Effectiveness of N-acetylcysteine in treating patients with coronavirus disease 2019 may be in doubt but in uncertainty

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Coronavirus disease 2019 (COVID-19), a pandemic infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the leading cause of morbidity and mortality worldwide in the past 3 years.[1–3] Despite far-advanced prevention strategies, including mask, hand-washing and vaccination, many people still attack by SARS-CoV-2. Most (81%) infected subjects develop mild-to-moderate diseases, presenting fever, respiratory symptoms (cough and sore throat), a loss of taste and/or smell, headache, myalgias and various kinds of gastrointestinal symptoms as nausea, vomiting and/or diarrhea in mild diseases and lower respiratory tract diseases such as shortness of breath with exertion and moderate pneumonia.[4] However, a certain percentage of infected individuals, particularly for those vulnerable to infectious disease pandemic will become severe COVID-19,[5–7] presenting apparent shortness of breast at rest (a respiratory rate of ≥30 breaths/min, an oxygen saturation of ≤93% on room air at sea level of a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of <300 mgHg and subsequently develop critical COVID-19 with evidence of respiratory failure, shock, or multiorgan failure.[4,8,9] Therefore, a prompt and immediate effective treatment may be needed to prevent the occurrence of critical illness, life-threatening status or even mortality.[9,10] Unfortunately, the availability and accessibility of therapeutic agents to COVID-19 are inadequate, given their expensive cost, prescription requirement, and insufficient production capacity to catch up the speed of spread of COVID-19 pandemics, contributing to an urgent need of focusing on repurposing licensed drugs (antiviral and immunomodulating) or agents that had existing clinical or nonclinical toxicology data for the alternative therapeutics to COVID-19.[4,10] A publication in the March issue of the *Journal of the Chinese Medical Association* entitled "Is N-acetylcysteine effective in treating patients with coronavirus disease 2019? A meta-analysis." attempted to discuss the potential candidate (N-acetylcysteine: NAC, a traditional pharmacological effect on promoting respiratory hygiene) by drug repurposing for the treatment of COVID-19,[10] based on its potential antioxidative and anti-inflammatory effects.[11–14]

The authors conducted a systematic review and meta-analysis, including four studies and 355 patients to compare the outcomes between the use and nonuse of NAC in the management of patients with COVID-19.[10] The evaluated outcomes included intubation rate (three studies), oxygenation index (three studies), intensive care unit (ICU) stay (two studies), hospital stay (three studies), and mortality (three studies).[10] The results revealed none of the aforementioned evaluated items showed a statistically significant difference between the use and nonuse of NAC in the management of patients with COVID-19, with odd ratio (OR) of 0.55, 95% confidence interval (CI) 0.16 to 1.89; difference in means (DM) 80.84, 95% CI –38.16 to 199.84; DM –0.74, 95% CI –3.19 to 1.71; MD –1.05, 95% CI –3.02 to 0.92; and OR 0.58, 95% CI 0.23 to 1.45, respectively.[10] The aforementioned clinical observations failed to translate the basic and fundamental benefits of NAC, a precursor of glutathione (GSH), involved in GSH replenishment and containing many physiological and anti-pathological intracellular effects, to clinical effectiveness for the treatment of patients with COVID-19.[11]

NAC works either directly or indirectly on cells facing oxidative stress injury.[11] The former regenerates free form of Cys34 of human serum albumin to provide the main and predominant extracellular antioxidant role and the latter is deacetylated to yield L-cysteine (L-cys) to enhance the production of the rate-limiting enzyme glutamate-cysteine ligase, which is a limited enzyme to synthesize GSH.[11] All react with electrophilic metabolites in the cell nucleus, bind reactive DNA metabolites and block reactive oxidative intermediates,[11] contributing to the major and predominant intracellular effects, as a drug with mucolytic and antioxidant activity, for respiratory diseases and the treatment of acetaminophen poisoning (150 mg/kg intravenous [IV] at the standard practice to work as an approved antidote against acetaminophen intoxication to achieve a 100% efficacy if administered within 8 hours from ingestion).[12–14] Therefore, the role of NAC is worthy of our attention in the management

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of various kinds of inflammatory diseases, contributing to the need to comment the present meta-analysis.

Since the administration of NAC varied greatly in clinical routine practice, and it can be applied via IV, orally (PO) as well as inhalation (3% hypertonic saline and NAC nebulizer therapy).[14] NAC has an extremely safe profile and an excellent oral and topical bioavailability with ability to break the disulfide bonds to depolymerize the mucin and thus reduce the affinity of SARS-CoV-2 for the angiotensin-converting enzyme 2 sites, with subsequently preventing the virus entering into the cell.[11] Therefore, we welcome that the authors would like to explore the thoughtful process based on replicable data from the systematic review and meta-analysis. As shown by authors,[10] NAC is not beneficial for the treatment of patients with COVID-19 with regard to respiratory outcome, mortality, duration of ICU and hospital stay.[10] However, all, except one reports are based on IV form to administer NAC.[10] Therefore, it should be clarifying why the NAC should be administered in the IV form, since oral and inhalation route can be well-tolerated in patients with "mild to moderate" COVID-19 diseases. This hypothesis seemed to be supported by the present meta-analysis, because oral NAC (1.2 g/d) could reduce the intubation rate and mortality.[10] Unfortunately, this finding was obtained from a retrospective study (observation study),[10] which may not reach a high-level evidence to convince the audience.

Additionally, the case number (n = 355) of the present meta-analysis is small.[10] Furthermore, the IV dose of NAC varies greatly among three studies (21 g/d, 40 mg/kg/d, and 1.2 to 1.5 g/d, respectively.[10] It is hard to use "un-uniform" doses of NAC to compare and/or summarize their results. We are relatively doubtful for the in-effectiveness of NAC in the management of patients with COVID-19. At least, we believe that the effectiveness of NAC cannot be unlimitedly extending to all patients with COVID-19 without further large scale studies to investigate it.

Similar to the results made by present meta-analysis,[10] a recent meta-analysis enrolled three randomized controlled trials (RCTs) and five nonrandomized studies with 315 subjects and 20 826 subjects, respectively, and in term of in-hospital mortality, the summary effects of all RCTs and nonrandomized studies were 0.85 of OR (95% CI 0.43-1.67) and 1.02 of OR (95% CI 0.47-2.23), respectively.[15] Need for ICU admission and invasive ventilation was 0.86 of OR (95% CI 0.44-1.69) and 0.91 of OR (95% CI 0.54-1.53), respectively.[15] Based on the results obtained from a meta-analysis, the authors suggested the certainty of evidence about the use of NAC for the treatment of patients with COVID-19 was very low; thus, the authors did not recommend the routine use of NAC for patients with COVID-19 in clinical practice.[15]

Based on the absence of benefits from both meta-analyses,[10,15] it is hard to suggest the routine use of NAC in the management of patients with COVID-19. Furthermore, one study also failed to support the role of NAC for patients with COVID-19, even the study has conducted to use inhalation route.[14] The authors further highlighted the prescription of NAC may be lack evidence-based efficacy and is even a harmful intervention, and of most importance, a non-cost-effective care, and this misunderstanding or un-effective therapeutic choice may burnout the facility of medical care and subsequently result in crisis of medical service.[14] All contribute to reconsideration of need of using NAC in the clinical routine practice.

Although the meta-analyses failed to support the clinical benefits of NAC in the management of patients with COVID-19, some observational studies (real world data) have shown favorable results in patients with COVID-19 receiving NAC treatment.[15] Due to the conflicted data, a lots of uncertainties of NAC effect and the discrepancy between in theory and in practice still bother us. It may be too mature to make a conclusion as in-effectiveness of NAC for the treatment of patients with COVID-19. We should be always in aware of the possibility of misinterpretation.[16,17] The theoretical benefits of NAC may be varied greatly if the prescription routes are different. Unfortunately, this hypothesis is never being tested. To overcome the limitation, much solid evidence based on high-quality studies is needed to test the real effect of NAC for the treatment of patients with COVID-19. We hope to see more and more large scale of prospective randomized trials to evaluate the safety and effectiveness of NAC in the management of patients with COVID-19, although COVID-19 may no longer be considered a catastrophic pandemic.

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