REVIEW ARTICLE

Efficacy of Paracetamol or Ibuprofen in The Management of COVID-19 Fever: A Systematic Review

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ABSTRACT

The Global outbreak of COVID-19 pandemic affected almost all countries and territories worldwide. The outbreak was first identified from Wuhan, China, in December 2019 and was declared a pandemic in March 2020. Virus incubation time is usually 7 days and initial symptoms includes fever, cough, flu, muscle fatigue and difficulty in breathing. Ibuprofen and paracetamol are the two most commonly used over the counter (OTC) drugs to treat fever due to COVID-19. Some researchers discouraged the use of ibuprofen initially due to possible adverse effects related with longevity of infection, increased morbidity, and mortality rate. This study aimed to compare the effectiveness of paracetamol and ibuprofen as anti-pyretic drugs to treat fever caused in COVID-19 infection. A systematic review of major databases i.e., PubMed, Cochrane library, Web of Science, Google scholar and ClinicalTrials.gov was performed, to screen the studies conducted on managing fever using paracetamol and ibuprofen. Review of the selected articles based on the inclusion/exclusion criteria was performed by two independent researchers. The titles of selected publications were screened for relevance to the preset criteria followed by review of the abstracts. Finally, the full-length articles were evaluated for the final selection of studies to be included. Outcomes of use of ibuprofen and paracetamol were estimated by analyzing selected case control and cohort studies. Overall, eleven observational studies were selected for the compilation of systematic review, based upon the preset inclusion/ exclusion criteria. All studies included adult COVID-19 patients both male and female from different age groups. Paracetamol users were compared with ibuprofen users and no adverse effects of ibuprofen were found related to longevity of infection, complications, increased mortality rate and ventilation support requirement, when treating fever or pain caused by COVID-19. However, further studies and randomized control trials need to be conducted to assess and compare the effectiveness of these drugs to manage fever caused by coronavirus disease.

Key Words: *COVID-19, COVID-19 Management, Ibuprofen, Paracetamol, Systematic Review.*

Introduction

Around the globe the emergence of new viral diseases has been a burden to the economy and health. The cases of unknown upper respiratory tract infection flooded the hospitals of Wuhan, China in December 2019.[1] The causative agent for this disease was identified as a novel coronavirus, later named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and the disease was known as coronavirus disease or COVID-19[1]. Later, several cases of COVID-19 were reported throughout the world and was declared a global pandemic by the World Health Organization (WHO) in March, 2020.[2] Virus usually takes about seven days to incubate and initial symptoms include fever, sore throat, cough, headache, fatigue, diarrhea and loss of smell/taste.[3,4] In fact, as many as 45–89% of adult patients suffering from COVID-19 report fever, even with mild to moderate disease.[5,6] There are few antipyretics over the counter available, among those ibuprofen and paracetamol are most commonly used. Ibuprofen belongs to NSAIDs, a class of drugs which includes anti-inflammatory properties. Although, paracetamol has anti-pyretic characteristics, but it has no antiplatelet and anti-inflammatory properties like NSAIDS.[7] NSAIDs/ibuprofen could lead to high expression of angiotensin-converting enzyme 2 (ACE-2) receptors and hence they can result in a

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superior infection, that is why paracetamol was also recommended in place of NSAIDs/ibuprofen.[8]

The debate around the usage of ibuprofen for patients of COVID-19 was ignited by the reporting of adverse effects among four young patients, without any previous morbidity, who had used ibuprofen to relieve COVID-19 fever.[9] The French health minister also cautioned the public against ibuprofen use as an antipyretic during COVID-19.[9] This led to an eighty percent decrease in ibuprofen use for COVID-19 fever in France. In addition, Randomized Controlled Trials (RCTs) conducted showed that the use of ibuprofen for the treatment of respiratory infection related symptoms could possibly be a factor in prolonging the duration of symptoms and therefore, the recommendation for ibuprofen use for such infections should be withdrawn.[10] As a result, paracetamol was preferred for treating COVID-19 fever, rather than ibuprofen and other NSAIDs.[8] However not only the WHO, but also the Healthcare Products Regulatory Agency UK and the Italian Society for Pharmacology later reversed the statements against ibuprofen prescription to COVID-19 patients, owing to absence of any conclusive evidence against the use of ibuprofen.

This study aims to compare the effectiveness of paracetamol and ibuprofen for managing fever caused by COVID-19.

Methodology

The current Systematic Review has employed the criteria included in the Preferred Reporting Items for Systematic Review (PRISMA; Figure 1). The protocol for this review was published in the International Prospective Register of Systematic Reviews, PROSPERO (Registration number CRD42020198538) (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020198538).

Inclusion Criteria

1. Studies on hospitalized COVID-19 patients
2. Studies on infected individuals aged 18 years and above
3. Clinical studies published in English only
4. Studies published between December 2020 and June 08, 2022
5. Observational studies

Exclusion Criteria

1. Studies on pregnant women and children
2. Studies published in languages other than English or studies on animals.

Databases used and Strategy for Data Synthesis

The review was based on search results obtained from the databases of the Google Scholar, ClinicalTrials.gov, Web of Science, Cochrane Library and MEDLINE and using the search strategy previously published in the protocol. Each database was systematically searched for the three main concepts of COVID-19, ibuprofen, and paracetamol, using synonyms of the three terms. Explicit search strategy has already been published on PROSPERO (Registration no: CRD42020198538).

The studies thus retrieved were all exported to Microsoft Office 365 Excel (Microsoft Corporation, USA) file. After the process of removing the duplicates, screening the titles, abstracts, and full text articles was completed by two reviewers, by using the inclusion/exclusion criteria as mentioned above. The full text articles were assessed for the quality of evidence according to the Quality assessment criteria (Table 1). Results shared by the two independent reviewers were compared and disagreements were resolved by seeking advice of the third reviewer.

Study selection process

The search of the Google scholar, ClinicalTrials.gov, MEDLINE, Web of Science databases and Cochrane Library yielded a total of 1,069 publications. Seventy-one, duplicate records were removed to yield a total of 998 publications. The titles of the remaining 998 publications were screened for relevance to research topic by the two independent reviewers and 926 were excluded. Remaining 72 publications were reviewed for abstracts and 40 studies were excluded due to non-relevance to the subject, only being commentaries or summaries of available treatments with just a passing reference to the treatment of fever and pain in COVID-19. Thirty-two full text articles were assessed for inclusion in the final stage of the review; of which only eleven studies were found eligible to be included in the final review. Reasons for non-inclusion are as follows: some of the publications explained the underlying mechanism of action of ibuprofen and paracetamol describing how they produce their effects in COVID-19. Only those studies were selected which investigated the effectiveness of either NSAIDs/ibuprofen or paracetamol or compared the effectiveness of these

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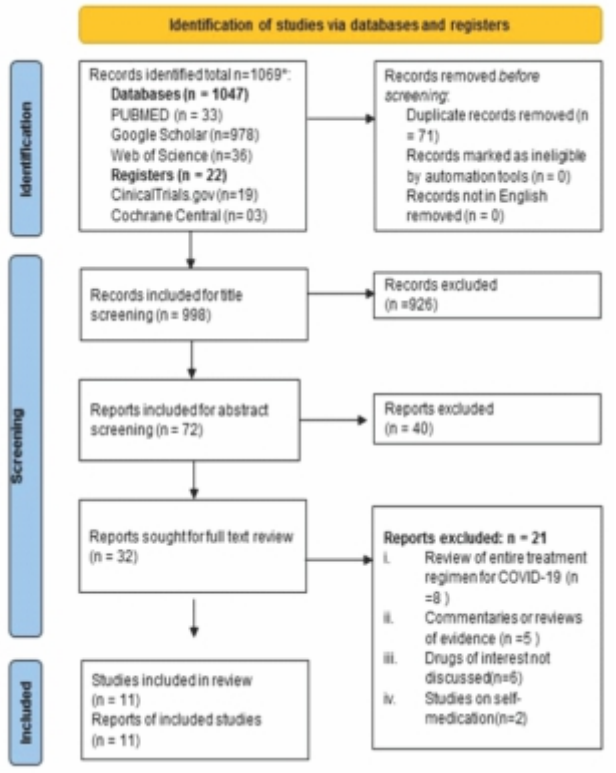
two drugs.

Risk of bias assessment

The criteria of risk bias assessment for observational studies, was used (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). Participation rate was 50%, research question and population were clearly defined, and inclusion/exclusion criteria were explicitly described in all of studies. In all of the studies, sample size calculation was not clearly defined along with power description (Table I).

Figure 1: Flowchart Diagram for Systematic Review on Efficacy of Paracetamol or Ibuprofen in the Management of COVID-19 Fever



Results

Results of all selected/screened studies are given in table 2. In the Danish Cohort, NSAID user were identified by being prescribed with NSAID/ibuprofen from 30 days before being diagnosed with COVID-19 infection.[11] The filling of the prescription did not imply that the patients had taken the medicine as well. However, it is outweighed by the large sample size of 9,236 individuals in the study. In the study conducted by Bruce *et al.*, 2020,[12] sample information was extracted from the COPE (COVID-19 in geriatric population) study, and it analyzed the intake of NSAIDs/ibuprofen in patients among 65, 65-79 and 80 years or more in age. Despite their dissimilarities all the included studies report that the practice/intake of NSAIDs/ibuprofen does not have a significant effect on the death rate and stay in hospital.

In the South Korean cohort, the association of NSAIDs/ibuprofen and adverse clinical outcomes was analyzed in 1,824 hospitalized COVID-19 patients.[13] NSAID/ibuprofen users had a higher proportion of adverse outcomes including in hospital deaths, ICU admissions, use of mechanical ventilation and sepsis compared to the non NSAID users. In another study conducted on Danish cohort of 4,002 individuals, 264 patients were identified as ibuprofen users. Based on the time of diagnosis of COVID-19 infection, the patients were divided into higher than fourteen days vs less than or equal to fourteen days before diagnosis.[14] No significant association was found between ibuprofen use and 30-day severe COVID-19 infection complications defined as severe respiratory complications, ICU admission or death.

Another study conducted on two cohorts consisting of current NSAID users and nonusers, found no evidence for COVID-19 related deaths in both cohorts.[15] To characterize the demographics, clinical symptoms, the course of treatment, and stay in hospital, patients (n=307) were followed after being discharged from hospital.[16] Estimated length of stay in hospital due to COVID-19 infection was found to be 5.59 days longer for patients receiving supportive care (NSAIDs/ibuprofen & Paracetamol) than for those receiving azithromycin + hydroxychloroquine or hydroxychloroquine alone.

Rinott *et al.*,2020 in their retrospective study, specifically classified patients into Paracetamol and Ibuprofen users.[17] In Abu Esba *et al.*, 2021 study, the NSAID users were classified into acute and chronic users of NSAIDs/ibuprofen, to assess the effect of NSAIDs/ibuprofen use. Neither of the NSAID users' group showed any increase in risk of mortality or the hospital admission, increase in length of stay or time to improvement.[18] A study conducted on a large UK cohort, compared the severity and susceptibility of COVID-19, among NSAIDs/ibuprofen using patients and paracetamol users. No association was found

Table I. Risk of Bias Assessment according to the criteria of US National Institute of Heart, Lung and Respiratory Diseases (Low Risk ✓High risk ✕Unclear (Not reported=NR, cannot determine=CD, Not Available=NA)

No.	Criteria	Lars Christian Lund; 2020: Denmark	Eilidh Bruce;2020: UK	Han Eol Jeong;2020: South Korea	Kristian Kragholm;2020: Denmark	Angel YS Wong; 2021:UK	Mary EyramAshinyo;2020: Ghana	Ehud Rinott, 2020: Israel	Laila Carolina Abu Esba;2021: Saudi Arabia	Joht Singh Chandan;2021: UK	Justin T. Reese:2021: USA	Heather M. Campbell;2022: USA
1.	Was the research question or objective in this paper clearly stated?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2.	Was the study population clearly specified and defined?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
3.	Was the participation rate of eligible persons at least 50%?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
4.	Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
5.	Was a sample size justification, power description, or variance and effect estimates provided?	Unclear	unclear	unclear	Unclear	unclear	unclear	unclear	unclear	✓	unclear	unclear
6.	For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	✓	✓	✓	✓	✓	✕	✕	✓	✓	✓	✓
7.	Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

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8.	For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	✓	✓	✓	✓	✗	✓	✓	✗	✗	✗	✓
9.	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
10.	Was the exposure(s) assessed more than once over time?	NR	NR	✗	NR	✗	NR	NR	NR	NR	✗	✗
11.	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
12.	Were the outcome assessors blinded to the exposure status of participants?	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
13.	Was loss to follow-up after baseline 20% or less?	Less	NA	NA	NA	NA	NA	CD	NA	NA	NA	NA
14.	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

Table II: Studies Included in The Systematic Review

No.	Study Title	First Author; Year: Country	Study Type	Sample size	Age (y)	Subjects	Study groups	Treated patients	Route of Administration	Main findings
1	Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: A Danish nationwide cohort study [11]	Lars Christian Lund;2020: Denmark	Cohort study	9,236 (NSAID users=248, Non-NSAID users=8,988)	Median age= 50 years	COVID-19 patients	All Danish residents who had a positive PCR test for SARS-CoV-2 during the period 27 February 2020 to 20 April 2020 were included in the study	Users of NSAID users were compared to individuals without NSAID use in the corresponding time window	Not specified	Use of NSAIDs was not associated with 30-day mortality, hospitalization, ICU admission, mechanical ventilation, or renal replacement therapy in Danish individuals who tested positive for SARS-CoV-2.
2	Prior routine use of non-steroidal anti-inflammatory drugs (NSAIDs) and important outcomes in hospitalized patients with COVID-19 [12]	Eilidh Bruce;2020:UK	Prospective Cohort study	1222	3 groups, 1: under 65 years, 2: 65-79 years, 3: over 80 years	COVID-19 patients	Adults ≥18 years admitted to 10 hospitals in the United Kingdom and one in Italy with the diagnosis of COVID-19	Hospitalized patients	All types except topical NSAIDS	This study found that the routine use of NSAIDs might confer a modest survival benefit and is not associated with poorer outcomes
3	Association between non steroidal anti-inflammatory drug use and adverse clinical outcomes among adults hospitalized with coronavirus 2019 in South Korea: A nationwide study [13]	Jeong, Han Eol, 2020, South Korea	Cohort study	1824	Mean age (NSAID users= 54 years and non NSAID users=47.8 years)	Hospitalized COVID-19 patients	1824 adults hospitalized for COVID-19 were divided into two groups; 354 NSAID users and 1470 nonusers	Hospitalized COVID-19 patients	oral and intravenous administration	NSAID use was associated with worse COVID-19–related outcomes compared with nonuse among patients hospitalized with COVID-19

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4	Association between prescribed ibuprofen and severe COVID-19 infection: A nationwide register-based cohort study [14]	Kristian Kragholm, 2020, Denmark	Cohort Study	4,002	Median age for individuals with Ibuprofen prescription claim=58 years while for No ibuprofen prescription claim=57 years	COVID-19 patients	COVID-19 patients were divided into ibuprofen and non-ibuprofen users	COVID-19 patients	Not specified	In this nationwide study, there was no significant association between ibuprofen drug prescription claims and severe COVID-19 diagnosis.
5	Use of non-steroidal anti-inflammatory drugs and risk of death from COVID-19: an OpenSAFELY cohort analysis based on two cohorts [15]	Angel YS Wong, 2021, UK	Cohort study	**Cohort 1:** 536,423 current NSAID users and 1,927,284 non-users, **Cohort2:** 175,495 current NSAID users and 1,533,286 non-users	Cohort 1 : Median age=53 years, Non-users=49. Cohort2: Median age=63 years among current users and non-users=68	NSAID users of COVID-19 patients	The first cohort was all people with ≥1 oral NSAID prescription within the 3 years before study start (1 March 2020), identified from the general population. The second cohort was all people with a diagnosis of rheumatoid arthritis (RA)/osteoarthritis (OA) before study start.	COVID-19 patients	Not specified	No evidence of a harmful effect of routinely prescribed NSAIDs on COVID-19 related death found.
6	Clinical characteristics, treatment regimen and duration of hospitalization among COVID-19 patients in Ghana: a retrospective cohort study [16]	Mary Eyram Ashinyo, 2020' Ghana	Retrospective Cohort Study	307	Mean age=37.9 years	COVID-19 patients	COVID-19 patients discharged from the hospital after treatment	The patients were categorized into five groups based on the type of treatment they received during hospitalization: (1) chloroquine+azithromycin, (2) hydroxychloroquine+azithromycin, (3) azithromycin only, (4) hydroxychloroquine only and (5) Supportive treatment only (vitamin C and analgesics (paracetamol or ibuprofen).	Not specified	Based on the data of 244 fully recovered patients, the use of the azithromycin +chloroquine combination or hydroxychloroquine alone shortened the duration of hospitalization compared to the use of azithromycin only

										or supportive treatment.
7	Ibuprofen use and clinical outcomes in COVID-19 patients [17]	Ehud Rinott, 2020: Israel	Retrospective Cohort Study	403 (Cases=179, Controls= 224) COVID-19 patients	Median age=40 year	Confirmed cases of COVID-19	COVID-19 patients with fever	One hundred and seventy-nine (44%) patients had fever, with 32% using paracetamol and 22% using ibuprofen (Both hospitalized and non-hospitalized)	Not specified	When compared to exclusive paracetamol users, no differences were observed in mortality rates or the need for respiratory support among patients using ibuprofen.
8	Ibuprofen and NSAID Use in COVID-19 Infected Patients Is Not Associated with Worse Outcomes: A Prospective Cohort Study [18]	Laila Carolina Abu Esba;2021: Saudi Arabia	Prospective Cohort Study	503	Group 1: acute ibuprofen users=34.5; group 2: aspirin/NSAID users=38; group 3: aspirin/NSAID chronic users=57; group 4: any NSAID users, acute/ chronic combined=47.5. Non-NSAID users=36	Adult COVID patients	Group 1: acute ibuprofen users during infection only; group 2: aspirin/NSAID acute use during infection; group 3: aspirin/NSAID chronic users; group 4: any NSAID users, acute/ chronic combined. Non-NSAID users were the control group.	Both hospitalized and non-hospitalized	Not specified	Acute ibuprofen use was not associated with a greater risk of mortality relative to nonusers (adjusted hazard ratio (HR) 0.632 [95% CI 0.073–5.441; P = 0.6758]). NSIAD chronic use was also not associated with greater risk of mortality (adjusted HR, 0.492 [95% CI 0.178–1.362; P = 0.1721])
9	Nonsteroidal Anti-inflammatory Drugs and Susceptibility to COVID-19 [19]	Jot Singh Chandan, 2021, UK	Cohort study	13,202	Mean age in matched cohort=68 years	Diagnosis of osteoarthritis in COVID-19 patients	Patients prescribed an NSAID were compared to those prescribed either co-codamol (paracetamol and codeine) or co-dydramol (paracetamol and dihydrocodeine).	Osteoarthritis patients already prescribed with NSAIDS	All types except topical NSAIDS	Prescriptions of NSAIDs (excluding topical preparations) in primary care do not increase susceptibility to COVID-19 or all-cause mortality, including in older patients.
10	NSAID use and clinical outcomes in	Justin T Reese; 2022: USA	Retrospective Cohort Study	857061 (NSAIDS users:19,746,	Median age of cohort=47.6 years	COVID-19 patients	Individuals diagnosed with COVID-19 were	COVID-19 patients	Not specified	The findings of the study did not show an

	COVID-19 patients: a 38-center retrospective cohort study [20]			Non-NSAID users= 19,746)			then divided into those individuals treated with the medication			association in hospitalized COVID-19 patients between NSAID use and increased COVID-19 severity, or increased risk of invasive ventilation, AKI, ECMO, and all-cause mortality. There is a significant association between NSAID use and decreased risk of these outcomes.
11	Chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen and relationship with mortality among United States Veterans after testing positive for COVID-19 [21]	Campbell HM, 2022, USA	Retrospective Cohort Study	28,856 patients	Mean age=57.8 years	COVID-19 patients	COVID-19 patients divided into sporadic NSAID users, chronic NSAID monotherapy users, chronic acetaminophen users	Studied NSAIDs included aspirin > 150mg/day, ibuprofen, naproxen, meloxicam, celecoxib, and diclofenac.	Not specified	The results of this study show no association between chronic use of any of the six NSAIDs studied or with acetaminophen and all-cause mortality in Veterans diagnosed with COVID-19 infection. Clinically important association was also not revealed when chronic acetaminophen use was substituted for sporadic NSAID use.

between increased risk of mortality and ibuprofen/NSAID use, when compared to paracetamol.[19]

In the study conducted by Reese *et al.*, electronic health record data from 38-centers was analyzed for a retrospective cohort analysis. Cases using NSAID were matched with 19,746 COVID-19 inpatients to create a propensity-matched cohort. NSAIDs/ibuprofen use was not associated with increase in severity of COVID-19 outcomes. The prescription of NSAIDs/ibuprofen was also not associated with high rate of mortality.[20] Campbell *et al.*, 2022 studied the impact of continuous usage of specific NSAID/ibuprofen and paracetamol on death/mortality. No significant differences in mortality were established between chronic use of NSAIDs/ibuprofen and paracetamol use.[21]

Discussion

During the early days of COVID-19 outbreak, speculations based on unpublished data on the NSAIDs/ibuprofen particularly ibuprofen and COVID-19 symptoms worsening, caused quite a stir around the world. Harmful effects of NSAIDs/ibuprofen were attributed to the up regulation of ACE2 receptors which facilitate the viral entry in the different organs such as lungs, heart, kidney, and intestines, hence contributing to worse outcomes of COVID-19 infection.[22] Evidence from *in vitro* as well as cohort studies shows that ibuprofen is not associated with harmful impacts in COVID infection.[21,23,24] Despite the intrinsic limitations of the observational studies, this systematic review has shown that with NSAIDs/ibuprofen, there was no harmful effect observed, either in terms of increased mortality or morbidity. It was suggested that a modest survival benefit for older patients treated with NSAIDs/ibuprofen might exist.[1] We found that no Randomized Controlled Trial (RCT) was done to assess the ibuprofen effects in comparison with paracetamol in people infected with COVID-19.

With regards to the treatment of COVID-19 fever, Rinott *et al.*, concluded that there was no increased death rate or the requirement of ventilator in patients on ibuprofen exclusively compared to those taking paracetamol.[17] Most of the studies included found no association between increased mortality in COVID-19 patients prescribed with ibuprofen or NSAIDs/ibuprofen. However, a study conducted in a South Korean cohort indicated a greater proportion of complication related to COVID-19 and death among NSAID users compared to the nonusers.[25]

There are few studies on the efficacy of paracetamol as an antipyretic agent for COVID-19. We have taken care to include only studies that were conducted on COVID-19 patients since SARS-CoV-2 is a novel virus, has a different behavior as compared to different viruses of the same family such as MERS viruses originated from middle east countries.[26] The studies showed slight variations, with some including both hospitalized as well as non-hospitalized individuals diagnosed with COVID-19,[17,18] while others included only hospitalized COVID-19 patients.[12,25] While Rinott *et al.*, studied the findings on patients receiving NSAIDs/ibuprofen during the treatment period and did not explore the pre-admission use of NSAIDs/ibuprofen,[17] Bruce *et al.*,2020 emphasized the pre-COVID treatment history and clearly documented the prior use of NSAIDs/ibuprofen as well the presence/absence of co-morbidities.[12]

The present study has a few limitations. Firstly, only limited published studies on the efficacy of paracetamol and NSAIDS/Ibuprofen for management of COVID-19 fever were available. While all the eleven included studies were observational, the prospective nature of the studies excludes the possibility of reverse causality. Secondly, despite the limitations of the included studies, their results indicate that the exclusion of NSAIDs/ibuprofen from COVID-19 management plan, is not supported by empirical evidence and RCTs are much needed. Currently we have no results from clinical trials, only cohort studies were included for the compilation of this systematic review. Although we followed all the standard protocols for searching and screening studies, the probability of missing some studies still exist. Moreover, studies on children and pregnant women were excluded, so the results of current study can not be applied to them.

Conclusion

According to the results of the present systematic review, there is no evidence refuting the efficacy and/or safety of ibuprofen in comparison with paracetamol and that the use of ibuprofen should not be prohibited during the treatment of fever and pain accompanying the COVID-19 infection.

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CONFLICT OF INTEREST

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DATA SHARING STATMENT

The data that support the findings of this study are available from the corresponding author upon request.

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