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# Impact of Antidiabetic Drugs on Clinical Outcomes of COVID-19: A Nationwide Population-Based Study

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**Background:** Inconsistent results have been reported regarding the association between the use of antidiabetic drugs and the clinical outcomes of coronavirus disease 2019 (COVID-19). This study aimed to investigate the effect of antidiabetic drugs on COVID-19 outcomes in patients with diabetes using data from the National Health Insurance Service (NHIS) in South Korea.

**Methods:** We analyzed the NHIS data of patients aged ≥20 years who tested positive for COVID-19 and were taking antidiabetic drugs between December 2019 and June 2020. Multiple logistic regression analysis was performed to analyze the clinical outcomes of COVID-19 based on the use of antidiabetic drugs.

**Results:** A total of 556 patients taking antidiabetic drugs tested positive for COVID-19, including 271 male (48.7%), most of whom were in their sixties. Of all patients, 433 (77.9%) were hospitalized, 119 (21.4%) received oxygen treatment, 87 (15.6%) were admitted to the intensive care unit, 31 (5.6%) required mechanical ventilation, and 61 (11.0%) died. Metformin was significantly associated with the lower risks of mechanical ventilation (odds ratio [OR], 0.281; 95% confidence interval [CI], 0.109 to 0.720; $P$=0.008), and death (OR, 0.395; 95% CI, 0.182 to 0.854; $P$=0.018). Dipeptidylpeptidase-4 inhibitor (DPP-4i) were significantly associated with the lower risks of oxygen treatment (OR, 0.565; 95% CI, 0.356 to 0.895; $P$=0.015) and death (OR, 0.454; 95% CI, 0.217 to 0.949; $P$=0.036). Sulfonylurea was significantly associated with the higher risk of mechanical ventilation (OR, 2.579; 95% CI, 1.004 to 6.626; $P$=0.049).

**Conclusion:** In patients with diabetes and COVID-19, metformin exhibited reduced risks of mechanical ventilation and death, DPP-4i was linked with lower risks of oxygen treatment and death, while sulfonylurea was related to the increased risk of mechanical ventilation.

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## INTRODUCTION

Diabetes mellitus is known to be associated with the severity of coronavirus disease 2019 (COVID-19) along with factors such as old age, male gender, obesity, and comorbidities like hypertension, chronic obstructive pulmonary disease (COPD), and chronic liver disease [1,2]. Previous studies have reported that patients with diabetes who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are at a higher risk of requiring mechanical ventilation, intensive care unit (ICU) admission, and death than those without diabetes [3-8].

Considering the association between diabetes and COVID-19 severity, as well as the common occurrence of diabetes in COVID-19 patients [9], the relationship between antidiabetic drugs and COVID-19 severity has been investigated. In the Coronavirus SARS-CoV-2 and Diabetes Outcomes (CORONADO) study, an observational study conducted across 53 French medical centers for 3 weeks involving 1,317 hospitalized COVID-19 patients with diabetes, the use of different antidiabetic drugs, including metformin, sulfonylurea, meglitinides, dipeptidylpeptidase-4 inhibitors (DPP-4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), and insulin, was not associated with an increased risk of the composite endpoint (tracheal intubation for mechanical ventilation and death within 7 days of admission) [10]. However, other studies have reported conflicting results regarding the impact of antidiabetic drugs on the clinical outcomes of patients with diabetes and COVID-19. Some studies have indicated potential benefits, including reduced ICU admissions and mortality, whereas others have suggested no impact or increased disease severity [11-14]. Furthermore, even randomized controlled trials (RCTs) involving metformin or DPP-4i have not shown consistent results regarding the association between the use of antidiabetic drugs and disease severity in COVID-19 [15-19]. This highlights the need for further research on the impact of antidiabetic drugs on the clinical outcomes of COVID-19 in the general diabetic population.

Therefore, we aimed to investigate the association between the use of antidiabetic drugs and clinical outcomes of COVID-19 in patients with diabetes. Especially, we sought to analyze the impact of the most commonly used antidiabetic drugs in Korea, such as metformin, DPP-4i, and sulfonylurea [20]. This study was conducted using data from the National Health Insurance Service (NHIS) of South Korea, which is a nationwide population-based dataset.

## METHODS

### Study population

Using data from the NHIS in South Korea, patients with diabetes who tested positive for COVID-19 between December 2019 and June 2020 were analyzed. The study period was set at approximately 6 months from December 2019, when patients with COVID-19 were first identified in Wuhan, China. The NHIS is a national healthcare program covering the entire South Korean population. The NHIS data included information on the subjects' test results, prescription drugs, and diagnostic codes expressed as the Korean Classification of Disease seventh revision (KCD-7) and a modified version of the International Classification of Disease (ICD-10). Among subjects ≥20 years for whom claim data was available between December 2019 and June 2020, patients with diabetes who tested positive for COVID-19 were analyzed, regardless of hospitalization status. Patients who had received at least one of the following diabetes medications was defined as patients with diabetes: metformin, DPP-4i, sulfonylurea, sodium-glucose cotransporter-2 inhibitors, thiazolidinediones, GLP-1RAs, alpha-glucosidase inhibitors, meglitinides, or insulin, within the year before the COVID-19 diagnosis. Drug combinations were not considered. The characteristics of the subjects at the time of the COVID-19 diagnosis were analyzed and their clinical outcomes were compared.

### COVID-19 tests

COVID-19 tests were conducted using diagnostic kits or real-time polymerase chain reaction on nasopharyngeal swabs or sputum samples. The South Korean government implemented screening tests for COVID-19 in the following cases: (1) patient exhibiting fever or respiratory symptoms within 14 days of contact with a confirmed COVID-19 patient during their symptom-exhibiting period; (2) a physician suspecting COVID-19 due to reasons such as pneumonia of unknown etiology; (3) patient developing fever or respiratory symptoms within 14 days after entering South Korea from abroad; and (4) individuals with an epidemiological link to a domestic COVID-19 cluster experiencing fever or respiratory symptoms within 14 days. Fever was

defined as a temperature ≥37.5°C, and respiratory symptoms were defined as symptoms like coughing or shortness of breath.

### Definitions of disease

Comorbidities were defined using diagnostic codes. Hypertension was defined by diagnostic codes I10–I13 and I15; dyslipidemia, E78; asthma, J45 and 46; COPD, J41–J44; ischemic heart disease, I20–I25; stroke, I121–I122; cancer, C; end-stage renal disease, V001, V003, and V005; and diabetic retinopathy, H360. Blood test findings were established using the most recent medical reports from 2017. Low income was defined as being in the bottom 20% of income or receiving medical aid and smoking status (never and smoker) was determined based on a self-reported questionnaire. The Charlson comorbidity index (CCI) score was calculated using the diagnosis code corresponding to the disease [21]. The history of drug use for angiotensin-converting enzyme inhibitor (ACEi), angiotensin II receptor blocker (ARB), steroids, and immunosuppressants was defined as the history of drug prescription within 1 month before the COVID-19 diagnosis. Hospitalization, oxygen treatment, ICU admission, ventilator use, and mortality were evaluated as outcomes. Hospitalization, oxygen treatment, ICU admission, and ventilator use were defined through treatment codes, and mortality through treatment outcome classification codes.

### Statistical analysis

Continuous variables are expressed as mean±standard deviation, and categorical variables are presented as numbers and proportions. *T* tests and chi-square tests were used to compare the baseline characteristics and clinical outcomes between patients who did and did not use antidiabetic drugs. The association between the use of antidiabetic drugs and clinical outcomes was analyzed using multiple logistic regression with covariates such as sex, age, region, smoking status, low income, body mass index (BMI), drugs being used, and CCI score. *P* value <0.05 was considered statistically significant in all analyses. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

### Ethical statement

This study was approved by the Institutional Review Board (IRB) of the Kangbuk Samsung Hospital (IRB no. KBSMC 2020-04-040). Patient data were de-identified, and according to the Bioethics and Safety Act in South Korea, consent from the study participants was waived.

## RESULTS

### Baseline characteristics

After excluding subjects with missing claim data from December 2019 to June 2020, 115,235 individuals were analyzed. Among them, 17,270 patients were taking at least one antidiabetic drugs, and among patients taking antidiabetic drugs, 556 patients tested positive for COVID-19 (Fig. 1). Of the 556 patients, 271 (48.7%) were male, most of whom were in their sixties (202 patients [36.3%]) (Table 1). The majority of patients (65.8%) were residents of Daegu. The average BMI was 25.3±3.6 kg/m². Among these patients, 461 (82.9%) were on metformin, 358 (64.4%) on DPP-4i, and 205 (36.9%) on sulfonylureas. A total of 172 patients (30.9%) were receiving insulin therapy.

When patients were divided based on the use of metformin, DPP-4i, and sulfonylurea, there were no significant differences observed in sex and BMI. Age distribution showed no significant differences based on metformin and sulfonylurea usage, but significant age distribution differences were noted with DPP-4i use. Glucose levels were significantly higher in all three drug usage groups compared to the non-usage groups. While there were no significant differences in CCI scores based on metformin and DPP-4i usage, the sulfonylurea group exhibited significantly higher CCI scores (5.0±2.5 vs. 4.4±2.4, *P*=0.002). The proportion of patients using insulin and steroids was significantly lower in the metformin and DPP-4i groups, whereas there were no significant differences in patients using ACEi, ARB, or immunosuppressants between those using each drug and those not using them.

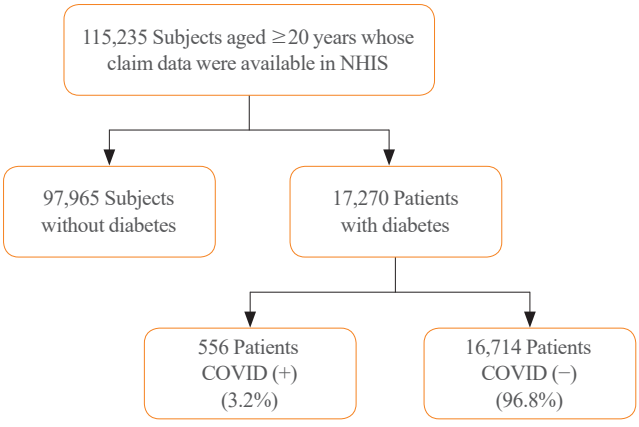


**Fig. 1.** Study subjects. NHIS, National Health Insurance Service; COVID-19, coronavirus disease 2019.

**Table 1.** Baseline Characteristics of Diabetic Patients with Coronavirus Disease 2019 according to the Use of Antidiabetic Drugs

| Characteristic | Total | Metformin | | | DPP-4i | | | SU | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No | Yes | *P* value | No | Yes | *P* value | No | Yes | *P* value |
| Number | 556 | 95 | 461 | | 198 | 358 | | 351 | 205 | |
| Male sex | 271 (48.7) | 54 (56.8) | 217 (47.1) | 0.083 | 102 (51.5) | 169 (47.2) | 0.330 | 163 (46.4) | 108 (52.7) | 0.155 |
| Age, yr | | | | 0.420 | | | 0.002 | | | 0.626 |
| 20–29 | 2 (0.4) | 1 (1.1) | 1 (0.2) | | 1 (0.5) | 1 (0.3) | | 2 (0.6) | 0 | |
| 30–39 | 8 (1.4) | 2 (2.1) | 6 (1.3) | | 4 (2.0) | 4 (1.1) | | 6 (1.7) | 2 (1.0) | |
| 40–49 | 32 (5.8) | 4 (4.2) | 28 (6.1) | | 12 (6.1) | 20 (5.6) | | 21 (6.0) | 11 (5.4) | |
| 50–59 | 119 (21.4) | 17 (17.9) | 102 (22.1) | | 33 (16.7) | 86 (24.0) | | 81 (23.1) | 38 (18.5) | |
| 60–69 | 202 (36.3) | 31 (32.6) | 171 (37.1) | | 60 (30.3) | 142 (39.7) | | 127 (36.2) | 75 (36.6) | |
| 70–79 | 131 (23.6) | 25 (26.3) | 106 (23.0) | | 53 (26.8) | 78 (21.8) | | 77 (21.9) | 54 (26.3) | |
| ≥80 | 62 (11.2) | 15 (15.8) | 47 (10.2) | | 35 (17.7) | 27 (7.5) | | 37 (10.5) | 25 (12.2) | |
| Region | | | | 0.846 | | | 0.833 | | | 0.259 |
| Seoul | 27 (4.9) | 4 (4.2) | 23 (5.0) | | 9 (4.6) | 18 (5.0) | | 14 (4.0) | 13 (6.3) | |
| Daegu | 366 (65.8) | 60 (63.2) | 306 (66.4) | | 127 (64.1) | 239 (66.8) | | 234 (66.7) | 132 (64.4) | |
| Gyeonggi-do | 25 (4.5) | 6 (6.3) | 19 (4.1) | | 11 (5.6) | 14 (3.9) | | 19 (5.4) | 6 (2.9) | |
| Gyeongsangbuk-do | 99 (17.8) | 17 (17.9) | 82 (17.8) | | 35 (17.7) | 64 (17.9) | | 57 (16.2) | 42 (20.5) | |
| Others | 39 (7.0) | 8 (8.4) | 31 (6.7) | | 16 (8.1) | 23 (6.4) | | 27 (7.7) | 12 (5.9) | |
| Smoking | 59 (10.6) | 8 (8.4) | 51 (11.1) | 0.447 | 20 (10.1) | 39 (10.9) | 0.771 | 35 (10.0) | 24 (11.7) | 0.521 |
| Low income | 165 (29.7) | 27 (28.4) | 138 (29.9) | 0.769 | 50 (25.3) | 115 (32.1) | 0.090 | 99 (28.2) | 66 (32.2) | 0.320 |
| Height, cm | 161.0±8.8 | 162.7±3.4 | 160.6±8.1 | 0.324 | 160.9±8.5 | 160.7±9.0 | 0.790 | 161.4±8.2 | 160.5±8.9 | 0.275 |
| Weight, kg | 65.7±11.7 | 65.5±4.8 | 65.8±10.7 | 0.901 | 65.8±11.1 | 65.6±11.8 | 0.842 | 66.1±12.3 | 65.3±10.8 | 0.474 |
| BMI, kg/m$^2$ | 25.3±3.6 | 24.6±1.4 | 25.4±3.3 | 0.332 | 25.4±3.4 | 25.4±3.6 | 0.976 | 25.3±3.9 | 25.3±3.2 | 0.881 |
| WC, cm | 85.8±8.9 | 86.1±3.8 | 85.8±8.0 | 0.894 | 85.5±8.7 | 86.1±8.9 | 0.496 | 85.6±9.2 | 85.3±8.4 | 0.676 |
| SBP, mm Hg | 128.3±15.0 | 128.8±5.8 | 128.2±13.9 | 0.871 | 128.0±16.6 | 128.6±14.1 | 0.639 | 127.4±15.1 | 128.8±14.2 | 0.289 |
| DBP, mm Hg | 76.9±10.1 | 75.8±3.6 | 77.2±9.4 | 0.578 | 76.0±9.9 | 76.9±9.6 | 0.318 | 76.3±10.0 | 76.4±9.2 | 0.996 |
| Glucose, mg/dL | 137.9±52.6 | 121.2±35.6 | 141.3±56.1 | 0.001 | 129.3±49.7 | 142.6±55.3 | 0.005 | 128.7±45.1 | 153.6±62.9 | <0.001 |
| AST, IU/L | 29.5±18.4 | 26.4±12.5 | 30.2±19.6 | 0.069 | 29.0±19.0 | 29.9±18.5 | 0.579 | 30.2±19.9 | 28.5±16.4 | 0.302 |
| ALT, IU/L | 31.4±25.0 | 26.0±18.8 | 32.5±26.3 | 0.022 | 29.5±22.0 | 32.4±26.9 | 0.197 | 31.9±27.1 | 30.5±22.0 | 0.538 |
| rGTP, IU/L | 42.0±51.2 | 35.3±33.2 | 43.4±54.9 | 0.165 | 46.7±69.7 | 39.5±38.6 | 0.119 | 43.2±49.7 | 40.1±55.5 | 0.490 |
| eGFR, mL/min/1.73 m$^2$ | 82.9±22.7 | 71.9±10.2 | 85.1±19.7 | 0.010 | 83.2±20.6 | 82.6±22.4 | 0.749 | 83.3±22.6 | 84.6±20.5 | 0.536 |
| Comorbidities | | | | | | | | | | |
| Hypertension | 425 (76.4) | 85 (89.5) | 340 (73.8) | 0.001 | 166 (83.8) | 259 (72.3) | 0.002 | 268 (76.4) | 157 (76.6) | 0.950 |
| Dyslipidemia | 501 (90.1) | 78 (82.1) | 423 (91.8) | 0.004 | 170 (85.9) | 331 (92.5) | 0.013 | 320 (91.2) | 181 (88.3) | 0.273 |
| Asthma or COPD | 122 (21.9) | 25 (26.3) | 97 (21.0) | 0.258 | 50 (25.3) | 72 (20.1) | 0.161 | 74 (21.1) | 48 (23.4) | 0.522 |
| IHD | 105 (18.9) | 22 (23.2) | 83 (18.0) | 0.243 | 40 (20.2) | 65 (18.2) | 0.555 | 64 (18.2) | 41 (20.0) | 0.608 |
| Stroke | 54 (9.7) | 8 (8.4) | 46 (10.0) | 0.641 | 20 (10.1) | 34 (9.5) | 0.818 | 28 (8.0) | 26 (12.7) | 0.071 |
| Cancer | 30 (5.4) | 10 (10.5) | 20 (4.3) | 0.015 | 15 (7.6) | 15 (4.2) | 0.091 | 17 (4.8) | 13 (6.3) | 0.451 |
| ESRD | 3 (0.5) | 3 (3.2) | 0 | <0.001 | 1 (0.5) | 2 (0.6) | 0.934 | 1 (0.3) | 2 (1.0) | 0.283 |
| DMR | 94 (16.9) | 9 (9.5) | 85 (18.4) | 0.034 | 23 (11.6) | 71 (19.8) | 0.013 | 51 (14.5) | 43 (21.0) | 0.050 |
| CCI score | 4.6±2.4 | 5.0±2.7 | 4.5±2.4 | 0.113 | 4.6±2.3 | 4.6±2.5 | 0.796 | 4.4±2.4 | 5.0±2.5 | 0.002 |

*(Continued to the next page)*

**Table 1.** Continued

| Characteristic | Total | Metformin | | | DPP-4i | | | SU | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No | Yes | *P* value | No | Yes | *P* value | No | Yes | *P* value |
| Medication | | | | | | | | | | |
| Insulin | 172 (30.9) | 54 (56.8) | 118 (25.6) | <0.001 | 75 (37.9) | 97 (27.1) | 0.008 | 107 (30.5) | 65 (31.7) | 0.763 |
| ACEi | 9 (1.6) | 3 (3.2) | 6 (1.3) | 0.192 | 3 (1.5) | 6 (1.7) | 0.886 | 5 (1.4) | 4 (2.0) | 0.635 |
| ARB | 197 (35.4) | 34 (35.8) | 163 (35.4) | 0.936 | 69 (34.9) | 128 (35.8) | 0.831 | 124 (35.3) | 73 (35.6) | 0.947 |
| Steroid | 135 (24.3) | 39 (41.1) | 96 (20.8) | <0.001 | 58 (29.3) | 77 (21.5) | 0.040 | 90 (25.6) | 45 (22.0) | 0.328 |
| Immunosuppressants | 2 (0.4) | 1 (1.1) | 1 (0.2) | 0.215 | 1 (0.5) | 1 (0.3) | 0.670 | 2 (0.6) | 0 | 0.279 |

Values are expressed as number (%) or mean±standard deviation. Statistical analysis was carried out by *T* test or chi-square test.
DPP-4i, dipeptidylpeptidase-4 inhibitor; SU, sulfonylurea; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; AST, aspartate aminotransferase; ALT, alanine aminotransferase; rGTP, gamma-glutamyltransferase; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease; ESRD, end-stage renal disease; DMR, diabetic retinopathy; CCI, Charlson comorbidity index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

**Table 2.** Clinical Outcomes of Diabetic Patients with Coronavirus Disease 2019 according to the Use of Antidiabetic Drugs

| Variable | Total | Metformin | | | DPP-4i | | | SU | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No | Yes | *P* value | No | Yes | *P* value | No | Yes | *P* value |
| Number | 556 | 95 | 461 | | 198 | 358 | | 351 | 205 | |
| Hospitalization | 433 (77.9) | 67 (70.5) | 366 (79.4) | 0.058 | 149 (75.3) | 284 (79.3) | 0.267 | 265 (75.5) | 168 (82.0) | 0.077 |
| Oxygen treatment | 119 (21.4) | 28 (29.5) | 91 (19.7) | 0.035 | 57 (28.8) | 62 (17.3) | 0.002 | 64 (18.2) | 55 (26.8) | 0.017 |
| ICU admission | 87 (15.6) | 23 (24.2) | 64 (13.9) | 0.012 | 35 (17.7) | 52 (14.5) | 0.327 | 52 (14.8) | 35 (17.1) | 0.480 |
| Ventilator support | 31 (5.6) | 14 (14.7) | 17 (3.7) | <0.001 | 14 (7.1) | 17 (4.8) | 0.253 | 16 (4.6) | 15 (7.3) | 0.171 |
| Death | 61 (11.0) | 25 (26.3) | 36 (7.8) | <0.001 | 36 (18.2) | 25 (7.0) | <0.001 | 38 (10.8) | 23 (11.2) | 0.886 |

Values are expressed as number (%). Statistical analysis was carried out by chi-square test.
DPP-4i, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; ICU, intensive care unit.

### Clinical outcome of COVID-19 according to the use of antidiabetic drugs

Of the total patients, 433 (77.9%) were hospitalized, and 119 (21.4%) received oxygen treatment. Additionally, 87 (15.6%) patients admitted to the ICU and 31 (5.6%) required mechanical ventilation. Sixty-one (11.0%) patients died (Table 2).

No significant differences in the number of hospitalized patients between those on and those not on metformin were observed. However, among patients on metformin, significantly fewer cases of patients were observed who received oxygen therapy (91 [19.7%] vs. 28 [29.5%], $P=0.035$), admitted to the ICU (64 [13.9%] vs. 23 [24.2%], $P=0.012$), required mechanical ventilation (17 [3.7%] vs. 14 [14.7%], $P<0.001$), and died (36 [7.8%] vs. 25 [26.3%], $P<0.001$).

Between patients receiving and not receiving DPP-4i, no significant differences in the number of patients hospitalized, admitted to the ICU, or required mechanical ventilation were observed. However, among patients receiving DPP-4i, significantly fewer patients received oxygen treatment (62 [17.3%] vs. 57 [28.8%], $P=0.002$) and died (25 [7.0%] vs. 36 [18.2%], $P<0.001$).

No significant differences in clinical outcomes, including hospitalization, ICU care, mechanical ventilation, or death, were observed between patients who were and who were not on sulfonylureas. In contrast, a significantly higher proportion of patients on sulfonylureas received oxygen therapy (55 [26.8%] vs. 64 [18.2%], $P=0.017$).

### Risk of clinical outcomes according to the use of antidiabetic drugs

The risk of adverse clinical outcomes according to the administration of antidiabetic drugs was analyzed (Table 3). The use of metformin was not associated with the risks of hospitalization, oxygen treatment or ICU admission. However, it was signifi-

**Table 3.** Logistic Regression Analyses for the Risk of Clinical Outcomes according to the Use of Antidiabetic Drugs

| Variable | Metformin | | DPP-4i | | SU | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | *P* value | OR (95% CI) | *P* value | OR (95% CI) | *P* value |
| Hospitalization | 1.271 (0.705–2.292) | 0.425 | 1.026 (0.634–1.661) | 0.916 | 1.567 (0.953–2.575) | 0.077 |
| Oxygen treatment | 0.703 (0.397–1.245) | 0.227 | 0.565 (0.356–0.895) | 0.015 | 1.473 (0.925–2.344) | 0.102 |
| ICU admission | 0.612 (0.332–1.130) | 0.117 | 0.959 (0.564–1.631) | 0.877 | 1.324 (0.778–2.254) | 0.301 |
| Ventilator support | 0.281 (0.109–0.720) | 0.008 | 1.090 (0.430–2.762) | 0.856 | 2.579 (1.004–6.626) | 0.049 |
| Death | 0.395 (0.182–0.854) | 0.018 | 0.454 (0.217–0.949) | 0.036 | 1.093 (0.508–2.353) | 0.820 |

Statistical analysis was carried out by multiple logistic regression weighting with covariates such as sex, age, region, smoking, low income, body mass index, systolic blood pressure, glucose, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, hypertension, dyslipidemia, asthma or chronic obstructive pulmonary disease, ischemic heart disease, stroke, cancer, end-stage renal disease, angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, steroid, insulin, immunosuppressants, Charlson comorbidity index score.
OR, odds ratio; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; SU, sulfonylurea; ICU, intensive care unit.

cantly associated with the lower risks of mechanical ventilation (odds ratio [OR], 0.281; 95% confidence interval [CI], 0.109 to 0.720; *P*=0.008), and death (OR, 0.395; 95% CI, 0.182 to 0.854; *P*=0.018). Use of DPP-4i was not associated with the risks of hospitalization, ICU admission, or mechanical ventilation. However, DPP-4i users were significantly associated with the lower risks of oxygen treatment (OR, 0.565; 95% CI, 0.356 to 0.895; *P*=0.015) and mortality (OR, 0.454; 95% CI, 0.217 to 0.949; *P*=0.036) compared to non-users. Use of sulfonylureas was not associated with the risks of hospitalization, oxygen treatment, ICU care, or death. However, the use of sulfonylurea was significantly associated with the higher risk of mechanical ventilation (OR, 2.579; 95% CI, 1.004 to 6.626; *P*=0.049).

## DISCUSSION

This study analyzed the effect of antidiabetic drugs on the clinical outcomes of COVID-19 in patients with diabetes using nationwide population-based cohort data. In patients with diabetes and COVID-19, the administration of metformin was associated with the lower risks of mechanical ventilation and death, the use of DPP-4i was associate with the lower risks of oxygen treatment and death, while sulfonylurea usage was associated with the higher risk of mechanical ventilation.

Metformin, the most widely used antidiabetic drug, decreases hepatic glucose output and increases glucose utilization in the peripheral tissues [22]. Although its frequency of occurrence is low, metformin is known to cause lactic acidosis in infections and sepsis, emphasizing the need for caution [23]. Conversely, metformin has shown anti-inflammatory actions, such as reducing the levels of interleukin-1β and interleukin-6, and the risk of thrombosis and inflammasome activation [24,25]. Furthermore, ex vivo studies using lung tissue infected with COVID-19 have shown that metformin inhibits viral replication and lipopolysaccharide (LPS)-induced lung injury [26,27]. Considering the research findings regarding metformin's anti-inflammatory actions and its effect on inhibiting lung injury, it was anticipated that metformin could demonstrate positive effects in patients with COVID-19. Similarly to the results of this study, in a RCT that included 1,323 overweight or obese patients diagnosed with COVID-19, metformin significantly improve the composite outcome of emergency department visits, hospitalization, or death [15]. In another study that investigated the effects of metformin compared to placebo in COVID-19 patients, metformin significantly reduced oxygen requirements [17]. Furthermore, previous studies have reported a 13% to 90% reduction in mortality in COVID-19 patients with the use of metformin [11,28,29]. However, there are research findings indicating that metformin either does not significantly impact the clinical outcomes of COVID-19 patients or, conversely, increases disease severity [16,30]. Considering the varying proportions of patients with diabetes and durations of metformin administration across studies, further research is deemed necessary.

Dipeptidylpeptidase-4 (DPP-4) is an enzyme located on the cell surface that interacts with several peptide hormones to regulate the immune response [31]. DPP-4 is associated with inflammation and acts as a receptor for coronavirus [32,33]. A previous study showed that DPP-4i can reduce LPS-induced lung injury [34]. Therefore, it was anticipated that DPP-4i would improve the clinical outcomes of COVID-19 by regulating the interaction between SARS-CoV-2 and human host cells and exerting anti-inflammatory effects. In an RCT comparing linagliptin+insulin

to insulin alone among patients admitted with SARS-CoV-2 infection and hyperglycemia of 140 to 400 mg/dL, regardless of a previous diagnosis of diabetes, the use of linagliptin+insulin resulted in a significantly lower risk of mechanical ventilation than insulin alone (3 [8.8%] vs. 12 [34.3%], $P$=0.010) [18]. Similar to the RCT, the administration of DPP-4i lowered the risk associated with oxygen treatment in this study. DPP-4 is present in immune and endothelial cells, pneumocytes, pleural mesothelium, and lymphatic vessels, is rarely detected in the conducting airway of the human respiratory tract, and increases in incidence in the distal airway [33]. Spatial localization in the alveolar region of DPP-4 may have influenced the reduction of oxygen treatment by DPP-4i administration. Furthermore, DPP-4i may have an impact on the immune response and lung injury, which could potentially contribute to reduced mortality.

Sulfonylurea was developed by observing hypoglycemia during the treatment of patients with typhoid with para-amino-sulfonamide-isopropyl-thiodiazole [35] and has been reported to be effective in preventing and treating Pneumocystis carinii pneumonitis due to its structural similarity to trimethoprim-sulfamethoxazole, a sulfonamide antibiotic [36]. SARS-CoV-2 activates the nodlike receptor pyrin 3 (NLRP3) inflammasome, leading to neuroinflammation and brain injury [37], and sulfonylurea has been reported to exert neuroprotective effects by inhibiting the NLRP3 inflammasome signaling pathway and suppressing the release of pro-inflammatory cytokines [38,39]. Although the structural similarities between sulfonylureas and antibiotics and their anti-inflammatory actions are known, in this study, the administration of sulfonylureas was associated with the higher risk of mechanical ventilation. Contrary to the findings of this study, in retrospective studies that analyzed the effects of sulfonylureas on clinical outcomes in patients hospitalized for COVID-19, the use of sulfonylureas did not have a significant effect on ICU admission, mechanical ventilation, or death [7,40]. In addition, meta-analyses have reported both neutral and slightly decreased mortality outcomes associated with sulfonylurea use, suggesting the need for additional research [13,41].

This study had several limitations. While hyperglycemia in patients with diabetes is known to be associated with poor clinical outcomes of COVID-19 [42], the glycated hemoglobin (HbA1c) levels of the subjects were not considered, as the NHIS data do not include HbA1c results. Instead, the glycemic control status of the subjects was indirectly reflected by the fasting plasma glucose results. Additionally, the study period coincided with the initial outbreak of COVID-19 in South Korea, when there were concentrated outbreaks in certain regions, leading to challenges in accommodating COVID-19 patients and when standardized COVID-19 management practices were not established. Differences in healthcare accessibility and management approaches could have influenced the clinical outcomes. However, we tried to overcome geographical disparities in healthcare accessibility by adjusting for the subjects' regional data. Owing to South Korea's policy, most COVID-19 confirmed patients were hospitalized regardless of the severity of the disease, resulting in a higher proportion of hospitalized patients in this study. Hospitalization due to COVID-19 is one of the factors in evaluating the severity of the disease, but the results of the current study might not be appropriate for assessing for severity of COVID-19 expressed in hospitalization rates. Moreover, in this study, there was a significantly lower proportion of patients using steroids among those using metformin and DPP-4i. Steroids possess immunosuppressive properties, and it has been reported that patients with immunocompromised status due to steroid administration have a higher mortality risk when infected with COVID-19 [43]. The reason for the difference in steroid use among medication groups is uncertain, but instead, we attempted to adjust for outcome differences based on steroid usage by analyzing steroids as a covariate. However, this study has the strength of analyzing the impact of antidiabetic drugs on the clinical outcomes of all diabetic patients with COVID-19 in South Korea because it used data from the NHIS, a public health care system covering the entire population. In addition, as South Korea actively conducts COVID-19 tests and has successfully managed the COVID-19 pandemic, its national data are considered to accurately reflect the prevalence and clinical outcomes of COVID-19.

In patients with diabetes infected with COVID-19, use of metformin was associated with reduced risks of mechanical ventilation and death; DPP-4i was linked to lower risks of oxygen treatment and death; and sulfonylureas was related to increased risk of mechanical ventilation. Similar to SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV), infectious diseases caused by these new viruses will continue to occur. Given that patients with diabetes are vulnerable to such infections, assessing the effects of antidiabetic medications on infectious diseases is imperative. Further research is required to provide guidelines for the use of antidiabetic drugs in patients with various infectious diseases.

## CONFLICTS OF INTEREST

Won-Young Lee is an editor-in-chief and Eun-Jung Rhee is a

deputy editor of the journal. But they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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## AUTHOR CONTRIBUTIONS

Conception or design: E.J.R., W.Y.L. Acquisition, analysis, or interpretation of data: S.J.M., J.H.J., K.D.H. Drafting the work or revising: H.N.J., S.J.M., E.J.R., W.Y.L. Final approval of the manuscript: H.N.J., S.J.M., J.H.J., K.D.H., E.J.R., W.Y.L.

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