Ekowati et al (2023)
Vol 11(1): 7548
https://doi.org/10.20884/1.api.2023.11.1.7548

Acta Pharmaciae Indonesia:
Acta Pharm Indo
E-ISSN 2621-4520

RESEARCH ARTICLE Open Access

The effectiveness of N-acetylcysteine in alleviating clinical Symptoms of COVID-19 hospitalized patients at Santa Elisabeth Purwokerto General Hospital, Indonesia

Heny Ekowati*, Faradina Qorina Nadzif, Masita Wulandari Suryoputri, Nialiana Endah Endriastuti, Hanif Nasiatul Baroroh

ABSTRACT

Background: COVID-19 has been associated with increased innate immune system activation, leading to increased mucus production, inflammation, and tissue damage. N-Acetylcystysteine (NAC), an antioxidant and mucolytic, has demonstrated potential as a COVID-19 therapy.

Objective: The purpose of this study was to evaluate the effectiveness of NAC on the clinical symptoms of hospitalized COVID-19 patients at Santa Elisabeth Purwokerto General Hospital in Indonesia.

Methods: An observational analytical study design was employed, with data collected from the medical records of hospitalized COVID-19 patients at Santa Elisabeth Purwokerto General Hospital over the period of July 2020 to July 2021. The study included 209 patients who met the eligibility criteria.

Results: The results indicated that the use of NAC affected the clinical symptoms of cough, oxygen saturation (SPO2), and respiratory rate in patients with mild and moderate degrees of COVID-19 patients ($p<0.05$). However, it was found not to affect patients with severe degrees of the disease ($p>0.05$).

Conclusion: This study suggests that NAC may be a useful treatment option for patients with mild and moderate COVID-19. Further research is needed to confirm these findings and determine their effectiveness in severe cases.

Keywords: N-Acetylcysteine, COVID-19, clinical symptoms, effectiveness, Santa Elisabeth Purwokerto Hospital

Introduction

In 2019, the first pneumonia-like disease was reported in Wuhan, Hubei Province. It quickly spread to China, Thailand, Japan, and South Korea. On February 11, 2020, the WHO announced that the disease was caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and renamed Coronavirus Disease 2019 (COVID-19) [1]. As of December 19, 2022, there were 6,709,597 COVID-19-positive cases and 160,398 deaths in Indonesia [2]. Health Service announced 26 further positive cases in Banyumas Regency until November 16, 2022, for a total of 42,131 cases and 1,862 deaths [3]. Patients with COVID-19 generally exhibit pneumonia-like symptoms, including fever, dry cough, tiredness, sore throat, and shortness of breath. In patients with severe symptoms, hyperinflammation resulting in acute lung injury is believed to be the leading cause of death [4].

In the 1960s, N-acetylcysteine (NAC) was introduced as a safe mucolytic drug for respiratory diseases. Since then, it has been used in numerous hospital applications, including treating acute bronchopulmonary diseases, as an antidote for paracetamol intoxication, and as a potent antioxidant. NAC decreases the viscosity of mucus by breaking disulfide bridges between macromolecules [5]. Recently, NAC has been utilized

Laboratory of Pharmacology and Clinical Pharmacy, Department of Pharmacy, Faculty of Health Sciences, Universitas Jenderal Soedirman, Purwokerto 53123, Indonesia

*Corresponding author: Jl Dr. Soeparno Karangwangkal Purwokerto 53123, Indonesia. E-mail: heny.ekowati@unsoed.ac.id

as an adjunct medication for treating SARS-COV-2 infection. The risks, advantages, and effects of using NAC in COVID-19 are evaluated.

NAC contributes to glutathione production, increasing immune function and regulating the inflammatory response [6]. Additionally, it possesses mucolytic, antioxidant, and anti-inflammatory properties. NAC contributes to the synthesis of glutathione (GSH) [7], an antioxidant that inhibits the generation of pro-inflammatory cytokines [8]. NAC downregulates the pro-inflammatory cytokines via suppressing LPS-induced NF-κB activation. This led to decreased expression of IL-6 and reduced levels of IL-1 and TNF-α. NAC controls IL-10 and inhibits inflammatory cascade development [9].

Santa Elisabeth Purwokerto General Hospital, located in Banyumas Regency, serves as a referral center for COVID-19 patients. Since March 2020, the hospital has seen a rise in the number of patients admitted with varying symptoms ranging from mild to severe. NAC has gained popularity among the various treatments used for COVID-19 at this hospital. A study reported that NAC effectively improved the condition of a COVID-19 patient with respiratory failure who has administered NAC through inhalation [7]. Similarly, a study conducted by Ibrahim et al. (2020) demonstrated that administering NAC injections significantly improved the condition of ten severe COVID-19 patients dependent on respirators [10]. Given the promising results seen with the use of NAC, it is imperative to conduct further research at Santa Elisabeth Purwokerto General Hospital to assess the effectiveness of NAC in treating hospitalized COVID-19 patients. This study aimed to evaluate the effectiveness of NAC in alleviating clinical symptoms in COVID-19 patients hospitalized at Santa Elisabeth Purwokerto General Hospital in Banyumas Regency, Indonesia.

Methods

Research design

An observational analytical design was employed in this study. Data were retrospectively collected from the medical records of COVID-19 inpatients from July 2020 to July 2021. Ethical clearance for this study was obtained from the Health Research Ethics Commission, Faculty of Health Sciences, UNSOED, with reference number 325/EC/KEPK/III/2021.

Population and sample

The study population comprised COVID-19 inpatients at Santa Elisabeth Purwokerto General Hospital admitted between July 2020 and July 2021. The study sample consisted of patients who received NAC orally at 600 mg. A total sampling approach was employed to collect data from all eligible members of the population who met the inclusion and exclusion criteria.

The inclusion criteria were: (i) hospitalized patients aged over 18 years, (ii) a diagnosis of COVID-19 with or without comorbidities, (iii) administration of NAC for the treatment of COVID-19 either orally or intravenously, and (iv) availability of complete medical records, including medical record number, patient demographics (name, gender, age), treatment dates (admission and discharge from hospital), primary and secondary diagnoses, PCR swab or rapid-test results, patient-reported symptoms (cough and shortness of breath), clinical examination results [vital signs such as respiratory rate and oxygen saturation (SpO^2)], medical history, history of allergies, medication history, the therapy administered (drug name, preparation, dose, route of administration, and frequency of administration), and patient condition at the time of discharge. The exclusion criteria were COVID-19 hospitalized patients who were pregnant.

Instrument

The present study employed a Case Report Form (CRF) as a tool. The medical records of COVID-19 inpatients at Santa Elisabeth Purwokerto General Hospital were used as the primary source of data and the analysis was conducted based on the inclusion and exclusion criteria mentioned previously.

Analysis

Bivariate analysis was performed to examine the relationship between independent and dependent variables, using paired data. The clinical symptoms of COVID-19 patients were divided into mild, moderate, and severe categories before and after the administration NAC. Both subjective and objective data as well as vital signs were analyzed. The objective data were tested for normality distribution using Kolmogorov-Smirnov and the Shapiro-Wilk test. Numerical scale data such as temperature, respiratory rate, and oxygen saturation were analyzed using the paired T-test if the

Table 1. Sign test for cough in COVID-19 patients

Severity	Positive difference	Negative difference	Ties	P value
Mild	83	0	28	< 0.0001 (n = 111)
Moderate	43	0	31	< 0.0001 (n = 75)
Severe	9	0	14	> 0.180 (n = 23)

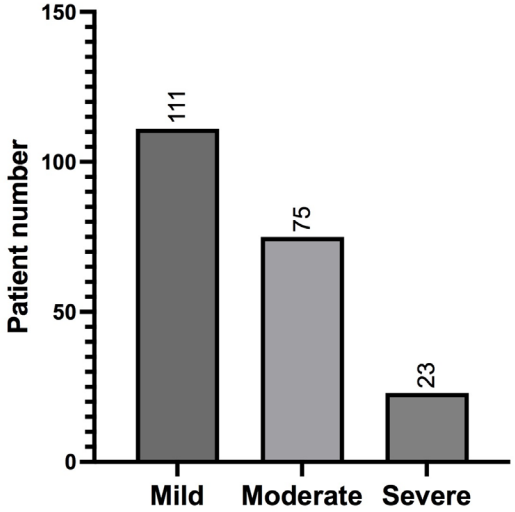

Figure 1. Characteristics of patients based on the severity degree

data were normally distributed, and the Wilcoxon test if otherwise. Data on a nominal scale such as coughing and shortness of breath was analyzed using the Sign Test. The results of these analyses aimed to determine the therapeutic effect of NAC on the clinical symptoms of COVID-19 patients. Patients were grouped according to the severity of their symptoms: mild, moderate, and severe.

Results

From 349 patients, the number of patients who met the inclusion criteria was 209. Figure 1 shows the distribution of patients based on the severity of their illness. The normality test for the severity of the patients revealed that the p-value for oxygen saturation, respiratory rate, and cough was less than 0.05. Data were collected at the time of hospital admission and discharge, and clinical symptoms were assessed after patients had taken NAC for at least 48 hours.

Patients with mild, moderate, and severe symptoms were subjected to statistical analysis to determine the effect of NAC therapy on their clinical symptoms. The cough parameter was evaluated using a Sign test, and patients were classified as coughing (value of 1) or not coughing (value of 2). The positive difference suggested that 83 patients with mild symptoms reported an improvement in their symptoms from coughing to no coughing. Ties indicated that 28 patients did not suffer any symptomatic changes. The positive difference indicated that 43 patients with moderate symptoms received an improvement in their symptoms from coughing to not coughing, while 32 patients did not experience any changes. The positive and negative differences and ties were assessed using a p-value less than 0.05, suggesting a statistically significant difference between the cough parameters before and after NAC treatment (Table 1).

Meanwhile, in patients with severe symptoms, the positive difference indicated that nine patients experienced an improvement in their symptoms from coughing to not coughing. Ties showed that 28 patients did not experience any changes in their coughing symptoms. The p-value was greater than 0.05, indicating no significant difference in the coughing parameters before and after using NAC (Table 1).

The Wilcoxon test was used to analyze the oxygen saturation and respiratory rate parameters. In patients with mild and moderate symptoms, the average oxygen saturation before NAC therapy was 97.12 ± 1.27 and 94.93 ± 4.00, and after treatment, it was 98.01 ± 0.83 and 95.04 ± 8.13 (respectively) ($p < 0.05$), indicating a significant difference in the oxygen saturation before and after NAC therapy (Figure 2, Figure 3). Similarly, in patients with mild and moderate symptoms, the average respiratory rate parameter before therapy was 21.59 ± 2.14 and 23.32 ± 3.58, and after treatment, it was 20.44 ± 1.46 and 21.25 ± 3.37 (respectively) ($p < 0.05$), indicating a significant difference in the respiratory rate value before and after NAC therapy (Figure 2, Figure 3).

In patient with severe symptoms, the average of oxygen saturation before NAC therapy was 83.91 ± 13.69, and after therapy, it was 79.22 ± 23.37 ($p > 0.05$),

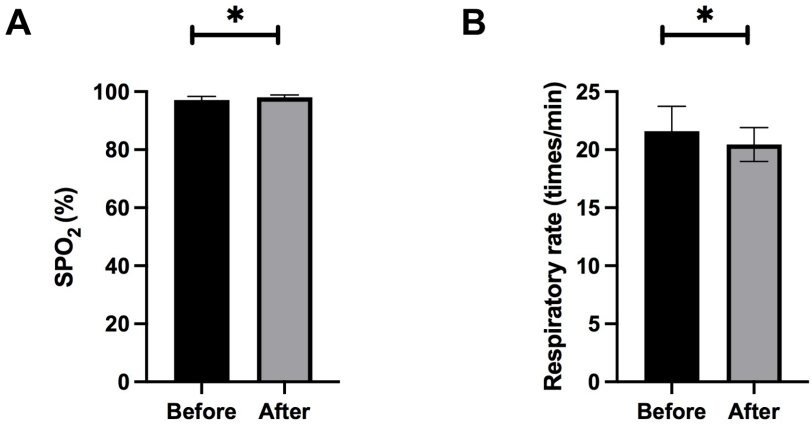

Figure 2. Wilcoxon test in patients with mild degree of COVID-19. (A) Oxygen saturation (SPO_2), (B) Respiratory rate

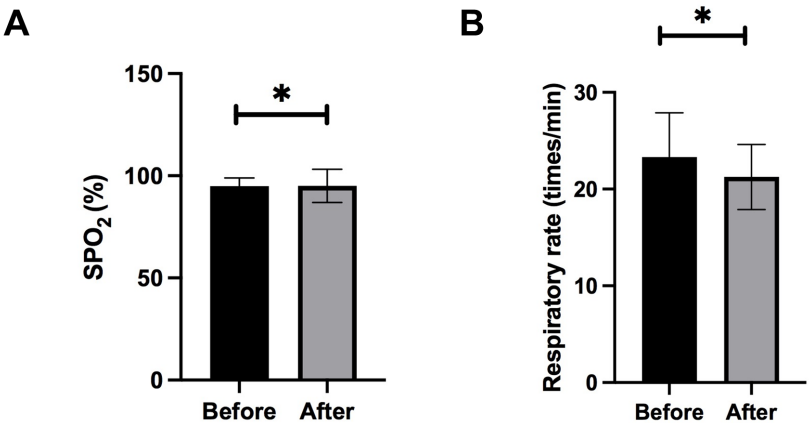

Figure 3. Wilcoxon test in patients with moderate degree of COVID-19. (A) Oxygen saturation (SPO_2), (B) Respiratory rate

indicating no significant difference in the oxygen saturation before and after NAC therapy. Similarly, the average respiratory rate parameter before therapy was 26.70 ± 9.57, and after therapy, it was 26.43 ± 9.57 (p >0.05), indicating no significant difference in the respiratory rate value before and after NAC therapy (Figure 4).

Discussions

Most patients treated in the Santa Elisabeth Purwokerto General Hospital had mild degrees of COVID-19 because this hospital was not the first referral for COVID-19 patients. Hence, the patients treated were mostly those with mild to moderate degrees of disease severity. Patients were grouped into three categories based on severity: mild, moderate, and severe. The classification was made according to the COVID management guidelines 3rd edition 2020, which categorizes patients based on symptoms and oxygen saturation values. A mild degree of disease was defined as a patient having a fever, cough, or sore throat with an oxygen saturation value greater than 95%. A moderate degree was defined as a patient experiencing symptoms of pneumonia, such as a fever, cough, or shortness of breath, with an oxygen saturation value of at least 93%. A severe degree was defined as a patient exhibiting symptoms of pneumonia, such as fever, cough, and shortness of breath, with an oxygen saturation value lower than 93% [11].

Out of a total of 100 patients, 43 patients (43%) were classified as mild, 25 patients (25%) as moderate, and 32 patients (32%) as severe. The most common degree of disease severity in COVID-19-positive patients at the Goeteng General Hospital was mild, which was in line with Rifaldi's study (2021) that found the largest population of COVID-19 positive patients had mild severity, accounting for 77 patients (53%) [12].

Of the 209 patients who met the inclusion criteria, 111 patients (53.11%) had a mild degree of disease severity, which was consistent with the findings of two

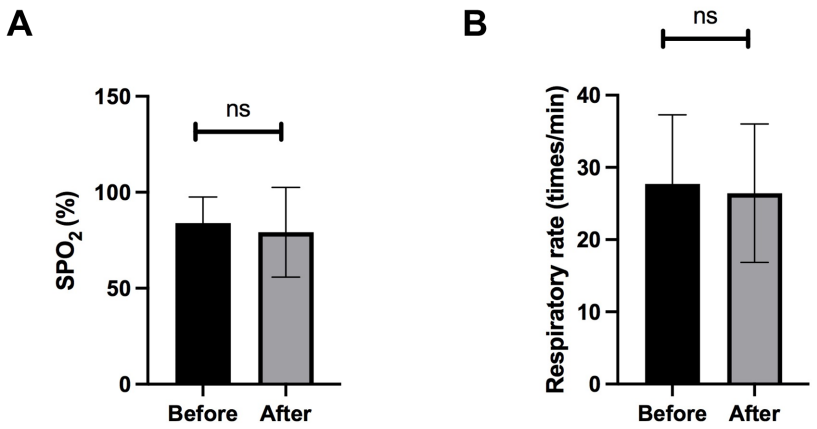

Figure 4. Wilcoxon test in patients with severe degree of COVID-19. (A) Oxygen saturation (SPO_2), (B) Respiratory rate

studies by Qi *et al.* (2021) dan Shoaib *et al.* (2021) who reported that most COVID-19 positive patients had mild degrees of severity [13] [14].

Studies have shown that COVID-19 is associated with a hyperinflammatory state [15] and NAC can help reduce hyperinflammation in COVID-19. Several reports have proposed NAC as a potential treatment for SARS-CoV-2, particularly in patients experiencing ARDS symptoms related to COVID-19 [16] [17]. NAC has been found to inhibit viral replication, modulate pro-inflammatory cytokine production, and inhibit oxidative damage, potentially reducing acute lung damage during COVID-19 [4].

Several reports have documented NAC clinical trials for various purposes. NAC (600 mg, twice daily) reduced influenza symptoms in 262 elderly persons in a double-blinded randomized placebo-controlled clinical trial by Millea (2009). NAC participants had less clinical illness and milder influenza episodes. NAC improved cell-mediated immunity more than placebo [18]. Szakmany et al. (2012) observed no significant effect of intravenous NAC on hospital stay, mechanical ventilation, or organ failure in sepsis and septic shock patients. Early and late NAC administration did not impact oxidative-inflammatory reactions [19].

Taher et al. (2021) conducted a study on NAC therapy for COVID-19, comparing NAC with a placebo in COVID-19 patients, but found no evidence of NAC's potential to treat patients with ARDS associated with COVID-19 [20]. Zhang et al. (2017) reported that although NAC in ARDS patients reduced the length of stay in the ICU, it did not significantly reduce mortality and did not increase oxygen saturation values [21].

In our study, we only evaluated the clinical symptoms of COVID-19 patients due to the incompleteness of their medical records, particularly laboratory data. Most laboratory examinations were performed only once upon admission to the hospital, which limits our ability to assess the impact of NAC therapy on reducing hyperinflammation in COVID-19 patients. A limitation of this study is that NAC was administered concomitantly with other COVID-19 therapy drugs, such as antivirals and symptomatic drugs, so the improvement in clinical symptoms may not solely be attributed to NAC therapy.

Conclusions

The impact of NAC on clinical symptoms was observed in patients with mild to moderate severity, but no significant effect was seen in patients with severe disease severity. The symptoms that were affected by NAC include cough, oxygen saturation, and respiratory rate.

Acknowledgment

We are grateful to Santa Elisabeth Hospital for allowing us to carry out this research.

Funding

We are grateful to Jenderal Soedirman University's Institute for Research and Community Service (LPPM), which funded this study under the UNSOED 2021 Riset Dasar Unggulan grant no. T/654/UN23.18/ PT.01.03/2021.

Author contributions

HE, NEE, MWS, and HNB designed this study; FQN assisted with data collection; HE and FQN wrote the

initial script; FQN assisted with statistical analysis; and all authors contributed to data interpretation and final approval of the manuscript.

Received: 19 December 2022
Revised: 2 February 2023
Accepted: 3 February 2023
Published online: 4 February 2023

References

1. Susilo, A., Rumende, C. M., Pitoyo, C. W., Santoso, W. D., Yulianti, M., Herikurniawan, H., Sinto, R., Singh, G., Nainggolan, L., Nelwan, E. J., Chen, L. K., Widhani, A., Wijaya, E., Wicaksana, B., Maksum, M., Annisa, F., Jasirwan, C. O. M. dan Yunihastuti, E. 2020. Coronavirus Disease 2019: Tinjauan Literatur Terkini, Jurnal Penyakit Dalam Indonesia, 7(1) : 45. https://doi.org/10.7454/jpdi.v7i1.415
2. Satuan Tugas Penanganan COVID-19, 2022. Peta Sebaran COVID 19 di Indonesia. https://covid19.go.id/.
3. Pemkab Banyumas. 2022. Update COVID-19 Banyumas-Pemkab Banyumas Tanggap COVID-19. http://covid19.banyumaskab.go.id/.
4. Shi, Z. dan Puyo, C. A. 2020. N-Acetylcysteine to Combat COVID-19: An Evidence Review, Therapeutics and Clinical Risk Management, 16 : 1047-1055. https://doi.org/10.2147/TCRM.S273700
5. Sahebnasagh, A., Saghafi, F., Avan, R., Khoshi, A., Khataminia, M., Safdari, M., Habtemariam, S., Ghaleno, H.R., Nabavi, S.M. 2020, The prophylaxis and treatment potential of supplements for COVID-19. European Journal of Pharmacology 887: 173530. https://doi.org/10.1016/j.ejphar.2020.173530
6. Wong, K. K., Lee, S. W. H. dan Kua, K. P. 2021. N-acetylcysteine as adjuvant therapy for covid-19 - a perspective on the current state of the evidence, Journal of Inflammation Research, 14 : 2993-3013. https://doi.org/10.2147/JIR.S306849
7. Liu, Yan, Wang, M., Luo, G., Qian, X., Wu, C., Zhang, Y., Chen, B., Leung, E. L. H. dan Tang, Y. 2020. Experience of N-acetylcysteine airway management in the successful treatment of one case of critical condition with COVID-19: A case report, Medicine, 99(42) : e22577. https://doi.org/10.1097/MD.0000000000022577
8. Febriana, L. 2021, Potensi Suplemen dalam Tatalaksana COVID-19, Continuing Medical Education, 48(2) : 93-96. https://doi.org/10.55175/cdk.v48i2.1303
9. Sujana, K. S. dan Maulida, M. 2021. Efektivitas N-Acetylsistein pada Pasien COVID-19," 48(7): 416-418. https://doi.org/10.55175/cdk.v48i7.1458
10. Ibrahim, H., Andras, P., Deane, S., Tyler, L., Zachary, K., Ronald, G., Kinan, Y., Cezar, S. dan Mathew, W. 2020. Therapeutic blockade of inflammation in severe COVID-19 infection with intravenous N-acetylcysteine," Clinical Imunology, 219(108544). https://doi.org/10.1016/j.clim.2020.108544
12. Rifaldi, F. (2021) 'Karakteristik Penderita Covid-19 Di RSUP.Dr Wahidin sudirohusodo Makasar Periode April-juni 2020.
13. Qi, J., He, D., Yang, D., Wang, M., Ma, W., Cui, H., Ye, F., Wang, F., Xu, J., Li, Z., Liu, C., Wu, J., Qi, K., Wu, R., Huang, J., Liu, S. dan Zhu, Y. (2021) "Severity-associated markers and assessment model for predicting the severity of COVID-19: a retrospective study in Hangzhou, China," BMC Infectious Diseases, 21(1), hal. 1-10. https://doi.org/10.1186/s12879-021-06509-6
14. Shoaib, N., Noureen, N., Munir, R., Shah, F. A., Ishtiaq, N., Jamil, N., Batool, R., Khalid, M., Khan, I., Iqbal, N. dan Zaidi, N. (2021) "COVID-19 severity: Studying the clinical and demographic risk factors for adverse outcomes," PLoS ONE, 16(8 August), hal. 1-10. https://doi.org/10.1371/journal.pone.0255999
15. Qin, C., Zhou, L., Hu, Z., Zhang, S., Yang, S., Tao, Y., Xie, C., Ma, K., Shang, K., Wang, W. dan Tian, D.-S. (2020) "Dysregulation of Immune Response in Patients with COVID-19 in Wuhan, China," SSRN Electronic Journal. https://doi.org/10.2139/ssrn.3541136
16. De Flora, S., Balansky, R. dan La Maestra, S. 2020. Rationale for the use of N-acetylcysteine in both prevention and adjuvant therapy of COVID-19," FASEB Journal : 13185-13193. https://doi.org/10.1096/fj.202001807
17. Izquierdo, J. L., Soriano, J. B., González, Y., Lumbreras, S., Ancochea, J., Echeverry, C. dan Rodríguez, J. M. (2022) "Use of N-Acetylcysteine at high doses as an oral treatment for patients hospitalized with COVID-19," Science Progress, 105(1), hal. 1-12. https://doi.org/10.1177/00368504221074574
18. Millea, P.J. 2009. N-Acetylcysteine: Multiple Clinical Applications. Am Fam Physician.80(3):265-269
19. Szakmany, T., Hauser, B., Radermacher, P. 2012. N-acetylcysteine for sepsis and systemic inflammatory response in adults. Cochrane Database of Systematic Reviews. Issue 9. Art. No.: CD006616. https://doi.org/10.1002/14651858.CD006616.pub2
20. Taher, A., Lashgari, M., Sedighi, L., Rahimi-bashar, F., Poorolajal, J. dan Mehrpooya, M. (2021) "A pilot study on intravenous N-Acetylcysteine treatment in patients with mild-to-moderate COVID19-associated acute respiratory distress syndrome," Pharmacological Reports. Springer International Publishing, 73(6), hal. 1650-1659. https://doi.org/10.1007/s43440-021-00296-2
21. Zhang, Y., Ding, S., Li, C., Wang, Y., Chen, Z. dan Wang, Z. (2017) "Effects of N-acetylcysteine treatment in acute respiratory distress syndrome: A meta-analysis," Experimental and Therapeutic Medicine, 14(4), hal. 2863-2868. https://doi.org/10.3892/etm.2017.4891