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The Clinical Characteristics and Outcomes of Patients with Moderate-to-Severe Coronavirus Disease 2019 Infection and Diabetes in Daegu, South Korea

Mi Kyung Kim[1,*], Jae-Han Jeon[2,*], Sung-Woo Kim[3], Jun Sung Moon[4], Nan Hee Cho[1], Eugene Han[1], Ji Hong You[1], Ji Yeon Lee[1], Miri Hyun[1], Jae Seok Park[1], Yong Shik Kwon[1], Yeon-Kyung Choi[2], Ki Tae Kwon[2], Shin Yup Lee[2], Eon Ju Jeon[3], Jin-Woo Kim[3], Hyo-Lim Hong[3], Hyun Hee Kwon[3], Chi Young Jung[3], Yin Young Lee[4], Eunyeoung Ha[4], Seung Min Chung[4], Jian Hur[4], June Hong Ahn[4], Na-young Kim[5], Shin-Woo Kim[5], Hyun Ha Chang[5], Yong Hoon Lee[5], Jaehee Lee[5], Keun-Gyu Park[5], Hyun Ah Kim[1], Ji-Hyun Lee[3]

[1]Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, Daegu,
[2]Department of Internal Medicine, Kyungpook National University Chilgok Hospital, School of Medicine, Kyungpook National University, Daegu,
[3]Department of Internal Medicine, Daegu Catholic University Hospital, Daegu Catholic University School of Medicine, Daegu,
[4]Department of Internal Medicine, Yeungnam University Hospital, Yeungnam University College of Medicine, Daegu,
[5]Department of Internal Medicine, Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea

Background: Coronavirus disease 2019 (COVID-19) is a global pandemic that had affected more than eight million people worldwide by June 2020. Given the importance of the presence of diabetes mellitus (DM) for host immunity, we retrospectively evaluated the clinical characteristics and outcomes of moderate-to-severe COVID-19 in patients with diabetes.
Methods: We conducted a multi-center observational study of 1,082 adult inpatients (aged ≥18 years) who were admitted to one of five university hospitals in Daegu because of the severity of their COVID-19-related disease. The demographic, laboratory, and radiologic findings, and the mortality, prevalence of severe disease, and duration of quarantine were compared between patients with and without DM. In addition, 1:1 propensity score (PS)-matching was conducted with the DM group.
Results: Compared with the non-DM group (n=847), patients with DM (n=235) were older, exhibited higher mortality, and required more intensive care. Even after PS-matching, patients with DM exhibited more severe disease, and DM remained a prognostic factor for higher mortality (hazard ratio, 2.40; 95% confidence interval, 1.38 to 4.15). Subgroup analysis revealed that the presence of DM was associated with higher mortality, especially in older people (≥70 years old). Prior use of a dipeptidyl peptidase-4 inhibitor or a renin-angiotensin system inhibitor did not affect mortality or the clinical severity of the disease.
Conclusion: DM is a significant risk factor for COVID-19 severity and mortality. Our findings imply that COVID-19 patients with DM, especially if elderly, require special attention and prompt intensive care.

Keywords: COVID-19; Diabetes mellitus; Mortality; Prognosis

INTRODUCTION

Within a few weeks of the first report of coronavirus disease 2019 (COVID-19) in Wuhan, China, the first case of COVID-19 was confirmed in South Korea [1]. Subsequently, there was an exponential increase in the number of COVID-19 cases in South Korea during February and March 2020 [2]. In May 2020, of the 11,344 virus-positive patients in the whole of Ko-

Corresponding authors: Hyun Ah Kim https://orcid.org/0000-0002-9125-7156
Department of Internal Medicine, Keimyung University Dongsan Hospital, Keimyung University School of Medicine, 1035 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Korea
E-mail: hyunah1118@dsmc.or.kr

Ji-Hyun Lee https://orcid.org/0000-0002-5671-0875
Department of Internal Medicine, Daegu Catholic University Hospital, Daegu Catholic University School of Medicine, 33 Duryugongwon-ro 17-gil, Nam-gu, Daegu 42472, Korea
E-mail: jhlee9@cu.ac.kr

*Mi Kyung Kim and Jae-Han Jeon contributed equally to this study as first authors.

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rea, 65% (6,880 patients) were in the fourth-largest city, Daegu, because of a large outbreak that was attributed to a religious assembly. Among the patients, those whose symptoms were mild were primarily cared for at "therapeutic living centers," whereas acutely and severely ill patients were admitted to five university hospitals in Daegu [3]. These hospitals had readily available high-flow nasal cannulae, mechanical ventilation, continuous renal replacement therapy (CRRT), extracorporeal membrane oxygenation (ECMO), and intensive care units (ICUs), the provision of which was managed by mutual cooperation among the staff of the hospitals. Therefore, patients with COVID-19 in the Daegu region who were admitted to these hospitals were moderately-to-severely ill, but were cared for appropriately and in a timely fashion.

Patients with diabetes mellitus (DM) or hyperglycemia are susceptible to infection because of defects in their innate immunity that result in defective phagocytosis and neutrophil chemotaxis [4,5]. Moreover, among several risk factors, DM *per se* is considered to be a major contributor to the severity and mortality rate associated with previously identified respiratory viral infections, including Middle East respiratory syndrome coronavirus and severe acute respiratory syndrome coronavirus 2 [6,7]. Therefore, DM is considered to be an important risk factor for the severity of and mortality associated with COVID-19. Furthermore, some previous studies have shown that DM increases the mortality rate of patients with COVID-19 [8,9], although others did not show a difference in mortality between COVID-19 patients with or without DM [10,11]. Because individuals with DM tend to be older and have more comorbidities than those without DM, the assessment of DM as an independent risk factor for COVID-19 outcomes is challenging. In addition, because COVID-19 infection, as its nomenclature suggests, is a novel viral disease, the impact of DM on the outcome of resulting disease has yet to be fully and appropriately assessed.

Therefore, in the present study, we determined whether the presence of DM affected the severity or mortality of COVID-19 by comparing patients with or without DM, and patients who were matched 1:1 using propensity score (PS)-matching.

METHODS

Study design and participants

We conducted a multi-center, retrospective, observational study. The study protocol was approved by the Institutional Review Board of Keimyung University Dongsan Hospital (2020-04-111) and individually by the Institutional Review Boards of each collaborating hospital. The necessity for informed consent was waived by the ethics boards of the hospitals because of the retrospective study design.

The study participants comprised adult patients (age >18 years) with COVID-19 that was laboratory-confirmed between 18 February 2020 and 31 March 2020. They were recruited from university hospitals (Daegu Catholic University Hospital, Keimyung University Dongsan Medical Center [Dongsan Hospital and Daegu Dongsan Hospital], Kyungpook National University Hospital, Kyungpook National University Chilgok Hospital, and Yeungnam University Hospital) in Daegu.

COVID-19 was diagnosed using a reverse transcription-polymerase chain reaction (RT-PCR) assay of nasal or pharyngeal swab specimens, and a confirmed case of COVID-19 was defined using a positive result on RT-PCR, irrespective of the clinical signs and symptoms present. A total of 1,100 patients were included in the study. Patients who were diagnosed with re-positive COVID-19 were excluded from the study. Patients who were admitted to more than two hospitals because of referral within the cohort were counted as a single case. After the exclusion of 18 patients, 1,082 were enrolled and allocated to a DM (n=235) or a non-DM (n=847) group. After PS-matching, 235 DM patients and 235 non-DM patients who had been matched for age, sex, and the presence of underlying disease (hypertension, cerebrovascular disease, cardiovascular disease, chronic kidney disease, chronic pulmonary disease, and cancer) were also compared (Fig. 1).

Data collection and definitions

We collected data from electronic medical records regarding the age, sex, vital signs, co-morbidities (hypertension, cerebrovascular disease, cardiovascular disease, chronic kidney disease, chronic pulmonary disease, and cancer), medication, laboratory findings, presence of pneumonia on chest radiographs or computed tomography (CT), treatment modality, and outcomes during hospitalization for all the participants. The major symptoms present (fever, cough, sputum, rhinorrhea, sore throat, myalgia, diarrhea, and shortness of breath) were also recorded. The laboratory findings included routine blood tests, glycosylated hemoglobin (HbA1c), C-reactive protein (CRP), procalcitonin, and serum indicators of liver or kidney injury. The presence of DM was defined on the basis of the participants' medical history and the diagnostic criteria for DM of the Kore-

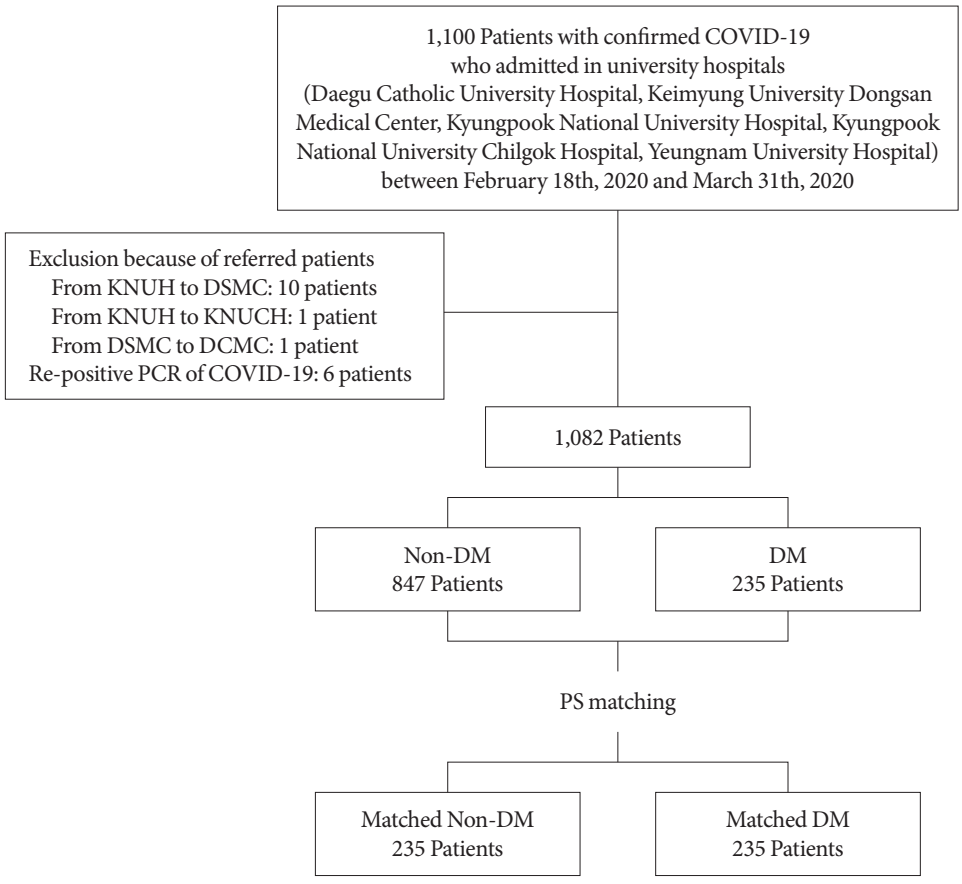

Fig. 1. Flow chart of the study. COVID-19, coronavirus disease 2019; KNUH, Kyungpook National University Hospital; DSMC, Dongsan Medical Center; KNUCH, Kyungpook National University Chilgok Hospital; DCMC, Daegu Catholic Medical Center; PCR, polymerase chain reaction; DM, diabetes mellitus; PS, propensity score.

an Diabetes Association [12]. Release from quarantine was defined using the instructions from the Korean Central Disease Control Headquarters: (1) clinically, the absence of a fever, without the necessity for an anti-pyretic agent, and an improvement in symptoms; (2) negative results of PCR tests performed twice at a 24-hour interval [13]; (3) severe disease defined as the necessity for the use of a high-flow nasal cannula, mechanical ventilation, CRRT, or ECMO, or admission to an ICU.

Quantification and statistical analysis

Statistical analyses were performed using SPSS Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). Continuous data are presented as means and standard deviations, and categorical data as frequency rates and percentages. Comparisons between two groups were made using Student's *t*-tests for continuous data and chi-square tests for categorical data. The risk of death and the corresponding hazard ratio (HR) were analyzed using the Kaplan-Meier method and a Cox proportional hazard model. Multivariate logistic analysis of the initial laboratory findings was performed to identify prognostic factors for severe disease and death from COVID-19. The relationships of severe disease and death with the current medication of patients with DM were also evaluated using multivariate logistic analysis. Differences with a two-sided $\alpha < 0.05$ were considered to be statistically significant.

RESULTS

Baseline characteristics of patients with COVID-19 on admission

The baseline characteristics of unmatched and PS-matched patients are shown in Table 1. A total of 1,082 patients with confirmed COVID-19 were enrolled, and 235 (21.81%) of these had

Table 1. Baseline characteristics of the full group of participants and of propensity score-matched patients with coronavirus disease 2019

Characteristic	Unmatched patients			1:1 PS-matched patients		
	Non-DM (*n*=847)	DM (*n*=235)	*P* value	Non-DM (*n*=235)	DM (*n*=235)	*P* value
Age, yr	56.5±18.0	68.3±11.9	<0.01	69.7±12.4	68.3±11.9	0.21
Male sex	278 (32.8)	106 (45.1)	<0.01	95 (40.4)	106 (45.1)	0.31
BMI, kg/m^2	23.5±3.6	24.2±3.2	0.03	24.0±3.24	24.2±3.16	0.62
SBP, mm Hg	133.2±20.7	137.6±19.6	<0.01	139.6±23.9	137.6±19.6	0.31
DBP, mm Hg	81.8±27.7	80.3±12.0	0.39	84.4±48.9	80.3±12.0	0.21
Body temperature, ℃	37.0±0.6	37.0±0.7	0.25	37.0±0.6	37.0±0.7	0.65
Co-morbidity						
Any co-morbidity	321 (37.9)	175 (74.5)	<0.01	168 (71.5)	175 (74.5)	0.47
Hypertension	227 (26.8)	147 (62.6)	<0.01	148 (63.0)	147 (62.6)	0.50
Heart disease	47 (5.5)	27 (11.5)	<0.01	22 (9.4)	27 (11.5)	0.27
Cerebrovascular disease	42 (5.0)	24 (10.3)	<0.01	27 (11.5)	24 (10.3)	0.38
Chronic kidney disease	14 (1.7)	18 (7.7)	<0.01	12 (5.1)	18 (7.7)	0.17
Chronic lung disease	56 (6.6)	16 (6.8)	0.51	18 (7.7)	16 (6.8)	0.43
Cancer	43 (5.1)	17 (7.2)	0.13	16 (6.8)	17 (7.2)	0.50
Symptoms and pneumonia						
Fever	356 (42.2)	110 (46.8)	0.12	102 (43.8)	110 (46.8)	0.29
Dyspnea	194 (23.0)	74 (31.5)	<0.01	58 (24.9)	74 (31.5)	0.07
Cough	430 (50.9)	100 (42.6)	0.01	107 (45.9)	100 (42.6)	0.26
Sputum	332 (39.3)	74 (31.5)	0.02	83 (35.6)	74 (31.5)	0.20
Rhinorrhea	136 (16.1)	20 (8.5)	<0.01	33 (14.2)	20 (8.5)	0.04
Sore throat	172 (20.4)	31 (13.2)	<0.01	43 (18.5)	31 (13.2)	0.08
Myalgia	266 (31.5)	60 (25.5)	0.04	65 (27.9)	60 (25.5)	0.32
Headache	245 (29.0)	41 (17.4)	<0.01	49 (21.0)	41 (17.4)	0.19
Diarrhea	168 (19.9)	29 (12.3)	<0.01	39 (16.7)	29 (12.3)	0.11
Pneumonia	582 (68.7)	206 (87.7)	<0.01	194 (82.6)	206 (87.7)	0.08
Medication						
Insulin	0	19 (8.1)		0	19 (8.1)	<0.01
Sulfonylurea	0	60 (25.5)		0	60 (25.5)	<0.01
Metformin	0	113 (48.1)		0	113 (48.1)	<0.01
α-Glucosidase inhibitor	0	2 (0.1)	0.03	0	2 (0.1)	0.03
Thiazolidinedione	0	7 (3.0)	<0.01	0	7 (3.0)	<0.01
DPP-4 inhibitor	0	85 (36.2)	<0.01	0	85 (36.2)	<0.01
SGLT-2 inhibitor	0	8 (3.4)	<0.01	0	8 (3.4)	<0.01
RAS inhibitor	105 (12.4)	70 (29.8)	<0.01	49 (20.9)	70 (29.8)	0.02
Calcium channel blocker	116 (13.7)	61 (26.0)	<0.01	70 (29.8)	61 (26.0)	0.05
β-Blocker	38 (4.5)	30 (12.8)	<0.01	23 (9.8)	30 (12.8)	0.32
Diuretic	35 (4.1)	40 (17.0)	<0.01	19 (8.1)	40 (17.0)	<0.01

(*Continued to the next page*)

Table 1. Continued

Characteristic	Unmatched patients			1:1 PS-matched patients		
	Non-DM (n=847)	DM (n=235)	P value	Non-DM (n=235)	DM (n=235)	P value
Laboratory findings on admission						
HbA1c, %	5.79±0.70	7.70±1.79	<0.01	5.72±0.44	7.70±1.79	<0.01
Glucose, mg/dL	109.9±30.6	186.7±101.1	<0.01	118.6±34.4	186.7±101.1	<0.01
WBCs, 10^3/μL	5.50±2.45	6.86±3.62	<0.01	5.99±3.06	6.86±3.62	<0.01
Neutrophils, %	60.4±14.6	69.0±15.1	<0.01	64.5±15.0	69.0±15.1	<0.01
Lymphocytes, %	28.8±12.5	21.5±12.1	<0.01	24.9±12.3	21.5±12.1	<0.01
Hb, g/dL	12.7±1.8	12.2±1.7	<0.01	12.7±4.0	12.2±1.7	0.11
Hct, %	38.1±4.6	36.4±4.9	<0.01	37.0±5.1	36.4±4.9	0.15
PLTs, 10^3/μL	226.2±83.3	234.0±104.3	0.23	223.9±84.3	234.0±104.3	0.25
CRP, mg/dL	7.2±21.2	10.6±18.8	0.03	9.0±22.6	10.6±18.8	0.38
Albumin, g/dL	3.93±0.49	3.64±0.56	<0.01	3.75±0.52	3.64±0.56	0.02
BUN, mg/dL	15.1±9.8	21.0±17.6	<0.01	19.1±12.6	21.0±17.6	0.18
Cr, mg/dL	0.91±1.16	1.27±1.70	<0.01	1.12±1.45	1.27±1.70	0.28
eGFR, mL/min/1.73 m^2	98.8±36.0	79.7±35.1	<0.01	85.7±34.9	79.7±35.1	0.06
AST, IU/L	44.4±216.8	40.8±42.6	0.80	51.9±311.9	40.8±42.6	0.59
ALT, IU/L	33.2±107.0	30.4±33.0	0.69	33.7±145.6	30.4±33.0	0.74
LDH, IU/L	458.8±260.8	552.6±432.1	<0.01	471.2±197.2	552.6±432.1	0.01
Procalcitonin, ng/mL	0.29±2.19	0.58±3.01	0.19	0.56±3.70	0.58±3.01	0.95

Values are presented as mean±standard deviation or number (%). P values were calculated using Student's t-test or the chi-square test.
PS, propensity score; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium glucose cotransporter-2; RAS, renin-angiotensin system; HbA1c, glycosylated hemoglobin; WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; PLT, platelet; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransaminase; LDH, lactate dehydrogenase.

DM (Table 1, Fig. 1). The mean ages of the participants were 56.5±18.0 and 68.3±11.9 years in the non-DM and DM group, respectively. Patients in their 50s were most common in the non-DM group, whereas in the DM group, patients in their 60s were most common, followed by those in their 70s (Supplementary Fig. 1). Five hundred and sixty-nine participants (67.2%) in the non-DM group and 129 (54.9%) in the DM group were women (P<0.01) (Table 1). After PS-matching, the percentages of women were 59.6% and 54.9%, respectively (P>0.05). As expected, patients with DM (73.7%) had more co-morbidities than those without DM (37.8%) (Table 1). After PS-matching, however, the prevalences of co-morbidities, such as hypertension, cerebrovascular accident, heart disease, chronic kidney disease, and cancer, did not differ between the two groups (Table 1). Among the participants with DM, 8.1% were using insulin. Metformin was the most commonly used oral antidiabetic drug (48.1%), followed by a dipeptidyl peptidase-4 (DPP-4) inhibitor (36.2%). With regard to antihypertensive drugs, renin-angiotensin system (RAS) inhibitors were the most commonly prescribed type of drug in the DM group, whereas calcium channel blockers were the most commonly prescribed type of drug in the non-DM group (Table 1).

Approximately 16% of the participants did not present with any symptoms. Cough, sputum, rhinorrhea, sore throat, myalgia, headache, and diarrhea, which are indicative of upper respiratory tract infection or viral infection, were more prevalent in the non-DM group of the unmatched cohort (Table 1). By contrast, dyspnea and radiographically diagnosed pneumonia were significantly more prevalent in the DM group (Table 1). Although PS-matching abrogated the differences in the prevalence of the majority of the symptoms listed above, rhinorrhea remained more common in the non-DM group (Table 1). Two-thirds of the participants were diagnosed as having pneumonia by radiologic examination following their admission. Pneumo-

Table 2. In-hospital management and outcomes of patients with coronavirus disease 2019

Variable	Unmatched patients			1:1 PS-matched patients		
	Non-DM	DM	*P* value	Non-DM	DM	*P* value
Treatment						
ICU	73 (8.6)	57 (24.3)	<0.01	34 (14.5)	57 (24.3)	<0.01
High flow O_2	52 (6.1)	35 (14.9)	<0.01	23 (9.8)	35 (14.9)	0.06
Ventilator	38 (4.5)	37 (15.7)	<0.01	18 (7.7)	37 (15.7)	<0.01
CRRT	8 (0.9)	15 (6.4)	<0.01	3 (1.3)	15 (6.4)	<0.01
ECMO	5 (0.6)	10 (4.3)	<0.01	3 (1.3)	10 (4.3)	0.04
Duration						
Confirmation-release[a], day	29.4±13.6	33.2±14.3	<0.01	31.9±13.4	33.2±14.3	0.39
Hospital length[a], day	24.6±13.3	29.3±15.1	<0.01	27.5±13.9	29.3±15.1	0.22
Outcome						
Release	759 (89.6)	182 (77.4)	<0.01	207 (88.1)	182 (77.4)	<0.01
Severe disease	94 (11.1)	65 (27.7)	<0.01	45 (19.1)	65 (27.7)	0.02
Death	41 (4.8)	44 (18.7)	<0.01	18 (7.7)	44 (18.7)	<0.01

Values are presented as number (%) or mean±standard deviation. All *P* values were calculated using Student's *t*-test or the chi-square test.
PS, propensity score; DM, diabetes mellitus; ICU, intensive care unit; CRRT, continuous renal replacement therapy; ECMO, extracorporeal membrane oxygenation.
[a]Only includes patients who had been released from quarantine.

nia was more prevalent on X-ray or chest CT in the DM group than in the non-DM group, although this difference was not significant in the PS-matched cohort ($P=0.08$). Analysis of the laboratory findings on admission showed higher HbA1c, serum glucose concentration, white blood cell (WBC) count, serum CRP, lactate dehydrogenase (LDH) activity, blood urea nitrogen, and creatinine; and lower lymphocyte count and serum albumin in participants with DM in the unmatched cohort. Furthermore, even after PS-matching, there were significantly higher serum glucose, HbA1c, LDH, and neutrophil count; and significantly lower lymphocyte count and serum albumin concentration. However, the serum CRP and creatinine concentrations were not significantly different (Table 1).

In-hospital management and outcomes

The number of deaths in the entire cohort was 85 (mortality rate, 7.85%) (Table 2). During hospitalization, 152 participants (14.04%) had severe disease, which was defined as a reliance on one or more of ICU care, high-flow O_2 nasal cannulae, mechanical ventilation, CRRT, or ECMO (Table 2). In the PS-matched cohort, more of the participants with DM developed severe disease than those without DM (Table 2). The prevalence of quarantine release was also significantly lower in the DM group (Table 2). In addition, in the unmatched cohort, the period of time between COVID-19 confirmation and quarantine release, and the duration of stay in hospital, were significantly longer in participants with DM than in those without DM (Table 2). However, after PS-matching, these differences were not statistically significant (Table 2).

The mortality rate was significantly higher in the DM group than in the non-DM group (18.7% vs. 7.7%) (Table 2). Not only in the entire cohort (Fig. 2A), but also in PS-matched participants, the DM group exhibited higher mortality than the non-DM group, as illustrated by the cumulative death rate (HR, 2.40; 95% confidence interval [CI], 1.38 to 4.15) (Fig. 2B).

We also stratified the PS-matched cohort according to their age and sex. Subgroup analysis showed that DM significantly increased the risk of mortality in participants aged ≥70 years (HR, 3.29; 95% CI, 1.72 to 6.32) (Fig. 3B), whereas DM did not increase this risk in participants aged <70 years (HR, 1.06; 95% CI, 0.36 to 3.32) (Fig. 3A). DM was associated with higher mortality, irrespective of sex (Fig. 3C and D).

Identification of the baseline laboratory parameters that influence the severity of COVID-19-related disease and death

Multivariate logistic analysis showed that high baseline WBC

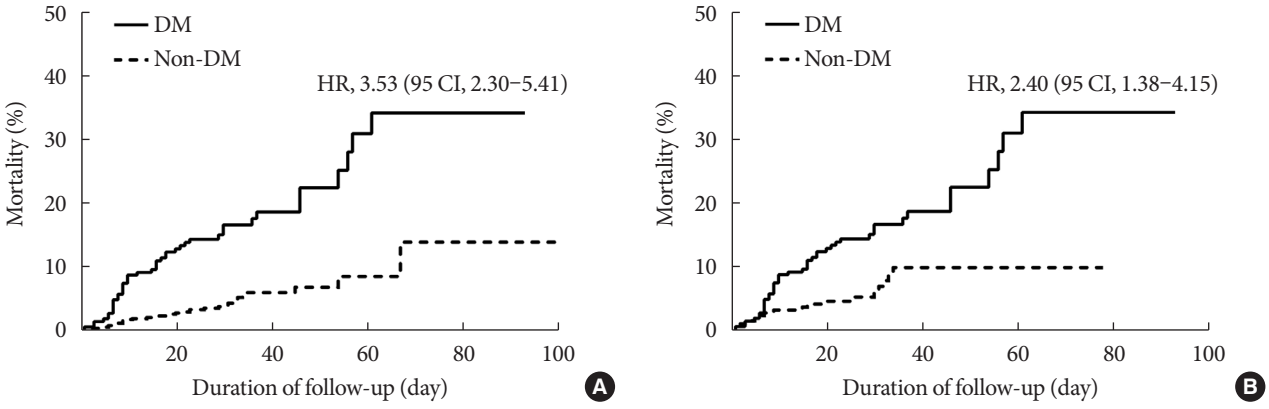

Fig. 2. Mortality due to coronavirus disease 2019 in all patients (A) and propensity score-matched patients (B). The data were analyzed using the Kaplan-Meier method, and hazard ratios were calculated using a Cox proportional hazards model. Data are expressed as hazard ratio (HR) (95% confidence intervals [CI]). DM, diabetes mellitus

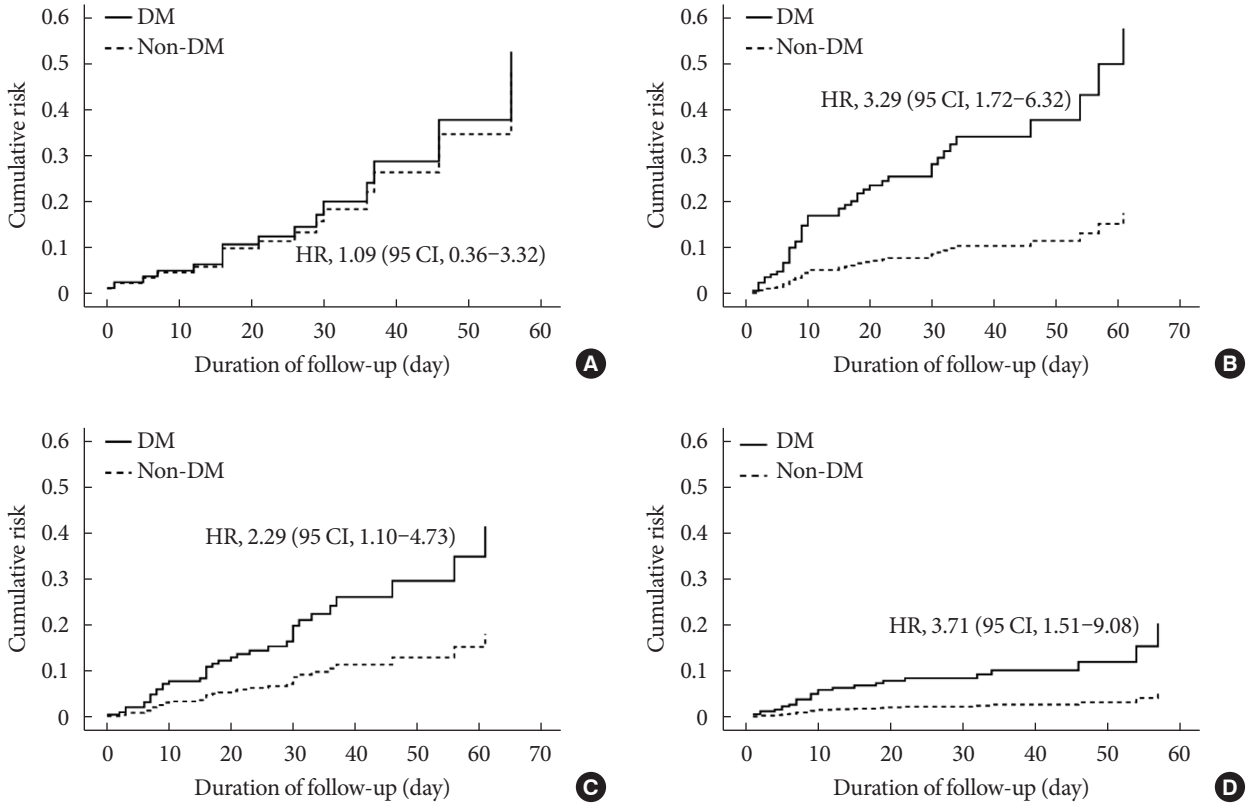

Fig. 3. Mortality of coronavirus disease 2019 patients in subgroups defined according to age and sex. Patients aged <70 years (A) and >70 years (B); and male (C) and female (D) patients. Data were analyzed using a Cox proportional hazards model. Data are expressed as hazard ratio (HR) (95% confidence intervals [CI]). The model was adjusted for age, sex, and the presence of underlying diseases.

count, high hemoglobin concentration, low platelet count, low albumin concentration, and high aspartate aminotransferase (AST) activity were associated with a higher risk of death in participants with DM (Table 3). Low platelet count, high AST activity, low alanine aminotransaminase (ALT) activity, and high LDH activity were associated with severe disease (Table

Table 3. Multivariate model for the prediction of severe disease or death in coronavirus disease 2019 patients

Variable	Non-DM patients		DM patients	
	Severe disease	Death	Severe disease	Death
Glucose, mg/dL	1.01 (1.00–1.02)	1.02 (1.00–1.04)	1.00 (1.00–1.01)	1.00 (0.99–1.00)
WBCs, 10^3/μL	1.01 (0.86–1.18)	1.02 (0.78–1.34)	1.12 (1.00–1.28)	1.22 (1.06–1.41)[a]
Hb, g/dL	1.13 (0.93–1.36)	0.97 (0.55–1.74)	1.14 (0.82–1.59)	1.55 (1.07–2.26)[b]
PLT, 10^3/μL	1.00 (0.99–1.01)	0.99 (0.97–1.00)	0.99 (0.99–1.00)[b]	0.99 (0.99–1.00)[b]
CRP, mg/dL	1.03 (1.01–1.05)[a]	1.03 (0.99–1.07)	0.99 (0.96–1.01)	0.99 (0.96–1.02)
Albumin, g/dL	0.15 (0.04–0.55)[a]	0.53 (0.04–7.76)	0.38 (0.14–1.02)	0.19 (0.06–0.56)[a]
eGFR, mL/min/1.73 m^2	1.00 (0.99–1.02)	1.00 (0.98–1.03)	0.99 (0.97–1.00)	0.99 (0.98–1.01)
AST, IU/L	1.09 (1.04–1.14)[a]	1.10 (1.02–1.19)[b]	1.05 (1.02–1.08)[a]	1.03 (1.00–1.06)[b]
ALT, IU/L	0.93 (0.88–0.98)[a]	0.93 (0.85–1.01)	0.96 (0.92–0.99)[a]	0.96 (0.92–1.01)
LDH, IU/L	1.00 (1.00–1.01)	1.00 (0.99–1.00)	1.00 (1.00–1.01)[b]	1.00 (1.00–1.00)

Data were analyzed using multivariate logistic regression, and all data are expressed as odds ratios (95% confidence intervals). The model was adjusted for age, sex, and the presence of underlying diseases.
DM, diabetes mellitus; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransaminase; LDH, lactate dehydrogenase.
[a]$P<0.01$, [b]$P<0.05$.

3). Among participants with DM, the baseline random serum glucose and CRP concentrations were not associated with severe disease or death (Table 3). However, among non-DM participants, high CRP concentration, low albumin concentration, high AST activity, and low ALT activity were predictors of severe disease. Of these, only high AST activity was also a predictor of death (Table 3).

Analysis of the relationships between the use of particular medications and in-hospital mortality

Angiotensin-converting enzyme 2 (ACE2) inhibitor and DPP-4 inhibitor use appear to affect the pathogenesis of coronaviruses [14,15]. Therefore, we next investigated whether the prior use of such medications affected the prognosis or mortality rate of participants with COVID-19, after adjustment for age, sex, and the presence of underlying diseases. As shown in Supplementary Table 1, the use of neither a RAS inhibitor nor a DPP-4 inhibitor was associated with higher prevalence of severe disease or death. Instead, the use of metformin or insulin tended to be associated with less severe disease and lower mortality, although these findings did not achieve statistical significance (Supplementary Table 1).

DISCUSSION

In the present study, we showed that patients with DM are at higher risk of severe COVID-19-related disease and mortality. Given the importance of the relationship between COVID-19 and DM, an international panel of experts has recently made practical recommendations for the management of DM in patients with COVID-19 [16]. Our findings underscore the importance of taking extra care of patients with DM who contract COVID-19.

In the present study, 21.8% of patients with COVID-19 had DM. A previous meta-analysis showed a mean prevalence of DM of 11% among patients with COVID-19 [9]. Because of the exponential increase in COVID-19 infections, doctors from the Daegu Medical Associations performed telephone consultations to check the status of patients who were confined at home and classified them on the basis of their disease severity. They were hospitalized if they exceeded a threshold score on a scoring system that consisted of the severity of disease, age, the presence of underlying disease, and social factors. Asymptomatic or mild cases were admitted to a "therapeutic living center" and closely monitored, whereas those with moderate-to-severe disease were admitted to university hospitals [3]. On the basis of the scoring system, most of the participants in the present study were classified as having moderate-to-severe disease.

The prevalence of DM in the present study cohort was almost twice that of the general population, presumably because individuals with severe disease who were at high risk of severe disease or death were preferentially admitted to the university

hospitals. Notably, unlike in other recently published studies [17,18], female patients made up the larger proportions of both the non-DM and DM groups in the present study. This is in contrast to the Chinese data [18] and data from another region of Korea [19]. This difference might be attributable to a specific demographic characteristic: the exponential spread of the virus in Daegu was initiated in a female-dominated religious group.

DM is an independent risk factor for the severity of and mortality associated with COVID-19 [9,20]. A previous large cohort study (a cohort of 7,336 COVID-19 patients with or without DM) showed that DM increases the mortality of patients and that strict glucose control improves the outcomes of COVID-19 [17]. An analysis of 1,950 COVID-19 patients also revealed that DM is a risk factor (HR, 1.59; 95% CI, 1.03 to 2.45) [8]. In addition, a meta-analysis showed that DM in patients with COVID-19 is associated with two-fold higher mortality compared with patients without DM [9]. These findings are highly suggestive that DM is an important factor in the prognosis of COVID-19. Nevertheless, several COVID-19 studies have not shown significant differences in disease severity or mortality in patients with or without DM, presumably because of the small numbers of participants [10,21]. In addition, a recent observational study showed that DM is not an independent risk factor for COVID-19-related mortality [11].

The findings of the present study also show that DM is associated with a higher risk of severe disease and mortality, regardless of sex. Furthermore, we identified a relationship between the presence of DM and higher mortality due to COVID-19 in older patients, but this relationship was not present in younger patients. A series of recent studies suggest that old age is a risk factor for mortality in patients with DM [11,22], but this evidence is insufficient to conclude that DM is not a risk factor for COVID-19-related mortality in young patients. However, on the basis of the results of the present study, it is possible to surmise that DM is more likely to be a risk factor in older patients than in younger patients.

In the present study, we did not identify any relationships between the use of specific medications and the outcomes associated with COVID-19 in DM patients. DPP-4 is a receptor for the human coronavirus-Erasmus Medical Center (hCoV-EMC) [15]. Although it is not clear whether this is also the case for COVID-19, and early studies have failed to identify relationships between the exposure to DPP-4 inhibitors and the outcomes of COVID-19 [23], an upregulation of DPP-4 in patients with type 2 DM remains a plausible explanation for the greater severity of COVID-19 in patients with DM [24]. Furthermore, it has been suggested that the ACE2 receptor is the primary receptor for coronavirus spike protein [16,25]. Greater glycosylation of both the spike protein and the ACE2 receptor, secondary to hyperglycemia, may modulate the binding of the virus and therefore might account for the greater severity of COVID-19 in hyperglycemic patients. In the present study, the disease was slightly less severe in patients who were administering metformin or insulin, but this trend did not achieve statistical significance. Furthermore, the use of RAS inhibitors did not affect mortality. The effect of medication on the mortality associated with COVID-19 remains controversial [23,26-28]. Therefore, our findings are in line with recent recommendations that unless contraindicated, the continuation of current medication is strongly recommended [17,29].

The present study had some limitations. First, after the diagnosis of the 31st case of COVID-19 in South Korea, there was an exponential increase in the number of COVID-19 diagnoses in Daegu. Because of a shortage of infrastructure and training of medical staff, there was incomplete documentation regarding exposure history and laboratory testing conducted in the patients. In particular, and as previously documented [22], HbA1c values for a considerable proportion of the participants were missing; therefore, our analysis of the impact of the degree of baseline glycemic control (i.e., HbA1c on admission) on the severity and mortality associated with COVID-19 was limited. Second, of the confirmed cases of COVID-19 in Daegu, 65.6% were associated with a single religious group, so it is unlikely that the data collected are representative of the general population. Furthermore, these patients were admitted to university hospitals because of their moderate-to-severe disease, and therefore the data are not representative of COVID-19 patients with mild disease. However, in spite of these limitations, the present study has a substantial strength: it is the first multicenter study to investigate the association between COVID-19 and DM in Daegu, Korea, the site of the first outbreak of COVID-19 outside Wuhan, China.

Our findings regarding severe COVID-19 patients corroborate a series of recent observations that DM is a risk factor for severe COVID-19-related disease, as well as mortality. Accumulating evidence and our own data both also suggest that old age is an independent risk factor for COVID-19 infection and the severity of the disease. The present findings strongly suggest that DM contributes to higher COVID-19-related mortality, especially in the elderly. Therefore, special attention should

be paid to older patients with DM during the treatment of COVID-19.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2020.0146.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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

ORCID

Mi Kyung Kim *https://orcid.org/0000-0001-5750-3598*
Jae-Han Jeon *https://orcid.org/0000-0002-9217-968X*
Hyun Ah Kim *https://orcid.org/0000-0002-9125-7156*
Ji-Hyun Lee *https://orcid.org/0000-0002-5671-0875*

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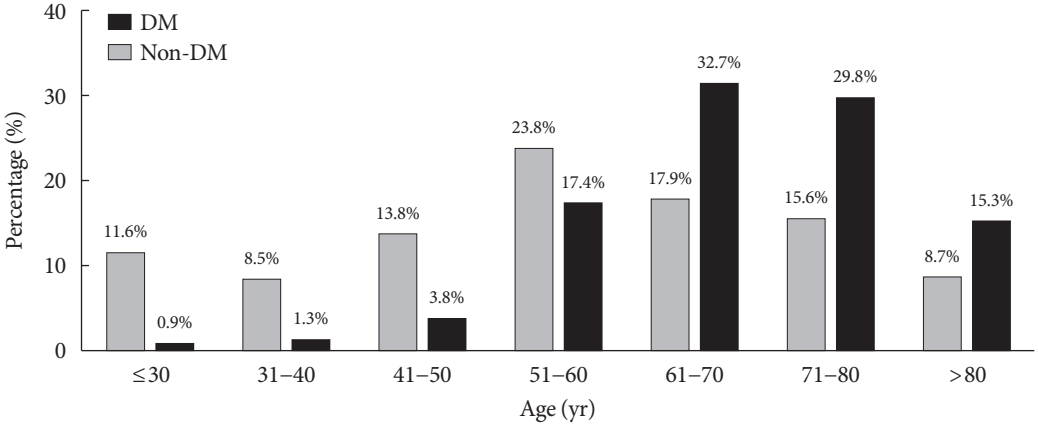
Supplementary Table 1. Odds ratios for severe disease and death in diabetes patients, according to their medication

	Severe disease		Death	
	Odds ratio	*P* value	Odds ratio	*P* value
Insulin	0.24 (0.04–1.39)	0.11	0.26 (0.03–2.63)	0.25
Sulfonylurea	1.16 (0.47–2.89)	0.74	0.84 (0.23–3.09)	0.79
Metformin	0.48 (0.19–1.24)	0.13	0.36 (0.10–1.23)	0.10
DPP-4 inhibitor	1.05 (0.44–2.49)	0.92	1.47 (0.45–4.78)	0.52
SGLT-2 inhibitor	1.75 (0.23–13.50)	0.59	5.05 (0.48–53.26)	0.18
RAS inhibitor	0.66 (0.24–1.76)	0.40	1.37 (0.37–5.07)	0.64

Data were analyzed using multivariate logistic regression and are expressed as odds ratios (95% confidence intervals). The model was adjusted for age, sex, and the presence of underlying diseases.
DPP-4, dipeptidyl peptidase-4; SGLT-2, sodium glucose cotransporter-2; RAS, renin-angiotensin system.



Supplementary Fig. 1. Age distribution of patients with or without diabetes mellitus (DM).