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Review Article

Associations between serum levels of interleukin-23 and the susceptibility and development of ankylosing spondylitis: a meta-analysis

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Abstract: Purpose: A meta-analysis was undertaken to examine the correlation between ankylosing spondylitis (AS) progression and serum levels of interleukin-23 (IL-23) in AS patients. Methods: PubMed, EBSCO, Cochrane Library database, Springer link, Elsevier Science Direct, Web of science, Wanfang (Chinese) Database, and Chinese National Knowledge Infrastructure (CNKI) (last updated search in Match, 2017) were exhaustively searched for pertinent case-control studies using keywords related to IL-23 and AS. The search results were screened using presupposed inclusion and exclusion criteria, and the data from selected high-quality studies was analyzed with STATA software11.0. Results: Seventeen case-control studies were finally included in this meta-analysis and contained a combined total of 909 AS patients and 757 healthy controls. The main result of this meta-analysis showed that serum IL-23 levels in AS patients were strikingly higher than healthy controls (SMD = 1.078, 95% *CI* = 0.963~1.193, P < 0.001). Subgroup analysis based on ethnicity demonstrated that serum IL-23 level was also markedly higher in AS patients, both in Asians and Caucasians. ESR, CRP levels and BASDAI score were distinctly associated with serum IL-23 levels. Conclusion: Meta-analysis of seventeen high-quality studies revealed a strong correlation between elevated IL-23 serum levels and AS susceptibility. Therefore, serum IL-23 levels could confers risk susceptibility to AS, and therefore could be used as markers for the development of AS.

Keywords: Ankylosing spondylitis, interleukin-23, serum level, meta-analysis

Introduction

Ankylosing spondylitis (AS) is a clinically well-known and a severe form of spondyloarthropathies. It is a major violation of the human central axis bone and the large peripheral joints [1]. The main extra-articular manifestations of AS are enthesitis and synovitis, which might offer clues for the diagnosis [2]. Its estimated occurrence is 0.2%~0.5% worldwide with a higher prevalence among young adult males [3-5]. The exact pathological mechanisms involved in the development of AS still remain unknown. But the underlying mechanisms as reported are largely related to inflammation. Inflammation and ankylosis are main symptoms of AS. Changes in the structure of the joint, new bone formation and joint fusion are caused by chronic inflammation. Therefore, AS symptoms may also occur outside the spine and joints [6]. Various inflammatory mediators, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, and IL-17 cytokines, are reported to playing a dominant role in these inflammatory and proliferative cascades of AS [7-9].

IL-23, a member of IL-12 family, is a pro-inflammatory heterodimeric cytokine which consists of the IL-23 p19 and p40 subunits [10]. IL-23 has been shown to participate in many inflammatory disorders, such as inflammatory bowel disease, psoriasis and coronary heart disease [11-14]. In recent years, the role of cytokines in the pathogenesis of the inflammatory dis-

eases is getting more and more attention, and IL-23 may play an important role in AS progression [4, 15]. The importance of inflammatory pathways in AS is highlighted by the pronounced reduction in inflammation and disease activity following blockade of TNF, IL-17, and IL-12/23, however, further insight into the inflammatory networks operating in AS is urgently needed. IL-12 is used to be recognized as central gene in autoimmune inflammation, and now plentiful studies demonstrated that IL-23 also plays an important role, as a key reaction effector molecule in the final phase [16]. IL-23 is required in the process of proliferation and survival of Th17 cell, as well as in the immune response [17]. Our previous studies showed that polymorphism in IL-23 receptor is associated with susceptibility to AS [18] IL-23 is a pleiotropic cytokine involved in both pro-inflammatory and anti-inflammatory pathways [19]. Importantly, overexpression and abnormal activation of IL-23 signaling pathways is an indicator of aggressive disease course in autoimmunity and cancer, and elevated levels of IL-23 is implicated in the pathogenesis of several autoimmune diseases, including AS. Nevertheless, recent studies have shown that the serum level of IL-23 are susceptibility to AS [20, 21] while with inconsistent results [22, 23].

The role of IL-23 is suspected in the pathogenesis of AS, and previous studies on systemic inflammation in AS are hampered by small sample sizes and selected patient groups [19]. Furthermore, the clinical relevance of their serum levels and its implication to AS pathology continues to be hotly debated. In this context, we undertook a meta-analysis based approach to investigate the robust association between IL-23 serum levels with AS development.

Materials and methods

Literature retrieval and data collection

PubMed, EBSCO, Cochrane Library database, Springer link, Elsevier Science Direct, Web of science, Wanfang Database, and Chinese National Knowledge Infrastructure (CNKI) were comprehensively searched by two authors (Renfang Han and Qing Xia) independently to identify potential studies relevant to IL-23 serum levels in AS patients. A third reviewer (Faming Pan) was consulted for a final decision in case of any discrepancies between the two reviewers. The database search retrieved studies published prior to Match 2017 and the language of publication was not restricted. The search terms were: (ankylosing spondylitis or ankylosing spondyloarthritis or ankylosis spondylitis or AS) and (interleukin-23 serum levels or IL-23 serum levels or interleukin-23 serum levels). We also manually examined the bibliographies of selected studies to identify additional relevant articles. Only published studies with full text were included. All the retrieved references were managed in EndNote X7 (Thomson Reuters).

Inclusion and exclusion criteria

Study selection for meta-analysis was based on the following inclusion criteria: (1) the published study must be a case-control study; (2) study must report the correlation between serum IL-23 levels and AS; (3) sufficient information must be available on country, ethnicity, publication year, sample size, gender, IL-23 detection methods, serum IL-23 levels. The exclusion criteria were: (1) inconsistent diagnostic criteria for AS; (2) studies that are not case-control studies; (3) incomplete original data.

Data collection

The study screening and selection procedures were undertaken independently by two reviewers (Renfang Han and Qing Xia). The relevant information extracted from finally selected studies included: authors' information, year of publication, country, ethnicity, sample size, number of patients and controls, gender, age, detection methods, and serum IL-23 levels. In case of any disagreements during study selection or data extraction, a third investigator (Faming Pan) was consulted for resolution after careful reexamination of the data.

Quality assessment

The quality assessment of each eligible study was conducted using Newcastle-Ottawa Scale (NOS) criteria [24], and was performed blindly by two authors (Renfang Han and Qing Xia). Some discrepancies were solved by discussion with the third author (Faming Pan). Each study enrolled was judged on three broad dimen-

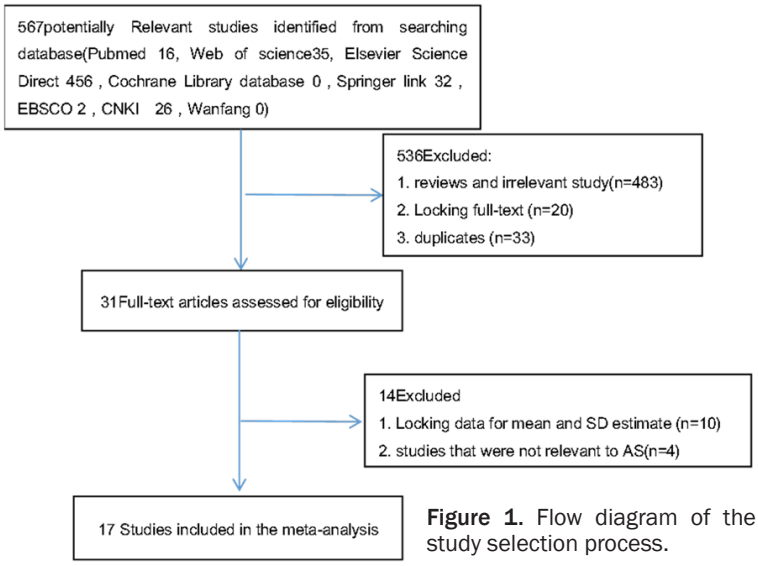

Figure 1. Flow diagram of the study selection process.

sions: the selection of the study subjects (4 items), the comparability of the study populations (1 item) and the ascertainment of the exposure in case-control studies (3 items). The total score for a single study ranges from 0 to 9. A study was considered to be of high quality if scored seven or more stars [25].

Statistical analysis

The difference in serum IL-23 levels between the case and control groups was compared by standardized mean difference (SMD) with 95% confidence intervals (95% *CI*), and the correlationship between serum IL-23 level and disease activity in AS was performed by CORs with 95% *CI*. The significance of the pooled SMDs and CORs was determined by Z-test and $P < 0.05$ was considered statistically significant. Cochran's Q-test ($P < 0.05$ was considered significant) and I^2 statistic were applied to determine between study heterogeneity. We quantified the effect of heterogeneity by using a recently developed measure, namely, $I^2 = 100\% \times (Q\text{-}df)/Q$, with values of 25%, 50% and 75% indicating as low, moderate, and high heterogeneity respectively. Random-effect model (the DerSimonian and Laird method) was used to calculate pooled estimates in case of significant heterogeneity ($P < 0.10$ or $I^2 > 50\%$). Otherwise, a fixed-effect model (the Mantel-Haenszel method) was adopted. Meta-regression analysis was performed to detect the source of heterogeneity. The funnel plots were carried out to assess potential publication bias and an asymmetric plot suggested a possible publication bias. Funnel plot asymmetry was further assessed by the method of Egger's liner regression tests and a $P < 0.05$ was considered significant. Sensitivity analysis was conducted to evaluate the stability of the meta-analysis. Sensitivity analysis was performed to calculate the influence of one single study in the overall outcomes. When any single study was deleted, the corresponding pooled SMDs were not substantially altered, suggesting that the results of this meta-analysis were stable. A two-side test was conducted, with $P < 0.05$ considered as being significant. All parameters of enrolled studies were offering mean ± SD. Besides, all standard errors of correlation coefficients (Sr) have been calculated by the flowing formula for combining correlation coefficients (CORs): $\text{sqrt}((1\text{-}r^2)/(N\text{-}1))$, r indicates the correlation coefficient, while N represents the sample size, namely the total number of participants. In addition, subgroup analysis was performed based on ethnicity. All statistical analyses were carried out in STATA software (STATA 11.0, Stata Corp, College Station, TX, USA).

Results

Eligible studies selected for meta-analysis of serum IL-23 levels and AS

Five hundred and sixty-seven candidate publications were considered through database searching (**Figure 1**). Of those, 536 reviews, abstracts and irrelevant publications were immediately excluded, thus leaving 31 studies for further selected. After screening the title and abstract, 14 of those studies were excluded (10 studies locking data for mean and SD estimate, 4 were not designed for AS). Eventually, 17 eligible studies were enrolled in the current meta-analysis [4, 16, 19-23, 26-37]. In total, the seventeen selected studies for meta-analysis contained a combined total of 909 AS patients and 757 healthy controls. Sample sizes in the studies varied from 19 to

Table 1. Comparison of meta-analysis studies for IL-23 with AS susceptibility

Auther	Year	Country	Type of research	Language	Case					Control					Source of control	Measurement
					N	Gender (M/F)	Mean age (years)	Mean	SD	N	Gender (M/F)	Mean age (years)	Mean	SD		
Ren JJ	2013	China	Case-Control	Chinese	60	32/28	32.75±7.28	1476.96	978.64	28	17/21	33.5±10.32	981.55	853.67	Hospital	ELISA
Wang	2009	China	Case-Control	Chinese	57	52/5	29.7±8.2	1159.71	139.45	38	30/8	27.7±6.9	438.50	93.42	Hospital	ELISA
Mahir	2015	Turkey	Case-Control	English	20	20/0	40.2±10.2	334.45	176.54	20	20/0	42.6±10.4	166.49	177.50	NA	ELISA
Sveas	2015	Norwegian	Cross-sectional	English	143	88/62	49.3±11.0	122.00	94.57	124	74/60	53.2±11.3	106.00	76.70	NA	ELISA
Zepa	2013	Latvia	Case-Control	English	39	NA	NA	194.60	261.40	39	NA	NA	200.30	256.30	NA	ELISA
Romero	2011	Colombia	Case-Control	English	19	15/5	32.3±9.1	5.20	3.90	46	NA	NA	3.10	0.70	Hospital	ELISA
Chen	2012	China	Case-Control	English	49	43/6	39.0±12.3	280.27	59.10	25	NA	NA	121.12	41.50	NA	ELISA
Yang	2011	China	Case-Control	Chinese	50	41/9	28.1±8.9	3149.20	1298.60	43	35/8	25.3±6.7	2399.00	719.60	NA	ELISA
Ren ML	2016	China	Case-Control	Chinese	48	43/5	26.2±5.2	54.19	5.40	49	NA	25.9±4.8	52.66	5.19	Hospital	ELISA
Cai	2016	China	Case-Control	Chinese	62	49/12	35.26±9.54	378.22	98.61	62	47/15	35.28±9.51	180.80	134.28	Hospital	ELISA
Tian	2016	China	Case-Control	Chinese	78	47/31	38.28±6.09	412.89	46.83	67	40/27	NA	179.82	21.79	Hospital	ELISA
Yuan	2015	China	Case-Control	Chinese	53	41/12	(23, 50)[a]	2.01	1.00	30	22/8	(22, 45)[a]	1.26	0.62	Hospital	ELISA
Liang	2012	China	Case-Control	Chinese	30	25/5	27.56±5.09	24.75	6.70	30	25/5	26.29±5.52	22.43	4.34	Hospital	ELISA
Ma	2012	China	Case-Control	Chinese	30	25/5	29.43±8.33	74.90	42.24	15	NA	NA	43.32	16.06	Hospital	ELISA
Zhao	2015	China	Case-Control	Chinese	83	65/18	24.81±10.12	379.23	98.26	65	46/19	26.17±9.76	180.82	34.29	Hospital	ELISA
Chen P	2014	China	Case-Control	Chinese	30	NA	NA	1256.10	105.47	30	NA	NA	234.76	16.09	Hospital	ELISA
Yang B	2016	China	Case-Control	Chinese	58	47/11	28.9±936	43.43	15.83	46	37/9	30.1±9.2	15.85	8.52	Hospital	ELISA

SD, standard deviation; ELISA, enzyme-linked immunosorbent assay; NA, not applicable; a, (minimum, Maximum).

Table 2. Assessment of quality of studies included

		Selection				Comparability		Outcome Assessment			
Authors	Year	1	2	3	4	1	2	1	2	3	Score
Ren JJ	2013	*	*	&	*	*	*	*	*	*	8
Wang	2009	*	*	&	*	*	*	*	*	*	8
Mahir	2015	*	*	&	*	*	*	*	*	&	7
Sveas	2015	*	*	&	*	*	*	*	*	*	8
Zepa	2013	*	*	-	*	*	*	*	*	&	7
Romero	2011	*	*	*	*	*	*	*	*	&	8
Chen	2012	*	*	-	*	*	*	*	*	-	7
Yang	2011	*	*	&	*	*	*	*	*	*	8
Ren ML	2016	*	*	&	*	*	*	*	*	*	8
Cai	2016	*	*	-	*	*	*	*	*	&	7
Tian	2016	*	*	&	*	*	*	*	*	*	8
Yuan	2015	*	*	&	*	*	*	*	*	*	8
Liang	2012	*	*	&	*	*	*	*	*	&	7
Ma	2012	*	*	-	*	*	*	*	*	*	8
Zhao	2015	*	*	&	*	*	*	*	*	*	8
Chen P	2014	*	*	&	*	*	*	*	*	-	7
Yang B	2016	*	*	&	*	*	*	*	*	*	8

*, 1 score; &, 0 score; NA, not applicable.

143 and the studies were published during 2009-2016. Nine studies were performed in Chinese population and the other four studies were performed in Caucasian populations, with one study each from Turkey, Columbia, Norwegian, and Latvia. Baseline characteristics for the 17 included studies are presented in **Table 1**. NOS scores for all the eligible studies ranged from 6 to 8 which are shown in **Table 2**.

Meta-analysis results for serum level of IL-23

A total of 17 studies reported the correlation between IL-23 serum level and AS. Our meta-analysis observed the existence of heterogeneity in the 17 published studies, thus random effect model was utilized (I^2 = 97.2%, P < 0.001). The main result of this meta-analysis showed that serum levels of IL-23 in AS patients were strikingly higher than healthy controls (SMD = 1.078, 95% CI = 0.963~1.193, P < 0.001) (**Figure 2**, **Table 3**). Subgroup analysis based on ethnicity demonstrated that serum IL-23 level was markedly higher in AS patients, compared with healthy controls, in both Asians (Asians: SMD = 1.528, 95% CI = 1.383~1.672, P < 0.001) and Caucasians (Caucasians: SMD = 0.301, 95% CI = 0.111~0.490, P = 0.002) (**Figure 2**, **Table 3**). ESR and CRP levels and BASDAI score were inversely associated with serum IL-23 levels (for ESR vs. IL-23: COR = 0.352, 95% CI = 0.263~0.441, P < 0.001; for CRP vs. IL-23: COR = 0.353, 95% CI = 0.263~0.441, P < 0.001; for BASDAI vs. IL-23: COR = 0.300, 95% CI = 0.204~0.396, P < 0.001, respectively), for details see **Table 4** and forest plots were shown in **Figure 2**, funnel plots were shown in **Figure 3**.

Sensitivity analysis and risk of publication bias

Three studies had the weight to significantly impact the pooled SMDs (**Figure 3**). Funnel plots were not symmetrically distributed, indicating publication bias. To some extent. Egger's test further confirmed the publication bias (P < 0.05) (**Figure 3**). However, after removing the three impact studies, the result of this meta-analysis does not significantly change. Through thorough analysis, we found that both of three studies satisfied the inclusion criteria and fail to meet the exclusion criteria; thus, we decided to enroll these articles at last.

Discussion

The development of AS involves a diverse range of genetic and environmental factors. Since the Genome Wide Association Studies (GWASs) were widely used in discovering the susceptibility genes for AS, and many susceptibility genes were recognized. Human leukocyte antigen (HLA)-B27 was the first molecule found to be highly associated with AS. Although HLA-B27 plays a critical role in AS pathogenesis, recent estimates suggest that it only accounts for 20.1% of the overall genetic predisposition and only 5-8% of HLA-B27 positive individuals of the general population develop the disease [38]. Additional non-MHC susceptibility loci should naturally be of concern [39], and it is even more important to find out the other potential factors to comprehensively clarify the pathogenesis of AS.

Sacroiliitis is the key feature of AS, accompanied by inflammation of the enthesitis and formation of syndesmophytes, with spinal ankylo-

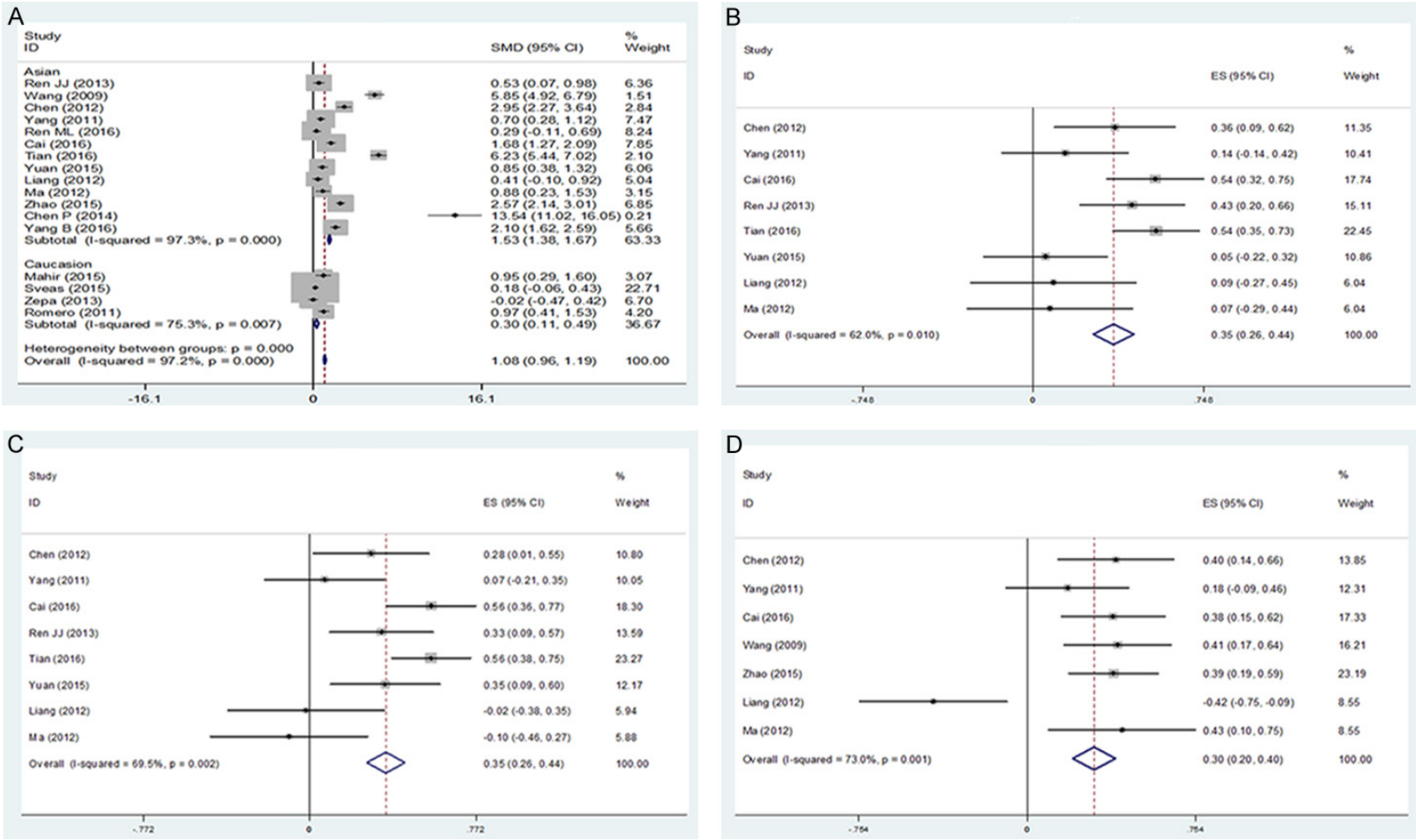

Figure 2. Meta-analysis for the association between serum IL23 levels and AS risk: A. Forest plots for serum IL23 level and AS. B. Forest plots for serum IL23 level and ESR. C. Forest plots for serum IL23 level and CRP. D. Forest plots for serum IL23 level and BASDAI.

Table 3. Sub meta-analysis studies for IL-23 with AS susceptibility (OR (95% CI))

	Qualified studies	Test of association				Test of heterogeneity	
		SMD	95% CI	*P*-value	Model	I^2 (%)	*P*-value
Caucasian	4	0.301	(0.111, 0.490)	0.002	Random	75.3	0.007
Asians	13	1.528	(1.383, 1.672)	< 0.001	Random	97.3	< 0.001
Overall	17	1.078	(0.963, 1.193)	< 0.001	Random	97.2	< 0.001

SMD, standardized mean difference; 95% CIs, 95% confidence intervals.

Table 4. Correlationship of serum IL-23 levels and disease activity in AS

Outcomes	No. of studies	COR	95% CI	*P*-value	Effect model
ESR vs. IL-23	8	0.352	(0.263, 0.441)	< 0.001	R
CRP vs. IL-23	8	0.353	(0.263, 0.441)	< 0.001	R
BASDAI vs. IL-23	7	0.300	(0.204, 0.396)	< 0.001	R

IL-23, Interleukin-23; No, number; COR, correlation coefficient; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

inhibit the production of pro-inflammatory cytokines, which may dramatically relieving AS symptoms. To investigate the contribution of other potential factors influencing the correlations of serum level of IL-23 with AS development, subgroup analyses were conducted. Stratified analysis in terms of ethnicity showed a significant association of elevated serum IL23 level with AS development in both Asian and Caucasian populations.

sis in later stages [40]. IL-23 drives a highly pathogenetic T cell population involved in the initiation of inflammatory disease and autoimmune diseases [41]. Recently some studies showed that serum levels of IL-23 in AS patients were significantly higher than those of healthy controls suggesting that the cytokine could serve as inflammatory biomarkers in spondyloarthritis. However, many case-control studies performed in different countries obtained conflicting results, and the cause of such difference was worth researching. The reason for the inconsistency such as country, economy, race and the use of non-steroidal anti-inflammatory drugs, should be taken into consideration. On the other hand, sample size is different and the sample size is small, so further to comprehensively evaluate the effect of IL-23 serum levels on the risk of AS, and a meta-analysis which is to increase the credibility of the conclusion by increasing the sample content, and to solve the inconsistency of the results was essential. These factors would influence the IL-23 level in the human body.

Our main results show that serum levels of IL-23 strikingly higher in AS patients than that of healthy controls, indicating that the cytokine play a prominent role in AS pathogenesis. The critical roles played by IL-23 and IL-23 receptor (IL-17 RA) regulated pathway in AS progression was further validated in studies that used anti-IL-23 RA monoclonal antibodies to

ESR and CRP are non-specific inflammatory markers that had long been selected for assessing systemic inflammation. ESR, CRP and BASDAI scores can well evaluate the inflammatory level and ankylosing situation of AS patients. The diagnostic value of ESR and CRP has been validated in AS [42]. Besides, BASDAI scores is a comprehensive self-administered instrument for assessing disease activity [43]. The three indicators can basically represent the disease activity in AS. In this meta-analysis, all of the three are strongly associated with the serum IL-23 levels of AS patients, which strongly testified the hazardous role of higher serum IL-23 levels in AS activity. Besides, we also have analyzed the two important factors (ESR and CRP) that were influenced by IL-23 levels from the current cognitive in biochemistry. Such co-evaluation may aid in a better understanding of autoimmunity etiopathogenesis in these systemic autoimmune diseases. ESR and CRP are important indicators of inflammation, and they are the basic laboratory indexes for judging the severity of infectious diseases. The positive correlation showed that the changes of IL-23 levels could be used to assess the severity of the disease.

However, our paper just introduces a degree of speculation. Limitations of the present meta-analysis must be acknowledged. First, included studies did not contain information on Th17 cells or other related cytokines, which

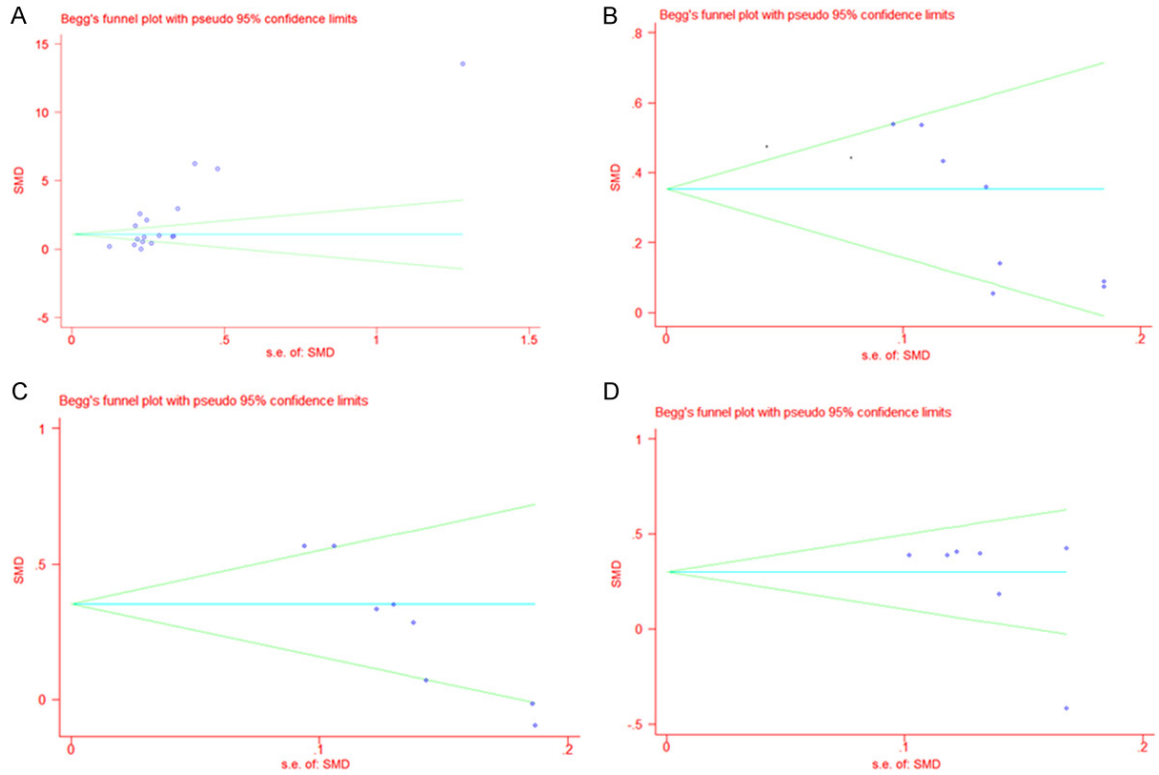

Figure 3. The funnel plots were carried out to assess potential publication bias and sensitivity analysis was conducted to evaluate the stability of the meta-analysis. A. Funnel plots for serum IL23 level and AS; B. Funnel plots for serum IL23 level and ESR; C. Funnel plots for serum IL23 level and CRP; D. Funnel plots for serum IL23 level and BASDAI.

may have led to an overestimation of the contribution of IL-23 to AS progression. Second, follow-up of treatment response was not performed in the selected studies and the serum IL-23 levels were not recorded after treatment. Finally, an accurate definition or cutoff point for 'high' or 'low' serum level for IL-23 was not provided in the included studies. But we are the first meta-analysis that identified the significant association of serum IL-23 level with AS susceptibility. The present study selected biomarkers for evaluation which are known to be important in the inflammatory and bone formation process characterizing AS.

Conclusion

In summary, we have pooled all available studies on serum IL-23 level and AS, and we firstly reported that high serum IL-23 level was a risk locus to AS, both in European populations and Asian populations. The study was to evaluate serum levels of IL-23 in patients with AS and to investigate their associations with clinical and biological variables assessing disease activity and function in patients with AS. To sum up, IL-23 is highly expressed in peripheral serum of patients with AS, and its amplitude is positively related to disease activity, and can be used for clinical efficacy and disease severity assessment. Further, more well-designed studies are needed to explore the association between serum IL-23 levels and AS.

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Disclosure of conflict of interest

None.

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