Effect of coronavirus disease 2019 pandemic on the lifestyle and glycemic control in patients with type 2 diabetes: a cross-section and retrospective cohort study

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Abstract. To investigate the acute effects of the coronavirus disease 2019 (COVID-19) on the lifestyle and metabolic parameters in patients with type 2 diabetes mellitus. This cross-sectional and retrospective cohort study induced 203 patients who completed a questionnaire regarding stress levels and lifestyles. Data regarding stress levels, sleep time, exercise, and total diet, snack, and prepared food intake were obtained from the questionnaires. The changes in the body weight or HbA1c levels were determined by comparing the values at the time the questionnaire was administered to those noted 3 months ago. Increased levels of stress and decreased exercise levels were reported in approximately 40% and >50%. During the COVID-19 pandemic. There was a negative correlation between stress and exercise ( \( r = -0.285, p < 0.001 \)) and a positive correlation between stress and prepared food intake ( \( r = 0.193, p = 0.009 \)). Decreased exercise levels ( \( r = -0.33, p < 0.001 \)) and increased snack consumption ( \( r = 0.24, p = 0.002 \)) were associated with increased body weight. Furthermore, increased total diet intake ( \( r = 0.16, p = 0.031 \)) was associated with increased HbA1c levels. These relationships remained significant for patients aged <65 years and patients who did not engage in regular exercise. Many patients experienced stress and lifestyle changes due to the COVID-19 pandemic, and these changes were associated with increased body weight and HbA1c levels.

Key words: COVID-19, Pandemic, Type 2 diabetes, Stress, Exercise

CORONAVIRUSES (CoV) are envelop-type viruses with a single-stranded, positive-sense ribonucleic acid genome that is known to cause respiratory infections in humans [1]. Although most human CoV infections are not severe, two major outbreaks of CoV infection have occurred in the past, namely severe acute respiratory syndrome coronavirus (SARS-CoV) infection in 2002–2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) infection in 2012 [2-4]. A new coronavirus, SARS-CoV-2, was distinguished as the pathogen causing coronavirus disease COVID-19 in Wuhan, China in December 2019 [5]. On March 11, 2020, the World Health Organization declared COVID-19 a pandemic [6]. By May 1, 2020, 233,560 deaths were reported among 3,269,667 confirmed cases worldwide and 430 deaths have been reported among 14,088 confirmed cases in Japan [7].

To block the spread of COVID-19, European countries have significantly curbed public life. In Japan, a state of emergency, with request-based measures of encouraging the populace to remain at home and businesses to limit operations, was declared on April 7, 2020. Therefore, the Japanese are also becoming more restrictive in their behavior. On the other hand, infectious disease outbreaks, including COVID-19, are associated with increased stress [8, 9]. Moreover, previous studies showed that disasters were associated with increased stress and worse glycemic control in patients with type 2 diabetes mellitus [10].

Patients with diabetes mellitus are more likely to develop COVID-19 and are at a higher risk of mortality [11-13]. Although patients with diabetes mellitus should be careful to avoid COVID-19 infection, there is a possibility that forcing these patients to restrict their life may
worsen their glucose control. However, the effect of the COVID-19 pandemic on the mental health and lifestyle of patients with type 2 diabetes mellitus is currently unknown. Therefore, in this cross-sectional study, we aimed to investigate the acute effects of the COVID-19 pandemic on the lifestyle changes in patients with type 2 diabetes mellitus. Furthermore, we also investigated the association between these changes and metabolic parameters, including body weight and hemoglobin A1c (HbA1c) levels, by conducting a retrospective cohort study.

**Materials and Methods**

**Study patients**

To clarify the natural history of the patients with diabetes mellitus, we are performing an ongoing opt-out survey among the patients with diabetes mellitus. This study was approved by the ethics committee of Kyoto Prefectural University of Medicine (ERB-C-1291). In this cross-sectional study, a questionnaire was administered to the patients with type 2 diabetes mellitus who visited a clinic at the Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine from April 16 to May 1, 2020. We excluded patients if they were admitted to the hospital during the past 3 months or provided incomplete answers to the questionnaires from the cross-sectional study and excluded those who changed their medication for diabetes during the past 3 months from the retrospective cohort study.

**Data collection and measurements**

Type 2 diabetes mellitus was diagnosed by the Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus [14]. According to the self-administered questionnaire, the patients were classified as a non-, past-, or current smoker and patients who regularly played any type of sport for more than once per week, before COVID-19 pandemic, were defined as regular exercisers. Nephropathy was defined according to the report of the Joint Committee on Diabetic Nephropathy [15]. Neuropathy was defined by the diagnostic criteria for diabetic neuropathy suggested by the Diagnostic Neuropathy Study Group [16]. Retinopathy was classified, as follows: no diabetic-retinopathy (NDR), simple diabetic-retinopathy (SDR), and proliferative diabetic retinopathy (PDR), which included pre-proliferative retinopathy [17]. Data regarding the body weight and HbA1c levels at the time the questionnaire was administered and the values noted 3 months ago were obtained from medical records, and the difference between the values corresponding to these two time-points was calculated as the change in the body weight or HbA1c levels. Based on the patient’s change in the body weight or HbA1c levels, we further classified them as weight gain or not, or worse glycemic control or not.

**Questionnaire**

Since the decreased contact time is essential to reduce the risk of disease transmission, we only asked the patients simple and a minimal number of questions. This questionnaire was performed by physician during medical examination. The questionnaire consisted of 6 short questions regarding stress and lifestyle factors. A visual analog scale (VAS; 0 = considerably reduced, 5 = no change, and 10 = considerably increased) was used for all questions and patients were asked to score how their stress levels, sleep time, exercise levels, and total diet, snack, and prepared food intakes have changed due to the COVID-19 pandemic (Supplemental Table 1). Based on the patient’s VAS scores, we further classified them as meeting or not meeting the following categories: increased stress (VAS ≥6), shortened sleep time (VAS ≤4), decreased exercise (VAS ≤4), increased total diet intake (VAS ≥6), increased snack consumption (VAS ≥6), and increased prepared food intake (VAS ≥6).

**Statistical analysis**

The statistical analyses were performed using the JMP version 13.1 software (SAS Institute Inc., Cary, NC) and p-values <0.05 were considered statistically significant. The mean or frequency of potential confounding variables was calculated. The continuous and categorical variables were presented as the means (±standard deviations) and absolute numbers, respectively. Spearman rank correlation was used to investigate the relationship among the changes in stress and lifestyle factors. Spearman rank correlation was also used to investigate the relationship between these changes in stress and lifestyle factors and changes in body weight or HbA1c levels. The differences in the change in body weight or HbA1c levels between the groups were evaluated using Mann-Whitney U test. Furthermore, the differences in the lifestyle factors between the groups were evaluated using Mann-Whitney U test. Subgroup analyses were performed to assess the relationship between the change in stress and lifestyle factors and change in metabolic parameters (i.e., body weight and HbA1c levels) according to sex, age (≥65 years or <65 years) and exercise habit.

**Results**

In this study, among 564 patients who were scheduled to visit our department, 87 patients received telemedicine and 127 patients did not visit. Among 350 patients who
The clinical characteristics of the study participants are shown in Table 1. The mean age of the study participants was 67.4 (±11.3) years, and 62.1% (n = 126/203) of them were men. Increased stress levels, decreased exercise levels, increased total diet, snack, and prepared food intake were observed in approximately 40%, >50%, and 20% of the participants during the COVID-19 pandemic, respectively.

The results of correlations of the change in stress and lifestyle factors during the COVID-19 pandemic are shown in Table 2. There was a negative correlation between stress and exercise levels and a positive correlation between stress and prepared food intake. In addition, there was a negative correlation between exercise levels and snack or prepared food intakes. Furthermore, there was a correlation among diet intakes.

Furthermore, we investigated the association between the changes in the stress or lifestyle factors and changes in metabolic parameters. Among 183 participants, 24 participants’ body weight data and 7 participants’ HbA1c data were not recorded. Overall, there was a slight increase in body weight (n = 159) from 65.6 (±15.3) kg to 65.8 (±15.2) kg (p = 0.126, by paired t test) and the HbA1c level (n = 176) from 7.5 (±1.0) % to 7.6 (±1.1) % (57.9 (±10.6) mmol/mol to 59.7 (±12.0) mmol/mol) (p = 0.001, by paired t test) after 3 months. The results of the assessment of the association between the changes in the stress or lifestyle factors and change in metabolic parameters are shown in Table 3. Decreased exercise levels and increased total diet or snack intake were associated with increased body weight. Furthermore, increased total diet intake was associated with increased HbA1c levels.

Fig. 2 and Fig. 3 show the differences in body weight or HbA1c level changes between the groups. The change in body weight was significantly greater in patients who reported decreased exercise levels (0.60 [±2.11] vs. −0.16 [±1.72]; p < 0.001), increased of total diet intake (0.80 [±2.06] vs. 0.13 [±1.93]; p = 0.010), and increased of snack consumption (0.70 [±1.76] vs. 0.13 [±2.00]; p = 0.017) and tended to be greater in those who reported increased stress levels (0.46 [±2.19] vs. 0.06 [±1.76]; p = 0.281), and shortened sleep time (0.74 [±2.01] vs. 0.11 [±1.67]; p = 0.059) compared to those who did not. The change in HbA1c level was significantly greater in patients who reported shortened sleep time (0.34 [±0.52] vs. 0.13 [±0.70]; p = 0.034) and increased total diet intake (0.38 [±0.88] vs. 0.11 [±0.61]; p = 0.038) and tended to be greater in those who reported increased snack consumption (0.38 [±0.88] vs. 0.11 [±0.61]; p = 0.077) compared to those who did not. Moreover, we investigated the differences of lifestyle factors between the patients with weight gain or not, or worse glycemic control or not (Table 4). Patients with weight gain were associated with decreased exercise, increased total diet or increased snack consumption.

The results of the sub-analysis are shown in Table 5. The relationship between decreased exercise levels and change in body weight or HbA1c significant for only in

| Table 1 Clinical characteristics of the study participants |
|---------------------------------|-----------------|
| **n** | 203 |
| **Age (year)** | 67.4 (11.3) |
| **Sex (men/women)** | 126/77 |
| **Duration of diabetes (year)** | 14.4 (10.1) |
| **Smoking (non-/past-/current smoker)** | 99/81/23 |
| **Exercise habit (no/yes)** | 133/70 |
| **Habitual alcohol intake (no/yes)** | 120/83 |
| **Nephropathy stage (1/2/3/4/5)** | 120/54/15/11/3 |
| **Neuropathy (no/yes)** | 161/42 |
| **Retinopathy (NDR/SDR/PDR)** | 154/20/29 |
| **Insulin usage (no/yes)** | 135/68 |
| **Oral medication for diabetes (no/yes)** | 33/170 |
| **Questionnaires** | |
| **Feel stress** | 6.0 (1.7) |
| **Increasing of stress (no/yes)** | 118/85 |
| **Sleep time** | 4.9 (1.4) |
| **Shorten sleep time (no/yes)** | 164/39 |
| **Exercise** | 3.7 (2.0) |
| **Decreasing of exercise (no/yes)** | 93/109 |
| **Total diet intake** | 5.2 (1.2) |
| **Increasing of total diet intake (no/yes)** | 163/40 |
| **Snack consumption** | 4.9 (1.6) |
| **Increasing of snack consumption (no/yes)** | 166/37 |
| **Prepared food intake** | 5.1 (1.3) |
| **Increasing of prepared food intake (no/yes)** | 173/30 |

NDR, non-diabetic retinopathy; SDR, simple diabetic retinopathy; PDR, proliferative diabetic retinopathy. All items of the change of stress or lifestyles factors were evaluated by used visual analog scale. 0 = considerably reduced, 5 = no change, 10 = considerably increased.
Fig. 1 Inclusion and exclusion flow

Table 2 The correlations of the change of stress and lifestyles factors

|                        | Stress | Sleep time | Exercise | Total diet intake | Snack consumption | Prepared food intake |
|------------------------|--------|------------|----------|-------------------|-------------------|----------------------|
| **Stress**             |        |            |          |                   |                   |                      |
| **Sleep time**         |        |            |          |                   |                   |                      |
| r = –0.098             |        |            |          |                   |                   |                      |
| p = 0.187              |        |            |          |                   |                   |                      |
| **Exercise**           |        |            |          |                   |                   |                      |
| r = –0.285             |        |            |          |                   |                   |                      |
| p < 0.001              |        |            |          |                   |                   |                      |
| r = 0.156              |        |            |          |                   |                   |                      |
| p = 0.035              |        |            |          |                   |                   |                      |
| **Total diet intake**  |        |            |          |                   |                   |                      |
| r = 0.115              |        |            |          |                   |                   |                      |
| p = 0.120              |        |            |          |                   |                   |                      |
| r = 0.054              |        |            |          |                   |                   |                      |
| p = 0.468              |        |            |          |                   |                   |                      |
| r = 0.052              |        |            |          |                   |                   |                      |
| p = 0.483              |        |            |          |                   |                   |                      |
| **Snack consumption**  |        |            |          |                   |                   |                      |
| r = 0.102              |        |            |          |                   |                   |                      |
| p = 0.170              |        |            |          |                   |                   |                      |
| r = 0.010              |        |            |          |                   |                   |                      |
| p = 0.896              |        |            |          |                   |                   |                      |
| r = –0.161             |        |            |          |                   |                   |                      |
| p < 0.001              |        |            |          |                   |                   |                      |
| r = 0.315              |        |            |          |                   |                   |                      |
| **Prepared food intake** |    |          |          |                   |                   |                      |
| r = 0.193              |        |            |          |                   |                   |                      |
| p = 0.009              |        |            |          |                   |                   |                      |
| r = 0.117              |        |            |          |                   |                   |                      |
| p = 0.114              |        |            |          |                   |                   |                      |
| r = –0.087             |        |            |          |                   |                   |                      |
| p = 0.241              |        |            |          |                   |                   |                      |
| r = 0.206              |        |            |          |                   |                   |                      |
| p = 0.005              |        |            |          |                   |                   |                      |
| r = 0.219              |        |            |          |                   |                   |                      |
| p = 0.003              |        |            |          |                   |                   |                      |
| r = 0.06               |        |            |          |                   |                   |                      |

Spearman rank correlation was performed to investigate the correlations. All items were evaluated by visual analog scale. 0 = considerably reduced, 5 = no change, 10 = considerably increased.

Table 3 The relationship between the change of stress or lifestyles factors and the change of metabolic parameters

|                              | Stress | Sleep time | Exercise | Total diet intake | Snack consumption | Prepared food intake |
|------------------------------|--------|------------|----------|-------------------|-------------------|----------------------|
| Change of body weight (n = 159) | r = 0.02 | r = –0.02 | r = –0.33 | r = 0.19          | r = 0.24          | r = 0.06             |
|                              | p = 0.767 | p = 0.770 | p < 0.001 | p = 0.016         | p = 0.002         | p = 0.449            |
| Change of Hemoglobin A1c (n = 176) | r = 0.06 | r = –0.07 | r = –0.09 | r = 0.16          | r = 0.08          | r = 0.03             |
|                              | p = 0.445 | p = 0.352 | p = 0.241 | p = 0.031         | p = 0.284         | p = 0.680            |

Spearman rank correlation was performed to investigate the correlations. All items of the change of stress and lifestyles factors were evaluated by visual analog scale. 0 = considerably reduced, 5 = no change, 10 = considerably increased.
men, whereas the relationship between increased snack consumption and change in body weight remained significant both in men and women. The relationship between decreased exercise levels or increased snack consumption and change in body weight remained significant for only patients aged <65 years. Furthermore, the relationship between the decreased exercise levels or increased snack or prepared food intake and changes in body weight or HbA1c levels remained significant for only patients who did not engage in regular exercise previously.

Discussion

In this study, we investigated the acute influence of the COVID-19 pandemic on the lifestyle of patients with type 2 diabetes mellitus. Based on our findings, patients with type 2 diabetes mellitus reported increased stress from the COVID-19 pandemic, which was associated with their exercise levels and diet intakes. Furthermore, these stress and lifestyle factors are associated with the changes in body weight and HbA1c.

Recent studies revealed that the COVID-19 pandemic is associated with increased stress in general populations [8, 9]. External stress may lead to less physical activity and poor diet [18, 19]. In addition, stress is thought to impact that metabolic parameters in patients with diabetes mellitus [20]. In previous studies, it has been reported that disasters, including earthquakes, floods, and hurricanes, were associated with increased stress and worse glycemic control in patients with type 2 diabetes mellitus [10, 21-27]. Although the association between stress and glycemic control was not observed in this study, unlike these previous disasters, the COVID-19 pandemic is ongoing and there are concerns that the impact on patients with diabetes mellitus will continue or become more severe. High glucose levels were associated with increased mortality in patients with SARS-CoV [28, 29].
and MERS-CoV [30]. Furthermore, high glucose levels are also reported to be associated with increased mortality in patients with COVID-19 [31]. Previous researchers have revealed that diet quality is associated with metabolic parameters, including glycemic control [32, 33], and that processed food intake is associated with calorie intake [34]. In addition, decreased exercise levels and increased snack consumption are associated with

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**Fig. 3** The difference of the change of hemoglobin A1c between the groups

The difference between groups was evaluated by Student t-test. *; indicated *p < 0.05.

A) Stress, feel high stress or not (visual analog scale [VAS] ≥6 or not)
B) Sleep time, shorten sleep time or not (VAS ≤4 or not)
C) Exercise, decreasing of exercise or not (VAS ≤4 or not)
D) Total diet intake, increasing of total diet intake or not (VAS ≥6 or not)
E) Snack intake, increasing of snack consumption or not (VAS ≥6 or not)
F) Prepared food intake, increasing of prepared food intake or not (VAS ≥6 or not)

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**Table 4** Differences of lifestyle factors between the patients with weight gain or worse glycemic control or not

| Body weight | Glycemic control |
|-------------|------------------|
| **Weight gain** | **Weight gain** | **p value** | **Worse glycemic control** | **Worse glycemic control** | **p value** |
| (−) | (+) | | (−) | (+) | |
| Stress | 6.1 (1.5) | 6.1 (1.5) | 0.566 | 5.8 (1.4) | 6.2 (1.8) | 0.153 |
| Sleep time | 4.8 (1.3) | 4.7 (1.4) | 0.822 | 4.9 (1.3) | 4.8 (1.5) | 0.594 |
| Exercise | 4.3 (2.0) | 2.9 (1.7) | <0.001 | 3.9 (2.0) | 3.6 (2.0) | 0.139 |
| Total diet intake | 4.9 (1.0) | 5.5 (1.3) | 0.011 | 4.9 (1.0) | 5.4 (1.3) | 0.059 |
| Snack consumption | 4.7 (1.6) | 5.4 (1.3) | 0.004 | 4.9 (1.6) | 5.1 (1.6) | 0.251 |
| Prepared food intake | 5.0 (1.2) | 5.2 (1.1) | 0.270 | 5.0 (1.1) | 5.1 (1.3) | 0.667 |

The differences in the lifestyle factors between the groups were evaluated using Mann-Whitney U test. Data were shown as mean (SD).
have currently decreased their physical activity levels. In evaluated by visual analog scale. 0 = considerably reduced, 5 = no change, 10 = considerably increased. The association between decreased exercise levels and the long term follow up. Moreover, there is a possibility and those who did not exercise regularly. These patients during pandemic. Therefore, we should focus on exercise Spearman rank correlation was performed to investigate the correlations. All items of the change of stress and lifestyles factors were changes in body weight was significant for age under 65 and those who did not exercise regularly. These patients have currently decreased their physical activity levels. In addition, the association between increased snack consumption and changes in body weight was significant. This result revealed that consumed snacks is one of the important treating targets of not increase body weight during pandemic. Therefore, we should focus on exercise of patients who are <65 years or without a regular exercise habit and diet, especially snack. On the other hand, it is possible that the spread of COVID-19 infection has caused patients with diabetes to rethink their lifestyles. Thus, there is a possibility that the glycemic control and body weight would be better in the long term follow up. Moreover, there is a possibility that the results vary greatly depending on the timing of the survey. The survey was conducted in mid-April to early May, when we are most concerned about infection. Thus, further studies are needed for these associations. In addition, this study was performed in a single university medical center, thus there is a possibility that the back‐ground of patients in this study differs from that of the general Japanese population with diabetes, although average age and BMI are almost same as a previous study [36].

There are several limitations of this study. Firstly, the sample size was relatively small, and the participants were limited to a single center. In addition, this study only included the patients who visited our department. Therefore, the data of patients who did not visit were not included. There is a possibility that patients who did not visit our department experienced more stress or changes in lifestyle and, therefore, poor glycemic control. Secondly, the questionnaire of this study was simple and subjective and did not include quantitative evaluation. However, under the pandemic situation, the decreased contact time is essential to reduce the risk of disease transmission. Therefore, we only asked the patients simple and a minimal number of questions. Third, the causal relationship between the COVID-19 pandemic and the results of this survey is not wholly clarified. Because the

### Table 5 Sub-analysis of the relationship between the change of stress or lifestyles factors and the change of metabolic parameters

|                          | Exercise habit (-) | Total diet intake | Snack consumption | Prepared food intake |
|--------------------------|--------------------|-------------------|-------------------|---------------------|
| Change of body weight, n = 104 | $r = -0.34$ | $r = 0.17$ | $r = 0.16$ | $r = -0.03$ |
| Change of HbA1c, n = 110  | $p < 0.001$ | $p = 0.091$ | $p = 0.113$ | $p = 0.790$ |
| Change of body weight, n = 55  | $r = -0.30$ | $r = 0.25$ | $r = 0.38$ | $r = 0.18$ |
| Change of HbA1c, n = 66  | $p = 0.028$ | $p = 0.06$ | $p = 0.004$ | $p = 0.178$ |
| Change of body weight, n = 53  | $r = -0.44$ | $r = 0.06$ | $r = 0.29$ | $r = -0.14$ |
| Change of HbA1c, n = 57  | $p = 0.001$ | $p = 0.670$ | $p = 0.037$ | $p = 0.323$ |
| Change of body weight, n = 106  | $r = -0.26$ | $r = 0.26$ | $r = 0.20$ | $r = 0.20$ |
| Change of HbA1c, n = 119  | $p = 0.008$ | $p = 0.007$ | $p = 0.042$ | $p = 0.037$ |
| Change of body weight, n = 104  | $r = -0.37$ | $r = 0.17$ | $r = 0.35$ | $r = 0.08$ |
| Change of HbA1c, n = 116  | $p = 0.001$ | $p = 0.082$ | $p < 0.001$ | $p = 0.424$ |
| Change of body weight, n = 55  | $r = -0.09$ | $r = 0.08$ | $r = 0.16$ | $r = 0.02$ |
| Change of HbA1c, n = 60  | $p = 0.318$ | $p = 0.376$ | $p = 0.078$ | $p = 0.867$ |

Spearman rank correlation was performed to investigate the correlations. All items of the change of stress and lifestyles factors were evaluated by visual analog scale. 0 = considerably reduced, 5 = no change, 10 = considerably increased.
questionnaire was collected only 1 time point for individu-ual patients and answer for the question was based on the memory of the patients during the 3 months, answers could be strongly affected by the most recent feeling. Furthermore, there were no control in this study. Fourth, here is a possibility of change of answers if patients did not know their recent HbA1c, because the questionnaire was performed by physician during medical examination. Lastly, this study included only Japanese patients; therefore, it is not clear whether our findings can be generalized to the populations of other countries.

In conclusion, many patients with type 2 diabetes mellitus reported increased stress levels and changes in lifestyle factors during the COVID-19 pandemic. These lifestyle changes were associated with changes in the body weight and HbA1c levels, even during the short-term (i.e., 3 months). Given that the pandemic is ongoing, we should pay more attention to the management of stress and lifestyle factors in patients with type 2 diabetes mellitus to prevent the worsening of their glycemic control. Further research of exercise therapy or diet intervention without close contact with others is needed.

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Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. We affirmed that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned.

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None.

Conflicts of Interest

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**Contribution Statements**

C.M. and Y. Ho obtained and analyzed data and wrote manuscript. These authors equally contributed to this work. Y. Ha. planned, and designed the work, obtained, analyzed and interpreted data and contributed to discussion. T.O. analyzed and interpreted data and contributed to discussion. F.T., R.K., H.N., T.S., N.N., E.U., M.H., and M.Y. obtained data and contributed to discussion. M.F. contributed to the conception of the work, obtained and interpreted data and contributed to discussion. All authors checked the final version, and agree to be responsibility for the work to ensure that any questions related to the accuracy or completeness of any of the work are appropriately investigated and resolved. Corresponding author, Yoshitaka Hashimoto, takes full responsibility for the work and publish the manuscript.

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