Metformin use and risk of COVID-19 among patients with type II diabetes mellitus: an NHIS-COVID-19 database cohort study

Tak Kyu Oh1 · In-Ae Song1

Abstract

Aims The relationship between metformin therapy and the risk of coronavirus disease (COVID-19) has not been reported among patients with type 2 diabetes mellitus (DM). We aimed to investigate whether metformin therapy was associated with the incidence of COVID-19 among type 2 DM patients in South Korea.

Methods The National Health Insurance Service-COVID-19 cohort database, comprising COVID-19 patients from 1 January 2020 to 4 June 2020, was used for this study. Among them, adult patients with type 2 DM were included in this study. Metformin users were defined as those who had been prescribed continuous oral metformin for over a period of ≥ 90 days, and the control group was defined as all other patients.

Results Overall, 27,493 patients with type 2 DM (7204, metformin user group; 20,289, control group) were included. After propensity score matching, 11,892 patients (5946 patients in each group) were included in the final analysis. In the logistic regression analysis, the odds of metformin users developing COVID-19 was 30% lower than that of the control group [odds ratio (OR): 0.70, 95% confidence interval (CI): 0.61–0.80; P < 0.001]. However, in the multivariate model, metformin use was not associated with hospital mortality when compared with that of the control group (OR: 1.26, 95% CI: 0.81–1.95; P = 0.301).

Conclusions Metformin therapy might have potential benefits for the prevention of COVID-19 among patients with type 2 DM in South Korea. However, it did not affect the hospital mortality of type 2 DM patients diagnosed with COVID-19.

Keywords Antidiabetic drug · Cohort study · Metformin · Type 2 diabetes

Introduction

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread worldwide [1]. The World Health Organization had declared the Chinese outbreak of COVID-19 as a Public Health Emergency of International Concern on 30 January, 2020 [2], and it was declared a pandemic on 11 March, 2020 [3]. As of 10 August 2020, approximately 5 million COVID-19 cases and 150,000 COVID-19-related deaths have been reported in the USA [4]. COVID-19 represents a global public health crisis, with no available vaccine for its prevention [5, 6].

Previous studies have identified important risk factors for worsening outcomes among COVID-19 patients [7, 8], and diabetes mellitus (DM) is known to be an important risk factor for increased mortality among COVID-19 patients. Furthermore, a recent study in the USA reported that pre-existing type 2 DM is a risk factor for developing COVID-19 [9, 10]. Metformin, a biguanide agent, is most commonly prescribed for the management of type 2 DM [11]. Several studies have focussed on the effect of metformin therapy on the outcomes of COVID-19 [12–15] because metformin decreases the levels of tumour necrosis factor (TNF)-α, interleukin (IL)-6, and IL-10, which are known to play important roles in the inflammatory response in COVID-19 patients [16]. Furthermore, metformin also increases the
activation of adenosine monophosphate (AMP)-activated protein kinase (AMPK), which has important downstream effects in COVID-19 [17, 18]. Some recent studies have also reported the benefit of metformin therapy in reducing mortality in COVID-19 patients [12, 15]. However, the relationship between the risk of COVID-19 and metformin therapy in patients with DM has not been reported yet.

Therefore, we aimed to investigate whether metformin therapy is associated with the incidence of COVID-19 among type 2 DM patients in South Korea. Additionally, we examined the effect of metformin therapy on hospital mortality among type 2 DM patients diagnosed with COVID-19.

Methodology

Study design and population

As a population-based cohort study, this study was conducted according to the Reporting of Observational Studies in Epidemiology guidelines [19]. The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (X-2004-604-905) and the Health Insurance Review and Assessment Service (NHIS-2020-1-291). The requirement of informed consent was waived because data analyses were performed retrospectively using anonymised data retrieved from the South Korean National Health Insurance Service (NHIS) database. Using the NHIS-COVID-19 cohort database, individuals aged ≥ 20 years and diagnosed with type 2 DM were included in the study.

NHIS-COVID-19 cohort database

The NHIS-COVID-19 cohort database was developed to investigate the risk of COVID-19 among the South Korean population with the cooperation of the NHIS and Korea Centers for Disease Control and Prevention (KCDC). The KCDC provides information, such as the confirmation date of COVID-19, results of treatment, and demographic details, on patients diagnosed with COVID-19 recorded since 1 January 2020. COVID-19 patients undergoing treatment in hospitals while this study was conducted were not included in this database as their treatment results were not yet determined. Using this patient information, the NHIS formed the control population using stratification methods in regard to age, sex, and residence, in February 2020. In the NHIS-COVID-19 cohort database, all disease diagnoses per the International Classification of Diseases (ICD)-10 codes and prescription information concerning drugs and/or procedures from 2015 to 2020 were included. For our study, data were extracted by an independent medical record technician at the NHIS centre who was not affiliated with our study, as of June 26 2020. In South Korea, patients who were diagnosed with COVID-19 were admitted to the hospital if they had severe symptoms such as pneumonia. However, if they had mild or no symptoms, they were isolated and closely monitored in certain government-managed centres. If the COVID-19 patients in the government-managed centres developed any severe symptoms, they were transferred to a hospital immediately for proper treatment.

Exposure variable: metformin use

Among type 2 DM patients, prescription information from 2019 to 2020 was extracted, and the metformin user group was defined as those who had been prescribed continuous oral metformin over a period of ≥ 90 days, and the control group included all the other patients.

Endpoints of the study

The primary endpoint of our study was the development of COVID-19 among type 2 DM patients. It was evaluated from 1 January 2020 to 4 June 2020. The secondary endpoint was hospital mortality among patients who were diagnosed with COVID-19.

Covariates

The following information was collected as covariates: (1) demographic characteristics (age and sex), (2) place of residence (Seoul, Gyeonggi-do, Daegu, Gyeongsangbuk-do, and other areas), (3) underlying disability, (4) income level in 2020, (5) the Charlson Comorbidity Index, which was calculated based on the registered ICD-10 diagnostic codes (Table S1) from January 1, 2019 to December, 31 2019, and (6) other anti-diabetic medications (meglitinide, dipeptidyl peptidase-4 [DPP4]-inhibitors, thiazolidinediones, sulfonylureas, and insulin). Age was divided into seven groups (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and ≥ 80 years). In South Korea, as a sole public insurance system, all comorbidities are registered by physicians into the NHIS database to receive insurance coverage. For example, patients with chronic kidney disease or liver diseases should be registered in the NHIS database following diagnosis by physicians.

Statistical analysis

The baseline characteristics of the type 2 DM patients in our study are presented as numbers with percentages for categorical variables and mean value with standard deviation for continuous variables. We performed propensity score matching to reduce confounders in observational studies using the nearest neighbour method with a 1:1 ratio,
without replacement, and a calliper width of 0.2 [20]. Logistic regression analysis was performed for calculating propensity scores as a logistic model, and all covariates were included in the propensity score model. The absolute standardized mean difference (ASD) was used for determining the balance between the metformin user group and the control group, before and after propensity score matching. ASDs between the two groups were set to below 0.2 for determining whether the two groups were well balanced through propensity score matching. After confirming adequate balance between the two groups through propensity score matching, we performed the univariate logistic regression analysis for assessing the development of COVID-19 in the propensity score-matched cohort.

For sensitivity analysis, the multivariate logistic regression analysis was conducted for assessing the development of COVID-19 in the entire cohort to (1) determine whether the results obtained from the propensity score-matched cohort were generalizable to the entire cohort and (2) investigate the risk of developing COVID-19 among metformin users with other important covariates in context, not isolated. All covariates were included in the multivariate model for adjustment, and the Charlson Comorbidity Index and comorbidities that were used to calculate the Charlson Comorbidity Index were included in a different model to avoid multicollinearity. Finally, we performed the multivariate logistic regression analysis for hospital mortality among type 2 DM patients diagnosed with COVID-19 for investigating whether metformin use affected mortality compared with that of the control group. The Hosmer–Lemeshow statistics were used for confirming the goodness of fit of multivariate models at \( P > 0.05 \), and it was confirmed that there was no multicollinearity in all multivariate models of the entire cohort with a variance inflation factor of <2.0. The results of the logistic regression models are presented as odds ratios (ORs) with 95% confidence intervals (CIs). A receiver operator characteristic (ROC) curve analysis was performed for validating the use of logistic regression analysis in our study. R software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria) and SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA) were used for all analyses, and a \( P \) value of <0.05 was considered statistically significant.

## Results

During the extraction date, i.e. 26 June 2020, the NHIS-COVID-19 cohort comprised 8070 COVID-19 patients and 121,050 other patients in the control population. Among the 8070 patients, 4790 patients were aged < 20 years and 2290 patients with incomplete medical records were excluded from the analysis. Thus, 122,040 patients were initially screened, and among them, 27,493 patients with type 2 DM (7204 patients in the metformin user group and 20,289 patients in the control group) were included in the study. A total of 2047 cases of type 2 DM patients (7.4%) were diagnosed with COVID-19 in 2020, and hospital mortality occurred in 174 patients (8.5%) among the COVID-19 patients. After propensity score matching, 11,892 patients (5946 patients in each group) were included in the final analysis. The results of the comparison of characteristics between the metformin user group and control group are presented in Table 1. All ASDs were below 0.2, indicating that all covariates between the two groups were adequately balanced through propensity score matching. Figure S1 also shows that the distribution of propensity scores became similar after propensity score matching. The patient selection flow chart is presented in Fig. 1.

### COVID-19 risk among patients with type 2 DM

The results of the development of COVID-19 among type 2 DM patients before and after propensity score matching are presented in Table 2. In the propensity-matched cohort, 390 of the 5946 (6.6%) metformin users were diagnosed with COVID-19 in 2020, while 541 of the 5946 (9.1%) control group patients were diagnosed with COVID-19. In the logistic regression analysis, the odds of metformin users developing COVID-19 was 30% lower than that of the control group patients (OR: 0.70, 95% CI: 0.61–0.80; \( P < 0.001 \)). The results of the multivariate logistic regression model for developing COVID-19 in the entire cohort are presented in Table 3. In the multivariate model, the metformin user group was associated with a 12% lower incidence of COVID-19 than the control group (OR: 0.88, 95% CI: 0.78–0.99; \( P = 0.039 \)). The Hosmer–Lemeshow statistics showed goodness of fit in the three models (\( P > 0.05 \)), and the area under the curve (AUC) of the multivariate models in the ROC analyses was 0.81 (95% CI: 0.80–0.81).

### Hospital mortality among patients with type 2 DM and COVID-19

The results of the multivariate logistic regression model for hospital mortality in COVID-19 patients with type 2 DM are presented in Table 4. In the multivariate model, the metformin user group was not associated with hospital mortality compared with the control group (OR: 1.26; 95% CI: 0.81–1.95; \( P = 0.301 \)). The Hosmer–Lemeshow statistics showed goodness of fit in the three models (\( P > 0.05 \)), and the AUC of the multivariate model in the ROC analysis was 0.83 (95% CI: 0.82–0.83).
Table 1  Comparison of characteristics between metformin users and control group before and after propensity score matching

| Age        | Metformin n=7,204 | Control n=20,289 | After propensity score matching (n=11,892) |
|------------|-------------------|------------------|-------------------------------------------|
|            | ASD               |                  | ASD                                       |
| 20–29      | 65 (0.9)          | 1174 (5.8)       | 61 (1.0)                                  |
| 30–39      | 105 (1.5)         | 909 (4.5)        | 100 (1.7)                                 |
| 40–49      | 408 (5.7)         | 1710 (8.4)       | 350 (5.9)                                 |
| 50–59      | 1547 (21.5)       | 4548 (22.4)      | 1296 (21.8)                               |
| 60–69      | 2372 (32.9)       | 5407 (26.6)      | 1906 (32.1)                               |
| 70–79      | 1704 (23.7)       | 3787 (18.7)      | 1373 (23.1)                               |
| ≥ 80       | 1003 (13.9)       | 2754 (13.6)      | 860 (14.5)                                |
| Sex, male  | 3221 (44.7)       | 7752 (38.2)      | 2669 (44.9)                               |

Residence

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Income level in 2020

|                      | Metformin n=5,289 | Control n=20,289 |
|----------------------|-------------------|------------------|
|                      | ASD               | ASD             |

Charlson comorbidity index in 2020

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Peripheral vascular disease

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Renal disease

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Rheumatic disease

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Dementia

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Peptic ulcer disease

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Hemiplegia or paraplegia

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Moderate or severe liver disease

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Mild liver disease

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Chronic pulmonary disease

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Cerebrovascular disease

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Congestive heart failure

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Myocardial infarction

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Malignancy

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Metastatic solid tumour

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

AIDS/HIV

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Other anti-diabetic medication

|                      | Metformin n=5,946 | Control n=5,946 |
|----------------------|-------------------|-----------------|
|                      | ASD               | ASD             |

Presented as number with percentage or mean with standard deviation

ASD absolute value of standard mean difference; AIDS acquired immune deficiency syndrome; HIV human immunodeficiency virus
Discussion

Using the NHIS-COVID-19 cohort database, we showed that metformin therapy was associated with a lower incidence of COVID-19 in type 2 DM patients in South Korea. Both the propensity score modelling and multivariate logistic regression modelling were demonstrated for the entire cohort. This is the first study to report that metformin therapy might have a protective effect against the risk of COVID-19 among type 2 DM patients. However, our study did not show a beneficial association between metformin therapy and hospital mortality.

The benefits of metformin therapy on lowering the risk of COVID-19 among patients with type 2 DM can be supported by a few studies. First, the effect of metformin on the immune system should be considered. Metformin is known to enhance the immunomodulatory effect in animal studies via adipose-derived mesenchymal stem cells [21]. Many previous epidemiologic studies have shown that metformin therapy might enhance the immune system by pleiotropic effect [22, 23], which might affect the risk of COVID-19 among type 2 DM patients. Second, metformin is beneficial for obese people as it aids in weight loss [24], and it might affect obesity reduction in type 2 DM patients, which is known to be a significant risk factor for COVID-19, in addition to DM [25]. Third, the anti-inflammatory effects of metformin might affect the risk of COVID-19 among patients with type 2 DM because metformin decreases the levels of TNFα, IL-6, and IL-10, which are known to play important roles in the inflammatory response during COVID-19 [16].
Metformin is known to activate AMPK via liver kinase B1 and inhibit the mammalian target of rapamycin (mTOR) pathway. The mTOR signalling pathway plays a key role in the pathogenesis of influenza. Metformin also indirectly attenuates AKT activation through the phosphorylation of

**Table 3** Multivariable logistic regression model for diagnosis of COVID-19 in South Korea

| Variable                      | Multivariable model | P-value |
|-------------------------------|---------------------|---------|
| Metformin user                | 0.88 (0.78, 0.99)   | 0.039   |
| Age, year                     |                     |         |
| 20–29                         | 1                   |         |
| 30–39                         | 0.79 (0.57, 1.09)   | 0.158   |
| 40–49                         | 0.98 (0.75, 1.27)   | 0.859   |
| 50–59                         | 0.73 (0.58, 0.93)   | 0.010   |
| 60–69                         | 0.60 (0.48, 0.77)   | < 0.001 |
| 70–79                         | 0.44 (0.34, 0.56)   | < 0.001 |
| ≥ 80                          | 0.36 (0.28, 0.48)   | < 0.001 |

**Income level 2020 (Feb)**

| Q4 (Highest)                  | 1                   |
| Q3                            | 0.84 (0.73, 0.97)   | 0.018   |
| Q2                            | 0.77 (0.68, 0.89)   | < 0.001 |
| Q1 (Lowest)                   | 0.80 (0.71, 0.90)   | < 0.001 |
| unknown                       | 1.01 (0.69, 1.48)   | 0.975   |
| Sex, male                     | 1.06 (0.96, 1.17)   | 0.252   |

**Residence at February, 2020**

| Seoul                         | 1                   |
|                               |                     |
| Gyeonggi-do                   | 0.95 (0.74, 1.20)   | 0.647   |
| Daegu                         | 1.05 (0.77, 1.44)   | 0.743   |
| Gyeongsangbuk-do              | 1.07 (0.82, 1.39)   | 0.610   |
| Other area                    | 0.89 (0.67, 1.18)   | 0.414   |
| Underlying disability         | 1.05 (0.92, 1.21)   | 0.486   |
| Charlson comorbidity index, 1 point | 1.19 (1.18, 1.20) | < 0.001 |
| Peripheral vascular disease   | 0.73 (0.63, 0.84)   | < 0.001 |
| Renal disease                 | 0.99 (0.79, 1.24)   | 0.922   |
| Rheumatic disease             | 0.94 (0.77, 1.14)   | 0.525   |
| Dementia                      | 2.04 (1.73, 2.40)   | < 0.001 |
| Peptic ulcer disease          | 1.05 (0.93, 1.19)   | 0.460   |
| Hemiplegia or paraplegia      | 2.58 (1.87, 3.57)   | < 0.001 |
| Moderate or severe liver disease | 0.73 (0.37, 1.41) | 0.347   |
| Mild liver disease            | 2.03 (1.84, 2.24)   | < 0.001 |
| Chronic pulmonary disease     | 3.54 (3.20, 3.91)   | < 0.001 |
| Cerebrovascular disease       | 0.98 (0.84, 1.14)   | 0.777   |
| Congestive heart failure      | 2.10 (1.83, 2.41)   | < 0.001 |
| Myocardial infarction         | 2.61 (2.10, 3.24)   | < 0.001 |
| Malignancy                    | 1.51 (1.37, 1.67)   | < 0.001 |
| Metastatic solid tumour       | 0.91 (0.76, 1.09)   | 0.302   |
| AIDS/HIV                      | 4.65 (1.17, 18.59)  | 0.030   |

**Other anti-diabetic drug**

| Meglitinide                   | 0.78 (0.18, 3.36)   | 0.737   |
| Dipeptidyl peptidase-4 inhibitors | 1.01 (0.87, 1.17) | 0.860   |
| Thiazolidinediones            | 1.06 (0.84, 1.34)   | 0.619   |
| Sulfonylureas                 | 0.88 (0.75, 1.04)   | 0.126   |
| Insulin                       | 0.83 (0.63, 1.09)   | 0.183   |

**Table 4** Multivariable logistic regression model for hospital mortality in COVID-19 patients with type 2 DM (n = 2047, death = 174, 8.5%)

| Variable                      | Multivariable model | P-value |
|-------------------------------|---------------------|---------|
| Metformin user                | 1.26 (0.81, 1.95)   | 0.301   |
| Age, 10 year increases        | 2.56 (2.07, 3.17)   | < 0.001 |

**Income level**

| Q1 (Lowest)                   | 1                   |
| Q2                            | 1.09 (0.62, 1.91)   | 0.764   |
| Q3                            | 0.97 (0.58, 1.62)   | 0.909   |
| Q4 (highest)                  | 0.67 (0.43, 1.05)   | 0.078   |

**Residence**

| Seoul                         | 1                   |
| Gyeonggi-do                   | 2.27 (0.59, 8.75)   | 0.234   |
| Daegu                         | 2.88 (0.63, 13.19)  | 0.174   |
| Gyeongsangbuk-do              | 2.14 (0.53, 8.62)   | 0.287   |
| Other area                    | 1.74 (0.39, 7.76)   | 0.466   |
| Underlying disability         | 1.02 (0.67, 1.55)   | 0.932   |
| Charlson comorbidity index, 1 point | 1.27 (1.04, 1.55) | 0.017   |
| Peripheral vascular disease   | 1.14 (0.74, 1.77)   | 0.546   |
| Renal disease                 | 1.84 (1.05, 3.21)   | 0.033   |
| Rheumatic disease             | 0.88 (0.43, 1.78)   | 0.717   |
| Dementia                      | 1.73 (1.11, 2.69)   | 0.016   |
| Peptic ulcer disease          | 1.31 (0.87, 1.98)   | 0.199   |
| Hemiplegia or paraplegia      | 3.18 (1.54, 6.56)   | 0.002   |
| Moderate or severe liver disease | 4.25 (1.02, 17.70) | 0.047   |
| Mild liver disease            | 0.75 (0.52, 1.09)   | 0.131   |
| Chronic pulmonary disease     | 1.78 (1.22, 2.61)   | 0.003   |
| Cerebrovascular disease       | 0.61 (0.38, 0.99)   | 0.044   |
| Congestive heart failure      | 1.90 (1.29, 2.79)   | 0.001   |
| Myocardial infarction         | 1.18 (0.67, 2.06)   | 0.571   |
| Malignancy                    | 0.92 (0.62, 1.34)   | 0.649   |
| Metastatic solid tumour       | 1.54 (0.93, 2.57)   | 0.094   |
| AIDS/HIV                      | 0.00 (0.00-)        | 0.982   |

**Other anti-diabetic drug**

| Meglitinide                   | 0.00 (0.00-)        | 0.987   |
| Dipeptidyl peptidase-4 inhibitors | 1.24 (0.74, 2.08) | 0.410   |
| Thiazolidinediones            | 1.14 (0.53, 2.47)   | 0.736   |
| Sulfonylureas                 | 1.43 (0.83, 2.48)   | 0.198   |
| Insulin                       | 2.27 (0.99, 5.17)   | 0.052   |

AUC: 0.83 (95% CI: 0.82, 0.83) OR odds ratio; CI confidence interval; AIDS acquired immune deficiency syndrome; HIV human immunodeficiency virus

Metformin is known to activate AMPK via liver kinase B1 and inhibit the mammalian target of rapamycin (mTOR) pathway. The mTOR signalling pathway plays a key role in the pathogenesis of influenza. Metformin also indirectly attenuates AKT activation through the phosphorylation of
insulin receptor substrate 1, resulting in inhibition of the mTOR signalling cascade [26]. The mTOR pathway plays a major role in COVID-19 pathogenesis, and metformin might work against SARS-CoV-2 infection [27]. However, the relationship between the risk of COVID-19 and metformin therapy among patients with type 2 DM remains controversial, and future studies are needed.

The impact of metformin therapy on outcomes such as mortality among type 2 DM patients with COVID-19 also remains controversial. Recent cohort studies have reported that metformin therapy is associated with a lower mortality among patients with DM [12, 15, 28]. However, our study did not find such an association between metformin therapy and hospital mortality among type 2 DM patients. A higher rate of hospital mortality might be caused by acute respiratory distress syndrome (ARDS) among COVID-19 patients [29]. However, a cohort study reported that prior metformin therapy was not associated with mortality among patients with ARDS [30]. However, the scoring system of severity among COVID-19 patients was not included in our study, and the results might be controversial. Therefore, more studies are needed to confirm the effects of metformin therapy on mortality among COVID-19 patients.

Although other anti-diabetic drugs were not associated with the risk of COVID-19 infection and in-hospital mortality in the multivariable model of the entire cohort in this study, their potential benefits should be evaluated. For example, a previous report indicated that DPP4-inhibitor may have a protective effect against COVID-19 [31, 32] because DPP4-inhibitor might reduce the entry and replication of SARS-CoV-2 in human tissue [33]. However, in this study, other anti-diabetic drugs, including DPP4-inhibitor, were covariates; hence, more studies are needed to elucidate the relationship between various anti-diabetic drugs and the progression COVID-19.

Our study has several limitations. First, some important variables, such as body mass index, smoking, and history of alcohol use, were not included in the analysis because the NHIS database did not provide those data. Second, both propensity score modelling and multivariate adjustment reduce known and measured confounders. There might be residual confounders that should be considered when interpreting the results of this study. Third, we did not consider the effect of metformin use in combination with other anti-diabetic drugs, which might have affected the results of this study. Fourth, our analysis was based on the metformin prescription data in the NHIS database; it did not assess compliance among those classified as metformin users. Fifth, we did not evaluate some important information that reflects the severity of DM, such as duration of diabetes and HbA1c levels; therefore, the appropriate control of blood glucose in the patients with type 2 DM in this study might have affected the results. Considering these limitations, the results of this study should be interpreted cautiously, and further prospective, large population-based cohort studies are needed to confirm these findings. Sixth, the validity of our study findings may be compromised by selection bias during the enrolment of study participants. Some COVID-19 patients were admitted to the hospital for treatment, while others were not admitted to the hospital and did not receive in-hospital treatment. Hospital admission or lack of it could affect the association between metformin use and in-hospital mortality. Lastly, for analysing hospital mortality, the disease severity of COVID-19 patients have not been evaluated and adjusted sufficiently; therefore, the results should be interpreted carefully.

In conclusion, our study showed that metformin therapy might have potential benefits for the prevention of COVID-19 among patients with type 2 DM in South Korea. However, it did not affect hospital mortality of type 2 DM patients diagnosed with COVID-19. Since there were unmeasured confounders in this study, our findings should be carefully interpreted, and further studies are needed to confirm the effects of metformin therapy on the risk and mortality of COVID-19.

Author contributions TK Oh designed the study, analysed the data, interpreted the data, and drafted the manuscript; In-Ae Song contributed to the study conceptualization, acquisition of data, and reviewed the manuscript. All authors have given approved the final version of the manuscript.

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethics approval The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (X-2004–604-905) and the Health Insurance Review and Assessment Service (NHIS-2020–1-291).

Informed consent The requirement of informed consent was waived because data analyses were performed retrospectively using anonymised data retrieved from the South Korean National Health Insurance Service database.

References

1. Wang Y, Wang Y, Chen Y, Qin Q (2020) Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. J Med Virol 92(6):568–576. https://doi.org/10.1002/jmv.25748

2. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention (2020) The epidemiological characteristics of an outbreak of 2019 novel
coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi 41(2):145–151. https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.003

3. Bedford J, Enria D, Giesecke J et al (2020) COVID-19: towards controlling a pandemic. The Lancet 395(10229):1015–1018

4. Moore JTJMM, Report MW (2020) Disparities in incidence of COVID-19 among underrepresented racial/ethnic groups in counties identified as hotspots during June 5–18, 2020—22 states, February–June 2020. 69

5. Rothan HA, Byrareddy SN (2020) The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 109:102433. https://doi.org/10.1016/j.aut.2020.102433

6. Tu H, Tu S, Gao S, Shao A, Sheng JJJoI (2020) The epidemiological and clinical features of COVID-19 and lessons from this global infectious public health event

7. Cai H (2020) Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med 8(4):e20. https://doi.org/10.1016/S2213-2600(20)30117-X

8. Guan WJ, Ni ZY, Hu Y et al (2020) Clinical characteristics of COVID-19 in China. N Engl J Med 382(18):1708–1720. https://doi.org/10.1056/NEJMoa2002032

9. Gu T, Mack JA, Salvatore M et al (2020) COVID-19 outcomes, risk factors and associations by race: a comprehensive analysis using electronic health records data in Michigan medicine. medRxiv. https://doi.org/10.1101/2020.06.16.20133140

10. Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A, Del Prato S (2020) COVID-19 in people with diabetes: understanding the reasons for worse outcomes. Lancet Diabetes Endocrinol 8(9):782–792. https://doi.org/10.1016/S2213-8587(20)30238-2

11. Bailey CJ (2017) Metformin: historical overview. Diabetologia 60(9):1566–1576. https://doi.org/10.1007/s00125-017-4318-z

12. Crouse A, Grimes T, Li P et al (2020) Metformin use is associated with reduced mortality in a diverse population with Covid-19 and diabetes. medRxiv. https://doi.org/10.1101/2020.07.29.20164020

13. El-Arabey AA, Abdalla M (2020) Metformin and COVID-19: a novel deal of an old drug. J Med Virol. https://doi.org/10.1002/jmv.25958

14. Esami Z (2020) A proposed mechanism for the possible therapeutic potential of Metformin in COVID-19. Diabetes Res Clin Pract. https://doi.org/10.1016/j.diabres.2020.108282

15. Luo P, Qiu L, Liu Y, Liu XL, Zheng JL, Xue HY, Liu WH, Liu D, Li J (2020) Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. Am J Trop Med Hyg 103(1):69–72. https://doi.org/10.4269/ajtmh.20-0375

16. Tufan A, Avanalgu Guler A, Matucci-Cerinic M (2020) COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci. https://doi.org/10.3906/sag-2004-168

17. Cameron AR, Morrison VL, Levin D et al (2016) Anti-Inflammatory effects of metformin irrespective of diabetes status. Circ Res 119(5):652–665. https://doi.org/10.1161/CIRCRESAHA.116.308445

18. Ingraham NE, Barakat AG, Reilkoff R et al (2020) Understanding the renin-angiotensin-aldosterone-SARS-CoV axis: a comprehensive review. Eur Respir J. https://doi.org/10.1183/13993003.00912-2020

19. Von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP (2007) The strengthening of the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 147(8):573–577

20. Rosenbaum PR, Rubin DB (1984) Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 79(387):516–524

21. Jang SG, Lee J, Hong SM, Kwok SK, Cho ML, Park SH (2020) Metformin enhances the immunomodulatory potential of adipose mesenchymal stem cells through STAT1 in an animal model of lupus. Rheumatology (Oxford) 59(6):1426–1438. https://doi.org/10.1093/rheumatology/kez631

22. Negrotto L, Farez MF, Correale J (2016) Immunologic effects of metformin and pioglitazone treatment on metabolic syndrome and multiple sclerosis. JAMA Neurol 73(5):520–528. https://doi.org/10.1001/jamaneurol.2015.4807

23. Prattichizzo F, Giuliani A, Mensa E et al (2018) Pleiotropic effects of metformin: Shaping the microbiome to manage type 2 diabetes and postpone ageing. Ageing Res Rev 48:87–98. https://doi.org/10.1016/j.arr.2018.10.003

24. Seifarth C, Schehler B, Schneider HJ (2013) Effectiveness of metformin on weight loss in non-diabetic individuals with obesity. Exp Clin Endocrinol Diabetes 121(1):27–31. https://doi.org/10.1055/s-0032-1327734

25. Zhou Y, Chi J, Lv W et al (2020) Obesity and diabetes as high-risk factors for severe coronavirus disease 2019 (Covid-19). Diabetes Metab Res Rev. https://doi.org/10.1002/dmrr.3377

26. Clements A, Gao B, Yeap SHO, Ali SS, Gurney H (2011) Metformin in prostate cancer: two for the price of one. Ann Oncol 22(12):2556–2560. https://doi.org/10.1093/annonc/mdr037

27. Sharma S, Ray A, Sadasivam B (2020) Metformin in COVID-19: a possible role beyond diabetes. Diabetes Res Clin Pract 164:101813. https://doi.org/10.1016/j.diabres.2020.101813

28. Bramante C, Ingraham N, Murray T et al (2020) Observational study of metformin and risk of mortality in patients hospitalized with Covid-19. medRxiv. https://doi.org/10.1101/2020.06.19.20135095

29. Zangrillo A, Beretta L, Scandroglio AM (2020) Characteristics, treatment, outcomes and cause of death of invasively ventilated patients with COVID-19 ARDS in Milan. Italy, Crit Care Resusc

30. Oh TK, Song IA (2020) Prior metformin therapy and 30-day mortality in patients with acute respiratory distress syndrome: a nationwide cohort study. Ann Palliat Med 9(3):903–911. https://doi.org/10.21037/apm.2020.04.25

31. Solerte SB, Di Sabatino A, Galli M, Fiorina P (2020) Dipeptidyl peptidase-4 (DPP4) inhibition in COVID-19. Acta Diabetol 57(7):779–783. https://doi.org/10.1007/s00592-020-01539-z

32. Solerte SB, D’Addio F, Trevisan R et al (2020) Sitagliptin treatment at the time of hospitalization was associated with reduced mortality in patients with type 2 diabetes and COVID-19: a multicenter, case-control, retrospective, observational study. Diabetes Care 43(12):2999–3006. https://doi.org/10.2337/dc20-1521

33. Qi F, Qian S, Zhang S, Zhang Z (2020) Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. Biochem Biophys Res Commun 526(1):135–140. https://doi.org/10.1016/j.bbrc.2020.03.044

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.