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Correlation between serum β2-microglobulin level and systemic lupus erythematosus disease activity

A PRISMA-compliant meta-analysis

Tao You, BM[a], Xiaoyin Lin, BM[a], Chunhong Zhang, BM[a], Weilun Wang, BM[a], Meihong Lei, PhD[a,*]

Abstract

Background: Numerous studies have explored whether serum beta 2-microglobulin (β2-MG) can be used as a biomarker for monitoring systemic lupus erythematosus (SLE) disease activity, but the results are conflicting. Therefore, we performed a systematic meta-analysis to further investigate the correlation between serum β2-MG level and SLE disease activity.

Methods: PubMed, Web of Science, Embase, and CNKI databases were thoroughly searched for eligible studies through April 2022. Standardized mean differences with 95% confidence intervals (95% CIs) were used to depict the differences in serum β2-MG levels between groups compared in the studies. The correlation between serum β2-MG level and SLE disease activity was assessed using Fisher *z*-values.

Results: Sixteen articles with combined 1368 SLE patients were included in this meta-analysis. Serum β2-MG levels were significantly higher in SLE patients than in healthy controls (pooled standardized mean difference: 3.98, 95% CI: 2.50–5.46, $P < .01$). In addition, patients with active SLE had an increased serum β2-MG concentration compared to their inactive SLE counterparts. Furthermore, a positive correlation was observed between serum β2-MG levels and SLE disease activity (pooled Fisher $z = 0.78$, 95% CI: 0.61–0.96, $P < .01$).

Conclusions: This study suggests that patients with SLE have higher serum β2-MG levels than healthy controls and that serum β2-MG levels are positively correlated with SLE disease activity. Thus, serum β2-MG level may be a promising biomarker for monitoring SLE disease activity.

Abbreviations: CI = confidence interval, SLE = systemic lupus erythematosus, SLEDAI = SLE disease activity index, SMD = standardized mean difference, β2-MG = beta 2-microglobulin.

Keywords:: β 2-MG, disease activity, systemic lupus erythematosus

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder characterized by alternate phases of flares and remissions, which often leads to chronic inflammation and damage to multiple organs with substantial morbidity and mortality.[1–3] The pathogenesis of SLE is intricate and remains incompletely understood, yet excessive B- and T-cell activation, autoantibody production, and imbalance between immune complex formation and its clearance have been widely proposed to be key drivers in the development and progression of SLE.[4,5] The selection of a therapeutic regimen for SLE depends on the degree of disease activity, and therefore methods to determine this activity level are of great importance in clinical practice.[6]

Several inflammatory biomarkers, such as sedimentation rate and C-reactive protein level, are commonly used to evaluate the degree of SLE activity.[7] However, these inflammatory markers lack specificity and are unreliable. In addition, many other serological markers, including anti-C1q antibodies, anti-dsDNA, and C3 complement components, have also been measured to assess SLE disease activity but have not been found to correlate with all SLE manifestations.[8] Furthermore, there are some standardized disease activity assessment tools that integrate laboratory and clinical manifestations, such as the SLE Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group index (BILAG). Nevertheless, it is time-consuming and inconvenient in daily practice to assess SLE disease activity using these assessment tools. Hence, it is imperative to develop novel and efficient tools to evaluate SLE disease activity.

Beta 2-microglobulin (β2-MG) is a low-molecular-weight protein (11 kDa) that is extensively expressed on the surface of all

TY and XL contributed equally to this work.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

This study is a meta-analysis and systematic review, so it unnecessary to obtain Ethical Approval.

[a] *Department of Endocrinology and Rheumatology, The Affiliated Dongnan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen City, Fujian Province, China.*

**Correspondence: Meihong Lei, Department of Endocrinology and Rheumatology, The Affiliated Dongnan Hospital of Xiamen University, School of Medicine, Xiamen University, Xiamen City, Fujian Province, China (e-mail: 83009253@qq.com).*

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nucleated cells.[9] In physiological conditions, the daily formation of β2-MG is 50 to 200 mg with a plasma half-life of 2 hours, and its serum level is low.[10] It has been well established that lymphocyte activity during lymphoproliferative and autoimmune disease processes has a significant effect on β2-MG levels.[11,12] Interestingly, mounting evidence shows that serum β2-MG levels are often elevated in patients with autoimmune diseases, including SLE, rheumatoid arthritis (RA), and Sjogren syndrome, compared to their healthy counterparts.[13,14] More importantly, numerous clinical studies have reported that serum β2-MG level is associated with SLE disease activity, suggesting that serum β2-MG may be used as a tool for evaluating SLE disease activity.[15–18] In contrast, some studies have found no significant relationship between serum β2-MG level and SLE disease activity. The conclusions of these studies may be biased due to limited sample size; however, a review of their findings in comparison to other studies is necessary. Therefore, in this study, we conducted a comprehensive meta-analysis of the published literature to evaluate the association between serum β2-MG levels and SLE disease activity.

2. Methods

2.1. Database search strategy

This meta-analysis was performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. A systematic search was conducted in PubMed, Web of Science, Embase, and CNKI databases from the earliest entry through April 2022 for relevant literature on the correlation between serum β2-MG levels and SLE disease activity.

2.2. Eligibility criteria

The inclusion criteria for eligible studies were as follows: case–control or retrospective cohort design; patients divided into SLE and health control groups or active SLE and inactive SLE groups based on the SLE Disease Activity Index (SLEDAI) score; reported Spearman correlation coefficient or Pearson correlation coefficient value for the correlation between serum β2-MG level and SLE disease activity, and (or) serum β2-MG levels (presented as mean and standard deviation/error) in active SLE patients and inactive counterparts; and published in English or Chinese. The exclusion criteria were as follows: nonhuman research, conference abstracts, or review literature; unrelated topics; enrollment of overlapping populations; and unavailability of data for the pooled analysis.

2.3. Data extraction and quality assessment

Data were extracted by 2 independent investigators from eligible studies which included the first author's name, publication year, study region, sample sizes of active/inactive SLE patients and normal controls, mean age, sex ratio, detection method for serum β2-MG, Spearman or Pearson correlation coefficient (r) value for describing the correlation between serum β2-MG levels and SLE disease activity, mean value, and standard deviation or error of serum β2-MG levels. When only the Spearman correlation coefficient value was provided in the included studies, we converted it into a Pearson correlation coefficient value as previously described. Two investigators independently evaluated the quality of potentially eligible studies with reference to the Newcastle–Ottawa Scale,[19] and studies scored 0 to 3, 4 to 6, and 7 to 9 points were regarded as low, moderate, and high quality, respectively.

2.4. Statistical analysis

STATA version 12.0 (Stata Corporation, College Station, TX) was used to perform the statistical analysis. The differences between serum β2-MG levels in SLE patients versus healthy controls and active SLE patients versus inactive SLE counterparts were depicted by standardized mean differences (SMDs) with 95% confidence intervals (95% CIs). In addition, the correlation between serum β2-MG levels and SLE disease activity was evaluated using pooled correlation coefficients. For this, we first transformed the Pearson correlation coefficients into Fisher r- to z-values, and then subjected these data to meta-analysis, the results of which were stated as the Fisher z values with 95% CIs.[20–22] The heterogeneity among the included studies was assessed using Cochran Q test and I^2 index.[23] When the P value was <0.05, or (and) I^2 was >50%, there was considered to be significant heterogeneity, and subsequently a random-effect model was selected for calculating the pooled results. To decipher the potential sources of heterogeneity, subgroup and meta-regression analyses were performed based on sample size, study region, method of detecting serum β2-MG level, and definition of disease activity. Sensitivity analysis was performed to evaluate the influence of each eligible study on the combined results. Funnel plots and Begg and Egger tests were utilized to evaluate publication bias.[24–26] A P value <.05 was defined as statistically significant.

3. Results

3.1. Literature selection

A total of 143 studies were initially retrieved from a systematic search of PubMed, Web of Science, Embase, and CNKI databases. Among these, 62 duplicates were excluded. After screening the titles and abstracts of the remaining 81 articles, 53 articles were removed due to their classification as case reports, letters, conference abstracts, reviews, nonclinical studies, or unrelated topics. Next, the full texts of the remaining 28 studies were carefully reviewed, and another 12 articles were excluded due to unavailability of necessary data mentioned in the inclusion criteria and overlapping patient data. Thus, 16 studies involving a combined 1368 SLE patients and 423 healthy controls were included in this meta-analysis.[15–18,27–38] The details of the study selection process are presented in Figure 1.

3.2. Study characteristics

The included studies were published between 2010 and 2021. The sample sizes of eligible studies ranged from 23 to 200 patients or participants. There were 9 articles enrolling patients from China,[17,28,30,31,33–37] and 7 articles from the United States,[18] Korea,[27] Spain,[29] Brazil,[6] Egypt,[15] and Iran.[16] In 7 studies, serum β2-MG levels were measured using an enzyme-linked immunosorbent assay (ELISA).[15,17,27,29,33,36,38] All the included studies reported the correlation coefficient between serum β2-MG levels and SLE disease activity. The serum β2-MG levels in SLE patients and healthy controls were compared in 7 studies,[15,17,28,30,33,34,36] and 10 studies compared the serum β2-MG levels between active SLE patients and inactive patients.[15,17,28,30,31,33–37] The Newcastle–Ottawa Scale scores of the included studies ranged from 6 to 7, indicating that the included studies were of high quality. The detailed baseline characteristics of the eligible studies are summarized in Table 1.

3.3. Meta-analysis of serum β2-MG levels in SLE patients and correlation with disease activity

A total of 7 studies reported serum β2-MG levels in SLE patients and their healthy counterparts.[15,17,28,30,33,34,36] There was significant heterogeneity (I^2 = 96.7%, P < .01), so chose a random-effect model to perform a meta-analysis comparing the serum β2-MG levels between SLE patients and healthy controls. As shown in Figure 2, serum β2-MG levels were

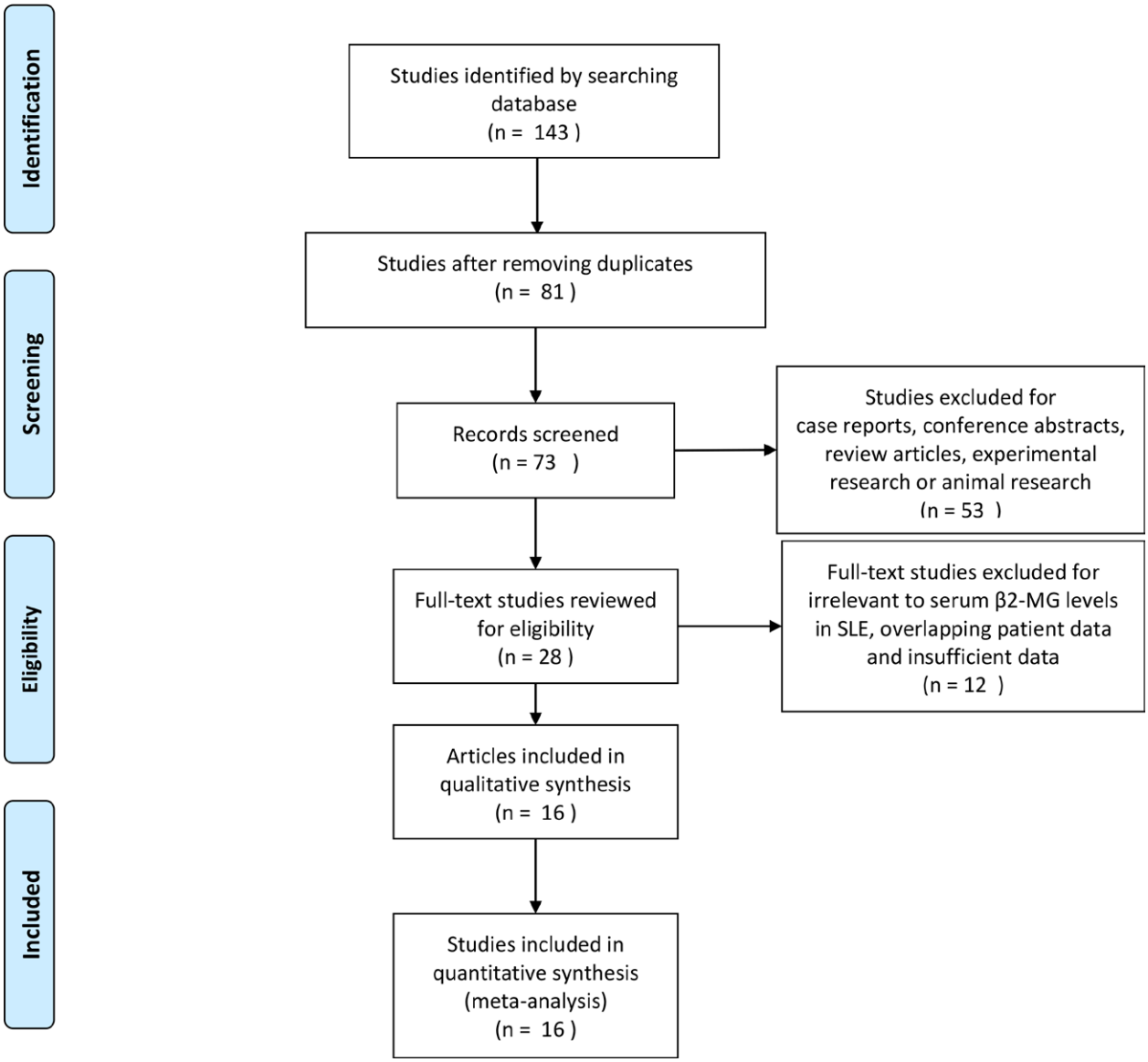

Figure 1. PRISMA flowchart for identifying eligible studies. PRISMA = Preferred Reporting Items for Systematic Review and Meta-Analysis.

significantly higher in SLE patients than in their healthy counterparts (pooled SMD: 3.98, 95% CI: 2.50–5.46, $P < .01$). In addition, a total of 10 articles compared serum β2-MG levels between active and inactive SLE patients.[15,17,28,30,31,33–37] The random-effects model was used for the pooled analysis, again due to substantial heterogeneity ($I^2 = 94.5\%$, $P < .01$). We found that active SLE patients had a significantly higher level of serum β2-MG than inactive SLE patients (pooled SMD: 1.89, 95% CI: 1.20–2.58, $P < .01$; Fig. 3). Furthermore, all of the included studies evaluated the correlation of the serum β2-MG level with SLE disease activity by calculating the correlation coefficients.[15–18,27–38] In view of the significant heterogeneity ($I^2 = 88.9\%$, $P < .01$), we again selected a random-effect model to synthetize the correlation coefficients and confirmed the positive correlation between serum β2-MG level and SLE disease activity (pooled Fisher $z = 0.78$, 95% CI: 0.61–0.96, $P < .01$; Fig. 4).

3.4. Subgroup analysis and meta-regression analysis

To investigate the potential sources of heterogeneity in the pooled results, we performed subgroup and meta-regression analyses by sample size, study region, detection method, and definition of SLE disease activity. The results showed that the serum β2-MG level was significantly higher in active SLE patients than in inactive SLE patients (Table 2) and was positively correlated with SLE disease activity (Table 3) in all subgroups regardless of sample size, study region, detection method, and definition of SLE disease activity. However, significant heterogeneity remained in each subgroup analysis and our meta-regression analyses did not yield significant results (Tables 2 and 3).

3.5. Sensitivity analysis and publication bias

A sensitivity analysis was performed to evaluate the influence of each eligible study on the combined results. As shown in Figure 5A, the overall pooled SMDs describing the differences between active and inactive SLE patients in serum β2-MG levels were not substantially altered after removing any individual study. Consistently, we found no significant change in the overall pooled Fisher z-values (Fig. 5B). Begg and Egger tests were then conducted to investigate whether there was any publication bias among the included studies for the meta-analyses comparing the serum β2-MG levels between active SLE patients and inactive SLE patients and to

Table 1

Characteristics of eligible studies.

		SLE			Control					
		Sample size	Mean age							
Study	Country	Active/ inactive	Active/inactive	Female (%)	Sample size	Mean age	Female (%)	Detection methods	Definition of active SLE	NOS
Aghdashi, 2019	Iran	50	32.01 ± 1.61	NA	25	30.28 ± 1.11	NA	ELISA	SLEDAI ≥ 8	6
Guo, 2019	China	28/34	34.42 ± 5.87	NA	35	34 ± 9	NA	ELISA	SLEDAI ≥ 10	6
Hermansen, 2012	USA	26	41	100	10	28	100	Multiplex	SLEDAI ≥ 3	6
Kim, 2010	Korea	100	32.8 ± 10.9	NA	50	29.5 ± 5.9	NA	ELISA	NA	6
Li, 2020	China	31/28	43. 96 ± 12. 73	91	65	43. 48 ± 12. 65	91	LEITA	SLEDAI ≥ 10	6
Liang, 2020	China	28/20	34. 69 ± 4.97	73	42	33. 58 ± 4. 25	71	ELISA	SLEDAI ≥ 10	6
Liu, 2015	China	100/40	38 ± 12	62	50	39 ± 14	NA	LEITA	NA	6
Liu, 2021	China	94/106	36.34 ± 8.87	90	100	35.45 ± 9.56	85	ELISA	SLEDAI ≥ 10	7
Nashwa, 2019	Egypt	20/20	30.50 ± 5.21/30.65 ± 5.07	80	20	30.35 ± 4.40	80	Nephelometry	SLEDAI ≥ 4	6
Silva, 2012	Spain	42	37.1 ± 13.1	88	NA	NA	NA	ELISA	SLEDAI-2K ≥ 6	6
Skare, 2014	Brazil	129	40.1 ± 11.3	96.9	NA	NA	NA	Chemilumi-nescence	NA	6
Wang, 2021	China	23/27	43.57 ± 5.16/44.51 ± 5.37	48	NA	NA	NA	NA	SLEDAI-2K ≥ 10	6
Wei, 2021	China	23/29	38. 82 ± 9. 27/37. 97 ± 8. 90	71	26	37. 49 ± 8. 73	69	NA	SLEDAI ≥ 10	6
Xu, 2017	China	40/67	38.83 ± 13.38	94	NA	NA	NA	Radioimmuno-assay	SLEDAI ≥ 10	6
Zhang, 2019	China	76/118	34.2 ± 13.6/39.9 ± 14.4	89	NA	NA	NA	NA	SLEDAI ≥ 10	6
Żychowska, 2018	China	69	34.5 ± 11	90	NA	NA	NA	ELISA	NA	6

ELISA = enzyme-linked immunosorbent assay, LEITA = Latex-enhanced immunoturbidimetric assay, NA = not available, NOS = Newcastle–Ottawa Scale, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

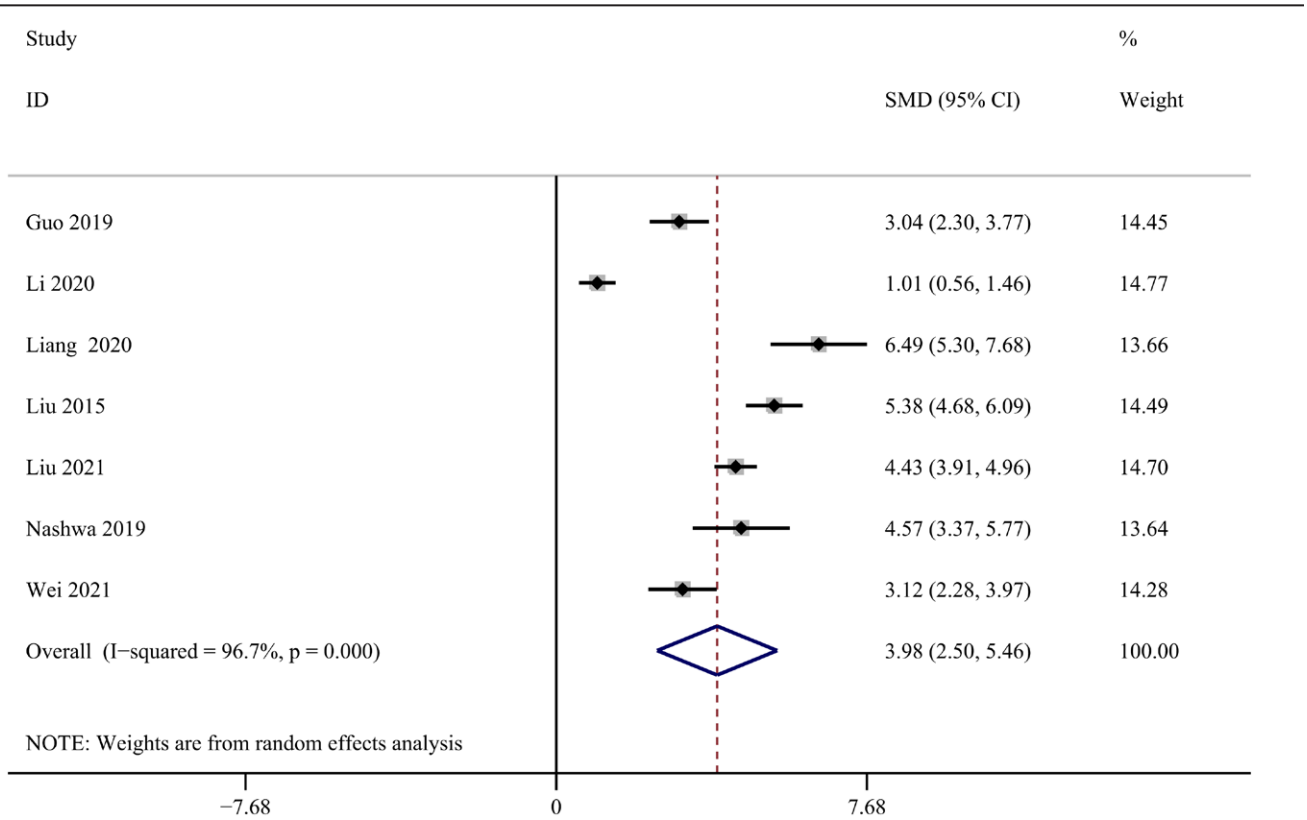

Figure 2. Meta-analysis comparing the serum β2-MG levels between SLE patients and health controls. β2-MG = beta 2-microglobulin, CI = confidence interval, SLE = systemic lupus erythematosus, SMD = standardized mean difference.

evaluate the correlation between serum β2-MG levels and SLE disease activity. The funnel plots for the pooled analysis of SMD and Fisher *z* were symmetrical (Fig. 6). Meanwhile, the *P* values of Begg tests (SMD, *P* = .858; Fisher z, *P* = .367) and Egger tests (SMD: *P* = .860, Fisher z: *P* = .579) were >.05. Hence, we found no significant publication bias in the included studies.

4. Discussion

Early detection of SLE progression and precise monitoring of disease activity are of great clinical significance, as they help to establish an optimized and individualized treatment plan for SLE patients.[6] Therefore, research has recently focused on

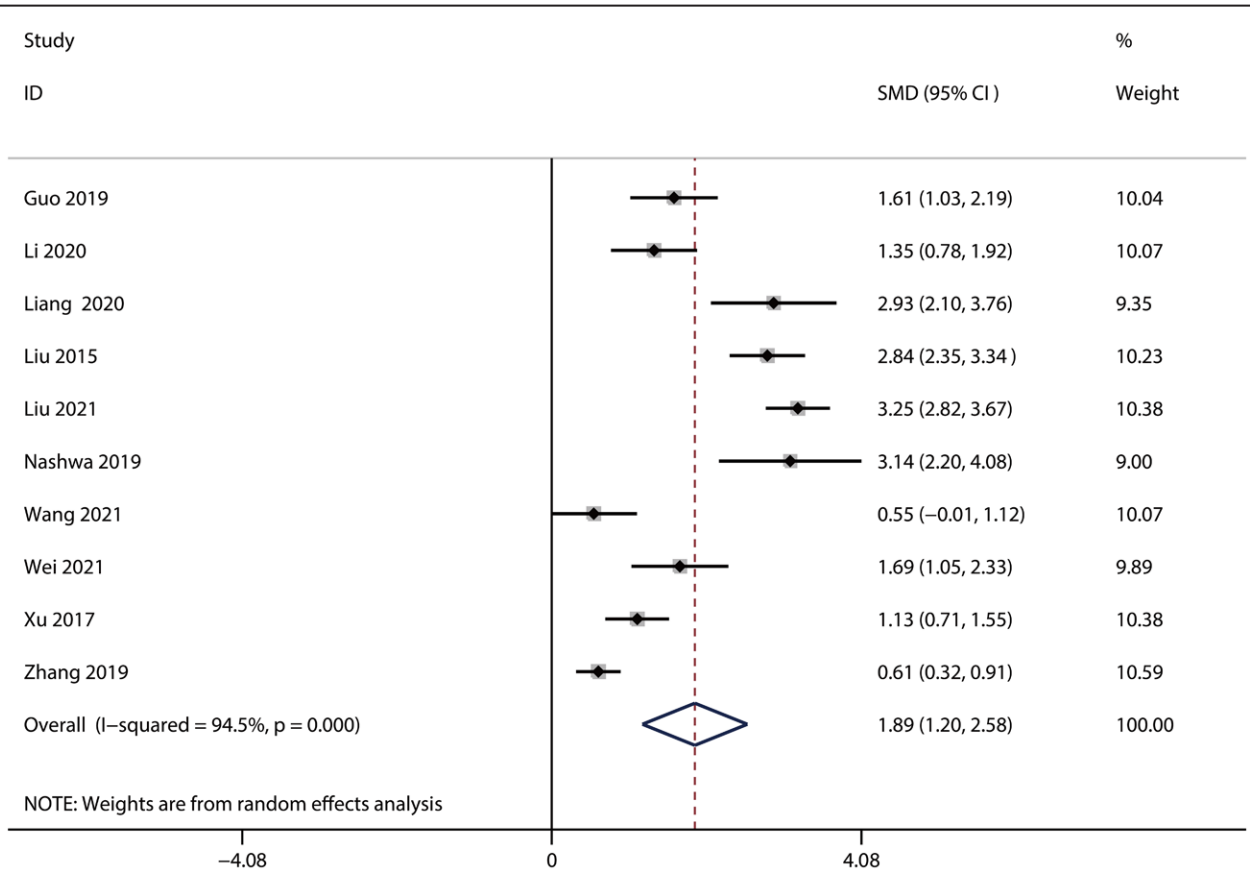

Figure 3. Meta-analysis comparing the serum β2-MG levels between active patients and inactive patients. β2-MG = beta 2-microglobulin, CI = confidence interval, SMD = standardized mean difference.

developing sensitive biomarkers of SLE disease activity. Growing evidence has shown that serum β2-MG levels are increased in SLE patients versus healthy controls and are closely related to SLE disease activity, suggesting the potential of serum β2-MG as a biomarker for monitoring SLE disease activity.[15–18,27–38] Nevertheless, it has also been reported in other studies that there is no significant correlation between serum β2-MG level and SLE disease activity. Therefore, further studies are needed to determine the relationship between serum β2-MG levels and SLE disease activity.

In the present study, we initially performed a systematic meta-analysis of published literature to explore whether serum β2-MG levels are associated with SLE disease activity. In this meta-analysis, a total of 16 studies involving a combined 1368 SLE patients and 423 healthy controls were included. Consistent with most published studies, our pooled analysis showed that the serum β2-MG level was significantly higher in SLE patients than in healthy controls (pooled SMD:3.98, 95% CI: 2.50–5.46, $P < .01$). Moreover, we found a positive correlation between serum β2-MG levels and SLE disease activity (pooled Fisher z = 0.78, 95% CI: 0.61–0.96, $P < .01$; pooled SMD:1.89, 95% CI: 1.20–2.58, $P < .01$). Importantly, in our subgroup and sensitivity analyses, the pooled estimation for the correlation of the serum β2-MG level with SLE disease activity was not dramatically altered. Meanwhile, we did not observe significant publication bias among the included studies. Thus, our meta-analysis is considered robust and reliable and may provide further evidence supporting the potential of serum β2-MG as a biomarker to monitor SLE disease activity.

To date, the cause of increased serum β2-MG concentrations in patients with SLE remains largely unknown. The elevated lymphocyte turnover may partly explain this phenomenon because both T and B cells are aberrantly activated in SLE patients, accompanied by the overproduction of β2-MG.[38,39] Similarly, in addition to SLE, many other lymphoproliferative disorders and autoimmune diseases have also been characterized by β2-MG overproduction and increased serum β2-MG levels.[40,41] It has been well established that a large number of autoantibodies are synthesized and released, and some antibodies can target β2-MG to form the immune complex in SLE patients. Notably, this immune complex is too large to be filtered completely by the kidney, which may provide another explanation for increased serum β2-MG levels in SLE patients.[42,43]

In an experimental study, SLE mice with β2-MG deficiency had typical cutaneous symptoms but experienced a lower risk of kidney damage compared to control mice. This result indicated a potential influence of β2-MG on the clinical course of SLE.[44] In addition, Kim et al[27] suggested that serum β2-MG levels were much higher in SLE patients with serositis, oral ulcers, or lupus nephritis than in patients without these tissue and organ damage conditions. Furthermore, increasing evidence shows that there is a positive relationship between serum β2-MGl level and multiple cytokines involved in the pathogenesis of SLE, such as interleukin (IL)-6, IL-8, IL-18, and interferon-α.[18] Interestingly, immunosuppressive treatment has been shown to markedly reduce the serum β2-MGl level in SLE patients.[45] Overall, these reports are in favor of the finding in our meta-analysis that serum β2-MG level is positively correlated with SLE disease activity. Therefore, serum β2-MG may be used as a biomarker to monitor SLE disease activity, alone or in combination with other tools.

Although our meta-analysis has clinical significance in SLE management, several limitations must be considered. First, all the included studies were retrospectively designed, under which conditions data collection bias may be unavoidable. Second, there was significant heterogeneity in our pooled analysis, which may

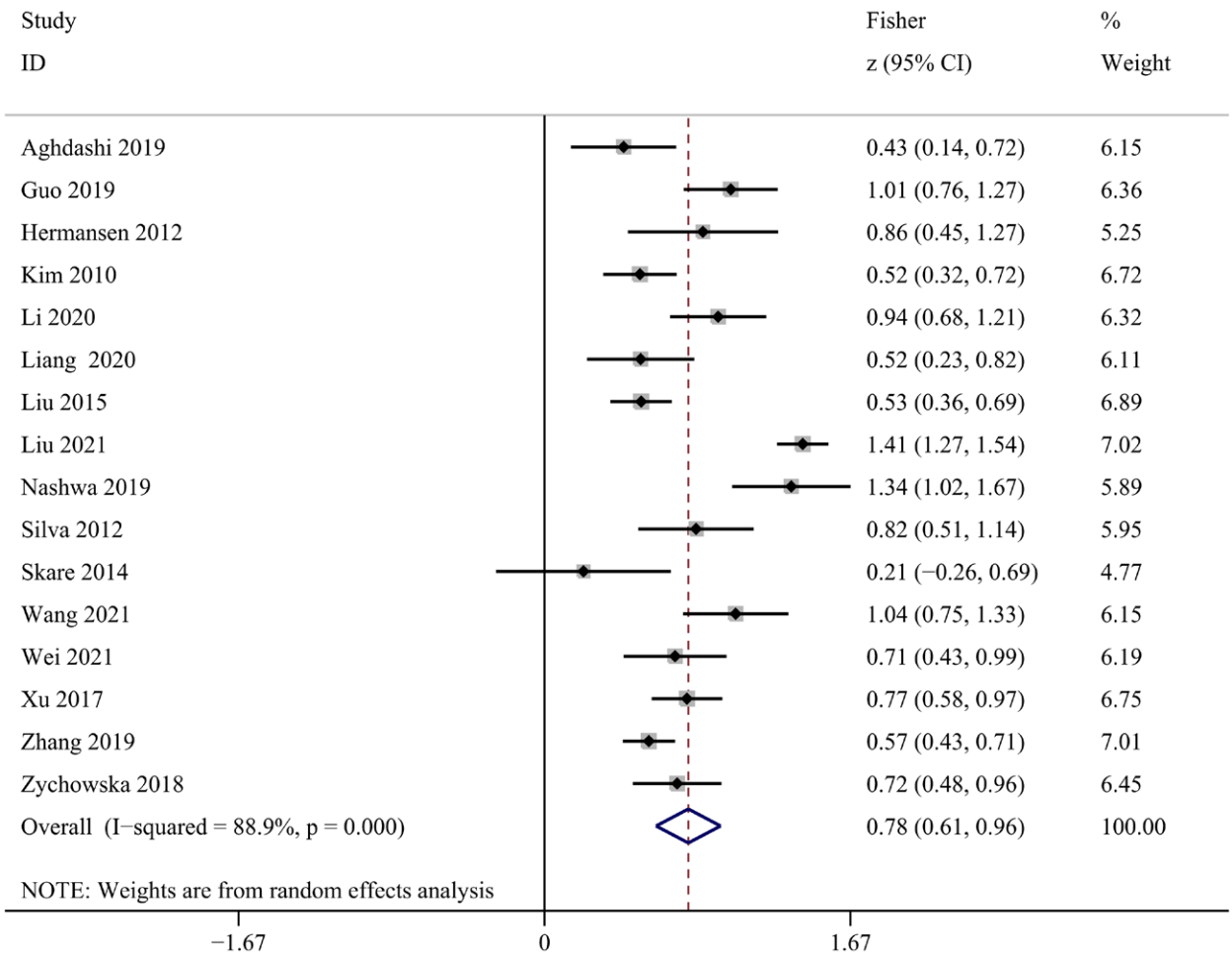

Figure 4. Meta-analysis evaluating the correlation between the serum β2-MG level and SLE disease activity. β2-MG = beta 2-microglobulin, CI = confidence interval, SLE = systemic lupus erythematosus.

Table 2

Subgroup analyses for the pooled results of differences in serum β2-microglobulin levels between active and inactive SLE patients.

				Heterogeneity		Meta-regression		
Variables	**No. of studies**	**Pooled estimate (95% CI)**	***P* value**	**I^2 (%)**	***P* value**	**Tau2**	**I^2 (%)**	***P* value**
Sample size						0.94	94.78	.26
n <100	6	1.822 (1.117–2.528)	<.01	85.3	<.01			
n ≥100	4	1.951 (0.639–3.263)	<.01	97.7	<.01			
Country						0.95	94.78	.26
Other country	1	3.145 (2.204–4.085)	<.01	–	–			
China	9	1.762 (1.046–2.478)	<.01	94.8	<.01			
Measuring methods						0.85	92.1	.17
ELISA	3	2.594 (1.509–3.68)	<.01	90.2	<.01			
Other methods	7	1.576 (0.878–2.275)	<.01	92.6	<.01			
Definition of activity						1.1	94.9	.64
SLEDAI ≥10	7	1.777 (0.975–2.58)	<.01	94.8	<.01			
Other methods	3	2.162 (0.486–3.838)	.01	95.2	<.01			

CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

have led to overestimation or underestimation of the correlation between serum β2-MG levels and SLE disease activity. Third, most of the included studies were conducted in Asia, particularly China. Thus, it may be too early to expand our conclusions to populations outside Asia. Fourth, in addition to the SLEDAI score, many other tools or biomarkers, such as the BILAG score and components such as C3, IL-6, IL-8, IL-18, and interferon-α, can reflect SLE disease activity. However, in this study, only the correlation between serum β2-MG level and the SLEDAI score was systematically assessed, because sufficient data regarding the other tools or biomarkers were unavailable for the pooled analysis. Last but not least, the potential utility and specificity of serum β2-MG in evaluating SLE disease activity have not been investigated in the context of other inflammatory conditions either.

Table 3

The correlation between serum β2-microglobulin level and disease severity of SLE in different subgroups.

Variables	No. of studies	Pooled estimate (95% CI)	*P* value	Heterogeneity		Meta-regression		
				I^2 (%)	*P* value	Tau2	I^2 (%)	*P* value
Sample size						0.09	89.57	.42
n <100	10	0.838 (0.677–0.998)	<.01	67.6	<.01			
n ≥100	6	0.687 (0.341–1.032)	<.01	95.3	<.01			
Country						0.09	89.03	.45
China	9	0.835 (0.593–1.077)	<.01	92	<.01			
Other country	7	0.708 (0.467–0.95)	<.01	77.9	<.01			
Measuring methods						0.09	88.38	.96
ELISA	7	0.783 (0.457–1.109)	<.01	92.8	<.01			
Other methods	9	0.778 (0.601–0.954)	<.01	78.2	<.01			
Definition of activity						0.08	88.18	.42
SLEDAI ≥10	7	0.853 (0.567–1.139)	<.01	92.7	<.01			
Other methods	9	0.721 (0.526–0.917)	<.01	78	<.01			

CI = confidence interval, ELISA = enzyme-linked immunosorbent assay, SLE = systemic lupus erythematosus, SLEDAI = Systemic Lupus Erythematosus Disease Activity Index.

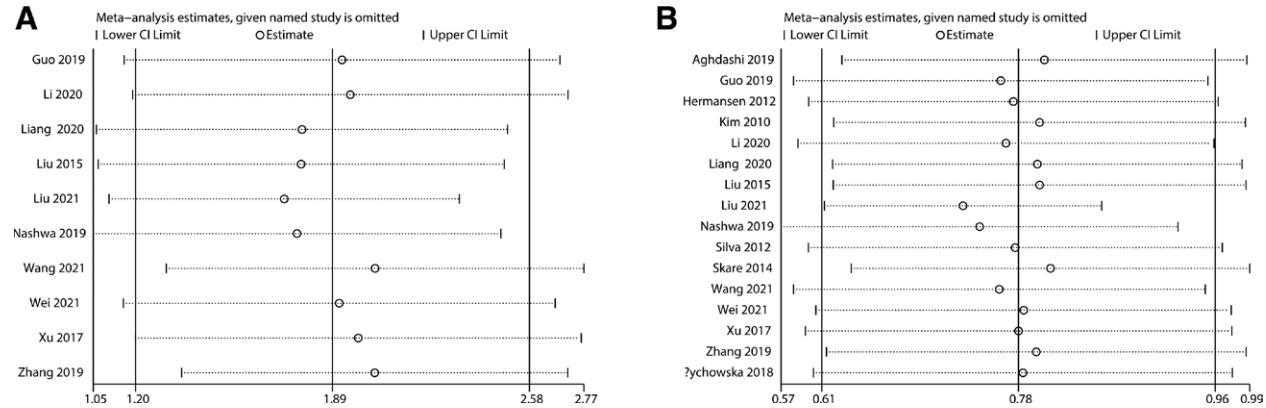

Figure 5. Sensitivity analysis of the pooled results about the difference in the serum β2-MG levels between active SLE patients and inactive SLE patients (A), and the correlation of the serum β2-MG level with SLE disease activity (B). β2-MG = beta 2-microglobulin, CI = confidence interval, SLE = systemic lupus erythematosus.

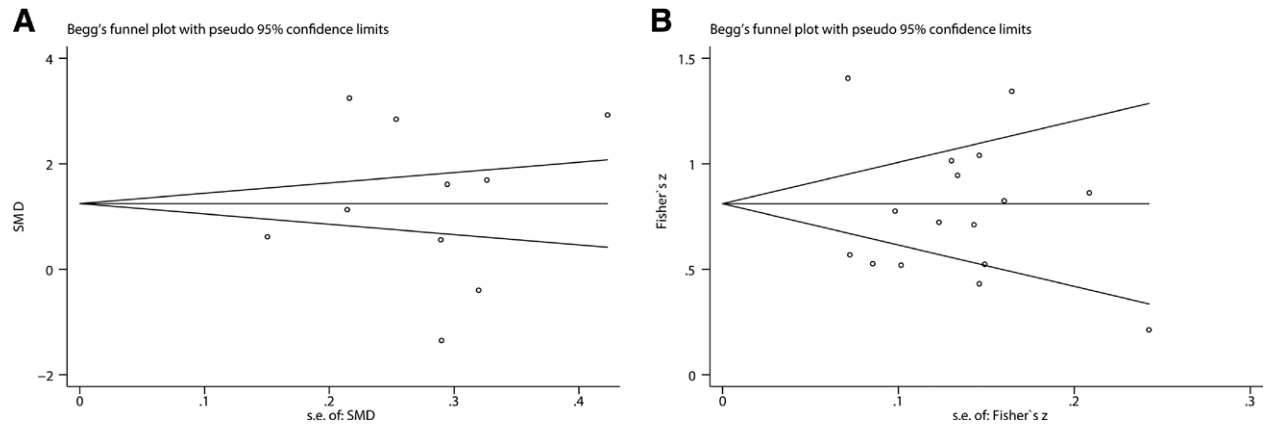

Figure 6. Funnel plots of the pooled results about the difference in the serum β2-MG levels between active SLE patients and inactive SLE patients (A), and the correlation of the serum β2-MG level with SLE disease activity (B). β2-MG = beta 2-microglobulin, SLE = systemic lupus erythematosus, SMD = standardized mean difference.

5. Conclusions

In sum, our study indicates that serum β2-MG levels are significantly higher in SLE patients than in healthy controls. Moreover, serum β2-MG levels positively correlated with SLE disease activity, implying that serum β2-MG may be a promising biomarker for monitoring SLE disease activity. Nevertheless, more prospective studies on diverse populations with large sample sizes should be conducted to validate these findings.

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Author contributions

Meihong Lei was responsible for designing this research. Tao You, Xiaoyin Lin, and Chuanhong Zhang extracted the data and conducted the statistical analysis. Tao You and Weilun Wang drafted the manuscript.

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