META-ANALYSIS

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Prevalence of NSAID use among people with COVID-19 and the association with COVID-19-related outcomes: Systematic review and meta-analysis

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Aim: Recent reports of potential harmful effects of nonsteroidal anti-inflammatory drugs (NSAIDs) in treating patients with coronavirus disease 2019 (COVID-19) have raised great concern.

Methods: We searched the PubMed, EMBASE, Cochrane Library and MedRxiv databases to examine the prevalence of NSAID use and associated COVID-19 risk, outcomes and safety.

Results: Twenty-five studies with a total of 101 215 COVID-19 patients were included. Prevalence of NSAID use among COVID-19 patients was 19% (95% confidence interval [CI] 14-23%, no. of studies [n] = 22) and NSAID use prior to admission or diagnosis of COVID-19 was not associated with an increased risk of COVID-19 (adjusted odds ratio [aOR] = 0.93, 95% CI 0.82-1.06, I^2 = 34%, n = 3), hospitalization (aOR = 1.06, 95% CI 0.76-1.48, I^2 = 81%, n = 5), mechanical ventilation (aOR = 0.71, 95% CI 0.47-1.06, I^2 = 38%, n = 4) or length of hospital stay. Moreover, prior use of NSAIDs was associated with a decreased risk of severe COVID-19 (aOR = 0.79, 95% CI 0.71-0.89, I^2 = 0%, n = 7) and death (aOR = 0.68, 95% CI 0.52-0.89, I^2 = 85%, n = 10). Prior NSAID administration might also be associated with an increased risk of stroke (aOR = 2.32, 95% CI 1.04-5.2, I^2 = 0%, n = 2), but not myocardial infarction (aOR = 1.49, 95% CI 0.25-8.92, I^2 = 0, n = 2) and composite thrombotic events (aOR = 1.56, 95% CI 0.66-3.69, I^2 = 52%, n = 2).

Dr Zhao, Dr Huang and Dr Huang are co-first authors.

Conclusion: Based on current evidence, NSAID use prior to admission or diagnosis of COVID-19 was not linked with increased odds or exacerbation of COVID-19. NSAIDs might provide a survival benefit, although they might potentially increase the risk of stroke. Controlled trials are still required to further assess the clinical benefit and safety (e.g., stroke and acute renal failure) of NSAIDs in treating patients with COVID-19.

KEYWORDS

aspirin, coronavirus disease 2019, ibuprofen, meta-analysis, naproxen, nonsteroidal anti-inflammatory drugs, systematic review

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), currently prevalent worldwide, is an acute respiratory illness caused by a novel virus called severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2). This virus can infect host cells expressing the angiotensin-converting enzyme (ACE2) receptor.[1,2]

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen and naproxen, are widely applied inexpensive over-the-counter drugs due to their anti-inflammatory properties.[3] Moreover, since most COVID-19 patients initially show signs of fever and pain, NSAIDs may be the most commonly prescribed drugs for the general population with COVID-19.[4] However, concerns were initially raised by French researchers reporting several COVID-19 patients whose symptoms worsened after taking ibuprofen, an NSAID.[5] In addition, considerable reports have revealed various side effects of NSAIDs and argued against their administration in COVID-19 patients.[5,6] Safety issues have therefore been raised about the use of NSAIDs in COVID-19. Subsequently, the European Medicines Agency (EMA) and the World Health Organization (WHO) have claimed that NSAIDs, at least not all NSAIDs, should not be precluded when COVID-19 is clinically indicated, based on the limited evidence of COVID-19 epidemiology.[7,8]

NSAIDs exert their effects by suppressing cyclooxygenase enzymes to reduce prostaglandin synthesis. Substances like prostaglandin are closely related to signs of pain, fever and inflammation in patients with COVID-19.[9] However, studies have suggested that exposure to NSAIDs, including ibuprofen, may increase the risk of COVID-19. Moreover, it has been speculated that NSAID use in COVID-19 patients may worsen the disease and increase the odds of ICU admission and death.[10] By contrast, other studies have reported that prior exposure to NSAIDs did not significantly increase the risk of COVID-19 and was associated with a lower risk of death in hospitalized COVID-19 patients.[11–13] Considering the debate over ibuprofen use in COVID-19 and the rapidly unfolding situation of the current COVID-19 pandemic, this study aimed to (1) assess the prevalence use of NSAIDs in the general COVID-19 population, (2) systematically investigate the association of NSAIDs with the risk of COVID-19 and related outcomes, and (3) assess the

What is already known about this subject

- Recent studies have raised concern about the link between NSAIDs and the risk of COVID-19 infection as well as associated clinical outcomes.

What this study adds

- The prevalence of NSAID use prior to admission or diagnosis of COVID-19 was 18%.
- Prior exposure to NSAIDs was not associated with an elevated COVID-19 infection.
- Prior use of NSAIDs was linked with a reduced risk of severe COVID-19 infection and reduced all-cause death.
- Prior use of NSAIDs might be associated with an increased risk of stroke, but not myocardial infarction, overt thrombosis, major bleeding and acute renal failure.

safety (particularly vascular complications) of NSAIDs in treating patients with COVID-19.

2 | METHODS

This study was performed in accordance with PRISMA 2020 guidelines[14] (Supporting Information Table S1) and registered in PROSPERO (international prospective register of systematic reviews, registration number CRD42019132063).

Two independent researchers (X.L. and Ss.H.) searched the PubMed, Cochrane Library, EMBASE and MedRxiv databases from December 2019 to January 2021 for relevant studies reporting the prevalence of NSAID use and associated outcomes in COVID-19 patients, without language restrictions. The search was performed using the following Medical Subject Headings words:

"anti-inflammatory agents, non-steroidal" OR "aspirin" OR "ibuprofen" OR "naproxen" AND "COVID-19" OR "SARS-CoV-2". Pooled odds ratios (ORs) were calculated using random effects models. Hazard ratio and risk ratio were regardes as OR. All analyses were performed using Stata 16.0 (Stata Corp LP, College Station, TX, USA) and Review Manager (RevMan) version 5.3 (The Cochrane Collaboration 2014; Nordic Cochrane Center, Copenhagen, Denmark). Full details of the literature search strategy, study selection criteria, quality assessment and statistical analysis are reported in the Supporting Information.

2.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[15-18]

3 | RESULTS

3.1 | Study selection

After searching the databases, we obtained 879 potentially relevant articles (PubMed = 377, Cochrane Library = 0, EMBASE = 419, and MedRxiv = 83). Of these, 91 were duplicated publications. In addition, 735 studies were excluded after examining their titles and abstracts. Of the remaining 53 articles, 28 were excluded after a detailed review of the full text for the following reasons: (1) eight reports assessed other respiratory infections; (2) seven reports were letters, reviews or case reports; (3) six studies assessed suspected COVID-19 cases instead of confirmed cases; (4) four articles were based on other
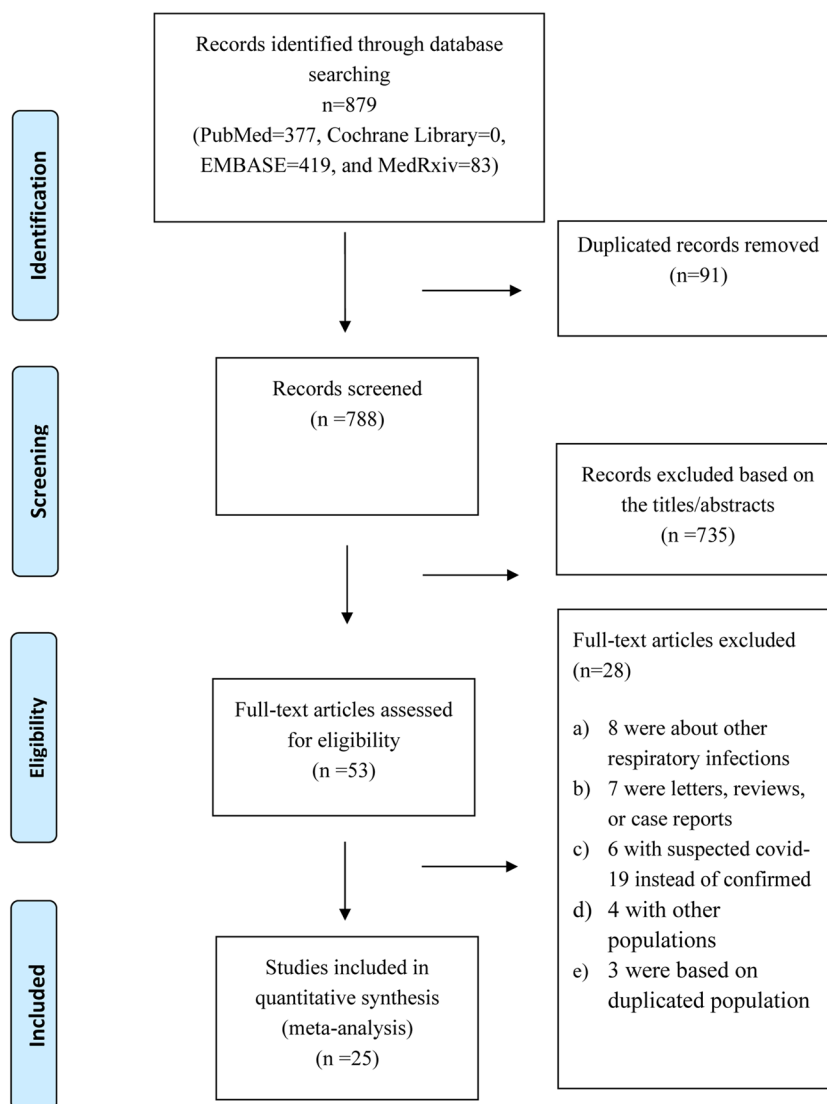

FIGURE 1 Flow chart of study selection

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TABLE 1 Basic information of included studies of the association between NSAIDs and COVID-19

Study, year, country	Type of NSAIDs	Definition of exposure to NSAIDs	Dose of NSAIDs	Study design	Data source
Alamdari, 2020, Iran	NSAIDs	Prescribed NSAIDs in electronic medical record	Not available	Retrospective cohort	Hospitalized in Shahid Modarres Hospital
Abu Esba, 2020, Riyadh	NSAIDs	Prescribed NSAIDs for 30 days in 6 months before admission or patient self-reported chronic use or NSAID use during admission	Not available	Prospective cohort	King Abdulaziz Medical City and King Abdullah Specialist Children's Hospital
Bruce, 2020, UK	NSAIDs	Prescribed NSAIDs prior to admission	Not available	Retrospective cohort	Hospitalized in COVID-19 in older people study
Argenziano, 2020, USA	NSAIDs	NYP/CUIMC electronic health record prior to admission	Not available	Retrospective cohort	Hospitalized at NYP/CUIMC
Choi, 2020, Korea	Ibuprofen	Prescribed NSAIDs in medical records prior to admission	Not available	Retrospective cohort	Hospitalized at Armed Forces Daegu Hospital
Chang, 2020, USA	NSAIDs	Prescribed NSAIDs 90 days before Diagnosis of COVID-19	Not available	Case-control cohort	UCLA health system
Chow, 2020, USA	Aspirin	Administration of aspirin within 24 hours to 7 days before hospital admission	Not available	Retrospective cohort	Hospitalized COVID-19 patients in CRUSH COVID study
Castro, 2020, USA	Ibuprofen	At least one prescription or medication order of NSAIDs in the 1 year to 30 days before COVID-19 admission	Not available	Retrospective cohort	Hospitalized in two academic medical centers and four community affiliate hospitals
Huh, 2020, South Korea	NSAIDs	Prescribed NSAIDs ≤7 days before diagnosis of COVID-19	Not available	Case-control	National hospitalized patients in HIRA database
Imam, 2020, USA	NSAIDs	Prescribed NSAIDs in electronic medical record prior to admission	Not available	Retrospective cohort	Hospitalized in Beaumont Health's eight hospitals
Jehi, 2020, USA	NSAIDs	Prescribed NSAIDs in electronic medical record prior to admission	Not available	Retrospective cohort	Inpatient or outpatients in Cleveland Clinic
Jeong, 2020[b], South Korea	NSAIDs	Prescribed NSAIDs within 7 days before cohort entry	Not available	Retrospective cohort	National hospitalized patients in HIRA database
Lund, 2020, Denmark	NSAIDs	Prescribed NSAIDs within 30 days before diagnosis of COVID-19 (defined as current use)	Not available	Retrospective cohort	Danish health and administrative registries
McKeigue, 2020, Scotland	NSAIDs	Prescribed NSAIDs in 240 days before diagnosis of COVID-19	Not available	Case-control	REACT-SCOT study
Meizlish, 2020, USA	Aspirin	In-hospital aspirin use	Not available	Retrospective cohort	Yale New Haven health system
Nguyen, 2020, USA	NSAIDs	Outpatient medication NSAIDs in electronic medical records	Not available	Retrospective cohort	Hospitalized in University of Chicago Medical Center
Osborne, 2020, USA	Aspirin	Prescribed aspirin up to 30 days before diagnosis of COVID-19	Not available	Retrospective cohort	VA national corporate data warehouse
Rentsch, 2020, USA	NSAIDs	Prescribed NSAIDs in the year before diagnosis of COVID-19 14 days	Not available	Retrospective cohort	VA national corporate data warehouse

TABLE 1 (Continued)

Study, year, country	Type of NSAIDs	Definition of exposure to NSAIDs	Dose of NSAIDs	Study design	Data source
Reilev, 2020, Denmark	NSAIDs	Prescribed NSAIDs within 6 months prior to diagnosis of COVID-19	Not available	Retrospective cohort	Nationwide data in Danish
Rinott, 2020, Israel	Ibuprofen	Used ibuprofen within a week before diagnosis of COVID-19	Not available	Retrospective cohort	Shamir Medical Centre
Ruiz-Antorán, 2020, Spain	NSAIDs	Prescribed NSAIDs in electronic medical records prior to admission	Not available	Retrospective cohort	Hospitalized in 18 tertiary Spanish hospitals
Ramachandran, 2020, USA	NSAIDs	Prescribed NSAIDs in electronic medical records prior to admission	Not available	Retrospective cohort	Hospitalized in Care Academic Medical Center in Brooklyn
Subudhi, 2020, USA	NSAIDs	Prescribed NSAIDs in medical record prior to admission	Not available	Retrospective cohort	Massachusetts General Brigham healthcare database
Sahai, 2020, USA	Aspirin	Prescribed aspirin new or ongoing administration during admission	81 mg	Retrospective cohort	Hospitalized Cleveland Clinic patients
Wong et al, 2020, USA	NSAIDs	Prescribed NSAIDs in the 4 months before diagnosis of COVID-19	Not available	Retrospective cohort	National Health Service England database

Abbreviations: COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate, FIB-4, fibrosis 4 score; VACS, Veterans; HIRA, Korean Health Insurance Review & Assessment Service; NYP/CUIMC, New York-Presbyterian/Columbia University Irving Medical Center; CRUSH COVID, multicenter Collaborative Research to Understand the Sequelae of Harm in COVID; REACT-SCOT, Rapid Epidemiological Analysis of Comorbidities and Treatments as risk factors for COVID-19 in Scotland; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure.

[a]The outcome of death was not included because of cross-sectional design.

[b]The use of NSAIDs was not included because of duplicated population (Huh et al., 2021, South Korea).

[c]The outcomes of ICU admission and death were not included because of duplicated population (Lund et al., 2020, Danish).

[d]The CAN score is a tool that assesses patients' risk of morbidity and mortality using a wide array of data available in the EHR, including socio-demographics, clinical diagnoses, vital signs, medications, laboratory values and healthcare utilization data. DOI:0.2106/JBJS.OA.19.00061.

TABLE 1 (Continued)

Study, year, country	Sample size	Mean age	Female (%)	Diagnosis of COVID-19	Outcomes included	Adjusted variables
Alamdari, 2020, Iran	459	61	139 (30.3)	SARS-COV-2 PCR-positive	Prevalent use NSAIDs	Not applicable[a]
Abu Esba, 2020, Riyadh	503	50	215 (42.7)	SARS-COV-2 PCR-positive	Prevalent use NSAIDs Hospitalisation Mechanical ventilation Severe COVID-19 30-day mortality	Age, sex, comorbidities: hypertension, DM, dyslipidemia, asthma or COPD, cardiovascular disease, renal or liver impairment, and malignancy
Bruce, 2020, UK	1222	61	532 (43.5)	Clinical or laboratory confirmed diagnosis of COVID-19	In-hospital mortality	Age group, sex, smoking status, CRP levels, diabetes, hypertension, CAD, reduced renal function
Argenziano, 2020, USA	1000	63	404 (40.4)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs	Not applicable
Choi, 2020, Korea	293	29	79 (27.0)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs	Not applicable
Chang, 2020, USA	843	49	438 (52.0)	SARS-COV-2 PCR-positive	Incidence of NSAIDs use Risk of COVID-19 Hospitalisation Severe covid-19	Age, sex, CAD, congestive HF, COPD, type 2 DM, hyperlipidemia, HTN, obesity, and chronic renal disease
Chow, 2020, USA	412	60	168 (40.8)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Mechanical ventilation ICU admission In-hospital mortality	Age, BMI, ethnicity, HTN, DM, CAD, beta-blocker, renal disease
Castro, 2020, USA	7360	>60	3495 (47.5)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Mechanical ventilation ICU Death	Age at admission, gender, race, ethnicity, Charlson comorbidity index and the presence of a prior diagnosis in the health system
Huh, 2020, South Korea	5172	44	2883 (55.7)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Risk of COVID-19	Age, sex, region of residence, comorbidities, healthcare, utilization, hydroxychloroquine, ACEI/ARB, metformin, thiazolidinedione, statins, sirolimus, mycophenolate, amiodarone, camostat, systemic steroid
Imam, 2020, USA	1305	61.0	603 (46.2)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Death Renal failure	Age greater than 60 years, comorbidities were computed into the Charlson comorbidity index ACEI/ARB
Jehi, 2020, USA	4536	NA	2426 (53.5)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Hospitalisation	Univariate analysis
Jeong, 2020[b], South Korea	1824	49	1074 (590)	SARS-COV-2 PCR-positive	Mechanical ventilation ICU admission Death Cardiovascular composite	PS matched for age, sex, health insurance type, hypertension, hyperlipidaemia, DM, asthma, COPD, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions, ACEI/ARB, β-blockers, CCB, diuretics, nitrates

TABLE 1 (Continued)

Study, year, country	Sample size	Mean age	Female (%)	Diagnosis of COVID-19	Outcomes included	Adjusted variables
Lund, 2020, Denmark	1120	54	655 (58.5)	SARS-COV-2 PCR-positive	Hospitalisation ICU admission Death	PS matched for age, sex, antihypertensives, antidiabetic drugs immunosuppressants, opioids, benzodiazepines, first- and second-generation antipsychotics, systemic glucocorticoids, inhaled corticosteroids asthma, COPD, cardiovascular disease, ischemic stroke, chronic kidney failure, liver disease, alcohol-related disorders, dementia, cancer, overweight or obesity, hemiplegia and paraplegia, osteoarthrosis, rheumatoid arthritis, dysmenorrhea
McKeigue, 2020, Scotland	2378	NA	NA	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Severe COVID-19	Proton pump inhibitors, antihistamines, antipsychotic drugs, opioid analgesics
Meizlish, 2020, USA	2785	>60	1389 (49.9)	SARS-COV-2 PCR-positive	In-hospital death	Propensity matched for age, BMI, DDmax, admission RI score, sex and African-American race
Nguyen, 2020, USA	689	55	393 (57.0)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs	Not applicable
Osborne, 2020, USA	26 346	58	2859 (10.9)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs 30-day mortality	Age, gender and CAN* mortality score
Rentsch, 2020, USA	585	66	27 (4.6)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Risk of COVID-19 Hospitalisation ICU admission	Age, sex, race, ACE/ARB use, HTN, temperature, CKD, COPD, DM, vascular disease, systolic blood pressure, oxygen saturation, albumin, eGFR, FIB-4, haemoglobin, lymphocyte count, VACS index score
Reilev, 2020, Denmark	9519	49	5509 (58.0)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Risk of COVID-19	Univariate analysis[c]
Rinott, 2020, Israel	403	45	220 (54.6)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Mechanical ventilation Severe COVID-19 Death	Univariate analysis
Ruiz-Antorán, 2020, Spain	506	67	182 (36.0)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Death	Univariate analysis
Ramachandran, 2020, USA	295	66	133 (45.0)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs	Not applicable
Subudhi, 2020, USA	1144	>60	515 (45.0)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs ICU admission Death	Univariate analysis
Sahai, 2020, USA	1994	60	1018 (51)	SARS-COV-2 PCR-positive	Prevalent use of NSAIDs Mortality Safety outcomes	Propensity matched for age, platelets, gender, race, ethnicity, smoking, oppressors, COPD, emphysema, asthma, diabetes, hypertension, CAD, HF, cancer, ongoing immunosuppressive treatment

TABLE 1 (Continued)

Study, year, country	Sample size	Mean age	Female (%)	Diagnosis of COVID-19	Outcomes included	Adjusted variables
Wong et al, 2020, USA	2 463 707	53	1 410 922 (57.2)	ICD-10	COVID-19-related death	Age, sex, obesity, smoking, hypertension, HF, other heart disease, DM, COPD, asthma, other respiratory diseases such as cystic fibrosis, cancer, immunosuppressive conditions, current other medication use, region

Abbreviations: COVID-19, coronavirus disease 2019; OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate, FIB-4, fibrosis 4 score; VACS, Veterans; HIRA, Korean Health Insurance Review & Assessment Service; NYP/CUIMC, New York-Presbyterian/Columbia University Irving Medical Center; CRUSH COVID, multicenter Collaborative Research to Understand the Sequelae of Harm in COVID; REACT-SCOT, Rapid Epidemiological Analysis of Comorbidities and Treatments as risk factors for COVID-19 in Scotland; COPD, chronic obstructive pulmonary disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; BMI, body mass index; CKD, chronic kidney disease; DM, diabetes mellitus; CAD, coronary artery disease; HF, heart failure.

[a]The outcome of death was not included because of cross-sectional design.

[b]The use of NSAIDs was not included because of duplicated population (Huh et al., 2021, South Korea).

[c]The outcomes of ICU admission and death were not included because of duplicated population (Lund et al., 2020, Danish).

[d]The CAN score is a tool that assesses patients' risk of morbidity and mortality using a wide array of data available in the EHR, including socio-demographics, clinical diagnoses, vital signs, medications, laboratory values and healthcare utilization data. DOI:0.2106/JBJS.OA.19.00061.

diseases (e.g., rheumatologic diseases, cancers and coronary artery diseases); and (5) three reports were based on the same population. Finally, 25 publications (23 cohorts) were included in this meta-analysis (Figure 1).

3.2 | Study characteristics and quality

The basic characteristics of the included studies are shown in Table 1. The mean age of patients ranged from 64 to 67 years. Prevalence of exposure to NSAIDs was assessed using the electronic medical record database. The definition of NSAIDs use varied across studies. All studies defined NSAID use prior to admission or diagnosis of COVID-19 (range from 7 days to 1 years), except one study with in- NSAID hospital use.[19] The doses of NSAIDs were not reported in almost all studies, except one[20] in which 81 mg aspirin was administered. The diagnosis of COVID-19 was confirmed by SARS-COV-2 PCR in most studies; one[21] used ICD-10, and another[12] combined clinical and SARS-COV-2 PCR findings. The majority of studies were retrospective or prospective cohort observational studies, and three reports[22–24] were case-control studies. The assessment results showed that all articles were of medium to high quality (Supporting Information Tables S2 and S3), although some studies did have insufficient descriptions of the methods for controlling the confounding factors and length of follow-up.

3.3 | Prevalence of NSAID use in patients with COVID-19

Twenty-two articles with 106 421 patients (Supporting Information Table S4) reported the use of NSAIDs in COVID-19 cases. The pooled results showed NSAID use prevalence of 19% (95% confidence interval [CI] 14-23%) in COVID-19 patients, with significant heterogeneity ($I^2 = 99\%$) (Figure 2). Prior NSAID use frequency was 18% (95% CI 13-22%, $I^2 = 99\%$) when excluding the study by Meizlish et al, which only covered in-hospital NSAID use. Subgroup analysis showed no statistical differences in the prevalence of NSAID use across age groups, study designs, regions and sample sizes (Supporting Information Figure S1a-d).

3.4 | The impact of NSAIDs on the risk of COVID-19

Five studies[22,23,25–27] with 17 239 cases among 343 286 individuals reported the effect of NSAID use on the risk of COVID-19 infection. Pooled analysis showed that NSAID use prior to admission or diagnosis of COVID-19 did not increase the risk of COVID-19 infection (crude odds ratio [OR] = 0.93, 95% CI 0.78-1.12, $I^2 = 83\%$) (Supporting Information Figure S2a). Three studies[22,23,26] evaluated the association between NSAIDs and COVID-19 infection by multivariate analysis. The results after adjustments were consistent with the raw analysis (adjusted OR = 0.93, 95% CI 0.82-1.06, $I^2 = 34\%$) (Figure 3A).
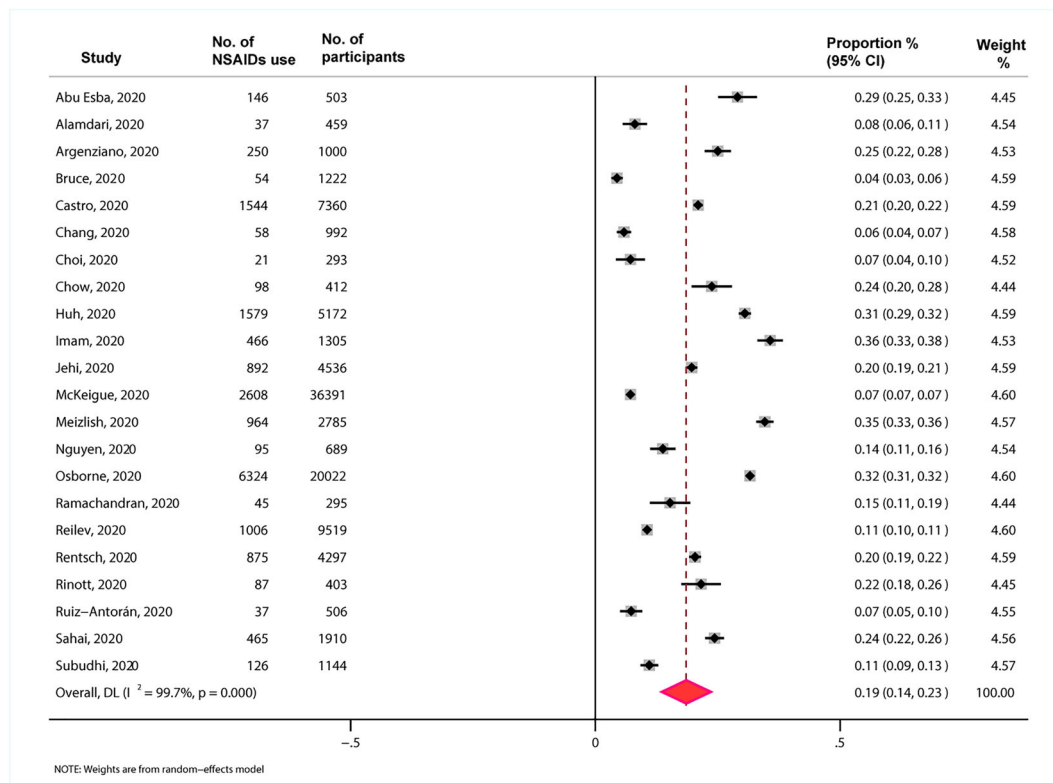
FIGURE 2 Forest plot for the prevalence of NSAID use in patients with COVID-19

3.5 | The impact of NSAID use on hospitalization in patients with COVID-19

There were nine publications[22,27–34] with 10 955 cases/30921 COVID-19 patients assessing the association between NSAIDs and hospitalization. The pooled results based on unadjusted analysis showed that the use of NSAIDs did not significantly elevate the risk of admission (crude OR = 1.05, 95% CI 0.63-1.73, I^2 = 97%) (Supporting Information Figure S2b). Three studies further reported the adjusted results, with a summary OR of 1.06 (95% CI 0.76-1.48, I^2 = 81%) (Figure 3B). Subgroup analysis after adjustment showed that neither ibuprofen nor naproxen prior use significantly increased the risk of severe (e.g., ICU admission) COVID-19 (ibuprofen: OR = 0.82, 95% CI 0.54-1.23, I^2 = 45%; naproxen: OR = 0.66, 95% CI 0.50-0.87) (Supporting Information Figure S3).

3.6 | Length of hospitalization

There were three publications that reported the association between hospitalization length and NSAID use (Supporting Information Table S5). A meta-analysis could not be conducted due to insufficient data. Jeong et al[10] reported a median length of hospitalization of 12 days among NSAID users versus 13 days among nonusers in COVID-19 patients. Another retrospective cohort including 412 American COVID-19 patients reported that there was no significant difference in the length of hospital stay between aspirin users and no-aspirin users.[11] A prospective cohort study that included 503 patients in Asia also showed that neither acute nor chronic use of NSAIDs increased the length of hospital stay compared to non-NSAID users[29] (P = .63). Overall, all included studies reported a nonsignificant difference in the length of hospital stay between NSAID prior users and non-NSAID users.

3.7 | Mechanical ventilation

Six studies[10,11,27,29,30,34] with 459/11857 patients were included for the assessment of mechanical ventilation. The pooled results of both crude (crude OR = 1.34, 95% CI 0.60-3.02, I^2 = 79%) and adjusted (adjusted OR = 0.71, 95% CI 0.47-1.06, I^2 = 38%) analyses showed no significant risk of mechanical ventilation in COVID-19 patients with prior use of NSAIDs (Supporting Information Figures S2c and 3c). Adjusted subgroup analysis showed prior use of aspirin, ibuprofen and naproxen did not significantly increase the risk of severe COVID-19 (aspirin: OR = 0.56, 95% CI 0.47-1.06; ibuprofen: OR = 0.75, 95% CI 0.22-2.50, I^2 = 58%; naproxen: OR = 0.36, 95% CI 0.03-3.96) (Supporting Information Figure S4).

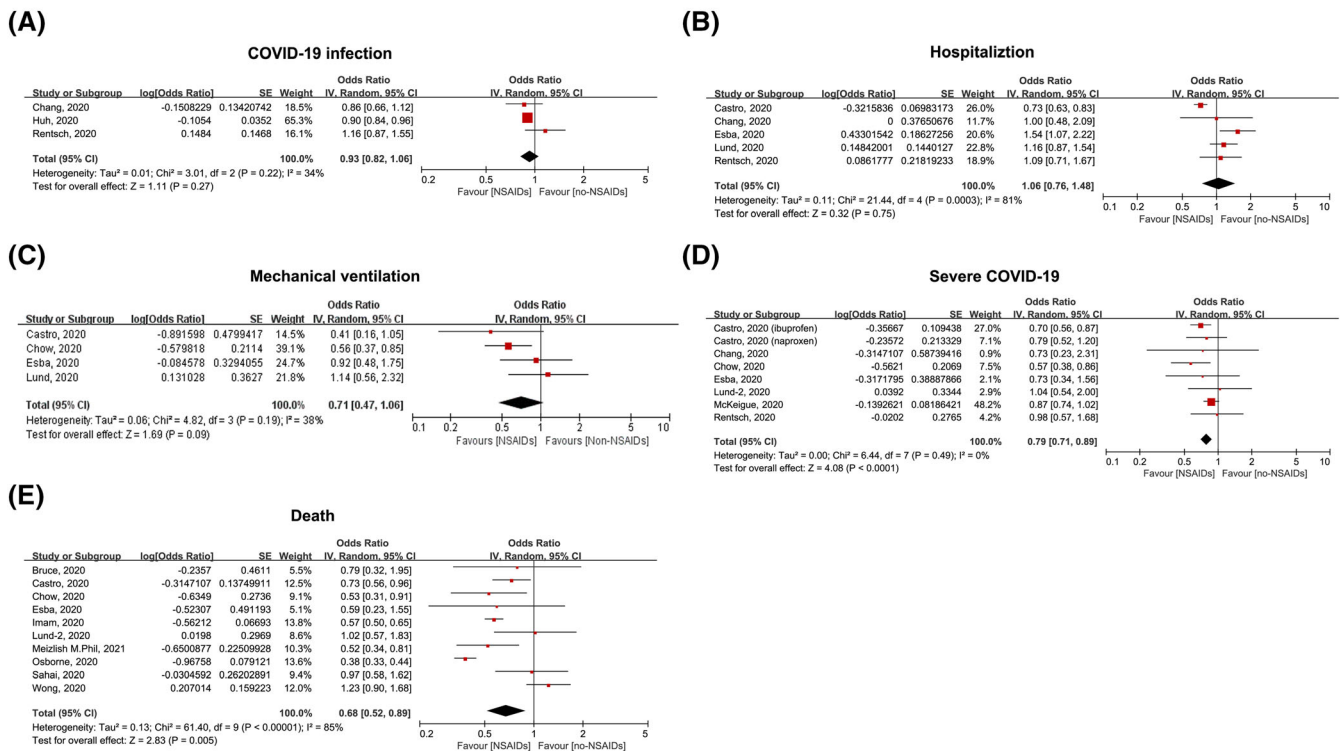**Association between NSAIDs and COVID-19, pooled by adjusted results**

FIGURE 3 Forest plot for the association between NSAIDs and COVID-19, pooled by adjusted results. (A) Risk of COVID-19 infection. (B) Risk of hospitalization. (C) Risk of mechanical ventilation. (D) Risk of severe COVID-19 (e.g., ICU admission). (E) Risk of death. NSAIDs, nonsteroidal anti-inflammatory drugs; ICU, intensive care unit.

3.8 | Impact of NSAID use on severe COVID-19 infection

Twelve articles involving 6284 severe COVID-19 cases among 69 942 patients[10,11,22,24–27,29,30,34–36] assessed the association between prior use of NSAIDs and COVID-19 severity. As shown in Supporting Information Figure S2d, NSAID use before COVID-19 admission was not significantly associated with the development of severe COVID-19 (crude OR = 0.90, 95% CI 0.66-1.21, I^2 = 85%). Furthermore, pooled OR in multivariate analysis showed significantly reduced risk of severe COVID-19 infection (adjusted OR = 0.79, 95% CI 0.71-0.89, I^2 = 0%) (Figure 3D). Adjusted subgroup analysis showed prior exposure of aspirin, ibuprofen and naproxen did not significantly increase the risk of severe COVID-19 (aspirin: OR = 0.57, 95% CI 0.38-0.86; ibuprofen: OR = 0.98, 95% CI 0.59-1.65, I^2 = 81%; naproxen: OR = 0.79, 95% CI 0.52-1.20) (Supporting Information Figure S5).

3.9 | Impact of NSAID use on death in patients with COVID-19

We included 14 studies[10–12,19–21,27,29,30,34,36–39] with 2966 cases among 35 595 patients when assessing the link between death and NSAID. We observed a decreased but nonsignificant risk of death after NSAID use in COVID-19 patients (crude OR = 0.73, 95% CI 0.53-1.02, I^2 = 80%) (Supporting Information Figure S2e).

Notably, the pooled results of adjusted analysis showed that NSAID use could significantly decreased the mortality of COVID-19 patients (adjusted OR = 0.68, 95% CI 0.52-0.89, I^2 = 85%) (Figure 3E). The results were stable (adjusted OR = 0.72, 95% CI 0.54-0.96, I^2 = 86%) after excluding one study on in-hospital use of NSAIDs. Subgroup analysis after adjustment showed aspirin, ibuprofen and naproxen did not significantly increase COVID-19-related death (aspirin: OR = 0.41, 95% CI 0.22-2.50, I^2 = 4%; ibuprofen: OR = 0.83, 95% CI 0.69-0.99, I^2 = 0; naproxen: OR = 0.92, 95% CI 0.72-1.17) (Supporting Information Figure S6).

3.10 | Safety of NSAID use in patients with COVID-19

Adverse cardiovascular events caused by NSAIDs, including major bleeding, heart failure and major coronary events, have been well documented in the general population.[40] Therefore, we focused on the potentially harmful effects of NSAIDs on vascular complications in COVID-19 patients. Four studies reported NSAID-related safety outcomes (myocardial infarction, stroke, major bleeding, composite thrombotic events or renal failure).[10,11,20,37] The pooled results showed prior prescription of NSAIDs significantly increased the risk of stroke (OR = 2.32, 95% CI 1.04-5.2, I^2 = 0%) (Figure 4A), but not myocardial infarction (OR = 1.49, 95% CI 0.25-8.92, I^2 = 0%), composite thrombotic events (including deep vein thrombosis,

NSAIDs and safety outcomes in COVID-19

Stroke

(A)

Study or Subgroup	NSAIDs Events	Total	no-NSAIDs Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Jeong, 2020	7	354	13	1470	75.9%	2.26 [0.90, 5.71]
Sahai, 2020	5	444	2	444	24.1%	2.52 [0.49, 13.04]
Total (95% CI)		798		1914	100.0%	**2.32 [1.04, 5.20]**
Total events	12		15			

Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.04 (P = 0.04)

Myocardial infraction

(B)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Jeong, 2020	0	354	4	1470	37.5%	0.46 [0.02, 8.56]
Sahai, 2020	3	444	1	444	62.5%	3.01 [0.31, 29.08]
Total (95% CI)		798		1914	100.0%	**1.49 [0.25, 8.92]**
Total events	3		5			

Heterogeneity: Tau² = 0.00; Chi² = 1.00, df = 1 (P = 0.32); I² = 0%
Test for overall effect: Z = 0.43 (P = 0.66)

Composite thrombtic events

(C)

Study or Subgroup	NSAIDs Events	Total	no-NSAIDs Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chow, 2020	9	98	28	314	52.9%	1.03 [0.47, 2.27]
Sahai, 2020	17	444	7	444	47.1%	2.49 [1.02, 6.05]
Total (95% CI)		542		758	100.0%	**1.56 [0.66, 3.69]**
Total events	26		35			

Heterogeneity: Tau² = 0.20; Chi² = 2.10, df = 1 (P = 0.15); I² = 52%
Test for overall effect: Z = 1.02 (P = 0.31)

Acute kidney failure

(D)

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Imam, 2020	-0.174353	0.2557776	65.0%	0.84 [0.51, 1.39]
Jeong, 2020	1.141033	0.7653084	35.0%	3.13 [0.70, 14.03]
Total (95% CI)			100.0%	**1.33 [0.39, 4.55]**

Heterogeneity: Tau² = 0.54; Chi² = 2.66, df = 1 (P = 0.10); I² = 62%
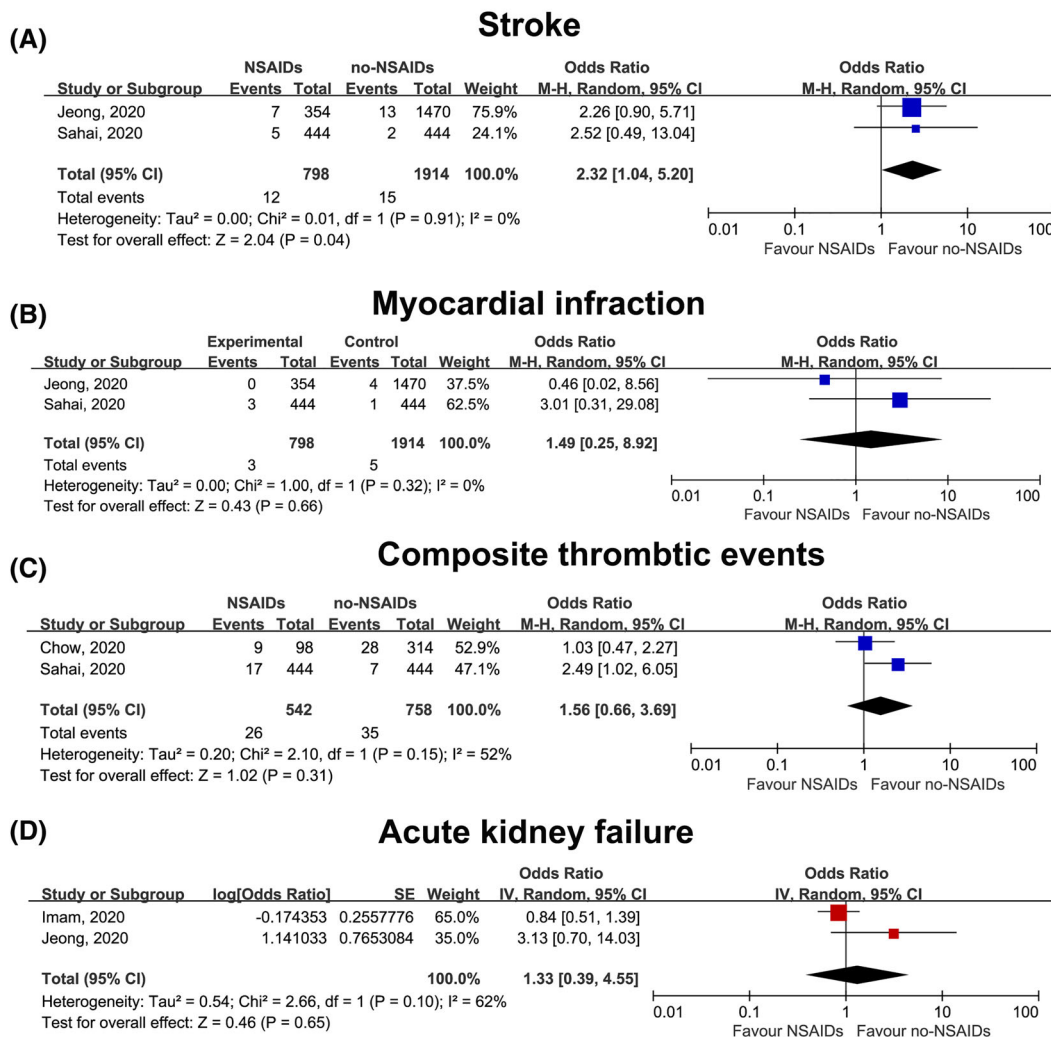Test for overall effect: Z = 0.46 (P = 0.65)

FIGURE 4 Forest plots for the associations between nonsteroidal anti-inflammatory drugs and safety outcomes in COVID-19 patients. (A) Stroke. (B) Myocardial infarction. (C) Composite thrombotic events. (D) Acute kidney failure.

pulmonary embolism, peripheral arterial occlusion, ischemic stroke and myocardial infarction) (OR = 1.56, 95% CI 0.66-3.69, I^2 = 52%) (Figure 4B,C) and renal failure (OR = 1.33, 95% CI 0.39-4.55, I^2 = 62%) (Figure 4E). Chow et al[11] found no significant difference (crude OR = 0.79, 95% CI 0.31-1.99) in major bleeding (intracranial or gastrointestinal bleeding) between NSAID and non-NSAID groups in raw analysis.

3.11 | Publication bias and sensitivity

No publication bias for COVID-19 susceptibility was detected by the funnel plot or Egger's test (P > .1), although these tests were not recommended for outcome assessment based on a small number of studies (N < 10) (Supporting Information Figure S6).

4 | DISCUSSION

At present, no consensual guidelines are available regarding NSAID use in COVID-19, reflecting a paucity of data in this regard. Our results showed the prevalence of NSAID use was 18% among the general population with COVID-19, which suggested the use of NSAIDs in COVID-19 patients was not uncommon. Furthermore, based on current evidence, we found prior exposure to NSAIDs, including aspirin, ibuprofen and naproxen, was not associated with an increased risk of COVID-19 or worse outcomes in patients with COVID-19. Notably, significantly increased risk of thrombotic stroke was found in COVID-19 patients with prior use of NSAIDs (OR = 2.32, P < .04) in two observational studies.[10,20]

There has been sound evidence that the SARS-CoV-2 spike glycoprotein directly binds to the host cell's ACE2 receptor, which is highly expressed in human lung tissue, gastrointestinal tract and

arterial smooth muscle cells.[41] Indeed, the ACE receptor in humans plays an important role in the pathophysiology of SARS-CoV-2 infection.[41] Great concerns have been raised about several drugs with the potential of increasing ACE2 expression that might contribute to the spread of COVID-19 in the general population, including ACE inhibitors (ACEIs), angiotensin 2 receptor blockers (ARBs) and NSAIDs.[5] In a previous report, we demonstrated that ACEIs/ARBs were not associated with an increased risk of COVID-19 infection and worsened outcomes in COVID-19.[42] Similarly, regarding NSAIDs, a potential increase in COVID-19 risk with the use of NSAIDs was not found in the present study. There are several possible explanations for these findings. First, although animal studies showed that ACE2 receptor expression was significantly upregulated by ibuprofen use,[43] a recent report found two commonly used NSAIDs (ibuprofen and meloxicam) had no effect on ACE2 expression, viral entry and viral replication in a mouse SARS-CoV-2 infection model.[44] Furthermore, no human studies have assessed the effect of ibuprofen on ACE2 expression, particularly its expression in the lung tissue. Second, whether or not there is a positive correlation between ACE2 expression level and the risk of COVID-19 infection remains unknown. The most recent evidence has derived from COVID-19 and inflammatory bowel diseases. Elevated ACE2 protein expression was observed in the terminal ileum and colon in patients with inflammatory bowel disease compared with controls.[45] However, there is currently no evidence showing an increased risk of inflammatory bowel disease or associated aggravated outcomes in the context of COVID-19.[45] Collectively, based on current experimental and clinical data, we suggest that there is no evidence of a positive correlation between NSAIDs and the risk of COVID-19.

Recent reports of potential harms (e.g., worsening symptoms) by NSAIDs in patients with COVID-19 have attracted widespread attention, and several medical regulatory agencies still have inconsistent opinions based on limited evidence.[5] In the present study, we also found that the use of NSAIDs provided a potential benefit in treating COVID-19. Indeed, NSAID use reduced the incidence of severe COVID-19 infection and all-cause mortality after adjustment for confounders. These results corroborated our previous findings about ACEI/ARB, although our study also concerned the side effects of NSAID for treating COVID-19 based on similar reasons.[42] Several potential mechanisms might explain these results. First, although some literature reviews and investigators recommend avoiding NSAIDs based on previous studies showing adverse outcomes in ibuprofen users in the treatment of acute respiratory tract infections, these results might be subject to selection bias.[46,47] The NSAID group might have higher disease severity compared with the non-NSAID group. For example, although Joeng et al[10] found a worsened composite outcome (in-hospital death, ICU admission, mechanical ventilation use or sepsis) in the NSAID group, an elevated adverse event rate was not found compared with individuals administered paracetamol, a drug used for similar indications as NSAIDs.[10] Furthermore, the pathophysiology and transmission of COVID-19 are thought to be different when compared with other respiratory diseases.[48] Therefore, the harmful effects of NSAIDs in individuals infected by other respiratory viruses might not be generalized to COVID-19. In contrast, a recent propensity-score matched study with 7747 individuals has shown that use of NSAIDs is not associated with 30-day intensive care unit admission or death of patients hospitalized with influenza.[49] Second, NSAIDs are well-known anti-inflammatory drugs that inhibit the cyclooxygenase (COX) isoforms COX-1 and COX-2. It is well-established that hyper-inflammatory responses underlie the pathology of severe COVID-19. Indeed, cytokine production is significantly increased in COVID-19.[50] NSAIDs may decrease the production of a subset of proinflammatory cytokines, including interleukin 6 and tumour necrosis factor alpha, which may reduce the incidence of cytokine storm in COVID-19,[48] leading to a better prognosis.

It has been shown that the capabilities of different NSAIDs in suppressing the enzymatic activities of COX-1 and/or COX-2 differ, resulting in a variety of therapeutic effects.[6,51] In subgroup analyses, we found that all types of NSAIDs (aspirin, ibuprofen and naproxen) were safe for the primary care of all COVID-19 patients, consistent with our main results. However, because only a few articles were included in the subgroup analysis, more research was needed to confirm the effects of different NSAIDs on COVID-19.

Our results might be generalized to a diverse population. In accordance with the above findings, several cohort studies also found no outcome worsening in COVID-19 patients with coexisting comorbidities, including rheumatic disease[52] and coronary artery diseases.[53] For example, a national cohort study including 1 708 781 individuals with rheumatoid arthritis/osteoarthritis showed that the use of NSAIDs was not associated with a reduced COVID-19-related mortality after adjusting for cofounding factors.[52] Furthermore, another cohort with a small sample size (N = 183) in China found that low-dose aspirin use prior to admission was not associated with mortality in patients with coronary artery diseases hospitalized with COVID-19 infection (OR = 0.944, P = .89).[53] Collectively, these results suggest that NSAID treatment is safe for other patient populations, and individuals taking NSAIDs for secondary prevention should continue their treatment.

A previous study found NSAID use was associated with an increased risk of ischemic stroke in patients with acute respiratory infections.[54] Consistently, we also found a significantly increased risk of stroke in COVID-19 patients who received NSAIDs, but no elevated incidence of composite thrombotic events (including deep vein thrombosis, pulmonary embolism, peripheral arterial occlusion, ischemic stroke and myocardial infarction) in hospitalized COVID-19 patients was observed by pooling two studies. The somewhat contradictory results are interesting. Possible differences between infection-induced thrombosis and similar clinical features of COVID-19 can be distinguished by the examination of overt thrombosis (e.g., deep vein thrombosis, pulmonary embolism and myocardial infarction) versus microthrombosis, which is usually the cause of thrombotic stroke. It is well known that the presence of microthrombi is not necessarily correlated with overt thrombosis.[55–57] Microthrombosis can be better diagnosed with video-microscopy, dark-field images and spectral images,[56,57] therefore further studies should use more effective tools to comprehensively elucidate the effect of aspirin or other NSAIDs on microthrombosis.

It is well known that NSAIDs can increase the risk of major bleeding, e.g., upper gastrointestinal complications.[51] Chow et al[11] found no significant increase in major bleeding in patients administered aspirin, which might be explained by the fact that patients with COVID-19 frequently acquired a hypercoagulable state and thrombocytopenia is uncommon in COVID-19 patients. However, considering the observational study design and limited sample size, ongoing COVID-19 clinical trials involving aspirin or other NSAIDs would be helpful to provide more sound evidence for safety outcomes.

4.1 | Study strengths and limitations

The greatest strength of this study was its large sample size. We examined the prevalence of NSAID use in COVID-19 cases and comprehensively assessed the related outcomes, including the risk of COVID-19, hospital admission, severity, mechanical ventilation and death, as well as safety outcomes. As readily available and inexpensive drugs, these results revealed the benefits of the clinical use of NSAIDs during the COVID-19 pandemic.

We recognized the possible limitations of this study as well. This was a meta-analysis including observational studies. This intrinsic limitation precluded us from inferring a causal relationship. The included patients were adult individuals, and the effects of NSAIDs in young and children patients should be further studied. Measured and unmeasured factors such as various underlying diseases might influence the results. For example, it was thought that there was a large gender difference in susceptibility to COVID-19. However, the limited data prevented sex-specific subgroup analysis. Some data, including age and specific drug doses, were incomplete in most included studies and could not be further combined. However, Wong et al[21] reported that high-dose or low-dose ibuprofen/naproxen was not linked with an increased risk of COVID-19-related death in the general population, which suggests NSAIDs at common clinical doses are safe. Significant heterogeneity was observed across the included studies, which might result from the differences in exposure to NSAIDs, types of NSAIDs and analytical strategies. Specifically, exposure definition varied greatly across included studies. The majority of studies defined NSAID use within 7 days to 1 year prior to admission or diagnosis of COVID-19 as prior use of NSAIDs. Only one study assessed in-hospital NSAID use. Thus, our results should be explained as the effect of prior use of NSAIDs in COVID-19, rather than the effect of current treatment of NSAIDs in hospitalized COVID-19 patients. Well-designed randomized controlled clinical trials (e.g., with a large sample size or using the COVID Outcomes Scale recommended by the WHO) are required for further assessment of the clinical benefit and safety (e.g., stroke and acute renal failure) of NSAIDs in the prevention and treatment of COVID-19.

Age is an important confounding factor that might influence our results. Elderly people with comorbidities are more prone to routinely take NSAIDs.[58] Although most of our data were adjusted for age, we could not fully exclude the potential age-related bias. However, patients of the NSAID group in most included studies were older, and age-related adverse events could not be underestimated. Wong et al[21] reported that NSAID use was not linked with COVID-19-related death both in young and older populations, and the estimated effect did not differ by age in all adjusted models. In general, current evidence suggests there is no correlation between age and NSAID use in COVID-19.

5 | CONCLUSION

The current findings support the notion that prior exposure to NSAIDs is not associated with an elevated susceptibility to COVID-19 or exacerbation of COVID-19. In addition, prior NSAID use might be beneficial to improve COVID-19 outcomes to some extent. Thus, proper use of NSAIDs in COVID-19 is recommended, rather than absolute rejection of NSAID drugs. It is worth pointing out that this meta-analysis was mostly based on observational studies, and ongoing trials (NCT0432563339, NCT0438276840, NCT0433462941 and NCT04344457) are expected to demonstrate more precise roles of NSAIDs in the management of COVID-19. Moreover, future research should not only focus on the use of NSAIDs as a therapeutic option, but also continue to examine the effects of pre-admission NSAID use on the risk of COVID-19, as well as COVID-19 outcomes and mortality in the general population.

COMPETING INTERESTS
All authors declare that they have no conflicts of interest.

CONTRIBUTORS
P.Y. and X.L. were responsible for the entire project and revised the manuscript. H.Z., Ss.H. and K.M. performed data extraction, statistical analysis and data interpretation. X.L. and Ss.H. drafted the first version of the manuscript. All authors participated in the interpretation of the results and prepared the final version of the manuscript.

AVAILABILITY OF SUPPORTING DATA
All data generated or analysed during this study were included in this published article (and its supplementary information files).

CONSENT FOR PUBLICATION
Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.