

# HbA1c measurement may save COVID-19 inpatients from overlooked diabetes

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## Keywords

COVID-19, Diabetes mellitus, Glycated Hemoglobin A1c

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## ABSTRACT

**Aims/Introduction:** To investigate overlooked diabetes in patients with coronavirus disease 2019 (COVID-19).

**Materials and Methods:** In total, 462 COVID-19 inpatients were included in this retrospective study. The presence of diabetes before COVID-19 admission, and the HbA1c and blood glucose levels at admission were examined.

**Results:** Of the 462 patients, 116 had diabetes. Seventy-six patients had been diagnosed with diabetes before COVID-19 admission, and 40 patients were diagnosed for the first time. Of the patients with diabetes 72% required insulin. Patients with diabetes were significantly ( $P < 0.05$ ) older, more likely to be male, heavier, and showed a lower eGFR. Patients with overlooked diabetes showed a lower HbA1c (average 7.1% vs 7.5%), a lower casual blood glucose (average 157 vs 179 mg/dL), and they used less insulin per day during hospitalization (average 16.0 units vs 34.5 units) than patients with previously diagnosed diabetes. Patients with overlooked diabetes tended to have more severe COVID-19 than those with pre-diagnosed diabetes. Multivariable logistic regression analyses showed that the increased odds ratios (ORs) of aggravation in all patients with COVID-19 were associated with age [OR 1.04], BMI [OR 1.05], and diabetes [OR 2.15]. The risk factors for aggravation in patients with COVID-19 and diabetes were age [OR 1.05] and HbA1c [OR 1.45].

**Conclusions:** Diabetes is a predictor of COVID-19 aggravation. Furthermore, in COVID-19 patients with diabetes, high HbA1c levels are a risk factor for severe COVID-19. A total of 8.7% of COVID-19 inpatients were diagnosed with diabetes after HbA1c was measured on admission. Therefore, it is important to measure HbA1c in COVID-19 patients.

## INTRODUCTION

A total of 537 million adults are living with diabetes worldwide, and this number is increasing yearly<sup>1</sup>. Diabetes has been reported to be associated with coronavirus disease 2019 (COVID-19) severity and mortality<sup>2–6</sup>. For patients with COVID-19, the presence of diabetes changes the assessment of the risk of severe disease, subsequent treatment, and the necessity for hospitalization. Therefore, health center staff and attending physicians evaluate the patients' comorbidities and medical history before starting treatment. Previous epidemiological studies in Japan have shown that the prevalence of diabetes in the general population is 11.9%, of which 52.2% were newly diagnosed at the time of the survey<sup>7</sup>. The National Health and

Nutrition Survey of Japan by the Ministry of Health, Labour and Welfare reported that 23.4% of patients with diabetes do not receive treatment<sup>8</sup>.

We hypothesized, therefore, that some patients with COVID-19 may have diabetes according to their HbA1c and blood glucose levels on admission, even if they state that they do not have diabetes during the initial patient interview. A recent Japanese report suggested that patients with newly diagnosed diabetes upon admission for COVID-19 were at higher risk for severe COVID-19 than patients with pre-existing diabetes<sup>9</sup>.

Furthermore, a previous study in Israel reported that HbA1c levels are associated with the severity of COVID-19<sup>10</sup>. It has been suggested that poor pre-infection glycemic control affects the outcome of COVID-19.

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Whether a patient has diabetes is an important concern in the treatment of COVID-19, but few reports have examined the rate of overlooked diabetes in COVID-19 patients. We figured that it is possible to overlook diabetes by simply interviewing the patient and to cause aggravation of COVID-19 in patients with overlooked diabetes. Measuring the HbA1c levels and identifying potential patients with diabetes may change the treatment strategy for COVID-19 and contribute to an improved prognosis. This study aimed to investigate the rate of overlooked diabetes and its clinical characteristics in Japanese COVID-19 patients requiring hospitalization.

## MATERIALS AND METHODS

### Study design and patients

This retrospective study included 462 patients aged 16–101 years who were admitted to the National Hospital Organization Kanazawa Medical Center, Japan, between April 1, 2020 and September 1, 2021. During this period, 467 patients aged 16 years or older were admitted for COVID-19 treatment. Five patients were excluded from the analysis because HbA1c was not measured. All participants were Japanese. They were diagnosed according to the COVID-19 clinical guidelines in Japan. In this study, diabetes was defined as (1) having been diagnosed before admission (medical records) (2) having an HbA1c level  $\geq 6.5\%$  on admission, and a fasting blood glucose of  $\geq 7.0$  mmol/L (126 mg/dL) or a random blood glucose of  $\geq 10.0$  mmol/L (200 mg/dL) during hospitalization. The patient's clinical data, laboratory data, and treatment details were extracted from the electronic medical record by the endocrinologist.

### Procedures

SARS-CoV-2 infection was proven using reverse transcription-polymerase chain reaction (RT-PCR), nicking enzyme amplification reaction, or antigen testing. Patients underwent blood tests (including blood count, biochemistry, and coagulation) and computed tomography (CT) of the chest as a routine examination on admission. The treatment plan for COVID-19 was decided by the attending physician in consultation with a pulmonologist, referring to the latest Japanese clinical guidelines for COVID-19 treatment. Patients who received steroids for the treatment of COVID-19 underwent blood glucose monitoring using a simple blood glucose meter. If the pre-prandial blood glucose level was  $>200$  mg/dL, the patients were administered insulin on a sliding scale according to the blood glucose levels. If the blood glucose level was still inadequately controlled, an endocrinologist initiated intensive insulin therapy. The maximum number of total units of insulin used per day during hospitalization was defined as the amount of insulin used.

### Definition of severity

COVID-19 severity (mild, moderate, severe, or critical) was determined by reference to the COVID-19 treatment guidelines by the National Institutes of Health and the COVID-19 clinical guidelines in Japan. Briefly, the mild grade was defined as mild

symptoms and no changes on lung CT scans; the moderate grade was defined as the presence of respiratory symptoms, blood oxygen saturation  $\leq 96\%$ , and changes on lung CT scans; the severe grade was defined as blood oxygen saturation  $\leq 93\%$ ; and the critical grade was defined as a need for ventilator use or intensive care unit admission. The worst severity was recorded throughout the hospitalization period.

### Statistical analysis

Categorical variables are presented as the value, and continuous variables are summarized as average  $\pm$  standard deviation. Categorical data were analyzed using Fisher's exact test. The Holm *post hoc* test was additionally used to compare three or more groups. The Mann–Whitney U test was used to compare non-normal continuous variables data. The Kruskal–Wallis test with the Steel *post hoc* test was used for the comparison of three or more groups of continuous variables. Ordinal logistic regression analysis was used to perform multivariable analyses to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for factors associated with clinical outcomes. We chose age, body-mass index (BMI), sex, estimated glomerular filtration rate (eGFR), and the presence of diabetes in multivariable regression models to identify risk factors for advancing severity in all patients with COVID-19. To explore the risk factors for advancing severity in patients with COVID-19 with diabetes, age, sex, BMI, eGFR, HbA1c levels, and usage of insulin per day were chosen as variables in the multivariable regression model. Logistic regression analysis was used to compare the two groups according to whether they had been treated previously for diabetes. Statistical significance was set at  $P < 0.05$ . Analyses were performed using EZR software ver1.54 (Jichi Medical University, Saitama, Japan).

## RESULTS

### Characteristics of the population

Of the 462 patients included in this study (Table 1), 249 (53.8%) were men and 213 (46.1%) were women. The average age was 56.8, and the average BMI was 23.5 kg/m<sup>2</sup>. A total of 116 patients had diabetes. One hundred and thirteen patients had type 2 diabetes, one had steroid-induced diabetes, one had diabetes after pancreatic cancer surgery, and one had diabetes due to malignancy. There were no patients with type 1 diabetes. Compared with patients without diabetes, patients with diabetes were significantly older (average 67.8 years old vs 53.1 years old), more likely to be male (70.6% vs 48.2%), had a higher BMI (average BMI 25.3 kg/m<sup>2</sup> vs 22.9 kg/m<sup>2</sup>), and showed a higher creatinine level (average 0.94 mg/dL vs 0.82 mg/dL), lower eGFR (average 65.3 mL/min/1.73 m<sup>2</sup> vs 76.1 mL/min/1.73 m<sup>2</sup>), and had more severe COVID-19.

### Comparison of overlooked and pre-diagnosed patients with diabetes

Seventy-six patients had been diagnosed with diabetes previously and had started treatment before admission due to

**Table 1** | Baseline characteristics of patients with COVID-19 admitted to our hospital

	COVID-19 (n = 462)	Non-diabetes (n = 346)	Diabetes (n = 116)
Age (year)	56.8 ± 19.8	53.1 ± 20.3	67.8* ± 13.7
Sex, % (no.)			
Male	53.8% (249)	48.2% (167)	70.6%* (82)
Female	46.1% (213)	51.7% (179)	29.3% (34)
Height (cm)	162.9 ± 10.1	162.8 ± 10.0	163.0 ± 11.0
Weight (kg)	63.0 ± 16.9	61.4 ± 16.3	68.0* ± 18.0
BMI (kg/m <sup>2</sup> )	23.5 ± 4.8	22.9 ± 4.6	25.3* ± 5.3
Creatinine (mg/dL)	0.85 ± 0.49	0.82 ± 0.50	0.94* ± 0.42
eGFR (mL/min/1.73m <sup>2</sup> )	73.4 ± 21.8	76.1 ± 21.7	65.3* ± 20.4
COVID-19 Severity, % (no.)			
Mild	28.5% (132)	35.5% (123)	7.7% (9)*
Moderate	50.0% (231)	48.5% (168)	54.3% (63)*
Severe	16.2% (75)	12.4% (43)	27.5% (32)*
Critical	4.9% (23)	3.1% (11)	10.3% (12)*

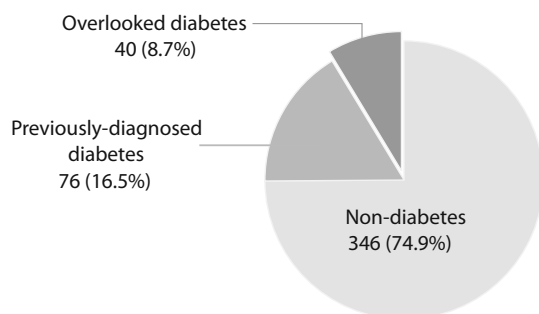
Data are presented as mean ± standard deviation. Clinical characteristic parameters were compared between patients with and without diabetes using the Mann–Whitney U test. Categorical data were analyzed using Fisher’s exact test. \**P* < 0.05. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c.

COVID-19, on the other hand, the remaining 40 patients were diagnosed with diabetes for the first time upon admission (Figure 1). In other words, 34.4% of 116 patients with diabetes and COVID-19 were diagnosed with diabetes only after the HbA1c was measured upon admission. Two patients with previously (pre)-diagnosed diabetes had begun diabetes treatment but had self-interrupted treatment before admission.

The clinical characteristics of the patients with diabetes are shown in Table 2. Overlooked patients with diabetes showed lower HbA1c levels compared with pre-diagnosed patients (average 7.1% vs 7.5%; respectively, *P* < 0.05), lower casual blood glucose (average 157 mg/dL vs 179 mg/dL; respectively *P* < 0.05), and used less insulin per day during hospitalization (average 16.0 units vs 34.5 units,

respectively; *P* < 0.05). Otherwise, there were no significant differences in the clinical background, age, sex, BMI, and eGFR. More than 80% of both patients with overlooked diabetes and patients with pre-diagnosed diabetes were hospitalized within 2 days of diagnosis. The proportion of patients hospitalized within 3–4 days of diagnosis was 5.0% for overlooked diabetes and 15.8% for pre-diagnosed diabetes. 15.0% of patients with overlooked diabetes and 3.9% of patients with pre-diagnosed diabetes required more than 5 days from the date of diagnosis to hospitalization. The time from diagnosis to hospitalization for COVID-19 was significantly longer for patients with overlooked diabetes than for pre-diagnosed diabetes (*P* = 0.038).

Ordinal logistic analysis was performed with the severity of disease as the dependent variable for both overlooked and pre-diagnosed diabetes. HbA1c tended to be associated with severity in overlooked diabetes [OR 4.41, 95%CI 1.12–27.70, *P* = 0.094], and age was associated with severity in pre-diagnosed diabetes [OR 1.06, 95%CI 1.01–1.12, *P* = 0.021]. Logistic analysis of overlooked diabetes and pre-diagnosed diabetes showed that overlooked diabetes patients tended to have more severe COVID-19 [OR 1.57, 95%CI 0.93–2.69, *P* = 0.072]. Of the overlooked patients with diabetes, 70.0% required insulin therapy to control the fasting blood glucose level to <200 mg/dL. Similarly, 73.6% of the patients with pre-diagnosed diabetes required insulin therapy during hospitalization. Eighty-four patients with diabetes were administered steroids for COVID-19 treatment. The maximum total insulin dose per day during hospitalization for patients with COVID-19 with diabetes, according to COVID-19 severity, is provided in Figure 2. Compared with mild cases, the moderate, severe, and critical cases tended to have more patients requiring more insulin. In



**Figure 1** | The proportion of overlooked diabetes in 462 patients with COVID-19. A total of 25.1% of patients with COVID-19 had diabetes. Forty patients were diagnosed with diabetes for the first time on admission – they were not aware that they had diabetes.

**Table 2** | Clinical characteristics of patients with overlooked diabetes and patients with pre-diagnosed diabetes

	Overlooked diabetes (n = 40)	Pre-diagnosed diabetes (n = 76)
Age (year)	68.2 ± 14.2	67.6 ± 13.6
Sex, % (no.)		
Male	67.2% (27)	72.4% (55)
Female	32.8% (13)	27.6% (21)
Height (cm)	162.7 ± 9.3	163.8 ± 11.2
Weight (kg)	65.6 ± 12.4	69.5 ± 20.2
BMI (kg/m <sup>2</sup> )	24.7 ± 3.5	25.6 ± 6.1
Creatinine (mg/dL)	0.85 ± 0.22	0.98 ± 0.49
eGFR (mL/min/1.73m <sup>2</sup> )	67.9 ± 18.4	64.0 ± 21.3
Severity, % (no.)		
Mild	2.5% (1)	10.5% (8)
Moderate	57.5% (23)	52.6% (40)
Severe	25.0% (10)	28.9% (22)
Critical	15% (6)	7.8% (6)
HbA1c (%)	7.1 ± 1.4	7.5* ± 1.1
Casual blood glucose (mg/dL)	157 ± 92	179* ± 66
Insulin utilization rate during hospitalization (%)	70.0%	73.6%
Steroid utilization rate during hospitalization (%)	82.5%	68.9%
Total insulin units per day (units)	16.0 ± 21.3	34.5* ± 33.8

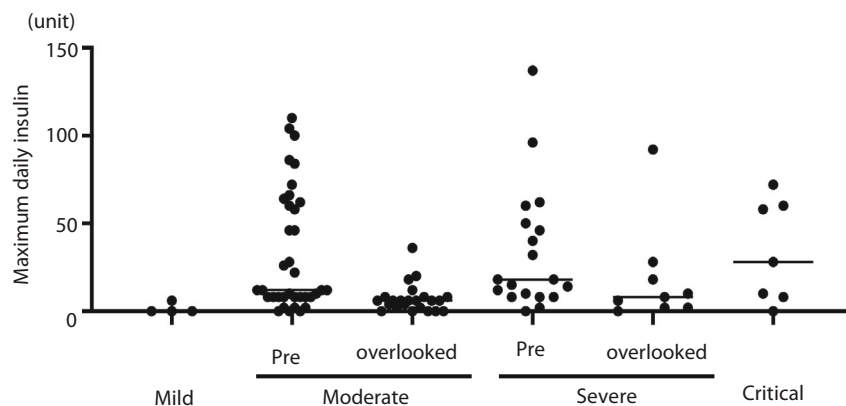
Data are presented as mean ± standard deviation. The clinical characteristic parameters were compared using the Mann–Whitney U test. Categorical data were analyzed using Fisher's exact test. \**P* < 0.05. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c.

moderate and severe cases, patients with pre-diagnosed diabetes tended to require more insulin than those with overlooked diabetes.

#### Risk factors associated with COVID-19 severity grading

In our cohort, the COVID-19 severity grading was mild in 28.5% of cases, moderate in 50.0%, severe in 16.2%, and critical in 4.9%. The clinical features were compared according to the severity of COVID-19 (Table 3a).

Patients with moderate, severe, and critical grades of COVID-19 were significantly older and showed a lower eGFR than those with a mild grade; the BMI of patients with mild COVID-19 was significantly lower than that of patients with moderate and severe COVID-19. There was no significant difference in the BMI between mild grade and critical grade. We performed ordinal logistic regression for multivariable analyses to identify risk factors associated with COVID-19 severity. Multivariable logistic regression analyses showed increased odds of



**Figure 2** | Maximum total insulin units per day administered during hospitalization to the patients with COVID-19 with diabetes by COVID-19 severity. The plots show the maximum total insulin units per day for each patient with diabetes. Because of the large number of patients, patients with COVID-19 of moderate and severe severity were divided into pre-diagnosed diabetes and overlooked diabetes groups. Pre, previously diagnosed patients with diabetes; Overlooked, patients with overlooked diabetes.

**Table 3** | Clinical characteristics by COVID-19 severity and risk of severe disease (a) Data from overall 462 patients with COVID-19; (b) Data from the 116 patients with COVID-19 and diabetes

(a)	Mild (n = 132)	Moderate (n = 231)	Severe (n = 75)	Critical (n = 23)
Age (year)	47.2 ± 21.8	57.7* ± 17.5	66.0* ± 15.6	72.8* ± 17.1
Sex, % (no.)				
Male	46.2% (61)	52.5% (122)	66.6%* (50)	65.2% (15)
Female	53.8% (71)	47.1% (109)	33.3% (25)	34.7% (8)
Height (cm)	162.7 ± 9.1	163.1 ± 10.0	163.8 ± 10.6	160.5 ± 14.1
Weight (kg)	60.3 ± 14.9	63.9 ± 17.0	67.1* ± 19.0	58.5 ± 17.8
BMI (kg/m <sup>2</sup> )	22.6 ± 4.8	23.7* ± 4.6	24.8* ± 5.4	22.5 ± 5.7
BMI, % (no.)				
BMI < 18.5	14.3% (19)	9.5% (22)	12.1% (9)	26.0% (6)
18.5 ≤ BMI < 25	62.1% (82)	59.5% (137)	43.2% (32)	43.4% (10)
25 ≤ BMI < 30	16.6% (22)	21.3% (49)	31.0% (23)	17.3% (4)
30 ≤ BMI	6.8% (9)	9.5% (22)	13.5% (10)	13.0% (3)
Creatinine (mg/dL)	0.81 ± 0.31	0.84* ± 0.31	0.94* ± 0.45	0.83 ± 0.26
eGFR (mL/min/1.73 m <sup>2</sup> )	82.7 ± 22.6	70.8* ± 19.3	65.5* ± 19.4	72.4* ± 30.9
Diabetes, % (no.)	6.8% (9)	27.2%* (63)	42.6%* (32)	52.1%* (12)
Overlooked diabetes	1	23	10	6
Pre-diagnosed diabetes	8	40	22	6
Non-diabetes, % (no.)	93.2% (123)	72.7% (168)	57.3% (43)	47.8% (11)
Predictive factors	Odds ratio(95% Confidence Interval)			P value
Age	1.04 (1.02–1.05)			<0.001
Male	1.37 (0.93–2.01)			0.103
BMI	1.05 (1.01–1.09)			0.018
eGFR	0.99 (0.98–1.01)			0.834
Diabetes	2.15 (1.36–3.40)			0.001
(b)	Mild (n = 9)	Moderate (n = 63)	Severe (n = 32)	Critical (n = 12)
Age (year)	67.7 ± 15.1	66.4 ± 12.9	68.8 ± 18.4	72.2 ± 20.7
Sex, % (no.)				
Male	44.4% (4)	69.8% (44)	81.2% (26)	66.6% (8)
Female	55.5% (5)	30.1% (19)	18.7% (6)	33.3% (4)
Height (cm)	161.2 ± 8.7	164.4 ± 9.5	164.2 ± 9.4	158.0 ± 17.6
Weight (kg)	68.6 ± 24.5	69.0 ± 16.1	68.2 ± 18.4	63.1 ± 21.6
BMI (kg/m <sup>2</sup> )	26.1 ± 8.0	25.4 ± 4.4	25.2 ± 5.9	24.7 ± 6.4
BMI, % (no.)				
BMI < 18.5	11.1% (1)	3.1% (2)	9.3% (3)	16.6% (2)
18.5 ≤ BMI < 25	44.4% (4)	50.7% (32)	50.0% (16)	41.6% (4)
25 ≤ BMI < 30	22.2% (2)	33.3% (21)	25.0% (8)	16.6% (2)
30 ≤ BMI	22.2% (2)	12.6% (8)	15.6% (5)	25.0% (3)
Creatinine (mg/dL)	0.73 ± 0.29	0.95 ± 0.36	1.01 ± 0.56	0.82 ± 0.23
eGFR (mL/min/1.73 m <sup>2</sup> )	78.2 ± 24.9	63.3 ± 18.9	64.0 ± 21.4	69.7 ± 20.0
HbA1c (%)	7.0 ± 1.2	7.3 ± 1.0	7.4 ± 1.0	8.0 ± 2.4
Casual blood glucose (mg/dL)	158.7 ± 52.5	159 ± 57.1	178.3 ± 70.9	222.4 ± 149.5
Total insulin unit per day (units)	6.0 ± 0.0	22.6* ± 30.0	28.6* ± 33.8	33.7 ± 29.2
Insulin utilization rate (%)	11.1%	80.9%	75.0%	50.0%
Steroid utilization rate (%)	0.0%	80.6%	87.5%	50.0%
Predictive factors	Odds ratio (95% Confidence Interval)			P value
Age	1.05 (1.01–1.09)			0.028
Sex (male)	2.43 (1.01–6.08)			0.052
BMI	0.99 (0.90–1.09)			0.925

**Table 3.** (Continued)

Predictive factors	Odds ratio (95% Confidence Interval)	P value
eGFR	1.01 (0.98–1.03)	0.354
HbA1c	1.45 (1.00–2.10)	0.046
Total insulin unit per day	1.00 (0.98–1.02)	0.354

Mean  $\pm$  SD. Data are presented as mean  $\pm$  standard deviation. Clinical parameters were compared according to COVID-19 severity using the Kruskal-Wallis test with the Steel *post hoc* test. Categorical data were analyzed using the Fisher's exact test with the Holm *post hoc* test. \* $P < 0.05$ . Age, sex, BMI, eGFR, and the presence of diabetes were examined by multivariable analysis for correlation with COVID-19 severity. In patients with diabetes, age, sex, BMI, eGFR, HbA1c, and the total insulin unit per day were examined by multivariable analysis for correlation with COVID-19 severity. BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c.

aggravation in all patients with COVID-19 associated with age (OR 1.04 [95% CI 1.02–1.05]), BMI (OR 1.05 [95% CI 1.01–1.09]), and diabetes (OR 2.15 [95% CI 1.36–3.40]).

In addition, we compared the clinical features according to COVID-19 severity in patients with both COVID-19 and diabetes (Table 3b). Patients with moderate, severe, and critical COVID-19 did not differ significantly from those with mild grade COVID-19 regarding age, sex, BMI, eGFR, blood HbA1c, and glucose levels. Patients with a BMI between 18.5 and 25 kg/m<sup>2</sup> were the most found, regardless of the disease severity. Even in the critical-grade patients, 16.6% were thin, with a BMI < 18.5 kg/m<sup>2</sup>. The steroid utilization rate was 79.2% in patients with moderate, severe, and critical grades of COVID-19 and diabetes. None of the patients with mild-grade COVID-19 and diabetes used steroids for COVID-19.

In the multivariable analysis, the risk factors for aggravation in patients with COVID-19 and diabetes were age (OR 1.05 [95% CI 1.01–1.09]) and HbA1c levels (OR 1.45 [95% CI 1.00–2.10]). In contrast to the analysis of all the patients, no significant association was found for sex, BMI, or eGFR.

## DISCUSSION

In the patients with both diabetes and COVID-19, 34.4% had overlooked diabetes. This value is higher than the prevalence of diabetes in the general Japanese population (23.4%)<sup>8</sup>. In other words, 8.7% of our patients with COVID-19 were diagnosed with diabetes only after the HbA1c had been measured on admission. A previous epidemiological study in Japan showed that 6.2% of the general population have undiagnosed diabetes<sup>7</sup>; therefore, in our entire cohort, which included patients without diabetes, there were relatively more patients with untreated diabetes than in the general Japanese population. Previous studies have shown that diabetes does not increase the risk of COVID-19 infection<sup>4,5,11</sup>. In contrast, pre-diagnosed diabetes is associated with COVID-19 severity and mortality<sup>2,5,11</sup>. Our cohort consisted of patients with COVID-19 who were judged to require inpatient care based on their symptoms, past medical history, and comorbidities; therefore, the large number of patients with newly diagnosed diabetes may have been due to the severity of the disease in many patients, who were deemed

unsuitable for home care. Interviewing patients before starting COVID-19 treatment without checking the HbA1c and blood glucose levels could mean missing potential patients with diabetes and lead to severe COVID-19.

Studies in India and China have reported that newly diagnosed cases of diabetes have a higher risk of mortality and severity with COVID-19 compared with pre-diagnosed cases<sup>12,13</sup>. A recent Japanese report also suggested that COVID-19 patients with newly diagnosed diabetes may have severe COVID-19<sup>9</sup>. The study showed that newly diagnosed (overlooked) patients with diabetes had higher HbA1c than pre-diagnosed patients with diabetes, and 93.5% of their patients were severe or critical COVID-19 cases. Poorer glycemic control may have led to more severe cases of COVID-19, requiring hospitalization and treatment at their hospital, which specializes in the treatment of infectious diseases. On the other hand, our COVID-19 patients were mostly mild or moderate because our facility is a local hospital. Although our patients with overlooked diabetes had better glycemic control than pre-diagnosed patients, multivariate analysis showed that COVID-19 could be more severe. One possible reason for this could be that patients with newly diagnosed diabetes are unaware of their diabetes, and their medical providers also do not know that the patients have diabetes, which may delay hospitalization and initiation of treatment and increase the risk of severe disease. In our study, the time from diagnosis to hospitalization for COVID-19 was significantly longer for patients with overlooked diabetes than for patients with pre-diagnosed diabetes. Our result suggests that patients with diabetes are more likely to develop severe COVID-19, even in newly diagnosed cases. It is important to measure HbA1c to identify potential patients with diabetes for COVID-19 treatment.

Previous reports have indicated that diabetes is associated with COVID-19 severity, which is supported by our data. In our analysis, among patients with COVID-19, age [OR 1.04] and BMI [OR 1.05] were also associated with COVID-19 severity, but the presence of diabetes had a higher odds ratio [OR 2.15]. In a meta-analysis of 47 pooled studies<sup>2</sup>, COVID-19 patients with diabetes had a significantly higher risk of severe disease [OR 2.20]. In a retrospective study using a U.S. medical

database, COVID-19 combined with type 2 diabetes was significantly associated with the need for inpatient and intensive care<sup>14</sup>. In a Japanese registry study, the presence of diabetes as a comorbidity was associated with severe COVID-19 on admission [OR = 1.34]<sup>15</sup>. The mechanism by which diabetes affects the severity of COVID-19 is unclear. Whether the worse prognosis is due to diabetes *per se* or to concomitant morbidities and risk factors remains to be fully elucidated. Previous studies examining comorbidities of diabetes have found that, in patients with COVID-19, those with diabetes more commonly had hypertension, cardiovascular, neurological, and chronic kidney diseases. Cardiovascular, neurological, and chronic kidney diseases are all associated with a risk of in-hospital death and poor prognosis<sup>16,17</sup>. It is well known that pro-inflammatory cytokines play an important role in the severity of COVID-19. Overproduction of proinflammatory cytokines (TNF $\alpha$ , IL-6, IL-1 $\beta$ , and CXCL10) leads to the so-called 'cytokine storm', which increases the risk of vascular permeability, multiple organ failure, and death. A multicenter study in a Chinese population of patients with COVID-19<sup>17</sup> showed that those with diabetes had a higher incidence of lymphopenia and elevated levels of inflammatory biomarkers (C-reactive protein and procalcitonin). Patients with diabetes are in a constant state of chronic inflammation and may be more susceptible to the cytokine storm<sup>4</sup>. Coagulation abnormalities due to vascular endothelial damage are also known to contribute to COVID-19 severity. In a retrospective Chinese study of patients with diabetes and COVID-19, non-survivors had longer prothrombin times and higher concentrations of D-dimer<sup>18</sup>. In general, chronic hyperglycemia causes vascular and neurological disorders; therefore, these conditions may be related to the severity of COVID-19.

Our data showed that higher HbA1c levels were a factor in disease severity in patients with COVID-19 and diabetes. These results are consistent with those of previous studies. A retrospective cohort study of the association between pre-infection glycemic control and disease severity in patients with type 2 diabetes and COVID-19 in Israel found a gradual dose-response relationship between HbA1c level and the risk of severe COVID-19<sup>10</sup>. A population-based cohort study in England also suggested a higher risk of mortality from COVID-19 in patients with either type 1 or type 2 diabetes with HbA1c levels >10.0% than in those with HbA1c levels of less than 6.5%<sup>19</sup>. In addition, a Japanese study showed that HbA1c levels might be a risk factor for severe disease requiring oxygenation in patients with COVID-19<sup>20</sup>.

Based on previous reports and our data, hyperglycemia before or after hospitalization may be associated with the severity of COVID-19. Although HbA1c levels reflect glycemic control before hospitalization, patients with diabetes with higher HbA1c levels often continue to have hyperglycemia and require more insulin during hospitalization. In our patients with COVID-19 and diabetes, insulin was required for glycemic control in 73.6% of the patients with pre-diagnosed diabetes and 70.0% of the patients with overlooked diabetes. During

hospitalization, many patients required additional insulin treatment for adequate blood glucose control, supplementing their pre-hospitalization diabetes treatment (appropriate diet and treatment with oral hypoglycemic agents). The use of glucocorticoids in the treatment of patients with severe COVID-19 appears to be one of the reasons for hyperglycemia and higher insulin requirements during hospitalization. Although the mechanism by which COVID-19 causes hyperglycemia is not clear, it has been shown that patients with COVID-19 develop hyperglycemia due to increased insulin resistance, independent of the use of glucocorticoids. Another explanation is reduced adiponectin expression due to adipose tissue infection by SARS-CoV-2<sup>21</sup>. In a previous report that analyzed glycemic control and prognosis after hospitalization in COVID-19, mortality was higher in the group with poor glycemic control<sup>22,23</sup>. Therefore, blood glucose monitoring and treatment of hyperglycemia are important in hospitalized patients with COVID-19.

Obesity is also considered to be a factor in the severity of COVID-19. Our finding that a high BMI is a risk factor [OR 1.05] for severe disease is consistent with previous reports. A report from the USA showed that patients with obesity and COVID-19 have a higher intensive care unit admission rate<sup>24</sup>. A report from China found that obesity increased the risk of severe COVID-19 by approximately 3-fold, resulting in a longer hospital stay<sup>25</sup>. Obesity is an inflammatory state characterized by chronic activation of the immune system, which adversely affects immune function and the host's defense mechanisms, resulting in high infection rates. In addition, changes in pulmonary physiology, increased receptors for viral entry, increased viral diversity and titers, and prolonged viral shedding periods affect SARS-CoV-2 infection in obesity<sup>26</sup>. In a Japanese registry study<sup>15</sup>, obesity was found to be a risk factor for severe COVID-19 at the time of hospitalization, which is consistent with our results.

By contrast, in Japanese patients with diabetes, the absence of obesity may not indicate a lower risk of severe COVID-19. Interestingly, in our cohort of patients with both COVID-19 and diabetes, we were unable to demonstrate an association between BMI and severe disease. In patients with diabetes and severe COVID-19 from our cohort, 13.0% were obese (BMI  $\geq$  30 kg/m<sup>2</sup>) and 26.0% were thin (BMI < 18.5 kg/m<sup>2</sup>). Asian Americans have a significantly higher risk of type 2 diabetes than whites despite having a substantially lower BMI<sup>27</sup>. Compared with Caucasians, Japanese individuals have relatively low obesity, which is the main cause of increased insulin resistance. Furthermore, experiments comparing insulin resistance and insulin secretion capacity in Japanese and Caucasian populations have shown that Japanese individuals have low insulin secretion capacity<sup>28</sup>. Japanese patients with diabetes are more likely to be thin (even for type 2 diabetes) than those in Europe and the USA because of the predominance of endogenous insulin hyposecretion. Japanese patients with type 2 diabetes with a long disease duration often show emaciation and malnutrition

accompanied by insulin secretion deficiency. Such patients are old, have many comorbidities, such as cardiovascular disease, hypertension, and malignancies, and may be affected severely by infectious diseases due to malnutrition and immunodeficiency.

This study has some limitations. We included patients in the early stages of the COVID-19 pandemic when no effective treatment had been established. The severity of the disease may vary depending on the time of infection, type of virus variant, and the availability of medical care, and should be discussed with caution<sup>29</sup>.

This study and previous reports have shown that diabetes is a risk factor for COVID-19 severity and hyperglycemia during COVID-19 treatment is a poor prognostic factor. Therefore, the presence of diabetes may alter the indications for hospitalization. In Japan, at the time of COVID-19 diagnosis, public health center staff interview COVID-19 patients about their symptoms, medical history, and comorbidities. Patients with an underlying disease are given a higher priority for hospitalization. However, if the number of hospital beds is insufficient, patients with respiratory failure may not be admitted. The Japanese clinical guidelines<sup>30</sup> recommend oral steroid administration as an option for patients with severe COVID-19 who are treated at home and cannot be hospitalized. In our study, we found that many patients with diabetes were not recognized by simply interviewing the patients. If a potential patient with diabetes is missed and steroids are administered at home without hospitalization, hyperglycemia may occur, leading to severe COVID-19 and death. The severity of COVID-19 may vary depending on the time of infection, type of virus variant, availability of medical care, and local factors; however, it is possible that diabetes is being overlooked in any given region and at any given time. In our region, when the number of infected patients increased and more patients were treated at home or in accommodation, the local government expanded the number of medical facilities where outpatients underwent CT scans and blood tests to determine indications for hospitalization. To detect overlooked diabetes and to provide appropriate COVID-19 treatment, it is worth measuring HbA1c and blood glucose levels at the time of the initial diagnosis and hospitalization.

Limitations of this study are the relatively small number of patients and the single-center, retrospective design. We also performed a subgroup analysis only in patients with diabetes, but the number of patients included was small. Our hospital began inpatient treatment of COVID-19 patients at the beginning of the pandemic. The cohort in this study includes cases from that period, and treatment for COVID-19 varied depending on when the patients were admitted.

Diabetes is a predictor of disease severity in COVID-19. However, in our study, 8.7% of patients with COVID-19 were diagnosed with diabetes only after the HbA1c levels were measured on admission. In patients with both COVID-19 and diabetes, a high HbA1c level is a risk factor for severe disease. Therefore, it is important to measure HbA1c levels in patients with COVID-19.

## DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The Research Ethics Commission of the National Hospital Organization Kanazawa Medical Center approved this study and waived the requirement for informed consent from the study participants because of the study's retrospective design (approval R03-065). All clinical investigations were conducted by the guidelines of the Declaration of Helsinki and its recent revisions.

Informed consent: This study was conducted without informed consent, but the patients were allowed to actively opt-out of participating.

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

Animal studies: N/A.

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