Received: 1 January 2018 | Accepted: 15 February 2018

DOI: 10.1111/sji.12649

REVIEW

WILEY Scandinavian Journal of Immunology

Expression of interleukin-17 in primary Sjögren's syndrome and the correlation with disease severity: A systematic review and meta-analysis

L.-W. Zhang[1] | P.-R. Zhou[1] | P. Wei[1] | X. Cong[2] | L.-L. Wu[2] | H. Hua[1]

[1]Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China

[2]Department of Physiology and Pathophysiology, Peking University Health Science Center, Key Laboratory of Molecular Cardiovascular Sciences, Ministry of Education, and Beijing Key Laboratory of Cardiovascular Receptors Research, Beijing, China

Correspondence
H. Hua, Department of Oral Medicine, Peking University School and Hospital of Stomatology, Beijing, China.
Email: honghua1968@aliyun.com

Funding information
National Natural Science Foundation of China, Grant/Award Number: 81771090

Abstract

The aberrant expression of interleukin-17 (IL-17) has been reported in primary Sjögren's syndrome (pSS). Abnormalities in IL-17 can promote the production of pro-inflammatory cytokines and aggravate autoimmune disorders. The aim of this study was to investigate alterations of IL-17 in patients with pSS and explore the correlation between IL-17 and disease severity. Eight databases were searched for original studies reporting the expression of IL-17 in patients with pSS and controls. Eligible reports were included in the pooled analysis, and subgroup evaluations were performed according to different types of controls and IL-17 measurement methods. Newcastle-Ottawa Scale criteria were used to assess the risk of bias of the included studies. In total, 45 articles are included in the meta-analysis. The expression of IL-17 is significantly increased in patients with pSS compared to controls. Furthermore, patients with pSS without immunosuppressive treatment show markedly higher IL-17 levels. In addition, patients with pSS with positive rheumatoid factors tend to express a higher level of IL-17 than patients with negative rheumatoid factors. Negative correlations between IL-17 levels and ocular parameters are also found in patients with pSS. The results are similar after adjustment by "trim and fill" methods. In conclusion, the expression of IL-17 is obviously increased in patients with pSS, especially among those without immunosuppressive treatment. In addition, IL-17 level correlates with the disease severity of pSS. These findings demonstrate the significance of IL-17 overexpression in patients with pSS and may provide insights for the development of therapeutic interventions targeting IL-17 for pSS.

1 | INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease in which the exocrine glands are the main tissue damaged, especially salivary and lacrimal glands. As one of most common autoimmune diseases, SS affects 0.5% to 1.0% of the population and is most commonly observed in women in the fifth decade of life.[1] SS can present as primary Sjögren's syndrome (pSS) or secondary Sjögren's syndrome (sSS) according to whether the patient has another autoimmune disease.[2] Clinically, dryness is the overwhelming complaint, although other general features (fatigue and chronic pain) and extraglandular manifestations (including lymphoma) are also involved.[3,4] The diagnostic criteria set by the American-European Consensus Group (AECG), American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) all highlight the significance of the ocular, oral and histopathological symptoms, as well as autoantibodies, in the classification of pSS.[5,6] Unfortunately, no curative agents exist for SS.

Therapeutic approaches include topical and systemic treatments to manage the sicca and systemic symptoms, with the aim of improving the quality of life.[7,8] The long-term prognosis of patients with pSS is unclear. Non-Hodgkin lymphoma (NHL) represents the most severe complication, affecting approximately 5% of patients with pSS. The risk of NHL occurrence in patients with pSS has been previously estimated to be sevenfold to 19-fold higher than that of the general population.[9]

Despite years of efforts directed towards defining the genetic factors, environmental events, and hormonal mechanisms associated with, and immunological basis for the development of SS, the underlying aetiology remains poorly understood.[10] However, the exaggeration of innate and adaptive immune responses has been proven beyond doubt. The adaptive immune system is activated pathogenically by signals arising from the aberrant innate immune response, resulting in B and T cell abnormalities in salivary gland lesions and the peripheral blood of SS mouse models and patients.[11,12] The ensuing abnormal inflammatory cytokines and autoantibodies could invade the salivary glands, as well as other target organs, contributing to the incidence and development of SS.[12] Among the aberrant cytokines, interleukin-17 (IL-17) is an important pro-inflammatory cytokine that is mainly secreted by Th17 cells. Under normal conditions, IL-17 plays a potent role in immunity against extracellular bacteria and fungi, by activating or recruiting cytokines and chemokines.[13,14] However, IL-17 is not always beneficial for host defence. IL-17 is involved in the pathogenesis of multiple autoimmune diseases, including systemic lupus erythematosus, psoriasis, inflammatory bowel diseases and rheumatoid arthritis.[13] It has also been reported that IL-17 could induce cytokines and chemokines to promote lymphocyte recruitment, activation and migration to target tissues.[15] Furthermore, IL-17 could potentiate aberrant autoimmune responses by favouring B and T cell survival and protecting T cells from apoptosis.[16] As the first studies showed that IL-17 was present in salivary gland lesions from patients with pSS,[17,18] the pathologic role of IL-17 in SS has attracted ever greater attention. In patients with pSS, an increase in IL-17 has been found in both the serum and the affected glandular lesions, indicating that IL-17 may play a key role in the development of both the glandular and systemic manifestations of the disorder.[19,20] Genetically, IL-17$^{-/-}$ mice were completely resistant to SS induction, showing no evidence of disease symptoms or histopathological changes in salivary glands. In contrast, transfer of Th17 cells rapidly induced the onset of SS-like sialadenitis in immunized IL-17$^{-/-}$ mice.[21] In addition, the single nucleotide polymorphism rs4711998 in *IL-17* has been reported to be associated with a germinal centre-like structure in salivary glands, which is a possible predictor of later lymphoma development in patients with pSS.[22] These results further suggest that IL-17 plays a pathogenic role in the induction of glandular damage, as well as in the poor prognosis of patients with pSS.

Even though many studies have reported the expression of IL-17 in patients with pSS, no comprehensive and systematic study has summarized the alterations of IL-17 expression in patients with pSS. Meanwhile, the connection between IL-17 and SS symptoms has not been clearly elucidated. Thus, we perform the systematic review and meta-analysis to evaluate alterations of IL-17 in patients with pSS and their significance to disease severity.

2 | MATERIALS AND METHODS

2.1 | Search strategy

This review was performed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[23] We searched PubMed, Embase, Web of Science, Ovid, Cochrane Database, Wanfang Data, CNKI and VIP Information databases for original articles published up to 1 December 2017, using the keywords "Sjögren's Syndrome" OR "Sjögrens Syndrome" OR "Sjögren Syndrome" OR "Sicca Syndrome" AND "interleukin-17" OR "IL-17", without any limitations. The authors of meeting abstracts that met the inclusion criteria were contacted for original data (no additional data were provided). Complementary manual searching was performed using the reference lists of relevant original or review articles. The searches were conducted by 2 independent investigators (L Zhang and P Zhou). Any discrepancies were resolved by discussion or by input from the third reviewer (H Hua).

The controls involved in the meta-analysis were divided into 2 types. The first control type was non-sicca control, which included individuals without sicca symptoms. Most individuals in this group were healthy, but some patients with mild topical oral lesions, such as chronic gingivitis and mucoceles, were also included. The second control type was non-SS control, which included patients displaying subjective complaints of dry mouth or eyes, but who did not have SS. The cause of sicca in non-SS controls could be attributed to certain non-autoimmune factors, including non-specific chronic sialoadenitis, head and neck radiation therapy, use of certain medications and disorders of the nervous system.[24] There was no overlap between the 2 control groups.

2.2 | Study selection

Inclusion criteria were as follows: (i) original human studies reporting the expression of IL-17 or IL-17-producing T

cells in the serum, tears, saliva or salivary glands of patients with pSS; (ii) patients with SS met standard diagnostic criteria, such as ACR and AECG criteria for pSS; (iii) mean and standard deviation (SD) of IL-17 expression were available or could be calculated from the original data; and (iv) a non-sicca control or non-SS control group was essential in the meta-analysis to evaluate the expression of IL-17 in patients with pSS. We set no limitations on age, sex or disease duration, with or without clinical treatment for patients with pSS. Exclusion criteria were as follows: (i) SS cases and controls suffered from other systemic autoimmune diseases; and (ii) studies conducted in animal models or cell lines.

2.3 | Data extraction and quality assessment

For statistical analysis, the following items were extracted: authors, country of origin, number of cases, SS diagnostic criteria, age, disease duration, medical treatment history of patients with pSS, mean and SD of IL-17 expression, clinical, serological and histological parameters, including the salivary flow rate, anti-Sjögren's syndrome-related antigen A (Ro/SSA) and anti-Sjögren's syndrome-related antigen B (La/SSB) autoantibodies. Data extraction and management were performed independently by 2 reviewers (L Zhang and P Zhou). Any disagreement was resolved by discussion or by input from the third reviewer (H Hua).

Study quality and bias were assessed using the Newcastle-Ottawa Scale (NOS) criteria, from the following perspectives: (i) the selection of the study groups (4 scores); (ii) the comparability of the groups (2 scores); and (iii) the ascertainment of the exposure and outcome of interest (3 scores).[25] The detailed definition of the assessment is shown in Table S1. A study would be graded as low, moderate or high quality according to scores of 0-3, 4-6 and 7-9, respectively.[26] Two reviewers (L Zhang and P Zhou) independently assessed the quality of the eligible studies. Disagreement was resolved by discussion or by input from the third reviewer (H Hua).

2.4 | Statistical analysis

Statistical analysis was conducted using Stata software (ver. 14.0; Stata Corp., College Station, TX, USA). The data (sample size, mean ± SD) were evaluated with respect to changes of IL-17 levels in patients with pSS vs controls. For certain articles presenting only graphical results, GetData Graph Digitizer software (GetData Pty Ltd., Kogarah, NSW, Australia) was used to convert the graphs into numerical data. Among the studies providing data as median ± interquartile range (IQR) or median ± range, we estimated the mean ± SD following a standard method.[27] The expression of IL-17 in serum, saliva, tear and salivary glands, as well as the proportion of IL-17$^+$CD4$^+$ T cells in CD4$^+$ T cells, was analysed. To specifically compare IL-17 expressions in patients with pSS with those in non-sicca and non-SS controls, the meta-analysis was conducted according to different control types. Moreover, considering that the studies used different measurement methods, subgroup analysis was used to estimate the results obtained using different methods. Besides, when comparing the IL-17 expression among patients with pSS without immunosuppressive treatment and 2 different controls, subgroup analysis according to the sample types was conducted, simultaneously. Standardized mean difference (SMD) and 95% confidence interval (CI, Hedges' g) were calculated as the pooled effect estimates. In addition, I^2 was performed to evaluate the heterogeneity of the studies, which ranged from 0% to 100%; 25% and 50% were used as cut-offs for modest and high heterogeneity, respectively.[28] If no significant heterogeneity was detected, a fixed-effect model would be used to calculate the pooled effect size. Otherwise, a random effect model would be used. The published Pearson correlation coefficients (r) of IL-17 and clinical or serological markers were also summarized. Fisher transformation was used to convert each correlation coefficient into an approximately normal distribution, and then the estimate and its 95% CI were transformed back to the original scale.

The publication bias was assessed by funnel plot. The SMD and standard error were used as the x- and y-axes of the funnel plot, respectively. Egger's regression was used to detect plot asymmetry. If asymmetry is indicated, the "trim and fill" method would be used to adjust summary estimates for the underlying bias. The basic idea of the trim and fill method is to add studies to the funnel plot until it becomes symmetric. This method trims small studies and fills hypothetical studies until funnel plot symmetry is achieved, can also estimate the number and outcomes of missing studies and then recalculate the revised pooled effect size using original and filled studies.[29] For continuous data, SMD and its variance are recommended as variables for the trim and fill method. The filled funnel plots, with SMD and its standard error as the axes, would be output. Thus, we could evaluate the bias caused by missing articles and estimate the validity and generalizability of the meta-analysis by comparing the original and revised effect sizes.

3 | RESULTS

3.1 | Characteristics of the included studies

Based on the search strategy, 1699 studies are retrieved from the relevant databases, and 1611 are excluded after our primary screening due to duplication or not meeting

the inclusion criteria. In addition, we record all reasons for study exclusion, disagreements between the 2 reviewers and third reviewer comments. Finally, 45 articles covering 65 studies[18,20,30-72] are included in the meta-analysis, with 31 articles including non-sicca controls, 4 including non-SS controls and 9 including both types of controls. The other included study compares IL-17 expression between patients with pSS with weak or strong lymphocytic infiltration, although no control is involved. In total, 1716 patients with pSS, 892 non-sicca cases and 309 non-SS cases are included in the meta-analysis. In addition, 23 articles covering 32 studies include patients that have not taken steroids or immunosuppressants for at least 3 months before sample collection, 6 articles include a mix of patients with and without immunosuppressive treatment, and 16 articles lack a description of treatment history. Therefore, IL-17 levels are also compared between patients with pSS without immunosuppressive treatment and controls.

For the risk of bias assessment, 35 articles are considered high quality (NOS score, 7-9) and 10 are considered moderate quality (4-6), thus indicating that most studies have low risk of bias. The flow diagram for article selection is shown in Figure 1, and the baseline characteristics of the included articles are summarized in Table 1.

Of the 45 articles included in the meta-analysis, IL-17 expression (mean ± SD) could be extracted directly from 31 articles, whereas GetData Graph Digitizer is used to digitize the graphical data from the other 14 articles. Pooled data from the studies show that the level of IL-17 in patients with pSS is elevated compared to that in controls (including non-sicca and non-SS controls), although significant heterogeneity is found (SMD, 1.74, 95% CI: 1.38~2.10; I^2, 94.6%; data not shown). Furthermore, the pooled effect size of the 32 studies including patients not taking immunosuppressants shows a much higher level of IL-17 expression (SMD, 2.52, 95% CI: 1.98~3.06; I^2, 94.6%; data not shown). A stratified analysis is then conducted to assess the alteration of IL-17 expression in patients with pSS compared to the different control groups.

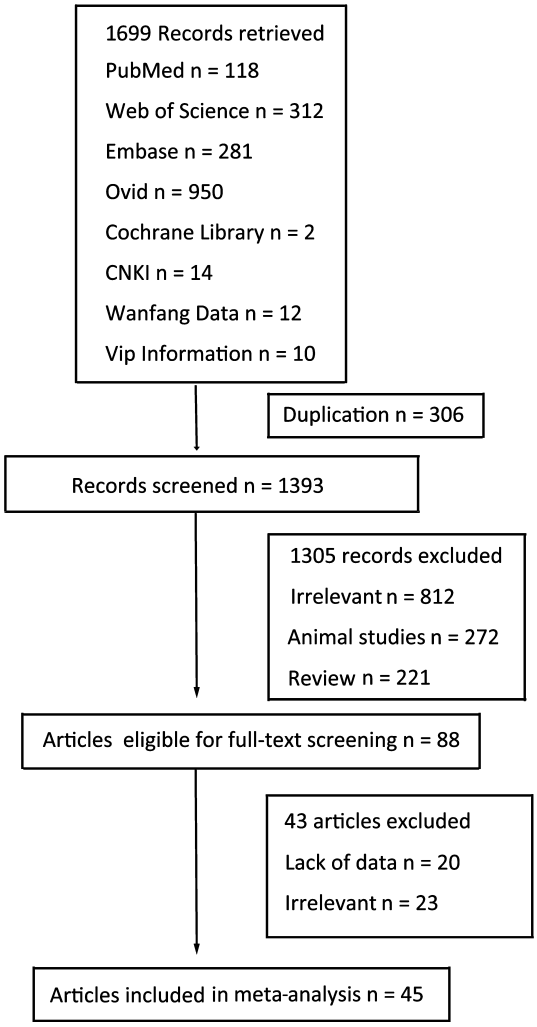

FIGURE 1 Flow diagram of study selection in the meta-analysis

3.2 | Comparison of IL-17 expression between patients with pSS and non-sicca controls

In the meta-analysis, 40 articles covering 49 studies report the expression of IL-17 in patients with pSS and non-sicca controls, including 35 studies report the expression of IL-17 in serum, 6 report IL-17 levels in tears, 4 report IL-17 levels in saliva, and 4 report IL-17 levels in the salivary glands. Among the 35 studies reporting IL-17 in serum, flow cytometry is used in 9 studies, enzyme-linked immunosorbent assays (ELISA) in 18, multiplex bead assays in 7 and polymerase chain reaction (PCR) in 1 study. The expression of IL-17 in the serum of patients with pSS is significantly increased regardless of the detection method used (Figure 2A). However, although the overall result from the tear assessment shows higher expression of IL-17 in patients with pSS, a significant difference is only achieved in studies that utilize ELISA for measurement (Figure 2B). The pooled effect size from the 4 studies measuring IL-17 in salivary glands by PCR reveals that patients with pSS overexpress IL-17 (Figure 2C). For the saliva assessment, a significant increase in IL-17 in patients with pSS is found from the overall result, but the studies using multiplex bead assays show no statistical significance between 2 groups (Figure S1A).

Among the 49 studies, 24 studies from 22 articles include patients with pSS who have either never received steroids or immunosuppressants or have not received these drugs for at least 3 months before enrolment. Of these studies, 7 use flow cytometry, 8 use ELISA, 4 use

TABLE 1 Characteristics of individual studies included in the meta-analysis

Study	Sample type	Sample size			Expression of IL-17			NOS score
		pSS	Non-sicca	Non-SS	pSS	Non-sicca	Non-SS	
Alunno[30]	Serum	15	10		5.0 ± 0.4	4.6 ± 0.4		8
Alunno[31]	Serum	30	16		6.0 ± 3.7	4.3 ± 1.4		7
Kang[32]	Saliva	30	25	30	1.3 ± 2.3	0.1 ± 0.2	1.2 ± 1.5	7
Kang[33]	Tear	33	28	38	530.4 ± 446.3	45.3 ± 57.4	422.9 ± 389.7	6
Kwok[34]	Serum	40	20		139.0 ± 55.6	27.4 ± 9.7		7
Lee[35]	Tear	40	35	40	13.2 ± 12.7	2.8 ± 3.5	4.0 ± 5.2	6
Lin[36]	Serum	38	30		1.1 ± 1.4	0.2 ± 0.2		8
Liu[37]	Tear	15	15	15	305.2 ± 12.1	26.3 ± 5.2	41.1 ± 3.5	6
Miletic[38]	Serum	30	15		12.9 ± 28.0	0.2 ± 0.6		8
Oh[39]	Serum	12	10		37.0 ± 46.7	1.1 ± 1.6		4
Ohyama[40]	Saliva	90	36	30/22	468.4 ± 110.9	134.5 ± 64.2	93.0 ± 69.8/ 227.9 ± 80.6	7
Sudzius[41]	Serum	37	13	13	1.1 ± 0.6	1.1 ± 0.5		7
Tan[42]	Tear	20	20	20	89.8 ± 33.3	27.2 ± 18.4	63.7 ± 26.0	7
Tanaka[43]	SG	15	18		304.5 ± 409.0	2.3 ± 2.4		6
Wang [44]	Serum	35/15	50		0.4 ± 0.03/0.3 ± 0.01	0.2 ± 0.04		8
Alunno[45]	Serum	15/15	15		22.4 ± 7.7/7.7 ± 4.0	4.5 ± 1.0		8
Benchabane[46]	Serum	44	15		99.6 ± 25.1	21.0 ± 3.3		7
Benchabane[46]	Saliva	44	15		4.4 ± 1.6	0.3 ± 0.2		7
Ciccia [47]	SG	19		16	6.8 ± 6.9		0.9 ± 0.3	7
Deng[48]	Serum	31	28		11.8 ± 6.1	39.3 ± 29.4		6
Fei[49]	Serum	54	17		2.3 ± 3.5	0.4 ± 0.7		8
Gan[50]	Serum	109	42		10.4 ± 3.9	10.3 ± 1.9		7
Gao[51]	Tear	20	20	20	1.9 ± 0.2	1.0 ± 0.01	1.5 ± 0.2	7
Katsifis[20]	Serum	30/11	30/11		163.6 ± 246.5/149.4 ± 120.4	35.0 ± 21.9/ 60.1 ± 26.9		5
Maehara[52]	SG	54	16		1.4 ± 0.5	0.4 ± 0.1		8
Maehara[53]	SG	15	15		28.5 ± 21.5	4.4 ± 3.3		8
Moriyama[54]	SG	36	15		338.7 ± 551.8	0.9 ± 5.4		8
Moriyama[54]	Serum	36	15		0.5 ± 0.4	0.1 ± 0.6		8
Moutsopoulos[55]	Serum	22	11		146.2 ± 177.8	60.4 ± 21.8		7
Nguyen[18]	Saliva	21	19		1.2 ± 1.0	0.9 ± 1.0		7
Nguyen [18]	Serum	21	19		12.4 ± 43.8	6.0 ± 12		7
Pollard[56]	Serum	28	10		469.0 ± 1074.0	13.0 ± 14.8		6
Tan[57]	Tear	20	20	20	440.7 ± 126.1	6.2 ± 11.6	364.3 ± 126.9	7
Tan[57]	Serum	20	20	20	964.9 ± 124.8	342.0 ± 85.1	718.9 ± 115.9	7
Verstappen[58]	Serum	20	11		0.9 ± 0.6	0.7 ± 0.3		6
Zhang [59]	Serum	87	30		130.6 ± 90.3	58.7 ± 37.1		7
Ciccia[60]	SG	15		10	4.6 ± 0.4		2.0 ± 0.3	7
Szodoray[61]	Serum	25	14		1.0 ± 0.6	1.2 ± 0.7		5
Reksten [62]	Serum	97/18			83.0 ± 128.0/76.0 ± 76.0			7
Grados[63]	Serum	21	28		80.0 ± 49.0	15.5 ± 5.5		8

(Continues)

TABLE 1 (Continued)

Study	Sample type	Sample size			Expression of IL-17			NOS score
		pSS	Non-sicca	Non-SS	pSS	Non-sicca	Non-SS	
Ciccia[64]	SG	20		10	4.8 ± 2.2		1.0 ± 0.3	8
Mieliauskaite[65]	SG	25		25	4.6 ± 1.4		3.8 ± 1.2	7
Han[66]	Serum	15/15/15	15		22.7 ± 6.6/ 15.8 ± 6.3/21.6 ± 7.3	11.2 ± 6.1		7
Zhu [67]	Serum	32	26		2.2 ± 5.2	1.4 ± 1.2		7
Zhu[68]	Serum	89	38		37.6 ± 14.5	10.0 ± 2.7		7
Zhu[69]	Serum	60	30		10.0 ± 2.0	12.8 ± 1.4		7
Sun [70]	Serum	20	20		124.5 ± 24.8	28.4 ± 19.6		7
Shi[71]	Serum	25/28	15		110.8 ± 25.1/211.8 ± 76.6	142.8 ± 45.5		7
Wang[72]	Serum	50	40		38.6 ± 10.5	6.1 ± 3.2		7

NOS, Newcastle-Ottawa Scale; SG, Salivary gland.

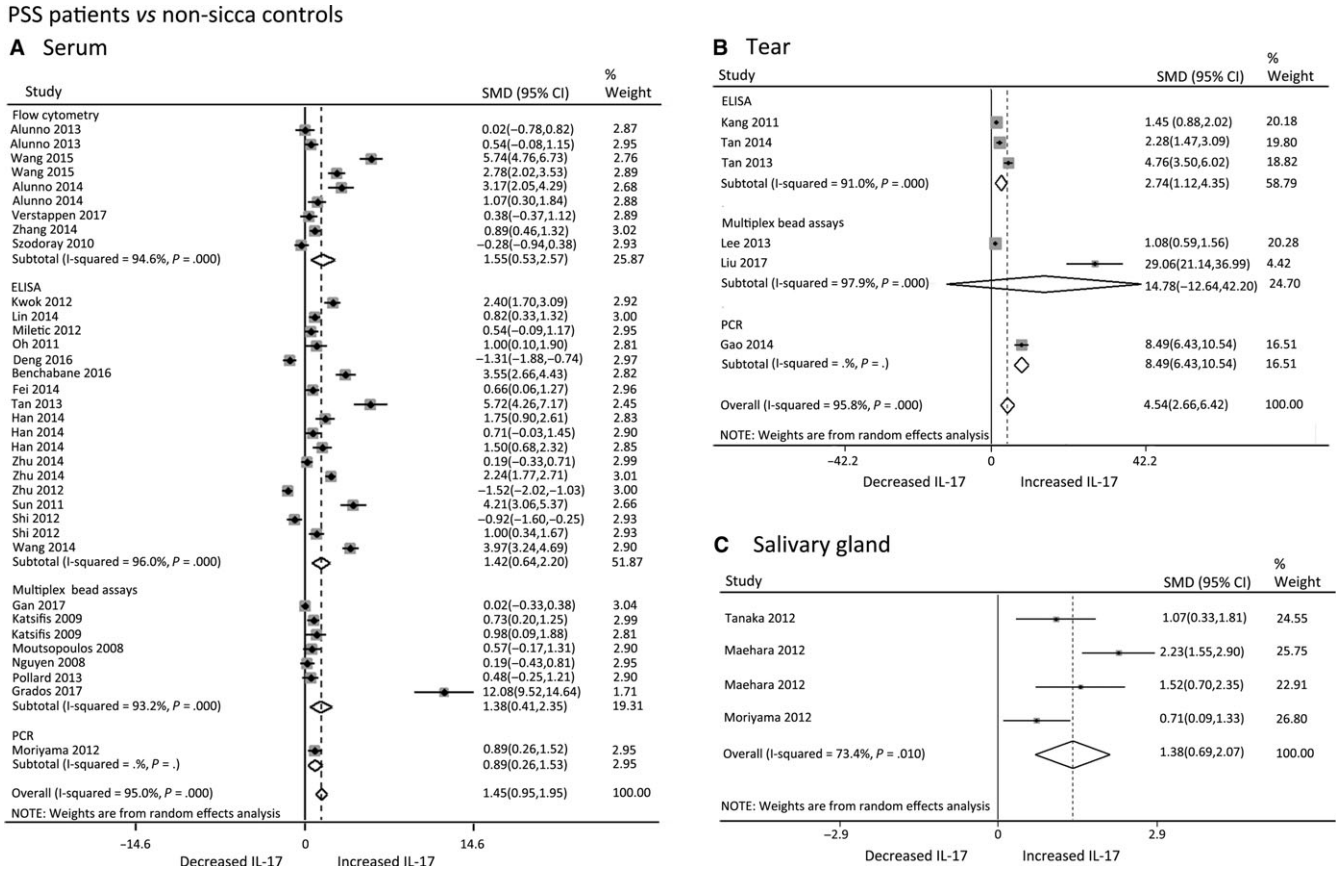

FIGURE 2 Comparison of IL-17 expression levels between patients with pSS and non-sicca controls. Comparison of IL-17 levels in serum (A), tear (B) and salivary gland (C) between patients with pSS and non-sicca controls

multiplex bead assay, and 5 use PCR. We compare the IL-17 level between those patients with pSS and non-sicca controls. The pooled SMD also shows overexpression of IL-17 in patients with pSS regardless of the detection method (Figure 3). On the other hand, among the 24 studies, 15 studies report the IL-17 expression in serum, 5 studies report IL-17 level in tear, 3 studies report IL-17 level in salivary gland, and the other 1 reports IL-17 level in saliva. The pooled effect size from each subgroup still shows the overexpression of IL-17 in patients with pSS without immunosuppressive treatment (Figure S2).

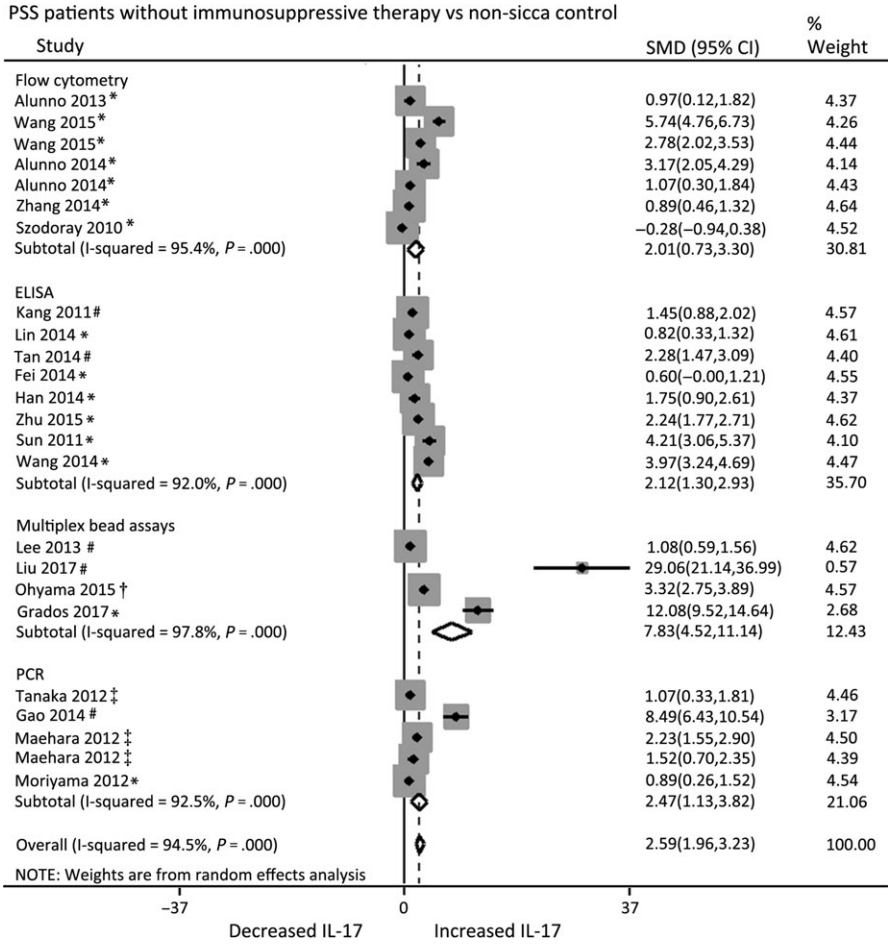

FIGURE 3 Comparison of IL-17 expression levels between patients with pSS without immunosuppressive therapy and non-sicca controls. The samples from different bodily fluids or salivary gland are mixed, * means samples are from serum, # means samples are from tear, ‡ means samples are from salivary gland, and †means samples are from saliva

3.3 | Comparison of IL-17 expression between patients with pSS and non-SS controls

In total, 13 articles covering 14 studies report the expression of IL-17 in patients with pSS and non-SS controls, including 1 study that reports the expression of IL-17 in serum, 6 that report it in tears, 3 in saliva and 4 in the salivary glands. Pooled analysis of IL-17 expression in pSS serum is unavailable due to the limited number of studies. Three of the studies in tears use ELISA, 2 use multiplex bead assays, and 1 uses PCR. The overall result shows overexpression of IL-17 in tears from patients with pSS, although significant difference is only found among studies using ELISA (Figure 4A). A significant difference is also found in studies conducted in salivary glands (Figure 4B). However, no significant difference is found among studies measuring IL-17 in the saliva of patients with pSS (Figure S1B).

Similarly, 7 articles covering 8 studies include patients with pSS without immunosuppressive therapy. Two of these studies use ELISA, 4 use multiplex bead assays, and 2 use PCR. Compared with non-SS controls, a significant increase in IL-17 in patients with pSS without immunotherapy is found from the overall result (Figure 5). Moreover, among the 8 studies, 5 studies report the IL-17 expression in tear, 1 study reports the IL-17 expression in salivary gland, and 2 studies report the IL-17 expression in saliva. The pooled effect size from each subgroup also shows the high level of IL-17 in patients with pSS without immunosuppressive treatment (Figure S3).

3.4 | Correlation of IL-17 and disease severity

In addition to evaluating alterations of IL-17 in patients with pSS, we explore the correlation between IL-17 levels and disease severity in patients with pSS. Controls are not essential for the analysis. Unfortunately, no study reports the correlation between IL-17 levels and salivary secretion or pSS prognostic factors. In total, 12 studies are included to assess the correlation of histological, serological and ocular severity with IL-17.

3.4.1 | Lymphocytic infiltration

Seven studies report IL-17 levels in patients with pSS with weak or strong lymphocytic infiltration. Four studies measure the IL-17 level in serum, 2 studies measure the IL-17

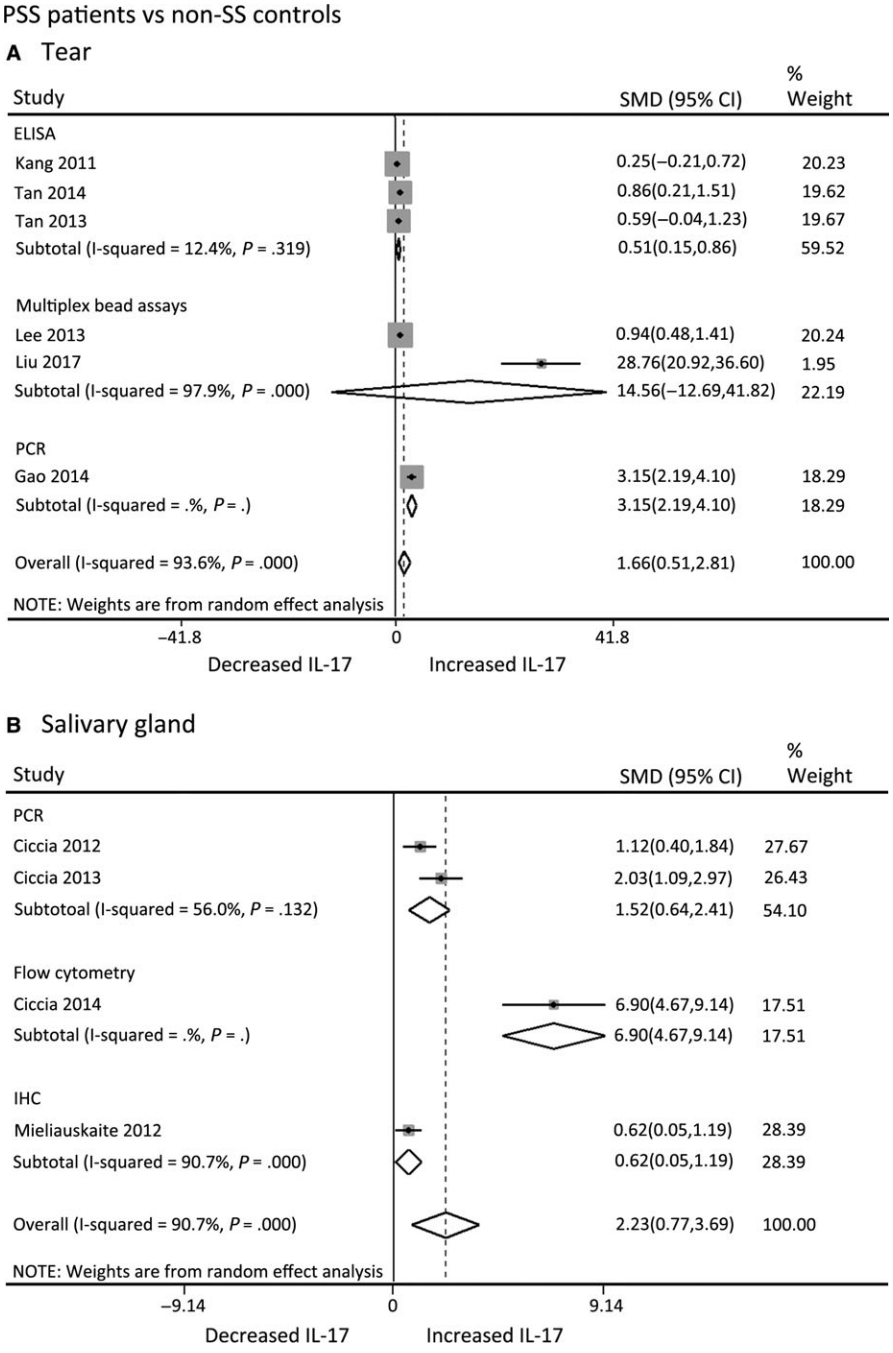

FIGURE 4 Comparison of IL-17 expression between patients with pSS and non-SS controls. Comparison of IL-17 levels in tear (A) and salivary gland (B) between patients with pSS and non-SS controls

level in salivary gland, and the other 1 study measures the IL-17 level in saliva; meanwhile, 3 studies use multiplex bead assays to measure the expression of IL-17, 2 use ELISA, and 2 use PCR. However, neither the subgroup results nor the overall result shows the significant difference of IL-17 among patients with different infiltration severity (Figure 6A).

3.4.2 | Serological parameters

Two studies evaluate the difference in IL-17 expression in serum between patients with pSS that are positive and negative for anti-Ro/SSA and anti-La/SSB antibodies; the results reveal no statistically significant difference between these 2 patient groups (Figure S4). In contrast, rheumatoid factor (RF)-positive patients tend to show higher IL-17 expression compared to negative RF patients with pSS (Figure 6B).

3.4.3 | Ocular parameters

Three studies report the correlation between IL-17 expression levels in tear and tear film break-up time (TBUT), as well as the Schirmer I test. Pooled data show a negative

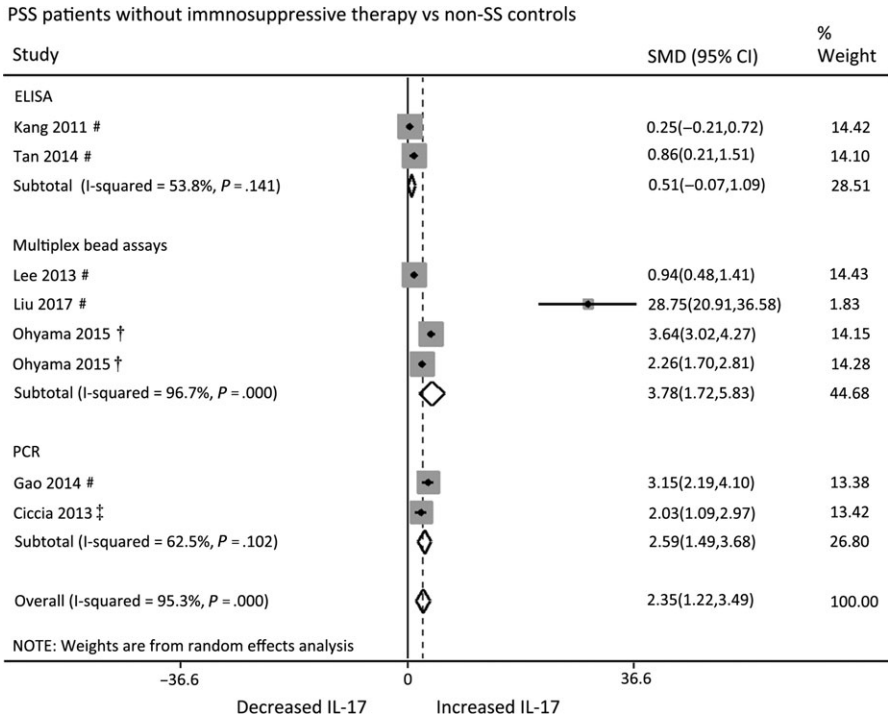

FIGURE 5 Comparison of IL-17 expression levels between patients with pSS without immunosuppressive therapy and non-SS controls. The samples from different bodily fluids or salivary gland are mixed, # means samples are from tear, ‡ means samples are from salivary gland, and †means samples are from saliva

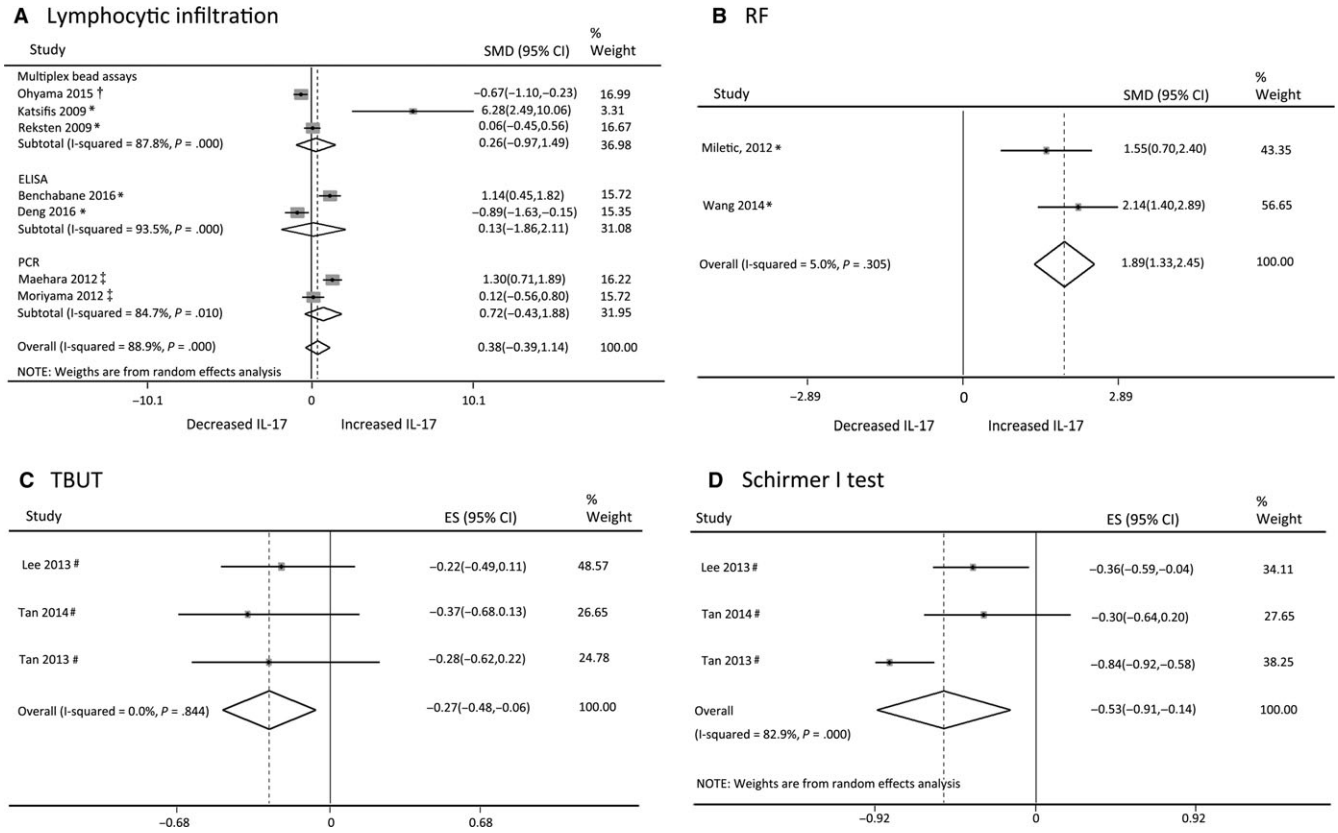

FIGURE 6 Correlations of IL-17 expression levels with disease severity in patients with pSS. (A) Comparison of IL-17 expression levels between patients with pSS with weak and strong lymphocytic infiltration. (B) Comparison of IL-17 levels between patients with pSS with positive and negative RF. Correlation of IL-17 expression levels with TBUT (C) and the Schirmer I test (D) in patients with pSS. The samples from different bodily fluids or salivary gland are mixed, * means samples are from serum, # means samples are from tear, ‡ means samples are from salivary gland, and †means samples are from saliva

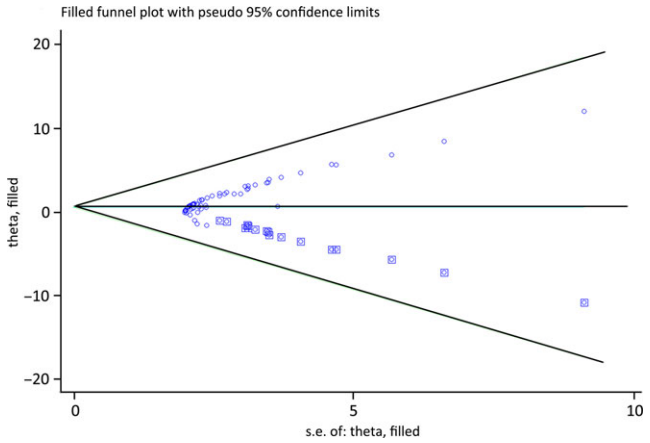

FIGURE 7 Funnel plot of studies adjusted by trim and fill method

correlation between IL-17 levels and TBUT. Similarly, a negative correlation is found between IL-17 and the Schirmer I test (Figure 6C,D).

3.5 | Publication bias

The asymmetry of the funnel plot and the results of Egger's regression ($P < .01$) both indicate the presence of publication bias. Therefore, the "trim and fill" method is used to adjust for bias. Compared to the previous pooled effect size (SMD, 1.74, 95% CI: 1.38~2.10), the pooled SMD after adjustment (SMD, 0.67, 95% CI: 0.10~1.25) still remains significant, although the increased level of IL-17 expression is reduced. This suggests that the results of the meta-analysis are still valid, although publication bias must nevertheless be considered (Figure 7).

4 | DISCUSSION

Sjögren's syndrome is a complex and multifactorial autoimmune disease, the pathogenesis of which still remains unclear. The most accepted aetiology of SS relates to aberrant inflammation, which leads to destruction of the epithelium in the exocrine glands and lymphocytic infiltration.[73] The impact of abnormal cytokine production in SS has attracted considerable attention.[74] As an important pro-inflammatory cytokine, IL-17 is related to a wide range of pathological inflammatory conditions, including autoimmune diseases, metabolic disorders and cancers.[15] In autoimmune disorders, IL-17 can promote the expression of chemokines, which drive recruitment of inflammatory cells, including monocytes, neutrophils, dendritic cells and Th17 cells.[75] Meanwhile, IL-17 can increase the expression of various pro-inflammatory cytokines, which may in turn aggravate inflammation and cause organ destruction.[75] In addition, IL-17 could stimulate the release of matrix metalloproteinases, destroying components of the extracellular matrix and resulting in compromised function of the exocrine glands.[76,77] In recent years, several articles have explored the aberrant expression of IL-17 in patients with pSS. The aim of this comprehensive meta-analysis is to clarify alterations of IL-17 in the serum, tears, saliva and salivary glands of patients with pSS, as well as its correlation with disease severity.

Non-sicca controls and non-SS controls are both included in the meta-analysis. In contrast to the non-sicca controls, lymphocytic infiltration could occur in the exocrine glands of non-SS controls.[32] Furthermore, cytokine expression and release could also be aberrant in non-SS controls.[37] Therefore, it is essential and meaningful to include the 2 different controls simultaneously. When compared with non-sicca controls, a significant increase in IL-17 is found in the serum, tears, saliva and salivary glands of patients with pSS, with the largest difference in IL-17 levels seen in tears. Similarly, a significant difference is found in IL-17 levels in the tears and salivary glands of patients with pSS compared with non-SS controls. These data indicate the important role of IL-17 in the pathogenesis of pSS.

Among the autoimmune disorders, SS remains one of the most difficult to manage. The treatment of pSS is based on symptomatic management of sicca manifestations and the use of immunosuppressive agents for systemic disease.[3] We evaluate 23 articles that include patients without systemic treatment to exclude the influence of immunosuppressants. The results further confirm the elevated expression of IL-17 in patients with pSS. Compared with the pooled effect size derived from all 45 articles, alterations of IL-17 in patients without immunosuppressive treatment seem to be greater, which indicate a possible effect of immunosuppressants on alleviating inflammation.

Lymphocytic infiltration in exocrine glands is the most important histological characteristic of patients with pSS. Previous studies have shown that IL-17 is mainly expressed in the periductal and perivascular infiltrates of the salivary glands,[20,43,78] with the level of expression correlated with the severity of glandular inflammation.[79] However, among the 7 studies reporting IL-17 expression under conditions of weak and strong lymphocytic infiltration, no significant overexpression of IL-17 in severe inflammatory patients is found. Notably, no consistent cut-off value is used for distinguishing weak from strong infiltration among the 7 studies. Four studies evaluate inflammation using Greenspan's focus score[80]; a score of 6 is used as a cut-off value for distinguishing weak and strong infiltration. Three articles use the AECG classification criteria for pSS (focus score $\geq$1 foci/4 mm^2 for the minor salivary gland); 2 of these studies use a focus score of 1 as a cut-off for weak and

strong infiltration, and the other study defines weak infiltration as 1-2 foci per lobule of labial salivary glands. This inconsistency may be attributable to the high heterogeneity among the included studies, which could bias the pooled effect size. This must be kept in mind when interpreting the results.

In addition, our results indicate that there is no difference in IL-17 expression between patients who are positive and negative for anti-Ro/SSA and anti-La/SSB antibodies. Similar results have been reported previously.[50] Ro/SSA and La/SSB are extractable nuclear antigens, while anti-Ro/SSA and anti-La/SSB antibodies are among the most common autoantibodies found in patients with pSS, being present in 50%-70% of patients.[81] Previous studies have suggested that anti-Ro/SSA and anti-La/SSB antibodies are associated with a longer disease duration, more severe dysfunction of the exocrine glands and stronger lymphocytic infiltration in the salivary glands.[81] However, this analysis, as along with other previous reports, fails to find a correlation between IL-17 levels and those of the 2 antibodies. Surprisingly, RF, an important serological marker of pSS, is significantly related to elevated expression of IL-17 in patients. Furthermore, a previous study also found that RF levels were positively correlated with IL-17 expression.[50] These results indicate that, to some extent, IL-17 combined with certain serological parameters has some utility in the evaluation of disease severity in patients with pSS.

The salivary flow rate, TBUT and Schirmer I test are important for evaluating the severity of dryness. However, few studies explore the correlation between IL-17 levels and the salivary flow rate. Regarding the ocular parameters, the TBUT and Schirmer I test are negatively correlated with tear IL-17 levels in patients with pSS. These ocular parameters could constitute an important reference for clinicians to determine the severity of pSS and develop treatment plans. These results reveal a possible correlation between IL-17 and dry eye symptoms in patients with pSS. However, considering the small number of studies involved, additional studies are still needed to confirm the results.

Although the SS Foundation has developed clinical practice guidelines for the management of the oral, ocular and rheumatologic or systemic manifestations of patients with pSS in 2016, no curative therapy for SS exists.[82] Given the need for treatments for these patients, cytokine imbalances and the proven physiopathological mechanisms offer therapeutic opportunities.[83] Biological treatment has attracted significant attention recently. B cell depletion therapy with rituximab has shown beneficial effects on glandular morphology, dryness and several extraglandular manifestations in patients with pSS.[84] Regarding IL-17, monoclonal antibodies targeting IL-17 or the IL-17 receptor have proven effective in alleviating the course of psoriasis, inflammatory bowel disease and arthritis, but have not yet been applied in patients with pSS.[3] The evidence provided by this meta-analysis suggests that IL-17 is aberrantly expressed in pSS and correlated with disease severity, which could provide a theoretical basis for the development and application of therapies targeting IL-17 for the treatment of pSS.

Lymphoma is a leading cause of mortality in patients with pSS.[85] Reported predictors of lymphoma include lymphadenopathy, parotid enlargement, palpable purpura, low C4 serum levels and cryoglobulins.[86] Although no study specifically evaluated the correlation between IL-17 and the development of lymphoma in pSS, a relationship between IL-17 and lymphoproliferative disease has been posited. Circulating IL-17 levels are significantly increased in patients with anaplastic large cell lymphoma and acute lymphoblastic leukaemia.[87,88] In addition, relatively lower serum IL-17 expression is a positive predictor of 3-year progression-free survival for patients with extranodal natural killer/T cell lymphoma.[89] Moreover, IL-17 may be prognostic factor for B lymphoma by inducing radiation resistance. IL-17 could suppress p53 expression and thereby repress irradiation-triggered apoptosis of lymphoma cells.[90] Therefore, we speculate that IL-17 is a key prognostic factor for lymphoma. Further studies are still needed to reveal the risk conferred by IL-17 overexpression with respect to the onset of lymphoma in patients with pSS.

Overall, there are several limitations to our analysis, necessitating significant caution when interpreting the results. The main limitation is the high heterogeneity of some estimates. It is difficult to elucidate the source of the heterogeneity, but we assume that diversity in the study designs, sample sizes, disease durations and measurement errors all contribute. Second, the number of included articles and the overall sample size are small in the contest of assessing the significance of IL-17 for disease severity. Even though a negative correlation is found between IL-17 levels and ocular parameters, the available evidence is still not sufficient to draw a firm conclusion. Third, the underlying publication bias must be considered. Although our literature search is as comprehensive as possible, Egger's regression still shows the presence of small-study effects. However, overexpression of IL-17 is still determined in the patients with pSS, although the adjusted result shows that the increase in IL-17 levels is somewhat reduced. The results indicate that studies with a small sample size or negative findings may not always be published. All of these limitations should be borne in mind when interpreting the results.

In conclusion, by analysing the data of studies that have investigated IL-17 levels in patients with pSS, especially in those not receiving immunosuppressive therapies, this meta-analysis provides robust evidence that IL-17 is

increased in patients with pSS. Certain parameters that are important in pSS, such as RF and ocular signs, are found to be correlated with the expression level of IL-17. These findings suggest that IL-17 may participate in the onset and progression of pSS and may provide evidence that could inform the development of therapeutic approaches for pSS targeting IL-17.

ACKNOWLEDGMENT

This work is supported by the National Natural Science Foundation of China (Grant numbers 81771090 and 81371163).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

ORCID

L.-W. Zhang http://orcid.org/0000-0003-4762-7989

REFERENCES

1. Zhang Q, Wang X, Chen H. Sjögren's syndrome is associated with negatively variable impacts on domains of health-related quality of life: evidence from Short Form 36 questionnaire and a meta-analysis. *Patient Prefer Adherence*. 2017;11:905-911.
2. Both T, Dalm VA, van Hagen PM, van Daele PL. Reviewing primary Sjogren's syndrome: beyond the dryness - from pathophysiology to diagnosis and treatment. *Int J Med Sci*. 2017;14:191-200.
3. Retamozo S, Flores-Chavez A, Consuegra-Fernández M, Lozano F, Ramos-Casals M, Brito-Zerón P. Cytokines as therapeutic targets in primary Sjogren syndrome. *Pharmacol Ther*. 2017. https://doi.org/10.1016/j.pharmthera.2017.10.01
4. Isaksen K, Jonsson R, Omdal R. Anti-CD20 treatment in primary Sjögren's syndrome. *Scand J Immunol*. 2008;68:554-564. https://doi.org/10.1111/j.1365-3083.2008.02185.x.
5. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis*. 2002;61:554-558.
6. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjogren's syndrome: a consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis*. 2017;76:9-16.
7. Shih KC, Lun CN, Jhanji V, Thong BY, Tong L. Systematic review of randomized controlled trials in the treatment of dry eye disease in Sjogren syndrome. *J Inflamm (Lond)*. 2017;14:26.
8. Carsons SE, Vivino FB, Parke A, et al. Treatment guidelines for rheumatologic manifestations of Sjogren's syndrome: use of biologic agents, management of fatigue, and inflammatory musculoskeletal pain. *Arthritis Care Res (Hoboken)*. 2017;69:517-527.
9. Fragkioudaki S, Mavragani CP, Moutsopoulos HM. Predicting the risk for lymphoma development in Sjogren syndrome: an easy tool for clinical use. *Medicine (Baltimore)*. 2016;95:e3766.
10. Peck AB, Nguyen CQ. What can Sjogren's syndrome-like disease in mice contribute to human Sjogren's syndrome? *Clin Immunol*. 2017;182:14-23.
11. Furuzawa-Carballeda J, Sánchez-Guerrero J, Betanzos JL, et al. Differential cytokine expression and regulatory cells in patients with primary and secondary Sjögren's syndrome. *Scand J Immunol*. 2014;80:432-440.
12. Goules AV, Kapsogeorgou EK, Tzioufas AG. Insight into pathogenesis of Sjögren's syndrome: dissection on autoimmune infiltrates and epithelial cells. *Clin Immunol*. 2017;182:30-40.
13. Chizzolini C, Dufour AM, Brembilla NC. Is there a role for IL-17 in the pathogenesis of systemic sclerosis? *Immunol Lett*. 2018;195:61-67.
14. Gaffen SL. An overview of IL-17 function and signaling. *Cytokine*. 2008;43:402-407.
15. Alunno A, Carubbi F, Bartoloni E, et al. Unmasking the pathogenic role of IL-17 axis in primary Sjogren's syndrome: a new era for therapeutic targeting? *Autoimmun Rev*. 2014;13:1167-1173.
16. Boggio E, Clemente N, Mondino A, et al. IL-17 protects T cells from apoptosis and contributes to development of ALPS-like phenotypes. *Blood*. 2014;123:1178-1186.
17. Sakai A, Sugawara Y, Kuroishi T, Sasano T, Sugawara S. Identification of IL-18 and Th17 cells in salivary glands of patients with Sjogren's syndrome, and amplification of IL-17-mediated secretion of inflammatory cytokines from salivary gland cells by IL-18. *J Immunol*. 2008;181:2898-2906.
18. Nguyen CQ, Hu MH, Li Y, Stewart C, Peck AB. Salivary gland tissue expression of interleukin-23 and interleukin-17 in Sjögren's syndrome: findings in humans and mice. *Arthritis Rheum*. 2008;58:734-743.
19. Szodoray P, Alex P, Jonsson MV, et al. Distinct profiles of Sjogren's syndrome patients with ectopic salivary gland germinal centers revealed by serum cytokines and BAFF. *Clin Immunol*. 2005;117:168-176.
20. Katsifis GE, Rekka S, Moutsopoulos NM, Pillemer S, Wahl SM. Systemic and local interleukin-17 and linked cytokines associated with Sjögren's syndrome immunopathogenesis. *Am J Pathol*. 2009;175:1167-1177.
21. Lin X, Rui K, Deng J, et al. Th17 cells play a critical role in the development of experimental Sjögren's syndrome. *Ann Rheum Dis*. 2015;74:1302-1310.
22. Reksten TR, Johnsen SJ, Jonsson MV, et al. Genetic associations to germinal centre formation in primary Sjogren's syndrome. *Ann Rheum Dis*. 2014;73:1253-1258.
23. Knobloch K, Yoon U, Vogt PM. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement and publication bias. *J Craniomaxillofac Surg*. 2011;39:91-92.
24. Labbé A, Liang Q, Wang Z, et al. Corneal nerve structure and function in patients with non-sjogren dry eye: clinical correlations. *Invest Ophthalmol Vis Sci*. 2013;54:5144-5150.
25. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses 2011. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed December 12, 2017.

26. Wang XF, Zhu YT, Wang JJ, et al. The prognostic value of interleukin-17 in lung cancer: a systematic review with meta-analysis based on Chinese patients. *PLoS One*. 2017;12:e0185168.
27. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
28. Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. *J Eval Clin Pract*. 2008;14:951-957.
29. Lin L, Chu H. Quantifying publication bias in meta-analysis. *Biometrics*. 2017. https://doi.org/10.1111/biom.12817
30. Alunno A, Bistoni O, Bartoloni Bocci E, et al. IL-17-producing double-negative T cells are expanded in the peripheral blood, infiltrate the salivary gland and are partially resistant to corticosteroid therapy in patients with Sjögren's syndrome. *Reumatismo*. 2013;65:192-198.
31. Alunno A, Bistoni O, Bartoloni E, et al. IL-17-producing CD4-CD8- T cells are expanded in the peripheral blood, infiltrate salivary glands and are resistant to corticosteroids in patients with primary Sjögren's syndrome. *Ann Rheum Dis*. 2013;72:286-292.
32. Kang EH, Lee YJ, Hyon JY, Yun PY, Song YW. Salivary cytokine profiles in primary Sjögren's syndrome differ from those in non-sjögren sicca in terms of TNF-α levels and Th-1/Th-2 ratios. *Clin Exp Rheumatol*. 2011;29:970-976.
33. Kang MH, Kim MK, Lee HJ, Lee HI, Wee WR, Lee JH. Interleukin-17 in various ocular surface inflammatory diseases. *J Korean Med Sci*. 2011;26:938-944.
34. Kwok SK, Cho ML, Her YM, et al. TLR2 ligation induces the production of IL-23/IL-17 via IL-6, STAT3 and NF-kB pathway in patients with primary Sjogren's syndrome. *Arthritis Res Ther*. 2012;14:R64.
35. Lee SY, Han SJ, Nam SM, et al. Analysis of tear cytokines and clinical correlations in Sjögren syndrome dry eye patients and non-Sjögren syndrome dry eye patients. *Am J Ophthalmol*. 2013;156:247-253.
36. Lin W, Jin L, Chen H, et al. B cell subsets and dysfunction of regulatory B cells in IgG4-related diseases and primary Sjögren's syndrome: the similarities and differences. *Arthritis Res Ther*. 2014;16:R118.
37. Liu R, Gao C, Chen H, Li Y, Jin Y, Qi H. Analysis of Th17-associated cytokines and clinical correlations in patients with dry eye disease. *PLoS One*. 2017;12:e0173301.
38. Miletic M, Stojanovic R, Pajic O, et al. Serum interleukin-17 & nitric oxide levels in patients with primary Sjögren's syndrome. *Indian J Med Res*. 2012;135:513-519.
39. Oh JY, Kim MK, Choi HJ, et al. Investigating the relationship between serum interleukin-17 levels and systemic immune-mediated disease in patients with dry eye syndrome. *Korean J Ophthalmol*. 2011;25:73-76.
40. Ohyama K, Moriyama M, Hayashida JN, et al. Saliva as a potential tool for diagnosis of dry mouth including Sjögren's syndrome. *Oral Dis*. 2015;21:224-231.
41. Sudzius G, Mieliauskaite D, Butrimiene I, Siaurys A, Mackiewicz Z, Dumalakiene I. Activity of T-helper cells in patients with primary Sjogren's syndrome. *In Vivo*. 2013;27:263-268.
42. Tan X, Sun S, Liu Y, et al. Analysis of Th17-associated cytokines in tears of patients with dry eye syndrome. *Eye (Lond)*. 2014;28:608-613.
43. Tanaka A, Moriyama M, Nakashima H, et al. Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz disease. *Arthritis Rheum*. 2012;64:254-263.
44. Wang K, Shi L, Yu Z, et al. Cyclosporine A suppresses the activation of the Th17 cells in patients with primary Sjögren's syndrome. *Iran J Allergy Asthma Immunol*. 2015;14:198-207.
45. Alunno A, Carubbi F, Bistoni O, et al. CD4(-)CD8(-) T-cells in primary Sjögren's syndrome: association with the extent of glandular involvement. *J Autoimmun*. 2014;51:38-43.
46. Benchabane S, Boudjelida A, Toumi R, Belguendouz H, Youinou P, Touil-Boukoffa C. A case for IL-6, IL-17A, and nitric oxide in the pathophysiology of Sjögren's syndrome. *Int J Immunopathol Pharmacol*. 2016;29:386-397.
47. Ciccia F, Guggino G, Rizzo A, et al. Potential involvement of IL-22 and IL-22-producing cells in the inflamed salivary glands of patients with Sjogren's syndrome. *Ann Rheum Dis*. 2012;71:295-301.
48. Deng F, Chen J, Zheng J, et al. Association of BAFF and IL-17A with subphenotypes of primary Sjögren's syndrome. *Int J Rheum Dis*. 2016;19:715-720.
49. Fei Y, Zhang W, Lin D, et al. Clinical parameter and Th17 related to lymphocytes infiltrating degree of labial salivary gland in primary Sjögren's syndrome. *Clin Rheumatol*. 2014;33:523-529.
50. Gan Y, Zhao X, He J, et al. Increased interleukin-17F is associated with elevated autoantibody levels and more clinically relevant than interleukin-17A in primary Sjögren's syndrome. *J Immunol Res*. 2017;2017:4768408.
51. Gao C, Chen HJ, Jin Y, Qi H. Expression of Th17 related cytokines on ocular surface of dry eye and its significance. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2014;32:641-646.
52. Maehara T, Moriyama M, Hayashida JN, et al. Selective localization of T helper subsets in labial salivary glands from primary Sjögren's syndrome patients. *Clin Exp Immunol*. 2012;169:89-99.
53. Maehara T, Moriyama M, Nakashima H, et al. Interleukin-21 contributes to germinal centre formation and immunoglobulin G4 production in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. *Ann Rheum Dis*. 2012;71:2011-2019.
54. Moriyama M, Hayashida JN, Toyoshima T, et al. Cytokine/chemokine profiles contribute to understanding the pathogenesis and diagnosis of primary Sjögren's syndrome. *Clin Exp Immunol*. 2012;169:17-26.
55. Moutsopoulos NM, Katsifis GE, Angelov N, et al. Lack of efficacy of etanercept in Sjögren syndrome correlates with failed suppression of tumour necrosis factor alpha and systemic immune activation. *Ann Rheum Dis*. 2008;67:1437-1443.
56. Pollard RP, Abdulahad WH, Bootsma H, et al. Predominantly proinflammatory cytokines decrease after B cell depletion therapy in patients with primary Sjogren's syndrome. *Ann Rheum Dis*. 2013;72:2048-2050.
57. Tan XH, Sun S, Zhu TT, Ren TL, Wu ZF, Wang K. Expression of interleukin-17 and interleukin-22 in supernatant of peripheral blood mononuclear cell and tear in dry eye patient. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2013;31:668-673.
58. Verstappen GM, Kroese FG, Meiners PM, et al. B cell depletion therapy normalizes circulating follicular Th cells in primary Sjögren syndrome. *J Rheumatol*. 2017;44:49-58.
59. Zhang R, Sun T, Song L, Zuo D, Xiao W. Increased levels of serum galectin-3 in patients with primary Sjögren's syndrome: associated with interstitial lung disease. *Cytokine*. 2014;69:289-293.
60. Ciccia F, Guggino G, Rizzo A, et al. Rituximab modulates IL-17 expression in the salivary glands of patients with primary Sjögren's syndrome. *Rheumatology (Oxford)*. 2014;53:1313-1320.
61. Szodoray P, Horvath IF, Papp G, et al. The immunoregulatory role of vitamins A, D and E in patients with primary Sjogren's syndrome. *Rheumatology (Oxford)*. 2010;49:211-217.
62. Reksten TR, Jonsson MV, Szyszko EA, Brun JG, Jonsson R, Brokstad KA. Cytokine and autoantibody profiling related to

histopathological features in primary Sjogren's syndrome. *Rheumatology (Oxford)*. 2009;48:1102-1106.
63. Grados A, Ebbo M, Piperoglou C, et al. T cell polarization toward TH2/TFH2 and TH17/TFH17 in patients with IgG4-related disease. *Front Immunol*. 2017;8:235.
64. Ciccia F, Alessandro R, Rodolico V, et al. IL-34 is overexpressed in the inflamed salivary glands of patients with Sjogren's syndrome and is associated with the local expansion of pro-inflammatory CD14(bright)CD16+ monocytes. *Rheumatology (Oxford)*. 2013;52:1009-1017.
65. Mieliauskaite D, Dumalakiene I, Rugiene R, Mackiewicz Z. Expression of IL-17, IL-23 and their receptors in minor salivary glands of patients with primary Sjögren's syndrome. *Clin Dev Immunol*. 2012;2012:187258.
66. Han D, Shi LP, Liu ZD. The expression and significance of IL-6 and IL-17 in peripheral blood of Sjogren's syndrome patients. *Chin J Trauma Disabil Med*. 2014;22:37-38.
67. Zhu KD. *The Expression and Significance of IL-17 in the Peripheral Blood of the Patients with Rheumatoid Arthritis, Primary Sjogren's Syndrome, and Systemic Lupus Erythematosus*. Suzhou: Soochow University; 2014.
68. Zhu GH, Zhang YF, Gao YJ, Yan F. Expression of peripheral blood T lymphocyte subsets, IL-17 and IL-10 in primary Sjogren′s syndrome. *Lab Med Clin*. 2015;12:2664-2668.
69. Zhu JD, Wang ZQ, Zhang PN. The imbalance of immunity between Th17 and CD4 + CD25 + regulatory T cell in patients with Sjogren's syndrome. *J Radioimmunol*. 2012;25:301-303.
70. Sun Y, Jiang L, Sun DD, et al. The expression of IL-17 in four rheumatoid diseases. *Chin J Cell Mol Immunol*. 2011;27:85-89.
71. Shi YT. *The Level and the Clinical Significance of Interleukin-17 in Primary Sjogren's Syndrome with Interstitial Lung Disease*. Shenyang: China Medical University; 2012.
72. Wang XY, Zou WH, Wu Q, Gu JH. Determination of serum interleukin-17 and significance in patients with primary Sjogren' s syndrome. *Chin J Gen Prac*. 2014;12:620-621.
73. Brito-Zerón P, Baldini C, Bootsma H, et al. Sjögren syndrome. *Nat Rev Dis Primers*. 2016;2:16047.
74. Youinou P, Pers JO. Disturbance of cytokine networks in Sjögren's syndrome. *Arthritis Res Ther*. 2011;13:227.
75. van den Berg WB, McInnes IB. Th17 cells and IL-17 a–focus on immunopathogenesis and immunotherapeutics. *Semin Arthritis Rheum*. 2013;43:158-170.
76. Gliozzi M1, Greenwell-Wild T, Jin W, et al. A link between interferon and augmented plasmin generation in exocrine gland damage in Sjögren's syndrome. *J Autoimmun*. 2013;40:122-133.
77. Wang X, Zheng XY, Ma C, et al. Mitigated Tregs and augmented Th17 cells and cytokines are associated with severity of experimental autoimmune neuritis. *Scand J Immunol*. 2014;80:180-190.
78. Alunno A, Ibba-Manneschi L, Bistoni O, et al. Mobilization of lymphatic endothelial precursor cells and lymphatic neovascularization in primary Sjögren's syndrome. *J Cell Mol Med*. 2016;20:613-622.
79. Generali E, Costanzo A, Mainetti C, Selmi C. Cutaneous and mucosal manifestations of Sjögren's syndrome. *Clin Rev Allergy Immunol*. 2017;53:357-370.
80. Greenspan JS, Daniels TE, Talal N, Sylvester RA. The histopathology of Sjögren's syndrome in labial salivary gland biopsies. *Oral Surg Oral Med Oral Pathol*. 1974;37:217-229.
81. Shen L, Suresh L. Autoantibodies, detection methods and panels for diagnosis of Sjögren's syndrome. *Clin Immunol*. 2017; 182:24-29.
82. Vivino FB, Carsons SE, Foulks G, et al. New treatment guidelines for Sjögren's disease. *Rheum Dis Clin North Am*. 2016;42:531-551.
83. Sambataro D, Sambataro G, Dal Bosco Y, Polosa R. Present and future of biologic drugs in primary Sjögren's syndrome. *Expert Opin Biol Ther*. 2017;17:63-75.
84. Verstappen GM, van Nimwegen JF, Vissink A, Kroese FGM, Bootsma H. The value of rituximab treatment in primary Sjögren's syndrome. *Clin Immunol*. 2017;182:62-71.
85. Singh AG, Singh S, Matteson EL. Rate, risk factors and causes of mortality in patients with Sjögren's syndrome: a systematic review and meta-analysis of cohort studies. *Rheumatology (Oxford)*. 2016;55:450-460.
86. Nishishinya MB, Pereda CA, Muñoz-Fernández S, et al. Identification of lymphoma predictors in patients with primary Sjögren's syndrome: a systematic literature review and meta-analysis. *Rheumatol Int*. 2015;35:17-26.
87. Ariffin H, Azanan MS, Abd Ghafar SS, et al. Young adult survivors of childhood acute lymphoblastic leukemia show evidence of chronic inflammation and cellular aging. *Cancer*. 2017;123:4207-4214.
88. Sueki Y, Nozaki Y, Kawashima I, et al. Anaplastic large cell lymphoma with paraneoplastic neutrophilia: an association between IL-17 elevation and aggressive disease progression. *Int J Hematol*. 2014;99:773-776.
89. Shang CX, Ma JC, Nan Z, Li Y, He WC, Pan XY. Change of plasma interleukin-17 level in patients with extranodal NK/T-cell lymphoma and its clinical significance. *Zhongguo Shi Yan Xue Ye Xue Za Zhi*. 2017;25:796-801.
90. Li Q, Xu X, Zhong W, et al. IL-17 induces radiation resistance of B lymphoma cells by suppressing p53 expression and thereby inhibiting irradiation-triggered apoptosis. *Cell Mol Immunol*. 2015;12:366-372.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Zhang L-W, Zhou P-R, Wei P, Cong X, Wu L-L, Hua H. Expression of interleukin-17 in primary Sjögren's syndrome and the correlation with disease severity: A systematic review and meta-analysis. *Scand J Immunol*. 2018;87: e12649. https://doi.org/10.1111/sji.12649