



Ibuprofen and NSAID Use in COVID-19 Infected Patients Is Not Associated with Worse Outcomes: A Prospective Cohort Study

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ABSTRACT

Introduction: Ibuprofen disappeared from the pharmacy shelves during the 2019 coronavirus (COVID-19) pandemic. However, a while later, information circulated that ibuprofen should be avoided as it could worsen COVID-19 symptoms. The aim of our study was to assess the association of acute and chronic use of

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nonsteroidal anti-inflammatory drugs (NSAIDs) with worse COVID-19 outcomes.

Methods: We did a prospective cohort study between April 12 and June 1, 2020. Adults consecutively diagnosed with COVID-19 were included. Information on NSAID use was collected through a telephone questionnaire, and patients were followed up for COVID-19 infection outcomes, including death, admission, severity, time to clinical improvement, oxygen requirement and length of stay.

Results: Acute use of ibuprofen was not associated with a greater risk of mortality relative to non-use (adjusted hazard ratio [HR] 0.632 [95% CI 0.073–5.441; $P = 0.6758$]). Chronic NSAID use was also not associated with a greater risk of mortality (adjusted HR 0.492 [95% CI 0.178–1.362; $P = 0.1721$]). Acute ibuprofen use was not associated with a higher risk of admission compared to non-NSAID users (adjusted odds ratio OR 1.271; 95% CI 0.548–2.953). NSAID users did not have a significantly longer time to clinical improvement or length of stay. **Conclusion:** Acute or chronic use of ibuprofen and other NSAIDs was not associated with worse COVID-19 disease outcomes.

Keywords: COVID-19; COVID-19 outcomes; Ibuprofen; NSAIDs

Key Summary Points

Why carry out this study?

The concern about ibuprofen and NSAID use circulating in the media during the COVID-19 outbreak was based solely on anecdotal observation, and a correspondence published in the Lancet posed the theoretical explanation that, due to the port of entry of COVID-19 that may be upregulated by some drugs, they may worsen COVID-19 outcomes.

The aim of our study was to assess the association of acute and chronic use of NSAIDs with worse COVID-19 outcomes.

What was learned from the study?

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; $P = 0.6758$]). NSAID chronic use was also not associated with greater risk of mortality (adjusted HR, 0.492 [95% CI 0.178–1.362; $P = 0.1721$]).

NSAID users did not have a significantly longer time to clinical improvement or length of hospital stay.

The proposed potential benefit of ACE2 through the removal of angiotensin II in viral-mediated lung injury possibly means that upregulating ACE2 might be beneficial, with no evidence of harm seen in our study; more research could be conducted to explore the potential repurposing of NSAIDs for COVID-19 treatment.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.13103009>.

INTRODUCTION

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) commonly used during any infection accompanied by fever. It is an effective antipyretic and analgesic and is available over the counter (OTC). Acetaminophen and ibuprofen are the two most extensively used antipyretics [1].

Ibuprofen disappeared from the pharmacy shelves when quarantine measures were announced to combat the 2019 coronavirus (COVID-19) disease pandemic, which led to global shortages of ibuprofen [2]. However, a while later information circulated on the news saying that ibuprofen should be avoided as it could worsen COVID-19 symptoms [3–5].

The concern with ibuprofen in the media during the COVID-19 outbreak was fueled by the Health Minister of France, who shared on social media that NSAIDs including ibuprofen could worsen COVID-19 infections [6]. This was based solely on observation, and no reference to any published data was ever made. Such opinions are influenced by indication bias as patients usually step up to ibuprofen and other NSAIDs when their symptoms get worse.

Shortly thereafter, a correspondence published in the Lancet posed the theory that due to the port of entry of COVID-19, which binds to their target cells through angiotensin-converting enzyme 2 (ACE2), some drugs that upregulate the expression of ACE2, giving ibuprofen as an example, may facilitate infection with COVID-19 [7].

Later on, many health agencies shared statements reporting that the concern with ibuprofen and other NSAIDs had no solid evidence to support the recommendations to avoid its use in COVID-19-infected patients or the general population to minimize the risk of transmission [8–11].

Nevertheless, the theory and observation are worth further research. ACE2 plays an important role in the viral entry to cells and is also an important mediator in the renin-angiotensin system, which is important in the mechanism of multiple drugs, not only ibuprofen [12]. In the search for literature related to the effect ibuprofen or NSAIDs may directly have on

ACE2, only one animal study was found. This study was in diabetic rats and reported an increase in ACE2 in the heart tissue after treatment with ibuprofen [13]; however, a similar effect cannot be easily extrapolated to non-diabetic human patients or lung tissue.

Nevertheless, if any of these speculations and observations that ibuprofen worsens symptoms or increases the risk of transmission are true, the implications for the healthcare systems may be huge because of its wide OTC use not only in the context of COVID-19-associated fever but also in patients that chronically use it for pain [14, 15].

Implications of public fear based on little clinical evidence could be that patients with chronic pain switch from NSAIDs to alternatives such as opioids, which could worsen the opioid epidemic. Alternatively, if higher doses of acetaminophen are used to avoid NSAIDs, an increase in liver injury cases may occur.

Contrarily, a few animal studies demonstrated that ACE2 plays a critical role in viral-induced lung injury, showing worse survival in ACE2 knockout mice, and proposed a potential benefit of ACE2 through the removal of angiotensin II in viral-mediated lung injury [16, 17]. This possibly means that upregulating ACE2 might be beneficial. In fact, recombinant ACE2 did seem to improve lung injury in a phase II trial involving acute respiratory distress syndrome (ARDS) patients [18].

With the theoretical, anecdotal observations and serious implications together with theories of benefit, the aim of our study was to provide an evaluation of outcomes in COVID-19-infected patients taking ibuprofen or other NSAIDs, both acutely and/or chronically, which is essential to rule out any drug safety concerns and determine whether comorbid conditions and age confound this association. In addition, results may set a path to further study whether ACE2 upregulation has a valid therapeutic potential.

METHODS

Study Design and Participants

This prospective observational cohort study took place at the Ministry of National Guard

Health Affairs (MNGHA) in Riyadh, Saudi Arabia, which includes King Abdulaziz Medical City, a 1500-bed hospital, and King Abdullah Specialist Children's Hospital, a 600-bed hospital that was also utilized for COVID-19-infected patients during the outbreak. In total, the facilities provide 100 adult intensive care unit (ICU) beds, which was increased to 200 beds during the peak of COVID-19 cases. Patients seen at the facility were MNGHA-eligible patients, MNGHA employees and later throughout the study period, as a directive from the Ministry of Health, any patient in Saudi Arabia, regardless of status, who would be eligible for treatment at any governmental hospital if infected with COVID-19.

We prospectively identified adult patients (aged ≥ 18 years) who were diagnosed with a laboratory-confirmed case of COVID-19 from April 12 to June 1, 2020, who had a valid mobile contact number in our electronic medical records (EMR) and were willing to participate in the study. Laboratory testing for COVID-19 was done using the reverse transcription-polymerase chain reaction (RT-PCR). No sample size calculation was performed; it was determined by the study period. The list of patients with a COVID-19-positive result was obtained daily throughout the study period. The study was approved by the ethics committee of King Abdullah International Medical Research Center (KAIMRC) for both participating centers, King Abdulaziz Medical City and King Abdullah Specialist Children's Hospital. The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. A telephone consent form was developed and approved by the IRB.

Exposure of Interest: Use of Ibuprofen and Other NSAIDs

The exposure of interest was patients' acute use of ibuprofen or NSAIDs (including aspirin) during infection and chronic NSAID use before the confirmed COVID-19 infection. The exposures of interest were divided into four groups: group 1: acute ibuprofen users during infection only; group 2: other 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.

Owing to the common use of these drugs as OTC medications, information about patient exposure was captured through a short telephone questionnaire in addition to electronic prescription filling information from the patient's EMR to identify chronic NSAID use. Chronic NSAID use was defined as > 1 (30-day) filling in a 6-month period prior to the index date or patient self-reported chronic use.

All patients, whether admitted or not, were interviewed via telephone to identify OTC antipyretics used during infection and chronic aspirin/NSAID use. The questionnaire was administered within 5 days of the confirmed laboratory result to minimize the risk of recall bias. Patients who were unable to answer or had their telephone switched off were excluded from the study.

Questionnaire Administered by Telephone to COVID-19-Positive Patients

The questionnaire included questions about the onset of symptoms, whether the patient experienced fever, use of antipyretics including acetaminophen, ibuprofen or any other NSAID during the infection (patients were given a list of common brand names of ibuprofen) and chronic use of aspirin/NSAIDs within the past 6 months.

Data Collection

We recorded data from the patients' EMR on demographics, comorbidities, admission for COVID-19, electronic prescription of antipyretics including NSAIDs during infection and, within the past 6 months, standard of care received, number of antibiotics prescribed during the infection and the outcomes of interest listed below.

Outcomes

The primary outcome was 30-day mortality. Secondary analysis included severe COVID-19 infection and hospital admission.

Additional outcomes for admitted patients included time to clinical improvement, oxygen support required and length of hospital stay.

Time to clinical improvement was defined as the time from admission to an improvement of 2 points (from the status at admission) on the World Health Organization's recommended seven-category ordinal scale or live discharge from the hospital, whichever came first [19].

Additional outcome for patients not admitted included a prescription for an antibiotic during the patient's infection with COVID-19, indicating worse symptoms in patients not admitted.

Patients were followed up from the index date until primary outcome occurrence, discharge or up to 30 days.

Statistical Analysis

All descriptive statistics were reported as counts or means. For comparison of demographic variables and comorbidities among cohorts, independent-sample *t* tests were used for numeric variables, while χ^2 or Fisher exact tests were used for categorical variables.

We estimated hazard ratios (HRs) with 95% confidence intervals for mortality using the Cox proportional hazards model. Log-binomial regression models were used to determine whether any of the NSAID groups were associated with an increase in the relative risk (RR) of outcomes upon adjustment for covariates. The time to clinical improvement and length of stay were portrayed by Kaplan-Meier plot and compared with a log-rank test.

Adjusted models included the following covariates: age, sex and comorbidities: hypertension, diabetes mellitus (DM), dyslipidemia, asthma or chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), renal or liver impairment, and malignancy.

The institutional review board (IRB) at King Abdullah International Medical Research Center (KAIMRC) (protocol RC20/209/R) approved this study for both King Abdulaziz Medical City and King Abdullah Specialist Children's Hospital. A telephone consent form was developed

and approved by the IRB; all participants verbally consented.

RESULTS

For this cohort study designed to examine outcomes among patients with COVID-19, 503

COVID-19-infected patients were included; the first patient was included on April 12, 2020, and the last on June 1, 2020. Baseline characteristics of the study groups are shown in Table 1. Patient selection is shown in Fig. 1. Overall, 17% of patients were asymptomatic, 70% reported mild symptoms, 7% were considered moderate, and 6% were severe.

Table 1 Baseline characteristics of patients with COVID-19 by NSAID user groups and non-NSAID users

Characteristics	Group 1 ^a (<i>n</i> = 40 [7.9%])	Group 2 ^b (<i>n</i> = 17 [3.4%])	Group 3 ^c (<i>n</i> = 96 [19%])	Group 4 ^d (<i>n</i> = 146 [29%])	Group 5 ^e (<i>n</i> = 357 [71%])
Sex					
Male (<i>n</i> = 288)	23 (57.5)	8 (47.06)	51 (53.1)	76 (52)	212 (59.4)
Female (<i>n</i> = 215)	17 (42.5)	9 (52.94)	45 (46.9)	70 (48)	145 (40.6)
Age, median (IQR)	34.5 (27–43.5)	38 (34–44)	57 (38.5–67.5)	47.5 (33–63)	36 (27–49)
Comorbidities					
Hypertension (<i>n</i> = 103)	16 (40)	8 (47)	76 (79.2)	97 (66.4)	119 (33.3)
Diabetes (<i>n</i> = 113)	2 (5)	2 (11.8)	49 (51)	51 (34.9)	52 (14.6)
Dyslipidemia (<i>n</i> = 88)	3 (7.5)	3 (17.7)	56 (58.3)	60 (41.1)	53 (14.8)
Asthma or COPD (<i>n</i> = 26)	4 (10)	1 (5.9)	41 (42.7)	45 (30.8)	43 (12)
CVD (<i>n</i> = 27)	0	0	10 (10.4)	13 (8.9)	13 (3.6)
Renal impairment (<i>n</i> = 16)	0	1 (5.9)	17 (17.7)	18 (12.3)	9 (2.5)
Liver impairment (<i>n</i> = 6)	0	0	6 (6.3)	6 (4.1)	10 (2.8)
Malignancy (<i>n</i> = 7)	0	0	1 (1)	1 (0.7)	5 (1.4)
Hypothyroidism (<i>n</i> =)	0	1 (5.9)	3 (3.1)	4 (2.7)	3 (0.8)
	2 (5)	0	5 (5.2)	7 (5)	7 (2)

COPD chronic obstructive pulmonary disease, *COVID-19* coronavirus disease 2019, *CVD* cardiovascular disease, *IQR* interquartile range, *NSAID* nonsteroidal anti-inflammatory drugs

^a Group 1: patients that used ibuprofen only during infection

^b Group 2: Other aspirin/NSAID acute use during infection

^c Group 3: chronic NSAID users

^d Group 4: acute and chronic NSAID users combined

^e Group 5: non-NSAID user

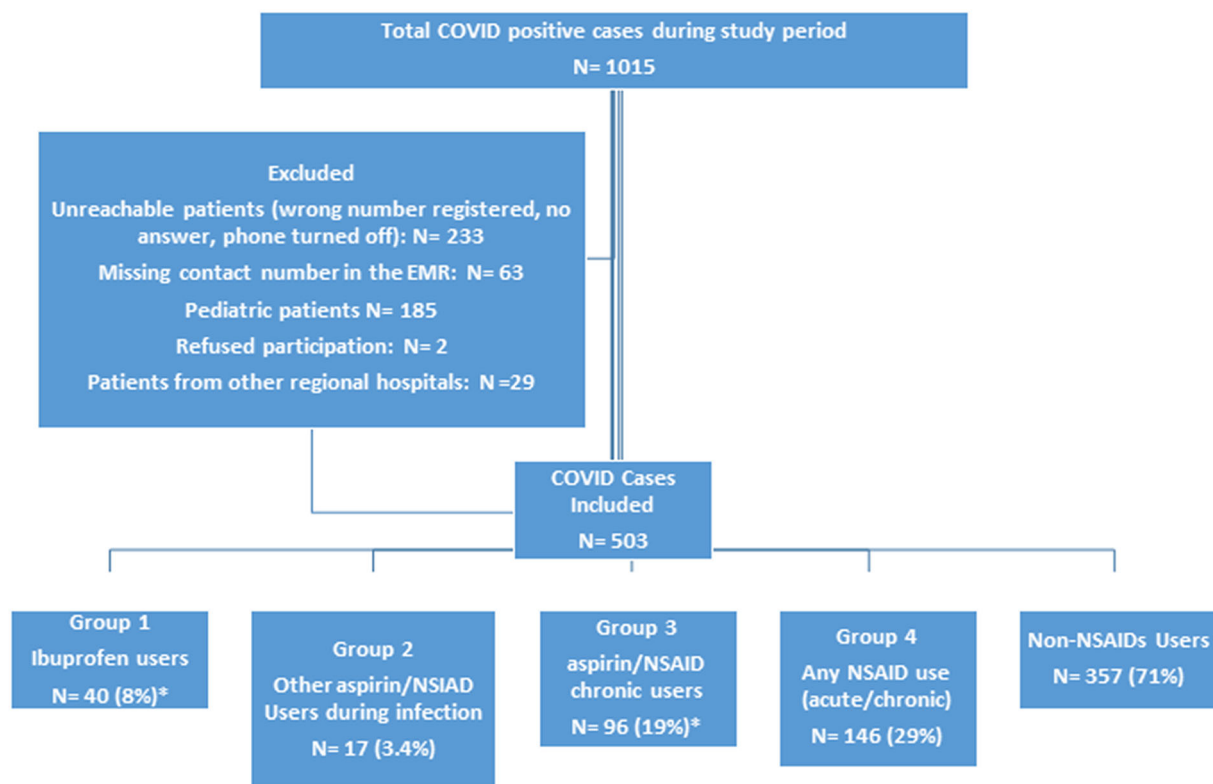


Fig. 1 Patient selection. *NSAID* nonsteroidal anti-inflammatory drugs, *COVID-19* coronavirus disease 2019, *EMR* electronic medical record, *N* number. *Seven (1.4%)

Of the 503 patients included, 40 (7.95%) used ibuprofen during infection (group 1), 17 (3.4%) used other NSAIDs during infection (group 2), 96 (19%) used NSAIDs chronically before infection (group 3), 146 (29%) had any NSAID use, with acute and/or chronic users combined (group 4), and 357 (71%) were non-NSAID users. Seven patients (1.4%) were both chronic users of NSAIDs and used ibuprofen acutely during their infection. (Table 1).

Chronic NSAID users were older than non-NSAID users (57 years [IQR 38.5–67.5] vs. 36 years [IQR 27–49]). Chronic NSAID users were more likely to have comorbid conditions than non-NSAID users (e.g., 41% vs. 14.8% with DM and 12.3% vs. 2.5% with CVD). NSAID use was slightly higher in men than in women (52% vs. 48%).

For the type of NSAIDs used, see supplemental Tables 1 and 2. For other COVID-19-

patients were both chronic users of NSAIDs and used ibuprofen acutely during their infection

related supportive drugs used in this cohort of patients, see supplemental Table 3.

Antibiotic, oseltamivir and acetaminophen use was higher in all NSAID user groups compared to non-NSAID users, as shown in supplemental Table 3. The mean accumulative dose of ibuprofen in group 1 was 3575 mg (SD 3421), and the mean number of days of treatment with ibuprofen was 3.3 days (SD 2.2).

Mortality

A total of 18 (3.8%) patients died during the study period in the cohort of patients included: 2.5% died in group 1, 5.9% in group 2, 6.3% in group 3, 4.8% in group 4 and 3.1% in the non-NSAID users. Table 2 shows the unadjusted and adjusted HRs from the Cox regression analysis.

Acute ibuprofen use during infection was not associated with a greater risk of mortality

Table 2 Hazard ratios for mortality in NSAID users vs. non-NSAID users

Primary outcome	No. (%)	Unadjusted model	Age- and sex-adjusted model	Fully adjusted model ^a
Mortality	Group 1 ^b (<i>n</i> = 40)	Group 5 Non-NSAID users ^f (<i>n</i> = 357)	Hazard ratio (95% CI) <i>p</i> value	Hazard ratio (95% CI) <i>p</i> value
	1 (2.5)	11 (3.1)	0.518 0.5269 (0.067–3.981)	0.632 0.6706 (0.073–5.441)
	Group 2 ^c (<i>n</i> = 17)	Group 5 Non-NSAID users ^f (<i>n</i> = 357)	Hazard ratio (95% CI) <i>p</i> value	Hazard ratio (95% CI) <i>p</i> value
	1 (5.9)	11 (3.1)	5.340 0.1370 (0.587–48.590)	5.815 0.1153 (0.435–77.752)
	Group 3 ^d (<i>n</i> = 96)	Group 5 Non-NSAID users ^f (<i>n</i> = 357)	Hazard ratio (95% CI) <i>p</i> value	Hazard ratio (95% CI) <i>p</i> value
	6 (6.3)	11 (3.1)	0.620 0.3440 (0.230–1.669)	0.392 0.0775 (0.133–1.157)
	Group 4 ^e (<i>n</i> = 146)	Group 5 Non-NSAID users ^f (<i>n</i> = 357)	Hazard ratio (95% CI) <i>p</i> value	Hazard ratio (95% CI) <i>p</i> value
	7 (4.8)	11 (3.1)	0.660 0.3942 (0.254–1.716)	0.492 0.1553 (0.178–1.362)

NSAID nonsteroidal anti-inflammatory drugs

^a Fully adjusted model: includes the following covariates: age, sex, comorbidities: hypertension, diabetes, dyslipidemia, asthma or chronic obstructive pulmonary disease, cardiovascular disease, renal or liver impairment, and malignancy

^b Group 1: patients who used ibuprofen only during infection

^c Group 2: Other aspirin/NSAID acute users during infection

^d Group 3: chronic NSAID users

^e Group 4: acute and chronic NSAID users combined

Table 3 Relative risk of mortality, admission, oxygen support and severe COVID-19 in acute ibuprofen users

	Unadjusted Relative risk (95% CI [‡])	<i>p</i> value	Age-, sex-adjusted Relative risk (95% CI [‡])	<i>p</i> value	Fully adjusted ^a Relative risk (95% CI [‡])	<i>p</i> value
Mortality	0.6809 (0.0906–5.1162)	0.7087	2.6926 (0.3293–22.0175)	0.3555	2.6951 (0.3302–21.9964)	0.3547
Admission	0.9138 (0.4636–1.8013)	0.7946	1.2625 (0.6340–2.5140)	0.5072	1.1819 (0.5917–2.3606)	0.6359
Oxygen support	0.8904 (0.2752–2.8812)	0.8463	1.5232 (0.4603–5.0408)	0.4907	1.4482 (0.4361–4.8089)	0.5454
Severe COVID-19	0.8574 (0.2039–3.6056)	0.8337	1.9180 (0.4377–8.4039)	0.3876	1.8484 (0.4202–8.1314)	0.4163

COVID-19 coronavirus disease 2019

^a Fully adjusted model, which includes the following covariates: age, sex, comorbidities: hypertension, diabetes, dyslipidemia, asthma or chronic obstructive pulmonary disease, cardiovascular disease, renal or liver impairment and malignancy

[‡] Confidence interval

relative to non-NSAID users in the unadjusted analysis (HR 0.518 [95% CI 0.067–3.981]; $P = 0.5269$) and was not significant after adjusting for age, sex and comorbidities (HR 0.632 [95% CI 0.073–5.441]; $P = 0.6758$).

In addition, chronic NSAID use was not associated with greater risk of mortality relative to non-NSAID users in the unadjusted analysis (HR 0.660 [95% CI 0.254–1.716]; $P = 0.3942$) and not significant after accounting for age, sex and comorbidities (HR 0.492 [95% CI 0.178–1.362]; $P = 0.1721$).

Relative Risk of Mortality, Admission, Oxygen Support and Severe COVID-19 Disease

The adjusted RR of mortality, admission, oxygen support and severe COVID-19 disease in acute ibuprofen users (group 1) was not significantly higher than in non-NSAID users (Table 3).

The adjusted RR of mortality in acute/chronic NSAID users combined (group four) was not significantly higher than that of non-NSAID

Table 4 Relative risk of death, admission, oxygen support and severe COVID-19 disease in acute and chronic NSAID users combined

	Unadjusted Relative risk (95% CI [‡])	<i>p</i> value	Age-, sex-adjusted Relative risk (95% CI [‡])	<i>p</i> value	Fully adjusted ^a Relative risk (95% CI [‡])	<i>p</i> value
Death	1.556 (0.6032–4.0139)	0.3605	0.6653 (0.2558–1.7303)	0.4034	0.5927 (0.2261–1.5536)	0.2874
Admission	2.4058 (1.6895–3.4258)	< 0.0001	1.7450 (1.2017–2.5341)	0.0034	1.5419 (1.0605–2.2420)	0.0234
Oxygen support	1.8339 (0.9953–3.3790)	0.0518	1.0182 (0.5351–1.9371)	0.9563	0.9189 (0.4818–1.7525)	0.7975
Severe COVID-19	1.7260 (0.8244–3.6139)	0.1477	0.8289 (0.3870–1.7756)	0.6293	0.7282 (0.3398–1.5605)	0.4147

COVID-19 coronavirus disease 2019, NSAID nonsteroidal anti-inflammatory drugs

^a Fully adjusted model, including the following covariates: age, sex, comorbidities: hypertension, diabetes, dyslipidemia, asthma or chronic obstructive pulmonary disease, cardiovascular disease, renal or liver impairment, and malignancy

[‡] Confidence interval

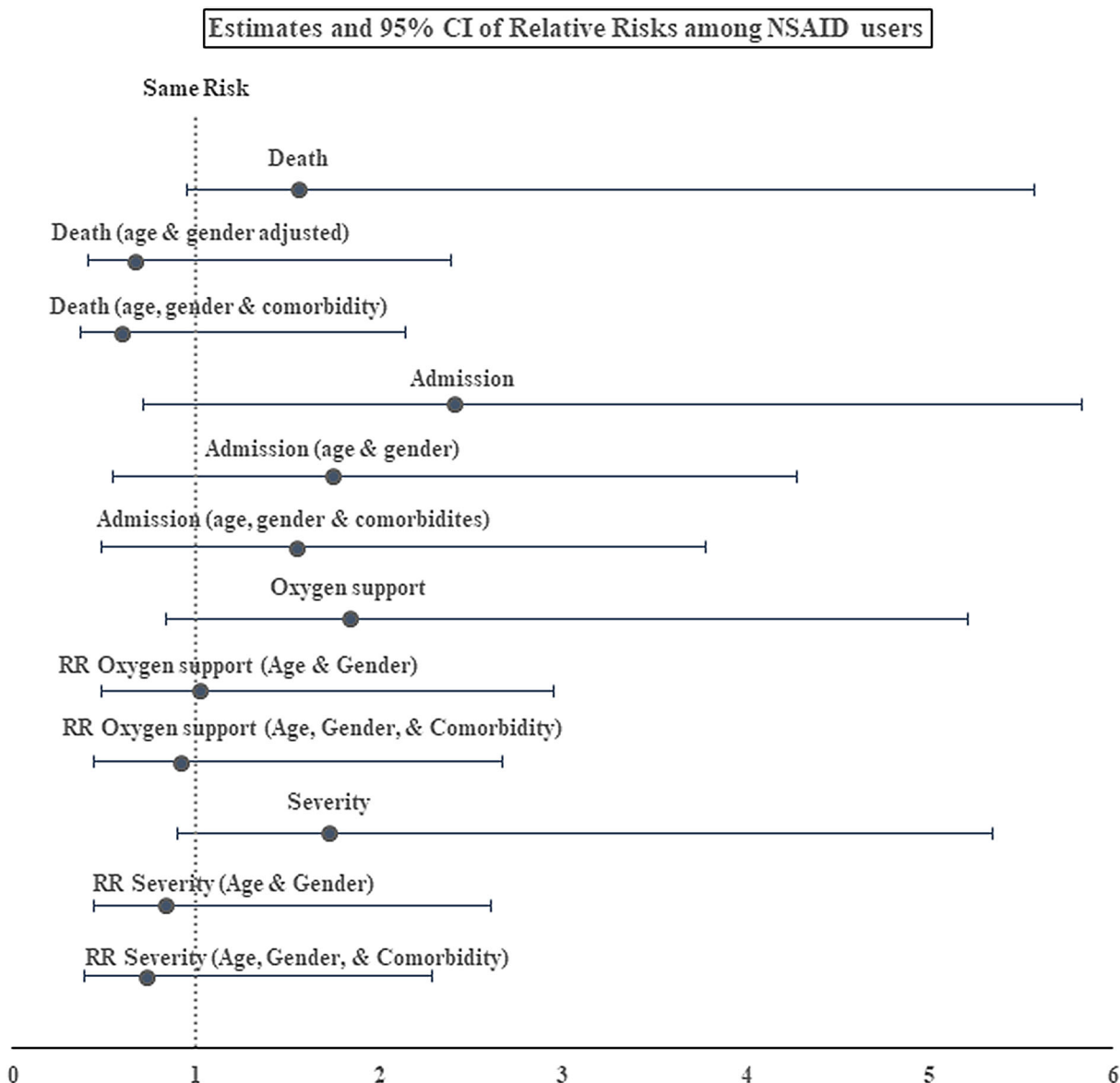


Fig. 2 Relative risk for death, admission, oxygen support requirement and severity, unadjusted and adjusted, for any NSAID use (group 4^a) vs. non-NSAID users. *NSAID*

nonsteroidal anti-inflammatory drugs. ^aGroup 4: acute and chronic NSAID users combined

users (RR 0.5927 [95% CI 0.2261–1.5536]; $P = 0.2874$); similarly, NSAID users were not at a higher risk of oxygen support requirement and severe COVID-19 disease compared to non-NSAID users. See Table 4 for unadjusted and adjusted RRs of outcomes in acute/chronic NSAID users (group 4). Figure 2 shows unadjusted and adjusted RRs for the different outcomes in NSAID users (group 4).

Admission

In our cohort, 22.5% of patients in group 1, 35.3% in group 2, 49% in group 3 and 41.8% in group 4 were admitted vs. 17.4% in the non-NSAID user group. The adjusted RR of admission was higher in acute/chronic NSAID users (group 4) compared to non-NSAID users (RR 1.5419 [95% CI 1.0605–2.2420]; $P = 0.0234$).

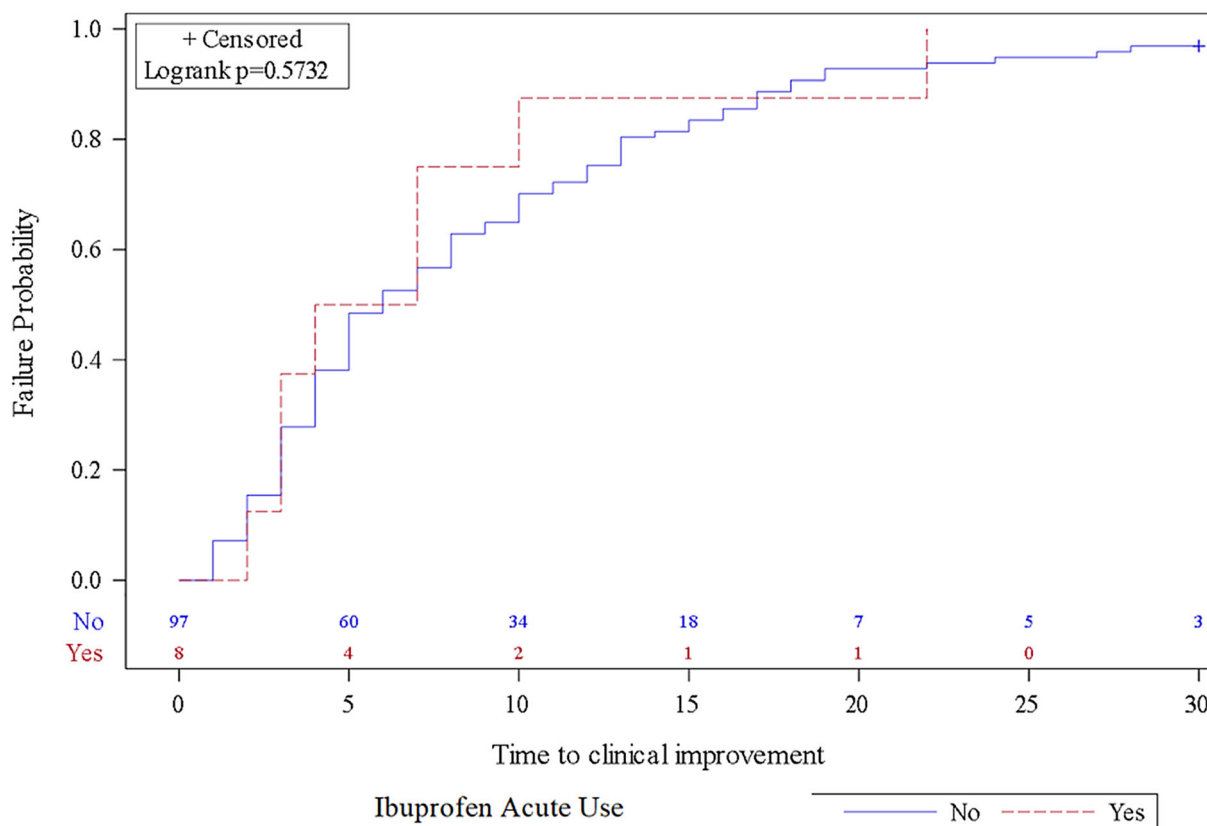


Fig. 3 Kaplan-Meier plot for time to clinical improvement: ibuprofen use (Group 1^a) vs. non-NSAID users. NSAID nonsteroidal anti-inflammatory drugs. ^a Group 1: patients that used ibuprofen only during infection

Odds of Admission for Ibuprofen Users (Group 1)

Acute ibuprofen use was not associated with a higher risk of admission compared to non-NSAID users (adjusted odds ratio OR 1.271; [95% CI 0.548–2.953]). The OR for admission was however higher with age (OR 1.038; 95% CI 1.021–1.055) and comorbidities (OR 3.276; 95% CI 1.916–5.601).

Time to Clinical Improvement

There was no difference in time to clinical improvement between any NSAID user groups compared to non-NSAID users; see Figs. 3, 4 and 5. KM plots for time to clinical improvement in each group. Time to clinical improvement in acute ibuprofen users did not significantly differ from that of non-NSAID users (median 5.50 days vs. 6 days; adjusted HR 0.998; 95%

confidence interval [CI] 0.474–2.101; $P = 0.9963$), in NSAID chronic users vs. non-NSAID users (median, 6 days vs. 5 days; adjusted HR for clinical improvement, 1.000; 95% confidence interval [CI] 0.646–1.549; $P = 0.9991$) and in acute/chronic NSAID users combined vs. non-NSAID users (median, 6 days vs. 5 days; adjusted HR for clinical improvement, 0.996; 95% confidence interval [CI] 0.667–1.487; $P = 0.9857$).

Length of Hospital Stay

There was no significant difference between the length of stay in acute/chronic NSAID users compared to non-NSAID users (median, 7 days vs. 8 days; adjusted hazard ratio for the length of stay, 1.091; $P = 0.6353$). See the KM plot for the length of stay (Fig. 6).

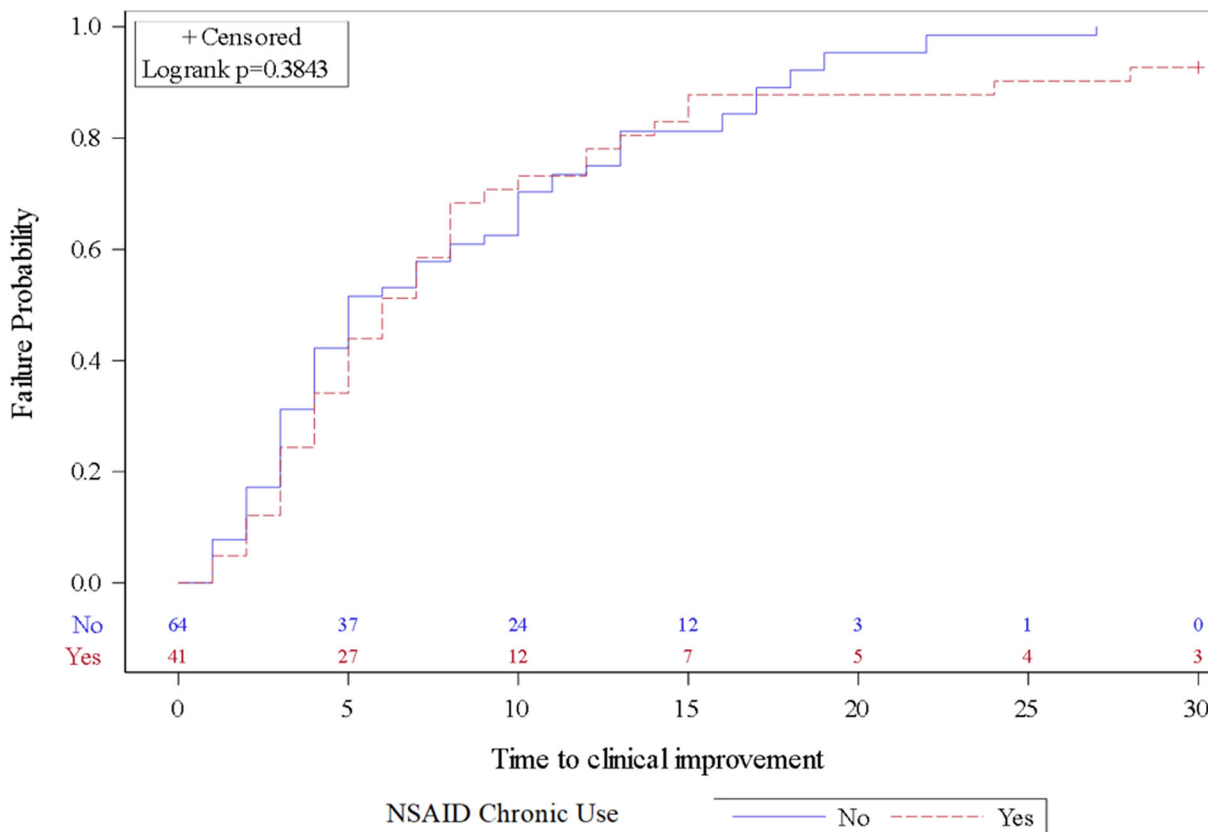


Fig. 4 Kaplan-Meier plot for time to clinical improvement: NSAID chronic use (group 3^a) vs. non-NSAID users. *NSAID* nonsteroidal anti-inflammatory drugs. ^aGroup 3: chronic NSAID users

Antibiotic Use

Of the 380 patients who were not admitted, 100 (26.3%) were prescribed an antibiotic; 24 (6.3%) of them had more than one antibiotic prescription. Acute ibuprofen users and chronic NSIAD users were not prescribed antibiotics significantly more than non-NSAID users (adjusted RR 1.5475 (0.8153–2.9372)]; *P* = 0.1817) and (adjusted RR 1.1536 (0.6802–1.9567)]; *P* = 0.5960), respectively. (Table 5).

DISCUSSION

Despite the risk of indication bias, not favoring outcomes in patients taking ibuprofen, as patients with more severe symptoms would probably be more likely to take it, we found no association between the acute use of ibuprofen

during infection with any of the outcomes assessed including mortality, admission, severity and length of hospital stay.

We also found no association between the acute and chronic use of NSAIDs and a higher risk of mortality, severe COVID-19 disease and need for oxygen support, with no difference in time to clinical improvement and length of hospital stay compared to non-NSAID users in admitted patients. Although there was a higher risk of admission among chronic NSAID users, this outcome may have been confounded by patients admitted for concomitant conditions requiring medical care as we did not exclude patients who were admitted for other reasons and happened to be COVID-19 positive. In addition, in the early stages of this study, patients at MNGHA were admitted regardless of the severity of symptoms while waiting to be transferred to quarantine.

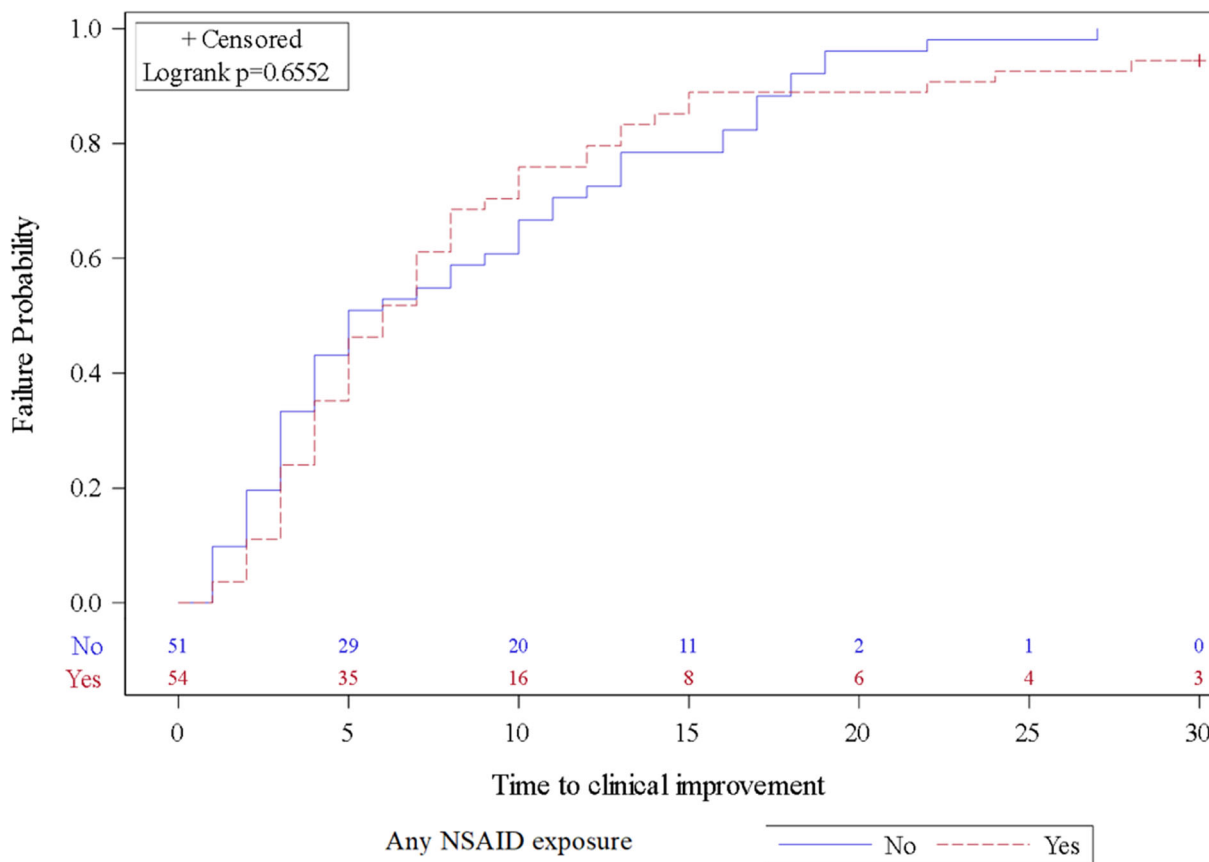


Fig. 5 Kaplan-Meier plot for time to clinical improvement: any NSAID use (group 4^a) vs. non-NSAID users. NSAID nonsteroidal anti-inflammatory drugs. ^aGroup 4: acute and chronic NSAID users combined

Concern about NSAIDs worsening lung infection is not new or specific to COVID-19; in fact, previous pharmacoepidemiologic data and pharmacovigilance analysis report that NSAID exposure increases the risk of severe pulmonary complications, supported by experimental data and pharmacologic plausibility [20]. These concerns and analyses were led by the French Regional Pharmacovigilance Centers, possibly explaining why early alerts on ibuprofen in COVID-19 came from France.

In a study published early on in the COVID-19 pandemic, samples of plasma of infected patients had significantly higher angiotensin II levels compared to healthy individuals. The levels were linearly associated with viral load and lung injury. In addition, the authors suggested angiotensin receptor blocker (ARB) drugs as potential repurposing treatments for COVID-19 [21]. This study contradicts the theory that

upregulation of ACE2 is associated with adverse outcomes, as ACE2 acts as a negative regulator and decreases angiotensin II levels. Therefore, a clinical trial to test the benefit of ibuprofen in COVID-19 patients is currently ongoing [22]. An excellent narrative review outlines the theories and evidence on the mechanistic effect of ibuprofen on ACE2 [23].

Other NSAIDs such as naproxen have also been studied for their antiviral potential and showed potent in vitro activity against severe acute respiratory syndrome-related coronavirus (SARS-CoV) [24] and antiviral activity against influenza A and B viruses in animal models [25, 26]. This is why naproxen has also been listed as a potential agent and is currently being studied in a clinical trial in COVID-19-infected patients [27, 28].

Our study has several limitations. First, this was an observational study; no causal

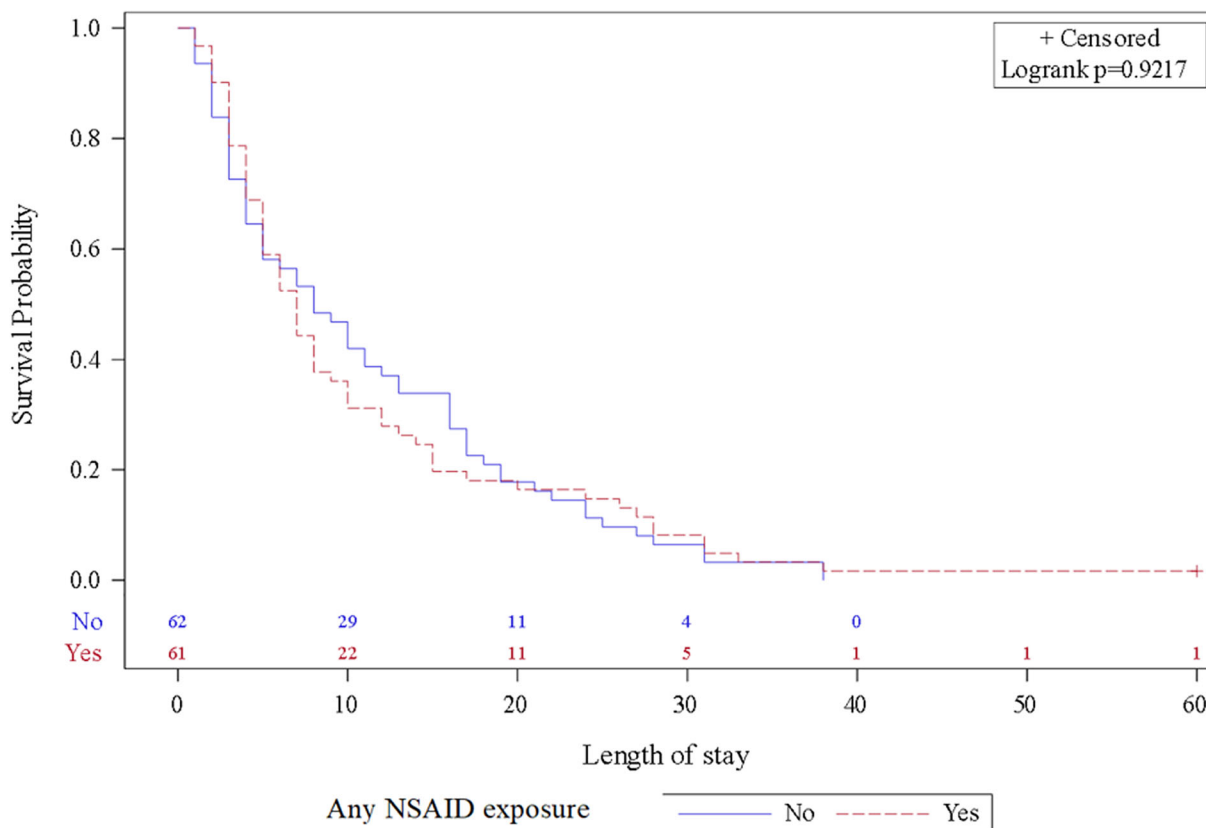


Fig. 6 Kaplan-Meier plot for length of stay in any NSAID user (group 4^a) vs. non-NSIAD users. *NSAID* nonsteroidal anti-inflammatory drugs. ^aGroup 4: acute and chronic NSAID users combined

Table 5 Relative risk of antibiotic prescribing in NSAID users

	Unadjusted Relative risk (95% CI [‡])	<i>p</i> value	Age-, sex-adjusted Relative risk (95% CI [‡])	<i>P</i> value	Fully adjusted ^a Relative risk (95% CI [‡])	<i>p</i> value
Group 1 ^b	1.3914 (0.7437–2.6032)	0.3013	1.6691 (0.8836–3.1529)	0.1144	1.5475 (0.8153–2.9372)	0.1817
Group 3 ^c	1.6888 (1.0346–2.7566)	0.0361	1.2549 (0.7424–2.1211)	0.3965	1.1536 (0.6802–1.9567)	0.5960
Group 4 ^d	1.7879 (1.1821–2.7041)	0.0059	1.5720 (1.0255–2.4097)	0.0379	1.4351 (0.9272–2.2214)	0.1051

NSAID nonsteroidal anti-inflammatory drugs

^a Fully adjusted model, which includes the following covariates: age, sex, comorbidities: hypertension, diabetes, dyslipidemia, asthma or chronic obstructive pulmonary disease, cardiovascular disease, renal or liver impairment, and malignancy

^b Group 1: patients that used ibuprofen only during infection

^c Group 3: chronic NSAID users

^d Group 4: acute and chronic NSAID users combined

conclusion can be reached, and connections should be interpreted as associations. Second, as this study was conducted at an early stage of the pandemic outbreak in Saudi Arabia, screening

strategies in the beginning may have introduced selection bias relative to strategies at a later period. Third, the main analysis of this study compared NSAID users with non-NSAID

users, but confounding by indication may have influenced the results.

However, the study strength is that prescription fillings, patient questionnaires and in-hospital electronic administration records were used to confirm exposure to NSAIDs.

CONCLUSION

This study found no association between ibuprofen or any other NSAID and worse COVID-19 outcomes. Both acute and chronic exposure to NSAIDs did not show any significant association with COVID-19-related mortality, and no significant difference in time to clinical improvement or length of stay compared to non-NSAID users was found.

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Compliance with Ethics Guidelines. The study has received approval from the ethics committee of King Abdullah International Medical Research Center (KAIMRC) for both participating centers, King Abdulaziz Medical City and King Abdullah Specialist Children's Hospital. The study was performed in accordance with the Helsinki Declaration of 1964

and its later amendments. A telephone consent form was developed and approved by the IRB.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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