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Impact of diabetes and Krebs von den Lungen-6 on coronavirus disease 2019 severity: A single-center study from Japan

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ABSTRACT

Aims/Introduction: Diabetes mellitus is reported as a risk factor for increased coronavirus disease 2019 (COVID-19) severity and mortality, but there have been few reports from Japan. Associations between diabetes mellitus and COVID-19 severity and mortality were investigated in a single Japanese hospital.

Materials and Methods: Patients aged ≥20 years admitted to Osaka City General Hospital for COVID-19 treatment between April 2020 and March 2021 were included in this retrospective, observational study. Multivariable logistic regression analysis was carried out to examine whether diabetes mellitus contributes to COVID-19-related death and severity.

Results: Of the 262 patients included, 108 (41.2%) required invasive ventilation, and 34 (13.0%) died in hospital. The diabetes group (n = 92) was significantly older, more obese, had longer hospital stays, more severe illness and higher mortality than the non-diabetes group (n = 170). On multivariable logistic regression analysis, age (odds ratio [OR] 1.054, 95% confidence interval [CI] 1.023–1.086), body mass index (OR 1.111, 95% CI 1.028–1.201), history of diabetes mellitus (OR 2.429, 95% CI 1.152–5.123), neutrophil count (OR 1.222, 95% CI 1.077–1.385), C-reactive protein (OR 1.096, 95% CI 1.030–1.166) and Krebs von den Lungen-6 (OR 1.002, 95% CI 1.000–1.003) were predictors for COVID-19 severity (R^2 = 0.468). Meanwhile, age (OR 1.104, 95% CI 1.037–1.175) and Krebs von den Lungen-6 (OR 1.003, 95% CI 1.001–1.005) were predictors for COVID-19-related death (R^2 = 0.475).

Conclusions: Diabetes mellitus was a definite risk factor for COVID-19 severity in a single Japanese hospital treating moderately-to-severely ill patients.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first identified near Wuhan, China, in November 2019[1], and has subsequently spread worldwide. After the World Health Organization declared a pandemic condition on 11 February 2020, the number of infections and deaths continued to increase, and more than 240 million people have been infected and more than 4.9 million people had died worldwide by the end of October 2021[2]. In Japan, more than 1.7 million people have been infected, and approximately 18,000 people have died in the same period[3]. Despite development and commercialization of effective vaccines, it remains a great issue for public health.

Diabetes mellitus has been reported to be a risk factor for increased COVID-19 severity and mortality[4,5], as well as old age[6], obesity[7], smoking[8], chronic kidney disease[9], chronic obstructive pulmonary disease[10], hypertension[11], cardiovascular disease[12] and malignancy[13]. Wu *et al.*[14] reported from China that the mortality rate in patients with diabetes mellitus was approximately threefold higher compared with the overall mortality rate. Barron *et al.*[15] also reported from the UK that the

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adjusted odds ratio for COVID-19-related mortality was 1.80 in patients with type 2 diabetes mellitus. However, whether all patients would have received appropriate treatment during the pandemic is uncertain. In contrast, Japan is one of the few countries where the number of patients with COVID-19 is low compared with many other countries in the world, and all people have access to public health insurance, which means that, to date, almost all severe cases have received adequate treatment. Thus, examining the relationship between diabetes mellitus and COVID-19 in Japan might provide useful information as to whether diabetes mellitus is a risk factor for COVID-19 severity and death, even with appropriate medical care. To answer this question, whether diabetes mellitus contributes to COVID-19 severity and mortality, was examined in a retrospective, observational study.

MATERIALS AND METHODS

Study design

This was a retrospective, observational study of COVID-19 patients at Osaka City General Hospital (Osaka, Japan), a regional core hospital mainly treating moderately-to-severely ill COVID-19 patients. Patients admitted for treatment of COVID-19 between 1 April 2020 and 31 March 2021 were included in the present study. All patients were treated according to Japanese COVID-19 treatment guidelines[16]. The use of the data was approved by the Osaka City General Hospital Ethics Committee, and written, informed consent was obtained from all participants.

Patients' information

Patients were enrolled using the following inclusion criteria: (i) age ≥20 years; and (ii) diagnosis of SARS-CoV2 infection by reverse transcription polymerase chain reaction or antigen test. Patients were excluded using the following exclusion criteria: (i) age <20 years; (ii) transferred to another hospital within 3 days of admission; (iii) transferred to another hospital for continued active treatment; (iv) received palliative care because of no request for aggressive treatment; and (v) missing all or almost all data on laboratory and clinical characteristics. As a result, 262 patients were included in the present study (Figure 1).

Diabetes mellitus was defined as a confirmed diagnosis of diabetes mellitus in the past and/or on treatment, or hemoglobin A1c (HbA1c) ≥6.5% and plasma glucose ≥200 mg/dL on admission. Based on Japanese and National Institutes of Health (NIH) guidelines[16,17], the severity of COVID-19 was defined using the following criteria: mild, those who did not require oxygen administration (Japanese guidelines: mild-to-moderate I illness; NIH guidelines: mild-to-moderate illness); moderate, those who required non-invasive oxygen administration (Japanese guidelines: moderate II illness; NIH guidelines: severe illness); and severe, those who required intubation and invasive ventilation (Japanese guidelines: severe illness; NIH guidelines: critical illness). The duration of hospitalization was defined as the length of stay in Osaka City General Hospital. Discharge from hospital included discharge home, transfer for rehabilitation purposes and transfer due to stable illness.

Data collection and end-point definitions

The medical records were examined, and data were collected and checked by six researchers. From the electronic medical records, the following information was extracted: age, sex, weight and body mass index (BMI), smoking history, medical history and comorbidities, vital signs on admission, laboratory findings, and treatment and progress after admission. Laboratory findings included complete blood count, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, albumin, blood urea nitrogen, creatinine, uric acid, cholesterol, triglycerides, plasma glucose, HbA1c, C-reactive protein (CRP), Krebs von den Lungen-6 (KL-6) and D-dimer. The estimated glomerular filtration rate was calculated by the Japanese formula[18], using serum creatinine levels and age. Given the emergency conditions, laboratory parameters were not available for all patients, therefore, analyses were based on non-missing data. The number of missing parameters were KL-6: 21 cases; and D-dimer: 14 cases, respectively.

Patients were divided into the diabetes group and the non-diabetes group for analysis. The primary outcome was defined as COVID-19-related death during hospitalization. The secondary outcomes were defined as COVID-19 severity, days of hospitalization and days of invasive ventilation.

Statistical analysis

Continuous variables are expressed as medians and interquartile range (IQR), and categorical variables are expressed as counts and percentages. Patients were grouped by COVID-19 severity and the presence of diabetes mellitus. Comparisons between groups were carried out with Mann–Whitney's *U*-test for non-parametric continuous variables. Categorical variables were compared using the χ^2-test. Multivariable logistic regression analysis was carried out to examine factors contributing to COVID-19-related death and severity. Two models were designed for the analysis: model 1 was adjusted for age, sex, BMI, smoking status (current or ex-), presence of hypertension, coronary heart disease, respiratory disease, malignant neoplasm, estimated glomerular filtration rate, neutrophil, platelets, CRP, KL-6, D-dimer and the presence of diabetes mellitus; and model 2 included HbA1c instead of the presence of diabetes mellitus. For multivariable logistic regression analysis, patients who had mild or moderate severity were defined as the non-severe group. The significance level was set at $P = 0.05$. IBM SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA) was used for the analysis.

RESULTS

A total of 262 patients (184 [70.2%] men, 78 [29.8%] women) were included. The median age was 64 years (IQR 47–74 years), and the median BMI was 24.1 kg/m^2 (IQR 21.8–

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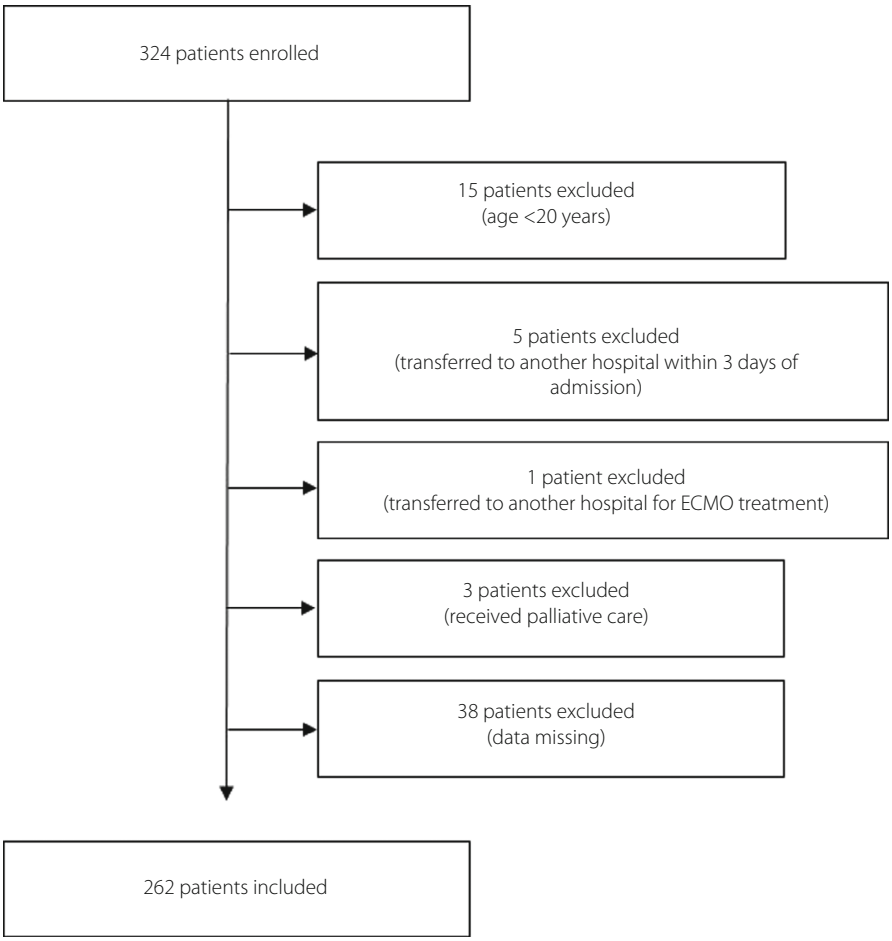

Figure 1 | Patient flow chart. ECMO, extracorporeal membrane oxygenation.

27.4 kg/m^2). Almost half of the patients were current or ex-smokers (133, 50.8%). The severe group that required invasive ventilation included 108 (41.2%) patients, seven of whom required extracorporeal membrane oxygenation management, and 34 (13.0%) died in hospital. The moderate group requiring non-invasive oxygen therapy included 96 (36.6%) patients, and the remaining 58 (22.1%) patients were classified in the mild group. Patients who required treatment with glucocorticoids, remdesivir and anticoagulants were 172 (65.6%), 127 (48.5%) and 164 (62.6%), respectively. The relationship between COVID-19 severity and treatment is shown in Table S1. A total of 92 (35.1%) patients had a diagnosis of diabetes mellitus before or at the time of admission. Other comorbidities and vital signs on admission are shown in Table 1.

Differences between patients with and without diabetes mellitus

The diabetes group was significantly older (70 vs 60 years, $P < 0.001$) and more obese (BMI 25.0 kg/m^2 vs 23.7 kg/m^2, $P = 0.026$) compared with the non-diabetes group. Systolic blood pressure was significantly higher (133 mmHg vs 126 mmHg, $P = 0.002$) and SpO_2 was significantly lower (94% vs 96%, $P < 0.001$) on admission. The diabetes group had a significantly longer hospital stay (15 days vs 12 days, $P = 0.003$), more severe illness (64.1% vs 29.4%, $P < 0.001$) and higher mortality (22.8% vs 7.6%, $P < 0.001$) compared with the non-diabetes group, whereas there was no difference in the duration of invasive ventilation (13 days vs 11 days, $P = 0.727$). Hypertension (63.0% vs 34.7%, $P < 0.001$) and dyslipidemia (46.7% vs 15.9%, $P < 0.001$) were significantly more common in the diabetes group, whereas there were no differences in other comorbidities between the two groups (Table 2). In the diabetes group, white blood cells, neutrophils, lactate dehydrogenase, blood urea nitrogen, creatinine, CRP, KL-6 and D-dimer were significantly higher, whereas albumin and estimated glomerular filtration rate were significantly lower, compared with the non-diabetes group (Table 3). The median HbA1c in the diabetes group was 7.4% (IQR 6.9–8.6%), and the median plasma glucose on admission was 181 (IQR 132–250) mg/dL.

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Table 1 | Patients' baseline characteristics

	All patients (n = 262)
Sex, *n* (%)	
Male	184 (70.2)
Female	78 (29.8)
Median age, years (IQR)	64 (47–74)
Median BMI, kg/m^2 (IQR)	24.1 (21.8-27.4)
Smoking (current or ex-)	133 (50.8)
Severity, *n* (%)	
Mild	58 (22.1)
Moderate	96 (36.6)
Severe	108 (41.2)
COVID-19 treatment, *n* (%)	
Glucocorticoids	172 (65.6)
Remdesivir	127 (48.5)
Anticoagulants	164 (62.6)
ECMO	7 (2.7)
In-hospital mortality, *n* (%)	34 (13.0)
Original comorbidities, *n* (%)	
Diabetes mellitus	92 (35.1)
Medications	
Sulfonylurea	11 (12.0)
Glinide	3 (3.3)
DPP-4 inhibitor	34 (37.0)
Metformin	18 (19.6)
α-GI	5 (5.4)
SGLT-2 inhibitor	16 (17.4)
Thiazolidinedione	5 (5.4)
GLP-1 analog	5 (5.4)
Insulin	11 (12.0)
No medication	40 (43.5)
Hypertension	117 (44.7)
Dyslipidemia	70 (26.7)
Coronary heart disease	24 (9.2)
Cerebrovascular disease	21 (8.0)
Respiratory disease	40 (15.3)
Immunosuppressant drugs	23 (8.8)
Malignant neoplasm	31 (11.8)
Vital signs on admission, median (IQR)	
Temperature (°C)	37.2 (36.6–37.9)
Pulse (b.p.m.)	85 (75–97)
Systolic blood pressure (mmHg)	128 (114–144)
Diastolic blood pressure (mmHg)	76 (65–83)
Respiratory rate (breaths/min)	20 (18–24)
SpO_2 (%)	95 (93–98)

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; ECMO, extracorporeal membrane oxygenation; GLP-1, glucagon-like peptide-1; IQR, interquartile range; SGLT-2, sodium–glucose cotransporter 2; α-GI, alpha-glucosidase inhibitor.

Multivariable logistic regression analysis for COVID-19 severity and death

The results of multivariable logistic regression analysis for COVID-19 severity and COVID-19-related death are shown in Tables 4 and 5. Analysis for COVID-19 severity showed that age (odds ratio [OR] 1.054, 95% confidence interval [CI] 1.023–1.086), BMI (OR 1.111, 95% CI 1.028–1.201), presence of diabetes mellitus (OR 2.429, 95% CI 1.152–5.123), neutrophil count (OR 1.222, 95% CI 1.077–1.385), CRP (OR 1.096, 95% CI 1.030–1.166) and KL-6 (OR 1.002, 95% CI 1.000–1.003) were predictors of severity (model 1, R^2 = 0.468). Meanwhile, just two factors, age (OR 1.104, 95% CI 1.037–1.175) and KL-6 (OR 1.003, 95% CI 1.001–1.005), were predictors of death (model 1, R^2 = 0.475). The results of model 2, using HbA1c instead of the presence of diabetes mellitus, were similar to those of model 1 (R^2 = 0.448 for severity and R^2 = 0.472 for COVID-19-related death).

DISCUSSION

In the present retrospective study, diabetes mellitus was found to affect COVID-19 severity in a Japanese core hospital mainly treating moderately-to-severely ill patients. The diabetes group had significantly more severe disease, higher mortality and longer hospital stay than the non-diabetes group. In addition, white blood cells, neutrophil count, CRP, KL-6 and D-dimer were significantly higher, and albumin and the estimated glomerular filtration rate were significantly lower, suggesting that there were more severe cases in the diabetes group. On multivariable logistic regression analysis, diabetes was a predictor of COVID-19 severity along with age, BMI, neutrophil count, CRP and KL-6, whereas only age and KL-6 were predictors of death. The strengths of the present study include that all patients were treated with standard COVID-19 therapy, eliminating the impact of possible inadequate treatment as a result of triage during the pandemic. In addition, recent meta-analyses have reported that diabetes mellitus increases the risk of COVID-19-related death, as well as the severity[19,20], but these studies mainly analyzed reports from China, the USA, Latin America and Europe, with few reports from Asian countries other than China, especially from Japan. The present results show that diabetes mellitus is also a risk factor for COVID-19 severity in Japan.

Diabetes mellitus is significantly correlated with the severity of coronavirus infections, including SARS-CoV-2 infection[21]. Angiotensin-converting enzyme 2 (ACE2) might play an important role in the relationship between diabetes mellitus and COVID-19 severity. ACE2 has been identified as the receptor for the coronavirus spike protein[22], and has protective effects primarily regarding inflammation. COVID-19 infection reduces ACE2 expression, inducing cellular damage, hyperinflammation and respiratory failure. Acute hyperglycemia has been shown to upregulate ACE2 expression on cells that might facilitate viral cell entry. However, chronic hyperglycemia is known to downregulate ACE2 expression, making the cells vulnerable to the inflammatory and damaging effect of the virus[21]. On multivariable logistic regression analysis in the present study, diabetes mellitus was associated with COVID-19 severity, but not with death. Although the sample size might have been

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Table 2 | Characteristics of patients with/without diabetes mellitus

	Non-diabetes (n = 170)	Diabetes (n = 92)	P-value
Sex, n (%)			
Male	114 (67.1)	70 (76.1)	0.127
Female	56 (32.9)	22 (23.9)	
Median age, years (IQR)	60 (42–72)	70 (57–77)	<0.001
Median BMI, kg/m^2 (IQR)	23.7 (21.6–26.6)	25.0 (22.2–28.3)	0.026
Smoking (current or ex-), n (%)	83 (48.8)	50 (54.3)	0.185
Severity, n (%)			
Mild-to-moderate	120 (70.6)	33 (35.9)	<0.001
Severe	50 (29.4)	59 (64.1)	
COVID-19 treatment, n (%)			
Glucocorticoids	95 (55.9)	77 (83.7)	<0.001
Remdesivir	74 (43.5)	53 (57.6)	0.030
Anticoagulants	84 (49.4)	80 (87.0)	<0.001
ECMO	2 (1.2)	5 (5.4)	0.041
In-hospital mortality, n (%)	13 (7.6)	21 (22.8)	<0.001
Median hospitalization time, days (IQR)	12 (7–17)	15 (11–22)	0.003
Median invasive ventilation time, days (IQR)	11 (6–19)	13 (5–21)	0.727
Original comorbidities, n (%)			
Hypertension	59 (34.7)	58 (63.0)	<0.001
Dyslipidemia	27 (15.9)	43 (46.7)	<0.001
Coronary heart disease	12 (7.1)	12 (13.0)	0.109
Cerebrovascular disease	11 (6.5)	10 (10.9)	0.211
Respiratory disease	25 (14.7)	15 (16.3)	0.731
Immunosuppressant drugs	15 (8.8)	8 (8.7)	0.972
Malignant neoplasm	20 (11.8)	11 (12.0)	0.963
Median vital signs on admission (IQR)			
Temperature (°C)	37.2 (36.7–37.9)	37.1 (36.5–37.8)	0.183
Pulse (b.p.m.)	84 (75–96)	89 (76–100)	0.159
Systolic blood pressure (mmHg)	126 (113–138)	133 (120–153)	0.002
Diastolic blood pressure (mmHg)	76 (66–82)	74 (63–84)	0.751
Respiratory rate (breaths/min)	20 (18–24)	22 (18–25)	0.439
SpO_2 (%)	96 (94–98)	94 (93–96)	<0.001

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; IQR, interquartile range.

too small to investigate the association between diabetes mellitus and COVID-19 mortality in the present study, diabetes treatment might have affected this result. Several studies have reported that patients on chronic insulin treatment had a higher risk of COVID-19-related death[23,24]. It has also been reported that dipeptidyl peptidase-4 inhibitors might be associated with decreased mortality[25,26]. In the present study, there were few insulin users and more dipeptidyl peptidase-4 inhibitor users in the diabetes group, which might explain the lack of a relationship between diabetes mellitus and COVID-19-related death.

Other than diabetes mellitus, the present multivariable logistic regression analysis showed that the neutrophil count and CRP were associated with COVID-19 severity. It has been reported that a high neutrophil : lymphocyte ratio[27] and elevated CRP[19] are associated with increased COVID-19 severity and mortality, which is consistent with the present results. Although elevated D-dimer levels and low platelet counts have also been reported to be associated with increased COVID-19 severity and mortality[19,28], no association was observed among these factors in the present study. This might have been due to the fact that almost all patients in the severe group received anticoagulation therapy as standard treatment. In addition, age contributed to both COVID-19 severity and mortality, whereas BMI contributed only to severity and not to mortality in the present study. Gao *et al.*[7] reported that the risk of COVID-19-related death was higher in those with BMI <23 kg/m^2 and >28 kg/m^2, whereas the median BMI in the present study was not very different, 24.1 kg/m^2 for all patients and 23.4 kg/m^2 for those who died (Figures S1–S3.). Multivariable logistic regression analysis also showed that BMI was a predictor of neither COVID-19 severity nor COVID-19-related death, even if categorized <23 kg/m^2 or >28 kg/m^2 (Tables S2 and S3). Racial differences between white people and Asian people

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Table 3 | Laboratory parameters of patients with/without diabetes mellitus

	All patients (n = 262)	Non-Diabetes (n = 170)	Diabetes (n = 92)	P-value
WBC ($\times 10^3/mm^3$)	6.39 (4.70–9.14)	6.15 (4.54–5.89)	7.15 (5.21–10.21)	0.042
Neutrophil ($\times 10^3/mm^3$)	5.08 (3.35–7.72)	4.78 (3.15–7.14)	5.43 (4.18–8.24)	0.039
Lymphocyte ($\times 10^3/mm^3$)	0.80 (0.60–1.13)	0.80 (0.60–1.14)	0.78 (0.59–1.10)	0.431
Hemoglobin (g/dL)	13.6 (12.3–14.9)	13.6 (12.3–14.8)	13.6 (12.3–15.0)	0.982
Platelets ($\times 10^4/mm^3$)	20.1 (14.7–25.0)	20.1 (14.7–24.3)	20.0 (14.6–27.9)	0.402
AST (U/L)	43 (28–58)	42 (27–56)	44 (30–60)	0.385
ALT (U/L)	31 (20–46)	31 (20–47)	32 (21–46)	0.664
LDH (U/L)	361 (259–448)	332 (234–426)	384 (312–475)	0.001
Albumin (g/dL)	3.2 (2.9–3.6)	3.3 (2.9–3.8)	3.1 (2.7–3.4)	<0.001
BUN (mg/dL)	15.5 (11.0–23.0)	14.0 (10.5–21.0)	20.1 (13.2–27.6)	<0.001
Creatinine (mg/dL)	0.77 (0.62–0.98)	0.76 (0.59–0.95)	0.82 (0.7–1.03)	0.009
eGFR (mL/min)	76 (58–93)	78 (63–98)	70 (51–83)	0.003
Uric acid (mg/dL)	4.6 (3.5–6.0)	4.5 (3.3–5.8)	4.7 (3.6–6.5)	0.123
Total cholesterol (mg/dL)	154 (129–179)	155 (139–179)	144 (123–175)	0.103
LDL cholesterol (mg/dL)	81 (63–104)	81 (69–104)	80 (56–103)	0.156
HDL cholesterol (mg/dL)	42 (34–53)	46 (35–54)	39 (31–49)	0.092
Triglyceride (mg/dL)	128 (91–171)	125 (88–151)	134 (95–182)	0.126
Plasma glucose (mg/dL)	125 (103–170)	112 (96–135)	181 (132–250)	<0.001
Hemoglobin A1c (%)	6.2 (5.7–7.0)	5.9 (5.6–6.1)	7.4 (6.9–8.6)	<0.001
C-reactive protein (mg/dL)	6.65 (2.92–11.89)	5.49 (2.06–11.31)	7.77 (4.45–12.34)	0.015
KL-6 (U/mL)	304 (211–482)	259 (193–380)	404 (262–639)	<0.001
D-dimer (μg/mL)	1.1 (0.8–1.7)	1.0 (0.7–1.5)	1.3 (0.9–2.4)	<0.001

Data are presented as medians and interquartile range (Q1–Q3). ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; KL-6, Krebs von den Lungen-6; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; WBC, white blood cell.

Table 4 | Multivariable logistic regression analysis for severity

	Model 1: R^2 = 0.468			Model 2: R^2 = 0.448		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age (years)	1.054	1.023–1.086	0.001	1.056	1.024–1.089	0.001
Sex (male)	1.104	0.462–2.639	0.823	1.105	0.462–2.640	0.823
BMI (kg/m^2)	1.111	1.028–1.201	0.008	1.108	1.025–1.198	0.010
Smoking (current or ex-)	0.838	0.390–1.800	0.650	0.775	0.358–1.679	0.518
Hypertension	0.971	0.440–2.143	0.942	1.177	0.532–2.605	0.688
Coronary heart disease	0.327	0.097–1.099	0.071	0.321	0.096–1.072	0.065
Cerebrovascular disease	2.353	0.584–9.478	0.229	2.370	0.559–10.053	0.242
Respiratory disease	1.484	0.586–3.758	0.405	1.541	0.604–3.931	0.365
Malignant neoplasm	0.804	0.265–2.439	0.700	0.684	0.231–2.024	0.493
eGFR (mL/min)	0.997	0.984–1.011	0.688	0.996	0.983–1.009	0.554
Neutrophil ($\times 10^3/mm^3$)	1.222	1.077–1.385	0.002	1.205	1.063–1.367	0.004
Platelets ($\times 10^4/mm^3$)	0.997	0.993–1.002	0.268	0.998	0.994–1.003	0.436
C-reactive protein (mg/dL)	1.096	1.030–1.166	0.004	1.083	1.019–1.151	0.011
KL-6 (U/mL)	1.002	1.000–1.003	0.042	1.001	1.000–1.003	0.062
D-dimer (μg/mL)	0.994	0.957–1.032	0.752	0.998	0.961–1.038	0.935
Diabetes (model 1)	2.429	1.152–5.123	0.020			
HbA1c, % (model 2)				1.302	1.013–1.674	0.039

Models were adjusted for age, sex, body mass index (BMI), smoking (current or ex-), presence of hypertension, coronary heart disease, respiratory disease, malignant neoplasm, estimated glomerular filtration rate (eGFR), neutrophil, platelets, C-reactive protein, , Krebs von den Lungen-6 (KL-6), D-dimer, and model 1: presence of diabetes mellitus and model 2: hemoglobin A1c (HbA1c). CI, confidence interval.

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Table 5 | Multivariable logistic regression analysis for coronavirus disease 2019-related death

	Model 1: R^2 = 0.475			Model 2: R^2 = 0.472		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
Age (years)	1.104	1.037–1.175	0.002	1.101	1.033–1.175	0.003
Sex (male)	0.459	0.108–1.942	0.290	0.540	0.124–2.359	0.413
BMI (kg/m^2)	1.028	0.893–1.183	0.704	1.013	0.880–1.166	0.861
Smoking (current or ex-)	1.278	0.377–4.331	0.694	1.066	0.299–3.793	0.922
Hypertension	0.775	0.217–2.769	0.695	1.078	0.293–3.968	0.910
Coronary heart disease	2.195	0.567–8.497	0.255	2.171	0.548–8.596	0.270
Cerebrovascular disease	0.428	0.072–2.552	0.352	0.478	0.077–2.961	0.427
Respiratory disease	0.897	0.211–3.815	0.883	0.946	0.223–4.017	0.940
Malignant neoplasm	1.305	0.315–5.406	0.714	1.162	0.282–4.783	0.835
eGFR (mL/min)	0.982	0.960–1.006	0.134	0.983	0.960–1.006	0.150
Neutrophil ($\times 10^3$/mm^3)	1.149	0.990–1.334	0.068	1.160	1.000–1.347	0.051
Platelets ($\times 10^4$/mm^3)	0.994	0.987–1.001	0.068	0.994	0.987–1.000	0.068
C-reactive protein (mg/dL)	1.021	0.935–1.114	0.650	1.010	0.924–1.104	0.823
KL-6 (U/mL)	1.003	1.001–1.005	0.001	1.003	1.001–1.004	0.001
D-dimer (μg/mL)	0.994	0.957–1.032	0.744	0.998	0.961–1.036	0.910
Diabetes mellitus (model 1)	1.698	0.575–5.013	0.338			
HbA1c, % (model 2)				1.252	0.833–1.880	0.280

Models were adjusted for age, sex, body mass index (BMI), smoking (current or ex-), presence of hypertension, coronary heart disease, respiratory disease, malignant neoplasm, estimated glomerular filtration rate (eGFR), neutrophil, platelets, C-reactive protein, Krebs von den Lungen-6(KL-6), D-dimer, and model 1: presence of diabetes and model 2: hemoglobin A1c (HbA1c). CI, confidence interval.

might be involved in the relationship between BMI and COVID-19-related death. Remarkably, KL-6 was strongly associated with COVID-19 severity and death in the present study. KL-6 is considered to be a part of human MUC1 mucin expressed on type II alveolar epithelial cells, with positive chemotaxis for human fibroblasts[29]. As its serum levels increase when alveolar epithelial cells are damaged and regenerate, it has been used as a biomarker for interstitial pneumonia[30]. Elevated serum KL-6 indicates the severity of interstitial lung injury and pulmonary fibrosis caused by COVID-19; thus, it might have been a predictor of severity and mortality. KL-6 was measured by 90.3% of mild-to-moderate cases, and 96.3% of severe cases, suggesting that the effect of selection bias is very small. Several studies suggest that KL-6 is a useful biomarker for predicting the severity of COVID-19 and death[31,32], which also supports the present results.

The limitations of the present study include that the sample size was small and might have been insufficient to detect factors that contribute to mortality. In addition, patient selection bias existed due to it being a study at a single center that treats mainly patients with moderate-to-severe disease. Furthermore, due to the lack of data on plasma glucose levels after hospitalization, the impact of glycemic management on prognosis could not be investigated. Finally, almost all patients were Japanese, and the effect of racial differences cannot be ignored.

In conclusion, diabetes mellitus was found to be a definite risk factor for COVID-19 severity in a single center that mainly treats patients with moderate-to-severe disease in Japan. Further studies are needed to determine whether diabetes mellitus is associated with COVID-19 mortality in Japan, and whether glycemic control during hospitalization reduces the risk of COVID-19 severity and mortality.

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DISCLOSURES

Dr Hosoi reports receiving lecturer's fees from Ono, Sanofi and Eli Lilly. The other authors report no conflict of interest.
Approval of the research protocol: The protocol for this research project has been approved by a suitably constituted ethics committee of the institution and it conforms to the provisions of the Declaration of Helsinki (ethics committee of Osaka City General Hospital, Approval No. 1810073).
Informed consent: All informed consent was obtained from the participants and/or families.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1 | Body mass index histogram for all patients.

Figure S2 | Body mass index histogram of the surviving patients.

Figure S3 | Body mass index histogram of deceased patients.

Table S1 | The relationship between coronavirus disease 2019 severity and treatment.

Table S2 | Multivariable logistic regression analysis for severity (body mass index categorized).

Table S3 | Multivariable logistic regression analysis for coronavirus disease 2019-related death (body mass index categorized).

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