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N-Acetylcysteine Therapy and Hospital Length of Stay Among SARS-CoV-2 Delta Variant Patients

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Abstract

Background: *The SARS-CoV-2 Delta variant surge was marked by high transmissibility and clinical severity, leading to substantial increases in hospitalizations and mortality. N-acetylcysteine (NAC) has been proposed as an adjunctive therapy for its mucolytic, antioxidant, and anti-inflammatory properties, particularly its ability to inhibit pro-inflammatory cytokines and restore glutathione levels. However, clinical evidence on its impact on hospital length of stay during the Delta variant surge remains limited.* ***Objective:*** *This study aimed to investigate the association between NAC therapy and length of hospital stay (LOS) among patients hospitalized with the SARS-CoV-2 Delta variant.* ***Methods:*** *A retrospective, cross-sectional observational study was conducted at Muhammadiyah Lamongan Hospital in Indonesia. Using purposive sampling, data were extracted from the medical records of 444 adult patients (≥18 years) with PCR-confirmed SARS-CoV-2 infection who were hospitalized between June and August 2021. All subjects received NAC therapy (≥1200 mg/day) as part of their clinical management. LOS was categorized as short (<10 days) or long (≥10 days) based on established clinical criteria.* ***Results:*** *The study population was predominantly male (50.5%), with the largest age group being 56–65 years (32.2%). The most prevalent comorbidities were pneumonia (60.4%), diabetes mellitus (21.0%), and hypertension (6.8%). Regarding clinical outcomes, 81.98% (n=364) of patients receiving NAC therapy were hospitalized for less than 10 days, while 18.02% (n=80) were hospitalized for 10 days or longer.* ***Conclusion:*** *Hospitalized patients with the SARS-CoV-2 Delta variant receiving NAC therapy predominantly had shorter hospital stays (≤10 days). These findings provide preliminary evidence of NAC's potential as a beneficial adjunctive treatment to expedite recovery.*

Keywords: *Acetylcysteine; COVID-19; Length of Stay; SARS-CoV-2 Delta Variant*

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is a global problem, particularly during the surge of the SARS-CoV-2 Delta variant, which is associated with increased transmissibility and greater clinical severity [1,2]. This has led to a substantial rise in hospitalizations and mortality, especially in developing countries such as Indonesia [3,4]. Data indicate 6,451,016 deaths worldwide from 594,367,247 confirmed cases [5]. Indonesia is among the countries adversely affected by COVID-19. In early June 2021, the death rate in Indonesia due to COVID-19 reached 157,420 from 6,323,715 confirmed cases [6]. Clinically, COVID-19 ranges from mild symptoms to severe disease, characterized by fever, cough, shortness of breath, repeated chills, muscle aches, headaches, sore throats, diarrhea, loss of smell, and loss of taste. About 20% of patients become seriously ill, with dyspnea, a reduction in peripheral capillary oxygen saturation (PaO2/FiO2 < 300 mmHg), and an increased oxygen requirement [7,8], emphasizing the need for effective therapeutic strategies to improve clinical outcomes, including reducing the length of hospital stay [9].

Research on the effectiveness of treatments and prevention is extensive because COVID-19 is a new pandemic and its clinical use remains limited. The drugs being tested include antimicrobials, adjunctive therapies, and nutritional supplements. These include: remdesivir, chloroquine, hydroxychloroquine, lopinavir, ritonavir, favipiravir, anticoagulants, azithromycin, bronchodilators, corticosteroids, convalescent plasma, fibrinolytics, interleukin-1 antagonists, interleukin-6 receptor antagonists, Janus kinase inhibitors, vitamin C, vitamin D, vitamin E, vitamin B complex, zinc, selenium, N-Acetylcysteine, quercetin, and melatonin [10, 11]. The role of these supplements in COVID-19 is based on their antioxidant, immunomodulatory, and anti-inflammatory effects. COVID-19 infection is associated with oxidant-antioxidant imbalances, resulting in inflammation and tissue damage. Glutathione is an antioxidant widely found in the body. It helps protect cells from oxidative stress, either directly or indirectly by providing cysteine residues as precursors for glutathione synthesis. One drug with this mechanism of action is N-Acetylcysteine. The dosage used is ≥1200 mg per day, administered orally or intravenously, divided into 2-3 doses. In addition, N-Acetylcysteine may reduce the release of pro-inflammatory cytokines by suppressing lipopolysaccharide activity [12,13].

Despite these potential benefits, current evidence on the clinical effectiveness of NAC in COVID-19 remains limited and inconclusive, particularly among patients infected with the Delta variant. Most studies have focused on severity and mortality outcomes, with limited data on hospitalization-related outcomes such as length of stay [14]. This gap is clinically important because shorter hospital stays are linked to better patient recovery and a reduced healthcare burden. Therefore, this study aimed to evaluate the association between NAC use and length of hospital stay among patients hospitalized with COVID-19 due to the SARS-CoV-2 Delta variant.

MATERIALS AND METHODS

Materials

This study used a retrospective cross-sectional design based on medical records from Muhammadiyah Lamongan Hospital. It included medical records of adult patients with laboratory-confirmed COVID-19 who were hospitalized between June and August 2021, during the SARS-CoV-2 Delta variant surge in Indonesia. Purposive sampling was used to select eligible subjects based on predefined criteria. The inclusion criteria were: (1) patients aged ≥18 years; (2) laboratory-confirmed COVID-19 caused by SARS-CoV-2, diagnosed by polymerase chain reaction (PCR); (3) hospitalization during the June–August 2021 Delta variant surge; and (4) receipt of N-acetylcysteine (NAC) therapy during hospitalization, with or without comorbidities.

Tools

Data were retrospectively extracted from patients' medical records using a structured data extraction form developed for this study. Medical records served as the primary source of clinical and demographic information. The extracted variables included sociodemographic characteristics (age and sex), clinical characteristics (comorbidities, hospitalization status, and NAC therapy administration), and clinical outcomes. The primary clinical outcome was length of hospital stay (LOS), defined as the duration from hospital admission to discharge. LOS exceeding 10 days was categorized as high, whereas LOS below 10 days was classified as low, based on previously established criteria.

Ethical approval was obtained from the Institutional Ethics Committee of LPPM Universitas Muhammadiyah Lamongan (No. 128/EC/KEPK-S2/02/2022). Muhammadiyah Lamongan Hospital granted permission to access medical records. Patient confidentiality was maintained by anonymizing all identifiable patient information during data extraction and analysis.

RESULTS AND DISCUSSION

In this study, 444 COVID-19 patients met the inclusion and exclusion criteria and were included in the analysis based on the availability of complete medical records. As shown in Table 1, the largest proportion of patients was aged 55–65 years (27.1%), while the smallest proportion was observed in patients aged >75 years (2.8%). These findings differ from previous studies conducted by Bulut and Kato (2020) in Germany, which reported that the majority of COVID-19 cases occurred in individuals aged 20–59 years (66,896 cases), whereas patients aged 60–79 years accounted for 18,307 cases [16]. According to Mei Jeng (2020), the rate of infection among children with SARS-CoV-2 appears to be considerably reduced, and symptoms are comparatively mild compared to those in adults [17]. A study shows that children have a low risk of COVID-19, and disproportionate precautions are very detrimental to them [18]. The sex of the patients was predominantly male (50.45%) compared to female (49.54%) (Table 1).

Table 1. Demographic characteristics of the study participants

Characteristic	Category	n	%
Age (years)	<45	120	27.0
	45–55	101	22.7
	56–65	143	32.2
	66–75	65	14.6
	>75	15	3.4
Sex	Male	224	50.5
	Female	220	49.5

Note. Data are presented as *n* (%). Age categories were created based on the distribution of participants' ages in the study population.

In another study in Iran, COVID-19 patients were predominantly male [10]. Huang et al. (2020) also reported that COVID-19 cases were more prevalent among males [11]. In the present study, the predominance of older patients may reflect a higher risk of severe disease requiring hospitalization among middle-aged to elderly individuals, particularly during the Delta variant surge, which has been associated with increased disease severity. Additionally, older patients are more likely to have comorbidities, which may increase the likelihood of hospital admission and prolong clinical monitoring [12][13].

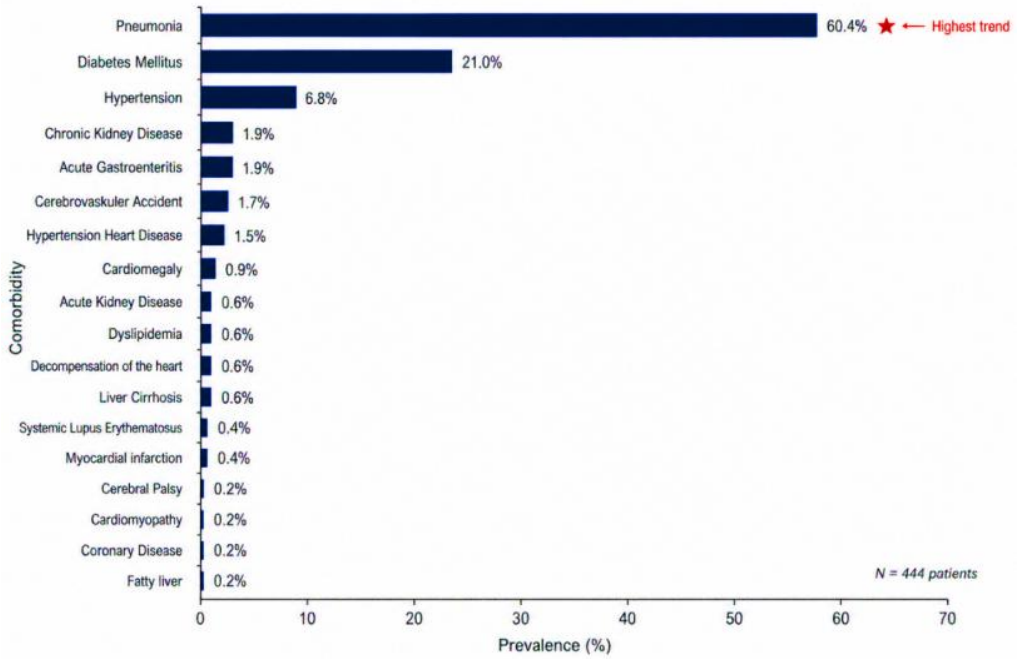

Figure 1. Prevalence of comorbidities among hospitalized COVID-19 patients (N = 444)

According to Figure 1, the most common comorbidities among patients were pneumonia, diabetes mellitus, and hypertension, accounting for 60.4%, 21%, and 6.8%, respectively. This pattern indicates that

respiratory conditions dominate the clinical profile of patients, while metabolic and cardiovascular diseases also contribute substantially to disease burden. Overall, the findings suggest that COVID-19 patients commonly present with pneumonia-related complications alongside chronic comorbidities, highlighting the importance of early detection and comprehensive management of underlying diseases to reduce severity and improve clinical outcomes [14,15]. Diabetic patients often exhibit a pro-inflammatory state, which predisposes them to exaggerated inflammatory responses, such as cytokine storms, during COVID-19. This hyperinflammatory state can lead to acute respiratory distress syndrome (ARDS) and multi-organ failure [16]. Furthermore, elevated levels of inflammatory cytokines, such as IL-6 and IL-10, are linked to worse outcomes in diabetic COVID-19 patients, including prolonged hospitalization and a higher risk of death [17]. Previous studies have reported that hypertension was the most prevalent comorbidity among hospitalized COVID-19 patients [18–20]. A meta-analysis shows that hypertensive patients had a significantly higher mortality rate than non-hypertensive patients, with some studies reporting a 3.48-fold increased risk of death [21].

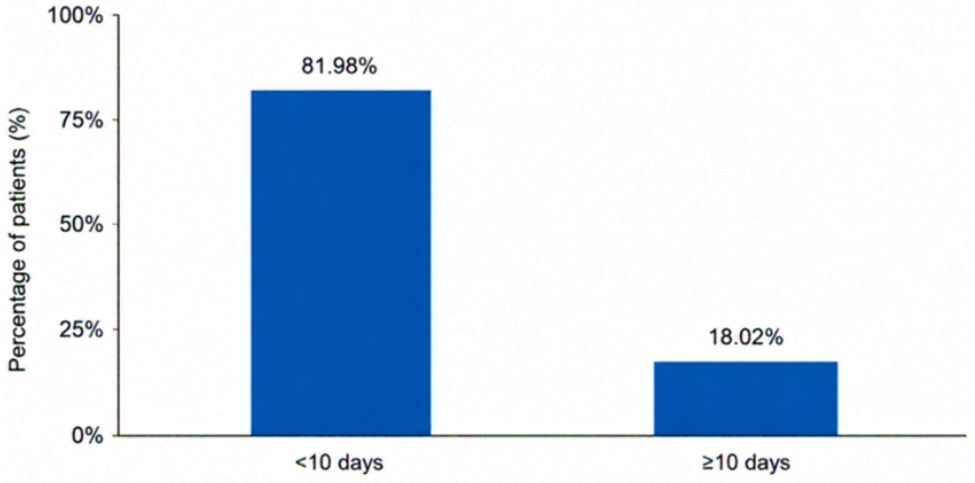

Figure 2. Distribution of patients according to length of stay (N = 444). Most patients (81.98%) had a hospital stay of less than 10 days, whereas 18.02% remained hospitalized for 10 days or longer

Among patients receiving N-acetylcysteine (NAC) in Figure 2, the length of hospitalization was predominantly less than 10 days (81.98%), while only 18.02% had a hospital stay exceeding 10 days. The 10-day cutoff was selected based on previous studies and clinical considerations, indicating that 10 days is a meaningful threshold for distinguishing between shorter and longer exposure periods. These findings show that most patients had a hospital length of stay of less than 10 days. However, because the present study was descriptive in nature and included only a single observation point, no conclusions can be drawn regarding the association between NAC administration and hospitalization duration. A study compared two groups of COVID-19 patients: those receiving standard therapy and those receiving standard therapy plus NAC (1,200 mg/day intravenously). The NAC group had a significantly shorter hospital stay (12.2 days) than the standard therapy group (15.3 days; $p < 0.05$) [22]. Another study involving patients with moderate COVID-19 found that adding NAC to standard care reduced hospital length of stay compared with the control group, though specific durations were not reported [23].

Patient characteristics and comorbid conditions may influence variations in length of hospitalization. Increased creatinine levels in patients with chronic kidney disease, as well as underlying liver disease, have been identified as factors associated with prolonged hospital stay [19,24,25]. In addition, several other factors may contribute to the length of hospitalization among patients with COVID-19. Laboratory and biomarker factors associated with prolonged hospitalization among patients with COVID-19 include elevated inflammatory markers such as C-reactive protein (CRP), D-dimer, ferritin, and neutrophil-to-lymphocyte ratio (NLR) [26], electrolyte imbalances, including hyponatremia on admission [27], and reduced lymphocyte counts, particularly among patients with diabetes mellitus [28]. Furthermore, treatment and healthcare resource-related factors may also influence the length of hospital stay among patients with COVID-19. Early initiation of antiviral therapy has been associated with shorter hospitalization duration [29], whereas inadequate healthcare resources and delays in treatment administration may contribute to prolonged LOS [30].

N-Acetylcysteine is a mucolytic used in chronic obstructive pulmonary disease at a dose of 600 mg/day. In addition to its mucolytic effects, N-acetylcysteine is an immunomodulator. Immunomodulator therapy, such

as N-acetylcysteine, is needed to reduce multi-organ dysfunction and the use of mechanical ventilation [31]. Several studies have shown that administering N-acetylcysteine is beneficial for COVID-19 patients by suppressing pro-inflammatory cytokine production, inhibiting viral replication, and acting as an antioxidant to reduce inflammation [32–35]. NAC also reduces pro-inflammatory cytokine levels, including TNF-α, IL-6, and IL-1β, which contribute to systemic inflammation and organ damage [36,37]. In patients with acute respiratory distress syndrome (ARDS), NAC has been shown to alleviate hypoxemia by improving the SpO_2/FiO_2 ratio, indicating enhanced blood oxygenation [38,39].

CONCLUSION AND SUGGESTION

This study evaluated the association between N-acetylcysteine (NAC) administration and length of hospital stay (LOS) among 444 patients infected with the SARS-CoV-2 Delta variant. The results showed that a significant majority of patients (81.98%) who received NAC therapy had a LOS of less than 10 days, while only 18.02% remained hospitalized longer. These findings suggested that the antioxidant and anti-inflammatory properties of NAC, including its ability to inhibit pro-inflammatory cytokines, may have contributed to improved clinical recovery and shorter hospital stays during the Delta variant surge.

Despite these promising outcomes, the interpretation of the results was limited by the study's retrospective, descriptive design and the lack of a non-NAC comparison group. Consequently, it was suggested that further well-designed analytical investigations, particularly randomized controlled trials, be conducted to definitively establish the clinical effectiveness and therapeutic role of NAC as an adjunctive treatment. Furthermore, future research was recommended to investigate the impact of different dosages and routes of administration to optimize NAC protocols and improve clinical outcomes in COVID-19 management.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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