JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

Check for updates

Association of acute-to-chronic glycemic ratio and outcomes in patients with COVID-19 and undiagnosed diabetes mellitus: A retrospective nationwide cohort study

Masaki Uchihara[1], Takehiro Sugiyama[2,3,4], Ryotaro Bouchi[1,2]*, Nobuaki Matsunaga[5], Yusuke Asai[5], Hiroyuki Gatanaga[6], Mitsuru Ohsugi[1,2], Norio Ohmagari[6,7], Hiroshi Kajio[1], Kohjiro Ueki[1,8]

[1]Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine, Toyama, Tokyo, Japan, [2]Diabetes and Metabolism Information Center, Research Institute, National Center for Global Health and Medicine, Toyama, Tokyo, Japan, [3]Institute for Global Health Policy, Bureau of International Health Cooperation, National Center for Global Health and Medicine, Toyama, Tokyo, Japan, [4]Department of Health Services Research, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan, [5]AMR Clinical Reference Center, National Center for Global Health and Medicine, Tokyo, Japan, [6]AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan, [7]Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan, and [8]Department of Molecular Diabetic Medicine, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Toyama, Tokyo, Japan

Keywords
Acute-to-chronic glycemic ratio, COVID-19, Undiagnosed diabetes mellitus

***Correspondence**
Ryotaro Bouchi
Tel.: +81-3-3202-7181
Fax: +81-3-3202-7364
E-mail address:
rybouchi@hosp.ncgm.go.jp

J Diabetes Investig 2023; 14: 623–629

doi: 10.1111/jdi.13979

ABSTRACT

Aims/Introduction: To assess the association of undiagnosed diabetes mellitus and its acute-to-chronic glycemic ratio with clinical outcome in patients hospitalized with coronavirus disease 2019 (COVID-19) using a large-scale nationwide registry in Japan.

Materials and Methods: Overall, 4,747 patients were included between July 2021 and January 2022. We evaluated blood glucose and glycated hemoglobin levels at admission, and calculated the acute-to-chronic glycemic ratio for each non-diabetes mellitus, undiagnosed diabetes mellitus and pre-existing diabetes mellitus group. The primary composite outcome comprised in-hospital mortality, invasive mechanical ventilation, extracorporeal membrane oxygenation support, intensive care unit admission and transfer to a more advanced medical facility.

Results: Compared with the non-diabetes mellitus group, the undiagnosed diabetes mellitus group was significantly associated with a worse COVID-19 outcome (odds ratio 2.18, 95% confidence interval 1.50–3.18). In patients with undiagnosed diabetes mellitus, the 3rd tertile of the acute-to-chronic glycemic ratio was linked with a worse COVID-19 outcome compared with the 1st tertile (odds ratio 3.33, 95% confidence interval 1.43–7.77), whereas glycated hemoglobin levels were not; among patients with pre-existing diabetes mellitus, glycated hemoglobin levels were linked with a worse outcome.

Conclusions: Among patients with undiagnosed diabetes mellitus with COVID-19, the magnitude of elevation of blood glucose from chronic to acute levels is associated with worse outcomes.

INTRODUCTION

The complications of diabetes mellitus and hyperglycemia at admission are known risk factors for worse outcomes with the coronavirus disease 2019 (COVID-19)[1]. Emerging evidence regarding the association between diabetes and COVID-19, including our previous study, shows that the prognosis is poor in patients with undiagnosed diabetes mellitus at admission, which accounts for 15–30% of the patients with diabetes mellitus hospitalized for COVID-19[2–5]. However, these results in large cohorts and the reasons for these associations remain unclear.

In patients with diabetes mellitus who had cardiovascular disease or COVID-19, factors including acute-to-chronic (A/C) glycemic ratio, stress hyperglycemia ratio or glycemic gap have

Received 11 November 2022; revised 28 December 2022; accepted 11 January 2023

© 2023 The Authors. *Journal of Diabetes Investigation* published by Asian Association for the Study of Diabetes (AASD) and John Wiley & Sons Australia, Ltd
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

20401124, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jdi.13979 by Cochrane Japan, Wiley Online Library on [13/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

been found to be strongly associated with the outcome rather than blood glucose or glycated hemoglobin (HbA1c) levels on admission[6–9]; this suggests that the magnitude of acute blood glucose elevation from chronic levels could be harmful. However, these indicators have not been previously confirmed in patients with undiagnosed diabetes mellitus. Specifically, some patients with undiagnosed diabetes mellitus might have an acute deterioration in their glucose tolerance after COVID-19. Consequently, acute hyperglycemia in patients with undiagnosed diabetes mellitus would be expected to have a more substantial impact than in those with pre-existing diabetes mellitus, and might also be an indicator of the severity of COVID-19. Furthermore, data from National Center for Global Health and Medicine, Tokyo, Japan suggested that, in patients with undiagnosed diabetes mellitus, hyperglycemia immediately after hospitalization might lead to severe conditions[2]. Therefore, we investigated the association of undiagnosed diabetes mellitus and its glycemic ratio with the clinical outcome in patients hospitalized with COVID-19 using a large-scale nationwide registry in Japan.

MATERIALS AND METHODS

Study design

The present retrospective observational study used the data from the COVID-19 Registry Japan (COVIREGI-JP), a large-scale registry of patients hospitalized with COVID-19 in Japan[10]. The healthcare facilities voluntarily participating in the registry enrolled the patients. The inclusion criteria for enrollment were a positive severe acute respiratory syndrome coronavirus 2 test and inpatient treatment at a healthcare facility. The study data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based data capture application hosted at Joint Center for Researchers, Associates and Clinicians data center of the National Center for Global Health and Medicine. As of January 2022, >740 facilities across Japan joined the registry, enrolling >57,000 patients with COVID-19. We extracted data from the registry on age, sex, smoking history, vaccination, body mass index (BMI), medication, comorbidity, laboratory findings and outcomes. Comorbidities were scored with the Charlson Comorbidity Index, which encompasses 19 medical conditions, assembled by Charlson *et al.*[11] The study protocol was approved by the National Center for Global Health and Medicine ethics review committee (NCGM-G-003494-0). In addition, the present study was carried out following the principles of the Declaration of Helsinki. The STROBE-statement of this study is shown in Appendix S1.

Patients and definition of outcomes

In the analysis, we included patients enrolled in the COVIREGI-JP who tested positive for severe acute respiratory syndrome coronavirus 2 and were hospitalized between 1 July 2021 and 31 January 2022. However, patients aged <18 years, with a history of using steroids for >1 month, pregnant, transferred from another hospital, unfinalized data, or incomplete data on outcomes or glycemic profiles were excluded; we then carried out complete data analyses.

The enrolled patients were categorized into the following three groups: non-diabetes mellitus, undiagnosed diabetes mellitus and pre-existing diabetes mellitus. The undiagnosed diabetes mellitus was defined as patients having HbA1c ≥6.5% (48 mmol/mol) without a prior history of diabetes mellitus. Conversely, pre-existing diabetes mellitus was determined based on self-reported history of diabetes mellitus, previous medical records before admission, reported diagnosis of diabetes mellitus or treatment with glucose-lowering medications. The HbA1c data were measured at admission.

In addition, patients were stratified according to their respective tertiles of blood glucose and A/C glycemic ratio at admission among all patients complicated with diabetes mellitus (excluding the non-diabetes mellitus group). The A/C glycemic ratio was calculated based on the following formula[8,12]:

$$\text{A/C glycemic ratio} = \text{glucose at admission (mg/dL)} / \text{estimated chronic glucose (mg/dL)}$$

$$\text{Estimated chronic glucose levels (mg/dL)} = (28.7 \times \text{HbA1c [\%]}) - 46.7$$

Furthermore, patients were categorized into three groups according to HbA1c levels: group 1 (HbA1c <7.0%), group 2 (HbA1c 7.0–7.9%) and group 3 (HbA1c ≥8.0%).

The primary composite outcome comprised worse COVID-19 events, including in-hospital death, invasive mechanical ventilation, extracorporeal membrane oxygenation support, intensive care unit admission and transfer to another medical facility seeking more advanced care to day 60 of hospitalization.

Statistical analysis

In the analysis of patient backgrounds, categorical variables were presented as count (%), and continuous variables were presented as the mean and standard deviation or the median and interquartile range, respectively. The differences among the groups were compared using the Student's *t*-test or Mann–Whitney *U*-test and the χ^2-test or Fisher's exact tests for the continuous and dichotomous variables, respectively, where appropriate.

We carried out a multivariable logistic regression analysis to identify the association between undiagnosed diabetes mellitus and pre-existing diabetes mellitus groups compared with the non-diabetes mellitus group with worse COVID-19 outcomes. In addition, we also carried out a multivariable logistic regression analysis to evaluate the association between the glycemic parameters and worse COVID-19 outcomes in undiagnosed diabetes mellitus and pre-existing diabetes mellitus groups. We included age, sex, BMI, vaccination and Charlson Comorbidity Index as independent variables in these models. In addition,

© 2023 The Authors. *Journal of Diabetes Investigation* published by AASD and John Wiley & Sons Australia, Ltd

20401124, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jdi.13979 by Cochrane Japan, Wiley Online Library on [13/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

continuous variables (age and BMI) were included with their quadratic terms. Statistical significance was set at $P < 0.05$. Statistical analyses were carried out using Stata SE 17.0 (StataCorp, College Station, TX, USA).

RESULTS

Among 9,631 patients hospitalized between 1 July 2021 and 31 January 2022, a total of 4,747 patients were included in the analysis (Figure 1), of which the non-diabetes mellitus, undiagnosed diabetes mellitus and pre-existing diabetes mellitus groups comprised 3,722 (78.4%), 287 (6.0%) and 738 (15.5%) patients, respectively. Notably, patients with undiagnosed diabetes mellitus accounted for 27.2% (287/1,055) of all the patients with diabetes mellitus. Tables 1 and 2 presents the baseline characteristics and outcomes. Overall, the primary outcome event was recorded in 189 (5.1%), 47 (16.4%) and 115 (15.6%) patients in the non-diabetes mellitus, undiagnosed diabetes mellitus and pre-existing diabetes mellitus groups, respectively. Compared with the non-diabetes mellitus group, the undiagnosed diabetes mellitus and pre-existing diabetes mellitus groups were significantly associated with a worse COVID-19 outcome (odds ratio [OR] 2.18, 95% confidence interval [CI] 1.50–3.18 and OR 2.08, 95% CI 1.57–2.77, respectively). An additional analysis with HbA1c as a covariate did not change the results, which also showed that the undiagnosed diabetes mellitus and pre-existing diabetes mellitus groups were significantly associated with the worse COVID-19 outcome compared with the non- diabetes mellitus group (OR 1.73, 95% CI 1.16–2.59 and OR 1.51, 95% CI 1.05–2.18). Furthermore, to consider the effect of COVID-19 related diabetes in an additional analysis, we also defined newly-diagnosed diabetes mellitus as patients with either new-onset diabetes mellitus (having both HbA1c <6.5% [48 mmol/mol] and random blood glucose ≥200 mg/dL [10.0 mmol/L] on admission without a prior history of diabetes) or undiagnosed diabetes mellitus. As a result, the newly-diagnosed diabetes mellitus group were significantly associated with a worse COVID-19 outcome compared with the non-diabetes mellitus group (OR 2.17, 95% CI 1.50–3.14).

Additionally, in patients with undiagnosed diabetes mellitus, the analysis of A/C glycemic ratio tertiles, adjusted for age, sex, BMI, vaccination and comorbidities, showed that the 3rd tertile was associated with the worse COVID-19 outcome compared

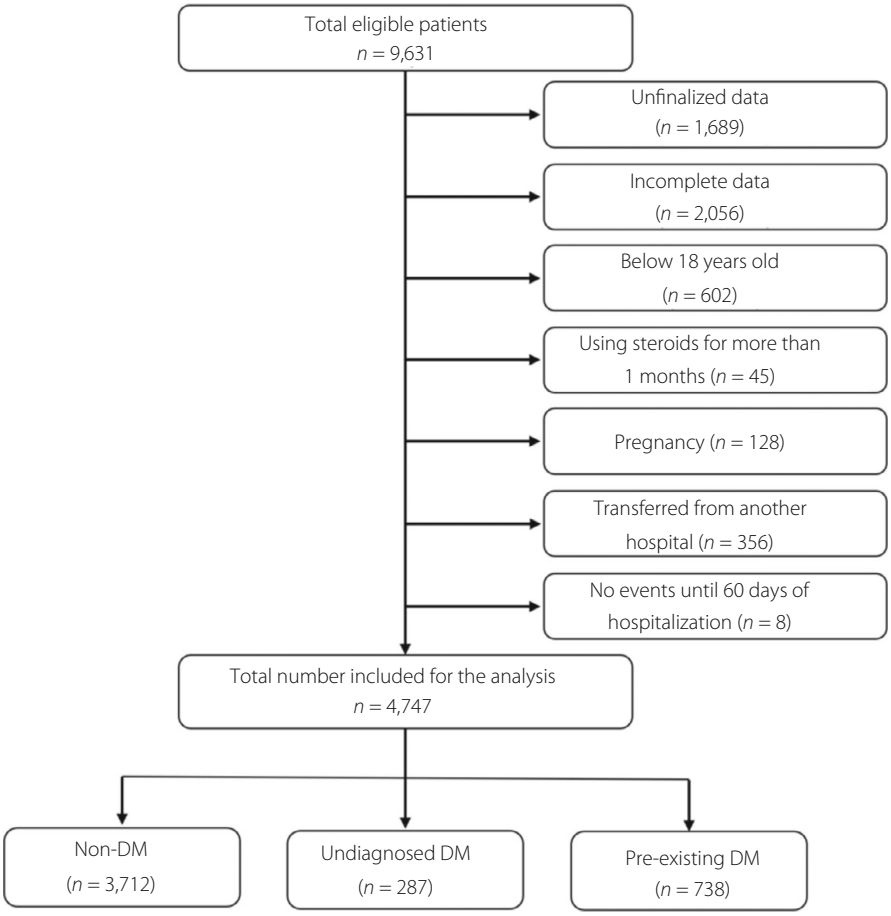

Figure 1 | Population flow chart showing the selection of patients for inclusion in the analysis. DM, diabetes mellitus.

© 2023 The Authors. *Journal of Diabetes Investigation* published by AASD and John Wiley & Sons Australia, Ltd

Table 1 | Patient characteristics and outcomes

	Non-DM (n = 3,722)	Undiagnosed DM (n = 287)	Pre-existing DM (n = 738)	P-values
Age, years (mean ± SD)	48.0 ± 17.3	55.5 ± 14.7	58.7 ± 15.2	<0.001
Sex female, n (%)	1,556 (41.8%)	93 (32.4%)	206 (27.9%)	<0.001
BMI (n = 4,440), kg/m^2 (mean ± SD)	24.4 ± 5.8	27.7 ± 5.7	27.1 ± 5.6	0.026
Smoking history				
Never smoked	1,805 (48.5%)	122 (42.5%)	300 (40.7%)	<0.001
Former smoked	716 (19.2%)	65 (22.6%)	193 (26.0%)	
Currently smoking	842 (22.6%)	73 (25.4%)	174 (23.6%)	
Unknown	359 (9.7%)	27 (9.4%)	71 (9.6%)	
Vaccination				
Never	2,924 (78.6%)	223 (77.7%)	503 (68.2%)	<0.001
Once	349 (9.4%)	45 (15.7%)	103 (14.0%)	
More than twice	449 (12.1%)	19 (6.6%)	132 (17.9%)	
Comorbidities				
Charlson Comorbidity Index, except for DM (mean ± SD)	0.24 ± 0.79	0.32 ± 0.98	0.43 ± 1.14	<0.001
Hypertension	715 (19.2%)	93 (32.4%)	371 (50.1%)	<0.001
Hyperlipidemia	333 (9.0%)	47 (16.4%)	218 (29.5%)	<0.001
Cerebrovascular disorders	118 (3.2%)	11 (3.8%)	49 (6.6%)	<0.001
Myocardial infarction	38 (1.0%)	5 (1.7%)	23 (3.1%)	<0.001
COPD	52 (1.4%)	3 (1.1%)	18 (2.4%)	0.111
Moderate-to-severe renal dysfunction[†]	33 (0.9%)	5 (1.7%)	18 (2.4%)	0.002
Cancer	74 (2.0%)	5 (1.7%)	15 (2.0%)	0.980
Laboratory findings				
Median blood glucose at admission, mg/dL (IQR)	106 (97–121)	138 (119–180)	164 (127–228)	<0.001
Median HbA1c, % (IQR)	5.7 (5.4–5.9)	6.8 (6.6–7.4)	7.4 (6.6–8.5)	<0.001
Median HbA1c, mmol/mol (IQR)	38.8 (35.5–41.0)	50.8 (48.6–57.4)	57.4 (48.6–69.4)	<0.001
Median A/C glycemic ratio (IQR)	0.92 (0.83–1.03)	0.90 (0.79—1.11)	1.00 (0.82–1.25)	<0.001
Median hemoglobin (n = 4,745), g/dL (IQR)	14.5 (13.4–15.6)	14.9 (13.7–16.0)	14.7 (13.4–15.9)	<0.001
Outcomes				
Primary outcome event	189 (5.1%)	47 (16.4%)	115 (15.6%)	<0.001
Invasive MV	27 (0.7%)	15 (5.2%)	35 (4.7%)	<0.001
ICU admission	109 (2.9%)	32 (11.2%)	87 (11.8%)	<0.001
ECMO	5 (0.1%)	1 (0.4%)	3 (0.4%)	0.169
Transfer to a more advanced medical facility	60 (1.6%)	11 (3.8%)	30 (4.1%)	<0.001
Mortality	38 (1.0%)	9 (3.1%)	28 (3.8%)	<0.001
Oxygen demand	1,289 (34.6%)	199 (69.3%)	411 (55.7%)	<0.001

Continuous variables are presented as mean ± standard deviation (SD) and median (interquartile range [IQR]); categorical variables are presented as number (percentage). [†]Creatinine ≥3 mg/dL, during dialysis, after kidney transplant or urinary nephropathy. A/C, acute-to-chronic; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; ECMO, extracorporeal membrane oxygenation support; HbA1c, glycated hemoglobin; ICU, intensive care unit; IQR, interquartile range; MV, mechanical ventilation.

Table 2 | Association of primary outcomes according to diabetes classification

	OR[†] (95% CI)	P-values
Non-DM (n = 3,722)	Reference	
Undiagnosed DM (n = 287)	2.18 (1.50–3.18)	<0.001
Pre-existing DM (n = 738)	2.04 (1.54–2.70)	<0.001

[†]Adjusted for age, sex, body mass index (BMI), vaccination and Charlson comorbidity index. CI, confidence interval; DM, diabetes mellitus; OR, odds ratio.

with the 1st tertile (OR 3.33, 95% CI 1.43–7.77), whereas HbA1c levels were not associated with the outcome (Table 3). In contrast, in patients with pre-existing diabetes mellitus, although the A/C ratio was not associated with a worse COVID-19 outcome, the 2nd and 3rd tertiles of blood glucose and group 3 (HbA1c ≥8%) were significantly associated with a worse COVID-19 outcome compared with the 1st tertile of blood glucose and group 1 (HbA1c <7.0%), respectively (Table 3). In a sensitivity analysis of only patients with oxygen demand, the undiagnosed diabetes mellitus group was significantly associated with a worse COVID-19 outcome

© 2023 The Authors. *Journal of Diabetes Investigation* published by AASD and John Wiley & Sons Australia, Ltd

20401124, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jdi.13979 by Cochrane Japan, Wiley Online Library on [13/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

20401124, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jdi.13979 by Cochrane Japan, Wiley Online Library on [13/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 3 | Association of primary outcomes according to glycemic parameters

Glycemic parameters	Undiagnosed DM (n = 287) OR† (95% CI)	P-values	Pre-existing DM (n = 738) OR† (95% CI)	P-values
A/C glycemic ratio 1st tertile (<0.86)	Reference		Reference	
A/C glycemic ratio 2nd tertile (0.86–1.12)	1.03 (0.45–2.34)	0.948	1.35 (0.77–2.35)	0.296
A/C glycemic ratio 3rd tertile (>1.12)	3.33 (1.43–7.77)	0.005	1.53 (0.87–2.68)	0.141
Blood glucose at admission 1st tertile (<134 mg/dL)	Reference		Reference	
Blood glucose at admission 2nd tertile (134–196 mg/dL)	1.74 (0.80–3.78)	0.162	2.81 (1.52–5.20)	0.001
Blood glucose at admission 3rd tertile (>196 mg/dL)	2.59 (1.03–6.50)	0.042	2.25 (1.20–4.23)	0.011
Group 1 (HbA1c <7.0%)	Reference		Reference	
Group 2 (HbA1c 7.0–7.9%)	0.88 (0.39–2.02)	0.765	1.55 (0.88–2.73)	0.126
Group 3 (HbA1c ≥8.0%)	1.90 (0.78–4.60)	0.157	1.95 (1.10–3.46)	0.021

†Adjusted for age, sex, body mass index, vaccination and Charlson comorbidity index. A/C, acute-to-chronic; CI, confidence interval; DM, diabetes mellitus; HbA1c, glycated hemoglobin; OR, odds ratio.

than the non-diabetes mellitus group. The association between the A/C glycemic ratio and worse COVID-19 outcomes in patients with undiagnosed diabetes mellitus was also evident (Tables S1 and S2).

DISCUSSION

The findings of the present study showed that the undiagnosed diabetes mellitus group, as well as the pre-existing diabetes mellitus group, was associated with worse COVID-19 outcomes compared to the non-diabetes mellitus group. In addition, in patients with undiagnosed diabetes mellitus, the A/C glycemic ratio was associated with a poor prognosis, whereas HbA1c levels were unrelated to the outcome. Conversely, in patients with pre-existing diabetes mellitus, HbA1c levels, rather than the A/C glycemic ratio, were associated with severe outcomes of COVID-19. To the best of our knowledge, this is the first study to investigate the value of the A/C glycemic ratio independently for patients with undiagnosed diabetes mellitus and pre-existing diabetes mellitus. At the same time, previous reports have examined the usefulness of the parameters of acute hyperglycemia in patients with diabetes mellitus as a whole[5,6,9].

Although an association between undiagnosed diabetes mellitus and poor prognosis has been reported in patients with COVID-19, a relatively small number of patients were reported in these studies[2,13,14]. The present study results corroborated this association by utilizing an extensive national registry. Additionally, the result that undiagnosed diabetes mellitus accounted for 27.2% of diabetes mellitus is closely comparable with our past single-center study result of 30.6%[2], which is higher than the previous meta-analysis result of 14.4%[5]. Differences in the study duration and geography in these studies might have affected the prevalence of undiagnosed diabetes mellitus; nevertheless, the potentially high majority of patients with undiagnosed diabetes mellitus reinforces the importance of screening for diabetes mellitus on admission.

Furthermore, the present data showed that in patients with undiagnosed diabetes mellitus, the higher the A/C glycemic ratio, which implies a greater magnitude of baseline chronic to subsequent acute blood glucose elevation, the poorer the prognosis of COVID-19. In patients with undiagnosed diabetes mellitus who had COVID-19, stress-induced transient insulin resistance and acute insulin deficiency have been indicated as clinical manifestations[15–17]. Although the mechanism of the association between acute hyperglycemia and poor outcome of COVID-19 has not been fully elucidated, the potential causative factors include reduced host cellular defenses due to altered leukocyte function, activation of nuclear factor κB, and mitochondrial and vascular endothelial dysfunction by oxidative stress[3,18]. In patients with undiagnosed diabetes mellitus, these acute pathologies might have also been linked with a poorer prognosis. Furthermore, levels of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α, are typically elevated in patients with severe COVID-19[17,19]. These cytokines might deteriorate β-cell function and insulin resistance, and potentially result in hyperglycemia[20]. Unfortunately, as the present data did not include these exploratory biomarkers, further studies are required to consider the effects of cytokines and acute stress on hyperglycemia and the prognosis of COVID-19 in patients with undiagnosed diabetes mellitus. Additionally, whether the alterations in glucose metabolism that abruptly developed in severe COVID-19 are long-lasting or temporary remains unclear[21]. Our COVID-19 registry does not contain long-term glucose metabolism status and thus cannot contribute to this vital issue.

We found that HbA1c levels at admission were associated with worse COVID-19 outcomes in patients with pre-existing diabetes mellitus. These different results between the patients with undiagnosed diabetes mellitus and pre-existing diabetes mellitus might propose a different pathogenesis of a poor prognosis of COVID-19. For example, chronic hyperglycemia reduces the expression of angiotensin-converting enzyme 2, which predisposes cells to damage and inflammation[1]. Diabetes and hyperglycemia also affect lung volume and diffusion capacity, which might lead to a deterioration in the respiratory condition[13].

© 2023 The Authors. *Journal of Diabetes Investigation* published by AASD and John Wiley & Sons Australia, Ltd

In addition to COVID-19, undiagnosed diabetes mellitus is also known to be associated with poor outcomes in patients with acute stroke and myocardial infarction[22,23]; however, whether the mechanism is stress-induced hyperglycemia or caused by other pathologies remains controversial. Furthermore, a previous study reported the prognostic impact of a high A/C ratio in patients with diabetes mellitus hospitalized with acute myocardial infarction[9]. Therefore, to elucidate the effects of sudden acute glycemic change on severe illness in patients with undiagnosed diabetes mellitus, future studies should assess the correlation between the A/C glycemic ratio and prognosis.

The present study had some limitations. First, there were no data on blood glucose levels after admission, which made it impossible to assess the duration of the hyperglycemia during hospitalization. Second, as only hospitalized patients with COVID-19 were included, patients who were recuperating at home or in a hotel were not assessed in this study. Third, because physicians at each facility decide the treatment regimen and intensive care unit admission, it cannot be ruled out that the treatment differences between facilities might have affected the results.

In conclusion, we showed that among patients with undiagnosed diabetes mellitus who had COVID-19, the magnitude of the elevation of blood glucose from chronic to acute levels is linked with worse COVID-19 outcomes. Therefore, assessing the A/C glycemic ratio would be beneficial in patients with undiagnosed diabetes mellitus rather than independently evaluating blood glucose and HbA1c levels. We also re-emphasize the importance of glycemic control in the daily care of patients with pre-existing diabetes mellitus.

ACKNOWLEDGMENTS

The authors particularly acknowledge all the individuals enrolled in this study, and their medical staff for their participation.

Funding related to the conduct of this study was provided by the National Center for Global Health and Medicine COVID-19 Gift Fund.

DISCLOSURE

The authors declare no conflict of interest.
Approval of the research protocol: The study protocol was approved by the Institutional Review Board of the National Center for Global Health and Medicine, Tokyo, Japan (approval number: NCGM-G-003494-0).
Informed consent: We applied the opt-out method to obtain consent for this study.
Registry and the registration no. of the study/trial: N/A.
Animal studies: N/A.

DATA AVAILABILITY STATEMENT

The data supporting this study's findings are available from the COVIREGI-JP, but restrictions apply to the availability of these data, which were used under license for the current research and therefore are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the COVIREGI-JP. RB is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

REFERENCES

1. Bornstein SR, Rubino F, Khunti K, *et al*. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; 8: 546–550.
2. Uchihara M, Bouchi R, Kodani N, *et al*. Impact of newly diagnosed diabetes on coronavirus disease 2019 severity and hyperglycemia. *J Diabetes Investig* 2022; 13: 1086–1093.
3. Vargas-Vázquez A, Bello-Chavolla OY, Ortiz-Brizuela E, *et al*. Impact of undiagnosed type 2 diabetes and pre-diabetes on severity and mortality for SARS-CoV-2 infection. *BMJ Open Diabetes Res Care* 2021; 9: e002026.
4. Shrestha DB, Budhathoki P, Raut S, *et al*. New-onset diabetes in COVID-19 and clinical outcomes: a systematic review and meta-analysis. *World J Virol* 2021; 10: 275–287.
5. Sathish T, Kapoor N, Cao Y, *et al*. Proportion of newly diagnosed diabetes in COVID-19 patients: a systematic review and meta-analysis. *Diabetes Obes Metab* 2021; 23: 870–874.
6. Ramon J, Llauradó G, Güerri R, *et al*. Acute-to-chronic glycemic ratio as a predictor of COVID-19 severity and mortality. *Diabetes Care* 2022; 45: 255–258.
7. Clausen CL, Leo-Hansen C, Faurholt-Jepsen D, *et al*. Glucometabolic changes influence hospitalization and outcome in patients with COVID-19: an observational cohort study. *Diabetes Res Clin Pract* 2022; 187: 109880.
8. Marenzi G, Cosentino N, Milazzo V, *et al*. Prognostic value of the acute-to-chronic glycemic ratio at admission in acute myocardial infarction: a prospective study. *Diabetes Care* 2018; 41: 847–853.
9. Mondal S, DasGupta R, Lodh M, *et al*. Stress hyperglycemia ratio, rather than admission blood glucose, predicts in-hospital mortality and adverse outcomes in moderate-to severe COVID-19 patients, irrespective of pre-existing glycemic status. *Diabetes Res Clin Pract* 2022; 190: 109974.
10. Matsunaga N, Hayakawa K, Terada M, *et al*. Clinical epidemiology of hospitalized patients with coronavirus disease 2019 (COVID-19) in Japan: Report of the COVID-19 registry Japan. *Clin Infect Dis* 2021; 73: e3677–e3689.
11. Charlson ME, Pompei P, Ales KL, *et al*. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
12. Nathan DM, Kuenen J, Borg R, *et al*. Translating the A1C assay into estimated average glucose values. *Diabetes Care* 2008; 31: 1473–1478.
13. Paolo G, Luca M, Boscari F, *et al*. Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by

© 2023 The Authors. *Journal of Diabetes Investigation* published by AASD and John Wiley & Sons Australia, Ltd

20401124, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jdi.13979 by Cochrane Japan, Wiley Online Library on [13/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

aggravating respiratory deterioration. *Diabetes Res Clin Pract* 2020; 168: 108374.
14. Li H, Tian S, Chen T, *et al*. Newly diagnosed diabetes is associated with a higher risk of mortality than known diabetes in hospitalized patients with COVID-19. *Diabetes Obes Metab* 2020; 22: 1897–1906.
15. Cromer SJ, Colling C, Schatoff D, *et al*. Newly diagnosed diabetes vs. pre-existing diabetes upon admission for COVID-19: associated factors, short-term outcomes, and long-term glycemic phenotypes. *J Diabetes Complications* 2022; 36: 108145.
16. Atkinson MA, Powers AC. Distinguishing the real from the hyperglycaemia: does COVID-19 induce diabetes? *Lancet Diabetes Endocrinol* 2021; 9: 328–329.
17. Ceriello A, De Nigris V, Prattichizzo F. Why is hyperglycaemia worsening COVID-19 and its prognosis? *Diabetes Obes Metab* 2020; 22: 1951–1952.
18. Lontchi-Yimagou E, Sobngwi E, Matsha TE, *et al*. Diabetes mellitus and inflammation. *Curr Diab Rep* 2013; 13: 435–444.
19. Hayama H, Ide S, Kitami Y, *et al*. Interleukin-6 is upregulated and may be associated with myocardial injury in some patients who have recovered from COVID-19. *Glob Health Med* 2022; 4: 61–63.
20. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The common soil hypothesis revisited. *Arterioscler Thromb Vasc Biol* 2004; 24: 816–823.
21. Rubino F, Amiel SA, Zimmet P, *et al*. New-onset diabetes in Covid-19. *N Engl J Med* 2020; 383: 789–790.
22. Cho KH, Kwon SU, Lee JS, *et al*. Newly diagnosed diabetes has high risk for cardiovascular outcome in ischemic stroke patients. *Sci Rep* 2021; 11: 12929.
23. Ertelt K, Brener SJ, Mehran R, *et al*. Comparison of outcomes and prognosis of patients with versus without newly diagnosed diabetes mellitus after primary percutaneous coronary intervention for ST-elevation myocardial infarction (the HORIZONS-AMI study). *Am J Cardiol* 2017; 119: 1917–1923.

SUPPORTING INFORMATION

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

Table S1 | Association of primary outcomes according to diabetes classification in a sensitivity analysis in patients with oxygen demand.

Table S2 | Association of primary outcomes according to glycemic parameters in a sensitivity analysis in patients with oxygen demand.

Appendix S1 | STROBE statement – checklist of items that should be included in reports of observational studies.

© 2023 The Authors. *Journal of Diabetes Investigation* published by AASD and John Wiley & Sons Australia, Ltd

20401124, 2023, 4, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/jdi.13979 by Cochrane Japan, Wiley Online Library on [13/06/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License