Ibuprofen and NSAIDs use in COVID-19 infected patients is Not Associated with Worse Outcomes

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Abstract

Background: Ibuprofen disappeared off the pharmacy shelves during the COVID-19 pandemic. However, a while later circulating information was that ibuprofen should be avoided as it could worsen COVID-19 symptoms. The aim of our study was to assess the association of NSAID acute and chronic use 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.

Findings: Ibuprofen acute 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]). Ibuprofen acute 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.

Interpretation: Ibuprofen and other NSAID acute or chronic use were not associated with worse COVID-19 disease outcomes.

Introduction

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

Ibuprofen disappeared off pharmacy shelves when quarantine measures were announced to combat the Coronavirus disease 2019 (COVID-19) pandemic, which led to global shortages in ibuprofen.² However, a while later circulating information on the news was 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 infection.⁶ This was based solely on observation, and reference to any published data was never made. Such opinions are influenced by indication bias as patients usually step-up to ibuprofen, and other NSAIDs when their symptoms get worse.

But then shortly after, a correspondence published in the Lancet posed a 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 up-regulate the expression of ACE2, and gave ibuprofen as an example, may facilitate infection with COVID-19.⁷

Many health agencies, later on, shared statements that the concern with ibuprofen and other NSAIDs had no solid evidence to support 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 is true, implications may be huge on healthcare systems due to 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.

Rather contradicting, 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 up-regulating 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 the serious implications puzzled with theories of benefit, an observational study on outcomes in COVID-19 infected patients taking ibuprofen, or other NSAIDs both acutely, or chronically, is essential to rule out any drug safety concerns, and whether comorbid conditions and age confound this association. Besides, results may set path to further research on whether ACE2 up-regulation 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 NGHHA eligible patients, NGHHA employees, and later throughout the study period, as a directive by the Ministry of Health, any patient regardless of status in Saudi Arabia would be eligible for treatment if infected with COVID-19 at any governmental hospital.

We prospectively identified adult patients (aged 18 years and above) who were diagnosed with a laboratory-confirmed 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 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 were obtained daily throughout the study period.

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 one: Ibuprofen acute user during infection only; Group two: Other aspirin/NSAID acute use during infection; Group three: Aspirin/NSAID chronic users, and Group four: any NSAID user acute/chronic combined. Non-NSAID users were the control group.

Owing to the common use of these drugs as OTC, 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 six-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 aspirin/NSAID chronic use. The questionnaire was administered within five days from 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 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 six months.

Data collection

We recorded data from the patient's EMR on demographics, co-morbidities, admission for COVID-19, electronic prescription of antipyretics including NSAIDs during infection, and within the past six 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 two 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; 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.

Role of the funding source

No funding was received for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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 (figure 1). Overall, 17% of patients were asymptomatic, 70% reported mild symptoms, 7% were considered moderate, and 6% were severe.

Of the 503 patients included; 40 (7.95%) used ibuprofen during infection (group one), 17 (3.4%) used other NSIADs during infection (group two), 96 (19%) used NSAIDs chronically before infection (group three), 146 (29%) had any NSAID use acute and/or chronic users combined (group four), 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 users were slightly higher in men than in women (52% vs 48%).

For type of NSAIDs used, see supplemental table 1 and 2. For other COVID-19 related supportive drugs used in this cohort of patients, see supplemental table 3.

Antibiotics, oseltamavir, and acetaminophen use were 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 one was 3575 mg (SD 3421), and the mean 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 vs 3.1% in the non-NSAID users. Table 2 shows the unadjusted and adjusted HRs from the Cox regression analysis.

Ibuprofen acute use during infection was not associated with a greater risk of mortality 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, NSIAD chronic use was not associated with greater risk of mortality relative to non-NSIAD 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 Sever COVID-19:

The adjusted RR of mortality, admission, oxygen-support, and sever COVID-19 disease in acute ibuprofen users (group one) 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 non-NSIAD 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 sever COVID-19 disease compared to non-NSAID users. See table 4 for unadjusted and adjusted RR of outcomes in acute/chronic NSAID users (group four), and figure 2; shows unadjusted and adjusted RR for the different outcomes in NSIAD user (group four).

Admission: In our cohort, 22.5% of patients in group one, 35.3% in group two, 49% in group three, and 41.8% in group four were admitted vs 17.4% in the non-NSAID user group. The adjusted RR of admission was higher in acute/chronic NSAID users (group four) compared to non-NSAID users (RR 1.5419 [95% CI 1.0605 - 2.2420]; $p=0.0234$).

Odds of Admission in Ibuprofen Users (group 1): Ibuprofen acute 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 users groups compared to non-NSAID users, see figure 3, 4, and 5 KM plots for time to clinical improvement in each group. Time to clinical improvement in ibuprofen acute users' did not significantly differ from non-NSAID users (median, 5.50 days vs. 6 days; adjusted HR, 0.998; 95% confidence interval [CI], 0.474 to 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 to 1.549; $P=0.9991$), and 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 to 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 length of stay, 1.091; $P=0.6353$). See figure 6 KM plot for length of stay.

Antibiotic Use:

Of the 380 patients that 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)]; $p=0\cdot1817$), (adjusted RR 1·1536 (0·6802 - 1·9567)]; $p=0\cdot5960$), respectively. (table 5).

Discussion

Despite the risk of indication bias, not favoring outcomes in patients taking ibuprofen, as it is likely that patients with more severe symptoms would be more likely to take it; we found no association between the use of ibuprofen acutely 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, 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 that were admitted for other reasons, and happened to be COVID-19 positive. In addition, in the early stages of this study, patients at NGHHA were admitted regardless of severity of symptoms; while awaiting to be transferred to quarantine.

Concerns with NSAIDs worsening lung infection is not new or specific to COVID-19, in fact previous pharmacoepidemiological data, and pharmacovigilance analysis report that NSAID exposure increases the risk of severe pulmonary complications, supported by experimental data, and pharmacological 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 of the COVID-19 pandemic, samples of plasma of infected patients had significantly higher Angiotensin II levels compared to healthy individuals, levels were linearly associated with viral load, and lung injury. In addition, the authors suggested that angiotensin receptor blocker (ARB) drugs as potential repurposing treatments for COVID-19.²¹ This study contradicts the theory that up-regulating ACE2 is associated with adverse outcomes, as ACE2 acts as a negative regulator and decreases Angiotensin II, therefore, a clinical trial to test the benefit of ibuprofen in COVID-19 patients is currently ongoing.²²

Other NSAIDs like naproxen have also been fairly researched for its antiviral potential, and showed potent in vitro activity against SARS-CoV²³ and antiviral activity against influenza A and B viruses in animal models.^{24,25} Which 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.^{26,27}

Our study has several limitations. First, this was an observational study; no causal conclusion can be made, and connections should be interpreted as associations. Second, as this study was conducted at an early stage of the pandemic outbreak in Saudi, 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 questionnaire, and in-hospital electronic administration records were used to confirm the study of 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 found no significant difference in time to clinical improvement or length of stay compared to non-NSAID users.

Declarations

Ethical Guidelines

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.

Competing Interests

We declare no competing interests.

Data sharing

The data are available upon request to corresponding author. Queries and applications for datasets should be directed to Laila Carolina Abu Esba; email: abuesbala@ngha.med.sa

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Tables

Table 1. Baseline Characteristics of Patients with COVID-19 by NSAID User Groups, and Non-NSAID Users:

Characteristics	Group 1 ^a (n = 40 [7·9%])	Group 2 ^b (n = 17 [3·4%])	Group 3 ^c (n = 96 [19%])	Group 4 ^d (n = 146 [29%])	Group 5 ^e (n = 357 [71%])
Sex					
Male (n=288)	23 (57·5)	8 (47·06)	51 (53·1)	76 (52)	212 (59·4)
Female (n= 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	16 (40)	8 (47)	76 (79·2)	97 (66·4)	119 (33·3)
Hypertension (n= 103)	2 (5)	2 (11·8)	49 (51)	51 (34·9)	52 (14·6)
Diabetes (n=113)	3 (7·5)	3 (17·7)	56 (58·3)	60 (41·1)	53 (14·8)
Dyslipidemia (n=88)	4 (10)	1 (5·9)	41 (42·7)	45 (30·8)	43 (12)
Asthma or COPD (n=26)	4 (10)	0	10 (10·4)	13 (8·9)	13 (3·6)
CVD (n= 27)	0	1 (5·9)	17 (17·7)	18 (12·3)	9 (2·5)
Renal impairment (n=16)	0	0	6 (6·3)	6 (4·1)	10 (2·8)
Liver impairment (n=6)	0	0	1 (1)	1 (0·7)	5 (1·4)
Malignancy (n=7)	0	1 (5·9)	3 (3·1)	4 (2·7)	3 (0·8)
Hypothyroidism (n=)	2 (5)	0	5 (5·2)	7 (5)	7 (2)

Abbreviations: 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

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 (n = 40)	Group 5 Non-NSAID users ^f (n = 357)	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	p value
	1 (2.5)	11 (3.1)	0.518 (0.067-3.981)	0.5269	0.626 (0.073-5.410)	0.6706	0.632 (0.073-5.441)	0.6758
	Group 2 ^c (n = 17)	Group 5 Non-NSAID users ^f (n = 357)	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
	1 (5.9)	11 (3.1)	5.340 (0.587 - 48.590)	0.1370	6.072 (0.643 - 57.293)	0.1153	5.815 (0.435 - 77.752)	0.1833
	Group 3 ^d (n = 96)	Group 5 Non-NSAID users ^f (n = 357)	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	p value
	6 (6.3)	11 (3.1)	0.620 (0.230 - 1.669)	0.3440	0.382 (0.132 - 1.112)	0.0775	0.392 (0.133 - 1.157)	0.0900
	Group 4 ^e (n = 146)	Group 5 Non-NSAID users ^f (n = 357)	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
	7 (4.8)	11 (3.1)	0.660 (0.254 - 1.716)	0.3942	0.479 (0.173 - 1.322)	0.1553	0.492 (0.178 - 1.362)	0.1721

Abbreviations: 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 that used ibuprofen only, during infection

^c Group 2: Other aspirin/NSAID acute User 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 Sever COVID-19 in Acute Ibuprofen users:

	Unadjusted Relative risk (95% CI‡)	p value	Age, sex adjusted Relative risk (95% CI‡)	p value	Fully adjusted ^a Relative risk (95% CI‡)	p 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

Abbreviations: COVID-19, coronavirus disease 2019

^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.

Table 4: Relative Risk of Death, Admission, Oxygen-Support, and Severe COVID-19 in Acute and Chronic NSAID users combined:

	Unadjusted Relative risk (95% CI‡)	p value	Age, sex adjusted Relative risk (95% CI‡)	p value	Fully adjusted ^a Relative risk (95% CI‡)	p 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)	<.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

Abbreviations: COVID-19, coronavirus disease 2019; 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.

Table 5: Relative Risk of Antibiotic Prescribing in NSAID Users:

	Unadjusted Relative risk (95% CI†)	P value	Age, sex adjusted Relative risk (95% CI†)	P value	Fully adjusted ^a Relative risk (95% CI†)	P 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

Abbreviations: 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 that used ibuprofen only, during infection

^c Group 3: chronic NSAID users

^d Group 4: acute, and chronic NSAID users combined

Figures

Figure 1

Patient Selection: Abbreviations: NSAID, Nonsteroidal anti-inflammatory drugs; COVID-19, coronavirus disease 2019; EMR, Electronic Medical Record; N, Number. * 7 (1.4%) patients were both chronic users of NSAIDs and used ibuprofen acutely during their infection

Estimates and 95% CI of Relative Risks among NSAID Users

Figure 2

Relative Risk for Death, Admission, Oxygen Support Requirement, and Severity, Unadjusted and Adjusted, for any NSAID use (Groups 4a) vs Non-NSAID Users. Abbreviations: NSAID, Nonsteroidal anti-inflammatory drugs; a Group 4: acute, and chronic NSAID users combined

Figure 3

Kaplan-Meier plot for Time to Clinical Improvement Acute Ibuprofen Use (Group 1 a) vs Non-NSAID Users. Abbreviations: NSAID, Nonsteroidal anti-inflammatory drugs; a Group 1: patients that used ibuprofen only, during infection

Figure 4

Kaplan-Meier plot for Time to Clinical Improvement in NSAID Chronic Users (Group 3a) vs Non-NSAID Users. Abbreviations: NSAID, Nonsteroidal anti-inflammatory drugs; a Group 3: chronic NSAID users

Figure 5

Kaplan-Meier plot for Time to Clinical Improvement any NSAID Use (Group 4 a) vs Non-NSAID Users. Abbreviations: NSAID, Nonsteroidal anti-inflammatory drugs; a Group 4: acute, and chronic NSAID users combined

Figure 6

Kaplan-Meier plot for Length of Stay in any NSAID User (Group 4 a) vs Non-NSAID Users. Abbreviations: NSAID, Nonsteroidal anti-inflammatory drugs; a Group 4: acute, and chronic NSAID users combined

Supplementary Files

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- [SupplementalTables.docx](#)