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Meta-Analysis

Circulating macrophage migration inhibitory factor levels and its polymorphisms in systemic lupus erythematosus: A meta-analysis

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Abstract: The present study aimed to systemically review the evidence regarding the relationship between circulating macrophage migration inhibitory factor (MIF) levels and systemic lupus erythematosus (SLE), as well as the associations between several polymorphisms in the *MIF* gene and SLE susceptibility. We performed a meta-analysis of serum/plasma levels of MIF in SLE patients and controls and evaluated evidence of associations between the *MIF -173 C/G* allele and *-794CATT*$_{5-8}$ polymorphisms and the associated risk for SLE. Nine studies were included in this meta-analysis. Meta-analysis indicated that MIF levels were significantly higher in the SLE group than in the control group (SMD = 1.154, 95% CI = 0.369–1.938, $P = 0.004$). Stratification by ethnicity showed significantly higher MIF levels in the SLE group representing Asian populations (SMD = 1.911, 95% CI = 0.871–2.951, $P < 0.001$). MIF levels were significantly higher in the SLE group than in the control group in the age-and/or sex matched population, but not in the unmatched population (SMD = 1.236, 95% CI = 0.579–1.893, $P < 0.001$; SMD = 1.118, 95% CI = -0.027–2.263, $P = 0.056$). However, results of the meta-analysis showed no association between SLE and the *MIF -173 C* allele, the *-794CATT*$_7$ allele, and the *-794CATT*$_7$*-MIF-173C* haplotype with high heterogeneity. Our meta-analysis demonstrated significantly higher circulating MIF levels in patients with SLE, but no evidence of associations between *MIF -173 C/G* and *-794CATT*$_{5-8}$ polymorphisms and SLE susceptibility.

Key words: MIF; Level; Polymorphism; SLE.

Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterized by aberrant immune regulation, B-cell hyperactivity, excessive production of autoantibodies, and immune-complex deposition leading to intense inflammation and multiple organ damage. Although the etiology of SLE remains unclear, it has been known to be multifactorial and to be caused by interactions between genetic and environmental factors (1).

Macrophage migration inhibitory factor (MIF) is an important regulator of the innate and adaptive immune responses. MIF functions as a potent pro-inflammatory cytokine and is secreted by activated T lymphocytes and macrophages (2). MIF upregulates the production of interleukin-6, interferon-gamma, and tumor necrosis factor-alpha, as well as adhesion molecules, chemokines, and matrix metalloproteinases (3). MIF plays a critical role in the regulation of T-cell activation and produces signals that stimulate B-cell proliferation, thereby leading to B-cell hyperactivity. MIF also inhibits p53-dependent apoptosis and counteracts the anti-inflammatory effects of glucocorticoids (4). Anti-MIF treatment reduces glomerulonephritis in lupus-prone mice, and MIF levels were reported to be elevated in the blood of SLE patients when compared to healthy controls (5). The *MIF* gene is located in chromosome 22q11.2. Two functional promoter polymorphisms of the MIF gene have been studied (6), one of which is a G to C transition at -173 (rs755622) and the other a $(CAAT)_{5-8}$ tetranucleotide repeat at -794. The *MIF -173 C* allele generates a putative binding site of the activating enhancer binding protein 4 transcription factor and is associated with upregulated MIF mRNA and protein expression in a cell-type–dependent manner (7). The *MIF -173 C* allele is in strong linkage disequilibrium with the *-794CATT*$_7$ allele, and the *-794CATT*$_7$*-MIF-173C* haplotype correlates with increased MIF production (8). As a result, the *MIF* gene has been recognized as a candidate gene in SLE.

Studies investigating circulating MIF levels in SLE patients in comparison to healthy controls, and the *MIF -173 C/G* and *-794CATT*$_{5-8}$ polymorphisms have demonstrated associations with SLE pathogenesis and disease susceptibility in some, but not all, studies (9-17). In this study, we performed a meta-analysis to overcome the limitations of the individual studies and resolve inconsistencies in the obtained findings (18). The aim of our meta-analysis was to systematically review evidence on serum/plasma MIF levels in SLE patients compared to those in controls and to determine whether the *MIF -173 C/G* allele and *-794CATT*$_{5-8}$ polymorphisms are associated with SLE susceptibility.

Materials and Methods

Identification of eligible studies and data extraction

We performed a literature search for studies that examined MIF levels in SLE patients and controls, evalua-

ted the relationship between circulating (serum or plasma) MIF levels, or tested for associations between *MIF* polymorphisms and SLE. The MEDLINE, EMBASE, and Cochrane databases were searched to identify all available articles (up to February 2017). The following key words and terms were used in the search: "macrophage migration inhibitory factor," "MIF," "polymorphism," "systemic lupus erythematosus," and "SLE." In addition, all references cited in the original studies were reviewed to identify additional studies that were not included in the abovementioned electronic databases. Studies were considered eligible based on the following inclusion criteria: (1) they were studies with case-control design, (2) they provided data on MIF levels in both affected and control groups, and (3) they tested the *MIF -173 C/G* allele and/or *-794CATT*$_{5\text{-}8}$ polymorphisms in both SLE and control groups. No language or race/ethnicity restrictions were applied. Studies were excluded if the following criteria were met: (1) they contained overlapping or insufficient data, or (2) they were reviews or case reports. Data provided in the methods and results were extracted from original studies by two independent reviewers. Discrepancies between the reviewers were resolved by consensus. The meta-analysis was performed in accordance with PRISMA guidelines (19). The following data were extracted from each study: primary author, year of publication, country, ethnicity, adjustments for age and/or sex, number of participants, mean and standard deviation (SD) of MIF levels, and the allele and genotype frequencies of the *MIF -173 C/G* allele and *-794CATT*$_{5\text{-}8}$ polymorphisms. When data were presented as medians, interquartile ranges, or ranges, the mean and SD values were derived using previously described formulas (20, 21).

Evaluation of statistical associations

We performed a meta-analysis to examine the relationship between MIF levels and SLE risk and to examine the differences in the allelic effects of the *MIF -173 C/G* polymorphisms and *MIF -794CATT*$_7$ allele. In addition, corresponding differences with the *-794CATT*$_7$*-MIF-173C* haplotype were examined. For continuous data, results were presented as standardized mean differences (SMDs) and 95% confidence intervals (CIs). For dichotomous data, odds ratios (ORs) and 95% CIs were calculated. We assessed within-study and between-study variations and heterogeneities using Cochran's Q-statistics (22). The heterogeneity test was used to test the null hypothesis that all studies were evaluating the same effect. When the Q-statistic was significant ($P < 0.10$), which indicated heterogeneity across studies, a random effects model was used for the meta-analysis; otherwise, a fixed effects model was applied (23). It was assumed that all studies estimated the same underlying effect and specifically considered within-study variation (22). We quantified the effect of heterogeneity using $I^2 = 100\% \times (Q\text{-}df)/Q$ (24), where I^2 is a measure of the degree of inconsistency between studies and indicates the percentage of total variation across studies that was caused by heterogeneity and not by chance. I^2 values ranged from 0% and 100%, and I^2 values of 25%, 50%, and 75% were referred to as low, moderate, and high estimates, respectively (24). Statistical analyses were performed using the Comprehensive Meta-Analysis computer program (Biosta, Englewood, NJ, USA).

Evaluation of heterogeneity and publication bias

To identify potential sources of heterogeneity in the meta-analysis, meta-regression analysis was performed using the following variables: ethnicity, adjustment, publication year, sample size, and data type. A sensitivity test was conducted to evaluate the influence of each individual study on the pooled odds ratio (OR) by omitting each study individually. Although funnel plots are often used to detect publication bias, they require diverse study types with varying sample sizes, and their interpretation involves subjective judgment. Therefore, we assessed publication bias using Egger's linear regression test (25), which measures funnel plot asymmetry using a natural logarithm scale of the ORs.

Results

Studies included in the meta-analysis

We identified a total of 122 studies using electronic and manual search methods, out of which 12 were selected for full-text review based on the title and abstract and three were excluded because they either lacked data (26, 27) or provided duplicate data (28). A total of nine articles met our inclusion criteria (9-17) (Figure 1), and one of the eligible studies contained data on two different groups (13), which were treated independently and consisted of 648 SLE patients and 917 controls evaluated for MIF levels, and 2,118 SLE patients and 2,523 controls (Table 1). Nine studies examined MIF levels in affected and control groups, and four studies evaluated polymorphisms in the *MIF* gene in both SLE and control groups (Table 1). Four studies examined the *MIF -173 C/G* polymorphism, four studied the *-794CATT*$_7$ allele, and three studied the *-794CATT*$_7$*-MIF-173C* haplotype. More detailed information about the studies included in the meta-analysis is summarized in Table 1.

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

Meta-analysis revealed that individuals in the SLE group had significantly higher MIF levels than those

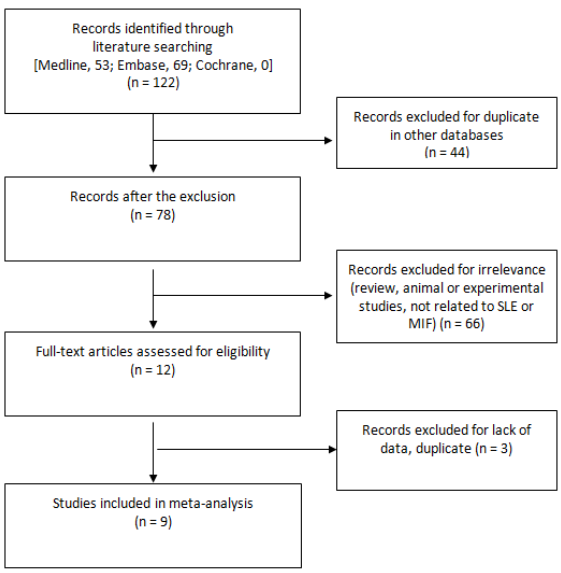

Figure 1. Flow chart showing the study selection.

Table 1. Detailed information on the individual studies included in the meta-analysis.

A. MIF level.

Author	Country	Ethnicity	Cohort size (N)		Data type	Statistical findings		
			Cases	Control		SMD	Magnitude[a]	*P* value
Feng, 2017(9)	China	Asian	35	21	Calculated	1.766	Large	< 0.001
Yanchun, 2015(10)	China	Asian	106	38	Original	1.585	Large	< 0.001
Cruz-Mosso, 2014(11)	Mexico	Latin American	135	200	Calculated	1.449	Large	< 0.001
Wang, 2012(12)	China	Asian	40	22	Calculated	0.495	Small	0.066
Sreih-1, 2011(13)	USA	Caucasian	116	55	Original	0.784	Medium	< 0.001
Sreih-2, 2011(13)	USA	African American	44	44	Original	0.122	No effect	0.567
Chen, 2004(14)	China	Asian	55	18	Original	2.030	Large	< 0.001
Foote, 2004(15)	Australia	Unknown	90	279	Original	0.401	Small	0.001
Mizue, 2000(16)	Japan	Asian	27	240	Original	3.677	Large	< 0.001

[a] Magnitude of Cohen's d effect size, where 0.2 to 0.5 indicates a small effect, 0.5 to 0.8 indicates a medium effect, and ≥ 0.8 indicates a large effect. *SMD*: Standardized mean difference.

B. MIF polymorphisms.

Author	Country	Ethnicity	Cohort size (N)		MIF polymorphism tested	Statistical findings (*P*-value)
			Cases	Controls		
Cruz-Mosso, 2014(11)	Mexico	Latin American	186	200	*MIF -173 C/G, -794CATT$_{5-8}$*	*MIF -173 C allele (p = 0.03), -794CATT$_7$ (p = 0.02)*
Sreih-1, 2011(13)	USA	Caucasian	1,042	1,395	*MIF -173 C/G, -794CATT$_{5-8}$*	*MIF -173 CC (p = 0.36), -794CATT$_7$ (p = 0.049)*
Sreih-2, 2011(13)	USA	African American	179	173	*MIF -173 C/G, -794CATT$_{5-8}$*	*MIF -173 CC (p = 0.007), -794CATT$_7$ (p = 0.25)*
Sanchez, 2006(17)	Spain	Caucasian	711	755	*MIF -173 C/G, -794CATT$_{5-8}$*	*MIF -173 CC (p = 0.004), -794CATT$_7$ (NS)*

NS: not significant.

in the control group (SMD = 1.154, 95% CI = 0.369–1.938, *P* = 0.004) (Table 2, Figure 2). Stratification by ethnicity showed significantly higher MIF levels in the SLE group in Asian populations (SMD = 1.911, 95% CI = 0.871–2.951, *P* < 0.001) (Table 2). MIF levels were significantly higher in the SLE group than in the control group in the age-and/or sex matched population, but not in the unmatched population (SMD = 1.236, 95% CI = 0.579–1.893, *P* < 0.001; SMD = 1.118, 95% CI = -0.027–2.263, *P* = 0.0560) (Table 2).

Meta-analysis of the MIF -173 C/G allele and -794CATT$_{5-8}$ polymorphisms and SLE susceptibility

Meta-analysis showed no association between SLE susceptibility and the *MIF -173 C* allele in a pooled cohort of affected individuals when compared to pooled controls (OR = 1.083, 95% CI = 0.842–1.939, *P* = 0.536) (Table 3). Stratification by ethnicity indicated no association between the *MIF -173 C* allele and SLE susceptibility in Caucasians and Asians (Table 3). In addition, meta-analysis of the *-794CATT$_7$* allele showed the same pattern as that observed for the C allele of the *MIF -173 C/G* polymorphism (Table 3). Meta-analyses of the *-794CATT$_7$-MIF-173C* haplotype showed no association with SLE susceptibility in the overall and Caucasian populations (Table 3).

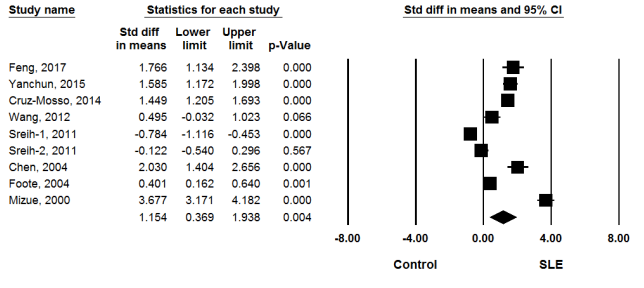

Figure 2. Meta-analysis of the relationship between circulating MIF levels and SLE susceptibility for all patients.

Table 2. Meta-analysis of the association between circulating MIF levels and SLE susceptibility.

Groups	Population	No. of studies	Test of association			Test of heterogeneity		
			SMD	95% CI	p-val	Model	p-val	I^2
All	Pooled	9	1.154	0.369 - 1.938	0.004	R	< 0.001	97.3
Ethnicity	Asian	5	1.911	0.871 - 2.951	< 0.001	R	< 0.001	94.8
	Non-Asian	4	0.242	-0.707 - -1.191	0.617	R	< 0.001	97.5
Age- and/or sex-matched	Yes	3	1.236	0.579 - 1.893	< 0.001	R	< 0.001	83.8
	No	6	1.118	-0.027 - 2.263	0.056	R	< 0.001	98.3

SMD: Standardized mean difference. * Magnitude of Cohen's d effect size: 0.2–0.5, small effect; 0.5–0.8, medium effect; ≥ 0.8, large effect. R: Random effects model.

Table 3. Meta-analysis of the associations of the *MIF -173 C/G* allele and *-794CATT$_{5-8}$* polymorphisms with SLE susceptibility.

Polymorphism	Population	No. of studies	Test of association			Test of heterogeneity		
			OR	95% CI	p-val	Model	p-val	I^2
-173 C/G C vs. G	Overall	4	1.083	0.842-1.939	0.536	R	0.002	79.0
	Caucasian	2	1.133	0.324-1.559	0.442	R	0.011	84.1
	AA	1	0.748	0.549-1.021	0.067	NA	NA	NA
	LA	1	1.390	1.018-1.899	0.038	NA	NA	NA
-794CATT$_7$ allele vs. others	Overall	4	1.011	0.766-1.333	0.940	R	0.010	73.3
	Caucasian	2	0.957	0.735-1.247	0.747	R	0.082	61.9
	AA	1	0.694	0.419-1.150	0.156	NA	NA	NA
	LA	1	1.467	1.061-2.029	0.020	NA	NA	NA
-794CATT$_7$-MIF-173C vs. others	Overall	3	0.886	0.394-1.990	0.769	R	< 0.001	93.8
	Caucasian	2	1.171	0.406-3.377	0.771	R	< 0.001	96.4
	AA	1	0.470	0.261-0.848	0.012	NA	NA	NA

R: Random effects model. F: Fixed effects model. NA: Not available. AA: African American. LA: Latin American.

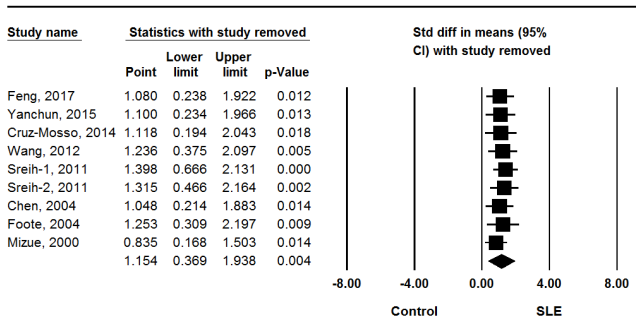

Figure 3. Sensitivity analysis on the relationship between circulating MIF levels and SLE susceptibility.

Heterogeneity, sensitivity test, meta-regression, and publication bias

Between-study heterogeneity was identified during the meta-analyses of MIF levels in SLE patients (Table 2). Meta-regression analysis revealed that ethnicity, adjustment, and data type (all $P < 0.001$), but not sample size and publication year (all $P > 0.05$), influenced heterogeneity in our meta-analysis. Heterogeneity was detected in the meta-analyses of the *MIF -173 C/G* allele and *-794CATT$_{5-8}$* polymorphisms (Table 3). Sensitivity analysis showed that no individual study significantly affected the pooled OR, indicating the robustness of this meta-analysis (Figure 2). The obtained funnel plot showed no evidence of asymmetry, and the results of Egger's regression test indicated no evidence of publication bias (Egger's regression test *p*-values = 0.397).

Discussion

In this meta-analysis, evidence for the association between circulating MIF levels and SLE susceptibility, and between polymorphisms in MIF genes and SLE susceptibility was evaluated. Results of our meta-analysis showed that circulating MIF levels were significantly higher in individuals in the SLE group than in those in the control group. However, results revealed no association of the *MIF -173 C/G* allele, the *-794CATT$_7$* allele, and the *-794CATT$_7$-MIF-173C* haplotype with SLE susceptibility. The data suggest that MIF levels play a role in the autoimmune and inflammatory processes in SLE by providing evidence that higher MIF levels are strongly correlated with SLE pathogenesis.

MIF is released by various immunologic effector cells and is known to promote the production of several proinflammatory cytokines (2). MIF plays a key role in the regulation of innate immunity and in the differentiation of the adaptive response. MIF contributes to the pathogenesis of autoimmune inflammatory diseases, including SLE (5). MIF expression is increased in both renal and skin lesions in lupus-prone MRL/lpr mice (29). Although individuals in the SLE group had significantly higher MIF levels than did those in the control group, stratification by ethnicity showed significantly higher MIF levels in the SLE group in Asian populations, but not in non-Asian groups. The non-Asian groups consisted of Caucasian, Latin American, African American, and unknown populations. Thus, ethnic heterogeneity cannot be ruled out as the reason for the observed differences between Asian and non-Asian groups.

The *MIF -173 G/C* polymorphism creates a binding site in activator protein-4, which is involved in intracellular transport (30). The CATT-repeat region within the *MIF* gene includes several putative Pit-1 transcription factor binding sites. Human T-cells transfected with *MIF -173 C* luciferase reporter constructs showed higher activity than cells transfected with the *MIF -173 T* construct, and the disease-associated *-794CATT$_7$-MIF-173C* haplotype showed the highest activity and higher levels of circulating MIF (31). Given the potential link between MIF and risk for autoimmune or inflammatory diseases, MIF polymorphisms, which can influence MIF expression, have been studied as potential causes of autoimmune or inflammatory diseases (32). Our meta-analysis showed no association between SLE and the *MIF -173 C* allele, *-794CATT$_7$* allele, and *-794CATT$_7$-MIF-173C* haplotype with high heterogeneity. Results of the meta-analysis on the *MIF -173 C* allele, *-794CATT$_7$* allele, and the *-794CATT$_7$-MIF-173C* haplotype are not consistent with the results reported from previous functional studies on MIF polymorphisms. However, epidemiologic results occasionally may not coincide with results from functional studies in this regard, considering that SLE is a complex disease and multiple genes, different genetic backgrounds, and environmental factors contribute to its development. Moreover, results of our meta-analysis on MIF polymorphisms can be due to a Type II error (false

negative) or heterogeneity. Two studies on Caucasian populations even showed different results regarding the association of the *MIF -173 C/G* allele and *-794CATT*$_{5-8}$ polymorphisms with SLE susceptibility (13, 17).

This meta-analysis has several shortcomings that need to be considered. First, most of the studies included in the meta-analysis had small sample sizes evaluating the association between MIF levels and SLE risk; in addition, only a small number of studies evaluated the associations of the *MIF -173 C/G* allele and *-794CATT*$_{5-8}$ polymorphisms with SLE risk. Thus, this meta-analysis lacks statistical power. Second, the studies examined were heterogeneous in terms of demographic characteristics and clinical features. Heterogeneity, confounding factors, and limited clinical information provided in these studies populations may confound the results. These limitations did not allow further analysis, although a sensitivity test and a meta-regression analysis were conducted. Third, publication bias may adversely affect our analysis because studies with negative findings may not have been published or identified in the search. The possibility of the bias cannot be eliminated. Nevertheless, this meta-analysis also has its strengths. Our meta-analysis is the first study that provides two parallel lines of evidence examining both MIF levels and MIF polymorphisms in SLE patients. While individual studies had limited cohort sizes ranging from 27 to 135 participants for MIF levels and from 179 to 1,042 for MIF polymorphisms, our pooled analysis included a total of 648 SLE patients examined for MIF levels and 2,118 SLE patients with SLE examined for MIF polymorphisms. Compared to individual studies, our study provided accurate data through increased statistical power and resolution, which was achieved by pooling the results of independent analyses.

In conclusion, our meta-analysis demonstrated that circulating MIF levels were significantly higher in SLE patients than in controls. However, the *MIF -173 C/G* allele and *-794CATT*$_{5-8}$ polymorphisms were not found to be associated with SLE susceptibility. Results of meta-analysis suggested that circulating MIF likely plays a role in SLE pathogenesis. However, further studies are warranted to determine whether MIF levels directly contribute to the development and progression of SLE.

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Conflict of interest statement

The authors have no financial and non-financial conflicts of interest to declare.

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