Association Between Neuropsychiatric Event and Systemic Lupus Erythematosus Clinical Manifestation: A Meta-Analysis

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ABSTRACT

To uncover the clinical characteristics and investigate the underlying causes of psychiatric manifestations in patients with systemic lupus erythematosus (SLE), including its subset, neuropsychiatric systemic lupus erythematosus (NPSLE). Through comprehensive database searches in PubMed, Embase, Medline, and Cochrane, from their inception to August 2023, the study focused on adult SLE and NPSLE cases. From the selected studies, data were synthesised *via* a random-effects meta-analysis, encompassing a total of 2,997 subjects across six studies. The findings highlighted differences in medical indicators such as discoid rash, hypertension, mean disease duration, and various autoantibodies between SLE and NPSLE patients, indicating a nuanced approach to treatment is necessary, particularly with NPSLE requiring extended treatment periods. The analysis suggests that the causality behind these manifestations is multifactorial, encompassing mental state, autoantibody profiles, and environmental factors, thus providing valuable insights into the clinical management and understanding of SLE and NPSLE. This study emphasises the complexity of SLE, particularly in its neuropsychiatric manifestations, and underscores the importance of targeted treatment strategies.

Key Words: *Systemic lupus erythematosus, Neuropsychiatric systemic lupus erythematosus, Neuropsychiatric event, Meta-analysis.*

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with an unknown cause and a dismal prognosis.[1] The majority of its neurological symptoms are aseptic meningitis, cerebrovascular disease, epilepsy, acute bewilderment, cognitive decline, etc.[2] Patients with neuropsychiatric (NP) manifestations find it challenging to address their neuropsychiatric systemic lupus erythematosus (NPSLE) during treatment due to the variability of clinical presentations and the complexity of illness pathogenesis.[3] This complicates clinical diagnosis, delays treatment, and impacts prognosis. In order to accomplish early recognition, prevention, diagnosis, and treatment of the disease, it is crucial to discuss the disease's associated clinical manifestations. The purpose of this investigation was to compare the clinical presentation of patients with NPSLE *versus* patients with SLE.

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METHODOLOGY

The authors conducted database searches using PubMed, Embase, Medline, and Cochrane. The computerised search included terms associated with SLE patients, NPSLE patients, psychiatric systems, encephalopathy, and study design. The search form is a follows: "[Title/Abstract] = ('SLE' OR 'Systemic lupus erythematosus')" and [Title/Abstract] = ('NPSLE' OR 'Neuropsychiatric systemic lupus erythematosus' OR 'Neuropsychiatric'). All of the articles' cited sources were examined and the authors were contacted for additional information, if needed.

Studies that compared the medical outcomes of patients with SLE and those with NPSLE were considered if they were single-centre, case-control, or cross-sectional studies conducted in English. The International Classification of Diseases (ICD) code, American College of Rheumatology (ACR) criteria, or a clinician review / diagnosis were used to classify SLE or NPSLE.[4,5] Single-centre, case-control, or cross-sectional English-language studies were evaluated that compared the medical outcomes of patients with SLE and those with NPSLE. SLE and NPSLE are classified using the ICD code, ACR criteria, or a clinician review / diagnosis.[6-11]

Inclusion criteria consisted of single-centre studies, case-control studies, or cross-sectional studies investigating lupus encephalopathy risk factors and medical indicators, published in English databases between 2000 and 2023. The included research needed to contain an NPSLE group (experiment group) and an SLE group (control group), with all instances meeting the

clearly defined diagnostic standards for SLE and NPSLE. Studies were required to exclude neuropsychiatric symptoms caused by infection, renal insufficiency, brain tumour, acute cerebral haemorrhage, diabetes, and other factors. It was also necessary that patients in the experimental group and the control group were from the same time period, with a clearly indicated, adequate sample size, including any variations in sample size due to mortality or loss of follow-up in the trial. Furthermore, the literature had to present reliable statistical impacts and indications.

Exclusion criteria comprised studies without a clear experimental group and control group; those lacking clear diagnostic criteria for SLE and NPSLE; studies without original data, making it impossible to calculate the combined effect size; clinical case reports with less than ten subjects; studies that were case reports rather than clinical trials; and studies where the quality of the paper or dissertation was subpar.

In a case-control study, the NOS quality scoring standard was used to assess the quality of the collected literature in eight areas, including whether the case definition and diagnosis were appropriate, whether the cases were representative or continuous, and whether the controls were community controls or hospital controls.[12] The score for yes was 1 point and 0 point for no. A score between 6 and 8 indicated high-quality research, a score between 3 and 5 indicated moderate-quality research, and a score of 2 or less indicated low-quality research.

Statistics on medical indicators in the medical literature were compiled, as well as meta-analyses of the indicators, for which six studies reported data. Using Revman 5.4, MD values and 95% CI were computed for continuous variables, whereas OR values and 95% CI were computed for binary variables. The I^2 test was used to determine whether heterogeneity existed among the studies. If I^2 was less than 50%, heterogeneity among studies was low, and the fixed effect model was used to analyse the data. If I^2 was less than 50%, heterogeneity among studies was substantial, and the random-effect model was used to analyse the data. Using subgroup analysis, the data for the heterogeneous investigations were processed.

RESULTS

To search the English literature, the following databases were consulted: PubMed, Embase, Medline, and Cochrane. There were 196 pertinent articles retrieved. Six English studies were included according to inclusion and exclusion criteria (Figure 1).

According to the first author, publication date, sample size for each group, age of survey respondents, and detection indicators, a total of six English studies were included. The literature was published between 2000 and 2018 (Table I). Five of the six included works were of high quality, while one was of average quality (Table II). Publication bias was evaluated by applying funnel plots of the Anti-dsDNA with the greatest number of included studies. The Anti-ds DNA funnel plot is visually symmetric, which suggests that there is no publication bias (Figure 2).

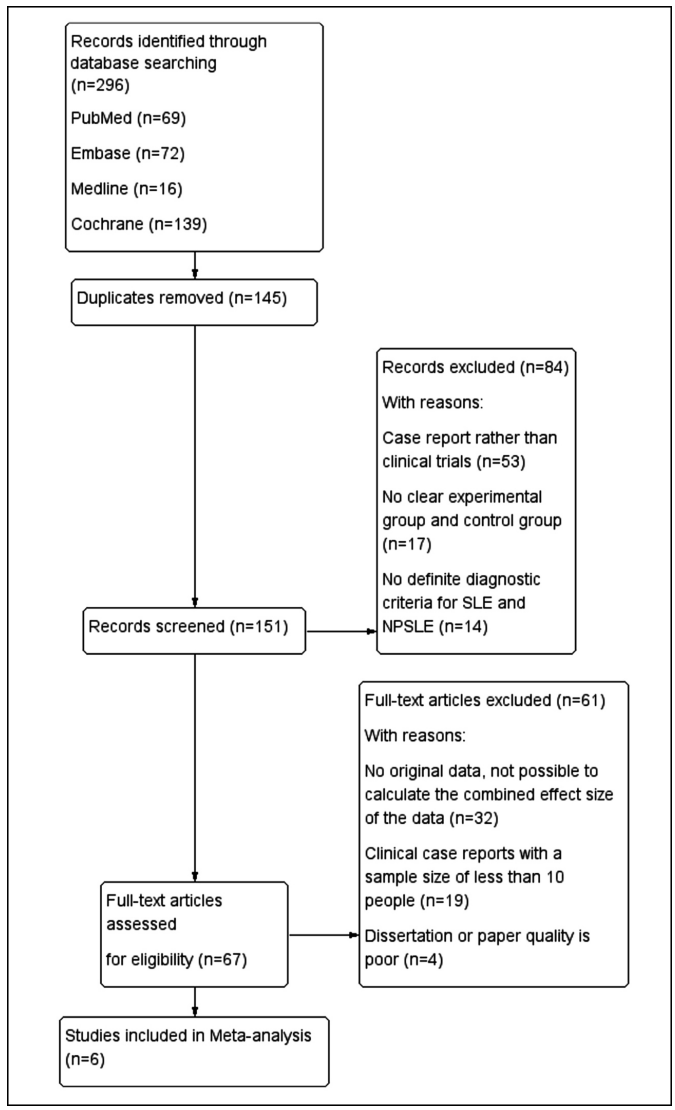

Figure 1: Flow diagram for screening literature characteristics and quality evaluation.

This meta-analysis describes the clinical symptoms and medical indicators of SLE and NPSLE patients. There were a total of 2,997 patients enrolled. In the six studies included in the primary and/or sensitivity analysis, patients were evaluated for malar rash, discoid rash, mucosal ulcer, arthritis, serositis, and other symptom-contrast results. On the patients' medical indicators, including anti-dsDNA antibody, anti-Sm antibody, ANA, and anti-RNP antibody, a statistical analysis was performed. Statistically significant results were reported (Figure 2A).

Five out of six studies, listed values for NPSLE (experimental group) and SLE (control group), with a total of 823 experimental group and 2,090 control group. In accordance to the heterogeneity test, there was a small amount of heterogeneity in the results, and subgroup analysis was not necessary because I^2 was less than 50% ($I^2 = 41\%$, $p = 0.15$); therefore, a fixed effect model was employed for the meta-analysis. The findings revealed that NPSLE patients were marginally less likely to have discoid rash than SLE patients, with a total effect size of OR = 0.74, 95% CI (0.54, 1.00), $p = 0.05$ (Figure 2B).

Table I: Features of the included studies.

Study	Year	Sample size		Study type	Medical tests
		NPSLE	SLE		
Ahn *et al.*[6]	2018	216	692	Single-centre study	Age Disease duration Malar rash Oral ulcers Discoid rash Photo-sensitivity Serositis Haematologic disorder Anti-dsDNA Anti-Ro Anti-La Anti-RNP Anti-Sm ANA
Karassa *et al.*[7]	2000	32	96	Case-control study	Age Disease duration Discoid rash Serositis Haemolytic anaemia Leucopaenia Anti-ds DNA Anti-Sm Anti-SSA Anti-SSB Anti-RNP LA ANA
Abdul Sattar *et al.*[8]	2013	48	36	Single-centre study	Age Disease duration Haematologic disorder Serositis Anti-dsDNA Anti-Ro Anti-La Anti-RNP
Padovan *et al.*[9]	2010	153	247	A single centre	Age Disease duration Hypertension Malar rash Discoid rash Photo-sensibility Mucosal ulcer Serositis Haemolytic anaemia Leucopaenia Anti-dsDNA Anti-Sm ANA
Mok *et al.*[10]	2000	96	422	Case-control study	Age Disease duration Malar rash Oral ulcers Discoid rash Photo-sensitivity Renal disease Leucopaenia Serositis ANA Anti-dsDNA Anti-Ro Anti-La Anti-RNP Anti-Sm
Govoni *et al.*[11]	2011	326	633	Cross-sectional study	Age Disease duration Malar rash Oral ulcers Discoid rash Photo-sensitivity Serositis LA Anti-dsDNA Anti-Ro Anti-La Anti-RNP Anti-Sm

Note: ANA, Antinuclear antibodies; dsDNA, Double-stranded deoxyribonucleic acid; LA, Lupus anticoagulant; RNP, Ribonucleoprotein.

Table II: NOS quality evaluation of the included research.

Study	Year	1	2	3	4	5	6	7	8	Total
Karassa *et al.*[7]	2000	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	7
Padovan *et al.*[9]	2010	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	7
Mok *et al.*[10]	2000	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	7
Govoni *et al.*[11]	2011	Yes	No	Yes	Yes	Yes	No	Yes	Yes	6
Ahn *et al.*[6]	2018	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	7
Abdul Sattar *et al.*[8]	2013	Yes	Yes	Yes	Yes	No	Yes	Yes	No	6

Note: 1. Whether the definition and diagnosis of cases are appropriate; 2. Whether the cases are representative or continuous; 3. Whether the control was community control or hospital control; 4. Whether the control group had no medical history; 5. Whether cases and controls are comparable; 6. Whether case and control investigation and evaluation methods are blind or reliably recorded; 7. Whether the investigation methods of cases and controls are the same; 8. Whether the non-response rates were the same for cases and controls.

Four out of six studies provided listed values for NPSLE (experimental group) and SLE (control group), with 615 people in the experimental group and 1,203 people in the control group. The $I^2 = 0\%$, p = 0.57 heterogeneity test revealed that there was no heterogeneity in the results. As a result, the fixed effect model was utilised for the meta-analysis. NPSLE patients had a slightly decreased risk of developing hypertension than SLE patients, with a total effect size of OR = 0.75, 95% CI (0.59, 0.96), p = 0.02 (Figure 2C).

A total of 5 out of the 6 studies, included listed values for NPSLE (experimental group) and SLE (control group), including a total of 827 experimental group and 2,042 control group. There was almost no heterogeneity according to the heterogeneity test ($I^2 = 3\%$, p = 0.39). Therefore, the fixed-effect model was used for the meta-analysis. It is shown that NPSLE patients' disease duration is longer than SLE patients. The combined effect size was MD = 1.24, 95% CI (0.78, 1.70, p <0.01) (Figure 2D).

Enzyme-linked immunosorbent assay (ELISA) and the Farr radioimmunoassay were the most common anti-dsDNA detection techniques described in the literature. All six included studies listed the NPSLE (experimental group) and SLE (control group) values for the 870 participants in the experimental group and the 2,124 participants in the control group. The heterogeneity test revealed that the results were homogeneous ($I^2 = 0\%$, p = 0.45). For meta-analysis, a fixed effect model was therefore employed. The results demonstrated that the anti-dsDNA index was lower in NPSLE patients than in SLE patients, with a combined effect size of OR = 0.84, 95% CI (0.71, 0.99), p = 0.04 (Figure 3A).

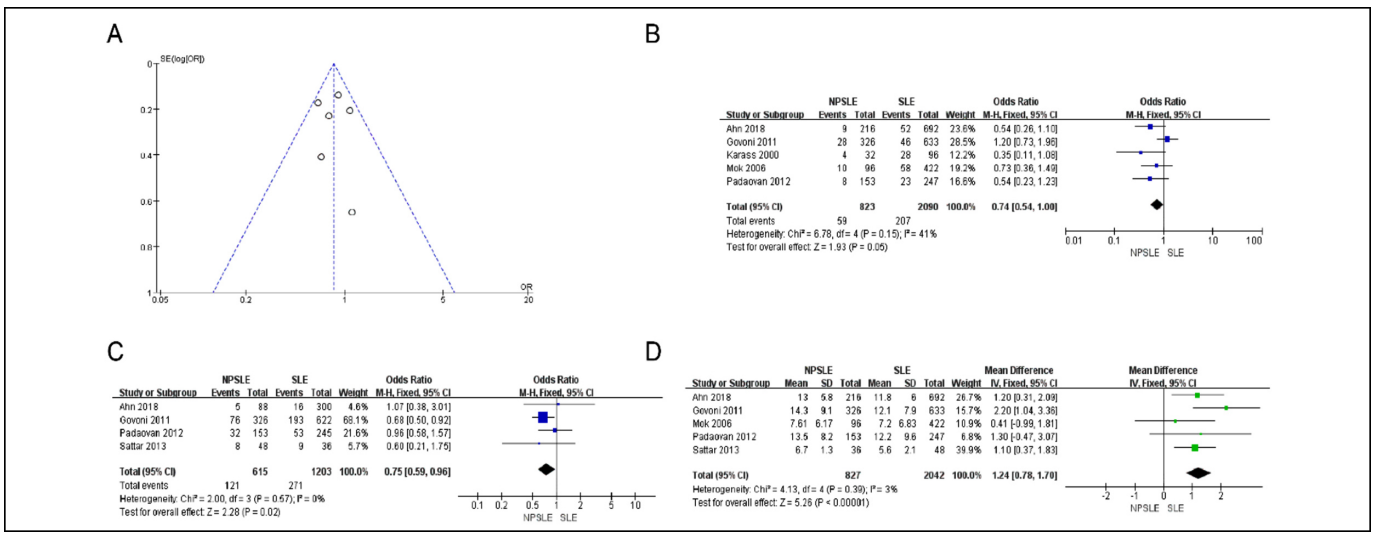

Figure 2: Forest plot. Medical index contrast of anti-dsDNA between NPSLE patients and SLE patients.
(A) Funnel plot of the studies included in the present meta-analysis. (B) Forest plot of the relationship between discoid rash and NPSLE patients / SLE patients. (C) Forest plot of the relationship between hypertension and NPSLE patients / SLE patients. (D) Forest plot of the relationship between mean disease duration and NPSLE patients / SLE patients.

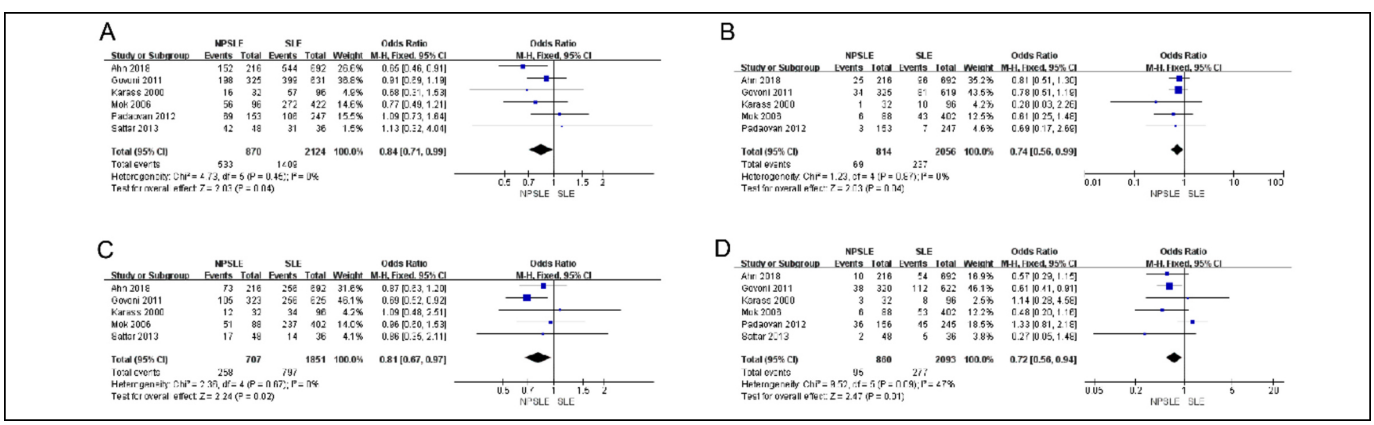

Figure 3: Forest plot.
(A) Forest plot of the relationship between anti-dsDNA and NPSLE patients / SLE patients. (B) Forest plot of the relationship between anti-Sm and NPSLE patients / SLE patients. (C) Forest plot of the relationship between anti-SSA and NPSLE patients / SLE patients. (D) Forest plot of the relationship between anti-SSB and NPSLE patients / SLE patients.

ELISA and the Farr radioimmunoassay comprised the majority of anti-Sm detection methods described in the included literature. In 5 out of the 6 included studies, values for NPSLE (experimental group) and SLE (control group) were provided, with a total of 870 participants in the experimental group and 2,124 participants in the control group. The heterogeneity test revealed that the results were homogeneous (I^2 = 0%, p = 0.87). For meta-analysis, a fixed effect model was therefore employed. Figure 3 B demonstrates that the anti-Sm index was lower in NPSLE patients than in SLE patients, with a combined effect size of [OR = 0.84, 95% CI (0.71, 0.99), p = 0.04].

In the included literature, the anti-SSA assay was immunoblotting or ELISA. Five out of the six studies listed values for NPSLE (experimental group) and SLE (control group), with 707 experimental group members and 1,851 control group members. The heterogeneity test revealed that the results were homogeneous (I^2 = 0%, p = 0.67). For meta-analysis, a fixed effect model was therefore employed. Anti-SSA index was lower in NPSLE patients than in SLE patients, with a combined effect magnitude of OR = 0.81, 95% CI (0.67, 0.97), p = 0.02 (Figure 3C).

Immunoblotting and ELISA were cited in the literature as anti-SSB detection methods. The six included studies listed the NPSLE (experimental group) and SLE (control group) values for all 860 participants in the experimental group and 2,093 participants in the control group. High heterogeneity was indicated by the heterogeneity test (I^2 = 47%, p = 0.09), but I^2 was less than 50%. Consequently, the fixed effect model was retained for meta-analysis. Anti-SSB index was lower in NPSLE patients than in SLE patients, with a combined effect magnitude of OR = 0.72, 95% CI (0.56, 0.94), p = 0.01 (Figure 3D).

DISCUSSION

When SLE impacts either the central nervous system or the peripheral nervous system, it can lead to the development of neuropsychiatric syndromes.[13] The identification of neuropsychiatric syndromes concurrent with systemic lupus erythematosus (today known as NPSLE) is one of the challenges in the medical profession because it may require so many other symptom patterns.[14] These neuropsychiatric syndromes can sometimes be mistaken for symptoms of contagious diseases or manifestations of an acute attack, due to their overlapping clinical presentations. Headaches are the most common neurological symptom of SLE, although the existence of a specific lupus headache and the optimal method to worry in SLE cases remains debatable.[15] Other common neuropsychiatric manifestations of SLE include cognitive pathology, mood disturbance, cerebrovascular disease, seizures, polyneuropathy, anxiety disorder, and in rare cases, personality disorders.[16]

Lupus patients exhibit some apparent symptoms.[17] Extended cutaneous (discoid) lupus, sub-acute cutaneous lupus, and intense cutaneous lupus are the three most common forms of wounds. People with discoid lupus can develop scaly, dark-coloured skin lesions.[18] Lupus erythematosus cutis intense manifests as a rash. Some individuals develop the characteristic zygomatic dermatitis associated with this condition.[19] The meta-analysis revealed that patients with NPSLE had a less pronounced discoid rash than patients with SLE.

Positive ANA test results are observed in some connective tissue disorders and other autoimmune diseases, as well as in healthy individuals.[20] Anti-dsDNA antibodies are highly specific for SLE; they are found in 70 percent of cases, but in only 0.5 percent of individuals without SLE.[21] Although not always, these anti-dsDNA protein titers tend to indicate disease processes.[22] Anti-U1 RNP (which also appears in general pathology and various connective tissue diseases), SSA (or anti-Ro), and SSB (or anti-La); both of which are more prevalent in sicca syndrome.[23] SSA and SSB pose a heightened risk for cardiac conduction block in neonates with lupus.[24] This meta-analysis delineates a comprehensive examination of the clinical symptoms and medical indices, distinguishing patients with systemic SLE from those with NPSLE. This study encompasses a substantial cohort of 2,997 patients across six studies, offering a robust dataset for evaluating the prevalence of key symptoms such as malar rash, discoid rash, mucosal ulcers, and the incidence of conditions such as arthritis and serositis. Furthermore, the scrutinised variations in significant medical indices including anti-dsDNA, anti-Sm, ANA, and anti-RNP antibodies among these patient groups. The present study's investigation into the medical indices revealed lower levels of anti-dsDNA in NPSLE patients compared to those with SLE. Given the homogeneous nature of these results (I^2 = 0%, p = 0.45), this observation points to a potentially distinct immunological profile in NPSLE, which may have implications for diagnosis and treatment. The consistent findings regarding the anti-Sm index further corroborate this distinction, with both indices showing lower levels in NPSLE patients [OR = 0.84, 95% CI (0.71, 0.99), p = 0.04]. The data presented in this study illuminate the nuanced differences between SLE and NPSLE, highlighting the importance of tailored diagnostic criteria and management plans. However, it is essential to acknowledge the limitations of this analysis, including the variability in diagnostic criteria across studies and potential publication bias. Future research should focus on longitudinal studies to explore the progression of these conditions and the impact of various treatment modalities on patient outcomes. Furthermore, incorporating recent studies and expanding the dataset could enhance the robustness and applicability of these findings.

CONCLUSION

This meta-analysis of six studies involving 2,997 patients reveals notable differences between SLE and NPSLE in terms of clinical symptoms and medical indicators. The findings suggest that SLE patients generally present with more pronounced medical indicators than those with NPSLE, who require longer treatment durations. Although the analysis highlights the distinctions between SLE and NPSLE, it falls short of pinpointing the exact causes of these differences. Future research is essential to delve deeper into these variations and their implications for treatment and management strategies.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
YL: Conceptualised the study, led the research design, and was the principal investigator.
QG, PY: Contributed significantly to the data collection and analysis, and played critical roles in interpreting the results.
YL, QG, PY, LZ, NY, XS: Drafted the manuscript.
LZ, NY: Reviewed the literature and revised the manuscript critically.
XS: Contributed to the study's methodology development and performed the statistical analysis.
All authors approved the final version of the manuscript to be published. Each author agreed to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

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