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Original Article

COVID-19 clinical outcomes and N-acetylcysteine (CoViNAC study): a GRADE compliant meta-analysis of randomized controlled trials with molecular docking and dynamics simulation studies with Mpro of SARS-CoV-2

Seshadri Reddy Varikasuvu[1*], Munikumar Manne[2], Subodh Kumar[3], Shiv Kumar Mudgal[4], Vikash Raj[5], Saurabh Varshney[6], Pratima Gupta[7], Ashoo Grover[8], Chanchal Goyal[9], Vanita Lal[1], Harminder Singh[3], Mona Lisa[10], SARANSH Workshop Members

[1] *Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), Deoghar, India*
[2] *Director of Academics and Training, Bioinformatics Division, Manna Biotech Private Limited, Hyderabad-500076, Telangana, India*
[3] *Pharmacology, All India Institute of Medical Sciences (AIIMS), Deoghar, India*
[4] *Nursing, All India Institute of Medical Sciences (AIIMS), Deoghar, India*
[5] *Orthopaedics, All India Institute of Medical Sciences (AIIMS), Deoghar, India*
[6] *Otorhinolaryngology, All India Institute of Medical Sciences (AIIMS), Deoghar, India*
[7] *Microbiology, All India Institute of Medical Sciences (AIIMS), Deoghar, India*
[8] *Scientist-G & Head, Delivery Research Division, ICMR, New Delhi, India*
[9] *Scientist-E, ICMR, New Delhi, India*
[10] *Department of Pathology, All India Institute of Medical Sciences (AIIMS), Deoghar, India.*

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Abstract

N-acetylcysteine (NAC) has been proposed as an adjuvant therapy for COVID-19, but evidence from randomized controlled trials (RCTs) remains inconclusive. This systematic review and meta-analysis evaluated NAC's efficacy in improving mortality and recovery/discharge rates. Additionally, molecular docking and molecular dynamics simulation (MDMS) studies were conducted to assess NAC's interaction with the SARS-CoV-2 main protease (Mpro), a key enzyme for viral replication. A systematic search identified 12 RCTs, with 11 trials (1125 patients) included in the mortality analysis. NAC significantly reduced mortality (RR=0.59, 95% CI 0.39–0.88, p=0.01; I^2=62%), indicating a 41% decreased risk of death. Six RCTs (656 patients) showed improved recovery/discharge rates (RR=1.09, 95% CI 1.03–1.14, p=0.003; I^2=0%). MDMS studies demonstrated stable NAC binding at the Mpro catalytic site, interacting with His41 and Cys145, crucial for enzymatic activity. These findings suggest NAC significantly improves clinical outcomes in COVID-19 and may inhibit viral replication by targeting Mpro. This integrated evidence substantiates NAC's potential as a critical adjuvant therapy.

Keywords: COVID-19, N-acetylcysteine, Mortality, Meta-analysis, SARS-CoV-2.

1. Introduction

Ever since its emergence, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19), has impacted millions of deaths. Globally, a total of 768,983,095 confirmed COVID-19 cases including 352,943 newly reported ones in the past week are reported to the World Health Organization (WHO), of which 6,953,743 are the number of deaths as of 2nd August 2023.[1]

Being called the 'Achilles Heel' of the virus, the SARS-CoV-2 main protease (M^{pro}), a vital enzyme for viral replication has been proposed to be one of the most attractive targets for anti-viral agents against SARS-CoV-2.[2–4] COVID-19 is characterized by hyper-inflammatory cytokine storm, oxidant-antioxidant dyshomeostasis, immunopathogenic injury, and organ dysfunction causing increased deaths.[5–8] To combat the COVID-19 epidemic, the scientific community across the world has demonstrated great efforts towards novel medication and adjuvant therapies involving anti-inflammatory and anti-oxidant compounds.[9–11]

N-acetylcysteine (NAC), a precursor for cellular gluta-

* Corresponding author.
E-mail address: lifeschemistry@live.com (S. R. Varikasuvu).
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thione levels shown to exhibit antioxidant and anti-inflammatory properties is routinely used for treating acetaminophen overdose. As a mucolytic for chronic respiratory diseases, NAC has been demonstrated to improve immunity, reduce pro-inflammation, and inhibit viral replication.[12–14] The use of NAC as an adjuvant treatment for COVID-19 has been hypothesized and confirmed in several case series.[15–18] While there is a strong evidence in the form of observational cohort studies on the role of NAC in improving COVID-19 outcomes, quality evidence through randomized controlled trials (RCTs) and a meta-analysis of RCTs is still required.[19–23] Many of the registered trials are active and yet to be completed, there is a greater need for clinical evidence synthesis based on the available RCTs using NAC treatment in COVID-19. Therefore, we aim to conduct this systematic review with a comprehensive meta-analysis of RCTs addressing the efficacy of NAC treatment mainly in relationship to COVID-19 mortality and recovery/discharge outcomes. Further, we formulated and tested the hypothesis that NAC might interact and influence the catalytic site of M^{pro} involved in viral replication, using molecular docking and molecular simulation (MDMS) studies.

2. Material and methods

This systematic review and meta-analysis was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[24] The protocol as NACOVID-study was registered on PROSPERO: CRD42022308776. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology based on domains including 'study design', 'risk of bias', 'inconsistency', 'indirectness', and 'imprecision' was used to assess the certainty of evidence (GRADEpro, Version 20. McMaster University, 2014).[25]

2.1. Literature search strategy and study selection

The literature search was conducted with no language restrictions using PubMed/MEDLINE, Cochrane Library, EMBASE, Web of Science, WHO, and ClinicalTrials.gov from inception. Literature search was latest updated on December 23, 2024. The search strategy included both the MeSH and broad text-word search terms: ("acetylcysteine"[Supplementary Concept] OR "acetylcysteine"[All Fields] OR "n acetylcysteine"[All Fields] OR "acetylcysteine"[MeSH Terms]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields])). The other terms used for SARS-CoV-2/COVID-19 are Coronavirus and 2019-nCoV Disease. The bibliographies of published articles were also hand-searched manually for additional studies.

The inclusion criteria as per the PICO (participants, intervention, comparator, and outcomes) approach were: (1) RCTs comparing supplementation of NAC to placebo/control in COVID-19; (2) RCTs reporting the use of NAC supplementation on one or more of the following clinical outcomes (as defined by the authors as primary or secondary); need for the ICU admission, need for invasive mechanical ventilation, mortality events, recovery/discharge rates and any adverse events related to NAC supplementation. No pre-specified limitations were applied for dose, route, and type of NAC supplementation. The exclusion criteria were: (1) studies with no control/comparator group; and (2) study types other than RCTs such as observational studies and trial protocols. In the case of duplicate articles, only a recent report with all relevant information was included. The literature search and study selection were independently done by two reviewers, and in case of any discrepancy, the corresponding authors were contacted for additional information.

2.2. Data extraction and risk of bias assessment

The information extracted from eligible RCTs include: first author names, study country and setting, sample sizes, randomization, blinding, NAC form and dose, and number of events for clinical outcomes (need for ICU admission, invasive mechanical ventilation, mortality, and recovery/discharge events) in treatment and comparator groups. Two investigators (S.R.V. and S.K.) independently extracted the data and assessed the quality for potential risks of bias (RoB) in the RCTs using the Cochrane RoB 2.0 tool [26]. Each study was rated as having either 'low risk', 'high risk', or 'some concerns'. Any discrepancies were resolved upon discussion with professor-level investigators (S.V. and P.G.).

2.3. Data analysis

For this random-effects meta-analysis of RCTs, the intention-to-treat population was used to report the effect sizes as risk ratio (RR) with 95% CI for the dichotomous clinical outcomes such as need for ICU admission, mechanical ventilation, mortality and recovery events between treated and control groups. The overall effect size for RR was presented Z-score. A Z-score with a p-value of <0.05 was considered statistically significant. The between-study heterogeneity was examined by the I^2 statistics and the values >50% were considered to indicate a high degree of heterogeneity [27]. We assessed publication bias by visual inspection of the funnel plot, and by the Begg's and Egger's regression tests for the mortality outcome. The sub-group analysis was conducted based on route of NAC supplementation. The sensitivity analysis was performed by leaving out one study at a time. The methodology of MDMS studies of NAC with M^{pro} is detailed in the Supplementary material; Appendix 1.

3. Results

We reviewed 402 articles for eligibility, identifying 14 potential studies for inclusion. However, two of these studies were excluded as they were not RCTs) [28,29]. Therefore, a total of 12 RCTs were included in the final analysis [30–41]. The PRISMA flow diagram is presented in Fig. 1. Of these, all are registered clinical trials; one is multicentric [33], seven are single-center trials, one is open-labeled [34], two are single-blinded [32,35], and four are double-blinded [30,31,36,37]. One study reported two

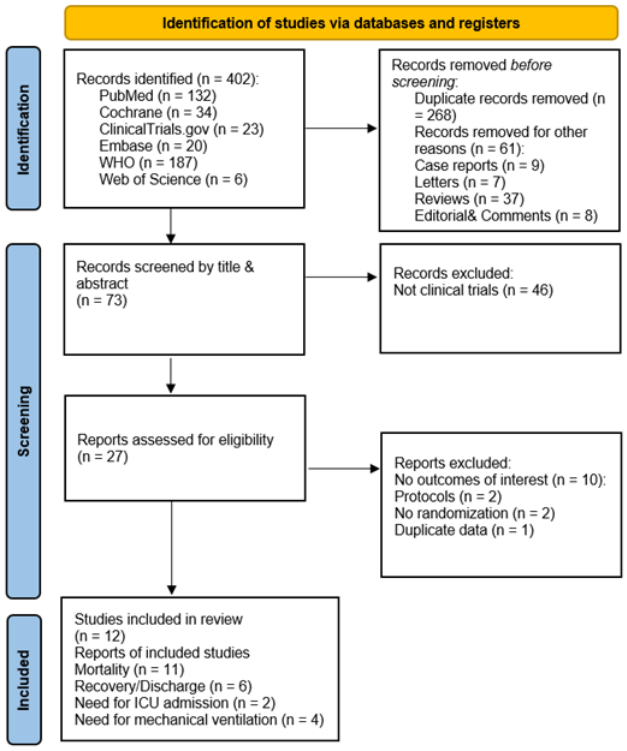

Fig. 1. The PRISMA flow diagram of this meta-analysis.

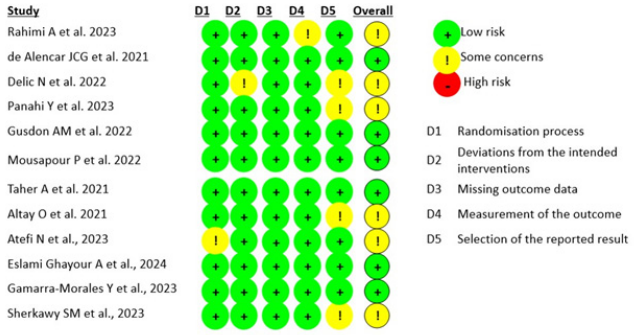

Fig. 2. The Risk of bias assessment of included studies.

observations as an open-label phase-2 and also a double-blinded phase-3 trial on two separate patient cohorts [30]. NAC treatment was compared to placebo in six studies [30,31,33,35–37], and standard treatment alone with no placebo information in two other studies [32,34]. While the allocation ratios were 3:1 in two studies [30,33], all other studies reported an allocation ratio of 1:1. The criteria for inclusion and exclusion, study settings, participant characteristics and treatment strategies, NAC form, dosage, and route of supplementation, reported adverse events and various other study characteristics are presented in Supplementary Appendix 2. All the studies enrolled adult COVID-19 patients aged >18 years with a minimum mean age of 35y to a maximum of 68.5 y across the individual studies. While COVID-19 diagnosis was done in six of the trials by laboratory RT-PCR confirmation [30,32–36], no RT-PCR information was available in one trial [37], whereas both suspected and confirmed cases were enrolled in one trial [31]. COVID-19 was reported to be symptomatic mild-moderate in three trials [30,34,36], and severe in the remaining five trials [31–33,35,37]. The route of NAC supplementation was oral in four studies [30,38,39,41], and inhalational in two studies [32,34]. Whereas the remaining six trials used intravenous NAC [31,33,35–37,40], of which one trial used dendrimer-NAC conjugate nanotherapy [33]. Of the 12 trials, the overall ROB was assessed to be low in 6 trials, while others were assessed to have some concerns as shown in Fig. 2.

3.1. Meta-analysis

The pooled evidence (Fig. 3) from 11 RCTs [31–41] indicated a decreased mortality rate in the NAC intervention group (90/564 = 15.9%) than in the comparator group (166/561 = 29.5%). This between-group difference in the mortality outcome was statistically significant (11 RCTs, RR = 0.59, p=0.01, I^2=62%). The results exploring reasons for heterogeneity through sub-group and sensitivity analyses are presented in Fig. 4, and Fig. 5, respectively. The funnel plot analysis (Fig. 6.) with Begg's (p = 0.05) and Egger's tests (p = 0.11) on the mortality outcome indicated no significant publication bias.

With a statistically significant difference (six observations from 5 RCTs [30,33,36,37,38], RR = 1.09, p=0.003, Fig. 7), the recovery/discharge rate was higher (374/436 = 85.7%) in the NAC intervention group than in the comparator group (145/220 = 65.9%), with no significant heterogeneity (I^2 = 0%). The GRADE assessment of certainty of evidence for all the outcomes is presented in Table 1.

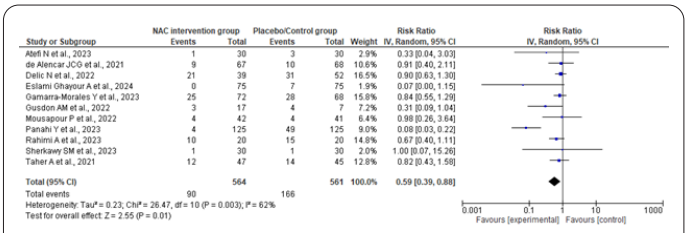

Fig. 3. The Forest plot for the mortality outcome between NAC and control groups.

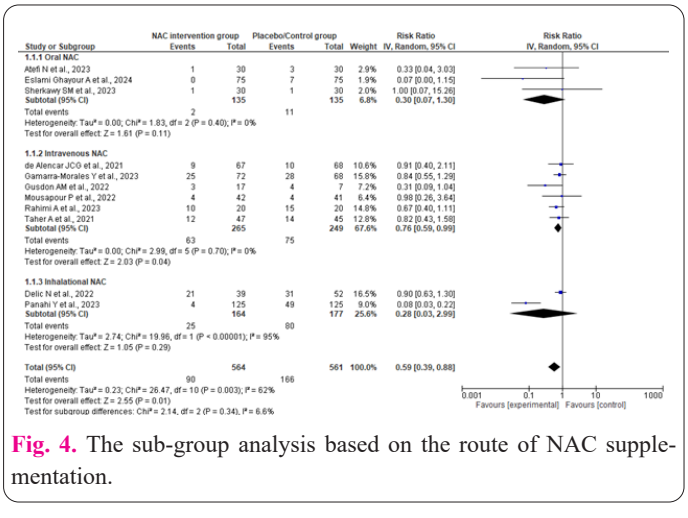

Fig. 4. The sub-group analysis based on the route of NAC supplementation.

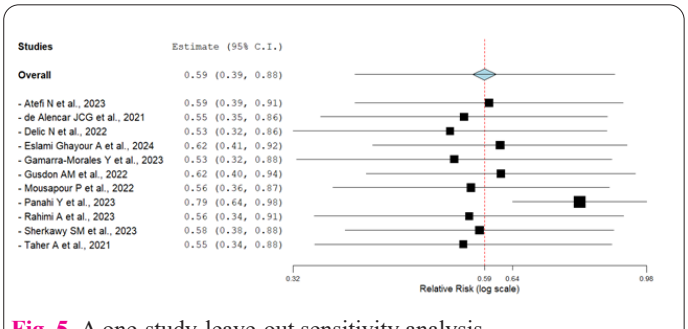

Fig. 5. A one-study-leave-out sensitivity analysis.

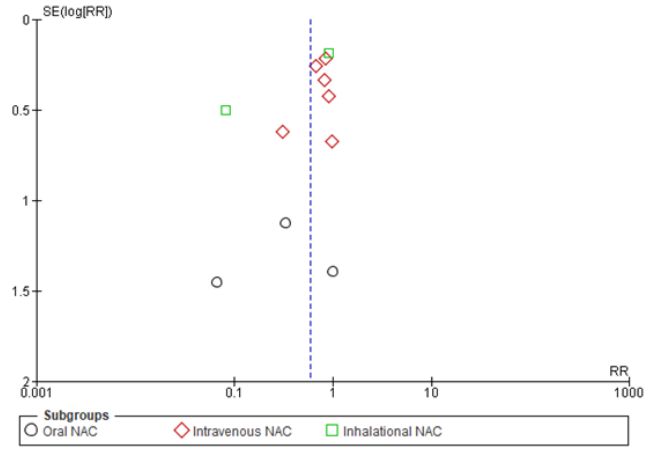

Fig. 6. The Funnel plot for publication bias.

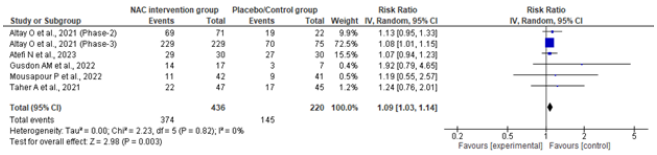

Fig. 7. The Forest plot for the Recovery/Discharge outcome between NAC and Control groups.

The certainty of evidence for the mortality outcome was assessed to be 'moderate' due to serious inconsistency, whereas the certainty of evidence for recovery/discharge outcome was assessed as 'low' due to serious imprecision and strongly suspected publication bias.

3.2. Molecular docking and dynamic simulations

As depicted in Fig. 8, NAC showed stable interactions at the catalytic site of M^{pro}, suggesting its possible therapeutic role in affecting the enzyme required for viral replication. The results of MDMS studies are described in the supplementary Appendix 1.

4. Discussion

This meta-analysis of randomized controlled trials (RCTs) reveals noteworthy improvements in clinical outcomes such as mortality and recovery/discharge rates, among COVID-19 patients who received N-acetylcysteine (NAC) as an adjunct to standard treatment, in comparison to those in the placebo/comparator group.

The collective evidence from 11 RCTs [31–41] indicated a significantly lower mortality risk in the NAC-treated group as compared to the comparator group (RR=0.59, p=0.01), however with a significant between-study heterogeneity (I^2=62%, p=0.003). We speculate that this high heterogeneity could be due to different routes of NAC administration. Accordingly, the sub-group analysis indicated that the route of NAC intervention (intravenous or inhalation or oral) is the main source of moderate heterogeneity observed (I^2=62%). Two studies [32,34] using inhalational NAC are the source of heterogeneity. A repeated meta-analysis combining these two studies yielded an I^2 value of 95%, and a statistically non-significant RR of 0.28 (95% CI: 0.03-2.99, p=0.29). The sub-group meta-analysis including three studies [38,39,41] using oral NAC, showed no statistically significant difference in RR for the mortality outcome (RR=0.30, 95% CI: 0.07-1.30,

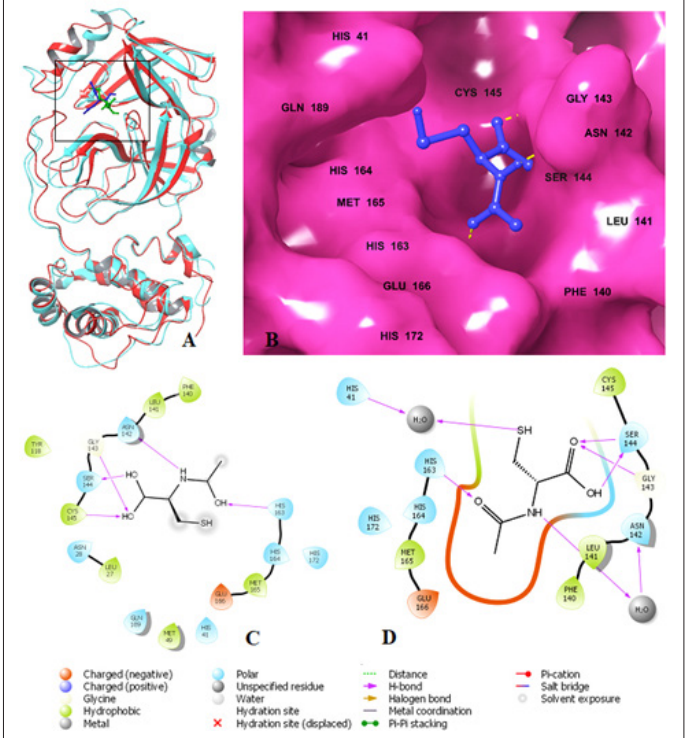

Fig. 8. The molecular docking and dynamics simulation of Mpro with NAC. (A). The superimposed structures depict the molecular interactions of Mpro (cyan) with NAC (blue) after the docking process and the interactions of Mpro (red) with NAC (green) after conducting molecular dynamics (MD) simulations. The root mean square deviation (RMSD) values of the post-docking and dynamics simulation for Mpro are 2.96 Å and for NAC, are 3.86 Å. (B). The active site of the Mpro with NAC (C). Post-docking interactions (D). Post-dynamics simulations interactions

p=0.11), with no heterogeneity (I^2=0%). Notably, the subgroup meta-analysis including six studies using intravenous NAC [31,33,35-37,40], showed a statistically significant mortality reduction in NAC group (RR=0.76, 95% CI: 0.59-0.99, p=0.04), with no heterogeneity (I^2=0%). These findings collectively suggest that, while the studies in the inhalational NAC subgroup are significant contributors to the observed heterogeneity, intravenous route of NAC intervention was found to be effective in reducing mortality.

The sensitivity analysis (Fig. 5) revealed that excluding the study by Panahi et al. [34] reduced the overall I^2 for heterogeneity from 62% to 0%, indicating that this study was the primary contributor to the observed heterogeneity. Therefore, we further examined the forest plot to assess study weight distributions and various characteristics of Panahi et al.'s study [34] that might have influenced heterogeneity and the overall outcome. As shown in the forest plot (Fig. 2), this study was assigned a weight of 9%, which falls within the midrange compared to other studies. A closer inspection of the forest plot revealed a substantially higher number of events in the control arm (49/125) compared to the intervention arm (4/125), which likely contributed to the heterogeneity. Although Panahi et al.'s study [34] was the primary source of heterogeneity, its exclusion did not alter the overall pooled outcome (RR = 0.79, 95% CI = 0.64–0.98). Moreover, the statistical significance for mortality (P = 0.03) was retained even after excluding this study, demonstrating the robustness of the meta-analysis.

Table 1. The GRADE assessment of certainty of evidence

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo	With NAC and COVID-19		Risk with placebo	Risk difference with NAC and COVID-19
Mortality											
1125 (11 RCTs)	not serious	serious[a]	not serious	not serious	none	⊕⊕⊕◯ Moderate[a]	166/561 (29.6%)	90/564 (16.0%)	**RR 0.59** (0.39 to 0.88)	166/561 (29.6%)	**121 fewer per 1,000** (from 180 fewer to 36 fewer)
Recovery/Discharge											
656 (5 RCTs)	not serious	not serious	not serious	serious[b]	publication bias strongly suspected[c]	⊕⊕◯◯ Low[b,c]	145/220 (65.9%)	374/436 (85.8%)	**RR 1.09** (1.03 to 1.14)	145/220 (65.9%)	**59 more per 1,000** (from 20 more to 92 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. I-squared value of 62%. The main source of heterogeneity is coming from studies using Inhalational NAC, particularly a study by Panahi et al., which contributes to the heterogeneity.

b. the lower level of 95% CI is 1.03, which is very close to the line of no effect

c. The Begg's test and Egger's test for funnel plot asymmetry show statistically significant p-values of 0.03 and 0.04, respectively.

We conducted a detailed analysis of study characteristics to identify potential contributors to heterogeneity and overall outcomes. Clinical heterogeneity due to COVID-19 severity, variations in standard treatments, mortality events, and NAC dosage/forms could not be ruled out. Among studies using intravenous NAC, dosing and formulation varied across severe and mild-moderate COVID-19 cohorts. Standard treatment protocols and mortality rates also differed. Two studies reported similar mortality rates between NAC and control groups [31,37]. Notably, a recent study using dendrimer-NAC nanotherapy improved clinical outcomes (mechanical ventilation or death up to 60 days) in severe COVID-19 [33], possibly due to enhanced NAC bioavailability, overcoming its sulfhydryl group binding limitations [42,43]. For NAC inhalation therapy, one study [34] found a significant mortality reduction despite higher age in the NAC group, whereas another [32] reported no effect, potentially due to all patients being on mechanical ventilation. NAC inhalation primarily acts as a mucolytic in the lower respiratory tract, while other routes provide antioxidant effects. Additionally, it has been linked to improved oxidative balance [44,45], better ventilatory function, higher SpO_2, and reduced lung damage in COVID-19 patients [28,34].

The overall findings of this meta-analysis support the beneficial role of NAC as an adjuvant therapy in reducing mortality, further reinforced by the significantly higher recovery/discharge rates in NAC-treated COVID-19 patients compared to the control group. Evidence from six observations across five RCTs [30,33,36–38] demonstrated a significantly higher recovery/discharge rate ($P = 0.003$) in the NAC group, with no significant heterogeneity ($I^2 = 0\%$). Notably, this meta-analysis excludes RCTs using inhalational NAC [32,34] but includes a study evaluating oral NAC combined with metabolic activators (L-serine, L-carnitine, and nicotinamide riboside) [30].

The literature extensively describes NAC as a safe precursor for restoring cellular GSH levels, enhancing T-lymphocyte response, modulating inflammatory pathways, and protecting cells. Its therapeutic potential in blocking nuclear factor kappa-light-chain-enhancer of B cells (NF-κB) activation, mitigating cytokine storms, and alleviating respiratory distress in COVID-19 has been reported [17,34,36]. Additionally, as an NF-κB inhibitor, NAC exhibits antiviral properties by preventing RNA virus replication, including SARS-CoV-2 [33,46]. Considering the promising findings of our meta-analysis and evidence that SARS-CoV-2 main protease (Mpro), essential for viral replication, could be a potential NAC target, we conducted molecular docking and dynamic simulations (Supplementary Material). The results revealed stable hydrogen bond formations and van der Waals interactions (VdWi) between NAC and key amino acids of Mpro. Notably, after MD simulations, NAC maintained stable interactions with key residues across all five catalytic sub-pockets, including His41 and Cys145, which form the catalytic dyad of Mpro. Additionally, since nucleophilic water maintenance by His164 and Asp187 is crucial for zwitter activation and resetting of the catalytic dyad (Cys145–His41) [4], NAC's water-mediated interactions with His41 and VdWi with His164 suggest its potential to bind Mpro and interfere with viral replication. Furthermore, NAC's favorable safety profile, with no serious adverse effects, may be attributed to the absence of Mpro homologs in humans, minimizing interactions with human proteases and reducing the likelihood of side effects.

This study uniquely integrates a comprehensive meta-analysis with molecular docking and dynamic simulations of NAC with Mpro. However, certain limitations exist. While heterogeneity was addressed through subgroup and sensitivity analyses, clinical variability in COVID-19 severity, comorbidities, sample sizes, study settings, randomization, blinding, data collection, and treatment protocols remains an inherent factor. Notably, none of the included trials reported significant loss to follow-up or severe adverse events related to NAC supplementation (Supplementary Appendix 1). This, along with NAC's favorable safety profile, reinforces its potential as a well-tolerated intervention.

In summary, this meta-analysis demonstrated that adding N-acetylcysteine (NAC) to standard treatment improved both mortality and recovery/discharge rates in COVID-19 patients. These findings are further supported by molecular docking and simulation studies, which highlight NAC's potential to target key residues in the catalytic site of Mpro (Cys145 and His41) and influence its activation (Cys145–His41) and resetting (His164). However, given the variability and limited number of trials across oral, intravenous, and inhalational NAC therapies, further well-designed studies with larger sample sizes are warranted.

Conflict of interests

The authors have no conflicts with any step of the article preparation.

Consent for publication

The authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

No human or animals were directly used in the present research.

Informed consent

The authors declare that no patients were directly used in this study.

Availability of data and material

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

The conceptualization of the study was done by SRV, MM, SK, SKM, ML, and SV. Data curation, analysis, methodology, and software development were collaboratively undertaken by SRV, MM, SK, SKM, and PG. Supervision and validation responsibilities were managed by AG, CG, HS and SRV. The original draft of the manuscript was written by SRV, MM, ML, SK and SKM, while the review and editing process involved contributions from SV, PG, AG, CG, and HS. All the alphabetically-listed names under the **'SARANSH Workshop Members'** have equally contributed to updating this systematic review and meta-analysis, contributing valuable inputs and critical review comments during their participation from 20-23 Jan 2025. All authors approved the final manuscript.

SARANSH Workshop Members

Abha Kumari (Bihar), A Naga Syamsundara Kiran (West-Bengal), Asha Premlata Omega Oraon (Jharkhand), Akshay A Shelke (Bihar), Anup Sharma (West-Bengal), Aprajita Jha (Bihar), Ashish Pundhir (West-Bengal), Ashutosh Kumar (Bihar), Balarko Chakraborty (Jharkhand), Bijita Dutta (West-Bengal), Bulbul Purkait (West-Bengal), Digamber Chaubey (Bihar), Divyam Goyal (Delhi), Garima Chauhan (West-Bengal), Gaurav Jain (Jharkhand), Gaurav Shandilya (Bihar), Jaseena C V (Bihar), Maneesh Kumar (Bihar), Nabendu Sen (West-Bengal), Nishi (Jharkhand), Pawan Kumar (Jharkhand), Pradip Kumar Tiwari (Jharkhand), Priti Abha (Bihar), Rajesh De (West-Bengal), Rajesh Kumar (Jharkhand), Rakesh Kumar (Bihar), Rakesh Kumar (IGIMS-Bihar), Ram Sanjay Pund (Bihar), Sairavi Kiran Biri (Jharkhand), Sana Irfan (Jharkhand), Saptarshi Guha Thakurta (Jharkhand), Saurav (Bihar), Sommya Kumari (Bihar), Sudarsan Behera (Jharkhand), Sunil Kumar Mishra (Jharkhand), Suparna Kanti Pal (West-Bengal), Sweta Jha (Bihar), V Udaya Kumar (Bihar).

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References

1. WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data n.d. https://covid19.who.int/ (accessed August 5, 2023).
2. Huff S, Kummetha IR, Tiwari SK, et al (2022). Discovery and Mechanism of SARS-CoV-2 Main Protease Inhibitors. J Med Chem 65(4):2866-2879. doi:10.1021/acs.jmedchem.1c00566.
3. Luan B, Huynh T, Cheng X, Lan G, Wang HR (2020). Targeting Proteases for Treating COVID-19. J Proteome Res 19(11):4316-4326. doi:10.1021/acs.jproteome.0c00430.
4. Hu Q, Xiong Y, Zhu GH, et al (2022). The SARS-CoV-2 main protease (Mpro): Structure, function, and emerging therapies for COVID-19. MedComm (2020) 3(3):e151. doi:10.1002/mco2.151.
5. Varikasuvu SR, Varshney S, Dutt N, et al (2021). D-dimer, disease severity, and deaths (3D-study) in patients with COVID-19: a systematic review and meta-analysis of 100 studies. Sci Rep 11(1):21888. doi:10.1038/s41598-021-01462-5.
6. Hojyo S, Uchida M, Tanaka K, et al (2020). How COVID-19 induces cytokine storm with high mortality. Inflamm Regen 40:37. doi:10.1186/s41232-020-00146-3.
7. Varikasuvu SR, Dutt N, Thangappazham B, Varshney S (2021). Diabetes and COVID-19: A pooled analysis related to disease severity and mortality. Prim Care Diabetes 15(1):24-27. doi:10.1016/j.pcd.2020.08.015.
8. Varikasuvu SR, Varshney S, Dutt N (2021). Markers of coagulation dysfunction and inflammation in diabetic and non-diabetic COVID-19. J Thromb Thrombolysis 51(4):941-946. doi:10.1007/s11239-020-02270-w.
9. Varikasuvu SR, Thangappazham B, Vykunta A, et al (2022). COVID-19 and vitamin D (Co-VIVID study): a systematic review and meta-analysis of randomized controlled trials. Expert Rev Anti Infect Ther 20(6):907-913. doi:10.1080/14787210.2022.2035217.
10. Vollbracht C, Kraft K (2022). Oxidative Stress and Hyper-Inflammation as Major Drivers of Severe COVID-19 and Long COVID: Implications for the Benefit of High-Dose Intravenous Vitamin C. Front Pharmacol 13:899198. Published 2022 Apr 29. doi:10.3389/fphar.2022.899198.
11. Manne M, Goudar G, Varikasuvu SR, et al (2021). Cordifolioside: potent inhibitor against Mpro of SARS-CoV-2 and immunomodulatory through human TGF-β and TNF-α. 3 Biotech 11(3):136. doi:10.1007/s13205-021-02685-z.
12. Ibrahim H, Perl A, Smith D, et al (2020). Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine. Clin Immunol 219:108544. doi:10.1016/j.clim.2020.108544.
13. Zhou N, Yang X, Huang A, Chen Z (2021). The Potential Mechanism of N-acetylcysteine in Treating COVID-19. Curr Pharm Biotechnol 22(12):1584-1590. doi:10.2174/1389201021999201228212043.
14. Milara J, Martínez-Expósito F, Montero P, et al (2022). N-acetylcysteine Reduces Inflammasome Activation Induced by SARS-CoV-2 Proteins In Vitro. Int J Mol Sci 23(23):14518. doi:10.3390/ijms232314518.
15. Carothers C, Birrer K, Vo M (2020). Acetylcysteine for the Treatment of Suspected Remdesivir-Associated Acute Liver Failure in COVID-19: A Case Series. Pharmacotherapy 40(11):1166-1171. doi:10.1002/phar.2464.
16. Chen B, Raja K, Pierre-Louis F, et al (2023). Intravenous N-Acetylcysteine in Management of COVID-19: A Case Series. J Pharm Pract 36(4):1008-1014. doi:10.1177/08971900221080283.
17. Wong KK, Lee SWH, Kua KP (2021). N-Acetylcysteine as Adjuvant Therapy for COVID-19 - A Perspective on the Current State of the Evidence. J Inflamm Res 14:2993-3013. Published 2021 Jul 6. doi:10.2147/JIR.S306849.
18. Izquierdo-Alonso JL, Pérez-Rial S, Rivera CG, Peces-Barba G (2022). N-acetylcysteine for prevention and treatment of COVID-19: Current state of evidence and future directions. J Infect Public Health 15(12):1477-1483. doi:10.1016/j.jiph.2022.11.009.
19. Afaghi S, Moghimi N, Malekpour Alamdari N, et al (2023). N-acetylcysteine as adjuvant therapy for hospitalized Covid-19 patients: A single-center prospective cohort study. Caspian J Intern Med 14(3):543-552. doi:10.22088/cjim.14.3.553.
20. Galindo-Andúgar MA, Arias Arias Á, Alfonso García Guerra J, Fernández Visier I, Manuel Fernández Ibáñez J, Bellido Maldonado A (2023). Impact of N-Acetylcysteine in the mortality of patients hospitalized with COVID-19: a retrospective cohort study. Rev Clin Esp (Barc) 223(8):479-485. doi:10.1016/j.rceng.2023.07.006.
21. Paraskevas T, Kantanis A, Karalis I, et al (2023). N-acetylcysteine efficacy in patients hospitalized with COVID-19 pneumonia: a systematic review and meta-analysis. Rom J Intern Med 61(1):41-52. doi:10.2478/rjim-2023-0001.
22. Izquierdo JL, Soriano JB, González Y, et al (2022). Use of N-Acetylcysteine at high doses as an oral treatment for patients hospitalized with COVID-19. Sci Prog 105(1):368504221074574. doi:10.1177/00368504221074574.
23. Assimakopoulos SF, Aretha D, Komninos D, et al (2021). N-acetyl-cysteine reduces the risk for mechanical ventilation and mortality in patients with COVID-19 pneumonia: a two-center

retrospective cohort study. Infect Dis (Lond) 53(11):847-854. doi :10.1080/23744235.2021.1945675.

24. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6(7):e1000097. doi:10.1371/journal.pmed.1000097.
25. Guyatt GH, Oxman AD, Vist GE, et al (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 336(7650):924-926. doi:10.1136/bmj.39489.470347.AD.
26. Sterne JAC, Savović J, Page MJ, et al (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898. doi:10.1136/bmj.l4898.
27. Turner RM, Davey J, Clarke MJ, Thompson SG, Higgins JP (2012). Predicting the extent of heterogeneity in meta-analysis, using empirical data from the Cochrane Database of Systematic Reviews. Int J Epidemiol 41(3):818-827. doi:10.1093/ije/dys041.
28. Gaynitdinova V V., Avdeev SN, Merzhoeva ZM, et al (2021). N-acetylcysteine as a part of complex treatment of moderate COVID-associated pneumonia. Pulmonologiya 31:21–9. doi: 10.18093/0869-0189-2021-31-1-21-29.
29. Gamarra-Morales Y, Herrera-Quintana L, Molina-López J, et al (2023). Response to Intravenous N-Acetylcysteine Supplementation in Critically Ill Patients with COVID-19. Nutrients 15(9):2235. doi:10.3390/nu15092235
30. Altay O, Arif M, Li X, et al (2021). Combined Metabolic Activators Accelerates Recovery in Mild-to-Moderate COVID-19. Adv Sci (Weinh) 8(17):e2101222. doi:10.1002/advs.202101222.
31. de Alencar JCG, Moreira CL, Müller AD, et al (2021). Double-blind, Randomized, Placebo-controlled Trial With N-acetylcysteine for Treatment of Severe Acute Respiratory Syndrome Caused by Coronavirus Disease 2019 (COVID-19). Clin Infect Dis 72(11):e736-e741. doi:10.1093/cid/ciaa1443.
32. Delić N, Matetic A, Domjanović J, et al (2022). Effects of Different Inhalation Therapy on Ventilator-Associated Pneumonia in Ventilated COVID-19 Patients: A Randomized Controlled Trial. Microorganisms 10(6):1118. doi:10.3390/microorganisms10061118.
33. Gusdon AM, Faraday N, Aita JS, et al (2022). Dendrimer nanotherapy for severe COVID-19 attenuates inflammation and neurological injury markers and improves outcomes in a phase2a clinical trial. Sci Transl Med 14(654):eabo2652. doi:10.1126/scitranslmed.abo2652.
34. Panahi Y, Ghanei M, Rahimi M, et al (2023). Evaluation the efficacy and safety of N-acetylcysteine inhalation spray in controlling the symptoms of patients with COVID-19: An open-label randomized controlled clinical trial. J Med Virol 95(1):e28393. doi:10.1002/jmv.28393.
35. Rahimi A, Samimagham H, Hajiabdolrrasouli L, et al (2023). Efficacy of N-acetyl Cysteine in Severe COVID-19 Patients: A Randomized Controlled Phase III Clinical Trial. Jundishapur J Nat Pharm Prod18:1–9. doi: 10.5812/jjnpp-129817.
36. Taher A, Lashgari M, Sedighi L, et al (2021). A pilot study on intravenous N-Acetylcysteine treatment in patients with mild-to-moderate COVID19-associated acute respiratory distress syndrome. Pharmacol Rep 73(6):1650-1659. doi:10.1007/s43440-021-00296-2.
37. Mousapour P, Hamidi Farahani R, Mosaed R, Asgari A, Hazrati E (2022). Efficacy and safety of acetylcysteine for the prevention of liver injury in COVID-19 intensive care unit patients under treatment with remdesivir. Gastroenterol Hepatol Bed Bench 15(3):241-248. doi:10.22037/ghfbb.v15i3.2565.
38. Atefi N, Goodarzi A, Riahi T, et al (2023). Evaluation of the efficacy and safety of oral N-acetylcysteine in patients with COVID-19 receiving the routine antiviral and hydroxychloroquine protocol: A randomized controlled clinical trial. Immun Inflamm Dis 11(11):e1083. doi:10.1002/iid3.1083.
39. Eslami Ghayour A, Nazari S, Keramat F, Shahbazi F, Eslami-Ghayour A (2024). Evaluation of the efficacy of N-acetylcysteine and bromhexine compared with standard care in preventing hospitalization of outpatients with COVID-19: a double blind randomized clinical trial. Rev Clin Esp (Barc) 224(2):86-95. doi:10.1016/j.rceng.2023.12.011.
40. Gamarra-Morales Y, Herrera-Quintana L, Molina-López J, et al (2023). Response to Intravenous N-Acetylcysteine Supplementation in Critically Ill Patients with COVID-19. Nutrients 15(9):2235. doi:10.3390/nu15092235.
41. Sherkawy SM, El Wakeel LM, Schaalan MF, Moharram AN, Abouelwafa MA (2023). Impact of N-Acetylcysteine on Modulating Inflammation of Hospitalized Patients with COVID-19 Infections: A Prospective Randomized Trial. Arch Pharm Sci ASU 7(1):129-146. doi: 10.21608/aps.2023.212265.1122.
42. Olsson B, Johansson M, Gabrielsson J, Bolme P (1988). Pharmacokinetics and bioavailability of reduced and oxidized N-acetylcysteine. Eur J Clin Pharmacol 34(1):77-82. doi:10.1007/BF01061422.
43. Kannan S, Dai H, Navath RS, et al (2012). Dendrimer-based postnatal therapy for neuroinflammation and cerebral palsy in a rabbit model. Sci Transl Med 4(130):130ra46. doi:10.1126/scitranslmed.3003162
44. Di Marco F, Foti G, Corsico AG (2022). Where are we with the use of N-acetylcysteine as a preventive and adjuvant treatment for COVID-19?. Eur Rev Med Pharmacol Sci 26(2):715-721. doi:10.26355/eurrev_202201_27898.
45. Lana JFSD, Lana AVSD, Rodrigues QS, et al (2021). Nebulization of glutathione and N-Acetylcysteine as an adjuvant therapy for COVID-19 onset. Adv Redox Res 3:100015. doi:10.1016/j.arres.2021.100015.
46. Shi Z, Puyo CA (2020). N-Acetylcysteine to Combat COVID-19: An Evidence Review. Ther Clin Risk Manag 16:1047-1055. doi:10.2147/TCRM.S273700.