J Rheum Dis 2025;32(1):48-56
https://doi.org/10.4078/jrd.2024.0095
pISSN: 2093-940X, eISSN: 2233-4718

Original Article

Associations between circulating interleukin-18 levels and adult-onset Still's disease: a meta-analysis

Young Ho Lee, M.D., Ph.D., Gwan Gyu Song, M.D., Ph.D.

Division of Rheumatology, Department of Internal Medicine, Korea University Medical Center, Korea University College of Medicine, Seoul, Korea

Objective: This study aimed to investigate the link between circulating interleukin-18 (IL-18) levels and adult-onset Still's disease (AOSD).

Methods: A thorough search was performed on MEDLINE, Embase, and Web of Science to find relevant articles. A meta-analysis was conducted to compare serum/plasma IL-18 levels in AOSD patients to those in control subjects.

Results: The meta-analysis included 13 studies with a total of 562 AOSD patients and 790 controls. The results showed a significant increase in IL-18 levels in the AOSD group compared to the control group (standard mean difference [SMD]=1.899, 95% confidence interval [CI]=1.078~2.720, p<0.001). When stratified by ethnicity, higher IL-18 levels were found in both Asian and European populations with AOSD. Subgroup analysis, regardless of variable adjustments, consistently indicated significantly higher IL-18 levels in the AOSD group. Significant elevations in IL-18 levels were observed in both small (n<50) and large groups (n>50), as well as in original and imputed data groups after data type stratification. Free IL-18 levels were significantly higher in the active group compared to the inactive group (SMD=0.900, 95% CI=0.532~1.268, p<0.001). The meta-analysis showed a positive correlation between IL-18 levels and ferritin (correlation coefficient=0.542, 95% CI=0.431~0.637, p<0.001) and C-reactive protein.

Conclusion: This meta-analysis demonstrated a significant increase in circulating IL-18 levels and a positive correlation between IL-18 levels and ferritin and C-reactive protein levels in patients with AOSD.

Keywords: Adult-onset Still's disease, Interleukin-18, Ferritin, Polymorphism, Genetic, Meta-analysis

INTRODUCTION

Adult-onset Still's disease (AOSD) is a systemic inflammatory condition marked by a range of clinical symptoms such as spiking fever, transient skin rash, joint pain or arthritis, sore throat, and enlarged liver or spleen [1,2]. Diagnostic laboratory findings often include neutrophilic leukocytosis, abnormal liver function tests, high serum ferritin levels, and increased acute-phase reactants. Despite significant medical advancements, the precise cause of AOSD remains unknown. Active AOSD is characterized by immune-mediated inflammation, typically triggered by abnormal immune responses in genetically predisposed individuals exposed to environmental factors [3].

Interleukin-18 (IL-18), initially identified as interferon-γ-inducing factor, plays a critical role in AOSD pathogenesis. IL-18 has various functions, such as inducing interferon-γ synthesis in T cells and natural killer (NK) cells, promoting Th1-type immune responses, and enhancing proliferative responses and cytokine production in activated T cells [4]. IL-18 has been linked to several inflammatory conditions, including acute liver injury,

Received August 1, 2024; **Revised** September 18, 2024; **Accepted** October 17, 2024, **Published online** October 29, 2024

Corresponding author: Young Ho Lee, https://orcid.org/0000-0003-4213-1909
Division of Rheumatology, Department of Internal Medicine, Korea University Anam Hospital, Korea University College of Medicine, 73 Goryeodae-ro, Seongbuk-gu, Seoul 02841, Korea. **E-mail:** lyhcgh@korea.ac.kr

inflammatory arthritis, allergic inflammation, and other autoimmune diseases. The biological effects of IL-18 align with the key features of AOSD, indicating a potential connection between IL-18 dysregulation and AOSD [5]. The IL-18 gene, located on chromosome 11q22.2q22.3, includes promoters upstream of exons 1 and 2. Two significant single nucleotide polymorphisms (SNPs) at positions 607 and 137 in the promoter region of IL-18 exon 1 are of particular interest [6]. Given IL-18's crucial role in the cytokine network and its overexpression in AOSD, researchers have focused on studying the relationship between blood IL-18 levels, IL-18 gene polymorphisms, and AOSD susceptibility.

Although many studies have investigated these associations, debates continue about whether serum IL-18 levels are reliable markers of disease activity [7-19]. Additionally, the role of IL-18 polymorphisms in AOSD onset remains controversial, with earlier studies yielding inconsistent results. To resolve these issues, a comprehensive review and meta-analysis are needed to better understand the complex relationship between IL-18 and AOSD [20]. The objectives of this study were to systematically review evidence on serum/plasma IL-18 levels in AOSD patients versus controls, determine IL-18 serum levels in active versus inactive AOSD, correlate these levels with other disease activity markers, and investigate the link between IL-18 polymorphisms and AOSD susceptibility.

MATERIALS AND METHODS

Selection of relevant studies and data compilation

We conducted a comprehensive search of scientific literature to identify studies that measured circulating IL-18 levels (plasma or serum), explored the association between AOSD and IL-18 gene polymorphisms, and analyzed the relationship between these IL-18 levels and AOSD. Searches were performed on PubMed, Embase, and Cochrane Databases for all relevant publications up to June 2024. The search terms included "interleukin-18," "serum OR plasma OR circulating OR blood," "polymorphism," and "adult-onset Still's disease." Additionally, we manually reviewed the references of retrieved articles to identify any further relevant studies not indexed in these databases.

Eligible studies were required to be case-control, cohort, or cross-sectional in design and to provide data on IL-18 levels in both affected and control groups, as well as information on IL-18 gene polymorphisms in both AOSD and control groups. We excluded studies that provided duplicate data, case reports, reviews, or those lacking sufficient information. For each selected study, we collected data on the author, publication year, country, ethnicity, age, sex, number of participants, mean and standard deviation of IL-18 levels, and genotype and allele frequencies of IL-18 polymorphisms. When data were reported as ranges, medians, or interquartile ranges, we converted these to means and standard deviations using established formulas [21,22].

Two independent evaluators, who were part of the initial study, reviewed and disclosed the study methods and findings. Discrepancies between reviewers were resolved by consensus. Each study's quality was assessed using the Newcastle-Ottawa Scale [23], and we adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines throughout the process [24].

Statistical correlation analysis

We performed a meta-analysis to examine the allelic effects of various IL-18 gene variations and the association between AOSD and IL-18 levels. The results are presented as 95% confidence intervals (CIs) for continuous data and mean and standard deviation. For dichotomous data, we calculated 95% CIs and odds ratios (ORs). Variations and heterogeneities within and across studies were assessed using Cochran's Q tests [25]. A heterogeneity test was used to test the null hypothesis that each study estimated the same effect. For meta-analysis, a fixed-effects model was used unless the Q-statistic indicated significant heterogeneity ($p<0.10$), in which case a random-effects model was applied [26]. The influence of heterogeneity was quantified using $I^2=100\% \times (Q-df)/Q$ [27], which determines whether total variation across trials is due to chance or heterogeneity and measures the inconsistency between studies. I^2 values ranged from 0% to 100%, with thresholds of 25%, 50%, and 75% representing low, moderate, and high levels of I^2, respectively [27]. Statistical analyses were conducted using the Comprehensive Meta-Analysis software (Biostat Inc., Englewood, NJ, USA).

Evaluation of risks and publication bias

To explore potential sources of heterogeneity in the meta-analysis, we used explanatory variables such as ethnicity, publication year, sample size, matched variables, data type, and study quality. Sensitivity analysis was performed by eliminating one study at a time to determine its effect on the overall effect size. Funnel plots and Egger's linear regression test were used to assess the presence of publication bias [28], utilizing standard

mean differences (SMDs) or ORs on a natural logarithmic scale to evaluate funnel plot asymmetry.

RESULTS

Studies included in the meta-analysis

We identified 573 publications using both manual and computerized search methods. From these, 19 were selected for full-text review based on their titles and abstracts, while six were excluded due to a lack of IL-18 data. Ultimately, 13 studies, comprising 562 AOSD patients and 790 controls, were included in the meta-analysis (Figure 1) [7-19]. Ten studies analyzed IL-18 levels in affected and control groups in a meta-analysis (Table 1) [7-16], and three studies on IL-18 polymorphisms were included in the systematic review (Table 2) [17-19]. Each study received a quality grade between six and seven. The demographics of the participants and quality assessments are summarized in Tables 1 and 2.

Comparison of circulating IL-18 levels between AOSD patients and healthy controls

The meta-analysis revealed that IL-18 levels were significantly higher in the AOSD group compared to the control group (SMD=1.899, 95% CI=1.078~2.720, p<0.001) (Table 3, Figure 2) [7-16]. Subgroup analyses were conducted based on ethnicity, age, sex, sample size, and data type. Both Asian and European populations exhibited higher IL-18 levels in the AOSD group according to ethnicity-based stratification (Table 3). Subgroup analysis consistently showed significantly higher IL-18 levels in the AOSD group across all variables. Higher IL-18 levels were also observed in both small (n<50) and large groups (n>50), as well as in original and imputed data groups (Table 3). No significant difference in IL-18 levels was found between active and inactive disease groups. There were two studies on free IL-18 in AOSD [13,29]. Free IL-18 levels were significantly higher in the active group compared to the inactive group (SMD=0.900, 95% CI=0.532~1.268, p<0.001) (Table 3).

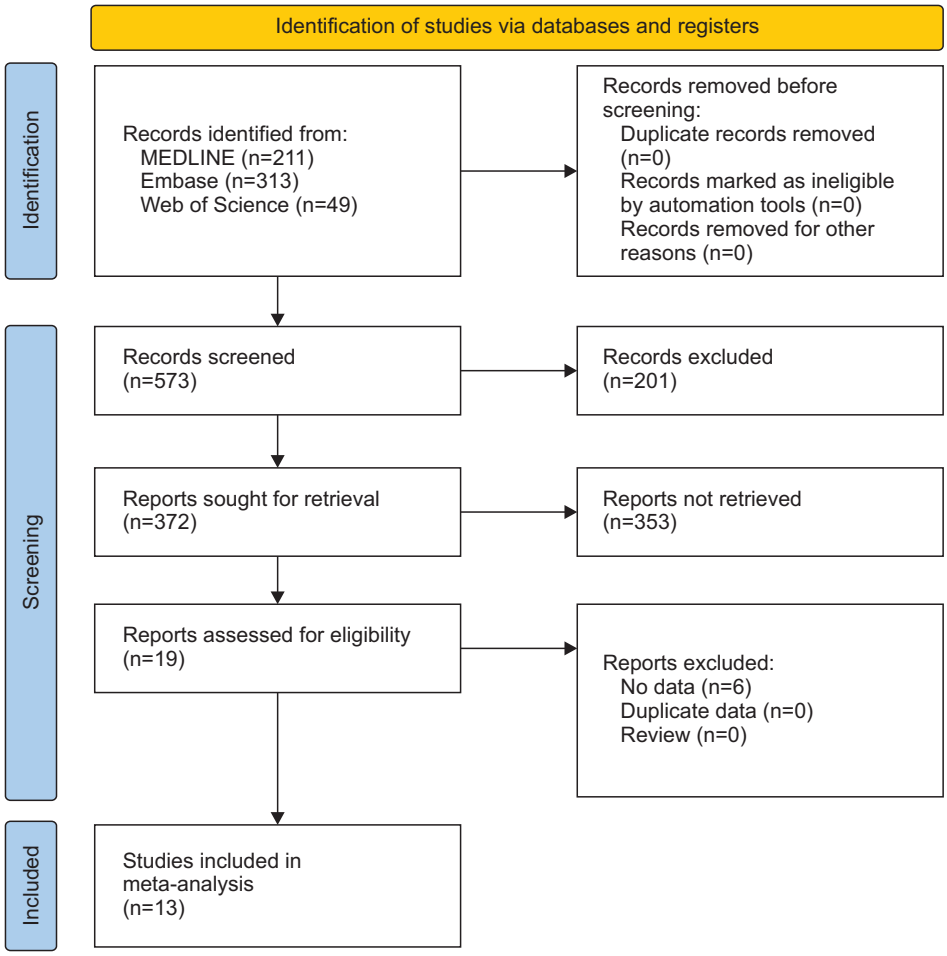

Figure 1. Flowchart depicting the study selection process for the meta-analysis.

Table 1. Characteristics of individual studies included in the meta-analysis (IL-18 level)

Author	Country	Ethnicity	Cohort size (n)		IL-18 level (pg/mL or ng/L)		Statistical finding			Study quality†
			Case	Control	Case	Control	SMD	Magnitude*	p-value	
Chen et al. [9]	China	Asian	23	31	3496.00	7.56	1.173	Large	<0.001	6
Ichikawa et al. [10]	Japan	Asian	25	12	2267.60	72.10	5.855	Large	<0.001	6
Hung et al. [11]	Taiwan	Asian	66	128	977.70	142.10	3.676	Large	<0.001	7
Kim et al. [12]	Korea	Asian	13	19	3016.20	30.00	1.976	Small	<0.001	6
Jung et al. [13]	Korea	Asian	80	30	27219.60	211.50	0.603	Moderate	<0.001	7
Colafrancesco et al. [7]	Italy	European	16	21	2424.70	227.00	0.689	Moderate	0.043	6
Kim et al. [14]	Korea	Asian	36	33	7560.30	139.20	1.355	Large	<0.001	6
Priori et al. [8]	UK	European	21	21	2366.70	212.00	0.639	Moderate	0.043	6
Chen et al. [15]	Taiwan	Asian	50	20	506.18	60.23	1.070	Large	<0.001	6
Choi et al. [16]	Korea	Asian	14	15	65.90	10.00	2.950	Large	<0.001	6

IL-18: interleukin-18, SMD: standard mean difference, n: number. *Magnitude of Cohen's d effect size where 0.2 to 0.5 is a small effect, 0.5 to 0.8 is a medium effect, and ≥0.8 is a large effect. †Newcastle-Ottawa Scale.

Table 2. Characteristics of individual studies included in systematic review (IL-18 polymorphisms)

Author	Country	Ethnicity	Cohort size (n)		IL-18 gene and polymorphism tested	Statistical finding (p-value)	NOS score
			Case	Control			
Chen et al. [17]	China	Asian	96	164	−607 C/A	−607 AA (p<0.05)	7
Her et al. [18]	Korea	Asian	70	204	−607 C/A, −137 G/C	−607 C/A (p=0.044), −137 G/C (NS)	7
Sugiura et al. [19]	Japan	Asian	16	92	C to T substitution at position −5890 (SNP1), A to G at position −5316 (SNP2), T to C at position −5207 (SNP3), T to C at position −4762 (SNP4), C to G at position −4675 (SNP5), T to C at position −3268 (SNP6), C to T at position −2835 (SNP7), T to C at position −2565 (SNP8), G to T at position −689 (SNP9), C to A at position −640 (SNP10), and a 9 bp (AACAGGACA) insertion between positions −6311 and −6310	SNP1, 2, 4, 5, 6, 9, and 10 and the 9 bp insertion (p<0.05)	7

IL-18: interleukin-18, n: number, NS: not significant, NOS: Newcastle-Ottawa Scale.

Correlation between IL-18 levels and activity markers

The meta-analysis demonstrated a positive correlation between IL-18 and ferritin levels (correlation coefficient=0.542, 95% CI=0.431~0.637, p<0.001) (Table 4, Figure 3A) [7,13-16]. Additionally, IL-18 showed positive correlations with C-reactive protein (CRP) (correlation coefficient=0.306, 95% CI=0.168~0.431, p<0.001) (Table 4, Figure 3B) [7,13-16].

IL-18 polymorphisms and AOSD: a systematic review

Three studies were included in this review. One study suggested that the A allele and AA genotype at position −607 of IL-18 gene polymorphisms could be genetic risk factors for AOSD in the Korean population. Patients with AOSD had a significantly higher frequency of AA genotypes at −607 compared to controls (AA vs. CA and CC, OR=1.90, 95% CI=1.01~3.58, p=0.044) [18]. Another study indicated that the SNP 607/AA genotype, associated with lower IL-18 levels, might be a genetic protective

Table 3. Meta-analysis of the association between circulating IL-18 levels and AOSD

Group	Population	No. of study	Test of association			Test of heterogeneity		
			SMD*	95% CI	p-value	Model	p-value	I^2
All	Overall	10	1.899	1.078~2.720	<0.001	R	<0.001	94.2
Ethnicity	Asian	8	2.228	1.254~3.201	<0.001	R	<0.001	94.9
	European	2	0.662	0.208~1.117	0.004	F	0.915	0
Matched for age and sex	Yes	6	2.406	1.259~3.553	<0.001	R	<0.001	94.9
	No	4	1.601	0.326~1.876	0.005	R	0.001	82.5
Sample size	n>50	5	1.577	0.437~2.717	0.001	R	<0.001	96.0
	n<50	5	2.298	0.896~3.700	0.001	R	<0.001	92.5
Data type	Original	4	1.174	0.660~1.688	<0.001	R	0.018	70.0
	Calculated	6	2.413	1.034~3.791	0.001	R	<0.001	95.7
Disease activity	Active vs. Inactive group	3	2.099	−0.390~4.589	0.098	R	<0.001	94.1
Disease activity (free IL-18)	Active vs. Inactive group	3	0.900	0.532~1.268	<0.001	F	0.936	0

IL-18: interleukin-18, AOSD: adult-onset Still's disease, SMD: standardized mean difference, CI: confidence interval, n: number, F: fixed effects model, R: random effects model, NA: not available. *Magnitude of Cohen's d effect size (SMD): 0.2~0.5, small effect; 0.5~0.8, medium effect; ≥0.8, large effect.

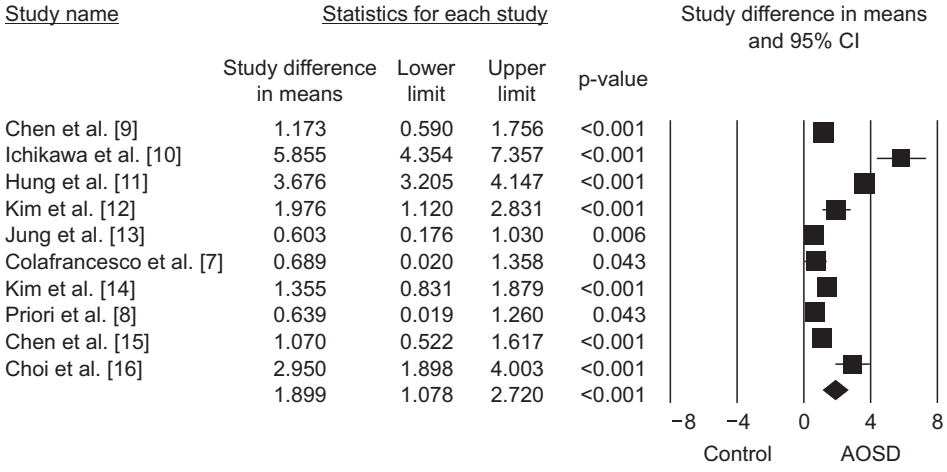

Figure 2. Meta-analysis illustrating the relationship between circulating IL-18 levels and AOSD. IL-18: interleukin-18, AOSD: adult-onset Still's disease, CI: confidence interval.

Table 4. Meta-analysis of the correlation coefficient between IL-18 level and ferritin, CRP in AOSD

Parameter	No. of study	Test of association			Test of heterogeneity		
		Correlation coefficient	95% CI	p-value	Model	p-value	I^2
Ferritin	5	0.542	0.431~0.637	<0.001	F	0.267	23.1
CRP	5	0.306	0.168~0.431	<0.001	F	0.735	0

IL-18: interleukin-18, CRP: C-reactive protein, AOSD: adult-onset Still's disease, CI: confidence interval, F: fixed effects model.

factor against AOSD in the Chinese population. Significantly lower frequencies of the –607/AA genotype were observed in AOSD patients compared to controls (18.8% vs. 31.1%, respectively; p<0.05). Median serum IL-18 levels were significantly lower in AOSD patients with the AA genotype compared to those with the CA or CC genotypes [17]. The last Japanese

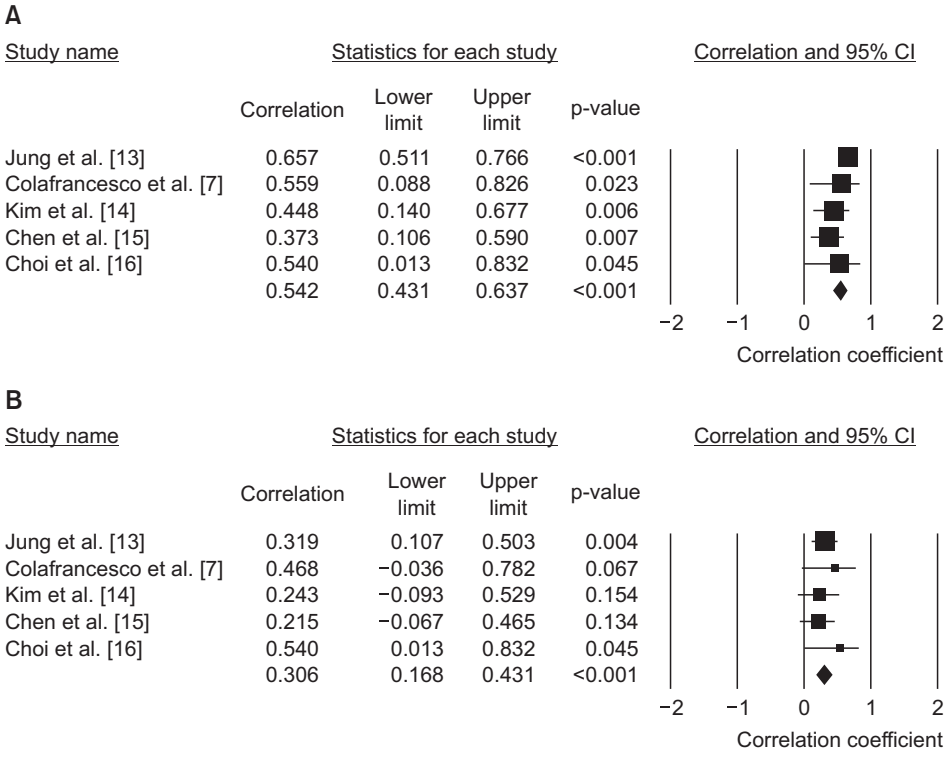

Figure 3. Meta-analysis showing the correlation coefficient between circulating IL-18 levels and ferritin (A), as well as CRP (B). IL-18: interleukin-18, CRP: C-reactive protein, CI: confidence interval.

study investigated a 6.7 kb region upstream of exon 2 of the IL-18 gene, which included promoter activity, and identified seven SNPs and a single 9 bp insertion frequently present in AOSD patients [19]. This study found a significantly higher frequency of individuals carrying the S01/S01 genotype in AOSD patients compared to healthy controls (OR=7.81, 95% CI=2.48~24.65, p<0.001) [19].

Heterogeneity, sensitivity test, and publication bias

Heterogeneity was observed in the meta-analysis of IL-18 levels in AOSD patients (Table 3). A significant portion of the variability was attributed to different effect sizes, although the effect sizes were consistently oriented across studies. Significant heterogeneity was noted in the meta-analysis of IL-18 levels in relation to sample size and ethnicity (p<0.05); however, study quality, data format, and publication year had no significant impact on heterogeneity based on meta-regression tests. Sensitivity analysis indicated that the inclusion or exclusion of any single study did not affect the meta-analysis results, demonstrating reliability. We found no evidence of publication bias, as indicated by the absence of asymmetry in the funnel plot and non-significant Egger's regression test results (p>0.05).

DISCUSSION

This study shows that the significant increase in circulating IL-18 levels among patients with AOSD compared to controls underscores the potential role of this cytokine in the disease's pathogenesis. Higher IL-18 levels observed in both Asian and European populations with AOSD suggest the broad applicability of these results across different ethnic groups. This meta-analysis revealed a positive correlation between IL-18 levels and established inflammation markers, ferritin, and CRP, strengthening the argument that IL-18 is involved in the inflammatory processes associated with AOSD. The lack of significant differences in IL-18 levels between active and inactive disease groups is noted. This discrepancy may be due to the comparison of total IL-18 levels rather than free IL-18 levels. It is possible that free IL-18 levels differ between active and inactive patients with AOSD [29]. Therefore, free IL-18 levels or the IL-18/IL-18 binding protein ratio imbalance may serve as more useful biomarkers for AOSD [30]. We included a comparison based on free IL-18 levels as a subgroup analysis. Free IL-18 levels were significantly higher in the active group compared to the inactive group (SMD=0.900, 95% CI=0.532~1.268, p<0.001).

The IL-18 gene polymorphisms, particularly the –607 C/A polymorphism, may be a susceptibility factor for AOSD,

implying a potential genetic predisposition related to the regulatory regions of IL-18. The A allele at position 607 in the IL-18 promoter region may be linked to susceptibility to AOSD in the Korean population [18]. This allele, part of haplotype of the IL-18 gene reported by Sugiura et al. [19], was associated with AOSD development in a Japanese population. However, lower frequencies of single-nucleotide polymorphisms (607/AA) were observed in Chinese patients with AOSD compared to healthy controls [17], suggesting variation in genetic susceptibility among ethnic groups. Genetic studies suggest that the regulatory regions of IL-18 are associated with AOSD development. The A allele at position –607 in the IL-18 promoter region was associated with the susceptibility to AOSD in Korean and Japanese populations, but the SNP –607/AA genotype was a protective factor against occurrence of AOSD in the Chinese population. Population-specific genetic backgrounds and environmental influences likely contribute to the observed differences in the role of the –607/AA genotype in AOSD susceptibility between Korean, Japanese, and Chinese populations.

Elevated IL-18 levels enhance the activation of various immune cells, leading to an exaggerated inflammatory response [1]. IL-18 contributes directly to disease activity through multiple mechanisms, including the promotion of pro-inflammatory Th1 responses, the induction of cytokine and chemokine production, the activation of NK cells, and the promotion of apoptosis and tissue damage [31]. IL-18's ability to promote Th1-type immune responses may be a key mechanism underlying AOSD [3]. The upregulation of Th1 cytokines, such as interferon-γ, may perpetuate the inflammatory cascade, contributing to the clinical manifestations of AOSD. The positive correlation between IL-18 levels, ferritin, and CRP levels suggests that IL-18 amplifies inflammatory responses, stimulating the production of these acute-phase reactants and contributing to the systemic inflammation and clinical manifestations of AOSD. The correlation with ferritin, a marker of macrophage activation, implies that IL-18 may be involved in macrophage dysregulation, contributing to the hyperinflammatory state observed in AOSD [32]. Polymorphisms in the IL-18 gene, such as the –607 C/A variant, may modulate IL-18 expression. Genetic predisposition through variations in the regulatory regions of IL-18 could influence IL-18 production and release, contributing to AOSD susceptibility. Genetic variations may lead to an altered immune response, affecting the balance between pro- and anti-inflammatory signals, potentially triggering or exacerbating AOSD. Higher IL-18 concentrations have been measured in AOSD patients with macrophage activation syndrome (MAS) than patients with an active disease without MAS [33]. IL-18 plays a central role in the pathogenesis of MAS in AOSD by driving the hyperinflammatory response, promoting cytokine storms, and contributing to the dysfunction of immune cells like NK cells [5]. IL-18 has a role comparable to IL-1β, but unlike IL-1β, which is not reliably detected in peripheral blood, IL-18 or free IL-18 can be measured in peripheral blood using ELISA (enzyme-linked immunosorbent assay) [34]. This makes IL-18, along with ferritin and CRP, an important biomarker for diagnosing AOSD, evaluating disease activity, and predicting outcomes, such as the risk of progression to MAS. On the other hand, IL-6 is more strongly linked to articular symptoms rather than systemic manifestations in AOSD.

It is important to acknowledge the limitations of this meta-analysis. First, the limited number of included studies may have reduced the statistical power. Second, considerable variability among the included studies may have compromised the reliability of the conclusions. We performed the subgroup analysis and meta-regression test to explore potential sources of heterogeneity. Subgroup analysis showed no heterogeneity in Europeans and meta-regression test revealed ethnicity and sample size had significant impact on heterogeneity. Third, the predominant use of a cross-sectional design in the included studies poses challenges in establishing a causal relationship between IL-18 and AOSD. Therefore, longitudinal studies or larger cohort studies are necessary to establish causality between IL-18 and AOSD. Nevertheless, this meta-analysis has strengths. To our knowledge, this is the first study to concurrently examine two key aspects: IL-18 levels and polymorphisms in IL-18-encoding loci in patients with AOSD. Despite individual trial cohort sizes ranging from 13 to 204 patients, our combined analysis included 562 patients. Moreover, our approach, which combined findings from multiple independent analyses, enhanced the statistical power and resolution of the study [35].

CONCLUSION

This meta-analysis revealed a significant elevation in circulating IL-18 levels in patients with AOSD compared to controls, showed a positive correlation between IL-18 levels and ferritin and CRP levels, and suggested an association between IL-18 polymorphisms and AOSD susceptibility. These findings sug-

gest a crucial role for IL-18 in the pathogenesis of AOSD. However, further investigations are necessary to determine the direct contribution of IL-18 to AOSD pathogenesis.

FUNDING

None.

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

Y.H.L. has been an editorial board member since March 2013, but has no role in the decision to publish this article.

AUTHOR CONTRIBUTIONS

Y.H.L. was involved in conception and design of study, acquisition of data, analysis and/or interpretation of data, drafting the manuscript, revising the manuscript critically for important intellectual content. G.G.S. was involved in conception and design of study, analysis and interpretation of data, and drafting the manuscript.

ORCID

Young Ho Lee, https://orcid.org/0000-0003-4213-1909
Gwan Gyu Song, https://orcid.org/0000-0003-3492-2225

REFERENCES

1. Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. J Autoimmun 2018;93:24-36.
2. Lee JH, Ha YJ, Kang EH, Chang SH, Lee YJ. A case of macrophage activation syndrome during the treatment of adult-onset Still's disease with tocilizumab. J Rheum Dis 2022;29:123-8.
3. Wang MY, Jia JC, Yang CD, Hu QY. Pathogenesis, disease course, and prognosis of adult-onset Still's disease: an update and review. Chin Med J (Engl) 2019;132:2856-64.
4. Kaplanski G. Interleukin-18: biological properties and role in disease pathogenesis. Immunol Rev 2018;281:138-53.
5. Baggio C, Bindoli S, Guidea I, Doria A, Oliviero F, Sfriso P. IL-18 in autoinflammatory diseases: focus on adult onset Still disease and macrophages activation syndrome. Int J Mol Sci 2023;24:11125.
6. Motavaf M, Safari S, Alavian SM. Interleukin 18 gene promoter polymorphisms and susceptibility to chronic hepatitis B infection: a review study. Hepat Mon 2014;14:e19879.
7. Colafrancesco S, Priori R, Alessandri C, Perricone C, Pendolino M, Picarelli G, et al. IL-18 serum level in adult onset Still's disease: a marker of disease activity. Int J Inflam 2012;2012:156890.
8. Priori R, Barone F, Alessandri C, Colafrancesco S, McInnes IB, Pitzalis C, et al. Markedly increased IL-18 liver expression in adult-onset Still's disease-related hepatitis. Rheumatology (Oxford) 2011;50:776-80.
9. Chen PK, Lan JL, Huang PH, Hsu JL, Chang CK, Tien N, et al. Interleukin-18 is a potential biomarker to discriminate active adult-onset Still's disease from COVID-19. Front Immunol 2021;12:719544.
10. Ichikawa T, Shimojima Y, Kishida D, Ueno KI, Sekijima Y. The implication of interferon-γ-producing immunocompetent cells for evaluating disease activity and severity in adult-onset Still's disease. Int J Rheum Dis 2021;24:1176-85.
11. Hung WT, Chen YM, Hung SI, Chen HH, Gung NR, Hsieh CW, et al. CARD8 SNP rs11672725 identified as a potential genetic variant for adult-onset Still's disease. Life (Basel) 2021;11:382.
12. Kim HA, Choi B, Suh CH, Han MH, Jung JY, Sayeed HM, et al. Highly expression of CD11b and CD32 on peripheral blood mononuclear cells from patients with adult-onset Still's disease. Int J Mol Sci 2017;18:202.
13. Jung KH, Kim JJ, Lee JS, Park W, Kim TH, Jun JB, et al. Interleukin-18 as an efficient marker for remission and follow-up in patients with inactive adult-onset Still's disease. Scand J Rheumatol 2014;43:162-9.
14. Kim HA, An JM, Nam JY, Jeon JY, Suh CH. Serum S100A8/A9, but not follistatin-like protein 1 and interleukin 18, may be a useful biomarker of disease activity in adult-onset Still's disease. J Rheumatol 2012;39:1399-406.
15. Chen DY, Lan JL, Lin FJ, Hsieh TY. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. J Rheumatol 2004;31:2189-98.
16. Choi JH, Suh CH, Lee YM, Suh YJ, Lee SK, Kim SS, et al. Serum cytokine profiles in patients with adult onset Still's disease. J Rheumatol 2003;30:2422-7.
17. Chen DY, Chen YM, Chen HH, Hsieh CW, Lin CC, Lan JL. Functional association of interleukin 18 gene –607 (C/A) promoter polymorphisms with disease course in Chinese patients with adult-onset Still's disease. J Rheumatol 2009;36:2284-9.
18. Her MY, Kim SK, Sung YK, Lee HS, Uhm WS, Kim TH, et al. Association of interleukin-18 polymorphisms with adult onset Still's disease in Korea. J Korean Rheum Assoc 2006;13:116-22.
19. Sugiura T, Kawaguchi Y, Harigai M, Terajima-Ichida H, Kitamura Y, Furuya T, et al. Association between adult-onset Still's disease and interleukin-18 gene polymorphisms. Genes Immun 2002;3:394-9.
20. Lee YH. An overview of meta-analysis for clinicians. Korean J Intern Med 2018;33:277-83.
21. 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.
22. Ridout KK, Ridout SJ, Price LH, Sen S, Tyrka AR. Depression and telomere length: a meta-analysis. J Affect Disord 2016;191:237-47.
23. Wells G, Shea B, O'connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonran-

domised studies in meta-analyses. Ottawa, Ottawa Hospital Research Institute, 2000.
24. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
25. Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. BMJ 1997;315:1533-7.
26. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
27. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.
28. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
29. Park JH, Kim HS, Lee JS, Kim JJ, Jung KH, Park YW, et al. Natural killer cell cytolytic function in Korean patients with adult-onset Still's disease. J Rheumatol 2012;39:2000-7.
30. Girard C, Rech J, Brown M, Allali D, Roux-Lombard P, Spertini F, et al. Elevated serum levels of free interleukin-18 in adult-onset Still's disease. Rheumatology (Oxford) 2016;55:2237-47.
31. Ihim SA, Abubakar SD, Zian Z, Sasaki T, Saffarioun M, Maleknia S, et al. Interleukin-18 cytokine in immunity, inflammation, and autoimmunity: biological role in induction, regulation, and treatment. Front Immunol 2022;13:919973.
32. Tomaras S, Goetzke CC, Kallinich T, Feist E. Adult-onset Still's disease: clinical aspects and therapeutic approach. J Clin Med 2021;10:733.
33. Inoue N, Shimizu M, Tsunoda S, Kawano M, Matsumura M, Yachie A. Cytokine profile in adult-onset Still's disease: comparison with systemic juvenile idiopathic arthritis. Clin Immunol 2016;169:8-13.
34. Tapia VS, Daniels MJD, Palazón-Riquelme P, Dewhurst M, Luheshi NM, Rivers-Auty J, et al. The three cytokines IL-1β, IL-18, and IL-1α share related but distinct secretory routes. J Biol Chem 2019;294:8325-35.
35. Lee YH. Meta-analysis of genetic association studies. Ann Lab Med 2015;35:283-7.