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Original Article

Associations Between Circulating Interleukin-17 Levels and Systemic Lupus Erythematosus and Between Interleukin-17 Gene Polymorphisms and Disease Susceptibility: A Meta-analysis

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Objective. To systematically investigate the relationship between circulating interleukin-17 (IL-17) levels and systemic lupus erythematosus (SLE) and associations between polymorphisms in *IL17* genes and SLE susceptibility. **Methods.** We performed a meta-analysis of serum/plasma IL-17 levels in patients with SLE and controls and evaluated the associations between the *IL17A* rs2275913, *IL17F* rs763780, and *IL17F* rs2397084 polymorphisms and *IL17F* copy number variations (CNVs) and risk of SLE. **Results.** Thirteen studies focusing on 2,096 patients with SLE and 2,587 controls were included. Our meta-analysis revealed that IL-17 levels were significantly higher in the SLE group than the control group (standardized mean difference = 1.045, 95% confidence interval [95% CI] = 0.521 ~ 1.568, $p < 0.001$). Subgroup analysis using sample size showed increased IL-17 levels in samples from large ($n > 100$) but not small ($n < 90$) SLE groups. We found no evidence of associations between SLE and the *IL17A* rs2275913, *IL17F* rs763780, and *IL17F* rs2397084 polymorphisms. However, a significant association was found between SLE and *IL17F* CNVs in a pooled cohort of affected individuals compared to that in pooled controls (odd ratio = 3.663, 95% CI = 2.466 ~ 5.221, $p < 0.001$). **Conclusion.** This meta-analysis revealed significantly higher circulating IL-17 levels in patients with SLE and showed evidence of associations between *IL17F* CNVs and SLE. **(J Rheum Dis 2020;27:37-44)**

Key Words. Interleukin-17, Polymorphism, Systemic lupus erythematosus

INTRODUCTION

Systemic lupus erythematosus (SLE) is characterized by immune regulation disruption and multisystem involvement and is mediated by autoantibodies and immune complex deposits [1]. Disrupted immune regulation via dysregulation of B- and T-cell activation and aberrant production of cytokines plays a key role in SLE pathogenesis [2]. Although the etiology of SLE is incompletely understood, it is clear that genetic components play key roles in SLE pathogenesis [2,3].

A subtype of T cells, Th17 cells, secrete interleukin-17 (IL-17), which is a pleiotropic pro-inflammatory cytokine that enhances T-cell priming and stimulates epithelial, endothelial, and fibroblastic cells to produce multiple proinflammatory mediators such as tumor necrosis factor-alpha (TNF-α), IL-1β, IL-6, and chemokines [4]. IL-17 plays a critical role in innate and adaptive immune systems by promoting inflammation, cytokine production, B-cell proliferation, and autoantibodies production [4]. IL-17 consists of six protein members [IL-17A, IL-17B, IL17-C, IL-17D, IL-17E (IL-25), and IL-17F] of which IL-17A and IL-17F are responsible for the activity of Th17 cells in the induction of other cytokines and chemokines [5]. *IL17A* and *IL17F* are both located on chromosome 6p12, which is a genomic region linked to SLE [6]. In addition to the ability of IL-17 to regulate inflammatory reactions and immune responses and because of their chro-

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mosomal location, these genes are considered potential candidate genes for SLE.

Several studies investigating circulating IL-17 levels in patients with SLE compared to healthy controls and testing polymorphisms in different *IL17*-encoding genes have found associations with SLE susceptibility [7-19]. Thus, we performed a meta-analysis to overcome the limitations of individual studies and to resolve the inconsistencies in their findings. The aim of our meta-analysis was to review systematically available evidence on serum/plasma IL-17 levels in patients with SLE compared to those found in controls and to determine whether polymorphisms in *IL17*-encoding genes were associated with SLE susceptibility.

MATERIALS AND METHODS

Identification of eligible studies and data extraction

We performed a literature search for studies that examined IL-17 levels in patients with SLE and controls, evaluated the relationship between circulating (serum or plasma) IL-17 levels, or tested for associations between polymorphisms in *IL17* genes and SLE. PUBMED, EMBASE, and Cochrane databases were searched to identify all available articles (up to August 2019). The following key words and terms were used in the search: "IL-17", "level OR serum OR plasma", "polymorphism", "systemic lupus erythematosus", and "SLE". In addition, all references cited were reviewed to identify additional studies that were not included in the above-mentioned electronic databases. Studies were considered eligible based on the following inclusion criteria: (1) they were case-control, cohort, or cross-sectional studies; (2) they provided data on IL-17 levels in both affected and control groups; (3) they included at least 10 patients with SLE; and (4) they tested *IL17* gene polymorphisms in SLE and control groups. Studies were excluded if: (1) they contained overlapping or insufficient data or (2) they were reviews or case reports. Data on the methods and results were extracted from original studies by two independent reviewers. Discrepancies between the reviewers were resolved by consensus. We performed the meta-analysis in accordance with PRISMA guidelines [20]. The following information was extracted from each study: primary author, year of publication, country, ethnicity, adjustments for age and sex, number of participants, mean and standard deviation (SD) of IL-17 levels, and allele and genotype frequencies of polymorphisms in *IL17* genes. When data were presented as medians, interquartile ranges, or ranges, the mean and SD values were derived using previously described formulae [21,22].

Evaluation of statistical associations

We performed a meta-analysis to examine the relationship between IL-17 levels and SLE and to evaluate the allelic effect of the minor allele versus the major allele of different polymorphisms in *IL17* genes. For continuity of data, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). Odd ratios (ORs) and 95% CIs were calculated for dichotomous data. We assessed within-study and between-study variations and heterogeneities using Cochran's Q-statistics [23]. The heterogeneity test was used to assess the null hypothesis that all studies were evaluating the same effect. When the Q-statistic was significant ($p<0.10$), indicating heterogeneity across studies, a random effect model was used for the meta-analysis; otherwise, a fixed effect model was applied [24]. It was assumed that all studies estimated the same underlying effect and specifically considered within-study variation [23]. We quantified the effect of heterogeneity using $I^2=100\% \times (Q\text{-}df)/Q$ [25], where I^2 was a measure of the degree of inconsistency between studies and determines whether the percentage total variation across studies was due to heterogeneity and not chance. I^2 ranged from 0% and 100%. I^2 values of 25%, 50%, and 75% were referred to as low, moderate, and high estimates, respectively [25]. Statistical determinations were performed using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

Evaluation of heterogeneity, sensitivity test, and publication bias

To examine potential sources of heterogeneity observed in the meta-analysis, a meta-regression analysis was performed using the following variables: ethnicity, adjustment for age and/or sex, publication year, sample size, and data type. A sensitivity test to assess the influence of each individual study on the pooled effect size was performed by omitting each study individually. Although funnel plots are often used to detect publication bias, they require diverse study types of varying sample sizes, and their interpretation involves subjective judgment. Therefore, we assessed publication bias using Egger's linear regression test [26], which measures funnel plot asymmetry using a natural logarithm scale of the effect size.

Table 1. Characteristics of individual studies included in the meta-analysis

A. IL-17 level

Author	Country	Ethnicity	Cohort size (n)		IL-17 level (pg/mL or ng/L)		Statistical findings		
			Cases	Controls	Cases	Controls	SMD	Magnitude*	p-value
Cheng et al., 2019 [7]	China	Asian	45	50	40.82	14.94	1.524	Large	0.000
Jin et al., 2018 [8]	China	Asian	55	55	4.58	4.01	0.438	Small	0.023
Shahin et al., 2017 [9]	Egypt	Arab	57	42	79.75	24.80	1.649	Large	0.000
Peliçari Kde et al., 2015 [10]	Brazil	Latin American	67	47	48.97	34.05	0.803	Large	0.000
AlFadhi et al., 2016 [11]	Kuwait	Arab	50	8	13.90	16.70	−0.655	Medium	0.089
Boghdadi et al., 2014 [12]	Egypt	Arab	40	30	44.12	7.00	1.919	Large	0.000
Rana et al., 2012 [13]	India	Asian	40	20	766.95	175.70	2.009	Large	0.000
Cheng et al., 2009 [14]	China	Asian	24	32	159.50	106.67	0.569	Medium	0.039

IL-17: interleukin-17, SMD: standard mean difference. *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.

B. *IL17* polymorphisms

Author	Country	Ethnicity	Cohort size (n)		*IL17* gene and polymorphism tested	Statistical findings (p-value)
			Cases	Controls		
Pasha et al., 2019 [15]	Egypt	Arab	80	80	rs2275913	rs2275193 (p=0.048)
Montúfar-Robles et al., 2019 [16]	Mexico	Latin American	367	499	rs2275913	NS
Paradowska et al., 2016 [17]	Poland	European	139	106	rs763780, rs2397084	rs763780 (p=0.001), rs2275193 (NS)
Hammad et al., 2016 [18]	Egypt	Arab	115	259	rs2275913, rs763780, rs2397084	NS
Yu et al., 2011 [19]-1	China	Asian	576	953	IL-17F CNV	IL-17F CNV (p<0.001)
Yu et al., 2011 [19]-2	China	Asian	441	406	IL-17F CNV	IL-17F CNV (p<0.001)

CNV: copy number variation, NS: not significant.

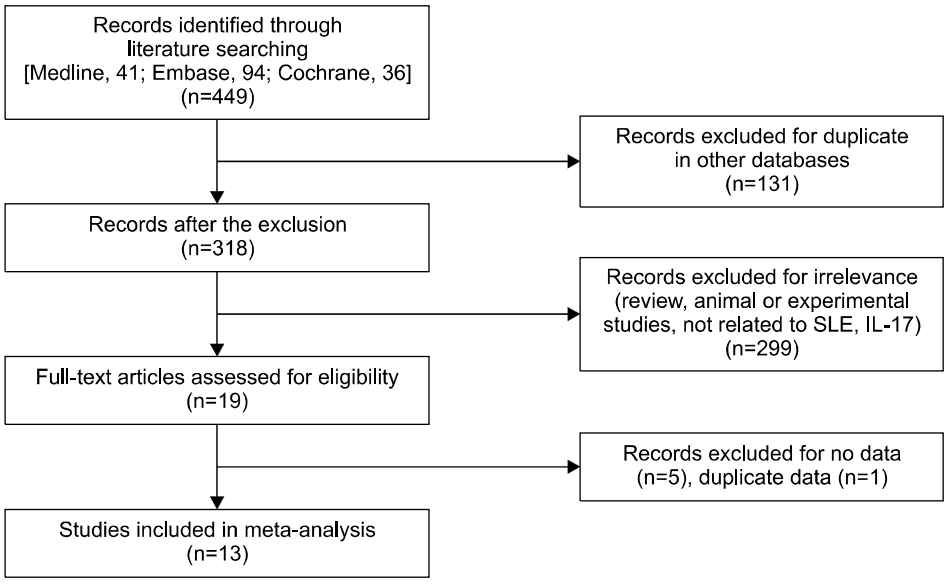

Figure 1. Flow diagram of the study selection process. SLE: systemic lupus erythematosus, IL-17: interleukin-17.

RESULTS

Studies included in the meta-analysis

We identified 449 studies using electronic and manual search methods of which 19 were selected for full-text review based on the title and abstract, and six were excluded because they either lacked data or provided duplicated data. Therefore, 13 articles met our inclusion criteria [7-19] (Figure 1). One of the eligible studies contained data on two different groups [19], which were treated independently. Fourteen comparisons were examined in the meta-analysis, which consisted of 2,096 patients with SLE and 2,587 controls (Table 1). Eight studies examined IL-17 levels in affected and control groups, and six comparative studies from five articles evaluated polymorphisms in *IL17* genes in both the SLE and control groups (Table 1). Meta-analysis of *IL17*-related polymorphisms was performed if there were at least two comparisons. Because of the limited number of candidate-gene association studies, four types of meta-analyses were performed: rs2275913 in *IL17A* and rs763780, rs2397084, and copy number variations (CNVs) in *IL17F*. Characteristic features of the studies included in the meta-analysis are summarized in Table 1.

Meta-analysis of circulating IL-17 levels in patients with SLE compared to those in controls

Using meta-analysis, we found that IL-17 levels were significantly higher in the SLE group than those in the control group (SMD=1.045, 95% CI=0.521～1.568, p< 0.001) (Table 2, Figure 2). Stratification based on ethnicity revealed higher IL-17 levels in the SLE group among Asian and Latin American populations but not in Arabs (Table 2). Subgroup analysis using sample size showed significantly higher IL-17 levels for large (n> 100) but not small (n<90) sample groups in the SLE group compared to those found in the control group (Table 2).

Table 2. Meta-analysis of the association between circulating IL-17 levels and SLE

Groups	Population	No. of studies	Test of association			Test of heterogeneity		
			SMD	95% CI	p-value	Model	p-value	I^2
All	Pooled	8	1.045	0.521～1.568	<0.001	R	<0.001	88.7
Phenotype	SLE	5	1.370	0.806～1.935	<0.001	R	<0.001	83.8
	LN	3	0.806	−0.006～1.618	0.052	R	0.001	85.7
Ethnicity	Asian	4	1.113	0.399～1.827	0.002	R	<0.001	88.1
	Arab	3	0.999	0.358～2.355	0.149	R	<0.001	93.8
	Latin American	1	0.803	0.416～1.190	<0.001	NA	NA	NA
Sample size	n≤90*	4	0.974	0.153～2.106	0.091	R	<0.001	92.4
	n>90	4	1.091	0.523～1.659	<0.001	R	<0.001	86.4

IL-17: interleukin-17, SLE: systemic lupus erythematosus, SMD: standard mean difference, CI: confidence interval, n: number, R: random effects model, LN: lupus nephritis, NA: not available. *Number of patients with SLE.

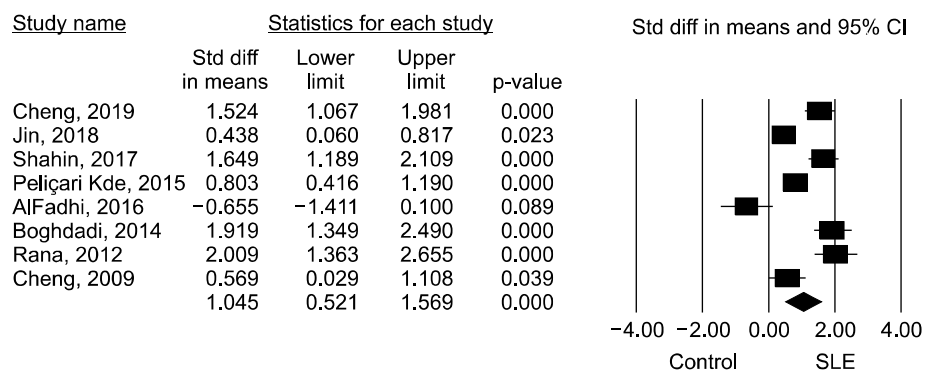

Figure 2. Meta-analysis of the relationship between circulating IL-17 levels and SLE. IL-17: interleukin-17, SLE: systemic lupus erythematosus, Std diff: standard difference, CI: confidence interval.

Meta-analysis of *IL17A* rs2275913, *IL17F* rs763780, and *IL17F* rs2397084 polymorphisms and *IL17F* CNVs and SLE susceptibility

Our meta-analysis revealed no evidence of an association between the *IL17A* rs2275913, *IL17F* rs763780, and *IL17F* rs2397084 polymorphisms and SLE susceptibility (Table 3, Figure 3). However, our meta-analysis showed a significant association between SLE and *IL17F* CNVs in a pooled cohort of affected individuals compared to those found in pooled controls (OR=3.663, 95% CI=2.466～5.221, $p<0.001$) (Table 3, Figure 3).

Heterogeneity and publication bias

Between-study heterogeneity was identified during the meta-analyses of IL-17 levels in patients with SLE (Table 2). However, meta-regression analysis showed that ethnicity, data type, sample size, and adjustment for age and/or sex had no effect on heterogeneity in our meta-analysis of IL-17 levels in patients with SLE (all $p>0.05$). Sensitivity analysis showed that no individual study significantly affected the pooled SMD, indicating that the results of this meta-analysis were robust. No heterogeneity was found in the meta-analyses of polymorphisms in *IL17* genes, with the exception of rs22759136 in *IL17A* and rs763780 in *IL17F*. However, the studies included in the meta-analysis for rs763780 showed the same directionality of the ORs (Figure 2). Publication bias results from a disproportionate number of positive studies and poses a problem for meta-analyses. However, we found no evidence of publication bias for any of the study subjects (i.e., the funnel plot showed no evidence of asymmetry, and from Egger's regression test all $p>0.05$).

DISCUSSION

In this meta-analysis, evidence for elevated circulating IL-17 levels in SLE and for association between polymorphisms in *IL17* genes and SLE susceptibility were evaluated. Our meta-analysis of 13 studies, which included 2,096 patients with SLE and 2,587 controls, showed that circulating IL-17 levels were significantly higher in the SLE group than the control group. The reason of significantly higher IL-17 levels for large but not small sample groups is unclear, but it may be explained by statistical power due to sample size. In addition, we showed a significant association between *IL17F* CNVs and SLE susceptibility. These findings indicate that an increased IL-17 level may play a role in the pathogenesis of SLE and that CNVs from *IL17*-encoding genes may be associated with SLE risk. Our meta-analysis provides evidence that higher IL-17 levels are correlated with pathogenesis of SLE and, therefore, supports the involvement of Th17 cells in SLE. Th17 cells have been increasingly recognized as important mediators of autoimmune diseases [27]. Th17 cells are associated with the production of mediators of inflammation; thus, they have potentially pathogenic roles in autoimmune disease [27]. IL-17, a major effect factor of Th17 cells, is a potent pro-inflammatory cytokine that is produced by activated T lymphocytes and is also a potent inducer of TNF-α, IL-1-β, IL-6, IL-8, and G-CSF [4]. Our findings that IL-17 levels increase in the patients with SLE support a role of IL-17 in the pathophysiology of SLE.

Given the potential link between IL-17 and autoimmune diseases, polymorphisms in *IL17* genes, which can affect IL-17 expression, have been studied as potential causes of

Table 3. Meta-analysis of tests of association between polymorphisms in *IL17* genes and SLE

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-value	Model	p-value	I^2
IL-17A rs2275913 G vs. A	Pooled	3	1.074	0.800～1.441	0.637	R	0.125	51.9
IL-17F rs763780 G vs. A	Pooled	2	2.122	0.898～5.017	0.087	R	0.058	72.2
IL-17F rs2397084 G vs. A	Pooled	2	0.804	0.549～1.19	0.264	F	0.896	0
IL-17F CNVs A vs. NA	Pooled	2	3.663	2.466～5.441	0.001	F	0.719	0

SLE: systemic lupus erythematosus, OR: odds ratio, CI: confidence interval, R: random effect model, F: fixed effect model, A: amplification, NA: nonamplification, CNVs: copy number variations.

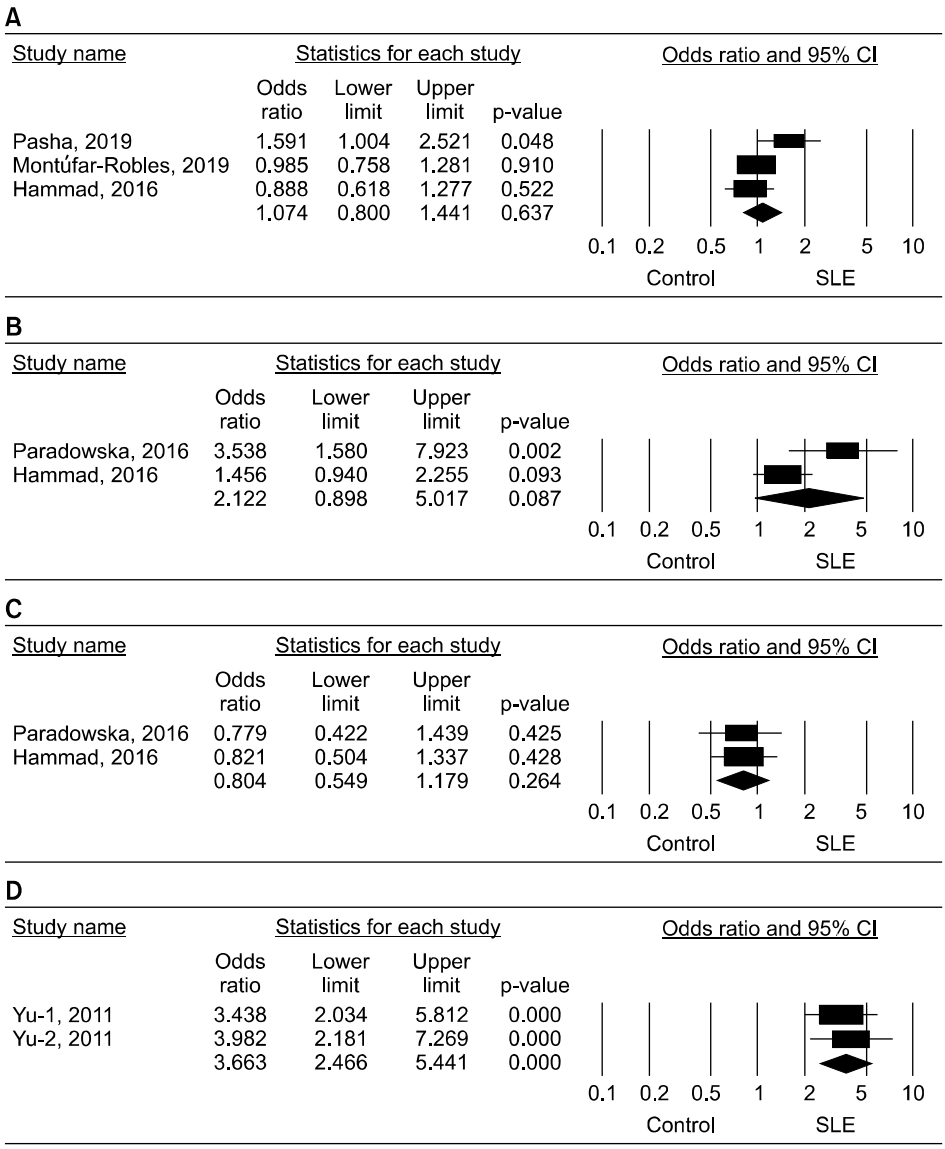

Figure 3. Odds ratios and 95% confidence intervals (CIs) of studies and pooled data for allelic association between *IL17A* rs2275913 (A), *IL17F* rs763780 (B), *IL17F* rs2397084 (C), and *IL17F* copy number variation (D) polymorphisms and systemic lupus erythematosus (SLE).

autoimmune diseases [28,29]. Our meta-analysis revealed an association between *IL17F* CNVs and SLE, in agreement with the results of functional studies conducted on the *IL17F* CNV polymorphism [19]. Increased copy numbers of IL-17F correlated with elevated mRNA levels [19]. Based on these findings and on those showing that *IL17F* CNVs are associated with both altered expression of IL-17, which can lead to elevated IL-17 levels, we propose a link between these variants and the development of SLE. However, our results on the association between the *IL17A* rs2275913, *IL17F* rs763780, and *IL17F* rs2397084 polymorphisms and SLE risk are not consistent with the functional studies of the polymorphisms. This may be because of the difference in clinical characteristics of the studied populations. In addition, genetic association results sometimes do not coincide with the results of functional studies for complex autoimmune diseases such as SLE. Multiple genes, genetic backgrounds, and environmental factors contribute to SLE development. Our negative results for the *IL-17* polymorphisms might also be due to Type II error.

This meta-analysis has a few limitations. First, most of the recruited studies had small sample sizes, and a limited number of studies tested for evidence of an association between different polymorphisms in *IL17* genes and its levels and SLE. Therefore, our meta-analysis may be underpowered. Second, the studies examined were heterogeneous with regard to both demographic characteristics and clinical features. Heterogeneity, confounding factors, and limited clinical information in these study

populations may confound the results. Third, publication bias may adversely affect our analysis because studies with negative findings may not be published or identified in our search. Although we used Egger's regression test, the possibility of bias cannot be eliminated. Fourth, inflammatory cytokine level such as IL-17 varies according to disease activity, pre and post-treatment, and treatment drug types, even if measured in the same person. However, it is not possible to verify that all IL-17 levels of SLE patients were measured under the same conditions because individual papers do not indicate that they were all measured under the same conditions. Nevertheless, this meta-analysis also has its strengths. To the best of our knowledge, our meta-analysis is the first study that provides two parallel lines of evidence examining both IL-17 levels and polymorphisms in *IL17*-encoding genes in patients with SLE. While individual studies had a limited cohort size ranging from 24 to 576 participants, our pooled analysis had 2,096 patients. In addition, compared to individual studies, our study was able to provide data that were accurate by increasing the statistical power and resolution of the analysis through pooling the results of these independent analyses.

CONCLUSION

In conclusion, our meta-analysis demonstrated that circulating IL-17 levels were significantly higher in patients with SLE than the controls and that *IL17F* CNVs were associated with SLE susceptibility. Based on these findings, we conclude that IL-17 may have an important role in the pathogenesis of SLE. However, further studies are warranted to determine whether IL-17 levels directly contribute to the development of SLE.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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/or interpretation of data, drafting the manuscript.

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