Italian Journal of Food Science, 2025; 37 (1): 43–59

N-acetylcysteine as a promising treatment for COVID-19: A comprehensive meta-analysis of systemic manifestations and clinical outcomes

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Academic Editor: Prof. Tommaso Beccari - Università degli Studi di Perugia, Italy

Received: 10 August 2024; Accepted: 7 October 2024; Published: 1 January 2025

ORIGINAL ARTICLE

Abstract

The COVID-19 pandemic presents systemic disorders, primarily affecting respiratory and cardiovascular systems. N-acetylcysteine (NAC) possesses antioxidative, anti-inflammatory, and immune-modulating properties, suggesting a potential therapy against COVID-19. In the current study, a meta-analysis was conducted to investigate the effectiveness of NAC supplementation against COVID-19. A literature search was conducted from April 2019 to December 2023 using Rev-Man 5.3 incorporating 14 studies with 20,980 participants. Results revealed significant differences in total and native thiol, and hydrogen sulfides in COVID-19 patients. NAC-treated patients exhibited significant reduction in C-reactive protein and D-dimer levels, along with higher pO_2/FiO_2 ratios, minimal stay in hospital, and lower mortalities supporting the efficacy of NAC toward COVID-19.

Keywords: acetylcysteine; COVID-19; glutathione; NAC; pandemics; thiol

Introduction

COVID-19 is a global pandemic caused by the novel coronavirus SARS-CoV-2 (Tang and Licina, 2022). The disease has a broad clinical spectrum, ranging from asymptomatic to severe cases. It poses significant challenges, particularly in severe cases involving cytokine storms, oxidative stress, and coagulation abnormalities (Khezri *et al.*, 2022). The global engineering community has shown significant interest in the pandemic, examining and bolstering the significance of aerosol transmission of SARSCoV2 as the primary catalyst for the spread of the COVID-19 pandemic (Tang and Licina, 2022).

N-acetylcysteine (NAC) is a long-standing compound that has been utilized for many years as a mucolytic agent, aimed at enhancing the clearance of airways in cases of chronic respiratory disorders (Faverio *et al.*, 2022; Izquierdo-Alonso *et al.*, 2022). NAC is a potent

antioxidant and precursor of glutathione, which is well-established in mitigating oxidative stress and inflammation (Kim *et al.*, 2003). The theoretical basis for considering NAC as a potential therapeutic agent for COVID-19 is due to its antioxidant, anti-inflammatory, and mucolytic properties (Tang and Licina, 2022). Loureirin A, a flavonoid derived from the medicinal plant, Dragon's Blood, is recognized for its attributes in combating inflammation and preventing blood clots. Its mode of action appears to disrupt certain factors associated with the COVID-19 disease process (Khezri *et al.*, 2022). Previous research has explored the potential application of NAC in treating various respiratory diseases, including COVID-19 (Blasi *et al.*, 2016; Tang and Licina, 2022; Zhang *et al.*, 2017).

Nonetheless, a thorough compilation of existing evidence is required to comprehensively analyze the impact of NAC on the outcomes of COVID-19 treatment (Tang and Licina, 2022). Similarly, colchicine, a medication frequently employed in the treatment of rheumatic and musculoskeletal diseases (RMDs), is presently under investigation for its effectiveness against COVID-19 due to its anti-inflammatory properties (Madrid-García *et al.*, 2021). The current body of research indicates that thiol antioxidants, including NAC, probably function as metal binders that moderate zinc's involvement in the interdependent effects of pyrrolidine dithiocarbamate (PDTC) on AP-1 and NF-κB (Kim *et al.*, 2003). However, NAC's mechanism of action in COVID-19 treatment remains unclear, and further research is needed to establish its efficacy and safety in managing COVID-19 (Tang and Licina, 2022).

We conducted this comprehensive meta-analysis of systemic manifestations and clinical outcomes of NAC as a food supplement of potential therapeutic action against COVID-19.

Methods

The research was carried out as per the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for systematic reviews (Moher *et al.*, 2009). The review was subjected to a thorough assessment following "A Measurement Tool to Assess Systematic Reviews 2" (AMSTAR 2) checklist (Kanukula *et al.*, 2024) and was also registered under PROSPERO.

Search strategy

We searched the following databases: Medline (through PubMed), Scopus, Web of Science (WOS), Cochrane, Virtual Health Library (VHL), and Global Index Medicus (GHL). A manual search was performed to minimize results bias by searching for references of included studies (extracted from PubMed, Scopus, WOS, Cochrane VHL, and GHL) and related articles from April 2019 to December 2023. Broad search filters were applied to find all the studies by using the following MeSH terms: ("N-Acetyl-L-cysteine" OR "N Acetyl L cysteine" OR "N-Acetylcysteine" OR "N Acetylcysteine" OR "NAC" OR "Thiol" OR "H_2S" OR "Hydrogen Sulfide" OR "RSS" OR "reactive sulfur species" AND ("Coronavirus 2, SARS" OR "Coronavirus Disease 2019 Virus" OR "2019 Novel Coronavirus" OR "Wuhan Seafood Market Pneumonia Virus" OR "SARS-CoV-2Virus" OR "2019-nCoV" OR "COVID-19Virus" OR "Wuhan Coronavirus" OR "Coronavirus, Wuhan" OR "COVID19Viruses" OR "Viruses, COVID19" OR "Severe Acute Respiratory Syndrome Coronavirus 2").

Study selection

Inclusion criteria

Studies meeting the following criteria were included:

- Population: Studies on COVID-19 patients were categorized into two groups, with and without NAC protocols.
- Outcome: Studies reporting demographic, clinical, laboratory, and mortality rate findings.
- Study design: All clinical trials or observational studies that reported one or more outcomes of NAC, H_2S, thiol, or RSS for patients infected with COVID-19 compared with other therapeutic protocols or placebo.
- Language: Only studies written in the English language, published in international publications and with enough information for qualitative and quantitative analyses, were included.

Exclusion criteria

- The studies that did not suggest sufficient data were omitted.
- Animal research, posters, duplicate papers, or conference papers were not included.
- Only a few review articles were included in the current systematic review but not in the meta-analysis.

Screening

The studies identified in the search were imported into EndNote X9.1 (Clarivate Analytics, https://clarivate.com/) to eliminate duplicates. Two independent reviewers then assessed all documents for appropriateness. The eligibility was evaluated in two phases: first, the titles and abstracts were examined; following this, the full articles corresponding to the selected abstracts were retrieved and appraised for eligibility. In cases of divergence in

viewpoints, resolution was achieved through discussion involving a third reviewer. The search process and details of study selection are visually depicted in the PRISMA diagram (Figure 1).

Data extraction

We gathered demographic details, medical history, clinical manifestations, lab results, treatments, and clinical results. Two separate evaluators collected this information onto a consistent Microsoft Excel spreadsheet. Subsequently, a third, independent reviewer cross-verified the compiled data to ensure precision. Any discrepancies were settled through deliberation.

Quality assessment

Assessing the risk of bias for observational studies

Two reviewers assessed the caliber of the studies encompassed by utilizing the National Institute of Health (NIH) quality assessment tool tailored for observational cohort, case-control, controlled interventional studies, and cross-sectional studies (Health, 2013). This assessment tool entails 14 inquiries covering aspects such as sample size, participant selection, exposure evaluation, and outcome assessment. Studies garnering a score of ≥ 9 points were classified as high quality, those scoring 5–8 points were categorized as moderate quality, and studies achieving 1–4 points were categorized as low quality (Health, 2013).

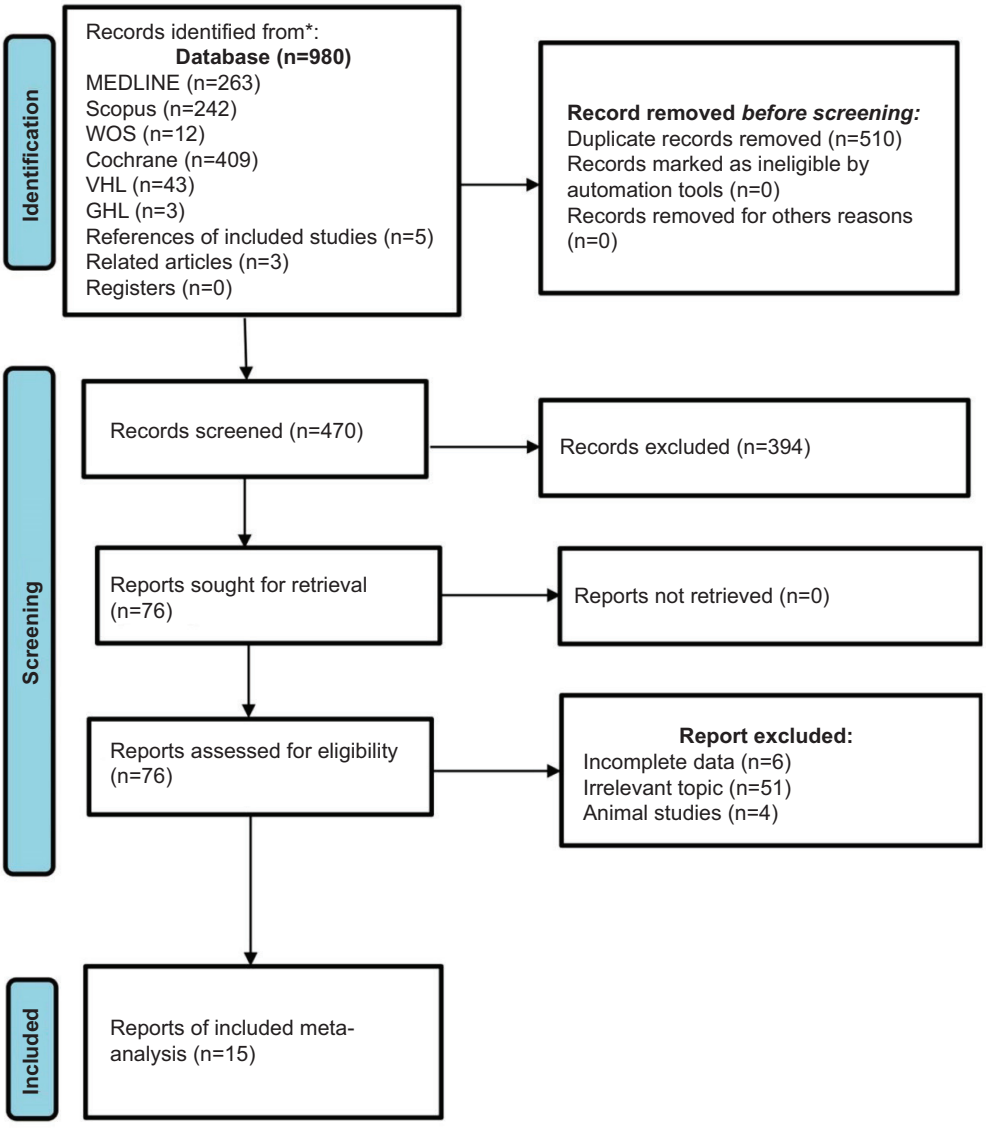

Figure 1. PRISMA flow diagram of included studies and screening process.

Assessing the risk of bias for randomized control studies

To evaluate the potential bias in each of the studies incorporated, we employed the Cochrane Risk of Bias instrument outlined in the Cochrane Handbook of Systematic Reviews of Interventions (Version 5.1.0) (Kanukula *et al.*, 2024).

Assessing the risk of bias across studies

To evaluate bias within the encompassed studies, we analyzed the outcomes reported in each study to eliminate the possibility of selectively presenting certain results. As indicated by Egger *et al.*, the appraisal of publication bias through the employment of funnel plot methodology is dependable when the cumulative number of studies exceeds 10 (Egger *et al.*, 1997). Therefore, although our meta-analysis included 14 studies, the assessment of publication bias was not reliable because each outcome comprised fewer than 10 pooled studies, so we did not assess the existence of publication bias by Egger's test for funnel plot asymmetry.

Data synthesis

Rev-Man 5.3 software (Review Manager Version 5.3, Cochrane Collaboration, John Wiley & Sons, Inc., NY, USA) was employed in the data meta-analysis. Seven studies are represented by mean and standard deviation (Çakırca *et al.*, 2021; Gaynitdinova *et al.*, 2021; Ibrahim *et al.*, 2020; Kalem *et al.*, 2021; Mete *et al.*, 2021; Şekeroğlu *et al.*, 2021; Taher *et al.*, 2021), two studies are represented by the median and interquartile range (Assimakopoulos and Marangos, 2020; Aykac *et al.*, 2021), and five studies are represented by median range (de Alencar *et al.*, 2021; Avdeev *et al.*, 2022; Chen *et al.*, 2023; Faverio *et al.*, 2022; Ramadhan *et al.*, 2021). The data was transformed into mean and standard deviation values according to the method described by McGrath (McGrath *et al.*, 2020). For statistical analysis, the studies were inserted directly by mean and standard deviation for the outcomes that did not report baseline values. On the other hand, mean difference and standard error for studies reported baseline values. Six studies are represented as dichotomous data and were inserted as events for statistical analysis (Alencar *et al.*, 2021; Assimakopoulos and Marangos, 2020; Avdeev *et al.*, 2022; Faverio *et al.*, 2022; Ibrahim *et al.*, 2020; Izquierdo *et al.*, 2022; Taher *et al.*, 2021). We evaluated heterogeneity by visually examining the forest plots to observe the degree of overlap in the 95% confidence intervals of the pooled estimates. We also assessed heterogeneity using the chi-square test and quantified it using the I2 test. Heterogeneity was regarded as present when the P-value exceeded 0.1 and the I2 value exceeded 50%. There was evidence of heterogeneity in the data. A random-effects model was selected to solve this heterogeneity, and sensitivity analysis was conducted. The P-value for the overall mean difference (MD), less than the statistically significant value, was set at 0.05. UN inconsistency (I2), Chi-square (X2), and Tau-square tests were run to check for heterogeneity. A leave-one-out analysis in each scenario was conducted to examine the effect of a single study on the overall effect. We also excluded an outlying study to examine the pooled effect and to account for heterogeneity. These analyses solve the problem of heterogeneity.

Results

Data analysis

From our initial literature search, we identified 980 distinct records. After conducting a preliminary assessment of titles and abstracts, 76 studies met the criteria for further full-text scrutiny. Eventually, a total of fourteen studies (encompassing 20,980 patients) were deemed suitable for incorporation in this meta-analysis (Faverio *et al.*, 2022; Izquierdo *et al.*, 2022; Kalem *et al.*, 2021; Ramadhan *et al.*, 2021). The progression of study selection is visually outlined in the PRISMA flowchart, as depicted in Figure 1.

Baseline characteristics

Fifteen studies were incorporated, with a total population of 20,980 COVID-19 patients, including 3475 administered NAC versus 17,705 without NAC. Two case series studies were conducted in the USA by Ibrahim *et al.* (2020) and Chen *et al.* (2021). Another two were conducted in Russia, one was an RCT by Gaynitdinova *et al.* (2021) and another one a case-control (Avdeev *et al.*, 2022); one case-control in Greece (Assimakopoulos and Marangos, 2020); one RCT in Brazil (Alencar *et al.*, 2021); one case-control in Italy (Faverio *et al.*, 2022); one cohort in Indonesia (Ramadhan *et al.*, 2021); one cross-sectional in Spain (Izquierdo *et al.*, 2022); one RCT in Iran (Taher *et al.*, 2021); and five cohorts in Turkey; (Aykac *et al.*, 2021; Çakırca *et al.*, 2021; Kalem *et al.*, 2021; Mete *et al.*, 2021; Şekeroğlu *et al.*, 2021). The summary of the included studies and their population characteristics are shown in Tables 1 and 2.

Quality assessment

Quality assessment in individual studies

The quality of the included studies was assessed using the National Institute of Health (NIH) scale for observational studies, and the assessment results showed 11 studies to be of high quality. Four studies scored 11 conducted by Avdeev *et al.* (2022), Aykac *et al.* (2021), Kalem *et al.* (2021), and Sekeroğlu *et al.* (2021). Four studies

Table 1. Summary of the included studies and their population characteristics.

Study ID	Sample size N/C (F.)	Age (mean)	Sex, male N/C (F.)	Primary symptoms	Hypertension N/C (F.)	Diabetes N/C (F.)	Cancer N/C (F.)	CLDs N/C (F.)	Cardiac D. N/C (F.)	CKD N/C (F.)	Ads N/C (F.)
Taher *et al*. (2021)	47/45	59/55	15/24	N/A	N/A	10/12	N/A	8/6	16/10	N/A	N/A
de Alencar *et al*. (2021)	67/68	59/58	43/37	N/A	32/31	29/22	8/9	45/44	N/A	N/A	3/2
Gaynitdinova *et al*. (2021)	24/22	66/57	N/A	N/A	N/A	N/A	N/A	45/39	N/A	N/A	N/A
Faverio *et al*. (2022)	585/321	63/68	409/192	N/A	275/151	84/69	47/37	N/A	319/187	41/31	N/A
Assimakopoulos and Marangos, (2020)	42/40	61/64	28/27	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Izquierdo *et al*. (2022)	2071/17137	70/66	1089/10282	N/A	1227/9379	590/4519	8/10	236/1247	319/2783	N/A	N/A
Avdeev *et al*. (2021)	24/22	66/57	16/13	N/A	N/A	7/4	8/11	5/3	18/16	3/1	N/A
Ramadhan *et al*. (2021)	16/75	53/52	12/44	SOB, Cough, Fever, Anosmia, Ageusia	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mete *et al*. (2021)	43/43	59/57	22/22	Cough, fever, dyspnea, fatigue, and myalgia	11/9	4/7	N/A	M/A	2/6	N/A	N/A
Kalem *et al*. (2021)	144/70	49/51	94/41	Fever, cough, and shortness of breath	25/15	19/5	N/A	N/A	8/2	N/A	N/A
Aykac *et al*. (2021)	40/34	52/47	21/19	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Şekeroğlu *et al*. (2021)	33/3	56/53	18/16	Fever, cough, and shortness of breath	12/10	4/4	N/A	N/A	5/1	2/3	N/A
Çakırca *et al*. (2021)	46/40	60/63	25/28	N/A	15/17	12/6	N/A	6/9	9/6	N/A	N/A
Chen *et al*. (2023)	10	62	4	N/A	8	3	N/A	N/A	N/A	N/A	N/A
Ibrahim *et al*. (2020)	10	35	10	Fever, cough, and shortness of breath	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Ads, auto immune diseases; CLDs, chronic lung diseases; CKD, chronic kidney diseases; F, frequency; N/C, (N-acetylcysteine/control).

Table 2. Summary for included studies designs and main findings.

Study ID	Country	Study design	Protocol (dose/duration/administration)		Main findings
			N-acetylcysteine	Control therapy	
Taher *et al*. (2021)	Iran	RCT	40 mg/kg/day for 3 days	Vitamin C (1000 mg bid), vitamin D3 (1000 IU bid), zinc (50 mg daily), cortisone	The prospective advantages of intravenous NAC in treating patients with mild-to-moderate these findings did not support COVID-19.
de Alencar *e al*. (2021)	Brazil	RCT	21 g (approximately 300 mg/kg) for 20 h	Ceftriaxone 2g/day and Azithromycin 500 mg/day	High doses of NAC administration had no impact on how severely Covid-19 evolved.
Gaynitdinova *et al.* (2021)	Russia	RCT	1200–1500 mg/day intravenously with 8–10 drops	Hydroxychloroquine 200 mg (800 mg/day for 1 day); 400 mg/day from the 2nd to the 7th day; Azithromycin 500 mg/day for 5 days; Enoxaparin 0.4 mg/day subcutaneously; Dexamethasone 8 – 12 mg/day	The study confirmed the effectiveness of NAC as a part of the complex treatment of moderated COVID-associated pneumonia
Faverio *et al*. (2022)	Italy	Retrospective monocentric	300 mg intravenously three times daily	Hydroxychloroquine, prophylactic heparin, and in cases of oxygen supplementation requirements, remdesivir was administered.	This study provides no evidence that NAC affects short- and long-term outcomes, such as in-hospital mortality, ICU hospitalization, DLCO impairment, and 6-month chest radiography changes.
Assimakopoulos and Marangos (2021)	Greece	Retrospective cohort	600 mg bid orally for 14 days	N/A	This study showed that oral NAC therapy (1200 mg/d) decreased ventilator need and death in COVID-19 pneumonia patients.
Izquierdo *et al*. (2022)	Spain	Retrospective cohort	600 mg every 8 h orally	Corticosteroids, Hydroxychloroquine, Azithromycin, Enoxaparin, and Acenocoumarin	Although these patients were older, more frequently male, and had comorbidities, oral treatment with NAC at a high dose was associated with significantly lower mortality in COVID-19 admitted patients.
Avdeev *et al*. (2021)	Russia	Case-Control	A daily dose from 1200 to 1800 mg IV	Local protocol, all patients received hydroxychloroquine, azithromycin, corticosteroids, prophylactic low molecular weight heparin, and tocilizumab if indicated	Overall, this study found that NAC therapy significantly improved oxygenation parameters and reduced CRP, the NEWS2 score, and the length of hospitalization in COVID-19 hospitalized patients. Further randomized prospective trials with a larger cohort are needed to confirm these findings.
Ramadhan *et al*. (2021)	Indonesia	Cohort	A bottle of 5 g NAC IV (1200–1800 mg/day)	Antivirals, azithromycin, vitamin C, vitamin D, and vitamin E	After adjuvant NAC therapy, there is a positive correlation and a significant decrease in serum TNF and SpO2/FiO2 ratio, which improves hypoxemia in COVID-19 patients.
Mete *et al*. (2021)	Turkey	Prospective	N/A	Favipiravir, Sulfate, Levofloxacin, and enoxaparin sodium	This finding strongly suggests that thiol/disulfide homeostasis and nitrosative stress can both contribute to COVID-19 pathogenesis. This was the first study to show that antiviral therapy can prevent serum thiol depletion and decrease serum NO levels in COVID-19 patients.
Kalem *et al*. (2021)	Turkey	Prospective	N/A	Antioxidants, fish oil, supplemental vitamins, iron supplements.	NT and TT levels are substantially predictive of COVID-19 diagnosis and disease severity.
Aykac *et al.* (2021)	Turkey	Prospective cohort	N/A	N/A	In this study, the authors discover that parameters that reveal oxidant and antioxidant capacity, such as TT and NT, appear to be good candidates for accurate prediction of clinical course among COVID-19 patients.
Şekeroğlu *et al*. (2021)	Turkey	Prospective cohort	N/A	N/A	The thiol-disulfide balance was disrupted in COVID-19 patients in this study. Monitoring the thiol-disulfide balance during patient follow-up and treatment may be beneficial.
Çakırca *et al.* (2021)	Ireland	Prospective	N/A	N/A	Thiol was the best predictor of ICU requirement in COVID-19-infected patients, followed by OSI, TAS, and TOS in this study. Antioxidants, such as thiol molecules, can be used as adjunctive therapy in COVID-19 disease.
Chen *et al*. (2023)	USA	Case series	1000 mg/kg (141.67 mg/kg IV) every 12 h for 1–6 doses	N/A	This retrospective case series found no benefit for NAC; however, more research is needed to determine whether differences in drug regimens would result in positive results.
Ibrahim *et al*. (2020)	USA	Case series	600 mg (IV) every 12 h for 1 week	Hydroxychloroquine received only one dose (400 mg)	This study shows that the mechanism of action of NAC may involve blocking viral infection and the resulting cytokine storm, which calls for further confirmatory research in the context of controlled clinical trials.

scored 10 (Assimakopoulos and Marangos, 2020; Çakırca *et al.*, 2021; Faverio *et al.*, 2022; Mete *et al.*, 2021), two studies scored 9 (Ramadhan *et al.*, 2021; Izquierdo *et al.*, 2022), and two studies scored 8 and 6, respectively (Chen *et al.*, 2023; Ibrahim *et al.*, 2020). The results of the quality assessment are shown in Table S1.

Quality assessment for randomized control trials by using the ROB1 scale

The Cochrane Risk of Bias assessment tool was applied to evaluate the quality of the incorporated RCT studies. The studies conducted by Gaynitdinova *et al.* (2021), Taher *et al.* (2021), and de Alencar *et al.* (2021) displayed a range of quality from moderate to high. An overview of the quality assessment aspects for the included studies is depicted in Figure S1.

Evaluating the risk of bias across studies

To evaluate bias across the studies included, we examined the reported results to identify any indications of selective outcome reporting. As noted by Egger *et al.* (1997), the assessment of publication bias lacks reliability when there are fewer than 10 combined studies. Therefore, even though our meta-analysis encompassed 14 studies, the evaluation of publication bias was deemed unreliable because each outcome consisted of fewer than 10 aggregated studies. Consequently, we refrained from conducting Egger's test for funnel plot asymmetry to determine the presence of publication bias.

Statistical analysis

Acetylcysteine derivative differences between mild and severe COVID-19 patients

Kalem *et al.* (2021) revealed thiol-disulfide homeostasis (TDH) as a new parameter that indicates oxidative stress and has a substantial predictive value in COVID-19 diagnosis and severity. Severe COVID-19 patients had lower native thiol (NT) and total thiol (TT) levels than healthy controls and mild to moderate patients ($P < 0.001$). Native thiol reflected only reduced thiols, and TT reflected both reduced and oxidized thiols, while half of the difference between TT and NT was accepted as the disulfide level. Five studies compared TT levels between COVID-19 patients with mild symptoms (n = 273) and COVID-19 patients with severe symptoms (n = 163) (Aykac *et al.*, 2021; Çakırca *et al.*, 2021; Kalem *et al.*, 2021; Mete *et al.*, 2021; Şekeroğlu *et al.*, 2021), and four of them compared NT and disulfide levels (n = 227, 123 for each, respectively) between the same two groups (Aykac *et al.*, 2021; Mete *et al.*, 2021; Şekeroğlu *et al.*, 2021). The overall MD between the two groups had significantly higher TT, NT, and disulfide levels in COVID-19 patients with mild symptoms. For TT (MD: 103.15; 95% CI: 91.31–114.99; $P < 0.00001$), NT (MD: 101.9; 95% CI: 86.23–117.58; $P < 0.00001$), and di-sulfide levels (MD: 4.93; 95% CI: 3.18–6.68; $P < 0.00001$) were compared with those in the COVID-19 with severe symptoms group (Figure 2).

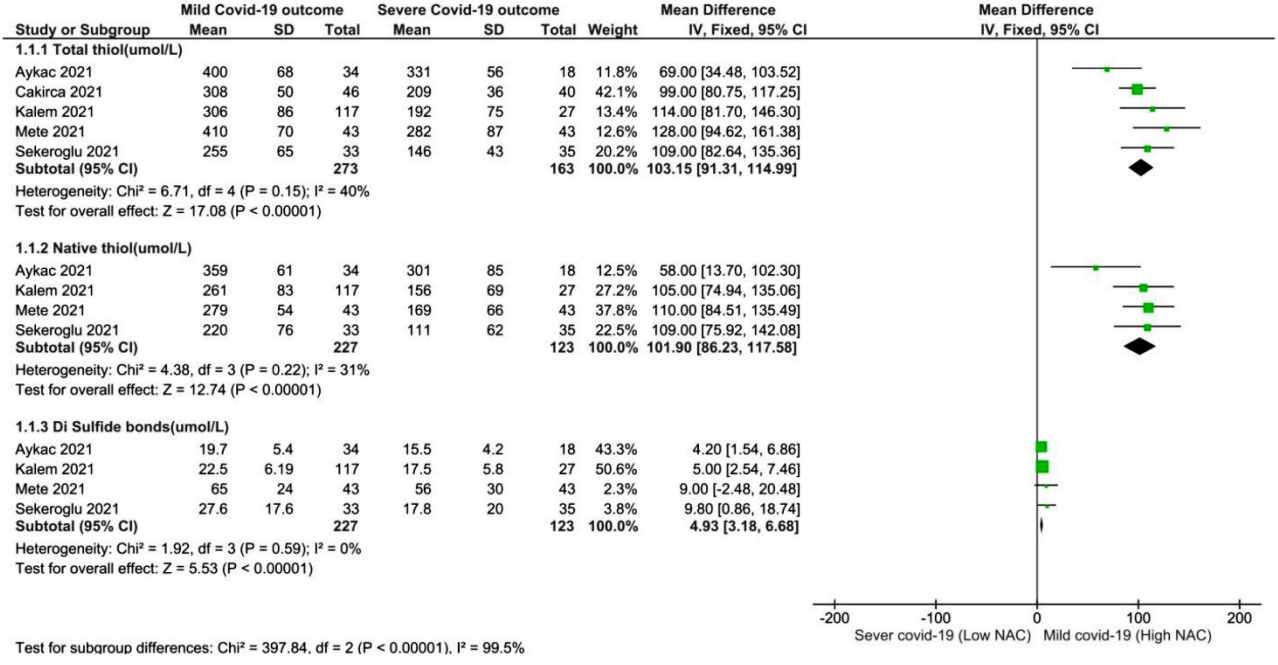

Figure 2. Acetylcysteine derivative differences between mild and severe COVID-19 patients.

Lymphocyte differences between high and low NAC derivatives in COVID-19 patients

Sex studies compared the absolute numbers of lymphocytes between mild COVID-19 patients with symptoms who had high NAC derivatives (n = 326) and severe COVID-19 patients with symptoms who had low NAC derivatives (n = 256) (Assimakopoulos and Marangos, 2020; Çakırca *et al.*, 2021; Gaynitdinova *et al.*, 2021; Kalem *et al.*, 2021; Mete *et al.*, 2021; Şekeroğlu *et al.*, 2021). The overall MD between the two groups was significantly higher in COVID-19 patients with mild symptoms (SMD: 0.64; 95% CI: 0.47–0.81; P < 0.00001) (Figure 3).

Acetylcysteine derivatives in inflammation and cytokine storms

Four studies compared C-reactive protein (CRP) levels between COVID-19 patients who were treated with NAC in their protocol (n =157) and COVID-19 patients without NAC in their protocol (n = 152) (Alencar *et al.*, 2021; Assimakopoulos and Marangos, 2020; Avdeev *et al.*, 2022; Gaynitdinova *et al.*, 2021), and three studies compared ferritin levels between COVID-19 patients who were treated with NAC in their protocol (n = 68) and COVID-19 patients without NAC in their protocol (n = 68) (Assimakopoulos and Marangos, 2020; Chen *et al.*, 2023; Ibrahim *et al.*, 2020).

The overall SMD between the two groups had significantly lower CRP for COVID-19 patients who were treated with NAC in their protocol (SMD: –12.09, 95% CI: –23.98 to –0.19; P = 0.05), but the overall MD between the two groups had no significant difference in ferritin (MD: –0.39, 95% CI: –1.09–0.3; P < 0.27) (Figure 4).

Acetylcysteine derivatives in coagulation

Two studies compared D-dimer levels between COVID-19 patients treated with NAC in their protocol (n = 66) and COVID-19 patients without NAC in their protocol (n = 62) (Assimakopoulos and Marangos, 2020; Avdeev *et al.*, 2022). The overall MD between the two groups was significantly lower in D-dimer for COVID-19 patients who were treated with NAC in their protocol (MD: –203.53, 95% CI: –366.33 to –40.73); P = 0.01) (Figure 4).

Respiratory index

Five studies compared the levels of pO_2/FiO_2 between COVID-19 patients who were treated with NAC in their protocol (n = 709) and COVID-19 patients without NAC in their protocol (n = 458) (Assimakopoulos and Marangos, 2020; Avdeev *et al.*, 2022; Faverio *et al.*, 2022; Gaynitdinova *et al.*, 2021; Taher *et al.*, 2021). The overall MD between the two groups had significantly higher levels of pO_2/FiO_2 for COVID-19 patients who were treated with NAC in their protocol (MD: 35.45, 95% CI: 28.71–42.2); P < 0.00001) (Figure 5).

Length of hospital stay

Five studies compared days of hospital stay between COVID-19 patients who were treated with NAC in their protocol (n = 734) and COVID-19 patients without NAC in their protocol (n = 486) (de Alencar *et al.*, 2021; Avdeev *et al.*, 2022; Faverio *et al.*, 2022; Gaynitdinova *et al.*, 2021; Taher *et al.*, 2021). The overall MD between the two groups showed that COVID-19 patients who were treated with NAC in their protocol spent fewer days in hospital (MD: –5, 95% CI: –4.09 to –1.66); P < 0.00001) (Figure 5).

Length of ICU stay

Three studies compared days spent in the intensive care unit between COVID-19 patients who have been treated with NAC in their protocol (n = 686) and COVID-19 patients without N-acetylcysteine in their protocol (n = 442) (de Alencar *et al.*, 2021; Faverio *et al.*, 2022; Taher *et al.*, 2021). The overall MD between the two groups showed that COVID-19 patients who were treated with NAC in their protocol spent fewer days in the hospital (MD: –2.18, 95% CI: –3.96 to –0.4; P = 0.02) (Figure 5).

Mortality rate

Five studies compared the mortality rate between COVID-19 patients treated with NAC in their protocol (n = 2251) and COVID-19 patients without NAC in their protocol (n = 17312) (de Alencar *et al.*, 2021; Assimakopoulos and Marangos, 2020; Avdeev *et al.*, 2022; Izquierdo *et al.*, 2022; Taher *et al.*, 2021). The overall odds ratio between the two groups showed that the COVID-19 patient group treated with NAC in their protocol had a lower rate of mortality (OR: 0.56, 95% CI: 0.35–0.9); P = 0.02) (Figure 5).

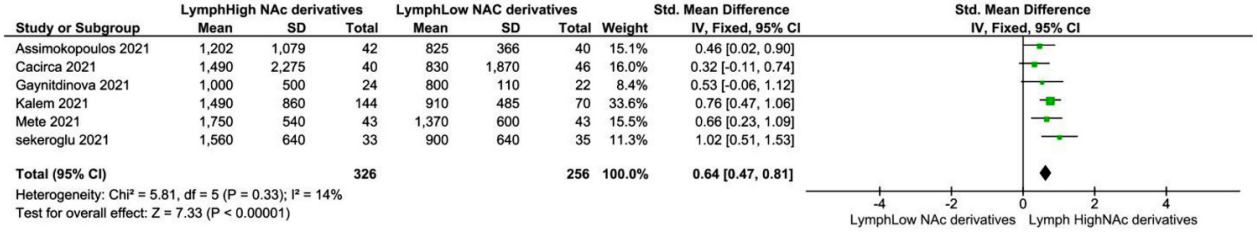

Figure 3. Lymphocyte differences between high and low NAC derivatives in COVID-19 patients.

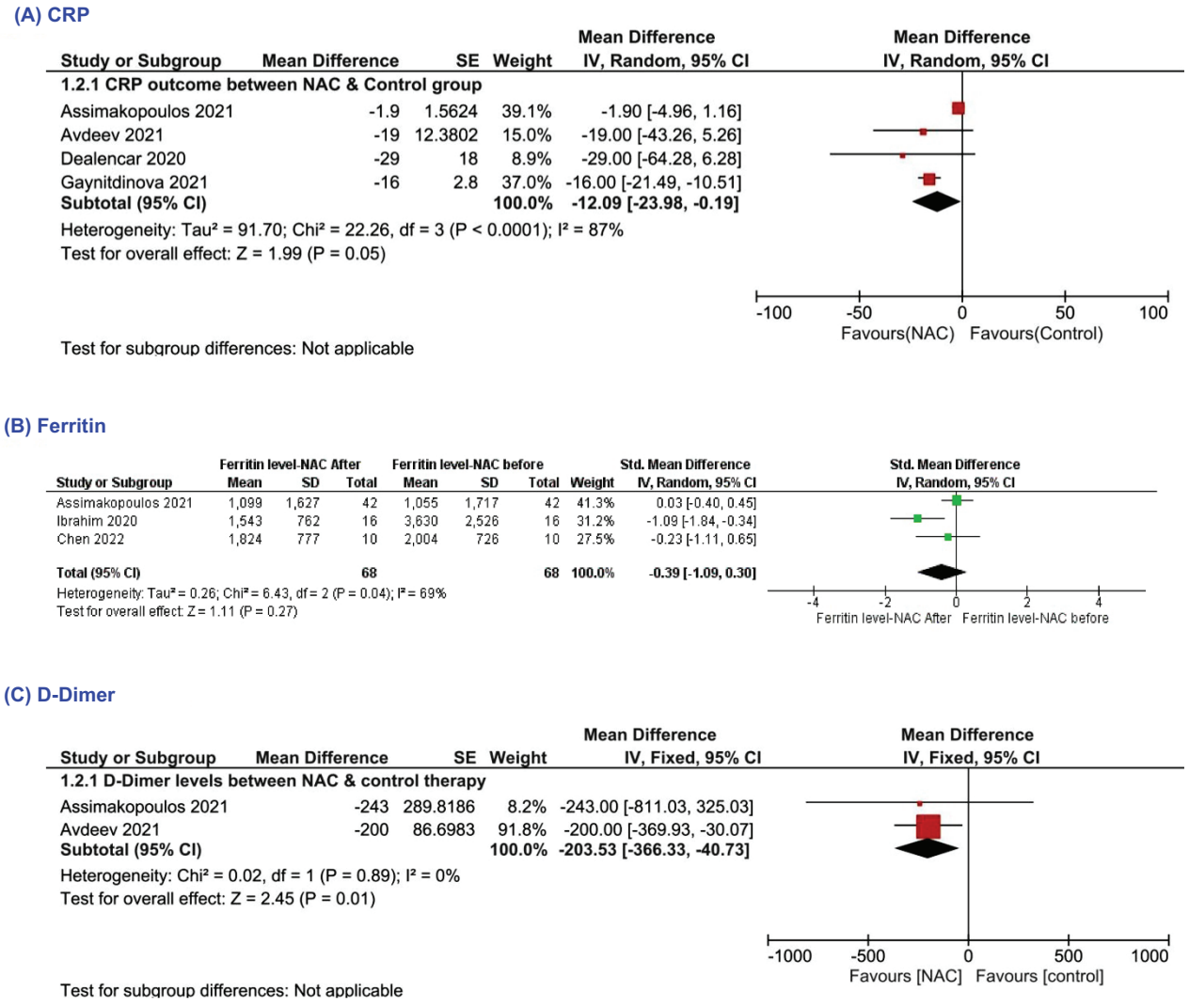

Figure 4. Effect of acetylcysteine derivatives on CRP, ferritin, and D-Dimer.

Sensitivity analysis

There was evidence of heterogeneity in some outcomes. To solve this, a random effects model was selected for those outcomes, and sensitivity analysis was conducted to solve heterogeneity and determine if it affected the outcomes of the current study. We conducted a sensitivity analysis in the case of CRP and ferritin heterogeneity. By excluding one outlier in 2021, the heterogeneity of CRP was adjusted, and the heterogeneity of ferritin was adjusted as well when the study of Ibrahim in 2020 was excluded. At the same time, the outcome was not affected before and after the sensitivity test for the two outcomes (Figures S2 and S3).

Discussion

In our meta-analysis, NAC was shown to combat the first pathological stage of COVID-19 by preventing or decreasing viral entry and replication. In COVID-19 patients treated with NAC, increased TT (both reduced and oxidized thiols), NT (reduced thiols), and disulfide levels (half of the difference between TT and reduced thiols) impaired the binding fusion and replication of SARS-CoV-2 and subsequently the severity of the disease, leading to mild symptoms. Aykac *et al.* (2021), Cakirca *et al.* (2021), Kalem *et al.* (2021), Mete *et al.* (2021), and Şekeroğlu *et al.* (2021) have revealed that patients with high-dose NAC have demonstrated mild symptoms compared to severe symptoms in low-dose patients, which supports the studies of Dai *et al.* (2021), who reported that NAC could break disulfide bonds residing in the mucus, it could break disulfide bonds in many proteins in the context of SARS-CoV-2 infection, as disulfide bonds are present in the S2 spike protein, ACE2, transmembrane protease serine two and RNA-dependent RNA polymerase so that NAC might combat viral entry into host cells and replication (Bourgonje *et al.*, 2021;

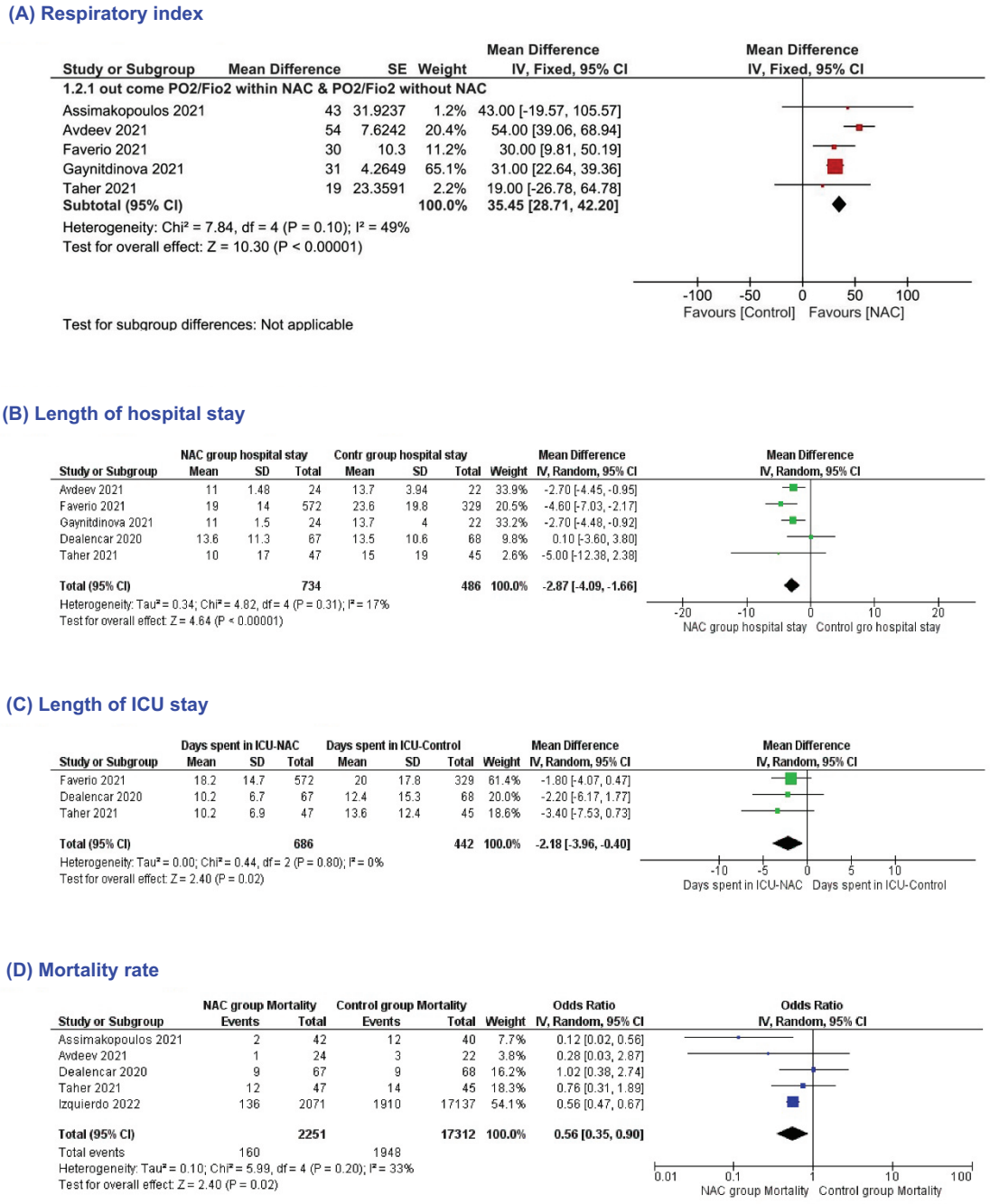

Figure 5. Effect of acetylcysteine derivatives on respiratory index, length of hospital stay, length of ICU stay, and mortality rate.

Dai *et al.*, 2021). Dai *et al.* pointed out that the interaction between ACE2 and the SARS-CoV-2 S protein relied on intra- and intermolecular disulfide bonds. These bonds played a crucial role in the binding mechanism and were influenced by the balance of thiol-disulfide interactions within the extracellular surroundings (Dai *et al.*, 2021). The binding between the SARS-CoV-2 S protein and ACE2 was entirely disrupted when all disulfide bonds were converted into sulfhydryl groups, as demonstrated by molecular dynamics simulations (Dai *et al.*, 2021). Reducing only the disulfide bonds in ACE2 to sulfhydryl groups resulted in a decreased binding strength, whereas diminishing the disulfide bonds in the SARS-CoV-2 S protein had a relatively minor impact in comparison.

Additionally, Dai *et al.* reported that NAC and H_2S combat binding by downregulating all binding cofactors (glucose-regulated protein 78 (GRP78), transferrin receptor (TFR), protein kinase receptor AXL, kidney injury molecule-1 (KIM-1) and neuropilin 1 (NRP1)

(Cazzola *et al.*, 2021; Dai *et al.*, 2021). The potential exists for NAC to attach itself to Cys-145, a crucial site in Mpro structure. This interaction could lead to the suppression of its protease activity and subsequently hinder the replication of the virus (Shi and Puyo, 2020). Both Mpro and PLpro, which are cysteine proteases, hold equal significance in the viral life cycle (Iciek *et al.*, 2022). Bourgonje *et al.* also noted that the RdRp domain within the nsp12-nsp7-nsp8 complex encompasses disulfide bonds at cysteines C301–C306 and C487–C645. NAC or other hydrogen sulfide (H_2S) contributors might access the RdRp domain to dissolve these disulfide bonds (Bourgonje *et al.*, 2021). Shi and Puyo (2020) outlined that RNA viruses depend on active support from the NF-κB pathway within host cells for replication, and curtailing NF-κB considerably hampers the replication rate. Additionally, Pons *et al.* (2020) suggested that glutathione (GSH), known for its inhibitory effect on NF-κB activation, might potentially diminish viral replication. In addition to inhibiting viral entry and replication, the NAC can modulate the immune response to SARS-CoV-2, preventing severe inflammation. Jasim *et al.* (2022) and Gorini *et al.* (2021) reported that H_2S enhances T-cell activation; activated CD4+ and CD8+ T cells are involved in viral elimination, leading to mild to moderate upper respiratory tract symptoms (Gorini *et al.*, 2021; Jasim *et al.*, 2022). Zoofaghari *et al.* demonstrated that administering a substantial dose of oral NAC (1200 mg) has the potential to enhance adaptive immunity. This is achieved through the elevation of lymphocyte glutathione levels and the modulation of neutrophil activity in the context of COVID-19. Consequently, this approach leads to a reduction in symptoms (Zoofaghari *et al.*, 2022). In the current meta-analysis, NAC and its metabolites combat the second phase of COVID-19 (pneumonia without cytokine storm, with or without hypoxia) by preventing the causes of acute inflammation. Assimakopouos and Marangos (2020), Avdeev *et al.* (2021), de Alencar *et al.* (2021), and Gaynitdinova *et al.* (2021) revealed that the overall standardized mean difference (SMD) of CRP (acute phase reactant) was significantly lower in COVID-19 patients who were treated with NAC in their protocol ($P = 0.05$) than in the untreated group.

Our study found NAC to combat the third extrapulmonary phase: pneumonia with cytokine storm, coagulation, multiorgan failure, and mortality by preventing or decreasing the causes. According to Dai *et al.*, hydrogen sulfide (H_2S) can safeguard various organs from harm due to its wide array of biological effects. These effects encompass antiviral properties, mitigation of inflammation, revival of endothelial function, restraint of hypoxia or ischemia-induced damage, and disruption of the harmful loop between COVID-19 and excessive sympathetic activation (Dai *et al.*, 2021). Our meta-analysis findings showed a clear improvement in the patient states at the hospital stay, ICU stay, and mortality levels. Assimakopouos and Marangos (2020), Avdeev *et al.* (2021), Faverio *et al.* (2022), Gaynitdinova *et al.* (2021), and Taher *et al.* (2021) revealed that pO_2/FiO_2 showed higher levels in COVID-19 patients treated with NAC in their protocol ($P < 0.00001$) than in the nontreated group. This outcome aligned with the findings of Corman *et al.*, who noted that H_2S serves as an activating agent for hypoxic detection in the carotid bodies. Both CBS and CSE genes are expressed in the carotid body, leading to increased production of H_2S under hypoxic conditions (Bourgonje *et al.*, 2021). Furthermore, Iciek *et al.* documented the intravenous administration of NAC to patients with COVID-19 who were reliant on ventilators. The study revealed a positive clinical advancement in all treated patients (Iciek *et al.*, 2022). Faverio *et al.* (2022), de Alencar *et al.* (2021), and Taher *et al.* (2021) demonstrated that patients treated with NAC in their protocol spent fewer days in the ICU ($P = 0.02$) than the control group. Assimakopouos and Marangos (2020), Avdeev *et al.* (2021), de Alencar *et al*. (2021), and Taher *et al.* (2021) showed that the overall odds ratio between NAC-treated COVID-19 patients and the nontreated group (OR: 0.56, 95% CI: 0.35–0.9); $P = 0.02$), indicating a lower rate of mortality in the NAC-treated group. All these findings agree with the following studies: Bourgonje *et al*. (2021) and Zoofaghari *et al*. (2022) stated that a rapid increase in circulating cysteine levels was observed within hours following NAC supplementation and that cysteine by its thiol group could directly scavenge ROS in different stages of COVID-19, preventing cytokine storms, pulmonary edema, and ROS-induced respiratory failure (Bourgonje *et al.*, 2021; Zoofaghari *et al.*, 2022). At the levels of cytokine storm and subsequent coagulopathy, Assimakopouos and Marangos (2021) and Avdeev *et al.* (2021) found a significantly lower overall MD in D-dimer for COVID-19 patients treated with NAC in their protocol ($P = 0.01$) in contrast to the untreated group, this aligns with previous research. Cruz *et al.* (1993) highlighted that NAC, whether directly through its unbound thiol form or indirectly through conversion to L-cysteine or reduced glutathione, diminishes the disulfide link within the vWF A1 domain-a pivotal factor in vWF's capacity to attach to platelet GPIb-dependent on its concentration (Cruz *et al.*, 1993), and lysis of vWF causes lysis of the thrombus. According to the findings of Federici *et al.*, 1993, factor VIII (FVIII) and von Willebrand factor (VWF) are separate yet interconnected glycoproteins present in the bloodstream. They exist as a closely associated complex (FVIII/VWF) within the plasma (Cruz *et al.*, 1993). VWF serves as the transporter of FVIII within the plasma, and recent research has verified its essential role as a critical collaborator with FVIII. VWF has substantial involvement in various aspects of FVIII, encompassing its functionality, generation, stabilization, structure, and susceptibility to immune responses

(Cruz *et al.*, 1993). Therefore, proteolysis of VWF leads to loss of stabilization of factor VIIII, so NAC has an anti-coagulant effect (Cruz *et al.*, 1993).

Kim *et al.* (2021) observed that N, N'-diacetyl-L-cystine (DiNAC) effectively dissolved blood clots in as little as 1.5 min, leading to an average decrease in surface area by approximately 71 ± 20%. These findings open up a new potential application for DiNAC as a thrombolytic agent to address sudden blockages in arteries. This could help minimize the chances of excessive bleeding due to hyper-fibrinolysis (Kim *et al.*, 2021). Martinez de Lizarrondo *et al.* (2017) also indicated that NAC serves as a secure and efficient substitute for existing antithrombotic medications in reestablishing blood vessel openness after arterial blockages. Simultaneous administration of NAC along with a nonpeptidic GpIIb/IIIa inhibitor enhanced its ability to dissolve blood clots by expediting thrombus breakdown and averting reocclusion. The utilization of NAC represents a notable and innovative strategy for addressing neuropsychiatric symptoms, such as those seen in post-COVID or long COVID syndrome (Sears and Hewett, 2021; Smaga *et al.*, 2021). The conceivable methods through which NAC might exert its effects, either directly or indirectly, involve the modulation of various neurotransmitters (such as glutamate, GABA, and H_2S), maintenance of oxidative balance (including GSH and H_2S), and control of inflammatory agents (Schwalfenberg, 2021; Smaga *et al.*, 2021). The discharge and reabsorption of neurotransmitters within glutamatergic and GABAergic synapses, engaging with an astrocyte (Walls *et al.*, 2015). L-cysteine undergoes swift oxidation to form cysteine, which serves as a substrate for the cysteine/glutamate antiporter (system xC). Cysteine is conveyed into the cell and traded for glutamate, thereby governing the extracellular glutamate levels. Once within the cell, cysteine is converted back to cysteine, which is the essential element setting the pace for the synthesis of GSH (Smaga *et al.*, 2021). However, we acknowledge the heterogeneity among the studies, potential publication bias, and variations in NAC administration protocols which might be a limitation of the current study.

Conclusions

Our findings suggest that NAC's antioxidant, antiviral, immune-modulating, and anti-inflammatory effects could make it a valuable adjunctive therapy in managing COVID-19 patients. For future researchers, we recommend conducting well-designed randomized controlled trials that focus on specific stages of the disease to provide a more targeted understanding of NAC's effects. Mechanistic studies are needed to elucidate the underlying pathways NAC influences viral replication, inflammation, and coagulation. Moreover, exploring optimal dosage, timing, and administration methods of NAC in different patient populations will be critical for refining its therapeutic potential.

Supplementary Data

Table S1 (Quality assessment of the included studies was performed according to the National Institute of Health (NIH) quality assessment); Figure S1 (Rob1 scale for randomized control trial quality assessment); Figure S2 (Sensitivity analysis for CRP); Figure S3 (Sensitivity analysis for ferritin).

AI Declaration Statement

The authors declare that no AI and AI-assisted technologies were not used in this study.

Author Contributions

H. Saleh, A. Zaid, A. Abdeen, and S. Ibrahim were involved in the idea validation. A. Zaid, H. Saleh, S. Almahdy, and S. Elmalawany contributed to the search strategy. Data screening was performed by S. Almahdy and S. Elmalawany. Data extraction was conducted by A. Abdeen, I. Alsaati, and S. Ibrahim. S. Elmalawany, I. Alsaati, and S. Ibrahim contributed to the quality assessment. Data analysis was performed by A. Zaid, H. Saleh, S. Almahdy, and S. Elmalawany. All authors were involved in writing the original draft. Writing, review, and editing of the manuscript was conducted by A. Zaid, A. Abdeen, and S. Ibrahim.

Funding

The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number RI-44-0571.

Conflict of Interest

The author's declare no conflicts of interest.

Acknowledgments

The authors extend their appreciation to the Deputyship for Research & Innovation, Ministry of Education in Saudi Arabia for funding this research work through the project number RI-44-0571.

Competing Interests

The authors declare no relevant financial or nonfinancial conflicts of interest.

Data Availability Statement

The original contributions presented in this study can be found in the article and supplementary material. Further inquiries can be directed to the corresponding authors.

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Supplementary

Table S1. Quality assessment of the included studies was performed according to the National Institute of Health (NIH) quality assessment.

Study	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	C13	C14	Score
Assimakopoulos 2021	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	CD	10
Avdeev 2021	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	CD	11
Faverio 2021	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	CD	10
Ramadhan 2021	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes	CD	9
Chen 2022	Yes	Yes	Yes	No	No	No	No	No	Yes	No	Yes	No	Yes	CD	6
Izquierdo 2022	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	CD	9
Mete 2021	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	CD	10
Ibrahim 2020	Yes	Yes	Yes	NO	No	No	Yes	Yes	Yes	No	Yes	No	Yes	CD	8
Aykac 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	CD	11
Cakirca 2021	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	CD	10
Kalem 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	CD	11
Sekeroglu 2021	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	CD	11

C, criterion; CD, cannot be determined.

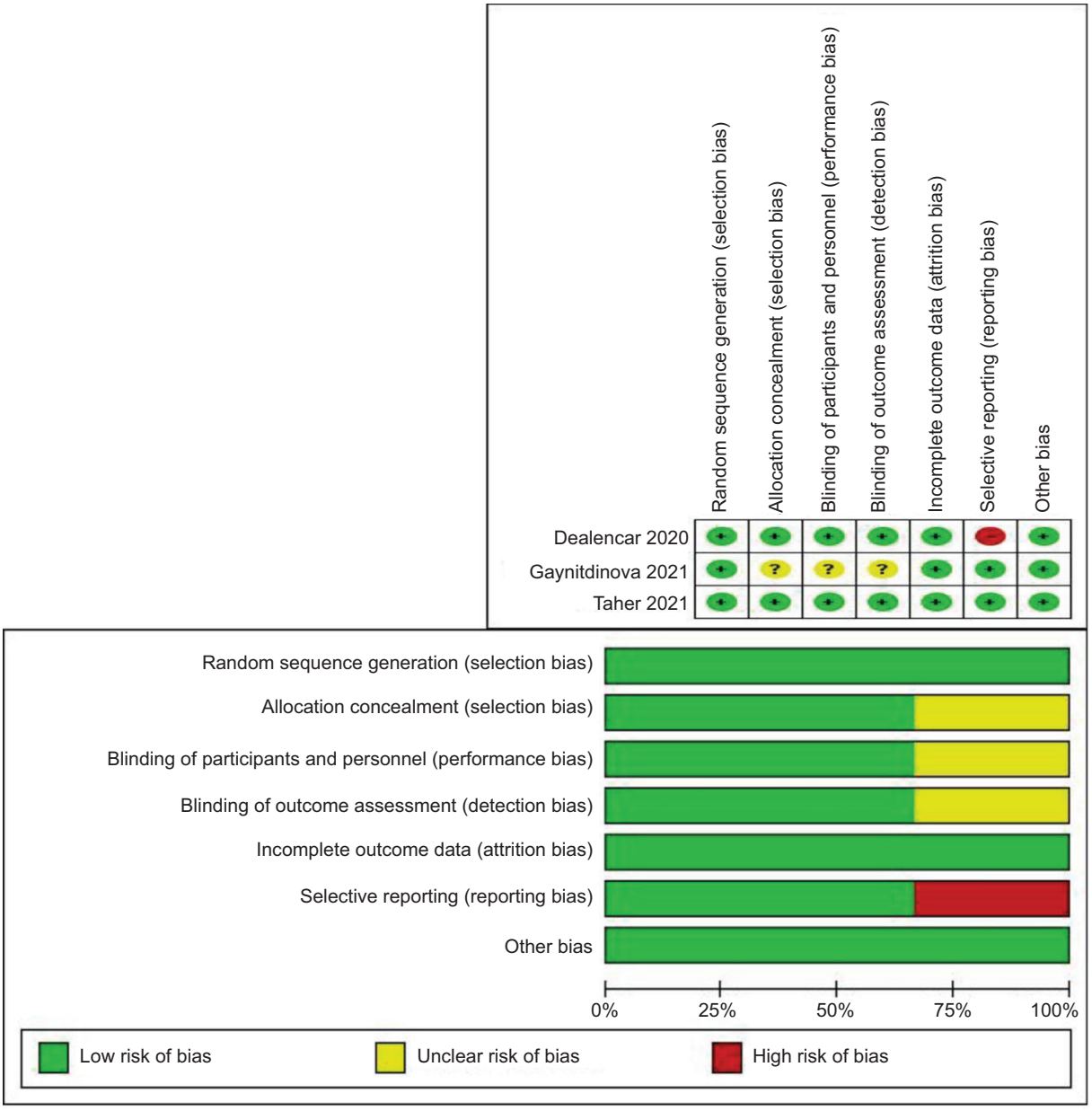

Figure S1. Rob1 scale for randomized control trial quality assessment.

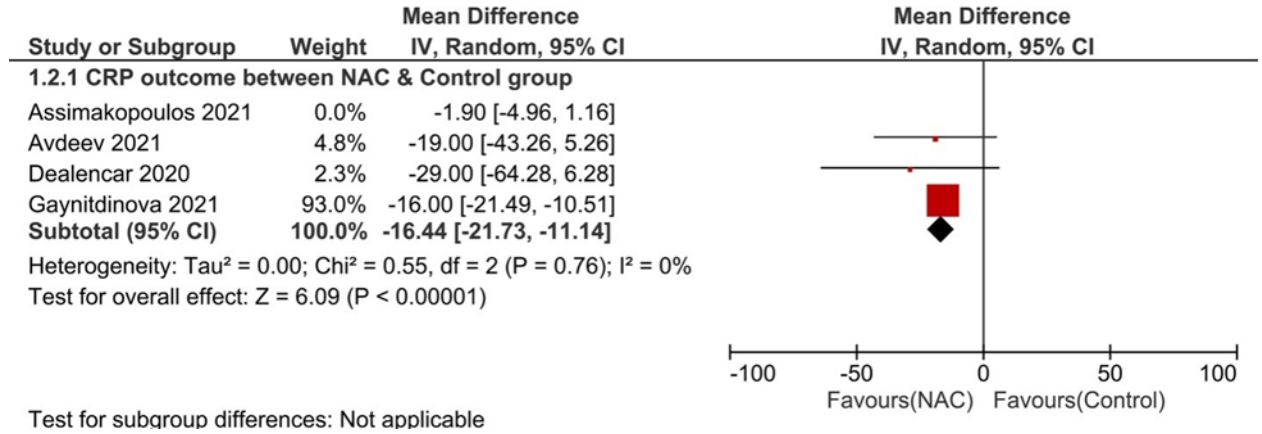

Figure S2. Sensitivity analysis for CRP.

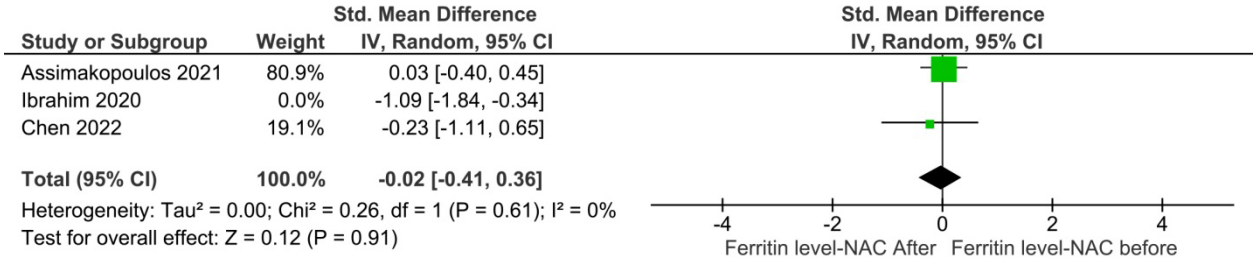

Figure S3. Sensitivity analysis for ferritin.