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Glycated hemoglobin level on admission associated with progression to severe disease in hospitalized patients with non-severe coronavirus disease 2019

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ABSTRACT

Aims/Introduction: Poor glycemic control is known to be associated with severe infection development. This retrospective observational study examined whether glycemic control before coronavirus disease 2019 (COVID-19) onset contributes to progression from non-severe to severe COVID-19.

Materials and Methods: Glycated hemoglobin (HbA1c) was measured on hospital admission in 415 patients with non-severe COVID-19. The outcome was determined from time of hospital admission to severe progression, based on clinical practice guidelines for COVID-19 in Japan.

Results: The median value for HbA1c on admission was 6.1%, with diabetes present in 138 patients (33.3%). Among the total cohort, 93 (22.4%) progressed to severe COVID-19 with a median (interquartile range) time of 4 days (3–7 days), whereas 322 (77.6%) were discharged after 13 days (10–17 days). A multivariable Cox proportional hazards regression model showed that HbA1c level on admission was independently associated with progression to severe COVID-19 (hazard ratio for 1% increase 1.237, 95% confidence interval 1.037–1.475; $P = 0.018$), with findings consistent among several sensitivity analyses. In subgroup analyses, such an association was significant in patients with diabetes, as well as older age, current smoking habit, lower estimated glomerular filtration rate, higher C-reactive protein level, moderate II COVID-19, dyslipidemia and chronic respiratory disease, with no remarkable inconsistency among the subgroups. Finally, higher HbA1c level (≥7%) was more strongly associated with severe COVID-19 progression than diabetes.

Conclusions: The results suggest that poor glycemic control before COVID-19 onset contributes to progression from non-severe to severe COVID-19, even in patients with severe COVID-19 risk factors regardless of the presence of diabetes.

INTRODUCTION

The numbers of patients who progress from non-severe to severe coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), have been dramatically increasing worldwide[1–3]. As individuals with severe COVID-19 have a high risk of mortality and require advanced medical care[4–6], careful follow up for progression, as well as administration of therapeutic agents, are needed when treating patients with non-severe COVID-19. However, it is

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difficult to fully implement such treatment strategies, due to the dramatic increase in patients with COVID-19 and insufficient medical resources. Thus, elucidation of factors associated with progression of patients from non-severe to severe COVID-19 is essential for effective treatment.

Glycated hemoglobin (HbA1c) represents average blood glucose level during a period of a few months, and is considered to be the gold standard for evaluating glycemic control[7,8]. Poor glycemic control before an infection, reflected by high HbA1c level, as well as diabetes, is known to be associated with severe infections and infection-related mortality[9–13]. Of importance, diabetes has been reported to have a relationship with severe COVID-19 progression and COVID-19-related mortality[14–16], whereas poor glycemic control has also been shown to be associated with COVID-19-related mortality[17–19]. Unfortunately, studies that examined the association of glycemic control before onset of COVID-19, assessed by HbA1c level, with progression from non-severe to severe COVID-19 are limited.

To elucidate whether glycemic control before onset of COVID-19 contributes to progression from non-severe to severe COVID-19, we examined the association between HbA1c level on admission and progression to severe COVID-19 in patients initially hospitalized for non-severe COVID-19 at Osaka City Juso Hospital, Osaka, Japan, which was designated by the Osaka prefecture government as a priority medical institution for COVID-19 and the first in Japan to specialize in receiving patients with a non-severe status.

MATERIALS AND METHODS

Study design

The present retrospective observational study included 415 hospitalized patients with non-severe COVID-19 (mild, moderate I moderate II). We examined the association between HbA1c level on admission and progression to severe COVID-19 during hospitalization in this cohort.

Participants

From November 2020 to May 2021, 555 patients with COVID-19 were admitted to Osaka City Juso Hospital. Excluded from the present analysis were those with severe COVID-19 on admission (n = 6), who received treatment for COVID-19 before admission (n = 3), or transferred to our hospital from a tertiary hospital after improvement from severe to non-severe COVID-19 (n = 39). Furthermore, patients who were aged <20 years (n = 12), pregnant (n = 10), self-discharged (n = 2), transferred to other hospitals due to mental illness (n = 1) or missing relevant data (n = 67) were excluded. As a result, 415 patients with non-severe COVID-19 (214 men, 201 women) were enrolled as participants in the present retrospective observational study. This investigation was carried out in full accordance with the principles of the Declaration of Helsinki, and Ethical Guidelines for Clinical Studies by the Ministry of Health, Labor and Welfare, Japan. The present study protocol was approved by the Ethics Committee of Osaka City Juso Hospital (approval No. 3-A1) and Osaka City University Graduate School of Medicine (approval No. 2021–159), and carried out with an opt-out option, which was explained in instructions on the websites of both facilities. After approval of the study protocol, all data subjected to analysis were collected from relevant patient medical records.

Diagnosis and COVID-19 severity classification

The diagnosis and severity classification of COVID-19 for each patient were based on clinical practice guidelines for COVID-19 published by the Japanese Ministry of Health, Labor and Welfare[20–23]. Briefly, COVID-19 was confirmed using a nucleic acid amplification test, which included real-time polymerase chain reaction, loop-mediated isothermal amplification and transcription-mediated amplification assays, and a quantitative or qualitative antigen test for SARS-CoV-2. Severity classification was based on respiratory symptoms and oxygenation, as follows: mild, percutaneous oxygen (SpO_2) saturation ≥96%, no respiratory symptoms or coughing only without shortness of breath; moderate I (patient does not suffer from respiratory failure), SpO_2 saturation 93–96%, shortness of breath and pneumonia findings; moderate II (patient suffers from respiratory failure), SpO_2 ≤93%, oxygen (O_2) administration required; and severe condition, admission to an intensive care unit or mechanical ventilator required.

Clinical assessments

Information for each participant regarding height, bodyweight, current smoking habit, present and past illness, use of medication, date of onset of COVID-19 based on onset of symptoms, severity of COVID-19, treatment, and outcome (progression to severe COVID-19 or discharge) was obtained. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Blood was drawn at the time of admission with or without fasting, then routine blood examinations including random plasma glucose (RPG), serum creatinine and C-reactive protein (CRP) were carried out using a routine standard laboratory method at the hospital[24]. HbA1c was determined using high-performance liquid chromatography[25]. Estimated glomerular filtration rate (eGFR) was calculated using an equation designed for Japanese individuals, as previously described[26]. The diagnosis of diabetes was based on a previous history of treatment for the disease or an HbA1c level on admission ≥6.5%[27]. Hyperglycemia during hospitalization was defined as plasma glucose level ≥180 mg/dL during hospitalization[28], based on blood samples drawn periodically and as required for medical conditions, as well as on admission. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg or treatment for the condition[29], whereas dyslipidemia was defined based on the criteria of the Japan Atherosclerosis Society or treatment for the condition[30]. Abnormal findings indicating pneumonia were evaluated based on chest computed tomography or X-ray findings.

Management of patients with COVID-19 during hospitalization

All patients were treated in accordance with the most current guidelines available at the time[20–23]. O_2 was administered when SpO_2 was <93% at room air, with the dose of O_2 adjusted to maintain an SpO_2 value between 93% and 96%. Criteria used for discharge from dedicated beds for COVID-19 were as follows: (i) 10 days from date of onset of symptoms and 72 h after symptom resolution; or (ii) 24 h after resolution of symptoms if the patient had negative results in polymerase chain reaction or quantitative antigen tests twice, with at least 24 h between tests[20–23]. In contrast, patients with progression from non-severe to severe COVID-19 were transferred to a tertiary hospital with an intensive care unit available unless no life-prolonging treatment was required.

Outcome

The outcome of this study was time (days) from hospital admission to severe COVID-19 progression. Patients who did not progress to severe COVID-19 and met the discharge criteria were assumed to have not progressed to severe COVID-19 after discharge.

Statistical analysis

Baseline demographics and clinical characteristics are presented as number (percentage) for categorical variables. and median (interquartile range [IQR]) for continuous variables. To investigate the association between HbA1c level on admission and progression from non-severe to severe COVID-19, a multivariable Cox proportional hazards regression model was used with adjustments for the following known risk factors: age, sex, BMI, current smoking status, eGFR, CRP level, days from disease onset to hospital admission and COVID-19 severity on admission (primary Cox model). To evaluate which glycemic-related characteristics were more strongly associated with severe COVID-19 progression, the same Cox models were used, with HbA1c level on admission replaced by the presence or absence of higher HbA1c on admission (≥7%), higher RPG on admission (≥140 mg/dL) or diabetes (secondary Cox model). The association between HbA1c level on admission and severe COVID-19 progression was also evaluated visually using Kaplan–Meier curves showing the cumulative incidence of severe COVID-19 progression stratified by HbA1c level on admission (≥7%, 6–6.9% and <6% for all patients, and ≥7% and <7% for diabetes patients) determined using log-rank tests.

The consistency of the results was analyzed for the following subgroups: age (≥75, <75 years), sex (male, female), BMI (≥25, <25 kg/m^2), current smoking habit (presence, absence), eGFR (≥60, <60 mL/min/1.73 m^2), CRP (≥30, <30 mg/L), days from disease onset to hospital admission (<4, 4–6, ≥7 days), COVID-19 severity (mild, moderate I, moderate II), diabetes (presence, absence), hypertension (presence, absence), dyslipidemia (presence, absence) and chronic respiratory disease (presence, absence). To examine the robustness of the results, several sensitivity analyses were carried out. For sensitivity analysis 1, the presence or absence of coexisting diseases (diabetes, hypertension, dyslipidemia, chronic respiratory disease) was additionally adjusted. Second, use of non-diabetic medication was additionally adjusted (sensitivity analysis 2). Third, use of anti-diabetic medication was additionally adjusted (sensitivity analysis 3). Fourth, use of COVID-19 medications was additionally adjusted (sensitivity analysis 4). Fifth, the presence or absence of hyperglycemia during hospitalization was additionally adjusted (sensitivity analysis 5). Sixth, the value for 'days from disease onset to hospital admission' was included as a stratification factor in the Cox model with use of the categories '<4 days', '4–6 days' and '≥7 days' (sensitivity analysis 6). Seventh, 'COVID-19 severity' was included as a stratification factor in the Cox model (sensitivity analysis 7). Eighth, the time to severe COVID-19 progression for discharged patients was censored at the date of discharge for the analysis (sensitivity analysis 8).

The R software package, version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria), was used for data analysis. All reported *P*-values are two-tailed and were considered statistically significant at <0.05.

RESULTS

Clinical characteristics of patients with non-severe COVID-19

The characteristics of all enrolled patients (n = 415) are presented in Table 1. The median value for HbA1c on admission was 6.1%, and diabetes was present in 138 patients (33.3%). The number of patients with mild, moderate I and moderate II COVID-19 was 218 (52.5%), 83 (20.0%) and 114 (27.5%), respectively.

Glycemic control status and medications used for COVID-19 during hospitalization

During hospitalization, 118 patients presented with hyperglycemia defined as plasma glucose level ≥180 mg/dL. Medications given for COVID-19 included favipiravir in 317 (76.4%), steroids in 271 (65.3%), ciclesonide in 95 (22.9%), remdesivir in 22 (5.3%) and baricitinib in two (0.5%) patients.

Progression from non-severe to severe COVID-19

Among the present 415 patients with non-severe COVID-19 at the time of hospitalization, 93 (22.4%) progressed to severe COVID-19, and 322 (77.6%) were discharged. The median time from hospital admission to severe COVID-19 progression was 4 days (IQR 3–7; range 1–14), whereas that to discharge was 13 days (IQR 10–17; range 5–48).

Association of HbA1c level on admission with progression from non-severe to severe COVID-19

Results from the primary Cox model are shown in Table 2. HbA1c level on admission was significantly associated with severe COVID-19 progression (hazard ratio [HR] for 1% increase 1.237, 95% confidence interval [CI] 1.037–1.475; P = 0.018), whereas other variables, including age, sex, BMI, CRP level and

Table 1 | Clinical characteristics of patients with coronavirus disease 2019

Age (years)	78.0 (61.0–83.0)
Male (*n*)	214 (51.6)
BMI (kg/m^2)	23.1 (21.1–25.7)
Smoker (*n*)	156 (37.6)
RPG (mg/dL)	120.0 (104.0–142.5)
HbA1c (%)	6.1 (5.8–6.5)
eGFR (mL/min/1.73 m^2)	66.0 (50.0–81.0)
CRP (mg/L)	36.0 (8.0–72.8)
Days from disease onset to hospital admission	5.0 (3.0–8.0)
0–3 days (*n*)	142 (34.2)
4–6 days (*n*)	139 (33.5)
>6 days (*n*)	134 (32.3)
Abnormal pneumonia findings	196 (47.2)
COVID-19 severity	
Mild (*n*)	218 (52.5)
Moderate I (*n*)	83 (20.0)
Moderate II (*n*)	114 (27.5)
Coexisting diseases	
Diabetes (*n*)	138 (33.3)
Hypertension (*n*)	246 (59.3)
Dyslipidemia (*n*)	224 (54.0)
Chronic respiratory disease (*n*)	52 (12.5)
Medication: non-diabetic	
ACE inhibitors/ARBs (*n*)	119 (28.7)
Statins (*n*)	116 (28.0)
Immunosuppressants (*n*)	6 (1.4)
Medication: anti-diabetic	
Sulfonylureas (*n*)	22 (5.3)
Metformin (*n*)	37 (8.9)
DPP-4 inhibitors (*n*)	56 (13.5)
Pioglitazone (*n*)	5 (1.2)
SGLT2 inhibitors (*n*)	24 (5.8)
Glinides (*n*)	4 (1.0)
α-Glucosidase inhibitors (*n*)	6 (1.4)
GLP-1 receptor agonists (*n*)	4 (1.0)
Insulin (*n*)	13 (3.1)

Total $n = 415$. Values are expressed as median (interquartile range) or number (%). ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; RPG, random plasma glucose; SGLT2, sodium-glucose cotransporter 2.

COVID-19 severity, were also significantly ($P < 0.05$) associated with progression to severe. Kaplan–Meier analysis also showed that patients with a higher HbA1c level on admission had a significantly ($P < 0.001$) greater rate of severe COVID-19 progression (Figure 1a). Additionally, the presence of a higher HbA1c level on admission was most strongly associated with severe COVID-19 progression (HR 1.786, 95% CI 1.079–2.956; $P = 0.024$), as compared with higher RPG on admission (HR 0.873, 95% CI 0.542–1.404; $P = 0.574$) or diabetes (HR 1.146, 95% CI 0.723–1.816; $P = 0.561$; Table 3).

Subgroup and sensitivity analyses of association between HbA1c level on admission and severe COVID-19 progression

There was no remarkable inconsistency observed among the series of subgroups related to sex (male, female), BMI (≥25, <25 kg/m^2) or COVID-19 severity (mild, moderate I, moderate II). However, it was interesting to note that the association between HbA1c level on admission and severe COVID-19 progression was significantly (P for interaction = 0.048) greater in patients with chronic respiratory disease, as compared with those without (Figure 2). In addition, the association of HbA1c level on admission with severe COVID-19 progression was significant ($P = 0.038$) in patients with diabetes (Figure 2), which was also shown by Kaplan–Meier analysis results (Figure 1b). Furthermore, the relationship of HbA1c level on admission with severe COVID-19 progression was significant in patients with older age, current smoking habit, lower eGFR, higher CRP level, moderate II COVID-19 and dyslipidemia. Results from the series of sensitivity analyses were consistent with the main results (Figure 2), whereas anti-diabetic medications given and glycemic control status during hospitalization each showed no significant association with severe COVID-19 progression.

DISCUSSION

In the present study, HbA1c level on admission was found to be significantly associated with severe COVID-19 progression in patients initially hospitalized for non-severe COVID-19 (Table 2, Figure 1a), which was confirmed in several different sensitivity analyses carried out (Figure 2). In subgroup analyses, that association was also significant in patients with diabetes and other risk factors for severe progression, with no remarkable inconsistency found among the series of subgroups (Figures 1b and 2). Finally, higher HbA1c level on admission (≥7%) was more strongly associated with severe progression than coexistence of diabetes (Table 3). The present results show that poor glycemic control before onset of COVID-19 contributes to progression from non-severe to severe COVID-19, even in patients with risk factors for severe progression regardless of the presence of diabetes.

Previous studies have shown that HbA1c level determined before onset of COVID-19 is associated with progression to severe COVID-19, independent of known risk factors[31,32]. However, measurement of HbA1c level was carried out either 1 or 10 years before COVID-19 onset in those studies, thus their findings do not accurately reflect glycemic control near before onset of COVID-19. As for the association of HbA1c level determined near onset of COVID-19 in individuals with severe COVID-19 progression, several inconsistent results have been reported[33,34]. Liu *et al.*[33] showed that HbA1c level on admission was significantly associated with severe COVID-19 progression in hospitalized patients with diabetes, although the number of participants included in their study was small ($n = 64$). In contrast, Cariou *et al.*[34] reported that HbA1c level from 6 months before to 7 days after admission was not significantly associated with severe COVID-19 progression in 846

Table 2 | Multivariable Cox proportional analysis of factors associated with severe coronavirus disease 2019 progression (primary Cox model)

Variables	HR (95% CI)	*P*-value
Age (per 10 year increase)	1.555 (1.267–1.910)	<0.001
Male (ref. female)	1.884 (1.140–3.112)	0.013
BMI (per 5 kg/m^2 increase)	1.372 (1.051–1.792)	0.020
Smoker (ref. non-smoker)	1.010 (0.639–1.597)	0.967
eGFR (per 10 mL/min/1.73 m^2 increase)	1.010 (0.918–1.112)	0.834
CRP (per 50 mg/L increase)	1.423 (1.147–1.766)	0.001
Days from disease onset to hospital admission (per 3 day increase)	1.066 (0.866–1.311)	0.547
COVID-19 severity: Moderate I (ref. Mild)	1.393 (0.722–2.687)	0.323
COVID-19 severity: Moderate II (ref. Mild)	3.736 (2.138–6.527)	<0.001
HbA1c (per 1% increase)	1.237 (1.037–1.475)	0.018

BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; HR, hazard ratio.

patients with diabetes. However, analysis of that association was adjusted only with age and sex, and not with other important risk factors for severe COVID-19 progression, such as BMI, CRP level and severity on admission. Furthermore, to the best of our knowledge, no other studies that compared various subgroups or carried out sensitivity analysis of the association between HbA1c level and severe COVID-19 progression have been reported. Thus, the present study is the first to present consistent and robust findings (Figure 2) clarifying the association of HbA1c level at the time of admission, considered to reflect glycemic control near before onset of COVID-19, with severe COVID-19 progression, after full adjustment using known risk factors for severe progression in analyses of a relatively large number of patients originally hospitalized for non-severe COVID-19 (n = 415; Table 2).

In general, poor glycemic control before an infection is known to be associated with the severity and mortality of a variety of infections[9–12], whereas intensive glycemic control before infection has been shown to substantially reduce the incidence of vaginal and foot infections in patients with type 1 diabetes[35]. Those findings also show that glycemic control before an infection contributes to the possibility of severe progression. In the same manner, the present results showing an association between HbA1c level on admission and severe COVID-19 progression (Table 2, Figure 1a) suggest that poor glycemic control before onset of COVID-19 contributes to progression to severe COVID-19, whereas HbA1c level at the time of admission predicts progression to severe COVID-19 in patients with non-severe COVID-19.

In the present study, the association with severe COVID-19 progression was weaker for higher RPG than for higher HbA1c level on admission (Table 3). Although previous meta-analyses have shown fasting plasma glucose level to be associated with COVID-19 prognosis[36,37], no such findings have shown a robust association of admission RPG level[36]. Determination of

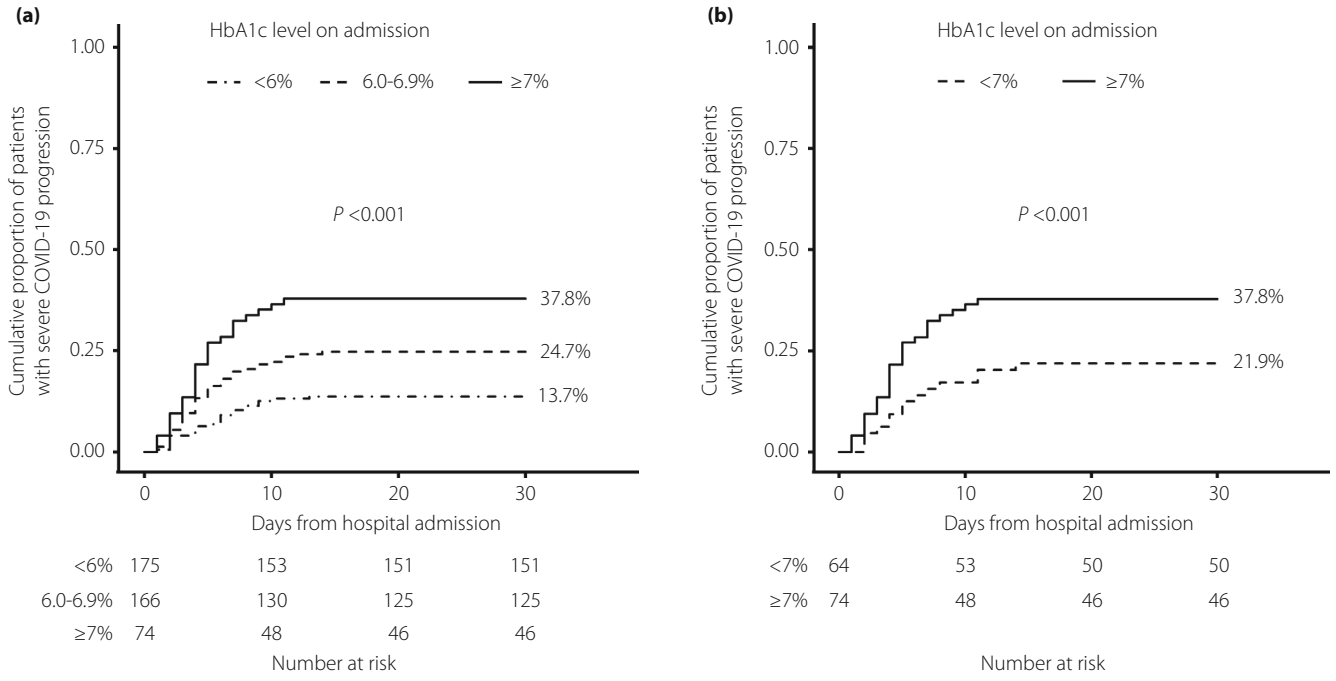

Figure 1 | Kaplan–Meier analysis estimates for cumulative incidence of severe coronavirus disease 2019 (COVID-19) progression stratified by glycated hemoglobin (HbA1c) level on admission in (a) all patients and (b) diabetes patients.

Table 3 | Association of higher glycated hemoglobin level, higher random plasma glucose level or diabetes with severe coronavirus disease 2019 progression (secondary Cox model)

Variable	HR (95% CI)	*P*-value
Model 1		
HbA1c level ≥7% (ref. <7%)	1.786 (1.079–2.956)	0.024
Model 2		
RPG level ≥ 140 mg/dL (ref. <140 mg/dL)	0.873 (0.542–1.404)	0.574
Model 3		
Diabetes: presence (ref. absence)	1.146 (0.723–1.816)	0.561

All Cox models were adjusted for the following known risk factors: age, sex, body mass index (BMI), smoking status, estimated glomerular filtration rate (eGFR), CRP, C-reactive protein (CRP) level, days from disease onset to hospital admission and COVID-19 severity on admission. CI, confidence interval; COVID-19, coronavirus disease 2019; HbA1c, glycated hemoglobin; HR, hazard ratio; RPG, random plasma glucose.

fasting plasma glucose rather than RPG at the time of admission might be more important for predicting the prognosis of COVID-19, as well as analysis of the association of HbA1c or plasma glucose level in affected patients.

Previous studies have shown a significant association of HbA1c level with mortality related to COVID-19[17–19]. Interestingly, Yanagisawa *et al.*[38] noted that HbA1c level on admission was significantly associated with oxygen therapy requirement, which basically corresponds to moderate II COVID-19. In contrast, the present findings showed a significant association of HbA1c level on admission with progression to severe COVID-19. Together, the results obtained in the present study along with those previously presented suggest that poor glycemic control contributes to any stage of the clinical course related to COVID-19 progression.

Although the presence of diabetes has been reported to be associated with severe COVID-19 progression[14–16], the underlying mechanisms have yet to be fully clarified. In the present study, the presence of higher HbA1c level on admission was more strongly associated with severe COVID-19 progression than the presence of diabetes (Table 3). In subgroup analyses as well, HbA1c level on admission remained associated with severe COVID-19 progression in patients with diabetes (Figures 1b and 2). Therefore, poor glycemic control might be an important factor related to the association of diabetes with severe COVID-19 progression, with glycemic control before COVID-19 onset possibly of critical importance in diabetes patients for the prevention of progression to a severe status.

Other studies have noted chronic respiratory disease, as well as older age, smoking habit, chronic renal failure, high inflammation, severity of COVID-19 and dyslipidemia to be risk factors for severe COVID-19 progression[39–44]. Notably, in the present subgroup analyses, the association between HbA1c level on admission and severe COVID-19 progression was significantly greater in patients with chronic respiratory disease, whereas it was also significant in those with older age, smoking habit, lower eGFR, higher CRP level, moderate II COVID-19 and dyslipidemia, in addition to diabetes, with no remarkable inconsistency found among the subgroups (Figure 2). Therefore, poor glycemic control might contribute to progression to severe COVID-19 independent of the presence or absence of risk factors for severe COVID-19 progression, including patients with risk factors for severe progression other than diabetes.

Poor glycemic control status is considered to reduce the availability of COVID-19 medications, especially steroids, as those deteriorate glycemic control. However, steroid administration was noted significantly more often in patients with a higher HbA1c level (≥7%) as compared with those with a lower level (<7%; 83.8% vs 61.3%, $P < 0.001$). Also, steroids were administered to all of the 93 patients who progressed to severe COVID-19. Thus, poor glycemic control did not lead to hesitation regarding steroid administration. In contrast, based on a robust association of HbA1c level on admission with severe COVID-19 progression after adjustments for COVID-19 medications, including steroids (Figure 2), proactive administration of COVID-19 medications might be important for prevention of COVID-19 progression in patients with poor glycemic control status.

The present study had some important limitations. First, HbA1c level was measured on admission, but not at the onset of COVID-19 in the present participants. Inflammation in patients with COVID-19 leads to hyperglycemia, whereas SARS-CoV-2 is considered to directly infect pancreatic β-cells, also leading to hyperglycemia[45,46]. Although we considered HbA1c level on admission as an indicator of glycemic control before onset of COVID-19, hyperglycemia caused by COVID-19 that developed from the time of disease onset until hospital admission might have had effects on HbA1c levels measured at the time of admission, even though the period from disease onset to hospital admission was short (5.0 [3.0–8.0] days). Second, patients who had received a vaccination against SARS-CoV-2 or underwent treatment for COVID-19 before admission were not included in the present analysis. Furthermore, it is unfortunate that we could not carry out a survey of SARS-CoV-2 strains. Third, the association between HbA1c level and severe COVID-19 progression in non-hospitalized patients was not investigated, as the participants were enrolled from among hospitalized patients with non-severe COVID-19. Fourth, the severity classification of COVID-19 defined by the Japanese Ministry of Health, Labor and Welfare[20–23] is not consistent with that used in other countries, although severe COVID-19 in the classification used in Japan basically corresponds to the critical COVID-19 severity classification used in other countries[47–49]. Fifth, this was a single-center study. However, Osaka City Juso Hospital has been accepting non-severe COVID-19 patients from throughout Osaka Prefecture in response to instructions from the Osaka Prefecture government, thus there was no selection bias. Sixth, due to the observational design of

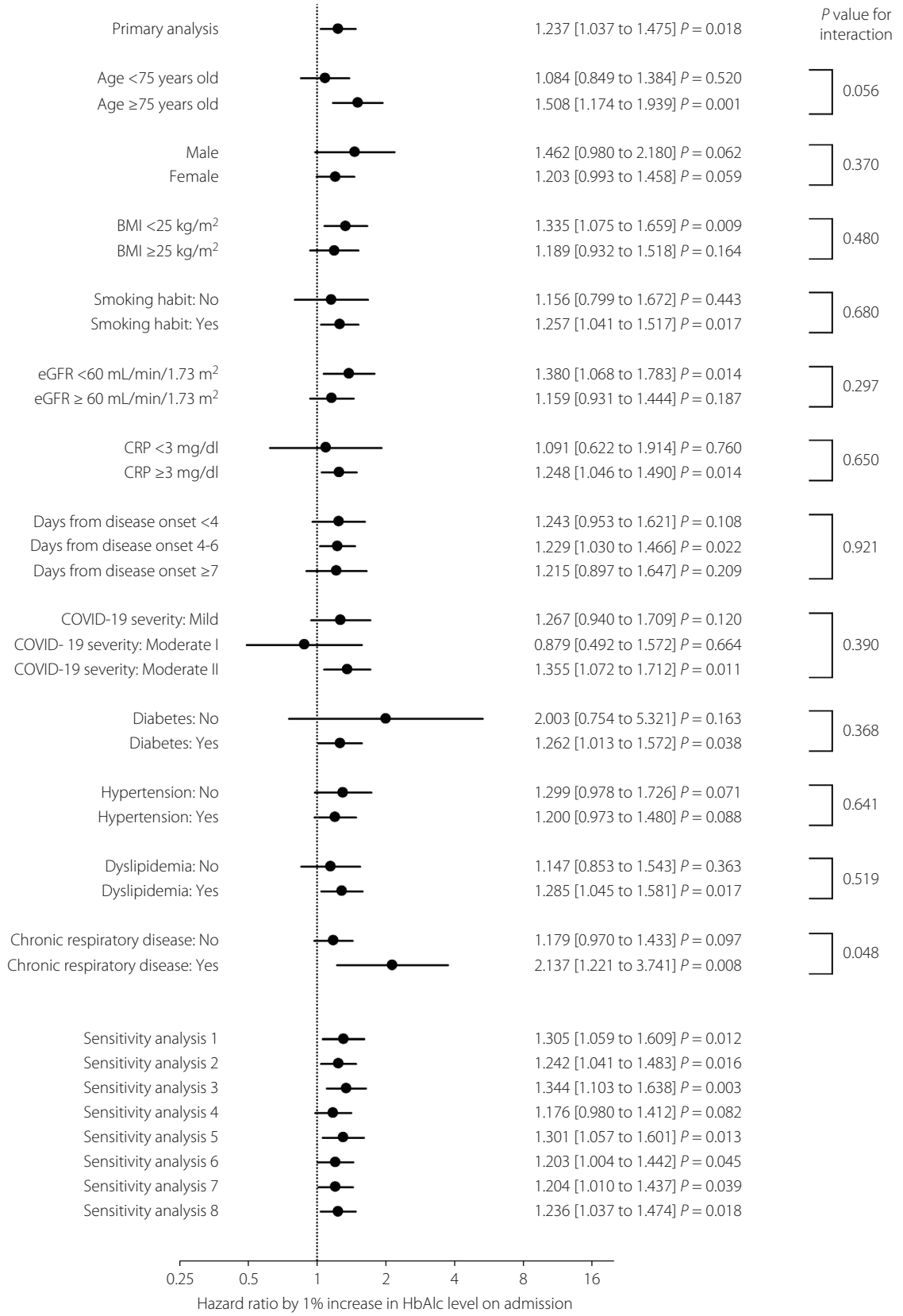

Figure 2 | Subgroup and sensitivity analyses of association between glycated hemoglobin (HbA1c) level on admission and severe coronavirus disease 2019 (COVID-19) progression. Forrest plot shows hazard ratio (HR) and 95% confidence interval (CI) as circles and lines. BMI, body mass index; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate.

this study, even though relationships were explored in predictive terms, the results cannot be interpreted to show causal relationships. Finally, due to the small number of death cases (n = 36), we were not able to fully investigate the association of HbA1c level on admission with COVID-19-related mortality in the present study.

The present results showed that HbA1c level on admission was significantly associated with severe COVID-19 progression in patients hospitalized for non-severe COVID-19, and that association was also significant in patients with diabetes, as well as other risk factors for severe progression. It is suggested that poor glycemic control before onset of the disease contributes to severe COVID-19 progression, thus management of glycemic control before onset of COVID-19 is of critical importance for diabetes patients, as well as non-diabetic individuals.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The present study protocol was approved by the Ethics Committee of Osaka City Juso Hospital (approval No. 3-A1) and Osaka City University Graduate School of Medicine (approval No. 2021–159).

Informed consent: The need for informed consent was waived owing to the retrospective nature of the investigation and the opt-out method of inclusion.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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