Use of non-steroidal anti-inflammatory drugs and adverse outcomes during the COVID-19 pandemic: A systematic review and meta-analysis

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Summary

Background There are concerns that the use of non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of adverse outcomes among patients with coronavirus COVID-19. This study aimed to synthesize the evidence on associations between the use of NSAIDs and adverse outcomes.

Methods A systematic search of WHO COVID-19 Database, Medline, the Cochrane Library, Web of Science, Embase, China Biology Medicine disc, China National Knowledge Infrastructure, and Wanfang Database for all articles published from January 1, 2020, to November 7, 2021, as well as a supplementary search of Google Scholar. We included all comparative studies that enrolled patients who took NSAIDs during the COVID-19 pandemic. Data extraction and quality assessment of methodology of included studies were completed by two reviewers independently. We conducted a meta-analysis on the main adverse outcomes, as well as selected subgroup analyses stratified by the type of NSAID and population (both positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or not).

Findings Forty comparative studies evaluating 4,867,795 adult cases were identified. Twenty-eight (70%) of the included studies enrolled patients positive to SARS-CoV-2 tests. The use of NSAIDs did not reduce mortality outcomes among people with COVID-19 (number of studies [N] = 29, odds ratio [OR] = 0.93, 95% confidence interval [CI]: 0.75 to 1.14, I^2 = 89%). Results suggested that the use of NSAIDs was not significantly associated with higher risk of SARS-CoV-2 infection in patients with or without COVID-19 (N = 10, OR = 0.96, 95% CI: 0.86 to 1.07, I^2 = 78%; N = 8, aOR = 1.01, 95% CI: 0.94 to 1.09, I^2 = 26%), or an increased probability of intensive care unit (ICU) admission (N = 12, OR = 1.28, 95% CI: 0.94 to 1.75, I^2 = 82% ; N = 4, aOR = 0.89, 95% CI: 0.65 to 1.22, I^2 = 60%), requiring mechanical ventilation (N = 11, OR = 1.11, 95% CI: 0.79 to 1.54, I^2 = 63%; N = 5, aOR = 0.80, 95% CI: 0.52 to 1.24, I^2 = 66%), or administration of supplemental oxygen (N = 5, OR = 0.80, 95% CI: 0.52 to 1.24, I^2 = 63%; N = 2, aOR = 1.00, 95% CI: 0.89 to 1.12, I^2 = 0%). The subgroup analysis revealed that, compared with patients not using any NSAIDs, the use of ibuprofen (N = 5, OR = 1.09, 95% CI: 0.50 to 2.39; N = 4, aOR = 0.95, 95% CI: 0.78 to 1.16) and COX-2 inhibitor (N = 4, OR = 0.62, 95% CI: 0.35 to 1.11; N = 2, aOR = 0.73, 95% CI: 0.45 to 1.18) were not associated with an increased risk of death.

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Interpretation Data suggests that NSAIDs such as ibuprofen, aspirin and COX-2 inhibitor, can be used safely among patients positive to SARS-CoV-2. However, for some of the analyses the number of studies were limited and the quality of evidence was overall low, therefore more research is needed to corroborate these findings.

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Keywords: NSAIDs; COVID-19; Systematic review; Meta-analysis

Research in context

Evidence before this study

We searched seven databases and resources from January 1, 2020, through November 7, 2021, with no restriction by language, for any systematic reviews comparing the clinical adverse outcomes between patients receiving NSAIDs. We used database-specific combinations of the following index terms and phrases: COVID-19, SARS-CoV-2, Coronavirus disease-19, 2019-novel coronavirus, 2019-nCoV, Nonsteroidal Anti-Inflammatory, Non-Steroidal Anti-Inflammatory, NSAID*, Antipyretic*, Ibuprofen*, Aspirin, Acetaminophen, and their derivatives. Previous related meta-analyses have only focused on a subset of NSAIDs and included indirect evidence on middle east respiratory syndrome-related coronavirus (MERS) and severe acute respiratory syndrome (SARS) and non-peer-reviewed preprints. Other meta-analyses did not perform subgroup analyses, nor did they grade the quality of evidence for their findings.

Added value of this study

We did a comprehensive systematic review and meta-analysis of forty observational studies across 14 countries and five continents. Our findings suggest that NSAIDs such as ibuprofen, aspirin, and COX-2 inhibitor can be used safely during the COVID-19 pandemic. The use of NSAIDs was not significantly associated with higher risk of SARS-CoV-2 infection, or an increased probability of intensive care unit (ICU) admission, requiring mechanical ventilation, or administration of supplemental oxygen.

Implications of all the available evidence

Our findings suggest that NSAIDs can be used safely in patients to relieve pain, inflammation, and fever during the COVID-19 pandemic. For future studies, there is a lack of high-quality multicenter cohort studies with a large sample size indicating NSAIDs' impact on the quality of life and long-term survival.

Introduction

Since December 2019, a new infectious disease, coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2, has swept across the world and brought huge challenges to the public health and medical service systems worldwide.[1] Current evidence suggests that fever is one of the main clinical symptoms of COVID-19, with 88.7% of hospitalized adults and 63.3% of hospitalized children with COVID-19 presenting fever. Therefore, symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen is often used in COVID-19 patients.[2–4] However, a study published on March 11, 2020, questioned the safety of ibuprofen in the treatment of COVID-19, suggesting that SARS-CoV-2 could invade human cells by combining with Angiotensin-Converting Enzyme 2 (ACE2), with the goal of infestation. Ibuprofen can strengthen the binding ability of ACE2 and SARS-CoV-2 and enhance the infection process of the virus. The possibility that ibuprofen use can deteriorate the course of COVID-19 should thus not be excluded, and ibuprofen should be used with caution in patients during the pandemic.[5]

Based on the above research results, Olivier Véran, the Minister of Solidarity and Health of France issued a warning via social media on 14 March 2020, stating that "the use of anti-inflammatory drugs (ibuprofen, cortisone, etc.) may aggravate the course of COVID-19, and paracetamol is recommended if fever symptoms occur".[6] On March 17, 2020, the World Health Organization (WHO) also issued a statement that "it is recommended that patients with COVID-19 avoid taking ibuprofen".[7] However, at the same time, the European Medicines Agency (EMA) issued a statement that there is no scientific evidence of an association between ibuprofen and COVID-19 deterioration. The EMA further noted that they would closely monitor the situation and review any new information.[8] In France, the issuance of the above warnings led to an 80% drop in the prescription rate of ibuprofen in general.[9]

The evidence on the impact of ibuprofen and other NSAIDs for patients with COVID-19 is still controversial. The first prospective cohort study of ibuprofen and other NSAIDs for treating adults with COVID-19 showed that among 503 adults with confirmed SARS-CoV-2 infection, the use of ibuprofen during the acute phase was not associated with the risk of death (hazard

ratio [HR]=0.63, 95% CI: 0.07 to 5.44) or the risk of hospital admission (OR = 1.27, 95% CI: 0.55 to 2.95), compared with no ibuprofen use. Long-term use of NSAIDs was also not found to be associated with a higher risk of death (HR=0.49, 95% CI: 0.18 to 1.36).[10] However, another retrospective cohort study from South Korea showed that among 1824 hospitalized adult patients with COVID-19, there was an increased risk of adverse outcomes in patients who used NSAIDs (OR=1.54, 95% CI: 1.13 to 2.11) compared with patients who did not use NSAIDs (n = 87).[11] Currently, the research results on whether NSAIDs can be safely used in patients with COVID-19 or not are inconsistent. To answer this question, we included all comparative studies which enrolled patients that took NSAIDs during the COVID-19 pandemic, to conducted this comprehensive systematic review and meta-analysis to explore the association between the use of NSAIDs and adverse outcomes among patients during the COVID-19 pandemic.

Methods

Our systematic review and meta-analysis were performed in accordance with the *Cochrane Handbook*.[12] We report the results in accordance with the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) statement.[13]

Data sources and searches

We performed a systematic literature search of the WHO COVID-19 Database, Medline (via PubMed), The Cochrane Library, Web of Science (WOS), China Biology Medicine disc (CBM), China National Knowledge Infrastructure (CNKI), and Wanfang Database for studies published from January 1, 2020, through November 7, 2021. We used database-specific combinations of the following index terms and phrases: COVID-19, SARS-CoV-2, Coronavirus disease-19, 2019-novel coronavirus, 2019-nCoV, Nonsteroidal Anti-Inflammatory, Non-Steroidal Anti-Inflammatory, NSAID*, Antipyretic*, Ibuprofen*, Aspirin, Acetaminophen, and their derivatives. Supplementary searches were conducted on Google Scholar (https://scholar.google.nl/). Finally, we reviewed the references from the included articles manually to identify any missed potentially relevant records. The inclusion of studies was not restricted by the publication status or language. An information retrieval specialist helped to develop the search strategy. Details of the search strategies are available in eTable 1 in Supplementary.

Inclusion and exclusion criteria

We included all comparative studies in comparing the clinical adverse outcomes during the COVID-19 pandemic (in the time period starting from the end of 2019) between patients receiving and not receiving any NSAIDs. All included studies must be conducted during the COVID-19 pandemic, but the patients could positive or negative to SARS-CoV-2 test. We made no restrictions on age, gender, ethnicity, region, other individual factors, or the COVID-19 status.

We excluded multiple publications on the same population. Studies reporting insufficient details were also excluded unless we were able to retrieve the original data.

Study selection process

Study selection was conducted independently by two investigators. For this purpose, four investigators were divided into two groups (Siya Zhao and Shuai Peng; Zhili Wang and Lidan Gan), and the records were split randomly between these groups. The retrieval consisted of three phases. In phase one, we screened titles and abstracts of search results to exclude literature that obviously did not meet the inclusion and exclusion criteria. In phase two, full-text articles were obtained for articles identified by one or both investigators as potentially relevant. The full texts of eligible articles were reviewed independently by the same two investigators. In phase three, any disagreements in the decision to include or exclude the study were adjudicated through discussion or consultation with a third investigator (Qi Zhou).

Data extraction

Two investigators (Siya Zhao and Lidan Gan) independently extracted data from the included studies using a standardized Microsoft Excel collection form. Disagreements were resolved through discussion or consultation with a third investigator (Qi Zhou) if necessary. The following information was extracted: (1) Basic information: the first author, year of publication, country of origin, sample size, types of study design and complications; (2) Characteristics of the exposure: types of NSAIDs taken; (3) Information on outcomes: mortality, probability of SARS-CoV-2 infection, probability of ICU admission rate, probability of machine ventilation, probability of administration of respiratory support, a composite risk of adverse outcomes (defined as having at least one of the following: requirement for supplemental oxygen, mechanical ventilation, sepsis, ICU admission or death). Mortality was the primary outcome of our study. If sufficient data on characteristics or outcomes were not available, we contacted the authors of studies by e-mail to request them or calculated from other reported data according to methods recommended by the Cochrane Handbook, if available.

Assessment of the methodological quality

Two investigators (Qi Zhou and Siya Zhao) independently assessed the risk of bias in each study included

in the systematic review. We used the Newcastle-Ottawa Scale to assess the methodological quality.[14] The tool consists of eight items: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, the demonstration that outcome of interest was not present at the start of study, comparability of cohorts on the basis of the design or analysis, assessment of outcome, sufficient follow-up for outcomes to occur, and adequacy of follow up of cohorts. Each item was rated as either none, one point or two points. We resolved disagreements by discussion or by consultation with another investigator (Yaolong Chen).

Assessment of the certainty of the evidence

We assessed the certainty of the evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[15,16] for all outcomes. We rated the certainty of the evidence for each outcome based on considerations of five factors that may lead to rating down the quality of evidence (risk of bias, inconsistency, imprecision, indirectness, and publication bias), and three factors that may lead to rating up the quality of evidence (dose-response gradient, large magnitude of effect and plausible confounders or biases). The quality of evidence is initially assigned as high for randomized controlled trials (RCTs) without serious defects in methodology, and low for observational studies, after which the quality is gradually up- or downgraded based on the eight factors mentioned before. The quality of the evidence is finally rated as 'high', 'moderate', 'low' or 'very low'. We performed the assessment using the GRADEpro software and generated a summary of findings (SoF) table.[17,18]

Data analysis

I^2 statistic was used to quantify the amount of heterogeneity, with I^2 of greater than 50% representing substantial heterogeneity.[19] We did our data analyses with RevMan 5.4 software and STATA15.0 (StataCorp, College Station, Texas). We used a random effects model and calculated odds ratios (OR) with 95% confidence intervals (CI) for dichotomous outcomes, and mean differences (MD) with 95% CI for continuous outcomes.[20] We present the pooled results over all studies and performed subgroups analyses by the type of NSAID (ibuprofen vs. aspirin vs. COX-2 inhibitor vs. other drugs) and population (C+:all patients tested positive for SARS-CoV-2 vs. C±/C-: part or no patients tested positive for SARS-CoV-2). We also performed a meta-analysis of adjusted OR, risk ratio (RR) and HR. If both unadjusted and adjusted ORs were reported from the same study, we extracted both and pooled the unadjusted estimates in the main analysis and the adjusted estimates in the secondary analysis. RR and HR from other studies were regarded as OR. If not available, ORs could be obtained through calculating events and total numbers of patients in two groups. If more than one adjusted ORs were reported, we used the one adjusted for the maximum number of covariables. We also performed a sensitivity analysis to assess the robustness of our findings by excluding one research every analysis. Publication bias was assessed by a funnel plot.[21]

Role of the funding source

There was no funding source for this study.

Results

Characteristics of the included studies

A total of 2312 references were identified in our search. After screening on titles, abstracts and full texts, forty comparative studies involving 4867,795 individuals were included in this review, in which eight are from the United States of America (USA), six are from South Korea, and four are from the United Kingdom (UK) (Figure 1).[10,11,22–59] Twenty-eight (70%) of the included studies enrolled patients positive to SARS-CoV-2 tests. All forty studies included only adult cases. Thirty-seven studies were retrospective and the remaining three prospective. Characteristics of the included studies are described in Table 1. Thirty-four (85%) of the included studies did not specify whether the assessment of the outcome was blinded. Moreover, we found a risk of bias in the ascertainment of the exposure in seven studies. Overall, the methodological quality of the included studies was good (eTable 2 in Supplementary).

Mortality

Twenty-nine studies with 4241,022 cases assessed the association between NSAID exposure and mortality in patients who were positive or negative to SARS-CoV-2 tests during the COVID-19 pandemic. The use of NSAIDs did not increase the odds of death (OR = 0.93, 95% CI: 0.75 to 1.14, I^2 = 89%) (Figure 2). In the analysis of adjusted estimates, NSAID use was associated with better-adjusted mortality (aOR = 0.74, 95% CI: 0.61 to 0.90, I^2 = 82%) (Figure 3).

The results of subgroup analysis of unadjusted mortality showed that significant associations were not found in the subgroup analyses stratified by the type of NSAID (ibuprofen: OR = 1.09, 95% CI: 0.50 to 2.39; aspirin: OR = 0.93, 95% CI: 0.58 to 1.48; COX-2 inhibitor: OR = 0.62, 95% CI: 0.35 to 1.11) and the population (C+: OR = 0.94, 95% CI: 0.74 to 1.20; C±/C-: OR = 0.91, 95% CI: 0.55 to 1.50). However, subgroup analysis showed that administration of aspirin (aOR = 0.55, 95% CI: 0.40 to 0.78), ibuprofen (aOR = 0.95, 95% CI: 0.78 to 1.16) and COX-2 inhibitor

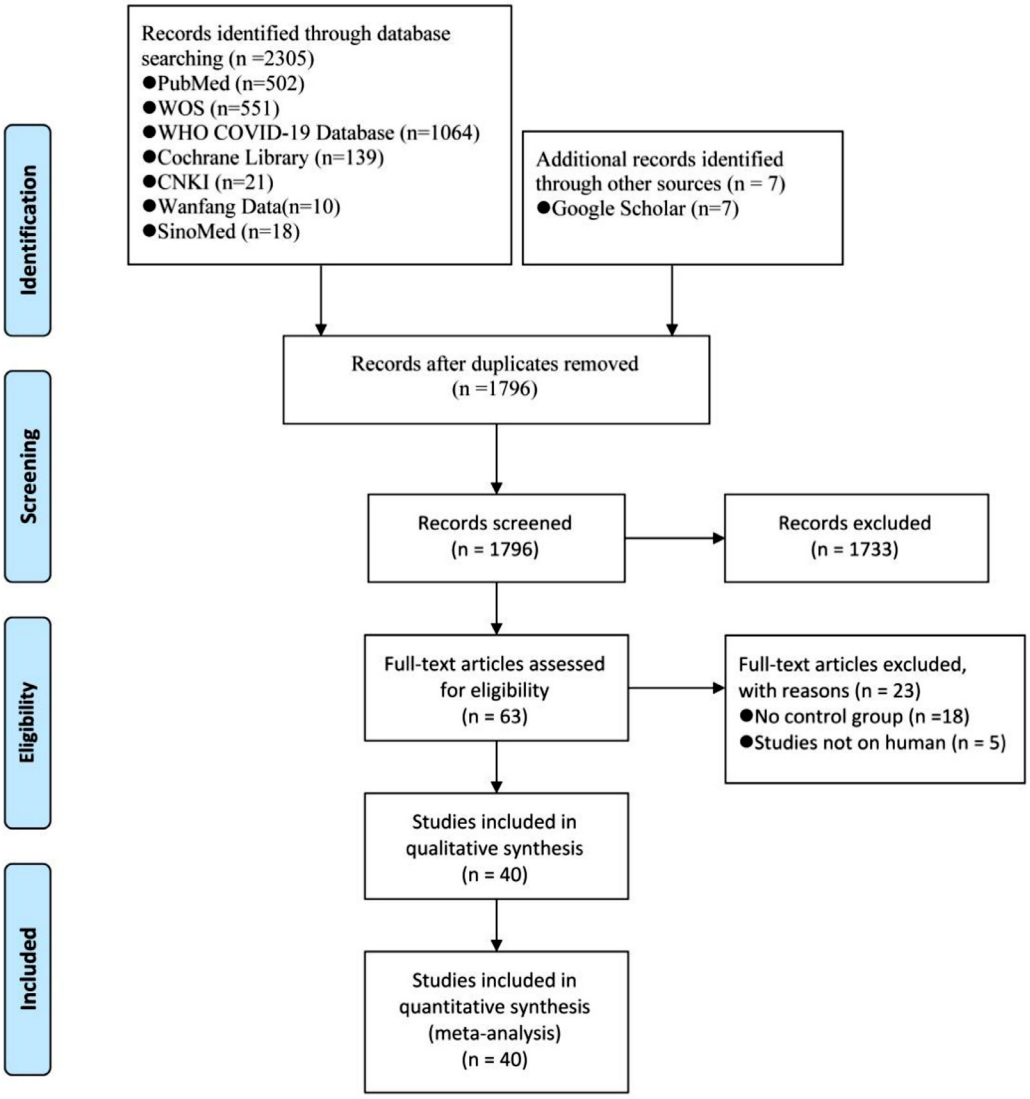

Figure 1. *Literature search and screening process from*: Moher D, Liberati A, Tetzlaff J, Altman D G. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement BMJ 2009; 339 :b2535 doi:10.1136/bmj.b2535.

(aOR = 0.73, 95% CI: 0.45 to 1.18) were not statistically different in terms of mortality in patients with COVID-19. The results of the subgroup analysis of the population showed a statistical difference, which means that taking NSAIDs may reduce the mortality among patients positive to SARS-CoV-2 tests (N = 24, OR = 0.94, 95% CI: 0.74 to 1.20, I^2=88%; N = 15, aOR=0.72, 95% CI: 0.56 to 0.82, I2=84%). However, the point estimate aORs from different populations (C +, aOR = 0.72, 95% CI: 0.56 to 0.92; C±/C-, aOR=0.87, 95% CI: 0.77 to 0.98) (eFigure 1 in Supplementary) all lied within the 95% CI for the total aOR of the association between NSAID and mortality (aOR = 0.74, 95% CI: 0.61 to 0.90) (Figure 3). Therefore, the adjusted mortality did not differ significantly across patients with or without COVID-19.

Risk of SARS-CoV-2 infection

Ten studies with 581,055 cases assessed the association between NSAID exposure and the risk of SARS-CoV-2 infection in patients who were negative to SARS-CoV-2 tests during the COVID-19 pandemic. The use of NSAIDs did not increase the odds of SARS-CoV-2 infection (OR = 0.96, 95% CI: 0.86 to 1.07, I^2=78%) (Figure 4). Similar results were found in the adjusted analysis (aOR = 1.01, 95% CI: 0.94 to 1.09, I^2=26%) (eFigure 2 in Supplementary).

ICU admission

Twelve studies (n = 27,689) evaluated the association between NSAID exposure and ICU admission in patients who were positive or negative to SARS-CoV-2

Study ID	Country	Study design	Population	Type of drugs	Dosage (daily)	Sample size		Age (year) *		Male (%)		Diabetes mellitus (%)		Hypertension (%)		COPD-Chronic pulmonary disease (%)		Cardiovascular disease (%)		Outcomes
						E	C	E	C	E	C	E	C	E	C	E	C	E	C	
Abdelwahab et al., 2021 a	Egypt	RS	C+	Aspirin	81–162 mg	31	36	56.0 ± 16.1	44.0 ± 16.5	51.6	33.3	38.7	11.1	48.4	13.9	NR	NR	25.8	0	④
Abdelwahab et al., 2021 b	Egypt	RS	C+	Aspirin	81–162 mg	35	123	61.0 ± 14.3	58.0 ± 14.7	48.6	46.3	48.6	43.1	62.9	45.5	NR	NR	22.9	3.3	④
Abu Esba et al., 2020	Saudi Arabia	PS	C+	Unspecified	NR	146	357	47.5(33.0–63.0)	36.0 (27.0–49.0)	52.1	59.4	41.1	14.8	34.9	14.6	NR	NR	12.3	2.5	①⑤⑦
Aghajani et al., 2021	Iran	RS	C+	Aspirin	NR	336	655	65.8 ± 14.3	58.5 ± 17.4	56.0	54.0	47.6	21.8	62.5	30.0	NR	NR	40.8	8.7	① ④
Alamdari et al., 2020	Iran	RS	C+	Unspecified	NR	37	422	61.8 ± 11.9	69.7	NR	NR	NR	NR	NR	NR	NR	NR	①		
Argenziano et al., 2020	USA	RS	C+	Unspecified	NR	250	750	63.0 (50.0–75.0)	59.6	37.2	60.1	6.6	NR	NR	③⑦					
Blanch-Rubió et al., 2020	Spain	RS	C±	Unspecified	NR	318	1784	66.4 (13.3)	19.5	NR	NR	NR	NR	NR	NR	NR	NR	②		
Bruce et al., 2020	UK	RS	C+	Unspecified	NR	54	1168	NR	NR	46.3	56.9	20.4	27.3	31.5	51.1	NR	NR	NR	NR	①
Chandan et al., 2021	UK	RS[&]	Osteoarthritis	Unspecified	NR	8595	8595	68.4 ± 10.4	68.1 ± 10.5	34.8	34.2	17.0	15.9	NR	NR	8.1	7.1	13.7	9.7	①②
Chow et al., 2021	USA	RS	C+	Aspirin	81 mg	98	314	61.0 (55.0–72.0)	52.0 (37.0–65.0)	62.2	58.3	55.1	29.0	78.6	52.5	NR	NR	34.7	5.7	①③④
Costantino et al., 2020	France	RS	Rheumatic diseases	Unspecified	NR	318	337	51.0 ± 13.4	38.2	NR	NR	NR	NR	NR	NR	NR	NR	②		
Drake et al., 2021	UK	PS[&]	C+	Unspecified	NR	4211	67,968	70.1 ± 18.7	70.2 ± 18.4	46.4	46.4	21.1	21.5	NR	NR	18.7	16.5	35.1	30.3	①③④⑤
Gianfrancesco et al., 2020	Australia	RS	RA	Unspecified	NR	111	420	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	⑦
Gupta et al., 2020	USA	PS	C+	Unspecified	NR	191	2024	60.5 (14.5)	64.8	NR	NR	NR	NR	NR	NR	NR	NR	①		
Hong et al., 2020	China	PS	C+	COX-2 inhibitor	200–400 mg	36	7	49.3 ± 14.8	49.5 ± 18.3	47.2	57.1	8.3	14.2	8.3	14.2	NR	NR	5.6	14.2	①
Huh et al., 2021	South Korea	RS	C±	Unspecified	NR	7080	36,966	NR	NR	59.5	NR	NR	NR	NR	NR	NR	NR	NR	②	
Hwang et al., 2020	South Korea	RS	C+	Unspecified	NR	5	98	67.6 ± 15.3	50.5	NR	NR	NR	NR	NR	NR	NR	NR	①		
Imam et al., 2020	USA	RS	C+	Unspecified	NR	466	839	61.0 ± 16.3	53.8	NR	NR	NR	NR	NR	NR	NR	NR	①		
Jehi et al., 2020	USA	RS	C+	Unspecified	NR	892	3644	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	⑦
Jeong et al., 2020	South Korea	RS[&]	C+	Unspecified	NR	354	1470	54.1 ± 17.6	47.8 ± 19.1	41.5	41.0	17.0	11.0	28.0	19.0	20.0	15.0	NR	NR	①③④⑥
Karruli et al., 2021	Italy	RS	C+	Aspirin	Low dose	5	27	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	①
Kim et al., 2021 a	South Korea	RS[&]	C±	Aspirin	NR	136	136	NR	NR	63.2	61.8	67.6	72.1	79.4	82.4	9.6	8.1	48.5	49.3	①②③④⑤⑥
Kim et al., 2021 b	South Korea	RS[&]	C±	Aspirin	NR	526	526	NR	NR	58.0	56.8	50.8	49.8	75.5	76.2	9.7	7.2	36.3	35.0	①②③④⑤⑥

Table 1 (Continued)

Study ID	Country	Study design	Population	Type of drugs	Dosage (daily)	Sample size		Age (year) *		Male (%)		Diabetes mellitus (%)		Hypertension (%)		COPD-Chronic pulmonary disease (%)		Cardiovascular disease (%)		Outcomes
						E	C	E	C	E	C	E	C	E	C	E	C	E	C	
Kragholm et al., 2020	Denmark	RS	C+	Ibuprofen	NR	264	3738	58.0(46—68.0)	57.0(45.0—73.0)	44.7	47.4	13.3	11.1	24.2	21.8	6.4	5.3	2.7	2.5	⑥
Liu et al., 2021	China	RS[&]	C+	Aspirin	81 mg	28	204	69.5 (61.0—77.0)	54.0 (42.0—65.0)	64.3	53.4	17.9	11.3	71.4	19.6	3.6	2.5	NR	NR	①
Lodigiani et al., 2021	Italy	RS	C+	Aspirin	NR	93	286	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	①③
Lund et al., 2020	Denmark	RS[&]	C+	Unspecified	NR	224	896	54.0(43.0—64.0)	54.0(41.0—66.0)	40.2	41.9	NR	NR	NR	NR	4.0	3.9	10.3	10.2	①③④⑦
Mancia et al., 2020	Italy	RS	C±	Unspecified	NR	5615	31,416	68.0 ± 13.0	63.0	NR	NR	NR	NR	NR	NR	NR	NR	②		
Martínez-Botía et al., 2021	Spain	RS[&]	C+	Unspecified	NR	366	1669	66.4 ± 15.8	67.3 ± 16.2	61.2	59.8	13.1	12.9	NR	NR	NR	NR	NR	NR	①③
Meizlish et al., 2021	USA	RS[&]	C+	Aspirin	81 mg	964	1821	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	①
Merzon et al., 2021	Israel	RS	C±	Aspirin	Low dose	1621	8856	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	①②⑦
Ong et al., 2020	Singapore	RS	C+	COX-2 inhibitor	60—90 mg	22	146	56.0 (53.8—61.0)	62.0 (55.8—68.3)	50.0	56.2	18.2	31.5	31.8	50.7	0	2.7	4.5	9.6	①③④⑤⑥
Osborne et al., 2021	USA	RS[&]	C+	Aspirin	NR	6300	6300	67.4 ± 10.8	67.3 ± 11.2	95.2	96.6	62.5	41.3	89.4	72.6	43.8	37.9	NR	NR	①
Park et al., 2021	South Korea	RS[&]	C+	Unspecified	NR	397	397	NR	NR	41.8	36.8	16.6	15.9	28.7	27.7	2.5	0.8	NR	NR	①④
Reilev et al., 2020	Denmark	RS	C±	Unspecified	NR	47,503	374,316	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	①②③⑦
Rinott et al., 2020	Israel	RS	C+	Ibuprofen	NR	87	316	40.0(24.5—64.0)	46.0(25.0—61.0)	52.9	55.1	11.4	8.8	NR	NR	NR	NR	13.7	12.6	①③④⑤
Sahai et al., 2021 a	USA	RS[&]	C+	Unspecified	NR	444	444	58.1 ± 17.0	58.2 ± 18.1	51.1	48.6	35.7	35.9	62.7	66.1	10.9	12.1	NR	NR	①
Sahai et al., 2021 b	USA	RS[&]	C+	Aspirin	81 mg	248	248	68.5 ± 13.6	69.5 ± 14.1	56.5	59.5	50.4	50	84.9	85	18.7	13.6	NR	NR	①
Son et al., 2021	South Korea	RS	C±	Aspirin	NR	844	10,631	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	②
Vahedian-Azimi et al., 2021	Iran	RS	C+	Aspirin	NR	237	350	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	①③
Vila-Corcoles et al., 2020	Spain	RS	C±	Unspecified	NR	1650	33,286	NR	NR	48.1	28.1	NR	NR	NR	NR	NR	NR	②		
Wong et al., 2021 a	UK	RS	General population	Unspecified	NR	536,423	1,927,284	53.0 (42.0—64.0)	49.0 (36.0—60.0)	40.8	43.3	11.0	9.0	23.9	18.4	2.9	2.2	NR	NR	①
Wong et al., 2021 b	UK	RS	Rheumatoid arthritis	Unspecified	NR	175,495	1,533,286	63.0 (55.0—71.0)	68.0 (58.0—76.0)	37.0	37.9	14.7	15.4	37.7	40.8	4.8	5.6	NR	NR	①
Yuan et al., 2021	China	RS	C+	Aspirin	75—150 mg	52	131	69.7 ± 1.1	71.8 ± 0.9	59.6	51.9	25.0	20.6	61.5	53.4	1.9	5.3	NR	NR	

***Table 1*: Characteristics of the included studies.**

① Mortality; ② Risk of SARS-CoV-2 infection; ③ ICU admission; ④ Mechanical ventilation; ⑤ Supplemental oxygen; ⑥ Composite adverse outcome; ⑦ Hospital admission; C+: Patients positive to SARS-CoV-2 tests; C±: Partial or none patients positive to SARS-CoV-2 tests; E: Exposure group; C: Control group; NR: Not report; RS: Retrospective study; PS: Prospective study; *: Data are reported as mean ± SD or median (interquartile range); &: Propensity score—matched cohort study.

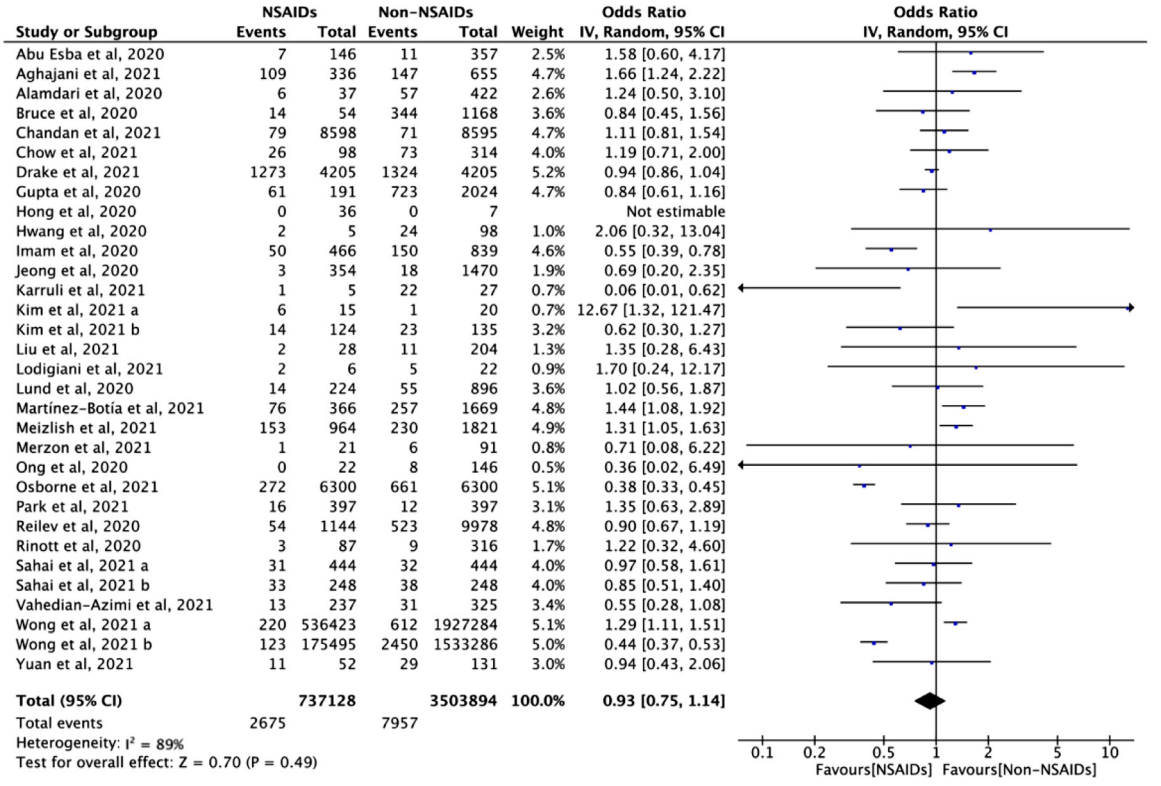

Figure 2. *The association between NSAID exposure and mortality among patients who were positive or negative to SARS-CoV-2 tests during the COVID-19 pandemic*. "Events" is the number of deaths; "Total" is population size; "Weight" is study weight in the analysis. "IV" is inverse variance statistical method of meta-analysis; "Random" is random effects model; "95% CI" is the 95% confidence intervals for the mortality; Each horizontal line in the graphical display represents a study, its width represents 95% CI of the interval estimation of the odds ratio effect of mortality, and the blue midpoint of the line symbolizes the point estimate of the unadjusted odds ratio effect of mortality; "I^{2}" represents the quantity of heterogeneity (0–100%); "Test for overall effect: $Z = 0.70$ ($P = 0.49$)" confirms no statistical difference illustrated by the diamond crossing the line of effect (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

tests during COVID-19 pandemic. The use of NSAIDs in patients was not associated with the probability of ICU admission (OR = 1.28, 95% CI: 0.94 to 1.75, I^2 = 82%) (Figure 5). Similar results were found in the adjusted analysis (aOR = 0.89, 95% CI: 0.65 to 1.22, I^2 = 60%) (eFigure 2 in Supplementary).

. Mechanical ventilation

Eleven studies (n = 14,717) evaluated the association between NSAID exposure and mechanical ventilation rate in patients who were positive or negative to SARS-CoV-2 tests. The use of NSAIDs did not increase the probability of requiring mechanical ventilation (OR = 1.11, 95% CI: 0.79 to 1.54, I^2 = 63%), compared to those not taking NSAIDs (Figure 6). In the adjusted analysis, there was also no increase in the odds of mechanical ventilation with the use of NSAID (aOR = 0.80, 95% CI: 0.52 to 1.24, I^2 = 66%), compared with no NSAID use (eFigure 2 in Supplementary).

Other outcomes

No association between NSAIDs exposure and administration of supplemental oxygen (OR = 0.80, 95% CI: 0.52 to 1.24, I^2 = 57%), composite adverse outcome (OR = 1.32, 95% CI: 0.75 to 2.33, I^2 = 75%), hospital admission (OR = 1.58, 95% CI: 1.06 to 2.36, I^2 = 93%) among patients who were positive or negative to SARS-CoV-2 tests during the COVID-19 pandemic (see eFigure 3 in Supplementary). And the adjusted ORs between NSAIDs exposure and administration of supplemental oxygen (aOR = 1.00, 95% CI: 0.89 to 1.12, I^2 = 0%), composite adverse outcome (aOR = 1.07, 95% CI: 0.66 to 1.73, I^2 = 72%), hospital admission (aOR = 1.07, 95% CI: 0.74 to 1.55, I^2 = 62%) also did not show association (see eFigure 2 in Supplementary).

Sensitivity analysis

We performed a sensitivity analysis on the mortality meta analysis by excluding one study at a time because

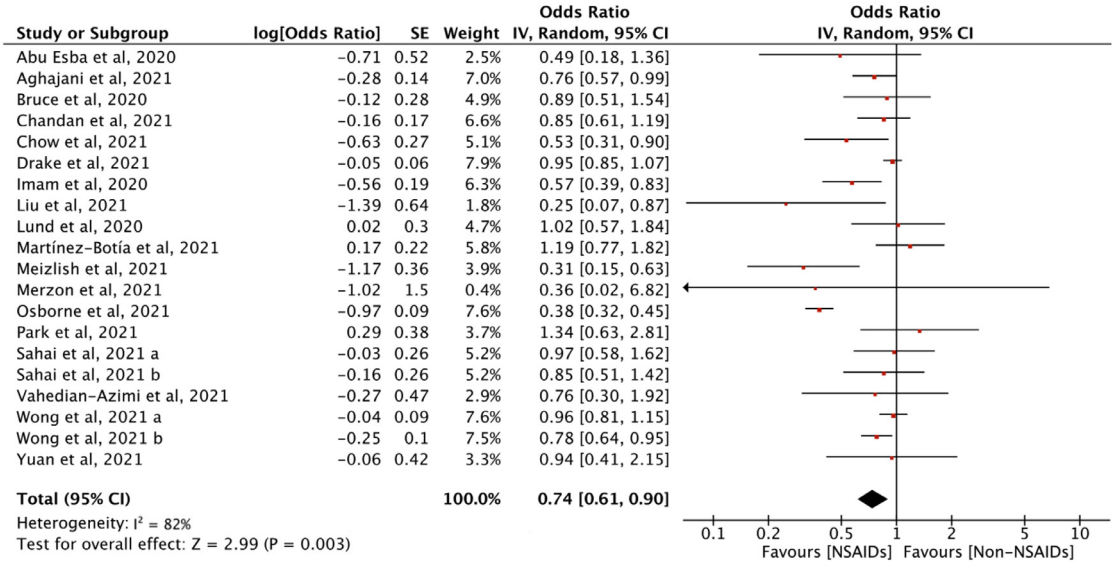

Figure 3. *Adjusted odds ratio of the association between NSAID and mortality among patients who were positive or negative to SARS-CoV-2 tests during the COVID-19 pandemic*. "Log[Odds Ratio]" is the natural logarithms (ln) of odds ratio for each included study; "SE" is the standard error of Log[Odds Ratio]; "Weight" is study weight in the analysis. "IV" is inverse variance statistical method of meta-analysis; "Random" is random effects model; "95% CI" is the 95% confidence intervals for the adjusted mortality; Each horizontal line in the graphical display represents a study, its width represents 95% CI of the interval estimation of the odds ratio effect of adjusted mortality, and the red midpoint of the line symbolizes the point estimate of the adjusted odds ratio effect of mortality; "I^2" represents the quantity of heterogeneity (0−100%); "Test for overall effect: $Z = 2.99$ ($P = 0.003$)" confirms the statistical difference illustrated by the diamond on the left side of the line of effect (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

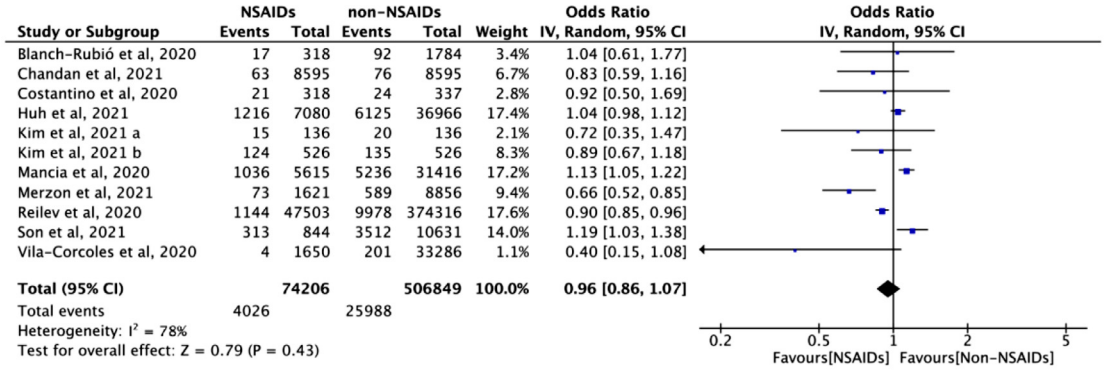

Figure 4. *The association between NSAID exposure and risk of SARS-CoV-2 infection among patients who were negative to SARS-CoV-2 tests during the COVID-19 pandemic*. "Events" is the number of SARS-CoV-2 infection; "Total" is population size; "Weight" is study weight in the analysis. "IV" is inverse variance statistical method of meta-analysis; "Random" is random effects model; "95% CI" is the 95% confidence intervals for the risk of SARS-CoV-2 infection; Each horizontal line in the graphical display represents a study, its width represents 95% CI of the interval estimation of the odds ratio effect of risk of SARS-CoV-2 infection, and the blue midpoint of the line symbolizes the point estimate of the unadjusted odds ratio effect of risk of SARS-CoV-2 infection; "I^2" represents the quantity of heterogeneity (0−100%); "Test for overall effect: $Z = 0.79$ ($P = 0.43$)" confirms no statistical difference illustrated by the diamond crossing the line of effect (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

of the high heterogeneity ($I^2 = 89\%$). A major cause of the high heterogeneity was the difference between the very precise estimates in the two sub-studies by Wong et al.[37] and Osborne et al.[56] (eFigure 4 in Supplementary). The sample size of Wong et al.[37] and Osborne et al.[56] were observed to be high as compared with other included studies, which might affect the results. Where the population included in the study of

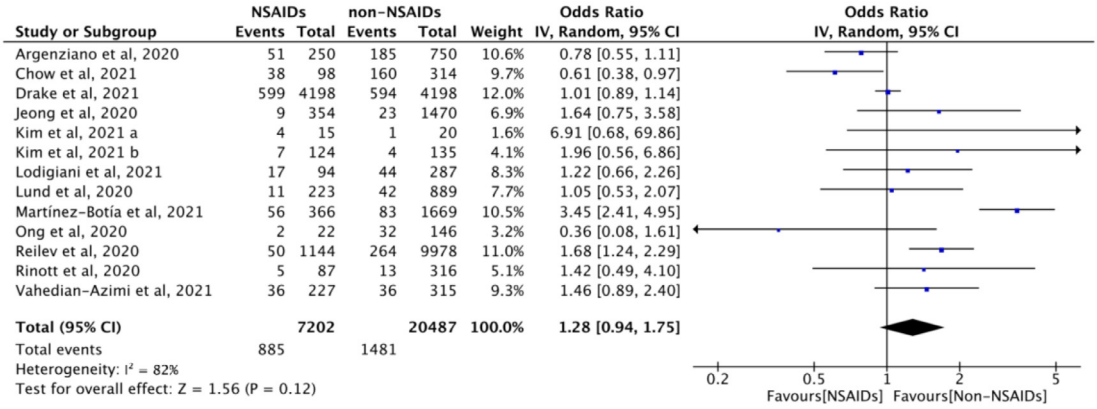

Figure 5. *The association between NSAID exposure and ICU admission among patients who were positive or negative to SARS-CoV-2 tests during the COVID-19 pandemic*. "Events" is the number of ICU admission; "Total" is population size; "Weight" is study weight in the analysis. "IV" is inverse variance statistical method of meta-analysis; "Random" is random effects model; "95% CI" is the 95% confidence intervals for the ICU admission; Each horizontal line in the graphical display represents a study, its width represents 95% CI of the interval estimation of the odds ratio effect of risk of ICU admission, and the blue midpoint of the line symbolizes the point estimate of the unadjusted odds ratio effect of risk of ICU admission; "I^2" represents the quantity of heterogeneity (0−100%); "Test for overall effect: $Z = 1.56$ ($P = 0.12$)" confirms no statistical difference illustrated by the diamond crossing the line of effect. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

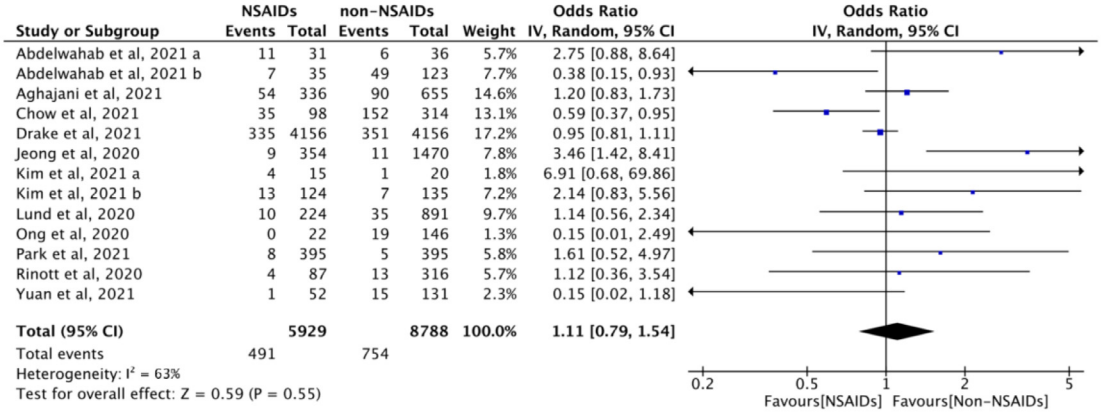

Figure 6. *The association between NSAID exposure and mechanical ventilation among patients who were positive or negative to SARS-CoV-2 tests during the COVID-19 pandemic*. "Events" is the number of patients mechanical ventilation; "Total" is population size; "Weight" is study weight in the analysis. "IV" is inverse variance statistical method of meta-analysis; "Random" is random effects model; "95% CI" is the 95% confidence intervals for the mechanical ventilation; Each horizontal line in the graphical display represents a study, its width represents 95% CI of the interval estimation of the odds ratio effect of mechanical ventilation, and the blue midpoint of the line symbolizes the point estimate of the unadjusted odds ratio effect of mechanical ventilation; "I^2" represents the quantity of heterogeneity (0−100%); "Test for overall effect: $Z = 0.59$ ($P = 0.55$)" confirms no statistical difference illustrated by the diamond crossing the line of effect. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

Wong et al.[37] was non-COVID-19 patients and the drug administrated in the study of Osborne et al.[56] was aspirin. Since the results of the sensitivity analysis found that type of NSAID were sources of heterogeneity between studies, so the sources of heterogeneity found in the sensitivity analysis were consistent with sources of heterogeneity found in subgroup analysis.

Quality of evidence and publication bias

Based on the pooled results, we downgraded the quality of evidence for some outcomes by one level due to imprecision (wide confidence interval) or inconsistency. Consequently, the quality of the evidence was classified as "Very low" and "Low" for unadjusted and adjusted mortality, respectively. The GRADE quality summary of

findings for all outcomes is shown in eTable 3 in Supplementary. The funnel plot for the studies of mortality as an outcome is provided. It shows a lack of small studies showing lower or no risk with NSAIDs. There was no significant evidence of publication bias (eFigure 5 in Supplementary).

Discussion

This systematic review and meta-analysis included forty studies with a total of 4881,423 adult patients. We found that the use of NSAIDs did not aggravate mortality, ICU admission rate, mechanical ventilation rate, or any other adverse outcome, although the quality of evidence was low or very low. According to our results, there is no need for patients and clinicians to be concerned about the routine use of NSAIDs to relieve pain, inflammation and fever due to COVID-19.

Fever induced by viral infection is usually self-limiting and does not require specific antiviral therapy. Symptomatic and supportive treatments are the main part of the management of patients with COVID-19 at present. The risk of hemodynamic instability caused by fever is high, and NSAIDs (in particular ibuprofen and acetaminophen) are one of the most commonly used antipyretic and analgesic drugs to reduce the body temperature of fever patients and treat acute pain worldwide. Therefore, the current recommendations of some guidelines indicate that the use of antipyretic drugs such as ibuprofen, acetaminophen or any other NSAIDs should not be contraindicated in patients with COVID-19.[60,61] The WHO made a rapid systematic review based on 73 studies about SARS, MERS and COVID-19 and found no effect of NSAIDs on the risk of ischemic and hemorrhagic stroke and myocardial infarction in adults with acute respiratory infections. Moderate to high-quality evidence suggests that there is no significant association between ibuprofen or acetaminophen use and all-cause mortality, hospitalization, acute renal failure or acute gastrointestinal bleeding on febrile children. Most included studies found either no adverse events or only mild or moderate adverse events, and there was no evidence indicating that NSAIDs have an impact on the quality of life or long-term survival.[62]

In our study, both unadjusted and adjusted mortality were analyzed. When the results of the two analyze agreed, we drew conclusions based on the direction of agreement, and when the results of the two analyses did not agree, they were discussed and drew reasonable conclusions primarily based on the adjusted results and quality of the evidence. After the subgroup analysis, we found that ibuprofen, COX-2 inhibitor, and other NSAIDs all could not reduce the risk of death, and the results of analysis of unadjusted and adjusted mortality were consistent. While the adjusted analysis found that aspirin could reduce mortality in patients with COVID-19, however this was not confirmed by the unadjusted analysis. The results of our review were in line with these previous findings.[63–68]

This is a comprehensive systematic review and meta-analysis of the correlation between the use of NSAIDs and unfavorable outcomes of COVID-19, and it thus can be expected to reflect the best available evidence on this topic. The study is reported according to the Cochrane guidelines and the PRISMA statement. We performed a meta-analysis of included studies and were thus able to draw quantitative conclusions. Our study has however also some limitations. The forty studies included were all observational studies, some of them had small sample sizes, and all studies presented with a risk of bias in the implementation of blinding methods of outcome evaluators. To get the pooled adjusted OR, HR and RR in the original research were deirectly merged with OR in the meta-analysis, so there are limitations in the results of the adjusted OR. The results of high quality multicenter cohort study with large sample size are therefore still lacking. The clinical heterogeneity among the studies was large and we could thus not draw conclusions or give specific recommendations for different sub-populations (based on e.g. age or severity of disease), or the timing of medication, dosage, or any other aspect, to conduct quantitative analysis. Due to the particularity and urgency of the public health situation, our study was not registered on the international registration platform PROSPERO. The participants of all included studies were all exclusively adults, so the results cannot necessarily be generalized for children.

The use of NSAIDs (especially, ibuprofen, COX-2 inhibitor and low-dose aspirin) was not found to be associated with higher mortality, ICU admission rate, machine ventilation rate or administration of respiratory support. Despite the concerns that NSAID could enhance the ability of SARS-CoV-2 to invade human cells, there is no evidence to support that NSAID would worsen the prognosis of COVID-19.

Contributions

Qi Zhou and Siya Zhao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Yaolong Chen, Enmei Liu and Xiaohui Wang.

Acquisition, analysis, or interpretation of data: Qi Zhou, Siya Zhao, Lidan Gan, Zhili Wang, Shuai Peng, Yaolong Chen.

Drafting of the manuscript: Qi Zhou, Siya Zhao, Lidan Gan, Zhili Wang, Shuai Peng.

Critical revision of the manuscript for important intellectual content: Qiyuan Li; Zijun Wang, Xiao Liu; Hui Liu; Qianling Shi; Zhengxiu Luo; Janne Estill; Yaoliong Chen; Xiaohui Wang and Enmei Liu.

Statistical analysis: Qi Zhou and Siya Zhao.

Supervision: Enmei Liu; Yaolong Chen and Xiaohui Wang.

The decision for the manuscript submission and publication: Yaolong Chen.

Declaration of interests

None.

Data sharing statement

The data analyzed during the current systematic review and meta-analysis is available from the corresponding author on reasonable request.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101373.

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