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The Risk of Diabetes on Clinical Outcomes in Patients with Coronavirus Disease 2019: A Retrospective Cohort Study

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Background: To determine the role of diabetes mellitus (DM) in the coronavirus disease 2019 (COVID-19), we explored the clinical characteristics of patients with DM and compared risk factors such as age, glycemic control, and medications to those without DM.
Methods: This was a retrospective cohort study of 117 confirmed patients with COVID-19 which conducted at a tertiary hospital in Daegu, South Korea. The primary outcome was defined as the severe and critical outcome (SCO), of which the composite outcomes of acute respiratory distress syndrome, septic shock, intensive care unit care, and 28-day mortality. We analyzed what clinical features and glycemic control-related factors affect the prognosis of COVID-19 in the DM group.
Results: After exclusion, 110 participants were finally included. DM patients ($n=29$) was older, and showed higher blood pressure compared to non-DM patients. DM group showed higher levels of inflammation-related biomarkers and severity score, and highly progressed to SCO. After adjustment with other risk factors, DM increased the risk of SCO (odds ratio [OR], 10.771; $P<0.001$). Among the DM patients, SCO was more prevalent in elderly patients of ≥70 years old and age was an independent risk factor for SCO in patients with DM (OR, 1.175; $P=0.014$), while glycemic control was not. The use of medication did not affect the SCO, but the renin-angiotensin system inhibitors showed protective effects against acute cardiac injury (OR, 0.048; $P=0.045$).
Conclusion: The COVID-19 patients with DM had higher severity and resulted in SCO. Intensive and aggressive monitoring of COVID-19 clinical outcomes in DM group, especially in elderly patients is warranted.

Keywords: Aged; COVID-19; Diabetes mellitus; Prognosis; Risk factors; Severe acute respiratory syndrome coronavirus 2

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic virus, which causes pneumonia, originated in Wuhan, China, in 2019 and is spreading rapidly to other countries [1]. By April 11, 2020, 1,610,909 cases of coronavirus disease 2019 (COVID-19) had been confirmed in 213 countries, and 99,690 COVID-19 patients had died worldwide. The

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Chinese Center for Disease Control and Prevention reported 81% as mild cases, 14% as severe cases, and 5% as critical cases [2].

Diabetes mellitus (DM) has an estimated prevalence of 9.3% globally, and is a serious disease that impacts the health status associated with other diseases [3]. In a population-based cohort study, DM was clearly shown to be associated with increased mortality from pneumonia [4], and hyperglycemia on admission is associated with poor clinical outcome for both diabetic and nondiabetic patients with community-acquired pneumonia [5]. Respiratory tract infections, including bacterial pneumonia, influenza, and tuberculosis, are more common, and are more serious in patients with DM than in those without DM [6]. The pathophysiology of increased mortality in diabetic patients with pneumonia is as follows: (1) decreased T lymphocyte response; (2) decreased neutrophil function; (3) depression of the antioxidant system; and (4) disorders of humoral immunity by the complement system [6].

Previous studies reported that 25% to 45% of patients with COVID-19 have more than one coexisting disorder. Among them, about 10% of patients in China have DM [7,8]. A recent study showed that diabetic patients are more susceptible to an inflammatory storm, eventually leading to rapid progression and poor prognosis in COVID-19 patients [9].

In this study, we determined the clinical characteristics of COVID-19 patients with DM compared to those without DM. In addition, we analyzed the severity and clinical outcomes of COVID-19 patients with DM according to age, glycemic control status, and medications.

METHODS

Study design and subjects

We performed a retrospective cohort study of 117 patients with SARS-CoV-2 infection hospitalized at Yeungnam University Medical Center, in Daegu, South Korea. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and was reviewed and approved by the Institutional Review Board of Yeungnam University Hospital (YUH IRB 2020-03-057). The requirement for informed consent was waived because of the retrospective study design.

During the study period, all consecutive adult patients (age >18 years) with SARS-CoV-2 infection admitted to the hospital were eligible for inclusion. SARS-CoV-2 infection was confirmed by real-time reverse transcriptase-polymerase chain reaction assay of nasal and pharyngeal swab samples. Patients who were taken to other hospitals and whose final clinical results were unknown were excluded from the analysis. After excluding seven patients, 110 patients were finally included in this study, and 26.4% (n=29) had DM (Fig. 1).

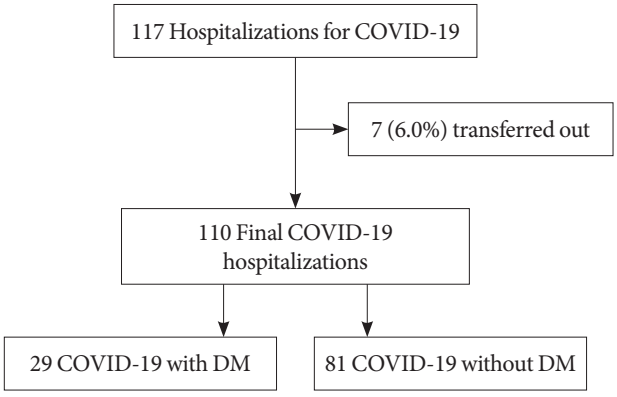

Fig. 1. Patient selection. COVID-19, coronavirus disease 2019; DM, diabetes mellitus.

Data collection and definitions

The patients' electronic medical records were reviewed. Data on patients' age, sex, comorbidities, symptoms, vital signs, radiological findings, severity based on the National Early Warning Score (NEWS), treatment, and clinical outcomes were collected. DM was defined as any of the following criteria: (1) a known history of diabetes; (2) taking oral or injected antihyperglycemic agents; (3) history of abnormal blood glucose levels based on diagnostic criteria for type 2 DM of the Korean Diabetes Association [10]. Data on glycosylated hemoglobin (HbA1c) level, DM duration, oral antihyperglycemic agents (OHAs), insulin, and renin-angiotensin system (RAS) inhibitors were collected from patients with DM.

NEWS [11] is an early warning score facilitating the early detection of and response to deterioration of patient's condition and consists of seven parameters: pulse oximetry, oxygen, pulse, systolic blood pressure, respiration rate, temperature, and central nervous system status. Each parameter is assigned a score of 0 to 3 points. The score reflects the degree to which the parameters differ from the normal range.

Acute respiratory distress syndrome (ARDS) was diagnosed according to the Berlin definition [12]. Septic shock was defined according to the Third International Consensus Definitions for sepsis and septic shock (Sepsis-3) [13]. Acute cardiac injury was defined as a serum troponin I level above the 99th

percentile upper reference limit or new abnormal electrocardiography and echocardiography findings [14]. Acute kidney injury was defined according to the Kidney Disease Improving Global Guidelines (KDIGO) for acute kidney injury [15].

In this study, we used the term "severe and critical outcome (SCO)" as an index of poor clinical outcome. SCO was defined as the composite outcome of ARDS, septic shock, intensive care unit (ICU) care, and 28-day mortality, referring to the classification of the Chinese Center for Disease Control and Prevention [2].

Statistical analysis

Continuous variables are expressed as mean±standard deviation and were compared by Student's *t*-test or the Mann-Whitney *U* test. Categorical variables were compared by the chi-squared test or Fisher's exact test. To determine the effects of DM and medications on SCO, multiple logistic regression analysis was performed after adjusting for covariates. In all analyses, two-tailed $P<0.05$ was taken to indicate statistical significance. All statistical analyses were performed using SPSS software version 24.0 (IBM Co., Armonk, NY, USA).

RESULTS

Baseline characteristics and clinical outcomes of COVID-19 patients according to the presence of DM

Table 1 shows the baseline characteristics of all patients and a comparison of patients with and without DM. The mean age of the total patient population was 56.9 years and the male to female ratio was 1:1.3. Smokers accounted for 14.5%. A total of 29 patients had DM (26.4%). DM patients had a higher mean age than patients without DM ($n=81$) (66.3±8.9 years vs. 53.5±17.9 years, respectively; $P<0.001$). Systolic and diastolic blood pressures were higher in patients with DM than in those without DM (both $P<0.05$). Hypertension was the most common comorbidity among all participants (33.6%), and more than half of the DM patients had a diagnosis or were taking medication for hypertension. On physical examination, there were no differences in symptoms between groups, except headaches were more frequent among non-DM patients ($P=0.020$). Bilateral pneumonia was common in DM patients, but the difference in radiologic findings (unilateral pneumonia, bilateral pneumonia, and multiple ground-glass opacity) compared to non-DM patients was not statistically significant ($P=0.191$). DM patients had higher white blood cell counts, neutrophil counts, lactate dehydrogenase, serum glucose, and C-reactive protein levels and lower albumin level compared to non-DM patients (all $P<0.05$).

Table 2 shows the severity, clinical outcomes, and treatment strategy of COVID-19 patients with and without DM. DM patients, compared to subjects without DM, had higher NEWS (4.0±4.2 vs. 1.9±2.1, $P=0.015$) and rates of progression to mortality (17.2% vs. 1.2%), ARDS (37.9% vs. 8.6%), septic shock (24.1% vs. 1.2%), ICU care (27.6% vs. 6.2%), and acute cardiac injury (27.6% vs. 6.2%) (all $P<0.01$). In addition, DM patients had higher rates of oxygen and invasive mechanical ventilation treatments (both $P<0.01$) and prescription of hydroxychloroquine medication ($P=0.022$).

The rates of progression to SCO were significantly higher with patients aged ≥70 years old compared to subjects <70 years old (42.3% vs. 9.6%, $P=0.01$), and in DM patients compared to subjects without DM (44.8% vs. 7.5%, $P<0.001$). The effect of age and DM on the risk of SCO in COVID-19 was analyzed (Fig. 2A). After adjustments for age, sex, smoking status, and the presence of comorbidities, age of ≥70 years old (odds ratio [OR], 7.106; $P=0.005$) and DM (OR, 10.771; $P<0.001$) significantly increased the risk of SCO, whereas hypertension, chronic lung disease, and malignancy had no effect on severity of outcomes.

Analysis of factors affecting SCO in COVID-19 patients with DM

We extracted diabetic patients ($n=29$) and explored the effects of age, DM control status, and medications on clinical outcomes. Twelve were newly diagnosed with DM on admission. Comparisons of clinical characteristics and outcomes according to age with a cutoff of 70 years are presented in Table 3. Compared to DM patients <70 years old ($n=18$), older DM patients (≥70 years old, $n=11$) were significantly older (60.9±6.2 years vs. 75.3±3.6 years, respectively; $P<0.001$) but there was no difference in sex ratio ($P=0.702$). The HbA1c and serum glucose levels, DM duration, and medication histories of OHAs, insulin and RAS inhibitors were not different between groups (all $P>0.05$). NEWS was not different between groups (3.3±4.1 vs. 5.3±4.5, respectively; $P=0.204$), but SCO was more frequent in DM patients ≥70 years old (27.8% vs. 72.7%, respectively; $P=0.027$).

The effects of age, HbA1c, and serum glucose level on SCO in COVID-19 patients with DM were evaluated (Fig. 2B). After adjustments, age significantly increased the risk of SCO

Table 1. Comparison of baseline anthropometric, symptom, and laboratory characteristics between coronavirus disease 2019 patients with and without diabetes

Variable	All patients (*n*=110)	With DM (*n*=29)	Without DM (*n*=81)	*P* value
Age, yr	56.9±17.0	66.3±8.9	53.5±17.9	<0.001
Male sex	48 (43.6)	14 (48.3)	34 (42.0)	0.664
Smoker	16 (14.5)	7 (24.1)	9 (11.1)	0.123
Packs per year	29.2±26.7	26.6±17.9	31.2±32.9	0.918
Vital signs on admission				
Body temperature, °C	37.2±0.7	37.1±0.7	37.2±0.6	0.501
Heart rate, beats/min	86.0±13.8	86.8±15.2	85.7±13.3	0.719
Respiratory rate	21.0±2.8	22.1±4.4	20.6±1.9	0.085
Systolic BP, mm Hg	128.1±18.6	136.2±19.9	125.2±17.4	0.006
Diastolic BP, mm Hg	79.9±12.2	84.0±13.2	78.5±11.6	0.038
Comorbidities				
Hypertension	37 (33.6)	16 (55.2)	21 (25.9)	0.006
Chronic lung disease	4 (3.6)	2 (6.9)	2 (2.5)	0.283
Malignancy	6 (5.5)	2 (6.9)	4 (4.9)	0.653
Cardiovascular disease	10 (9.1)	5 (17.2)	5 (6.2)	0.125
Cerebrovascular disease	4 (3.6)	3 (10.3)	1 (1.2)	0.055
Symptoms on admission				
Fever	62 (56.4)	16 (55.2)	46 (56.8)	1.000
Cough	58 (52.7)	11 (37.9)	47 (58.0)	0.083
Sputum	38 (34.5)	7 (24.1)	31 (38.3)	0.183
Myalgia	37 (33.6)	8 (27.6)	29 (35.8)	0.497
Dyspnea	37 (33.6)	12 (41.4)	25 (30.9)	0.362
Headache	26 (23.6)	2 (6.9)	24 (29.6)	0.020
Diarrhea	11 (10.0)	1 (3.4)	10 (12.3)	0.282
Radiological findings				0.191
Unilateral pneumonia	17 (15.5)	2 (6.9)	15 (18.5)	
Bilateral pneumonia	46 (41.8)	18 (62.1)	28 (34.6)	
Multiple ground-glass opacity	39 (35.5)	9 (31.0)	30 (37.0)	
Laboratory results				
White blood cell count, $\times 10^9$/L	6.7±3.3	7.8±2.9	6.3±3.4	0.040
Neutrophil count, $\times 10^9$/L	4.7±3.3	6.0±3.1	4.3±3.3	0.022
Platelets, $\times 10^9$/L	244.1±103.5	237.7±92.0	246.3±107.8	0.700
Albumin, g/dL	3.7±0.6	3.4±0.6	3.9±0.5	<0.001
Lactate dehydrogenase, IU/L	625.9±331.7	801.4±453.3	559.0±243.7	0.010
Serum glucose, mg/dL	133.6±61.8	192.1±94.2	112.7±20.3	<0.001
eGFR, mL/min/1.73 m^2 (MDRD)	89.9±23.5	82.6±23.8	92.5±23.0	0.050
C-reactive protein, mg/dL	5.8±8.4	9.9±10.2	4.3±7.1	0.011
Procalcitonin, ng/mL	0.5±2.6	1.2±4.6	0.2±1.3	0.260

Values are presented as mean±standard deviation or number (%).
DM, diabetes mellitus; BP, blood pressure; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

Table 2. Comparison of clinical outcomes and treatment between coronavirus disease 2019 patients with and without diabetes

Variable	All patients (*n*=110)	With DM (*n*=29)	Without DM (*n*=81)	*P* value
Severity scoring				
NEWS	2.5±3.0	4.0±4.2	1.9±2.1	0.015
Clinical outcomes				
28-day mortality	6 (5.5)	5 (17.2)	1 (1.2)	0.005
ARDS	18 (16.4)	11 (37.9)	7 (8.6)	0.001
Septic shock	8 (7.3)	7 (24.1)	1 (1.2)	<0.001
ICU care	13 (11.8)	8 (27.6)	5 (6.2)	0.005
Acute cardiac injury	13 (11.8)	8 (27.6)	5 (6.2)	0.005
Acute kidney injury	9 (8.2)	5 (17.2)	4 (4.9)	0.052
Treatment				
Oxygen	38 (34.5)	18 (62.1)	20 (24.7)	0.001
HFNC	10 (9.1)	4 (13.8)	6 (7.4)	0.451
IMV	11 (10.0)	8 (27.6)	3 (3.7)	0.001
CRRT	3 (2.7)	2 (6.9)	1 (1.2)	0.169
ECMO	4 (3.6)	3 (10.3)	1 (1.2)	0.055
Antibiotics	108 (98.2)	27 (93.1)	81 (100.0)	0.068
Lopinavir/ritonavir	106 (96.4)	27 (93.1)	79 (97.5)	0.283
Hydroxychloroquine	91 (82.7)	28 (96.6)	63 (77.8)	0.022
Glucocorticoid	21 (19.1)	8 (27.6)	13 (16.0)	0.270

Values are presented as mean±standard deviation or number (%).
NEWS, National Early Warning Score; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; HFNC, high flow nasal cannula; IMV, invasive mechanical ventilation; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.

Table 3. Comparison of clinical characteristics and outcomes between younger (<70 years) and older (≥70 years) coronavirus disease 2019 patients with diabetes

Variable	Age <70 yr (*n*=18)	Age ≥70 yr (*n*=11)	*P* value
Age, yr	60.9±6.2	75.3±3.6	<0.001
Male sex	9 (50)	4 (36.4)	0.702
HbA1c, %	7.8±1.7	7.36±2.0	0.611
Serum glucose, mg/dL	178.9±69.0	213.6±126.1	0.465
DM duration, yr	2.8±4.4	9.0±11.6	0.133
Newly diagnosed DM	9 (50.0)	3 (27.3)	0.317
Medications			
Oral anti-hyperglycemic drugs			
No medication	10 (58.8)	3 (30.0)	0.236
On Medication	7 (41.2)	7 (70.0)	
Metformin	6 (35.3)	5 (50.0)	0.687
DPP4i	5 (29.4)	1 (10.0)	0.363
Sulfonylurea	2 (11.8)	2 (20.0)	0.613
Others (TZD, SGLT2i, AGI)	2 (11.8)	2 (20.0)	0.613
Insulin	1 (10.0)	0	0.675
RAS inhibitors	8 (47.1)	6 (60.0)	0.695
NEWS	3.3±4.1	5.3±4.5	0.204
Severe and critical outcome[a]	5 (27.8)	8 (72.7)	0.027

Values are presented as mean±standard deviation or number (%).
HbA1c, glycosylated hemoglobin; DM, diabetes mellitus; DPP4i, dipeptidyl peptidase 4 inhibitor; TZD, thiazolidinedione; SGLT2i, sodium-glucose transport protein 2 inhibitor; AGI, α-glucosidase inhibitor; NEWS, National Early Warning Score.
[a]Composite outcome of acute respiratory distress syndrome, septic shock, intensive care unit care, and mortality within 28 days.

(OR, 1.175; *P*=0.014), whereas HbA1c and serum glucose had no effect on SCO. We also evaluated the effects of medications on SCO, acute cardiac injury, and acute kidney injury in COVID-19 patients with DM (Fig. 3). The usage of metformin or RAS inhibitors had no effect on SCO, but RAS inhibitors showed protective effects against acute cardiac injury (OR, 0.048; *P*=0.045).

We investigated whether poor glycemic control affects the prognosis of COVID-19 patients (Supplementary Table 1). Compared to diabetic patients with HbA1c <8% (*n*=21), poorly controlled (HbA1c ≥8%, *n*=8) patients had higher levels of HbA1c (6.9±0.5 vs. 10.0±1.9, respectively) and serum glucose (163.9±56.0 vs. 266.4±133.5, respectively), and had longer duration of DM (2.5±3.9 vs. 11.4±12.5, respectively) (all *P*<0.05). However, age, sex ratio, medication histories, NEWS, and SCO were not different between groups (all *P*>0.05).

DISCUSSION

The results of the present study showed that the elderly over 70 years old and the presence of DM significantly impacted the clinical course of COVID-19. Patients with DM showed higher severity scores (NEWS) and more frequently progressed to SCO than patients without DM. Among DM patients, age significantly affected SCO, and RAS inhibitors showed beneficial effects against acute cardiac injury.

In recent reports of COVID-19 from China, the prevalence of comorbid DM was 7.4% to 20%, and patients with cardio-

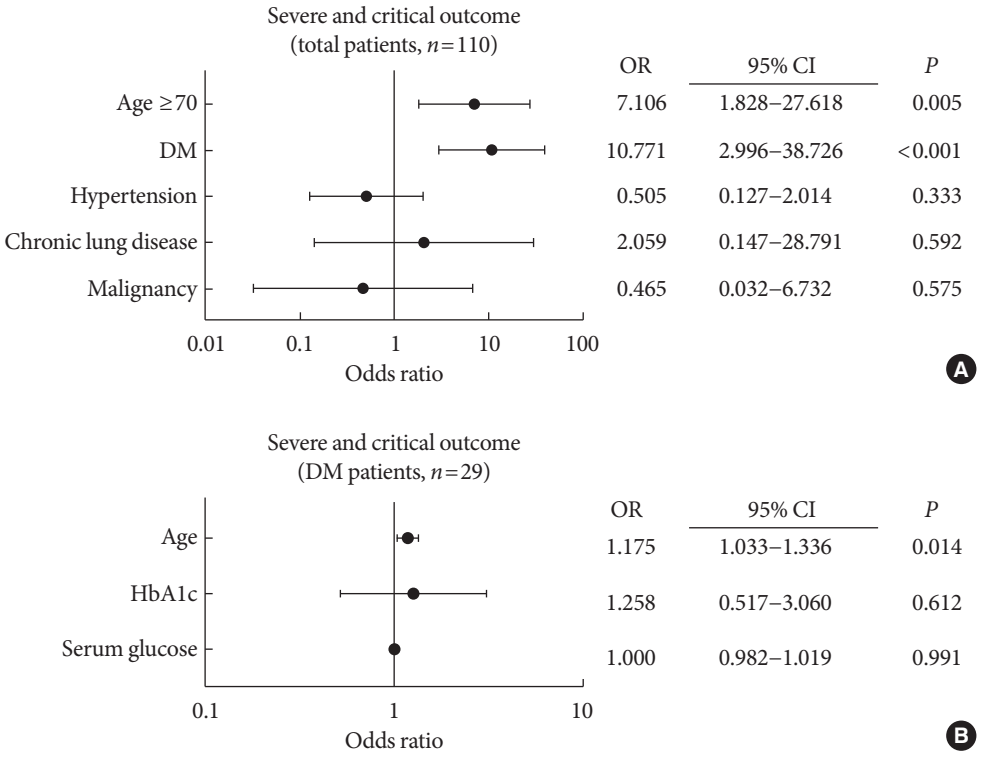

Fig. 2. Diabetes mellitus (DM) and age as a risk factor for severe and critical outcomes in patients with coronavirus disease 2019. Severe and critical outcomes: composite outcome of acute respiratory distress syndrome, septic shock, intensive care unit care, and mortality within 28 days. Multivariate logistic regression analysis was adjusted by (A) age (<70:≥70 years old), sex, smoking status, and the presence of comorbidities (diabetes mellitus, hypertension, chronic lung disease, and malignancy) in the total number of patients and (B) age (continuous), sex, smoking status, and glycosylated hemoglobin (HbA1c), and serum glucose levels among diabetic patients. The odds ratios (ORs) are presented in $\log_{10}$. CI, confidence interval.

metabolic disease had a severe clinical course [16]. Various results have been reported as to whether DM is a significant risk factor for disease progression of COVID-19. Guo et al. [9] reported higher levels of inflammation-related biomarkers in DM patients compared to non-DM patients. Zhou et al. [17] reported significant numbers of patients with DM in the non-survivor group, but the presence of DM did not significantly increase the risk of mortality. Wu et al. [8] reported that, after 40 days of follow-up, the presence of DM increased the risk of progressing to ARDS but did not affect mortality rate. In the present study, patients with DM had high levels of inflammation-related biomarkers and increased risk of SCO, including 28-day mortality. These data indicate that special attention should be paid to COVID-19 patients with comorbid DM.

The impacts of DM on the clinical course of SARS and Middle East respiratory syndrome (MERS) have been verified previously. The presence of DM and fasting plasma glucose level ≥126 mg/dL increased the risk of death in SARS by 6.3 and 3.3 times, respectively, and emphasized that adequate blood glucose control during treatment could improve prognosis [18]. In a meta-analysis in MERS cases, DM patients had 1.8 times increased risk of death [19]. In diabetic mice exposed to MERS-CoV, the duration of the severe disease phase was prolonged and the recovery was delayed, independently of viral titer, which was due to dysregulation of the immune response [20]. Previous reports and the results of the present study indicated that the progression of COVID-19 is also affected by DM.

Angiotensin-converting enzyme 2 (ACE2) acts as a cellular receptor for SARS-CoV and SARS-CoV2 [21], enabling acute viral replication. Accordingly, the causes of increased susceptibility to COVID-19 in diabetic patients was suggested to be related to diminished T cell function, increased susceptibility to cytokine storm, and increased ACE2 expression [22]. In addition, there is emerging evidence that the usage of drugs that increase ACE2 expression, such as RAS inhibitors (ACE inhibitors and angiotensin II receptor blockers), thiazolidinediones,

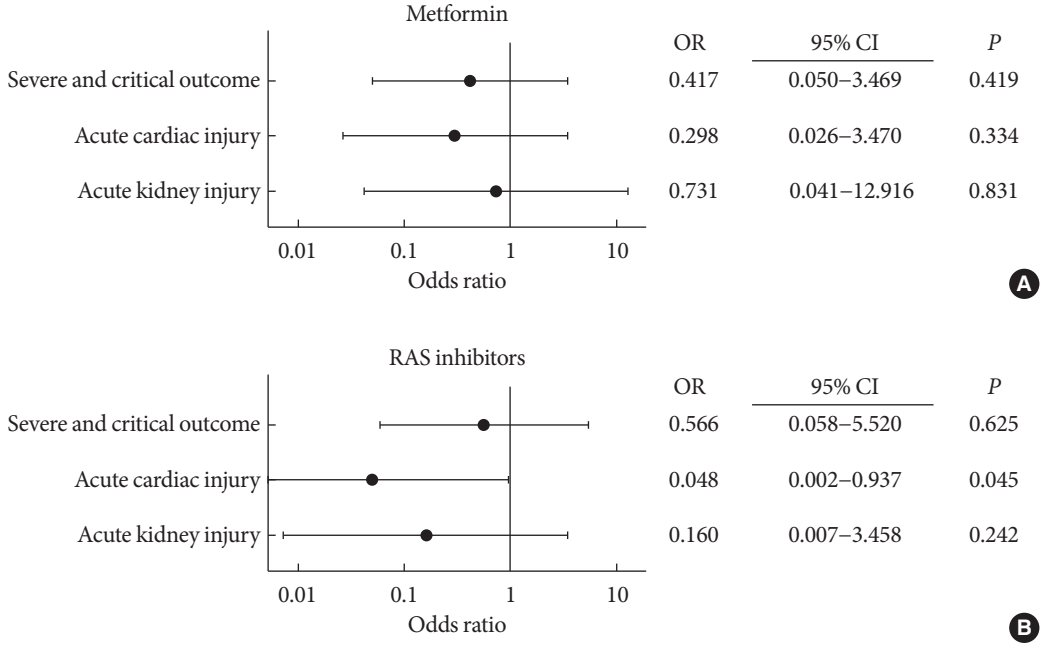

Fig. 3. Effects of (A) metformin and (B) RAS inhibitors on severe and critical outcomes, acute cardiac injury, and acute kidney injury in diabetic patients with coronavirus disease 2019. Severe and critical outcomes: composite outcome of acute respiratory distress syndrome, septic shock, intensive care unit care, and mortality within 28 days. Multivariate logistic regression analysis was adjusted by age, sex, smoking status, and glycosylated hemoglobin level. The odds ratios (ORs) are presented in $\log_{10}$. CI, confidence interval.

and ibuprofen, may accelerate the development of COVID-19 [23]. In addition, glucagon like peptide-1 agonist [24] and atorvastatin [25] upregulate ACE2, so they should be used with caution. In the case of MERS-CoV, dipeptidyl peptidase 4 (DPP4) was shown to be a functional cellular receptor [26], so it was suggested that the use of DPP4 inhibitors may slow the progression of COVID-19 infection [27]. In the present study, neither RAS inhibitors nor metformin exacerbated the course of COVID-19, so the discontinuation or modification of these drugs does not appear to be necessary.

This study had some limitations. First, we included only our experience in a single tertiary center in Korea and recognize that there are limitations to generalizing these findings to other situations. However, the proportion of moderate to high-risk (NEWS ≥5) patients among the participants in this study was about 20%, which was a similar pattern to those of previous studies. Amidst the global pandemic of COVID-19, each country and city is showing quite different outcomes, depending on their healthcare systems and resources [28]. These findings may provide insight for the operation of healthcare systems that are similar to those of South Korea. Second, we cannot exclude the effects of glycemic control or DM complications on prognosis of COVID-19 patients. There are no data regarding the optimal glycemic target for patients with COVID-19 and DM, and our study only showed the clinical outcomes according to HbA1c level. In the present study, the poorly controlled group, as defined by HbA1c ≥8%, did not show different outcomes with regard to severity or mortality. Surprisingly, however, we found that about 40% of the patients in the DM group had been newly diagnosed with DM, indicating heterogeneity within the DM group. Further large-scale studies on glycemic control and COVID-19 prognosis would provide more insight. Meanwhile, healthcare providers should pay attention to the possibility of "hidden diabetes" in COVID-19 patients.

This study had some strengths. To our knowledge, this is the first study suggesting effects of antidiabetic medications or glycemic control (indicated by HbA1c) on the clinical course of COVID-19. These findings provide insight into factors that affect the course of COVID-19 in patients with DM. In contrast to concerns raised previously, OHA and RAS inhibitors did not significantly affect the severity of COVID-19, suggesting that patients with DM do not have to stop taking their medications.

In conclusion, COVID-19 patients with DM had higher severity and higher rates of severe outcomes, including 28-day mortality, than those without DM. After adjustment for other risk factors, DM was an independent risk factor for SCO in COVID-19 patients. Among patients with DM, older age significantly increased the risk of SCO but RAS inhibitors and OHA did not affect the outcomes. Given these potentially devastating effects of DM, especially in older patients, intensive and aggressive monitoring is needed in COVID-19.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0105.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

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

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