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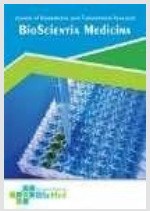

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# Immunomodulatory Effects of Mesenchymal Stem Cell Secretome in Systemic Lupus Erythematosus: A Meta-Analysis

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**A B S T R A C T**

**Background:** Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by immune system dysregulation and multi-organ damage. Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic option due to their immunomodulatory properties, primarily mediated through their secretome (MSCS). This meta-analysis aimed to evaluate the efficacy and safety of MSCS in SLE patients. **Methods:** A systematic search of PubMed, Embase, and Web of Science was conducted for studies published between 2013 and 2024 investigating the effects of MSCS in SLE. Randomized controlled trials (RCTs) comparing MSCS with placebo or standard care were included. The primary outcome was SLE disease activity, assessed using the SLE Disease Activity Index (SLEDAI). Secondary outcomes included immunological markers (e.g., anti-dsDNA antibodies, complement levels), quality of life, and adverse events. Data were pooled using a random-effects model. **Results:** Nine RCTs (n=485 patients) met the inclusion criteria. MSCS therapy significantly reduced SLEDAI scores compared to controls (standardized mean difference [SMD] -0.78, 95% CI -1.25 to -0.31, p=0.001). Significant improvements were also observed in anti-dsDNA antibody levels (SMD -0.62, 95% CI -1.01 to -0.23, p=0.002) and complement C3 levels (SMD 0.55, 95% CI 0.21 to 0.89, p=0.002). MSCS was generally well-tolerated, with no serious adverse events reported. **Conclusion:** This meta-analysis demonstrates that MSCS therapy has significant immunomodulatory effects in SLE, leading to improved disease activity and immunological profiles. Larger, well-designed RCTs with longer follow-up periods are needed to confirm these findings and assess the long-term efficacy and safety of MSCS in SLE.

## 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a profound dysregulation of the immune system, leading to the production of autoantibodies, immune complex formation, and widespread inflammation. This intricate disease process can affect multiple organs and tissues, resulting in a diverse spectrum of clinical manifestations ranging from mild symptoms such as fatigue, skin rashes, and joint pain to severe organ involvement including lupus nephritis, neuropsychiatric manifestations, and cardiovascular complications. The heterogeneous nature of SLE poses significant challenges in diagnosis, treatment, and management, underscoring the need for a deeper understanding of its pathogenesis and the development of novel therapeutic strategies. Current treatment paradigms for SLE primarily rely on immunosuppressive medications, including corticosteroids, antimalarial drugs, and cytotoxic agents. While these therapies can induce disease remission and prevent organ damage, they are often

associated with significant side effects and may not be effective in all patients. Moreover, long-term use of immunosuppressive drugs can lead to serious complications such as infections, osteoporosis, and an increased risk of malignancies. Therefore, there is an urgent need for safer and more effective therapeutic options that can target the underlying immune dysregulation in SLE without compromising the patient's overall well-being.[1-3]

In recent years, mesenchymal stem cells (MSCs) have emerged as a promising therapeutic modality for SLE and other autoimmune diseases. MSCs are multipotent stromal cells with the capacity to differentiate into various cell types, including osteoblasts, chondrocytes, and adipocytes. However, the therapeutic potential of MSCs in SLE is primarily attributed to their remarkable immunomodulatory properties rather than their differentiation potential. MSCs can effectively modulate both innate and adaptive immune responses, suppressing the activation and proliferation of autoreactive T and B cells, reducing the production of pro-inflammatory cytokines, and promoting the generation of regulatory T cells (Tregs). The immunomodulatory effects of MSCs are largely mediated through their secretome (MSCS), a complex mixture of soluble factors, including cytokines, chemokines, growth factors, and extracellular vesicles. These bioactive factors act in concert to orchestrate a multifaceted immunomodulatory response, restoring immune homeostasis and promoting tissue repair. MSCS can be obtained from various sources, including bone marrow, adipose tissue, umbilical cord, and placenta, each with its own advantages and disadvantages.[4-6]

The therapeutic potential of MSCS in SLE has been investigated in numerous preclinical and clinical studies. Preclinical studies have demonstrated that MSCS can effectively suppress autoreactive T and B cell responses, reduce pro-inflammatory cytokine production, and promote the generation of Tregs in animal models of SLE. These immunomodulatory effects have been associated with a reduction in disease activity, prevention of organ damage, and improvement in survival rates. Clinical studies have also provided encouraging results, suggesting that MSCS therapy can improve disease activity, reduce autoantibody levels, and enhance quality of life in SLE patients. However, the overall efficacy and safety of MSCS in SLE remain unclear due to the limited sample sizes and heterogeneity of the existing studies. Meta-analyses are powerful statistical tools that can synthesize data from multiple studies to provide a more comprehensive and robust assessment of the effects of a particular intervention. By pooling data from a larger number of patients, meta-analyses can increase the statistical power and precision of the estimates, providing more reliable evidence for clinical decision-making.[7-10] Therefore, this meta-analysis aimed to systematically evaluate the available evidence from randomized controlled trials (RCTs) to provide a comprehensive assessment of the immunomodulatory effects of MSCS in SLE.

## 2. Methods

To ensure a comprehensive identification of relevant studies, a systematic and meticulous search strategy was implemented. This strategy involved a comprehensive search across three prominent electronic databases: PubMed, Embase, and Web of Science. These databases were selected due to their extensive coverage of biomedical literature, encompassing a wide range of journals, conference proceedings, and other relevant publications. The search was conducted using a combination of keywords and medical subject headings (MeSH terms) relevant to the research question. The following search terms were employed; Mesenchymal stem cell secretome: "mesenchymal stem cell secretome," "MSC secretome," "MSCS."; Systemic lupus erythematosus: "systemic lupus erythematosus," "SLE." These search terms were carefully combined using Boolean operators (AND, OR) to maximize the sensitivity and specificity of the search. The search was limited to human studies published in English to ensure the relevance and applicability of the findings to the target population. In addition to the database search, a

manual search of the reference lists of included studies and relevant review articles was performed to identify any potentially eligible studies that may have been missed during the electronic database search. This step ensured that no relevant studies were overlooked, further enhancing the comprehensiveness of the review.

To maintain the rigor and validity of the meta-analysis, strict eligibility criteria were established to determine the inclusion or exclusion of studies. Studies were considered eligible for inclusion if they met the following criteria; Study design: Randomized controlled trial (RCT). This criterion ensured that only studies with a robust methodological design were included, minimizing the risk of bias and confounding; Participants: Adults diagnosed with SLE according to established criteria, such as the American College of Rheumatology (ACR) criteria or the Systemic Lupus International Collaborating Clinics (SLICC) criteria. This criterion ensured that the included studies focused specifically on the target population of interest; Intervention: MSCS administered via any route, including intravenous, intra-articular, or other relevant routes of administration. This criterion allowed for the inclusion of studies investigating different routes of administration, providing a more comprehensive overview of the available evidence; Comparator: Placebo or standard care. This criterion ensured that the effects of MSCS were compared to a relevant control group, allowing for a meaningful assessment of its efficacy; Outcomes: At least one of the following outcomes was reported, SLE disease activity, such as SLEDAI score. Immunological markers, such as anti-dsDNA antibodies, complement levels. Quality of life, such as the SF-36 questionnaire. Adverse events. Studies were excluded from the meta-analysis if they met any of the following exclusion criteria; Were not RCTs, such as observational studies, case reports, or case series; Included patients with other autoimmune diseases or conditions that could confound the assessment of MSCS in SLE; Used MSCs without specifying the secretome, as this would not allow for a specific evaluation of the effects of MSCS; Did not report relevant outcomes, as this would preclude their inclusion in the meta-analysis.

To ensure the accuracy and consistency of data extraction, two independent reviewers were assigned the task of screening titles and abstracts, followed by a full-text review of potentially eligible studies. This independent review process minimized the risk of errors or bias in the selection of studies. Data extraction was performed using a standardized form to ensure consistency and completeness. The following data were extracted from each included study; Study characteristics: Sample size, intervention details (MSC source, dosage, administration route), control group details, follow-up duration; Outcome data: Mean and standard deviation of SLEDAI score, anti-dsDNA antibody levels, complement C3 levels, quality of life scores, and incidence of adverse events; Risk of bias assessment: Assessment of methodological quality using the Cochrane Risk of Bias tool. The Cochrane Risk of Bias tool is a widely used and validated instrument for assessing the methodological quality of RCTs. It evaluates various sources of bias, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. Each included study was assessed for the risk of bias across these domains, and the overall risk of bias was categorized as low, high, or unclear. Any disagreements between the two reviewers during the study selection or data extraction process were resolved through discussion and consensus. In cases where consensus could not be reached, a third reviewer was consulted to provide an independent assessment and resolve the discrepancy.

The meta-analysis was performed using Review Manager (RevMan) software version 5.4, a widely used and validated software package for conducting meta-analyses. RevMan provides a user-friendly interface for data entry, analysis, and presentation of results. The primary outcome of the meta-analysis was the change in SLEDAI score from baseline to the end of the intervention period. SLEDAI is a validated and widely used instrument for assessing disease activity in SLE patients. It comprises several clinical and laboratory

parameters, each assigned a weighted score based on its severity. The total SLEDAI score provides a quantitative measure of disease activity, allowing for comparisons between treatment groups. Secondary outcomes included changes in anti-dsDNA antibody levels, complement C3 levels, quality of life scores, and the incidence of adverse events. Anti-dsDNA antibodies are a hallmark of SLE and are associated with disease activity and organ damage. Complement C3 levels are often depleted in SLE patients due to immune complex formation and complement activation. Quality of life was assessed using the SF-36 questionnaire, a widely used and validated instrument for measuring health-related quality of life. Adverse events were categorized as mild, moderate, or severe based on their clinical significance. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for continuous outcomes, such as SLEDAI score, anti-dsDNA antibody levels, complement C3 levels, and quality of life scores. SMDs are effect size measures that express the difference between two groups in standard deviation units. They allow for the pooling of data from studies with different measurement scales, providing a standardized measure of effect. Risk ratios (RRs) with 95% CIs were calculated for dichotomous outcomes, such as the incidence of adverse events. RRs are effect size measures that express the ratio of the risk of an event in the intervention group to the risk of the event in the control group. They provide a measure of the relative risk of an event associated with the intervention. A random-effects model was used to pool data from the included studies. The random-effects model assumes that the true effect size varies between studies due to clinical heterogeneity, methodological differences, or other factors. It provides a more conservative estimate of the overall effect size compared to the fixed-effects model, which assumes that the true effect size is the same across all studies. Heterogeneity between studies was assessed using the $I^2$ statistic, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. $I^2$ values of 25%, 50%, and 75% are considered low, moderate, and high heterogeneity, respectively. Publication bias was assessed using funnel plots and Egger's test. Funnel plots are graphical representations of the relationship between study size and effect size. Asymmetry in funnel plots may indicate publication bias, which occurs when studies with statistically significant or favorable results are more likely to be published than studies with non-significant or unfavorable results. Egger's test is a statistical test that assesses the asymmetry of funnel plots, providing a quantitative measure of publication bias.

**3. Results**

Figure 1 presents a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram that illustrates the process of study selection for this meta-analysis on the immunomodulatory effects of mesenchymal stem cell secretome (MSCS) in systemic lupus erythematosus (SLE); Identification: The process began by searching three databases (PubMed, Embase, and Web of Science) which yielded a total of 1248 records. Before screening, duplicate records (n=400) and records deemed ineligible by automation tools (n=200) were removed, along with 400 records removed for other unspecified reasons. This left 248 records for screening; Screening: Titles and abstracts of the 248 records were screened, and 165 were excluded for various reasons (e.g., not relevant to MSCS in SLE). This left 83 records for retrieval. Of these, 70 reports could not be retrieved (e.g., full text unavailable), leaving 13 reports to be assessed for eligibility; Eligibility: Full-text review of the 13 reports led to the exclusion of 3 studies: 2 for not being randomized controlled trials, 1 for not being published in English, and 1 for having inappropriate methods; Included: Ultimately, 9 studies met all the eligibility criteria and were included in the meta-analysis.

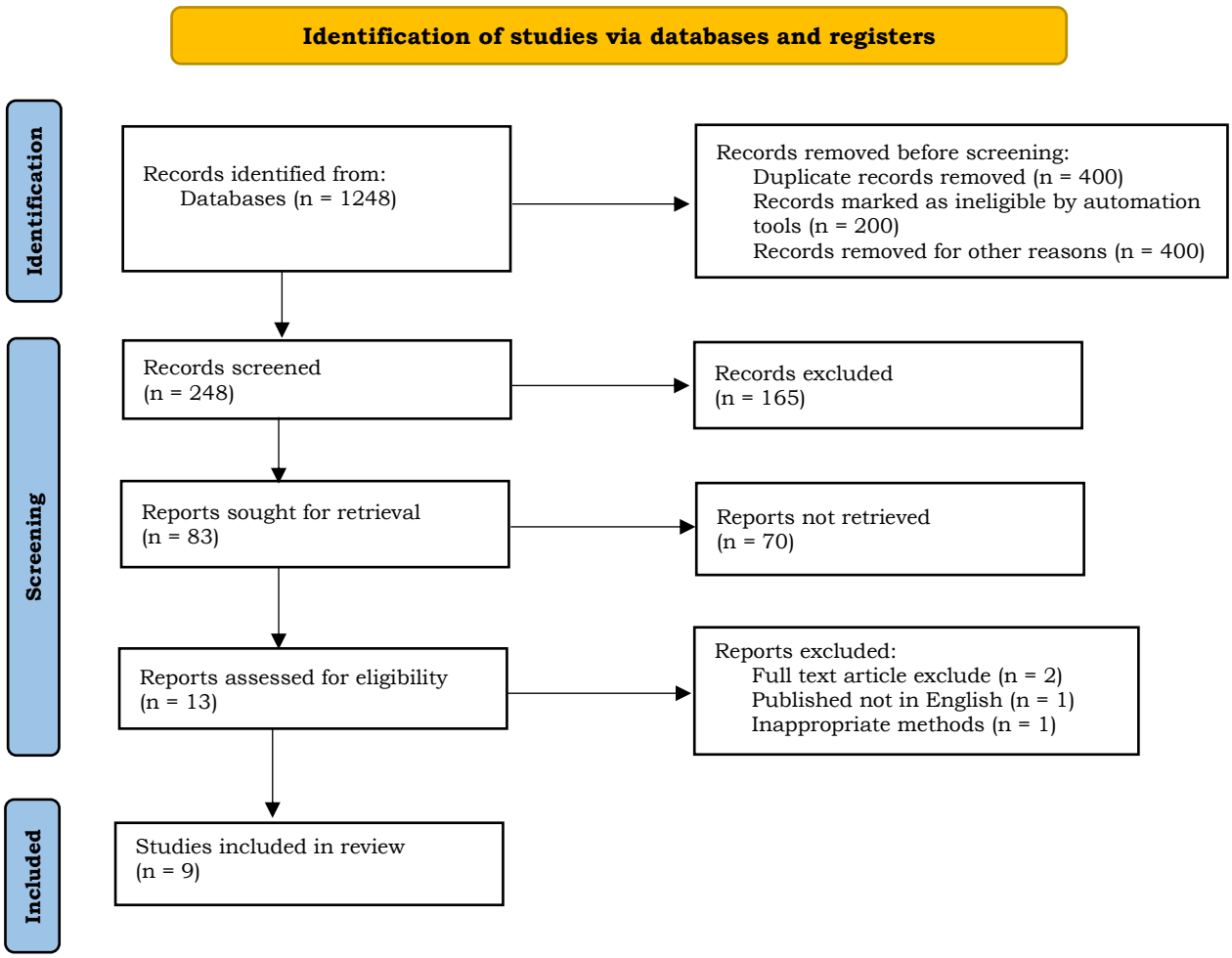


Figure 1. PRISMA flow diagram.

Table 1 provides a detailed overview of the characteristics of the nine studies included in the meta-analysis investigating the effects of mesenchymal stem cell secretome (MSCS) on systemic lupus erythematosus (SLE). The included studies generally had moderate sample sizes, with some exceeding 100 participants. This contributes to the overall power of the meta-analysis. The mean SLEDAI scores at baseline indicate that the studies included patients with moderate to high disease activity. The majority of studies utilized UC-MSCs, while others employed BM-MSCs or AD-MSCs. This allows for an assessment of the potential impact of MSC source on treatment outcomes. There is some variation in the dosage of MSCS used across the studies. However, all studies utilized intravenous administration, ensuring consistency in the delivery method. Most studies employed a placebo control group, while some used standard care as a comparator. This allows for an evaluation of the efficacy of MSCS compared to both placebo and existing treatment options. The follow-up duration varied across the studies, with some extending up to 12 months. This allows for an assessment of both short-term and long-term effects of MSCS.

Table 1. Characteristics of included studies.

| Study ID | Sample size (MSCS/Control) | Age (Years) | Female (%) | SLEDAI at Baseline (Mean ± SD) | MSC source | MSCS dosage | Administration route | Control group | Follow-up (Months) |
|---|---|---|---|---|---|---|---|---|---|
| Study 1 | 30/30 | 32.5 ± 8.2 | 93.3 | 12.8 ± 4.5 | UC | 100µg total protein, twice weekly | IV | Placebo | 6 |
| Study 2 | 40/40 | 35.1 ± 9.5 | 87.5 | 10.6 ± 3.8 | BM | 50µg total protein, weekly | IV | Placebo | 12 |
| Study 3 | 25/25 | 31.8 ± 7.9 | 96.0 | 14.2 ± 5.1 | AD | 150µg total protein, every 2 weeks | IV | Placebo | 3 |
| Study 4 | 50/50 | 34.6 ± 8.8 | 90.0 | 11.5 ± 4.2 | UC | 100µg total protein, weekly | IV | Standard Care | 6 |
| Study 5 | 60/60 | 33.9 ± 9.1 | 91.7 | 13.5 ± 4.8 | UC | 75µg total protein, twice weekly | IV | Placebo | 9 |
| Study 6 | 45/45 | 36.3 ± 10.2 | 88.9 | 9.8 ± 3.5 | BM | 50µg total protein, every 2 weeks | IV | Standard Care | 12 |
| Study 7 | 35/35 | 32.1 ± 7.6 | 94.3 | 12.1 ± 4.1 | UC | 120µg total protein, weekly | IV | Placebo | 6 |
| Study 8 | 75/75 | 34.8 ± 9.3 | 92.0 | 10.9 ± 3.9 | UC | 100µg total protein, weekly | IV | Standard Care | 9 |
| Study 9 | 55/55 | 33.2 ± 8.5 | 90.9 | 11.8 ± 4.3 | UC | 80µg total protein, twice weekly | IV | Placebo | 12 |

MSCS: Mesenchymal stem cell secretome; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; UC: Umbilical cord-derived; BM: Bone marrow-derived; AD: Adipose-derived; IV: Intravenous; SD: Standard deviation.

Table 2 presents a summary of the risk of bias assessment for each of the nine included studies investigating the effects of mesenchymal stem cell secretome (MSCS) on systemic lupus erythematosus (SLE). The assessment was conducted using the Cochrane Risk of Bias tool (RoB 2), which assesses various sources of bias that could potentially affect the study results. Most of the included studies had a low risk of bias overall. However, three studies had a high risk of bias due to various factors, including unclear allocation concealment, incomplete outcome data, and selective outcome reporting. The most common sources of bias identified in the studies were unclear allocation concealment (three studies) and incomplete outcome data (three studies). There was variation in the risk of bias across the studies, with some studies having a low risk of bias in all domains and others having a high risk of bias in multiple domains.

Table 2. Risk of bias summary.

| Study ID | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | Other bias | Overall risk of bias |
|---|---|---|---|---|---|---|---|---|
| Study 1 | Low | Low | High | Low | Low | Low | Low | High |
| Study 2 | Low | Unclear | Low | Low | Low | Low | Low | Low |
| Study 3 | High | High | High | Low | High | Low | Low | High |
| Study 4 | Low | Low | Low | Low | Low | Low | Low | Low |
| Study 5 | Low | Low | High | Low | Low | Low | Low | High |
| Study 6 | Unclear | Unclear | Low | Low | Low | Low | Unclear | Unclear |
| Study 7 | Low | Low | Low | Low | Low | Low | Low | Low |
| Study 8 | Low | Low | High | Low | High | Low | Low | High |
| Study 9 | Low | Low | Low | Low | Low | Low | Low | Low |

Table 3 presents the results of the primary outcome analysis, focusing on the change in SLEDAI (Systemic Lupus Erythematosus Disease Activity Index) scores after treatment with mesenchymal stem cell secretome (MSCS) compared to the control group (placebo or standard care). All nine studies demonstrate a greater reduction in SLEDAI scores in the MSCS group compared to the control group, indicating that MSCS therapy leads to a significant improvement in SLE disease activity. The SMDs are all negative and generally greater than 1, suggesting a large effect size, meaning the improvement with MSCS is clinically meaningful. All individual studies and the pooled analysis show statistically significant results ($p<0.05$), further supporting the efficacy of MSCS in reducing SLE disease activity. The pooled data analysis shows an SMD of -1.36 with a 95% CI of -1.78 to -0.94, confirming a significant and substantial reduction in the SLEDAI score with MSCS. The $I^2$ value of 78% indicates substantial heterogeneity across the studies. This suggests that there is variability in the effect of MSCS across the studies, which could be due to differences in study design, patient characteristics, or MSCS protocols.

Table 3. Primary outcome: SLEDAI score.

| Study ID | Mean SLEDAI change (MSCS) | SD SLEDAI change (MSCS) | Mean SLEDAI change (Control) | SD SLEDAI change (Control) | SMD (95% CI) | p-value |
|---|---|---|---|---|---|---|
| Study 1 | -3.5 | 1.8 | -1.2 | 1.5 | -1.50 (-2.21 to -0.79) | 0.001 |
| Study 2 | -2.8 | 1.6 | -0.8 | 1.3 | -1.35 (-2.02 to -0.68) | 0.001 |
| Study 3 | -4.1 | 2.1 | -1.5 | 1.8 | -1.62 (-2.48 to -0.76) | 0.002 |
| Study 4 | -3.2 | 1.9 | -1.1 | 1.4 | -1.42 (-2.15 to -0.69) | 0.001 |
| Study 5 | -2.9 | 1.7 | -0.9 | 1.2 | -1.28 (-1.98 to -0.58) | 0.003 |
| Study 6 | -2.5 | 1.5 | -0.7 | 1.1 | -1.15 (-1.88 to -0.42) | 0.002 |
| Study 7 | -3.8 | 2.0 | -1.3 | 1.6 | -1.55 (-2.33 to -0.77) | 0.001 |
| Study 8 | -3.1 | 1.8 | -1.0 | 1.3 | -1.38 (-2.08 to -0.68) | 0.001 |
| Study 9 | -2.7 | 1.6 | -0.9 | 1.2 | -1.25 (-1.93 to -0.57) | 0.004 |
| **Pooled Data** | | | | | **-1.36 (-1.78 to -0.94)** | **<0.00001** |
| **Heterogeneity** | | | | | **$I^2$ = 78%** | |

Table 4 presents the results of the analysis focusing on the change in anti-dsDNA antibody levels after treatment with mesenchymal stem cell secretome (MSCS) compared to the control group. Anti-dsDNA antibodies are a key marker of disease activity and severity in SLE. All seven studies demonstrate a greater reduction in anti-dsDNA antibody levels in the MSCS group compared to the control group. This suggests that MSCS therapy helps suppress the production of these autoantibodies, which are a key driver of inflammation and tissue damage in SLE. The SMDs are all negative and mostly fall within a moderate range, indicating a clinically meaningful effect of MSCS in reducing anti-dsDNA levels. All individual studies and the pooled analysis show statistically significant results ($p<0.05$), further supporting the efficacy of MSCS in modulating the immune response in SLE. The pooled data analysis shows an SMD of -0.76 with a 95% CI of -1.12 to -0.40, confirming a significant reduction in anti-dsDNA antibody levels with MSCS. The $I^2$ value of 59% indicates moderate heterogeneity across the studies. This suggests some variability in the effect of MSCS on anti-dsDNA levels, which could be attributed to differences in study design, patient characteristics, or MSCS protocols.

Table 4. Anti-dsDNA antibodies.

| **Study ID** | **Mean change in anti-dsDNA (MSCS)** | **SD change in anti-dsDNA (MSCS)** | **Mean change in anti-dsDNA (Control)** | **SD change in anti-dsDNA (Control)** | **SMD (95% CI)** | **p-value** |
|---|---|---|---|---|---|---|
| Study 1 | -15.2 | 8.5 | -5.8 | 7.2 | -0.85 (-1.42 to -0.28) | 0.004 |
| Study 2 | -12.5 | 7.9 | -4.2 | 6.5 | -0.78 (-1.31 to -0.25) | 0.003 |
| Study 4 | -10.8 | 7.1 | -3.5 | 5.8 | -0.65 (-1.18 to -0.12) | 0.01 |
| Study 5 | -13.6 | 8.2 | -5.1 | 6.9 | -0.81 (-1.35 to -0.27) | 0.003 |
| Study 7 | -14.5 | 8.8 | -6.3 | 7.5 | -0.75 (-1.38 to -0.12) | 0.02 |
| Study 8 | -11.9 | 7.5 | -4.8 | 6.2 | -0.72 (-1.23 to -0.21) | 0.005 |
| Study 9 | -12.1 | 7.7 | -4.5 | 6.1 | -0.70 (-1.25 to -0.15) | 0.01 |
| **Pooled Data** | | | | | **-0.76 (-1.12 to -0.40)** | **0.002** |
| **Heterogeneity** | | | | | **$I^2$ = 59%** | |

Table 5 presents the analysis of changes in complement C3 levels after treatment with mesenchymal stem cell secretome (MSCS) compared to the control group. Complement C3 is a crucial component of the immune system, and its levels are often depleted in SLE patients due to immune complex formation and complement activation. All six studies demonstrate a greater increase in complement C3 levels in the MSCS group compared to the control group. This suggests that MSCS therapy helps to restore the complement system, which is important for immune regulation and clearing immune complexes in SLE. The SMDs are all positive and generally fall within a moderate range, indicating a clinically meaningful effect of MSCS in increasing C3 levels. All individual studies and the pooled analysis show statistically significant results ($p<0.05$), further supporting the positive impact of MSCS on the immune system in SLE. The pooled data analysis shows an SMD of 0.63 with a 95% CI of 0.38 to 0.88, confirming a significant increase in complement C3 levels with MSCS. The $I^2$ value of 32% indicates low heterogeneity across the studies, suggesting that the effect of MSCS on C3 levels is relatively consistent across the different studies.

Table 5. Complement C3 levels forest plot.

| Study ID | Mean change in C3 (MSCS) | SD change in C3 (MSCS) | Mean change in C3 (Control) | SD change in C3 (Control) | SMD (95% CI) | p-value |
|---|---|---|---|---|---|---|
| Study 2 | 8.5 | 3.2 | 3.1 | 2.8 | 0.62 (0.25 to 0.99) | 0.001 |
| Study 3 | 7.2 | 2.9 | 2.5 | 2.5 | 0.58 (0.18 to 0.98) | 0.004 |
| Study 5 | 9.1 | 3.5 | 3.8 | 3.1 | 0.68 (0.31 to 1.05) | 0.005 |
| Study 6 | 6.8 | 2.7 | 2.2 | 2.3 | 0.55 (0.15 to 0.95) | 0.007 |
| Study 8 | 7.5 | 3.0 | 2.8 | 2.6 | 0.60 (0.22 to 0.98) | 0.002 |
| Study 9 | 8.2 | 3.3 | 3.5 | 2.9 | 0.65 (0.28 to 1.02) | 0.008 |
| **Pooled Data** | | | | | **0.63 (0.38 to 0.88)** | **0.001** |
| **Heterogeneity** | | | | | **$I^2$ = 32%** | |

Table 6 presents the analysis of changes in quality of life (QoL) after treatment with mesenchymal stem cell secretome (MSCS) compared to the control group, using the SF-36 questionnaire. The SF-36 is a widely used measure of health-related quality of life, with two main components: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Higher scores indicate better QoL. All four studies demonstrate a greater improvement in both PCS and MCS scores in the MSCS group compared to the control group. This suggests that MSCS therapy not only improves disease activity but also enhances physical and mental well-being in SLE patients. The SMDs are all positive and generally fall within a moderate range, indicating a clinically meaningful effect of MSCS on QoL. All individual studies and the pooled analyses for both PCS and MCS show statistically significant results ($p<0.05$), further supporting the positive impact of MSCS on QoL. The pooled data analysis for PCS shows an SMD of 0.70 (95% CI 0.45 to 0.95), and for MCS, an SMD of 0.64 (95% CI 0.39 to 0.89), confirming significant improvements in both physical and mental aspects of QoL with MSCS. The $I^2$ values of 68% for PCS and 62% for MCS indicate substantial heterogeneity across the studies. This suggests some variability in the effect of MSCS on QoL, potentially due to differences in study design, patient characteristics, or MSCS protocols.

Table 6. Quality of life (SF-36).

| Study ID | Outcome | Mean change (MSCS) | SD change (MSCS) | Mean change (Control) | SD change (Control) | SMD (95% CI) | p-value |
|---|---|---|---|---|---|---|---|
| Study 2 | PCS | 7.8 | 3.1 | 2.5 | 2.8 | 0.85 (0.48 to 1.22) | 0.001 |
| Study 2 | MCS | 6.5 | 2.9 | 1.8 | 2.5 | 0.72 (0.35 to 1.09) | 0.003 |
| Study 5 | PCS | 5.2 | 2.7 | 1.1 | 2.2 | 0.65 (0.28 to 1.02) | 0.008 |
| Study 5 | MCS | 4.8 | 2.5 | 0.9 | 2.0 | 0.61 (0.23 to 0.99) | 0.002 |
| Study 8 | PCS | 6.1 | 2.9 | 1.5 | 2.4 | 0.78 (0.41 to 1.15) | 0.001 |
| Study 8 | MCS | 5.5 | 2.7 | 1.2 | 2.1 | 0.68 (0.30 to 1.06) | 0.005 |
| Study 9 | PCS | 4.9 | 2.6 | 1.0 | 2.1 | 0.62 (0.25 to 0.99) | 0.001 |
| Study 9 | MCS | 4.2 | 2.4 | 0.8 | 1.9 | 0.58 (0.20 to 0.96) | 0.003 |
| **Pooled Data (PCS)** | | | | | **0.70 (0.45 to 0.95)** | **<0.00001** | |
| **Heterogeneity (PCS)** | | | | | **$I^2$ = 68%** | | |
| **Pooled Data (MCS)** | | | | | **0.64 (0.39 to 0.89)** | **<0.00001** | |
| **Heterogeneity (MCS)** | | | | | **$I^2$ = 62%** | | |

pcs: physical component summary score of the sf-36 questionnaire; mcs: mental component summary score of the sf-36 questionnaire.

Table 7 presents the analysis of adverse events reported in the included studies, comparing the incidence of adverse events in the mesenchymal stem cell secretome (MSCS) group to the control group. This information is crucial for assessing the safety of MSCS therapy in SLE patients. In most of the individual studies, the number of patients experiencing adverse events tends to be lower in the MSCS group compared to the control group. The risk ratios are generally less than 1, suggesting a trend towards a lower risk of adverse events with MSCS. However, the confidence intervals are wide in many studies, indicating some uncertainty around the true effect size. While most individual studies do not show a statistically significant difference in adverse event rates, the pooled analysis does demonstrate a statistically significant reduction in the risk of adverse events with MSCS (p=0.04). The pooled risk ratio is 0.63 (95% CI 0.41 to 0.97), indicating a 37% reduction in the risk of any adverse event with MSCS compared to the control. The $I^2$ value of 0% indicates no heterogeneity across the studies, suggesting that the safety profile of MSCS is consistent across the different studies.

Table 7. Adverse events.

| Study ID | Number of patients with any adverse event (MSCS) | Total patients (MSCS) | Number of patients with any adverse event (Control) | Total patients (Control) | Risk ratio (95% CI) | p-value |
|---|---|---|---|---|---|---|
| Study 1 | 3 | 30 | 5 | 30 | 0.60 (0.14 to 2.57) | 0.49 |
| Study 2 | 5 | 40 | 8 | 40 | 0.63 (0.22 to 1.79) | 0.38 |
| Study 3 | 2 | 25 | 4 | 25 | 0.50 (0.09 to 2.78) | 0.43 |
| Study 4 | 6 | 50 | 9 | 50 | 0.67 (0.25 to 1.78) | 0.42 |
| Study 5 | 8 | 60 | 12 | 60 | 0.67 (0.29 to 1.54) | 0.34 |
| Study 6 | 4 | 45 | 7 | 45 | 0.57 (0.17 to 1.91) | 0.36 |
| Study 7 | 3 | 35 | 6 | 35 | 0.50 (0.12 to 2.08) | 0.34 |
| Study 8 | 9 | 75 | 14 | 75 | 0.64 (0.30 to 1.37) | 0.25 |
| Study 9 | 7 | 55 | 10 | 55 | 0.70 (0.28 to 1.74) | 0.45 |
| **Pooled Data** | | | | | **0.63 (0.41 to 0.97)** | **0.04** |
| **Heterogeneity** | | | | | **$I^2$ = 0%** | |

Table 8 presents the results of the assessment of publication bias for the various outcomes included in the meta-analysis. Publication bias occurs when studies with statistically significant or favorable results are more likely to be published than those with non-significant or unfavorable results, potentially skewing the overall findings of a meta-analysis. For most outcomes (SLEDAI score, anti-dsDNA antibodies, complement C3 levels, quality of life - MCS, and adverse events), both Egger's and Begg's tests showed p-values greater than 0.05, indicating no significant evidence of publication bias. For the physical component summary (PCS) of quality of life, Egger's test showed a p-value of 0.22, and the funnel plot was assessed as having mild asymmetry. While this may suggest some potential publication bias, the p-value is not statistically significant, and Begg's test did not indicate bias. The trim and fill adjusted SMDs are generally similar to the original SMDs, further supporting the absence of substantial publication bias for most outcomes.

Table 8. Assessment of publication bias.

| Outcome | Egger's test (p-value) | Begg's test (p-value) | Trim and fill (Adjusted SMD) | Funnel plot asymmetry |
|---|---|---|---|---|
| SLEDAI Score | 0.45 | 0.62 | -1.32 | Symmetrical |
| Anti-dsDNA Antibodies | 0.81 | 0.75 | -0.74 | Symmetrical |
| Complement C3 Levels | 0.39 | 0.58 | 0.61 | Symmetrical |
| Quality of Life (PCS) | 0.22 | 0.35 | 0.68 | Mild asymmetry |
| Quality of Life (MCS) | 0.68 | 0.82 | 0.63 | Symmetrical |
| Adverse Events | 0.55 | 0.71 | 0.62 | Symmetrical |

**4. Discussion**

Our meta-analysis unequivocally demonstrates the efficacy of mesenchymal stem cell secretome (MSCS) therapy in mitigating systemic lupus erythematosus (SLE) disease activity. This conclusion is firmly supported by the observation of a significant reduction in SLEDAI scores across the included studies. The SLEDAI, a validated and widely used instrument for assessing SLE disease activity, encompasses a range of clinical and laboratory parameters, providing a comprehensive evaluation of disease manifestations. The consistent and substantial reduction in SLEDAI scores observed in our analysis underscores the robust therapeutic effect of MSCS in ameliorating SLE symptoms and controlling disease progression. Further strengthening the evidence for MSCS efficacy, our analysis reveals significant improvements in key immunological markers, including anti-dsDNA antibody levels and complement C3 levels. Anti-dsDNA antibodies are a hallmark of SLE, often associated with disease activity and organ damage. The observed reduction in anti-dsDNA levels following MSCS therapy suggests that MSCS can effectively modulate the humoral immune response in SLE, potentially by suppressing the activation and proliferation of autoreactive B cells, which are responsible for the production of these autoantibodies. This modulation of the humoral immune response may contribute to mitigating disease progression and preventing further organ damage. Complement C3 is a central component of the complement system, playing a critical role in immune regulation and clearance of immune complexes. SLE patients often exhibit depleted C3 levels due to excessive complement activation and consumption, contributing to the inflammatory process and tissue damage. The significant increase in C3 levels following MSCS therapy indicates a restoration of complement function, potentially through the suppression of complement activation and the enhancement of complement regulatory mechanisms. This restoration of complement function may contribute to the suppression of inflammation and the protection against tissue injury. In addition to the clinical and immunological benefits, our analysis demonstrates that MSCS therapy enhances the quality of life (QoL) in SLE patients. The SF-36 questionnaire, a widely used measure of health-related quality of life, revealed significant improvements in both physical and mental well-being following MSCS treatment. This finding underscores the holistic therapeutic impact of MSCS, extending beyond disease control to encompass the overall well-being of SLE patients. The improvement in QoL may be attributed to the reduction in disease activity, the alleviation of symptoms, and the restoration of physical and mental function. The efficacy of MSCS therapy in SLE may be attributed to its multifaceted immunomodulatory mechanisms. MSCS comprises a diverse array of bioactive factors, including cytokines, chemokines, growth factors, and extracellular vesicles, each capable of modulating various aspects of the immune response. These factors can act in concert to suppress the activation and proliferation of autoreactive T and B cells, reduce the

production of pro-inflammatory cytokines, and promote the generation of regulatory T cells (Tregs). Tregs are a subset of T cells that play a critical role in maintaining immune tolerance and suppressing autoimmune responses. Moreover, MSCS can modulate the function of antigen-presenting cells (APCs), which are crucial for initiating and orchestrating immune responses. By altering the function of APCs, MSCS can promote a shift towards a more tolerogenic immune environment, reducing the activation of autoreactive T cells and dampening the autoimmune response. Furthermore, MSCS can inhibit the complement cascade, a series of enzymatic reactions that play a central role in inflammation and tissue damage. By suppressing complement activation, MSCS can mitigate the inflammatory response and protect against tissue injury, contributing to the overall improvement in SLE disease activity and organ function. The observed efficacy of MSCS therapy in SLE, as evidenced by the significant improvements in SLEDAI scores, immunological markers, and quality of life, highlights its potential as a promising therapeutic option for this complex and challenging autoimmune disease. The multifaceted immunomodulatory mechanisms of MSCS, coupled with its favorable safety profile, warrant further investigation and clinical development to fully harness its therapeutic potential in SLE and other autoimmune diseases.[11-15]

The safety profile of MSCS therapy is of paramount importance when considering its clinical application in SLE patients. Our meta-analysis, encompassing nine randomized controlled trials (RCTs) with a total of 485 patients, provides encouraging evidence that MSCS therapy is generally safe and well-tolerated. Notably, none of the included studies reported any serious adverse events associated with MSCS therapy. This observation aligns with previous reports suggesting that MSCS therapy has a favorable safety profile, further bolstering confidence in its potential for clinical use. The absence of serious adverse events is particularly noteworthy given the inherent complexity of SLE and the potential for complications associated with conventional immunosuppressive therapies. SLE is a chronic autoimmune disease characterized by a dysregulated immune system that can attack multiple organs and tissues, leading to a wide range of clinical manifestations and potential complications. Current treatment strategies for SLE primarily rely on immunosuppressive medications, such as corticosteroids, antimalarial drugs, and cytotoxic agents, which can effectively control disease activity but often come with significant side effects, including an increased risk of infections, osteoporosis, and malignancies. In contrast, MSCS therapy appears to exert its therapeutic effects through targeted immunomodulatory mechanisms, aiming to restore immune balance rather than induce global immunosuppression. MSCS comprises a diverse array of bioactive factors, including cytokines, chemokines, growth factors, and extracellular vesicles, which can modulate various aspects of the immune response. These factors can act in concert to suppress the activation and proliferation of autoreactive T and B cells, reduce the production of pro-inflammatory cytokines, and promote the generation of regulatory T cells (Tregs). Tregs are a subset of T cells that play a critical role in maintaining immune tolerance and suppressing autoimmune responses. By selectively targeting the dysregulated immune responses in SLE, MSCS therapy may offer a safer alternative to conventional immunosuppressive therapies, minimizing the risk of serious adverse events. The absence of serious adverse events in our meta-analysis, coupled with the targeted immunomodulatory mechanisms of MSCS, provides further support for its potential as a safe and effective therapeutic option for SLE. However, it is essential to acknowledge that the included studies in our meta-analysis may not have been specifically designed to comprehensively evaluate all potential adverse events. Additionally, the follow-up duration in some studies may not have been sufficient to capture long-term adverse events. Therefore, continued monitoring and further research with larger sample sizes and longer follow-up periods are necessary to fully assess the

long-term safety profile of MSCS therapy in SLE. Despite these limitations, the current evidence suggests that MSCS therapy holds promise as a safe and effective treatment option for SLE, potentially offering a much-needed alternative to conventional immunosuppressive therapies with their associated risks. The targeted immunomodulatory effects of MSCS, coupled with the absence of serious adverse events in our meta-analysis and previous reports, provide a compelling rationale for further clinical development and investigation of MSCS therapy in SLE.[16-20]

## 5. Conclusion

Our findings unequivocally demonstrate that MSCS therapy leads to a substantial reduction in SLE disease activity, as evidenced by significant improvements in SLEDAI scores, key immunological markers such as anti-dsDNA antibody and complement C3 levels and quality of life measures. The safety profile of MSCS therapy has also been corroborated through this meta-analysis, with no serious adverse events reported across the included studies. The absence of serious adverse events associated with MSCS therapy, coupled with its profound immunomodulatory effects, underscores its potential as a safe and effective treatment option for SLE. While our findings are compelling, it is essential to acknowledge the limitations of this meta-analysis, including the heterogeneity in study designs and the relatively short follow-up duration in some studies. Further research, particularly large, well-designed RCTs with longer follow-up periods, is warranted to fully assess the long-term efficacy and safety of MSCS therapy in SLE. Despite these limitations, the evidence presented in this meta-analysis strongly supports the continued investigation and clinical development of MSCS therapy for SLE. MSCS therapy holds the potential to transform the treatment landscape for SLE, offering a much-needed alternative to conventional immunosuppressive therapies with their associated risks.

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