Original Article

The association between immunosuppressants use and COVID-19 adverse outcomes: national COVID-19 cohort in South Korea

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Background: There is uncertainty of the effect of immunosuppression, including corticosteroids, before COVID-19 infection on COVID-19 outcomes. The aim of this study was to investigate the relationship between prehospitalization immunosuppressants use (exposure) and COVID-19 patient outcomes.

Methods: We conducted a population-based retrospective cohort study using a nationwide healthcare claims database of South Korea as of May 15, 2020. Confirmed COVID-19 infection in hospitalized individuals aged 40 years or older were included for analysis. We defined exposure variable by using inpatient and outpatient prescription records of immunosuppressants from the database. Our primary endpoint was a composite endpoint of all-cause death, intensive care unit (ICU) admission, and mechanical ventilation use. Inverse probability of treatment weighting (IPTW)-adjusted logistic regression analyses were used, to estimate odds ratio (OR) and 95% confidence intervals (CI), comparing immunosuppressants users and non-users.

Results: We identified 4,349 patients, for which 1,356 were immunosuppressants users and 2,993 were non-users. Patients who used immunosuppressants were at increased odds of the primary endpoint of all-cause death, ICU admission and mechanical ventilation use (IPTW OR =1.32; 95% CI: 1.06–1.63), driven by higher odds of all-cause mortality (IPTW OR =1.63; 95% CI: 1.21–2.26). Patients who used corticosteroids (n=1,340) were at increased odds of the primary endpoint (IPTW OR =1.33; 95% CI: 1.07–1.64).

Conclusions: Immunosuppressant use was associated with worse outcomes among COVID-19 patients. These findings support the latest guidelines from the CDC that people on immunosuppressants are at high risk of severe COVID-19 and that immunocompromised people may benefit from booster COVID-19 vaccinations.

Keywords: Immunosuppressants; COVID-19

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Introduction

In December 2019, an outbreak of a novel coronavirus was reported in Wuhan, China, which was later named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the Coronavirus Study Group of the International Committee on Taxonomy of Viruses (1,2). The SARS-CoV-2 virus rapidly spread around the world, causing the COVID-19 disease in infected patients; on March 12, 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic (3).

As the scientific community raced to find possible active agents for treatment and cure of COVID-19, supportive care therapies were developed and tested (3,4). Immunosuppressants, specifically corticosteroids, were employed, as it could help COVID-19 patients by mitigating cytokine storms (5). However, there are concerns that it can worsen viral shedding and, therefore, increase mortality due to COVID-19 (6).

The current WHO clinical guidelines, as of November 2021, provides a strong recommendation for corticosteroids use in severe and critical patients with COVID-19 infection (7). However, in patients with mild to moderate COVID-19 infections who do not require oxygen support, corticosteroid use was associated with a trend towards higher mortality, although not statistically significant in the RECOVERY trial (17.8% *vs.* 14.0%; RR =1.19; 95% CI: 0.92–1.55) (8). As a result, there is uncertainty of the effect of immunosuppression, including corticosteroids, started before COVID-19 infection, on COVID-19 outcomes since patients on immunosuppression could have a wide spectrum of COVID-19 disease presentations, from asymptomatic to critical COVID-19 infections. It is possible that patients with non-severe COVID-19 infections could receive harm from baseline corticosteroids use.

The aim of this study was to investigate the relationship between immunosuppressants use, including corticosteroids, and COVID-19 patient outcomes. We present the following article in accordance with the STROBE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-3465/rc).

Methods

Data source and study population

The Health Insurance Review and Assessment Service (HIRA) of South Korea is the sole nationwide government agency that operates a fee-for-service reimbursement system, which covers 98% of the Korean population. Its administrative claims database includes the beneficiary's sociodemographic characteristics, healthcare utilization history, diagnosis results (International Classification of Diseases 10th Revision, ICD-10), as well as prescription from both inpatient and outpatient settings. On March 27, 2020, the #OpenData4COVID19 project by the Ministry of Health and Welfare (MoHW) of Korea released a patient-level, deidentified COVID-19 data based on the HIRA insurance claims database, which is the first nationwide dataset of COVID-19 patients. The HIRA COVID-19 database included data for all individuals who received a reverse transcription-polymerase chain reaction (RT-PCR) test for COVID-19 as of May 15, 2020, which was linked to their claims data for the previous 3 years.

The HIRA data consisted of 234,427 consecutive individuals who were tested for SARS-CoV-2 between January 1, 2020 and May 15, 2020. In total, 7,590 were identified as positive for COVID-19, designated by the coding in the #OpenData4COVID19 project (Table S1). Among them, 4,610 individuals were aged 40 years or older. We excluded those who were less than 40 years old, as it is less likely that these younger individuals would experience severe COVID-19 outcomes. For precise outcome measurements, we further restricted the analysis to individuals who were hospitalized for COVID-19, resulting in 4,349 individuals in our study cohort (*Figure 1*). The cohort entry date was defined as the admission date of COVID-19 hospitalization. In South Korea, individuals who were confirmed to be positive for COVID-19 during this time interval required hospitalization until full recovery, defined by the cessation of fever without medication use and two negative test results within 24 hours (9). However, there were a small number of confirmed COVID-19 patients who were not hospitalized due to the temporal shortage of health facilities.

This study was approved by the Human Investigation Review Board of Public Institutional Bioethics Committee designated by the MOHW, which waived the requirement of informed consent due to retrospective study design and anonymity of the HIRA database (IRB #P01-2020-1262-001). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Endpoints

Our primary endpoint was a composite of all-cause death, intensive care unit (ICU) admission, and mechanical

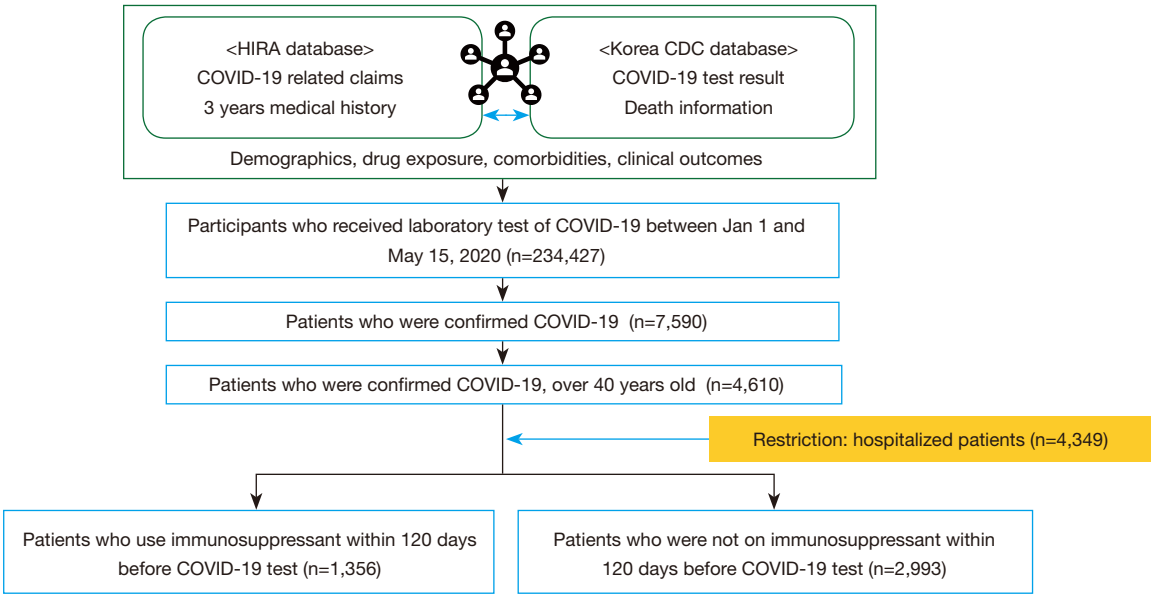

Figure 1 Population-based cohort study design using the HIRA and KDCA database of South Korea. HIRA, Health Insurance Review and Assessment Service; CDC, Centers for Disease Control and Prevention; KDCA, Korean Disease Control and Prevention Agency.

ventilation use. As secondary endpoints, we evaluated the individual components of the primary composite endpoint. In-hospital ICD-10 diagnostic codes and the national procedure codes were used to define the outcomes (Table S1). We measured these study outcomes between the cohort entry date through the end of follow-up (discharge, or end of study).

Exposures

We classified individuals who had inpatient and outpatient prescription records of immunosuppressants at least once within 120 days prior to the cohort entry (ascertainment window: −120 to 0 d) as immunosuppressants users. Other individuals were defined as non-users. Among immunosuppressants users, corticosteroids users were assessed as a separate exposure group and compared to the non-immunosuppressants-users in sensitivity analysis. Our definition follows an intention-to-treat approach. Immunosuppressants were identified by the anatomical therapeutic chemical classification codes (ATC) (Table S1).

Statistical analysis

We described baseline characteristics of immunosuppressants users and non-users as counts with percentages (for categorical variables) and means with standard deviations (for continuous variables). We calculated the absolute standard difference (aSD) to measure distributional imbalances between two groups for each variable. Empirically, aSD ≤0.1 is preferred for balance between groups.

We conducted outcome analysis by estimating odds ratios (ORs) using a logistic regression analysis where each individual was weighted by the inverse probability of treatment weight (IPTW) (10,11) To be specific, we estimated the propensity score (PS), the probability for an individual to receive immunosuppressants, using logistic regression, which included age in years, square of age, sex, and type of health insurance at cohort entry, as well as 20 pre-exposure comorbidities and 12 pre-exposure co-medications (Appendix 1) as explanatory variables. We defined comorbidity variables using diagnostic codes and co-medications (Table S1). Then, the IPTW, 1/PS to immunosuppressants users and 1/(1-PS) to non-users, was assigned to each individual. The effect of immunosuppressants use on primary and secondary endpoints was then estimated using weighted univariable logistic regression. We reported the estimated OR and the 95% confidence intervals (CI). In addition, for comparison purposes, we fitted unweighted univariate logistic regression models and unweighted multivariate logistic regression models, adjusting for age, sex, insurance type, history of

diabetes and history of hypertension.

We conducted a subgroup analysis for the risk of the primary endpoint. We considered stratifications by the following: (I) sex; (II) age, classified into groups with age <65 and ≥65 years; (III) the history of autoimmune disease, cancer and HIV, and (IV) the history of autoimmune disease. For each subgroup analysis, we conducted a trivariable IPTW-weighted logistic regression that includes the exposure (immunosuppressants use), stratification variable and the interaction of those two. We obtained the P value of the interaction term (P for interaction) for each stratification to examine the effect modification.

We checked the sensitivity of results against the scope of working definitions. First, we redefined the study population by those who were aged ≥40 years and confirmed positive, which relaxed the restriction of hospitalization. Second, we also considered an exclusion for individuals who used immunosuppressants for a short period but stopped prior to hospitalization, and thus we narrowed down the window of ascertaining exposure from 120 to 90 days. Lastly, we narrowed down the definition of the exposure group from immunosuppressants users to corticosteroids users. For each change of the settings, we repeated our main analysis.

To examine the sensitivity of results against the selection of statistical tools, the following alternative approaches were considered. First, we excluded subjects with extreme PS values, that is, PS <0.025 or PS >0.975 (IPTW with trimming). Second, we additionally included the fitted PSs to other covariates in our unweighted multivariable logistic regression model (outcome adjustment model). Third, we used the standardized mortality ratio (SMR) weight, defined as 1 for immunosuppressants users and PS/(1-PS) for non-users, in place of IPTW in our main model (SMR weighting). Finally, we considered a PS matching approach (PS matching). All statistical analyses were conducted using R 3.5.2. P values less than 0.05 were considered statistically significant.

Results

A total of 4,349 patients were included in the main analysis, for which 1,356 (31%) used immunosuppressants within 120 days of hospitalization for COVID-19. Users of immunosuppressants were older, and a larger proportion had hyperlipidemia and hypertension. A larger proportion of immunosuppressants users also used acetaminophen, systematic antibiotics, and NSAIDs (*Table 1*).

Patients who used immunosuppressants were at increased odds of the primary endpoint of all-cause death, ICU admission and mechanical ventilation use (IPTW OR =1.32; 95% CI: 1.06–1.63). When assessing the component outcomes individually, immunosuppressants users were at higher odds of all-cause mortality—IPTW OR =1.63; 95% CI: 1.21–2.26 (*Table 2*).

There existed no effect modification by age, sex, history of autoimmune diseases, cancer and HIV, and history of autoimmune disease (*Table 3*). The results of the sensitivity analysis remained consistent with the main analysis (Tables S2-S5). When redefining the study population to include all confirmed patients with COVID-19 (IPTW OR =1.33; 95% CI: 1.07–1.65), changing the exposure ascertainment window to 90 days (IPTW OR =1.43; 95% CI: 1.15–1.77), and applying other statistical methods [IPTW with trimming (IPTW OR =1.32; 95% CI: 1.06–1.63), outcome adjustment model (OR =1.29; 95% CI: 1.05–1.58), SMR weighting (OR =1.30; 95% CI: 1.03–1.64), and PS matching (OR =1.32; 95% CI: 1.07–1.64)], immunosuppressants use was associated with an increased odd of the primary endpoint consistent with the main analysis (Table S2).

When assessing the component outcomes individually, immunosuppressants users were at higher odds of all-cause mortality while redefining the study population to include all confirmed patients with COVID-19 (IPTW OR =1.67; 95% CI: 1.23–2.26), changing the exposure ascertainment window to 90 days (IPTW OR =1.85; 95% CI: 1.36–2.52), and applying other statistical methods [IPTW with trimming (IPTW OR =1.65; 95% CI: 1.21–2.26), outcome adjustment model (OR =1.59; 95% CI: 1.18–2.13), SMR weighting (OR =1.51; 95% CI: 1.05–2.16), PS matching (OR =1.57; 95% CI: 1.14–2.17)] (Tables S3-S5).

Among 1,356 immunosuppressants users in the main analysis, 1,340 (98.8%) were corticosteroid users. They were at increased odds of the primary endpoint (IPTW OR =1.33; 95% CI: 1.07–1.64) (Table S2). When assessing the component outcomes individually, corticosteroids users were only at higher odds of all-cause mortality—IPTW OR =1.67; 95% CI: 1.22–2.76 (Tables S3-S5), which is consistent with the analysis for immunosuppressants use.

Discussion

This study reports on a nationwide cohort of South Korean COVID-19 patients. This dataset was completely enumerated and statistically controlled for confounding using PSs. The results suggest that patients administered immunosuppressants were at increased odds of all-cause

Table 1 Baseline sociodemographic and clinical characteristics of adult patients (≥40 years old) with COVID-19 in South Korea, as of May 15, 2020

Characteristic	Before IPTW			After IPTW[§]		
	User* (n=1,356)	Non-user (n=2,993)	aSD	User* (n=4,349)	Non-user (n=4,360)	aSD
Age (years; mean ± SD)	61.4±12.0	59.7±12.7	0.14	60.2±12.7	60.2±12.5	0.00
40–49	229 (16.9)	679 (22.7)	0.15	954 (21.9)	901 (20.7)	0.03
50–59	424 (31.3)	983 (32.8)	0.03	1,406 (32.3)	1,404 (32.2)	0.00
60–69	371 (27.4)	692 (23.1)	0.10	1,010 (23.2)	1,068 (24.5)	0.03
70–79	205 (15.1)	366 (12.2)	0.08	563 (13.0)	595 (13.6)	0.02
80–89	113 (8.3)	220 (7.4)	0.04	339 (7.8)	319 (7.3)	0.02
90+	14 (1.0)	53 (1.8)	0.06	77 (1.8)	72 (1.7)	0.01
Sex						
Male	483 (35.6)	1,126 (37.6)	0.04	1,591 (36.6)	1,600 (36.7)	0.00
Female	873 (64.4)	1,867 (62.4)	0.04	2,759 (63.4)	2,760 (63.3)	0.00
Health insurance type						
Medical insurance	1,192 (87.9)	2,639 (88.2)	0.01	3,846 (88.4)	3,848 (88.3)	0.01
Medical aid	164 (12.1)	354 (11.8)	0.01	503 (11.6)	512 (11.7)	0.01
Comorbidities						
Arrhythmias	57 (4.2)	62 (2.1)	0.12	118 (2.7)	117 (2.7)	0.00
Asthma	208 (15.3)	239 (8.0)	0.23	441 (10.1)	450 (10.3)	0.01
Atrial fibrillation	32 (2.4)	43 (1.4)	0.07	74 (1.7)	79 (1.8)	0.01
Autoimmune disease	177 (13.1)	75 (2.5)	0.40	255 (5.9)	267 (6.1)	0.01
Chronic lung disease	525 (38.7)	901 (30.1)	0.18	1,459 (33.6)	1,457 (33.4)	0.00
Coronary artery disease	134 (9.9)	192 (6.4)	0.13	331 (7.6)	336 (7.7)	0.00
Dementia	80 (5.9)	234 (7.8)	0.08	321 (7.4)	319 (7.3)	0.00
Diabetes mellitus	275 (20.3)	562 (18.8)	0.04	853 (19.6)	844 (19.4)	0.01
Heart failure	71 (5.2)	117 (3.9)	0.06	199 (4.6)	181 (4.1)	0.02
Hyperlipidemia	516 (38.1)	910 (30.4)	0.16	1,432 (32.9)	1,433 (32.9)	0.00
Hypertension	407 (30.0)	742 (24.8)	0.12	1,133 (26.1)	1,142 (26.2)	0.00
Immunosuppression[#]	159 (11.7)	219 (7.3)	0.15	389 (8.9)	383 (8.8)	0.01
Kidney disease	22 (1.6)	37 (1.2)	0.03	51 (1.2)	55 (1.3)	0.01
Liver disease	67 (4.9)	129 (4.3)	0.03	196 (4.5)	192 (4.4)	0.00
Other cerebrovascular diseases	98 (7.2)	150 (5.0)	0.09	238 (5.5)	248 (5.7)	0.01
Peripheral vascular disease	148 (10.9)	246 (8.2)	0.09	385 (8.9)	390 (8.9)	0.00
Pneumonia including tuberculosis	129 (9.5)	182 (6.1)	0.13	311 (7.1)	308 (7.1)	0.00
Psychiatric disorders	408 (30.1)	706 (23.6)	0.15	1,082 (24.9)	1,111 (25.5)	0.01

Table 1 (*continued*)

Table 1 (*continued*)

Characteristic	Before IPTW			After IPTW[§]		
	User* (n=1,356)	Non-user (n=2,993)	aSD	User* (n=4,349)	Non-user (n=4,360)	aSD
Stroke or TIA	105 (7.7)	198 (6.6)	0.04	287 (6.6)	299 (6.9)	0.01
Thromboembolism	71 (5.2)	161 (5.4)	0.01	225 (5.2)	229 (5.3)	0.00
Medications						
Acetaminophen	409 (30.2)	539 (18.0)	0.29	960 (22.1)	960 (22.0)	0.00
Antibacterials	628 (46.3)	994 (33.2)	0.27	1,627 (37.4)	1,641 (37.6)	0.00
Anticoagulants	50 (3.7)	58 (1.9)	0.11	113 (2.6)	112 (2.6)	0.00
Antidementia	100 (7.4)	248 (8.3)	0.03	334 (7.7)	341 (7.8)	0.01
Antidepressants	159 (11.7)	255 (8.5)	0.11	429 (9.9)	416 (9.5)	0.01
Antidiabetics	199 (14.7)	415 (13.9)	0.02	620 (14.3)	626 (14.4)	0.00
Antiplatelets	220 (16.2)	359 (12.0)	0.12	566 (13.0)	581 (13.3)	0.01
Antipsychotics	186 (13.7)	422 (14.1)	0.01	573 (13.2)	607 (13.9)	0.02
Antivirals	56 (4.1)	82 (2.7)	0.08	136 (3.1)	137 (3.1)	0.00
Anxiolytics	264 (19.5)	439 (14.7)	0.13	698 (16.1)	711 (16.3)	0.01
Lipid lowering agents including statin	392 (28.9)	673 (22.5)	0.15	1,064 (24.5)	1,083 (24.8)	0.01
NSAIDs	844 (62.2)	1,294 (43.2)	0.39	2,138 (49.2)	2,152 (49.4)	0.00

Mean and standard deviation were reported for continuous variables. Frequency and percentage were reported for categorical variables. Users: immunosuppressants within 120 days. *, patients prescribed within 120 days prior to cohort entry were regarded as immunosuppressants users, and otherwise patients were defined as non-users; [§], weighted cohort using the IPTW; [#], immunosuppression includes HIV, history of organ transplant, transplant rejection, noninfectious enteritis and colitis, ulcerative colitis, and Crohn's disease. IPTW, inverse probability of treatment weighting; aSD, absolute standardized difference; TIA, transient cerebral ischemic attack; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2 OR of adverse clinical outcomes associated with immunosuppressants use compared with non-users patients with COVID-19

Outcomes	Cumulative incidence (%)		Unadjusted*		Adjusted[§]		IPTW adjusted[#]	
	Non-user	User	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Composite primary outcome	311 (10.4)	185 (13.6)	1.36 (1.12–1.66)	0.002	1.31 (1.07–1.60)	0.01	1.32 (1.06–1.63)	0.01
All-cause death	126 (4.2)	91 (6.7)	1.64 (1.24–2.16)	0.001	1.68 (1.23–2.30)	0.001	1.63 (1.21–2.26)	<0.01
Mechanical ventilation use	72 (2.4)	51 (3.8)	1.59 (1.10–2.28)	0.01	1.48 (1.02–2.14)	0.004	1.12 (0.76–1.65)	0.57
ICU admission	212 (7.1)	118 (8.7)	1.25 (0.99–1.58)	0.06	1.22 (0.96–1.54)	0.10	1.11 (0.87–1.44)	0.38

*, unweighted univariable logistic regression model; [§], unweighted multivariable logistic regression model adjusted for age, sex, insurance type, history of diabetes and history of hypertension; [#], IPTW-weighted univariable logistic model. OR, odds ratio; IPTW, inverse probability of treatment weighting; CI, confidence interval; ICU, intensive care unit.

mortality, mechanical ventilation and ICU admission.

Our results support the guideline from the Center for Disease Control and Prevention in the United States, classifying patients with prior use of corticosteroids and other immunosuppressive medication as a high risk group of patients for severe COVID-19 infection (12). In support of this assertion are papers by Brenner *et al.* (13), Michelena *et al.* (14), Di Giorgio *et al.* (15), Marlais *et al.* (16) and

Table 3 Forest plot summarizing the OR of primary endpoint associated with immunosuppressants use compared with non-users when stratified for age, sex, history of autoimmune disease, cancer and HIV, and history of autoimmune disease

Characteristic	N	Cumulative incidence (%)		IPTW adjusted OR	
		Non-user	User	OR (95% CI)	P value
Total	4,349	311 (10.4)	185 (13.6)	1.32 (1.06–1.63)	0.01
Age group (years)				P for interaction =0.24	
<65	2,944	132 (6.4)	66 (7.5)	1.15 (0.83–1.59)	0.39
≥65	1,405	179 (19.4)	119 (24.7)	1.49 (1.21–2.00)	<0.01
Sex				P for interaction =0.23	
Male	1,609	145 (12.9)	93 (19.3)	1.48 (1.08–2.01)	0.01
Female	2,740	166 (8.9)	92 (10.5)	1.14 (0.85–1.52)	0.39
History of autoimmune disease, cancer and HIV				P for interaction =0.95	
No	3,883	284 (10.3)	143 (12.8)	1.25 (0.99–1.58)	0.05
Yes	466	27 (12.1)	42 (17.4)	1.28 (0.72–2.26)	0.39
History of autoimmune disease				P for interaction =0.99	
No	4,097	303 (10.4)	161 (13.7)	1.28 (1.02–1.59)	0.03
Yes	252	8 (10.7)	75 (13.6)	1.28 (0.52–3.13)	0.58

OR, odds ratio; IPTW, inverse probability of treatment weighting; CI, confidence interval.

Montero-Escribano *et al.* (17).

Notably, corticosteroids are known to reduce mortality, mechanical ventilation and duration of hospital stay relative to standard-of-care in patients with severe and critical COVID-19, as noted by the living systematic review and meta-analysis by Siemieniuk *et al.* (18) and WHO clinical guideline (7). Andersen *et al.* (19) reported contrary results to our paper, in that adverse outcomes were not associated with immunosuppressants use before COVID-19. However, their paper reported on a sicker patient population who might have received benefit from corticosteroids, whereas our analysis reports on a nationwide cohort of all patients admitted for COVID-19 to South Korean hospitals, which include patients with non-severe COVID-19 infection. In South Korea in the time interval assessed, typically all COVID-19 patients were admitted to hospitals, even if they were asymptomatic or had mild symptoms, in an attempt to limit spread of the COVID-19 infection. As a result, our study provides a more complete picture with all spectrum of COVID-19 patients, from asymptomatic to critical COVID-19. As corticosteroids use is beneficial in patients with severe to critical stages in COVID-19 infection and could possibly be harmful in patients with non-severe COVID-19 infection, as seen from RECOVERY trial (8), it comes as no surprise that our study results show increased odds of primary endpoint or mortality in immunosuppressants or corticosteroid users given that most COVID-19 infections are non-severe (20).

While not directly assessed, our study results support the receipt of booster COVID-19 vaccinations for immunocompromised people taking immunosuppressant medications. These findings also urge caution around blanket-continuation of immunosuppressants for COVID-19 patients who were on immunosuppressants prior to COVID-19 diagnosis; patients might need to be assessed on a per-case basis, weighing the risk of adverse COVID-19 outcomes with the benefits of continuing immunosuppressants. Consideration may need to be given to lowering the degree of immunosuppression if a patient was on immunosuppressants and has a non-severe COVID-19 infection, although establishing a dose response to immunosuppressants was not possible with the current cohort dataset.

There are several notable strengths of this study. As South Korea used a strict nationwide patient management system for COVID-19, the use of a population-based cohort mitigated any potential sampling bias issue; 94.3% of all confirmed COVID-19 patients ≥40 years of age (n=4,610) were hospitalized (n=4,349) regardless of presence

of symptom or severity of disease in our study. There could be very little chance of outcome misclassification since outcomes such as all-cause death and outcomes defined from procedures codes (i.e., ICU admissions and mechanical ventilation use) are unlikely to be misclassified in the main analysis restricted to hospitalized COVID-19 patients, given the cross-referencing of these records with national death records and reimbursement review processes, respectively. Consistent results across rigorous statistical methods, including IPTW, PS matching, SMR and thorough sensitivity analyses, suggest our results are robust. Additionally, including chronic co-medications as confounders could have mitigated healthy user bias.

This study was also not without limitations. We do not have data regarding the severity of COVID-19 at the time of COVID-19 diagnosis, which is a limitation of using claims data. In addition, there may still exist residual confounding by confounders that are typically not captured in a claims database (e.g., body mass index, baseline blood pressure, laboratory test values). Also, our result is limited by the observational nature of our study design. At last but not least, the involvement of interstitial lung disease (ILD), an important aggravating factor of COVID-19 patients, could not be adjusted in this study because the frequency of ILD in this dataset was rare.

In conclusion, our study of a large nationwide cohort of hospitalized COVID-19 patients in South Korea finds that use of immunosuppressants or corticosteroids increases the odds of all-cause mortality, mechanical ventilation and ICU admissions. These findings lend credence to the latest guidelines from the CDC that people on immunosuppressants are at high risk of severe COVID-19 and could benefit from booster COVID-19 vaccinations.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3465/rc

Data Sharing Statement: Available at https://apm.amegroups.com/article/view/10.21037/apm-21-3465/dss

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Human Investigation Review Board of Public Institutional Bioethics Committee designated by the MoHW, which waived the requirement of informed consent due to retrospective study design and anonymity of the HIRA database (IRB #P01-2020-1262-001). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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