

Sakaguchi Kota (Orcid ID: 0000-0002-5169-6613)
Watari Takashi (Orcid ID: 0000-0002-9322-8455)
Tokuda Yasuharu (Orcid ID: 0000-0002-9325-7934)

Evidence-based Prescription of Corticosteroids for COVID-19 patients : A Comparison between General Medicine and Other Specialty in Japan

Kota Sakaguchi MD, MBA ¹ Takashi Watari MD, MHQS, Ph.D,¹⁻³ Yasuharu Tokuda MD, MPH,^{4,5} Ph.D⁴

1 Shimane University Hospital, General Medicine Center, Shimane, Japan

2 Medicine Service, VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA

3 Department of Medicine, University of Michigan Medical School. Ann Arbor, Michigan, USA

4 Muribushi Okinawa Clinical Training Center, Okinawa, Japan

5Tokyo Foundation for Policy Research, Tokyo, Japan

ORCID.

Kota Sakaguchi: 0000-0002-5169-6613

Takashi Watari: 0000-0002-9322-8455

Yasuharu Tokuda: 0000-0002-9325-7934

Corresponding author: Kota Sakaguchi MD, MBA

Shimane University Hospital, General Medicine Center, Shimane, Japan 89-1 Enya-cho, Izumo city, Shimane prefecture, Japan

Phone: +81-853-23-2111 Fax: +81-853-20-2375 E-mail: bananakuriimu@gmail.com

Running title: COVID-19 prescriptions

Acknowledgments: We thank the team members, Dr. Yoshihiko Shiraishi, Dr. Ichiro Kato, Dr. Seiji Odagawa, Dr. Takeshi Endo, Dr. Nobuyuki Ueno, and Mrs. Kazumi Iwatani from Shimane University Hospital, General Medicine Center, for sharing their wisdom during this

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/jgf2.602](https://doi.org/10.1002/jgf2.602)

This article is protected by copyright. All rights reserved.

research. In addition, we thank Dr. Kiyosu Taniguchi and Dr. Kenji Shibuya for helping with the data collection in Japan.

Manuscript word count: 988

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding statement: This study was supported by the national academic research grant funds [JSPS KAKENHI: 20H03913]. The sponsor of the study had no role in the study design, data collection, analysis, or preparation of the manuscript.

Conflict of interest: None declared.

Ethics approval statement: This study was conducted per the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines. This study was approved by the Institutional Ethics Committee of the Muribushi Okinawa Center for Teaching Hospitals (No.2021-9).

Patient consent statement: N/A

Evidence-based Prescription of Corticosteroids for COVID-19 patients: A Comparison between General Medicine and Other Specialty in Japan

Abstract

Background

The difference of evidence-based prescription for COVID-19 patients between general medicine and other specialty in Japan is unclear.

Methods

A retrospective observational study using a hospital-based administrative database was conducted for the differences between departments for prescriptions of glucocorticoids in COVID-19 patients.

Results

Of 65,156 patients, 23,348 met indication for glucocorticoids. General medicine physicians in Japan were more likely to prescribe corticosteroids for COVID-19 patients than other departments after its evidence was published (adjusted odds ratio, 1.32; $p < 0.001$; 95% confidence interval, 1.11–1.56).

Conclusions

General medicine physicians were more likely to practice evidence-based care for COVID-19 patients.

Keywords: Glucocorticoids; COVID-19; pandemic; prescription; pharmacoepidemiology

Introduction

It is crucial to determine the quality of general care for COVID-19 patients to assess patient outcomes. In several countries, general practitioners had to contribute as the mainstay of outpatient and inpatient care because infectious disease specialists and respiratory physicians could not treat all patients during the COVID-19 pandemic.^{1,2} Numerous clinical trials have been conducted to date, with the aim of establishing an effective treatment. In particular, the report of an absolute risk reduction in 28-day mortality by administering dexamethasone to COVID-19 hospitalized patients requiring oxygen therapy and mechanical

ventilation on June 16, 2020, was a breakthrough.³ In the UK, based on this scientific evidence, the administration rate of corticosteroids to eligible patients increased from 27.5% in the week before June 16, 2020, to 75–80% in January 2021, and the successful implementation of new treatment methods with a high evidence level was recognized, mainly in general medicine departments.⁴

However, the circumstances surrounding the implementation of corticosteroids in COVID-19 patients by general medicine departments in Japan are unclear. Potential inequalities in treatment according to specialty during pandemics are critical to individuals, communities, and nations. Therefore, we aimed to elucidate the quality of general care for COVID-19 patients. We examined the past situation of glucocorticoid prescription for COVID-19 patients after solid evidence had been published and whether there were differences by specialty in Japan during this pandemic.

Methods

The current study used the largest nationwide hospital administrative database, called Diagnosis and Procedure Combination (DPC) data in Japan, containing data from 25% (438 of 1,750) of all acute care hospitals (DPC hospitals). The DPC dataset used in the current study was collected from the Ministry of Health, Welfare, and Labour of the government of Japan by Medical Data Vision (MDV), Co., Tokyo, Japan (as of April 1, 2021).⁵ In the dataset, the age and gender distribution of registered patients is comparable to the distribution of patients at healthcare institutions nationwide as published by the government of Japan, thus representing the national data.¹ The current study collected the MDV DPC data from January 1, 2010, to November 30, 2021, and focused on patients of all ages with confirmed (RT-PCR test positive) acute COVID-19 (International Classification of Diseases and Related Health Problems, 10th Revision diagnosis code U071) who required admission, with

acute COVID-19 as the major cause for the admission. The data from the first admission were used in the current study.

Variables

The data used in this study included demographics, clinical characteristics, corticosteroid use, and departmental characteristics (general medicine, respiratory medicine, emergency medicine, internal medicine, pediatrics, cardiology, and gastroenterology) (Table 1). We followed the Japanese Medical Specialty Organization for specialty classification by the physicians.⁶

Standard descriptive statistics were used to calculate the number, percentage, mean, median, and interquartile range (IQR) for each piece of data. The chi-square test or Fisher's exact test was used for comparisons of categorical data. For continuous variables, t-tests or Wilcoxon rank-sum tests were employed. Additionally, multivariate linear and logistic regression analyses were performed to examine the factors associated with cognitive bias. Variables were adjusted based on their clinical relevance and previous studies.³ The criteria used for the explanatory variables were factors associated with steroid prescriptions among COVID-19 patients in previous studies³ and factors that were significant at $p < 0.05$, based on univariate screening and univariate regression. Specifically, general internal medicine was selected for the multiple logistic regression analysis of the presence of steroid prescriptions. All analyses were performed using the Stata statistical software (Stata Corp. 2015, Stata 17 Base Reference Manual). All tests were two-tailed, and statistical significance was set at $p < 0.05$. This study was approved by the appropriate ethics committee.

Results

Of the 65,184 COVID-19 patients (female, 42.5%; mean age \pm SD, 53.7 \pm 0.08) included in this study, 23,348 (35.8%) received oxygen therapy, with dexamethasone indicated. In fact, 14,763 (63.2%) patients were prescribed dexamethasone, and the clinical characteristics of these patients included a high proportion of diabetes (11,221 patients [48.1%]) and smoking (10,905 patients [46.7%]) (Table 1). The general medicine department prescribed corticosteroids significantly more often than other departments (adjusted odds ratio, 1.27; $p=0.006$; 95% CI, 1.07–1.51). Moreover, we found that diabetes (adjusted odds ratio, 1.32; 95% CI, 1.25–1.40) and mechanical ventilation (adjusted odds ratio, 1.08; 95% CI, 1.11–1.56) were factors in the patient background for high corticosteroid prescription (Table 2).

Discussion

This is the first study to analyze corticosteroid prescription and the department of admission for COVID-19 patients using a large Japanese database. We found that the general medicine department was significantly more likely to use corticosteroids in COVID-19 patients requiring oxygen therapy and mechanical ventilation at the time of admission than other departments. In addition to individual behavioral change, factors involved in decision-making must be considered when implementing new therapeutic interventions, and in several cases, the complexity of the intervention and difficulty in reaching consensus with others have been identified as barriers.⁷ In previous studies, the Department of General Medicine collaborated with nurses and other frontline care team members during COVID-19 treatment, which facilitated consensus building regarding new healthcare delivery methods and information sharing.^{8,9} This may have been a factor in the rapid introduction of corticosteroids with a high level of evidence and decision-making based on scientific evidence.

This study had several limitations. First, it only analyzed data from COVID-19 patients in DPC-registered hospitals in Japan. This is an inadequate sample size compared with the number of patients published by the MHLW.¹⁰ Second, due to the characteristics of the data described above, there may be insufficient assessment of the expertise of physicians involved in the prescription of corticosteroids.

In conclusion, we evaluated the characteristics of corticosteroid prescriptions for COVID-19 patients after data on treatment with a high level of evidence was published and found that general medicine departments prescribed more corticosteroids for COVID-19 patients than other departments. This was a result of the application of treatment by general medicine departments immediately after data with high level of evidence regarding the treatment was published.

References

1. Bowden K, Burnham EL, Keniston A, et al. Harnessing the power of hospitalists in operational disaster planning: COVID-19. *J Gen Intern Med.* 2020;35:2732–7.
2. Garg M, Wray CM. Hospital medicine management in the time of COVID19: preparing for a sprint and a marathon. *J Hosp Med.* 2020;15:305–7.
3. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med.* 2021;384:693–704.
4. Närhi F, Moonesinghe SR, Shenkin SD, et al. Implementation of corticosteroids in treatment of COVID-19 in the ISARIC WHO Clinical Characterisation Protocol UK: prospective, cohort study. *Lancet Digit Health.* 2022;4:e220–34.

5. Medical Data Vision Co., Ltd. MDV Database. Available from: <https://en.mdv.co.jp>. Accessed 14 Apr 2022.
6. Japanese Medical Specialty Board. 2018. [cited 25 June 2019]. Available from: <https://www.japan-senmon-i.jp/>. Accessed 29 Aug 2020.
7. Craig P, Dieppe P, Macintyre S, et al. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.
8. Kim MK, Rabinowitz LG, Nagula S, et al. A primer for clinician deployment to the medicine floors from an epicenter of COVID-19. *NEJM Catalyst*. 2020.
9. Biala D, Siegel EJ, Silver L, Schindel B, Smith KM. Deployed: pediatric residents caring for adults during COVID-19's First Wave in New York City. *J Hosp Med*. 2020;15:763–4.
10. Japan Ministry of Health, Labour and Welfare. Coronavirus (COVID-19). Available from: <https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html>. Accessed 20 Mar 2022.

Ethics approval statement: This study was conducted per the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines. This study was approved by the Institutional Ethics Committee of XXXX.

Patient consent statement: N/A

Tables

Table 1. The characteristics and comorbidities of patients with COVID-19 in Japan.

	June 16, 2020–November 30, 2021
Demographic and clinical characteristics	
Total no. of patients	23,348
Age, mean (SD), y	53.7 (0.08)
Age group, no. (%)	
>65	11,540 (49.3)
Sex, no. (%)	
Male	14,806 (63.4)
Female	8,542 (36.6)
Comorbidities, no. (%)	
Congestive heart failure	3,710 (15.9)
Acute myocardial infarction	297 (1.3)
Hypertension	10,075 (43.2)
Stroke	1,120 (4.8)
Chronic kidney disease	1,391 (6.0)
Diabetes	11,221 (48.1)
Obesity (BMI > 30)	5,497 (23.5)
Chronic lung disease	6,034 (25.8)
Rheumatologic arthritis	16 (0.1)
Smoking	10,905 (46.7)
Cancer	1,341 (5.7)
ARDS	1,179 (5.1)
Dementia	1,846 (7.9)
ICU admission	2,945 (12.6)
Mechanical ventilation	2,393 (10.3)
Steroid use	14,763 (63.2)

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: ARDS, acute respiratory syndrome; BMI, body mass index; ICU, intensive care unit.

Table 2. Predictor variables and steroid use of patients with COVID-19.

Variables	Adjusted OR (95% CI)	P value
GIM	1.27 (1.07-1.51)	0.006
Age > 65 years	0.73 (0.69-0.78)	<0.001
Male sex	1.14 (1.08-1.21)	<0.001
Obesity (BMI>30)	0.88 (0.81-0.95)	0.002
Smoking	0.92 (0.86-0.97)	0.002
Coma	0.46 (0.30-0.69)	<0.001
Shock	0.42 (0.07-2.55)	0.349
Cancer	0.92 (0.82-1.04)	0.203
Liver cirrhosis	1.10 (0.78-1.56)	0.579
Chronic lung disease	1.07 (0.10-1.14)	0.064
Diabetes	1.32 (1.25-1.40)	<0.001
Stroke	0.87 (0.75-1.01)	0.067
Heart failure	0.98 (0.90-1.07)	0.701
Chronic kidney disease	1.09 (0.96-1.24)	0.170
Dementia	0.54 (0.49-0.60)	<0.001
ICU	1.02 (0.93-1.13)	0.633
Mechanical ventilation	1.08 (0.97-1.19)	0.177

Abbreviations: OR, odds ratio; CI, confidence interval; GIM, general internal medicine; Adjusted logistic regression models

**COI Self-Report Form: Journal of General and Family Medicine,
an official Journal of Japan Primary Care Association**

All Authors' Name: _____

Title of the paper: _____

All authors must describe the COI status, within one year before the paper submission, with any companies, organizations, and/or groups **related to the content of the publication**. The Corresponding Author should guarantee that he/ she has obtained all potential Conflict of Interest from all authors and must disclose them in the table below.

Item	Applicability	If "Yes," please list the name of the author and the name of all related entities.
(1) Assuming a position of a board member or advisor in a profit-making business, legal entity, or organization run by you, your spouse, or your first-degree relative 1 million yen or more annual compensation from a single business, entity, or group		
(2) Stock holdings 1 million yen or more annual dividends or 5% or more interests in the applicable business		
(3) Patent royalties 1 million yen or more annual income per patent		
(4) Honoraria for lectures 1 million yen or more total annual income from a single company or organization		
(5) Honoraria for manuscripts 500 thousand yen or more total annual income from a single company or organization annual income from a single business or group		
(6) Total clinical research grants (e.g. commissioned research, joint research) 2 million yen or more total annual research grants paid from a single company or organization to you or your department		
(7) Total scholarship grants (incentives), etc. 2 million yen or more total annual scholarship contributed by a single company or organization to you or your department		
(8) Courses endowed by companies, etc. (Fill in if you belong to any course endowed by a company, etc.)		
(9) Receiving travel expenses or gifts 50 thousand yen or more annually from a single company or organization		

(This COI report will be kept for two years after the publication of the paper. The content of your report will not be disclosed to a third party.)

Corresponding author's name _____

Signature _____ Date _____

Tables

Table 1. The characteristics and comorbidities of patients with COVID-19 in Japan.

	June 16, 2020–November 30, 2021
Demographic and clinical characteristics	
Total no. of patients	23,348
Age, mean (SD), y	53.7 (0.08)
Age group, no. (%)	
>65	11,540 (49.3)
Sex, no. (%)	
Male	14,806 (63.4)
Female	8,542 (36.6)
Comorbidities, no. (%)	
Congestive heart failure	3,710 (15.9)
Acute myocardial infarction	297 (1.3)
Hypertension	10,075 (43.2)
Stroke	1,120 (4.8)
Chronic kidney disease	1,391 (6.0)
Diabetes	11,221 (48.1)
Obesity (BMI > 30)	5,497 (23.5)
Chronic lung disease	6,034 (25.8)
Rheumatologic arthritis	16 (0.1)
Smoking	10,905 (46.7)
Cancer	1,341 (5.7)
ARDS	1,179 (5.1)
Dementia	1,846 (7.9)
ICU admission	2,945 (12.6)
Mechanical ventilation	2,393 (10.3)
Steroid use	14,763 (63.2)

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: ARDS, acute respiratory syndrome; BMI, body mass index; ICU, intensive care unit.

Table 2. Predictor variables and steroid use of patients with COVID-19.

Variables	Adjusted OR (95% CI)	P value
GIM	1.27 (1.07-1.51)	0.006
Age > 65 years	0.73 (0.69-0.78)	<0.001
Male sex	1.14 (1.08-1.21)	<0.001
Obesity (BMI>30)	0.88 (0.81-0.95)	0.002
Smoking	0.92 (0.86-0.97)	0.002
Coma	0.46 (0.30-0.69)	<0.001
Shock	0.42 (0.07-2.55)	0.349
Cancer	0.92 (0.82-1.04)	0.203
Liver cirrhosis	1.10 (0.78-1.56)	0.579
Chronic lung disease	1.07 (0.10-1.14)	0.064
Diabetes	1.32 (1.25-1.40)	<0.001
Stroke	0.87 (0.75-1.01)	0.067
Heart failure	0.98 (0.90-1.07)	0.701
Chronic kidney disease	1.09 (0.96-1.24)	0.170
Dementia	0.54 (0.49-0.60)	<0.001
ICU	1.02 (0.93-1.13)	0.633
Mechanical ventilation	1.08 (0.97-1.19)	0.177

Abbreviations: OR, odds ratio; CI, confidence interval; GIM, general internal medicine; Adjusted logistic regression models

Evidence-based Prescription of Corticosteroids for COVID-19 patients : A Comparison between General Medicine and Other Specialty in Japan

Kota Sakaguchi MD, MBA¹ Takashi Watari MD, MHQS, Ph.D,¹⁻³ Yasuharu Tokuda MD, MPH,^{4,5} Ph.D⁴

1 Shimane University Hospital, General Medicine Center, Shimane, Japan

2 Medicine Service, VA Ann Arbor Healthcare System, Ann Arbor, Michigan, USA

3 Department of Medicine, University of Michigan Medical School. Ann Arbor, Michigan, USA

4 Muribushi Okinawa Clinical Training Center, Okinawa, Japan

5Tokyo Foundation for Policy Research, Tokyo, Japan

ORCID.

Kota Sakaguchi: 0000-0002-5169-6613

Takashi Watari: 0000-0002-9322-8455

Yasuharu Tokuda: 0000-0002-9325-7934

Corresponding author: Kota Sakaguchi MD, MBA

Shimane University Hospital, General Medicine Center, Shimane, Japan 89-1 Enya-cho, Izumo city, Shimane prefecture, Japan

Phone: +81-853-23-2111 Fax: +81-853-20-2375 E-mail: bananakuriimu@gmail.com

Running title: COVID-19 prescriptions

Acknowledgments: We thank the team members, Dr. Yoshihiko Shiraishi, Dr. Ichiro Kato, Dr. Seiji Odagawa, Dr. Takeshi Endo, Dr. Nobuyuki Ueno, and Mrs. Kazumi Iwatani from Shimane University Hospital, General Medicine Center, for sharing their wisdom during this

research. In addition, we thank Dr. Kiyosu Taniguchi and Dr. Kenji Shibuya for helping with the data collection in Japan.

Manuscript word count: 988

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Funding statement: This study was supported by the national academic research grant funds [JSPS KAKENHI: 20H03913]. The sponsor of the study had no role in the study design, data collection, analysis, or preparation of the manuscript.

Conflict of interest: None declared.

Ethics approval statement: This study was conducted per the Declaration of Helsinki and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines. This study was approved by the Institutional Ethics Committee of the Muribushi Okinawa Center for Teaching Hospitals (No.2021-9).

Patient consent statement: N/A