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ORIGINAL ARTICLE

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

Tak Kyu Oh[1] · **In-Ae Song**[1]

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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

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✉ In-Ae Song
songoficu@outlook.kr

[1] Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam 13620, Korea

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

	Before propensity score matching ($n=27,493$)			After propensity score matching ($n=11,892$)		
	Metformin $n=7,204$	Control $n=20,289$	ASD	Metformin $n=5,946$	Control $n=5946$	ASD
Age						
20–29	65 (0.9)	1174 (5.8)		61 (1.0)	37 (0.6)	
30–39	105 (1.5)	909 (4.5)	0.252	100 (1.7)	66 (1.1)	0.048
40–49	408 (5.7)	1710 (8.4)	0.120	350 (5.9)	325 (5.5)	0.018
50–59	1547 (21.5)	4548 (22.4)	0.023	1296 (21.8)	1253 (21.1)	0.018
60–69	2372 (32.9)	5407 (26.6)	0.134	1906 (32.1)	1930 (32.5)	0.009
70–79	1704 (23.7)	3787 (18.7)	0.117	1373 (23.1)	1435 (24.1)	0.025
≥80	1003 (13.9)	2754 (13.6)	0.010	860 (14.5)	900 (15.1)	0.019
Sex, male	3221 (44.7)	7752 (38.2)	0.131	2669 (44.9)	2669 (44.9)	<0.001
Residence						
Seoul	292 (4.1)	878 (4.3)				
Gyeonggi-do	4729 (65.6)	13,731 (67.7)	0.004	250 (4.2)	247 (4.2)	0.007
Daegu	377 (5.2)	977 (4.8)	0.019	3929 (66.1)	3950 (66.4)	0.012
Gyeongsangbuk-do	1186 (16.5)	2970 (14.6)	0.049	307 (5.2)	291 (4.9)	0.003
Other area	620 (8.6)	1733 (8.5)	0.002	939 (15.8)	932 (15.7)	0.003
Underlying disability	1023 (14.2)	2647 (13.0)	0.033	521 (8.8)	526 (8.8)	0.036
Income level in 2020						
Q1	2089 (29.0)	5635 (27.8)		1728 (29.1)	1731 (29.1)	
Q2	1075 (14.9)	3361 (16.6)	0.046	900 (15.1)	843 (14.2)	0.027
Q3	1558 (21.6)	4326 (21.3)	0.007	1256 (21.1)	1289 (21.7)	0.014
Q4	2376 (33.0)	6669 (32.9)	0.002	1984 (33.4)	1996 (33.6)	0.004
Unknown	106 (1.5)	298 (1.5)	<0.001	78 (1.3)	87 (1.5)	0.013
Charlson comorbidity index in 2020	4.5 (3.4)	3.4 (3.4)	0.327	4.4 (3.4)	4.7 (3.4)	0.072
Peripheral vascular disease	1450 (20.1)	2687 (13.2)	0.172	1119 (18.8)	1119 (18.8)	<0.001
Renal disease	245 (3.4)	825 (4.1)	0.037	223 (3.8)	293 (4.9)	0.065
Rheumatic disease	342 (4.7)	1069 (5.3)	0.025	250 (4.2)	331 (5.6)	0.064
Dementia	676 (9.4)	1637 (8.1)	0.045	577 (9.7)	594 (10.0)	0.010
Peptic ulcer disease	1033 (14.3)	2960 (14.6)	0.007	853 (14.3)	950 (16.0)	0.047
Hemiplegia or paraplegia	71 (1.0)	238 (1.2)	0.019	60 (1.0)	69 (1.2)	0.015
Moderate or severe liver disease	27 (0.4)	76 (0.4)	<0.001	20 (0.3)	23 (0.4)	0.008
Mild liver disease	2336 (32.4)	4946 (24.4)	0.172	1923 (32.3)	2222 (37.4)	0.107
Chronic pulmonary disease	1364 (18.9)	3955 (19.5)	0.014	1170 (19.7)	1224 (20.6)	0.023
Cerebrovascular disease	1007 (14.0)	2304 (11.4)	0.076	803 (13.5)	859 (14.4)	0.027
Congestive heart failure	638 (8.9)	1687 (8.3)	0.019	531 (8.9)	571 (9.6)	0.024
Myocardial infarction	206 (2.9)	450 (2.2)	0.039	172 (2.9)	205 (3.4)	0.033
Malignancy	1892 (26.3)	5337 (26.3)	<0.001	1563 (26.3)	1623 (27.3)	0.023
Metastatic solid tumour	494 (6.9)	1333 (6.6)	0.011	428 (7.2)	470 (7.9)	0.028
AIDS/HIV	1 (0.0)	10 (0.0)	0.030	1 (0.0)	1 (0.0)	<0.001
Other anti-diabetic medication						
Meglitinide	24 (0.3)	12 (0.1)	0.048	15 (0.3)	12 (0.2	0.009
Dipeptidyl peptidase-4 inhibitors	2365 (32.8)	1767 (8.7)	0.514	1796 (30.2)	1677 (28.2)	0.043
Thiazolidinediones	736 (10.2)	528 (2.6)	0.251	586 (9.9)	498 (8.4)	0.049
Sulfonylureas	2414 (33.5)	1266 (6.2)	0.578	1655 (27.8)	1243 (20.9)	0.147
Insulin	476 (6.6)	438 (2.2)	0.327	360 (6.1)	356 (6.0)	0.003

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

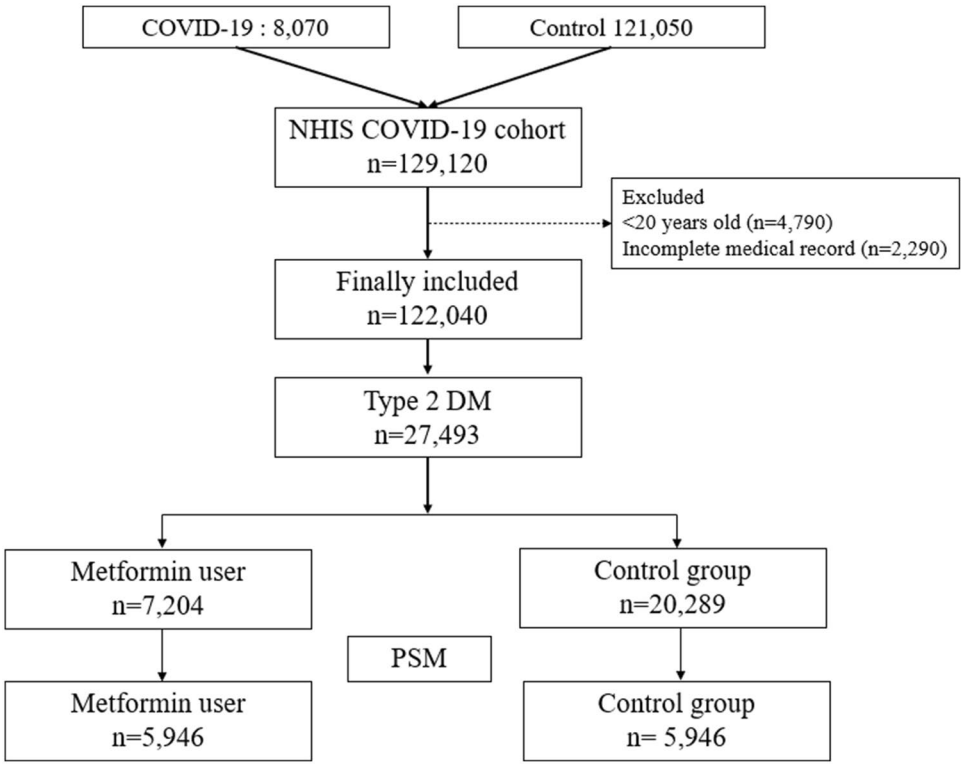

Fig.1 Flow chart depicting patient selection

Table 2 Development of COVID-19 before and after PSM

Variable	Development of COVID19	Logistic regression analysis OR (95% CI)	*P*-value
Before PSM			
Control	1567/20,289 (7.7)	1	
Metformin user	480/7204 (6.7)	0.85 (0.77, 0.95)	0.003
After PSM			
Control	541/5946 (9.1)	1	
Metformin user	390/5946 (6.6)	0.70 (0.61, 0.80)	< 0.001

PSM propensity score matching; *OR* odds ratio; *CI* confidence interval

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].

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

Variable	Multivariable model OR (95% CI)	*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

AUC of multivariable model: 0.81 (95% CI: 0.80, 0.81)

OR odds ratio; *CI* confidence interval; *AIDS* acquired immune deficiency syndrome; *HIV* human immunodeficiency virus

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 OR (95% CI)	*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
Unknown	0.20 (0.02, 1.76)	0.147
Sex, male	2.37 (1.63, 3.44)	< 0.001
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.

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