ORIGINAL ARTICLE

Clinical significance of prediabetes, undiagnosed diabetes and diagnosed diabetes on critical outcomes in COVID-19: Integrative analysis from the Japan COVID-19 task force

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Abstract

Aim: Diabetes mellitus (DM) is a known risk factor for severe coronavirus disease 2019 (COVID-19), but the clinical impact of undiagnosed diabetes and prediabetes in COVID-19 are unclear particularly in Japan. We clarify the difference in clinical characteristics, including age, sex, body mass index and co-morbidities, laboratory findings and critical outcomes, in a large Japanese COVID-19 cohort without diabetes, with prediabetes, undiagnosed diabetes and diagnosed diabetes, and to identify associated risk factors.

Materials and Methods: This multicentre, retrospective cohort study used the Japan COVID-19 Task Force database, which included data on 2430 hospitalized COVID-19 patients from over 70 hospitals from February 2020 to October 2021. The prevalence of prediabetes, undiagnosed diabetes and diagnosed diabetes were estimated based on HbA1c levels or a clinical diabetes history. Critical outcomes were

defined as the use of high-flow oxygen, invasive positive-pressure ventilation or extracorporeal membrane oxygenation, or death during hospitalization.

Results: Prediabetes, undiagnosed diabetes and diagnosed diabetes were observed in 40.9%, 10.0% and 23.0%, respectively. Similar to diagnosed diabetes, prediabetes and undiagnosed diabetes were risk factors for critical COVID-19 outcomes (adjusted odds ratio [aOR] [95% CI]: 2.13 [1.31-3.48] and 4.00 [2.19-7.28], respectively). HbA1c was associated with COVID-19 severity in prediabetes patients (aOR [95% CI]: 11.2 [3.49-36.3]), but not other groups.

Conclusions: We documented the clinical characteristics and outcomes of Japanese COVID-19 patients according to HbA1c levels or diabetes co-morbidity. As well as undiagnosed and diagnosed diabetes, physicians should be aware of prediabetes related to COVID-19 severity.

KEYWORDS

COVID-19, diabetes, hyperglycaemia, prediabetes state, undiagnosed diabetes

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is an ongoing pandemic. As the COVID-19 pandemic has progressed, several risk factors for increased severity of the disease have been reported. In particular, diabetes has been recognized as a risk factor for severe COVID-19.[1-3]

The prevalence of diagnosed diabetes is increasing worldwide, including in Japan. In 2021, the prevalence in the United States was estimated to be about 9.7%, while it was about 8.7% in Japan.[4] Diabetes has a similar prevalence in Japan and in the United States; thus it is of great social concern. High blood glucose levels lead to inflammation, impaired immune response, decreased intracellular bactericidal activity and an elevated risk of infectious lung diseases, such as COVID-19.[5,6] In fact, diagnosed diabetes and a high HbA1c level have recently been shown to be risk factors for COVID-19 severity.[5] Additionally, even undiagnosed diabetes that was identified at the time of COVID-19 diagnosis reportedly influences COVID-19 outcomes.[6-8]

In addition to undiagnosed and diagnosed diabetes, prediabetes is recognized as an important condition, with a growing population. Prediabetes is a state of high risk for diabetes that is defined by glycaemic variables that are higher than normal. Each year, about 5%-10% of people with prediabetes will progress to overt diabetes.[9] In Japan, about the same proportion of patients have prediabetes as have diagnosed diabetes.[10] The association between prediabetes and nephropathy, chronic kidney disease and cardiovascular disease has been reported previously.[11-13] The importance of prediabetes has further been evaluated in the area of infectious diseases. For instance, an association between prediabetes and the severity of community-acquired pneumonia has been reported.[14] Therefore, it remains possible that prediabetes may also influence the severity of COVID-19. Consequently, an integrated analysis of the association between abnormal glucose levels, including prediabetes, and COVID-19

outcomes, is needed. Although there has been one small-scale report on the relationship between prediabetes and COVID-19 severity,[7] there is a paucity of large-scale reports and comparisons among patients with abnormal glucose levels in this context. Despite increasing evidence on the role of diagnosed diabetes in COVID-19 severity, there is limited evidence available regarding the roles of prediabetes and undiagnosed diabetes.

Thus, in this study we performed an integrated analysis of a large Japanese cohort of COVID-19 patients, including those without diabetes, with prediabetes, with undiagnosed diabetes, and with diagnosed diabetes, to clarify the differences in clinical characteristics and critical COVID-19 outcomes in Japan. Moreover, we identified the risk factors associated with critical outcomes in each of these patient groups.

2 | METHODS

2.1 | Study design and settings

The study design and setting have been previously described.[15] All COVID-19 cases in this retrospective cohort study were recruited through the Japan COVID-19 Task Force. From February 2020 to October 2021, data were collected from consecutive inpatients aged 18 years or older who were diagnosed with COVID-19, based on SARS-CoV-2 polymerase chain reaction or antigen test results, at one of the affiliated hospitals (>70 hospitals). The data of patients who agreed to participate in the study were registered in an electronic case-record form. Patients meeting any of the following criteria were excluded: non-Japanese; incomplete medical records, such as an inability to evaluate critical outcomes during hospitalization (use of high-flow oxygen therapy, invasive positive-pressure ventilation [IPPV], extracorporeal membrane oxygenation [ECMO] or death). Additionally, we excluded patients in whom it was not possible to

evaluate a diagnosis of diabetes, or where there were no HbA1c data. Among the 3424 patients who met the inclusion criteria, we excluded 93 non-Japanese patients and 901 patients with incomplete medical records. Thus 2430 patients were included in the analysis (Figure S1).

Written or oral informed consent was obtained from all patients. This study was approved by the ethics committees of the Keio University School of Medicine (20200061) and related research institutions. All aspects of the study adhered to the principles of the Declaration of Helsinki adopted by the World Medical Association General Assembly (Fortaleza, Brazil) in October 2013.

2.2 | Data collection and definitions

We extracted the following information from the electronic case record forms: age, sex, body mass index (BMI), smoking history, known co-morbidities (such as hypertension, diabetes, cardiovascular disease and chronic kidney disease), laboratory findings upon admission and the presence of critical outcomes. Diagnosed diabetes was defined from the electronic case-record forms. The laboratory results were collected within 48 hours of the initial visit or admission. In patients without diagnosed diabetes, undiagnosed diabetes was defined by HbA1c levels of 6.5% or higher.[14,16] Prediabetes was defined by HbA1c levels of 5.7%-6.4%, according to the American Diabetes Association.[16] Critical outcomes were defined by the use of high-flow oxygen, IPPV or ECMO, or death during the course of hospitalization. All laboratory tests were performed according to the patient's clinical care needs. Individual clinicians determined co-morbidities, such as a history of hypertension, diabetes, cardiovascular disease and chronic kidney disease, by conducting interviews with each patient or evaluating the electronic medical records. The recorded data were reviewed by a team of respiratory clinicians. For missing core data, the first clinician to diagnose the disease was contacted to obtain the information. Missing patient background data were noted as unknown.

2.3 | Statistical analysis

Continuous and categorical variables are presented as means or percentages, respectively. The data were compared among patient groups, stratified by diabetes status and HbA1c levels using a one-way analysis of variance test. A post hoc Tukey test or Bonferroni correction was used. To investigate the relationship between each group and critical outcomes, we performed a multivariate logistic regression analysis to adjust for previously reported factors.[17-19] Specifically, the models were adjusted for patient characteristics, such as age (≥65 years), sex, BMI (≥25 kg/m^2), smoking history (smoked in the past) and co-morbidities (hypertension, cardiovascular disease and chronic kidney disease). We presented the adjusted odds ratio (aOR) with a 95% confidence interval (95% CI). Statistical significance was set at P less than .05. Statistically significant values with Bonferroni correction are listed in the figure legends. All statistical analyses were

conducted using the JMP 16 program (SAS Institute Japan Ltd., Tokyo, Japan). Figures were visualized by GraphPad Prism version 8.0 statistical software (GraphPad Prism Corp., La Jolla, CA) and the R Bioconductor package *ggalluvial* (https://www.r-project.org/).

3 | RESULTS

3.1 | Clinical characteristics of COVID-19 patients without diabetes, with prediabetes, undiagnosed diabetes and diagnosed diabetes

Table 1 summarizes the baseline characteristics of the 2430 patients included in this study. Of these patients, 562 patients (23.1%) had been diagnosed with diabetes previously. Additionally, some patients had other co-morbidities, such as diagnosed hypertension, cardiovascular disease and chronic kidney disease (n = 863 [35.7%], n = 253 [10.5%] and n = 191 [8.1%], respectively). Among the 1868 patients without a diagnosis of diabetes, 631 patients were without diabetes (HbA1c < 5.7%; 26.0%), 993 with prediabetes (HbA1c 5.7%-6.4%; 40.9%) and 244 with undiagnosed diabetes (HbA1c ≥ 6.5%; 10.0%). Compared with patients without diabetes, those in the other three patient groups were more probable to be older (P < .0001), have a high BMI (P < .0001) and have a smoking history (P = .002). Similar significantly higher frequencies were found for other co-morbidities, such as hypertension, cardiovascular disease and chronic kidney disease. In addition, a symptom of dyspnoea was more frequent in the three patient groups. By contrast, oro/nasopharyngeal symptoms (i.e. sore throat, nasal discharge, dysgeusia and dysosmia) were more frequent in patients with non-diabetes, a population without glycaemic abnormalities.

Notably, age, sex and BMI varied in each population (Figure 1). The proportion of individuals aged younger than 50 years was highest among patients without diabetes, followed by those with prediabetes, undiagnosed diabetes and diagnosed diabetes. Remarkably, the proportion of patients with prediabetes in this age group was less than or equal to those without diabetes, but higher than those in the undiagnosed or diagnosed diabetes groups. However, the proportion of those aged 60 years or older was lowest among patients without diabetes, followed by those with prediabetes, undiagnosed diabetes and diagnosed diabetes (Figure 1A). The proportion of patients with prediabetes in this age group was significantly less than that in the undiagnosed or diagnosed diabetes groups.

Similar percentage trends were observed for BMI. Thus the proportion of individuals with a BMI less than 25 kg/m^2 decreased gradually from patients without diabetes to those with undiagnosed or diagnosed diabetes. By contrast, the proportion of patients with BMI of 25 kg/m^2 or higher increased gradually among patients with undiagnosed or diagnosed diabetes (Figure 1B). The proportion of males in the groups also increased gradually from those without diabetes to the undiagnosed and diagnosed diabetes groups (Figure 1C).

In addition to the clinical background, there were differences in laboratory findings upon admission among those four groups (Table 2), more specifically, in the neutrocyte/lymphocyte ratio (P < .0001), liver function variables, such as aspartate aminotransferase, alanine

TABLE 1 A comparison of patient characteristics among each patient group

Variable	All patients n = 2430	Non-diabetes n = 631	Prediabetes n = 993	Undiagnosed diabetes n = 244	Diagnosed diabetes n = 562	P value
Age, mean (95% CI)	57.4 (56.7-58.1)	46.4 (45.0-47.8)	59.5 (58.6-60.4)	64.0 (61.9-66.0)	63.2 (61.8-64.5)	<.0001
Sex, n (%)						
Male	1677 (69.0)	406 (64.3)	670 (67.5)	174 (71.3)	427 (76.0)	
Female	753 (31.0)	225 (35.7)	323 (32.5)	70 (28.6)	135 (24.0)	<.0001
BMI, median (95% CI)	24.9 (24.7-25.2)	23.2 (22.8-23.6)	24.9 (24.5-25.3)	25.3 (24.6-26.1)	26.6 (26.1-27.1)	<.0001
Smoking history; ex-smoker, n (%)	1115 (48.3)	249 (41.1)	460 (48.6)	123 (53.3)	283 (54.1)	.002
Signs and symptoms, n (%)						
Disturbance of consciousness	89 (3.8)	13 (2.1)	30 (3.9)	20 (8.4)	26 (4.8)	<.0001
Fever	1967 (81.9)	511 (81.5)	817 (83.1)	194 (81.2)	445 (80.5)	NA
Cough	1533 (64.5)	374 (59.6)	666 (68.4)	161 (68.5)	332 (61.5)	.0007
Sputum	684 (29.0)	165 (26.6)	277 (28.7)	84 (35.9)	158 (29.5)	.06
Sore throat	593 (25.2)	191 (30.9)	245 (25.5)	50 (21.1)	107 (20.0)	.0002
Nasal discharge	350 (14.8)	116 (18.7)	128 (13.3)	33 (14.1)	73 (13.5)	.02
Dysgeusia	418 (17.7)	153 (24.6)	175 (18.1)	28 (11.9)	62 (11.6)	<.0001
Dysosmia	357 (15.2)	135 (21.7)	147 (15.2)	26 (11.2)	49 (9.1)	<.0001
Dyspnoea	929 (39.5)	149 (24.0)	399 (41.4)	133 (57.1)	248 (46.3)	<.0001
Co-morbidities, n (%)						
Hypertension	863 (35.7)	104 (16.5)	313 (31.6)	107 (44.0)	339 (60.9)	<.0001
Diabetes	562 (23.1)				562 (100.0)	
Cardiovascular disease	253 (10.5)	33 (5.3)	79 (8.0)	30 (12.4)	111 (19.8)	<.0001
Chronic liver disease	111 (4.7)	24 (3.9)	41 (4.2)	9 (3.8)	37 (6.9)	.05
Chronic kidney disease	191 (8.1)	29 (4.7)	51 (5.3)	12 (5.0)	99 (18.6)	<.0001

Note: P values reflect comparison of data among patient groups using χ^2 test.
Abbreviations: BMI, body mass index; CI, confidence interval.

aminotransferase and γ-glutamyl transpeptidase ($P < .0001$, $P < .0001$ and $P = .001$, respectively); renal function, such as blood urea nitrogen and creatinine ($P < .0001$); electrolytes such as sodium and potassium ($P < .0001$ and $P = .002$, respectively); lactate dehydrogenase ($P < .0001$); brain natriuretic peptide ($P < .0001$); ferritin ($P < .0001$); D-dimer ($P < .0001$); and C-reactive protein ($P < .0001$).

3.2 | Association between HbA1c levels or diagnosed diabetes and COVID-19 severity

To clarify the COVID-19 severity between patients without diabetes and those with prediabetes, undiagnosed diabetes and diagnosed diabetes, we assessed the complications and outcomes during hospitalization. Figure 2 indicates the incidence of complications (such as bacterial infection, thromboembolism and acute kidney injury) in each group. Along with patients with diagnosed diabetes, the frequency of complications among both patients with prediabetes and undiagnosed diabetes was higher than those without diabetes. Interestingly, there

was no significant difference in the complication rates between patients with undiagnosed diabetes and those with diagnosed diabetes.

Next, we compared the proportion of critical outcomes among the groups and interpreted the posthospitalization outcomes associated with COVID-19. The proportion of critical events, such as high-flow oxygen, non-invasive positive-pressure ventilation (PPV), IPPV (and ECMO) or death, was 6.3%, 18.9% and 34.0% in patients without diabetes, with prediabetes and with undiagnosed diabetes, respectively (Figure 3A). The proportion of patients with critical outcomes was higher in the prediabetes group than in the non-diabetes group (18.9% vs. 6.3%; $P < .0001$). It was even higher among patients with undiagnosed or diagnosed diabetes. Similar to complications, no difference in the proportion of critical outcomes was observed between patients with undiagnosed diabetes and those with diagnosed diabetes (34.0% vs. 31.9%). Figure 3B shows the oxygen demand status among patient groups (non-diabetes, prediabetes, undiagnosed diabetes and diagnosed diabetes) upon admission, the worst status for oxygen demand during hospitalization, and whether these patients were
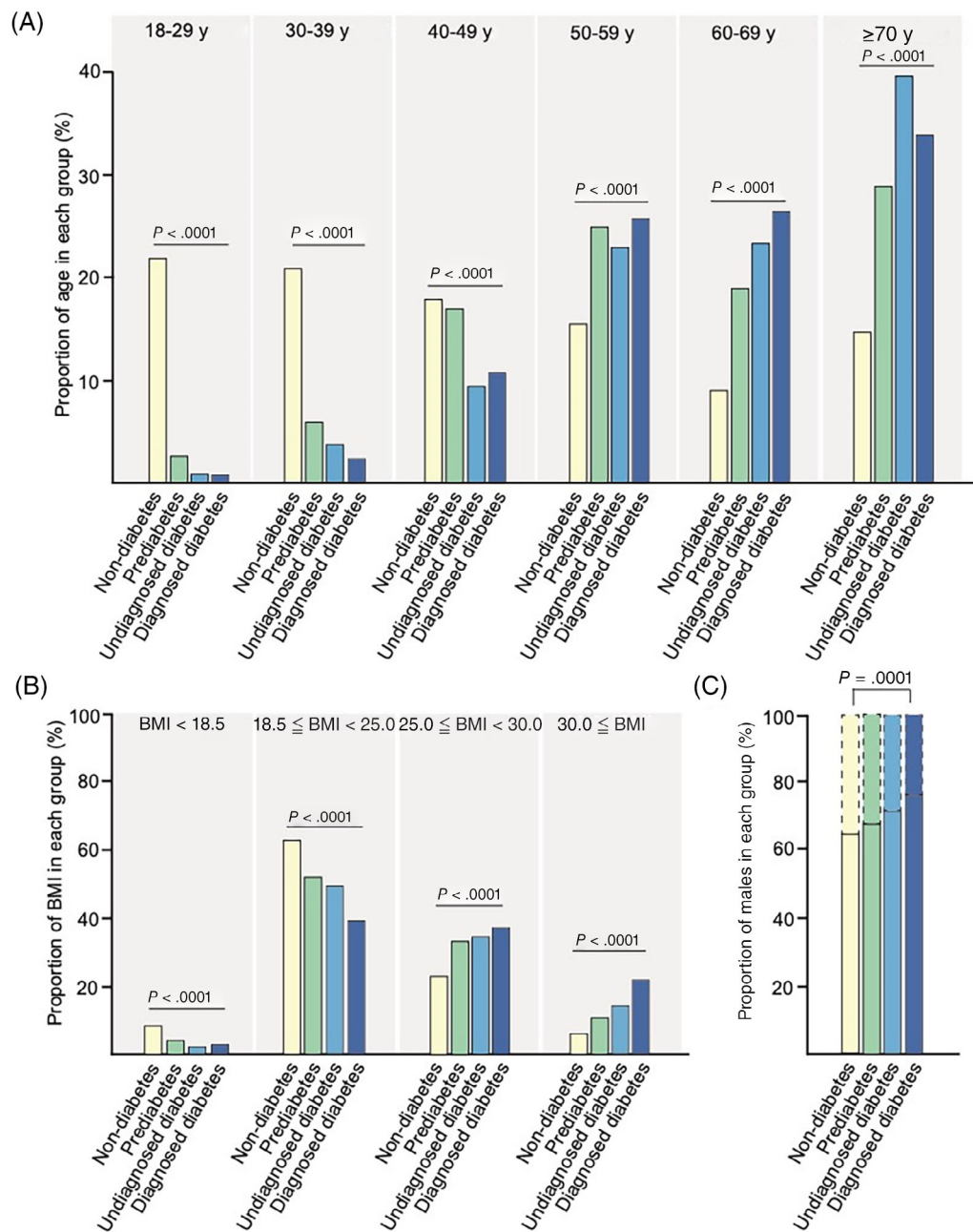
FIGURE 1 Age, BMI and sex distribution according to the patient groups. Statistical analysis was performed by χ^2 test. A, Age group (18-29, 30-39, 40-49, 50-59, 60-69 and ≥70 years) distributions in the patient groups. B, BMI group (<18.5, 18.5-24.9, 25.0-29.9 and ≥30.0 kg/m^2) proportions in the patient groups. C, Sex distribution in the patient groups. BMI, body mass index

alive or dead during hospitalization. Analysis of oxygen demand after admission for patients without oxygen demand at admission showed that 16.1% (n = 75), 34.0% (n = 199), 41.8% (n = 38) and 43.5% (n = 124) of the patients without diabetes, with prediabetes, with undiagnosed diabetes and diagnosed diabetes, respectively, required more than low-flow oxygen (Table S1). Multivariate logistic analysis revealed that prediabetes, undiagnosed diabetes and diagnosed diabetes were significantly associated with the occurrence of critical events, as compared with the absence of diabetes (Figure 3C; prediabetes: aOR 2.13, 95% CI 1.31-3.48; undiagnosed diabetes: aOR 4.00, 95% CI 2.19-7.28; diagnosed diabetes: aOR 3.96, 95% CI 2.38-6.58).

Thus, we indicated that, similar to undiagnosed and diagnosed diabetes, prediabetes was also independently associated with critical outcomes in COVID-19.

Based on these results, a strong relationship between COVID-19 outcomes and increasing HbA1c levels was suggested. Hence we performed more detailed categorical analysis. The average HbA1c levels increased gradually from patients without diabetes to higher consecutive levels among those with undiagnosed diabetes and diagnosed diabetes (Tukey test; non-diabetes: 5.39%, prediabetes: 5.98%, undiagnosed diabetes: 7.02%, diagnosed diabetes: 7.84%) (Figure 4A). In fact, HbA1c levels were significantly associated with the COVID-19

TABLE 2 A comparison of laboratory findings among each patient group

Variable	Non-diabetes n = 631	Prediabetes n = 933	Undiagnosed diabetes n = 244	Diagnosed diabetes n = 562	P value
Laboratory findings, median (95% CI)					
WBC ($\times 10^3$/dl)	5.1 (4.9-5.2)	5.8 (5.7-6.0)	7.0 (6.6-7.4)	6.5 (6.2-6.7)	<.0001
Neutrocyte (fraction, %)	66.2 (65.2-67.2)	72.0 (71.3-72.8)	76.0 (74.4-77.7)	73.6 (72.5-74.6)	<.0001
Lymphocyte (fraction, %)	24.2 (23.3-25.0)	20.0 (19.4-20.7)	16.9 (15.6-18.2)	18.4 (17.6-19.1)	<.0001
Neutrocyte/lymphocyte	4.3 (3.8-4.9)	6.8 (5.2-8.3)	11.3 (7.6-15.0)	6.9 (6.1-7.6)	.0002
Haemoglobin (g/dl)	14.3 (14.1-14.4)	14.3 (14.2-14.4)	14.0 (13.8-14.3)	14.1 (14.0-14.3)	NA
Platelets ($\times 10^4$/dl)	19.5 (18.8-20.2)	20.4 (19.8-21.1)	21.6 (20.4-22.8)	19.1 (18.3-19.9)	.003
Albumin (g/dl)	4.0 (3.9-4.1)	3.6 (3.6-3.7)	3.3 (3.3-3.4)	3.5 (3.4-3.5)	<.0001
T-Bil (mg/dl)	0.63 (0.61-0.66)	0.66 (0.64-0.69)	0.70 (0.65-0.75)	0.68 (0.65-0.71)	NA
γGTP (U/L)	50.8 (45.5-56.1)	79.3 (73.1-85.5)	90.5 (79.5-101.6)	71.9 (64.6-79.2)	.001
AST(U/L)	32.1 (30.0-34.2)	46.7 (43.6-49.7)	53.3 (48.3-58.3)	42.9 (39.6-46.3)	<.0001
ALT(U/L)	28.7 (26.6-30.8)	43.6 (40.6-46.6)	51.7 (46.7-56.7)	38.9 (35.6-42.2)	<.0001
BUN (mg/dl)	14.0 (13.2-14.9)	16.3 (15.7-16.9)	18.8 (17.3-20.2)	22.4 (21.5-23.4)	<.0001
Creatinine (mg/dl)	1.05 (0.94-1.17)	0.92 (0.87-0.98)	0.99 (0.81-1.17)	1.44 (1.33-1.56)	<.0001
LDH (U/L)	224 (217-231)	316 (306-326)	368 (348-389)	336 (322-349)	<.0001
CK (U/L)	123 (107-139)	193 (156-229)	193 (130-256)	197 (155-238)	NA
Na (mEq/L)	139 (138-139)	138.0 (137.8-138.2)	137.4 (137.0-137.9)	136.9 (136.6-137.2)	<.0001
K (mEq/L)	3.95 (3.92-3.98)	3.99 (3.93-4.04)	3.97 (3.88-4.06)	4.10 (4.04-4.16)	.002
Cl (mEq/L)	102.3 (102.0-102.6)	102.3 (100.4-104.1)	101.1 (98.7-103.6)	100.4 (98.8-102.0)	NA
BNP (pg/ml)	25.1 (17.9-32.3)	41.7 (29.7-53.8)	60.9 (11.7-110.2)	133.4 (101.3-165.6)	<.0001
Ferritin (ng/ml)	415 (373-457)	681 (631-731)	804 (700-909)	827 (759-895)	<.0001
D-dimer (ng/ml)	1.4 (0.95-1.94)	1.94 (1.60-2.29)	3.7 (2.8-4.6)	2.9 (2.3-3.6)	<.0001
Procalcitonin (ng/ml)	0.22 (0.10-0.34)	0.23 (0.14-0.32)	1.4 (0.0- 2.9)	2.2 (0.5-4.0)	NA
CRP (mg/dl)	2.9 (2.6-3.3)	5.6 (5.2-5.9)	14.3 (7.4-21.2)	7.4 (4.8-10.0)	<.0001

Note: P values reflect comparison of data among patient groups using one-way analysis of variance.
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; CK, creatine kinase; Cl, chloride; CRP, C-reactive protein; γGTP, guanosine-5'-triphosphate; K, potassium; LDH, lactate dehydrogenase; Na, sodium; T-Bil, total bilirubin; WBC, white blood cells.
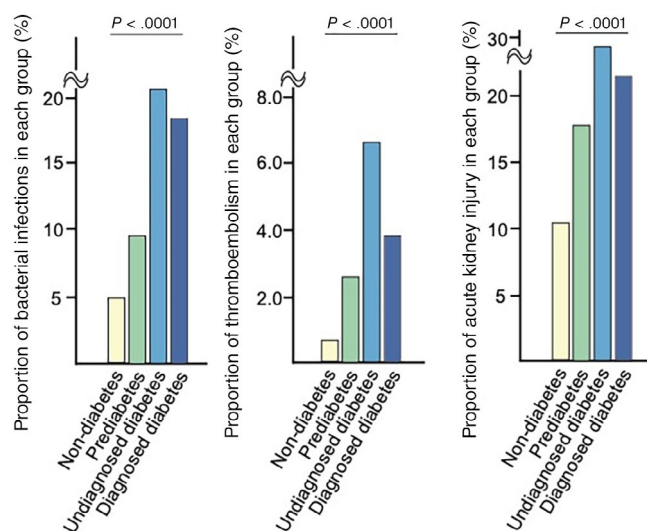

FIGURE 2 The proportion of complications (bacterial infection, thromboembolism and acute kidney injury) among the patient groups. Statistical analysis was performed by χ^2 test

outcome in the whole cohort by multivariate logistic analysis (aOR 1.26; 95% CI 1.14-1.38; P < .0001) (Figure 4B). As we had surmised, the proportion of patients with critical outcomes among those without diagnosed diabetes increased as HbA1c levels increased (HbA1c < 5.7%: 6.3%; HbA1c 5.7%-5.9%: 12.1%; HbA1c 6.0%-6.4%: 23.8%; HbA1c 6.5%-6.9%: 36.8%; HbA1c ≥ 7.0%: 28.4%) (Figure 4C). Conversely, the incidence of critical events was not significantly increased when stratified by HbA1c values among patients with diagnosed diabetes (Figure 4C).

3.3 | Factors related to COVID-19 severity in the non-diabetes, prediabetes, undiagnosed diabetes and diagnosed diabetes groups

To determine which of the patient characteristics at admission were associated with COVID-19 severity in each patient group, we performed logistic regression analysis (Table 3). Patient characteristics, such as age, sex, BMI and smoking history, and co-morbidities such as

FIGURE 3 The relationship between COVID-19 severity during hospitalization among the patient groups. A, The proportion of patients with critical outcomes among the patient groups. Statistical analysis was performed by χ^2 test with Bonferroni correction. *statistical analysis was significant (*P* value of <.0083 was considered statistically significant with Bonferroni correction). B, The oxygen demand status of each patient group on admission, and the worst oxygen demand status during hospitalization, and whether patients were alive or dead during hospitalization. C, Multivariate logistic regression analysis of the relationship between patient groups and critical outcomes. aOR, adjusted odds ratio; COVID-19, coronavirus disease 2019; IPPV, invasive positive-pressure ventilation
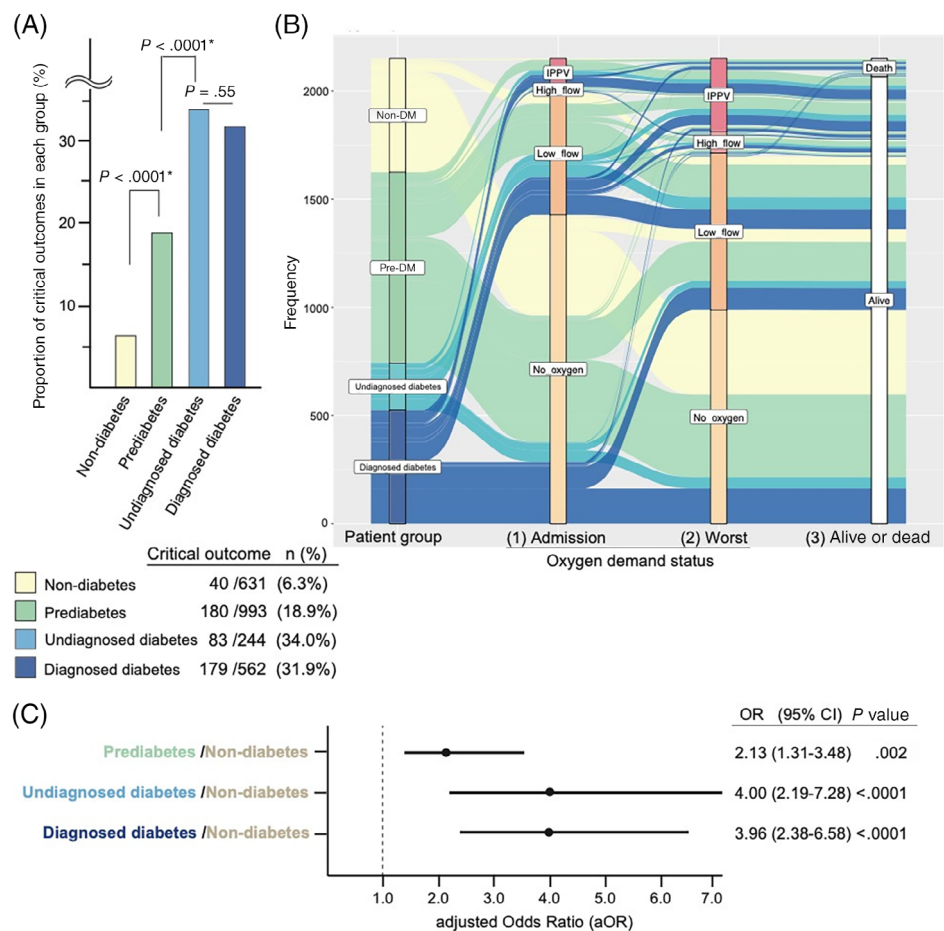

hypertension, cardiovascular disease and chronic kidney disease, were co-factors. Interestingly, factors related to critical outcomes differed among patient groups. In patients without diabetes, age (*P* < .0001), sex (*P* = .04) and hypertension and chronic kidney disease (*P* < .0001) were associated with critical outcomes. In patients with undiagnosed and diagnosed diabetes, BMI (*P* = .04 in those with undiagnosed diabetes) and chronic kidney disease (*P* = .00003 in those with diagnosed diabetes) were associated with critical outcomes. Contrary to those patient groups, HbA1c levels were associated with critical outcomes in patients with prediabetes in the multivariate logistic regression analysis (aOR 11.2, 95% CI 3.49-36.3, *P* < .0001) (Figure S2).

4 | DISCUSSION

No previous study has reported integrative analysis on the severity of COVID-19 in patients classified by diabetes co-morbidity or HbA1c levels in a large Japanese cohort, as performed here. We found that prediabetes and undiagnosed diabetes were independently related to COVID-19 severity, similar to diagnosed diabetes. This integrative analysis also identified factors associated with COVID-19 severity among each of the prediabetes, undiagnosed diabetes and diagnosed diabetes groups. Our findings could facilitate prediction of COVID-19 severity and optimization of patient allocation for special therapies and vaccination.

In this study, we also showed the prevalence of diabetes among COVID-19 patients. The proportion of diagnosed diabetes in our cohort was 23.1%. This is similar to previous reports from Western countries on the prevalence of diabetes among COVID-19 patients (22.8%-40.1%).[20-22] In another study from Japan, 14.2% of hospitalized COVID-19 patients were reported to have diabetes.[23] It was noteworthy that the prevalence of prediabetes in our cohort was 40.9%, which was almost twice that of diagnosed diabetes. This prevalence was similar to previous reports of community-acquired pneumonia.[14] Prediabetes is reported as a state of high risk for diabetes, which will eventually develop into diabetes in up to 70% of individuals. Considering that the prevalence of prediabetes was previously reported to be the same as that of diagnosed diabetes in a Japanese population, and is increasing annually,[9,10] this is a patient population that should not be overlooked.

Each patient group classified by the co-morbidity of diabetes and HbA1c levels showed particular patient characteristics and outcomes. Patients with diagnosed diabetes, undiagnosed diabetes and with prediabetes naturally included many risk factors associated with COVID-19 severity, such as older age,[24] male sex,[25] obesity,[26] hypertension,[27] cardiovascular disease[28] and chronic kidney disease.[29] This trend of patient background was similar to that in previous reports.[20] Previously, reports also described the strong confounding of diabetes regarding cardiovascular damage and COVID-19 severity.[30,31] However, having a cardiovascular disease was not a significant risk factor of critical
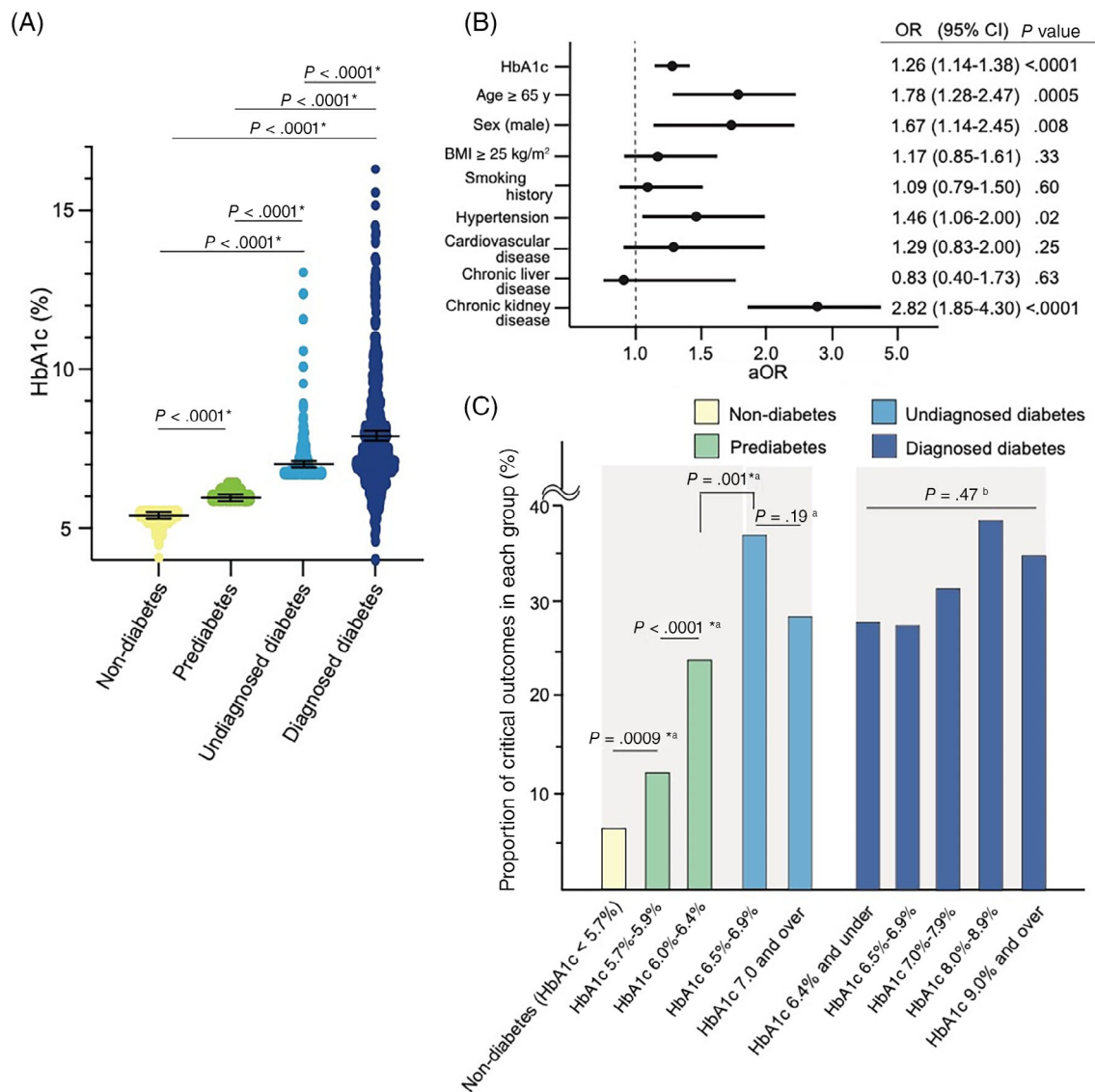
FIGURE 4 Stratified analysis in subdivisions based on HbA1c levels. A, Average HbA1c levels among the patient groups (non-diabetes, prediabetes, undiagnosed diabetes and diagnosed diabetes), using Tukey test for post hoc analysis. *statistical analysis was significant. B, Multivariate logistic regression analysis of the relationship between HbA1c levels and critical outcomes in the whole cohort (adjusted with age, sex, BMI, smoking history and co-morbidities (hypertension, cardiovascular disease, chronic kidney disease and chronic liver disease). C, The proportion of patients with critical outcomes in groups stratified by HbAlc levels. [a]statistical analysis was performed by χ^2 test with Bonferroni correction. [b]statistical analysis was only performed by χ^2 test. *statistical analysis was significant (P value of <.005 was considered statistically significant with Bonferroni correction). aOR, adjusted odds ratio; BMI, body mass index

outcomes in each group. The reason for this discrepancy is unknown; however, the lower prevalence of cardiovascular disease in our cohort, compared with Western studies, might be the reason. Additionally, the prevalence of severe COVID-19 was higher among these patients than in those without diabetes. The frequency of critical outcomes in our cohort was similar to that of previous Western reports.[21,22] In particular, undiagnosed diabetes was independently associated with COVID-19 severity, similar to diagnosed diabetes. Our results suggested that the population with undiagnosed diabetes has the same risk of severe COVID-19 as that with diagnosed diabetes, as suggested by previous studies.[6-8]

HbA1c levels above the standard value probably indicate pre-existing diabetes, which was aggravated by COVID-19, leading to metabolic complications.[7] HbA1c levels appropriately represent average blood glucose levels within the previous 2-3 months, and are not influenced by factors such as acute infection, stress or recent medications that could alter glucose metabolism, such as corticosteroids.[5,6] A previous report revealed that long-term metabolic inflammation caused by hyperglycaemia can also damage the immune system, reducing the body's ability to cope with infection, impairing the healing process and prolonging the recovery time.[6] Therefore, identifying patients with undiagnosed diabetes and prediabetes in regular medical

TABLE 3 Univariate logistic regression analysis of factors associated with critical outcomes in each patient group

Variable	Non-diabetes Univariable			Prediabetes Univariable			Undiagnosed diabetes Univariable			Diagnosed diabetes Univariable		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Age ≥ 65 y	5.03	2.61-9.70	<.0001	1.54	1.12-2.14	.009	1.23	0.72-2.09	.45	1.21	0.84-1.72	.3
Sex (male)	2.32	1.05-5.13	.04	1.31	0.92-1.88	.13	1.18	0.65-2.13	.59	1.32	0.86-2.03	.21
BMI ≥25 kg/m²	0.81	0.32-2.10	.66	1.87	1.19-2.94	.006	2.24	1.04-4.86	.04	0.83	0.53-1.30	.42
Smoking history	1.84	0.95-3.57	.07	1.06	0.75-1.48	.75	1.27	0.73-2.20	.41	1.06	0.73-1.53	.77
Hypertension	4.26	2.18-8.31	<.0001	1.77	1.27-2.47	.0008	0.83	0.48-1.41	.49	1.34	0.92-1.94	.12
Cardiovascular disease	2.14	0.71-6.42	.17	1.27	0.72-2.22	.41	0.79	0.35-1.83	.59	1.46	0.95-2.24	.09
Chronic liver disease	-	-	-	1.46	0.70-3.03	.32	0.95	0.23-3.90	.94	0.85	0.41-1.77	.67
Chronic kidney disease	8.37	3.51-19.94	<.0001	1.96	1.05-3.66	.04	2.01	0.63-6.45	.24	2.28	1.46-3.55	.0003
HbA1c	0.79	0.20-3.14	.73	9.07	4.19-19.66	<.0001	0.82	0.59-1.15	.23	1.02	0.92-1.13	.74

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

examinations (i.e. those with poor glycaemic control) provides awareness of the background glycaemic disorder, facilitates appropriate interventions for at-risk patients with coronavirus infections, including glucose monitoring and glycaemic control, and may improve their outcomes.

Moreover, we could clarify the importance of prediabetes by integrated analysis that included stratification by HbA1c levels. In this way we showed that prediabetes was also independently associated with COVID-19 severity, as compared with no diabetes. We also found that the proportion of patients with critical outcomes escalated as HbA1c levels increased (HbA1c < 5.7%: 6.3%; HbA1c 5.7%-5.9%: 12.1%; HbA1c 6.0%-6.4%: 23.8%; HbA1c 6.5%-6.9%: 36.8%). It was noteworthy that, even in patients with an HbA1c below 6.5%, there was a stepwise increase in the proportion of patients with severe COVID-19, from those with HbA1c 5.7%-5.9% to those with HbA1c 6.0%-6.4%. According to the American Diabetes Association, prediabetes patients with HbA1c 6.0%-6.4% have a very high risk of progression to diabetes.[16] A previous report suggested that insulin resistance starts years before diabetes development and that decreased β-cell function is already present in the prediabetes stage.[32] Prediabetes has also been linked to increased risk of early forms of nephropathy and chronic kidney disease, such as urinary albumin excretion.[33] Presumably this pathology progresses slowly and is less probable to present in the form of laboratory findings or co-morbidities. Taken together with our findings, assessing HbA1c may help to identify patients with prediabetes and prevent their progression to diabetes, but may also allow prediction of COVID-19 severity among patients with prediabetes.

HbA1c level was also identified as a factor associated with COVID-19 severity among patients with prediabetes by logistic regression analysis in each patient group. Factors previously reported to be associated with COVID-19 severity, such as age, hypertension and chronic kidney disease, were identified in the prediabetes and non-diabetes groups, while HbA1c was identified as a predictive factor only in the prediabetes group. Furthermore, among patients with diagnosed diabetes, chronic kidney disease was a factor associated with the severity of COVID-19. This could be because diabetic nephropathy is an important late complication of diabetes.[34]

This study had some limitations. First, we extracted the co-morbidity of diabetes by conducting interviews with each patient or by evaluating the medical records. The relevant criteria may have differed among individual institutions. In addition, we did not record regular patient medications. Thus, it was not possible to determine whether diabetes was currently being treated, had been treated previously, or was only recorded. We speculated that use of hypoglycaemic drugs may be effective in preventing severe COVID-19, as previously reported.[35] Second, no blood glucose, insulin and homeostasis model assessment of insulin resistance (HOMA-IR) data were collected in this study. Hyperglycaemia, insulin resistance and inflammatory responses observed in COVID-19 are probably intrinsically interlinked.[22,36] Therefore, it is necessary to interpret both HbA1c levels and blood glucose levels as a whole in relation to COVID-19 severity. In addition, HbA1c is less sensitive when it is less than 7%.[37] Thus we need to consider that stratification by HbA1c levels alone does not strictly reflect these patient groups. Third, of the 3424 participants that were initially included, 994 were excluded because of insufficient data and other reasons, which may be a possible selection bias. Consequently, further studies are needed to address the aforementioned limitations.

In conclusion, we elucidated the clinical characteristics and outcomes of COVID-19 patients as classified by HbA1c levels or by diabetes co-morbidity in a large Japanese COVID-19 cohort. Patients with prediabetes accounted for a large proportion of patients, and prediabetes was independently related to COVID-19 severity. Furthermore, we identified differences in risk factors for COVID-19 severity among patients without diabetes, with prediabetes, with undiagnosed diabetes, and with diagnosed diabetes. These findings may facilitate identification of patients with particularly increased risks of severe COVID-19 and may streamline allocation of certain treatments to these patients. More studies are required to evaluate the relationship between abnormal glycaemic control and COVID-19 severity.

AUTHOR CONTRIBUTIONS

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CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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