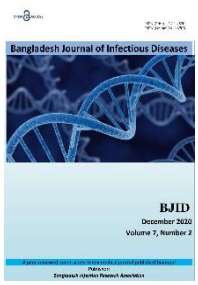
OPEN ACCESS Freely available online
http://www.banglajol.info/index.php/BJID/index
**Perspective**
**Bangladesh Journal of Infectious Diseases**
***June 2021, Volume 8, Number 1, Page 50-52***
ISSN (Online) 2411-670X
ISSN (Print) 2411-4820
DOI: https://doi.org/10.3329/bjid.v8i1.49980




# Non-steroidal anti-inflammatory drugs amid COVID-19 pandemic: An ally or an enemy?

Azhar Hussain[1], Jasndeep Kaler[2], Sohail Kumar[3], Dua Azim[4], Sundus Nasim[5]

[1]DHA., MBA, Medicine, Franklin University, Ohio, USA; [2]BS, Medicine, Xavier University School of Medicine, Oranjestad, Aruba; [3]MBBS, Internal Medicine, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan; [4]MBBS, Internal Medicine, Dow Medical College, Dow University of Health Sciences, Karachi, Pakistan; [5]MBBS, Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan

[**Received:** 29 October 2020; **Accepted:** 2 April 2021; **Published:** 1 June 2021**]**

**Abstract**

As the current global pandemic of the novel coronavirus diseases 2019 (COVID-19) continues to rage, the scientific and medical worlds are working to establish an effective therapy against the illness. Recently questions regarding non-steroidal anti-inflammatory drugs (NSAIDs) as a potential therapeutic option for COVID-19 have surfaced. While some studies hint towards the possible benefit of NSAIDs against SARS-CoV-2 infection, the current body of evidence also sheds light on the potential risk of using NSAIDs in COVID-19 patients. Thus, the available literature does not provide conclusive evidence for or against the use of NSAIDs for treating COVID-19 patients. Given the limited data available, we suggest cautionary approaches for the public to avoid possible harm until further evidence emerges. NSAIDs should not be used as the first-line agents for COVID-19 unless under medical supervision. Moreover, patients with chronic inflammatory conditions should continue the NSAIDs as per their regular prescriptions. [*Bangladesh Journal of Infectious Diseases, June 2021;8(1):50-52]*

**Keywords:** SARS-CoV-2; NSAIDS; ACE2; COVID-19

**Correspondence:** Sundus Nasim, Internal Medicine, Dow University of Health Sciences, Karachi, Pakistan; Mailing address: 17 Lincoln Court, Coram, NY 11727; **Email:** sundusnasim9@gmail.com; **Contact number**: +16315041798
**Conflict of interest:** The authors declare that they have no conflict of interest.
**Funding agency:** The study was not funded by any authority.
**Contribution to authors:** All the authors contributed equally.
**How to cite this article:** Hussain A, Kaler J, Kumar S, Azim D, Nasim S. Non-steroidal anti-inflammatory drugs amid COVID-19 pandemic: An ally or an enemy? Bangladesh J Infect Dis 2021;8(1):50-52


## Introduction

The current coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is undoubtedly the most significant global health concern of our time. Clinicians need to be vigilant as discoveries about the virus are emerging continuously. In addition to uncertainties pertaining to infection pathophysiology and ramifications, rising concerns regarding the use of widely-utilized medicines such as non-steroidal anti-inflammatory

drugs (NSAIDs) in the face of the pandemic have resulted in considerable speculations. On 16 March 2020, the Belgian Federal Agency for Medicines and Health Products released a statement saying 'It is well-known that NSAIDs and corticosteroids can lead to serious complications'. Moreover, Olivier Véran, the French Minister of Health, has complicated matters by advising people against the use of anti-inflammatory drugs like ibuprofen, suggesting that the NSAIDs could aggravate the COVID-19 infection. However, the current evidence does not confirm that the use of NSAIDs puts COVID-19 patients at a risk of more severe diseases.

**Role of NSAIDs against SARS-CoV-2**

NSAIDs work by inhibiting the cyclooxygenase (COX) isoenzymes, COX-1 and COX-2, which converts arachidonic acid (AA) into prostaglandins, thromboxanes, and leukotrienes. These AA derivatives protect the body against foreign bodies and regulate the immune mechanism of the host by mediating the inflammatory response.

The transmissibility of SARS-CoV-2 is via respiratory droplets through coughing, sneezing, or by direct contact with the infected individual. SARS-CoV-2 enters the alveolar epithelium cells through the angiotensin-converting enzyme 2 (ACE2) receptor. Clinically, SARS-CoV-2 mediated immune response is deemed two-phased[1]. The first phase is the immune defense-mediated protective phase that consists of incubation and non-severe stages of viral illness requiring the body's defense system to eliminate the virus and halt the progression of the disease. The second phase is the inflammation-driven destructive phase that comprises a severe stage characterized by lung damage due to the release of specific inflammatory mediators. These mediators, in turn, stimulate the alveolar macrophages to release an excess amount of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tissue necrosis factor-alpha (TNF- α), leading to a phenomenon known as the cytokine storm in COVID-19 patients. Thus, lung inflammation is the major cause of potentially fatal respiratory illness at a severe stage[1]. Therefore, it seems logical to suggest that the use of anti-inflammatory drugs such as NSAIDs in the initial phase may block the body's self-defence, resulting in rapid exacerbation of the viral illness. However, the use of anti-inflammatory drugs in later stages may benefit lung damage[2]. Currently, there is conflicting research as to how beneficial or detrimental NSAIDs may be to a COVID-19 positive patient.

An intriguing study conducted in 2006, demonstrated the antiviral activity of indomethacin against SARS-CoV-1 and canine coronavirus (CCoV), indicating its potency against SARS infections. The study also showed that this antiviral effect of indomethacin was not dependent on COX inhibition but rather on the blockade of viral RNA synthesis[3]. A widely prescribed NSAID, ibuprofen, was found to decrease IL-6 levels in human tissues and sputum[4,5]. Consequently, several clinical trials to test the efficacy and safety of anti-IL-6 agents against SARS-CoV-2 are actively recruiting. Another recent research has elucidated the antiviral effect of indomethacin against SARS-CoV-2 infected African monkey[6]. However, no such evidence supports its antiviral activity against SARS-CoV-2 in humans. Moreover, Naproxen, a potential COX-2 inhibitor, has previously shown to inhibit the nucleoprotein of the Influenza A virus[7]. Based on its anti-inflammatory and antiviral activity, a clinical trial is currently underway to evaluate its effectiveness when added to standard therapy in patients with severe COVID-19 admitted in ICU in terms of mortality at day 30[8].

Contrary to the afore-mentioned studies hinting towards the possible benefit of NSAIDs against SARS-CoV-2 infection, the current body of evidence also sheds light on the potential risk of using NSAIDs in COVID-19 patients. A review regarding NSAIDs suggests that the use of NSAIDs in patients with respiratory tract infections is associated with an increased risk of complications including prolonged illness, pleural effusions, complicated pneumonia, peritonsillar abscess, and disseminated infection[9].

The authors of the review hypothesized that such complications arise as a result of the inhibitory effect of NSAIDs on COX enzymes, which in turn inhibits resolvins and lipoxins synthesis and also reduces the infiltration of neutrophils into the lungs, ultimately delaying the healing process. Additionally, acute respiratory infections are known to be associated with an increased risk of myocardial infarction and stroke, and the intake of NSAIDs during the disease is associated with an even higher risk of developing these complications[10-11].

Nonetheless, a current study has implied that the use of ACE inhibitors and angiotensin-receptor blockers (ARBs) in COVID-19 patients might result

in poorer COVID-19 outcomes. The authors also stressed that ibuprofen might cause upregulation of the ACE receptors, the possible entry point of the SARS-CoV-2 virus[12]. Another study on diabetic rat models assessing the effects of ibuprofen on cardiac fibrosis demonstrated that the said drug increased the expression of ACE2 receptors[13]. It is, therefore, plausible that increased expression of ACE2 in patients utilizing NSAIDs could lead to a higher viral load of the SARS-CoV-2 and subsequent poorer outcomes. Moreover, there is speculation that the upregulation of ACE2 receptors may also facilitate the initial probability of contracting COVID-19.

## Conclusion

To summarize, NSAID therapy for COVID-19 patients can be considered a double-edged sword due to its dual nature. Whether it upregulates ACE2 receptors and exacerbates the lung damage resulting in poorer clinical outcomes or mitigates the cytokine storm resulting in improved clinical outcomes in COVID-19 patients, needs to be further investigated. While some researchers suggest NSAID therapy should continue, others suggest ceasing it until further evidence emerges to ensure the consequences of the medication. Nonetheless, it is imperative to mention that according to World Health Organization (WHO), at present, there is no evidence of severe adverse events, acute health utilization, long-term survival, or quality of life in patients with COVID-19 as a result of the use of NSAIDs[14].

Awaiting further researches, we suggest cautionary approaches for the public to avoid possible harm, as the existing literature does not currently provide conclusive evidence for or against the use of NSAIDs in the treatment of COVID-19 patients. NSAIDs should not be used as the first-line agents for COVID-19 unless under medical supervision. However, immunosuppressive drugs with well-established efficacy could be employed to manage the symptoms in critical stages of the infection cycle. We also suggest that patients with chronic inflammatory conditions should continue the NSAIDs as per their regular prescriptions.

## References


1. Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ. 2020;27:1451-4
2. Fukunaga K, Kohli P, Bonnans C, Fredenburgh LE, Levy BD. Cyclooxygenase 2 plays a pivotal role in the resolution of acute lung injury. J Immunol. 2005;174:5033-9.
3. Amici C, Di Caro A, Ciucci A, Chiappa L, Castilletti C, Martella V, et al. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther. 2006;11:1021-30.
4. Gallelli L, Galasso O, Falcone D, Southworth S, Greco M, Ventura V, et al. The effects of nonsteroidal anti-inflammatory drugs on clinical outcomes, synovial fluid cytokine concentration and signal transduction pathways in knee osteoarthritis. A randomized open label trial. Osteoarthr Cartil. 2013;21:1400-8.
5. Chmiel JF, Konstan MW, Accurso FJ, Lymp J, Mayer-Hamblett N, VanDevanter DR, et al. Use of ibuprofen to assess inflammatory biomarkers in induced sputum: Implications for clinical trials in cystic fibrosis. J Cyst Fibros. 2015;14:720-6.
6. Xu T, Gao X, Wu Z, Selinger DW, Zhou Z. Indomethacin has a potent antiviral activity against SARS CoV-2 in vitro and canine coronavirus in vivo. bioRxiv. 2020.
7. Lejal N, Tarus B, Bouguyon E, Chenavas S, Bertho N, Delmas B, et al. Structure-based discovery of the novel antiviral properties of naproxen against the nucleoprotein of influenza A virus. Antimicrob Agents Chemother. 2013;57:2231-42.
8. Efficacy of Addition of Naproxen in the Treatment of Critically Ill Patients Hospitalized for COVID-19 Infection. ClinicalTrials.gov. 2020. [Accessed 10 July 2020]. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04325633.
9. Voiriot G, Philippot Q, Elabbadi A, Elbim C, Chalumeau M, Fartoukh M. Risks Related to the Use of Non-Steroidal Anti-Inflammatory Drugs in Community-Acquired Pneumonia in Adult and Pediatric Patients. J Clin Med 2019;8:786.
10. Wen YC, Hsiao FY, Chan KA, Lin ZF, Shen LJ, Fang CC. Acute Respiratory Infection and Use of Nonsteroidal Anti-Inflammatory Drugs on Risk of Acute Myocardial Infarction: A Nationwide Case-Crossover Study. J Infect Dis 2017;215:503-9.
11. Wen YC, Hsiao FY, Lin ZF, Fang CC, Shen LJ. Risk of stroke associated with use of nonsteroidal anti-inflammatory drugs during acute respiratory infection episode. Pharmacoepidemiol Drug Saf. 2018;27:645-51.
12. Fang L, Karakiulakis G, Roth M. Antihypertensive drugs and risk of COVID-19? - Authors' reply. Lancet Respir Med. 2020;8:e32-3.
13. Qiao W, Wang C, Chen B, Zhang F, Liu Y, Lu Q, et al. Ibuprofen attenuates cardiac fibrosis in streptozotocin-induced diabetic rats. Cardiology. 2015;131:97-106.
14. The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19. World Health Organization. 2020. Available at: https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19. [Accessed 10 July 2020].