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Increased Insulin Requirements in Severe Cases of Covid-19 are Higher Than in Moderate Cases

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Purpose: Despite the low overall death rate of coronavirus disease 2019 (COVID-19), no study has examined the association between COVID-19 severity and the total daily insulin dose required for glycemic control. The aim of this study was to determine the maximum total daily insulin dose required according to COVID-19 severity, and the number of days required to reach the maximum insulin dose in patients with COVID-19 who used insulin during hospitalization.

Patients and Methods: This retrospective cohort study included participants aged 20–90 years with a confirmed diagnosis of COVID-19 who used insulin during hospitalization at Kyoto Prefectural University of Medicine Hospital between March 4, 2020, and May 31, 2021. Factors associated with maximum insulin dose during hospitalization were evaluated using linear regression analyses.

Results: The maximum insulin doses were 31.8, 76.8, and 230.7 U/day, and the numbers of days between COVID-19 diagnosis and the need for maximum insulin were 15.6, 17.1, and 13.7 days in patients without ventilator management, with ventilator management, and with ventilator and extracorporeal membrane oxygenation management, respectively. Multivariate linear regression analyses revealed that hemoglobin A1c level ($\beta = 15.87$, $P = 0.001$), use of a ventilator ($\beta = 50.53$, $P < 0.001$), and use of extracorporeal membrane oxygenation ($\beta = 150.36$, $P < 0.001$) were independent determinants of maximum insulin dose.

Conclusion: Patients with severe COVID-19 required a significantly higher maximum insulin dose than did those with moderate COVID-19. The maximum insulin dose was reached approximately 2 weeks after onset. Furthermore, the hemoglobin A1c level on admission and the use of a ventilator or extracorporeal membrane oxygenation during hospitalization were associated with the need for maximum insulin dose.

Plain language summary:

Why was the study done?

- More than 769 million infections and 6.9 million fatalities have resulted from the coronavirus disease 2019 (COVID-19), which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- In relation to the degree of sickness, what is the maximum daily insulin dosage and the number of days required to achieve the maximum insulin dose?

What did the researchers do and find?

- The maximum total daily insulin dose required according to COVID-19 severity and the number of days required to reach the maximum insulin dose in patients with COVID-19 who used insulin during hospitalization were determined in this study.
- The maximum daily insulin requirement in this study was reached approximately 2 weeks after the onset of COVID-19, regardless of severity.

What do these results mean?

- The results of this study may be useful as an indicator of insulin dosage and incremental acceleration in future COVID-19 clinical practice.
- Predicting the maximum amount of insulin and the time required to reach this maximum during hospitalization will lead to more appropriate glycemic management.

Keywords: COVID-related diabetes, SARS-CoV-2, insulin resistance, glycemic control, retrospective cohort study

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Introduction

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused more than 769 million infections and 6.9 million deaths[1] since its outbreak in December 2019, making it an urgent global challenge. Although the overall mortality rate of COVID-19 is low, poor prognosis has been reported when patients with COVID-19 have coexisting diabetes, especially type 2 diabetes.[2,3] Higher insulin doses that increase in parallel with illness severity have been reported to aid blood glucose level control in patients with severe COVID-19.[4] However, until recently, no study has examined the association between COVID-19 severity and the total daily insulin dose required for glycemic control.

In COVID-19 infection, it has been observed that in critically ill patients requiring ventilation, metabolic demands are increased and insulin requirements are greatly increased.[5] As one of the causes, SARS-CoV-2 has been reported to cause a decrease in insulin secretory capacity by invading and disrupting β-cells.[6] It has also been reported that high glycemic control during hospitalization is associated with increased mortality and length of hospital stay.[7]

In this study, we aimed to determine the maximum total daily insulin dose and the number of days required to reach the maximum insulin dose according to illness severity and factors associated with the need for maximum insulin dose in patients with COVID-19 who used insulin during hospitalization.

We believe that by clarifying these factors, we may be able to promptly adjust insulin doses and thereby achieve better glycemic control.

Materials and Methods

Study Design

All adult patients with a confirmed diagnosis of novel coronavirus-infected pneumonia and a moderate or severe disease level[8] requiring hospitalization and who were admitted to Kyoto Prefectural University of Medicine Hospital—one of the 55 publicly designated Class I infectious disease hospitals in Japan—between March 4, 2020, and May 31, 2021, were included in this retrospective cohort study. In this study, there were no similar previous reports and the sample size was determined from feasibility. COVID-19 patients who were expected to have severe disease, ie, patients with moderate stage I (no evidence of respiratory failure but evidence of pneumonia) with underlying diseases such as diabetes, or patients with moderate stage 2 (evidence of respiratory failure) or higher were admitted to Kyoto Prefectural University of Medicine Hospital.[8] The insulin dose was adjusted with the target of blood glucose control set at 140~180 mg/dL.[9] In addition, the Nutrition Support Team set the energy and protein targets according to the Japanese guidelines for nutritional therapy for critically ill patients,[10] and nutritional therapy was provided. Nutrition was primarily administered orally, with parenteral nutrition as needed. Nutrient requirements were calculated using the Harris-Benedict formula. The eligibility criteria for this study were as follows: confirmed diagnosis of COVID-19 by PCR using nasal swabs, age 20–90 years, and use of insulin during hospitalization. All procedures were approved by the Research Ethics Committee of Kyoto Prefectural University of Medicine (approval number ERB-C-1810-2) and were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients.

Data Collection

Blood samples were collected for biochemical measurements upon admission. The characteristics of each patient (age, sex, body mass index, smoking status, history of kidney disease, hypertension, and respiratory disease) were obtained from the initial questionnaire and medical information forms. Hemoglobin A1c (HbA1c) levels were expressed as the National Glycohemoglobin Standardization Program unit.

Definitions

In this study, patients were classified into three groups according to the COVID-19 treatment status: The "without ventilator management" group corresponded to patients with moderate COVID-19, while those with severe COVID-19

required ventilator management and were further divided into two groups based on whether they required extracorporeal membrane oxygenation (ECMO) management.[8] This study defined the maximum insulin dose as the maximum daily amount used during hospitalization. The date of diagnosis of COVID-19 was defined as the date when the patient became aware of symptoms known to be the initial symptoms of COVID-19, such as upper respiratory tract symptoms and fever. Renal disease was defined as present if the patient had been diagnosed with chronic kidney disease, glomerulonephritis, nephrotic syndrome, or autosomal dominant polycystic kidney disease prior to admission. Respiratory disease was defined as present if the patient had been diagnosed with lung cancer, chronic obstructive pulmonary disease, interstitial pneumonia, emphysema, asthma, or pulmonary tuberculosis. Cardiovascular disease was defined as present if the patient had been diagnosed with angina pectoris, myocardial infarction, valvular disease, and cerebral infarction. Insulin non-use or fasting serum CPR $\geq$ 0.6 mg/mL if on insulin at admission was defined as insulin-independent status. C-peptide immunoreactivity insulin resistance (CPR-IR) was used as a measure of insulin resistance and calculated as follows: CPR − IR = 20/(fasting C-peptide × fasting plasma glucose).[11]

Statistical Analyses

Baseline characteristics were summarized using means and standard deviations or numbers and percentages for the three groups. One-way analysis of variance (parametric analysis) and Kruskal–Wallis analysis (non-parametric variables) were applied to continuous variables, and chi-square tests were applied to categorical variables. Pairwise comparisons were performed using the Bonferroni test. Linear regression analysis was performed to examine the factors associated with maximum insulin dose. In addition to the unadjusted model (Model 1), we set up a multivariate model adjusted for COVID-19 severity risk factors, such as age, sex, body mass index, HbA1c level, hypertension, renal disease, respiratory disease, use of glucocorticoids, use of ventilator, and use of ECMO (Model 2). IBM SPSS Statistics version 19.0J (IBM Corp., Armonk, NY, USA) was used for statistical analyses, and two-sided P values <0.05 were considered significant.

Results

During the follow-up period of this retrospective study, there were 142 hospitalizations with confirmed novel coronavirus-infected pneumonia cases in our hospital. Of these, three patients were aged <20 years, 87 did not use insulin during hospitalization, and seven did not agree to participate in this study. Finally, 45 patients participated in this study (Figure 1). Patients with a history of type 1 diabetes were not included in the study. Of the 45 patients, 26 (57.8%) and 19 (42.2%) had severe and moderate COVID-19, respectively. The clinical characteristics of the three groups at baseline are

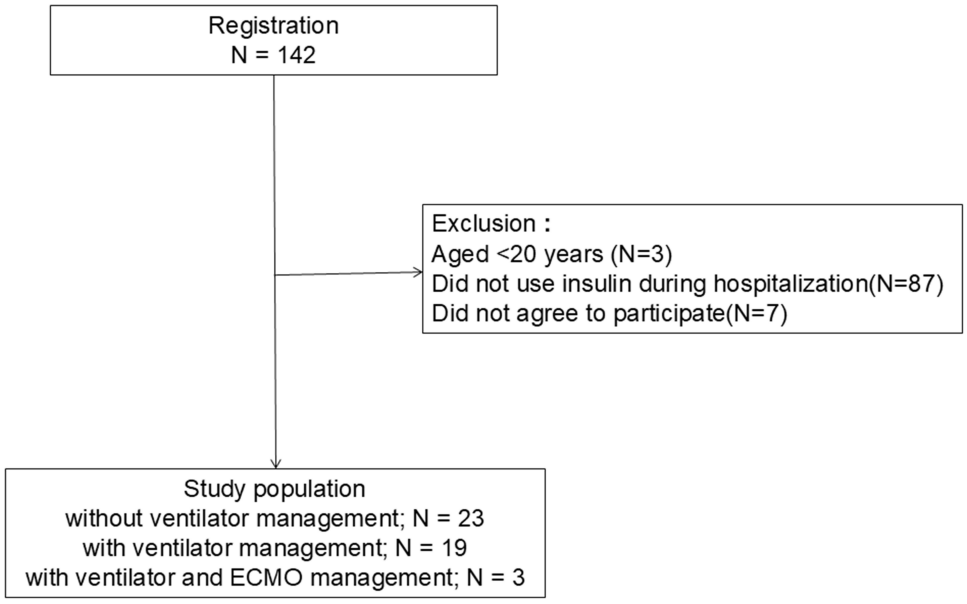

Figure 1 Flowchart for this study.

Table 1 Patient Characteristics

Characteristics	All (45)	Without Ventilator Management (19)	With Ventilator Management (23)	ECMO (3)	*p*
Male	39(86.7)	16(84.2)	20(87)	3(100)	0.39
Age, years	65.3±12.7	68.1±12.1	63.9±13.6	59.0±8.5	0.39
Body mass index, kg/m2	25.8±5.4	24.9±5.4	26.2±5.8	27.3±2.6	0.66
Hemoglobin A1c, %	7.5±1.9	7.4±1.2	7.4±2.4	8.9±2.5	0.28
Kidney disease	8(17.8)	3(15.8)	4(17.4)	1(33.3)	0.76
Hypertension	24(53)	10(52.6)	12(52.2)	2(66.7)	0.89
Respiratory disease	7(15.6)	4(21.1)	2(28.6)	1(33.3)	0.37
C-reactive protein	10.4±6.1	10.0±6.8	11.4±5.7	5.9±1.4	0.33
Ferritin	1335.8±1512.4	942.4±763.3	1676.5±1955.7	1214.7 ±420.7	0.30
Max insulin dose (U/day)	67.9±62.2	31.8±24.6	76.8±47.7*	230.7±274.0†	<0.001
Number of days from onset to reach max insulin (day)	16.2±7.4	15.6±5.1	17.1±9.3	13.7±2.9	0.87
Duration of hospitalization (day)	17.7±15.8	15.0±13.0	16.9±13.7	66.0±34.7†	0.036
Smoking	28(62.2)	11(57.9)	15(65.2)	2(66.7)	0.77
Use of glucocorticoids	41(91.1)	17(89.5)	21(91.3)	3(100)	0.84

Notes: Data are summarized by average±standard deviation or number (%). * *P*<0.01., † *P*<0.001. for difference versus without ventilator management group; ANOVA for comparison among the 3 subgroups.
Abbreviation: ECMO, extracorporeal membrane oxygenation management.

shown in Table 1. The mean values of age and HbA1c level were 65.3 ± 12.7 years and 7.5 ± 1.9%, respectively, and 39 (86.7%) of the patients were male. The proportions of patients without ventilator management, with ventilator management, and with ventilator and ECMO management were 42.2%, 51.1%, and 6.7%, respectively, with maximum insulin doses of 31.8, 76.8, and 230.7 U/day, respectively. The maximum insulin dose was significantly higher in the group with ventilator and ECMO than in the groups without ventilator and with ventilator, and significantly higher in the group with ventilator than in the group without ventilator (Table 1). The number of days between the diagnosis of COVID-19 and the need for maximum insulin were 15.6, 17.1, and 13.7 days in patients without ventilator management, with ventilator management, and with ventilator and ECMO management, respectively.

In the univariate analyses, HbA1c level (β = 16.85, P = 0.002), use of ventilator (β = 63.40, P < 0.001), and use of ECMO (β = 174.72, P < 0.001) were associated with the need for maximum insulin dose. Multivariate linear regression

Table 2 Regression Analysis on Max Insulin Dose

	Univariate		Multivariate	
	β	*p*	β	*p*
Age, years	−1.17	0.14	0.29	0.69
Sex (men = 1, women = 0)	14.60	0.62	−22.06	0.28
Body mass index, kg/m^2	3.44	0.06	−0.87	0.68

(*Continued*)

Table 2 (Continued).

	Univariate		Multivariate	
	β	*p*	β	*p*
Hemoglobin A1c, %	19.99	<0.001	19.25	<0.001
Hypertension	−2.06	0.92	7.17	0.62
Kidney disease	−11.84	0.65	−8.53	0.67
Respiratory disease	−6.42	0.82	−17.06	0.38
Smoking	−2.48	0.87	6.67	0.53
Use of glucocorticoids	14.19	0.69	28.63	0.21
Use of ventilator	69.00	‹ 0.001	59.27	‹ 0.001
Use of ECMO	170.34	‹ 0.001	125.86	‹ 0.001

Notes: β indicates linear regression coefficient. Adjusted for all variables in this table.
Abbreviation: ECMO, extracorporeal membrane oxygenation management.

analyses also revealed that HbA1c level (β = 15.87, P = 0.001), use of ventilator (β = 50.53, P < 0.001), and use of ECMO (β = 150.36, P < 0.001) were independent determinants of maximum insulin dose (Table 2).

CPR-IR values were 2.15 ± 3.09 and 3.11 ± 2.13 in severe and moderate COVID-19 groups, respectively (P = 0.643).

Discussion

To the best of our knowledge, this is the first study conducted to examine the association between COVID-19 severity and the need for maximum insulin dose and to investigate factors associated with the need for maximum insulin dose.

The results of this study revealed that the maximum insulin dose was significantly higher in patients with severe COVID-19 who used ventilators than in patients with moderate COVID-19 who did not use ventilators. In particular, patients in the ECMO management group required a higher maximum insulin dose of 230.7 U/day than did those in the other two groups. Regardless of COVID-19 severity, the maximum insulin dose was reached 14 to 17 days after onset of COVID-19 and 6 to 9 days after admission. Furthermore, HbA1c level at admission and ventilator or ECMO use during hospitalization were determinants of the need for maximum insulin dose. These results suggest that glycemic control status at admission and COVID-19 severity after admission are more related to the need for maximum daily insulin dose and that the maximum insulin requirement is reached approximately 2 weeks after the onset of COVID-19 and 1 week after admission.

There are various possible mechanisms by which COVID-19 severity is associated with total daily insulin dose. Increased insulin resistance has been reported to be the most significant factor influencing increased insulin requirements in patients with COVID-19.[12] In the present study, CPR-IR tended to be lower in severe cases, ie higher insulin resistance, but the difference was not significant. However, CPR-IR can be considered a useful indicator in cases of mild insulin resistance and is therefore considered a reference value in this study.

We used CPR-IR calculated by CPR at admission and fasting blood glucose level, which may be applicable in a wide range of clinical settings. However, detailed application criteria and cutoff values would require further study.

Inflammatory mediators released by inflammation directly affect the action of insulin, thereby contributing to the onset and progression of insulin resistance. Similarly, inflammation may have increased insulin resistance in severe cases of COVID-19.[12,13] Previous reports have suggested that excessive inflammation and disproportionate immune response may be involved in the rapid deterioration of disease in patient with diabetic-complicated COVID-19, as cytokine storms have often been observed in COVID-19-related death.[14,15] The increased insulin requirement under ventilator and ECMO management in the present study may indicate the involvement of cytokine storms.[16] However, the indicators of a cytokine storm, such as tumor necrosis factor-α, interferon, interleukin (IL)-1β, monocyte chemoattractant protein-1

(chemokine (C-C motif) ligand 2), and IL-6, were not identified in this study, and future studies are required.[15,17] CRP and ferritin were evaluated as markers to assess inflammation in this study, but no significant association was found between elevated insulin levels and inflammatory markers. This may be because this study included hospitalized patients at a moderate or advanced stage of disease and with high inflammatory marker levels overall. Acute hyperglycemia is known to occur as a defense mechanism against the loading of pathological stresses such as ischemia and hypoxia.[18] In the present study, hypoxia and other pathological stresses may have caused hyperglycemia in cases where ventilator or ECMO management was implemented.[19]

In contrast, insulin secretory capacity reduces in patients with severe COVID-19,[6] suggesting a mechanism in which SARS-CoV-2 binds to angiotensin-converting enzyme 2 in the pancreas, directly injuring the pancreatic head and reducing insulin secretory capacity.[6] However, none of the patients in the present study was insulin-dependent at the time of admission.

In the present study, the maximum total daily insulin doses were achieved 14 to 17 days after the onset of COVID-19, regardless of severity. This is roughly consistent with the typical course of COVID-19 that has been reported,[11] which is severe after 10 days from the onset of illness. A specific application of these results would be to predict the maximum amount of insulin and the time required to reach the maximum amount during hospitalization, which would lead to more appropriate glycemic control.

This study has the following limitations. First, the participants were Japanese only, and the results may not be generalizable to other ethnic groups. Second, the sample size was small, particularly as only three patients were managed with ECMO. Therefore, a sensitivity analysis was performed excluding the three ECMO cases, but the results remained the same. The aim is to increase the number of patients and revisit this issue in the future. Third, in this study, pancreatic endocrine function was not assessed after admission, making it difficult to determine whether the need for high-dose insulin was due to pancreatic endocrine insufficiency or insulin resistance. Finally, Kyoto Prefectural University of Medicine Hospital is the only facility in Kyoto that is designated as a Class I infectious disease hospital, where COVID-19 patients, who are expected to be severely ill, are mainly admitted. Therefore, although the above results do not necessarily apply to all facilities, we believe they can help guide treatment in severe COVID-19 practice.

Conclusion

COVID-19 severity and the amount of insulin required are closely associated. Increased insulin resistance may be involved as a major factor. The maximum daily insulin requirement in this study was reached approximately 2 weeks after the onset of COVID-19, regardless of severity. The results of this study may be useful as an indicator of insulin dosage and incremental acceleration in future COVID-19 clinical practice.

Data Sharing Statement

The datasets of the current study are available from the corresponding author upon reasonable request.

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Author Contributions

T.M. designed the study, analyzed, and interpreted the data, and drafted and revised the manuscript. E.U., M.H., K.S., N. K., Y.K., Y.H., D.I., T.H., M.Y., T.S, and M.F. collected, analyzed, and interpreted the data and revised the manuscript. All authors approved the final version of the manuscript. E.U. is the guarantor of this work and, as such, has full access to all the study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no competing interests.

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