Ibuprofen and COVID-19 Severity

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Purpose: Investigate whether ibuprofen prescription prior to COVID-19 infection is associated with the worst severity that COVID-19 patients reach during the course of their disease.

Data: Data were examined for 33,567 COVID-19 positive patients with data on prior ibuprofen prescription. Data are pooled from 23 health systems that represent 146 hospitals, spanning 11 states and covering 89 million patients, collected from April 13 to April 20, 2020.

Observations: In this sample, COVID-19 positive patients who had been prescribed ibuprofen prior to infection were less likely to require admission and less likely to die.

Background

In a letter to The Lancet Respiratory Medicine published online in March, Fang et al. speculated that use of medications that upregulate angiotensin-converting enzyme 2 (ACE2) increases the risk of severe COVID-19 disease.[1] That speculation was based on a finding that SARS-CoV-2 uses ACE2 to bind to its target cell. While the authors focused primarily on two types of medications, ACE-inhibitors and angiotensin II receptor blockers, they also suggested that ibuprofen can increase ACE2 levels.

Those early speculations led to suggestions that patients should stop using NSAIDs, including ibuprofen, to treat symptoms of COVID-19.[2] These suggestions were controversial due to the scarcity of supporting data. Recent review of existing literature concluded that evidence is urgently needed to better understand the relationship between prescribed ibuprofen and COVID-19.[3,4] This analysis was undertaken in part to determine if there was any evidence of a relationship in a larger data set.

Methods

Chronic outpatient ibuprofen usage is difficult to know with certainty. An imperfect but accepted approach in other population-based observational research related to ibuprofen has been to look to prescription information.[5,6] In this report, the ibuprofen group includes patients that were prescribed scheduled ibuprofen of any dosage with a start date prior to March 1st 2020 with at least two refills indicated, and the prescription was still active on their medication list within the 30 days prior to their COVID-related admission or 30 days prior to their COVID-19 positive date. March 1st was chosen as the start of the month when the Lancet article was published, so prescription patterns prior to this time would not be affected by the article. Patients with prescriptions written “PRN” (taken as needed) were not defined as taking ibuprofen to restrict the population to patients most likely to be taking this prescription regularly.

Severity was defined by a six-point scale (1=No admission, 2=Admission, no respiratory support, 3=Admission with basic respiratory support, 4=Admission with advanced respiratory support, 5=ventilation, 6=Death). Advanced respiratory support includes patients with an oxygen flow rate above 30 L/min, or patients with a high-flow oxygen delivery method (includes BiPAP, high-flow nasal cannula, t-piece, blow-by, OptiFlow or CPAP if administered during the day). Basic respiratory support includes patients with an oxygen flow rate greater than zero and under 30 L/min.

Patients were classified as COVID-19 positive if they had a positive SARS-CoV-2 lab result or a COVID-19 diagnosis (U07.1 (ICD-10), 840539006 (SNOMED)). The severity for each patient was recorded for a 6-week evaluation period following the sample collection date of the first positive test or the first date a COVID-19 diagnosis was recorded, whichever was earlier.

Worst severity during the course of the COVID-19 illness is defined as highest level of medical care a patient required, or death. These analyses only include patients with a known outcome (never admitted or alive six weeks after a positive test, admitted and discharged, or died). This means the mortality rate is likely inflated, since currently hospitalized patients have not yet had an outcome.

We examined the association between ibuprofen prescription and the worst severity experienced by COVID-19 positive patients using an ordinal logistic regression model.[7] We verified whether the proportional odds assumption held by determining the probability of meeting a severity above each level for each group and calculating the difference in probability for each severity partition. In terms of power, we verified the sample size satisfied both the rule of thumb of having at least 15 events per variable,[8] as well as having adequate sample size and event fraction given the number of predictors considered.[9]

Observations

Table 1 provides the overall percentage of distribution by sex, age group, and severity based on chronic exposure to ibuprofen.

Distribution
by Sex, Age Group, and Severity

n = 33,567

Ibuprofen Prescription | No Ibuprofen Prescription

Sex

	Ibuprofen Prescription	No Ibuprofen Prescription
Female	61.1%	48.6%
Male	38.9%	51.4%

Age Group

	Ibuprofen Prescription	No Ibuprofen Prescription
19-44	36.1%	27.6%
45-54	20.7%	16.8%
55-64	23.6%	20.3%
65-74	13.3%	16.1%
75-84	4.8%	11.6%
85+	1.3%	7.5%

Severity

	Ibuprofen Prescription	No Ibuprofen Prescription
No Admission	57.1%	40.2%
Admission No Respiratory Support	12.8%	11.7%
Admission Basic Resp. Support	19.6%	27.6%
Admission Adv. Resp. Support	1.3%	2.7%
Ventilation	1.9%	2.5%
Death	7.3%	15.3%

Table 1. Distribution by sex, age group, and severity

The results of the ordinal logistic regression (Table 2) indicate that patients prescribed ibuprofen prior to infection experienced less severe illness.

Patients who were not chronically prescribed ibuprofen were 1.51 times as likely to reach a worse maximum severity level during the course of their evaluation period. This finding was shown to be significant ($p<0.0001$) by comparing the t-value against a normal distribution.

As a sensitivity analysis, we included all patients in the model regardless of follow-up and found that the effect of prescribed ibuprofen was very similar (OR=1.44). In assessing the assumption of proportional odds, the difference in predicted probabilities was small (<0.08) across all severity levels, providing no evidence of heterogeneous effect among the severity level partitions.

Results of Ordinal Logistic Regression Predicting Severity

n = 33,567

	Beta Value [95% Confidence Interval]	Odds Ratio [95% Confidence Interval]	Standard Error	t-value
Ibuprofen Prescription	0.42 [0.28,0.56]	1.51 [1.32,1.74]	0.06	6.01
Female	-0.53 [-0.58,-0.50]	0.58 [0.56,0.61]	0.021	-25.66
Age Group	2.61 [2.55,2.67]	13.60 [12.80,14.50]	0.032	80.74

Table 2. Results of ordinal logistic regression predicting severity

Figure 1 depicts the probabilities from the ordinal regression. Patients prescribed ibuprofen chronically (purple lines) show a higher probability of having less severe outcomes and a lower probability of having more severe outcomes across age groups and sex.

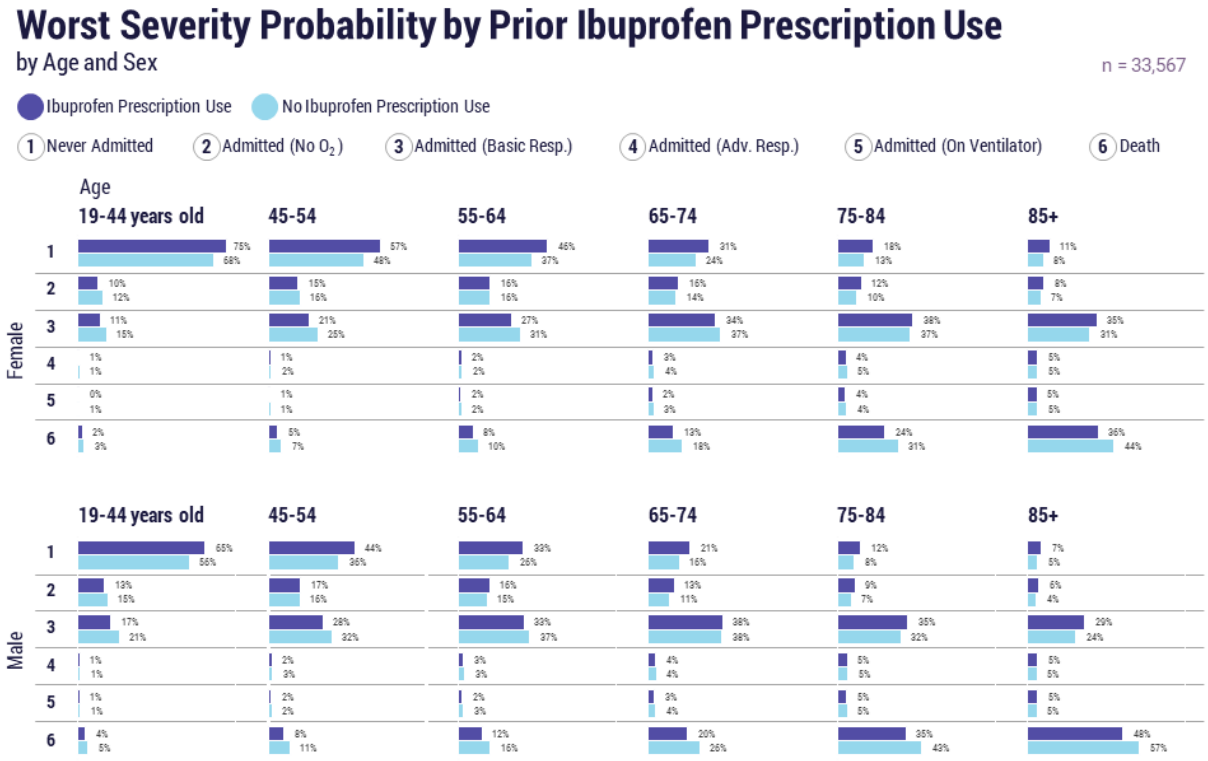

Figure 1. Severity probabilities by prior ibuprofen prescription, age group, and sex

Discussion

These preliminary observations suggest a possible association between chronic ibuprofen usage and improved outcomes experienced with COVID-19, although there may be other factors associated with both ibuprofen and lower severity of COVID-19 disease that are not addressed in this analysis.

There are several significant limitations of this analysis. First, patients prescribed ibuprofen tend to be younger, which suggests the possibility of residual confounding. If patients prescribed ibuprofen are consistently at the younger end of each age group, this may account for some of the observed effect. Future research with more granular age data is crucial to account for this potential source of bias. Although there was no evidence against the assumption of proportional odds, the inclusion of death prevents the severity scale from measuring a singular latent construct (severity of disease). Future research should examine the effect stratified by different levels of severity.

Also, we assumed that patients with prescriptions for ibuprofen written in a way that suggests chronic use are indeed taking the medication chronically, which may not always be true. Some patients may have taken their medications intermittently, some may have never taken their prescriptions, and some may have stopped taking their prescribed ibuprofen following the public concern for ibuprofen use during COVID-19 infection.[2] This would diminish the effect size observed here.

Another significant limitation of this analysis is the common use of over-the-counter ibuprofen. We attempted to focus on patients likely to use ibuprofen regularly by considering only those with a prescription in the ibuprofen group. We recognize that many patients in the unexposed group in this analysis could have used ibuprofen regularly as well. Similarly, the presence of ibuprofen users in the unexposed group would blunt the observed association with severity, so the presence of a significant association is notable.

Future population-based studies can investigate further by using different types of EHR data. We took a conservative approach by excluding patient-reported medications, but future analyses may examine the effect when these

medications are included. In addition, future studies may be able to use a more accurate measure of exposure by examining dispense data from pharmacies.

In addition, there are factors likely to be associated with chronic ibuprofen use that were not considered in this analysis. Patients with chronic prescriptions may be more likely to have regular access to care, which may account for the observed effect. Also, there may be an association between prescription for ibuprofen and certain chronic diseases. Future research should control for comorbidities to address this potential source of bias.

As we acknowledged in the methods, the study design outcome measurement was biased to include a higher death rate than the overall COVID-19 population, since expired patients require a shorter evaluation period for inclusion in the analysis. Given the observed negative association between ibuprofen prescription and worse outcomes, the findings are expected to overestimate the size of the true effect. In future research with longitudinal data, it would be more robust to take into consideration the uncertainty among recently tested patients by applying a cox proportional hazards model.

This analysis is also subject to common considerations regarding EHR data. It is possible that clinicians administered advanced respiratory support but failed to document this in the chart. Similarly, we know that some patients were diagnosed with COVID-19 before the ICD-10 code was available, and some organizations do not receive discrete results from their reference lab. We expect that these limitations are independent of ibuprofen exposure, so it is unlikely that they would bias the relationship between ibuprofen and severity.

Additional research should also evaluate COVID-19 outcomes across a broader scope of NSAIDs to determine whether this finding is consistent within the drug class. Finally, this analysis only included patients prescribed ibuprofen chronically in the group that was prescribed ibuprofen. Future research may seek to determine whether the effect is evident when patients begin taking ibuprofen closer in time to being infected or after becoming ill.

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