.[55 56] Besides, as the biopsy of the salivary gland was not mandatory and not widely conducted in patients of SLE, in most cases the diagnosis of sSS was made based on symptoms and signs alone. Above all, currently, only a few classification criteria are available for sSS, which have not been evaluated in large groups of patients with sSS. The 2002 criteria proposed by the American-European Consensus Group is the most objective one and most widely used, but it is also largely dependent on subjective judgement. It is, therefore, important to

further explore the pathogenesis of sicca symptoms in patients of SLE and illuminate the relationship between sSS and DED.

Some previous studies demonstrate that SLE is associated with general inflammation and damage of the ocular surface. SLE is an autoimmune disease which can affect nearly every organ of the body, characterised by chronic disturbance of the immune modulation and deposition of immune complexes in various organs and tissues.[3] The tear functional unit (TFU) and the ocular surface are also frequently found to be involved during the disease course of SLE. SLE can lead to severe ocular surface inflammation including keratitis, cicatrising conjunctivitis and scleritis.[2 7 57] Perivascular and subepithelial monocytes infiltration, deposition of immunoreactants and activation of natural killer cells and T-helper cells are found in conjunctival biopsies of patients with SLE.[7 58] Compared with healthy individuals, patients with SLE tend to have a higher density of Langerhans cells in the cornea, which are activated and have long dendritic processes.[59 60] The density of Langerhans cells is also found to be elevated in conditions of chronic DED and sSS.[61] Besides, the deposition of immune complexes in the corneal limbus in patients of SLE may stimulate the release of proinflammatory cytokines and trigger inflammatory cell infiltration.[2] Damage of the meibomian gland, characterised by the occlusion of meibomian gland orifices, decreased meibum quality and increased tear evaporation is found in patients of sSS associated with SLE.[62] Inflammatory cell infiltration and damage of the main and accessory lacrimal glands of patients with SLE may also lead to dry eye.[63] In conclusion, multiple mechanisms can be involved in the pathogenesis of DED in patients with SLE. Inflammatory vicious cycle is initiated on the ocular surface and can disturb the normal turnover of corneal and conjunctival epithelium.[64]

Limitations

There are several limitations of our study. First of all, as stated in the discussion above, there is no consensus on which set of diagnostic tests for DED should be chosen and currently many diagnostic tools are not sufficiently reliable and repeatable. Thus, highly heterogeneous prevalence of DED among studies has been noted. Second, as the racial information and the recruitment time are not available in most of the studies, we could not conduct further subgroup analysis based on the race of the patients and analyse the time trend. Third, to stabilise the variance of each study's proportion in our meta-analysis, we applied a two-step method with Freeman-Tukey double-arcsine transformation, which is a common approach and has been shown to be superior than other arcsine-based transformation methods.[65] However, some limitations have been proposed, including lack of intuitive interpretations, violation of the assumption of normal distribution in the random-effect model and complicated back-transformation.[66]

Implications for clinical application and future studies

Our meta-analysis demonstrated a relatively high prevalence of DED and sSS in patients of SLE. However, no further risk factors of DED in patients with SLE have been identified. Particularly, there were controversial results on whether the presence of serum markers such as anti-dsDNA, anti-Ro or anti-La were associated with increased risk of DED in patients with SLE in the previous studies.[3 11 14 17 20 29] Due to the scarcity of studies addressing these biomarkers, we did not collect enough data to conduct further subgroup analysis. More future studies are needed to illuminate the association of serum antibodies with the risk of DED and sSS in patients with SLE. Besides, whether other potential factors, such as specific subtypes of SLE, specific organ or tissue involvement, or specific therapy could be potential risk factors of DED in patients with SLE need to be further studied.

Overall, our study indicates that there is a relatively high prevalence of DED and sSS in patients with SLE. The study supports the need for patients with SLE to go through regular follow-up in ophthalmology and stomatology clinics. Efforts of multidisciplinary cooperation in the diagnosis and management are beneficial for patients with SLE.

CONCLUSIONS

DED and sSS are common in patients of SLE.

Contributors LW and YX conducted the literature search, study selection and manuscript writing. YD proposed the concept and revised the manuscript.

Funding The study was funded by the postdoctoral research funding of West China Hospital, Sichuan University (Grant number 2020HXBH044 and 2019HXBH036) and the Science & Technology Department of Sichuan Province funding project (No. 2021YFS0221 and No.2020YJ0022).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplemental information.

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