



# Increased circulating CXCL13 levels in systemic lupus erythematosus and rheumatoid arthritis: a meta-analysis

Yu-Qing Bao<sup>1,2</sup> · Jun-Ping Wang<sup>1,2</sup> · Zi-Wei Dai<sup>1</sup> · Yan-Mei Mao<sup>1,2</sup> · Jun Wu<sup>1,2</sup> · Heng-Sheng Guo<sup>1,2</sup> · Yuan-Rui Xia<sup>1,2</sup> · Dong-Qing Ye<sup>1,2</sup>

Received: 7 May 2019 / Revised: 3 August 2019 / Accepted: 6 September 2019 / Published online: 16 September 2019  
© International League of Associations for Rheumatology (ILAR) 2019

## Abstract

**Objectives** CXC ligand 13 (CXCL13) is known as B cell chemotactic factor (BLC), promoting the migration of B lymphocytes by communicating with its receptor CXCR5, which can be regarded as part of pathogenesis of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). This meta-analysis was to evaluate the circulating CXCL13 levels in SLE and RA.

**Methods** All articles were respectively gathered from PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) (by the end of 10 April 2019). According to random effects model, standardized mean difference (SMD) and 95% confidence interval (CI) of CXCL13 levels in SLE and RA were calculated by Stata 12.0 software.

**Results** Totally, 15 studies were selected (981 SLE patients and 380 healthy controls, 332 RA patients and 147 healthy controls). SLE and RA patients were significantly increased in circulating CXCL13 levels ( $SMD = 1.851$ , 95%  $CI$  0.604–3.098;  $SMD = 1.801$ , 95%  $CI = 1.145$ –2.457). Subgroup analyses showed that SLE patients from the Chinese group and systemic lupus erythematosus disease activity index (SLEDAI) score  $\geq 6$  group had higher circulating CXCL13 levels ( $SMD = 2.182$ , 95%  $CI$  0.135–4.229;  $SMD = 0.767$ , 95%  $CI$  0.503–1.030). However, there were no significant changes in CXCL13 concentrations in SLE patients from the English and SLEDAI score  $< 6$  group. Similarly, subgroup analyses presented that RA patients from different classifications showed higher circulating CXCL13 levels. There was no publication bias.

**Conclusions** This meta-analysis demonstrated increased circulating CXCL13 concentrations in SLE and RA patients. Circulating CXCL13 levels may act as biomarkers and therapy targets in the diagnosis and treatment of SLE and RA.

## Key Point

• First, CXC ligand 13 (CXCL13) is closely related to the pathogenesis of systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Second, this study may provide novel therapeutic targets for the treatment of SLE and RA patients. This meta-analysis provides a comprehensive analysis of circulating CXCL13 levels in patients with SLE and RA and also explores related influencing factors.

**Keywords** CXC ligand 13 · Meta-analysis · Rheumatoid arthritis · Systemic lupus erythematosus

## Introduction

The immune system is complicated, far-reaching, and difficult to predict. Multiple interconnected systems join together to

Yu-Qing Bao and Jun-Ping Wang contributed equally to this work.

✉ Dong-Qing Ye  
ydaqhmu@126.com; ydq@ahmu.edu.cn

<sup>1</sup> Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei 230032, Anhui, China

<sup>2</sup> Anhui Province Key Laboratory of Major Autoimmune Diseases, 81 Meishan Road, Hefei 230032, Anhui, China

maintain a perfect balance between physiological response and pathological autoimmunity. If not, the autoimmune disorders and consequent organ damage will follow. Hitherto, the exact causes of approximately 50% autoimmune diseases are still unknown [1]. Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are both typical chronic inflammatory autoimmune diseases. SLE or lupus is a progressive and lifelong autoimmune disorder, gradually damaging multiple organs including bones, muscles, heart, kidney, nerves, and blood [2–5] with a broad range of clinical manifestations, such as fatigue, fever, anorexia, dermatopathy, systemic infection, glomerulonephritis or nephrotic syndrome symptoms, myalgia or myasthenia, pericarditis or pericardial effusion, and neuronal damage [5]. RA is a long-lasting inflammatory joint

disease. If failure to control the disorder progression, the cartilage and bone will suffer heavy damage and eventually patients in RA even become disabled. At the outset, RA involves the joints. Subsequently, extra syndromes will occur, manifestations including rheumatoid nodules, pulmonary vasculitis, and the like. For now, because of the complicated pathogenesis of SLE and RA, it is difficult to identify and clarify accurate etiology, especially in the case of unhealable infection and electrolyte disturbance [6].

The etiology of autoimmune diseases is very complex, but the activation of autoimmune T cells and B cells is an inevitable part. Cytokines, including chemotactic factor synthesized and secreted by various immune or non-immune cells, are involved in a variety of immune responses. CXC chemotactic cytokine subfamily mainly acts on neutrophils and has a chemotactic effect on lymphocytes; CXC ligand 13 (CXCL13) is one of which, also known as B cell chemotactic factor (BLC). CXCL13 promotes the migration and aggregation of B lymphocytes by interacting with its receptor CXCR5, leading to the formation of germinal centers. Meanwhile, the germinal centers promote the further differentiation of B lymphocytes into plasma cells to produce corresponding antibody mountains. Thus, CXCL13 and CXCR5 play a key role in the differentiation of B lymphocytes into plasma cells to generate antibodies. The occurrence of SLE and RA is likely to be related to the over expression of CXCL13 and CXCR5 by generating an over-strong immune auxiliary effect. These discoveries provide strong evidence that CXCL13 will become an effective target for the treatment of SLE and RA [7, 8]. In the previous several decades, several studies have contributed to studying the CXCL13 expression level in many autoimmune diseases, especially in SLE and RA. Increased circulating CXCL13 levels in RA and SLE patients have been reported. Nevertheless, these reported results were individualized. Although there were three reviews having reported the association of circulating CXCL13 level with SLE [9–11], there is no quantitative analysis like a meta-analysis. In order to systematically quantify and evaluate the relationship between the circulating CXCL13 levels in SLE and RA, this article will employ a meta-analysis to acquire a more accurate and convincing estimation of the contact between circulating CXCL13 levels and SLE and RA.

## Materials and methods

### Search strategy

We searched PubMed, Web of Science, and China National Knowledge Infrastructure respectively to derive relevant articles up to 10 April 2019. “B lymphocyte chemoattractant,” “CXC ligand 13,” “CXCL13,” “BLC,” “BCA-1,” “Systemic Lupus Erythematosus,” “SLE,” “lupus,” “lupus nephritis,”

“Rheumatoid Arthritis,” and “RA” were all used as keys terms to look for related and eligible articles, increasing the opportunity for searching out more articles. For fear that we might miss some suitable articles, the references of the selected articles were screened carefully to ensure the reliability and validity of this meta-analysis.

### Inclusion criteria and exclusion criteria

Articles included in this meta-analysis were bound to meeting the following requirements: (a) case-control or cross-sectional studies; (b) studies based on adults; (c) SLE and RA patients must conform to the American College of Rheumatology (ACR) criteria or European League Against Rheumatism (EULAR) or Systemic Lupus International Collaborating Clinics (SLICC); (d) complete serum or plasma CXCL13 concentrations of both patients and controls were available; (e) if one article has published more than one time, we only used the latest edition.

Articles excluded in this meta-analysis are as follows: (a) reviews; (b) subjects are not humans; (c) lack of healthy controls. Detailed flow chart of article inclusion and exclusion process was presented in Fig. 1.

### Data extraction

From the eligible articles, the information was presented and listed as below: first author’s name and year of publication, region and ethnicity, kind of disease, language, original indicators, number of subjects, the mean age ( $\pm$  standard deviation), sex ratio, SLEDAI or disease activity score 28 (DAS28) score, duration years, assay method, study type, criteria for the classification of SLE or RA, and the mean CXCL13 concentrations ( $\pm$  standard deviation). It is worth noting that when the original full text only included median and inter-quartile range or median and range, we transformed the given data to figure out useful values [12]. On the basis of Newcastle-Ottawa scale (NOS), we assessed the methodological quality of all the selected articles. When divergence appeared, we strived to reach an agreement after panel discussion.

### Statistical analysis

For each article, the standardized mean difference (SMD) and 95% confidence intervals (95% CI) were elaborately shown by forest plot. The formula  $I^2 = ([Q - df]) \times 100\%$  was used to quantify the effect of heterogeneity once more. Assuming that the heterogeneity is significant ( $P < 0.05$ ), the random effects model was adopted to pool the SMD value; or else, the fixed-effect model was adopted. In order to evaluate the publication bias, Egger’s and Begg’s tests were used. Stata 12.0 software was used in this meta-analysis to perform all statistical analysis.

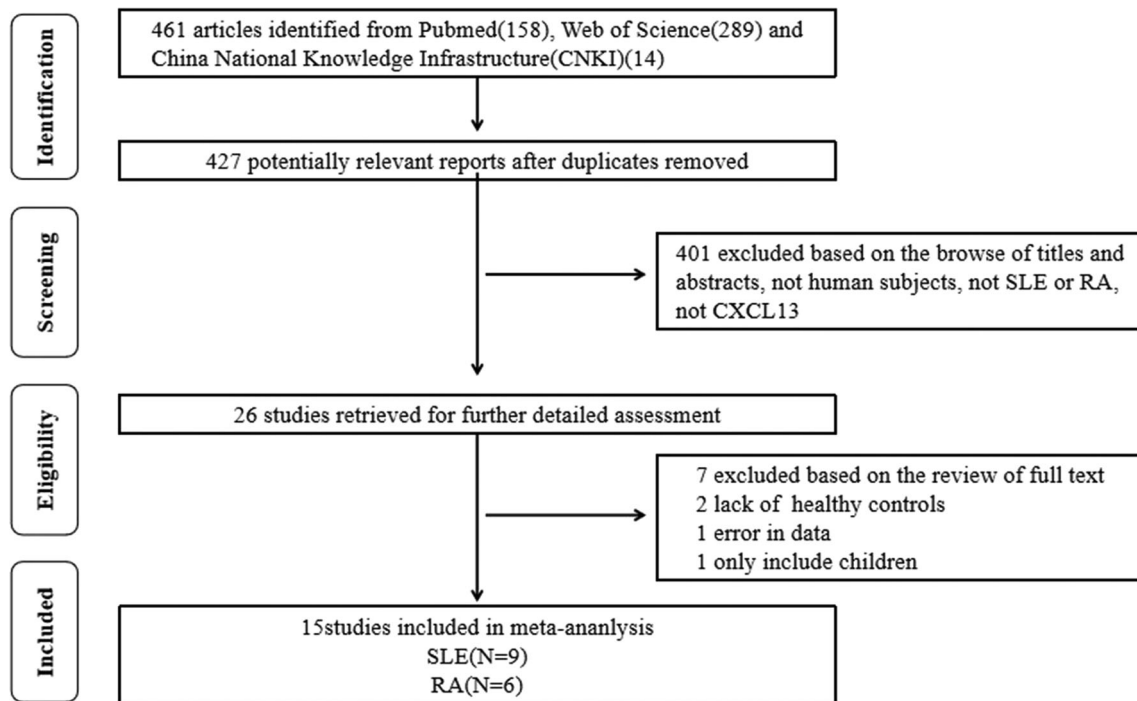


Fig. 1 Flowchart of selected articles

## Results

### Study characteristics

A total of 461 articles were retrieved from PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI); 435 articles were filtered out for the following reasons: duplicates, reviews, non-human subjects, and not SLE or RA. After carefully examining each article's title, abstract, and its full text, 15 eligible studies were included from the remaining 26 articles. Eventually, 981 SLE patients and 380 healthy controls as well as 332 RA patients and 147 healthy controls were chosen in this meta-analysis (Fig. 1). All of the 15 studies included were case-control studies; all of the diagnostic criteria for SLE and RA was ACR. Some studies also adopted EULAR or SLICC as criteria. The basic features of articles needed in this meta-analysis were shown in Table 1. Extracted data on circulating CXCL13 levels of 15 studies in this meta-analysis was presented in Table 2.

### Quality evaluation of included articles

A total of 15 articles were included in this meta-analysis, all of which were case-control studies. Of the 15 articles, 9 were SLE cases and 6 were RA cases. In these studies, the serum or plasma CXCL13 concentrations were all tested by ELISA. Studies included were almost gender and age matched. NOS scores of 15 studies are presented in Table 1.

### Meta-analysis results

All the meta-analysis results of SLE and RA were respectively presented in Table 3. The forest plots visually showed the significant heterogeneity (Figs. 2 and 3).

### Analysis in SLE

Among the included 9 studies, a significant statistical heterogeneity was discovered, which cannot be neglected ( $P < 0.001$ ,  $I^2 = 98.4\%$ ) (Table 3). Consequently, the random effects model was adopted for data analyzing, demonstrating that circulating CXCL13 concentrations in patients were significantly higher than that in control groups ( $SMD = 1.851$ , 95%  $CI$  0.604–3.098) (Fig. 2). For the sake of exploring the exact sources of heterogeneity, subgroup analyses were implemented. When classified by language and SLEDAI score, the Chinese group and SLEDAI score  $\geq 6$  group all had higher circulating CXCL13 levels respectively ( $SMD = 2.182$ , 95%  $CI$  0.135–4.229;  $SMD = 0.767$ , 95%  $CI$  0.503–1.030). When stratified by ethnicity, sample size, and original indicators, all patients in SLE showed increased circulating CXCL13 levels ( $SMD = 2.175$ , 95%  $CI$  0.540–3.809;  $SMD = 0.746$ , 95%  $CI$  0.451–1.041;  $SMD = 2.336$ , 95%  $CI$  0.544–4.128;  $SMD = 0.882$ , 95%  $CI$  0.576–1.187;  $SMD = 3.090$ , 95%  $CI$  0.437–5.743;  $SMD = 0.842$ , 95%  $CI$  0.619–1.066). However, there were no significant differences in the English group and SLEDAI score  $< 6$  group (Table 3). In order to investigate the publication bias, Egger's test

Table 1 Characteristics of included studies

Author (year)	Region (ethnicity)	Disease	Language	Original indicators	Case		Control		Assay method	Serum or plasma	Study type	Criteria for the classification of SLE or RA	NOS Ref.	
					Age (mean $\pm$ SD) years	Sex ratio (F/M)	SLEDAI or DAS 28 score	Duration (mean $\pm$ SD) years						Age (mean $\pm$ SD) years
Schiffer et al. (2009)	Hannover (Europe)	SLE	English	No mean $\pm$ SD	50 $\pm$ 22	80/11	7.0 $\pm$ 7.5	NA	45 $\pm$ 21	26/14	ELISA	Serum	Case-control ACR	7 [13]
Lee et al. (2010)	Taipei (Asia)	SLE	English	Mean $\pm$ SD	38 $\pm$ 13	399/26	5.6 $\pm$ 4.1	7.8 $\pm$ 6.6	43 $\pm$ 13	97/9	ELISA	Serum	Case-control ACR	6 [14]
Wong et al. (2010)	Hongkong (Asia)	SLE	English	No mean $\pm$ SD	41 $\pm$ 10	31/4	3.1 $\pm$ 3.0	12.0 $\pm$ 7.0	46 $\pm$ 7	23/0	ELISA	Plasma	Case-control ACR (1982)	5 [15]
Schiffer et al. (2011)	Hannover (Europe)	SLE	English	No mea $\pm$ SD	48 $\pm$ 25	34/3	8.8 $\pm$ 16.2	NA	42 $\pm$ 34	26/14	ELISA	Serum	Case-control ACR	7 [16]
Run et al. (2015)	Xiangyang (Asia)	SLE	Chinese	Mean $\pm$ SD	36 $\pm$ 5	32/48	NA	NA	36 $\pm$ 4	28/22	ELISA	Serum	Case-control ACR (1997)	7 [17]
Xie et al. (2015)	Shenzhen (Asia)	SLE	Chinese	Mean $\pm$ SD	32 $\pm$ 10	54/4	NA	NA	26 $\pm$ 5	19/3	ELISA	Serum	Case-control ACR (1982)	5 [18]
Dong et al. (2016)	Yantai (Asia)	SLE	Chinese	Mean $\pm$ SD	36 $\pm$ 6	76/14	NA	NA	36 $\pm$ 8	40/20	ELISA	Serum	Case-control ACR (1997)	5 [19]
Fang et al. (2017)	Fujian (Asia)	SLE	English	No mea $\pm$ SD	31 $\pm$ 8	32/4	8.3 $\pm$ 6.2	NA	42 $\pm$ 43	16/2	ELISA	Serum	Case-control ACR/SIJCC (2009)	7 [20]
He et al. (2018)	Pingxiang (Asia)	SLE	Chinese	No mean $\pm$ SD	NA	NA	NA	NA	NA	NA	ELISA	Serum	Case-control ACR (1997)	7 [21]
Rioja (2008)	Sheffield (Europe)	RA	English	No mean $\pm$ SD	64 $\pm$ 13	34/10	NA	NA	62 $\pm$ 13	13/3	ELISA	Plasma	Case-control ACR	8 [22]
Sahar et al. (2013)	Cairo (Africa)	RA	English	Mean $\pm$ SD	38 $\pm$ 10	NA	5.4 $\pm$ 0.9	NA	38 $\pm$ 10	NA	ELISA	Serum	Case-control ACR/EULAR	7 [23]
Nahed et al. (2013)	Cairo (Africa)	RA	English	Mean $\pm$ SD	44 $\pm$ 13	14/1	5.1 $\pm$ 0.9	6.1 $\pm$ 4.9	42 $\pm$ 12	9/1	ELISA	Plasma	Case-control ACR/EULAR	7 [24]
Zhang et al. (2013)	Hefei (Asia)	RA	Chinese	Mean $\pm$ SD	54 $\pm$ 14	81/21	NA	NA	55 $\pm$ 13	41/9	ELISA	Serum	Case-control ACR/EULAR (2009)	7 [25]
An et al. (2018)	Zhengzhou (Asia)	RA	Chinese	Mean $\pm$ SD	50 $\pm$ 15	61/20	NA	NA	49 $\pm$ 14	16/5	ELISA	Serum	Case-control ACR	7 [26]
Shadia et al. (2019)	Mansoura (Africa)	RA	English	Mean $\pm$ SD	39 $\pm$ 8	46/14	NA	4.4 $\pm$ 5.7	NA	NA	ELISA	Serum	Case-control ACR/EULA (2010)	7 [27]

**Abbreviations:** NA, not available; NOS, Newcastle-Ottawa Scale; SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; ELISA, enzyme-linked immunosorbent assay; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; SIJCC, Systemic Lupus International Collaborating Clinics; CXCL13, CXCL ligand 13; SLEDAI, SLE disease activity index; DAS 28, Disease Activity Score 28

**Table 2** Extracted data on circulating CXCL13 levels of 15 studies in this meta-analysis

Author	Case			Control		
	<i>N</i>	Mean (pg/ml)	SD (pg/ml)	<i>N</i>	Mean (pg/ml)	SD (pg/ml)
SLE						
Schiffer et al.	91	167.0	218.1	40	33.3	11.1
Lee et al.	405	168.5	14.5	106	107.4	8.8
Wong. et al.	35	109.1	69.1	23	49.2	19.6
Schiffer et al.	37	167.6	253.0	50	33.4	10.8
Run et al.	80	523.0	71.0	50	128.0	15.0
Xie et al.	58	247.7	176.5	22	167.2	145.4
Dong et al.	90	283.6	184.1	60	210.6	100.2
Fang et al.	36	310.6	375.2	18	49.1	35.4
He et al.	114	248.2	164.8	11	93.8	58.8
RA						
Rioja(2008)	44	74.6	32.0	16	43.3	12.9
Sahar et al.	30	165.4	49.4	20	15.7	5.9
Nahed et al.	15	164.7	90.7	10	11.5	2.2
Zhang et al.	102	242.2	119.9	50	131.6	34.6
An et al.	81	97.2	54.4	21	42.9	10.7
Shadia et al.	60	164	81.1	30	30.4	13.5

*N*, number; *SD* standard deviation

and Begg's test were both performed simultaneously. (Egger's  $t = 0.34$ ,  $P = 0.744$ ; Begg's  $z = 1.56$ ,  $P = 0.118$ ), indicating there was no publication bias.

### Analysis in RA

Obviously, the heterogeneity among the 6 studies was found to be of great difference ( $P < 0.001$ ,  $I^2 = 86.5\%$ ) (Table 3). Therefore, random effects model was chosen, ensuing that similar results were acquired exactly as that analyzed in RA: higher circulating CXCL13 concentrations in RA patients ( $SMD = 1.801$ , 95%  $CI = 1.145-2.457$ ) (Fig. 3). Accordingly, subgroup analyses, stratified by ethnicity, sample size, and original indicator, were also performed to explore the latent confounders. Results showed that RA patients in all groups had higher circulating CXCL13 concentrations ( $SMD = 1.105$ , 95%  $CI 0.841-1.369$ ;  $SMD = 2.645$ , 95%  $CI 1.503-3.788$ ;  $SMD = 1.384$ , 95%  $CI 0.838-1.929$ ;  $SMD = 2.355$ , 95%  $CI 0.685-4.026$ ;  $SMD = 1.962$ , 95%  $CI 1.175-2.749$ ;  $SMD = 1.105$ , 95%  $CI 0.499-1.712$ ) (Table 3). In order to ensure the accuracy, we used Egger's test and Begg's test to examine publication bias. Egger's  $t = 2.23$   $P = 0.090$ ; Begg's  $z = 1.50$ ,  $P = 0.133$  showing no publication bias.

### Discussion

CXCL13 is a B cell chemokine, which was first discovered in 1998. It is one of the members of the chemokine CXC family.

Current studies at home and abroad have shown that CXCL13 plays an important role in autoimmune diseases, especially in SLE and RA [28–30]. In 2001, Japanese scholars Ishikawa et al. [31] found that CXCL13 levels in the kidney of lupus BWF1 mice in the elderly group were higher than that in the young group. It was the first time connecting CXCL13 with SLE. In 2009, some German scholars Schiffer et al. [13] respectively detected the serum concentrations of CXCL13 in 91 SLE patients and 40 normal controls with the results showing that the serum CXCL13 concentrations in SLE patients were significantly higher, especially patients with LN. Moreover, CXCL13 level had a positive correlation with SLEDAI score and level of antibody against double-stranded (ds) DNA, which were statistically verified [9]. In 2015, the experiment of Wu et al. [32] in vivo found the decreased urinary protein, serum creatinine, and anti-dsDNA as well as the decreased deposition of kidney immune complex and secretion of inflammatory factor (IL-1, IL-6, IL-17, IL-33) in MRL/lpr mice after vaccinating, which fully indicating CXCL13 participated in the pathological process of SLE, and the application of anti-CXCL13 antibody might have certain therapeutic effect [29]. Based on these studies, CXCL13 is expected to become a new biomarker for SLE, even may reflect the degree of disease activity and renal involvement [32]. Edwards et al. [33] have proven that B cell-targeted therapy was highly effective to prevent disease progression in the treatment of RA. Rituximab was a successful example, contributing to managing 80% RA patients safely. CXCL13 is a critical B lymphocyte chemoattractant, playing vital role in

**Table 3** Subgroup analysis of CXCL13 levels in SLE and RA

Diseases	Stratification group	N	SMD (95% CI)	Heterogeneity test	
				P	I <sup>2</sup> (%)
SLE	Total		1.851 (0.604 to 3.098)	< 0.001	98.4
Ethnicity	Asia	7	2.175 (0.540 to 3.809)	< 0.001	98.7
	Europe	2	0.746 (0.451 to 1.041)	0.919	0.0
	Combined	9	1.851 (0.604 to 3.098)	< 0.001	98.4
Language	English	4	1.595 (− 0.130 to 3.319)	< 0.001	98.6
	Chinese	5	2.182 (0.135 to 4.229)	< 0.001	98.3
	Combined	9	1.851 (0.604 to 3.098)	< 0.001	98.4
Sample size	≥ 50	3	2.336 (0.544 to 4.128)	< 0.001	99.0
	< 50	6	0.882 (0.576 to 1.187)	0.685	0.0
	Combined	9	1.851 (0.604 to 3.098)	< 0.001	98.4
Original indicators	Mean ± SD	4	3.090 (0.437 to 5.743)	< 0.001	99.3
	Not mean ± SD	5	0.842 (0.619 to 1.066)	0.863	0.0
	Combined	9	1.851 (0.604 to 3.098)	< 0.001	98.4
SLEDAI score	≥ 6	3	0.767(0.503 to 1.030)	0.950	0.0
	< 6	2	2.809(− 0.556 to 6.174)	< 0.001	99.0
	Combined	5	1.595(− 0.130 to 3.319)	< 0.001	98.6
RA	Total		1.801(1.145 to 2.457)	< 0.001	86.5
Ethnicity	Europe and Asia	3	1.105(0.841 to 1.369)	1.000	0.0
	Africa	3	2.645(1.503 to 3.788)	0.003	82.7
	Combined	6	1.801(1.145 to 2.457)	< 0.001	86.5
Sample size	≥ 50	3	1.384(0.838 to 1.929)	0.015	76.2
	< 50	3	2.355(0.685 to 4.026)	< 0.001	91.4
	Combined	6	1.801(1.145 to 2.457)	< 0.001	86.5
Original indicators	Mean ± SD	5	1.962(1.175 to 2.749)	< 0.001	88.8
	No mean ± SD	1	1.105(0.499 to 1.712)	NA	NA
	Combined	6	1.801(1.145 to 2.457)	< 0.001	86.5

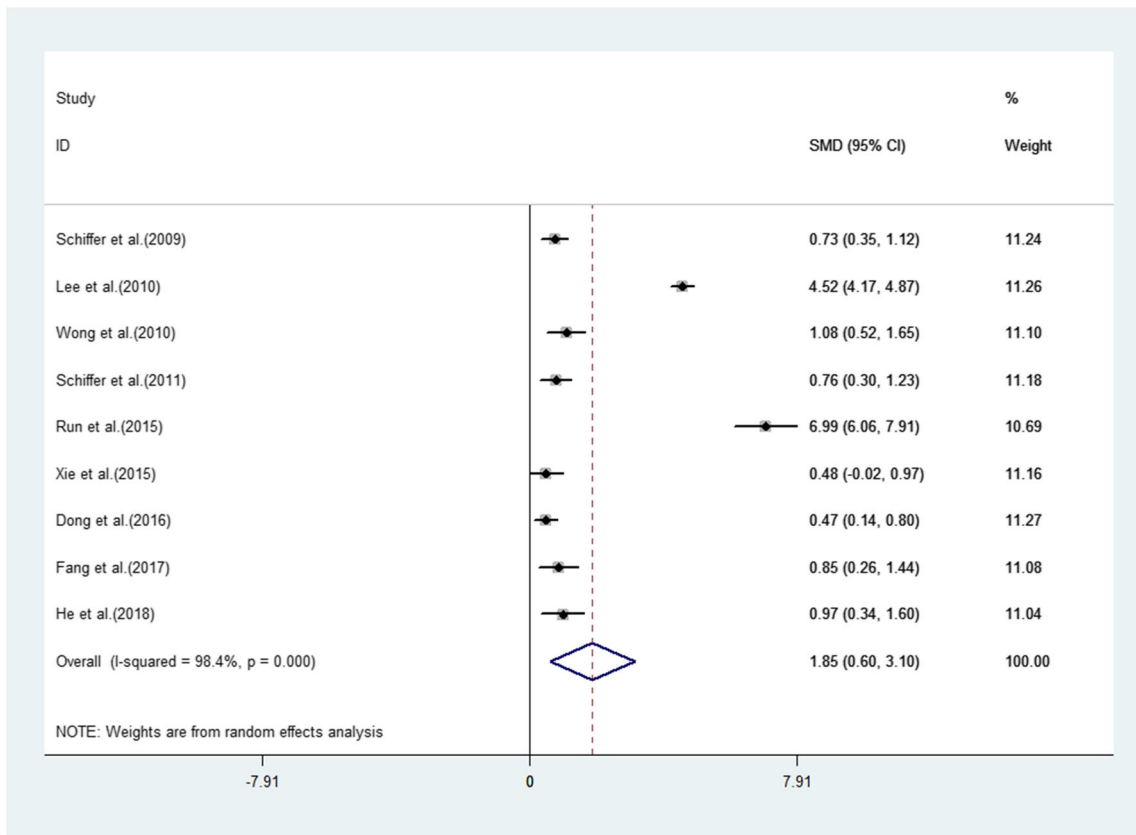
NA, not available; SLEDAI, SLE disease activity index; SD, standard difference; CI, confidence interval

the formation of B cell follicles in the lymphoid tissues. CXCL13 may serve as a novel biomarker to predict diseases severity. Jones et al. [34–37] also illustrated a similar perspective.

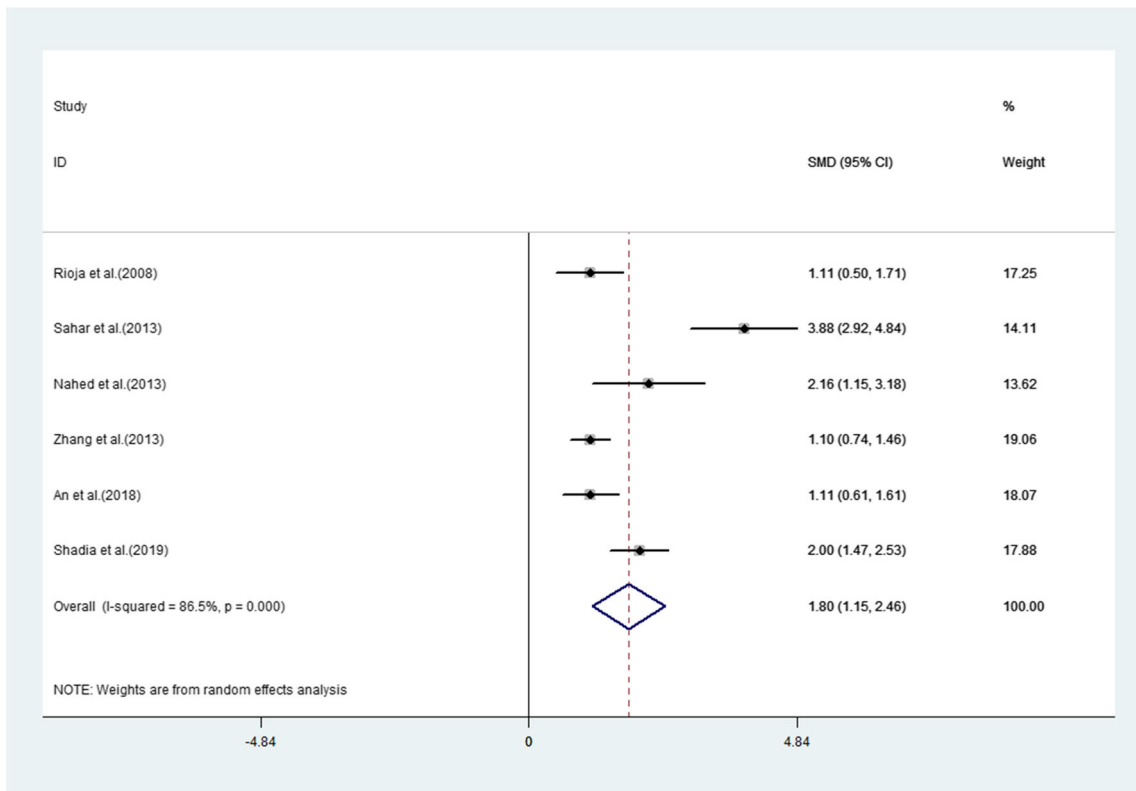
The pathogenic mechanism of SLE and RA is complex and influenced by multiple etiology, such as environment, genetics, epigenetics, endocrine, hormone, and individual susceptibility [1, 38, 39]. At present, 40% RA patients still have not received regular and reasonable treatment in China [40].

Various studies have reported that chemokine CXC family and corresponding receptors played a key role in the disease manifestation and progression. As it is well-known, SLE and RA are featured by the elevated production of auto-antibodies, which were generated long before clinical symptoms, resulting in more chronic and serious consequences. During the last decades, more than 150 auto-antibodies have been found in SLE, especially anti-dsDNA antibody, a sensitive biomarker to detect disease activity in SLE [9]. Different





**Fig. 2** Forest plot of 9 studies in circulating CXCL13 levels for SLE patients versus healthy controls, based on random effects model



**Fig. 3** Forest plot of 6 studies in circulating CXCL13 levels for RA patients versus healthy controls, based on random effects model

studies have indicated that Sjogren's syndrome (SS), adult-onset still's disease [41], SLE, and RA have association with members of CXC chemokines family and related receptors. Although CXCL13 has not been used in clinical practice, it cannot be denied that it is a very potential and promising biomarker. If ruling out serious infection and other diseases, CXCL13 is of great value for the diagnosis and prognosis of LN patients. In addition, anti-CXCL13 antibody can block CXCL13 and CXCR5 interaction and signaling pathway, which may provide a new therapeutic target for LN patients [10]. Synovitis is a common clinical manifestation in RA patients, characteristic of the formation of lymphoid follicles. In this process, CXCL13 plays a critical role by migrating B cells and T follicular helper cells to the follicle; thus, it can be shown that CXCL13 is expected to become a new biomarker for the early RA [34]. But without ignorance, CXCL13 plays a key role in the differentiation of B lymphocytes into plasma cells to generate antibodies. When generating an abnormal immune auxiliary effect, autoimmune diseases will occur consequently. Although this study proved that circulating CXCL13 levels may be of great value to the diagnosis of RA and SLE, we still need to pay attention to the differential diagnosis of autoimmune diseases.

In the meta-analysis, there were 15 articles selected in this study eventually, including 9 articles related to SLE and 6 articles related to RA. We estimated the association of circulating CXCL13 level with SLE and RA. The final results turned out to correspond with the original assumptions that there was correlation between CXCL13 levels and SLE ( $SMD = 1.851$ , 95%  $CI 0.604–3.098$ ) as well as RA ( $SMD = 1.801$ , 95%  $CI = 1.145–2.457$ ), suggesting that SLE and RA patients were significantly increased in circulating CXCL13 levels. Although Schiffer et al. [9], Li et al. [10], and Worthmann et al. [11] have never discussed this topic before, they just generalized and summarized rather than providing accurate quantitative description. In this study, the potential sources of heterogeneity were further explored due to strong heterogeneity. Therefore, subgroup analyses were performed to evaluate the exact sources of heterogeneity, and to minimize the potential confounding factors. For patients with SLE, we found that when classified by language and SLEDAI score, both the Chinese group and SLEDAI score  $\geq 6$  group had higher circulating CXCL13 levels. However, there were no significant differences in the English group and SLEDAI score  $< 6$  group. This finding suggested that ethnicity and SLEDAI score may be associated with circulating CXCL13 concentrations in SLE. For patients with RA, subgroup analyses, stratified by ethnicity, sample size, and original indicator, suggested that patients with RA in all subgroups had higher circulating CXCL13 concentrations. Furthermore, due to the limited data included in the selected studies, only five studies related to SLE were stratified by SLEDAI and only one study with the original indicator of mean (95% confidence interval), which may have a negative impact on the final results. Considering renal involvement is a

common clinical manifestation of SLE, lupus nephritis was also included in this study. It is worth noting that both Egger's test and Begg's test were implemented to prove no publication bias.

Admittedly, this article had some unavoidable limitations. First, we only retrieved three databases so the literature included might be not complete enough. Second, patients with LN or without LN might have a significant difference in CXCL13 concentrations; we could not guarantee that all articles included paid attention to this key point. Third, due to the lack of explicit data, we were incapable of analyzing the relationship DAS28 disease duration, some clinical symptoms and environmental characteristics with circulating CXCL13 levels of patients with SLE and RA, which might exactly be the sources of heterogeneity. Fourth, part of the data used in meta-analysis was approximate, resulting in a deviation. Fifth, the results of the pooled *SMD* in SLE and RA patients could rather be conservative because of using the random effects model.

In spite of these disadvantages above, this article also had advantages. First, it was the first comprehensive meta-analysis to clarify the relationship of CXCL13 concentrations with SLE and RA. Second, we included diverse literature from different countries, such as Egypt, America, Germany, and China. Third, no publication bias has been found, suggesting that there was no bias in selected articles.

## Conclusions

In summary, circulating CXCL13 level is higher in patients with SLE or RA, which may be prospective to become a novel auxiliary biomarker. More importantly, a new therapeutic target inspiring from CXCL13 nosogenesis can be detected and put into clinical practice.

**Acknowledgments** Thanks to the selfless help of the lab teachers and classmates.

**Funding information** This meta-analysis was funded by the Chinese national high level personnel special support plan.

## Compliance with ethical standards

**Disclosures** None.

## References

1. Coronel-Restrepo N, Posso-Osorio I, Naranjo-Escobar J, Tobón GJ (2017) Autoimmune diseases and their relation with immunological, neurological and endocrinological axes. *Autoimmun Rev* 16(7):684–692. <https://doi.org/10.1016/j.autrev.2017.05.002>
2. Agmon-Levin N, Blank M, Paz Z, Shoenfeld Y (2009) Molecular mimicry in systemic lupus erythematosus. *Lupus* 18(13):1181–1185. <https://doi.org/10.1177/0961203309346653>



3. D'Cruz DP, Khamashta MA, Hughes GR (2007) Systemic lupus erythematosus. *Lancet* 369(9561):587–596
4. Chines Society of rheumatology (2003) Guidelines for the diagnosis and treatment of systemic lupus erythematosus. *Chin J Rheumatol* 7(8):508–513
5. Fortuna G, Brennan MT (2013) Systemic lupus erythematosus: epidemiology, pathophysiology, manifestations, and management. *Dent Clin N Am* 57(4):631–655. <https://doi.org/10.1016/j.cden.2013.06.003>
6. Smolen JS, Aletaha D, McInnes IB (2016) Rheumatoid arthritis. *Lancet* 388(10055):2023–2038. [https://doi.org/10.1016/s0140-6736\(16\)30173-8](https://doi.org/10.1016/s0140-6736(16)30173-8)
7. Shi K, Hayashida K, Kaneko M, Hashimoto J, Tomita T, Lipsky PE, Yoshikawa H, Ochi T (2001) Lymphoid chemokine B cell-attracting chemokine-1 (CXCL13) is expressed in germinal center of ectopic lymphoid follicles within the synovium of chronic arthritis patients. *J Immunol* 166(1):650–655. <https://doi.org/10.4049/jimmunol.166.1.650>
8. Zhang X, Yang CX (2016) Research progress of CXCL-13 antibody in the treatment of autoimmune disease. *Pract Pharm Clin Remed* 19(8):1046–1049. <https://doi.org/10.14053/j.cnki.ppcr.201608032>
9. Schiffer L, Worthmann K, Haller H, Schiffer M (2015) CXCL13 as a new biomarker of systemic lupus erythematosus and lupus nephritis from bench to bedside? *Clin Exp Immunol* 179(1):85–89. <https://doi.org/10.1111/cei.12439>
10. Li LL (2016) Studies on the relationship between CXCL13 and systemic lupus erythematosus. *J Nantong Univ (Med Sci)* 36(4):287–290. <https://doi.org/10.16424/j.cnki.cn32-1087/r.2016.04.013>
11. Worthmann K, Gueler F, von Vietinghoff S, Davalos-MiBlitz A, Wiehler F, Davidson A, Witte T, Haller H, Schiffer M, Falk CS, Schiffer L (2014) Pathogenetic role of glomerular CXCL13 expression in lupus nephritis. *Clin Exp Immunol* 178(1):20–27. <https://doi.org/10.1111/cei.12380>
12. Luo DH, Wan X, Liu JM, Tong TJ (2017) How to estimate the sample mean and standard deviation from the sample size, median, extremes or quartiles. *Chin J Evid Based Med* 17(11):1350–1355
13. Schiffer L, Kumpers P, Davalos-MiBlitz AM, Haubitz M, Haller H, Anders HJ, Witte T, Schiffer M (2009) B-cell-attracting chemokine CXCL13 as a marker of disease activity and renal involvement in systemic lupus erythematosus (SLE). *Nephrol Dial Transplant* 24(12):3708–3712. <https://doi.org/10.1093/ndt/gfp343>
14. Lee HT, Shiao YM, Wu TH, Chen WS, Hsu YH, Tsai SF, Tsai CY (2010) Serum BLC/CXCL13 concentrations and renal expression of CXCL13/CXCR5 in patients with systemic lupus erythematosus and lupus nephritis. *J Rheumatol* 37(1):45–52. <https://doi.org/10.3899/jrheum.090450>
15. Wong CK, Wong PT, Tam LS, Li EK, Chen DP, Lam CW (2010) Elevated production of B cell chemokine CXCL13 is correlated with systemic lupus erythematosus disease activity. *J Clin Immunol* 30(1):45–52. <https://doi.org/10.1007/s10875-009-9325-5>
16. Schiffer L, Kielstein JT, Haubitz M, Lührs H, Witte T, Haller H, Kumpers P, Schiffer M (2011) Elevation of serum CXCL13 in SLE as well as in sepsis. *Lupus* 20(5):507–511. <https://doi.org/10.1177/0961203310383301>
17. Run YM, Rao H, Jiang H, Zhu YF, Cao H, Wang JM (2015) Detection of serum chemokine CXCL family contents in patients with systemic lupus erythematosus and its clinical significance. *J Hainan Med Univ* 21(12):1733–1736. <https://doi.org/10.13210/j.cnki.jhmu.20150827.006>
18. Xie WY, Nie LP, Yang YH (2015) The study of circulating CXCL13 level and expression of its receptor CXCR5 with system lupus erythematosus. *Chin J Lab Diagn* 19(10):1689–1692.6
19. Dong DQ, Zhang JM, Li HY, Sun WK (2016) Expressions of CXCR5 mRNA and CXCL13 mRNA in patients with systemic lupus erythematosus. *Chin J Clinic (Electronic Edition)* 10(18):2700–2704. <https://doi.org/10.3877/cma.j.issn.1674-0785.2016.18.005>
20. Fang C, Luo T, Lin L (2017) The correlational research among serum CXCL13 levels, circulating plasmablasts and memory B cells in patients with systemic lupus erythematosus: a STROBE-compliant article. *Medicine(Baltimore)* 96(48):e8675. <https://doi.org/10.1097/MD.00000000000008675>
21. He DN, Hu JK, Zhu JR, Dai SH, Liu YW, Hu N (2018) Serum CXCL13 and renal involvement in lupus nephritis. *Jiangxi Med J* 53(8):822–824+833. <https://doi.org/10.3969/j.issn.1006-2238.2018.8.012>
22. Rioja I, Hughes FJ, Sharp CH, Warnock LC, Montgomery DS, Akil M, Wilson AG, Binks MH, Dickson MC (2008) Potential novel biomarkers of disease activity in rheumatoid arthritis patients: CXCL13, CCL23, transforming growth factor alpha, tumor necrosis factor receptor superfamily member 9, and macrophage colony-stimulating factor. *Arthritis Rheum* 58(8):2257–2267. <https://doi.org/10.1002/art.23667>
23. Ahmed SF, Badr T, Hosny SM, Hamayed HFA (2013) Assessment of synovitis in early rheumatoid arthritis by CXCL13 serum levels and power Doppler ultrasonography: correlation with disease activity. *Egypt Rheumatologist* 35(1):21–27. <https://doi.org/10.1016/j.ejr.2012.09.001>
24. Sherif NM, Arafa MM, Ibrahim SE, Moussa SG (2013) CXC ligand 13 in rheumatoid arthritis and its relation to secondary Sjögren's syndrome. *Egypt Rheumatologist* 35(3):121–126. <https://doi.org/10.1016/j.ejr.2013.03.004>
25. Zhang MM, Zhang R, Xu JH (2013) Study of serum IL32 and chemokine CXCL13 in patients with rheumatoid arthritis. *Acta Univ Med Anhui* 48(12):1512–1515. <https://doi.org/10.19405/j.cnki.issn1000-1492.2013.12.024>
26. An LM, Chu TS, Liu W, Liu B, Zhu Q (2018) Expression and significance of serum CXCL13 in rheumatoid arthritis. *J Chin Pract Diagn* 32(3):248–250. <https://doi.org/10.13507/j.issn.1674-3474.2018.03.012>
27. Allam SI, Sallam RA, Elghannam DM, El-Ghaweet AI (2019) Clinical significance of serum B cell chemokine (CXCL13) in early rheumatoid arthritis patients. *Egypt Rheumatologist* 41(1):11–14. <https://doi.org/10.1016/j.ejr.2018.04.003>
28. Worthmann K, Gueler F, von Vietinghoff S, Davalos-MiBlitz A, Wiehler F, Davidson A, Witte T, Haller H, Schiffer M, Falk CS, Schiffer L (2014) Pathogenetic role of glomerular CXCL13 expression in lupus nephritis. *Clin Exp Immunol* 178(1):20–27. <https://doi.org/10.1111/cei.12380>
29. Oglesby A, Shaul AJ, Pokora T, Paramore C, Cragin L, Dennis G, Narayanan S, Weinstein A (2013) Adverse event burden, resource use, and costs associated with immunosuppressant medications for the treatment of systemic lupus erythematosus: a systematic literature review. *Int J Rheumatol*:347520. <https://doi.org/10.1155/2013/347520>
30. Latek D, Modzelewska A, Trzaskowski B, Palczewski K, Filipek S (2012) G protein-coupled receptors—recent advances. *Acta Biochim Pol* 59(4):515–529
31. Ishikawa S, Sato T, Abe M, Nagai S, Onai N, Yoneyama H, Zhang Y, Suzuki T, Hashimoto S, Shirai T, Lipp M, Matsushima K (2001) Aberrant high expression of B lymphocyte chemokine (BLC/CXCL13) by C11b+CD11c+ dendritic cells in murine lupus and preferential chemotaxis of B1 cells towards BLC. *J Exp Med* 193(12):1393–1402
32. Wu X, Guo J, Ding R, Lv B, Bi L (2015) CXCL13 blockade attenuates lupus nephritis of MRL/lpr mice. *Acta Histochem* 117(8):732–737. <https://doi.org/10.1016/j.acthis.2015.09.001>
33. Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR, Stevens RM, Shaw T (2004) Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 350(25):2572–2581

34. Jones JD, Hamilton BJ, Challener GJ, de Brum-Fernandes AJ, Cossette P, Liang P, Masetto A, Ménard HA, Carrier N, Boyle DL, Rosengren S, Boire G, Rigby WF (2014) Serum C-X-C motif chemokine 13 is elevated in early and established rheumatoid arthritis and correlates with rheumatoid factor levels. *Arthritis Res Ther* 16(2):R103. <https://doi.org/10.1186/ar4552>
35. Bugatti S, Manzo A, Benaglio F, Klersy C, Vitolo B, Todoerti M, Sakellariou G, Montecucco C, Caporali R (2012) Serum levels of CXCL13 are associated with ultrasonographic synovitis and predict power Doppler persistence in early rheumatoid arthritis treated with non-biological disease-modifying anti-rheumatic drugs. *Arthritis Res Ther* 14(1):R34. <https://doi.org/10.1186/ar3742>
36. Bugatti S, Manzo A, Vitolo B, Benaglio F, Binda E, Scarabelli M, Humby F, Caporali R, Pitzalis C, Montecucco C (2014) High expression levels of the B cell chemoattractant CXCL13 in rheumatoid synovium are a marker of severe disease. *Rheumatology (Oxford)* 53(10):1886–1895. <https://doi.org/10.1093/rheumatology/keu163>
37. Rosengren S, Wei N, Kalunian KC, Kavanaugh A, Boyle DL (2011) CXCL13: a novel biomarker of B-cell return following rituximab treatment and synovitis in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 50(3):603–610. <https://doi.org/10.1093/rheumatology/keq337>
38. Shapira Y, Agmon-Levin N, Shoenfeld Y (2010) Geoepidemiology of autoimmune rheumatic diseases. *Nat Rev Rheumatol* 6(8):468–476. <https://doi.org/10.1038/nrrheum.2010.86>
39. Wang JB, Pan HF, Ye DQ (2018) Association of Inc5150 gene polymorphisms with systemic lupus erythematosus. *Chin J Dis Control Prev* 22(9):929–932. <https://doi.org/10.16462/j.cnki.zhjbkz.2018.09.014>
40. Huang LL, Xu JH, Xu SQ, Xiao H, Chang L, Liu N, Ma Q (2016) Treat-to-target of rheumatoid arthritis and potential determinants. *Chin J Dis Control Prev* 20(6):586–589. <https://doi.org/10.16462/j.cnki.zhjbkz.2016.06.012>
41. Han JH, Suh CH, Jung JY, Nam JY, Kwon JE, Yim H, Kim HA (2015) Association of CXCL10 and CXCL13 levels with disease activity and cutaneous manifestation in active adult-onset still's disease. *Arthritis Res Ther* 17:260. <https://doi.org/10.1186/s13075-015-0773-4>

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.