

Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: a matched, prospective cohort study



Thomas M Drake, Cameron J Fairfield, Riinu Pius, Stephen R Knight, Lisa Norman, Michelle Girvan, Hayley E Hardwick, Annemarie B Docherty, Ryan S Thwaites, Peter J M Openshaw, J Kenneth Baillie, Ewen M Harrison*, Malcolm G Semple*, for the ISARIC4C Investigators†



Summary

Background Early in the pandemic it was suggested that pre-existing use of non-steroidal anti-inflammatory drugs (NSAIDs) could lead to increased disease severity in patients with COVID-19. NSAIDs are an important analgesic, particularly in those with rheumatological disease, and are widely available to the general public without prescription. Evidence from community studies, administrative data, and small studies of hospitalised patients suggest NSAIDs are not associated with poorer COVID-19 outcomes. We aimed to characterise the safety of NSAIDs and identify whether pre-existing NSAID use was associated with increased severity of COVID-19 disease.

Methods This prospective, multicentre cohort study included patients of any age admitted to hospital with a confirmed or highly suspected SARS-CoV-2 infection leading to COVID-19 between Jan 17 and Aug 10, 2020. The primary outcome was in-hospital mortality, and secondary outcomes were disease severity at presentation, admission to critical care, receipt of invasive ventilation, receipt of non-invasive ventilation, use of supplementary oxygen, and acute kidney injury. NSAID use was required to be within the 2 weeks before hospital admission. We used logistic regression to estimate the effects of NSAIDs and adjust for confounding variables. We used propensity score matching to further estimate effects of NSAIDs while accounting for covariate differences in populations.

Results Between Jan 17 and Aug 10, 2020, we enrolled 78 674 patients across 255 health-care facilities in England, Scotland, and Wales. 72 179 patients had death outcomes available for matching; 40 406 (56.2%) of 71 915 were men, 31 509 (43.8%) were women. In this cohort, 4211 (5.8%) patients were recorded as taking systemic NSAIDs before admission to hospital. Following propensity score matching, balanced groups of NSAIDs users and NSAIDs non-users were obtained (4205 patients in each group). At hospital admission, we observed no significant differences in severity between exposure groups. After adjusting for explanatory variables, NSAID use was not associated with worse in-hospital mortality (matched OR 0.95, 95% CI 0.84–1.07; $p=0.35$), critical care admission (1.01, 0.87–1.17; $p=0.89$), requirement for invasive ventilation (0.96, 0.80–1.17; $p=0.69$), requirement for non-invasive ventilation (1.12, 0.96–1.32; $p=0.14$), requirement for oxygen (1.00, 0.89–1.12; $p=0.97$), or occurrence of acute kidney injury (1.08, 0.92–1.26; $p=0.33$).

Interpretation NSAID use is not associated with higher mortality or increased severity of COVID-19. Policy makers should consider reviewing issued advice around NSAID prescribing and COVID-19 severity.

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) provide effective analgesia and are important in the treatment of inflammatory diseases. They form a part of the WHO pain ladder and have opioid-sparing properties, supported by data from randomised trials.¹ In March, 2020, the French health ministry and media discussed unpublished data showing that use of NSAIDs could increase the severity of COVID-19.^{2,3} Debate ensued, with some arguing that NSAIDs should be avoided as a result of these findings.^{3–5} This debate led to several regulatory authorities calling for urgent investigation of NSAIDs and COVID-19 severity.⁶

More recent studies have found no associations between NSAID use, admission to hospital, and worse outcomes for patients with COVID-19.^{7–13} These studies have been

done in several different populations. In the community, administrative data have not shown an increased risk of hospitalisation for patients with COVID-19 taking NSAIDs.^{7,11,13} Data on patients admitted to hospital with COVID-19 are more scarce but suggest that patients taking NSAIDs do not have poorer outcomes compared with not taking NSAIDs.^{10–12} Studies that focus on cohorts of hospitalised patients with COVID-19 have included participants from single centres or included only small numbers of patients taking NSAIDs.

Studies of patients with non-SARS-CoV-2 respiratory infection have found associations between NSAID (including cyclooxygenase [COX]-2 inhibitors) use and increased rates of complications.^{14–19} These studies found that NSAID use was associated with higher rates of

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*Contributed equally

†Members are listed in the appendix (pp 15–17)

Centre for Medical Informatics,

Usher Institute, University of

Edinburgh, Edinburgh, UK

(T M Drake MBChB,

C J Fairfield MBChB, R Pius PhD,

S R Knight MBChB,

L Norman PhD,

A B Docherty PhD,

Prof E M Harrison PhD);

Liverpool Clinical Trials Centre

(M Girvan BSc) and Health

Protection Research Unit in

Emerging and Zoonotic

Infections, Institute of

Infection, Veterinary and

Ecological Sciences, Faculty of

Health and Life Sciences

(H E Hardwick, M G Semple PhD),

University of Liverpool,

Liverpool, UK; National Heart

and Lung Institute, Imperial

College London, UK

(R S Thwaites PhD,

P J M Openshaw PhD);

Roslin Institute, University of

Edinburgh, Easter Bush

Campus, Edinburgh, UK

(J K Baillie PhD); and

Department of Respiratory

Medicine, Alder Hey Children's

Hospital, Liverpool, UK

(M G Semple)

Correspondence to:

Prof Ewen M Harrison, Centre for

Medical Informatics, Usher

Institute, University of

Edinburgh EH16 4UX, UK

ewen.harrison@ed.ac.uk

See Online for appendix

Research in context

Evidence before this study

There have been anecdotal reports that use of non-steroidal anti-inflammatory drugs (NSAIDs) is linked to COVID-19 severity and poor outcomes. NSAIDs are an important analgesic class, used in the management of acute pain and rheumatological diseases. We searched PubMed from inception to Jan 12, 2021, using the terms “NSAIDs” and “COVID-19”, with no language restrictions. Several studies, in various populations, have identified that patients taking NSAIDs who contract SARS-CoV-2 infection are not at higher risk of admission to hospital or death. However, the populations included in these studies are frequently small, based on routine administrative data, or are drawn from community populations and hence have relatively low rates of SARS-CoV-2 infection.

Added value of this study

This prospective, multicentre study at 255 UK healthcare facilities found that in patients who were admitted to hospital

with COVID-19, those taking NSAIDs before admission had the same outcomes as those who did not. We did not find any differences in mortality or disease severity, or in secondary outcomes including admission to critical care, use of ventilation, use of oxygen, or presence of acute kidney injury.

Implications of all the available evidence

Those taking NSAIDs do not appear to have poorer COVID-19 outcomes. To our knowledge, our prospective study includes the largest number of patients admitted to hospital with COVID-19 to date, and adds to the literature on the safety of NSAIDs and in-hospital outcomes. NSAIDs do not appear to increase the risk of worse in-hospital outcomes. NSAIDs are an important analgesic modality and have a vital opioid-sparing role in pain management. Patients and clinicians should be reassured by these findings that NSAIDs are safe in the context of the pandemic.

myocardial infarction, pleural empyema, and longer length of hospital stay. However, outcomes used in such pneumonia studies, for example empyema, are less frequent in patients with SARS-CoV-2 infection. There are recognised safety concerns with the use of NSAIDs, including increased incidence of stroke, gastrointestinal bleeding, myocardial infarction, acute kidney injury, and bleeding,^{14–17,20} which are more common in older people.

By contrast, a randomised trial in the UK found that ibuprofen reduced the symptom severity of acute respiratory tract infection in patients in the community.²¹ In preclinical models, there is evidence that NSAIDs decrease pulmonary oedema, lessen endothelial leakiness, and reduce the severity of acute respiratory distress syndrome (ARDS), leading to the suggestion they might be useful in the treatment of COVID-19, with at least one clinical trial currently underway.^{22–24}

We aimed to characterise the safety of NSAIDs and identify whether pre-existing NSAID use was associated with increased severity of COVID-19 disease.

Methods

Study design and participants

The International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterisation Protocol (CCP) for Severe Emerging Infection was developed in 2009 and activated in response to the SARS-CoV-2 pandemic on Jan 17, 2020. ISARIC-CCP-UK is an actively recruiting prospective cohort study across England, Scotland, and Wales. The protocol, revision history, case report forms, study information, and consent forms are available online. ISARIC CCP UK received ethical approval from the South Central—Oxford C Research Ethics Committee in England (13/SC/0149) and by the Scotland A Research Ethics Committee (20/SS/0028).

As required, patients gave written informed consent. The study is reported in line with the STROBE guidelines.²⁵

Patients of any age admitted to hospital with a confirmed or highly suspected SARS-CoV-2 infection leading to COVID-19 between Jan 17 and Aug 10, 2020, were eligible for inclusion in the study. Confirmation of SARS-CoV-2 infection was by reverse transcription-PCR, which was the only testing method available in the UK during the reported study period. Highly suspected cases were eligible for inclusion, given that SARS-CoV-2 was an emergent pathogen at time of protocol activation. We excluded patients who did not have death or discharge outcomes available.

Procedures

Data were collected by clinical research staff using a standardised case report form and entered into a Research Electronic Data Capture secure online database.²⁶ Data were captured across multiple timepoints, including admission, hospital stay (days 1, 3, 6, and 9), and discharge. Characteristics captured included age, sex, asthma, chronic cardiac disease, chronic haematological disease, chronic kidney disease, chronic neurological disease, chronic non-asthmatic pulmonary disease, HIV/AIDS, malignancy, liver disease, obesity, rheumatological disorder, and smoking history. Physiological parameters at admission were captured, including components of the National Early Warning Score 2 (NEWS2) and the quick Sequential Organ Failure Assessment (qSOFA).

Current medication or medication taken within the past 2 weeks was recorded on hospital admission. The NSAID group was defined as patients taking generic or branded NSAIDs available within the UK, determined using the NHS Technology Reference data update distribution service, which were mapped to entered drug names within

the study database. We defined exposure to NSAIDs as patients taking non-selective COX inhibitors or COX-2 specific inhibitors. Topical NSAID preparations were excluded. Aspirin was not considered an NSAID for the purposes of this analysis, as aspirin is frequently used for the treatment and prevention of conditions which are different to those for which NSAIDs are indicated.

Outcomes

The primary outcome was in-hospital mortality (including palliative discharge). Secondary outcomes were admission to critical care (level 3 intensive care unit or level 2 high dependency unit), use of invasive mechanical ventilation, use of non-invasive ventilation, use of supplementary oxygen, and occurrence of acute kidney injury. Acute kidney injury was defined according to the Kidney Disease: Improving Global Outcomes guidelines.²⁷ We followed up patients for the duration of their hospital admission. Patients who were admitted after Aug 3, 2020, were excluded to avoid bias from patients with a long hospital stay or who had not had adequate time to accrue secondary outcomes.

Statistical analysis

Categorical data are presented as frequencies and percentages. Normally distributed variables are summarised as mean (SD) and non-normally distributed variables as median (IQR). χ^2 test was used to compare categorical data, except where expected cell counts were five or fewer, in which case Fisher's exact test was used. Continuous variables were compared using Welch's *t*-test or the Kruskal-Wallis test, depending on the distribution of data.

We used propensity score matching to estimate the treatment effect of NSAIDs while accounting for covariate imbalance, using a multistep approach. First, multiple imputation by chained equations was done using available explanatory variables (age, sex, diabetes [type 1 or type 2], chronic cardiac disease, chronic renal disease, obesity, chronic pulmonary disease, ethnicity, dementia, and rheumatological disease) and outcomes (five imputed datasets with five iterations per dataset; distributions checked graphically, and convergence confirmed). Second, logistic regression was used to determine the log odds of NSAID use (propensity scores) using the variables stated above. For logistic regression models, patient-level explanatory variables were entered as fixed effects and in unmatched models, hospital was used as a random effect. We did not use random effects for matched models to ensure we could match on clinical characteristics, rather than restrict matches to within each centre. Following this, propensity score matching was done within each imputed dataset, and patients taking NSAIDs were matched (1:1) with their nearest neighbour not taking NSAIDs.²⁸ Balance was determined using standardised mean differences. Fourth, effects estimates were determined, and results were pooled using Rubin's rules.²⁹ Effect estimates are presented as odds ratios (ORs) for binary outcome data,

with corresponding 95% CIs. Imputed and matched data are presented as pooled models.

For unmatched models, clinically plausible variables associated with NSAID use and clinical outcomes were incorporated into the modelling approach. These variables included age, sex, and presence of chronic cardiac disease, chronic pulmonary disease, diabetes, obesity, chronic renal disease, rheumatological disease, and dementia. First order interactions were checked before final model selection, which was guided by minimisation of the Akaike Information Criterion. $p < 0.05$ was considered to indicate a statistically significant difference.

We did four separate sensitivity analyses. First, we included patients taking non-ibuprofen NSAIDs only, as these usually require a prescription in the UK and are more likely to be taken for longer periods than ibuprofen. Next, we did an analysis including patients who were admitted at least 7 days after symptom onset to investigate whether NSAID use had any effect in those without nosocomial infection. We then did an analysis confined to patients with rheumatic disease, as this group are likely to be on long-term NSAID treatment compared with individuals who might be taking NSAIDs for short-term analgesia. Finally, to ensure the secondary outcomes were robust and to establish whether death was likely to compete with these outcomes, we did three sensitivity analyses to see if death altered the direction or magnitude of the effect size. For the first sensitivity analysis we excluded those who died. For the second sensitivity analysis we used deterioration (death or requirement for critical care) as the outcome. Lastly, for the third sensitivity analysis, we looked at mortality by NSAID use only in those not admitted to critical care.

Data were analysed using R version 3.6.3, using the tidyverse, finalfit, mice, MatchThem, cobalt, and matchit packages.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

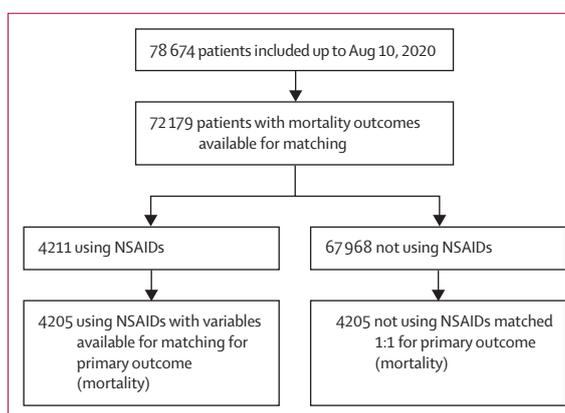


Figure 1: Study profile

	No NSAIDs (N=67 968)	NSAIDs (N=4211)	p value
Age at admission, years (n=71 987)	70.2 (18.4)	70.1 (18.7)	0.765*
Sex (n=71 915)	0.0008
Male	38 151 (56.1%)	2255 (53.6%)	..
Female	29 564 (43.5%)	1945 (46.2%)	..
Missing	253 (0.4%)	11 (0.3%)	..
Ethnicity (n=64 123)	0.116
Asian	3708 (5.5%)	230 (5.5%)	..
Black	2358 (3.5%)	118 (2.8%)	..
White	50 124 (73.7%)	3109 (73.8%)	..
Other	4201 (6.2%)	275 (6.5%)	..
Missing	7577 (11.1%)	479 (11.4%)	..
Smoking status (n=43 585)	0.0001
Current smoker	3588 (5.3%)	228 (5.4%)	..
Never smoked	22 896 (33.7%)	1394 (33.1%)	..
Former smoker	14 428 (21.2%)	1051 (25.0%)	..
Missing	27 056 (39.8%)	1538 (36.5%)	..
Chronic cardiac disease (n=67 454)	<0.0001
No	42 831 (63.0%)	2557 (60.7%)	..
Yes	20 588 (30.3%)	1478 (35.1%)	..
Missing	4549 (6.7%)	176 (4.2%)	..
Chronic kidney disease (n=66 964)	0.042
No	51 800 (76.2%)	3237 (76.9%)	..
Yes	11 167 (16.4%)	760 (18.0%)	..
Missing	5001 (7.4%)	214 (5.1%)	..
Chronic pulmonary disease (not asthma; n=67 171)	0.0030
No	51 933 (76.4%)	3219 (76.4%)	..
Yes	11 232 (16.5%)	787 (18.7%)	..
Missing	4803 (7.1%)	205 (4.9%)	..
Obesity (as defined by clinical staff; n=60 199)	<0.0001
No	49 993 (73.6%)	3039 (72.2%)	..
Yes	6590 (9.7%)	577 (13.7%)	..
Missing	11 385 (16.8%)	595 (14.1%)	..
Diabetes (n=65 135)	0.189
No diabetes	46 728 (68.8%)	2881 (68.4%)	..
Diabetes with complications	4484 (6.6%)	299 (7.1%)	..
Diabetes without complications	10 150 (14.9%)	593 (14.1%)	..
Missing	6606 (9.7%)	438 (10.4%)	..
Rheumatological disorder (n=66 228)	<0.0001
No	55 469 (81.6%)	3145 (74.7%)	..
Yes	6809 (10.0%)	805 (19.1%)	..
Missing	5690 (8.4%)	261 (6.2%)	..
Dementia (n=66 788)	0.0003
No	51 980 (76.5%)	3368 (80.0%)	..
Yes	10 845 (16.0%)	595 (14.1%)	..
Missing	5143 (7.6%)	248 (5.9%)	..

Data are mean (SD) or n (%). NSAID=Non-steroidal anti-inflammatory drug. *Welch's two-sample t-test used.

Table 1: Unmatched patient characteristics by NSAID use

Results

Between Jan 17 and Aug 10, 2020, we enrolled 78 674 patients across 255 health-care facilities in

	No NSAIDs (N=67 968)	NSAIDs (N=4211)	p value
Mortality (n=72 179)	0.227
No	46 712 (68.7%)	2932 (69.6%)	..
Yes	21 256 (31.3%)	1279 (30.4%)	..
Critical care admission (n=70 955)	0.467
No	57 507 (86.1%)	3599 (85.7%)	..
Yes	9250 (13.9%)	599 (14.3%)	..
Invasive ventilation (n=69 972)	0.396
No	60 254 (91.5%)	3821 (91.9%)	..
Yes	5562 (8.5%)	335 (8.1%)	..
Non-invasive ventilation (n=69 818)	0.0047
No	55 809 (85.0%)	3452 (83.3%)	..
Yes	9867 (15.0%)	690 (16.7%)	..
Supplemental oxygen (n=70 124)	0.62
No	22 826 (34.6%)	1420 (34.2%)	..
Yes	43 147 (65.4%)	2731 (65.8%)	..
Acute kidney injury (n=68 228)	0.034
No	48 258 (75.1%)	2945 (73.6%)	..
Yes	15 970 (24.9%)	1055 (26.4%)	..

NSAID=Non-steroidal anti-inflammatory drug.

Table 2: Unmatched outcomes by NSAID use

England, Scotland, and Wales (figure 1), representing around 60% of the total number of people admitted to hospital with COVID-19 over that time period. 72 179 patients had death outcomes available for matching. We observed no large differences in distribution of explanatory variables by missing mortality outcome (appendix p 1). In this cohort, 4211 (5.8%) patients were recorded as taking systemic NSAIDs before admission to hospital. In the unmatched data, patients who received NSAIDs were more likely to be female, and significantly more likely to have pre-existing rheumatological disease (table 1; appendix p 2). Propensity score matching produced balanced, well-matched treatment groups for each set of imputed and pooled models (appendix pp 3–8, 13).

1279 (30.4%) of 4211 patients in the NSAID group died versus 21 256 (31.3%) of 67 698 patients in the no NSAIDs group (table 2; appendix p 14). In the unmatched cohort, in-hospital mortality was no different between NSAID users and non-users (table 2). After matching, NSAID use was not associated with worse in-hospital mortality (matched OR 0.95, 95% CI 0.84–1.07; p=0.35; table 3).

In a sensitivity analysis of patients admitted to hospital at least 7 days after symptom onset (19 734 [27.3%] of 72 179 patients) who were taking NSAIDs matched to patients not taking NSAIDs who presented during the same timeframe, we found no difference in mortality

(matched OR 1.11, 95% CI 0.88–1.39; $p=0.37$). In patients with rheumatological disease (7614 [10.5%] of 72179), use of NSAIDs was not associated with increased mortality (matched OR 0.90, 0.68–1.19; $p=0.44$).

In the unmatched cohort, NSAID users were more likely to require non-invasive ventilation and sustain acute kidney injury (table 2). After matching, those taking NSAIDs were no more likely to require critical care admission (1.01, 0.87–1.17; $p=0.89$), invasive ventilation (0.96, 0.80–1.17; $p=0.69$), non-invasive ventilation (1.12, 0.96–1.32; $p=0.14$), or supplementary oxygen (1.00, 0.89–1.12; $p=0.97$), or to sustain acute kidney injury (1.08, 0.92–1.26; $p=0.33$), compared with those not taking NSAIDs (table 3; appendix p 14). In addition, on admission to hospital, matched patients on NSAIDs had similar qSOFA and NEWS2 scores to those who did not receive NSAIDs (table 3; figure 2). When we did a sensitivity analysis, excluding those who died, our findings did not change, and we did not observe an increase or decrease in associations between NSAIDs and any of the secondary outcomes (appendix p 9). We did a further two sensitivity analyses to ensure the secondary outcomes were robust. First, we combined death and critical care outcomes. Second, we looked at mortality in the population who did not require critical care. These analyses showed no association between NSAIDs and the chances of death or admission to critical care when these outcomes were combined (OR 0.94, 95% CI 0.83–1.06; $p=0.28$), nor any association with death in patients who were not admitted to critical care (0.92, 0.82–1.03; $p=0.16$).

The most common NSAID used was ibuprofen, followed by other NSAIDs—eg, diclofenac, ketorolac, naproxen, oxicams—and COX-2 inhibitors. We found no significant differences in mortality by type of NSAID (appendix p 10). We created matched groups to compare ibuprofen with no NSAID use, and ibuprofen with other NSAIDs, as a sensitivity analysis to explore whether NSAIDs associated with longer-term use had a different safety profile compared with ibuprofen. Use of ibuprofen was not significantly associated with increased mortality compared with those not taking NSAIDs (matched OR 0.90, 95% CI 0.71–1.13; $p=0.36$; appendix p 11) or any other NSAID (matched OR 0.82, 0.66–1.03; $p=0.082$; appendix p 12).

Discussion

In this study, patients admitted to hospital with COVID-19 who were taking NSAIDs did not have more severe disease than did patients who were not taking NSAIDs. Mortality, critical care admission, respiratory support, and acute kidney injury were also not significantly different across matched NSAID treatment groups. We found no evidence of harm caused by NSAID use in patients admitted to hospital with severe COVID-19.

	Effect estimate	p value
In-hospital mortality		
No NSAIDs	1 (ref)	..
NSAIDs (n=4205)	0.95 (0.84 to 1.07)	0.35
Secondary outcomes		
No NSAIDs	1 (ref)	..
NSAIDs		
Critical care admission (n=4198)	1.01 (0.87 to 1.17)	0.89
Invasive ventilation (n=4156)	0.96 (0.80 to 1.17)	0.69
Non-invasive ventilation (n=4142)	1.12 (0.96 to 1.32)	0.14
Oxygen (n=4151)	1.00 (0.89 to 1.12)	0.97
Acute kidney injury (n=4000)	1.08 (0.92 to 1.26)	0.33
Severity on admission		
Physiological scores		
qSOFA score (n=3793)	-0.02 (-0.06 to 0.02)	0.42
NEWS2 (n=3721)	-0.08 (-0.30 to 0.14)	0.46
Physiological parameters		
Heart rate (n=4102)	-0.40 (-1.39 to 0.59)	0.43
Respiratory rate (n=4096)	-0.17 (-0.66 to 0.32)	0.48
Saturation of peripheral oxygen (n=4076)	-0.00 (-0.27 to 0.26)	0.98
Systolic blood pressure (n=4085)	1.09 (-0.07 to 2.25)	0.066
Diastolic blood pressure (n=4071)	-0.21 (-0.93 to 0.51)	0.56
Effect estimates are either matched odds ratio (95% CI) or mean difference (95% CI). NSAID=non-steroidal anti-inflammatory drug. NEWS2=National Early Warning Score 2. qSOFA=quick Sequential Organ Failure Assessment.		
Table 3: Outcomes after propensity score matching between those using NSAIDs before admission and those not using NSAIDs		

Early on in the COVID-19 pandemic, questions were raised concerning the safety of NSAIDs in patients with COVID-19, with suggestions that these drugs were leading to more severe disease in some patients.^{2,30,31} Our data show that patients taking NSAIDs did not have more severe symptoms or poorer outcomes than those not taking NSAIDs. These data support community studies showing that NSAID users did not have higher rates of hospitalisation with COVID-19 and smaller studies of in-hospital outcomes, which found NSAID use was not associated with poorer outcomes. A propensity matched data linkage study of patients with osteoarthritis taking NSAIDs in the community setting found no difference in the risk of developing COVID-19 or dying from the disease.¹³ Compared with our data and previous studies our consortium has published, this data linkage study¹³ did not find any differences in risk factors for mortality after COVID-19, which is probably due to the very small numbers of patients with COVID-19 in the study. To our knowledge, our study is the largest study of in-hospital outcomes of patients with COVID-19 to date. Considering all the evidence, if there was an extreme effect of NSAIDs on COVID-19 outcomes or severity, this would have been observed in one or more of the studies that have been done, including the present study.

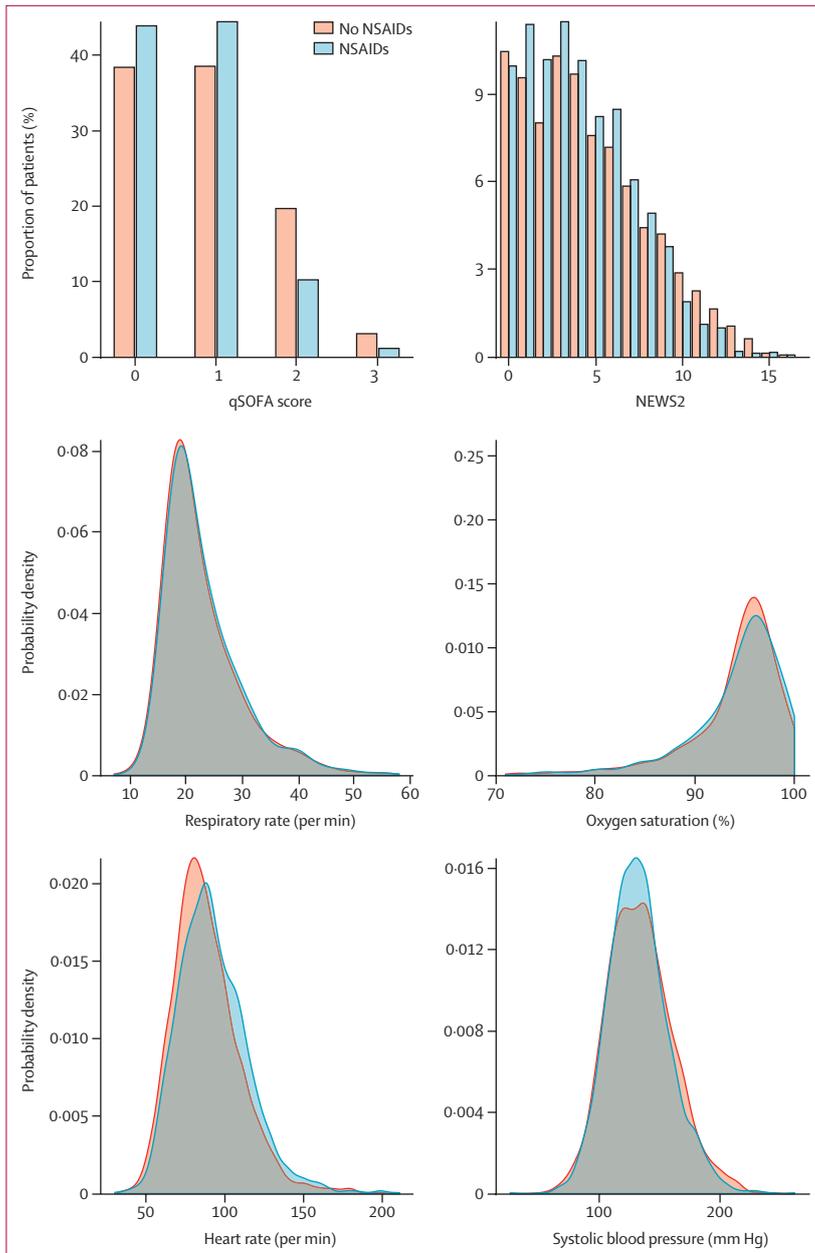


Figure 2: Physiological parameters on admission to hospital in NSAID users and those not taking NSAIDs
NSAID=non-steroidal anti-inflammatory drug. NEWS2=National Early Warning Score 2. qSOFA=quick Sequential Organ Failure Assessment.

To our knowledge, worldwide, this is the largest prospective study of patients admitted to hospital with COVID-19. We were able to collect real-time data on patients to study their outcomes and collect detailed comorbidity data. Clinical research staff collected data on medications that patients had been prescribed or were currently taking, or had been taking within the past 14 days. These data would otherwise be challenging to obtain from routine sources of health-care data. Although we have only captured data on patients admitted to

hospital with COVID-19 that are available within the ISARIC CCP, this represents around 60% of all patients hospitalised with COVID-19 in the UK during the period of the study. We did not capture data for patients who had the disease in the community and did not require hospital admission, or who died in the community without hospital admission. Despite this, we expect that most patients who had severe COVID-19 would be admitted to hospital and thus captured in our dataset. A further potential limitation of our study is the absence of information on the indication for NSAIDs and duration of use. These missing data make it difficult to know whether individuals were taking NSAIDs for long-term conditions, or symptomatic relief for COVID-19 symptoms. Similarly, it is unclear whether patients continued taking NSAIDs during their inpatient admission. Therefore, we are unable to make any recommendations on whether NSAIDs should be continued after admission to hospital. To address this, we did a sensitivity analysis comparing use of ibuprofen to no NSAIDs or use of other non-ibuprofen NSAIDs, as ibuprofen use is most likely to be short-term. We observed no increase in poorer outcomes in those who used ibuprofen compared with those who did not use NSAIDs. Similarly, older patients, who are at greatest risk of adverse outcomes from COVID-19, might be less likely to be taking NSAIDs compared with other, more healthy and fit populations, as older patients with greater numbers of comorbidities are less likely to be prescribed NSAIDs because of their side-effect profile; therefore, our matching might not have incorporated this patient group fully. However, as older patients are less likely to be taking NSAIDs and the safety debate concerns younger populations, this is unlikely affect our results and their relevance to clinical practice.

There are several other important limitations to our study that must be considered. First, the most used NSAID was ibuprofen, which might not be generalisable to every country. Different NSAIDs are known to have different side-effect profiles; therefore, clinical trials of a specific compound might not be generalisable to an entire drug class.³² Additionally, our data did not contain information on drug dosages or adherence, so we were unable to model dose–response data. Second, although our study captured data on most patients hospitalised with COVID-19 in the UK during the period it was done, a few centres did not participate. However, our data is concordant with other datasets that focused on smaller populations within our study, such as data from the Intensive Care National Audit and Research Centre.³³ Therefore, we consider our data to be meaningful and useful to help answer important clinical questions in patients with COVID-19. Another limitation is that to obtain the best possible matches for patients receiving NSAIDs, we did not include the date of admission as a matching variable. Mortality for patients admitted to hospital over the course of the pandemic has decreased,

but this is unlikely to have affected our conclusions given that the time period we conducted our study during was limited largely to the first UK wave of infection. Finally, our data lack a non-SARS-CoV-2 comparator group to provide a temporal comparison with other critical illness or respiratory conditions. Future research could include a comparator group to investigate if NSAIDs modify or moderate outcomes of interest in patients with COVID-19 compared with other illnesses.

Although use of NSAIDs could, in theory, be beneficial in patients with COVID-19, we did not identify any evidence to support this. Clinical studies have suggested that release of proinflammatory mediators in COVID-19—including interleukin (IL)-1 β , IL-6, and CCL2—is associated with more severe disease.^{34,35} Preclinical studies in non-COVID-19 models have found that release of these cytokines can be inhibited by treatment with NSAIDs, leading to discussion around whether NSAIDs might be useful as a therapy for COVID-19.^{23,36,37} In these studies, NSAIDs have been shown to suppress IL-6 production and expression through various mechanisms, including suppression of prostaglandin E2, which upregulates production of IL-6 and IL-8.^{36,37} Studies in bronchial epithelium have found that treatment with NSAIDs reduces expression of inflammatory mediators, including IL-6.³⁶ A clinical trial of dexamethasone, which also has been shown to modulate inflammation,³⁸ albeit probably through a separate mechanism, has been shown to reduce mortality in patients with COVID-19. Other immunomodulatory therapies are being trialled, including the IL-6 inhibitor tocilizumab. Results from the REMAP-CAP³⁹ and RECOVERY⁴⁰ trials showed that tocilizumab reduced the requirement for organ support and improved survival in patients with COVID-19, with further trials underway.^{41,42} In addition to these trials, a randomised trial of ibuprofen in patients with COVID-19 is also underway.²³

For clinicians and patients, our findings should provide reassurance that NSAIDs can be used as indicated in the community without increasing the severity of COVID-19. Our study did not capture whether NSAIDs were continued in hospital, so we cannot make any recommendations on whether these should be withheld or continued after hospital admission. There are important groups of patients who rely on NSAIDs for pain relief, including those with inflammatory joint diseases, bone pain, gout, postoperative pain, and menstrual pain, who would otherwise have few non-opioid options for pain relief. Taken together, clinicians should continue to prescribe and manage NSAIDs in the same way as before the COVID-19 pandemic began.

Future research in this area should focus on whether NSAIDs sufficiently modulate inflammation in COVID-19, by using both basic science and clinical approaches using appropriate outcomes that are directly measured. If benefit or harm is identified, finding the cellular mechanisms responsible for these effects will be

important to inform the biological understanding of COVID-19. Finally, including groups that compare NSAIDs with alternative analgesics should be considered to provide evidence for clinicians and patients on the risks associated with alternative medications. In conclusion, policy makers should consider reviewing issued advice around NSAID prescribing and COVID-19 severity. NSAID use is not associated with poorer outcomes in patients admitted to hospital with COVID-19.

Contributors

JKB, PJMO, MGS, and RST conceived the study, curated the data, acquired the funding, oversaw project administration and the data management platform, and wrote, reviewed, and edited the manuscript. EMH, TMD, RP, CJF, SRK, LN, and ABD investigated the study questions, analysed and visualised the data, wrote the original draft of the manuscript, and reviewed and edited the manuscript. HEH and MG were responsible for data management and study and site coordination. TMD, RP, LN, JKB, ABD, MGS, and EMH had access to and verified the raw data. The corresponding author had full access to all data and the final responsibility to submit for publication. All authors have full access to all the data in the study and have final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

Data, protocols, and all documentation around this analysis will be made available to academic researchers after authorisation from the independent data access and sharing committee. Data and analysis scripts are available on request to the Independent Data Management and Access Committee.

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For more information on **how to request access to the study data** see https://isaric4c.net/sample_access/

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References

- Ventafriida V, Saita L, Ripamonti C, De Conno F. WHO guidelines for the use of analgesics in cancer pain. *Int J Tissue React* 1985; 7: 93–96.
- Science Media Centre. Expert reaction to reports that the French Health Minister recommended use of paracetamol for fever from COVID-19 rather than ibuprofen or cortisone. March 16, 2020. <https://www.sciencemediacentre.org/expert-reaction-to-reports-that-the-french-health-minister-recommended-use-of-paracetamol-for-fever-from-covid-19-rather-than-ibuprofen-or-cortisone/> (accessed July 16, 2020).
- Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. *BMJ* 2020; 368: m1086.
- Torjesen I. Covid-19: ibuprofen can be used for symptoms, says UK agency, but reasons for change in advice are unclear. *BMJ* 2020; 369: m1555.
- Little P. Non-steroidal anti-inflammatory drugs and covid-19. *BMJ* 2020; 368: m1185.
- European Medicines Agency. EMA gives advice on the use of non-steroidal anti-inflammatories for COVID-19. March 18, 2020. <https://www.ema.europa.eu/en/news/ema-gives-advice-use-non-steroidal-anti-inflammatories-covid-19> (accessed July 16, 2020).
- Wong AYS, MacKenna B, Morton CE, et al. Use of non-steroidal anti-inflammatory drugs and risk of death from COVID-19: an OpenSAFELY cohort analysis based on two cohorts. *Ann Rheum Dis* 2021; published online Jan 21. <https://doi.org/10.1136/annrheumdis-2020-219517>.
- Abu Esba LC, Alqahtani RA, Thomas A, Shamas N, Alswaidan L, Mardawi G. Ibuprofen and NSAID use in COVID-19 infected patients is not associated with worse outcomes: a prospective cohort study. *Infect Dis Ther* 2021; 10: 253–68.
- Kragholm K, Gerds TA, Fosbøl E, et al. Association between prescribed ibuprofen and severe COVID-19 infection: a nationwide register-based cohort study. *Clin Transl Sci* 2020; 13: 1103–07.
- Bruce E, Barlow-Pay F, Short R, et al. Prior routine use of non-steroidal anti-inflammatory drugs (NSAIDs) and important outcomes in hospitalised patients with COVID-19. *J Clin Med* 2020; 9: 2586.
- Lund LC, Kristensen KB, Reilev M, et al. Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: a Danish nationwide cohort study. *PLoS Med* 2020; 17: e1003308.
- Jeong HE, Lee H, Shin HJ, Choe YJ, Filion KB, Shin JY. Association between NSAIDs use and adverse clinical outcomes among adults hospitalized with COVID-19 in South Korea: a nationwide study. *Clin Infect Dis* 2020; published online July 27. <https://doi.org/10.1093/cid/ciaa1056>.
- Chandan JS, Zemedikun DT, Thayakaran R, et al. Non-steroidal anti-inflammatory drugs and susceptibility to COVID-19. *Arthritis Rheumatol* 2021; 73: 731–39.
- Möller B, Pruijm M, Adler S, Scherer A, Villiger PM, Finckh A. Chronic NSAID use and long-term decline of renal function in a prospective rheumatoid arthritis cohort study. *Ann Rheum Dis* 2015; 74: 718–23.
- La Corte R, Caselli M, Castellino G, Bajocchi G, Trotta F. Prophylaxis and treatment of NSAID-induced gastroduodenal disorders. *Drug Saf* 1999; 20: 527–43.
- Kotsiou OS, Zarogiannis SG, Gourgoulianis KI. Prehospital NSAIDs use prolong hospitalization in patients with pleuropulmonary infection. *Respir Med* 2017; 123: 28–33.
- Basille D, Trouve C, Plouvier N, Andrejak C, Jounieaux V. Non-steroidal anti-inflammatory drugs may worsen the course of community-acquired pneumonia: a cohort study. *Eur Respir J* 2016; 48: OA3330.
- Lund LC, Reilev M, Hallas J, et al. Association of nonsteroidal anti-inflammatory drug use and adverse outcomes among patients hospitalized with influenza. *JAMA Netw Open* 2020; 3: e2013880.
- Voiriot G, Philippot Q, Elabbadi A, Elbim C, Chalumeau M, Fartoukh M. Risks related to the use of non-steroidal anti-inflammatory drugs in community-acquired pneumonia in adult and pediatric Patients. *J Clin Med* 2019; 8: 786.
- Wen Y-C, Hsiao F-Y, Chan KA, Lin Z-F, Shen L-J, Fang C-C. Acute respiratory infection and use of nonsteroidal anti-inflammatory drugs on risk of acute myocardial infarction: a nationwide case-crossover study. *J Infect Dis* 2017; 215: 503–09.
- Little P, Moore M, Kelly J, et al. Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. *BMJ* 2013; 347: f6041.
- Matute-Bello G, Frevert CW, Martin TR. Animal models of acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 2008; 295: L379–99.
- ClinicalTrials.gov. LIBERATE trial in COVID-19. <https://clinicaltrials.gov/ct2/show/NCT04334629?cond=covid-19+ibuprofen&draw=2&rank=3> (accessed July 16, 2020).
- ClinicalTrials.gov. Inhaled ibuprofen to treat COVID-19. <https://clinicaltrials.gov/ct2/show/NCT04382768?cond=covid-19+ibuprofen&draw=2&rank=1> (accessed July 16, 2020).
- von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening of reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; 4: e296.
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377–81.
- KDIGO. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline for Acute Kidney Injury. 2012. <https://kdigo.org/guidelines/acute-kidney-injury/> (accessed April 26, 2021).
- Ling AY, Montez-Rath ME, Mathur MB, Kappahhn K, Desai M. How to apply multiple imputation in propensity score matching with partially observed confounders: a simulation study and practical recommendations. April 16, 2019. <https://arxiv.org/abs/1904.07408> (accessed March 25, 2021).
- Fishgar F, Greifer N, Leyrat C, Stuart E. MatchThem: matching and weighting after multiple imputation. Set 24, 2020. <https://arxiv.org/abs/2009.11772> (accessed March 25, 2021).
- United States Food and Drug Administration. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. March 19, 2020. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19> (accessed Dec 3, 2020).
- Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020; 8: e21.
- Trelle S, Reichenbach S, Wandel S, et al. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011; 342: c7086.
- Intensive Care National Audit & Research Centre. COVID-19 reports. 2021. <https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports> (accessed Jan 28, 2021).
- Herold T, Jurinovic V, Arnreich C, et al. Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19. *J Allergy Clin Immunol* 2020; 146: 128–136.
- Chen Y, Wang J, Liu C, et al. IP-10 and MCP-1 as biomarkers associated with disease severity of COVID-19. *Mol Med* 2020; 26: 97.
- Ho JC, Tipoe G, Zheng L, et al. In vitro study of regulation of IL-6 production in bronchiectasis. *Respir Med* 2004; 98: 334–41.
- Canan CH, Gokhale NS, Carruthers B, et al. Characterization of lung inflammation and its impact on macrophage function in aging. *J Leukoc Biol* 2014; 96: 473–80.
- The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021; 384: 693–704.

-
- 39 The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. *N Engl J Med* 2021; **384**: 1491–502.
- 40 Horby PW, Pessoa-Amorim G, Peto L, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial. *medRxiv* 2021; published online Feb 11, 2021. <https://doi.org/10.1101/2021.02.11.21249258> (preprint).
- 41 O'Hare R. Arthritis drug effective in treating sickest COVID-19 patients. Nov 19, 2020. <https://www.imperial.ac.uk/news/209033/arthritis-drug-effective-treating-sickest-covid-19/> (accessed Dec 17, 2020).
- 42 Department of Health and Social Care. Interim Position Statement: Tocilizumab for patients admitted to ICU with COVID-19 pneumonia (adults). 2020. https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103715 (accessed April 26, 2021).