

N-acetylcysteine efficacy in patients hospitalized with COVID-19 pneumonia: a systematic review and meta-analysis

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Background: N-acetylcysteine (NAC) is a mucolytic agents with anti-inflammatory properties that has been suggested as an adjunctive therapy in patients with COVID-19 pneumonia.

Objectives: We conducted a systematic review and meta-analysis to evaluate available evidence on the possible beneficial effects of NAC on SARS-CoV-2 infection.

Methods: In September 2022, we conducted a comprehensive search on Pubmed/Medline and Embase on randomized controlled trials (RCTs) and observational studies on NAC in patients with COVID-19 pneumonia. Study selection, data extraction and risk of bias assessment was performed by two independent authors. RCTs and observational studies were analyzed separately.

Results: We included 3 RCTs and 5 non-randomized studies on the efficacy of NAC in patients with COVID-19, enrolling 315 and 20826 patients respectively. Regarding in-hospital mortality, the summary effect of all RCTs was OR: 0.85 (95% CI: 0.43 to 1.67, $I^2=0\%$) and for non-randomized studies OR: 1.02 (95% CI: 0.47 to 2.23, $I^2=91\%$). Need for ICU admission was only reported by 1 RCT (OR: 0.86, 95% CI: 0.44-1.69, $p=0.66$), while all included RCTs reported need for invasive ventilation (OR: 0.91, 95% CI: 0.54 to 1.53, $I^2=0$). Risk of bias was low for all included RCTs, but certainty of evidence was very low for all outcomes due to serious imprecision and indirectness.

Conclusion: The certainty of evidence in the included studies was very low, thus recommendations for clinical practice cannot be yet made. For all hard clinical outcomes point estimates in RCTs are close to the line of no effect, while observational studies have a high degree of heterogeneity with some of them suggesting favorable results in patients receiving NAC. More research is warranted to insure that NAC is both effective and safe in patients with COVID-19 pneumonia.

Key words: antioxidants, oxidative stress, COVID-19, N-acetylcysteine, critical care.

INTRODUCTION

Respiratory tract infections (RTI) can lead to plenty of complications including as respiratory failure and sepsis [1]. Antibiotics are the first line treatment for bacterial pneumonia but are of limited use in viral infection. In such cases, the use of adjunctive treatments are utilized by clinicians. The COVID-19 pandemic has highlighted our inability to treat causatively every patient, considering that as of 2022 the physician's options are still limited [2]. Airway inflammation and systematic redox imbalance are believed to be responsible for progression to severe disease and thus have been considered as therapeutic targets. Vitamins and antioxidants such as ascorbic acid and N-acetylcysteine (NAC) may restore that imbalance and could be helpful for COVID-19 patients along with antiviral therapies and other supplementation therapies [3]. Specifically, NAC has

been implicated in many molecular pathways associated with oxidative processes and has been proposed as a first-line therapy in SARS-CoV2 infection [4]. We conducted a systematic review and meta-analysis to evaluate available evidence on the possible beneficial effects of NAC on SARS-COV-2 infection

MATERIAL AND METHODS

The systematic review was designed and conducted according to the PRISMA guidelines. PROSPERO registration: CRD42022372419.

Inclusion criteria

Types of studies

We included randomized controlled trials (RCTs), cluster-RCTs and quasi-RCTs. Due to the low

amount of expected RCTs in this subject and the importance of summarizing all available evidence, we also included non-randomized studies (observational cohorts and case-controls). Editorials, letters, commentaries, cross-sectional studies, case series and case reports were not eligible for inclusion.

Types of participants

We included adult patients who required hospitalization for COVID-19 pneumonia. SARS-CoV-2 positivity must be proved with an RCT-PCR test. Patients must be presenting with respiratory signs and symptoms that are associated with COVID-19 (cough, respiratory distress, dyspnea).

Types of interventions (and co interventions)

In this review we considered to include studies on NAC irrespective of route of administration or dosage vs placebo or standard care (control). Due to the rapid changes in the standard care of treatments for patients with COVID-19, we did not exclude studies based on background therapy, that might range from agents that were used in the beginning of the pandemic (e.g. chloroquine) to newer antiviral and immunomodulatory drugs.

Type of outcome measures

Primary outcomes

- 1) All-cause mortality within hospitalization
- 2) Admission to ICU
- 3) Need for invasive ventilation

Secondary outcomes

- 1) Duration of hospitalization
- 2) Duration of ICU stay
- 3) Respiratory index
- 4) Inflammation biomarkers

Search methods

Electronic searches

In September 2022, we conducted a comprehensive search on PubMed/Medline and Embase, using the following terms: (N-Acetylcysteine OR N-Acetylcysteine OR Acetylcysteine OR N-Acetylcysteine OR Mucosolvin OR Trebon) AND (COVID-19 OR SARS-CoV2 OR Coronavirus).

Other search methods

References of included studies were searched for additional relevant literature not identified by the primary research.

Data collection and analysis

For each included study the follow data were extracted: first author, year of publication, population,

interventions (dose, route of administration, duration), comparisons, relevant outcomes and effect sizes. Additionally, for each study we collected information regarding randomization, blinding, intervention and stratification.

Selection of studies

After the removal of duplicate articles, screening was performed by two independent authors. Full text copies of all relevant manuscripts were retrieved. Conflicts were resolved after discussion between the two authors.

Data extraction and management

Data were extracted by two independent authors in two independent authors using pre-specified forms. Conflicts were resolved after discussion between the two authors.

Assessment of risk of bias in included studies

For RCTs risk of bias assessment was performed independently by two authors using the Cochrane ROB tool. The following domains were assessed:

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel

(performance bias)

4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

For non-randomized studies the Newcastle-Ottawa Scale was used. The following domains were assessed:

1. Selection
2. Comparability
3. Outcome/Exposure

Measures of treatment effect

Assessment of heterogeneity

Statistical heterogeneity will be assessed by examining the I^2 statistic and interpreted as following:

1. Less than 25%: no (none) heterogeneity
2. 25% to 49%: low heterogeneity
3. 50% to 74%: moderate heterogeneity
4. 75% or greater: high heterogeneity

Assessment of reporting bias

We planned to perform funnel plot analysis for each outcome, provided that there are at least 10 studies in the comparison and to use the “trim and fill method”, if important publication bias was discovered to determine its impact.

Data synthesis

Statistical analysis was performed using Stata v17 and RevmanWeb.

For each primary or secondary outcome that was reported by at least two RCTs, quantitative synthesis was performed using random-effect measures meta-analysis. Random-effects were used considering the expected clinical heterogeneity of the populations in frailty studies, the definition of frailty and different types of intervention. For categorical and continuous outcomes Odds and Mean Differences (or Standardized Mean Differences) with 95% Confidence Interval respectively were calculated. Wan's method for estimating the sample mean and SD from median and interquartile range was used [5].

Non-randomized studies were synthesized separately.

Subgroup analysis and investigation of heterogeneity

Acknowledging the heterogeneity due to different study design, data from RCTs and non-randomized studies were analyzed separately.

If substantial heterogeneity was identified within each study-design subgroup, we planned to perform additional subgroup analysis to investigate the effect of dosage and route of administration, provided that enough data was available.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of evidence of primary and secondary outcomes, starting from high certainty for RCTs and downgrading according to the trials' limitations.

The GRADE approach results in an assessment of the certainty of a body of evidence by one of the following four grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

RESULTS

Results of the search

Our search in Pub/Med and Embase resulted in 116 and 388 articles respectively. After duplicate removal, a total of 417 articles were screened resulting in 14 potentially eligible reports. 4 reported were excluded due to wrong study design (phase I trial, case series, protocol) [Figure 1].

Description of studies

We identified 4 RCTs and 6 non randomized studies eligible for inclusion in this systematic review. Although the articles by Avdeev and Gaytidnova were described as randomized and case control study respectively, they describe the same patient cohort [6, 7]. Thus, both reports were excluded from further analysis and the journal's editors were informed about the issue. Finally, we included 3 RCTs and 5 non-randomized studies, enrolling 315 and 20 826 patients respectively [Table 1].

Randomized controlled trials

All of the RCTs administered NAC intravenously, with each one using a different dosing regimen. The studies by Mousapour, Taher and de Alencar used 1 g/12 h 40 mg/kg/day and 21 g (divided into two doses) respectively [8–10].

In the study by Mousapour *et al.* 83 patients with severe COVID-19 pneumonia received 1g of NAC over 12 hours or the same volume of placebo [8]. The aim of this study was to evaluate NAC as prophylaxis for the prevention of liver injury in patients treated with remdesivir.

In the study by Taher *et al.* 92 patients with clinical and radiological findings compatible with severe COVID-19 pneumonia, were randomized to either 40 mg/kg/day of NAC intravenously for three days or placebo [9]. All patients received standard therapy and additional antioxidant supplements (vitamins and minerals). Their results were negative for all primary and secondary outcomes.

The study by de Alencar enrolled 140 patients with Sao2 >94% (without supplemental oxygen) and RR> 24 breaths per minute. The intervention group received 21 g of NAC divided into two doses (within 20 hours) [10]. No significant differences were found in the primary (endotracheal intubation and mechanical ventilation) or secondary outcomes.

Non-randomized studies

In a retrospective cohort study by Izquierdo *et al.*, 19,208 patients were included, and of those, 2071 (10.8%) were prescribed NAC at doses of 600 mg every 8 hours and compared with the rest 17,137 that were receiving standard treatment alone [11]. Results showcased that patients receiving NAC had lower mortality with or without concomitant administration of corticosteroids. However, NAC had no significant effect on the mean duration of hospitalization, Intensive Care Unit Admission, or use of invasive mechanical ventilation.

In Assimakopoulos *et al.*, 82 patients were hospitalized with moderate or severe COVID pneumonia, 42 receiving NAC 600 mg twice daily for 14 days or until discharge, and 40 receiving standard of care [12]. Results showed a decrease in severe

respiratory failure with a need for mechanical ventilation support and a reduction in 14- and 28-day mortality for the patients receiving NAC.

Faverio *et al.*, a retrospective observational cohort study, recruited 906 patients in Italy. 585 patients received at least 5 days of NAC, 300 mg NAC IV three times per day, which was switched to 600 mg per os daily when they became clinically stable [13]. The rest of the group (n=321) did not receive NAC or received for less than 5 days. By creating a pseudo-population, the authors adjusted the two groups for potential confounders. The short-term outcomes described higher mortality in patients receiving NAC, however, this was not statistically significant. ICU admission and ICU length of stay were similar in both groups. LOS for

patients discharged home was lower in the NAC group. No significant difference was described in long-term outcomes.

Khoonsari *et al.* reported that from 560 patients included in the study, NAC was used more often in patients who died [14]. However, the aim of the study was not to assess the effectiveness of NAC, instead, these data were described as part of the basic characteristics of the patients who survived and those who didn't.

Carillo Hernandez-Rubio *et al.* included 70 patients admitted to IRCU, showcasing that a higher proportion of patients needing endotracheal intubation were given NAC compared with patients who did not require intubation [15].

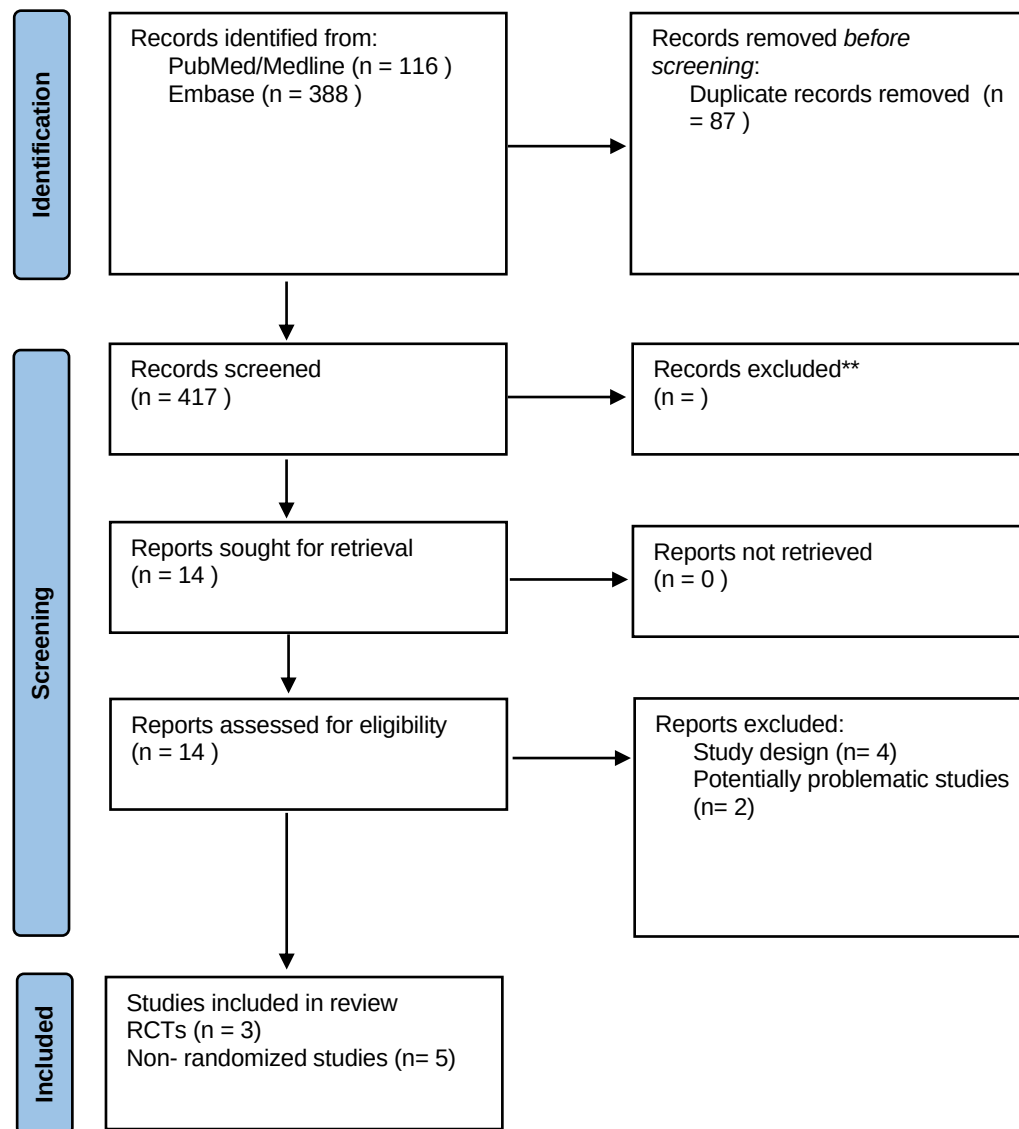


Fig. 1. PRISMA flowchart.

Table 1
Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes
Randomized Controlled Trials					
De Alencar [10]	double-blind, randomized, placebo-controlled trial	140 adult patients diagnosed with severe COVID-19 (suspected or confirmed) Inclusion criteria were oxyhemoglobin saturation (SaO ₂) of less than 94% while breathing ambient air and respiratory rate higher than 24 breaths/min. Exclusion criteria: SaO ₂ < 90% with supplemental oxygen, increased respiratory effort, imminent need for orotracheal intubation	21 g of NAC were administered intravenously for each patient in the NAC group (n=70), divided into 2 doses: 14 g in the first 4 hours and 7 g in the next 16 hours. N-acetylcysteine was diluted in 500 mL dextrose 5%. Patients in the placebo group (n=70) received the same amounts of dextrose 5% in water (1,000 mL in total) intravenously.	The primary clinical endpoint was the necessity for intubation and invasive mechanical ventilation. Secondary outcomes were time of invasive mechanical ventilation, admission to the ICU, length of ICU stay, and mortality.	This study was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), grants # 2016/14566-4 and 2020/04738-8.
Mousapour [8]	double-blind, randomized, placebo-controlled trial	83 adult patients with severe COVID-19 under treatment with remdesivir. All participating patients completed a 5-day course of remdesivir. Exclusion criteria: 1. Positive history of any underlying liver disease 2. Plasma levels of liver transaminases over 100 IU/L on the first day of ICU admission 3. Simultaneous use of any hepatotoxic drugs	One gram acetylcysteine will be administered intravenously every 12 hours for each patient in the intervention group, and each patient in the placebo group will receive the same volume of 0.9% sodium chloride.	Main outcome of interest will be considered as any significant difference in serum levels of markers of liver function. Need for supplemental oxygen, non-invasive ventilation, invasive ventilation and mortality are also reported.	This study was funded by Artesh University of Medical Sciences.
Taher [9]	double-blind, randomized, placebo-controlled trial	92 adult patients with a diagnosis of mild-to-moderate COVID19-associated ARDS Inclusion criteria: >18 years; had received a diagnosis of COVID-19 defined as either the positive SARS-CoV-2 on polymerase chain reaction testing (RT-PCR) in a respiratory tract specimen and/or clinical and radiological findings compatible with COVID-19 severe pneumonia, met	The intervention group (n=47) received NAC at a dose of 40 mg/kg/day diluted in 5% dextrose was administered as a continuous intravenous infusion for three consecutive days. The control group (n=45) received a placebo administered according to the	Primary outcomes: (1) overall 28-day mortality, (2) clinical status on study day 28, using an 8-point ordinal scale of the WHO Master Protocol and proportion of patients who met recovery criteria Secondary outcomes: (1) the proportion of patients needed	This research was supported by funding from the vice chancellor for research and technology, Hamadan University of Medical Sciences, Hamadan, Iran (No: 9903271878). This grant was not assigned to the manuscript

		the criteria for mild to moderate ARDS using the Berlin criteria. Patients with severe ARDS defined with a ratio $\text{PaO}_2/\text{FiO}_2$ ratio < 100 mm Hg and need for mechanical ventilation at the time of enrollment were excluded from the study	same schedule and in the same volume as the active drug. Additional treatment: All patients received supportive and/or COVID-19 standard treatments determined by their treating physician (corticosteroids, antioxidants, awake prone positioning) considered in the study patients.	mechanical ventilation and ventilator-free days, (2) mean change of ARDS severity based on the Berlin classification at 72 h and 96 h after intervention.	writing, editing, and publication fee.
Non Randomized Studies					
Assimakopoulos [12]	retrospective observational study	82 Patients with moderate or severe COVID-19 pneumonia. Moderate illness was defined as evidence of lower respiratory disease during clinical assessment or imaging, with $\text{SpO}_2 > 94\%$ on room air at sea level, while severe disease was defined as any of the following: $\text{SpO}_2 < 94\%$ on room air at sea level, a respiratory rate > 30 breaths/min, $\text{PaO}_2/\text{FiO}_2 < 300$ mm Hg, or lung infiltrates $> 50\%$. All patients enrolled should have a $\text{PO}_2/\text{FiO}_2 > 150$ mmHg on admission Exclusion criteria for this study included age < 18 years, severe respiratory failure requiring mechanical ventilation on admission, administration of IL-1 or IL-6 inhibitors (anakinra or tocilizumab respectively).	42 COVID-19 patients included who received N-acetylcysteine (NAC) 600 mg bid orally for 14 days or until hospital discharge (whatever comes first) plus standard of care. 40 patients selected by random sampling amongst those admitted at the same hospitals the same period and received standard of care, matched 1:1 by age and sex.	Severe respiratory failure, 14 and 28 day mortality, PO_2/FiO_2 ratio, inflammatory biomarkers.	
Faverio [13]	Retrospective observational cohort	906 consecutive adult patients hospitalized for SARS-CoV-2. Patients were excluded if they died or were discharged within 5 days from admission to avoid immortal time bias. A pseudo-population by weighting our cohort by the inverse of stabilised inverse probability of	300 mg NAC IV three times daily, switched to 600 mg per os daily when the patient reached clinical stability and continued until discharge.	Short term outcomes: mortality, ICU admission, duration of stay in the ICU, duration of hospitalization occurrence of atelectasis.	

		treatment weights (IPTW) adjusting for gender, age, days from symptoms onset to hospital admission, period of diagnosis, chest radiograph, ventilation support on admission, direct admission to the ICU, comorbidities diseases, cough and dyspnoea and concomitant commencement of systemic steroids or remdesivir.		Long term outcomes: DLCO impairment, chest radiograph abnormalities, walking distance (6 minutes), dyspnea score.	
Carillo Hernandez-Rubio [15]	Prospective cohort study	70 patients in an 11-bed IRCU led by a team of pneumologists with support from intensive care and anesthesia specialists in the first-level Infanta Elena University Hospital, Madrid, Spain. Inclusion criteria were the following: adult patients with a positive PCR for COVID-19 and admission to the IRCU with at least one of the following: respiratory rate (RR) > 30 breaths·minute ⁻¹ , severe dyspnea, use of accessory muscles or SpO ₂ <92% despite FiO ₂ >0.5 oxygen therapy.	44 of the included patients had received NAC, while 26 did not. The authors do not describe the dose and route of administration.	Rate of endotracheal intubation.	
Izquierdo [11]	observational retrospective cohort study	19,208 hospitalized patients with a diagnosis of PCR+ COVID-19, admitted from March 01, 2020, to January 24, 2021. Overall, mean ± SD age was 66.6 ± 20.9, and 53.6% were men. Compared with NAC-free patients, those treated with high-dose NAC were on average 4.2 years older, and more frequently male.	NAC was prescribed to 2,071 patients (10.8%) according to some local protocols that included this drug, as standard treatment, at doses of 600 mg every 8 h, together with other treatments, irrespective of the initial severity or clinical characteristics of COVID-19 patients.	Mortality, duration of hospitalization, Intensive Care Unit Admission, or use of invasive mechanical ventilation.	
Khoonsari [14]	Retrospective observational cohort	560 hospitalized patients with a confirmed diagnosis of COVID-19 were included. Confirmed cases were defined based on a positive test of RT-PCR assay of pharyngeal or nasal specimens	88 patients received NAC and 472 did not. The authors do not describe the dose and route of administration.	Mortality, liver enzyme levels.	

Risk of bias

All of the included RCTs (de Alencar, Mousapour, Taher) had low risk of bias overall [Table 2].

Allocation: Random sequence generation was judged adequate in all of the included studies. Allocation concealment was not adequately described in the studies by Mousapour and Taher.

Blinding: Risk of bias was low for all RCTs in both domains (participants and personnel and outcome assessors)

Incomplete outcome data: All three studies were judged to have low risk of bias in this domain.

Selective reporting: Outcomes were reported as per the registered protocol's description in all of the studies (de Alencar, Mousapour, Taher).

Other potential sources of bias: Funding for each study is reported in the Table of Study Characteristics [Table 1].

Quality assessment of non-randomized studies using the Newcastle-Ottawa tool is presented in Table 3 [Table 3].

Table 2

Risk of bias assessment in randomized controlled trials

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
De Alencar [10]	Low	Low	Low	Low	Low	Low	Low
Mousapour [8]	Low	Unclear	Low	Low	Low	Low	Low
Taher [9]	Low	Unclear	Low	Low	Low	Low	low

Table 3

Assessment of non-randomized studies using Newcastle-Ottawa score

Study	Total	Domains		
		Selection	Comparability	Outcome
Assimakopoulos [12]	4 (Moderate)	2	1	1
Faverio [13]	8 (High)	4	2	2
Izquierdo [11]	5 (Moderate)	4	0	1
Carillo Hernandez Rubio [15]	6 (Moderate)	2	2	2
Khoonsari [14]	6 (Moderate)	3	1	2

Effect of intervention

Mortality

RCTs: 3 studies (de Alencar, Taher) reported this outcome (OR: 0.85, 95% CI: 0.43 to 1.67, $I^2=0\%$) [Figure 2].

NRSI: 4 studies (Assimakopoulos, Faverio, Izquierdo, Khoonsari) reported this outcome. Meta-analysis of adjusted ORs of these non-randomized studies (random effects) results to and OR of: 1.02 (95% CI: 0.47 to 2.23) with very high heterogeneity ($I^2=91\%$). Among the included studies, Assimakopoulos *et al.* report the most beneficial findings with a crude OR (control vs

NAC) of 8.5 (95%CI: 2.1–57) and adjusted OR (control vs NAC) of 48 (4.4–1436) after adjustment for age, Charlson Index, severity of illness and lymphocytes. Adjustment for too many predictors per number of events (14 events in total) and potential overfitting of the multivariate model must be considered in this case. The biggest of the included studies (Izquierdo) reported a more modest but significantly beneficial effect in the NAC group compared to control (crude OR: 0.56; 95%CI: 0.47–0.67, adjusted for baseline covariates and corticosteroid use OR: 0.72; 95%CI: 0.60–0.87).

In the study by Faverio odds ratio (OR) of mortality (NAC vs control) from the IPTW weighted logistic

regression was 1.22 (95% CI 0.83–1.81, $p=0.3$). Lastly, in the study by Khoonsari a higher proportion of people who died were treated with NAC (NAC:25/88 vs Control 58/472), but the authors did not include NAC in their multivariable model, thus not adjusting for confounders.

Admission to ICU

RCTs: 1 study (de Alencar) reported this outcome (OR: 0.86, 95% CI:0.44–1.69, $p=0.66$).

NRSI: 2 studies (Izquierdo, Faverio) reported this outcome. Izquierdo *et al.* did not find significant difference between the two groups, but do not provide numerical data. After adjustment for the IPTW model (described in study characteristics), Faverio *et al.* did not observe differences between the two groups ($p=0.360$).

Need for invasive ventilation

RCTs: 3 studies (de Alencar, Taher, Mousapour) reported this outcome (OR:0.91, 95% CI:0.54 to 1.53, $I^2=0$) [Figure 3].

NRSI: 2 studies (Izquierdo, Hernandez) reported this outcome. Similarly to the previous outcome, Izquierdo *et al.* did not find significant difference between the two groups, but do not provide numerical data. In the study by Hernandez, patients who required invasive ventilation were more frequently treated with NAC ($p<0.01$).

Duration of hospitalization

RCTs: 2 studies (de Alencar, Taher) reported this outcome (MD (days): 0.16, 95% CI:-2.64 to 2.95, $I^2=0$) [Figure 4].

NRSI: 2 studies (Izquierdo, Faverio) reported this outcome. Izquierdo *et al.* did not find significant difference between the two groups, but do not provide numerical data. Faverio *et al.* observed a lower length of stay in the intervention group (weighted median (IQR) 15 (10–24) days) compared to the control group (weighted median (IQR) 17 (12–30) days, $p=0.013$).

Duration of ICU stay

RCTs: 2 studies (de Alencar, Taher) reported this outcome (MD (days): -0.73, 95% CI:-3.01 to 1.55, $I^2=28\%$) [Figure 5].

NRSI: Faverio *et al.* reported this outcome. They found no difference in the length of ICU between the two groups after adjustment for confounders.

Respiratory index

RCTs: 1 study (Taher) reported this outcome. The authors did not find a significant between group difference at 48 or 96 hours after randomization.

NRSI: Contrariwise, Assimakopoulos *et al.* found a significant difference in PO₂/FiO₂ ratio between the two groups (favoring intervention) in later timepoints ($p < .001$ at 7 days and $p < .05$ at 14 days, respectively).

Inflammatory biomarkers

RCTs: In the study by Mousapour *et al.*, CRP levels were lower in the intervention group compared to control 5 days after randomization. It must be noted that compared to control, in the intervention group CRP levels were higher at baseline.

NRSI: Assimakopoulos *et al.* found lower levels of WBCs, CRP, D-dimers and LDH but not ferritin in the intervention group compared to the control group in both timepoints (7 and 14 days).

Grade assessment

Due to the low number of patients and events in the included RCTs we downgraded 2 points for serious imprecision in all outcomes. Additionally, we downgraded 1 point for indirectness of evidence as we considered the NAC regimen in these RCTs not to be consistent with common clinical practice. Thus, the certainty of evidence for all outcomes is very low, not allowing us to make recommendations in favor or against the use of NAC in patients with COVID-19.

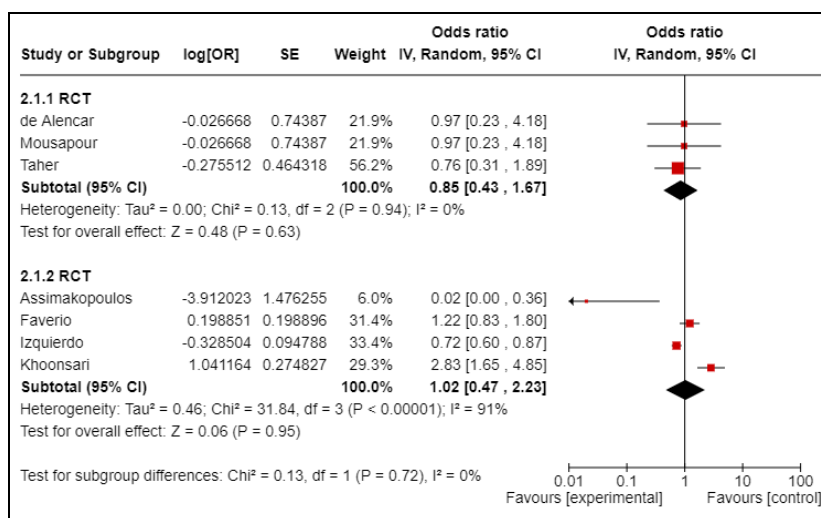


Fig. 2. Meta-analysis of in-hospital mortality.

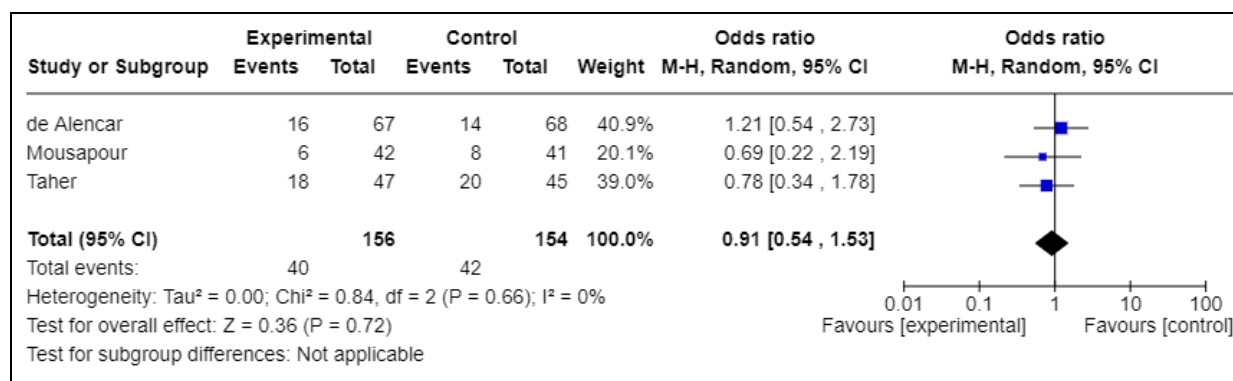


Fig. 3. Meta-analysis of need for invasive ventilation.

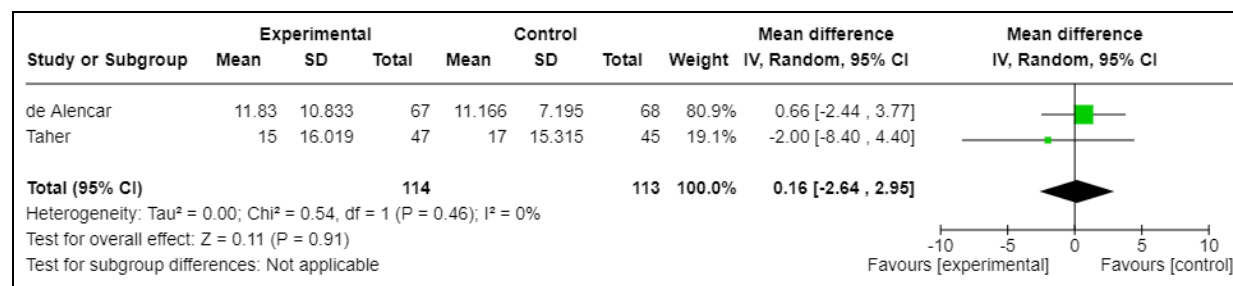


Fig. 4. Meta-analysis of duration of hospitalization.

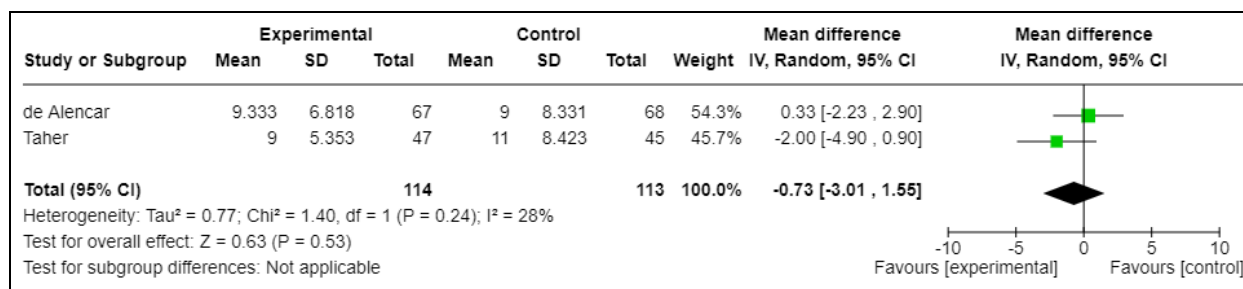


Fig. 5. Meta-analysis of duration of ICU stay.

DISCUSSION

In this systematic review we included 3 RCTs and 5 non-randomized studies on the efficacy of NAC in patients with COVID-19, enrolling 315 and 20826 patients respectively. The results of the RCTs were negative for all our primary and secondary outcomes. The results from non-randomized studies were mixed with high degrees of heterogeneity regarding in-hospital mortality. This may be explained by the different regimens used by the researchers. Overall, the quality of the evidence was very low, mainly due to the small number of patients included in the RCTs.

Two non-randomized studies have reported that NAC has beneficial results in COVID-19 patients, which has sparked the interest of many research teams worldwide [16]. A number of ongoing clinical trials

will hopefully allow us to reach safe conclusions in the near future.

Our knowledge from basic sciences and the clinical experience from other pulmonary diseases have made NAC an attractive adjuvant therapy for COVID-19 pneumonia [17]. NAC has many plausible effects in the pathways surrounding inflammation and oxidative stress. Additionally, recent a recent meta-analysis of NAC in patients with COPD exacerbations has reported significant effects in both clinical and pathophysiological endpoints [18]. A Cochrane review on mucolytics in patients with chronic bronchiolitis or COPD has found a small reduction in the likelihood of having an acute exacerbation, in days of disability per month and possibly hospitalizations, and more importantly no associations between intervention and adverse effects [19]. They also highlight the high degree of heterogeneity in this field.

Strengths and limitations: In this systematic review we have performed a robust search and thus we believe that all of the relevant available evidence has been analyzed. The exclusion of two eligible publications was unfortunate, but we consider it necessary to ensure certainty in our results. Additionally, we have reported evidence from non-randomized studies, but their shortcomings due to study design were considered during the analysis. Lastly, we expect that more research on this intervention will be soon published and we plan to update this review within a reasonable time period.

CONCLUSIONS

The certainty of evidence in the included studies was very low, thus recommendations for clinical practice cannot be yet made. For all hard clinical outcomes point estimates in RCTs are close to the line of no effect, while observational studies have a high degree of heterogeneity with some of them suggesting favorable results in patients receiving NAC. More research is warranted to insure that NAC is both effective and safe in patients with COVID-19 pneumonia.

Introducere: *N-acetil-cisteina (NAC) este un agent mucolitic cu proprietăți antiinflamatorii ce a fost sugerat ca tratament adjuvant la pacienții cu pneumonie COVID-19. Scopul studiului a fost de a realiza o sinteză sistematică și meta-analiză pentru a evalua evidențele actuale asupra beneficiilor NAC în infecția SARS-COV-2.*

Metode: *În luna septembrie 2022 a fost realizată căutarea pe Medline a studiilor clinic randomizate (RCT) și a studiilor observaționale ce au avut tratament NAC la pacienții cu pneumonie COVID-19. Extragerea datelor și evaluarea riscului de eroare sistematică au fost realizate de către doi observatori independenți.*

Rezultate: *Au fost incluse 3 RCT și 5 studii non-randomizate cu 315 respectiv 20 826 de pacienți incluși. Legat de mortalitatea intraspitalicească efectul din RCT a arătat OR: 0,85 (95% CI: 0,43 to 1,67, $I^2=0\%$), respectiv OR: 1,02 (95% CI: 0,47 – 2,23, $I^2=91\%$) la studiile non-randomizate. Internarea în secția de TI a fost evaluată doar într-un singur RCT (OR: 0,86, 95% CI:0,44–1,69, $p=0,66$), iar celelalte studii au raportat necesitatea ventilației invazive (OR:0,91, 95% CI:0,54 to 1,53, $I^2=0$). Riscul de eroare sistematică a fost redus la RCT-urile incluse.*

Concluzii: *Siguranța evidenței rezultatelor studiilor incluse a fost mică, așadar nu pot fi trase concluzii clare. Rezultatele RCT sunt apropiate de lipsa efectului, iar studiile observaționale au fost heterogene, unele sugerând rezultate favorabile. Totuși, studii ulterioare sunt necesare.*

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REFERENCES

1. ALIBERTI S, BRAMBILLA AM, CHALMERS JD, CILLONIZ C, RAMIREZ J, BIGNAMINI A, PRINA E, POLVERINO E, TARSIA P, PESCI A, TORRES A, BLASI F, COSENTINI R. *Phenotyping community-acquired pneumonia according to the presence of acute respiratory failure and severe sepsis*. Respir Res. 2014 Mar 4;15(1):27.
2. SIEMIENIUK RA, BARTOSZKO JJ, ZERAATKAR D, KUM E, QASIM A, MARTINEZ JPD, IZCOVICH A, LAMONTAGNE F, HAN MA, AGARWAL A, AGORITSAS T, AZAB M, BRAVO G, CHU DK, COUBAN R, DEVJI T, ESCAMILLA Z, FOROUTAN F, GAO Y, GE L, GHADIMI M, HEELS-ANSELL D, HONARMAND K, HOU L, IBRAHIM Q, KHAMIS A, LAM B, MANSILLA C, LOEB M, MIROSHNYCHENKO A, MARCUCCI M, MCLEOD SL, MOTAGHI S, MURTHY S, MUSTAFA RA, PARDO-HERNANDEZ H, RADA G, RIZWAN Y, SAADAT P, SWITZER C, THABANE L, TOMLINSON G, VANDVIK PO, VERNOOIJ RW, VITERI-GARCÍA A, WANG Y, YAO L, ZHAO Y, GUYATT GH, BRIGNARDELLO-PETERSEN R. *Drug treatments for COVID-19: living systematic review and network meta-analysis*. BMJ. 2020 Jul 30;370:m2980.
3. ASSIMAKOPOULOS SF, MARANGOS M. *N-acetyl-cysteine may prevent COVID-19-associated cytokine storm and acute respiratory distress syndrome*. Med Hypotheses. 2020;140:109778.
4. du PREEZ HN, ALDOUS C, KRUGER HG, JOHNSON L. *N-Acetylcysteine and Other Sulfur-Donors as a Preventative and Adjunct Therapy for COVID-19*. Adv Pharmacol Pharm Sci. 2022;2022:4555490.

5. WAN X, WANG W, LIU J, TONG T. *Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range*. BMC Med Res Methodol. 2014;14:135.
6. AVDEEV SN, GAYNITDINOVA VV, MERZHOEVA ZM, BERIKKHANOV ZG. *N-acetylcysteine for the treatment of COVID-19 among hospitalized patients*. J Infect. 2022;84(1):94–118.
7. GAYNITDINOVA V.V., AVDEEV S.N., MERZHOEVA Z.M., BERIKKHANOV Z.G., MEDVEDEVA I.V., GORBACHEVA T.L. *N-acetylcysteine as a part of complex treatment of moderate COVID-associated pneumonia*. PULMONOLOGIYA. 2021;31(1):21–29.
8. MOUSAPOUR P, HAMIDI FARAHANI R, MOSAED R, ASGARI A, HAZRATI E. *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. 2022;15(3):241–248.
9. TAHER A, LASHGARI M, SEDIGHI L, RAHIMI-BASHAR F, POOROLAJAL J, MEHRPOOYA M. *A pilot study on intravenous N-Acetylcysteine treatment in patients with mild-to-moderate COVID-19-associated acute respiratory distress syndrome*. Pharmacol Rep. 2021;73(6):1650–1659.
10. de ALENCAR JCG, MOREIRA CL, MÜLLER AD, et al. *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. 2021;72(11):e736–e741.
11. IZQUIERDO JL, SORIANO JB, GONZÁLEZ Y, et al. *Use of N-Acetylcysteine at high doses as an oral treatment for patients hospitalized with COVID-19*. Sci Prog. 2022;105(1):368504221074574.
12. ASSIMAKOPOULOS SF, ARETHA D, KOMNINOS D, et al. *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). 2021;53(11):847–854.
13. FAVERIO P, REBORA P, ROSSI E, et al. *Impact of N-acetyl-l-cysteine on SARS-CoV-2*.
14. KHOONSARI M, ZAMANI F, KARBALAIE NIYA M H, HEMMASI G, AJDARKOSH H, et al. *Liver Enzymes and Inpatient Deaths in COVID-19 Hospitalized Patients*. Hepat Mon. 2020;20(11):e109076.
15. CARRILLO HERNANDEZ-RUBIO J, SANCHEZ-CARPINTERO ABAD M, YORDI LEON A, et al. *Outcomes of an intermediate respiratory care unit in the COVID-19 pandemic*. PLoS One. 2020;15(12):e0243968.
16. TSERMPINI EE, GLAMOČLIJA U, ULUCAN-KARNAK F, REDENŠEK TRAMPUŽ S, DOLŽAN V. *Molecular Mechanisms Related to Responses to Oxidative Stress and Antioxidative Therapies in COVID-19: A Systematic Review*. Antioxidants (Basel). 2022;11(8):1609.
17. du PREEZ HN, ALDOUS C, KRUGER HG, JOHNSON L. *N-Acetylcysteine and Other Sulfur-Donors as a Preventative and Adjunct Therapy for COVID-19*. Adv Pharmacol Pharm Sci. 2022;2022:4555490.
18. JIANG C, ZOU J, LV Q, YANG Y. *Systematic review and meta-analysis of the efficacy of N-acetylcysteine in the treatment of acute exacerbation of chronic obstructive pulmonary disease*. Ann Palliat Med. 2021;10(6):6564–6576.
19. POOLE P, SATHANANTHAN K, FORTESCUE R. *Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease*. Cochrane Database Syst Rev. 2019;5(5):CD001287.

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