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Research Article

Migraine and Risk of Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis

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Background. Migraine is a frequently observed neurological disease in patients with systemic lupus erythematosus. However, the relationship between these two conditions is still a subject of controversy. *Objectives*. Our aim was to investigate the association between migraine and the risk of developing systemic lupus erythematosus through a meta-analysis of case-control studies. *Methods*. Following the Preferred Reporting Project for Systematic Reviews and Meta-Analysis statement, we conducted a comprehensive search of the following literature databases, including PubMed, Embase, and Web of Science, to identify relevant articles published up to June 2022 using the keywords "migraine" and "systemic lupus erythematosus" as subject headings. If heterogeneity was expected to be low ($I^2 \leq 50\%$), the pooled analysis was performed using a fixed-effects model calculated by the Mantel-Haenszel method. Analysis in this study was conducted using R software (http://www.r-project.org). *Results*. Six case-control experimental studies involving 908 participants were included in the meta-analysis. The overall combined relative risk of developing systemic lupus erythematosus in patients with migraine, compared to the control group, was 1.69 (95% confidence interval (CI): 1.26 to 2.27). The analysis revealed minimal evidence of heterogeneity and publication bias. *Conclusions*. Based on our meta-analysis, there is suggestive evidence that patients with migraine may have an elevated risk of developing systemic lupus erythematosus attacks.

1. Introduction

Systemic lupus erythematosus (SLE) is a severe systemic autoimmune disease that presents significant challenges in terms of diagnosis and treatment, leading to morbidity, mortality, and reduced quality of life [1]. Neuropsychiatric lupus (NPSLE) is a common manifestation of SLE [2]. Although several neurological symptoms are recognized as important features of SLE and indicative of central nervous system (CNS) involvement, limited research has been conducted specifically on the manifestation of migraine in the CNS [3]. Currently, no specific pathogenic mechanism has been identified to fully explain the development of SLE associated with migraine. Controversy surrounds the contribution of circulating cytokines, vascular injury, neuronal damage, and antiphospholipid antibodies (aPL) in triggering SLE in patients with migraine [4–6].

Migraine is a common occurrence in patients with SLE, with a reported prevalence of up to 70% [7]. However, the precise percentage of SLE patients affected by migraines remains uncertain [8]. This uncertainty may arise from factors such as small study sample sizes, diverse study designs, and the use of various classification criteria. Furthermore, the underlying pathophysiology of migraine and SLE remains unclear, and it is possible that autoimmunity may be the cause of both [9–11]. In this study, a meta-analysis was conducted to investigate the relationship between migraine and the risk of SLE. The goal was to elucidate the clinical connection between these two conditions and provide theoretical support for further basic research.

2. Materials and Methods

2.1. Standard Protocol Approvals, Registrations, Search Strategy, and Patient Consents. We searched the following literature databases: PubMed, Embase, and Web of Science (WOS) for publications published up to June 2022 pertaining to the subject headings "migraine" and "SLE." This systematic review and meta-analysis were registered in the International Prospective Register of Systematic Reviews under the number CRD42022345927. This study involved an analysis of publicly available documents and did not require an ethical committee review or direct patient interaction.

2.2. Study Selection. The literature search yielded a total of 1,003 articles, out of which 541 unique papers were included after screening for duplicates and removing irrelevant studies. A core reference database comprising 49 articles was established by assessing the inclusion/exclusion criteria in titles and/or abstracts. Full-text copies of these papers were obtained for quality assessment by the expert committee (Wang XJ, Tian DC, and Liu J). In these articles, the expert committee reached a consensus and selected six papers (Figure 1).

2.3. Inclusion and Exclusion Criteria. To be eligible, studies had to meet the following criteria: (1) study population: individuals with SLE or in good health; (2) exposure factor: migraine as the variable of interest; (3) outcomes: the risk of developing SLE associated with migraine; (4) study design: case-control studies; (5) language: written in English; and (6) study subjects: human participants. Moreover, the studies conducted by Goh et al. and Ainiala et al., which met the inclusion criteria but were excluded, were primarily due to small sample sizes or duplication of study populations [12, 13]. The following criteria were used for exclusion: (1) study types: case reviews, case reports, meta-analyses, and reviews; and (2) studies with unreliable odds ratios (OR) or hazard ratios (HR).

2.4. Data Extraction. From the included studies, we extracted various data items using a standardized data form, including the last name of the first author, publication year, research population, country, number of cases and participants, assessment of exposure, and outcome. The risk estimation was presented with the corresponding odds ratios (OR) and 95% confidence intervals (CI). Two authors (Hui X and Zhang LJ) independently conducted the research selection and, together with a third author (Zhang TT), performed data extraction. Any disputes were resolved through discussion.

2.5. Statistical Analysis. For binary outcomes, we calculated the OR and the corresponding 95% CI. In the meta-analysis, we combined data from multiple studies and obtained pooled ORs and 95% CIs using the Mantel-Haenszel method. The findings were presented using forest plots, which displayed individual studies and the combined results. Heterogeneity between the studies was assessed using the I^2 statistic and the X^2 test (p value > 0.10 was considered statistically significant). Heterogeneity levels were classified as low (I^2 value of 25%), moderate (50%), or high (75%). When there was little or no significant heterogeneity between the studies, fixed-effects models were used to combine the data. If heterogeneity was present ($I^2 = 50 - 75\%$), random-effects models were employed. If significant heterogeneity existed ($I^2 > 75\%$), the data were not pooled. Data analysis was performed using R software version 4.13 (with the meta package). Subsequently, to explore potential reasons for the observed heterogeneity, subgroup analysis and sensitivity analysis were conducted to evaluate the stability of the combined results.

2.6. Study Quality Assessment. The quality of the case-control studies included in the meta-analysis was assessed using the Newcastle-Ottawa scale (NOS) [14]. In each study, two authors independently used the checklist to reach a consensus on the score. Any conflicting assessments were discussed and resolved. If disagreements persisted between the two reviewers, a third reviewer was consulted to make the final decision. The study quality was also included as a moderator in the following analyses, with a score of 7-9 indicating good quality, 4-6 indicating a high risk of bias, and 0–3 indicating an extremely high risk of bias.

3. Results

3.1. Study Characteristics. The characteristics of the six case-control studies [15–20], published between 1982 and 2014, are presented in Table 1. Among these studies, one was conducted in the United States and five in Europe. Five studies included both men and women, while one study included only women [20]. The proportion of women exceeded 90% in all of these studies. Two articles [15, 16] identified migraine based on the International Classification of Headache Disorders (ICHD II) criteria, while alternative criteria were utilized in the remaining studies. Five studies [15–19] identified SLE using the American College of Rheumatology's (ACR) 1982 updated criteria, while the remaining study adopted the criteria of the American Rheumatism Association. Adjustments were made for various confounding factors. Two studies [15, 17] were corrected for univariate analysis, whereas four studies were adjusted for age and sex.

3.2. Main Analysis. Figure 2 displays the adjusted odds ratios (ORs) for each study as well as the summary OR for the association between migraine and SLE risk. The pooled relative risk for developing SLE in participants with migraine, compared to controls, was 1.69 (95% CI: 1.26-2.27, p value = 0.0004). This indicates that the prevalence of SLE is 1.69 times higher in patients with migraine compared to those without migraine, suggesting that migraine increases the risk of SLE.

3.3. Subgroup Analyses. Subgroups were categorized based on the presence of migraine with or without aura, country, and statistical model. Corresponding results showed no evidence of heterogeneity between subgroups, and hence the results were calculated based on the fixed-effects model. In

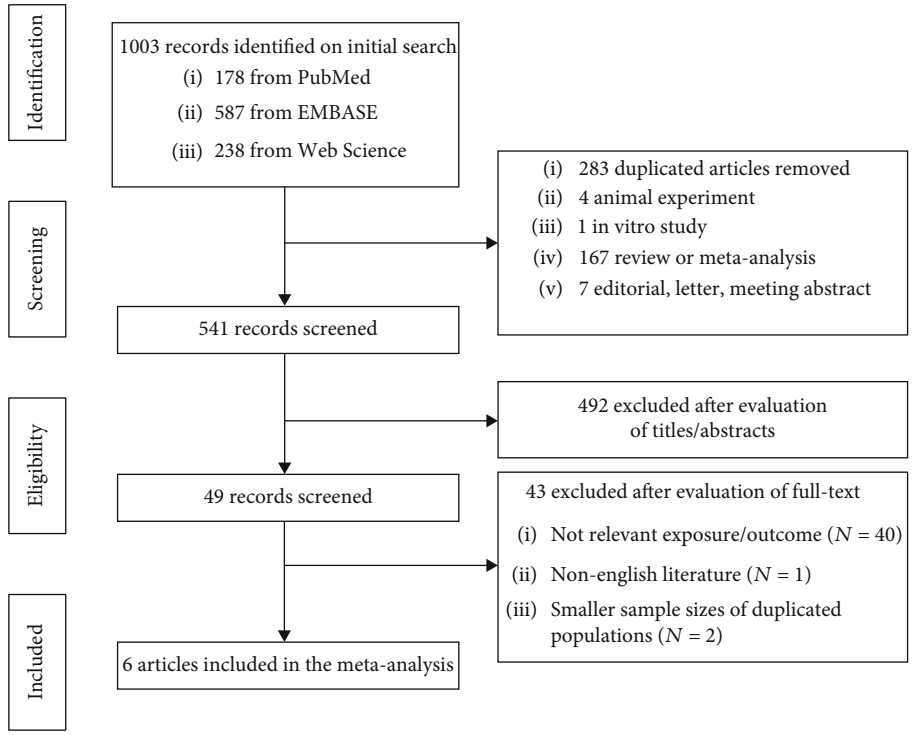

Figure 1: Flowchart of study selection.

Figure 2, the subgroup without aura did not show a statistically significant result (OR 1.20, 95% CI: 0.76-1.89), whereas in the subgroup with aura, exposure to migraine with aura was associated with an increased risk of SLE (OR 1.61, 95% CI: 1.00-2.57). Additionally, the subgroup analysis in Figure 3 demonstrated that exposure to migraine in the European (Norway, Greece, Brazil, Spain, and UK) subgroup (OR 1.52, 95% CI: 1.10-2.08) and North American (Brazil) subgroup (OR 1.79, 95% CI: 1.02-3.14) could increase the risk of SLE. Furthermore, the model-based subgroup analysis in Figure 4 indicated that migraine exposure in the univariate analysis group significantly contributed to the risk of SLE (OR 1.81, 95% CI: 1.18-2.79), whereas in the matched age and sex group, this association was not statistically significant (OR 1.52, 95% CI: 0.90-2.56).

3.4. Sensitivity Analysis. A sensitivity analysis was conducted to assess the influence of individual studies on the overall risk estimate by sequentially excluding each study. The analysis revealed that none of the studies significantly affected the overall risk estimate, which ranged from 1.54 (95% CI: 1.11-2.12) to 1.88 (95% CI: 1.37-2.59), as depicted in Figure 5.

3.5. Publication Bias. According to the results of the funnel plots in Figure 6, there was no evidence of publication bias regarding the risk of SLE in relation to migraine. The corresponding Egger tests repeatedly produced nonsignificant findings ($p = 0.77$), suggesting the absence of publication bias.

4. Discussion

4.1. Main Findings. In this study, migraine emerged as a significant risk factor for SLE, particularly evident in subgroup analyses focusing on migraine with aura, subgroup analyses based on diverse ethnic populations, and subgroup analyses utilizing various statistical models. Further research was imperative to unravel the underlying mechanisms and establish a causal relationship between migraine and SLE.

4.2. Mechanisms Underlying the Migraine-SLE Association. There were multiple possible mechanisms for the significant correlation between migraine and SLE risk. A potential mechanism underlying the onset of SLE attacks in migraine patients involved platelet activation and the impact of antiphospholipid antibodies on the modulation of their immune system [19–24]. Research had explored the potential associations between migraine and abnormalities in platelet activation [21]. Regulatory T cell function can be shut down by platelet activation through a sufficient increase in intracellular H_2O_2 [22], which breaks Tregs' grip on self-reactive T cells with an immunosuppressive effect [23]. Therefore, migraine patients can potentially disrupt their own immune systems through the activation of platelets.

Moreover, there was also emerging evidence suggesting that migraine represents a neurologic disorder with potential implications for autoimmune dysregulation [24]. Furthermore, migraine was the most prevalent neurological disease among patients with antiphospholipid syndrome, with high titers of antiphospholipid antibodies (up to 40%), which were

Table 1: Baseline characteristics of published studies examining migraine and risk of systemic lupus erythematosus.

*First author, year	Country	Study purpose	Sample size (cases/controls)	Age (years), female ratio	Migraine diagnostic criteria	SLE diagnostic criteria	Adjustments	NOS
*Tjensvoll et al., 2014 [15]	Norway	Exploring headache association in SLE versus pSS examination	175 (67/108)	Mean age (SD) in SLE/healthy subjects with headache: 43.3 ± 13.9 /46.7 ± 12.6; 87% in SLE and healthy subjects with headache	The International Classification of Headache Disorders (ICHD II) criteria	The 1982 revised American College of Rheumatology (ACR) criteria	NA	5
*Katsiari et al., 2011 [16]	Greece	Exploring the presence of migraine in SLE	144 (72/72)	Mean age (SD) in SLE/controls: 38.3 ± 2.4 /35.9 ± 8.3; 96%	The International Classification of Headache Disorders (ICHD II) criteria	The 1982 revised American College of Rheumatology (ACR) criteria	Matched for age (±2 years), gender, and educational level (±1 year)	5
*Lessa et al., 2006 [17]	Brazil	Exploring headache prevalence and classification in SLE patients	207 (115/92)	Mean age (SD) in SLE/controls: 36 ± 10 /46 ± 16; 92%	The International Headache Society criteria	The 1982 revised American College of Rheumatology (ACR) criteria	NA	7
*Fernández-Nebro et al., 1999 [18]	Spain	Exploring primary headaches in SLE: prevalence and forms	132 (71/71)	Mean age (SD) in SLE/healthy subjects: 36.6 ± 13.7/36.9 ± 12.9 ; 92 %	The revised criteria of the "ad hoc" Committee of the International Headache Society (IHS)	The 1982 revised American College of Rheumatology (ACR) criteria	Matched for age and sex from the same geographical area	4
*Markus and Hopkinson, 1992 [19]	UK	Exploring the relationship between migraines and headaches in SLE	180 (90/90)	Mean age in SLE/controls: 42.3/42.6; 96%	Episodic headaches lasting 2 to 72 h with total freedom between attacks	The 1982 revised American College of Rheumatology (ACR) criteria	Matched for age (±1 years) and gender	5
*Isenberg et al., 1982 [20]	UK	Exploring the relationship between migraine and SLE	60 (30/30)	Mean age (SD) in SLE/controls: 35.6 ± 9.5 /29.5 ± 6.6; 100%	Based on the definition of migraine with or without aura	The American Rheumatism Association's criteria	Matched for age and gender	4

NOS = Newcastle-Ottawa Quality Assessment Scale; NA = not available; SLE = systemic lupus erythematosus; pSS = primary Sjogren's syndrome. *Case-control study.

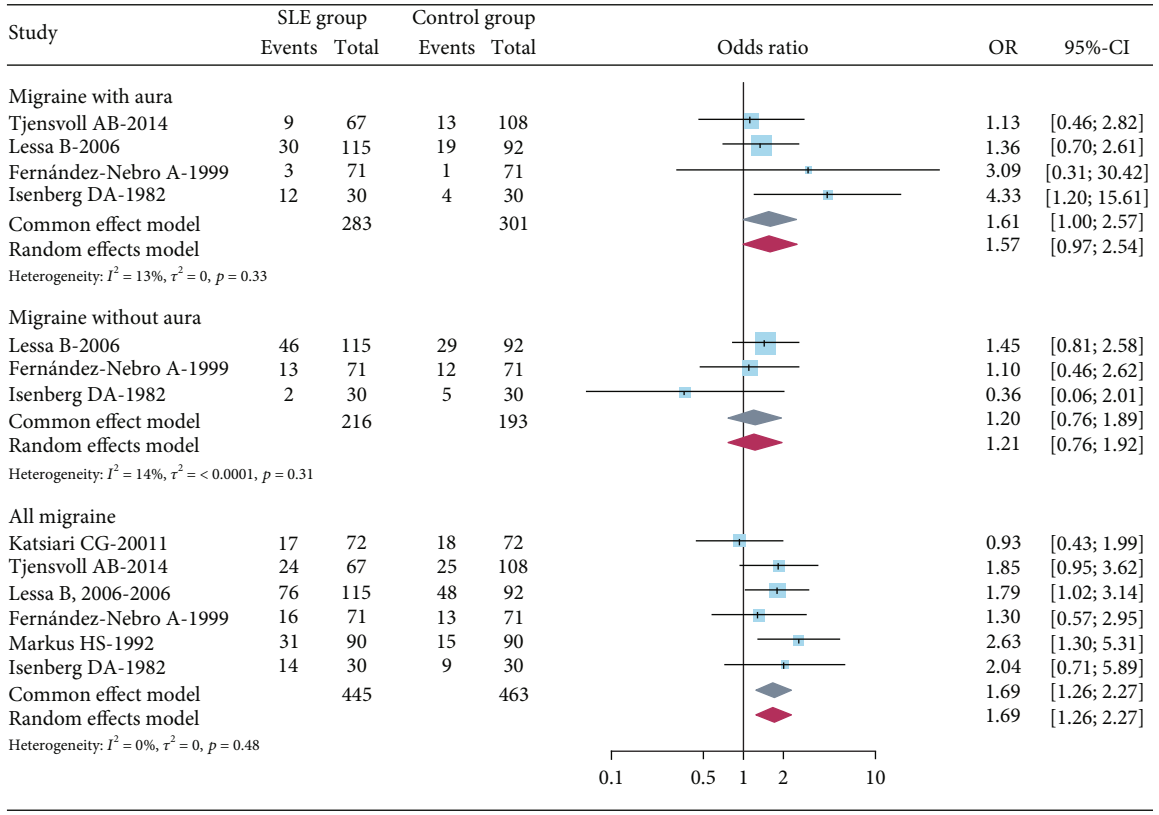

Figure 2: Forest plot of studies examining the association between systemic lupus erythematosus and risk of migraine.

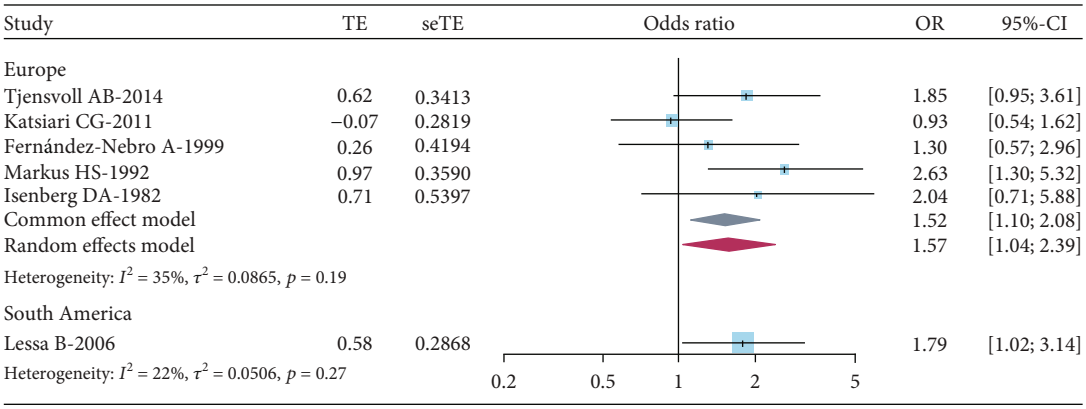

Figure 3: Forest plot of subgroup analysis relating migraine to SLE by the characteristic of the country.

closely associated with the autoimmune system [25]. The study also discovered that SLE patients had clinically significant antiphospholipid antibodies [26]. Hence, systemic platelet activation and antiphospholipid antibodies may be the reasons behind the increased risk of SLE associated with migraine, mediated through autoimmune mechanisms.

4.3. Heterogeneity and Sensitivity. A common concern in a meta-analysis is heterogeneity. Fortunately, there was little evidence of heterogeneity during our study. The following facts assisted in partially explaining this: inclusion and exclusion criteria were correctly defined and consistent study types were used; the majority of included studies exhibited consistency among patients in terms of age, gender, and other relevant factors [13–18].

Our subgroup and sensitivity analyses yielded very consistent and reliable results. There was a significant positive association between all subgroups except migraine without aura. In the subgroup analysis specifically examining migraine without aura, no significant association was found between migraine without aura and the risk of SLE. This could be attributed to the limited number of included studies ($n = 3$), resulting in inadequate statistical power.

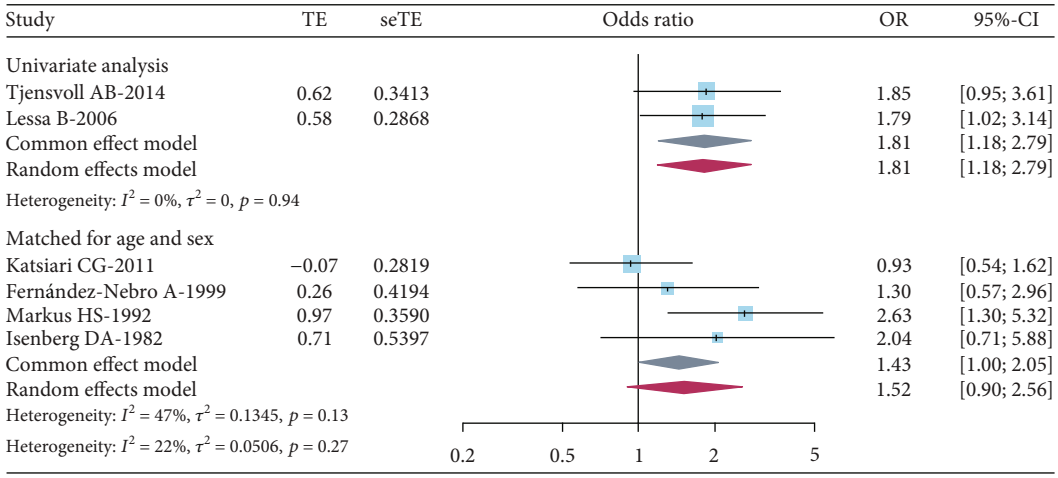

Figure 4: Forest plot of subgroup analysis relating migraine to SLE by the characteristic of the statistical model.

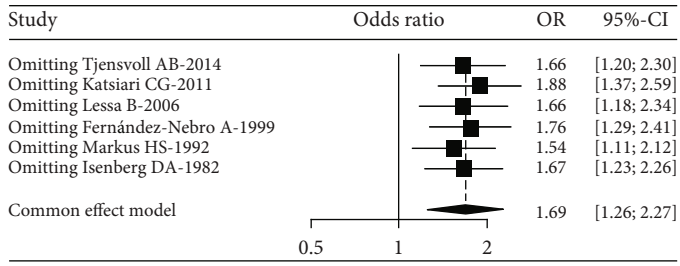

Figure 5: Sensitivity test for forest analysis.

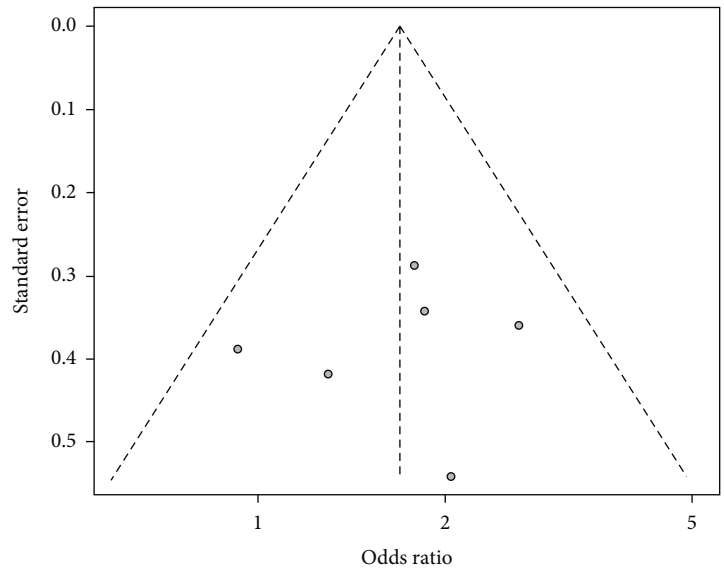

Figure 6: Funnel plot for case-control studies.

4.4. Advantages and Limitations. In this study, we analyzed the associations between migraine and SLE using a meta-analysis to obtain robust conclusions. To the best of our knowledge, this is the first comprehensive meta-analysis of the effects of migraine and the risk associated with SLE. Few studies have yet attempted to elucidate the pathogenic role of migraine in the risk of SLE; therefore, it would be interesting to investigate the exact mechanisms of migraine-mediated SLE. Furthermore, the presence of migraine would be considered a potential diagnostic indicator for the early detection of SLE. However, further investigation through high-quality studies was necessary to

confirm whether migraine indeed increases the risk of developing SLE.

Therefore, it is important to note several limitations of our meta-analysis. Firstly, since the studies were all retrospective, recall bias was a concern. Secondly, there was not enough research included in this analysis, especially in regard to subgroup analysis. Therefore, even if our statistical analysis did not yield a significant bias, there may be a potential publication bias. Thirdly, there could be some linguistic bias as English was the only language utilized in the study.

4.5. Clinical Implications. Finding the clinical connection between migraine and SLE will point fundamental research in the right direction for further examining the pathophysiology of both conditions and for creating efficient treatment regimens. Additionally, it will give clinicians a theoretical foundation on which to treat SLE or migraine.

5. Conclusions

Based on our meta-analysis, patients with migraine may have a higher risk of experiencing systemic lupus erythematosus attacks.

Data Availability

The data used to support the findings of this study are included within the article.

Additional Points

Key Message. Patients with migraine are more likely to develop SLE.

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

Authors' Contributions

Xianjun Wang and Dachen Tian contributed to the conception and design. Dachen Tian was responsible for the literature search. Xin Hui, Lijun Zhang, and Xianjun Wang were in charge of identifying relevant studies. Ji Liu, Mengen Wang, Xianjun Wang, and Dachen Tian evaluated the study quality. Tongtong Zhang, Xin Hui, and Lijun Zhang provided substantial contributions to the collection and assembly of data and data analysis and interpretation. Dachen Tian was in charge of graphs and tables. All authors contributed to the manuscript writing and final approval of the manuscript.

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