Association between NSAIDs use and adverse clinical outcomes among adults hospitalized with COVID-19 in South Korea: A nationwide study

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Summary: NSAIDs use was associated with an 54% increased risk of a primary composite outcome of in-hospital death, ICU admission, mechanical ventilation use, or sepsis, compared to non-use. We provide novel evidence to support the concern that NSAIDs may exacerbate COVID-19.

ABSTRACT

BACKGROUND: Non-steroidal anti-inflammatory drugs (NSAIDs) may exacerbate COVID-19 and worsen associated outcomes by upregulating the enzyme that SARS-CoV-2 binds to enter cells. To our knowledge, no study has examined the association between NSAID use and the risk of COVID-19-related outcomes.

METHODS: We conducted a cohort study using South Korea's nationwide healthcare database, which contains data of all subjects who received a test for COVID-19 (n=69,793) as of April 8, 2020. We identified adults hospitalized with COVID-19, where cohort entry was the date of hospitalization. NSAIDs users were those prescribed NSAIDs in the 7 days before and including cohort entry and non-users were those not prescribed NSAIDs during this period. Our primary outcome was a composite of in-hospital death, intensive care unit admission, mechanical ventilation use, and sepsis; our secondary outcomes were cardiovascular complications and acute renal failure. We conducted logistic regression analysis to estimate odds ratio (OR) with 95% confidence intervals (CI) using inverse probability of treatment weighting to minimize confounding.

RESULTS: Of 1,824 adults hospitalized with COVID-19 (mean age 49.0 years; female 59%), 354 were NSAIDs users and 1,470 were non-users. Compared with non-use, NSAIDs use was associated with increased risks of the primary composite outcome (OR 1.54 [95% CI 1.13-2.11]) but insignificantly associated with cardiovascular complications (1.54 [0.96-2.48]) or acute renal failure (1.45 [0.49-4.14]).

CONCLUSION: While awaiting the results of confirmatory studies, we suggest NSAIDs be used with caution among patients with COVID-19 as the harms associated with their use may outweigh their benefits in this population.

Keywords: coronavirus disease 2019; nonsteroidal anti-inflammatory drugs; adverse outcomes; nationwide study; pharmacoepidemiologic study

INTRODUCTION

Coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic.[1, 2] Concerns exist that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) may exacerbate COVID-19 by upregulating angiotensin-converting enzyme 2 (ACE2) expressions,[3, 4] the enzyme which SARS-CoV-2 binds to enter cells. In addition, NSAIDs inhibit cyclooxygenase (COX),[5] which could be involved in the pathogenesis of viral infections to result in tissue damage.[6, 7]

These concerns were based on unconfirmed anecdotal reports of four young COVID-19 patients who developed serious infectious complications following NSAIDs use.[8] The Health Minister of France subsequently recommended that paracetamol (acetaminophen) be used as first-line antipyretic agents over NSAIDs.

In contrast, the US Food and Drug Administration,[9] European Medicine Agency,[10] and Australia's Therapeutic Goods Administration[11] stated that there is insufficient evidence to draw conclusions regarding this safety concern and thus, current clinical practice should not be changed until further evidence becomes available. This position is supported by a recent systematic review of randomized trials and observational studies of respiratory viral infections, which concluded that there is currently no evidence to support that NSAIDs are harmful with respect to COVID-19.[12] Despite the widespread use of NSAIDs, to our knowledge, there is currently no published observational study that specifically assessed the association between NSAIDs use and clinical outcomes among COVID-19 patients.

This cohort study therefore aimed to examine the association between NSAIDs use, compared to non-use, and worsened clinical outcomes among adults hospitalized with

COVID-19 using South Korea's nationwide healthcare database containing all COVID-19 patients.

METHODS

Data source

We used the Health Insurance Review and Assessment Service (HIRA) database of South Korea, provided as part of the #OpenData4Covid19 project, a global research collaboration on COVID-19 jointly conducted by Ministry of Health and Welfare of Korea and HIRA.[13] Briefly, the South Korean government released the world's first de-identified COVID-19 nationwide patient data on March 27, 2020. Owing to South Korea's National Health Insurance system, which is the universal single-payer healthcare provider covering the entire Korean population of 50 million, and its fee-for-service reimbursement system, the database includes information from both inpatient and outpatient settings.

The HIRA COVID-19 database contains data of all subjects who received a test for COVID-19 as of April 8, 2020, linked to their administrative healthcare data from the previous 3 years (January 1, 2017 to April 8, 2020). The HIRA COVID-19 database includes anonymized patient identifiers, sociodemographic characteristics, healthcare utilization history, diagnoses (International Classification of Diseases, 10th Revision; ICD-10), and drug prescription information (Anatomical Therapeutic Chemical classification codes); use of over-the-counter drugs are not collected in this database (Supplementary Material 1).[14]

This study was approved by the Institutional Review Board of Sungkyunkwan University (SKKU 2020-03-012), which waived the requirement of obtaining informed consent.

Study design and participants

Of 69,793 individuals who received a diagnostic test for COVID-19 between January 1, 2020 to April 8, 2020, 5,707 tested positive for COVID-19 (Figure 1). The presence of COVID-19 was defined by positive findings on Korean Ministry of Food and Drug Safety approved diagnostic tests that used the reverse transcription polymerase chain reaction method targeting the RNA-dependent RNA polymerase, N, and E genes.[15] Confirmed COVID-19 cases were patients with a positive diagnostic test result and a recorded diagnosis of COVID-19, defined using domestic codes (Supplementary Material 2).

This population-based cohort study included 1,824 adults (aged ≥19 years) hospitalized with COVID-19 between January 20, 2020 (e.g., when the first patient was admitted) and April 8, 2020 in South Korea (Figure 1). In South Korea, patients diagnosed with COVID-19 are required to be admitted to hospital if they are symptomatic, and they remain hospitalized until fully recovered from COVID-19 (patients that met both clinical [cessation of fever without medication use] and testing criteria [negative results from two tests performed within a 24-hour interval]).[16] With the HIRA COVID-19 database covering all Koreans, our study enrolled all inpatients who were hospitalized for COVID-19, and cohort entry was defined by the date of admission for incident COVID-19 hospitalization.

Exposure to NSAIDs

We defined exposure using inpatient and outpatient prescription records of NSAIDs from the HIRA database, including both oral and intravenous formulations (Supplementary Material 2). We ascertained exposure to NSAIDs according to an intention-to-treat approach, in which exposure was defined in the index period of 7 days before and including cohort entry among hospitalized COVID-19 patients. Patients prescribed NSAIDs during this period were classified as NSAIDs users whereas those not prescribed NSAIDs during this period

were classified as non-users. To minimize any time-related biases such as immortal time,[17] follow-up was initiated from the date of cohort entry for both NSAIDs users and non-users.

Outcomes

Our primary outcome was a composite endpoint of in-hospital death, intensive care unit (ICU) admission, mechanical ventilation use, and sepsis. Our secondary outcomes were a composite endpoint of cardiovascular complications (myocardial infarction, stroke, heart failure), and acute renal failure. We defined outcomes using in-hospital ICD-10 diagnostic codes and procedures using the national procedure coding system (Supplementary Material 2). Study outcomes were measured between the cohort entry date and the earliest of the date of hospital discharge or end of study period (April 8, 2020).

Potential confounders

We assessed sociodemographic and clinical factors considered to be associated with NSAIDs use and risk of the outcomes of interest. For sociodemographic factors, we assessed age, sex, and health insurance type at cohort entry; age was grouped into 10-year bands. Clinical variables included comorbidities and use of co-medications assessed in the year before cohort entry (Supplementary Material 2). We used the expanded benefit coverage codes in addition to diagnosis codes to define malignancy to minimize false positives.

Statistical analysis

Baseline characteristics were summarized for NSAIDs users and non-users using counts (proportions) or mean (standard deviation) for categorical or continuous variables, respectively. We calculated the absolute standardized difference (aSD) to determine important imbalances between exposure groups, with aSD $\geq$0.1 considered important.

We estimated the cumulative incidence of the primary and secondary outcomes among NSAIDs users versus non-users. We used three outcome models using logistic regression to estimate odds ratio (OR) with 95% confidence intervals (CIs) of the association of interest. The first model was unadjusted. The second model included all covariates described above. The third model, considered our primary analysis, was weighted by propensity scores (PS) using the inverse probability of treatment weight (IPTW) approach.[18] The PS, or probability of receiving NSAIDs, was estimated using multivariable logistic regression analysis, with all confounders mentioned above included as independent variables. The *c*-statistic was used to determine model discrimination, with a value between 0.6 and 0.8 considered adequate to predict treatment status based on covariates included.[19] The IPTW approach involves weighting the inverse probability of receiving NSAIDs (1/PS for NSAIDs, and 1/(1−PS) for non-user groups).

Subgroup analyses

We conducted sex- and age-stratified analyses, with age classified into three groups (<45, 45-65, ≥65 years), for the risk of the primary outcome associated with NSAIDs use. In addition, we stratified by route of administration (oral versus intravenous) and by history of hypertension, hyperlipidemia, or diabetes mellitus. The PS were re-calculated in all subgroup analyses using multivariable logistic regression models.

Sensitivity analyses

Redefining the exposure ascertainment window

As there is currently no data available on how fast NSAIDs increase ACE2 tissue expressions, we varied the exposure ascertainment window to 14 days and 30 days before and including cohort entry. Patients prescribed NSAIDs during these periods were classified as NSAIDs users whereas those not prescribed NSAIDs were classified as non-users. Follow-up was initiated from cohort entry.

Head-to-head comparison of NSAIDs versus paracetamol

To examine the potential effects of confounding by indication, we compared NSAIDs to paracetamol as these are used for similar indications (Supplementary Material 2). We classified patients based on their exposure to NSAIDs or paracetamol in the 7 days before and including cohort entry, excluding those not exposed to one of the two drugs of interest and those who received both drugs during this exposure window. Follow-up was initiated from cohort entry for both exposure groups.

Redefining the primary composite outcome

As outcome misclassification of sepsis from inaccuracy of coding or reverse causality between NSAIDs use and sepsis is possible, we repeated our main analysis by using a redefined primary outcome that was a composite endpoint of in-hospital death, ICU admission, and mechanical ventilation use.

Alternative approaches involving propensity scores to control for confounding

First, to improve comparability between exposure groups, we excluded the most extreme 1% of PS values (IPTW with trimming). Second, we included the estimated PS, in addition to other covariates, into our multivariable logistic regression model. Third, we stratified on the PS in deciles. Last, we applied standardized mortality ratio weights (SMRW) (1 for NSAIDs, and PS/(1−PS) for non-user groups).[18]

All statistical analyses were performed using the SAS Enterprise Guide software (version 6.1).

RESULTS

Of 1,824 adults hospitalized with COVID-19 in South Korea, there were 354 NSAIDs users (19%) and 1,470 non-users (81%). NSAIDs users were older than non-users (mean age 54.1 years [standard deviation 17.6] versus 47.8 years [19.1], aSD 0.43), but had similar sex distribution (58% versus 59% female; aSD 0.01). Except for history of renal failure, NSAID users had a greater comorbidity burden and greater use of co-medications compared to non-users (Table 1).

Among 74 primary composite events, 22 occurred in NSAID users (cumulative incidence 6.2%) and 52 (3.5%) in non-users. Compared to non-use, NSAIDs use was associated with a 54% increased risk of the primary composite outcome (IPTW OR 1.54 [95% CI 1.13-2.11]). There were 31 events of cardiovascular complications (NSAIDs users: 9 [2.5%]; non-users: 22 [1.5%]) and 7 events of acute renal failure (NSAIDs users: 3 [0.9%]; non-users: 4 [0.3%]). Compared with non-use, use of NSAIDs had an insignificant positive association with cardiovascular complications (1.54 [0.96-2.48]) and acute renal failure (1.45 [0.49-4.14]) (Table 2). The detailed breakdown of study outcomes are shown in Supplementary Material 3.

There was no difference between the association between NSAID use and the risk of our primary composite endpoint by formulation of NSAIDs, sex, and histories of hypertension and hyperlipidemia (Figure 2). However, we found effect modification in age groups (p-for-interaction <0.0001) and history of diabetes mellitus (p-for-interaction 0.0180). The risk of the primary composite endpoint associated with NSAID use was significantly greater among middle-aged adults (45-64 years; 3.28 [1.98-5.43]) and among patients with no history of diabetes mellitus (1.70 [1.20-2.41]).

Findings from sensitivity analyses remained largely consistent, where all effect estimates showed positive associations between the primary outcome and NSAIDs users, as compared with non-users, when varying the exposure window, applying other methods involving PS, or redefining the primary outcome. When comparing to paracetamol, our sample size was greatly reduced, and there were no events that occurred in the NSAID group (cumulative incidence for NSAIDs users: 0.0%; paracetamol users 4.1%). Results of sensitivity analyses for the secondary outcomes were also generally consistent (Figure 3).

DISCUSSION

To the best of our knowledge, this is the first population-based cohort study to have investigated the association between NSAID use and adverse outcomes among patients with COVID-19. From 1,824 adults hospitalized with COVID-19 in South Korea, NSAIDs users, as compared with non-users, had a 54% increased risk of the primary composite outcome of in-hospital death, ICU admission, mechanical ventilation use, or sepsis (1.54 [1.13-2.11]). However, the risk of cardiovascular complications (1.54 [0.96-2.48]) and acute renal failure (1.45 [0.49-4.14]) were not associated with NSAIDs users when compared to non-users, likely due to limited number of outcome events. The association with the primary composite outcome remained largely consistent when the exposure period used to classify exposure

groups was varied or when applying different methods involving PS. This study provides novel, real-world evidence that supports the association between worsened clinical outcomes and NSAIDs users.

To our knowledge, this is the first study to date, to assess the safety of NSAIDs among COVID-19 patients. Nonetheless, our findings are consistent with indirect evidence from patients with acute respiratory infections or community-acquired pneumonia. A survey from regional pharmacovigilance centers in France reported 386 cases of serious infectious complications resulting in hospitalizations or death among patients who received NSAIDs (ibuprofen, ketoprofen) for acute respiratory infections.[20] However, given the limitations of pharmacovigilance assessments, causality could not be assessed. Moreover, a systematic review of observational studies found an increased risk of pleuropulmonary complications, disseminated infection, abscess, prolonged illness, delays in antibiotic prescriptions associated with NSAIDs in patients with community-acquired pneumonia.[21, 22] It is possible that NSAIDs use could have similarly worsened outcomes from SARS-CoV-2 pneumonia.

Our findings showed no increased risk of cardiovascular complications (1.54 [0.96-2.48]) and acute renal failure (1.45 [0.49-4.14]) among NSAIDs users when compared to non-users. This finding is inconsistent to the results of two case-crossover studies that found NSAIDs use during episodes of acute respiratory infections, as compared with non-use, was associated with increased risks of ischemic stroke (aOR 2.27 [2.00-2.58]) and myocardial infarction (aOR 3.41 [2.80-4.16]).[23, 24] Nevertheless, these studies were unable to conclude that use of NSAIDs increase the onset of cardiovascular complications as CIs were overlapping and further, did not examine the interaction between NSAIDs use and acute respiratory infections. Although the risks of myocardial infarction and stroke associated with NSAIDs use in the general population is well-established,[25, 26] our findings suggest that

risk of cardiovascular complications is not elevated with NSAIDs use in COVID-19 patients. Likewise, despite use of NSAIDs known to result in nephrotoxicity[27, 28], our findings suggest no additional risk of acute renal failure when COVID-19 patients were exposed to NSAIDs.

The underlying pathogenic link between NSAIDs and COVID-19 has yet to be elucidated. However, one animal study found increased ACE2 expressions with NSAIDs (ibuprofen)[29] in various organs such as the lung, heart, and kidneys.[4, 30, 31] Thus, ACE2 upregulation induced by NSAIDs could theoretically heighten the infectivity of SARS-CoV-2 to worsen clinical outcomes, resulting in multiple organ failure in severe cases. Other hypothetical mechanisms have also been suggested. NSAIDs could aggravate infections by upregulating COX-2 in activated B lymphocytes to interfere with antibody productions,[32] or by selectively inhibiting interferon-γ productions that are vital for immunity against foreign pathogens.[33] However, with inconsistent findings from animal studies and the precise biological mechanisms yet to be understood, it remains unclear as to whether these findings are readily transferable to humans.

We defined exposure using an approach analogous to an intention-to-treat, with exposure assessed in the 7 days before and including the day of cohort entry (hospital admission). We used this approach to avoid time-related biases that could be introduced by assessing in-hospital NSAID use as the date of prescription was not available for ~50% of in-hospital prescriptions. The length of hospital stay not only influences the probability of being exposed to NSAIDs while hospitalized but is also associated with worse prognosis. However, with exposure defined using pre-hospital medication use, our exposure assessment was independent of in-hospital outcomes and the duration of hospital stay. Although predicting the direction resulting from this bias is difficult as occurrence of confounders during hospitalization are accounted for in this study, the use of this exposure definition is likely to

bias our findings towards the null. This is because, by not accounting for NSAID use during hospitalization, the observed increased risk is suggested to be a conservative estimate.

Our study has several strengths. To our knowledge, this is the first population-based study conducted using all hospitalized patients with COVID-19 to assess the association between NSAID use and COVID-19 related outcomes. Moreover, we used a nationwide healthcare database of South Korea that includes information on healthcare utilization of all COVID-19 cases as of April 8, 2020. Therefore, our findings provide real-world evidence that is highly generalizable to everyday clinical practice. With its large source population, our data source was sufficiently large to assess this clinically important issue. In addition, our findings were consistent in sensitivity analyses that extended the index period.

Our study also has some limitations. First, outcome misclassification is possible. However, misclassification of in-hospital death is likely to be very small, and the validity of procedure codes to define ICU admission or mechanical ventilation use are also expected to be high as these codes are used for reimbursement processes by the health insurance authority. Also, the positive predictive value of diagnosis codes between claims data and electronic medical records was previously reported to be 82%,[34] and we believe its validity to be greater for sepsis, myocardial infarction, stroke, heart failure, and acute renal failure as we restricted to hospitalized patients receiving close monitoring. Second, our findings may have theoretically underestimated the association between NSAIDs users and clinical outcome due to depletion of susceptible patients,[35] as we included prevalent users of NSAIDs. However, our study period included the start of the COVID-19 pandemic in South Korea, making it unlikely that patients who were susceptible to adverse COVID-19 related outcomes were excluded prior to entering our cohort. Third, our results may be affected by confounding by indication given our use of an unexposed reference group. Despite attempting to address this by comparing NSAIDs users to paracetamol users, we were unable

to provide meaningful results as there were no events among NSAIDs users upon excluding those prescribed both NSAIDs and paracetamol during the exposure window. This therefore suggests that the 23 exposed events from our main analysis were exposed to both drugs during the exposure window, implying that these patients were severe cases who were prescribed both NSAIDs and paracetamol, either simultaneously or sequentially, to manage symptoms. Fourth, exposure misclassification is possible as over-the-counter use of NSAIDs are not recorded in the HIRA COVID-19 database. This would have underestimated NSAIDs use in our study, despite utilizing all prescriptions made from both inpatient and outpatient settings to ascertain prescription use of NSAIDs. Finally, residual confounding from unmeasured confounders may be present due to inherent limitations of claims data.

In summary, NSAID use was associated with worse COVID-19-related outcomes compared to non-use among patients hospitalized with COVID-19. While awaiting the results of confirmatory studies, we suggest NSAIDs be used with caution among patients with COVID-19 as the harms associated with their use may outweigh their benefits in this patient population.

NOTES

CONTRIBUTORS: All authors contributed to the study design and interpretation of the data. HEJ and HL designed the study, interpreted the data. HEJ wrote the manuscript. HL conducted the statistical analyses. HJS, YJC, and KBF interpreted the data and critically revised the manuscript. All authors reviewed and commented on drafts and approved the final manuscript and the decision to submit it for publication. JYS is the guarantor.

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Table 1. Baseline sociodemographic and clinical characteristics of adult patients hospitalized with COVID-19 in South Korea, as of Apr 8, 2020. Values are numbers (percentages) unless stated otherwise.

	Before IPTW[¶]			After IPTW[¶]		
	NSAIDs user n=354 (%)	Non-user n=1,470 (%)	aSD	NSAIDs user Weighted n=1,830 (%)	Non-user Weighted n=1,821 (%)	aSD
Age[†] (years; mean±std)	54.1 ± 17.6	47.8 ± 19.1	0.43	49.0 ± 21.2	48.9 ± 43.3	0.03
<30	44 (12)	398 (27)		452 (25)	442 (24)	
30-39	36 (10)	155 (11)		188 (10)	191 (10)	
40-49	54 (15)	205 (14)		260 (14)	260 (14)	
50-59	72 (20)	285 (19)		367 (20)	356 (20)	
60-69	79 (22)	197 (13)		262 (14)	271 (15)	
70-79	44 (12)	153 (10)		203 (11)	199 (11)	
80-89	22 (6)	66 (5)		88 (5)	88 (5)	
≥90	3 (1)	11 (1)		11 (1)	14 (1)	
Sex[†]			0.01			0.02
Male	147 (42)	603 (41)		734 (40)	746 (41)	
Female	207 (58)	867 (59)		1,096 (60)	1,075 (59)	
Health insurance type[†]			0.11			0.03
National health insurance	313 (88)	1,348 (92)		1,665 (91)	1,660 (91)	
Medical aid	41 (12)	122 (8)		165 (9)	162 (9)	
Comorbidities[‡]						
Hypertension	98 (28)	273 (19)	0.22	369 (20)	368 (20)	0.00
Hyperlipidemia	95 (27)	244 (17)	0.25	336 (18)	336 (18)	0.00
Diabetes mellitus	61 (17)	166 (11)	0.17	230 (13)	224 (12)	0.01
Malignancy	22 (6)	86 (6)	0.02	109 (6)	108 (6)	0.00
Asthma	34 (10)	82 (6)	0.15	113 (6)	113 (6)	0.00
COPD	71 (20)	220 (15)	0.13	302 (16)	289 (16)	0.02
Atherosclerosis	7 (2)	7 (0)	0.14	13 (1)	13 (1)	0.00
Chronic renal failure	5 (1)	28 (2)	0.04	42 (2)	33 (2)	0.03
Chronic liver disease	16 (5)	57 (4)	0.03	99 (5)	74 (4)	0.06
Rheumatoid arthritis	7 (2)	15 (1)	0.08	21 (1)	22 (1)	0.01
Osteoarthritis	87 (25)	208 (14)	0.27	294 (16)	291 (16)	0.00
Gastrointestinal conditions	252 (71)	848 (58)	0.28	1,107 (60)	1,097 (60)	0.00
Peripheral arterial disease	15 (4)	40 (3)	0.08	54 (3)	54 (3)	0.00
Atrial fibrillation	1 (0)	16 (1)	0.10	7 (0)	17 (1)	0.07
Other arrhythmia	10 (3)	17 (1)	0.12	32 (2)	27 (1)	0.02
Ischemic heart disease	25 (7)	56 (4)	0.13	82 (4)	80 (4)	0.00
Pneumonia	35 (10)	93 (6)	0.13	118 (6)	127 (7)	0.02
Psychiatric disorder[*]	28 (8)	83 (6)	0.09	110 (6)	110 (6)	0.00
Depression	25 (7)	71 (5)	0.09	97 (5)	94 (5)	0.01
Thyroid disease	16 (5)	69 (5)	0.01	91 (5)	86 (5)	0.01
Tuberculosis	2 (1)	5 (0)	0.03	6 (0)	7 (0)	0.01
Concomitant medications[‡]						
ACE inhibitors/ARBs	84 (24)	246 (17)	0.16	337 (18)	327 (18)	0.01
β-blockers	49 (14)	144 (10)	0.10	208 (11)	192 (11)	0.03
Calcium channel blockers	67 (19)	183 (12)	0.18	238 (13)	247 (14)	0.02
Diuretics	51 (14)	163 (11)	0.03	222 (12)	212 (12)	0.01
Nitrates	9 (3)	32 (2)	0.02	44 (2)	41 (2)	0.01
Anticoagulants	22 (6)	65 (4)	0.08	87 (5)	87 (5)	0.00
Inhaled therapy[‡]	26 (7)	85 (6)	0.06	105 (6)	110 (6)	0.01
Lipid lowering drugs	99 (28)	272 (19)	0.23	367 (20)	366 (20)	0.00
Opioids	222 (63)	756 (51)	0.23	1,015 (55)	974 (53)	0.04
Oral glucocorticoids	215 (61)	756 (51)	0.19	936 (51)	965 (53)	0.04
Platelet inhibitors	71 (20)	167 (11)	0.24	240 (13)	237 (13)	0.00

DPP-4 inhibitors	32 (9)	118 (8)	0.04	146 (8)	148 (8)	0.00
Metformin	44 (12)	132 (9)	0.11	172 (9)	172 (9)	0.00
Insulin	17 (5)	51 (3)	0.07	75 (4)	68 (4)	0.02
SGLT2 inhibitors	7 (2)	7 (0)	0.14	15 (1)	13 (1)	0.01
Sulfonylurea	25 (7)	59 (4)	0.13	82 (4)	81 (4)	0.00
Thiazolidinedione	8 (2)	17 (1)	0.09	21 (1)	24 (1)	0.01

Note: ACE, angiotensin converting enzyme; ARB, angiotensin-receptor II blocker; aSD, absolute standardized difference; COPD, chronic obstructive pulmonary disease; DPP-4, dipeptidyl peptidase 4; IPTW, inverse probability of treatment weighted; NSAIDs, nonsteroidal anti-inflammatory drugs; SGLT2, sodium-glucose co-transporter 2; std, standard deviation

[†]Assessed on cohort entry (date of hospitalization with COVID-19)

[‡]Assessed in the year prior to cohort entry

[‖] IPT weighted cohort, where the propensity score was estimated using a multiple logistic regression model that included the following independent variables: age, sex, health insurance type, comorbidities (hypertension, hyperlipidemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions, peripheral arterial disease, atrial fibrillation, other arrythmia, ischemic heart disease, pneumonia, psychiatric disorders, depression, thyroid disease), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates, anticoagulants, inhaled therapy for respiratory for respiratory disease, lipid lowering drugs, opioids, oral glucocorticoids, platelet inhibitors, dipeptidyl peptidase-4 inhibitors, metformin, insulin, sulfonylurea, sodium-glucose co-transporter-2 inhibitors) (*c*-statistics: 0.668 for NSAIDs users versus non-users)

[*]Psychiatric disorders include organic amnesic syndrome, delirium, other mental disorders, personality and behavioral disorders due to brain disease, mental and behavioral disorders due to use of alcohol, schizophrenia, persistent delusional disorders, hyperkinetic disorders, conduct disorders

[*]Inhaled therapy for respiratory disease β2 agonist inhalants, anticholinergic inhalants, and glucocorticoid inhalants

Table 2. Risk of adverse clinical outcomes associated with NSAIDs users compared with non-users among adult patients hospitalized with COVID-19

	Number of patients	Number of events	Cumulative incidence (%)	Odds ratio (95% confidence interval)		
				Unadjusted Model*	Adjusted Model†	IPT Weighted Model‡
All-cause death, ICU admission, mechanical ventilation use, sepsis						
Non-users	1,470	52	3.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
NSAIDs users	354	22	6.2	1.81 (1.08-3.02)	1.70 (0.96-3.00)	1.54 (1.13-2.11)
Cardiovascular complicationsǁ						
Non-users	1,470	22	1.5	1.00 (reference)	1.00 (reference)	1.00 (reference)
NSAIDs users	354	9	2.5	1.72 (0.78-3.76)	1.45 (0.57-3.72)	1.54 (0.96-2.48)
Acute renal failure						
Non-users	1,470	4	0.3	1.00 (reference)	1.00 (reference)	1.00 (reference)
NSAIDs users	354	3	0.9	3.13 (0.70-14.06)	NA**	1.45 (0.49-4.14)

Note: ICU, intensive care unit; IPT, inverse probability of treatment; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs

*Unadjusted univariable logistic regression model

†Fully adjusted multivariable logistic regression model with all potential confounders including age, sex, health insurance type, comorbidities (hypertension, hyperlipidemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions, peripheral arterial disease, atrial fibrillation, other arrythmia, ischemic heart disease, pneumonia, psychiatric disorders, depression, thyroid disease), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates, anticoagulants, inhaled therapy for respiratory for respiratory disease, lipid lowering drugs, opioids, oral glucocorticoids, platelet inhibitors, dipeptidyl peptidase-4 inhibitors, metformin, insulin, sulfonylurea, sodium-glucose co-transporter-2 inhibitors)

‡IPT weighted multivariable logistic regression model (main model), where the propensity score used was estimated using a multiple logistic regression model that included the following independent variables: age, sex, health insurance type, comorbidities (hypertension, hyperlipidemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions, peripheral arterial disease, atrial fibrillation, other arrythmia, ischemic heart disease, pneumonia, psychiatric disorders, depression, thyroid disease), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates, anticoagulants, inhaled therapy for respiratory for respiratory disease, lipid lowering drugs, opioids, oral glucocorticoids, platelet inhibitors, dipeptidyl peptidase-4 inhibitors, metformin, insulin, sulfonylurea, sodium-glucose co-transporter-2 inhibitors) (c-statistics: 0.668 for NSAIDs users versus non-users)

ǁ Cardiovascular complications include myocardial infarction, heart failure, and stroke

**Inestimable due to small number of events relative to the large number of confounders

FIGURE LEGENDS

Figure 1. Nationwide population-based cohort study design

Note: HIRA, Health Insurance Review and Assessment Service; NSAIDs, nonsteroidal anti-inflammatory drugs

The HIRA database of South Korea contains insurance benefit claims and longitudinal history of all medical services from the entire Korean population of 50 million inhabitants, based on fee-for-service payment system; thus, data from both inpatient and outpatient settings are available. A cohort of adult patients hospitalized with COVID-19 were identified from confirmed cases of COVID-19. Patients prescribed NSAIDs while hospitalized were classified as NSAIDs users and those not prescribed NSAIDs were classified as non-users. We assessed the risk of death, intensive care unit admission, mechanical ventilation use, or sepsis associated with NSAIDs users compared to non-users

Figure 2. Forest plot summarizing the risk of primary outcome[*] associated with NSAIDs when stratified for age, sex, formulation of NSAIDs and history of comorbidities

Note: IPT, inverse probability of treatment; NSAIDs, nonsteroidal anti-inflammatory drugs

[*]Primary outcome includes in-hospital death, intensive care unit admission, mechanical ventilation use, sepsis

[†]IPT weighted multivariable logistic regression model (main model), where the propensity score used was estimated using a multiple logistic regression model that included the following independent variables: age, sex, health insurance type, comorbidities (hypertension, hyperlipidemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions, peripheral arterial disease, atrial fibrillation, other arrythmia, ischemic heart disease, pneumonia, psychiatric disorders,

depression, thyroid disease), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates, anticoagulants, inhaled therapy for respiratory for respiratory disease, lipid lowering drugs, opioids, oral glucocorticoids, platelet inhibitors, dipeptidyl peptidase-4 inhibitors, metformin, insulin, sulfonylurea, sodium-glucose co-transporter-2 inhibitors) (c-statistics: 0.668 for NSAIDs users versus non-users)

‡Comparing patients prescribed oral formulation of NSAIDs to non-users

⁋ Comparing patients prescribed intravenous formulation of NSAIDs to non-users

Figure 3. Forest plot summarizing the results of sensitivity analyses comparing NSAIDs to paracetamol to minimize confounding by indication, and redefining the exposure ascertainment window to evaluate exposure misclassification

Note: ICU, intensive care unit; IPT, inverse probability of treatment; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs

†IPT weighted multivariable logistic regression model (main model), where the propensity score used was estimated using a multiple logistic regression model that included the following independent variables: age, sex, health insurance type, comorbidities (hypertension, hyperlipidemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions, peripheral arterial disease, atrial fibrillation, other arrythmia, ischemic heart disease, pneumonia, psychiatric disorders, depression, thyroid disease), and co-medications (angiotensin converting enzyme inhibitors,

angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates, anticoagulants, inhaled therapy for respiratory for respiratory disease, lipid lowering drugs, opioids, oral glucocorticoids, platelet inhibitors, dipeptidyl peptidase-4 inhibitors, metformin, insulin, sulfonylurea, sodium-glucose co-transporter-2 inhibitors) (c-statistics: 0.668 for NSAIDs users versus non-users)

‡Patients diagnosed with COVID-19 after receiving positive test results for COVID-19

ǁ Cardiovascular complications include myocardial infarction, heart failure, and stroke

Figure 1

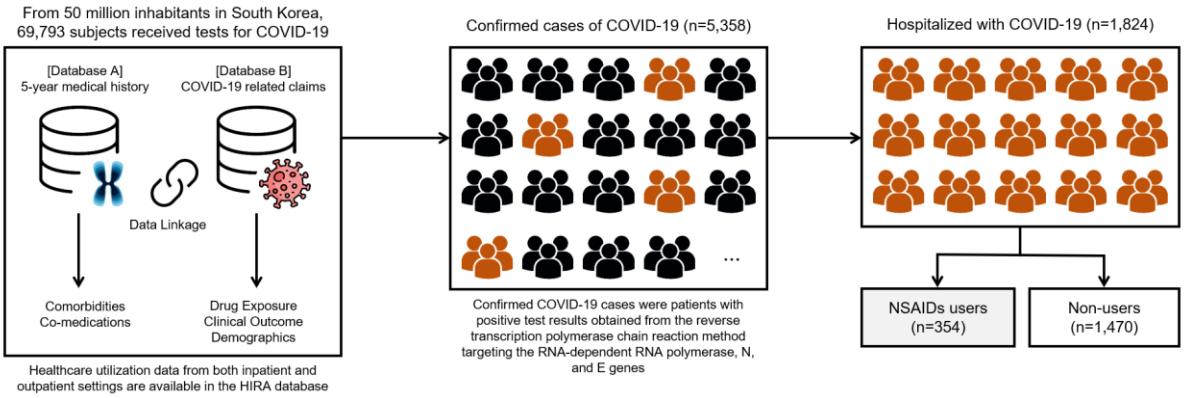

Figure 2

	Number of Patients	Cumulative incidence (%)		IPT weighted odds ratio† (95% confidence interval)			P interaction
		NSAIDs	Non-users				
Formulation of NSAIDs							
Oral formulations‡	1,687	5.5	3.5		1.52	(1.09-2.12)	0.1985
Intravenous formulations‖	1,607	7.3	3.5		1.96	(1.42-2.71)	
Age group (years)							
<45	750	1.9	1.9		0.72	(0.31-1.65)	
45-64	649	8.3	3.0		3.28	(1.98-5.43)	<0.0001
≥65	425	7.6	7.8		1.03	(0.64-1.68)	
Sex							
Male	750	8.8	5.5		1.15	(0.75-1.76)	0.2388
Female	1,074	4.4	2.2		1.70	(1.02-2.81)	
History of hypertension							
Yes	371	9.2	8.1		1.08	(0.63-1.86)	0.0663
No	1,453	5.1	2.5		2.25	(1.53-3.30)	
History of hyperlipidemia							
Yes	339	7.4	4.1		1.13	(0.54-2.37)	0.9340
No	1,485	5.8	3.4		1.37	(0.95-1.97)	
History of diabetes mellitus							
Yes	227	4.9	6.0		0.78	(0.33-1.82)	0.0180
No	1,597	6.5	3.2		1.70	(1.20-2.41)	

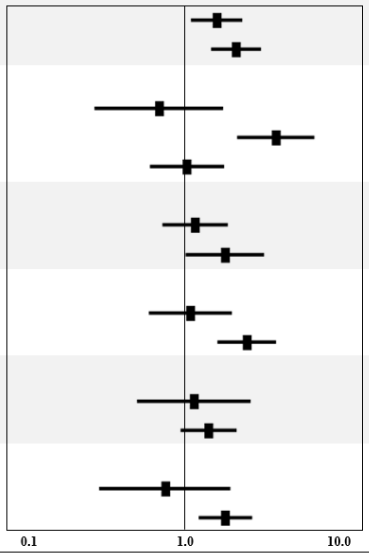

Figure 3

	Number of Patients	Cumulative incidence (%) NSAIDs	Cumulative incidence (%) Reference	IPT weighted odds ratio† (95% confidence interval)	
In-hospital death, ICU admission, mechanical ventilation use, sepsis					
Hospitalized COVID-19 patients					
NSAIDs users vs. non-users	1,824	6.2	3.5	1.54	(1.13-2.11)
NSAIDs users vs. paracetamol users	967	0.0	4.0	NA	
Varied exposure ascertainment window					
14 days before and including the date of cohort entry					
NSAIDs users vs. non-users	1,824	5.9	3.5	1.54	(1.12-2.11)
30 days before and including the date of cohort entry					
NSAIDs users vs. non-users	1,824	5.1	3.6	1.25	(0.90-1.73)
Propensity score methods (NSAIDs users vs. non-users)					
IPT weighted with trimming	1,789	6.0	3.4	1.38	(0.99-1.92)
Outcome model adjustment	1,824	6.2	3.5	1.47	(0.85-2.53)
Stratified propensity score in deciles	1,824	6.2	3.5	1.49	(0.88-2.52)
Standardized mortality ratio weighting	1,824	6.2	3.5	1.46	(0.75-2.85)
Redefining primary outcome (in-hospital death, ICU admission, mechanical ventilation use)					
NSAIDs users vs. non-users	1,824	4.8	2.7	1.63	(1.14-2.32)
Cardiovascular complications‡					
Hospitalized COVID-19 patients					
NSAIDs users vs. non-users	1,824	2.5	1.5	1.54	(0.96-2.48)
NSAIDs users vs. paracetamol users	967	3.2	1.3	0.87	(0.52-1.45)
Varied exposure ascertainment window					
14 days before and including the date of cohort entry					
NSAIDs users vs. non-users	1,824	2.1	1.6	1.33	(0.82-2.16)
30 days before and including the date of cohort entry					
NSAIDs users vs. non-users	1,824	2.6	1.3	1.95	(1.22-3.11)
Propensity score methods (NSAIDs users vs. non-users)					
IPT weighted with trimming	1,789	2.6	1.5	1.55	(0.96-2.49)
Outcome model adjustment	1,824	2.5	1.5	1.39	(0.61-3.20)
Stratified propensity score in deciles	1,824	2.5	1.5	1.47	(0.65-3.33)
Standardized mortality ratio weighting	1,824	2.5	1.5	1.41	(0.51-3.93)
Acute renal failure					
Hospitalized COVID-19 patients					
NSAIDs users vs. non-users	1,824	0.9	0.3	1.45	(0.49-4.14)
NSAIDs users vs. paracetamol users	967	1.6	0.2	0.52	(0.07-3.73)
Varied exposure ascertainment window					
14 days before and including the date of cohort entry					
NSAIDs users vs. non-users	1,824	0.7	0.3	1.47	(0.52-4.19)
30 days before and including the date of cohort entry					
NSAIDs users vs. non-users	1,824	0.8	0.2	1.54	(0.49-4.86)
Propensity score methods (NSAIDs users vs. non-users)					
IPT weighted with trimming	1,789	0.9	0.3	1.43	(0.49-4.15)
Outcome model adjustment	1,824	0.9	0.3	1.24	(0.21-7.19)
Stratified propensity score in deciles	1,824	0.9	0.3	1.73	(0.36-8.25)
Standardized mortality ratio weighting	1,824	0.9	0.3	1.69	(0.26-10.90)