International Journal of Clinical Medical Research

Determining the efficacy of N-acetyl cysteine in treatment of pneumonia in COVID-19 hospitalized patients: A meta-analysis

Mohamed E.A Shaaban[1], Ahmed I.M Mohamed[1]

*Correspondence:
Mohamed E.A Shaaban
Graduate of the Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt
Email:
m0hamed.essamit2000@gmail.com

[1] Graduate of the Faculty of Pharmacy, Beni-Suef University, Beni-Suef, Egypt.

Volume number 1
Issue number 2
Pages 36-42

Abstract

Background

Most patients infected with COVID-19 experienced cold-like symptoms. Some other patients developed more serious symptoms such as pneumonia. N-Acetylcysteine (NAC) is known to be effective against acute respiratory distress syndrome (ARDS) due to its anti-inflammatory and antioxidant properties. The effect of NAC on hospitalized COVID-19 patients was unknown. Therefore, this meta-analysis aimed to establish a relationship between the effects of NAC and non-NAC protocols in inpatients with COVID-19.

Method

By March 2022, a systemic review was conducted to assess the effects of NAC and non-NAC in inpatients with COVID-19. The clinical trials were identified in 20553 subjects admitted with COVID-19 at baseline. 2909 was treated with NAC and 17644 was treated without NAC. This study attempts to compare the effects of NAC and non-NAC in COVID-19 patients hospitalized with pneumonia. Statistical analysis uses the dichotomous method as a tool for odds ratio (OR) at 95% confidence interval (CI) to assess the effectiveness of NAC and non-NAC in COVID-19 patients hospitalized with pneumonia in random or fixed-effect model.

Results

Patients managed with NAC had fewer days in the ICU (OR, 2.79; 95% CI, -1.11-6.69, p = 0.16), lower mortality (OR, 0.69; 95% CI, 0.40-1.20, p = 0.19), and fewer number needed mechanical ventilation (OR, 0.74; 95% CI, 0.25-2.21, p = 0.59) compared with non-NAC in COVID-19 subjects hospitalized with pneumonia.

Conclusion

NAC has decreased the days stayed in the ICU, number of deaths, and number of patients needed mechanical ventilation in COVID-19 hospitalized with pneumonia, although, this difference was insignificant. Further studies are required that could affect the level of significance.

Keywords: COVID-19 disease, N-acetyl-cysteine, Mortality, Intensive care unit, Mechanical ventilation, Oxygen level, and pneumonia

Introduction

Coronaviruses are major pathogens of the respiratory system causing different disorders, including the common cold, Middle East respiratory syndrome, and severe acute respiratory syndrome. Today's global pandemic coronavirus disease 2019 (COVID-19 disease) has a high mortality rate, with an approximate 20% in some studies, and is 30–60 times more fatal than the common annual influenza. [1] SARS-CoV-2 virus-induced severe acute respiratory infection can lead to lung failure and the urge for mechanical ventilation. Infection with SARS-COV-2 virus can increase oxidative stress and induce activation of inflammatory factors by increasing the production of interleukin 8 and tumor necrosis factor α from lung cells, tumor necrosis factor α acts on mitochondria to produce reactive oxygen species (ROS) leading to pulmonary cell damage. [2,6]

It typically takes 7 days to develop computed tomography-confirmed pneumonia (COVID-19 disease) from the onset symptoms, like fever or dry cough, and another 2 days to develop acute respiratory distress syndrome (ARDS), ARDS is the major cause of death in COVID-19 disease patients, and it is related to dysregulated host immune responses after viral infection. [3]

However, there is still no gold standard treatment for it. NAC is a well-known multi-potential drug with a hypothetically probable acceptable effect on COVID-related consequences. NAC is a natural plant antioxidant found in onions. It is a precursor to glutathione derived from L-cysteine. NAC has several clinical benefits, including relief from cough, dry eyes, and influenza. It is also frequently used as an antidote for paracetamol overdose and to reduce nitrate tolerance. [4,5] NAC liquefies mucus by breaking down disulfide bonds to a sulfhydryl bond in mucoprotein. It could also decrease mucus elasticity and viscosity, making it easier to remove pulmonary secretions. [9] Besides that, it prevents bacterial and viral stimulation of mucin production and mucus hyper-secretion, leading to a decrease in dyspnea, improving lung function, and recovering blood oxygen saturation. [6, 10] NAC has both direct and indirect antioxidant properties. The direct effect is due to a free thiol group that interacts with and scavenges ROS. Its indirect antioxidant effect is due to its role as a glutathione precursor, which causes an increase in intracellular GSH levels. [11] NAC can also help to boost the immune system, decrease inflammation, and suppress viral replication by inhibiting interleukin 8, interleukin 6, and tumor necrosis α. [7, 12] It may be administered orally, intravenously, or nebulized. Because of the favorable risk-benefit ratio and its effects on glutathione synthesis, immune function, and inflammatory response, NAC has recently been proposed as adjunctive therapy to standard care for SARS-CoV-2 infection. [8] This meta-analysis aimed to establish the relationship between the effect of NAC and non-NAC protocol in hospitalized subjects with COVID-19 disease.

Method

Study protocol

In working on this meta-analysis, we followed the epidemiological statement according to established methodologies. [13]

Data pooling

Our search included only studies published in English. The size and type of study was not a selection criterion. Uncorrelated studies were excluded, e.g., editorials, perspectives, letters, commentary (Figure 1 shows the analysis mode). The study was organized and included in this meta-analysis when:

1. It is a prospective, cohort, or a retrospective randomized controlled trial
2. Subjects were hospitalized with pneumonia and diagnosed with COVID-19 disease
3. The intervention program must include NAC
4. The study discuss the effect of NAC versus non-NAC in COVID-19 disease patients hospitalized with pneumonia on different variables like mortality and/or number of patients who needed mechanical ventilation and/or number of patients admitted to ICU and/or like number of days stayed in the ICU

Among the intervention groups, the following exclusion criteria were adopted:

1- The studies that did not compare the effect of NAC versus non-NAC.
2- The studies with types of pneumonia other than that resulted from COVID-19 disease, and also non-human subjects.
3- Studies that did not focus on mortality rate.

Study selection

A systemic search on MEDLINE/PubMed and Google Scholar till March 2022 was performed. The selected medical subject terms and related words were: COVID-19 disease, N-acetyl cysteine, Intensive care unit, Pneumonia using the Boolean operators (OR, AND) as shown in Table 1.

Identification

PICOS was used as the primary search protocol strategy. [14] The P for the population who are COVID-19 patients hospitalized with pneumonia; I for intervention as drug protocol contain NAC or non-NAC. C for comparison was conducted to show the efficacy of NAC versus non-NAC on COVID-19 disease for various variables, and O for the outcome. Outcomes in the study were the number of deaths, the number of patients requiring mechanical ventilation, the number of patients admitted to ICU, and the number of days spent in the ICU. [15] The studies selected were pooled to EndNote X9 to remove duplicates. Besides, the screening of the studies' title and abstract was read to exclude any data that do not correlate with the effect of NAC versus non-NAC in COVID-19 disease patients hospitalized with pneumonia. The correlated data were collected from the remaining studies.

Screening

Subjects' characteristics from the correlated studies were pooled into a standardized form. The categorization was made into the standard form like the first author's surname, duration of the trial, place of practice, study design, study type, sample size, patients demographics, treatment methodology, follow-up periods, evaluation method (both qualitative and quantitative), statistical analysis, and primary outcome evaluation [16].

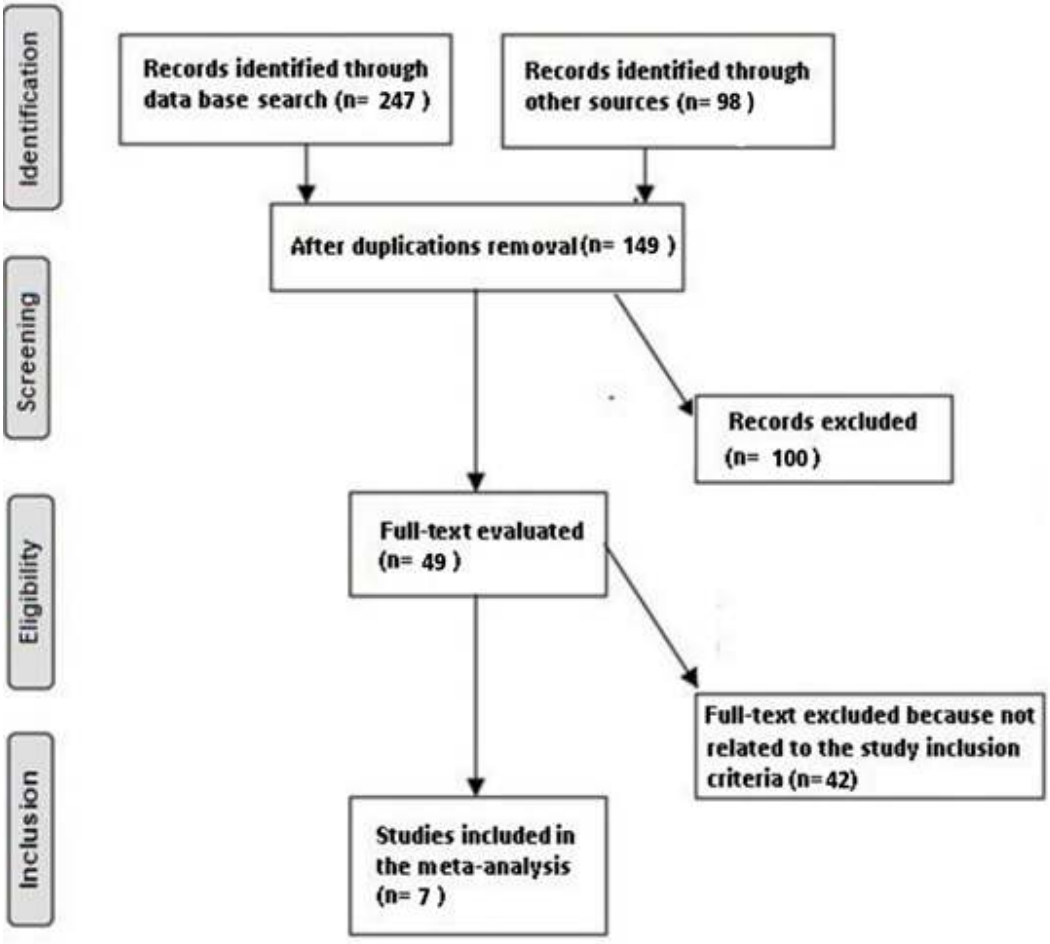

Figure 1. Schematic sketch of the study pattern

Table 1. Search Strategy for Each Database

Database	Search strategy
Pubmed	#1 "osteosarcoma"[MeSH Terms] OR "limb salvage surgery"[All Fields] OR "amputation"[All Fields] #2 "5-year overall survival"[MeSH Terms] OR "osteosarcoma"[All Fields] OR "5-year disease free survival rate"[All Fields] OR " local recurrence rate "[All Fields] #3 #1 AND #2
Embase	'osteosarcoma'/exp OR LSS'/exp OR amputation #2 '5-year OS/exp OR 'ICBG'/exp OR '5-year DFS rate' OR 'local recurrence rate' #3 #1 AND #2
Cochrane library	(osteosarcoma):ti,ab,kw OR (limb salvage surgery) :ti,ab,kw (Word variations have been searched) #2 (amputation):ti,ab,kw OR (5-year overall survival):ti,ab,kw OR (5-year disease free survival rate) :ti,ab,kw OR (local recurrence rate) :ti,ab,kw (Word variations have been searched) #3 #1 AND #2

The quality of the methodology was evaluated by the “risk of bias tool” adopted from the Cochrane Handbook for Systematic Reviews of Interventions Version 9. This meta-analysis recommends that if a study is following the inclusion criteria and the standards mentioned before, any conflicts that arose while collecting the data by two reviewers should be resolved by discussion or by the corresponding author to ensure the quality (Table 2). [17] Only the studies containing data on the use of NAC and non-NAC on COVID-19 subjects hospitalized with

pneumonia were included in the sensitivity test. In comparison, the impact of NAC and non-NAC is interpreted as a subcategory of sensitivity analysis.
A reexamination of the original article addressed for its any inconsistencies.

Table 2. Levels of risk of bias counted in the assessment criteria

Level of risk	Extend of meeting the criteria
Low	If all quality parameters are met
Moderate	If one of the quality parameters is not met/or partially met
High	if one of the quality parameters is not met/ not included

Statistical analysis

This meta-analysis compares the efficacy of NAC versus non-NAC in COVID-19 disease subjects hospitalized with pneumonia by these tools: relative risk or frequency rate and odds ratio (OR) with a 95% confidence interval (CI). The OR was calculated at a 95% CI on a random or fixed effect model using dichotomous method. The range of the (I2) index is established to be from 0 to 100%. The heterogeneity of the I2 index scale is specified as nil, low, moderate, and high as 0%, 25%, 50%, and 75%, respectively. [14] If I2 > 50%, this is considered Random-effect and if I2 < 50%, this is considered Fixed-effect. At the beginning of the evaluation, a subgroup analysis was accomplished by stratifying the initial evaluation for result categories. the result is considered statistically significant if the *p*-value is < 0.05. To evaluate the publication bias quantitatively and qualitatively, the Eager regression test was used (if $p \geq 0.05$). To do this, a logarithmic funnel plot of odds ratios is examined against their standard errors. [16] Reviewer Manager version 5.3 was used to provide the statistical findings and graphs (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark).

Results

There were 247 primary literatures (between 2020 and 2022), and only 7 of them fulfilled the inclusion criteria. [18-24] These 7 studies included 20553 COVID-19 disease patients hospitalized with pneumonia; 2909 were managed with NAC, and 17644 with non-NAC. All studies evaluated the effect of NAC compared to non-NAC in patients with COVID-19 disease who were hospitalized for pneumonia. Table 3 shows the data analyzed from the seven selected studies.

Table 3. Meta-analysis of 7 selected studies and their characteristic data.

Study	Country	Total	N-acetylcysteine	Non- N-acetylcysteine
Faverio, 2022 [18]	Italy	906	585	321
Ramadhan, 2021 [19]	Indonesia	91	75	16
Assimakopoulos, 2021 [20]	Greece	82	42	40
De Alencar, 2021 [21]	Brazil	128	65	63
Avdeev, 2022 [22]	Russia	46	24	22
Taher, 2021 [23]	Iran	92	47	45
Izquierdo, 2022 [24]	Spain	19208	2071	17137
	Total	**20553**	**2909**	**17644**

Management with NAC was insignificantly related to lower days stayed in the ICU (OR, 2.79; 95% CI, -1.11-6.69, $p = 0.16$) with moderate heterogenicity (I2 = 69%), lower death rate (OR, 0.69; 95% CI, 0.40-1.20, $p = 0.19$) with moderate heterogenicity (I2 = 74%), lower need of mechanical ventilation (OR, 0.74; 95% CI, 0.25-2.21, $p = 0.59$) with moderate heterogenicity (I2 = 73%), lower number of patients admitted to ICU (OR, 1.26; 95% CI, 0.26-5.95, $p = 0.77$) with high heterogenicity (I2 = 90%) compared with non-NAC in COVID-19 disease subjects hospitalized with pneumonia. as shown in [Figures 2-5].

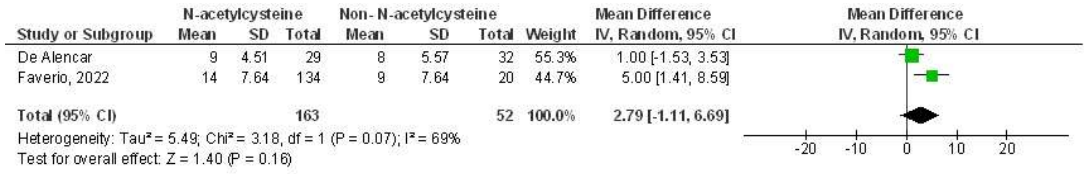

Figure 2. A Forest plot illustration: A comparative effect of NAC and non-NAC in COVID-19 disease subjects hospitalized with pneumonia on days stayed at ICU

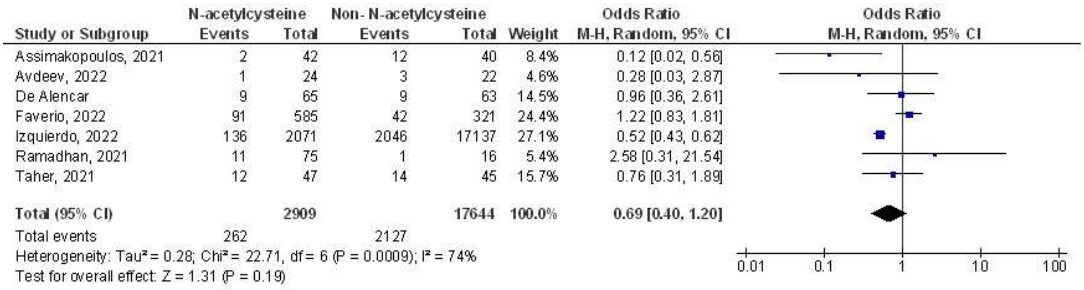

Figure 3. A Forest plot illustration: A comparative effect of NAC and non-NAC in COVID-19 disease subjects hospitalized with pneumonia on number of deaths

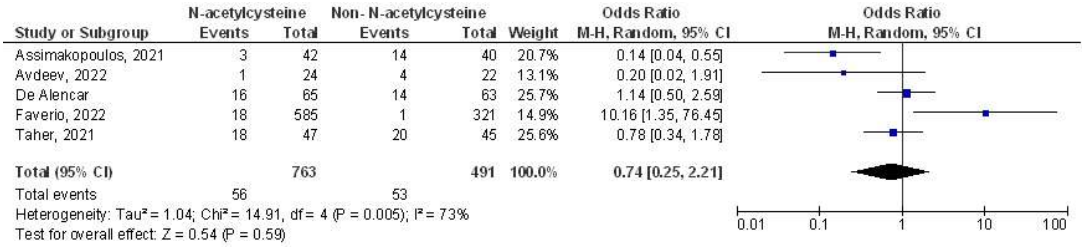

Figure 4. A Forest plot illustration: A comparative effect of NAC and non-NAC in COVID-19 disease subjects hospitalized with pneumonia on the number of patients who needed mechanical ventilation

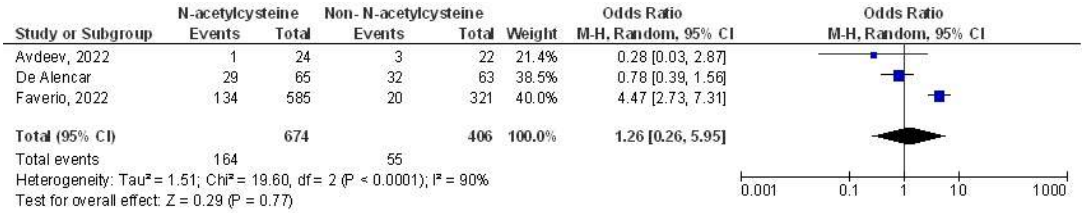

Figure 5. A Forest plot illustration: A comparative effect of NAC and non-NAC in COVID-19 disease subjects hospitalized with pneumonia on the number of patients admitted to ICU

The pooled data did not include items such as group age, ethnicity, or gender. Egger regression analysis funnel plot results during quantitative measurements showed no publication bias (p = 0.89). However, selected randomized association-based studies identified issues such as inadequate methodological tools. No selective reporting bias was identified in this meta-analysis.

Discussion

Glutathione reductase has been found in high levels in the most severely ill patients with COVID-19 disease. Reduced glutathione plays an important role in these cases because it affects the regulation of the immune response at various levels. This mechanism is evident in elderly patients suffering from persistent inflammation that induces cytokine production and oxidative stress. In these patients, a decrease in glutathione increases reactive oxygen species. This can explain the high mortality rate of elderly COVID-19 patients. [24] NAC is known to be a potent antioxidant and has been tested as an adjunct in the treatment of inpatients with COVID-19 disease suffering from pneumonia. [21] Our meta-analysis assessed the efficacy of using NAC versus non-NAC in inpatients with COVID-19 disease suffering from pneumonia in terms of death rate, mechanical ventilation needs, and the number of patients admitted to ICU. Our results show that there is a lower death number using NAC compared to non-NAC. However, this difference was insignificant as the *p*-value was high ($p = 0.19$), but this can be affected by the inclusion of more studies. Our meta-analysis contained only 7 studies that were considered to have a small sample size. Therefore, further studies comparing the effects of NAC versus non-NAC in patients with COVID-19 disease hospitalized with pneumonia should be conducted to validate the results.

Izquierdo, J. L., et al in their study found that oral administration of NAC was associated with improved survival in patients with COVID-19 disease who were hospitalized for pneumonia. Nonetheless, these patients were older and had more comorbidities. [24] Assimakopoulos, S. F., et al. in their study found that administration of NAC in COVID-19 disease patients hospitalized with moderate pneumonia prevents further deterioration while reducing the need for mechanical ventilation. [20] Several hypotheses tried to explain how NAC works against COVID-19 disease. Bourgonje, A. R., et al. in their study showed that hydrogen sulfide H2S plays an important role as a defense factor against COVID-19 disease. [25] Patients with COVID-19 disease have been found to have low serum levels of H2S.

This is negatively linked to inflammatory biomarkers like C-reactive protein and interleukin 6. [26] NAC can induce the endogenous production of H2S which made it a possible cure for COVID-19 disease. [25] COVID-19 disease increases oxidative stress in the body by increasing interleukin 6 and 8 and ROS. [2,6] NAC can restore the intercellular redox imbalance by replenishing the reduced glutathione. NAC provides L-cysteine as a precursor to GSH synthesis. [27] These data support our claim that further research is needed to validate our results and make them significant. Various standard of care protocols may also have influenced the outcome. This is not considered in the studies involved. Further research and analysis are needed to understand the effects of ethnicity, disease severity, drug dosage, and various treatment protocols. And none of the studies included responded to the effects of these research factors. In summary, treatment with NAC is insignificantly lower in mortality, ventilator need, number of patients admitted to the ICU, and days spent in the ICU compared to non-NAC in patients with COVID-19 disease subjects hospitalized with pneumonia.

Limitations

The effect of different treatment protocols was not discussed in this meta-analysis, as no study outlined this factor. Only 7 randomized trials were included in our meta-analysis; 4 of them were considered small and includes less than 100 subjects. The stage and severity of the disease were not disclosed in the studies.

Conclusion

NAC has decreased the days stayed in the ICU, number of deaths, need for mechanical ventilation, and number of patients admitted to ICU in COVID-19 disease hospitalized with pneumonia, although, this difference was insignificant.

Our meta-analysis found that NAC, when used with standard protocol, decreased the days stayed in the ICU, number of deaths, need for mechanical ventilation, and the number of patients admitted to ICU in COVID-19 disease hospitalized with pneumonia, although, this difference was insignificant. The outcome of this meta-analysis should be utilized with caution, as it included only 7 studies. More studies related to the effect of using NAC versus non-NAC in COVID-19 disease patients hospitalized with pneumonia should be made to validate these findings.

List of abbreviations

odd ratio (OR)
confidence intervals (CIs)
reactive oxygen species (ROS)
acute respiratory distress syndrome (ARDS)

References

1. Atefi, N., et al. (2020). "N-acetylcysteine and coronavirus disease 2019: May it work as a beneficial preventive and adjuvant therapy? A comprehensive review study." 25.
2. Rahimi, A., et al. (2021). "The efficacy of N-Acetylcysteine in severe COVID-19 disease patients: A structured summary of a study protocol for a randomised controlled trial." 22(1): 1-3.
3. Huang, C., et al. (2020). "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." 395(10223): 497-506.
4. Dominari, A., et al. (2021). "Bottom-up analysis of emergent properties of N-acetylcysteine as an adjuvant therapy for COVID-19 disease." 10(2): 34.
5. Šalamon, Š., et al. (2019). "Medical and dietary uses of N-acetylcysteine." 8(5): 111.
6. Zhang, R.-H., et al. (2014). "N-acetyl-l-cystine (NAC) protects against H9N2 swine influenza virus-induced acute lung injury." 22(1): 1-8.
7. Shi, Z., et al. (2020). "N-acetylcysteine to combat COVID-19 disease: an evidence review." 16: 1047.
8. Cevik, M., et al. (2020). "Virology, transmission, and pathogenesis of SARS-CoV-2." 371.
9. Santus, P., et al. (2014). "Oxidative stress and respiratory system: pharmacological and clinical reappraisal of N-acetylcysteine." 11(6): 705-717.
10. Sadowska, A. M., et al. (2006). "Role of N-acetylcysteine in the management of COPD." 1(4): 425.
11. Bachh, A. A., et al. (2007). "Effect of oral N-acetylcysteine in COPD–a randomised controlled trial." 14(1): 12-16.
12. Mata, M., et al. (2011). "N-acetyl-L-cysteine (NAC) inhibit mucin synthesis and pro-inflammatory mediators in alveolar type II epithelial cells infected with influenza virus A and B and with respiratory syncytial virus (RSV)." 82(5): 548-555.
13. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting.* Jama, 2000. **283**(15): p. 2008-2012.
14. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* Bmj, 2003. **327**(7414): p. 557-560.
15. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* Journal of clinical epidemiology, 2009. **62**(10): p. e1-e34.
16. Gupta, A., et al., *Obesity is independently associated with increased risk of hepatocellular cancer-related mortality: a systematic review and meta-analysis.* American journal of clinical oncology, 2018. **41**(9): p. 874.
17. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**.

18. Faverio, P., et al. (2022). "Impact of N-acetyl-l-cysteine on SARS-CoV-2 pneumonia and its sequelae: results from a large cohort study." 8(1).
19. Ramadhan, F., et al. (2021). "The Effects of N-Acetylcysteine as Adjuvant Therapy To Reduce TNF-A Level And Increase SPO2/FIO2 Ratio In Improving Hypoxemia In COVID-19 Patients." 9(3): 195-203.
20. Assimakopoulos, S. F., 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." 53(11): 847-854.
21. De Alencar, J. C. G., 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)." 72(11): e736-e741.
22. Avdeev, S. N., et al. (2022). "N-acetylcysteine for the treatment of COVID-19 among hospitalized patients." 84(1): 94-118.
23. Taher, A., et al. (2021). "A pilot study on intravenous N-Acetylcysteine treatment in patients with mild-to-moderate COVID19-associated acute respiratory distress syndrome." 73(6): 1650-1659.
24. Izquierdo, J. L., et al. (2022). "Use of N-Acetylcysteine at high doses as an oral treatment for patients hospitalized with COVID-19." 105(1): 00368504221074574.
25. Bourgonje, A. R., et al. (2021). "N-acetylcysteine and hydrogen sulfide in coronavirus disease 2019." 35(14): 1207-1225.
26. Renieris, G., Katrini, K., Damoulari, C., Akinosoglou, K., Psarrakis, C., Kyriakopoulou, M., ... & Giamarellos-Bourboulis, E. J. (2020). Serum hydrogen sulfide and outcome association in pneumonia by the SARS-CoV-2 corona virus. Shock (Augusta, Ga.).
27. Meyer, A., Buhl, R., Kampf, S., & Magnussen, H. (1995). Intravenous N-acetylcysteine and lung glutathione of patients with pulmonary fibrosis and normals. American journal of respiratory and critical care medicine, 152(3), 1055-1060.