



Inverse association between hypertension treatment and COVID-19 prevalence in Japan



Masako Kinoshita^{a,*}, Kazuaki Sato^{a,b}, Balachandar Vellingiri^c, Shawn J. Green^d, Masami Tanaka^{e,f}

^a Department of Neurology, National Hospital Organization Utano National Hospital, 8 Ondoyama-Cho, Narutaki, Ukyo-Ku, Kyoto 616-8255, Japan

^b Department of Neurology, Ijinkai Takada General Hospital, 28-1 Moriminami-cho, Ishida, Fushimi-ku, Kyoto 601-1495, Japan

^c Department of Human Genetics and Molecular Biology, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India

^d Lundquist Institute at Harbor-UCLA Medical Center, Lundquist Institute for Biomedical Innovation, Division of Cardiology, Harbor-UCLA Medical Center, 1124 W Carson St, Torrance, CA, 90502, United States

^e Kyoto MS Center, Kyoto Min-Iren Chuo Hospital, 16-1 Kasuga-Cho Nishinokyo, Nakagyo-Ku, Kyoto 604-8453, Japan

^f Department of Neurology, Kaikoukai Josai Hospital, 4-1 Kitahata-Cho, Nakamura-Ku, Nagoya 453-0815, Japan

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ABSTRACT

Objectives: Cell entry of SARS-CoV-2 depends on angiotensin-converting enzyme II. Angiotensin-converting enzyme II is homologous with, but acts antagonistically to, angiotensin-converting enzyme and has the critical function of protecting the lungs. Angiotensin-converting enzyme inhibitors are major antihypertensive agents. Thus, we aimed to analyze the impact of the prevalence of preexisting hypertension on the local spread of COVID-19.

Methods: Data on SARS-CoV-2 infection and the estimated number of patients who received medical treatment on the basis of disease classification using the International Statistical Classification of Diseases and Related Health Problems (10th Revision) in each prefecture were obtained from the official Japanese notifications database. We analyzed the association between the proportion of patients with each disease and SARS-CoV-2-infection prevalence.

Results: The ratio of patients treated for diseases of the circulatory system, especially hypertensive disorders, per population demonstrated the most significant negative correlation with SARS-CoV-2-infection prevalence (Spearman's rank correlation, $P < 0.01$). Age group analysis revealed a significant negative correlation in age groups 35–44, 45–54, 55–64, 75–84, and ≥ 85 .

Conclusions: Our findings suggest that hypertension treatment may play a protective role against the local spread of SARS-CoV-2 infection.

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Introduction

SARS-CoV-2 is the causative virus for COVID-19. Cell entry of SARS-CoV-2 depends on angiotensin-converting enzyme II (ACE2), which is a membrane-associated zinc peptidase, and transmembrane serine protease 2, which is a cellular serine protease (Zhou et al., 2020b; Hoffmann et al., 2020; Hirano and Murakami, 2020). ACE2 is homologous with, but acts antagonistically to, angiotensin-converting enzyme (ACE) and has the critical function of protecting the lungs from severe acute injury (Imai et al., 2005).

The renin-angiotensin-aldosterone system is an essential regulator of blood pressure. Thus, ACE inhibitors and angiotensin receptor blockers (ARBs) are commonly used as antihypertensive agents. Because both ACE inhibitors and ARBs increase ACE2 (Ferrario et al., 2005; Furuhashi et al., 2015), the possibility of these drugs having either the unfavorable effect of promoting SARS-CoV-2 cell entry or the beneficial effect of preventing acute lung distress in patients with hypertension remains controversial (Schiffirin et al., 2020; Shibata et al., 2020). Moreover, whether hypertension itself, as compared with other medical conditions, increases the risk of susceptibility to COVID-19 or disease severity, or impacts local COVID-19 spread, should be elucidated.

In a previous study, we demonstrated that routine infant Bacillus Calmette-Guérin (BCG) vaccination coverage in the younger generation had a significant impact on the prevention of local COVID-19 spread in Japan (Kinoshita and Tanaka, 2020). In

* Corresponding author.

E-mail addresses: machak@kuhp.kyoto-u.ac.jp (M. Kinoshita), neuroncc@kuhp.kyoto-u.ac.jp (K. Sato), geneticbala@buc.edu.in (B. Vellingiri), shawn.green@lundquist.org (S.J. Green), nra17777@nifty.com (M. Tanaka).

this study, we analyzed the effect of the proportion of local patients with preexisting hypertension and other medical conditions per population on the local prevalence of patients with COVID-19 infection, SARS-CoV-2 polymerase chain reaction-positive (PCR+) individuals, and COVID-19 deaths in Japanese prefectures.

Materials and methods

Prevalence of patients with COVID-19, SARS-CoV-2 PCR+ individuals, and COVID-19 deaths in each prefecture

Anonymous data on COVID-19 infection in Japan were obtained, as described in our previous study (Kinoshita and Tanaka, 2020). In

brief, the numbers of patients with COVID-19, SARS-CoV-2-PCR+ individuals, and COVID-19 deaths among Japanese residents in each prefecture were extracted from official notification records of the Ministry of Health, Labour and Welfare of Japan (Ministry of Health, Labour and Welfare of Japan, 2020). Data regarding patient age and sex were not available.

In Japan, COVID-19 diagnosis is on the basis of the Infectious Disease Surveillance System, in accord with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases. Until March 29, 2020, the Act applied to individuals with symptoms suggestive of SARS-CoV-2 infection. Thereafter, the Act has also been applied to the asymptomatic population, and the official number of patients has also included

Table 1

The estimated number of patients nationwide (thousands, per day) according to the Patient Survey in 2017 and its correlation with COVID-19 prevalence (* $P < 0.05$, ** $P < 0.01$).

Classification of diseases	Number of patients	Spearman's ρ
I. Certain infectious and parasitic diseases	189.6	-0.123
Intestinal infectious diseases	34.0	-0.199
Tuberculosis	4.3	0.304*
Viral infections characterized by skin and mucous membrane lesions	62.4	-0.079
Mycoses	39.9	0.064
II. Neoplasms	391.7	-0.398**
Malignant neoplasms	309.7	-0.417**
Carcinoma in situ of stomach	32.4	-0.342*
Carcinoma in situ of colon and rectum	48.4	-0.254
Carcinoma in situ of trachea, bronchus, and lung	34.9	-0.342*
III. Diseases of the blood and blood-forming organs and disorders involving the immune system	27.0	-0.037
IV. Endocrine, nutritional and metabolic diseases	475.9	-0.287
Disorders of the thyroid gland	33.1	0.000
Diabetes mellitus	242.9	-0.299*
V. Mental and behavioural disorders	512.9	-0.360
Schizophrenia, schizotypal and delusional disorders	216.2	-0.381**
Mood [affective] disorders	119.5	-0.140
Neurotic, stress-related and somatoform disorders	64.9	-0.073
VI. Diseases of the nervous system	291.1	-0.352*
VII. Diseases of the eye and adnexa	370.2	0.020
Cataract	90.9	-0.034
VIII. Diseases of the ear and mastoid process	101.8	-0.236
IX. Diseases of the circulatory system	1117.5	-0.469**
Hypertensive diseases	652.5	-0.456**
Other forms of heart disease	198.2	-0.296*
Ischaemic heart diseases	70.6	-0.257
Cerebrovascular diseases	231.9	-0.387**
X. Diseases of the respiratory system	725.8	-0.098
Acute upper respiratory infections	249.7	0.058
Pneumonia	43.4	-0.053
Acute bronchitis/bronchiolitis	93.5	-0.432**
Bronchitis/emphysema	30.8	-0.036
Asthma	124.6	-0.139
XI. Diseases of the digestive system	1359.3	0.097
Dental caries	277.1	0.061
Gingivitis and periodontal diseases	469.2	0.085
Gastric/duodenal ulcer	23.7	0.142
Gastritis and duodenitis	66.7	-0.107
Diseases of the liver	34.3	0.001
XII. Diseases of the skin and subcutaneous tissue	315.2	0.081
XIII. Diseases of the musculoskeletal system and connective tissue	948.5	-0.196
Inflammatory polyarthropathies	54.0	-0.830
Arthrosis	219.4	-0.087
Dorsopathies	443.2	-0.220
Disorders of bone density and structure	61.7	-0.211
XIV. Diseases of the genitourinary system	371.8	-0.226
Glomerular and renal tubulo-interstitial diseases, and renal failure	188.7	-0.103
Hyperplasia of prostate	33.3	-0.304*
Disorders of breast and female pelvic organs	94.2	-0.106
XV. Pregnancy, childbirth and the puerperium	33.4	-0.158
Hypertensive disorders in pregnancy	0.8	0.239
XVI. Certain conditions originating in the perinatal period	10.1	-0.153
XVII. Congenital malformations, deformations and chromosomal abnormalities	19.8	-0.053
XVIII. Symptoms, signs and abnormal findings, not elsewhere classified	93.2	-0.172
XIX. Injury, poisoning and certain other consequences of external causes	436.7	-0.057
Fracture	196	0.007

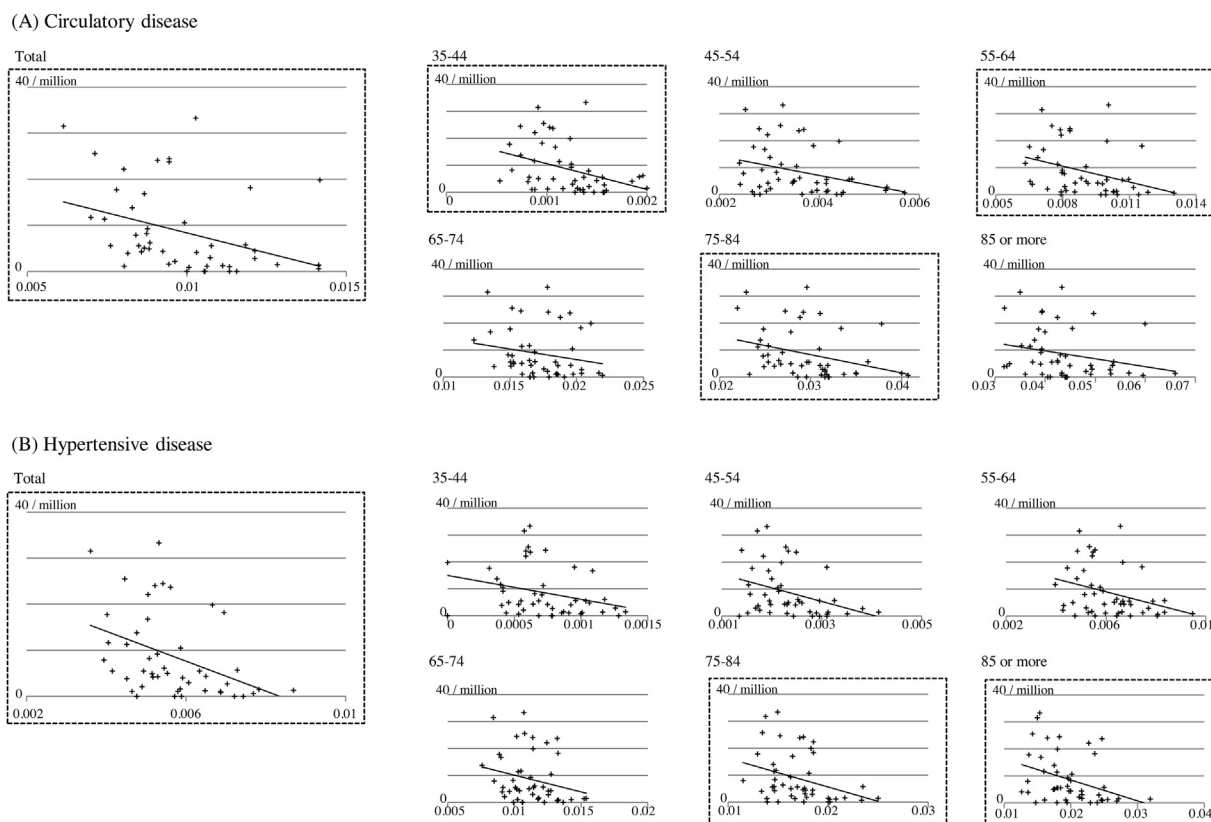


Figure 1. Correlation between the prevalence of patients with SARS-CoV-2 infection and (A) diseases of the circulatory system or (B) hypertensive diseases, by age group. Scatter plot of the prevalence of patients with SARS-CoV-2 infection (ordinate) against related factors (abscissa). Regression lines are shown for reference.

Table 2

Correlation coefficient (Spearman's ρ) between COVID-19 prevalence and diseases of the circulatory system, by age group.

Classification of diseases	Total*	35–44	45–54	55–64	65–74	75–84	≥85
IX. Circulatory	−0.469**	−0.421**	−0.295*	−0.412**	−0.297*	−0.441**	−0.321*
Hypertensive	−0.456**	−0.306*	−0.370*	−0.335*	−0.266	−0.367*	−0.383**

* $P < 0.05$.

** $P < 0.01$.

PCR+ individuals presenting no clinical symptoms. In April 2020, the Japanese Prime Minister declared a state of emergency. Thus, in this study, data collected as of March 29, 2020, were used.

The crude prevalence of SARS-CoV-2 infection in each prefecture was calculated as the number of patients divided by the number of individuals in each prefecture on October 1, 2019, as estimated by the Statistics Bureau, Ministry of Internal Affairs and Communications of Japan (Statistics Bureau, Ministry of Internal Affairs and Communications of Japan, 2020).

Preexisting diseases

The estimated number of patients who received medical treatment in each prefecture was obtained from the Patient Survey of October 2017. The Patient Survey is run every 3 years by the Health Statistics Office, Ministry of Health, Labour and Welfare (Statistics Bureau, Ministry of Internal Affairs and Communications of Japan, 2020). The diseases were classified on the basis of the International Statistical Classification of Diseases and Related Health Problems (10th Revision) (Table 1, Supplementary Tables 1A–1C). The ratio of the estimated number of patients treated for each disease per day to the estimated number of

individuals on October 1, 2019, in each prefecture was used as a surrogate for the local prevalence of patients with the disease. Though the number of patients per day, as estimated by the Patient Survey, was much smaller than the crude number of patients, the data were suitable for correlation analyses among prefectures or comparison among diseases. Data on patient age and sex were not available.

Statistical analyses

As per the Kolmogorov–Smirnov test, variables did not exhibit a normal distribution. Therefore, non-parametric Spearman's rank correlation coefficient was employed to evaluate the correlation of SARS-CoV-2 prevalence with each preexisting disease using SPSS (version 16.0; IBM Japan, Tokyo, Japan). The significance level was set at $P = 0.01$.

Results

Prevalence data of patients with COVID-19, SARS-CoV-2-PCR+ individuals, and COVID-19 deaths in each prefecture have previously been reported (Kinoshita and Tanaka, 2020). The

2017 Patient Survey demonstrated that circulatory system disease (Chapter IX, International Statistical Classification of Diseases and Related Health Problems [10th Revision]) was the second-largest classification of the estimated number of patients nationwide (Table 1).

The prevalence of patients with COVID-19 on March 29, 2020, showed a significant negative correlation with the ratio of patients per population with diseases of the circulatory system, especially hypertensive disorders and cerebrovascular diseases that form its subcategory, and schizophrenia ($P < 0.01$) (Figure 1, Table 1). Considering that our previous study demonstrated an inverse association between the elderly population and SARS-CoV-2-infection prevalence (Kinoshita and Tanaka, 2020) and that the proportion of patients with hypertensive disorders increases with age, we further analyzed the correlation between SARS-CoV-2 infection and hypertension by age group. A significant negative correlation was shown between SARS-CoV-2-infection prevalence and the ratio of hypertension in age groups 35–44, 45–54, 55–64, 75–84, and ≥ 85 (Figure 1 and Table 2).

Discussion

In this study, we analyzed the association of the ratio of local patients treated for preexisting hypertension and other medical conditions per population with SARS-CoV-2-infection prevalence in Japanese prefectures. The current study was the first to demonstrate that diseases of the circulatory system, especially treated hypertension, exhibited the strongest inverse correlation with the local spread of SARS-CoV-2 infection in Japan compared with a range of other diseases. Moreover, the correlation remained statistically significant after adjusting for the influence of age. Given prior reports indicating hypertension as a significant risk factor for COVID-19 incidence and severity (Zhou et al., 2020a; Wu et al., 2020), a plausible explanation for this unexpected inverse relationship is the potentially protective effect of antihypertensive medications.

The relationship between hypertension and COVID-19 has been controversial (Schiffrin et al., 2020). Initial studies in Wuhan, China, identified hypertension as the most common comorbidity in COVID-19 patients, especially those with lung injury (Zhou et al., 2020a; Wu et al., 2020). After the discovery of the cell-entry mechanism of SARS-CoV-2 (Zhou et al., 2020b; Hoffmann et al., 2020; Hirano and Murakami, 2020), the possibility of ACE inhibitors or ARBs having an unfavorable effect on COVID-19 secondary to the upregulation of ACE2 receptor sites theoretically facilitating viral cell entry has been a matter of great concern (Schiffrin et al., 2020; Shibata et al., 2020). However, in contrast to this line of reasoning, ACE2 has known protective pulmonary and vascular functions. Furthermore, decreased ACE2 expression is associated with worse outcomes in other respiratory diseases via down regulation of the ACE2/angiotensin-(1-7)/Mas axis. In concordance with this hypothesis, recent clinical studies in COVID-19 patients with hypertension have shown no increased risk of harm (Hasan et al., 2020) and further demonstrated a favorable role of renin-angiotensin system inhibitors (Meng et al., 2020; Adrish et al., 2020; Baral et al., 2020; Matsuzawa et al., 2020; Şenkal et al., 2020). A recent study revealed that ACE inhibitor use was associated with lower odds of COVID-19 among those aged ≥ 85 (An et al., 2021). In our study, the type of hypertensive medication could not be evaluated.

In Japan, calcium channel blockers are the most commonly used antihypertensives, and whereas ARBs are less often prescribed in hypertensive patients aged ≥ 75 , they are almost equally used in patients < 75 . In patients < 65 , ARBs narrowly become the most common antihypertensive medication class (Ishida et al., 2018). With the prevalence of hypertension increasing with age and our previous study demonstrating an inverse association between

ratios of the elderly population and SARS-CoV-2-infection prevalence (Kinoshita and Tanaka, 2020), an additional analysis was performed to adjust for the influence of age. Statistical significance was found in younger age groups, even those in their thirties or forties. The current study demonstrated a significant inverse correlation between cerebrovascular disease and COVID-19. Hypertension is one of the most important risk factors for cerebral infarction and cerebral hemorrhage, and absolute risk reduction can be achieved through optimal blood pressure control (Kannel et al., 1981; Tanaka et al., 1982; Thomopoulos et al., 2014). The use of ACE inhibitors or ARBs is recommended by the Japan Stroke Society considering the beneficial effects of improving insulin resistance, renal protection, and preventing atrial fibrillation (The Japan Stroke Society, 2019).

Severe COVID-19 outcomes are associated with endothelial dysfunction (Varga et al., 2020). ACE inhibitors and ARBs induce nitric oxide (NO) synthase, leading to the restoration of NO and improvement of endothelial dysfunction (Wagenaar et al., 2001; Palaniyappan et al., 2009). In addition, NO has direct antiviral activity in terms of preventing host-cell entry, virulence, or replication (Saura et al., 1999; Shulla et al., 2011; Green, 1995, 2020). Host defense via NO can be activated by BCG inoculation in animal studies (Green et al., 1994). This mechanism is possibly reinforced in Japan by the universal BCG vaccination policy. The abundant dietary nitrate content of traditional Japanese foods is a source of NO (Yamasaki 2020; Sobko et al., 2010).

In the present study, a significant inverse correlation was observed between schizophrenia and COVID-19. A recent study suggested the impact of a single nucleotide polymorphism (rs4702), located in the *FURIN*, on alveolar and neuron infection by SARS-CoV-2 *in vitro* (Dobrindt et al., 2020). The downregulation of *FURIN* expression, which is specific to the rs4702 G allele, has been associated with abnormal migration neurodevelopment leading to schizophrenia (Fromer et al., 2016; Hou et al., 2018; Schrode et al., 2019). The frequency of the rs4702 G allele in the Japanese population is relatively high (25.7%), whereas that in Yoruba Africans, the African ancestry in Southwest USA, or Luhya in Webuye, Kenya is negligible (SNPedia, 2020). Genetic preposition to SARS-CoV-2 infection warrants further studies.

In summary, the current study demonstrated that the proportion of patients treated for preexisting hypertension was inversely associated with local COVID-19 spread in Japan. Analysis by age group showed that the association remained statistically significant in patients in their thirties or forties. Antihypertensive medications, namely ACE inhibitors and ARBs, possibly play a protective role against COVID-19 via increases in ACE2 and NO.

Conflict of interest

None.

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Ethical approval

Ethical approval for this study was waived because we used previously published data that did not contain any personal information.

Author contributions

MK, KS, and MT contributed to the conceptualization and investigation. MK, KS, BV, SJG, and MT contributed to the

methodology. MK, KS, and MT performed data analysis. MK, KS, and TM contributed to the writing, original draft preparation, review, and editing. BV and SJG contributed to review and editing, and supervised the study. All authors contributed to the article and approved the submitted version.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.ijid.2021.05.071>.

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