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Original Article

Impact of regional heterogeneity on the severity of COVID-19

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ABSTRACT

The main objective of the study is to assess the impact of regional heterogeneity on the severity of COVID-19 in Japan. 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. Additionally, 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. 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. 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.

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 [1]. Although it has fluctuated, the epidemic has continued [2].

COVID-19 is more infectious than other respiratory tract infections [3], 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 [4]. 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 [5] 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 [6]. 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 [4,7]. 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, in other words, “regional heterogeneity” which includes multiple factors such as differences in the management of COVID-19 cases, diagnosis processes, capacity of healthcare facilities, and so forth. We had used the term to mean the various factors that affect the severity of COVID-19 cases at the time of admission, 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.

We included 27,865 cases registered between January 2020 and February 2021 in the COVID-19 Registry of Japan (COVIREGI-JP) [8]. 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-

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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) [9], which is a tool developed by the Royal College of Physicians to improve the detection of and response to clinical deterioration in adult patients and showed a good performance in the assessment of COVID-19 patients' severity [10], 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 (on March 17, 2021) [11] in each prefecture for model B.

The independent variable, the NEWS 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 1000 burnin. The sampling convergence was evaluated using the Gelman–Rubin statistics (R-hat below 1.1) and by visually inspecting a trace plot. All analyses were conducted using the R software version 4.0.5 [12].

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. Patients' informed consent was obtained in the form of opt-out on the registry website.

Table 1 presents the demographic characteristics of the hospitalized COVID-19 cases registered in COVIREGI-JP. Table S1 in the supplementary file represents the accumulated number of COVID-19 patients and population in each prefecture in Japan. Tables S2 and S3 in the supplementary file present the posterior distribution of the model parameters.

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.

In model A, posterior distribution of random effect of Kanagawa prefecture was 0.340 [95% Credible Interval (CrI) 0.269–0.410], and that of Iwate prefecture was -0.431 [95% CrI -0.593 to -0.268]. In model B, that of Kanagawa prefecture was 0.306 [95% CrI 0.213–0.402], and that of Iwate prefecture was -0.413 [95% CrI -0.579 to -0.249].

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

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 Bayes factor of model A over model B was 136988.360.

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.

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 [6]. 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

Table 1
Characteristics of registered patients.

Variable	Number
Sex	
Male	16152 (58%)
Female	11701 (42%)
Other	9 (0%)
Days from symptom onset to hospitalization	5 [2, 7]
Age	57 [41, 73]
0–64	16927 (60.7%)
65–	10938 (39.3%)
Ethnicity	
Japanese	26407 (95.8%)
Other ethnicity	1156 (4.2%)
Smoking history	
Former or current smoker	10246 (36.9%)
Never	12771 (46.0%)
Unknown	4771 (17.2%)
Drinking alcohol	
Daily (3 cans per day)	2087 (7.6%)
Occasional	9301 (34.1%)
None	9179 (33.6%)
Unknown	6738 (24.7%)
BMI	23.5 [20.9, 26.5]
Contact history within 14 days before onset	
Travel to COVID-19 countries	432 (1.6%)
Contact with COVID-19 patients	13934 (50.3%)
NEWS score	
0–4	21568 (77.4%)
5–6	2320 (8.3%)
7–	1759 (6.3%)
Unknown	2218 (8%)
No oxygen administration during admission	17530 (62.9%)
Oxygen administration during admission	8844 (31.7%)
Ventilator use during admission	1483 (5.3%)
Comorbidities	
No comorbidity	13659 (49.1%)
Any comorbidity	14206 (50.9%)
Cerebrovascular Disease	1738 (6.2%)
Bronchial Asthma	1479 (5.3%)
COPD/Chronic Lung Disease	1050 (3.8%)
Liver Dysfunction	688 (2.5%)
Hypertension	8239 (29.6%)
Hyperlipidemia	4001 (14.4%)
Diabetes Mellitus	4693 (16.8%)
Obesity diagnosed by physicians	1686 (6.1%)
Moderate to Severe Renal Dysfunction/Hemodialysis	471 (1.7%)
Solid Tumor/Metastatic Solid Tumor	1062 (3.8%)
Leukemia/Lymphoma	171 (0.6%)
Collagen Disease	356 (1.3%)
HIV/AIDS	55 (0.2%)
Outcome	
Discharge	20872 (74.9%)
Transfer to a different hospital	3326 (11.9%)
Transfer to non-medical facility	1331 (4.8%)
Transfer to long-term care facility	1043 (3.7%)
Death	1285 (4.6%)

Numbers with brackets represent absolute number and percentage.

Numbers with square brackets represent median value and interquartile range.

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 [13]. 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 [13]. 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

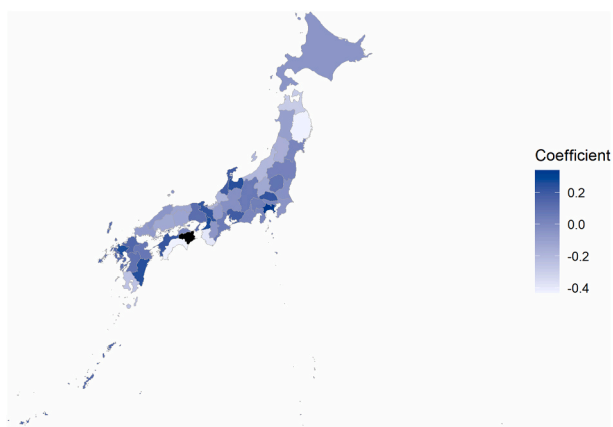


Fig. 1. Choropleth map of prefecture-specific random effect on the severity of COVID-19 cases at the time of admission in model A. Thick colors indicate higher risk of higher NEWS score on admission. Black color (Tokushima prefecture) represents N/A as there are no registered patients in this prefecture.



Fig. 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.

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 [14]. 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 [15].

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.

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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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.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jiac.2021.12.032>.

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