Journal of Clinical Medicine

MDPI

Article

Prior Routine use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Important Outcomes in Hospitalised Patients with COVID-19

Eilidh Bruce[1,2$#], Fenella Barlow-Pay[3$#], Roxanna Short[4], Arturo Vilches-Moraga[5], Angeline Price[5], Aine McGovern[6], Philip Braude[7], Michael Stechman[8], Susan Moug[3], Kathryn McCarthy[7], Jonathan Hewitt[8], Ben Carter[4#&], *Phyo K Myint[1,2#&]

1. Aberdeen Royal Infirmary, Aberdeen, Scotland
2. Institute of Applied Health Science, University of Aberdeen, Aberdeen Scotland
3. Royal Alexandra Hospital, Paisley, Scotland
4. Department of Biostatistics & Health Informatics, King's College London, England
5. Salford Royal NHS Trust, Salford, England
6. Glasgow Royal Infirmary, Glasgow, Scotland
7. North Bristol NHS Trust, Bristol, England
8. Cardiff University, Cardiff, Wales

[#] These authors contributed equally; [$] joint first authors; [&] joint last authors.

* Correspondence: phyo.myint@abdn.ac.uk; Tel.: +44 (0) 1224 437841

COPE study Collaborators (to be listed in PubMed under Collaborator List):

Study Registration Number: IRAS project ID 281951

Approval Number: UK Health Research Authority (Reference: 20/HRA/1898)

Protocol number: SPON1815-20

Received: date; Accepted: date; Published: date

Abstract: COVID-19 infection causes acute lung injury, resulting from aggressive inflammation initiated by viral replication. There has been much speculation about the potential role of non-steroidal inflammatory drugs (NSAIDs), which increase the expression of angiotensin converting enzyme 2 (ACE2), a binding target for SARS-CoV-2 to enter the host cell, which could lead to poorer outcomes in COVID-19 disease. The aim of this study was to examine the association between routine use of NSAIDs and outcomes in hospitalized patients with COVID-19 infection.

This was a multi-centre, observational study, with data collected from adult patients with COVID-19 admitted to eight UK hospitals. Of 1222 patients eligible to be included, 54 (4.4%) were routinely prescribed NSAIDs prior to admission. Univariate results suggested a modest protective

effect from the use of NSAIDs, but in the multivariable analysis, there was no association between prior NSAID use and time-to-mortality (adjusted HR [aHR] = 0.89, 95%CI 0.52-1.53, p=0.67) or length of stay (aHR 0.89, 95% CI 0.59-1.35, p=0.58).

This study found no evidence that routine NSAID use was associated with higher COVID-19 mortality in hospitalized patients, therefore patients should be advised to continue taking these medications until further evidence emerges. Our findings suggest that NSAID use might confer a modest benefit with regards to survival. However, as this finding was underpowered further research is required.

Keywords: covid-19; SARS-CoV-2; non-steroidal anti-inflammatory drugs; NSAIDs

1. Introduction

The pattern of acute lung injury seen in SARS-CoV-2 (commonly referred to as COVID-19) infection is thought to be a result of aggressive inflammation initiated by viral replication, however the exact pathophysiology behind this phenomenon remains largely unknown [1]. Following recognition that the angiotensin converting enzyme 2 receptor (ACE2) serves as a binding site for SARS CoV-2 to enter the host cell, a number of European authorities, including those in France and Belgium, issued federal reports suggesting that the use of non-steroidal inflammatory drugs (NSAIDs) in COVID-19 infection might adversely affect patients' clinical course and recovery [2]. There remains, however, a considerable uncertainty regarding the use of common NSAIDs and their effect on COVID-19.

NSAIDs are one of the most commonly prescribed and used pain medications worldwide, for both acute pain and chronic conditions such as rheumatological diseases and osteoarthritis [3,4], with analgesic, anti- inflammatory and anti-pyretic properties. Risks of NSAID use have been well studied in the general population, with particular focus on the association between their long-term use and increased risk of upper gastrointestinal effects (e.g. ulceration, bleeding), renal impairment and arterial thrombotic events (e.g. myocardial infarction, stroke) [4]. It has been speculated that ibuprofen may upregulate the cellular expression of (ACE2) [5], and in the context of COVID-19 it is therefore postulated that NSAID use could result in a higher viral infective load in respiratory tract. More recent work has also implicated NSAIDs in their association with high rates of complication (effusion, empyema, dissemination of infection) after acute respiratory tract infection [6,7], via the mechanism of NSAID mediated cyclo-oxygenase (COX) inhibition. It has been proposed that the inhibition of COX enzymes reduces recruitment of polymorphonuclear cells and inhibits synthesis of lipoxins and resolvins, ultimately delaying the resolution of inflammation.

However, there exists a conflict of opinion within the literature with regard to coronaviruses and very little research has been conducted to date. In vitro studies of the earlier SARS-CoV infection in animal models and human lung epithelium found indomethacin to have potent antiviral activity by inhibiting viral RNA synthesis [8], an effect that was independent of COX inhibition. Whilst the anti-inflammatory properties of NSAIDs are well known, it is unclear what, if any, their effect is on outcomes in acute respiratory tract infection.

Available published evidence is specifically lacking in describing outcomes for patients with COVID-19 infection who are NSAID users. The primary aim of this study is therefore to examine the association between prior routine use of NSAIDs and mortality and length of stay in patients admitted to hospital with COVID-19.

2. Methods

2.1 Study population

The study population was drawn from the COPE study (COVID-19 in Older People study) [9]. COPE study is a multicentre, observational study governed by the Older Persons Surgical Outcome Collaborative (OPSOC; www.opsoc.eu), our existing academic network of clinical centres. OPSOC runs a well-established programme of research with experience in collecting epidemiological data for both academic and service evaluation purposes. In the current study, a total of eight UK centres were included. They were all involved in delivery of unscheduled, in-patient treatment to patients with COVID-19. Data were gathered between 6th March and 28th April 2020. Patient outcomes were up to 28th April 2020. Detailed description of the study protocol and data collection methods has been previously reported [9].

In brief, data collection was undertaken prospectively using a standardised, computerised case report. This was populated after reviewing of patients' individual paper records, prescription administration records and information from electronic records. Each site's principal investigator supervised study personnel collecting data at a local level, all of whom had completed data collection training prior to their involvement in the study. Data was recorded securely at each site by adherence to data protection policy, and collated data was ultimately transferred in an anonymised format to King's College London for statistical analysis.

2.2 Participants

Patients aged 18 years or older who were admitted to hospital with a clinical or laboratory confirmed diagnosis of COVID-19 were included. Clinical diagnoses were made by clinicians at each site, based on signs, symptoms and/or radiological appearance consistent with COVID-19, whist laboratory confirmed diagnoses required positive PCR results from a swab for SARS-CoV-2. There were no exclusion criteria.

2.3 End points

The primary endpoint was the time-to-mortality from the date of admission or date of diagnosis, when the patient was diagnosed with COVID-19 five or more days after admission. Secondary outcomes included day 7 mortality and the time from admission or diagnosis (if diagnosed minimum of five days after admission) to discharge (length of stay).

2.4 Exposure

Data on the use of NSAIDs, including the number, type and dose of anti-inflammatory that each patient was taking prior to admission were collected from admission records and from online GP prescription records. NSAIDs included in the data collection were: propionic acid derivatives such as ibuprofen and naproxen, diclofenac, an acetic acid derivative and selective COX-2 inhibitors such

as celecoxib. Topical NSAIDs such as ibuprofen gels were not included due to their low level of systemic absorption and consequential limited systemic effects [10,11]. Low dose aspirin was not included as an NSAID in our data collection, as although it is a COX-inhibitor its effects are primarily anti-platelet at low doses, with minimal anti-inflammatory effects. History of coronary artery disease was included in the covariate data collection and adjusted for, and the majority of these patients will be taking aspirin.

2.5 Covariates

Additional clinical demographics collected included: age; sex; smoking status (current, previous, never); C-reactive protein (CRP) on admission; reduced renal function (eGFR <60 on admission) and the presence of comorbidities including diabetes mellitus, hypertension, and coronary artery disease (CAD).

2.6 Statistical analysis

Baseline demographic and clinical characteristics were compared by in hospital mortality status, and patients who were taking an NSAID versus those who were not. Time to-event outcomes (death, or discharge) were analysed with mixed-effects multivariable Cox's proportional baseline hazards models. The analyses were fitted with a random intercept to account for hospital variation, and adjusted for the base model of: NSAID prescribed (yes/no); patient age group; sex; smoking status; CRP; diabetes; hypertension; coronary artery disease; reduced renal function (eGFR<60). The adjusted hazard ratios (aHR) were estimated with associated 95% confidence intervals (95%CI). The baseline proportionality assumption was tested visually with log-log residuals. Each time to event analysis was reported with a Kaplan Meier survival plot. Day 7 mortality was analysed using a mixed-effects multivariable logistic model, fitting each hospital as a random intercept effect, and adjusted with covariates consistent with the time-to-event analyses. The adjusted odds ratio (aOR) were estimated and presented with corresponding 95% confidence interval (95%CI). Missing data were explored for patterns of missingness. Subgroup analyses were carried out to explore potentially moderating effects of NSAID use within different subgroups stratified by: age group; sex; smoking status; diabetes; hypertension; coronary artery disease; and renal impairment. Analysis was carried out using Stata version 15 [12] Kaplan Meier survival plots were visualised in R [13], with packages survival [14] and survminer [15].

Permission to undertake the study was received from The Health Research Authority (20/HRA/1898); Cardiff University acted as study sponsor.

3. Results

Data were collected from 1,222 patients with COVID-19 across eight UK sites, of whom 56.5% (n=690) were male. 4.4% of patients (n=54) were prescribed routine NSAIDs prior to admission. There were 19 patients with missing CRP data, these were inputted as CRP<40, and a further 20 patients with missing smoking status who were recorded as 'never smokers'. Overall in-hospital mortality was 29.3% (n=358), varying from 12.2-43.9% across hospital sites. In-hospital mortality was 25.9% (n=14) in the NSAID users and 29.5% (n=344) among the non-users (p=0.578). In-hospital mortality was higher in older age groups (39% in patients aged ≥80 years; 34.3% in those aged 65-79 years; 12.9% in

patients aged <65 years) and with the presence of co-morbidities including diabetes (32.4% in patients with diabetes vs. 28.1% in those without), hypertension (32.6% vs. 25.7%), coronary artery disease (39.2% vs. 26.3%) and reduced renal function (eGFR<60) on admission (38.7% vs. 23.1%). A complete breakdown of demographics and clinical characteristics by in-hospital mortality is shown in Table 1.

Table 1: Demographics, comorbidities and NSAID usage, by in hospital mortality

	Alive	Dead	Total	p-value[&]
	(n=864)	**(n=358)**	**(n=1222)**	
NSAID Prescription				
No	824 (70.6)	344 (29.5)	1168 (95.6)	0.578
Yes	40 (74.1)	14 (25.9)	54 (4.4)	
Sites				
Hospital A	119 (77.8)	34 (22.2)	153 (12.5)	<0.001
Hospital B	33 (76.7)	10 (23.3)	43 (3.5)	
Hospital C	108 (87.8)	15 (12.2)	123 (10.1)	
Hospital D	254 (66.8)	126 (33.2)	380 (31.1)	
Hospital E	76 (67.9)	36 (32.1)	112 (9.2)	
Hospital F	138 (56.1)	108 (43.9)	246 (20.1)	
Hospital G	100 (87.0)	15 (13.0)	115 (9.4)	
Hospital H	36 (72.0)	14 (28.0)	50 (4.1)	
Age				
Under 65 yrs	337 (87.1)	50 (12.9)	387 (31.7)	<0.001
65 to 79 yrs	266 (65.7)	139 (34.3)	405 (33.1)	
Over 80 yrs	261 (60.7)	169 (39.3)	430 (35.2)	
Sex				0.625
Female	380 (71.4)	152 (28.6)	532 (43.5)	
Male	484 (70.1)	206 (29.9)	690 (56.5)	
Smoking Status				
Never smokers	453 (73.2)	166 (26.8)	619 (50.7)	0.049
Ex-smokers	325 (66.7)	162 (33.3)	487 (39.9)	
Current smokers	74 (77.1)	22 (22.9)	96 (7.8)	
Missing	12	8	20	
Diabetes				
No	638 (71.9)	249 (28.1)	887 (72.6)	0.100
Yes	223 (67.6)	107 (32.4)	330 (27.0)	
Missing	3	2	5	
Hypertension				
No	448 (74.3)	155 (25.7)	603 (49.4)	0.008
Yes	414 (67.4)	200 (32.6)	614 (50.3)	
Missing	2	3	5	
Coronary Artery disease				
No	696 (73.7)	248 (26.3)	944 (77.3)	<0.001
Yes	166 (60.8)	107 (39.2)	273 (22.3)	
Missing	2	3	5	
Elevated CRP (>40)				
No	282 (84.4)	52 (15.6)	334 (27.3)	<0.001
Yes	571 (65.7)	298 (34.3)	869 (72.7)	
Missing	11	8	19	
Renal function (eGFR<60)				

No	568 (76.9)	171 (23.1)	739 (60.5)	<0.001
Yes	290 (61.3)	183 (38.7)	473 (38.7)	
Missing	6	4	10	

170 [&]Chi-squared was carried out between clinical characteristics and mortality

171

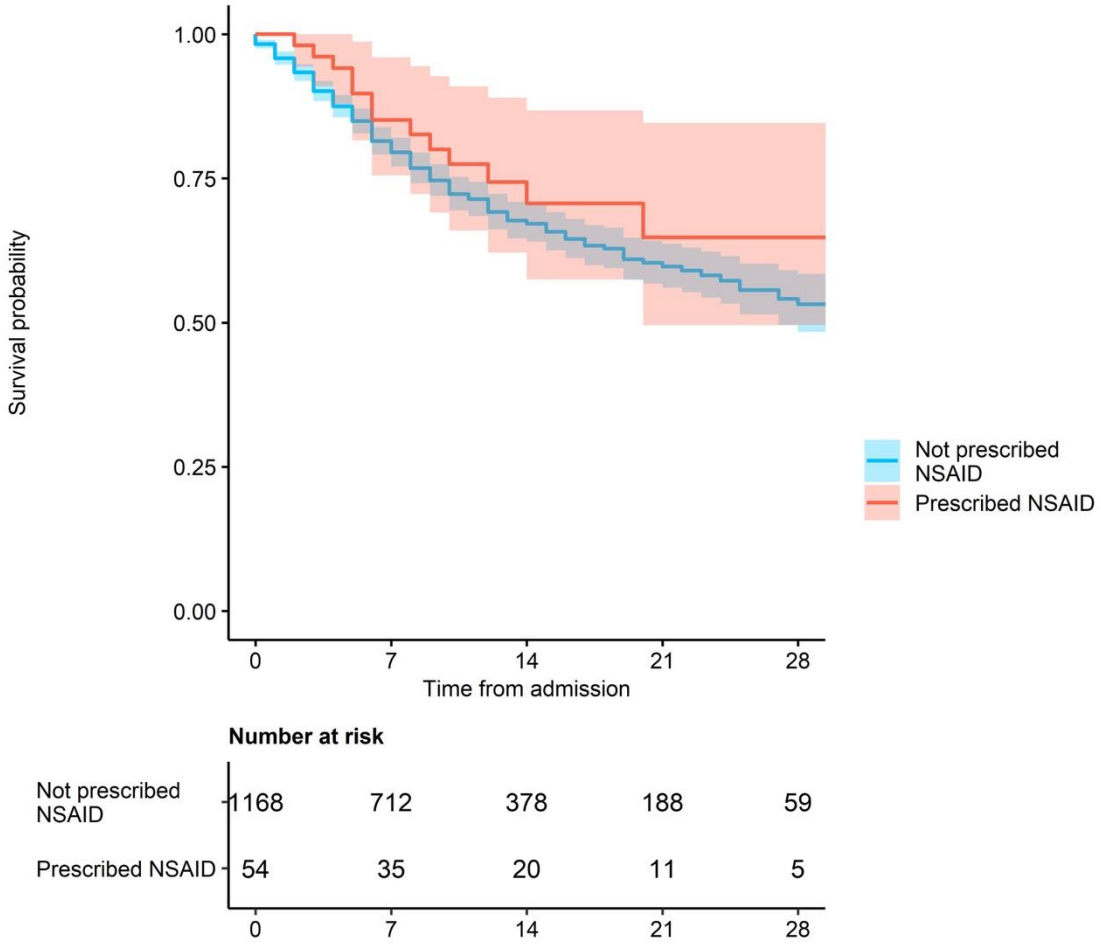
172 Overall NSAID use in the study population was 4.4% (n=54), ranging from 2.6-18.6% across the
173 eight hospital sites. Pre-admission NSAID use was higher in the younger age groups (<65 years 6.5%;
174 65-79 years 4.2%; ≥80 years 2.8%) and lower in patients with co-morbidities including diabetes (3.3%
175 in diabetic patients vs 4.9% in non-diabetics), hypertension (2.8% vs 6.1%), coronary artery disease
176 (3.3% vs 4.8%) and reduced renal function (3.0% vs 5.4%). The routine prescription of NSAIDs was
177 higher in those with an elevated CRP on admission; 5.1% of patients with an elevated CRP (>40mg.dl-
178 [1]) were prescribed routine NSAIDs prior to admission, compared to 3% of those without an elevated
179 CRP. Full patient demographics and clinical characteristics by NSAID use is shown in Supplementary
180 Table A1.

181 *3.1. Outcome analysis*

182 The primary endpoint was time to mortality, the Kaplan Meier Survival plot suggested a modest
183 protective effect due to NSAID use (Figure 1, Kaplan Meier curves), but in the crude analysis with
184 95%CI, we found no association between the routine use of NSAIDs, hazard ratio (HR) = 0.82 (95%CI
185 0.48-1.40, p=0.46, Table 2; indicated by overlapping shaded areas in Figure 1). Important covariates
186 which have previously been linked to poorer outcomes in COVID-19 disease, were associated with a
187 reduced time-to-mortality. These included: advancing age (compared to patients aged <65 years:
188 patients aged 65-79 years, HR=3.21, 95%CI 2.29-4.51; patients aged over 80 years, HR=3.94, 95%CI
189 2.52-5.50); reduced renal function (eGFR <60) on admission (HR=1.80, 95%CI 1.45-2.24, p<0.001), and
190 the presence or history of coronary artery disease (HR=1.47, p=0.001) and hypertension (HR=1.27,
191 95%CI 1.03-1.58, p=0.03).

192

Figure 1: NSAID use and Mortality (shaded areas indicate 95% confidence intervals):



In the multivariable analysis, there was no association between pre-admission NSAID use and time-to-mortality (adjusted HR [aHR] = 0.89, 95%CI 0.52-1.53, p=0.67, Table 2). Advancing age (65-79 vs under 65, aHR=3.14, 95%CI 2.20-4.48, p<0.001; over 80 vs under 65; aHR=4.00, 95%CI 2.81-5.71, <0.001), elevated CRP (>40mg/dl; aHR=2.75, 95%CI 2.01-3.76, p<0.001) and reduced renal function on admission (eGFR <60; aHR=1.40, 95%CI 1.11-1.75, p=0.004) were associated with mortality.

204 **Table 2:** Time to mortality. Crude and multivariable analysis

	Crude Hazard Ratio (HR) (n=1,181)		Adjusted Hazard Ratio (aHR)[&] (n=1,167)	
	HR, (95%CI)	p-value	aHR, (95%CI)	p-value
NSAID	0.82 (0.48-1.40)	0.46	0.89 (0.52-1.53)	0.67
Age				
Under 65	- Ref -		Ref -	
65 to 79	3.21 (2.29-4.51)	<0.001	3.14 (2.20-4.48)	<0.001
Over 80	3.94 (2.82-5.50)	<0.001	4.00 (2.81-5.71)	<0.001
Sex (Female)	- Ref		Ref -	
Male	0.88 (0.71-1.10)	0.25	0.88 (0.70-1.11)	0.28
Smoking status				
Ex-smokers	1.24 (1.0-1.55)	0.06	1.02 (0.80-1.28)	0.92
Current smokers	0.90 (0.56-1.42)	0.62	1.11 (0.68-1.82)	0.66
Elevated CRP (>40)	2.24 (1.65-3.05)	<0.001	2.75 (2.01-3.76)	<0.001
Patients with diabetes	1.09 (0.87-1.38)	0.45	1.03 (0.81-1.32)	0.80
Patients with CAD	1.47 (1.16-1.87)	0.001	1.09 (0.84-1.40)	0.53
Patients with hypertension	1.27 (1.03-1.58)	0.03	0.97 (0.77-1.22)	0.81
Patients with reduced renal function (eGFR<60)	1.80 (1.45-2.24)	<0.001	1.40 (1.11-1.76)	0.004

205 [&]The multivariable mixed-effects analysis was adjusted for: age group; sex; smoking; CRP; diabetes; CAD; hypertension; and
206 renal function
207
208 In the analysis for secondary outcomes, no association was found between pre-admission
209 NSAID use and day-7 mortality (adjusted Odds Ratio (aOR) = 0.79, p=0.60, Table 3) or time-to-
210 discharge (aHR=0.89, 95% CI 0.59-1.35, p=0.58, Table 3). Day-7 mortality was associated with older
211 age (compared to patients aged <65 years; 65-79 years aOR=3.80, p<0.001; ≥80 years aOR=5.14,
212 p<0.001), elevated CRP on admission (aOR=4.91, p<0.001) and reduced renal function (aOR=2.02,
213 p<0.001). An increased length of stay was associated with older age and elevated CRP on admission
214 (see Table 3).

Table 3: Day 7 mortality and Time to discharge. Multivariable analysis

	Adjusted Odds Ratio (OR) (n=1158)		Adjusted Hazard Ratio (aHR)[&] (n=1167)	
	aOR, (95%CI)	p-value	aHR, (95%CI)	p-
NSAID	0.79 (0.32-1.92)	0.602	0.89 (0.59-1.35)	0.58
Age				
Under 65	- Ref -		Ref -	
65 to 79	3.80 (2.26-6.37)	<0.001	0.76 (0.61-0.95)	0.02
Over 80	5.14 (3.04-8.69)	<0.001	0.56 (0.44-0.73)	<0.001
Sex (Female)	- Ref -		Ref -	
Male	0.81 (0.57-1.14)	0.227	0.92 (0.76-1.11)	0.37
Smoking status (Never)				
Ex-smokers	1.17 (0.83-1.67)	0.372	0.95 (0.78-1.15)	0.61
Current smokers	1.12 (0.54-2.33)	0.765	1.04 (0.73-1.48)	0.84
Elevated CRP (>40)	4.91 (2.99-8.06)	<0.001	0.69 (0.57-0.84)	<0.001
Patients with diabetes	1.04 (0.71-1.52)	0.838	0.84 (0.68-1.04)	0.12
Patients with CAD	1.46 (1.00-2.13)	0.051	1.12 (0.88-1.42)	0.36
Patients with	0.78 (0.55-1.10)	0.157	0.95 (0.79-1.16)	0.63
Patients with reduced renal function (eGFR<60)	2.02 (1.42-2.86)	<0.001	0.92 (0.75-1.13)	0.58

[&]The multivariable mixed-effects analysis was adjusted for: age group; sex; smoking; CRP; diabetes; CAD; hypertension; and renal function

Supplementary figures A1-A3 show subgroup analysis for patients prescribed NSAIDs, in relation to the three endpoints time-to-mortality, 7-day mortality and length of stay. Hazards ratios and odds ratios are adjusted for age group, sex, smoking status and co-morbidities. Due to the small number of NSAID users in our study population these analyses were underpowered and should be interpreted with caution and with a large degree of uncertainty.

4. Discussion

To the best of our knowledge, this study is the first to report on routine NSAID use and outcomes in hospitalized patients with COVID-19. We found that routine use of NSAIDs might confer a modest

survival benefit and lit is not associated with poorer outcomes. Uncertainty and speculation have surrounded this topic, and existing literature primarily references experience of these drugs in the setting of previous respiratory virus outbreaks [16]. Therefore, our findings provide novel information at a time where there is a significant lack of evidence and high demand for knowledge.

Whilst systematic reviews have concluded that there is insufficient evidence to determine the effect of NSAIDs in COVID-19 infection [16-19], advising against drastic changes to drug regimens, alternative literature advises that NSAIDs should be avoided until evidence emerges [20]. Many of the studies referenced within literature reviews are in relation to respiratory viruses other than SARS-CoV-2. It is thought that the pathophysiology and transmission of COVID-19 even shows differences in behaviour from other viruses within its family, such as severe acute respiratory virus (SARS) and Middle Eastern respiratory syndrome (MERS) [19]. Therefore, the findings of these studies may not be applicable in COVID-19 infection. However, very recently Rinott et al [21] published a retrospective cohort study of 403 cases of COVID-19 patients, recruiting those who used "any medication containing ibuprofen, paracetamol or dipyrone starting a week before diagnosis of COVID-19". Their conclusions therefore address the issue of acute use of NSAIDs, however found no significant association between ibuprofen usage and clinical outcomes (including mortality) when comparing the NSAID with cohorts using paracetamol or no- antipyretic.

Pre-admission NSAID use was lower in older age groups, which is in line with a recent European study of NSAID epidemiology [22]. NSAIDS account for 25% of adverse drug events reported in the United Kingdom [23], and it is thought that the elderly are more susceptible to the adverse effects of these drugs [4]. Conversely, the higher percentage of NSAID use in younger adults in this study may reflect their relative co-morbidity and subsequent susceptibility to hospitalization as a result of COVID-19.

Pre-admission NSAID use was also found to be lower in patients with co-morbidities across all age groups. This may be due to the relative contraindication of NSAIDs in these patients [24], and potential for drug interactions [25]. This low prevalence of NSAIDs routine use may be related to high proportion of patients with COVID-19 with background respiratory illness, where their use may be contraindicated. In analysis of biochemical markers, the routine prescription of NSAIDs was associated with elevated CRP on admission. This is expected, and is likely a reflection of pre- existing inflammatory conditions that require regular NSAID usage in this patient group in addition to COVID-19 infection.

Limitations of this study include a relatively small number of NSIAD users in our cohort thus study may be underpowered. It is possible that patients who have been using over-the-counter NSAIDs have not been captured. Conversely, as we collected data from prescriptions it is possible that some of the patients prescribed NSAIDs were not actually taking them in the days or weeks leading up to admission. We did not collect data on indication for, or duration of use of the agents, hence we cannot rule out possible confounding by indication.

There are intrinsic limitations associated with any observational study. However, the prospective relationship described reduces the possibility of reverse causality, whilst unselected cohort design reduced the selection bias. This study did not take into consideration a proportion of patients who were discharged from, or died in the Emergency Department or those patients with COVID-19 who remained in the community and were not treated in hospital. It is worth highlighting that our results specifically apply to the routine use of NSAIDs in patients who then develop COVID-19 infection. Our results therefore do not signify the safety of acute use of NSAIDs in the context of COVID-19 disease. This calls for future work examining the relationship between NSAID usage, by indication and duration as well as routine vs. acute usage, and mortality in Covid-19 in a high-powered study.

There are several strengths to our study. This was a multi-centre, prospective study, providing a large study population, which included patients from a range of specialties including medicine, surgery and medicine for the elderly. Through the inclusion of eight UK sites, the data are representative of populations across England, Scotland and Wales. Data was collected by trained personnel from paper and electronic records and prescription charts, which has resulted in minimal missing data.

This study has a number of direct implications on both clinical practice and research. Based on our results, patients and clinicians should not associate the routine use of NSAIDs with an increased risk of mortality in COVID-19 disease, and so we recommend that patients continue to comply with their baseline drug regimen. The association between NSAIDs and mortality in patients with COVID-19 warrants investigation via randomised controlled trials, as a method of further examining the potential beneficial effects that this study has suggested. Indeed, the LIBERATE Trial in COVID-19 [26] is an ongoing, multi-centre randomised controlled trial into lipid ibuprofen versus standard of care for acute hypoxic respiratory failure due to COVID-19. This is primarily in a critical care setting. However future investigation should not only concentrate on the use of NSAIDs as a therapeutic option, but continue to explore the effects of pre-admission NSAID use on outcomes and mortality in the general population affected by COVID-19. Future, higher powered studies would more reliably comment on the association of type, dose and duration of NSAID therapy with these important outcomes.

Our findings show no significant negative effect of routine NSAID use on mortality in patients with Covid-19 infection. Indeed, a modest beneficial effect of routine NSAID use on mortality may well exist, however cannot be concluded from the evidence presented here. This study has provided novel information into the impact of NSAID use and outcomes of COVID-19 disease, during a pandemic where there has been much uncertainty. Further evidence is required to explore this possible correlation and subsequently guide public health policy.

Author Contributions: Conceptualization, PKM, JH, BC and KM; methodology, PKM, BC.; software, BC, RS.; validation, BC, RS.; formal analysis, RS.; investigation, EB, FB-P.; resources, JH, PKM.; data curation, All.; writing—original draft preparation, EB, FB-P, BC, PKM.; writing—review and editing, All.; visualization, All.; supervision, PKM.; project administration, EB.; funding acquisition, Not applicable. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments:

We gratefully acknowledge the collaborators of the study listed below:

Ross Alexander, Emma Bhatti, Carly Bisset, Alice Cavenagh, Jemima Collins, Charlotte Davey, Siobhan Duffy, Jenny Edwards, Alice G Einarsson, Norman Galbraith, Madeline Garcia, James Hesford, Mark Holloway, Tarik Jichi, Joanna Kelly, Sheila Jones, Thomas Kneen, Thomas Lee, Kiah Lunstone, Emma Mitchell, Dolcie Paxton, Lyndsay Pearce, Terence J Quinn, Frances Rickard, Shefali Sangani, Rebecca Simmons, Sandeep Singh, Charlotte Silver, Thomas Telford, Alessia Verduri.

Conflicts of Interest: The authors declare no conflict of interest.

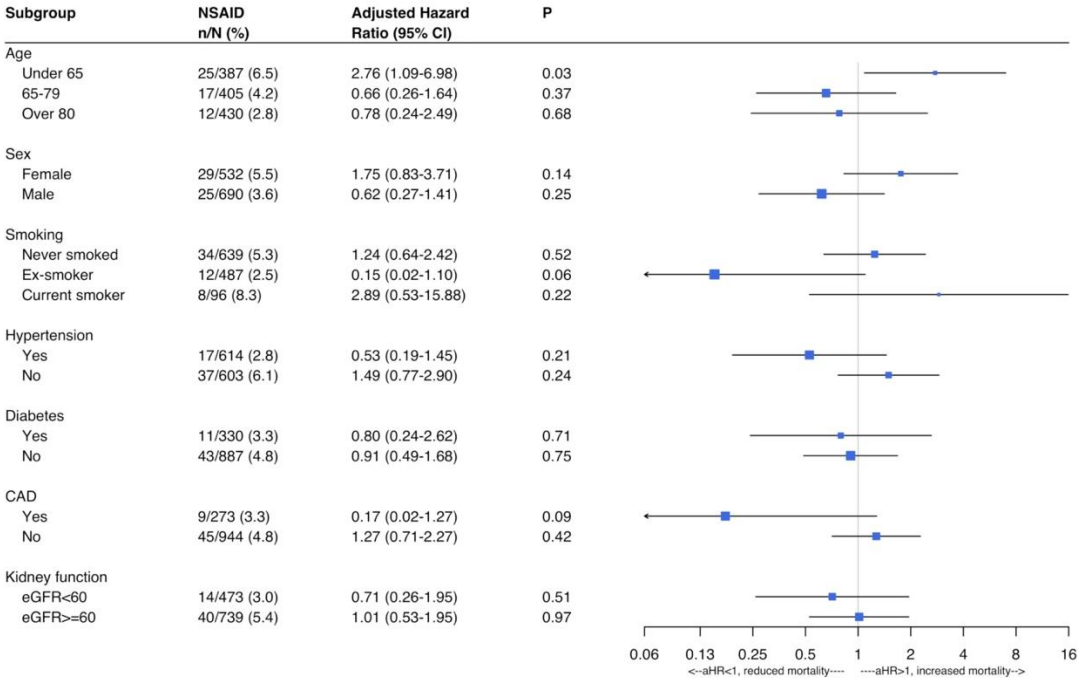
Appendix

Supplementary Table A1: Demographics and comorbidities, by NSAID Use

	No	Yes	Total
Sites	**(n=1168)**	**(n=54)**	
Hospital A	146 (95.4)	7 (4.6)	153 (12.5)
Hospital B	35 (81.4)	8 (18.6)	43 (3.5)
Hospital C	117 (95.1)	6 (4.9)	123 (10.7)
Hospital D	366 (96.3)	14 (3.7)	380 (31.1)
Hospital E	109 (97.3)	3 (3.0)	112 (9.2)
Hospital F	235 (95.5)	11 (4.5)	246 (20.1)
Hospital G	112 (97.4)	3 (2.6)	115 (9.4)
Hospital H	48 (96.0)	2 (4.0)	50 (4.1)
Age			
Under 65 yrs	362 (93.4)	25 (6.5)	387 (31.7)
65 to 79 yrs	388 (95.8)	17 (4.2)	405 (33.1)
Over 80 yrs	418 (97.2)	12 (2.8)	430 (35.2)
Sex			
Female	503 (94.6)	29 (5.5)	532 (43.5)
Male	665 (96.4)	25 (3.6)	690 (56.5)
Smoking Status			
Never smokers	585 (94.5)	34 (5.5)	619 (50.7)
Ex-smokers	475 (97.5)	12 (2.5)	487 (39.9)
Current smokers	88 (91.7)	8 (8.3)	96 (7.9)
Missing	20	0	20
Diabetes			
No	844 (95.2)	43 (4.9)	887 (72.6)
Yes	319 (96.7)	11 (3.3)	330(27.0)
Missing	5	0	5
Hypertension			
No	566 (93.9)	37 (6.1)	603 (49.4)
Yes	597 (97.2)	17 (2.8)	614 (50.3)
Missing	5	0	5
Coronary Artery disease			
No	899 (95.2)	45 (4.8)	944 (77.3)
Yes	264 (96.7)	9 (3.3)	273 (22.3)
Missing	5	0	5
Elevated CRP (>40)			
No	324 (97.0)	10 (3.0)	334 (27.3)
Yes	825 (94.9)	44 (5.1)	888 (71.1)

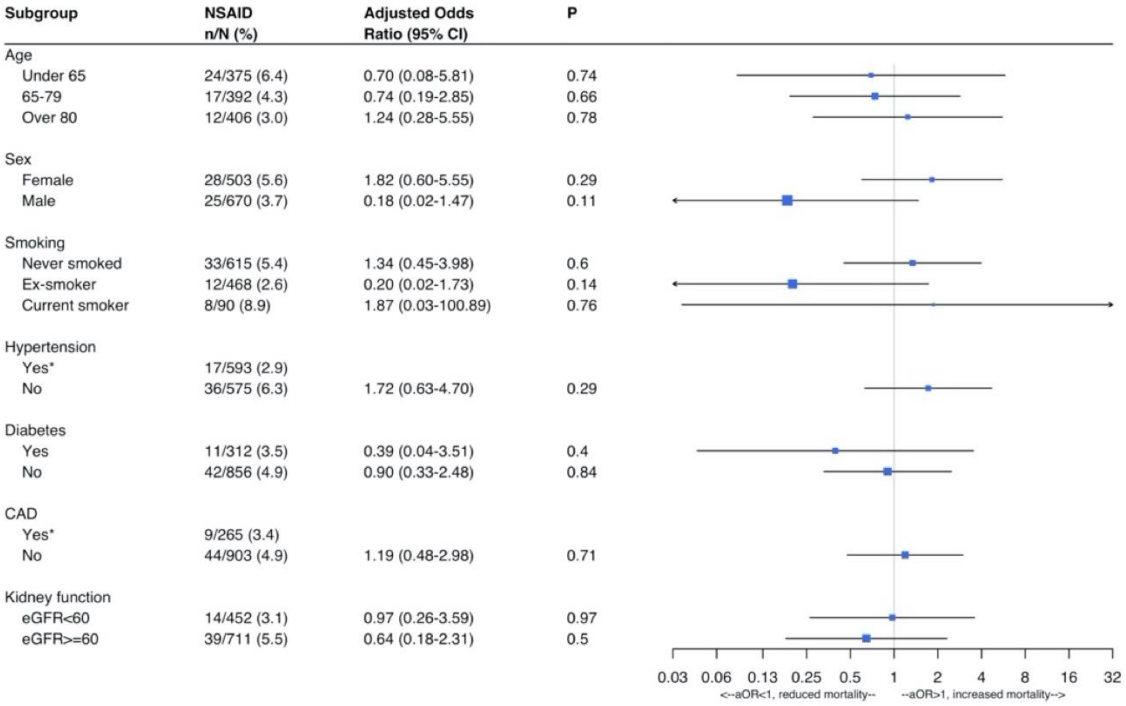
Missing	19	0	19
Renal function (eGFR<60)			
No	699 (94.6)	10 (5.4)	739 (60.5)
Yes	459 (97.0)	14 (3.0)	473 (38.7)
Missing	10	0	10

Supplementary Figure A1: Subgroups – Time to Mortality, Adjusted Hazard Ratio are presented from the Multivariable Cox PH model.



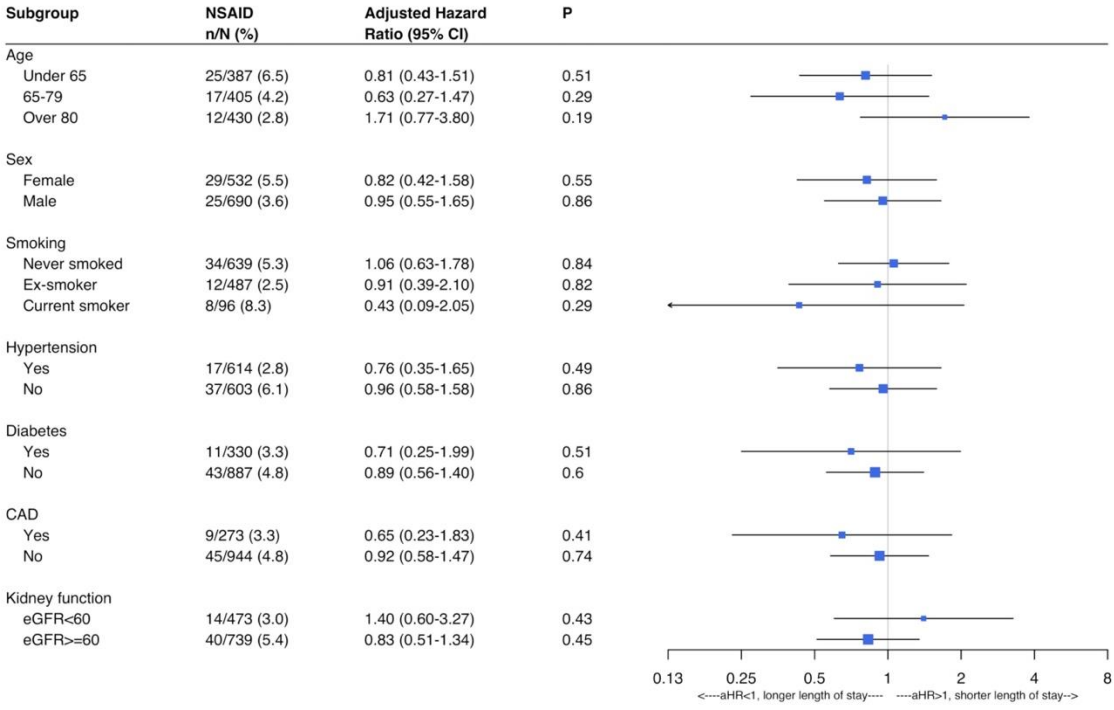
Note: Multivariable analyses adjusted for age group, sex, smoking status, hypertension, diabetes, CAD, kidney function, and elevated CRP

Supplementary Figure A2: Subgroup Analysis, Day-7 mortality. Mixed effects Logistic regression, Presenting the adjusted odds ratio from the logistic regression models.



Note: Multivariable analyses adjusted for age group, sex, smoking status, hypertension, diabetes, CAD, kidney function, and elevated CRP

Supplementary Figure A3: Subgroups – Time to Discharge, Adjusted Hazard Ratio are presented from the Multivariable Cox PH model.



Note: Multivariable analyses adjusted for age group, sex, smoking status, hypertension, diabetes, CAD, kidney function, and elevated CRP

References

1. Fu Y, Cheng Y, Wu Y. Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. Virol Sin. 2020. p. 12250.
2. Russell B, Moss C, Rigg A, Van Hemelrijck M. COVID-19 and treatment with NSAIDs and corticosteroids: should we be limiting their use in the clinical setting? Ecancermedicalscience. 2020; 14: 1023.
3. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. Aging Dis. 2018;9(1):143-150. Published 2018 Feb 1. doi:10.14336/AD.2017.0306
4. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Coxib and traditional NSAID trialists (CNT) collaboration. Lancet. 2013;382:769–779.
5. 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:E786.
6. Gracia-Ramos AE. Is the ACE2 Overexpression a Risk Factor for COVID-19 infection? [published online ahead of print, 2020 Apr4]. Arch Med Res. 2020;S0188-4409(20)30378-7. Doi:10.1016/j.arcmed.2020.03.011.
7. Basille D, Thomsen RW, Madsen M, et al. Nonsteroidal anti-inflammatory drug use and clinical outcomes of community- acquired pneumonia. Am J Rspir Crit Care Med 2018;198:128-31 doi:10.1164/rccm.201802-0229LE pmid:29461960.
8. Amici C, Di Caro A, Ciucci A, Chiappa L, Castilletti C, Martella V, Decaro N, Buonavoglia C, Capobianchi MR, Santoro MG. Indomethacin has a potent antiviral activity against SARS coronavirus. Antivir Ther. 2006;11(8):1021-30.
9. Hewitt J, Carter B, Vilches-Moraga A, et al. The effect of frailty on survival in patients with COVID-19 (COPE): a multicentre, European, observational cohort study [published online ahead of print, 2020 Jun 30]. *Lancet Public Health*. 2020;S2468-2667(20)30146-8. doi:10.1016/S2468-2667(20)30146-8
10. Heyneman, C.A., Lawless-Liday, C. & Wall, G.C. Oral versus Topical NSAIDs in Rheumatic Diseases. Drugs **60,** 555–574 (2000). https://doi.org/10.2165/00003495-200060030-00004
11. Honvo G, Leclercq V, Geerinck A, et al. Safety of Topical Non-steroidal Anti-Inflammatory Drugs in Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis. Drugs Aging. 2019;36(Suppl 1):45-64. doi:10.1007/s40266-019-00661-0
12. StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC
13. R Core Team (2019). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.
14. Therneau T (2020). A Package for Survival Analysis in R. R package version 3.1-12, https://CRAN.R-project.org/package=survival.
15. Alboukadel Kassambara, Marcin Kosinski and Przemyslaw Biecek (2019). survminer: Drawing Survival Curves using 'ggplot2'. R package version 0.4.6. https://CRAN.R-project.org/package=survminer
16. Russell B, Moss C, George G, et al. Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience. 2020;14:1022. Published 2020 Mar 27. doi:10.3332/ecancer.2020.1022
17. MaassenVanDenBrink, A., de Vries, T. & Danser, A.H.J. Headache medication and the COVID-19 pandemic. J Headache Pain **21,** 38 (2020). https://doi.org/10.1186/s10194-020-01106-5
18. Pergolizzi JV Jr, Varrassi G, Magnusson P, et al. COVID-19 and NSAIDS: A Narrative Review of Knowns and Unknowns [published online ahead of print, 2020 May 24]. Pain Ther. 2020;1-6. doi:10.1007/s40122-020-00173-5
19. Yousefifard M, Zali A, Zarghi A, Madani Neishaboori A, Hosseini M, Safari S. Non-steroidal anti-inflammatory drugs in management of COVID-19; a systematic review on current evidence [published online ahead of print, 2020 May 27]. Int J Clin Pract. 2020;e13557. doi:10.1111/ijcp.13557
20. Capuano A, Scavone C, Racagni G, Scaglione F; Italian Society of Pharmacology. NSAIDs in patients with viral infections, including Covid-19: Victims or perpetrators?. Pharmacol Res. 2020;157:104849. doi:10.1016/j.phrs.2020.104849
21. Rinott E, Kozer E, Shapira Y, Bar-Haim A, Youngster I. Ibuprofen use and clinical outcomes in COVID-19 patients [published online ahead of print, 2020 Jun 12]. *Clin Microbiol Infect*. 2020;S1198-743X(20)30343-8. doi:10.1016/j.cmi.2020.06.003

399 22. Gómez-Acebo I, Dierssen-Sotos T, de Pedro M, et al. Epidemiology of non-steroidal anti-inflammatory
400 drugs consumption in Spain. The MCC-Spain study. *BMC Public Health*. 2018;18(1):1134. Published 2018
401 Sep 21. doi:10.1186/s12889-018-6019-z
402 23. Zhang X, Donnan PT, Bell S, Guthrie B. Non-steroidal anti-inflammatory drug induced acute kidney injury
403 in the community dwelling general population and people with chronic kidney disease: systematic review
404 and meta-analysis. *BMC Nephrol*. 2017;18(1):256. Published 2017 Aug 1. doi:10.1186/s12882-017-0673-8
405 24. Pan Y, Zhang L, Wang F, Li X, Wang H; China National Survey of Chronic Kidney Disease Working Group.
406 Status of non-steroidal anti-inflammatory drugs use and its association with chronic kidney disease: a
407 cross-sectional survey in China. *Nephrology (Carlton)*. 2014;19(10):655-660. doi:10.1111/nep.12318
408 25. Lanas A et al. Risk of upper and lower gastrointestinal bleeding in patients taking nonsteroidal anti-
409 inflammatory drugs, antiplatelet agents, or anticoagulants. *Clin Gastroenterol Hepatol* 2014 Nov 14; [e-pub].
410 (http://dx.doi.org/10.1016/j.cgh.2014.11.007)
411 26. LIBERATE Trial in COVID-19 (LIBERATE). ClinicalTrials.gov Identifier: NCT04334629. Details accessed at
412 https://clinicaltrials.gov/ct2/show/study/NCT04334629 on 11th June 2020.
413

414