Supplementary document 1: The use of isCGM in Japan

Previously in Japan, FreeStyleLibre was prescribed only in patients treated under multiple daily insulin injection. Since 2022 April, the insurance coverage was expanded for all insulin using patients with diabetes, including patients with once-a-day insulin injection. For hospitalized patients, temporary use of FreeStyleLibre (Abbott Laboratories, Chicago, IL) for glucose management is not covered by insurance. For temporary use in inpatient glucose management, there is a different device, the FreeStyleLibre Pro (Abbott Laboratories, Chicago, IL), which is used for the purpose of testing 14-days of glycemic data. To scan the sensor glucose, a reader device is used, and one reader device carried by the medical staff is used to scan the sensors of multiple patients. The glucose profile report is only available after the 14-days of sensor use is completed, and remote monitoring of the data is not possible. Although FreeStyleLibre Pro is a cost-effective device, this is not suitable for glycemic control in hospitalized patients with infectious diseases, as in COVID-19 cases. On the contrary, the FreeStyleLibre system is a useful device since the users can scan the sensor using their own smartphone, and this enables the medical staff to remotely monitor the glycemic data.

Supplementary document 2: Materials and methods

Study design and participants

This exploratory research was conducted at the Central Hospital of the NCGM (CHNCGM), one of the designated institutions in Tokyo, Japan for severe COVID-19 cases during the pandemic. We retrospectively studied adult patients with diabetes and severe COVID-19 who required methylprednisolone therapy and were hospitalized at CHNCGM between April 1 and August 18, 2021. Among the 26 patients, 5 used isCGM and 21 used BGM only. As isCGM requires self-scanning, it was not used by intubated patients or older patients who found it difficult to conduct regular scanning. Therefore, in order to adjust the background, patients aged over 65 years and patients who were intubated were excluded from the analysis, leaving 14 patients in the BGM group. The diagnosis of COVID-19 was established based on the positivity of severe acute respiratory syndrome coronavirus 2 by the real-time reverse transcription-polymerase chain reaction test.

The study protocol was approved by the Institutional Review Board of the National Center for Global Health and Medicine (NCGM), Tokyo, Japan (approval number: NCGM-S-004328-00, approval date: October 21, 2021). We used the opt-out method to obtain informed consent for this study.

Data collection

The following information was collected from patients' electronic medical records: demographic data, comorbidities, vital signs, and laboratory findings at admission. Laboratory findings included blood cell counts, liver and kidney function test results, glycated hemoglobin A1c (HbA1c) levels, coagulation profile, and inflammatory markers. Other data included the worst severity of COVID-19 during hospitalization (critical, severe moderate, and mild), patient outcome (death, discharge, or hospital transfer), treatment regimens for COVID-19 (systemic corticosteroids, remdesivir, tocilizumab, baricitinib, and heparin), and respiratory support (e.g., nasal cannula or mask, high-flow nasal cannula, non-invasive positive pressure ventilation, and invasive ventilation).

Patients with diabetes included those with a known history of diabetes (defined based on self-reported history of diabetes, prior medical records of diabetes before admission, or treatment with glucose-lowering medications) and newly diagnosed diabetes (defined as having both an HbA1c level ≥6.5% [48 mmol/mol] and fasting plasma glucose level ≥126 mg/dL [7.0 mmol/L], or random blood glucose level ≥200 mg/dL [11.1 mmol/L] on admission with no history of diabetes).

The severity of COVID-19 was defined as follows: a critical condition requiring non-invasive positive pressure ventilation or invasive ventilation; a severe condition presenting clinical signs of pneumonia (fever, dyspnea, cough, and tachypnea) accompanied by a respiratory rate >30 breaths/min, severe respiratory distress, or oxygen saturation <94% on room air; a moderate condition presenting fever and respiratory symptoms with radiological findings of pneumonia; and a mild condition presenting mild clinical symptoms without signs of pneumonia on imaging. In this

study, patients with critical or severe conditions who required methylprednisolone therapy were analyzed.

Systemic corticosteroid therapies, including methylprednisolone pulse therapy (intravenous, 500–1000 mg daily for usually 3 consecutive days [up to 5 days] with gradual tapering according to the patient's respiratory status every 3–7 days) or methylprednisolone therapy (intravenous, 2 mg/kg for 5 consecutive days with gradual tapering according to the patient's respiratory status every 3–7 days) were selected by the infection and respiratory care specialists, taking into consideration the severity of respiratory failure. Treatment was initiated on the day of admission.

Inpatient glycemic control

Blood glucose levels of all patients were measured before each meal and at bedtime using a glucometer. In this study, patients with diabetes were categorized into two groups: those who used isCGM (FreeStyle Libre Flash glucose monitoring system, Abbott Laboratories, Chicago, IL) in addition to blood glucose monitoring (BGM) (isCGM group) and those who used only BGM (BGM group). There were no definite criteria for the use of isCGM. The decision was left to the diabetologist in charge, and the device was used with the patient's consent.

Diabetologists monitored patients' glycemic pattern to adjust the basal and bolus insulin doses according to food intake and glucocorticoid use. When necessary, continuous intravenous insulin infusion was used as an adjunct to basal insulin, and glucose-lowering medications was concomitantly administered. On average, insulin dose adjustments were performed approximately two to three times per day.

Based on measured blood glucose levels (4 points: before meals and at bedtime) during the first week of hospitalization, we calculated the daily time in range (TIR) for 70–180 mg/dL (3.9–10.0 mmol/L), time above range for >180 mg/dL (>10.0 mmol/L) and >250 mg/dL (>13.9 mmol/L), and time below range for < 70 mg/dL (3.9 mmol/L). To monitor the total daily insulin dose, subcutaneous long-acting insulin, fast-acting insulin, and intravenously injected insulin doses were recorded during the first 7 days of hospitalization.

Statistical analyses

Continuous variables were reported as mean ± standard deviation or median (interquartile range), and categorical variables were expressed as percentages. Differences in clinical characteristics between the groups were assessed using the Student t-test and chi-squared test for continuous and categorical variables, respectively. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). A dynamic graph of glucose levels was drawn using Python (version 3.8, Python Software Foundation, Wilmington, DE, USA) programming language modules NumPy, Matplotlib, and Seaborn.

Supplementary Table S1. Patient characteristics on admission

Variables	isCGM (n = 5)	BGM (n = 14)	p
Age, years	46.8 ± 11.2	53.5 ± 7.6	0.153
Sex male, n (%)	5 (100.0)	12 (85.7)	1
BMI, kg/m^2	29.5 ± 6.6	27.7 ± 4.0	0.450
Systolic blood pressure, mmHg	118.2 ± 16.7	133.8 ± 26.2	0.235
Body temperature, degree Celsius	37.5 ± 1.1	37.9 ± 1.1	0.499
Oxygen saturation, %	90.2 ± 7.6	89.4 ± 7.7	0.849
Oxygen concentration, L	3.4 ± 4.1	7.6 ± 4.7	0.098
Comorbidities, n (%)			
Hypertension	1 (20.0)	6 (42.9)	0.603
Dyslipidemia	0 (0.0)	7 (50.0)	0.106
CKD	0 (0.0)	1 (7.1)	1
COPD	0 (0.0)	1 (7.1)	1
Malignancy	0 (0.0)	0 (0.0)	-
Past or current smoker	2 (40.0)	5 (35.7)	1
Laboratory data			
Plasma glucose, mg/dL	219.4 ± 74.1	300.9 ± 157.2	0.286
HbA1c, %	8.4 ± 2.2	8.3 ± 1.7	0.858
Serum albumin, g/dL	3.1 ± 0.2	3.1 ± 0.5	0.914
AST, U/L	95.8 ± 16.6	67.6 ± 37.6	0.128
ALT, U/L	85.6 ± 37.4	54.6 ± 30.4	0.082
LDH, U/L	602.6 ± 223.5	551.5 ± 179.8	0.614
Serum creatinine, μmol/L	75.1 ± 8.9	90.2 ± 43.3	0.476

Lymphocyte count, /μl	1282.6 ± 273.7	760.7 ± 363.7	0.010
Neutrophil count, /μl	4553.4 ± 3105.1	7012.4 ± 2955.9	0.133
CRP, mg/dL	9.1 ± 7.7	13.7 ± 7.5	0.266
D-dimer, μg/mL	14.9 ± 30.9	11.1 ± 24.2	0.783

Data are expressed as number and percentage or mean ± standard deviation.
isCGM, intermittently scanned continuous glucose monitoring; BGM, blood glucose monitoring; BMI, body mass index; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HbA1c, glycated hemoglobin A1c; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Supplementary Table S2. Coronavirus disease 2019 (COVID-19) therapies and patient outcomes

Variables	Total (n = 19)	isCGM (n = 5)	BGM (n = 14)	p
Worst severity classification of COVID-19, n (%)				
Critical	11 (57.9)	2 (40.0)	9 (64.3)	0.603
Severe	8 (42.1)	3 (60.0)	5 (35.7)	0.603
Oxygen demand, n (%) [a]				
Nasal or mask	3 (15.8)	1 (20.0)	2 (14.3)	1
High flow nasal cannula	5 (26.3)	2 (40.0)	3 (21.4)	0.570
Non-invasive positive pressure ventilation	11 (57.9)	2 (40.0)	9 (64.3)	0.603
Glucocorticoid therapy, n (%)				
Methylprednisolone pulse therapy	13 (68.4)	3 (60.0)	10 (71.4)	1
Methylprednisolone therapy	6 (31.6)	2 (40.0)	4 (28.6)	1
Other COVID-19 medications, n (%)				
Remdesivir	17 (89.5)	4 (80.0)	13 (92.9)	0.468
Tocilizumab	11 (57.9)	4 (80.0)	7 (50.0)	0.338
Baricitinib	7 (36.8)	0 (0.0)	7 (50.0)	0.106
Heparin	18 (94.7)	5 (100.0)	13 (92.9)	1
Patient Outcomes, n (%)				
Death	0 (0)	0 (0)	0 (0)	-
Discharge	19 (100.0)	5 (100.0)	14 (100.0)	-

Data are expressed as count (percentage). [a]Worst delivery route.

isCGM, intermittently scanned continuous glucose monitoring; BGM, blood glucose monitoring.

Supplementary Table S3. Glycemic control in the first week of hospitalization

Variables	isCGM (n = 5)	BGM (n = 14)	p
Average blood glucose, mg/dL			
Day 1-7	197.4 ± 29.3	239.0 ± 24.9	0.007
Day 1-3	244.3 ± 26.8	276.8 ± 57.9	0.250
Day 4-5	181.7 ± 45.6	230.9 ± 39.8	0.035
Day 6-7	144.7 ± 32.1	200.1 ± 46.1	0.025
TIR 70 - 180 mg/dL (3.9–10.0 mmol/L), %			
Day 1-7	47.5 ± 22.7	25.8 ± 17.6	0.041
Day 1-3	19.7 ± 18.7	15.3 ± 17.9	0.651
Day 4-5	61.1 ± 33.9	23.3 ± 23.6	0.014
Day 6-7	75.0 ± 29.3	40.8 ± 30.1	0.042
TAR > 180 mg/dL (10.0 mmol/L), %			
Day 1-7	54.0 ± 21.6	74.2 ± 17.8	0.054
Day 1-3	82.3 ± 16.4	85.3 ± 17.7	0.750
Day 4-5	38.9 ± 33.9	76.7 ± 23.6	0.014
Day 6-7	27.5 ± 28.5	58.3 ± 31.3	0.071
TAR > 250 mg/dL (13.9 mmol/L), %			
Day 1-7	24.2 ± 14.9	43.0 ± 13.4	0.018

Day 1-3	45.0 ± 20.3	59.9 ± 27.3	0.285
Day 4-5	18.2 ± 27.7	39.8 ± 23.3	0.107
Day 6-7	0	25.0 ± 19.0	0.010
TBR < 70 mg/dL (3.9 mmol/L), %			
Day 1-7	0	0.3 ± 1.0	0.565
Day 1-3	0	0	-
Day 4-5	0	0	-
Day 6-7	0	0.9 ± 3.3	0.565

Data are presented as mean ± standard deviation. isCGM, intermittently scanned continuous glucose monitoring; BGM, blood glucose monitoring; TAR, time above range; TIR, time in range; TBR, time below range.

Supplementary Table S4. Total daily insulin dose in the first week of hospitalization

Days after admission	isCGM (n = 5)	BGM (n = 26)	p
Total daily insulin dose, units			
Day 1	11.6 ± 19.5	12.6 ± 19.3	0.924
Day 2	87.6 ± 81.3	33.4 ± 27.0	0.037
Day 3	114.6 ± 57.1	37.6 ± 26.4	0.001
Day 4	110.4 ± 47.3	47.4 ± 34.1	0.005
Day 5	90.0 ± 46.3	49.3 ± 33.7	0.050
Day 6	70.4 ± 40.4	53.1 ± 31.5	0.341
Day 7	56.6 ± 37.4	56.4 ± 32.5	0.992
Total daily insulin dose per body weight, units/kg			
Day 1	0.14 ± 0.24	0.18 ± 0.28	0.790
Day 2	0.88 ± 0.73	0.47 ± 0.40	0.123
Day 3	1.23 ± 0.54	0.52 ± 0.39	0.006
Day 4	1.19 ± 0.45	0.66 ± 0.52	0.057
Day 5	0.96 ± 0.42	0.67 ± 0.52	0.272
Day 6	0.77 ± 0.46	0.71 ± 0.47	0.811
Day 7	0.61 ± 0.39	0.75 ± 0.47	0.559

Data are presented as mean ± standard deviation. isCGM, intermittently scanned continuous glucose monitoring; BGM, blood glucose monitoring.