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SYSTEMATIC REVIEW

Efficacy of N-Acetylcysteine as an Adjuvant Therapy for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Aims/Background Rheumatoid arthritis (RA) is an inflammatory autoimmune disease and N-acetylcysteine (NAC) is considered a potential therapeutic agent for RA due to strong antioxidant and anti-inflammatory properties. Therefore, this systematic review and meta-analysis aimed to evaluate the efficacy of NAC as an adjuvant therapy for RA.

Methods A systematic search was conducted across five databases from inception to 1 August 2024, including CINAHL, Cochrane Library, EMBASE, PubMed, and Web of Science. The Cochrane risk-of-bias tool for randomized trials was used to assess the quality of the included studies. Sensitivity analysis was performed when significant heterogeneity was identified.

Results Four studies involving 204 patients were included in our meta-analysis. The results indicated that NAC alleviated disease activity in RA patients (Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR): mean difference (MD) = 0.54). Additionally, NAC reduced inflammatory markers (erythrocyte sedimentation rate (ESR): MD = 3.00). However, the beneficial effects of NAC on oxidative stress in RA patients were not observed.

Conclusion This meta-analysis demonstrated the efficacy of NAC in reducing inflammatory markers, improving joint tenderness, and swelling in patients with RA.

Key words: N-acetylcysteine; rheumatoid arthritis; oxidative stress; inflammation; meta-analysis

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Introduction

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease that not only affects the musculoskeletal system but also causes systemic changes, such as rheumatoid nodules, pulmonary fibrosis, vasculitis, pericarditis, and keratitis (Di Matteo et al, 2023). The pathogenesis of RA is highly complex, with genetic and environmental factors (such as dust exposure, viral infections, and alterations in the oral, gut, and lung microbiomes) known to play crucial roles in its development. However, the precise interplay between these genetic and environmental risk factors, and how their interaction leads to the progression of the disease, remains incompletely understood. The presence of self-reactive T cells and autoantibodies in the synovial membrane and blood is a hallmark of RA.

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The global prevalence of RA is estimated to be around 0.25%–1% (Finckh et al, 2022). Research indicates that RA is more common in developed countries and urban environments compared to developing countries and rural areas (GBD 2021 Rheumatoid Arthritis Collaborators, 2023). Additionally, RA is associated with high socioeconomic costs, as it can lead to progressive disability and premature mortality (Hsieh et al, 2020). Therefore, early diagnosis and timely, effective treatment are of critical importance.

Current treatment options for RA include non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease-modifying anti-rheumatic drugs (DMARDs). Over the past two decades, the introduction of biological DMARDs and targeted synthetic DMARDs has significantly improved RA management. However, a considerable number of RA patients still fail to achieve and sustain clinical remission, underscoring the urgent need for new treatment strategies.

Oxidative stress, defined as an imbalance between oxidants and antioxidants in favor of oxidants, leads to disruptions in redox signaling and control, as well as molecular damage (Forman and Zhang, 2021). Research suggests that oxidative stress plays a critical role in the progression of RA by damaging DNA, lipids, and proteins (Han et al, 2024). Antioxidant therapies have shown potential beneficial effects on both clinical and biochemical parameters in RA patients (da Fonseca et al, 2019; Djordjevic et al, 2023). N-acetylcysteine (NAC), a precursor of the antioxidant glutathione, possesses strong antioxidant and anti-inflammatory properties (Santus et al, 2024) and has beneficial effects in several immune-inflammatory diseases, including ulcerative colitis, systemic lupus erythematosus, and scleroderma (Abbasifard et al, 2023; Blagov et al, 2023; Xiao et al, 2024). Given the pivotal role of oxidative stress and inflammation in the development of RA (Mantle and Hargreaves, 2024), NAC is considered a potential therapeutic agent for RA. However, no comprehensive review currently summarizes the efficacy and safety of NAC therapy for rheumatoid arthritis. Therefore, this study is primarily exploratory, with the main objective of evaluating the impact of NAC on rheumatoid arthritis.

Methods

This study was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and adhered to the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al, 2021). The PRISMA checklist is available in **Supplementary Material 1**. The study protocol is registered on the PROSPERO database under registration number CRD42024576060.

Literature Search

To obtain usable research data, five databases were searched (CINAHL, Cochrane Library, EMBASE, PubMed, and Web of Science) from their inception to 1 August 2024. The search was restricted to English-language studies. The search algorithm was tailored to meet the specific requirements of each database, and the detailed search strategy is provided in **Supplementary Material 2**.

Eligibility Criteria and Literature Screening

The research question and eligibility criteria for this meta-analysis were formulated using the PICO (PICO stands for Population, Intervention, Comparison, Outcome) method as follows:

Population: Adult individuals with rheumatoid arthritis undergoing treatment with DMARDs.

Intervention: N-acetylcysteine.

Comparison: Placebo (Placebo tablets were identical to N-acetylcysteine in shape and color, containing inactive ingredients with no therapeutic activity).

Outcomes: Disease activity, inflammatory markers, and oxidative stress indicators.

Inclusion criteria for the study were: (1) randomized controlled trials (RCTs); (2) patients meeting the American College of Rheumatology diagnostic criteria for RA (Aletaha et al, 2010) and receiving DMARD treatment; (3) NAC as the intervention. Animal experiments and other clinical trial types were excluded.

Two researchers (TTH and KHR) independently evaluated all studies. In the first review round, the title and abstract were assessed to determine inclusion or exclusion. The researchers' votes were compared, and discrepancies were resolved through discussion. If no resolution was reached, the corresponding author (YXG) was consulted. In the second round, studies were assessed via full-text review, with discrepancies resolved in the same manner. Reasons for exclusion were documented.

Data Extraction

Two researchers (TTH and LX) independently extracted data from the articles. Numerical data were obtained from tables, text, or figures. If data were not directly reported, the WebPlotDigitizer tool (v4.8, Ankit Rohatgi) was used to extract information from graphs. Any discrepancies that arose during the process were discussed and resolved with the corresponding author (YXG). The included studies were summarized in a standardized table that included the first author's name, country, publication year, source of participants, protocol registration number, disease state, sample size, age, sex, intervention, duration, and outcomes.

Quality Evaluation

The Cochrane risk-of-bias tool for randomized trials (ROB1) was employed to assess the quality of the included studies. Two researchers (YH and YCH) independently utilized this tool during the evaluation process. The assessment criteria included attrition, detection, performance, reporting, selection bias, and other sources of bias. The evaluators' responses were categorized as low risk, unclear risk, or high risk of bias. Discrepancies between researchers were resolved by consulting the corresponding author (YXG).

Table 1. Main characteristics of included studies.

Study ID: Author (year)		Batooei et al (2018)	Hashemi et al (2019)	Jamali et al (2021)	Esalatmanesh et al (2022)
Country		Iran	Iran	Iran	Iran
Source of participants		The rheumatology out-patient clinics of Hamadan University of Medical Sciences	The specialty clinic affiliated to Hamadan University of Medical Sciences	The rheumatology outpatient's clinic of the Loghman Hakim University Hospital	The Autoimmune Diseases Research Center of Kashan University of Medical Sciences
Protocol ID		IRCT201507172296582	IRCT2015071722965N2	IRCT20190626044030N1	IRCT20101014004934N2
Disease state		Active (DAS28 >3.2)	Active (DAS28 >3.2)	Active (DAS28-ESR >3.2)	Active (DAS28 >3.1)
NAC group	Age (mean ± SD) Sex (male/female) Sample size Intervention	53.2 ± 12.5 5/22 27 NAC (600 mg twice a day) and conventional medications	53.91 ± 13.90 3/20 23 NAC (600 mg twice a day) and conventional medications	54.14 ± 9.11 3/19 22 NAC (600 mg twice a day) and conventional medications	48.21 ± 12.80 6/28 34 NAC (600 mg twice a day) and conventional medications
Placebo group	Age (mean ± SD) Sex (male/female) Sample size Intervention	51.6 ± 11.3 1/23 24 Placebo and conventional medications	50.68 ± 11.15 0/19 19 Placebo and conventional medications	54 ± 9.12 2/17 19 Placebo and conventional medications	53.25 ± 12.55 6/30 36 Placebo and conventional medications
Duration		12 weeks	12 weeks	8 weeks	3 months
Outcomes		DAS28-ESR, global health, number of tender joints, number of swollen joints, ESR	ESR, CRP, TAC, MDA, NO	DAS28-ESR, global health, number of tender joints, number of swollen joints, ESR	DAS28-ESR, ESR, CRP, TAC, MDA, NO

Abbreviations: DAS28-ESR, disease activity score 28-erythrocyte sedimentation rate; CRP, C-reactive protein; TAC, total antioxidant capacity; MDA, malondialdehyde; NO, nitric oxide; SD, standard deviation; NAC, N-acetylcysteine.

Data Analysis

RevMan 5.4 (5.4, Cochrane) was used to analyze the data and generate forest plots. Continuous data were assessed using mean difference (MD) or standard mean difference (SMD) with 95% confidence intervals (CI), while dichotomous data were assessed using risk difference (RD) with 95% CI. A difference was considered statistically significant when the *p*-value was less than 0.05. Statistical heterogeneity was assessed using the I^2 statistic or the Q-test. If I^2 exceeded 50% or the *p*-value was less than 0.1, indicating significant statistical heterogeneity, effect sizes were combined using a random effects model; conversely, a fixed effects model was applied. When significant heterogeneity was detected, the stability of the results was evaluated through sensitivity analysis.

Results

Literature Selection

After data retrieval, a total of 454 articles were identified. Following the removal of duplicates, 373 articles remained. After reviewing the titles and abstracts, we excluded 369 articles. A full-text review was conducted on the remaining four papers. Ultimately, four articles were included in our meta-analysis (Batooei et al, 2018; Esalatmanesh et al, 2022; Hashemi et al, 2019; Jamali et al, 2021). A flow diagram of the literature selection process is presented in Fig. 1.

Characteristics of the Included Studies

The four RCTs included in this meta-analysis were all conducted in Iran, with participants recruited from Hamadan University of Medical Sciences, Loghman Hakim University Hospital, and Kashan University of Medical Sciences. All included patients met the rheumatoid arthritis diagnostic criteria set by the American College of Rheumatology and were in an active state of the disease (Ramon Haddad et al, 2022). A total of 204 patients with rheumatoid arthritis were included in this meta-analysis, comprising 106 individuals (17 men and 89 women) in the NAC group and 98 individuals (9 men and 89 women) in the placebo group. All included studies administered NAC orally at a dose of 600 mg twice a day, with treatment durations ranging from 8 to 12 weeks. The main characteristics of the included RCTs are presented in Table 1.

Study Quality

The risk of bias for the included studies is presented in Fig. 2. Of the total studies, three described the randomization methods, while one study mentioned random grouping without specifying the randomization procedures. All participants and researchers were blinded throughout the trials in all four studies; however, only three studies reported the blinding of data collectors. All studies provided detailed descriptions of the number of patients who dropped out and the reasons for their dropout. In the included trials, a total of 67 patients (31 in the NAC group and 36 in the placebo group) dropped out for reasons including adverse effects, loss to follow-up, reluctance to continue treatment, and COVID-19 infection. Protocols

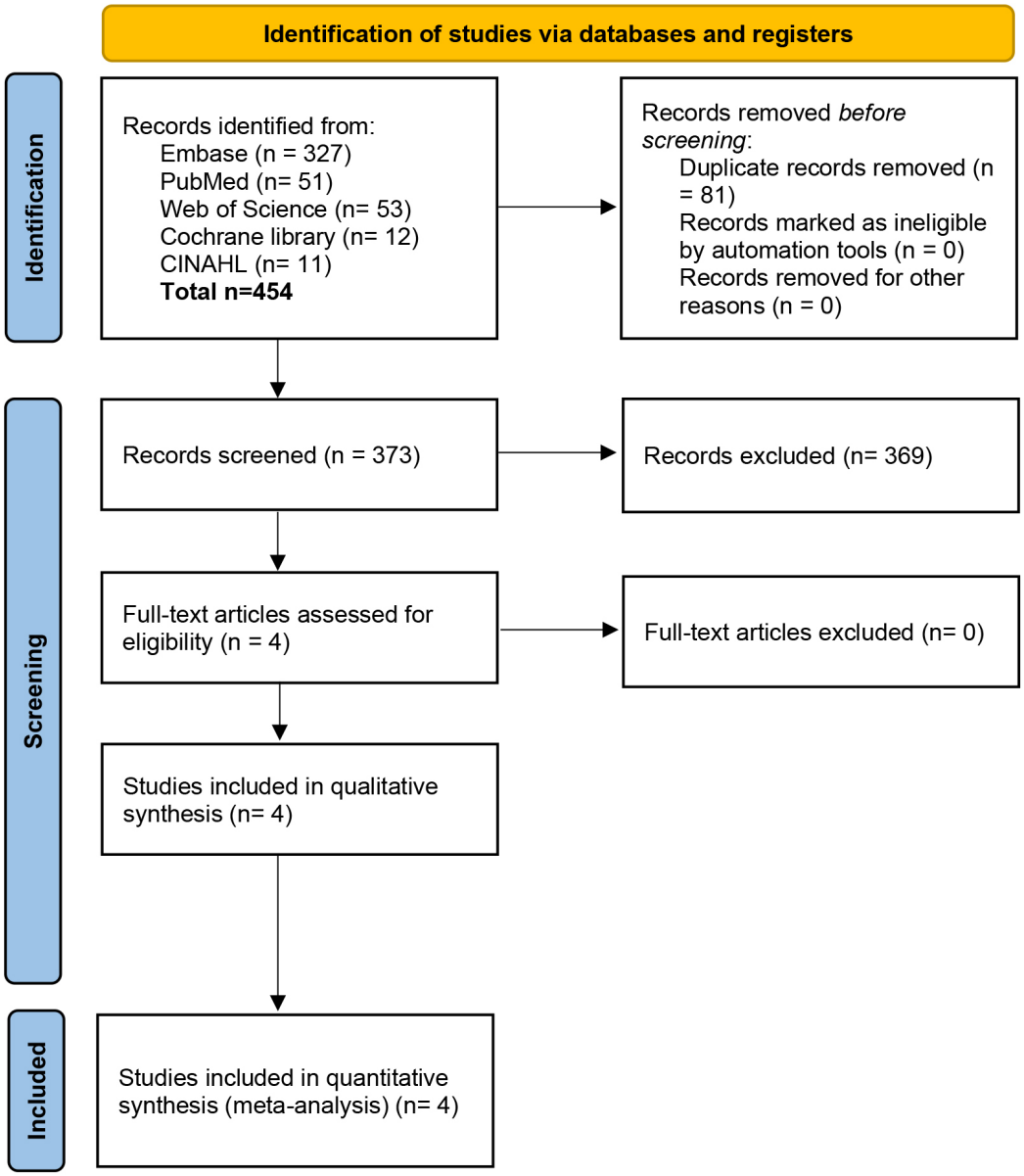

Fig. 1. The flowchart of the literature selection process.

were not available for two studies, while the outcomes of the other two studies were consistent with their protocols. No other sources of bias were identified. Details of the risk assessment are provided in **Supplementary Material 3**.

Outcomes

Disease Activity

DAS28-ESR

Three studies used the Disease Activity Score 28-erythrocyte sedimentation rate (DAS28-ESR) as the outcome indicator. The meta-analysis revealed a non-significant association between NAC and reduction in DAS28-ESR (n = 162, MD = 0.54, 95% CI [–0.21, 1.28], $p = 0.16$, $I^2 = 75\%$) (Fig. 3A). Due to significant heterogeneity, sensitivity analysis was performed by excluding studies individually, leading to reduced heterogeneity after excluding the Jamali et al (2021) study. The

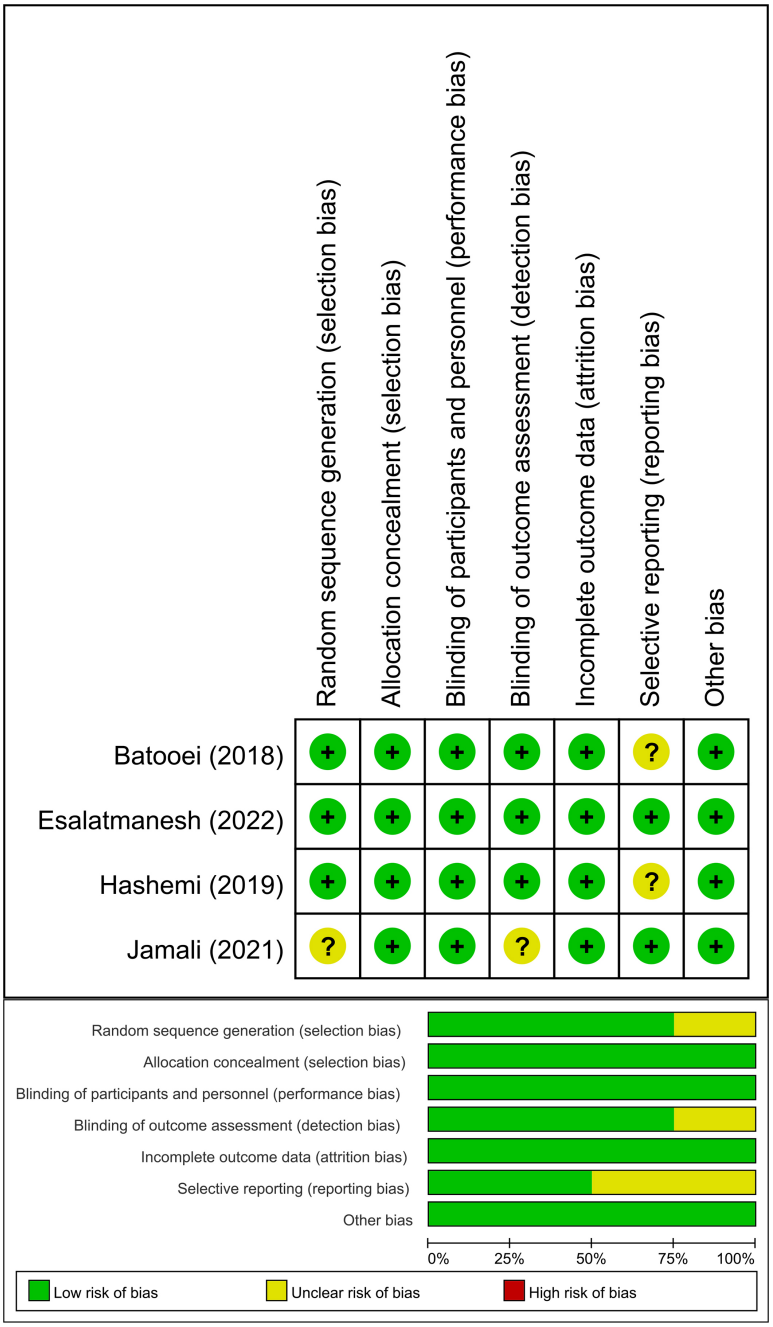

Fig. 2. Risk of bias of included studies.

re-evaluated results showed no significant association (n = 121, MD = 0.16, 95% CI [–0.32, 0.63], $p = 0.51$, $I^2 = 0\%$) (Fig. 3B).

Global Health

Two studies utilized the Global Health measure to assess patients' evaluations of their disease activity. The results indicated a significant association between NAC and improved Global Health scores (n = 92, MD = 7.52, 95% CI [0.89, 14.14], $p = 0.03$, $I^2 = 0\%$) (Fig. 3C).

Number of Tender Joints

Two studies reported the number of tender joints as the outcome indicator. The results demonstrated that the NAC group had a significantly lower number of tender joints compared to the placebo group (n = 92, MD = 1.72, 95% CI [0.12, 3.31], p = 0.03, I^2 = 0%) (Fig. 3D).

Number of Swollen Joints

Two studies used the number of swollen joints as the outcome indicator. The results indicated a significant association between NAC and a reduction in the number of swollen joints (n = 92, MD = 1.63, 95% CI [0.55, 2.71], p = 0.003, I^2 = 6%) (Fig. 3E).

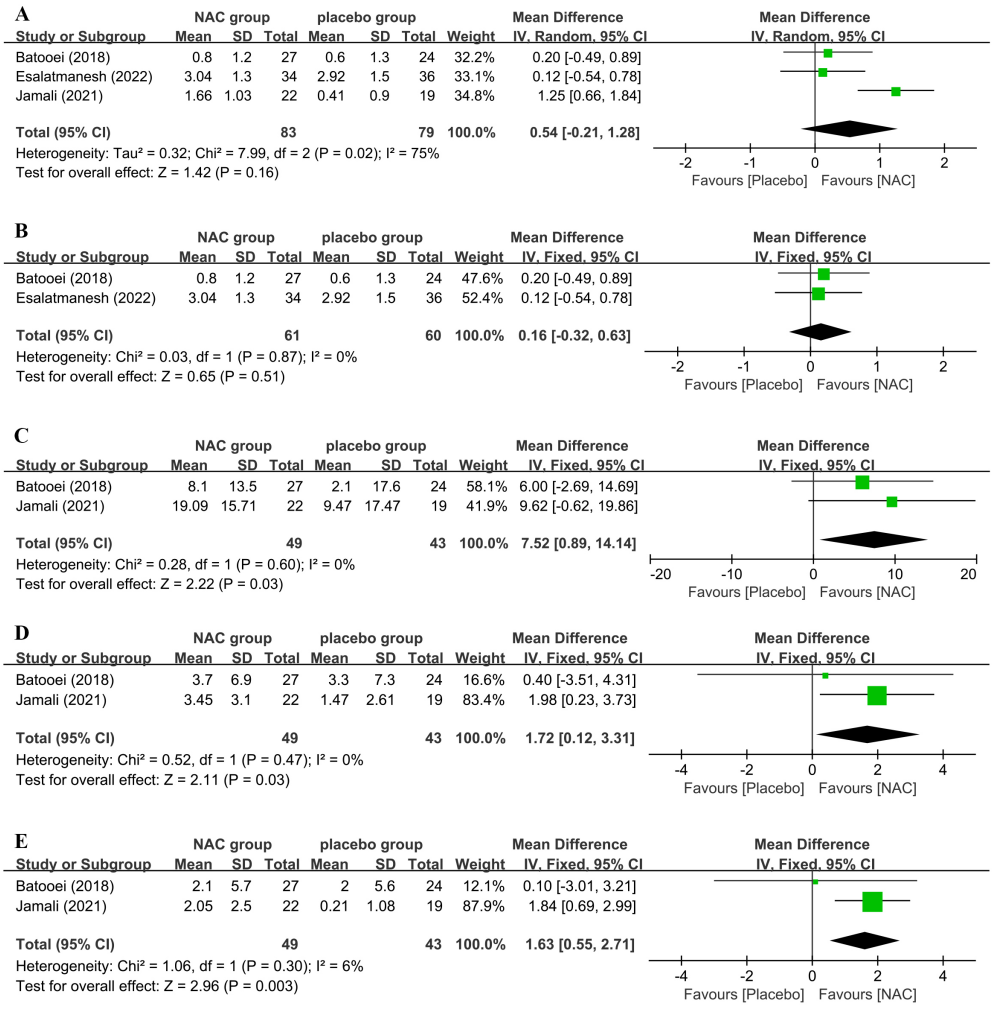

Fig. 3. Forest plot of disease activity. (A) Reduction in DAS28-ESR. (B) Sensitivity analysis of reduction in DAS28-ESR. (C) Global health. (D) Reduction in number of tender joints. (E) Reduction in number of swollen joints.

Inflammatory Indicator

ESR

Four studies used the erythrocyte sedimentation rate (ESR) as the outcome indicator. The meta-analysis results found a significant association between NAC and a reduction in the serum ESR level (n = 204, MD = 3.00, 95% CI [0.38, 5.63], $p = 0.02$, $I^2 = 37\%$) (Fig. 4A).

CRP

Two studies reported the C-reactive protein (CRP) as the outcome indicator. The meta-analysis revealed a notable link between NAC and a decline in the serum CRP level (n = 112, SMD = 0.42, 95% CI [0.04, 0.79], $p = 0.03$, $I^2 = 48\%$) (Fig. 4B).

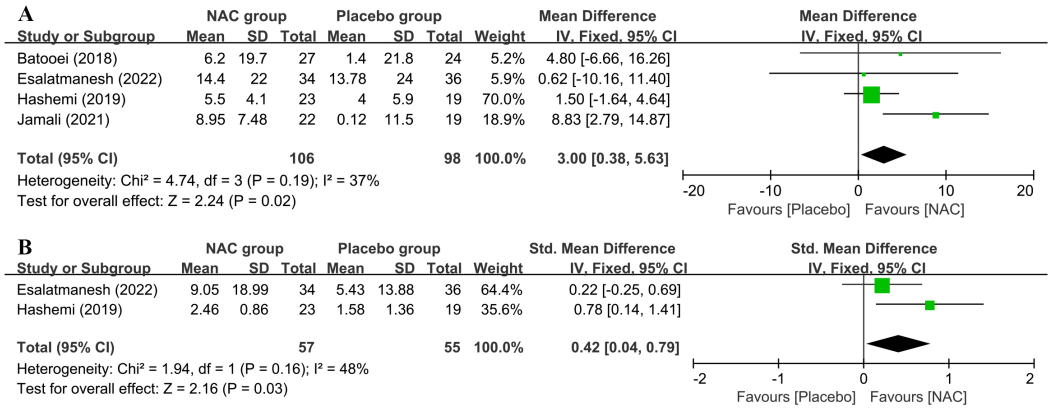

Fig. 4. Forest plot of inflammatory indicator. (A) Reduction in ESR. (B) Reduction in CRP.

Oxidative Stress Indicator

TAC

Two studies measured total antioxidant capacity (TAC) as the outcome indicator. According to the meta-analysis, NAC was not significantly associated with the serum TAC level (n = 112, SMD = 0.01, 95% CI = [–0.36, 0.38], $p = 0.96$, $I^2 = 37\%$) (Fig. 5A).

MDA

Two studies used malondialdehyde (MDA) as the outcome indicator. The meta-analysis data did not show a significant link between NAC and a decrease in the serum MDA level (n = 112, SMD = 1.22, 95% CI = [–0.14, 2.58], $p = 0.08$, $I^2 = 90\%$) (Fig. 5B).

NO

Two studies used nitric oxide (NO) as the outcome indicator. The outcomes of the meta-analysis did not reveal a notable association between NAC and a decline in the serum NO level (n = 112, SMD = 1.33, 95% CI = [–0.34, 3.00], $p = 0.12$, $I^2 = 93\%$) (Fig. 5C).

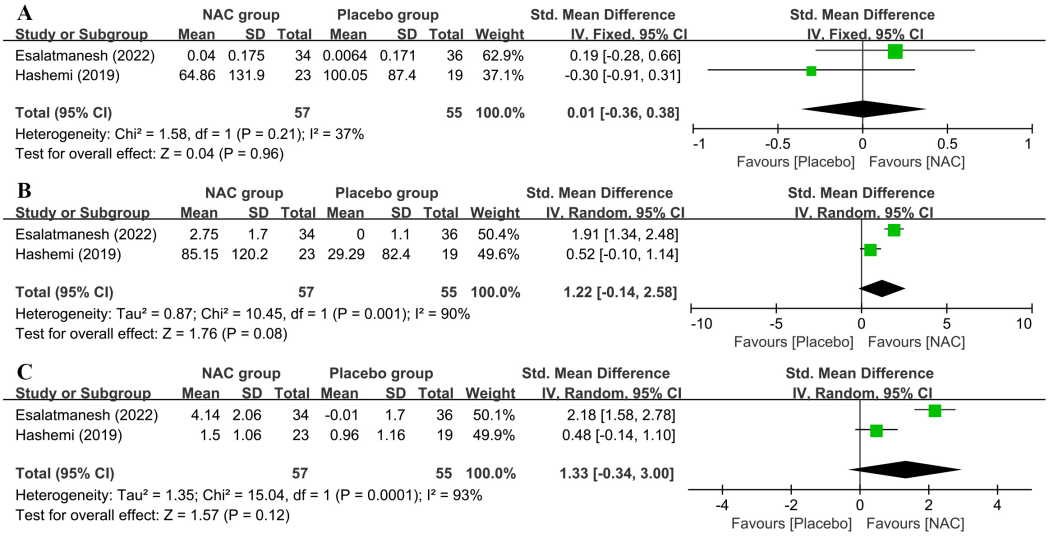

Fig. 5. Forest plot of oxidative stress indicator. (A) TAC. (B) Reduction in MDA. (C) Reduction in NO.

Adverse Effects

The safety of the intervention measures reported across the studies varied (Table 2). Two studies documented the number of patients withdrawing due to adverse reactions, totaling 5 in the NAC group and 3 in the placebo group. One study specifically outlined the reasons for withdrawal due to adverse reactions: 5 cases in the NAC group, including nausea (n = 3), gastric burning sensation (n = 1), and hypertension (n = 1), while only 1 case in the placebo group was noted, which included itching on the hands and face (n = 1). Importantly, no serious adverse reactions were reported, and the overall incidence rate of adverse drug reactions did not show statistical significance between the groups. Another study reported adverse reactions occurring during the trial period: 15 cases in the NAC group, including nausea (n = 9) and headache (n = 6), compared to 15 cases in the placebo group, which included nausea (n = 5), headache (n = 4), rhinorrhea (n = 3), mucus production (n = 2), and abdominal pain (n = 1). Due to inconsistencies in the adverse events reported in each study, no meaningful statistical analysis could be conducted to determine causality.

Discussion

NAC is metabolized in the liver to produce cysteine, a direct precursor for the intracellular synthesis of glutathione (GSH). By replenishing the depleted intracellular GSH pool, NAC can reduce the synthesis of reactive oxygen species (ROS) (Tenório et al, 2021). Additionally, NAC interacts directly with and neutralizes oxidants such as hydroxyl radicals, hypochlorous acid, and hydrogen peroxide, thereby exerting notable antioxidant effects (Eghtedari et al, 2022).

More importantly, NAC can exert anti-inflammatory effects by suppressing the activity of nuclear factor kappa B (NF-κB) and reducing levels of inflammatory cytokines (Panahi et al, 2023; Suresh et al, 2023; Wrotek et al, 2024). Given its

Table 2. Adverse effects (AE) reports of included studies.

Study ID: Author (year)	Batooei et al (2018)	Hashemi et al (2019)	Jamali et al (2021)	Esalatmanesh et al (2022)
Report content	AE that led to drop-out the trial	AE that led to drop-out the trial	AE that led to drug discontinuation	AE during the study
AE in NAC group	3*	2*	nausea (n = 3), heartburn (n = 1), hypertension (n = 1)	nausea (n = 9), headache (n = 6)
AE in placebo group	2*	1*	itching and dermal irritation on hands and face (n = 1)	nausea (n = 5), headache (n = 4), rhinorrhea (n = 3), mucus production (n = 2), abdominal pain (n = 1)

* Indicates that no specific symptoms were reported.

excellent antioxidant and anti-inflammatory properties, NAC is used in treating various diseases, including pulmonary, cardiovascular, hepatic, neurodegenerative, and psychiatric disorders (Clark et al, 2023; Cui et al, 2023; Mokra et al, 2023; Popescu et al, 2024; Zhang et al, 2024).

The application of NAC in autoimmune diseases has garnered increasing attention in recent years (Tieu et al, 2023). Research indicates that NAC can suppress synovial inflammation, regulate the differentiation of immune cells, and inhibit the degradation of chondrocytes as well as bone destruction (Kalyanaraman, 2022; Uehara et al, 2023; Wang et al, 2018; Yang et al, 2021; Zheng et al, 2024). Consequently, NAC is considered a potential adjunct therapy for RA. However, there remains some controversy regarding its clinical use in RA patients, highlighting the need for further investigation into its efficacy and safety in this population.

This systematic review evaluated the efficacy and safety of NAC as an adjunct therapy for RA. The review included four RCTs, and the results indicated that NAC can alleviate joint tenderness and swelling in RA patients while also reducing serum ESR and CRP levels. Although no significant difference was found in the DAS28-ESR, there was an improvement in the patients' overall global health. However, the beneficial effects of NAC on oxidative stress in RA patients were not observed. This lack of observed benefit may be attributed to the high heterogeneity among studies, and the limited number of included studies restricted further analysis. While our studies did not provide statistically significant results regarding the safety of NAC therapy in RA patients, the available evidence suggests that NAC appears to be a safe intervention (Jerome et al, 2024; Komakula et al, 2024). A comprehensive safety evaluation is warranted in the future.

Several strengths of this review are worth highlighting. This study conducted according to a protocol pre-registered on the PROSPERO website, represents the first systematic review and meta-analysis assessing NAC therapy for rheumatoid arthritis. The included studies generally had sufficient treatment durations (no less than 8 weeks), which aligns with the long disease duration typically observed in

RA patients. Additionally, the risk of bias across the studies was generally low, providing reasonable validity for interpreting the results.

However, the number of RCTs included in this meta-analysis was relatively small and limited to studies from the same country. This restriction in data availability hindered the possibility of conducting subgroup analyses for various outcome measures. Additionally, all interventions were administered as a single dose of 600 mg twice a day. In contrast, a randomized, placebo-controlled clinical trial in patients with systemic lupus erythematosus found that NAC significantly improved clinical outcomes, including arthritis, at higher doses of 2.4 g or 4.8 g daily (Lai et al, 2012). Furthermore, the included patients were all in a moderate-to-severe active state of the disease, preventing observations of NAC's effects in RA patients with varying levels of disease activity.

Given these limitations, it is essential to interpret the results of this meta-analysis with caution. Future clinical trials should be designed with larger sample sizes and establish gradients of disease activity and NAC dosage to investigate the quantitative-effectiveness relationship of NAC, as well as its safety and efficacy across different populations. A broader range of outcome indicators should also be included to provide a more comprehensive understanding of NAC's specific mechanisms of action. Additionally, building upon the framework of this study, future research may consider incorporating various study designs, such as open-label trials or real-world data studies, to enhance the comprehensiveness and practicality of the findings.

Conclusion

In summary, the current evidence indicates that NAC can reduce inflammatory markers and improve joint tenderness and swelling in patients with RA. However, due to the limitations of this study, further research is warranted. Future studies should focus on larger sample sizes, explore higher doses of NAC, and assess additional oxidative, inflammatory, and anti-inflammatory parameters. This approach will help draw more reliable, evidence-based conclusions regarding the efficacy and safety of NAC as an adjunct therapy for RA.

Key Points

- Oxidative stress is involved in the development of RA, and antioxidants have been shown to have therapeutic effects in patients with RA.
- N-acetylcysteine, an antioxidant, is considered a potential therapeutic agent for RA.
- Our study suggests that N-acetylcysteine improves joint tender and swelling, and reduces serum ESR and CRP levels in patients with RA.
- The results indicate that N-acetylcysteine does not significantly improve oxidative stress-related parameters in RA patients.
- Due to the limitations of this study, the present results should be interpreted with caution, and more clinical studies with large samples are warranted.

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available within the article and supplementary materials.

Author Contributions

TTH, KHR, and YXG designed the study, TTH, KHR, LX, YCH, HY and YXG collected and analyzed the data. All authors participated in drafting the manuscript and contributed to the important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgement

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://www.magonlinelibrary.com/doi/suppl/10.12968/hmed.2024.0560.

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