Cyclooxygenase inhibitor use is associated with increased COVID-19 severity

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Abstract

BACKGROUND

Cyclooxygenase (COX) inhibitors including non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to reduce pain, fever, and inflammation but have been associated with complications in community acquired pneumonia and other respiratory tract infections (RTIs). Conclusive data are not available about potential beneficial or adverse effects of COX inhibitors on COVID-19 patients.

METHODS

We conducted a retrospective, multi-center observational study by leveraging the harmonized, high-granularity electronic health record data of the National COVID Cohort Collaborative (N3C). Potential associations of eight COX inhibitors with COVID-19 severity were assessed using ordinal logistic regression (OLR) on treatment with the medication in question after matching by treatment propensity as predicted by age, race, ethnicity, gender, smoking status, comorbidities, and BMI. Cox proportional hazards analysis was used to estimate the correlation of medication use with morbidity for eight subcohorts defined by common indications for COX inhibitors.

RESULTS

OLR revealed statistically significant associations between use of any of five COX inhibitors and increased severity of COVID-19. For instance, the odds ratio of aspirin use in the osteoarthritis cohort (n=2266 patients) was 3.25 (95% CI 2.76 - 3.83). Aspirin and acetaminophen were associated with increased mortality.

CONCLUSIONS

The association between use of COX inhibitors and COVID-19 severity was consistent across five COX inhibitors and multiple indication subcohorts. Our results align with earlier reports associating NSAID use with complications in RTI patients. Further research is needed to characterize the precise risk of individual COX inhibitors in COVID-19 patients.

As of 3 April 2021, severe acute respiratory syndrome associated with coronavirus-2 (SARS-CoV-2) has infected more than 128 million people and caused more than 2.8 million deaths worldwide.[1] SARS-CoV-2 is the cause of the coronavirus disease of 2019 (COVID-19), a condition characterized by pneumonia, hyperinflammation, hypoxemic respiratory failure, a prothrombotic state, cardiac dysfunction, substantial mortality, and persistent morbidity in some survivors.[2]

Cyclooxygenase (COX) inhibitors represent a large and heterogeneous class of medications defined by their ability to inhibit COX, an enzyme that catalyzes the conversion of arachidonic acid to prostaglandins. The two COX isoforms differ in their distribution and physiologic roles. COX-1 is ubiquitously and constitutively expressed and produces prostaglandins implicated in homeostatic functions such as maintenance of gastrointestinal (GI) mucosal integrity. Many of the adverse effects of conventional non-steroidal anti-inflammatory drugs (NSAIDs) (including GI bleeding, peptic ulceration, hemorrhagic cerebrovascular accident, renal impairment, wheezing, and rash) are thought to be primarily related to inhibition of COX-1. In contrast, COX-2 is induced by cytokines and produces prostaglandins that mediate pain and inflammation.[3] Due to their widespread use, NSAIDs are common causes of serious adverse events that frequently necessitate hospitalization.[4]

NSAIDs have numerous potentially deleterious effects on immune function and may also mask warning signs of severe infection such as fever and pain during the course of community-acquired pneumonia. NSAID exposure in the early stage of community-acquired pneumonia has been associated with a delayed diagnosis and more severe clinical course,[5,6] but the quality of available research has been called into doubt and recent studies have failed to reproduce the proposed association.[7,8] Some NSAIDs have been associated with abnormalities of immune function.[9,10] Here, we investigate seven NSAIDs and acetaminophen, which has COX-2 inhibitory and other pharmacological activities.[11] For conciseness, we will refer to the group of NSAIDs and acetaminophen as COX inhibitors.

Existing evidence regarding the effect on COVID-19 of exposure to COX inhibitors is inconclusive. Indomethacin has a direct antiviral effect against the SARS-CoV virus,[12] and a clinical trial to assess the effects of adding naproxen to the treatment of critically ill patients hospitalized for COVID-19 infection is underway (ClinicalTrials.gov identifier: NCT04325633). On the other hand, an apparent increase in the severity of clinical symptoms was noted in French COVID-19 patients taking ibuprofen.[7] In the early months of the pandemic, a study was conducted with data from OpenSAFELY, a secure health analytics platform that covers 40% of all patients in England. The study ran from 1 March 2020 to 14 June 2020, looking at two (partially overlapping) cohorts: 2,463,707 patients in the general population with a history of NSAID use, and 1,708,781 patients with a diagnosis of rheumatoid arthritis or osteoarthritis. In both cohorts, the treatment group was defined as all patients who were prescribed NSAIDs within 4 months of the study's start date; all others were considered controls. The primary outcome was COVID-19 related death: no significant increase in mortality was shown in the treatment group of either cohort.[13] Other small cohort studies ranging in size from 293 to 1222 patients failed to show increased risks with use of various NSAIDs.[14–17] An observational study on 98 patients who had received aspirin within 24 hours of admission or 7 days before admission compared to 314 patients who had not received aspirin showed significant associations of aspirin use with decreased severity and mortality of COVID-19.[18]

Given the common use of COX inhibitors and the inconclusiveness of these prior studies, additional insight on potential risks of COX inhibitor use by COVID-19 patients is needed. Our research leverages data from the National COVID Cohort Collaborative (N3C), a centralized, harmonized, high-granularity electronic health record (EHR) repository with the largest, most representative U.S. cohort of COVID-19 cases and controls to date. We assessed associations of eight COX inhibitors with clinical severity and mortality of COVID-19 patients, demonstrating significant associations of five COX-inhibitors with increased COVID-19 severity and in two cases, mortality.

Methods

STUDY POPULATION

All patient data were accessed through the National COVID Cohort Collaborative (N3C) (covid.cd2h.org). N3C aggregates and harmonizes EHR data across 38 clinical organizations in the United States, including the Clinical and Translational Science Awards (CTSA) Program hubs. For this analysis, data were derived from the 24 centers that provided data for all predictors used in the regression analysis described below. Fourteen centers did not provide data on Body Mass Index (BMI) and were not included in this study. N3C harmonizes data across four clinical data models and provides a unified analytical platform in which data are encoded using the Observational Medical Outcomes Partnership (OMOP)[19] version 5.3.1 and provides shared phenotype definitions such as those for positive COVID-19 laboratory tests and COVID-19 clinical severity categories.[20,21]

ELIGIBILITY CRITERIA

Criteria for the current study were determined as follows. The COVID-19 positive cohort (Supplemental Table S1) was defined as those patients with any encounter after January 1, 2020 and positive SARS-CoV-2 laboratory test (polymerase chain reaction or antigen). For this study, data from up to February 2, 2021 were included. For each medication, we defined subcohorts based on an indication for use of one of eight COX inhibitors (acetaminophen, aspirin, celecoxib, diclofenac, ibuprofen, ketorolac, meloxicam, naproxen) that were neither sex-specific nor limited to pediatric age groups on the basis of information in the DrugCentral resource.[22] Subcohorts of COVID-19 patients who had a history of that indication prior to contracting COVID-19 were identified, as determined by a condition era[23] that began before the date of COVID-19 diagnosis. A treatment group within the subcohort was defined as patients whose drug era[23] for the medication in question began on or before the date of COVID-19

diagnosis and continued for at least one day. All other patients from the subcohort were used in propensity matching to define the control group. A secondary analysis was performed on all patients receiving the COX inhibitor regardless of indication.

Only patients with complete records (no missing values for any covariate used in propensity matching or logistic regression) were included for further analysis. We studied the drug-indication combinations for which there were at least 50 treated patients. OMOP concept ID codes for all drugs and drug indications used in this analysis are listed in Supplemental Tables S2 and S3.

OUTCOMES

The primary outcome of interest was the COVID-19 clinical severity category. Clinical severity was classified into five categories using the Clinical Progression Scale (CPS) established by the World Health Organization (WHO) for COVID-19 clinical research[24]: “mild” (outpatient, WHO severity 1-3); “mild ED” (outpatient with ED visit, WHO severity 3); “moderate” (hospitalized without invasive ventilation, WHO severity 4-6); “severe” (hospitalized with invasive ventilation or ECMO, WHO severity 7-9); and “mortality/hospice” (hospital mortality or discharge to hospice, WHO Severity 10).[21] For the purposes of the ordinal logistic regression (OLR) analysis described below, patients were assigned to severity groups according to the maximum clinical severity during their index encounter,[21] which was defined as the medical encounter during which a positive COVID-19 test was documented for the first time. Secondary outcomes were all-cause mortality recorded at any time following the COVID-19 diagnosis as well as analyses of the entire groups of COVID-19 patients treated with the medications of interest without restriction to indications.

STUDY DESIGN

For each of the eight COX Inhibitors, we constructed a codeset containing concept IDs representing all formulations of the medications (see Supplemental Table S3) using ATLAS (http://atlas-covid19.ohdsi.org/), the graphical user interface for the OMOP common data model.[25]

We explored the potential association between treatment with a pharmaceutical agent and severity of COVID-19. Two strategies were chosen to minimize the potential effects of confounding. To control for confounding due to covariate imbalance, we compared outcomes in a propensity-matched group of patients who had an indication associated with the COX inhibitor of interest. This resulted in subchorts of relatively homogeneous patient clusters. Propensity score matching was performed to correct residual covariate imbalance within these subcohorts.

Using the DrugCentral resource[22], we developed the following list of representative indications: osteoarthritis, rheumatoid arthritis, angina pectoris, migraine, myocardial infarction, pain, headache, and fever (OMOP concept id codes in Supplemental Table S2).[19] Figure 1 summarizes the procedure used to define the aspirin-osteoarthritis subcohort; other subcohorts were defined analogously.

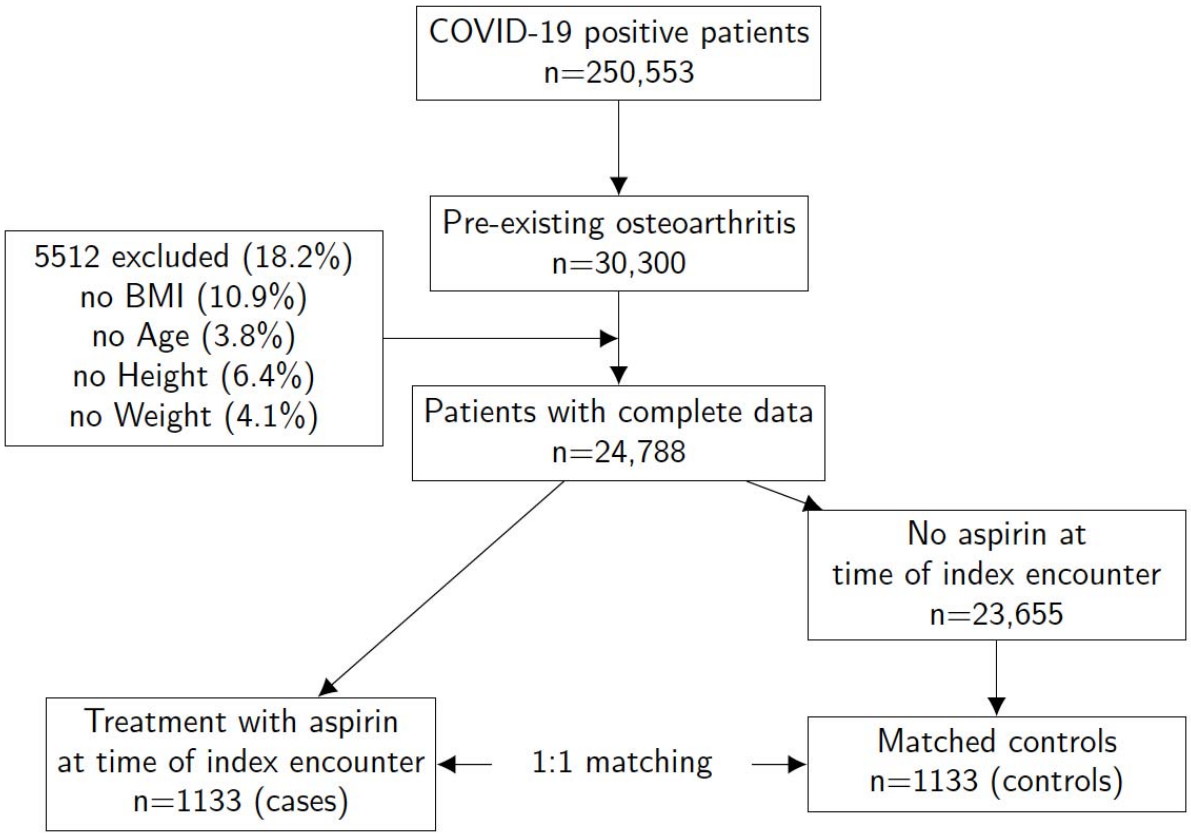

Figure 1. Definition of subcohorts by drug indication. In this example, the osteoarthritis subcohort is used to define case/control groups for treatment with aspirin. Other subcohorts were defined analogously.

Propensity matching

We performed propensity matching using the "nearest" method implemented in the R MatchIt package. Each patient from the treated group was matched to the patient in the untreated group with the closest propensity score. The propensity formula included age, race, ethnicity, gender, smoking status, Charlson Comorbidity Index, and BMI.

Ordinal logistic regression (OLR)

To investigate the association of treatment and other covariates with COVID-19 severity, we performed OLR using the *polr* function of the MASS R package. The dependent variable was COVID-19 severity, an ordered factor with levels "mild", "mild ED", "moderate", "severe", and

"mortality/hospice".[21] We assessed the relationship between COVID-19 severity and treatment with each medication under consideration as a part of multiple OLR with age, race, ethnicity, gender, smoking status, Charlson Comorbidity Index, and BMI as additional predictors. For treatment with the medication we recorded the t value, the corresponding p value, and the odds ratio along with its 95% confidence interval.

Cox proportional hazards modeling

A single index encounter was defined for each laboratory-confirmed positive patient as described previously.[21] Survival time was defined with respect to this encounter. For each patient, the latest visit and date of death (if observed) was recorded to measure right censoring (the last date for which death outcome can be ruled out) and survival, respectively. The *survival* R package was used to produce Kaplan-Meier survival curves, compute Cox proportional hazards regression using the same predictors as with OLR, and visualize Schoenfeld residuals.

RESULTS

We evaluated 250,533 patients with COVID-19 in a retrospective cohort study. Mean age was 41.6 years, and 115,828 patients (46.2%) were men. The Charlson Comorbidity Index was used to account for comorbidities,[26] and the Clinical Progression Scale (CPS) established by the World Health Organization (WHO) for COVID-19 clinical research was used to stratify patients according to severity.[24] A total of 6138 deaths were recorded in the COVID-19 cohort (1.9%). Supplemental Table S1 summarizes the demographics of the cohort.

We evaluated eight COX inhibitors. For each medication, we chose one or more representative indications with at least 50 cases, collected all individuals diagnosed with COVID-19 who additionally had been diagnosed with the representative drug indication, and then divided this cohort into individuals treated with the medication (cases) and those who were not (controls). We reasoned that this would define more balanced case and control groups than if we compared all COVID-19 patients who were receiving the medication with those who were not,

since medication use is a proxy for the distribution of comorbidities, some of which may correlate strongly with COVID-19 outcome. To further reduce the effect of confounders, we performed propensity matching[27] to match drug-treated and untreated patients according to age, race, ethnicity, gender, smoking status, Charlson Comorbidity Index, and BMI. Table 1 shows a representative cohort before and after propensity matching.

		Before propensity matching		After propensity matching	
	Aspirin	Control	SMD	Control	SMD
n	1133	23655	-	1133	-
Age	67.5 ± 12.0	61.4 ± 14.1	0.465	67.9 ± 11.9	0.035
BMI	32.1 ± 8.4	32.4 ± 8.2	0.037	32.2 ± 8.4	0.016
Charlson	2.55 ± 2.71	1.87 ± 2.47	0.264	2.53 ± 2.85	0.007
Race					
- African American	307 (27.2%)	5069 (21.4%)		271 (24.0%)	
- Asian	21 (1.9%)	360 (1.5%)		19 (1.7%)	
- Pacific Islander	1 (0.1%)	23 (0.1%)		0	
- White	715 (63.3%)	15900 (67.2%)		752 (66.6%)	
- Other	10 (0.9%)	289 (1.2%)		14 (1.2%)	
- Unknown	75 (6.6%)	2018 (8.5%)		73 (6.5%)	
Ethnicity					
- Hispanic or Latino	81 (7.2%)	1897 (8.0%)		84 (7.4%)	
- Not Hispanic or Latino	1018 (90.2%)	21145 (89.4%)		1013 (89.7%)	
- Unknown	30 (2.7%)	617 (2.6%)		32 (2.8%)	
Sex					
- Female	591 (52.3%)	14348 (60.6%)		599 (53.1%)	
- Male	538 (47.7%)	9310 (39.4%)		530 (46.9%)	
- Other	0 (0.0%)	1 (0.0%)		0	
Smoking status					
- Current or Former	142 (12.6%)	2746 (11.6%)		135 (12.0%)	

- Non smoker	987 (87.4%)	20913 (88.4%)		994 (88.0%)	
Severity Type					
- Mild	245 (21.7%)	13806 (58.4%)		576 (51.0%)	
- Mild ED	73 (6.5%)	2463 (10.4%)		109 (9.7%)	
- Moderate	621 (55.0%)	5879 (24.8%)		337 (29.8%)	
- Severe	66 (5.8%)	523 (2.2%)		23 (2.0%)	
- Mortality/hospice	124 (11.0%)	988 (4.2%)		84 (7.4%)	

Table 1. Aspirin-treated osteoarthritis subcohort. SMD: standardized mean difference.

OLR was performed to assess the relationship between use of the candidate medication and other covariates (age, race, ethnicity, gender, smoking status, Charlson comorbidity, and BMI) and COVID-19 severity (“mild”, “mild ED”, “moderate”, “severe”, “mortality/hospice”). Sixteen of the 21 cohort comparisons indicated a significant association of COX inhibitor use with increased COVID-19 severity (Table 2). Figure 2 shows the distribution of severity classes in osteoarthritis cohorts for aspirin, ibuprofen, and acetaminophen, as well as the distribution of severity classes in the entire COVID-19+ cohort for aspirin. In agreement with previous studies[28,29], we also consistently observed a significant association of age, male sex, and Charlson comorbidity with COVID-19 severity (Supplemental Table S1 - S21). OLR relies on an assumption of proportional odds, which we verified is tenable for these data (Supplemental Figure S22). We calculated the E-value for the observed values of the odds ratio to assess the sensitivity of our findings to uncorrected confounders.[30] The observed odds ratio of 3.3 for the association of aspirin with increased COVID-19 severity in the aspirin-osteoarthritis subcohort could not be explained away by an unmeasured confounder that was associated with both the treatment and the outcome by a odds ratio of less than 3.0-fold each above and beyond the confounders included in the regression. E-values for other subcohorts are shown in Supplemental Table S4.

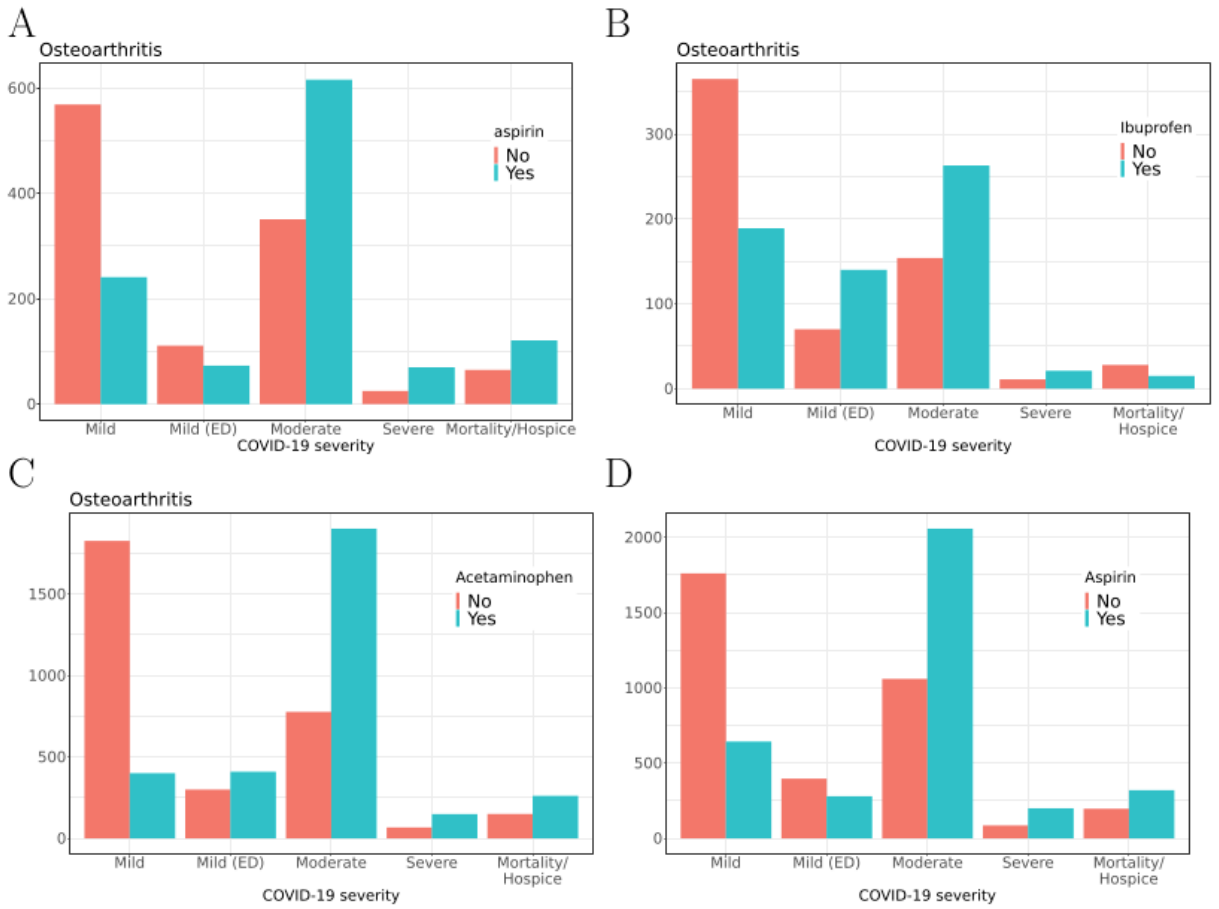

Figure 2. COVID-19 severity in a subcohort of osteoarthritis patients taking vs. not taking **A)** aspirin, **B)** ibuprofen or **C)** acetaminophen; and **D)** entire COVID-19 cohort taking vs. not taking aspirin. Severity of COVID-19 by group is shown on the x-axis, and number of patients is shown on the y-axis.

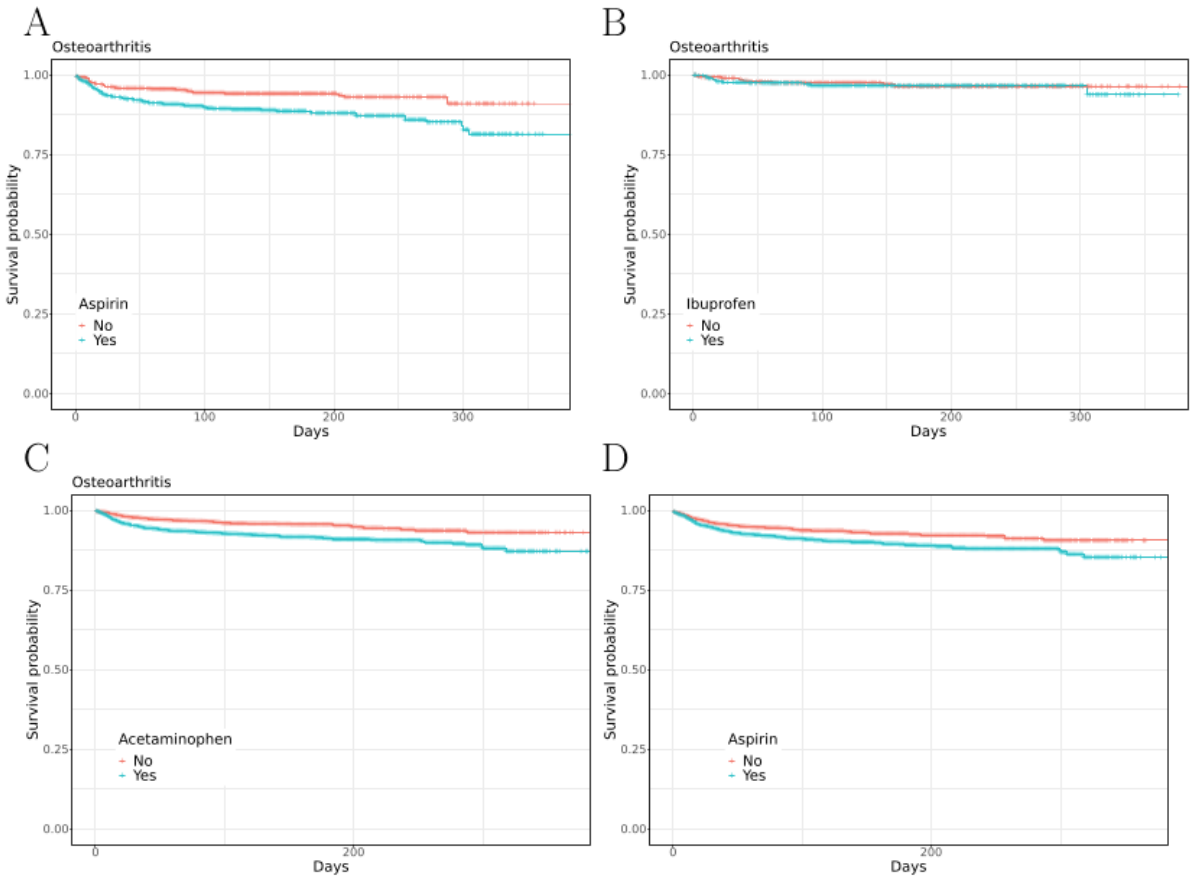

Figure 3. Kaplan-Meier survival curves for a subcohort of osteoarthritis patients taking vs. not taking **A)** aspirin, **B)** ibuprofen or **C)** acetaminophen and **D)** entire COVID-19+ cohort taking vs. not taking aspirin.

medication	indication	n
aspirin	angina pectoris***	696
	fever***	1,604
	migraine***	332
	myocardial infarction***	1,312
	osteoarthritis***	2,266
	pain***	5,464
	rheumatoid arthritis**	186
ibuprofen	fever***	2,480
	headache***	1,604
	osteoarthritis***	1,240
	pain***	5,774
naproxen	pain*	1,930
acetaminophen	osteoarthritis***	6,394
	pain***	21,094
	rheumatoid arthritis***	524
ketorolac	pain***	3,660
meloxicam	osteoarthritis	828
diclofenac	osteoarthritis	1,120
	pain	1,794
celecoxib	osteoarthritis	426
	pain	594

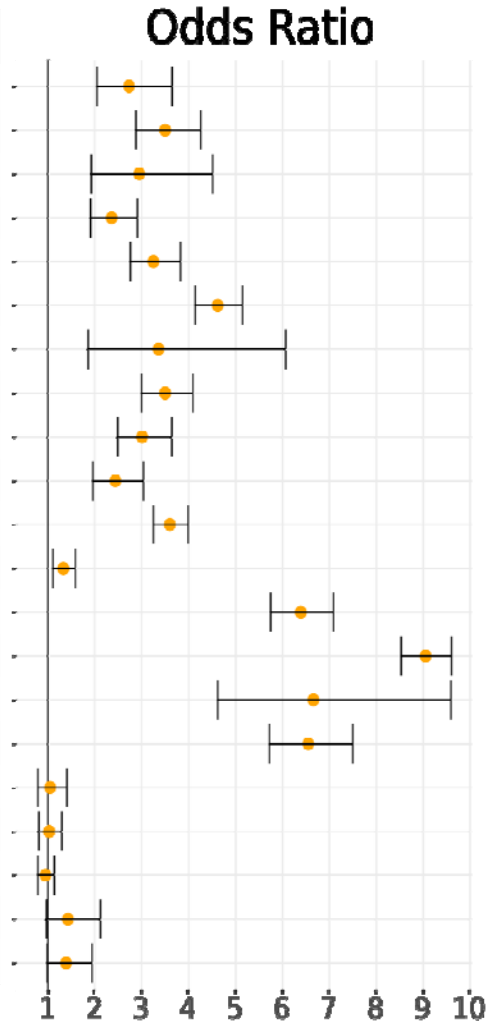

Table 2. Association of COX inhibitors with COVID-19 severity. For each combination of medication and disease indication, subcohorts were constructed using propensity matching. Ordinal logistic regression was used to assess association with COVID-19 severity. Odds ratios, 95% confidence intervals, and sample sizes (treated plus control) are shown. ***p < 0.001, **p < 0.01, *p < 0.05 after Bonferroni correction for 21 tests. Details for each subcohort are provided in Supplemental Tables S5-S25 and Supplemental Figures S1-S21.

To assess the effect of COX inhibitors on mortality, survival was measured in cohorts using the Cox proportional hazards model (Figure 3). The proportional hazards assumption was assessed by visualizing Schoenfeld residuals (Supplemental Fig. S23). We observed that aspirin and acetaminophen but not the other six tested COX inhibitors were associated with increased

mortality. Supplemental Tables S21-S60 and Supplemental Figures S1-S25 show detailed results. Comparable results were obtained by analyzing the entire cohort of COVID-19 per medication (Supplemental Figures S23-S31 and Tables S47-S62).

Discussion

Our findings show an association of COX inhibitors with increased COVID-19 severity across five of the eight tested agents (aspirin, ibuprofen, ketorolac, naproxen, and acetaminophen). Diclofenac, meloxicam, and celecoxib did not show significant associations with severity in our study. Interestingly, these three agents display selectivity for COX-2.[31]

COX-2 selective inhibitors were developed with the goal of avoiding the adverse GI effects associated with non-selective NSAIDs, but were found to be associated with a higher risk of cardiovascular adverse events including stroke and myocardial infarction.[32,33] Increased cardiovascular risk was subsequently shown to be associated also with non-selective NSAIDs in multiple studies.[34]

NSAIDs have multiple effects on the immune system, including inhibition of neutrophil adherence, decreased neutrophil degranulation and oxidant production, inhibition of neutrophil elastase activity and induction of neutrophil apoptosis, and inhibition of antibody production.[10,35] Several studies have documented an association between NSAID use and risk of severe pulmonary complications in the setting of community acquired pneumonia and acute viral infection.[5] Other studies have failed to find an association of NSAIDs with a worse prognosis among patients admitted with influenza.[8] Conceivably, the increased risk could be related to effects of NSAIDs on the immune system or to a delay in treatment related to the masking of symptoms of infection by an NSAID.[36] We did not observe an association of NSAID use with neutrophil counts in COVID-19 patients (data not shown). Insufficient data was available to assess other potential associations with immune cell function. Acetaminophen, which has a mechanism of action different from that of NSAIDs, has previously been associated with decreased mortality in critically ill patients.[37] These considerations, together with isolated reports

of exacerbation of the clinical course of COVID-19 following ibuprofen exposure, have led to recommendations against the use of ibuprofen for managing symptoms of COVID-19.[38]

Strengths and limitations of this study

Observational studies such as retrospective EHR cohort analysis are subject to confounding. In the case of our study, the decision of whether to treat a patient with a COX inhibitor could in principle be correlated with the outcome of interest (COVID-19 severity). We applied two strategies to mitigate confounding: (i) analysis of subcohorts according to indication, and (ii) propensity matching. However, in observational studies a risk of residual confounding persists because the efficacy of propensity matching is limited to known and measured factors. Exposure to the drugs of interest, most of which are available without a prescription, was likely to be captured incompletely in the EHR data used in the analysis. Thus, it is possible that there was unrecorded use of COX inhibitors in the untreated group.

Our study uses a five-level ordinal measure of COVID-19 outcome that may allow increased sensitivity compared with some previous efforts that use only COVID-19 mortality to measure outcome.

Conclusions

The many NSAIDs vary with respect to their ability to inhibit each isoenzyme (COX-1 and COX-2). Aspirin shows the lowest degree of COX-2 selectivity, while celecoxib is one of the most COX-selective NSAIDs.[39] In addition, celecoxib possess activities unrelated to COX inhibition.[40] Therefore, it appears plausible that the adverse effect profile of COX inhibitors in individuals with COVID-19 may differ from medication to medication. The results of our observational study demonstrated a significant association of the use of five of eight different COX inhibitors with increased clinical severity and mortality. We did not find evidence for an association of increased COVID-19 severity with diclofenac, meloxicam and celecoxib, which are selective for

COX-2,[31] raising the possibility of agent-specific risk profiles for individual COX inhibitors. Additionally, we demonstrate a significant association between COVID-19 severity and acetaminophen use, which does not provide support for recent recommendations for acetaminophen for symptom relief in COVID-19. While our findings suggest the importance for clinicians to carefully consider which COX inhibitor to prescribe, additional research will be required to confirm our results in other settings and to address the question of whether different COX inhibitors have different adverse effect profiles in treating COVID-19.

IRB

The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol #IRB00249128 or individual site agreements with NIH. The N3C Data Enclave is managed under the authority of the NIH; information can be found at https://ncats.nih.gov/n3c/resources.

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Conflicts of Interest

Katie Rebecca Bradwell: employee of Palantir Technologies; Melissa A. Haendel: co-founder Pryzm Health; Julie A. McMurry: Cofounder, Pryzm Health; Jasvinder Singh: JAS has received consultant fees from Crealta/Horizon, Medisys, Fidia, PK Med, Two labs Inc, Adept Field Solutions, Clinical Care options, Clearview healthcare partners, Putnam associates, Focus forward, Navigant consulting, Spherix, MedIQ, Jupiter Life Science, UBM LLC, Trio Health, Medscape, WebMD, and Practice Point communications; and the National Institutes of Health and the American College of Rheumatology. JAS owns stock options in TPT Global Tech, Vaxart pharmaceuticals and Charlotte's Web Holdings, Inc. JAS previously owned stock options in Amarin, Viking and Moderna pharmaceuticals. JAS is on the speaker's bureau of Simply Speaking. JAS is a member of the executive of Outcomes Measures in Rheumatology (OMERACT), an organization that develops outcome measures in rheumatology and receives arms-length funding from 12 companies.

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