

# Impact of regional heterogeneity on the severity of COVID-19

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## Abstract

**Background:** We aimed to assess the impact of regional heterogeneity on the severity of COVID-19 in Japan. **Methods:** We included 27,865 cases registered between January 2020 and February 2021 in the COVID-19 Registry of Japan to examine the relationship between the National Early Warning Score (NEWS) of COVID-19 patients on the day of admission and the prefecture where the patients live. A hierarchical Bayesian model was used to examine the random effect of each prefecture in addition to the patients' backgrounds. In addition, we compared the results of two models; one model included the number of beds secured for COVID-19 patients in each prefecture as one of the fixed effects, and the other model did not. **Results:** The results indicated that the prefecture had a substantial impact on the severity of COVID-19 on admission. Even when considering the effect of the number of beds separately, the heterogeneity caused by the random effect of each prefecture affected the severity of the case on admission. **Conclusions:** Our analysis revealed a possible association between regional heterogeneity and increased/decreased risk of severe COVID-19 infection on admission. This heterogeneity was derived not only from the number of beds secured in each prefecture but also from other factors.

**Title:** Impact of regional heterogeneity on the severity of COVID-19

**Running title:** Regional heterogeneity and COVID-19 management

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## Author contributions

Shinya Tsuzuki: Data Curation, Formal Analysis, Methodology, Visualization, Original Draft Preparation. Yusuke Asai: Data Curation, Methodology, Validation, Review and Editing. Nobuaki Matsunaga: Original Draft Preparation, Review and Editing. Haruhiko Ishioka: Original Draft Preparation, Review and Editing. Takayuki Akiyama: Data curation, Validation, Review and Editing. Norio Ohmagari: Conceptualization, Funding Acquisition, Project Administration, Review & Editing.

### **Data availability**

The data that support the findings of this study are available upon request to the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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### **Conflict of interest**

None declared.

### **Ethical approval**

This study was approved by the National Center for Global Health and Medicine (NCGM) ethics review committee (NCGM-G-003494-0). Information regarding opting out of our study is available on the registry website.

### **Patient consent**

Informed consent was obtained in the form of opt-out on the registry website.

### **Permission to reproduce material from other sources**

Not applicable.

### **Abstract**

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**Methods:** We included 27,865 cases registered between January 2020 and February 2021 in the COVID-19 Registry of Japan to examine the relationship between the National Early Warning Score (NEWS) of COVID-19 patients on the day of admission and the prefecture where the patients live. A hierarchical Bayesian model was used to examine the random effect of each prefecture in addition to the patients’ backgrounds. In addition, we compared the results of two models; one model included the number of beds secured for COVID-19 patients in each prefecture as one of the fixed effects, and the other model did not.

**Results:** The results indicated that the prefecture had a substantial impact on the severity of COVID-19 on admission. Even when considering the effect of the number of beds separately, the heterogeneity caused by the random effect of each prefecture affected the severity of the case on admission.

**Conclusions:** Our analysis revealed a possible association between regional heterogeneity and increased/decreased risk of severe COVID-19 infection on admission. This heterogeneity was derived not only from the number of beds secured in each prefecture but also from other factors.

Keywords: COVID-19; severity; regional heterogeneity; hierarchical Bayesian model

### **Introduction**

Coronavirus disease 2019 (COVID-19), which is caused by the SARS-CoV-2 virus, has become a global health threat, imposing a substantial disease burden on our society.<sup>1</sup> Although it has fluctuated, the epidemic has continued.<sup>2</sup>

COVID-19 is more infectious than other respiratory tract infections,<sup>3</sup> such as influenza, and is sometimes fatal to the elderly and those with underlying medical conditions. Considering these characteristics, the capacity of healthcare facilities for COVID-19 patients is an important factor in the management of newly infected COVID-19 patients.

When we consider countermeasures against COVID-19, the proportion of patients with severe disease is extremely important.<sup>4–6</sup> Mild and/or asymptomatic cases can be easily managed as they need no specific treatment. Conversely, severe cases often require intensive, multidisciplinary care. Furthermore, the duration of the disease in severe cases is generally longer than that of other viral pneumonias<sup>7</sup> and therefore places a greater burden on healthcare capacity. It is important, therefore, to precisely recognize the factors associated with the severity of COVID-19. For example, new variants may contribute to the severity of COVID-19 cases.<sup>8</sup> However, such variants are not the only determinants of severity; age, sex, past medical history, and many other factors have been attributed to the severity of COVID-19.<sup>5,9,10</sup> In addition, it is conceivable that there are other factors influencing the severity of COVID-19 aside from such biological aspects.

In Japan, the number and proportion of severe COVID-19 cases vary by prefecture. This phenomenon seems difficult to explain; nevertheless, there are differences in the management of COVID-19 cases among prefectures, and these differences may contribute to the capacity of healthcare facilities in each prefecture. Understanding the extent of such regional differences will help us tailor the countermeasures against COVID-19 more appropriately in each prefecture. The main objective of our study was to examine this regional heterogeneity quantitatively.

## Methods

We included 27,865 cases registered between January 2020 and February 2021 in the COVID-19 Registry of Japan (COVIREGI-JP)<sup>11</sup>. We used a Bayesian hierarchical model to construct a prefecture-specific random intercept to evaluate the effect of regional heterogeneity.

The capacity of medical facilities can be evaluated by the number of hospital beds; however, the differences in health policies against COVID-19 among local municipalities should also be taken into consideration as the planning of hospital bed distribution and the priority of hospitalization indication are influenced by the policy of each local municipality. Considering this, we constructed two models: one which included the number of beds secured for COVID-19 patients in each prefecture as a fixed effect (model B) and one which did not (model A).

The independent variable was the National Early Warning Score (NEWS)<sup>12</sup> of COVID-19 patients on the day of admission, and the explanatory variables for the fixed effect were sex, age of 65 years and older, and any risk factor of severe infection (cardiovascular disease, cerebrovascular disease, chronic respiratory disease, liver disease, diabetes, hypertension, obesity, dialysis or severe renal failure, and malignancy) for model A and the number of beds secured for COVID-19 patients in each prefecture for model B.

The independent variable, the NEWS score at the time of admission, was assumed to follow a Poisson distribution. We set four separate sampling chains, each consisting of 12,000 random samples, including 1,000 burnin. The sampling convergence was evaluated using the Gelman–Rubin statistics ( $\hat{R}$  below 1.1) and by visually inspecting a trace plot. All analyses were conducted using the R software version 4.0.5.<sup>13</sup>

## Results

Table 1 presents the demographic characteristics of the hospitalized COVID-19 cases registered in COVIREGI-JP. Tables 2 and 3 present the posterior distribution of the model parameters.

(Table 1)

(Table 2)

(Table 3)

All variables other than the number of beds included as fixed effects exhibited significant associations with the NEWS score at the time of admission in both models.

Figure 1 presents the choropleth graph of the median value of the posterior distribution of prefecture-specific random intercept in model A. Figure 2 presents the choropleth graph of the median value of the posterior distribution of prefecture-specific random intercept in model B.

(Figure 1)

(Figure 2)

Several prefectures exhibited a higher risk of higher NEWS scores upon admission, but these prefectures did not significantly change between model A and B. The Bayesian factor of model A over model B was 136988.360.

## Discussion

The results revealed the existing regional heterogeneity in the severity of COVID-19 cases at the time of admission in Japan. Our results suggest that the health policy of each prefecture might have an impact on the severity of hospitalized COVID-19 cases on admission.

A wide variety was observed in the median values of the posterior distribution of random effects for the different prefectures. That of Kanagawa prefecture in model A was 0.340 [95% Credible Interval (CrI) 0.269, 0.410], and that of Iwate prefecture was -0.431 [95% CrI -0.593, -0.268], indicating a substantial discrepancy in the severity of hospitalized COVID-19 cases between these two prefectures.

The posterior distribution of random effects in model B exhibited a similar trend to that in model A. The coefficient of Kanagawa prefecture in model B was 0.306 [95% CrI 0.213, 0.402], and that of Iwate prefecture was -0.413 [95% CrI -0.579, -0.249]. Other prefectures demonstrated similar results in both models, suggesting that factors other than the number of beds secured for COVID-19 patients (e.g., prioritization policy for COVID-19 case admission and number of physicians) had an impact on the severity of COVID-19 on admission.

We should take various factors into consideration when we interpret our results. The potential factors associated with the variation of the severity on admission could be viewed from two directions, namely, the local epidemiology of COVID-19 and the COVID-19 healthcare policy in each prefecture. From the former viewpoint, a regional surge in the number of COVID-19 patients or a rapid increase in the severity of disease due to new SARS-CoV-2 variants may contribute to the change in the severity on admission.<sup>8,14</sup> However, our analysis did not include patients with new SARS-CoV-2 variants as the study period was limited to before March 2021. While it is possible that COVID-19 cases due to new variants carry a greater risk of serious illness, there was a substantial regional heterogeneity in the severity of COVID-19 cases at the time of admission, as previous studies have demonstrated.<sup>15-17</sup> Presumably, variants are contributing factors to the severity of COVID-19 cases, but it should be noted that other factors also have a non-negligible influence on the severity of disease.

The latter point is relevant to policymakers (and healthcare providers) in the municipalities, mainly related to the on-site indication for hospitalization that is operated in each prefecture. The policy implemented to manage the waves of infection could be affected by the total medical capacity in the area. The number of beds secured for COVID-19 patients is one of the major resources.<sup>15,18</sup> The number of beds per population in each prefecture was included as one of the fixed effects in model B, and the random effect of each prefecture did not drastically change. Also, the number of physicians eligible for COVID-19 management may have an impact as this factor could create a bottleneck for patient acceptance.<sup>19</sup> However, it is difficult to precisely grasp the number of physicians who are engaging in COVID-19 patient management. This is because the

specialty of the medical doctor is not a good proxy for the number of physicians engaging in COVID-19 management under such an emergency period.<sup>20</sup>

The local government of each prefecture has established policy for the process of admission prioritization as a way of integrating the information from the regional medical situations, including the aforementioned factors, a strategy that may determine the variation in the severity on admission.<sup>21,22</sup> This means that there may be differences in whether a patient can be hospitalized and how long it takes for a patient to be hospitalized, even for clinically similar cases, depending on the prefecture they belong to.

Two types of strategy for symptomatic COVID-19 patients can be assumed. The following are simplified examples: 1) moderate to severe cases are admitted to hospital, whereas mild cases are managed at home or in a dedicated facility (severity on admission will increase), and 2) all patients, whether with mild or severe disease, are admitted to hospital (severity on admission will decrease). Both strategies have their own risks and benefits, and the local government of each prefecture has adopted each strategy depending on the height of each wave of the epidemic.

The strategy adopted should be evaluated by the outcomes of COVID-19 patients, damage to the medical system for non-COVID-19 diseases, and the impact on hospital and regional healthcare economy. A previous study in China demonstrated that the number of beds and medical staff per COVID-19 patient was negatively correlated with mortality.<sup>23</sup> Conversely, a recent study from Italy reported that greater access to hospitals did not affect the mortality of COVID-19 patients older than 80 years but affected that of patients younger than 80 years,<sup>24</sup> suggesting that the best approach may be to change the strategy according to age group or other properties of the patients. Evaluation of the regional policy could provide important insights to construct a better healthcare system against COVID-19 and other emerging infectious diseases.

Our analysis had several limitations. First, we examined data solely from Japan; thus, it is not appropriate to generalize our results globally. Nevertheless, it is easy to imagine that, even in other countries, there would be differences in health policies among local authorities and that they might have an impact on the management of COVID-19 cases. Second, we could not include other confounding factors, such as human resources and variance of SARS-CoV-2; these aspects should be addressed in future studies.

In conclusion, our analysis revealed a possible association between prefecture and an increased/decreased risk of severe COVID-19 infection at the time of admission. In addition, the number of beds secured for COVID-19 patients in each prefecture is not a single cause of such heterogeneity; therefore, other factors could be significant for the management of COVID-19 cases in Japan. Countermeasures against COVID-19 will be more appropriate if we take these insights into consideration.

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**Table 1. Characteristics of registered patients**

Variable		Number
Sex	Sex	
Male	Male	16152 (58%)
Female	Female	11701 (42%)
Other	Other	9 (0%)
Days from symptom onset to hospitalization	Days from symptom onset to hospitalization	5 [2, 7]
Age		57 [41, 73]
	0-64	16927 (60.7%)
	65-	10938 (39.3%)
Ethnicity		
Japanese	Japanese	26407 (95.8%)
Other ethnicity	Other ethnicity	1156 (4.2%)
Smoking history		
Former or current smoker	Former or current smoker	10246 (36.9%)
Never	Never	
Unknown	Unknown	12771 (46.0%)
		4771 (17.2%)
Drinking alcohol		
Daily (3 cans per day)	Daily (3 cans per day)	2087 (7.6%)
Occasional	Occasional	
None	None	9301 (34.1%)
Unknown	Unknown	9179 (33.6%)
		6738 (24.7%)
BMI	BMI	23.5 [20.9, 26.5]
Contact history within 14 days before onset	Contact history within 14 days before onset	
Travel to COVID-19 countries	Travel to COVID-19 countries	432 (1.6%)
Contact with COVID-19 patients	Contact with COVID-19 patients	13934 (50.3%)
NEWS score		
0-4	0-4	21568 (77.4%)
5-6	5-6	2320 (8.3%)
7-	7-	1759 (6.3%)
Unknown	Unknown	2218 (8%)
No oxygen administration during admission	No oxygen administration during admission	17530 (62.9%)
Oxygen administration during admission	Oxygen administration during admission	8844 (31.7%)
Ventilator use during admission	Ventilator use during admission	1483(5.3%)
Comorbidities	Comorbidities	
No comorbidity	No comorbidity	13659 (49.1%)
Any comorbidity	Any comorbidity	14206 (50.9%)
Cerebrovascular Disease	Cerebrovascular Disease	1738 (6.2%)
Bronchial Asthma	Bronchial Asthma	1479 (5.3%)
COPD/Chronic Lung Disease	COPD/Chronic Lung Disease	1050 (3.8%)
Liver Dysfunction	Liver Dysfunction	688 (2.5%)
Hypertension	Hypertension	8239 (29.6%)
Hyperlipidemia	Hyperlipidemia	4001 (14.4%)
Diabetes Mellitus	Diabetes Mellitus	4693 (16.8%)
Obesity diagnosed by physicians	Obesity diagnosed by physicians	1686 (6.1%)

Variable		Number
Moderate to Severe Renal Dysfunction/Hemodialysis	Moderate to Severe Renal Dysfunction/Hemodialysis	471 (1.7%)
Solid Tumor/Metastatic Solid Tumor	Solid Tumor/Metastatic Solid Tumor	1062 (3.8%)
Leukemia/Lymphoma	Leukemia/Lymphoma	171 (0.6%)
Collagen Disease	Collagen Disease	356 (1.3%)
HIV/AIDS	HIV/AIDS	55 (0.2%)
Outcome	Outcome	
Discharge	Discharge	20872 (74.9%)
Transfer to a different hospital	Transfer to a different hospital	3326 (11.9%)
Transfer to non-medical facility	Transfer to non-medical facility	1331 (4.8%)
Transfer to long-term care facility	Transfer to long-term care facility	1043 (3.7%)
Death	Death	1285 (4.6%)

Numbers with brackets represent absolute number and percentage.

Numbers with square brackets represent median value and interquartile range.

**Table 2. Posterior parameter distribution of hierarchical Bayesian model A**

Parameter	Median	95% credible interval	R-hat
Fixed effects			
Intercept	0.288	0.223, 0.353	1.005
Age 65 and older	0.293	0.275, 0.312	1.000
Male	0.194	0.177, 0.211	1.000
Having any risk factor	0.351	0.332, 0.370	1.000
Random effects			
Hokkaido	-0.051	-0.126, 0.024	1.004
Aomori	-0.283	-0.482, -0.078	1.001
Iwate	-0.431	-0.593, -0.268	1.001
Miyagi	0.010	-0.092, 0.110	1.002
Akita	-0.100	-0.439, 0.229	1.000
Yamagata	-0.166	-0.358, 0.023	1.000
Fukushima	0.027	-0.074, 0.131	1.002
Ibaraki	-0.036	-0.139, 0.066	1.002
Tochigi	0.091	-0.018, 0.206	1.001
Gunma	-0.132	-0.225, -0.039	1.003
Saitama	0.220	0.149, 0.291	1.004
Chiba	-0.053	-0.126, 0.017	1.004
Tokyo	0.007	-0.058, 0.074	1.005
Kanagawa	0.340	0.269, 0.410	1.004
Niigata	-0.201	-0.319, -0.084	1.002
Toyama	0.247	0.106, 0.385	1.001
Ishikawa	0.191	0.100, 0.283	1.002
Fukui	-0.179	-0.317, -0.043	1.001
Yamanashi	0.044	-0.181, 0.259	1.000
Nagano	0.067	-0.023, 0.153	1.003
Gifu	-0.030	-0.119, 0.057	1.003
Shizuoka	0.012	-0.078, 0.101	1.003

Parameter	Median	95% credible interval	R-hat
Aichi	0.190	0.118, 0.266	1.004
Mie	0.056	-0.044, 0.154	1.002
Shiga	-0.076	-0.168, 0.015	1.002
Kyoto	0.222	0.140, 0.303	1.003
Osaka	0.263	0.195, 0.330	1.005
Hyogo	0.116	0.043, 0.187	1.004
Nara	-0.054	-0.139, 0.032	1.003
Wakayama	-0.393	-0.553, -0.237	1.001
Tottori	-0.116	-0.317, 0.085	1.001
Shimane	-0.056	-0.303, 0.194	1.000
Okayama	-0.121	-0.233, -0.008	1.002
Hiroshima	-0.136	-0.217, -0.053	1.003
Yamaguchi	-0.078	-0.197, 0.037	1.001
Tokushima	0.001	-0.195, 0.194	1.000
Kagawa	0.214	0.100, 0.335	1.001
Ehime	-0.431	-0.661, -0.210	1.001
Kochi	0.144	0.070, 0.221	1.004
Fukuoka	0.257	-0.056, 0.571	1.000
Saga	0.126	0.025, 0.227	1.002
Nagasaki	0.099	0.004, 0.191	1.003
Kumamoto	0.073	-0.087, 0.233	1.001
Oita	0.246	0.117, 0.378	1.001
Miyazaki	-0.249	-0.412, -0.095	1.001
Kagoshima	0.140	0.063, 0.217	1.003
Okinawa	0.202	0.154, 0.257	1.002

**Table 3. Posterior parameter distribution of hierarchical Bayesian model B**

Parameter	Median	95% credible interval	R-hat
Fixed effects			
Intercept	0.387	0.193, 0.575	1.005
Age 65 and older	0.293	0.275, 0.312	1.000
Male	0.194	0.177, 0.211	1.000
Having any risk factor	0.351	0.332, 0.470	1.000
Number of beds secured for COVID-19 patients	-0.004	-0.010, 0.003	1.000
Random effects			
Hokkaido	-0.016	-0.115, 0.081	1.000
Aomori	-0.312	-0.517, -0.105	1.000
Iwate	-0.413	-0.579, -0.249	1.000
Miyagi	-0.030	-0.157, 0.089	1.000
Akita	-0.099	-0.434, 0.230	1.000
Yamagata	-0.182	-0.381, 0.003	1.000
Fukushima	0.024	-0.079, 0.125	1.000
Ibaraki	-0.052	-0.162, 0.051	1.000
Tochigi	0.073	-0.042, 0.189	1.000
Gunma	-0.153	-0.251, -0.052	1.001
Saitama	0.195	0.112, 0.278	1.001
Chiba	-0.070	-0.146, 0.008	1.001
Tokyo	0.045	-0.053, 0.139	1.000

Parameter	Median	95% credible interval	R-hat
Kanagawa	0.306	0.213, 0.402	1.001
Niigata	-0.205	-0.323, -0.090	1.000
Toyama	0.318	0.129, 0.513	1.000
Ishikawa	0.179	0.088, 0.273	1.001
Fukui	-0.155	-0.295, -0.006	1.000
Yamanashi	0.066	-0.153, 0.295	1.000
Nagano	0.049	-0.046, 0.141	1.000
Gifu	0.001	-0.103, 0.107	1.000
Shizuoka	-0.036	-0.159, 0.089	1.000
Aichi	0.152	0.054, 0.254	1.001
Mie	0.041	-0.062, 0.143	1.000
Shiga	-0.081	-0.174, 0.007	1.000
Kyoto	0.189	0.092, 0.291	1.001
Osaka	0.250	0.177, 0.321	1.001
Hyogo	0.075	-0.028, 0.177	1.001
Nara	-0.048	-0.133, 0.038	1.001
Wakayama	-0.338	-0.529, -0.154	1.000
Tottori	-0.033	-0.295, 0.218	1.000
Shimane	-0.031	-0.286, 0.215	1.000
Okayama	-0.137	-0.252, -0.021	1.001
Hiroshima	-0.169	-0.270, -0.068	1.001
Yamaguchi	-0.048	-0.179, 0.081	1.000
Tokushima	-0.011	-0.213, 0.179	1.000
Kagawa	0.193	0.069, 0.317	1.000
Ehime	-0.423	-0.653, -0.201	1.000
Kochi	0.102	-0.001, 0.211	1.001
Fukuoka	0.276	-0.034, 0.601	1.000
Saga	0.147	0.041, 0.255	1.000
Nagasaki	0.109	0.015, 0.203	1.000
Kumamoto	0.092	-0.069, 0.260	1.000
Oita	0.243	0.114, 0.374	1.000
Miyazaki	-0.257	-0.421, -0.101	1.000
Kagoshima	0.172	0.072, 0.265	1.000
Okinawa	0.200	0.153, 0.256	1.000

**Figure 1. Choropleth map of prefecture-specific random effect on the severity of COVID-19 cases at the time of admission in model A**

Thick colors indicate higher risk of higher NEWS score on admission.

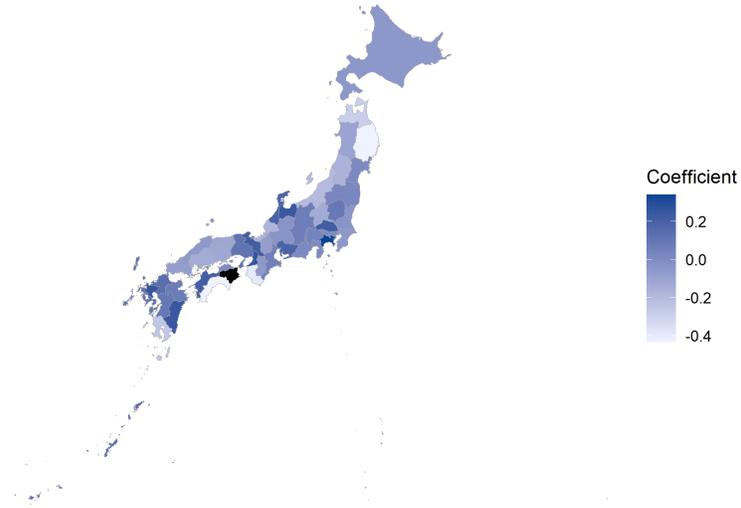
Black color (Tokushima prefecture) represents N/A as there are no registered patients in this prefecture.

**Figure 2. Choropleth map of prefecture-specific random effect on the severity of COVID-19 cases at the time of admission in model B**

Thick colors indicate higher risk of higher NEWS score on admission.

Black color (Tokushima prefecture) represents N/A as there are no registered patients in this prefecture.

Prefectural heterogeneity of impact on COVID-19 severity on admission



Prefectural heterogeneity of impact on COVID-19 severity on admission

