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

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SUMMARY

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. However, to our knowledge, no study has examined the association between NSAID use and the risk of COVID-19-related outcomes among hospitalised patients.

METHODS: We conducted a population-based 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 a cohort of adults hospitalised with COVID-19, where cohort entry was the date of hospitalisation. NSAIDs users were those prescribed NSAIDs in the 7 days before and including the date of 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 outcome was cardiovascular or renal complications. We conducted logistic regression analysis to estimate odds ratio (OR) with 95% confidence intervals (CI) using inverse probability of treatment weighting to minimize potential confounding.

FINDINGS: Of 1,824 adults hospitalised with COVID-19 (mean age 49·0 years, standard deviation 19·0 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 1·65, 95% CI 1·21-2·24) and of cardiovascular or renal complications (OR 1·87, 95% CI 1·25-2·80). Our main findings remained consistent when we extended the exposure ascertainment window to include the first three days of hospitalisation (OR 1·87, 95% CI 1·06-3·29).

INTERPRETATION: Use of NSAIDs, compared with non-use, is associated with worse outcomes among hospitalised COVID-19 patients. 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.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), which 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 are 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 Admnistration,[9] European Medicine Agency,[10] and Australia's Therapeutic Goods Admnistraiton[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 randomised 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 hospitalised 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 (national drug chemical code, prescription date, day's supply, dosage, route of administration). The national drug chemical codes used in South Korea are based on the drug's active chemical ingredient, and are mapped to the Anatomical Therapeutic Chemical (ATC) classification codes (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) hospitalised 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 hospitalised until fully recovered from COVID-19.[16] With the HIRA COVID-19 database covering all Koreans, our study enrolled all inpatients who were hospitalised for COVID-19, and cohort entry was defined by the date of admission for incident COVID-19 hospitalisation.

Exposure to NSAIDs

We defined exposure using inpatient and outpatient prescription records of NSAIDs from the HIRA database, including both oral and intravenous formulations (aceclofenac, diclofenac, etodolac, fenoprofen, flurbiprofen, dexibuprofen, ibuprofen, ibuproxam, ketoprofen, dexketoprofen, ketorolac, meloxicam, naproxen, piroxicam, celecoxib, polmacoxib, etoricoxib) (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 the date of 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 and was ended on the earliest of date of outcome occurrence or end of the study period (April 8, 2020).

Outcomes

Our primary outcome was a composite endpoint of in-hospital death, intensive care unit (ICU) admission, mechanical ventilation use, and sepsis. Our secondary outcome was a composite endpoint of cardiovascular or renal complications (myocardial infarction, stroke, heart failure, acute renal failure). We defined outcomes using in-hospital ICD-10 diagnostic codes and procedures using the national procedure coding system (Supplementary Material 2).

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 (national health insurance, medical aid) 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 using inpatient and outpatient data. The following comorbidities were defined using ICD-10 diagnostic codes: hypertension, hyperlipidaemia, diabetes mellitus, malignancy, asthma, chronic obstructive pulmonary disease, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions. We used the expanded benefit coverage codes in addition to diagnosis codes to define malignancy to minimize false positives. Use of co-medications were defined using ATC codes and included the following medications: angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor II blockers (ARBs), β-blockers, calcium channel blockers, diuretics, and nitrates (Supplementary Material 2).

Statistical analysis

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

We estimated the cumulative incidence of the primary and secondary composite outcomes among NSAIDs users versus non-users. We used three outcome models using logistic regression to estimate odds ratio (OR) and corresponding 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 the following variables included as independent variables: age, sex, health insurance type, hypertension, hyperlipidaemia, diabetes mellitus, malignancy, asthma, chronic obstructive pulmonary disease, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions, and use of co-medications (ACE inhibitors, ARBs, β-blockers, calcium channel blockers, diuretics, and nitrates). The *c*-statistic value 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

In 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, hyperlipidaemia, or diabetes mellitus.

Sensitivity analyses

Redefining the exposure ascertainment window

We varied the exposure ascertainment window to 7 days before and including the third day after the date of cohort entry among hospitalized COVID-19 patients. Patients prescribed NSAIDs during this period were classified as NSAIDs users whereas those not prescribed NSAIDs were classified as non-users. Follow-up was initiated from the third day after the date of cohort entry for both NSAIDs users and non-users and was ended on the earliest of date of outcome occurrence or end of the study period (April 8, 2020).

Head-to-head comparison of NSAIDs versus paracetamol

To examine the potential effects of confounding by indication, we compared NSAIDs users to paracetamol users as these two drugs are used for similar indications. Paracetamol and propacetamol (prodrug of paracetamol used in South Korea) were included in the paracetamol user group, with both oral and intravenous formulations included (Supplementary Material 2). We classified patients based on their exposure to NSAIDs or paracetamol in the 7 days before and including the day of cohort entry, excluding those not exposed to one of the two drugs of interest and those who received both NSAIDs and paracetamol during this exposure assessment window. Follow-up was initiated from the date of cohort entry for both NSAIDs users and paracetamol users and was ended on the date of outcome occurrence or end of the study period (April 8, 2020), whichever occurred first.

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

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (JYS) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Of 1,824 adults hospitalised 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 years] versus 47·8 years [standard deviation 19·1 years], 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). The median length of hospitalisation was 12·0 days among NSAIDs users and 13·0 days among non-users.

There was a total of 76 primary composite events (in-hospital death, ICU admission, mechanical ventilation use, or sepsis), 23 of which occurred in NSAID users (cumulative incidence 6·5%) and 53 (3·6%) among non-users. Compared to non-use, NSAIDs use was associated with an 65% increased risk of the primary composite outcome (IPTW OR 1·65, 95% CI 1·21-2·24). There were 44 secondary events of cardiovascular or renal complications (NSAIDs users: 28, 1·9%; non-users: 16, 4·5%). Compared with non-use, use of NSAIDs was associated with an increased risk of cardiovascular or renal complications (IPTW OR 1·87, 95% CI 1·25-2·80) (Table 2). The detailed breakdown of the primary and secondary outcomes by component of the composites are shown in Supplementary Material 3.

Results of subgroup analyses for the primary outcome revealed no difference between the association between NSAID use and the risk of our primary composite endpoint by age group (<45, 45-65, ≥65 years), sex, and histories of hypertension and hyperlipidaemia (Figure 2). However, use of intravenous NSAIDs was associated with a greater increased risk (IPTW OR 2·06, 95% CI 1·41-3·00) than use of oral NSAID formulations (IPTW OR 1·42, 95% CI 1·00-2·02; p-for-interaction 0·0486). In addition, the risk of the primary composite endpoint associated with NSAID use was greater among patients with no history of diabetes mellitus (IPTW OR 1·90, 95% CI 1·35-2·67) then among those with a history of diabetes

mellitus (IPTW OR 0·75, 95% CI 0·35-1·64; p-for-interaction 0·0151).

Findings from sensitivity analyses remained largely consistent, where the effect estimate for the primary outcome associated with NSAIDs users, as compared with non-users, was moderately increased (IPTW OR 1·87, 95% CI 1·06-3·29) when the exposure ascertainment window was extended to include the third day after hospital admission. When NSAIDs users were compared to paracetamol users, 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 outcome were generally consistent to that of our main findings, where when comparing NSAIDs users to paracetamol users, a null association was observed (IPTW OR 0·92, 95% CI 0·44-1·91) (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 hospitalised with COVID-19 in South Korea, NSAIDs users, as compared with non-users, had a 65% increased risk of the primary composite outcome of in-hospital death, ICU admission, mechanical ventilation use, or sepsis (IPTW OR 1·65, 95% CI 1·21-2·24). Moreover, the risk of cardiovascular or renal complications were further elevated in NSAIDs users (IPTW OR 1·87, 95% CI 1·25-2·80) compared to non-users. The association with the primary outcome remained largely consistent when the exposure ascertainment period used to classify exposure groups was varied (IPTW OR 1·87, 95% CI 1·06-3·29). 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 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 centres in France reported 386 cases of serious infectious complications resulting in hospitalisations 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 a particularly increased risk of cardiovascular or renal complications among NSAIDs users (IPTW OR 1·87, 95% CI 1·25-2·80) compared to non-

users. This finding is consistent to the results of two case-crossover studies conducted among patients with acute respiratory infections, which found that NSAIDs use, as compared with non-use, was associated with increased risks of ischemic stroke (aOR 2·27, 95% CI 2·00-2·58) and myocardial infarction (aOR 3·41, 95% CI 2·80-4·16).[23,24] In addition to the established risks of myocardial infarction and stroke associated with NSAIDs use in the general population,[25,26] our findings suggest an elevated risk of cardiovascular complications with NSAIDs use in COVID-19 patients. Moreover, use of NSAIDs that results in nephrotoxicity[27,28] may be more common among those seriously affected by COVID-19, as health conditions could be further exacerbated by fever and dehydration.

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 hospitalised 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. The use of this exposure definition would bias towards the null hypothesis (e.g., towards no association) as it does not account for NSAID use during hospitalization, suggesting that the observed increased risk is a conservative estimate.

Our study has several strengths. To our knowledge, this is the first population-based study conducted using all hospitalised 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 as we restricted to hospitalised patients receiving close monitoring. Second, our findings may have theoretically underestimated the association between NSAIDs users and clinical outcome due to depletion of susceptible,[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. Finally, residual confounding from unmeasured confounders (e.g. smoking history, body mass index) 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 hospitalised 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.

DISCLOSURES

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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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REFERENCES

1. World Health Organization. Coronavirus disease (COVID-19) Situation Dashboard. 2020. https://experience.arcgis.com/experience/685d0ace521648f8a5beeeee1b9125cd (accessed 27 Apr 2020).

2. Huang L, Zhang X, Zhang X, et al. Rapid asymptomatic transmission of COVID-19 during the incubation period demonstrating strong infectivity in a cluster of youngsters aged 16-23 years outside Wuhan and characteristics of young patients with COVID-19: a prospective contact-tracing study. *J Infect* 2020; **S0163-4453**(20): 30117-1.

3. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020.

4. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020; **S0092-8674**(20): 30229-4.

5. Caughey G, Clelend L, Penglis P, Gamble J, James M. Roles of cyclooxygenase (COX)-1 and COX-2 in prostanoid production by human endothelial cells: selective up-regulation of prostacyclin synthesis by COX-2. *J Immunol* 2001; **167**(5): 2831.

6. Lee S, Cheung C-Y, Nicholls J, et al. Hyperinduction of Cyclooxygenase-2-Mediated Proinflammatory Cascade: A Mechanism for the Pathogenesis of Avian Influenza H5N1 Infection. *The Journal of infectious diseases* 2008; **198**(4): 525-35.

7. Fung S-Y, Yuen K-S, Ye Z-W, Chan C-P, Jin D-Y. A Tug-Of-War Between Severe Acute Respiratory Syndrome Coronavirus 2 and Host Antiviral Defence: Lessons From Other Pathogenic Viruses. *Emerg Microbes Infect* 2020; **9**(1): 558-70.

8. Emma. UPDATE - Coronavirus: French health minister and WHO issue warning over taking anti-inflammatories. The Local France. 2020.

9. US Food and Drug Administration. FDA advises patients on use of non-steroidal

anti-inflammatory drugs (NSAIDs) for COVID-19. US Food and Drug Administration. 2020.

10. European Medicines Agency. EMA gives advice on the use of non-steroidal anti-inflammatories for COVID-19.: European Medicines Agency. 2020.

11. Therapeutic Goods Administration. No evidence to support claims ibuprofen worsens COVID-19 symptoms. Therapeutic Goods Administration. 2020.

12. World Health Organization. Scientific Brief: The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19. World Health Organization. 2020.

13. Health Insurance Review & Assessment Service, Ministry of Health and Welfare. #opendata4covid19. 2020. https://hira-covid19.net/ (accessed 15 Apr 2020).

14. Kim J, Yoon S, Kim L, Kim D. Towards Actualizing the Value Potential of Korea Health Insurance Review and Assessment (HIRA) Data as a Resource for Health Research: Strengths, Limitations, Applications, and Strategies for Optimal Use of HIRA Data. *J Korean Med Sci* 2017; **32**(5): 718-28.

15. World Health Organization. Laboratory testing for coronavirus disease 2019 (COVID-19) in suspected human cases: interim guidance. World Health Organization. 2020.

16. Ministry of Health and Welfare RoK. About COVID-19: Patient Treatment & Management. 2020. http://ncov.mohw.go.kr/baroView3.do?brdId=4&brdGubun=43 (accessed 19 May 2020).

17. Suissa S. Immortal Time Bias in Pharmaco-Epidemiology. *Am J Epidemiol* 2008; **167**(4): 492-9.

18. Desai R, Franklin J. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *BMJ* 2019; **367**: l5657.

19. Reducing bias in a propensity score matched-pair sample using greedy matching techniques. Proceedings of the Twenty-sixth Annual SAS Users Group international

conference; 2001. SAS Institute.

20. L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). Anti-inflammatoires non stéroïdiens (AINS) et complications infectieuses graves - Point d'Information. L'Agence nationale de sécurité du médicament et des produits de santé (ANSM). 2019.

21. Voiriot G, Philippot Q, Elabbadi A, Elbim C, Chalumeau M, Fartoukh M. Risks Related to the Use of Non-Steroidal Anti-Inflammatory Drugs in Community-Acquired Pneumonia in Adult and Pediatric Patients. *J Clin Med* 2019; **8**(6).

22. Little P. Non-steroidal anti-inflammatory drugs and covid-19. *BMJ* 2020.

23. Wen Y, Hsiao F, Chan K, Lin Z, Shen L, Fang C. Acute Respiratory Infection and Use of Nonsteroidal Anti-Inflammatory Drugs on Risk of Acute Myocardial Infarction: A Nationwide Case-Crossover Study. *The Journal of infectious diseases* 2017; **215**(4): 503-9.

24. Wen Y, Hsiao F, Lin Z, Fang C, Shen L. Risk of stroke associated with use of nonsteroidal anti-inflammatory drugs during acute respiratory infection episode. *Pharmacoepidemiology and drug safety* 2018; **27**(6): 645-51.

25. Schmidt M, Lamberts M, Olsen A, et al. Cardiovascular Safety of Non-Aspirin Non-Steroidal Anti-Inflammatory Drugs: Review and Position Paper by the Working Group for Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J* 2016; **37**(13): 1015-23.

26. Bhala N, Emberson J, Merhi A, et al. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet (London, England)* 2013; **382**(9894): 769-79.

27. Clavé S, Rousset-Rouvière C, Daniel L, Tsimaratos M. The Invisible Threat of Non-steroidal Anti-inflammatory Drugs for Kidneys. *Front Pediatr* 2017; **7**: 520.

28. Zhang X, Donnan P, Bell S, Guthrie B. Non-steroidal Anti-Inflammatory Drug

Induced Acute Kidney Injury in the Community Dwelling General Population and People With Chronic Kidney Disease: Systematic Review and Meta-Analysis. *BMC Nephrol* 2017; **18**(1): 256.

29. Qiao W, Wang C, Chen B, et al. Ibuprofen Attenuates Cardiac Fibrosis in Streptozotocin-Induced Diabetic Rats. *Cardiology* 2015; **131**(2): 97-106.

30. Li W, Moore M, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* 2003; **426**(6965): 450-4.

31. Kuba K, Imai Y, Rao S, et al. A Crucial Role of Angiotensin Converting Enzyme 2 (ACE2) in SARS Coronavirus-Induced Lung Injury. *Nat Med* 2005; **11**(8): 875-9.

32. Bancos S, Bernard M, Topham D, Phipps R. Ibuprofen and Other Widely Used Non-Steroidal Anti-Inflammatory Drugs Inhibit Antibody Production in Human Cells. *Cell Immunol* 2009; **258**(1): 18-28.

33. Inaoka M, Kimishima M, Takahashi R, Shiohara T. Non-steroidal Anti-Inflammatory Drugs Selectively Inhibit Cytokine Production by NK Cells and Gamma Delta T Cells. *Exp Dermatol* 2006; **15**(12): 981-90.

34. Health Insurance Review and Assessment Service. Evaluation and consideration methods of consistency between health insurance claims diagnostic codes and medical records: Health Insurance Review and Assessment Service. 2017.

35. Moride Y, Abenhaim L. Evidence of the depletion of susceptibles effect in non-experimental pharmacoepidemiologic research. *J Clin Epidemiol* 1994; **47**(7): 731-7.

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 hospitalised with COVID-19 were identified from confirmed cases of COVID-19. Patients prescribed NSAIDs while hospitalised 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, hyperlipidaemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers,

diuretics, nitrates) (c-statistics: 0·644 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, hyperlipidaemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates) (c-statistics: 0·644 for NSAIDs users versus non-users)

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

Cardiovascular or renal complications include myocardial infarction, heart failure, stroke, and acute renal failure

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

	Adult patients hospitalised with COVID-19 n=1,824 (%)	NSAIDs user n=354 (%)	Non-user n=1,470 (%)	aSD Before IPTW	aSD After IPTW
Age† (years; mean±std)	49·0 ± 19·0	54·1 ± 17·6	47·8 ± 19·1	0·43	0·03
<30	442 (24)	44 (12)	398 (27)		
30-39	191 (11)	36 (10)	155 (11)		
40-49	259 (14)	54 (15)	205 (14)		
50-59	357 (20)	72 (20)	285 (19)		
60-69	276 (15)	79 (22)	197 (13)		
70-79	197 (11)	44 (12)	153 (10)		
80-89	88 (5)	22 (6)	66 (4)		
≥90	14 (1)	3 (1)	11 (1)		
Sex†				0·01	0·02
Male	750 (41)	147 (42)	603 (41)		
Female	1,074 (59)	207 (58)	867 (59)		
Health insurance type†				0·01	0·02
National health insurance	1,661 (91)	313 (88)	1,348 (92)		
Medical aid	163 (9)	41 (12)	122 (8)		
Comorbidities‡					
Hypertension	371 (20)	98 (28)	273 (19)	0·22	0·00
Hyperlipidaemia	339 (19)	95 (27)	244 (17)	0·25	0·00
Diabetes mellitus	227 (12)	61 (17)	166 (11)	0·17	0.02
Malignancy	108 (6)	22 (6)	86 (6)	0·02	0.00
Asthma	116 (6)	34 (10)	82 (6)	0·15	0.00
COPD	291 (16)	71 (20)	220 (15)	0·13	0.00
Atherosclerosis	14 (1)	7 (2)	7 (0)	0·14	0.01
Chronic renal failure	33 (2)	5 (1)	28 (2)	0·04	0.04
Chronic liver disease	73 (4)	16 (5)	57 (4)	0·03	0.05
Rheumatoid arthritis	22 (1)	7 (2)	15 (1)	0·08	0.01
Osteoarthritis	295 (16)	87 (25)	208 (14)	0·27	0.01
Gastrointestinal conditions	1,100 (60)	252 (71)	848 (58)	0·29	0.02
Concomitant medications‡					
ACE inhibitors/ARBs	318 (17)	80 (23)	238 (16)	0·16	0.01
β-blockers	184 (10)	45 (13)	139 (9)	0·10	0.01
Calcium channel blockers	277 (15)	73 (21)	204 (14)	0·18	0.02
Diuretics	118 (7)	25 (7)	93 (6)	0·03	0.01
Nitrates	41 (2)	9 (3)	32 (2)	0·02	0.02

Note: ACE=angiotensin converting enzyme. ARB=angiotensin-receptor II blocker. aSD=absolute standardized difference. COPD=chronic obstructive pulmonary disease. IPTW=inverse probability of treatment weighted. NSAIDs=nonsteroidal anti-inflammatory drugs. std=standard deviation.

†Assessed on cohort entry (date of hospitalisation 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, hyperlipidaemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates) (*c*-statistics: 0·644 for NSAIDs users versus non-users)

Table 2. Risk of adverse clinical outcomes associated with NSAIDs users compared with non-users among adult patients hospitalised 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	53	3·6	1·00 (reference)	1·00 (reference)	1·00 (reference)
NSAIDs users	354	23	6·5	1·86 (1·12-3·08)	1·61 (0·94-2·77)	1·65 (1·21-2·24)
Cardiovascular or renal complications□						
Non-users	1,470	28	1·9	1·00 (reference)	1·00 (reference)	1·00 (reference)
NSAIDs users	354	16	4·5	2·44 (1·31-4·56)	2·32 (1·15-4·66)	1·87 (1·25-2·80)

Note: ICU=intensive care unit. IPT=inverse probability of treatment. 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, hyperlipidaemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates)

‡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, hyperlipidaemia, diabetes mellitus, asthma, chronic obstructive pulmonary disease, malignancy, atherosclerosis, chronic renal failure, chronic liver disease, rheumatoid arthritis, osteoarthritis, gastrointestinal conditions), and co-medications (angiotensin converting enzyme inhibitors, angiotensin-receptor II blockers, β-blockers, calcium channel blockers, diuretics, nitrates) (c-statistics: 0·644 for NSAIDs users versus non-users)

□Cardiovascular or renal complications include myocardial infarction, heart failure, stroke, and acute renal failure

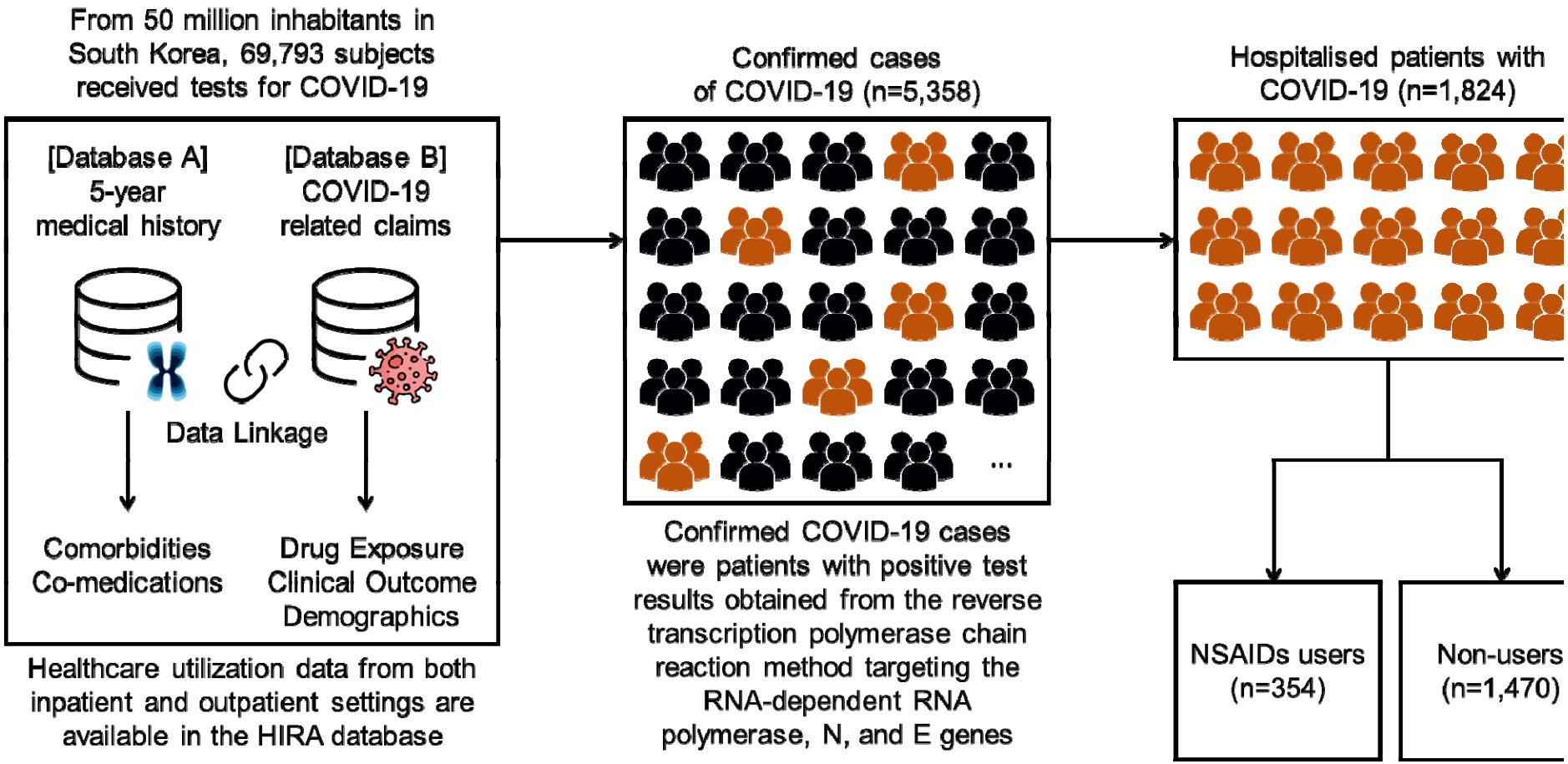

Figure 1. Nationwide population-based cohort study design

	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	3·6	1·42	(1·00-2·02)	0·0486
Intravenous formulations□	1,607	8·0	3·6	2·06	(1·41-3·00)	
Age group (years)						
<45	750	1·9	1·9	0·68	(0·30-1·55)	
45-64	649	8·3	3·0	3·46	(2·06-5·81)	0·9014
≥65	425	8·6	8·1	1·07	(0·66-1·74)	
Sex						
Male	750	8·8	5·6	1·14	(0·75-1·74)	0·0605
Female	1,074	4·8	2·2	2·54	(1·58-4·09)	
History of hypertension						
Yes	371	10·2	8·1	1·15	(0·69-1·92)	0·1966
No	1,453	5·1	2·6	2·02	(1·37-3·00)	
History of hyperlipidaemia						
Yes	339	8·4	4·1	1·94	(1·00-3·79)	0·4552
No	1,485	5·8	3·5	1·57	(1·11-2·23)	
History of diabetes mellitus						
Yes	227	6·6	4·9	0·75	(0·35-1·64)	0·0151
No	1,597	6·8	3·2	1·90	(1·35-2·67)	

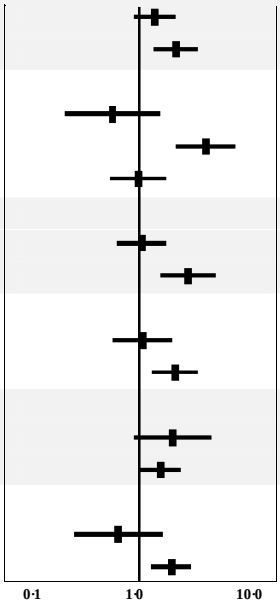

Figure 2. Forest plot summarizing the risk of primary outcome* associated with NSAIDs when stratified for age, sex, formulation of NSAIDs and history of comorbidities

	Number of Patients	Cumulative incidence (%)		IPT weighted odds ratio† (95% confidence interval)	
		NSAIDs	Reference		
All-cause death, ICU admission, mechanical ventilation use, sepsis					
Hospitalised COVID-19 patients					
NSAIDs users vs. non-users	1,824	6·7	3·6	1·65	(1·21-2·24)
NSAIDs users vs. paracetamol users	967	0·0	4·1	NA	
Varied exposure ascertainment window					
NSAIDs users vs. non-users	1,824	1·4	1·0	1·87	(1·06-3·29)
Cardiovascular or renal complications□					
Hospitalised COVID-19 patients					
NSAIDs users vs. non-users	1,824	4·5	1·9	1·87	(1·25-2·80)
NSAIDs users vs. paracetamol users	967	4·8	1·4	0·92	(0·44-1·91)
Varied exposure ascertainment window					
NSAIDs users vs. non-users	1,824	1·7	0·5	1·66	(0·78-3·50)

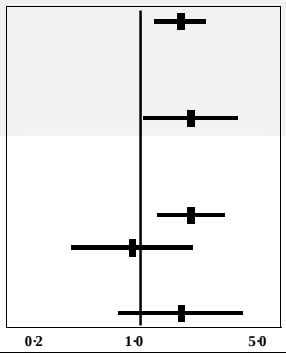

Figure 3. Forest plot summarizing the results of sensitivity analyses comparing NSAIDs to paracetamol to minimize confounding by indication, and redefining the exposure ascertainment window to evaluate exposure misclassification