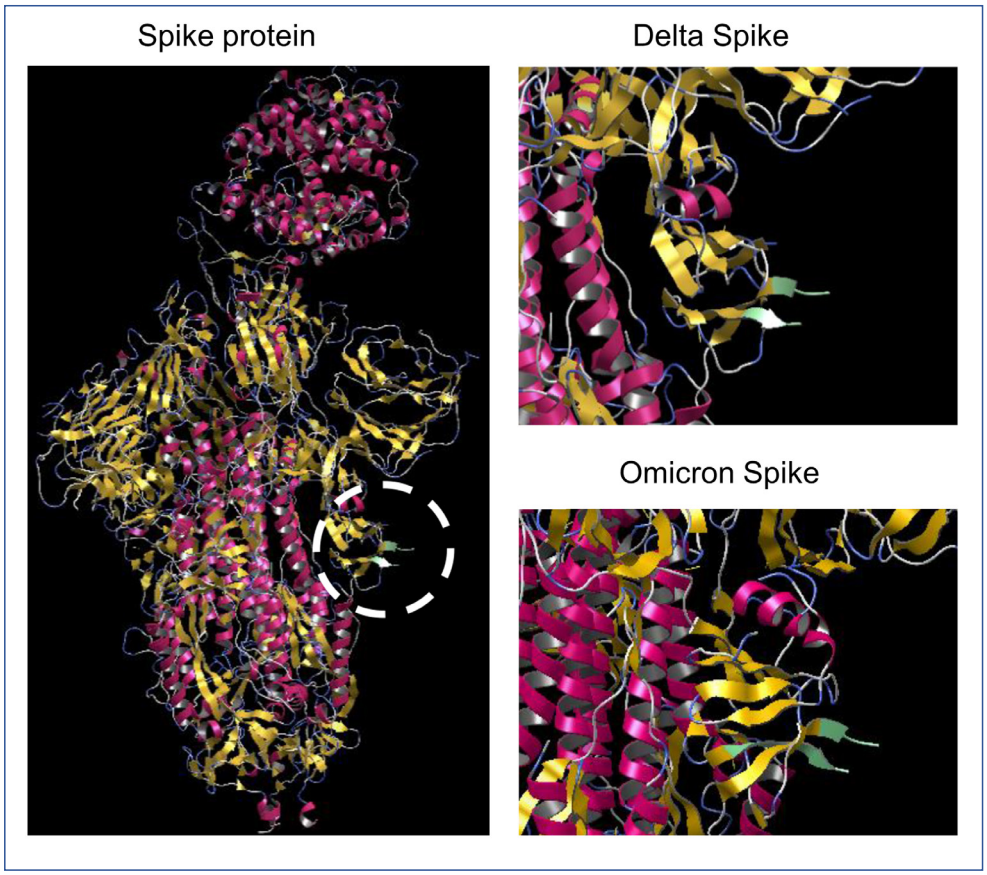
Print ISSN: 2434-9186 Online ISSN: 2434-9194

NCGM

GHM
Global Health & Medicine

Volume 4, Number 2
April, 2022

Special Topic: COVID-19 in Japan



Putative three-dimensional structures of the spike proteins of the Delta and Omicron variants (Page 87)

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Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English

Global Health & Medicine

Global Health & Medicine

Global Health & Medicine (Print ISSN 2434-9186, Online ISSN 2434-9194) is an international, open-access, peer-reviewed journal, published by the National Center for Global Health and Medicine (NCGM), which is a national research and development agency in Japan that covers advanced general medicine, basic science, clinical science, and international medical collaboration.

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Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
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Global Health & Medicine

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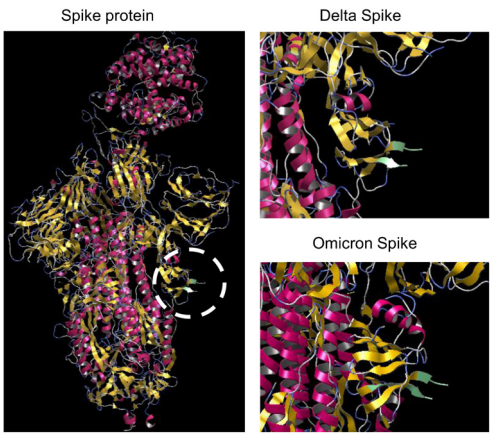
COVER FIGURE OF THIS ISSUE



Putative three-dimensional structures of the spike proteins of the Delta and Omicron variants. Structural data were derived from the protein data bank (PDB) database (Delta variant, PDB ID: 7w92, PDB DOI: 10.2210/pdb7W92/pdb; Omicron variant (BA.1), PDB ID: 7wk4, PDB DOI: 10.2210/pdb7WK4/pdb). Simulation was originally performed for this article using the open access software myPresto version 5.0. The left panel, the structure corresponding to the proposed superantigen is highlighted using a circle. The upper and lower right panels show the superantigen structures (enlarged) of the Delta and Omicron (BA.1) variants, respectively (Page 87).

Global Health & Medicine. 2022; 4(2):64-66.

EDITORIAL

DOI: 10.35772/ghm.2022.01036

COVID-19 in Japan: An update on national policy, research, clinical practice, and vaccination campaign

Peipei Song, Hiroaki Mitsuya*, Norihiro Kokudo*

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Abstract: As countries worldwide take steps such as vaccination campaigns to combat the COVID-19 pandemic, academia is actively promoting the timely sharing of scientific information across borders. As an international academic journal, *Global Health & Medicine* (GHM) has quickly accepted COVID-19-related papers and published results of series of studies since the beginning of 2020. In particular, the "First Special Issue on COVID-19" (April 2020) and the "Second Special Issue on COVID-19" (April 2021) included a wide range of articles presenting frontline data on the COVID-19 response in Japan, China, the United States, Italy, the United Kingdom, West Africa, and other various countries and areas worldwide. This "Third Special Issue on COVID-19" (April 2022) features the practical experiences of front-line clinicians, researchers, and other healthcare professionals from Japan and it presents updated data on *i*) national policy, *ii*) research, *iii*) clinical practice, and *iv*) the vaccination campaign. Our hope is that the rapid publication and sharing of information will help, in any way possible way, in the global fight against COVID-19.

***Keywords*:** COVID-19, SARS-CoV-2, vaccination, Omicron, BA.2 subvariant, XE subvariant, Japan

Japan has experienced six waves of the COVID-19 pandemic so far since the first domestic case of COVID-19 transmission was reported on January 16, 2020 (Figure 1). As of April 25, 2022, Japan had reported a cumulative total of 7,660,012 infected people and 29,308 deaths (*1*).

Japan's basic policy on COVID-19 is to curb the outbreak of infection, maintain the medical system, and focus on dealing with the severely ill. One of the most important response strategies, states of emergency, were declared four times, three of which were declared in 2021. During this period, Japan hosted the Tokyo 2020 Olympic (July 23-August 8, 2021) and Paralympic (August 24-September 5, 2021) Games, and began a massive vaccination campaign. As of April 25, 2022, the total number of vaccine doses administered has reached 268,822,890. Nationwide, 81.4% of the total population has received the first dose of the vaccine, 80.0% has received the second dose, and 50.8% has received the third dose (*2*).

As countries worldwide took steps such as vaccination campaigns to combat the COVID-19 pandemic, academia actively promoted the timely sharing of scientific information across borders. Indeed, facing with an unprecedented threat from COVID-19, the scientific community responded quickly to the outbreak by assisting the world by rapidly sharing research data and relevant findings (*3,4*). Such scientific information includes the route of transmission, transmissibility, history of human infection, effective clinical methods of managing at-risk populations and patients, laboratory information necessary to diagnose patients, and genetic sequencing information to assess virus stability.

Since its inception in October 2019, our journal – *Global Health & Medicine* (GHM) – has been dedicated to publishing high-quality original research that contributes to the advancement of global health and medicine, with the goal of creating a global information network for global health, basic sciences, and clinical sciences in the hope that they lead to novel clinical applications. Since its third issue (February 2020), GHM has quickly accepted COVID-19-related papers and published the results of many studies. In particular, the "First Special Issue on COVID-19" (April 2020) and the "Second Special Issue on COVID-19" (April 2021) included a wide range of articles presenting frontline data on the COVID-19 response in Japan, China, the United States, Italy, the United Kingdom, West Africa, and various countries and areas worldwide (Figure 2).

This "Third Special Issue on COVID-19" (April 2022) features the actual experiences of frontline clinicians and other healthcare professionals from Japan and it presents updated data on *i*) national policy, *ii*) research, *iii*) clinical practice, and *iv*) the vaccination campaign.

With respect to national policy, Dr. Ohmagari summarized the measures taken by the Tokyo Metropolitan Government in response to COVID-19 and

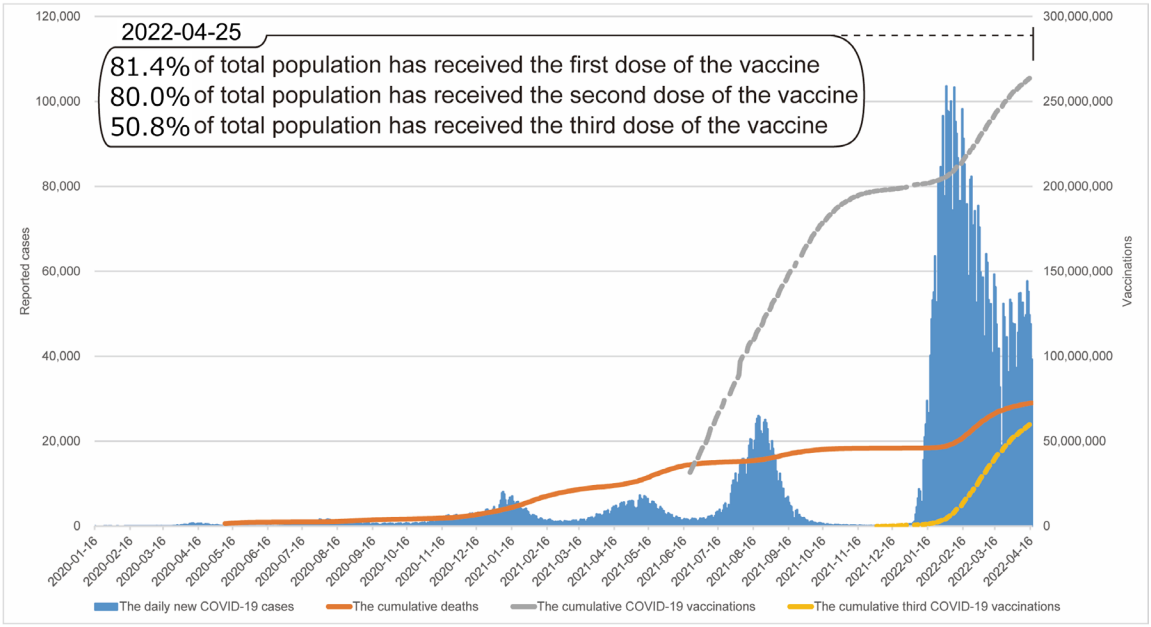

Figure 1. Number of reported COVID-19 cases and the vaccination campaign in Japan from 2020-2022. Data source: *https://www.mhlw.go.jp/stf/covid-19/open-data.html, https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html*

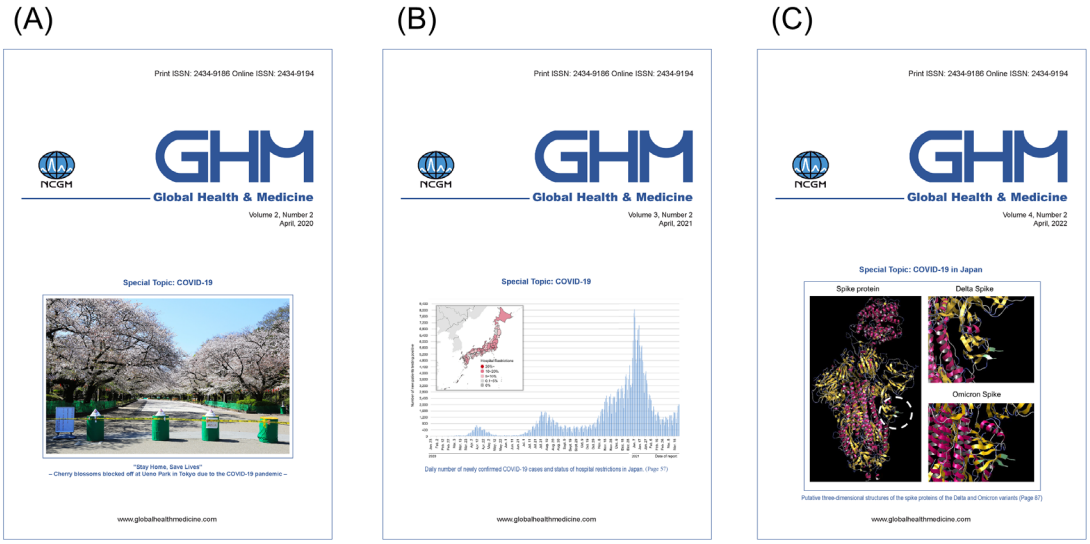

Figure 2. Series of special issues regarding COVID-19 published by *Global Health & Medicine*. (A) "First Special Issue on COVID-19" (April 2020), **(B)** "Second Special Issue on COVID-19" (April 2021), and **(C)** "Third Special Issue on COVID-19" (April 2022). The full articles are available from *http://globalhealthmedicine.com/site/archives.html*

he called for continued active maintenance of the health care system and the minimization of deaths, while normalizing social interactions. Akashi *et al.* presented their experience and implementation strategies to set up a "care and isolation facility" for mild COVID-19 cases in Tokyo by using existing hotels. Machida *et al.* described important national strategies, including legal measures by the government, infection control in high-risk areas, vaccine rollout, and prioritized hospitalization for high-risk patients in critical condition.

With respect to research, Ishizaka *et al.* reviewed the current status of "long COVID" in Japan and understanding of its molecular background. In addition, the feasibility of vaccination as a treatment for patients with long COVID was fully discussed.

With respect to clinical practice, Dr. Katagiri summarized the lessons learned for safe and adequate blood purification therapy in severe COVID-19. Tomidokoro *et al.* described the relationship between COVID-19 and cardiovascular diseases and its drastic consequences for Japanese patients in clinical settings. Minamimoto *et al.* analyzed the changes in the circumstances of cancer diagnoses during the COVID-19 pandemic in Tokyo, Japan, which they surmised based on FDG-PET/CT for cancer patients. The authors indicated that "the number of patients

receiving FDG-PET/CT in Tokyo was influenced by the COVID-19 epidemic; staging based on FDG-PET/CT had shifted to more advanced stages during the pandemic compared to that in pre-pandemic". Soh *et al.* shared their clinical experiences as emergency physicians performing endotracheal intubation for patients with COVID-19. Sekihara *et al.* analyzed the prognosis of Japanese patients with severe COVID-19 admitted to infectious disease intensive care unit during the pandemic caused by the Delta variant. Saito *et al.* described the clinical characteristics of and threshold cycle (Ct) values for the first 11 patients infected with the SARS-CoV-2 Omicron variant in Japan.

With respect to vaccination campaign, Nomoto *et al.* analyzed the impact of prioritized vaccinations for the elderly on the COVID-19 pandemic in Japan. Seto *et al.* emphasized the importance of promoting the proper use of anti-SARS-CoV-2 drugs and SARS-CoV-2 vaccines by hospital pharmacists and establishment of an adverse drug reaction reporting system. Matsumoto *et al.* reported the adverse reactions to and attitudes toward vaccines among young populations one month after receiving the second dose of mRNA-1273 in Japan. Dr. Ujiie emphasized the necessity of establishing an emergency regulatory approval system in Japan in response to the COVID-19 pandemic and challenges in developing domestically produced vaccines.

Although the past six waves of the pandemic in Japan have been relatively effectively contained nationwide, the uncertainty of the blow by the new Omicron variant and a potential seventh wave of the pandemic represent additional challenges in the immediate future. There are fears that as the highly infectious Omicron BA.2 (*5*) becomes mainstream, there will be even more infected people than during the past waves. In addition, Japan's first case of infection with the Omicron XE strain – a combination of the BA.1 and BA.2 subvariants, with a higher rate of infection than BA.2 subvariant – was also detected in a woman in her 30s who arrived at Narita Airport from the United States on March 26, 2022 (*6*).

Globally, national measures including vaccination campaigns, border quarantine, and domestic surveillance of mutant strains may continue in our combat with COVID-19. It is of note, however, that the requirement of mask wearing is being lifted in a number of countries and areas worldwide and no immediate increase of SARS-CoV-2-infected individuals has been seen in many such areas. In fact, the Centers for Disease Control and Prevention ruled that approximately 7 in 10 no longer need to wear masks in indoor public areas based on new guidance, as of April 25, 2022. On the other hand, there are surges in the numbers of newly infected in the US and other areas, prompting healthcare officials to re-expand recommendations to wear masks indoors in public spaces. Although we are to receive mixed signals in recommendations in the immediate future, it is obviously critical for us to stay vigilant on scientifically well-determined outcomes.

As an international academic journal, GHM will continue to work with authors to publish academic articles regarding COVID-19 in a determined effort to rapidly disseminate reliable information to promote science-based responses to combat this global pandemic.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Ministry of Health, Labour and Welfare. Current status of COVID-19 and the response to it by the Ministry of Health, Labour and Welfare (April 25, 2022 edition). *https://www.mhlw.go.jp/stf/newpage_25269.html* (accessed April 26, 2022). (in Japanese)
2. Prime Minister's Office of Japan. The new COVID-19 vaccine. *https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html* (April 25, 2022 edition). (accessed April 26, 2022). (in Japanese)
3. Mitsuya H, Kokudo N. Sustaining containment of COVID-19: Global sharing for pandemic response. Glob Health Med. 2020; 2:53-55.
4. Song P, Karako T. Scientific solidarity in the face of the COVID-19 pandemic: Researchers, publishers, and medical associations. Glob Health Med. 2020; 2:56-59.
5. Yu J, Collier AY, Rowe M, Mardas F, Ventura JD, Wan H, Miller J, Powers O, Chung B, Siamatu M, Hachmann NP, Surve N, Nampanya F, Chandrashekar A, Barouch DH. Neutralization of the SARS-CoV-2 Omicron BA.1 and BA.2 variants. N Engl J Med. 2022 Mar 16. doi: 10.1056/NEJMc2201849.
6. National Institute of Infectious Diseases. About the recombinant Omicron strain. *https://www.niid.go.jp/niid/ja/2019-ncov/2551-cepr/11073-cepr-b11529-re.html* (accessed April 16, 2022). (in Japanese)

Received April 20, 2022; Revised April 26, 2022; Accepted April 27, 2022.

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Global Health & Medicine. 2022; 4(2):67-70.

DOI: 10.35772/ghm.2022.01017

How did the Tokyo Metropolitan Government respond to COVID-19?

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Abstract: Tokyo Metropolitan Area is the most populous metropolitan area in the world. While cities around the world are struggling to cope with COVID-19, the number of new positives and deaths in Tokyo has so far been relatively contained compared to other large metropolitan areas. In Japan, infection control measures do not prohibit people from moving around during a COVID-19 outbreak. However, people are not only refraining from travel and social activities at the request of the government, but are also using their own judgment to avoid risk based on information about the infectious disease. This plays an extremely important role in Japan's infection control measures. Expectations are high in Japan for maintaining the health care system and minimizing deaths. It is necessary to steadily respond to these expectations while normalizing social functions.

***Keywords*:** health care system, infection prevention, policy, public awareness, Japan

Introduction

The population of Tokyo is 13,988,129 as of January 1, 2022 (*1*), and the Tokyo Metropolitan Area is the most populous metropolitan area in the world. In general, the COVID-19 epidemic tends to be more pronounced in metropolitan areas. Even in Japan, it is known that epidemic waves are often preceded by epidemics in metropolitan areas such as Tokyo and Osaka before other areas. For this reason, COVID-19 control in Tokyo is critically important for Japan as a whole. Although Tokyo is such a large metropolitan area, the total number of cases has been low so far compared to other metropolitan areas such as New York and London. In order to provide material for considering this difference, this article introduces the infection control measures for COVID-19 in Tokyo.

Overview of COVID-19 infections in Tokyo

As of February 17, 2022, the cumulative number of positive cases of COVID-19 in Tokyo was 863,984, and the estimated number of deaths as of the same date was 3,376 (*2*). The cumulative number of patients as of February 17, 2022 in New York, USA was 4,876,264, and the cumulative number of deaths as of the same date was 66,601 (*3*). The number of cumulative COVID-19 cases and deaths in Tokyo has remained relatively low.

Progress of the administrative response by Tokyo Metropolitan Government to date

In the event of a large-scale pandemic, Japan uses the Act on Special Measures against Novel Influenza, *etc*. to respond by declaring a state of emergency and issuing priority measures. This is implemented to prevent the spread of the pandemic in order to contain the negative impact on medical care and society itself. The declaration of a state of emergency is a request from the Prime Minister to the prefectural governors to take measures to protect the lives, health, and livelihood of the people. Specific measures to prevent the spread of infectious diseases are decided and announced, such as refraining from going out, restricting the holding of events, and shortening the business hours of restaurants.

The Priority Measures for Prevention of Spread of Infectious Diseases was newly introduced after the revision of the Infectious Diseases Control Law in 2021. The purpose is to enable intensive countermeasures to be taken even when a state of emergency has not been declared. Emergency declarations are issued on a prefectural basis. Priority measures, on the other hand, can be limited to specific areas, such as cities, towns, and villages, by the governor of the prefecture targeted by the government. In general, priority measures to prevent the spread of the disease are issued first while monitoring the impact of the disease on the prefecture. And if the situation is still not expected to improve, an emergency declaration is made. Compared to similar policies in other countries, the declaration of a state of emergency in Japan is a more relaxed response in terms of restricting people's activities.

Table 1 shows a summary of the administrative response of the Tokyo Metropolitan Government and

Table 1. Countermeasures taken by the Tokyo Metropolitan Government in response to the COVID-19 outbreak

Response	Teams	Functions
Administrative response	Task force headed by the Governor of Tokyo	Cross-sectional cooperation from various organizations in the metropolitan government.
	Tokyo Center for Infectious Disease Control and Prevention (Tokyo iCDC)	A permanent control tower to take charge of effective countermeasures against infectious diseases, including crisis management, research and analysis, and information collection and dissemination.
	Tokyo Metropolitan Government's monitoring meeting	Reports weekly on the status of new coronavirus infections in Tokyo, accompanied by a media briefing with the governor and experts responding at the same time.
Medical countermeasures	Call centers for patients at home care	Consultation for patients recovering at home when their health deteriorates or when they have difficulties in their daily lives.
	Health observation of patients at home by health centers and medical institutions	Regularly contact patients in home care who are at high risk of serious illness to determine if they need to be hospitalized.
	Recuperation at the hotel	Patients who have difficulty recuperating at home are cared for in hotels.
	Dispatch of physicians and medical teams to patients under home care	Dealing with various medical problems that occur during home care.
	Temporary medical facility to house patients on the hospitalization waiting list	Temporary medical facility to accommodate patients who are in need of hospitalization but cannot immediately secure a bed at an inpatient medical facility.
	Temporary medical facilities that can accommodate elderly people in need of care, patients requiring dialysis, and pregnant women	Due to the difficulty in securing beds for patients with special backgrounds, such as the elderly requiring nursing care, patients requiring dialysis, and pregnant women.
	Designation of medical facilities to admit patients with COVID-19	Tokyo has more than 7,000 beds.
	Dispatch of medical teams to elderly care facilities where patients have occurred	A means for elderly COVID-19 patients to receive neutralizing antibody therapy and oral antiviral therapy while in a senior care facility.
	Dispatch of infectious disease specialists to medical institutions and elderly care facilities where clusters have occurred	Elderly patients with mild illnesses would rather remain in a senior care facility and receive treatment to preserve their general condition and mental health.

medical measures for COVID-19 in Tokyo.

Administrative response of Tokyo Metropolitan Government

The Tokyo Metropolitan Government's response to the new coronavirus infection is being carried out under a task force headed by the Governor of Tokyo, with cross-sectional cooperation from various organizations in the metropolitan government. On October 1, 2020, the "Tokyo Center for Infectious Disease Control and Prevention (Tokyo iCDC)" was established by the Tokyo Metropolitan Government as a permanent control tower to take charge of effective countermeasures against infectious diseases, including crisis management, research and analysis, as well as information collection and dissemination. In times of peace, the Center will strengthen its intelligence functions such as policy planning, research and analysis utilizing networks with the national government, universities, *etc*., and information collection and dissemination such as public awareness raising and guideline creation, and human resource development. In addition, in times of emergency, such as the current one, it will perform the following functions respectively: crisis management, such as securing medical systems and coordinating hospitalization; and research and analysis, focusing on an analysis team that integrates the metropolitan government and external researchers.

The Tokyo Metropolitan Government's monitoring meeting reports weekly on the status of new coronavirus infections in Tokyo (*4*). The meeting and the subsequent press conference are all broadcast in real time on YouTube®. The content is also widely reported by mass media such as newspapers and television. This conference is a timely way to inform the people of Tokyo about the status of COVID-19 and its evaluation. There is also a lot of interest at the national level. It serves as a forum for risk communication between government agencies and the people of Tokyo. These results can be checked in real time by "Updates on COVID-19 in Tokyo", set up by the Tokyo Metropolitan Government (*2*). It has been reported that the Japanese people are collecting information and changing their behavior (*5*).

The establishment of risk communication forums such as the Tokyo Metropolitan Government's Monitoring Conference seems to have contributed to the change in behavior of citizens.

Medical countermeasures against COVID-19 in Tokyo

As of February 2022, Tokyo has about 7,000 beds available for COVID-19 patients who require inpatient care. Health observation of positive patients is conducted by public health centers or among medical doctors. During this process, there are patients whose condition deteriorates. In this case, the public health center usually requests the medical institution to admit the patient according to the patient's condition. However, there are cases where such coordination is difficult. During the COVID-19 pandemic, the number of available hospital beds can decrease, taking longer to admit patients who need to be hospitalized. Therefore, consequently 46 beds are reserved for patients who are on the waiting list for hospitalization despite the need for inpatient treatment. And 720 beds are reserved for oxygen and medical care delivery stations that provide medical care such as oxygen administration and neutralizing antibody therapy for patients with mild to moderate illnesses. In addition, to promote treatment with antibody drugs to prevent severe disease, the metropolitan government has established a call center to administer antibody drugs to patients upon request from patients or medical personnel. During a major epidemic, many patients with moderate to severe illnesses are admitted to inpatient beds, and the length of stay of these patients becomes longer, making it difficult to secure vacant beds. Therefore, to increase the utilization rate of bed, a coordination headquarters has been set up to promote transfer and discharge of patients.

In addition, there is a system of overnight treatment for those with mild or asymptomatic positive cases to prevent infection within the family. The Tokyo Metropolitan Government has about 11,000 rooms available.

Patients undergoing treatment at home are monitored by the public health center and medical institutions, and a call center has been set up to provide consultation services in case of sudden changes in their condition or for daily life support.

Olympic support

The Olympic and Paralympic Games Tokyo 2020 took place in the midst of the COVID-19 epidemic in Japan. In order to create a safe and secure environment for athletes and officials, the number of officials coming to Japan was reduced from the original plan to a quarter for the Olympics and a third for the Paralympics. As a watertight measure, officials were inspected twice before entering the country. Athletes were inspected daily in principle, while other officials were inspected periodically according to their roles. Strict restrictions were placed on the destinations, behavioral management, and health management of those involved. Basic infection control measures were taken to prevent the spread of the disease in the athletes' village and competition venues, such as thorough implementation of basic corona control measures; including masks, maintaining physical distance, and avoiding three densities.

In order to minimize contact with people living in Japan and to ensure the safety and security of the people, public transportation was not used in principle. As a general rule, all related personnel were transported using special vehicles for the event. For accommodations, self-arranged accommodations were required to meet the "Accommodation Guidelines", and if they could not meet these standards, they were changed to hotels arranged by the Organizing Committee. With regard to the infection status of those involved in the Games in Japan, the positive rate of tests during the Games for athletes and Games officials was 0.03% (304 (number of positive cases)/1,014,170 (number of tests)) (*6*). The results of the intense contact person testing area of the athletes' village were recorded. Participating athletes, coaches, medical attendants, and Paralympic Games running mates entered the village after being tested negative before leaving their home country and upon arrival at the airport. All participants were tested for saliva every morning, and those who tested positive were subjected to nasopharyngeal PCR testing. Those who were confirmed positive were quarantined to a hotel outside the athletes' village. Those who were in close contact with those athletes were then housed in a designated area and tested daily for nasopharyngeal PCR for 14 days before and after the games. As a result, a total of 3,426 tests were conducted in the test area during Tokyo 2020, with a total of 15 positive cases (*7*). Thus, although there was some spread of the infection in Japan, there was no major spread of the infection in the athletes' village. The positive rate of screening tests conducted in downtown Tokyo from July 1 to September 8 of the same year was 0.1%. The positive rate among Olympic officials was much lower than this. As for the status of medical care for athletes and Games officials, at the peak of the Games the pre-Olympic assumption was that at the same 8.5 times, two Games officials would be hospitalized, and the actual number was two. There was no one seriously ill. According to pre-convention estimates, 44.6 asymptomatic and mildly positive participants were expected to be housed at a lodging facility in Tokyo during the peak period, but the actual number was 49. During the Games, efforts were made to limit the impact on local medical care by identifying positive cases early, isolating them quickly, and using the accommodation and treatment facilities secured by the Organizing Committee. No clusters of cases were identified by the public health authorities, and no cases of the spread of

infection from people involved in the Games to the entire city were reported.

Thus, although the Tokyo Olympics and Paralympics were the first games held in the world after the start of the COVID-19 pandemic, the bubble was kept under safe conditions and the games were held without any major problems.

Conclusion

There are major differences in thinking among countries of how to combat the COVID-19 infection. Some countries are trying to minimize economic losses by resuming social activities as soon as possible, backed by aggressive vaccination promotion. On the other hand, there are countries that have a policy of minimizing the number of cases and deaths by strictly enforcing infection prevention measures and promoting vaccination, thereby minimizing the impact on healthcare and society. It will take some time for these countries to loosen their measures and reverse the situation.

Japan's and Tokyo's measures are similar to the latter. Tokyo citizens have extremely high expectations for the creation of a safe society, specifically to minimize the impact of COVID-19 on society and to maintain safe medical care and society. As the capital of the world's most aged country, Tokyo has a large number of elderly and other high-risk people. It is only natural that the people of Tokyo have high expectations for the creation of a city where these people can live in safety. It is not easy to establish infection control measures to protect the elderly, but many countries around the world will become super-aged societies in the future. The efforts made in Tokyo will provide other countries with important facts as examples of how to deal with infectious diseases in the super-aged society that will come in the future. At the same time, discussions and various efforts are being made to restore social activities. The consequences of these actions will be revealed by history.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Statistics of Tokyo. Population of Tokyo (estimate) *https://www.toukei.metro.tokyo.lg.jp/jsuikei/js-index.htm* (accessd January 1, 2022). (in Japanese)
2. Tokyo Metropolitan Government. Updates on COVID-19 in Tokyo. *https://stopcovid19.metro.tokyo.lg.jp/en/reference/* (accessd February 28, 2022).
3. USA FACTS. New York coronavirus cases and deaths. *https://usafacts.org/visualizations/coronavirus-covid-19-spread-map/state/new-york* (accessd April 7, 2022).
4. Bureau of Social Welfare and Public Health. COVID-19 Monitoring. *https://www.fukushihoken.metro.tokyo.lg.jp/english/health-crisis/monitoring.html* (accessd February 19, 2022).
5. Watanabe T, Yabu T. Japan's voluntary lockdown. PLoS One. 2021; 16:e0252468.
6. Results of COVID-19 Countermeasures at the Tokyo 2020 Games. *https://www.2020games.metro.tokyo.lg.jp/special/eng/guide/taikaijitorikumi/index.html* (accessd March 5, 2022).
7. Akashi H, Shimada S, Tamura T, Chinda E, Kokudo N. SARS-CoV-2 infections in close contacts of positive cases in the Olympic and Paralympic Village at the 2021 Tokyo Olympic and Paralympic Games. JAMA. 2022; 327:978-980.

Received March 10, 2022; Revised April 8, 2022; Accepted April 11, 2022.

Released online in J-STAGE as advance publication April 13, 2022.

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Global Health & Medicine. 2022; 4(2):71-77.

DOI: 10.35772/ghm.2022.01022

Reporting on the implementation to set up a "care and isolation facility" for mild COVID-19 cases in Tokyo

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Abstract: The increasing number of COVID-19 cases has placed pressure on medical facilities. Against this backdrop, the Tokyo Metropolitan Government established a facility for mild and asymptomatic COVID-19 cases by using existing hotels. These kinds of facilities were established in several countries, and represented a spectrum from hotel-like to hospital-like care. In this article, we focused on implementation and related strategies for establishing such a facility in Tokyo as implementation research, while ensuring patient and staff safety. This facility had three functions: care, isolation, and buffering. For the implementation strategy, we used several strategies from the Expert Recommendations for Implementing Change (ERIC) to implement functions similar to an ordinary hospital, but using fewer inputs. This experience can be applied to other resource-limited settings such as that in less developed countries.

***Keywords*:** COVID-19, isolation facility, implementation research, ERIC, Tokyo, Japan

Introduction

The world has been impacted by COVID-19. The increasing number of COVID-19 cases has placed pressure on medical facilities, leading to a shortage of medical personnel, beds, and medical devices. Additionally, adequate medical care cannot be provided in severe cases even in well-equipped hospitals. Tokyo was not exempt from this serious situation. Consequently, even people with moderate or severe cases had to remain at home due to the shortage of hospital beds and other resources; in severe cases, people infected with COVID-19 may have died without adequate medical care.

In Tokyo, in the beginning of the COVID-19 outbreak in 2020, people with severe, moderate, mild, and asymptomatic cases of COVID-19 were hospitalized. However, it was reported in the neighboring prefecture of Tokyo that some people with mild cases who stayed at home rapidly declined and died before hospitalization (*1*). Against this backdrop, the Tokyo Metropolitan Government (TMG) established a facility for mild and asymptomatic COVID-19 cases by using existing hotels. The National Center for Global Health and Medicine (NCGM) was asked to help establish this facility for people with COVID-19 who needed to stay at home just after being diagnosed in April, 2020.

Similar facilities were reported in other countries. For instance, in China, institutional isolation was reported to be able to contain COVID-19 infections in the relatively early stage of the outbreak (*2*). Their functions, such as care or isolation, differed from country to country and facility to facility (*3-5*).

In this article, we describe the implementation process to set up this so-called "care and isolation facility" for mild and asymptomatic COVID-19 cases by using existing hotels, and report our implementation strategies to prepare for a future resurgent epidemic of infectious diseases such as COVID-19.

Preparatory measures for the "care and isolation facility"

Implementation facility

We used the hotel that was prepared by the TMG, located in Tokyo with more than 450 rooms, as a "care and isolation facility". This care and isolation facility for mild and asymptomatic COVID-19 cases was not a formal medical care facility, but an ordinary existing hotel. However, this facility had to take care of the positive COVID-19 nasopharyngeal PCR test cases who were just diagnosed and required to remain at home for two weeks. This means that there was the possibility that

some cases could evolve and worsen while at the hotel. Therefore, we had to set up some level of medical care to detect and handle the worsening cases among mild and asymptomatic cases of COVID-19 in this facility.

Since this care and isolation facility was not an officially designated medical facility, it did not have any medical equipment, medical gas including oxygen, prescribed medicines, and so on. At the time, the nasopharyngeal PCR test was not conducted in the facility even though space was prepared for testing to detect negative to discharge, because it required skilled medical personnel; the saliva antigen test had not yet been introduced (*6*). Therefore, when people showed signs of the illness worsening, those with more severe symptoms were actively referred to hospitals. The TMG had some experience in establishing and running this kind of isolation facility for patients who had already been hospitalized and were recovering prior to discharge while waiting for their negative nasopharyngeal PCR results. However, this was the first time the TMG set up a care and isolation facility for mild and asymptomatic COVID-19 cases who had just been diagnosed by PCR test. Therefore, it was unknown how to set up this kind of facility to handle cases who may maintain their mild symptoms or worsen over time and require hospital admission for intensive care.

Administration and general support was also conducted by the TMG staff, but medical doctors were from the Tokyo Medical Association, and nurses from one of the Tokyo Metropolitan hospitals and a private job placement agency for nurses arranged by the TMG. The NCGM, consisting of medical doctors, nurses, and administrative staff, focused on support to establish the new medical care systems, clarify facility arrangements and materials, create forms, manuals, and documents, and set procedures and activities for the care and isolation facility for mild and asymptomatic COVID-19 case management.

Data collection and analysis

We identified the necessary functions, activities, forms, and systems to run this facility appropriately and adequately through discussions with the TMG staff, and implemented necessary procedures and installed these items using implementation strategies. We remained at the facility for five days after it started to receive positive COVID-19 cases and also followed up one week later and 40 days later. We interviewed the main managerial-level staff in charge of the operation of the TMG as counterparts.

Based on this information, we reviewed the implementation process combined with a research article review to understand the necessary components of the care and isolation facility and implementation strategies to set up a care and isolation facility. Then, we coded implementation strategies using Expert Recommendations for Implementing Change (ERIC) (*7*). Implementation strategies were categorized into nine clusters (*8*): *i*) use evaluative and iterative strategies, *ii*) provide interactive assistance, *iii*) adapt and tailor to the context, *iv*) develop stakeholder interrelationships, *v*) train and educate stakeholders, *vi*) support clinicians, *vii*) engage customers, *viii*) utilize financial strategies, and *ix*) change infrastructure. Implementation strategies are originally operationalized and reported by the elements of actor, action, action target, temporality, dose, implementation outcome affected, and justification (*9*); we modified and simplified this Proctor's specification.

Moreover, we evaluated their effectiveness based on the facility functions. We understood that these kinds of facilities have three functions, namely, care, isolation, and buffer, as shown in Figure 1. As a care center, we expected the care of positive cases who are both recovering and in the disease severity phase, and to avoid a critical situation such as death. As an isolation center, we expected the reduction of infection chains in families and communities. As a buffer center, we expected the containment of mild or asymptomatic cases, consequently avoiding an increase in congestion or the overburdening of hospitals that treat moderate or severe cases.

The implementation, implementation strategy and effectiveness for the "care and isolation facility"

Implementation: Identifying the necessary items, rules, activities and procedures

We identified what kinds of systems, facility arrangements, materials, forms, documents, procedures, and activities should be installed in this care and isolation facility. Next, we tried to identify the necessary items to provide safer care for patients and to keep staff safe, especially those who were not medical professionals, such as ordinary TMG administrative personnel. We also tried to install common systems, procedures, or tools that

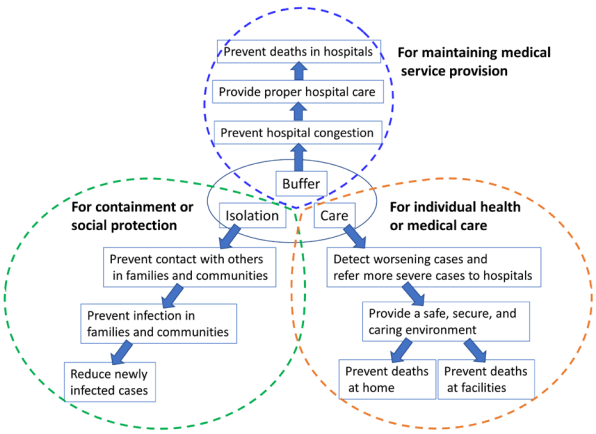

Figure 1. Three functions of the "Caring and Isolation Facility".

Table 1. Contents of implementation for the "care and isolation facility"

Items	Facility, Materials & Personnel	Forms & Documents	Procedures & Activities
Setting	- Zoning - PPE & sterilization materials - Communication tools with patients (telephone, *etc*.) - Doctors & nurses	- Registration form - Patient list	- Procedure to receive patients - Patient registration
Examination	- Daily medical examination by phone	- Daily individual patient medical records	- Vital sign check (BT, O2 saturation, BP, pulse) - Medical record keeping
Treatment	- Over-the-counter medicine		
Referral		- List of referral hospitals	- Special attention on worsening cases - Verbal examination
Administration on health	- Administration staff	- Daily work schedule - Daily patient schedule	- Handover meetings - General management meetings

are utilized in ordinary hospitals in Japan, namely, patient registration, individual patient medical records, checking vital signs, conducting daily medical examinations (doctor rounds), detecting more severe cases, referring them to the back-up hospitals, and so on.

These necessary items were considered based on evidence. For instance, the Medical Care Act of Japan stipulates that medical facilities should retain patient addresses, names, sex, age, disease names, chief complaints, treatments, dates of care, and so forth that are written in patient registration (*10*) and individual patients medical records (*11*). Moreover, the Japanese Nursing Association proposes that nursing records should be completed and retained (*12*). The purpose of nursing records are to prove nursing practice, secure the continuity of nursing care, and evaluate and improve nursing practice according to Nursing Work Standards (*12*).

The purpose of nursing records are as follows: *i*) to record all processes of nursing practice such as observation, assessment, planning, implementation, and evaluation; *ii*) to record the time taken to detect unusual events, as well as the situations of the events, procedures to deal with the events, and when unusual events or medical accidents occurred; and *iii*) to record contents that can be shared with other professionals, non-professionals, and persons who require nursing care (*12*). Moreover, making and keeping clinical records such as patient care records, prescriptions, laboratory test records, and hospital management records such as the number of inpatients and out-patients are stipulated in Japanese regulations (*10,13*).

Furthermore, this care and isolation facility had to handle infectious cases; therefore, it has to follow the rules of "securing infection control system in the medical facilities" as stipulated in the Regulation of Special Functioning Hospitals (*10*). The importance of zoning to manage dangerous communicable diseases is mentioned in the document (*14*), but this is generally common sense in the field of infection control. Other items were also based on common sense, such as the necessity of doctors and nurses.

It was unclear to what degree this care and isolation facility should follow these rules of medical care, since the facility was not a medical facility regulated by medical- or health-related laws, but merely a hotel. Therefore, we had to clarify what kinds of rules and activities should be in place to receive COVID-19 cases with the possibility of a rapidly changing health condition. According to this discussion, we decided to introduce and secure the activities and procedures shown in Table 1.

To determine the appropriate activities and procedures, we had to consider that the majority of staff from the TMG were ordinary administrative staff, not medical or health care professionals; therefore, we tried to not only reduce opportunities of direct contact between staff and patients with COVID-19, but also to secure a certain level of care by using a similar care level as that of medical facilities. Consequently, we introduced daily self-check interventions of body temperature and oxygen saturation, and information collection through a self-administered recording smartphone application and telephones as daily medical examinations. Furthermore, we had to prepare handover procedures, forms, and daily schedules for doctors from the Tokyo Medical Association, and nurses from one of the Tokyo Metropolitan hospitals and a private job placement agency, because they changed periodically (usually daily in the case of doctors); consequently, they may be unfamiliar with the care systems used in the facility, or uninformed about which systems had been installed, or the conditions of the patients. Based on these conditions, we had to consider specific implementation strategies.

Similar facilities were reported in Korea (*16*). One example was a "Life Treatment Center" that was used as an isolation facility. In this facility, "Doctors and nurses examine them twice a day through video calls. Medical data such as electrocardiogram (ECG), blood pressure, oxygen saturation, heart rate, and breathing rate were able to be acquired by vital sign monitors

and transmitted in real time to the monitoring center" (*17*). This facility utilized a very sophisticated system with medical devices. Another example was reported in China of a "medical isolation center" (*18*) or "temporary hospitals rapidly built by converting public venues, such as stadiums and exhibition centers, into health-care facilities to isolate patients with mild to moderate symptoms of an infectious disease from their families and communities, while providing medical care, disease monitoring, food, shelter, and social activities" (*3*). They recognized this facility as a hospital with social activities. In India, COVID Care Centers (CCCs) were established for individuals that returned positive PCR tests; individuals with asymptomatic and mildly symptomatic cases had to isolate. They used existing exhibition centers, trade centers, and educational institutions as isolation centers. Medical care, food, and shelter were provided in the CCCs, along with clinical monitoring by checking body temperature, blood pressure, oxygen saturation, pulse rate, and the provision of basic hematological and radiological interventions (*5*). In the UK, hotels were transformed into COVID-19 isolation centers to house patients who were recovering from the disease (*19*).

However, Japanese cases differed from those in Korea and China. In Japan, the facilities were not medical facilities such as hospitals, but merely accommodation in the form of hotels. In these non-medical facilities, they managed patients who were diagnosed with COVID-19 just before admission, but there were no sophisticated medical devices such as ECGs or other facilities for treatment. Hotel accommodation only has thermometers, oxygen saturation monitors, and PPE, but not oxygen concentrators or bulbs at this moment. Additionally, Japan's facilities did not require renovation or the massive construction of care hospitals as in China. Consequently, less input was necessary to set up the accommodation.

According to these examples, we can categorize these facilities as shown in Figure 2. The care facilities can be categorized midway between a hospital (medical care facility) and non-medical accommodation such as hotels, exhibition centers, and educational facilities. Therefore, the extent to which each care and isolation facility should be equipped depends on its needs. That is, the equipment can be changed according to the social and health situation. If the number of infected moderate cases should increase, the facilities would need to shift from hotel-like to hospital-like care.

Implementation strategy

We used several strategies to introduce the above procedures and activities to this care and isolation facility for mild and asymptomatic COVID-19 cases. The implementation strategies were coded using ERIC (*8*), and their results are summarized in Table 2.

	Non-medical		Medical
Fundamental functions	-Accommodation -Food		-Accommodation -Food
Examination	-Verbal rounds -BT, O_2 monitor	Intermediate	-Patient visits -BT, O_2 monitor -X-ray -Blood sampling (blood cell count)
Treatment	-Over-the-counter medicine	-O_2 cylinder -O_2 concentrator	-Prescribed medicine -Infusion -CPAP
Personnel	- Nurses (main), 24hrs		-Doctors & nurses, 24hrs

Figure 2. Spectrum of the "Care and Isolation Facility".

Several implementation strategies were used to perform implementations. However, the NCGM did not use implementation strategies to support clinicians, engage customers, and utilize financial strategies clusters in this facility. These implementation strategies were provided by the TMG.

Effectiveness

A shown in Figure 1, we used three dimensions, namely, care, isolation, and buffer, to think about efficacy. Regarding "care", around 140 individuals stayed in this facility (one hotel), which has a maximum capacity of 450 rooms; there were no deaths in the facility. It was reported in September 2021 that the first death occurred in one of the care and isolation facilities run by the TMG (*15*). Regarding "isolation", no staff were infected with COVID-19 during the first wave of the pandemic, and no cluster was observed in the facility. We were unable to evaluate the "buffer" aspect because we do not have comparative data of the burden of existing health facilities, and thus cannot conclude the real effects of this facility alone (with respect to patient numbers) on other hospitals.

However, the experience that was created at this care and isolation facility was later used in similar care and isolation facilities in Tokyo. Moreover, some of the manuals, forms, posters, and so forth were later placed on the website as general materials for use by other local governments.

Limitation

The question of whether it was permissible to collect personal health data and other information from the admitted individuals presented itself, since the care and isolation facility was not an officially-designated medical facility. In this regard, the kind of functions each care and isolation facility should have depends on the regulations or orders from national or local governments; therefore, perhaps only these authorities can definitively answer this question.

Furthermore, the contents of the manuals, documents, or procedures depends on the resources of the facility or

Table 2. Analysis by the Expert Recommendations for Implementing Change (ERIC)

Implementation strategies	Actor, Action, Target of the action, In the site	Temporality
Use evaluative and iterative strategies		
Conduct cyclical small tests of change	NCGM produced, tested, and revised records, manuals, and posters according to the daily practice after opening the facility.	First several days after opening the facility
Conduct local needs assessment	NCGM listened to the needs of TMG officials regarding what they wanted to do or what they expected us to do before starting the set-up of the new system to receive COVID-19 cases in this facility.	First several days after opening the facility
Develop and implement tools for quality monitoring	NCGM introduced criteria for referring patients to hospitals, such as oxygen saturation percentage in the initial stage.	First several days after opening the facility until handover to TMG staff
Develop and organize quality monitoring systems	NCGM introduced monitoring systems such as recording, reporting, and sharing information of admitted cases in the facility every day for the nurses, to check case conditions first, to record this information in all the case record books, and to share them with a doctor in charge and nurses the following day, and also the chief of the facility every morning and evening.	First several days after opening the facility until handover to TMG staff
Stage implementation scale up	NCGM organized opportunities for NCGM staff to observe other accommodations for mild or asymptomatic COVID-19 positive cases for airport quarantine that the NCGM had already supported before setting up this facility.	Several days before coming to this facility
Purposely re-examine the implementation	NCGM sent a new NCGM doctor to check the whole system to ensure that it works well and determine any areas that require correction for daytime duty and two doctors for night-time duty after the first installation of the new system. Approximately two weeks later, we conducted a discussion and hearing sessions with TMG officials and nurses in charge of case care.	Four days after the final days when we withdrew from the initial support
Provide interactive assistance		
Centralized technical assistance	NCGM sent our NCGM staff to this facility and advised TMG staff as medical/health assistance to set up this care and isolation facility every day in the initial stage.	First week
Facilitation	NCGM created, conducted, and confirmed handover processes from one shift of doctors and nurses to the next.	Initial four days
Facilitation	NCGM prepared the line list (all case list) on the white board and on PCs, amended some parts based on the discussion with TMG officials, and trained TMG officials on their use.	Initial four days
Adapt and tailor to context		
Promote adaptability	NCGM introduced and revised nurses' and doctors' work to check all cases by telephone instead of bedside care or patient rounds. Doctors only went into the each room if necessary.	First week
Develop stakeholder interrelationships		
Conduct local consensus discussions	NCGM discussed with TMG staff several changes of records, manuals, posters, and procedures in the daily discussion after starting the preparation and implementation of setting up the functions.	After starting the preparation and implementation of setting-up the functions
Visit other sites	NCGM visited other accommodations for mild or asymptomatic COVID-19 positive cases for airport quarantine before coming to the TMG site.	Before coming to the TMG site
Train and educate stakeholders		
Conduct ongoing training	NCGM conducted training several times on how to put on and remove PPE, how to use case lists, *etc*.	First week
Distribute education materials	NCGM prepared posters and manuals and posted them on the walls to share with relevant staff.	First week
Provide ongoing consultation	NCGM provided several consultations on infection control or other documents such as certificates to be given to cases that are going to be discharged.	The first two weeks
Use train-the-trainer strategies	NCGM trained the first batch of TMG staff as trainers, and we expected them to train the next batch.	First week
Change infrastructure		
Change physical structure and equipment	NCGM arranged case flows under the zoning and PPE changing spaces. In addition, the TMG prepared thermometers and oxygen saturation meters for all cases, and installed administrative equipment such as computers for case registration and white boards for case lists and referral contact information, *etc*.	First week
Change record systems	NCGM arranged and introduced new record systems of cases in this facility, such as lists of daily case names and other related information on the white board, and all case lists in the registration forms on PCs to register and record.	First week
Change service sites	TMG lent a hotel and set up zoning, food, room telephones, and other facilities. They sent their staff for logistics training to learn how to run the facility. We, the NCGM, used these settings to set up and manage this care and isolation facility.	First week

Global Health & Medicine. 2022; 4(2):71-77.

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local and national governments. For instance, the TMG had many oxygen saturations monitors; therefore, one monitor was placed in each room. However, in other hotels run by other organizations or local governments, there were only two monitors per floor. Therefore, the products that were used and made available differed from accommodation to accommodation. Thus, each organization should change the relevant standards, forms, or contents of manuals and posters so as to suit each facility.

Conclusion

Regarding implementation, Japan's facilities did not require renovation or the massive construction of care hospitals as in China. Looking at how policy makers could set up care and isolation facilities, especially in resource-limited settings, it is evident that it was easy to establish facilities with the three functions of care, isolation, and buffer by using existing facilities such as hotels instead of constructing new buildings or installing beds and other equipment. Consequently, less input was needed to set up the accommodation.

Regarding the implementation strategy, we used several strategies in ERIC to set up similar functions of an ordinary hospital by using fewer inputs. We think this can be applied to other resource-limited settings such as those found in less developed countries.

Acknowledgements

We would like to thank the National Center for Global Health and Medicine (NCCM) staff collaborators for their support of our operations most notably; Ikuma Nozaki, MD, PhD, and Motoyuki Tsuboi, MD, DTM&H, MSc-TMIH, and Sadatoshi Matsuoka, PhD for his advices on implementation research.

Funding: This study was supported by the National Center Consortium in Implementation Science for Health Equity (N-EQUITY) funded by the Japan Health Research Promotion Bureau (JH) Research Fund (Number 2019-(1)-4), and funded by the Ministry of Health, Labour, and Welfare Scientific Research Grant (Number 21BA1002).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. NHK. Repeated deaths by COVID-19 in home care in Tokyo. *https://www3.nhk.or.jp/news/html/20200425/k10012405741000.html* (accessed March 1, 2022). (in Japanese)
2. Dickens BL, Koo JR, Wilder-Smith A, Cook AR. Institutional, not home-based, isolation could contain the COVID-19 outbreak. Lancet. 2020; 395: 1541-1542.
3. Chen S, Zhang Z, Yang J, Wang J, Zhai X, Bärnighausen T, Wang C. Fangcang shelter hospitals: a novel concept for responding to public health emergencies. Lancet. 2020; 395: 1305-1314.
4. Kang E, Lee SY, Jung H, Kim MS, Cho B, Kim YS. Operating protocols of a community treatment center for isolation of patients with coronavirus disease, South Korea. Emerg Infect Dis. 2020; 26: 2329-2337.
5. Khrishnasamy N, Natarajan M, Ramachandran A, *et al*. Clinical outcomes among asymptomatic or mildly symptomatic COVID-19 patients in an isolation facility in Chennai, India. Am J Trop Med Hyg. 2021; 104: 85-90.
6. Norizuki M, Hachiya M, Motohashi A, Moriya A, Mezaki K, Kimura M, Sugiura W, Akashi H, Umeda T. Effective screening strategies for detection of asymptomatic COVID-19 travelers at airport quarantine stations: Exploratory findings in Japan. Glob Health Med. 2021; 3:107-111.
7. Powell BJ, Waltz TJ, Chinman MJ, Damschroder LJ, Smith JL, Matthieu MM, Proctor EK, Kircher JE. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. Implement Sci. 2015; 10:21.
8. Waltz TJ, Powell BJ, Matthieu MM, *et al*. Use of concept mapping to characterize relationships among implementation strategies and assess their feasibility and importance: results from the Expert Recommendations for Implementing Change (ERIC) study. Implement Sci. 2015; 10:109.
9. Proctor EK, Powell BJ, McMillen JC. Implementation strategies: recommendations for specifying and reporting. Implement Sci. 2013; 8: 139.
10. Ministry of Health, Labour and Welfare of Japan. Medical Care Act. July 30, 1948. *https://www.mhlw.go*.jp/web/t_doc?dataId=80090000&dataType=0&pageNo=1 (accessed March 1, 2022). (in Japanese)
11. Ministry of Health, Labour and Welfare of Japan. Ordinance for enforcement of the Medical Practitioners' Act. 1948. *https://elaws.e-gov.go.jp/document?lawid=323AC0000000201* (accessed March 1, 2022). (in Japanese)
12. Japanese Nursing Association. Guidelines on nursing records. *https://www.nurse.or.jp/home/publication/pdf/guideline/nursing_record.pdf* (accessed March 1, 2022). (in Japanese)
13. Ministry of Health, Labour and Welfare of Japan. Guidelines on provision of clinical information. *https://www.mhlw.go.jp/shingi/2004/06/s0623-15m.html* (accessed March 1, 2022). (in Japanese)
14. Disease Control and Prevention Center. National Center for Global Health and Medicine. How to think of zoning to deal with COVID-19 outbreak in acute care hospitals. *https://dcc.ncgm.go.jp/information/pdf/covid19_zoning_clue.pdf* (accessed March 1, 2022). (in Japanese)
15. The Asahi Shinbun Company. The first death case in COVID-19 care facility in Tokyo Metropolis. It was too late to finalize the criteria of admission. Asahi Shinbun Apital. *https://www.asahi.com/articles/ASP9G6HHWP9GUTIL05D.html* (accessed March 1, 2022). (in Japanese)
16. Seoul National University Hospital (SNUH), Seoul, South Korea. SNUH provides appropriate medical care to secure South Korea medical system in COVID-19 crisis. *https://www.prnewswire.co.uk/news-releases/snuh-provides-appropriate-medical-care-to-secure-south-korea-medical-*

system-in-covid-19-crisis-899976046.html (accessed March 1, 2022).
17. Yang Y, Kim H, Hwang J. Quarantine facility for patients with COVID-19 with mild symptoms in Korea: Experience from eighteen residential treatment centers. J Korean Med Sci. 2020; 35: e429.
18. ABC Net. China builds massive COVID-19 isolation centre as cases in Hebei province surge. *https://www.abc.net.au/news/2021-01-15/china-builds-shijiazhuang-covid19-isolation-centre-coronavirus/13061194* (accessed March 1, 2022).
19. pbctoday. Three hotels converted into Covid-19 isolation centres. *https://www.pbctoday.co.uk/news/planning-construction-news/covid-19-isolation-centre/75671/* (accessed March 1, 2022).

Received March 11, 2022; Revised April 1, 2022; Accepted April 4, 2022.

Released online in J-STAGE as advance publication April 9, 2022.

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Global Health & Medicine. 2022; 4(2):78-82.
MINI-REVIEW
DOI: 10.35772/ghm.2022.01025

Public health responses to COVID-19 in Japan

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Abstract: Two years have passed since the confirmation of the first case of coronavirus disease (COVID-19) in Japan. The aim of this article was to review the public health responses to COVID-19 in Japan. As of January 31, 2022, COVID-19-positive cases have cumulatively totaled 2,669,638 and deaths cases have cumulatively totaled 18,784. To deter COVID-19 transmission in the community, the government declared a state of emergency to minimize the impact on people's livelihoods and the economy. The prefectural (province) governor of an area under a "State of Emergency" may request special action to prevent the spread of infection among residents. A nationwide campaign, Avoid the "3 Cs" (Closed spaces, Crowded spaces, and Close-contact settings), has been widely acknowledged to have controlled infection in high-risk areas. In Japan, COVID-19 vaccines were supplied by Pfizer, Moderna, and AstraZeneca. Pfizer's vaccine received regulatory approval in Japan in February 2021, and Moderna and AstraZeneca's did so in May 2021. Public health centers (PHCs) under the jurisdiction of local governments are responsible for conducting Polymerase Chain Reaction (PCR) testing, coordinating the treatment of COVID-19-positive patients, and identifying persons in close contact with COVID-19 patients through an epidemiological study of each positive case. These public health responses have been implemented based on the assessment of the impact of each variant and support from a government panel of experts. Further studies may be need to be conducted develop more flexible and efficient public health responses.

Keywords: COVID-19 pandemic, measures against COVID-19, COVID-19 vaccine, public health center, government panel of experts

Introduction

Even now, two years after the confirmation of the first case of coronavirus disease (COVID-19) in Japan, COVID-19-related news has appeared every day, and there is still a sense of anxiety and tension. The aim of this article was to review the public health responses to COVID-19 in Japan.

Trends in COVID-19 cases in Japan

As of January 31, 2022, COVID-19-positive cases cumulatively totaled 2,669,638 and deaths cumulatively totaled 18,784. The "first wave" (about 700 cases per day at its peak) of a daily increase in cases was observed in April 2020, followed by a "second wave" (about 1,000 cases per day) in early August 2020 (about 1,600 cases per day), a "third wave" in early January 2021 (about 8,000 cases per day), a "fourth wave" in early May (about 7,000 cases per day), a "fifth wave" in mid-July (about 20,000), and then a "sixth wave" (about 100,000 cases per day) in February 2022 (Figure 1) (*1*).

The number of patients with severe COVID-19 has increased in accordance with the "waves" mentioned above. During the fifth wave (September 2021), the maximum number of seriously ill patients receiving care on the same day exceeded 2,000. Severe cases accounted for 9.8% of all positive cases from January to April 2020 and for 1.62% from June to August 2020 (*2*).

At the time this manuscript was written (the end of February 2022), the Omicron variant has been predominant, but the percentage of severe cases is reported to be decreasing due to people with a history of previous infection and COVID-19 vaccines. Special attention must be paid to the prevention of infection in the elderly, as 73% of cases of respiratory failure have been clustered in individuals over the age of 70 (*3*). The number of deaths exceeded 100 per day on some days in February and May of 2021 but tended to decline after July, and the increase slowed down after October 2021. With the spread of COVID-19, however, the number of deaths began to rise again, with approximately 270 deaths per day in late February of 2022 (*1*).

Legal measures by the government to deter COVID-19 transmission in the community

In 2009, Japan enacted the Act on Special Measures for Novel Influenza to protect the lives of citizens and minimize the impact on their livelihoods and the economy in the wake of the H1N1 influenza virus pandemic. In April 2020, the law was amended to allow for the declaration of a "State of Emergency" by the national government.

The prefectural (province) governor of an area under a "State of Emergency" may request special action to prevent the spread of infection among residents. Governors are authorized to encourage people to remain at home, to request the closure of commercial facilities such as restaurants, to restrict the use of facilities such as schools and welfare facilities, and to open temporary medical facilities to care for COVID-19 patients. The national government decided when to lift the state of emergency based on the status of the infection and the rate of bed occupation by COVID-19 patients. A State of Emergency was declared on a prefectural basis for two months from April 2020, two months from January 2021, two months from April 2021, and three months from July 2021.

In February 2021, the framework for a "Quasi-state of Emergency"(priority preventable measures) was implemented. As the name suggests, it is less restrictive than a "State of Emergency. The purpose of a "Quasi-state of Emergency" is to prevent the spread of the disease while minimizing the impact on the economy in situations where infection trends are not serious enough to warrant a State of Emergency. For example, the prefectural governor cannot request that commercial facilities suspend service, but he can request that their hours of operation be reduced.

The decision on whether to declare a State of Emergency or a Quasi-state of Emergency is determined by the "level" (*4*). Based on nationwide guidelines specified by the central government, each prefecture specifies numerical indicators. The guidelines for Japan and the indicators for one prefecture, Tokyo, are shown in Table 1.

The central government will make a comprehensive judgment and declare a Quasi-state of Emergency, level 2 or 3, or a State of Emergency, level 4. A Quasi-state of Emergency was declared from April to September 2021 and from January to March 2022 (as of Feb. 28, 2022) in prefectures where the spread of the disease is serious or in municipalities designated by prefectural governors.

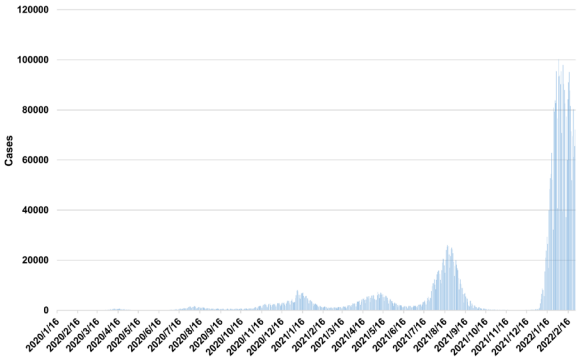

Figure 1. Trend in the number of newly confirmed cases with COVID-19 in Japan. Data source: *https://covid19.mhlw.go.jp/en*

Infection control in high-risk areas

A nationwide campaign to Avoid the "3 Cs" (Closed spaces, Crowded spaces, and Close-contact settings) has been widely favored by the public. Each prefectural government has implemented detailed measures. As of February 2022, the Tokyo Metropolitan Government has specified detailed measures for restaurants, coffee shops, bars, and other food and beverage-related establishments, including reduced business hours (closing at 8 or 9 PM), reduced hours when alcohol is served (from 11 AM to 8 PM), and reduced seating for a maximum of four at each table. The Metropolitan Government has also requested that citizens and karaoke establishments ensure the sterilization of microphones in rooms. For large-scale events, the upper limit of attendees should be half the

Table 1. Level of medical preparedness for COVID-19 nationwide and in Tokyo

Standards	Level 0	Level 1	Level 2	Level 3	Level 4
National Standard	No positive cases	General medical care is provided and care for patients with COVID-19 is available	Increasing the number of beds for COVID-19 to meet overall medical needs	Medical care for COVID-19 is not available without considerable restrictions on daily medical care	Medical care for COVID-19 is no longer available even though general medical care is restricted
Tokyo Standard	N/A	N/A	Bed utilization within three weeks will reach about 20% of the number of beds for patients with COVID-19 (7,229 beds)	Number of beds needed within three weeks will reach the number required (7,229 beds) or the utilization of beds or beds for patients with severe COVID-19 will exceed 50%.	Number of patients to hospitalize exceeds the number of allotted beds

Data source: Basic Approach to Future COVID-19 Countermeasures in Tokyo (accessed February 28, 2022). *https://www.bousai.metro.tokyo.lg.jp/_res/projects/default_project/_page_/001/020/633/20211125aa.pdf*

default capacity (5,000 concert attendees maximum) for events with cheering, and 20,000 for events without cheering (if their COVID-19 test is negative, the maximum number of people can enter the event up to the default capacity).

Panels to aid Government decision-making

The main bodies to discuss COVID-19 policies in Japan are *i*) the Headquarters for Countermeasures to Combat COVID-19, established by the Cabinet Secretariat and headed by the Prime Minister, with members including cabinet ministers, and *ii*) the Council to Promote Countermeasures against Novel Influenza and Other Infectious Diseases, which includes scholars as members. The COVID-19 Subcommittee under the Council includes medical experts on topics such as infectious diseases and epidemiology, as well as socioeconomic experts, and the COVID-19 Subcommittee. The results of discussions by the subcommittee are frequently reported in the press to attract public interest. The Ministry of Health, Labour, and Welfare (MHLW) has also established the "Advisory Board for Countermeasures against COVID-19," which advises the health minister on expert and technical matters in public health to promote measures against COVID-19 (*5*).

Ensuring COVID-19 immunization and vaccine rollout

In Japan, COVID-19 vaccines were supplied by Pfizer, Moderna, and AstraZeneca. Pfizer's vaccine received regulatory approval in Japan in February 2021, and Moderna and AstraZeneca's did so in May 2021 (*6*). Soon after the regulatory approval process, a vaccination campaign for healthcare personnel was launched in February 2021 and a campaign for the elderly was launched in April 2021 (*7*). In May 2021, the Ministry of Defense began operating large-scale vaccination centers in Tokyo and Osaka, leading cities in Japan, in order to significantly accelerate vaccination in urban areas. In June 2021, vaccination in the workplace was also initiated to expand the opportunities for vaccination. When the vaccination strategy initially started, two-dose vaccination was planned. In late 2021, however, administration of a third dose (a booster) was discussed in light of the global epidemic. The government established a vaccination plan with an interval of eight months between the second and third doses, taking into consideration field operations and the vaccine supply, but vaccinations with an interval of six months were then started in municipalities that had obtained a supply of vaccines and human resources. As of February 28, 2022, 80.3% of the total population has received the first dose of the vaccine, 79.1% have received the second dose, and 19.3% have received the third dose (*8*).

Looking at the healthcare field

When residents suspect they have COVID-19

In the early stage of the COVID-19 epidemic, residents were urged to call the health center or the COVID-19 consultation center if they suspected that they had COVID-19 symptoms. Medical facilities routinely visited by residents also began to offer consultations by phone. If the consultation indicated that the symptoms potentially COVID-19, residents were encouraged to undergo a Polymerase Chain Reaction (PCR) test or visit a designated health care provider. When the PCR test was positive, the residents were placed in a medical facility designated by the local government or in an overnight care facility, or they stayed in their homes. As of February 2022, symptomatic residents were directed to stay in designated facilities or in their homes for 72 hours after symptoms disappeared, and asymptomatic residents were directed to stay in a facility or at home for 7 days after the PCR test was positive to prevent the spread of COVID-19 (*9*).

Difficulty in allocating hospital beds

Due to the rapid increase in the number of COVID-19 patients since January 2022, medical facilities may no longer be able to respond to a request to admit a COVID-19 patient, and healthcare workers may not be able to provide medical care if they become infected. Media reports called for more effective government strategies to provide medical care (*10*). In areas with a larger number of infected people, patients diagnosed with COVID-19 cannot be admitted to medical facilities and are forced to recuperate at home or in designated hotels. If a COVID-19-positive resident was detected in a nursing home for the elderly, infection control in the home were typically insufficient, and the disease continued to spread rapidly inside the home. Since COVID-19 beds in hospitals were fully occupied, COVID-19 patients in homes for the elderly often could not be admitted.

Struggles at public health centers

Public health centers (PHC) under the jurisdiction of the prefectural government are responsible for conducting PCR testing, coordinating the treatment of COVID-19-positive patients, and identifying persons in close contact with COVID-19 patients through an epidemiological study of each positive case. These duties caused an excessive burden on PHCs, and they are on the verge of "collapse". Health centers have been noted to lag behind implementation of ICT compared to other institutions in the public sector. This has become a major obstacle to the smooth operation of health centers serving large numbers of people.

Health centers were unable to monitor a vast number of patients who were recuperating at home, and there were reported cases of patients who died at home without appropriate monitoring by healthcare personnel. When residents attempted to call PHCs for a consultation, the phone lines were always busy. The effect of this was that residents were unable to obtain necessary health guidance.

COVID-19 strategies now and in the future

A sustained call for basic infection control

There are no signs that COVID-19 is being constrained and the public is tiring of COVID-19 measures, so inevitably public interest in continuing basic infection control will gradually diminish. The key to limiting the spread of infection in the future is for the government to capitalize on techniques to communicate risk in order to call on the public to continue implementing routine infection control. Basic infection control, particularly in facilities for the elderly, is crucial to reducing preventable deaths.

Vaccine rollout

The supply of vaccine has become more consistent with each passing day. The third dose of the COVID-19 vaccine, a booster, should be rapidly administered to many citizens as possible, starting with priority vaccination groups, to prevent the spread of infection and to prevent serious complications. Due to a vaccine shortage, the start of COVID-19 vaccination has been delayed in Japan compared to other countries, and this has become a major topic of discussion. A national strategy has been launched to alleviate the causes of the delay in vaccine development and production in Japan. As one approach, the Cabinet Secretariat has established the Strategic Center of Biomedical Advanced Research and Development for Preparedness and Response (SCARDA), a governmental research funding agency, to strategically allocate research funds for clinical trials by research teams among industry, government, and academia (*11*).

Prioritized hospitalization for high-risk patients in critical condition

Through our COVID-19 experience, we have learned what conditions and pre-existing conditions predispose patients to develop severe COVID-19. Hospitalization should be limited to patients who require intensive medical care, and patients with more moderate COVID-19 should have their health monitored by a clinic or other lower-level facility. This reduces the excessive burden on medical facilities and maintains the provision of medical care. Facilities for the elderly should be expected to continue care as long as possible during an outbreak of COVID-19 among residents rather than immediately referring them to a hospital. Basic care and treatment can be provided to the infected person within the facility with attention to basic infection control. Efforts by those facilities would greatly reduce the burden on hospitals.

Focusing and streamlining the duties of PHCs

As mentioned earlier, PHCs have been almost completely exhausted by heavy workloads during the pandemic. From the viewpoint of the sustainability of operations by PHCs, their duties and operational tools should be reviewed and markedly changed. "An active epidemiological study and subsequent health monitoring" should be limited to residents who really need to be followed. Hospitalization and coordination of capacity among medical facilities could be done without PHCs. IT should be promoted to diminish faxes to prefectural headquarters and medical facilities.

Conclusion

Over the past two years, we have indeed encountered many unforeseen circumstances. We never imagined that we would be subjected to new systems that would restrict our everyday activities due to an infectious disease for such an extended period. This is probably the first time in the world that medical personnel, local governments, and pharmaceutical companies have endeavored to provide a new type of vaccine three times within one year.

This is the first time in Japan that hospitalization and outpatient visits have been restricted in order to prioritize the hospitalization of COVID-19 patients. We never thought that all the citizen of the nation would become aware of the duties of PHCs. Through these experiences, we were reminded of the importance of being flexible and responding to any situation. The public health responses mentioned earlier have been implemented based on an assessment of the impact of each variant and support from a government panel of experts. Further experiences and studies may be needed to develop more flexible and efficient public health responses.

The history of the fight against COVID-19 could be applicable to a future outbreak of an emerging and re-emerging infectious disease. Japanese have realized that the current healthcare system needs to be upgraded because it places too much of a burden on health centers and medical facilities, and they also experienced the limited availability of public health and medical care during the pandemic. The issues highlighted during this pandemic must be documented, and now is the chance to create a roadmap toward a solution based on the hardships all citizens have suffered.

Acknowledgements

When preparing this manuscript, the authors referred to "Trends in National Public Health ("kokumin eisei no doko" in Japanese), Journal of Health and Welfare Statistics 2021; 68(9), published by Health, Labour and Welfare Statistics Association, which contains the latest and richest information on COVID-19 in Japan. The authors wish to sincerely thank the Association for that information.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Ministry of Health, Labour, and Welfare of Japan. Visualizing the data: Information on COVID-19 infections. *https://covid19.mhlw.go.jp/en/* (accessed February 28, 2022).
2. Ministry of Health, Labour, and Welfare of Japan. 11 pieces of knowledge about COVID-19 “now," as of February 2022 *https://www.mhlw.go.jp/content/000788485.pdf* (accessed February 28, 2022). (in Japanese)
3. National Institute of Infectious Diseases of Japan. The mutant strain B.1.1.529 (Omicron strain) of SARS-CoV-2, 7th report. *https://www.niid.go.jp/niid/ja/2019-ncov/2551-cepr/10945-sars-cov-2-b-1-1-529-7.html* (accessed February 28, 2022). (in Japanese)
4. Government Announcement by the Cabinet Secretariat of Japan. "Indicators and Guidelines for the Implementation of Countermeasures in Response to Future Changes in the Status of Infection" August 7, 2020. *https://corona.go.jp/news/pdf/jimurenraku_0811.pdf* (accessed February 28, 2022). (in Japanese)
5. Ministry of Health, Labour, and Welfare of Japan. Advisory Board for Countermeasures against COVID-19. *https://www.mhlw.go.jp/stf/covid-19/seifunotorikumi.html#h2_3* (accessed February 28, 2022). (in Japanese)
6. The Japanese Association of Infectious Diseases Recommendations on COVID-19 vaccines, 4th version. *https://www.kansensho.or.jp/uploads/files/guidelines/2112_covid-19_4.pdf* (accessed February 28, 2022). (in Japanese)
7. Prime Minister's Office of Japan. Vaccinating order. *https://japan.kantei.go.jp/ongoingtopics/pdf/202105_vaccinating_order.pdf* (accessed February 28, 2022).
8. Prime Minister's Office of Japan. COVID-19 vaccines. *https://www.kantei.go.jp/jp/headline/kansensho/vaccine.html* (accessed February 28, 2022). (in Japanese)
9. Ministry of Health Labour, and Welfare of Japan. Coronavirus (COVID-19). *https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000164708_00079.html* (accessed February 28, 2022).
10. Nikkei Asia. Japan COVID crisis shows flaws in medical system: Nikkei and JCER. *https://asia.nikkei.com/Business/Health-Care/Japan-COVID-crisis-shows-flaws-in-medical-system-Nikkei-and-JCER* (accessed February 28, 2022).
11. Cabinet Office of Japan. Basic Approach to R&D Support by SCARDA (Draft) *https://www.kantei.go.jp/jp/singi/kenkouiryou/iyakuhin/dai6/siryou1-3.pdf* (accessed February 28, 2022). (in Japanese)

Received March 18, 2022; Revised March 30, 2022; Accepted April 4, 2022.

Released online in J-STAGE as advance publication April 10, 2022.

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Global Health & Medicine. 2022; 4(2):83-93.
REVIEW
DOI: 10.35772/ghm.2022.01013

Long COVID: current status in Japan and knowledge about its molecular background

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Abstract: Even after recovering from coronavirus disease 2019 (COVID-19), patients can experience prolonged complaints, referred to as "long COVID". Similar to reports in Caucasians, a follow-up study in Japan revealed that fatigue, dyspnea, cough, anosmia/dysgeusia, and dyssomnia are common symptoms. Although the precise mode of long COVID remains elusive, multiple etiologies such as direct organ damage by infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), autoimmunity, prolonged inflammatory reactions, and psychiatric impairment seem to be involved. Notably, SARS-CoV-2 is neurotropic, and viral RNA and proteins are continuously detectable in multiple organs, including the brain. Viral proteins exert a number of different toxic effects on cells, suggesting that persistent infection is a key element for understanding long COVID. Here, we first reviewed the current status of long COVID in Japan, and then summarized literature that help us understand the molecular background of the symptoms. Finally, we discuss the feasibility of vaccination as a treatment for patients with long COVID.

***Keywords*:** SARS-CoV-2, long COVID, persistency, viral proteins, autoantibody, vaccination

Introduction

Approximately 2 years have passed since severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in China in December 2019. Since then, more than 400 million people have been infected and approximately 6 million people have died from coronavirus disease 2019 (COVID-19) worldwide. After the acute phase of infection, patients can continue to suffer from various clinical symptoms that impair their quality of life, which is called "long COVID" or "long-haul COVID" (*1,2*). The World Health Organization recently defined this post-COVID status as "a clinical condition that occurs after 3 months of viral infection with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis" (*3*). A recent meta-analysis revealed that more than 50 symptoms have been identified in long COVID patients, approximately 80% of whom suffer from one or more symptoms (*4*). As possible causes of long COVID symptoms, multiple etiologies such as direct organ damage, constitutive inflammatory responses including autoimmunity, and psychiatric impairment seem to be involved.

A number of excellent reviews on the clinical symptoms of long COVID are available (*1,2*). Here, we summarize the current status of long COVID in Japan and discuss its possible modes and management by highlighting the persistence of viral infection.

Long COVID in Japan and knowledge about its main symptoms

Some individuals who were discharged from the National Center for Global Health and Medicine Hospital in Japan after recovery from COVID-19 have experienced long COVID symptoms for more than 60 days from initial symptom onset (*5*) (Table 1). Chronic manifestations of COVID-19 have been reported in several countries, including Spain (*6*), Norway (*7*), and Israel (*8*). Graded common symptoms are fatigue, dyspnea, dyssomnia, cough, chest pain, headache, and anosmia/dysgeusia. Most symptoms are prolonged from the acute phase of COVID-19 infection, although dyssomnia is a late-onset symptom that appears at least 30 days after initial symptom onset (*5*). Additionally, alopecia, fulminant myocarditis, and multi-system inflammatory syndrome can be observed at 6 weeks after symptom onset (*9,10*). Even after 1 year, a sizeable proportion of recovered COVID-19 patients still have most symptoms such as fatigue, dyspnea, arthralgia, memory loss, and concentration difficulties (*11*).

Table 1. Prevalence of long COVID symptoms

Variables	Japan	Spain	Norway	Israel
Number of patients	63	1969	312	544
Female (%)	33.3	46.4	51.3	56.4
Age, years, mean (SD)	48.1 (18.5)	61.1 (16.3)	46 (33-58)[†]	46.4 (15.5)
BMI, mean (SD)	23.7 (4.0)	-	24.6 (22.8-27.3)[†]	27.6 (5.6)
Comorbidity (%)				
Asthma/COPD	1.6	10.3	12.2	6.4
Hypertension	25.4	26.1	11.2	16.4
Chronic heart disease	1.6	11.9	7.1	-
Diabetes	14.3	12.0	4.2	8.3
Symptoms (%)				
Days from symptom onset at the time of observation	60 days	8.4 months (1.5)	6 months	123 days (80-204)[†]
Fatigue	15.9	61.3	29.9	75.6
Dyspnea	17.5	23.3	15.4	50.9
Cough	7.9	-	6.1	19.9
Chest pain	-	45.1[*]	-	30.5
Palpitations	-	7.1	6.1	12.3
Myalgia	-	45.1[*]	-	37.5
Arthralgia	-	45.1[*]	-	9.4
Paresthesia	-	12.0	3.6	24
Dyssomnia	16.1	34.2	5.3	37.5
Headache	-	45.1[*]	11.3	12.7
Memory loss	-	17.3	18.2	36.9
Concentration problems	-	7.1	19.0	39.0
Anosmia/dysgeusia	4.8	6.8	2.7	29.4
Worse physical activity status	-	-	-	26.1
Reference (DOI)	10.1093/ofid/ofaa507	10.3390/jcm11020413	10.1038/s41591-021-01433-3	10.3390/jcm11040898

[†]median (interquartile range); [*]pain symptoms (%) including chest pain, myalgia, arthralgia, and headache. SD, standard deviation; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

Fatigue

Fatigue is the most common complaint of long COVID. However, it is observed as a postinfectious syndrome not only in long COVID but also in various viral infections such as SARS-CoV-1, Middle East respiratory syndrome (*12*), Epstein-Barr (EB) virus, Q fever, and Ebola virus, showing a common symptom that resembles myalgia encephalomyelitis/chronic fatigue syndrome and fibromyalgia (*13*). A number of follow-up studies have identified fatigue and/or dyspnea in patients with long COVID, and approximately 70% of hospitalized COVID-19 survivors feel fatigue, but the symptoms improve continuously (*14,15*). Female sex has been identified as a risk factor for fatigue (*14*). Pre-existing comorbidities, symptoms at hospitalization, and severity during hospitalization have also been suggested as risk factors (*14*).

To assess physical condition, diffusion capacity for carbon monoxide and the 6-min walk test with lung computed tomography (CT) scans are commonly utilized. Abnormalities of diffusion capacity for carbon monoxide, chest X-rays, and reduced distance in the 6-min walk test are observed frequently in patients who received invasive mechanical ventilation (*16*). CT scans have detected persistent lung pathology in 63% of patients at 3 months, with findings of bilateral ground-glass opacities and/or reticulation in the lower lung lobes, but without radiological signs of pulmonary fibrosis. Although sequential follow-up evaluations revealed an improvement of symptoms and CT abnormalities (*16*), it was noted that respiratory changes persist in a non-negligible number of patients (approximately one-third) who require prolonged follow-up (*15*). Curiously, there is no difference in lowest oxygen saturation among patients with normal and reduced 6-min walk test distance, suggesting that the difference in walk distance is not directly related to physical abnormalities, but is associated with subjective factors. These observations imply the importance of comprehensive mental and physical care for patients with fatigue (*17*).

Observation that there is also a non-negligible number of patients with persistent respiratory changes (*15*) suggests that it is important to understand how lung damage occurs after viral infection. To identify the early events of lung injury during acute viral infection, Melms *et al.* performed single-nucleus RNA-sequencing analysis on snap-frozen lung tissues from individuals with COVID-19. They found nine major cell types (*i.e.*, epithelial cells, myeloid cells, fibroblasts, endothelial cells, T and natural killer lymphocytes, B lymphocytes and plasma cells, neuronal cells, mast cells, and antigen-presenting cells) in total 41 different cell types (*18*). Among these, alveolar type 1 (AT1) and type

2 (AT2) epithelial cells are involved in lung epithelial regeneration. AT2 cells express angiotensin converting enzyme 2 (ACE2), a receptor for SARS-CoV-2, and function as progenitors to AT1 cells. In COVID-19 lung samples, AT2 cells have decreased expression of a gene related to regeneration, whereas AT1 cells have no increased expression of a marker of late AT1 maturation. Data suggests that the regeneration program of the lung epithelium is impaired in the infected lung. Moreover, fibroblasts with high expression of the gene encoding collagen triple helix repeat containing-1, which was recently proposed as a marker of pathological fibroblasts, were identified (*18*).

Alopecia

Hair loss after viral infection was also reported as post-influenza alopecia in 1919, indicating that it is not specific to long COVID (*19*). Excessive hair loss occurs within 2-3 months after SARS-CoV-2 infection (*20*), and is mainly diagnosed as telogen effluvium. Telogen effluvium can be divided into acute or chronic when it continues for more than 6 months, which resolves at 6-12 months after removal of the activating factor. Proinflammatory cytokines including interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and interferon type I and II (IFN-I/II) are proposed as activating factors of telogen effluvium. As a therapeutic approach, hydroxychloroquine and glucocorticoids as anti-inflammatory agents have been tried (*21*).

Anosmia and dysgeusia

Viral load during infection is significantly associated with anosmia/dysgeusia (*22*). Consistent with the original report that ACE2 and transmembrane protease, serine 2 (TMPRSS2), a protease of the viral spike protein facilitating viral infection, are not expressed by olfactory neurons (*23*), single-cell RNA-sequencing analysis of cells derived from mouse nasal tissues revealed that ACE2 is expressed in dorsally located olfactory epithelial sustentacular cells and mouse olfactory bulb pericytes (*24*). Recently, a novel candidate receptor for SARS-CoV-2, neuropilin-1 (NRP1), has been reported. NRP1 binds to the Arg-Arg-Ala-Arg (RRAR) motif, which is located on the carboxy-terminal end of the S1 subunit of the viral spike protein (hereafter S1 protein) (*25*), and facilitates the cell entry of SARS-CoV-2. Different from ACE2, NRP1 is expressed in nasal epithelial cells and is responsible for infection of the nasal epithelium. Autopsy of two patients with anosmia revealed that SARS-CoV-2 infection induced axonal damage (*26*).

Analysis of an experimental mouse model of human ACE2 driven by the keratin 18 (K18-hACE2) promoter (*27*) demonstrated that SARS-CoV-2 infection impaired the ability to smell. Immunohistochemical analysis after viral infection revealed the nucleocapsid (N) protein of SARS-CoV-2 was expressed by sustentacular cells in the olfactory epithelium. Data strongly suggested that the mice were susceptible to anosmia after viral infection (*28*). If infection causes a functional abnormality of sustentacular cells, it is plausible that anosmia is reversible.

Analysis of three postmortem samples of the IXth (glossopharyngeal) and Xth (vagal) cranial nerves demonstrated the expression of ACE2, NRP1, and TMPRSS2, suggesting that SARS-CoV-2 can also infect these cranial nerves and induce dysgeusia by direct tissue damage (*29*).

Miscellaneous symptoms

In addition to these common complaints, patients with long COVID exhibit a variety of symptoms possibly related to psychiatric disorders that include attention disorder, post-activity polypnea, nausea or vomiting, memory loss, and paresthesia (*4*). To provide appropriate care to patients, it is necessary to exclude organic disorders in the central nervous system (CNS), further indicating the importance of identifying the tropism of SARS-CoV-2 in the CNS.

Policy for managing long COVID patients

At present, no solid clinical management approach has been established for long COVID. However, it is recommended that all patients with persistent symptoms, particularly those with multisystem complaints or symptoms lasting beyond 12 weeks, should be referred to a specialized outpatient COVID-19 recovery clinic, if available, or a subspecialty clinic relevant to the patient's specific symptoms (*30*).

The need for laboratory testing in patients with long COVID might be determined by the severity of symptoms and abnormal test results during the acute phase and current symptoms. For most patients who have recovered from mild acute COVID-19, routine laboratory testing is not conducted (*30*). In contrast, for patients recovering from more severe illness, it is reasonable to obtain complete blood counts; blood chemistry, including electrolytes, blood urea nitrogen, and serum creatinine. Liver function studies, including serum albumin should also be included. We generally do not monitor coagulation parameters and re-test serology. This approach is supported by the World Health Organization and the Centers for Disease Control and Prevention (*31,32*).

As for the treatment of long COVID, we often deal with each symptom individually. For instance, The American Academy of Physical Medicine and Rehabilitation has developed a multidisciplinary collaborative consensus guidance statement on the assessment and management of fatigue following

COVID-19 (33). Nevertheless, there is no established drug therapy for fatigue and non-pharmaceutical approaches such as "4-P" (Planning, Pacing, Prioritizing, and Positioning) are often recommended (*34*).

With regard to dysosmia and dysgeusia, there is scarce evidence for the use of specific pharmacologic agents. However, patients with persistent gustatory and/or olfactory dysfunction may benefit from olfactory training and self-guided programs. In a 2020 meta-analysis of four studies (two randomized controlled trials and two prospective cohort studies), 286 patients with pulmonary veno-occlusive disease received olfactory training and treatment protocols lasting from 4 to 9 months (*35*). Olfactory training was associated with an increased chance of a clinically important olfactory improvement (odds ratio 2.77, 95% confidence interval 1.67-4.58) compared with patients who did not receive such therapy. If the symptoms fail to resolve, further evaluation by an otolaryngologist may be needed, particularly in the setting of accompanying upper airway symptoms.

In other words, most symptoms caused by long COVID might not be critical; however, they may be difficult to resolve at the same time. The characteristics of patients who should be treated and how long they should be followed up for after the acute phase of COVID-19 are currently unknown. Given the circumstances, the clinical management of long COVID becomes inevitably vague and complicated.

Knowledge about molecular background of long COVID

Neurotropism of SARS-CoV-2

To understand the underlying mode of long COVID, especially related to psychological and/or autonomous function, it is important to know whether SARS-CoV-2 can infect the CNS. Generally, coronaviruses are neurotropic (*36*), and human CoV-229E and -OC43, which cause the common cold, are known to infect CNS tissues (*37*). Notably, reverse transcription-PCR analysis of cerebrospinal fluid of patients infected with SARS-CoV-1 detected the virus (*38*), and immunohistochemical analysis identified viral proteins in brain tissues (*39*). Additionally, infectious virus was isolated from autopsied brain tissue of a patient infected with SARS-CoV-1 (*39*). Moreover, evidence showing the ability of SARS-CoV-2 to infect the CNS was obtained by analysis of postmortem samples (*40,41*). Matschke *et al.* found SARS-CoV-2 viral proteins in cranial nerves originating from the lower brainstem and in isolated cells of the brainstem (*41*), whereas Meinhardt *et al.* detected RNA and the spike protein of SARS-CoV-2 in the medulla oblongata where the primary respiratory and cardiovascular control center is located (*40*). SARS-CoV-2 can enter the nervous system by crossing the neural-mucosal interface in the olfactory mucosa. Immunohistochemical analysis with anti-spike protein antibodies identified positive staining in cortical neurons (*28*).

The transmission of viral infection from the nasal cavity to the CNS was confirmed in transgenic K18-hACE2 mice (*28,42,43*). As reported for SARS-CoV-1, SARS-CoV-2 infection was detected in disconnected regions after nasal infection, implying the possibility that the virus may enter the CNS by different routes (*27*). It has been proposed that S1 protein internalizes the virus through ACE2 and affects blood-brain barrier integrity, resulting in SARS-CoV-2 invasion into the CNS (*44*). As an alternative route *via* a "Trojan horse" model, infected macrophages can possibly enter the CNS and form an infectious focus (*45*).

Risk factors for long COVID

Recently, a longitudinal multi-omics study identified several risk factors associated with long COVID that are measured at the initial point of COVID-19 diagnosis (*22*). These risk factors are as follows: *i*) SARS-CoV-2 RNA level in the blood early in infection, an indicator of viral load; *ii*) the existence of certain autoantibodies; *iii*) type 2 diabetes; and *iv*) reactivation of the EB virus. Among these, the presence of type 2 diabetes has been postulated as a risk factor for the severity of COVID-19 (*46*). It is plausible that the severity of tissue damage caused by viral infection influences the development of long COVID. In contrast, the EB virus, which infects individuals at a young age and becomes dormant in most people, is a well-known risk factor for systemic lupus erythematosus (*47*). An important next step is to determine how the level of viral RNA in the blood and the presence of autoantibodies are linked to the development of long COVID.

Viral proteins

In the acute phase of infection, host tissues are exposed to viral proteins, according to the severity of viral infection. The N protein of SARS-CoV-2 promotes IFN-I signaling and the production of inflammatory cytokines (*48*), leading to systemic inflammation and multi-organ damage (*49*). Notably, N protein is detected in serum during active viral replication (*50*), suggesting that circulating N protein causes symptoms related to long COVID through tissue damage.

In contrast, the spike protein has a variety of activities in several types of cells. In human monocytes/macrophages, it induces proinflammatory responses with an increase in the expression of TNF-α, major histocompatibility complex class II, nuclear factor-kappa B, and c-Jun N-terminal kinase (*51,52*). In pulmonary vascular cells, it activates cell growth

signaling with mitogen-activated protein kinase kinase phosphorylation and participates in cardiovascular/pulmonary abnormalities by thickening the pulmonary vascular wall (53). In microglia, the S1 subunit stimulates neuroinflammation through activation of nuclear factor-kappa B and p38 mitogen-activated protein kinase, resulting in neurological, cognitive, and neuropsychiatric symptoms (54). These observations indicate that S1 protein, which circulates in the blood (Matsunaga *et al.* unpublished data), could directly injure blood, vascular, and neuronal components and induce multiple symptoms of long COVID.

The potent inflammatory activity of S1 protein can be explained by the properties of an amino acid stretch homologous to superantigens. Cheng *et al.* found that the 678TNSPRRARSVASQ690 motif was homologous to the superantigenic 150TN-KKKATVQELD161 peptide of staphylococcal enterotoxin B (SEB) (*55,56*). SEB was first found as a superantigen with the ability to hyper-stimulate T cells expressing the Vβ T cell receptor gene (*55*). Such skewing of Vb2+ T cells was reported in severe/hyperinflammatory SARS-CoV-2 patients (*57*). Moreover, an anti-SEB monoclonal antibody (6D3) blocks SARS-CoV-2 infection (*57*). It was noted that the structural motif formed by three positively charged residues (R682, R683, and R685) in the spike protein was similar to the motif formed by K152, K153, and K154 in SEB (Figure 1, left panel, circle). The Omicron variant has mutations of two amino acids in the corresponding stretch (678TKSHRRAR RSVASQ690; mutated amino acids are underlined), but simulation of its three-dimensional structure suggested similar structural properties (Figure 1, right panel). It is necessary to observe whether infection with the Omicron variant also induces long COVID symptoms.

Autoimmunity in COVID-19

Autoantibodies have been proposed as a risk factor for long COVID (*22*), and several potential mechanisms linking autoimmunity and COVID-19 have been postulated: cross-reactivity between viral proteins and autoantigens (*58*), molecular mimicry (*59*), bystander activation (*60*), anti-idiotypic antibodies to antiviral antibodies (*61*), transient immune-suppression (*62*), and relaxed peripheral immune-tolerance for antibody screening (*63*). Among these, molecular mimicry by viral proteins of host molecules has been well characterized in a number of viruses including hepatitis B virus, hepatitis C virus, EB virus, cytomegalovirus, human T lymphotropic virus type-1, and Dengue virus (*64-67*).

Antibodies to viral proteins

In SARS-CoV-2 proteins, six amino acid sequences similar to host proteins (DAB adaptor protein 1, apoptosis-inducing factor mitochondria associated 1, and surfeit locus protein 1) that are expressed in the brainstem respiratory pacemaker have been identified (*68*). SARS-CoV-2 proteins also share five amino acid peptides with pulmonary surfactant and related proteins (*69*). Recently, it was reported that anti-spike protein antibodies cross-react with tissue proteins, including

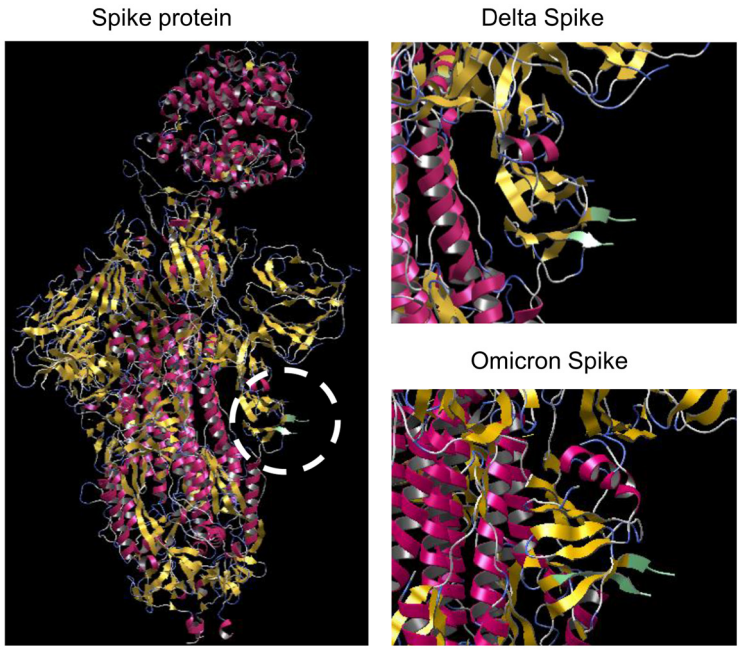

Figure 1. Putative three-dimensional structures of the spike proteins of the Delta and Omicron variants. Structural data were derived from the protein data bank (PDB) database (Delta variant, PDB ID: 7w92, PDB DOI: 10.2210/pdb7W92/pdb; Omicron variant (BA.1), PDB ID: 7wk4, PDB DOI: 10.2210/pdb7WK4/pdb). Simulation was originally performed for this article using the open access software myPresto version 5.0. The left panel, the structure corresponding to the proposed superantigen is highlighted using a circle. The upper and lower right panels show the superantigen structures (enlarged) of the Delta and Omicron (BA.1) variants, respectively.

Table 2. Autoimmune diseases accompanying SARS-CoV-2 infection

Target of autoantibody	Disease	Common symptom	Reference (DOI)
Angiotensin II receptor I	Severe inflammation	Endothelial damage, coagulopathy	10.1371/journal.pone.0259902
Double-stranded DNA	Systemic lupus erythematosus	Immune dysregulation	10.1007/s10067-020-05310-1
Red blood cell	Autoimmune hemolytic anemia	Anemia	10.1111/trf.16226
Platelet	Autoimmune thrombocytopenia	Purpura	10.1056/NEJMc2010472
Glycolipid	Guillain-Barré syndrome	Neurological manifestation	10.1016/S1474-4422(20)30109-5
Nucleus	Kikuchi-Fujimoto disease	Cervical lymphadenopathy mild fever	10.1111/bjh.17292
Neutrophil cytoplasm	Autoimmune vasculitis	Purpura	10.1007/s11239-020-02230-4
Central nervous system	Multiple sclerosis	Chronic inflammation, demyelination	10.1016/j.msard.2020.102377
La/SSB	Multisystem inflammatory syndrome in children	Inflammation in endothelial, gastrointestinal, and immune cells	10.3389/fped.2021.702318
Phospholipid	Antiphospholipid syndrome	Thrombosis	10.1016/j.medcli.2021.09.021
ACE2	Prothrombotic phenotype	Pulmonary hypertension, vasculopathy	10.1371/journal.pone.0257016
Jo-1	Anti-synthetase syndrome	Myopathy, arthritis	10.1186/s12890-020-01388-0

transglutaminase 3, transglutaminase 2, anti-extractable nuclear antigen, myelin basic protein, mitochondria, nuclear antigen, alpha-myosin, thyroid peroxidase, collagen, claudin 5 and 6, and S100 calcium-binding protein B (*70*). Loss of immune tolerance for eliminating cells with autoantibody production is likely due to transient immunosuppression after viral infection and following immune reconstitution. In COVID-19 patients, there are marked changes in various subpopulations of immune cells, including CD4+ and CD8+ T-lymphocytes (*71*), memory B-lymphocytes (*72*), monocytes/macrophages, and dendritic cells (*73*).

Autoantibodies to host molecules

In long COVID patients, a variety of autoantibodies have been identified (*74,75*) (Table 2). Both pre-existing and infection-induced autoantibodies are related to the severity, clinical symptoms, and post-acute symptoms including autoimmune conditions of COVID-19. Patients with anti-ACE2 autoantibodies have suppressed soluble ACE2 activity in plasma and symptoms associated with vasculopathies including pulmonary hypertension (*76*). The reduction or loss of ACE2 activity may lead to the increased activity of angiotensin II through angiotensin II receptor type 1 in the lung, heart, and kidney, which express ACE2 at high levels, resulting in enhanced inflammation (*77*) and prothrombotic phenotypes *(78,79*). The inflammatory stimuli triggered by autoantibodies may lead to the atypical phenotypes observed in long COVID (*80*).

Possible involvement of viral persistence

The number of clinical reports on recurrent infections with COVID-19 has been increasing (*81*), explained by viral relapse/reactivation in patients with persistent infection (*82,83*). Consistently, analysis using autopsy samples has detected persistent SARS-CoV-2 infection in multiple sites including the trachea, heart, lymph nodes, intestine, kidney, skeletal muscle, and brain. Strikingly, infection in the brain, including the cerebral cortex, brainstem, cerebellum, thalamus, hypothalamus, corpus callosum, and basilar artery regions, was detected for up to 230 days from initial symptom onset (*84*). This observation is consistent with reports on recurrent shedding of SARS-CoV-2 RNA in various body fluids such as urine, feces, and nasal mucous, implying the possibility that the viral genome remains transcriptionally active for a long time (*45*).

The persistence of SARS-CoV-2 is not surprising because RNA-sequencing analysis of 51 tissue types collected from healthy individuals at autopsy identified human CoV-229E transcripts in various tissues such as the brain, skin, and blood (*85*). Moreover, a number of RNA viruses, including hepatitis C virus, Ebola virus, Zika virus, respiratory syncytial virus, and measles virus, can establish persistent infections *(45,86*). As the most striking example, measles virus retained in the CNS causes sclerosing subacute panencephalitis (*87*). A link between persistent infection and fatigue-related symptoms has also been proposed because enteroviruses and their proteins are found in tissue samples obtained from patients with myalgia/chronic fatigue syndrome (*88*).

In the innate immune system, mammalian cells are equipped with pattern-recognition receptors for sensing viral RNA, which depend on endosomal Toll-like receptors and cytosolic retinoic acid-inducible gene I (RIG-I)-like receptors (*89*). Upon pattern-recognition receptor activation, downstream signaling cascades trigger the secretion of IFN-I/III, TNF-α, IL-1, and IL-6 (*90*). Recently, stimulator of interferon genes (STING), which was originally identified as a molecule that recognizes cytoplasmic DNA (*89*), was reported to function as an RNA-sensing molecule (*91*). STING cooperates with cyclic GMP-AMP synthase (cGAS), and the cGAS-STING pathway induces IFN-I production (91). Similar to SARS-CoV-1, multiple proteins of SARS-CoV-2 differentially block the pattern-recognition receptor pathway (*92*). Rui *et al.* demonstrated that protease 3CL of SARS-CoV-2

blocks the immune responses induced by the RIG-I-like receptor and cGAS-STING pathways (*92*). Furthermore, N protein antagonizes RIG-I-like receptor innate immune activation, whilst SARS-CoV-2 open reading frame (ORF) 3a specifically antagonizes the immune activation induced by cGAS-STING. It remains elusive how the inhibitory activity of viral proteins contributes to persistent transcription of viral RNA (*91*).

As an alternative mechanism for viral persistence, Zhang *et al.* reported that viral RNA is reverse-transcribed and integrated into the genome (*93*). In human cells, endogenous reverse transcriptase is derived from long interspersed element-1 (L1), an endogenous retroelement (*94*). L1 makes up about 17% of the human genome, and approximately 100 of the 5.0×10^5 copies present in a single cell are active for retrotransposition. L1 encodes ORF1 as well as ORF2, which has reverse transcriptase activity. It has been proposed that SARS-CoV-2 integrated into the genome is responsible for the continuous shedding of viral RNA. However, further study is required because the integration of viral DNA into the human genome was not reproducibly identified (*95*).

Although it remains elusive how viral proteins contribute to viral persistence, newly synthesized viral RNA and proteins will repetitively induce tissue inflammation and enhance the host immune reaction.

Therapeutic approaches for long COVID

As autoimmunity and persistent inflammatory conditions are likely to underlie the pathophysiological conditions of long COVID, Goel *et al.* investigated the effects of immunosuppressive agents on long COVID. Based on a 3-month follow-up analysis of 24 patients with long COVID who were administered glucocorticoid, they proposed that systemic steroids are helpful for recovery from long COVID. However, the number of enrolled patients was too small to draw a reliable conclusion (*96*).

There is an increasing number of reports examining the effectiveness of SARS-CoV-2 vaccination for the treatment of long COVID. Nehme *et al.* investigated the possible link between the improvement of long COVID after vaccination by analyzing its impact on the six main complaints (*i.e.*, fatigue, difficulty concentrating or memory loss, impaired sense of smell or taste, shortness of breath, and headache) (*97*). Out of 1,596 participants with symptoms developing after SARS-CoV-2 infection, 47.1% were vaccinated once or twice, while 65.3% of 228 participants without symptoms were vaccinated. Notably, the symptoms disappeared or improved in 35.5% of the vaccinated participants, while the symptoms were stable in 28.7% and worsened in 3.3%. Vaccination with two doses was associated with a decreased prevalence of dyspnea and change in the ability to taste. Additionally, Arnold *et al.* studied changes of symptoms after COVID-19 vaccination (*98*). Out of 78 participants, 44 had received vaccination, and at least one symptom was observed in 36 of the 44 vaccinated participants. A follow-up study was conducted for 8 months after vaccination to assess its effects on 159 symptoms. Out of these symptoms, 37 (23.2%) had improved, 9 (5.6%) had worsened, and 113 (71.1%) were unchanged. The Pfizer-BioNTech and Oxford-AstraZeneca vaccines had similar effects on the symptoms. In addition to these two peer-reviewed reports on the effectiveness of vaccination on long COVID, three additional non-peer-reviewed studies reported the favorable effects of COVID-19 vaccination. In contrast, Scherlinger *et al.* reported that COVID-19 vaccination was tolerable, because it was not linked with severe side effects, however it was not effective for long COVID (*99*). An improvement of symptoms was observed in 21.8% of participants, whereas they worsened in 31%. In their study, approximately one-third of participants did not receive vaccination due to expectations that it was a contraindication for long COVID and would worsen symptoms.

Intravenous immunoglobulin therapy (IVIg) has been used for patients in the acute phase of SARS-CoV-2 infection (*100*). Notably, IVIg has been used to treat patients with Guillain-Barré syndrome with favorable outcomes. Although the precise mechanism underlying Guillain-Barré syndrome is unknown, it is suggested that antibodies against surface glycoproteins of the pathogen cross-react with peripheral nerves through similar native proteins and damage cellular function. Among various functions, IVIg can neutralize autoantibodies and control cell-cell interactions by blocking Fc gamma receptors on immune cells. Moreover, IVIg, when prepared from convalescent SARS-CoV-2 patients, can neutralize viral proteins, suggesting that IVIg may be effective for long COVID patients, thus warranting its evaluation in clinical trials.

Conclusion

Direct tissue damage by SARS-CoV-2 infection, constitutive inflammatory responses including autoimmunity, and psychiatric impairment have been suggested as underlying etiologies of long COVID. Although it is unclear how constitutive inflammatory responses are induced, lines of evidence support the hypothesis that persistent infection is a putative cause of continuous inflammation. Additionally, clinical trials of the effects of COVID vaccination on long COVID patients have produced favorable outcomes, further implying that a persistent viral infection is involved in long COVID. Beside vaccination, it might be worthwhile to perform clinical trials using anti-viral compounds to see whether the symptoms of long COVID can be improved.

Funding: This work was supported by Grants-in-Aid from the National Center for Global Health and Medicine

(E20A2004D01, 20A2010, 20A2007D, 21A1006).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Nalbandian A, Sehgal K, Gupta A, *et al.* Post-acute COVID-19 syndrome. Nat Med. 2021; 27:601-615.
2. Mehandru S, Merad M. Pathological sequelae of long-haul COVID. Nat Immunol. 2022; 23:194-202.
3. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021. *https://apps.who.int/iris/handle/10665/345824* (accessed March 9, 2022).
4. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. Sci Rep. 2021; 11:16144.
5. Miyazato Y, Morioka S, Tsuzuki S, Akashi M, Osanai Y, Tanaka K, Terada M, Suzuki M, Kutsuna S, Saito S, Hayakawa K, Ohmagari N. Prolonged and late-onset symptoms of coronavirus disease 2019. Open Forum Infect Dis. 2020; 7:ofaa507.
6. Fernández-de-Las-Peñas C, Martín-Guerrero JD, Pellicer-Valero ÓJ, Navarro-Pardo E, Gómez-Mayordomo V, Cuadrado ML, Arias-Navalón JA, Cigarán-Méndez M, Hernández-Barrera V, Arendt-Nielsen L. Female sex is a risk factor associated with long-term post-COVID related-symptoms but not with COVID-19 symptoms: The LONG-COVID-EXP-CM multicenter study. J Clin Med. 2022; 11:413.
7. Blomberg B, Mohn KG, Brokstad KA, *et al.* Long COVID in a prospective cohort of home-isolated patients. Nat Med. 2021; 27:1607-1613.
8. Yelin D, Margalit I, Nehme M, *et al.* Patterns of long COVID symptoms: A multi-center cross sectional study. J Clin Med. 2022; 11:898.
9. Ishikura H, Maruyama J, Hoshino K, Matsuoka Y, Yano M, Arimura T, Katano H, Kato S, Kitamura T, Nakamura Y. Coronavirus disease (COVID-19) associated delayed-onset fulminant myocarditis in patient with a history of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. J Infect Chemother. 2021; 27:1760-1764.
10. Al-Falahi Z, Al-Harthi S, Farhan H, Al Busaidi I, Al Alawi AM. Late-onset COVID-19-related multi-system inflammatory syndrome in a middle-aged man. Cureus. 2021; 13:e15855.
11. Han Q, Zheng B, Daines L, Sheikh A. Long-term sequelae of COVID-19: A systematic review and meta-analysis of one-year follow-up studies on post-COVID symptoms. Pathogens. 2022; 11:269.
12. Ahmed H, Patel K, Greenwood DC, Halpin S, Lewthwaite P, Salawu A, Eyre L, Breen A, O'Connor R, Jones A, Sivan M. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. J Rehabil Med. 2020; 52:jrm00063.
13. Aucott JN, Rebman AW. Long-haul COVID: heed the lessons from other infection-triggered illnesses. Lancet. 2021; 397:967-968.
14. Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, *et al.* Fatigue and dyspnoea as main persistent post-COVID-19 symptoms in previously hospitalized patients: Related functional limitations and disability. Respiration. 2022; 101:132-141.
15. Fortini A, Rosso A, Cecchini P, Torrigiani A, Lo Forte A, Carrai P, Alessi C, Fabbrizzi F, Lovicu E, Sbaragli S, Faraone A. One-year evolution of DLCO changes and respiratory symptoms in patients with post COVID-19 respiratory syndrome. Infection. 2022; 50:513-517.
16. Sonnweber T, Sahanic S, Pizzini A, *et al.* Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. Eur Respir J. 2021; 57:2003481.
17. Lam GY, Befus AD, Damant RW, Ferrara G, Fuhr DP, Stickland MK, Varughese RA, Wong EY, Smith MP. Exertional intolerance and dyspnea with preserved lung function: an emerging long COVID phenotype? Respir Res. 2021; 22:222.
18. Melms JC, Biermann J, Huang H, *et al.* A molecular single-cell lung atlas of lethal COVID-19. Nature. 2021; 595:114-119.
19. Hazen H. Postinfluenzal alopecia. JAMA. 1919; 72:1452.
20. Starace M, Iorizzo M, Sechi A, *et al.* Trichodynia and telogen effluvium in COVID-19 patients: Results of an international expert opinion survey on diagnosis and management. JAAD Int. 2021; 5:11-18.
21. Fagan N, Meah N, York K, Bokhari L, Fletcher G, Chen G, Tobin DJ, Messenger A, Irvine AD, Sinclair R, Wall D. Shedding light on therapeutics in alopecia and their relevance to COVID-19. Clin Dermatol. 2021; 39:76-83.
22. Su Y, Yuan D, Chen DG, *et al.* Multiple early factors anticipate post-acute COVID-19 sequelae. Cell. 2022; 185:881-895.e20.
23. Bilinska K, Jakubowska P, Von Bartheld CS, Butowt R. Expression of the SARS-CoV-2 entry proteins, ACE2 and TMPRSS2, in cells of the olfactory epithelium: Identification of cell types and trends with age. ACS Chem Neurosci. 2020; 11:1555-1562.
24. Brann DH, Tsukahara T, Weinreb C, *et al.* Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv. 2020; 6:eabc5801.
25. Cantuti-Castelvetri L, Ojha R, Pedro LD, *et al.* Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. Science. 2020; 370:856-860.
26. Kirschenbaum D, Imbach LL, Ulrich S, Rushing EJ, Keller E, Reimann RR, Frauenknecht KBM, Lichtblau M, Witt M, Hummel T, Steiger P, Aguzzi A, Frontzek K. Inflammatory olfactory neuropathy in two patients with COVID-19. Lancet. 2020; 396:166.
27. Winkler ES, Bailey AL, Kafai NM, *et al.* SARS-CoV-2 infection of human ACE2-transgenic mice causes severe lung inflammation and impaired function. Nat Immunol. 2020; 21:1327-1335.
28. Zheng J, Wong LR, Li K, Verma AK, Ortiz ME, Wohlford-Lenane C, Leidinger MR, Knudson CM, Meyerholz DK, McCray PB Jr, Perlman S. COVID-19 treatments and pathogenesis including anosmia in K18-hACE2 mice. Nature. 2021; 589:603-607.
29. Vitale-Cross L, Szalayova I, Scoggins A, Palkovits M, Mezey E. SARS-CoV-2 entry sites are present in all structural elements of the human glossopharyngeal and vagal nerves: clinical implications. bioRxiv. 2022; 2021.12.30.474580.
30. UpToDate. Coronavirus disease 2019 (COVID-19). *https://www.uptodate.com/landing/covid19?source=promobox*

(accessed March 9, 2022).
31. World Health Organization. Support for rehabilitation: self-management after COVID-19-related illness. 2020. *https://apps.who.int/iris/bitstream/handle/10665/344472/WHO-EURO-2021-855-40590-59892-eng.pdf?sequence=1&isAllowed=y* (accessed March 9, 2022).
32. Centers for Disease Control and Prevention. COVID-19. *https://www.cdc.gov/coronavirus/2019-ncov/your-health/quarantine-isolation.html* (accessed March 9, 2022).
33. Herrera JE, Niehaus WN, Whiteson J, Azola A, Baratta JM, Fleming TK, Kim SY, Naqvi H, Sampsel S, Silver JK, Gutierrez MV, Maley J, Herman E, Abramoff B. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. PM R. 2021; 13:1027-1043.
34. Homerton University Hospital. Post COVID-19 patients infromation pack. Helping you to recover and manage your symptoms following COVID-19. *https://gp-website-cdn-prod.s3.amazonaws.com/downloads/1589364822-a2ac4f0d54141da323f4087888276478.pdf* (accessed March 9, 2022).
35. Kattar N, Do TM, Unis GD, Migneron MR, Thomas AJ, McCoul ED. Olfactory training for postviral olfactory dysfunction: Systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2021; 164:244-254.
36. Carod-Artal FJ. Neurological complications of coronavirus and COVID-19. Rev Neurol. 2020; 70:311-322.
37. Arbour N, Day R, Newcombe J, Talbot PJ. Neuroinvasion by human respiratory coronaviruses. J Virol. 2000; 74:8913-8921.
38. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis. 2004; 10:342-344.
39. Xu J, Zhong S, Liu J, Li L, Li Y, Wu X, Li Z, Deng P, Zhang J, Zhong N, Ding Y, Jiang Y. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. Clin Infect Dis. 2005; 41:1089-1096.
40. Meinhardt J, Radke J, Dittmayer C, *et al.* Olfactory transmucosal SARS-CoV-2 invasion as a port of central nervous system entry in individuals with COVID-19. Nat Neurosci. 2021; 24:168-175.
41. Matschke J, Lütgehetmann M, Hagel C, *et al.* Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol. 2020; 19:919-929.
42. Tseng CT, Huang C, Newman P, Wang N, Narayanan K, Watts DM, Makino S, Packard MM, Zaki SR, Chan TS, Peters CJ. Severe acute respiratory syndrome coronavirus infection of mice transgenic for the human Angiotensin-converting enzyme 2 virus receptor. J Virol. 2007; 81:1162-1173.
43. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. J Virol. 2008; 82:7264-7275.
44. DeOre BJ, Tran KA, Andrews AM, Ramirez SH, Galie PA. SARS-CoV-2 spike protein disrupts blood-brain barrier integrity *via* RhoA activation. J Neuroimmune Pharmacol. 2021; 16:722-728.
45. Proal AD, VanElzakker MB. Long COVID or post-acute sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms. Front Microbiol. 2021; 12:698169.
46. Raveendran AV, Misra A. Post COVID-19 syndrome ("Long COVID") and diabetes: Challenges in diagnosis and management. Diabetes Metab Syndr. 2021; 15:102235.
47. James JA, Kaufman KM, Farris AD, Taylor-Albert E, Lehman TJ, Harley JB. An increased prevalence of Epstein-Barr virus infection in young patients suggests a possible etiology for systemic lupus erythematosus. J Clin Invest. 1997; 100:3019-3026.
48. Zhao Y, Sui L, Wu P, Wang W, Wang Z, Yu Y, Hou Z, Tan G, Liu Q, Wang G. A dual-role of SARS-CoV-2 nucleocapsid protein in regulating innate immune response. Signal Transduct Target Ther. 2021; 6:331.
49. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, Hirayama AV, Mastroiani F, Turtle CJ, Harhay MO, Legrand M, Deutschman CS. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med. 2020; 8:1233-1244.
50. Zhang Y, Ong CM, Yun C, Mo W, Whitman JD, Lynch KL, Wu AHB. Diagnostic value of nucleocapsid protein in blood for SARS-CoV-2 infection. Clin Chem. 2021; 68:240-248.
51. Barhoumi T, Alghanem B, Shaibah H, Mansour FA, Alamri HS, Akiel MA, Alroqi F, Boudjelal M. SARS-CoV-2 coronavirus spike protein-induced apoptosis, inflammatory, and oxidative stress responses in THP-1-like-macrophages: Potential role of angiotensin-converting enzyme inhibitor (Perindopril). Front Immunol. 2021; 12:728896.
52. Shirato K, Kizaki T. SARS-CoV-2 spike protein S1 subunit induces pro-inflammatory responses *via* toll-like receptor 4 signaling in murine and human macrophages. Heliyon. 2021; 7:e06187.
53. Suzuki YJ, Nikolaienko SI, Dibrova VA, Dibrova YV, Vasylyk VM, Novikov MY, Shults NV, Gychka SG. SARS-CoV-2 spike protein-mediated cell signaling in lung vascular cells. Vascul Pharmacol. 2021; 137:106823.
54. Frank MG, Nguyen KH, Ball JB, Hopkins S, Kelley T, Baratta MV, Fleshner M, Maier SF. SARS-CoV-2 spike S1 subunit induces neuroinflammatory, microglial and behavioral sickness responses: Evidence of PAMP-like properties. Brain Behav Immun. 2022; 100:267-277.
55. Choi Y, Lafferty JA, Clements JR, Todd JK, Gelfand EW, Kappler J, Marrack P, Kotzin BL. Selective expansion of T cells expressing V beta 2 in toxic shock syndrome. J Exp Med. 1990; 172:981-984.
56. Deacy AM, Gan SK, Derrick JP. Superantigen recognition and interactions: Functions, mechanisms and applications. Front Immunol. 2021; 12:731845.
57. Cheng MH, Porritt RA, Rivas MN, Krieger JM, Ozdemir AB, Garcia G Jr, Arumugaswami V, Fries BC, Arditi M, Bahar I. A monoclonal antibody against staphylococcal enterotoxin B superantigen inhibits SARS-CoV-2 entry *in vitro*. Structure. 2021; 29:951-962 e3.
58. Yamamoto K. Possible mechanisms of autoantibody production and the connection of viral infections in human autoimmune diseases. Tohoku J Exp Med. 1994; 173:75-82.
59. Rojas M, Restrepo-Jiménez P, Monsalve DM, Pacheco Y, Acosta-Ampudia Y, Ramírez-Santana C, Leung PSC, Ansari AA, Gershwin ME, Anaya JM. Molecular mimicry and autoimmunity. J Autoimmun. 2018; 95:100-123.

60. Pacheco Y, Acosta-Ampudia Y, Monsalve DM, Chang C, Gershwin ME, Anaya JM. Bystander activation and autoimmunity. J Autoimmun. 2019; 103:102301.
61. Plotz PH. Autoantibodies are anti-idiotype antibodies to antiviral antibodies. Lancet. 1983; 2:824-826.
62. Canas CA. The triggering of post-COVID-19 autoimmunity phenomena could be associated with both transient immunosuppression and an inappropriate form of immune reconstitution in susceptible individuals. Med Hypotheses. 2020; 145:110345.
63. Woodruff MC, Ramonell RP, Saini AS, *et al.* Relaxed peripheral tolerance drives broad de novo autoreactivity in severe COVID-19. medRxiv. 2021; 2020.10.21.20216192.
64. Acay A, Demir K, Asik G, Tunay H, Acarturk G. Assessment of the frequency of autoantibodies in chronic viral hepatitis. Pak J Med Sci. 2015; 31:150-154.
65. Sutton RN, Emond RT, Thomas DB, Doniach D. The occurrence of autoantibodies in infectious mononucleosis. Clin Exp Immunol. 1974; 17:427-436.
66. Andersen P, Andersen HK. Smooth-muscle antibodies and other tissue antibodies in cytomegalovirus infection. Clin Exp Immunol. 1975; 22:22-29.
67. Vo HTM, Duong V, Ly S, Li QZ, Dussart P, Cantaert T. Autoantibody profiling in plasma of dengue virus-infected individuals. Pathogens. 2020; 9:1060.
68. Lucchese G, Floel A. Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons. Autoimmun Rev. 2020; 19:102556.
69. Kanduc D, Shoenfeld Y. On the molecular determinants of the SARS-CoV-2 attack. Clin Immunol. 2020; 215:108426.
70. Vojdani A, Kharrazian D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin Immunol. 2020; 217:108480.
71. Liu Y, Tan W, Chen H, Zhu Y, Wan L, Jiang K, Guo Y, Tang K, Xie C, Yi H, Kuang Y, Luo Y. Dynamic changes in lymphocyte subsets and parallel cytokine levels in patients with severe and critical COVID-19. BMC Infect Dis. 2021; 21:79.
72. Sosa-Hernández VA, Torres-Ruíz J, Cervantes-Díaz R, Romero-Ramírez S, Páez-Franco JC, Meza-Sánchez DE, Juárez-Vega G, Pérez-Fragoso A, Ortiz-Navarrete V, Ponce-de-León A, Llorente L, Berrón-Ruiz L, Mejía-Domínguez NR, Gómez-Martín D, Maravillas-Montero JL. B cell subsets as severity-associated signatures in COVID-19 patients. Front Immunol. 2020; 11:611004.
73. Sanchez-Cerrillo I, Landete P, Aldave B, *et al.* Differential redistribution of activated monocyte and dendritic cell subsets to the lung associates with severity of COVID-19. medRxiv. 2020; 2020.05.13.20100925.
74. Favaloro EJ, Henry BM, Lippi G. COVID-19 and antiphospholipid antibodies: Time for a reality check? Semin Thromb Hemost. 2022; 48:72-92.
75. Wang EY, Mao T, Klein J, *et al.* Diverse functional autoantibodies in patients with COVID-19. Nature. 2021; 595:283-288.
76. Takahashi Y, Haga S, Ishizaka Y, Mimori A. Autoantibodies to angiotensin-converting enzyme 2 in patients with connective tissue diseases. Arthritis Res Ther. 2010; 12:R85.
77. Jia H. Pulmonary angiotensin-converting enzyme 2 (ACE2) and inflammatory lung disease. Shock. 2016; 46:239-248.
78. Gue YX, Gorog DA. Reduction in ACE2 may mediate the prothrombotic phenotype in COVID-19. Eur Heart J. 2020; 41:3198-3199.
79. Lupi L, Adamo M, Inciardi RM, Metra M. ACE2 down-regulation may contribute to the increased thrombotic risk in COVID-19. Eur Heart J. 2020; 41:3200.
80. Knight JS, Caricchio R, Casanova JL, *et al.* The intersection of COVID-19 and autoimmunity. J Clin Invest. 2021; 131:e154886.
81. Choudhary MC, Crain CR, Qiu X, Hanage W, Li JZ. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) sequence characteristics of coronavirus disease 2019 (COVID-19) persistence and reinfection. Clin Infect Dis. 2022; 74:237-245.
82. Gousseff M, Penot P, Gallay L, *et al.* Clinical recurrences of COVID-19 symptoms after recovery: Viral relapse, reinfection or inflammatory rebound? J Infect. 2020; 81:816-846.
83. Lee JS, Kim SY, Kim TS, *et al.* Evidence of severe acute respiratory syndrome coronavirus 2 reinfection after recovery from mild coronavirus disease 2019. Clin Infect Dis. 2021; 73:e3002-e3008.
84. Chertow D, Stein S, Ramelli S, Grazioli A, Chung J-Y, Singh M, Yinda CK, Winkler C, Dickey J, Yiaya K. SARS-CoV-2 infection and persistence throughout the human body and brain. Research Square. 2021. DOI: 10.21203/rs.3.rs-1139035/v1.
85. Kumata R, Ito J, Takahashi K, Suzuki T, Sato K. A tissue level atlas of the healthy human virome. BMC Biol. 2020; 18:55.
86. McCarthy MK, Morrison TE. Persistent RNA virus infections: do PAMPS drive chronic disease? Curr Opin Virol. 2017; 23:8-15.
87. Sidhu MS, Crowley J, Lowenthal A, Karcher D, Menonna J, Cook S, Udem S, Dowling P. Defective measles virus in human subacute sclerosing panencephalitis brain. Virology. 1994; 202:631-641.
88. Chia J, Chia A, Voeller M, Lee T, Chang R. Acute enterovirus infection followed by myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and viral persistence. J Clin Pathol. 2010; 63:165-168.
89. Ishikawa H, Barber GN. STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. Nature. 2008; 455:674-678.
90. Vabret N, Britton GJ, Gruber C, *et al.* Immunology of COVID-19: Current state of the science. Immunity. 2020; 52:910-941.
91. Webb LG, Fernandez-Sesma A. RNA viruses and the cGAS-STING pathway: reframing our understanding of innate immune sensing. Curr Opin Virol. 2022; 53:101206.
92. Rui Y, Su J, Shen S, *et al.* Unique and complementary suppression of cGAS-STING and RNA sensing- triggered innate immune responses by SARS-CoV-2 proteins. Signal Transduct Target Ther. 2021; 6:123.
93. Zhang L, Richards A, Barrasa MI, Hughes SH, Young RA, Jaenisch R. Reverse-transcribed SARS-CoV-2 RNA can integrate into the genome of cultured human cells and can be expressed in patient-derived tissues. Proc Natl Acad Sci U S A. 2021; 118:e2105968118.
94. Goodier JL, Kazazian HH, Jr. Retrotransposons revisited: the restraint and rehabilitation of parasites. Cell. 2008; 135:23-35.
95. Smits N, Rasmussen J, Bodea GO, Amarilla AA, Gerdes P, Sanchez-Luque FJ, Ajjikuttira P, Modhiran N, Liang B, Faivre J, Deveson IW, Khromykh AA, Watterson D,

Ewing AD, Faulkner GJ. No evidence of human genome integration of SARS-CoV-2 found by long-read DNA sequencing. Cell Rep. 2021; 36:109530.
96. Goel N, Goyal N, Nagaraja R, Kumar R. Systemic corticosteroids for management of 'long-COVID': an evaluation after 3 months of treatment. Monaldi Arch Chest Dis. 2021. doi:10.4081/monaldi.2021.1981
97. Nehme M, Braillard O, Salamun J, Jacquerioz F, Courvoisier DS, Spechbach H, Guessous I. Symptoms after COVID-19 vaccination in patients with post-acute sequelae of SARS-CoV-2. J Gen Intern Med. 2022; doi: 10.1007/s11606-022-07443-2.
98. Arnold DT, Milne A, Samms E, Stadon L, Maskell NA, Hamilton FW. Symptoms after COVID-19 vaccination in patients with persistent symptoms after acute infection: A case series. Ann Intern Med. 2021; 174:1334-1336.
99. Scherlinger M, Pijnenburg L, Chatelus E, Arnaud L, Gottenberg JE, Sibilia J, Felten R. Effect of SARS-CoV-2 vaccination on symptoms from post-acute sequelae of COVID-19: Results from the nationwide VAXILONG study. Vaccines (Basel). 2021; 10:46.
100. Gupta S, Chandra A, Ray BK, Pandit A. Treatment related fluctuation and response to intravenous immunoglobulin therapy in post COVID-19 Guillain-Barre syndrome. Diabetes Metab Syndr. 2021; 15:102246.

Received March 9, 2022; Revised March 23, 2022; Accepted April 4, 2022.

Released online in J-STAGE as advance publication April 6, 2022.

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Global Health & Medicine. 2022; 4(2):94-100.
MINI-REVIEW
DOI: 10.35772/ghm.2022.01004

For safe and adequate blood purification therapy in severe COVID-19 — what we have learned so far

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Abstract: Acute kidney injury (AKI) is defined as an increase in serum creatinine within 48 h or 1 week, or a decrease in urine output within 6-24 h. Continuous renal replacement therapy (CRRT) plays an important role in patients with severe AKI. In addition to direct cytotoxicity caused by the severe acute respiratory syndrome coronavirus 2, patients with coronavirus disease (COVID-19) experience endothelial cell damage, increased thrombogenic inflammation, and impaired immune responses. It has been reported that the more severe the case, the greater overproduction of cytokines and the more advanced the multiorgan failure. The kidney is widely recognized as one of the primary target organs; and COVID-19 positive AKI has been reported to have a greater rate of subsequent decline in renal function than COVID-19 negative AKI. Blood purification therapy has been used to prevent or alleviate organ damage in patients with moderate-to-severe COVID-19. Cytokine regulation is one of the primary therapeutic goals for these patients. Even with the widespread use of vaccines and antibody therapy, a certain percentage of patients develop moderate-to-severe diseases.

***Keywords*:** blood purification, cytokines, acute kidney injury, Japan

Introduction

Acute kidney injury (AKI) is defined as an increase in serum creatinine within 48 h or 1 week, or a decrease in urine output within 6-24 h. At present, despite many opportunities to consider renal dysfunction as a part of multi-organ failure in the intensive care unit (ICU), drugs for AKI with clear clinical evidence have not reached clinical application. Acute hemodialysis, especially continuous renal replacement therapy (CRRT), plays an important role in severe AKI.

The spike protein (S protein) in the envelope of the new severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) binds to a receptor on the cell membrane (ACE2 receptor). It enters the cell through the transmembrane protease serine 2 (TMPRSS2). In addition to direct cell damage caused by the virus, endothelial cell damage, promotion of thrombotic inflammation, and impaired immune response are known to occur. In new coronavirus infections (coronavirus disease 2019; COVID-19), cytokine overproduction occurs, especially in severe cases, leading to progressive multi-organ failure. The kidney is widely recognized as the primary target organ (Figure 1) (*1*). Overseas, it has been reported that among COVID-19 cases, the incidence of AKI occurs in a range of 0.5-29% (*2*).

In general, AKI in a certain percentage of patients progresses to chronic kidney disease, and COVID-19-positive AKI has been reported to have a greater rate of subsequent decline in renal function than COVID-19-negative AKI (*3*). The initial symptoms of COVID-19 are similar to those of influenza, such as fever, cough, malaise, and dyspnea. The median time to hospitalization is 7 days. Diarrhea and taste and smell disorders may occur in some cases, although they are not inevitable. According to data from COVIREGI-JP, the Japanese registry for COVID-19 patients, 60% of hospitalized patients did not require oxygen administration, while 30% did, 9% required a ventilator or extracorporeal membrane oxygenation (ECMO), and 7.5% died. Predicting which patients will become critically ill is crucial for utilizing limited medical resources. We have reported that non-invasive urinary liver type fatty acid-binding protein (L-FABP) at the time of admission can be used to predict the severity of the disease (*4*).

Blood purification therapy is used to prevent or alleviate organ damage in patients with moderate-to-severe COVID-19. The goal is to remove circulating mediators, such as cytokines and damage-associated molecular patterns, including blood perfusion and plasma exchange for cytokine removal. However, when the disease progresses to multiple organ failure, blood purification is used to treat AKI and endotoxemia caused by various infections. The goal of therapy is to prevent

progression of organ failure, and renal replacement therapy (RRT), endotoxin adsorption, and plasma exchange are used to continue to remove cytokines (Figure 2) (*1*). This review aimed to investigate safe and adequate blood purification therapies for severe COVID-19.

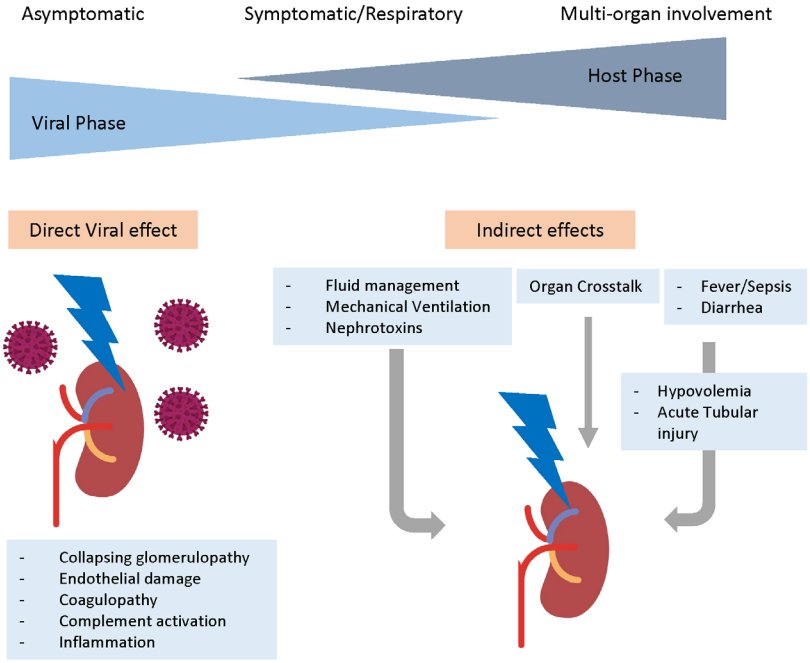

Figure 1. COVID-19 and acute kidney injury*. The effects of COVID-19 on the kidneys have been suggested to be direct viral damage and indirect effects. *Modified from *Ref. 1.*

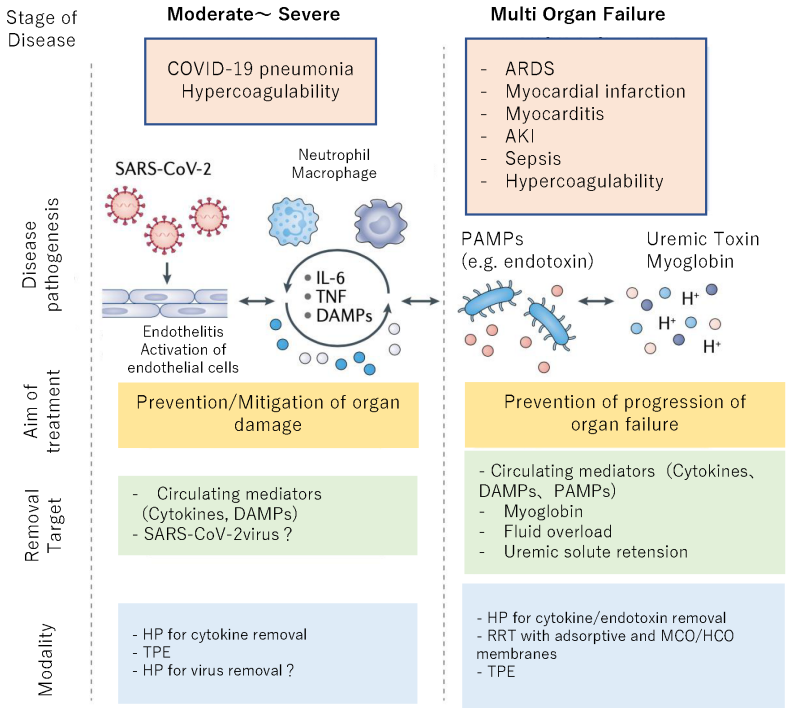

Figure 2. Blood purification therapy according to COVID-19 pathology*. Extracorporeal blood purification (EBP) has been proposed as a potential adjunctive therapy for critically ill patients with COVID-19 EBP may improve the condition by removing circulating immunomodulators. *Modified from *Ref. 1.* AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; DAMPs, damage-associated molecular patterns; HCO, high cut-off; HP, hemoperfusion; MCO, medium cut-off; PAMPs, PAMPs, pathogen-associated molecular patterns; RRT, renal replacement therapy; TPE, therapeutic plasma exchange.

CRRT

The benefits of early introduction of RRT include adjustment of positive water balance, electrolyte and acid-base balance, and elimination of inflammatory mediators. Meanwhile, the combination of vascular access insertion, anticoagulant use, and limited medical resources must be considered. The AKIKI study (*5*), published in 2016, is a French multicenter randomized controlled trial (RCT) that compared an early group of invasively treated patients with stage 3 AKI who started RRT within 6 h of study inclusion with a waitlist group that started RRT when an absolute indication for RRT emerged or when oliguria persisted for at least 72 h (51% of the waitlist group received RRT). No significant difference was observed in 60-day mortality between the early group and the waitlist group (48.5% *vs.* 49.7%; $p = 0.79$), while catheter-related infections and hypophosphatemia were significantly higher in the early group. The 2018 IDEAL-ICU study (*6*) was another French multicenter RCT. No significant difference in mortality at 90 days was observed (57.7% *vs.* 53.8%). In 2020, the STARRT-AKI study (*7*), the largest multicenter RCT ever conducted, was published in Canada. No significant difference in 90-day mortality (43.9% *vs.* 43.7%; $p = 0.92$) was identified, and RRT dependence was higher in the early start group. Based on the above, postponing RRT in patients with stage 3 AKI until it is indicated under close supervision is acceptable (*8*). The 2016 Japanese guidelines for the treatment of AKI, which were published before the results of STARRT-AKI were issued, stated that "there is little evidence that early initiation of blood purification improves prognosis, and the timing of initiation should be determined based on a wide range of clinical symptoms and conditions (strength of recommendation; no grade)".

The 25th Work Group (WG) of the Acute Disease Quality Initiative (ADQI) stated that there is no evidence that AKI due to COVID-19 should be managed differently from AKI due to other causes (*i.e.*, it should be managed in the same way as before) (*1*). The following are the proposals for WG (Table 1). First, the use of ultrasound for vascular access insertion and RRT administration should remain based on the KDIGO AKI guidelines (level of evidence: 1A). Second, the timing of RRT initiation, site of vascular access, and modality of acute RRT should be based on patient needs, the expertise of the institution, and availability of staff and equipment (NOT GRADED). Last, because COVID-19 often causes a hypercoagulable state, we suggest the use of continuous venous-venous hemodialysis or continuous venous-venous hemodiafiltration to reduce the filtration rate and reduce the risk of circuit coagulation when CRRT is performed (level of evidence: 2C).

In our hospital, when CRRT is performed, the first choice for a hemofilter is a membrane that can be expected to adsorb cytokines, such as polymethyl methacrylate membrane. When CRRT was first introduced in our institution in the first wave of severe COVID-19 cases, the problem was disposal of RRT effluents. In our study, the genomic material of SARS-CoV-2 was detected in the effluent (*9*). Considering the pore size of the hemofilter (7-10 nm) and the size of SARS-CoV-2 (approximately 100 nm), the virus appearing in total length in the CRRT effluent is unlikely. However, from the perspective of infection prevention for ICU staff and the psychological stress of treatment, drainage fluid is first solidified with a coagulant and then disposed of as regular infectious waste. Additionally, 24-hourly circuit replacement is advocated for CRRT due to concerns of circuit coagulation (*10*), and the circuit is changed every 24 h at most (Figure 3).

Table 1. Recommendations on RRT for COVID-19 patients*

Items	RRT Method	Responding to the growing demand for RRT
Introduction	Consider RRT when solutes and fluid retention are greater than renal function. (Consider a wide range of factors that can be corrected with RRT, not just BUN and sCre.)	If the response to conservative treatment such as bicarbonate administration and K adsorbents is poor, RRT should be considered.
Modalities	Choose prolonged RRT (*e.g.*, CRRT, SLED) if circulatory instability is present; consider treatments that reduce the risk of circuit coagulation, such as CVVHD and CVVHDF.	The modality of RRT can be influenced by the supply of machines and consumables on the medical side and the availability of trained staff. Consider short-duration IHD or CRRT if possible. Consider PIRRT with equipment. If equipment is not available, PD is an option.
Dialysis Prescription	For CRRT, a filtration rate of 20-25 mL/kg/hr is recommended. Target is 25-30 mL/kg/hr. Three times per week for IHD. For prolonged dialysis, prescribe with consideration for circuit coagulation.	In the case of PIRRT using short IHD or CRRT equipment, the water removal and filtration flow rate settings are adjusted to achieve the treatment goal.
Vascular Access	The right internal jugular vein is the first choice. Prone position, obesity, and hypercoagulability can affect access performance.	Create a system that can insert PD catheters for emergency evacuation.

*Modified from *Ref. 1.*

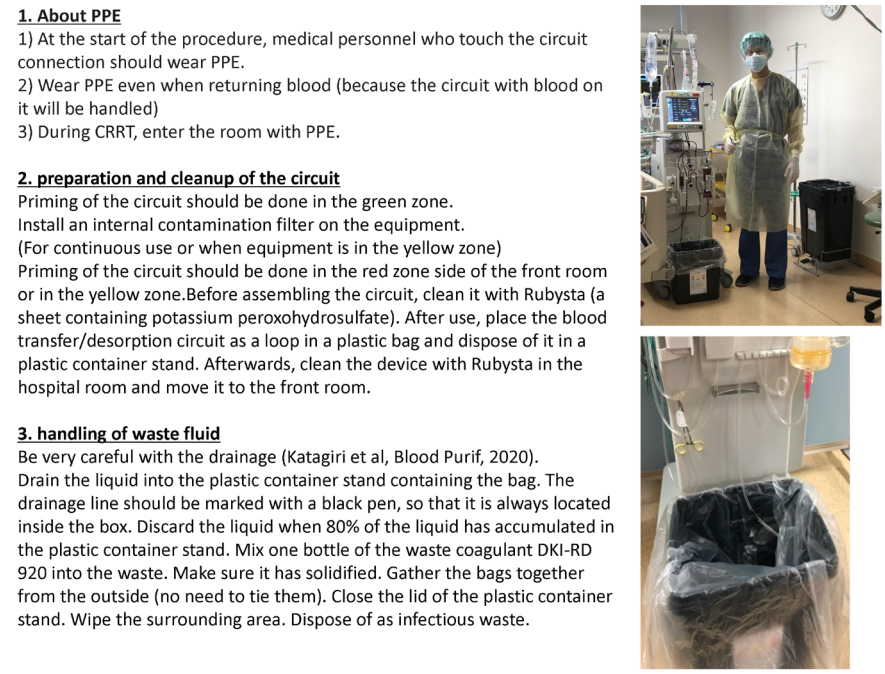

Figure 3. How to perform CRRT for COVID-19 in our hospital. In the beginning, we gathered information by hand and went through a trial and error process to ensure safe CRRT implementation.

PMX-DHP

Polymyxin B-immobilized fiber column direct hemoperfusion (PMX-DHP) therapy is a medical device that uses the polypeptide antibiotic polymyxin B to bind to lipid A, the active center of the endotoxin. In 2018, the EUPHRATES study (*11*) was published, which revealed that PMX-DHP was influential in treating sepsis (n = 450) with a high endotoxin activity assay of ≥ 0.6. The study compared PMX-DHP administered twice for 2 h within 24 h with sham treatment. The results indicated that the 28-day mortality rate was 37.7% in the PMX group and 34.5% in the sham group, which was not significantly different. Based on these results, the 2020 Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock also state that, "it is weakly recommended that PMX-DHP not be used in patients with septic shock (Grade 2B)".

PMX has been suggested to be effective not only as a sepsis treatment device, but also for respiratory diseases. In addition to endotoxin removal, PMX may be involved in the removal of mediators such as inflammatory cytokines causing a cytokine storm and adsorption of cellular components such as activated leukocytes that directly damage lung tissue. In 2014, as an advanced medical treatment B, the efficacy of PMX was studied in patients with acute exacerbation of idiopathic pulmonary fibrosis when it was added to the treatment. In our first case of PMX for COVID-19 (*12*), oxygen demand increased, the P/F ratio decreased to approximately 150 on the fifth day of hospitalization, and the central department requested PMX-DHP for 3 h over 2 days. Immediately after PMX-DHP administration, the patient demonstrated rapid fever resolution, and worsening of the respiratory condition was alleviated. Subsequently, we reported our experience with PMX-DHP in 12 patients during the so-called first wave (*13*), including those who required oxygenation at the time of PMX (n = 5), those who were on ventilators (n = 5), and those who had already received ECMO (n = 2) (Table 2). Since this was a single-center, backward-looking observational study, we cannot definitively state the efficacy of the treatment. Nevertheless, it may be helpful to consider it in patients with a P/F ratio < 300 or moderate disease II or higher requiring oxygenation, but before progressing to severe disease requiring ventilatory management or ECMO. In approximately half of the sessions, we experienced an increase in inlet pressure and short circuit coagulation within 15-30 min of the start of the procedure, which may be due to the presence of thrombosis in severe COVID-19 (circuit problems have decreased since then, probably due to the spread of anticoagulant therapy). Currently, we are continuing a multicenter prospective specific clinical study, and case reports suggesting that efficacy of PMX-DHP for COVID-19 continues to occur in Japan, Italy, and Thailand (*14-17*).

Plasma exchange therapy

Plasma exchange plays a role in acute hemodialysis by *i*) removing pathogenic substances from plasma (which are relatively large and cannot be removed by hemodialysis) and *ii*) efficiently replenishing plasma

Table 2. Results of PMX-DHP for COVID-19 patients at our hospital*

Variables	*n* = 12
Age	66.5 (36-83)
Sex	Male 9 (75.0 %), Female 3 (25.0 %)
Number of days since onset	6.5 (3-16)
BMI	25.4 (19.2-31.9)
Smoking	5 (41.7 %)
Hypertension	5 (41.7 %)
Diabetes	3 (25.0 %)
Oxygen administered at the start of PMX (no ventilator)	5 (41.7 %)
Ventilator at the start of PMX (no ECMO)	5 (41.7 %)
ECMO already in place at the start of PMX	2 (16.6 %)
Number of PMX attempts	One (2, 16.7 %), Two (10, 83.3 %)
Day 15 Severity	
improvement	7 (58.3 %)
constant	1 (8.3 %)
worsening	4 (33.3%)
P/F ratio	
Day 1	153.9 (69.0-327.1)
Day 4	214.1 (122.3-438.1)
Day 8	271.3 (172.8-464.8)
Inlet pressure rise	7/22 (31.8 %)
Circuit coagulation	5/22 (22.7 %)
Patient death	3 (25.0 %)

*Modified from *Ref. 13.*

proteins. Depending on the removal goal, simple plasma exchange (TPE), double filtration plasma exchange (DFPP), plasma adsorption, or even selective plasma exchange (SePE) can be used. Fresh frozen plasma (FFP) and albumin are options for replacement fluid, and the advantages and disadvantages of each need to be properly understood. Fibrin and factor 13 have a large molecular weight of 300 kDa and are removed by DFPP. Fibrinogen has a long half-life, and attention should be paid to appearance of bleeding tendencies. FFP replacement should be considered if fibrinogen levels are < 100-150 mg/dL prior to treatment.

Reports on the efficacy of TPE for COVID-19 continue to come from various regions (*18,19*), and only one RCT has been identified (*20*). This RCT compared the standard of care plus TPE (*n* = 43) with the standard of care (*n* = 44). The standard of care included ribavirin, dexamethasone, and anticoagulation; and the TPE used a centrifugation method rather than the membrane separation method. The results suggested that the number of days on ventilator and ICU stay as well as the SOFA score was lower in the TPE group than in the sham group. However, the mortality rate at day 35 was not significant in the TPE group. However, the usefulness of plasma exchange remains debatable (*21*).

Other blood purification therapies

LIXEL™ is covered by insurance for use in three hemodialysis sessions per week for the treatment of dialysis amyloidosis. LIXEL exerts its therapeutic effect by selectively adsorbing β2-microglobulin, the causative agent of dialysis amyloidosis, through hydrophobic interactions and molecular sieving effects, and has been reported to adsorb cytokines because of its structure (*22*). At our institution, maintenance hemodialysis patients with a history of dialysis for more than ten years who were admitted with moderate grade II COVID-19 were treated with LIXEL during dialysis (*23*). In Japan, Adacolam™, a blood cell removal purifier used during granulocyte monocyte ablation (GMA) therapy in ulcerative colitis, Crohn's disease, cystic psoriasis, and psoriatic arthritis, has been suggested as effective against COVID-19 (*24*). The main action of GMA is to adsorb and remove activated myeloid cells, although it is also expected to reduce inflammatory cytokines (*25*). oXiris™ is another biocompatible hemodialytic filter coated with heparin, which is used in RRT, is also known to adsorb and remove cytokines and endotoxins, and has antithrombotic properties. The adsorbent CytoSorb (CytoSorbents Corp, NJ, USA) is composed of porous polymer beads and adsorbs hydrophobic molecules of 5-55 kDa such as cytokines, myoglobin, and bilirubin (*26,27*). The adsorbent can be integrated into external circulation circuits such as ECMO and CRRT. The US Food and Drug Administration issued an emergency use authorization for the treatment of COVID-19 in 2020. Although its efficacy has been reported in some case reports, an RCT has reported that not only was there no effect on IL-6 reduction, but also 30-day mortality was significantly higher in the Cytosorb treatment group of critically ill patients randomized to ECMO (*28*). The increase in IL-6 in COVID-19 was slower than that in sepsis and ARDS, while the increase in D-dimer was more marked (*29*), suggesting that simply controlling IL-6 alone may not improve prognosis.

Conclusion

Blood purification therapy is complementary to drug therapy. Even with the widespread use of vaccines and antibody therapy (*30*), it is expected that a certain percentage of patients will develop moderate-to-severe diseases due to breakthrough infections. It is hoped that clinical studies will continue to accumulate evidence to investigate safe and adequate blood purification therapies for COVID-19.

Acknowledgements

We thank all the clinical staff at the National Center for Global Health and Medicine (NCGM) for their dedicated clinical practice and patient care.

Funding: This work was supported in part by Japan Agency for Medical Research and Development

(AMED; 20he0822003j0001) and Grants-in-Aid for Research from the National Center for Global Health and Medicine (21A-2002).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Nadim MK, Forni LG, Mehta RL, *et al.* COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol. 2020; 16:747-764.
2. Hirsch JS, Ng JH, Ross DW, Sharma P, Shah HH, Barnett RL, Hazzan AD, Fishbane S, Jhaveri KD; Northwell COVID-19 Research Consortium; Northwell Nephrology COVID-19 Research Consortium. Acute kidney injury in patients hospitalized with COVID-19. Kidney Int. 2020; 98:209-218.
3. Nugent J, Aklilu A, Yamamoto Y, Simonov M, Li F, Biswas A, Ghazi L, Greenberg H, Mansour G, Moledina G, Wilson FP. Assessment of acute kidney injury and longitudinal kidney function after hospital discharge among patients with and without COVID-19. JAMA Netw Open. 2021; 4:e211095.
4. Katagiri D, Ishikane M, Asai Y, *et al.* Evaluation of coronavirus disease 2019 severity using urine biomarkers. Crit Care Explor. 2020; 2:e0170.
5. Gaudry S, Hajage D, Schortgen F, *et al.* Initiation strategies for renal-replacement therapy in the Intensive Care Unit. N Engl J Med. 2016; 375:122-133.
6. Barbar SD, Clere-Jehl R, Bourredjem A, *et al.* Timing of renal-replacement therapy in patients with acute kidney injury and sepsis. N Engl J Med. 2018; 379:1431-1442.
7. STARRT-AKI Investigators; Canadian Critical Care Trials Group; Australian and New Zealand Intensive Care Society Clinical Trials Group; *et al.* Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med. 2020; 383:240-251.
8. Gaudry S, Hajage D, Benichou N, *et al.* Delayed versus early initiation of renal replacement therapy for severe acute kidney injury: a systematic review and individual patient data meta-analysis of randomised clinical trials. Lancet. 2020; 395:1506-1515.
9. Katagiri D, Ishikane M, Ogawa T, Kinoshita N, Katano H, Suzuki T, Fukaya T, Hinoshita F, Ohmagari N. Continuous renal replacement therapy for a patient with severe COVID-19. Blood Purif. 2021; 50:129-131.
10. Ronco C, Reis T. Kidney involvement in COVID-19 and rationale for extracorporeal therapies. Nat Rev Nephrol. 2020; 16:308-310.
11. Dellinger RP, Bagshaw SM, Antonelli M, Foster DM, Klein DJ, Marshall JC, Palevsky PM, Weisberg LS, Schorr CA, Trzeciak S, Walker PM; EUPHRATES Trial Investigators. Effect of targeted polymyxin B hemoperfusion on 28-day mortality in patients with septic shock and elevated endotoxin level: the EUPHRATES randomized clinical trial. JAMA. 2018; 320:1455-1463.
12. Kusaba Y, Izumi S, Takasaki J, Suzuki M, Katagiri D, Katsuno T, Matsumoto S, Sakamoto K, Hashimoto M, Ohmagari N, Katano H, Suzuki T, Hojo M, Sugiyama H. Successful recovery from COVID-19-associated acute respiratory failure with polymyxin B-immobilized fiber column-direct hemoperfusion. Intern Med. 2020; 59:2405-2408.
13. Katagiri D, Ishikane M, Asai Y, *et al.* Direct hemoperfusion using a polymyxin B-immobilized polystyrene column for COVID-19. J Clin Apher. 2021; 36:313-321.
14. Nihei Y, Nagasawa H, Fukao Y, Kihara M, Ueda S, Gohda T, Suzuki Y. Continuous extracorporeal treatments in a dialysis patient with COVID-19. CEN Case Rep. 2021; 10:172-177.
15. Ishiwari M, Togashi Y, Takoi H, Kikuchi R, Kono Y, Abe S. Polymyxin B haemoperfusion treatment for respiratory failure and hyperferritinaemia due to COVID-19. Respirol Case Rep. 2020; 8:e00679.
16. Thammathiwat T, Tungsanga S, Tiankanon K, Torvorapanit P, Chumpangern W, Udomkarnjananun S, Avihingsanon Y, Sriprasart T, Srisawat N, Jutivorakool K, Paitoonpong L, Putcharoen O, Townamchai N. A case of successful treatment of severe COVID-19 pneumonia with favipiravir and tocilizumab in post-kidney transplant recipient. Transpl Infect Dis. 2021; 23:e13388.
17. De Rosa S, Cutuli SL, Ferrer R, Antonelli M, Ronco C; COVID-19 EUPHAS2 Collaborative Group. Polymyxin B hemoperfusion in coronavirus disease 2019 patients with endotoxic shock: case series from EUPHAS2 registry. Artif Organs. 2021; 45:E187-E194.
18. Fernandez J, Gratacos-Ginès J, Olivas P, *et al.* Plasma exchange: an effective rescue therapy in critically Ill patients with coronavirus disease 2019 infection. Crit Care Med. 2020; 48:e1350-e1355.
19. Gluck WL, Callahan SP, Brevetta RA, Stenbit AE, Smith WM, Martin JC, Blenda AV, Arce S, Edenfield WJ. Efficacy of therapeutic plasma exchange in the treatment of penn class 3 and 4 cytokine release syndrome complicating COVID-19. Respir Med. 2020; 175:106188.
20. Faqihi F, Alharthy A, Alodat M, Asad D, Aletreby W, Kutsogiannis DJ, Brindley PG, Karakitsos D. A pilot study of therapeutic plasma exchange for serious SARS CoV-2 disease (COVID-19): A structured summary of a randomized controlled trial study protocol. Trials. 2020; 21:506.
21. Lu W, Kelley W, Fang DC, Joshi S, Kim Y, Paroder M, Tanhehco Y, Tran MH, Pham HP. The use of therapeutic plasma exchange as adjunctive therapy in the treatment of coronavirus disease 2019: A critical appraisal of the current evidence. J Clin Apher. 2021; 36:483-491.
22. Tsuchida K, Yoshimura R, Nakatani T, Takemoto Y. Blood purification for critical illness: cytokines adsorption therapy. Ther Apher Dial. 2006; 10:25-31.
23. Okuhama A, Ishikane M, Katagiri D, Kanda K, Nakamoto T, Kinoshita N, Nunose N, Fukaya T, Kondo I, Katano H, Suzuki T, Ohmagari N, Hinoshita F. Detection of SARS-CoV-2 in Hemodialysis Effluent of Patient with COVID-19 Pneumonia, Japan. Emerg Infect Dis. 2020; 26:2758-2761.
24. Kanekura T, Kawahara K. Adsorptive granulocyte and monocyte apheresis: A potentially relevant therapeutic option for COVID-19. Int J Infect Dis. 2020; 99:1-2.
25. Saniabadi AR, Hanai H, Takeuchi K, Umemura K, Nakashima M, Adachi T, Shima C, Bjarnason I, Lofberg R. Adacolumn, an adsorptive carrier based granulocyte and monocyte apheresis device for the treatment of inflammatory and refractory diseases associated with leukocytes. Ther Apher Dial. 2003; 7:48-59.
26. Rampino T, Gregorini M, Perotti L, Ferrari F, Pattonieri

EF, Grignano MA, Valente M, Garrone A, Islam T, Libetta C, Sepe V, Albertini R, Bruno R, Belliato M. Hemoperfusion with CytoSorb as adjuvant therapy in critically Ill patients with SARS-CoV2 pneumonia. Blood Purif. 2021; 50:566-571.
27. Supady A, Weber E, Rieder M, *et al.* Cytokine adsorption in patients with severe COVID-19 pneumonia requiring extracorporeal membrane oxygenation (CYCOV): a single centre, open-label, randomised, controlled trial. Lancet Respir Med. 2021; 9:755-762.
28. Alharthy A, Faqihi F, Memish ZA, Balhamar A, Nasim N, Shahzad A, Tamim H, Alqahtani SA, Brindley PG, Karakitsos D. Continuous renal replacement therapy with the addition of CytoSorb® cartridge in critically ill patients with COVID-19 plus acute kidney injury: a case-series. Artif Organs. 2021; 45:E101-E112.
29. Leisman DE, Ronner L, Pinotti R, Taylor MD, Sinha P, Calfee CS, Hirayama AV, Mastroiani F, Turtle CJ, Harhay MO, Legrand M, Deutschman CS. Cytokine elevation in severe and critical COVID-19: a rapid systematic review, meta-analysis, and comparison with other inflammatory syndromes. Lancet Respir Med. 2020; 8:1233-1244.
30. Terakawa K, Katagiri D, Shimada K, Sato L, Takano H. Safety of casirivimab/imdevimab administration in a SARS-CoV-2 positive maintenance dialysis patient in Japan. CEN Case Rep. 2022. doi: 10.1007/s13730-021-00671-1.

Received February 11, 2022; Revised March 15, 2022; Accepted March 25, 2022.

Released online in J-STAGE as advance publication March 31, 2022.

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Global Health & Medicine. 2022; 4(2):101-107.
DOI: 10.35772/ghm.2022.01006

REVIEW

Cardiovascular considerations during the COVID-19 pandemic: A focused review for practice in Japan

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Abstract: The COVID-19 pandemic is continuing to have drastic consequences for patients, healthcare workers, and the health system. Its cardiovascular implications have been well described in previous studies, but original reports from Japan are sparse. Validating overseas findings in the Japanese clinical settings is crucial to improve local COVID-19 care and to clarify the pandemic's impacts in the country. This review of available literature demonstrates that in Japanese patients and clinical settings too, there is a close relationship between COVID-19 and the cardiovascular system including cardiovascular complications. On the contrary, secondary effects on cardiovascular practice including service disruptions, telemedicine, and epidemiological changes in Japan have been relatively small.

***Keywords*:** COVID-19, Japan, cardiovascular complications, health system, epidemiology

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic is now entering its third year. Case fatality rates are lower than they were at the start of the pandemic, as more people around the globe are being vaccinated and less severe variants have become predominant. However, total infections worldwide have soared to over 400 million as of February 2022, continuing to exert extensive effects on our health and well-being. Even though Japan ranks the lowest among G7 nations in COVID-19 cases and deaths, the country is struggling on its own to apply lessons from overseas in the Japanese context.

An important consideration when drawing on global scientific literature regarding COVID-19 is that most previous studies do not take into account geographical and ethnic differences. The severity of COVID-19 is determined by a number of host factors like the baseline health condition and vaccination status, which have significant regional disparities. In addition, recent studies have suggested that genetic background may also be a determinant of severity (*1,2*). To provide more appropriate care in Japanese clinical settings, we must clarify the unique characteristics in Japanese cases.

Apart from infected individuals, the pandemic has had widespread collateral effects on society. Changes to the epidemiology of diseases and the healthcare system have resulted not only from the overwhelming rise in COVID-19 admissions but also from the lifestyle changes of the entire population. Such secondary consequences are observed across the globe but vary greatly in each region, depending on factors like public health policies, media coverage, and economic activities. Even though the direct burden from infections seems to be relatively small in Japan, collateral impacts on the non-infected population need to be taken into account to evaluate the comprehensive effects of the pandemic.

The close association between COVID-19 and the cardiovascular system and cardiovascular practice in general has been described previously (*3*). Here in this review, we will reinvestigate this association with an aim to be embraced in the Japanese context. We will first discuss the relationship between COVID-19 and the cardiovascular system, referring to unique findings in Japanese patients and clinical settings. Then, we will broaden our perspective to collateral consequences of the pandemic, depicting changes in clinical practice and epidemiology of cardiovascular diseases in Japan.

Role of cardiovascular comorbidities on the clinical course

Previous reports from around the world have shown that cardiovascular risk factors including male sex, advanced age, diabetes, hypertension, and obesity also pose a risk for poor prognosis in COVID-19 patients. Not surprisingly, cardiovascular comorbidities are also a predictor of severe illness. In one of the largest multi-national cohort studies of over 20,000 patients, the adjusted risk ratio for in-hospital mortality was 1.19

for heart failure and 1.41 for severe heart failure (New York Heart Association (NYHA) class III/IV) (*4*).

In Japanese COVID-19 patients too, cardiovascular comorbidity was confirmed to be one of the risk factors for severity along with age, diabetes, obesity, and chronic respiratory disease (*5*). The CLAVIS-COVID registry was organized by the Japanese Circulation Society to investigate the prognosis of hospitalized COVID-19 patients with prior cardiovascular diseases and/or risk factors. From the analysis of this extensive registry, the following observations have been made: the risk of complications was higher in those with multiple cardiovascular diseases or risk factors (*6*), statin users had lower severity (*7*), and increased lactate dehydrogenase (LDH) levels were associated with in-hospital mortality (*8*). Also, the 4C Mortality Score, developed based on UK cohorts predicting poor outcomes, was validated in Japanese cohorts as well (*9*). These results are compatible with findings in foreign studies. On the contrary, the threshold for increased mortality in obese patients was body mass index (BMI) of 30 in Japan, whereas in other countries the number was 40 (*10*). This suggests that even just mild obesity may predispose the patients to a poorer outcome in the Japanese population. In conclusion, predicting prognosis based on a cardiovascular standpoint is appropriate in the Japanese population as well, but there are probably subtle differences that need further investigation.

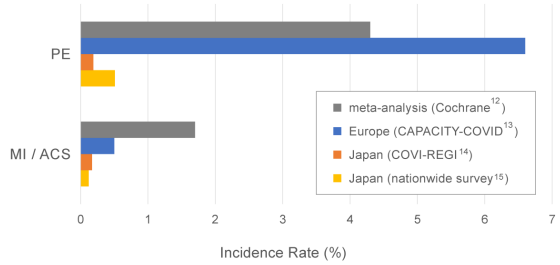

Figure 1. Reported incidence rates of thrombotic complications in hospitalized COVID-19 patients. Data adapted from four studies (*12-15*). The incidence rates appear to be substantially lower in Japanese cohorts, but differences in study designs and existence of numerous confounding factors make it virtually impossible to determine to what extent ethnic predispositions actually play a role.

Cardiovascular complications

Various types of cardiovascular complications may occur during the course of COVID-19, including arterial and venous thrombosis (*i.e.*, acute coronary syndrome, pulmonary embolism, and venous thromboembolism (VTE)), arrhythmias, and myocardial damage. According to a multicenter cohort study of over 65,000 hospitalized COVID-19 patients from UK healthcare facilities, there was a significant ethnic difference in the incidence of cardiovascular complications (*11*). Furthermore, compared to reports from other regions of the world, the incidence rates of cardiovascular complications such as thrombosis appear to be lower in Japan (*12-15*) (Figure 1). According to an analysis of Japan's largest inpatient registry of almost 20,000 COVID-19 patients (COVIREGI-JP), the incidences of cardiovascular complications were 0.59% for deep venous thrombosis, 0.19% for pulmonary embolism, 0.48% for ventricular tachycardia/fibrillation, 0.17% for myocardial ischemia, and 0.098% for myocarditis/pericarditis/cardiomyopathy (*14*). It is crucial, however, to bear in mind large variations in study settings. Complications may occur depending on the properties of the host (*i.e.*, baseline patient characteristics and vaccination status), the pathogen (*i.e.*, type of variant), and interventions (*i.e.*, prophylactic and supportive therapies) (Figure 2). One of the most critical determinants of complication occurrence is the severity of the infection. Complications occur more frequently in more severe cases. Even within COVID-19 patients that were hospitalized, the severity may vary greatly depending on factors like bed availability. Also, due to publication bias, the incidence rates might have been overestimated in initial reports. Therefore, a significant

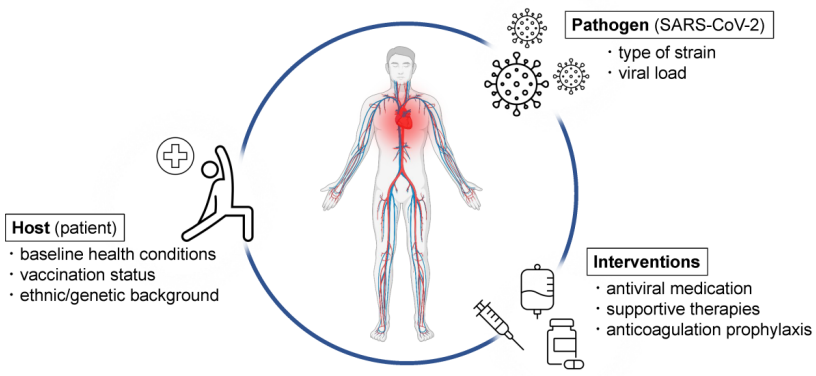

Figure 2. Determinants of cardiovascular complications in COVID-19. The effects of the infection on the cardiovascular system are dictated by various factors regarding the host, the pathogen, and medical interventions.

deviation is inevitable among different studies at different time points. Keeping in mind such pitfalls, we will carefully discuss regional and ethnic differences regarding thrombosis and myocardial damage.

Thrombosis

Apart from COVID-19, it has been previously revealed that thrombosis occurs less frequently in people of Asian descent compared to other races (*16*). Although the same trend is expected in COVID-related thrombosis, factors other than ethnicity, like disease severity of COVID-19 and thromboprophylaxis, play a similar if not a greater role in its occurrence. In order to reveal ethnic differences, studies of a patient population in one ethnically-diverse region are useful because region-specific variables are standardized to some extent. One such investigation which examined the incidence of thrombotic events among over 20,000 COVID-19 patients revealed that both arterial and venous thrombosis were more common in Black patients than in other races (*17*). While Asian patients tended to have a lower likelihood of VTE (odds ratio 0.64), the trend was only confirmed in the unadjusted model. On the contrary, in a smaller study of a mixed-ethnicity UK cohort of 613 patients, Asian patients were more likely to present with VTE compared to Caucasian and Afro-Caribbean patients (*18*). Limited reports thus far point to inconsistent conclusions.

Simple comparisons of incidence rates of thrombotic complications in hospitalized COVID-19 patients in and outside Japan may provoke interesting discussions. In Japan, a nationwide questionnaire-based survey revealed that thrombosis, the majority of which were VTEs, occurred in 1.86% of all hospitalized COVID-19 patients (n = 6,202) (*15*). More specifically, the number was 0.59% in mild or moderate patients, whereas the number was higher at > 13.5% in severe patients. Even when the severity of COVID-19 was accounted for, the numbers were quite low compared to reports from Western countries. Japanese patients may be less likely to develop COVID-19-related thrombosis.

In some clinical guidelines, uniform prophylactic anticoagulation is recommended for hospitalized COVID-19 patients due to the high risk of thrombosis (*19*). However, there is an ongoing debate whether racial predispositions should be considered for such practice (*20*). Anticoagulant-induced bleeding occurs more frequently in patients of Asian descent (*16*); this is the rationale behind non-adoption of routine postoperative anticoagulation for VTE prevention in Asia. In an observational study of 1,784 Japanese cohorts (*21*), although there was no difference in mortality between anticoagulated and non-anticoagulated COVID-19 patients overall, within the group treated with steroids (an indication of more severe infection), there was a trend towards lower mortality in the anticoagulated patients. In line with the study, a guideline issued by the Japanese Society of Phlebology and others recommends prophylactic-dose heparin only in patients that require oxygen support (*22*).

Whether or not there are other unique characteristics regarding COVID-related thrombosis in Japanese patients remains to be answered in future research. Only few studies have been published so far. As an example, despite possibly having lower thrombotic risks overall, in Japanese cohorts too, patients with obesity and severe COVID-19 were especially likely to develop VTE (*23*). Also, a small single-center study suggested that besides d-dimer, ferritin levels were also helpful biomarkers of thrombosis in COVID-19 patients (*24*). This may be an original finding in Japanese cohorts.

Myocardial injury

Myocardial injury in the context of COVID-19 infection usually refers to an elevation in cardiac troponin and is associated with disease severity and mortality (*25*). It is not unique to COVID-19; previous studies have described the same complication in other respiratory infections, including seasonal influenza (*26*). The primary mechanism is likely to be a mismatch in oxygen supply and demand rather than direct viral invasion into the myocardium. Myocardial injury may prevail in both early and convalescent phases of COVID-19.

Although there is insufficient data to compare its frequency in different populations, studies have confirmed the phenomenon in Japanese patients too. In a study of 209 recently recovered COVID-19 patients, 65% had positive high-sensitive troponin T (*27*). It is important to note that although the measurements were higher in those who suffered more severe infections, the majority of troponin-positive patients had only a mild illness. Furthermore, an additional analysis of the same patients revealed a decrease in left ventricular global longitudinal strain (LVGLS) on echocardiograms, suggesting that they may have poorer cardiovascular prognosis (*28*). Although these works are preliminary, these studies remind us to watch out for signs of cardiac dysfunction even after recovery from acute infection.

Secondary effects on cardiovascular practice

Service disruptions

The pandemic has restricted cardiovascular procedures globally, but the impact in Japan seems to have been small compared to other parts of the world (*29*). The Japanese Circulation Society conducted a nationwide survey in April and August of 2020 to evaluate the pandemic's impact on cardiovascular practice (*30,31*). According to the reports, transesophageal echocardiograms and diagnostic/therapeutic catheterizations were limited in over half of the

facilities during the first surge of the pandemic. Still, the restriction was much milder after the second surge. Large analyses of claims databases also support the perspective that disruptions in cardiovascular care were minimal or have faded away. According to one study, by September 2020, the number of elective percutaneous coronary interventions (PCIs) recovered to 98% of corresponding months in the previous two years (*32*). Another investigation showed that the number of physician visits declined only in April 2020 and that prescriptions for major chronic diseases (hypertension, diabetes, and dyslipidemia) were not affected (*33*). For emergent procedures, over 97% of hospitals managed to perform primary PCIs for ST elevation myocardial infarction (STEMI) even amid sharp COVID-19 surges (*34*). However, even in Japan, the door-to-balloon time was prolonged due to COVID-19 screening (*35,36*). Although reports so far have not shown increases in short-term mortality, recent evidence from overseas suggested that such delay resulted in an increase in infarct size and more frequent intramyocardial hemorrhage (*37*). Further optimization of COVID-19 screening protocols may be necessary.

Telemedicine

Some clinicians see the pandemic as a chance for digital transformation in healthcare. Although ICT-based healthcare entails unsolved issues such as digital divide, it has the potential to improve accessibility and efficiency (*38*). In the United States, the pandemic has led to a rapid expansion of online medical services, with the number of telehealth visits increasing tenfold in March 2021 compared to the same period in 2020 (*39*). Similar trends were seen in European countries like the UK, Germany, and France. In Japan, however, the adoption of telemedicine seems to be lagging behind. Although the Ministry of Health, Labor, and Welfare lifted some of the restrictions regarding online visits, the percentage of medical institutions offering virtual services reached a plateau after hitting 15% in June 2020 (*40*).

For cardiac rehabilitation (CR) also, Japan has been slow to adopt digital technology. According to a nationwide survey of CR facilities, group ambulatory CR was suspended in 70% of the facilities (*41*). Despite the suspension, only 8% offered remote CR programs, and, what is worse, only 30% of facilities not providing telerehabilitation had specific future plans for implementation. Another report revealed that CR interruption has actually resulted in a deterioration of hemodynamic measures of the patients overall (*42*).

Telemedicine does not necessarily require cutting-edge technology. For instance, most CR facilities in the UK have continued providing physical activity advice or training mainly by using less sophisticated technologies like telephones and pre-recorded online videos(*43*). In Japan too, a study proposed that making use of the country's reliable, high-speed postal service was effective to provide long-term remote electrocardiogram monitoring during the pandemic (*44*). These examples show that we should not passively wait for a revolutionary platform to emerge but instead actively make the best use of what is currently available.

Epidemiological changes

Functional emergency medical services and high care units are essential parts of acute cardiovascular care. In the early stages of the pandemic, disruption of overwhelmed healthcare systems resulted in a decline in hospitalizations for acute cardiovascular diseases worldwide (*45*). This section will focus on epidemiological changes of myocardial infarction and heart failure. In Japan during the pandemic, hospital admissions for acute coronary syndromes declined by only 5-10%, even in areas where COVID-19 was most prevalent (*46,47*). This contrasts with situations in areas hardest hit by the pandemic like the US, Spain, and Latin America, which saw declines of up to -50% (*48-50*). For heart failure exacerbations too, although a sudden decrease of -3.6% in hospitalizations was observed just after the declaration of the state of emergency in April 2020, there was no deterioration in in-hospital mortality (*51*). Despite the seemingly minor disruption, the phenomenon demands further investigation. It is speculated that the decreased cardiovascular admissions in Japan is a consequence of reluctance to seek medical attention. Media bias and health illiteracy may have been the root causes that incited excessive fear of viral exposure. Undeniably, it has been previously reported that the health literacy of Japanese people is poorer than that of Europeans (*52*). The public sector must work harder to deliver accurate and reliable health information to its citizens in comprehensible language.

Another aspect of cardiovascular diseases is that they are strongly associated with lifestyles. As the burden to the healthcare system is gradually being alleviated, impacts of post/with-COVID lifestyle changes on cardiovascular health are becoming more of a concern. For example, according to a recent US study that tracked health measures of more than 464,000 participants, blood pressure increased significantly during the pandemic compared to the previous year (*53*). The finding is alarming, given that even small rises in blood pressure measurements across a large population increase the long-term incidence of adverse cardiovascular events. In Japan, it appears that some people have adapted well to the pandemic and established healthier lifestyles, whereas others have increased their lifetime cardiovascular risk. For instance, in the working population, promotion of remote work and decreased overall work hours have

generally rendered them physically inactive (*54*). On the contrary, some people have become more health-conscious and developed healthier dietary habits (*55*). Effects on health parameters such as blood pressure and glycemic control are inconsistent among different studies (*56,57*). Future studies are awaited to assess the situation in more detail.

Conclusion

While the majority of publications regarding COVID-19 come from outside of Japan, Japanese patients have been underrepresented in most studies so far. There also remain great regional differences in clinical practice surrounding COVID-19. Thus, conclusions drawn from previous reports from different regions of the world may not always hold true for Japanese patients. We have summarized available scientific literature on the clinical characteristics of Japanese COVID-19 patients and the secondary impacts of the pandemic in Japan from a cardiovascular perspective. Studies from Japan were indeed limited, and knowledge gaps remain to be filled. Further research is called for in order to realize more precise approaches specific to Japanese clinical settings.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Ren W, Zhu Y, Lan J, *et al.* Susceptibilities of Human ACE2 Genetic Variants in Coronavirus Infection. J Virol. 2022; 96:e0149221.
2. COVID-19 Host Genetics Initiative. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. Eur J Hum Genet. 2020; 28:715-718.
3. Tomidokoro D, Hiroi Y. Cardiovascular implications of the COVID-19 pandemic. J Cardiol. 2022; 79:460-467.
4. CAPACITY-COVID Collaborative Consortium and LEOSS Study Group. Clinical presentation, disease course, and outcome of COVID-19 in hospitalized patients with and without pre-existing cardiac disease: a cohort study across 18 countries. Eur Heart J. 2022; 43:1104-1120.
5. Matsunaga N, Hayakawa K, Terada M, *et al.* Clinical epidemiology of hospitalized patients with coronavirus disease 2019 (COVID-19) in Japan: Report of the COVID-19 Registry Japan. Clin Infect Dis. 2021; 73:e3677-e3689.
6. Yamada T, Ogawa T, Minami K, Kusaka Y, Hoshiga M, Ukimura A, Sano T, Kitai T, Yonetsu T, Torii S, Kohsaka S, Kuroda S, Node K, Matsue Y, Matsumoto S. Multiple cardiovascular diseases or risk factors increase the severity of coronavirus disease 2019. Circ J. 2021; 85:2111-2115.
7. Ikari Y, Matsue Y, Torii S, Hasegawa M, Aihara K, Kuroda S, Sano T, Kitai T, Yonetsu T, Kohsaka S, Kishi T, Komuro I, Hirata KI, Node K, Matsumoto S. Association between statin use prior to admission and lower coronavirus disease 2019 (COVID-19) severity in patients with cardiovascular disease or risk factors. Circ J. 2021; 85:939-943.
8. Masumoto A, Kitai T, Matsumoto S, *et al.* Impact of serum lactate dehydrogenase on the short-term prognosis of COVID-19 with pre-existing cardiovascular diseases. J Cardiol. 2022; 79:501-508.
9. Kuroda S, Matsumoto S, Sano T, Kitai T, Yonetsu T, Kohsaka S, Torii S, Kishi T, Komuro I, Hirata KI, Node K, Matsue Y. External validation of the 4C Mortality Score for patients with COVID-19 and pre-existing cardiovascular diseases/risk factors. BMJ Open. 2021; 11:e052708.
10. Saito T, Yamaguchi T, Kuroda S, Kitai T, Yonetsu T, Kohsaka S, Torii S, Node K, Matsumoto S, Matsue Y, Kodama T. Impact of body mass index on the outcome of Japanese patients with cardiovascular diseases and/or risk factors hospitalized with COVID-19 infection. J Cardiol. 2022; 79:476-481.
11. Norris T, Razieh C, Zaccardi F, *et al.* Impact of cardiometabolic multimorbidity and ethnicity on cardiovascular/renal complications in patients with COVID-19. Heart. 2021; heartjnl-2021-320047.
12. Pellicori P, Doolub G, Wong CM, Lee KS, Mangion K, Ahmad M, Berry C, Squire I, Lambiase PD, Lyon A, McConnachie A, Taylor RS, Cleland JG. COVID-19 and its cardiovascular effects: a systematic review of prevalence studies. Cochrane Database of Systematic Reviews. Cochrane Database Syst Rev. 2021; 3:CD013879.
13. Linschoten M, Peters S, van Smeden M, Jewbali LS, Schaap J, Siebelink HM, Smits PC, Tieleman RG, van der Harst P, van Gilst WH, Asselbergs FW; CAPACITY-COVID collaborative consortium. Cardiac complications in patients hospitalised with COVID-19. Eur Heart J Acute Cardiovasc Care. 2020; 9:817-823.
14. Hiroi Y, Ohtsu H, Uemura Y, Hayakawa K, Asai Y, Kutsuna S, Terada M, Sugiura W, Ohmagari N. Cardiovascular complications of hospitalized patients with coronavirus disease 2019 in a Japanese registry in 2020. Circ J. 2022; 86:464-471.
15. Horiuchi H, Morishita E, Urano T, Yokoyama K; Questionnaire-survey Joint Team on The COVID-19-related thrombosis. COVID-19-related thrombosis in Japan: Final report of a questionnaire-based survey in 2020. J Atheroscler Thromb. 2021; 28:406-416.
16. Wang KL, Yap ES, Goto S, Zhang S, Siu CW, Chiang CE. The diagnosis and treatment of venous thromboembolism in Asian patients. Thromb J. 2018; 16:4.
17. Ilyas S, Henkin S, Martinez-Camblor P, Suckow BD, Beach JM, Stone DH, Goodney PP, Ebinger JE, Creager MA, Columbo JA. Sex-, race- and ethnicity-based differences in thromboembolic events among adults hospitalized with COVID-19. J Am Heart Assoc. 2021; 10:e022829.
18. Papageorgiou N, Providencia R, Saberwal B, *et al.* Ethnicity and COVID-19 cardiovascular complications: a multi-center UK cohort. Am J Cardiovasc Dis. 2020; 10:455-462.
19. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T, Levi M, Samama CM, Thachil J, Giannis D, Douketis JD; Subcommittee on Perioperative, Critical Care Thrombosis, Haemostasis of the Scientific,

Standardization Committee of the International Society on Thrombosis and Haemostasis. Scientific and Standardization Committee communication: Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. J Thromb Haemost. 2020; 18:1859-1865.
20. Iba T, Connors JM, Spyropoulos AC, Wada H, Levy JH. Ethnic differences in thromboprophylaxis for COVID-19 patients: should they be considered? Int J Hematol. 2021; 113:330-336.
21. Hara H, Uemura Y, Hayakawa K, *et al.* Evaluation of the efficacy of anticoagulation therapy in reducing mortality in a nationwide cohort of hospitalized patients with coronavirus disease in Japan. Int J Infect Dis. 2021; 112:111-116.
22. Mo M, Yamada N, Yamashita Y, Kobayashi T. Clinical guidance of prevention of venous thromboembolism in COVID-19. The Japanese Journal of Phlebology. 2021; 32:99-103. (in Japanese)
23. Yamashita Y, Maruyama Y, Satokawa H, *et al.* Incidence and clinical features of venous thromboembolism in hospitalized patients with coronavirus disease 2019 (COVID-19) in Japan. Circ J. 2021; 85:2208-2214.
24. Oba S, Hosoya T, Amamiya M, *et al.* Arterial and venous thrombosis complicated in COVID-19: A retrospective single center analysis in Japan. Front Cardiovasc Med. 2021; 8:767074.
25. Li JW, Han TW, Woodward M, Anderson CS, Zhou H, Chen YD, Neal B. The impact of 2019 novel coronavirus on heart injury: A systematic review and meta-analysis. Prog Cardiovasc Dis. 2020; 63:518-524.
26. Gao C, Wang Y, Gu X, Shen X, Zhou D, Zhou S, Huang J, Cao B, Guo Q; Community-Acquired Pneumonia-China Network. Association between cardiac injury and mortality in hospitalized patients infected with avian influenza A (H7N9) virus. Crit Care Med. 2020; 48:451-458.
27. Ide S, Hayama H, Asai Y, Terada M, Nomoto H, Kutsuna S, Ohmagari N, Hiroi Y. Evaluation of high-sensitivity cardiac troponin T levels in Japanese patients recently recovered from coronavirus disease 2019. Circ J. 2021; 85:944-947.
28. Hayama H, Ide S, Moroi M, Kitami Y, Bekki N, Kubota S, Uemura Y, Hara H, Kutsuna S, Ohmagari N, Hiroi Y. Elevated high-sensitivity troponin is associated with subclinical cardiac dysfunction in patients recovered from coronavirus disease 2019. Glob Health Med. 2021; 3:95-101.
29. Einstein AJ, Shaw LJ, Hirschfeld C, *et al.* International impact of COVID-19 on the diagnosis of heart disease. J Am Coll Cardiol. 2021; 77:173-185.
30. Mizuno A, Matsumoto C, Yoneoka D, Kishi T, Ishida M, Sanada S, Fukuda M, Saito Y, Yamauchi-Takihara K, Tsutsui H, Fukuda K, Komuro I, Node K. Cardiology department practices in the first wave of the coronavirus disease pandemic – A nationwide survey in Japan by the Japanese Circulation Society. Circ Rep. 2021; 3:137-141.
31. Mizuno A, Matsumoto C, Kishi T, Ishida M, Sanada S, Fukuda M, Komuro I, Hirata K, Node K. Cardiology department policy in Japan after coronavirus disease-2019 (COVID-19) – Descriptive summary of 2nd nationwide survey by the Japanese Circulation Society. Circ Rep. 2021; 3:100-104.
32. Watanabe S, Shin JH, Morishita T, Takada D, Kunisawa S, Imanaka Y. Medium-term impact of the coronavirus disease 2019 pandemic on the practice of percutaneous coronary interventions in Japan. J Atheroscler Thromb. 2021; doi: 10.5551/jat.63194.
33. Osawa I, Goto T, Asami Y, Itoh N, Kaga Y, Yamamoto Y, Tsugawa Y. Physician visits and medication prescriptions for major chronic diseases during the COVID-19 pandemic in Japan: retrospective cohort study. BMJ Open. 2021; 11:e050938.
34. Ishii H, Amano T, Kohsaka S, Morino Y, Yokoi H, Ikari Y. National survey of percutaneous coronary intervention during the COVID-19 pandemic in Japan: second report of the Japanese Association of Cardiovascular Intervention and Therapeutics. Cardiovasc Interv Ther. 2021; 1-5. doi: 10.1007/s12928-021-00776-5
35. Matsubara Y, Izumikawa T, Washimi S, Yamada T, Hashimoto S, Taniguchi N, Nakajima S, Hata T, Takahashi A. Impact of the SARS-CoV-2 pandemic on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction. Int Heart J. 2021; 62:1230-1234.
36. Kobayashi S, Sakakura K, Jinnouchi H, Taniguchi Y, Tsukui T, Watanabe Y, Yamamoto K, Seguchi M, Wada H, Fujita H. Comparison of door-to-balloon time and in-hospital outcomes in patients with ST-elevation myocardial infarction between before versus after COVID-19 pandemic. Cardiovasc Interv Ther. 2022; 1-10. doi: 10.1007/s12928-022-00836-4.
37. Lechner I, Reindl M, Tiller C, Holzknecht M, Troger F, Fink P, Mayr A, Klug G, Bauer A, Metzler B, Reinstadler SJ. Impact of COVID-19 pandemic restrictions on ST-elevation myocardial infarction: a cardiac magnetic resonance imaging study. Eur Heart J. 2021; ehab621. doi: 10.1093/eurheartj/ehab621.
38. Pinto FJ, Piñeiro D, Banerjee A, Perel P, Pervan B, Eiselé JL. World Heart Day 2021: COVID-19, digital health, and tackling cardiovascular disease. Lancet. 2021; 398:1467-1468.
39. Telehealth is here to stay. Nat Med. 2021; 27:1121.
40. 17th Committee Meeting on Review of Guidelines for the Appropriate Implementation of Online Medical Services Document 1: Verification results of the performance of telephone and online medical service from April to June 2021. *https://www.mhlw.go.jp/content/10803000/000840233.pdf* (accessed on February 15, 2022). (in Japanese)
41. Kida K, Nishitani-Yokoyama M, Oishi S, Kono Y, Kamiya K, Kishi T, Node K, Makita S, Kimura Y; Japanese Association of Cardiac Rehabilitation (JACR) Public Relations Committee. Nationwide survey of Japanese cardiac rehabilitation training facilities during the coronavirus disease 2019 outbreak. Circ Rep. 2021; 3:311-315.
42. Ogura A, Izawa KP, Tawa H, Kureha F, Wada M, Harada N, Ikeda Y, Kimura K, Kondo N, Kanai M, Kubo I, Yoshikawa R, Matsuda Y. Impact of the COVID-19 pandemic on phase 2 cardiac rehabilitation patients in Japan. Heart Vessels. 2021; 36:1184-1189.
43. O'Doherty AF, Humphreys H, Dawkes S, Cowie A, Hinton S, Brubaker PH, Butler T, Nichols S. How has technology been used to deliver cardiac rehabilitation during the COVID-19 pandemic? An international cross-sectional survey of healthcare professionals conducted by the BACPR. BMJ Open. 2021; 11:e046051.
44. Takami M, Fukuzawa K, Kiuchi K, Takemoto M, Nakamura T, Sakai J, Yatomi A, Nakasone K, Sonoda

Y, Yamamoto K, Takahara H, Suzuki Y, Tani K, Hirata KI. Practical utility of the postal service in delivering a self-fitted, wearable, long-term electrocardiogram monitoring device for outpatient care. Circ Rep. 2021; 3:294-299.
45. Bhatt AS, Moscone A, McElrath EE, Varshney AS, Claggett BL, Bhatt DL, Januzzi JL, Butler J, Adler DS, Solomon SD, Vaduganathan M. Fewer hospitalizations for acute cardiovascular conditions during the COVID-19 pandemic. J Am Coll Cardiol. 2020; 76:280-288.
46. Yasuda Y, Ishiguchi H, Ishikura M, Yoshida M, Imoto K, Sonoyama K, Kawabata T, Okamura T, Endo A, Kobayashi S, Tanabe K, Yano M, Oda T. Incidence and demographic trends for acute coronary syndrome in a non-epidemic area during the coronavirus disease pandemic in Japan – A 2-institutional observational study. Circ Rep. 2021; 3:95-99.
47. Watanabe Y, Miyachi H, Mozawa K, Yamada K, Oka E, Shiomura R, Sugizaki Y, Matsuda J, Nakata J, Tara S, Tokita Y, Iwasaki YK, Yamamoto T, Takano H, Shimizu W. Impact of the COVID-19 pandemic on ST-elevation myocardial infarction from a single-center experience in Tokyo. Intern Med. 2021; 60:3693-3700.
48. Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, Dixon S, Rade JJ, Tannenbaum M, Chambers J, Huang PP, Henry TD. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic. J Am Coll Cardiol. 2020; 75:2871-2872.
49. Rodríguez-Leor O, Cid-Álvarez B, Ojeda S, Martín-Moreiras J, Rumoroso JR, López-Palop R, Serrador A, Cequier A, Romaguera R, Cruz I, de Prado AP, Moreno R; on behalf of all the participants of the ACI-SEC Infarction Code Registry. Impact of the COVID-19 pandemic on interventional cardiology activity in Spain. REC Interv Cardiol. 2020; 2:82-89.
50. Mayol J, Artucio C, Batista I, Puentes A, Villegas J, Quizpe R, Rojas V, Mangione J, Belardi J; STEMI Working Group of Stent-Save a Life! LATAM and SOLACI (Latin American Society of Interventional Cardiology). An international survey in Latin America on the practice of interventional cardiology during the COVID-19 pandemic, with a particular focus on myocardial infarction. Neth Heart J. 2020; 28:424-430.
51. Morishita T, Takada D, Shin J, Higuchi T, Kunisawa S, Fushimi K, Imanaka Y. Effects of the COVID-19 pandemic on heart failure hospitalizations in Japan: interrupted time series analysis. ESC Heart Fail. 2022; 9:31-38.
52. Nakayama K, Osaka W, Togari T, Ishikawa H, Yonekura Y, Sekido A, Matsumoto M. Comprehensive health literacy in Japan is lower than in Europe: a validated Japanese-language assessment of health literacy. BMC Public Health. 2015; 15:505.
53. Laffin LJ, Kaufman HW, Chen Z, Niles JK, Arellano AR, Bare LA, Hazen SL. Rise in blood pressure observed among US adults during the COVID-19 pandemic. Circulation. 2022; 145:235-237.
54. Nagata S, Adachi HM, Hanibuchi T, Amagasa S, Inoue S, Nakaya T. Relationships among changes in walking and sedentary behaviors, individual attributes, changes in work situation, and anxiety during the COVID-19 pandemic in Japan. Prev Med Rep. 2021; 24:101640.
55. Shimpo M, Akamatsu R, Kojima Y, Yokoyama T, Okuhara T, Chiba T. Factors associated with dietary change since the outbreak of COVID-19 in Japan. Nutrients. 2021; 13:2039.
56. Endo K, Miki T, Itoh T, Kubo H, Ito R, Ohno K, Hotta H, Kato N, Matsumoto T, Kitamura A, Tamayama M, Wataya T, Yamaya A, Ishikawa R, Ooiwa H. Impact of the COVID-19 pandemic on glycemic control and blood pressure control in patients with diabetes in Japan. Intern Med. 2022; 61:37-48.
57. Aso Y, Iijima T, Tomaru T, Jojima T, Usui I. No negative impact of a national state of emergency by COVID-19 outbreak on hemoglobin A1c levels in patients with type 2 diabetes living in semi-rural Japan. Am J Med Sci. 2021; 362:104-105.

Received February 16, 2022; Revised March 14, 2022; Accepted March 26, 2022.

Released online in J-STAGE as advance publication March 31, 2022.

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Global Health & Medicine. 2022; 4(2):108-115.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2022.01016

Change in cancer diagnosis during the COVID-19 pandemic: Trends estimated from FDG-PET/CT

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Abstract: The aim of this study is to clarify changes in the circumstances of cancer diagnoses during the COVID-19 pandemic in Tokyo, Japan, estimated from [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) -positron emission tomography/computed tomography (PET/CT) for cancer patients. Cancer diagnosis in pandemic status (PANS) was evaluated by retrospective review of the findings of FDG-PET/CT examinations performed between 11 March 2020 and 28 December 2021 for initial staging and restaging for malignancy. Evaluation of cancer diagnosis in pre-pandemic status (pPANS) was conducted similarly in FDG-PET/CT examinations performed between 4 January 2018 and 10 March 2020. Of these, patients with malignant lymphoma (ML), lung cancer, esophageal cancer, and colorectal cancer who had a pathologically proven diagnosis or clinical diagnosis following therapy of the disease were selected for analysis. Initial cancer staging was determined by the diagnostic report of FDG-PET/CT. Change in cancer stage and in the number of FDG-PET/CT examinations performed was evaluated between pPANS and PANS, and according to term of the pandemic and vaccination status. The COVID-19 epidemic influenced the number of cancer patients who underwent FDG-PET/CT. There was a marked decrease in the number of cancer patients receiving FDG-PET/CT in Terms 1-3 (March 2020 to February 2021), but it recovered in Terms 4-6 (March 2021 to December 2021). There was no significant difference between PANS and pPANS in terms of the initial stage of cancer, but Stage IV ML and Stage II esophageal cancer were more frequent in PANS. Initial staging of ML, lung cancer, and esophageal cancer revealed more advanced cancer stages in Terms 4-6 compared with Terms 1-3. The number of patients receiving FDG-PET/CT in Tokyo was influenced by the COVID-19 epidemic. Staging based on FDG-PET/CT shifted to more advanced cancer stage during the pandemic compared with pre-pandemic.

***Keywords*:** COVID-19, pandemic, FDG-PET/CT, cancer stage, vaccination, Japan

Introduction

The novel coronavirus disease 2019 (COVID-19) outbreak spread across the world within a few months of the first report of its identification as severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) in January 2020 (*1*). On 11 March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic (*2*). In Tokyo, Japan, the first emergency declaration due to the COVID-19 outbreak was announced on 7 April 2020, and it had totally reached 4 times by the end of 2021.

The National Center for Global Health and Medicine (NCGM) is one of six National Centers in Japan with specific responsibility for management of infectious disease outbreaks. Since the first COVID-19 patient was confirmed in Japan in January 2020, the NCGM Center Hospital in Tokyo expanded its capacity for COVID-19 patients according to patient load, with peak capacity of 70 beds, including 8 intensive care unit beds (*3*). However, the hospital was forced to set priorities for the care of non-COVID-19 patients based on Business Continuity Planning (BCP) for dealing with the emergency situation. Based on BCP, hospitals temporally enacted restrictions on daily medical care systems and suspension of medical checkups including cancer screening. Social trends toward refraining from hospital consultation and regularly scheduled hospital or clinic visits occurred due to restrictions in the general medical care system and people's anxiety about contracting COVID-19. During the first wave of the pandemic in the United Kingdom (March - August 2020), an estimated 45% of people with potential cancer symptoms did not contact their doctor (*4,5*). Rodriguez *et al.* reported that COVID-19 had a marked impact on cancer care, with 46% of patients experiencing a change in care,

including treatment delay in 33% of patients and change of care location in 12%. The average duration of cancer-related care delays was greater than 4 weeks in 71.4% of clinic visits, 79.3% of laboratory testing or blood work, and 80.0% of imaging examinations (*6*). In the state of Victoria, Australia, approximately 2,500 cancer diagnoses were estimated to have been missed during the first 6 months of the pandemic (*7*). In Japan, the number of patients diagnosed with cancer was reported to have decreased after the pandemic (*8-10*), raising strong concern that a large number of patients would present with more advanced cancer in the future (*4*).

The glucose analog [^{18}F]-2-fluoro-2-deoxy-D-glucose (FDG) is a molecular imaging probe used to evaluate tissue glucose utilization and glucose metabolism. FDG-positron emission tomography/computed tomography (PET/CT) has utility in the staging, restaging, and assessment of therapeutic effects in malignancy, and is used in the management of patients with malignancy (*11*). PET/CT is also used as a part of the cancer screening program in Japan (*12*). Nuclear medicine departments have established effective procedures for patients and staff flow when facing known, suspected, and incidentally detected COVID-19 patients. These measures enabled transmission of the virus to be controlled while continuing to provide essential and critical services (*13,14*). With regard to nuclear medicine examinations including FDG-PET/CT, our department checked patients for clinical manifestations before the examination, and carefully surveyed the chest CT findings and noted any abnormal FDG uptake related to COVID-19, and alerted immediately to a doctor in charge if COVID-19 infection was suspected.

Under these conditions, it was unclear whether changes to medical care made in response to the COVID-19 pandemic had affected new cancer diagnoses and follow up in cancer patients. The aim of this retrospective study was to clarify change in the circumstances of cancer diagnosis during the COVID-19 pandemic, estimated based on FDG-PET/CT examinations performed in cancer patients.

Patients and Methods

Subjects

All study protocols in this retrospective observational study with waiver of patient informed consent were approved by our institutional review board (NCGM-S-004423-00). In evaluation of pandemic status (PANS), we surveyed FDG-PET/CT examinations performed between 11 March 2020 and 28 December 2021 (21.7 months) in patients aged ≥ 20 years, and selected those who had undergone FDG-PET/CT for initial staging and restaging (for the diagnosis of recurrence or new metastasis, or assessment of therapeutic effect in cases of malignant lymphoma [ML] only) of malignancy. In evaluation of pre-pandemic status (pPANS), we surveyed FDG-PET/CT examinations performed between 4 January and 10 March 2020 (26.3 months) in patients aged ≥ 20 years, and selected those who had undergone FDG-PET/CT for initial staging and restaging of malignancy, as described for PANS. With consideration to the number of available FDG-PET/CT examinations for each malignancy, we selected patients with ML, lung cancer, esophageal cancer, or colorectal cancer (excluding appendix and anal cancer) who had a pathologically proven diagnosis or a clinical diagnosis following therapy. Excluded cases were patients who underwent FDG-PET/CT for initial staging with no further definitive diagnosis of malignancy, and those with possible early-stage cancer observed clinically but without any definitive diagnosis.

Cancer stage based on FDG-PET/CT

Initial cancer stage was determined by the FDG-PET/CT diagnostic report made by board of nuclear medicine and diagnostic radiology, according to the 8th edition of the UICC-TNM classification for lung, esophageal, and colon cancer (*15*), and with the Lugano classification for malignant lymphoma (*16*). If no malignant lesion was identified on FDG-PET/CT, the patient was not included in this study even for lesions that were finally proven as malignant. Diagnostic report on brain MRI performed in the process of lung cancer staging was referred for checking the brain metastasis which could not identified by FDG-PET/CT.

Reference data and definitions

The number of cases of COVID-19 in Tokyo, Japan was obtained from the website established by the Tokyo Metropolitan Government (*17*). The trend of COVID-19 patients in Tokyo is presented in Figure 1A. After declaration of the COVID-19 outbreak as a global

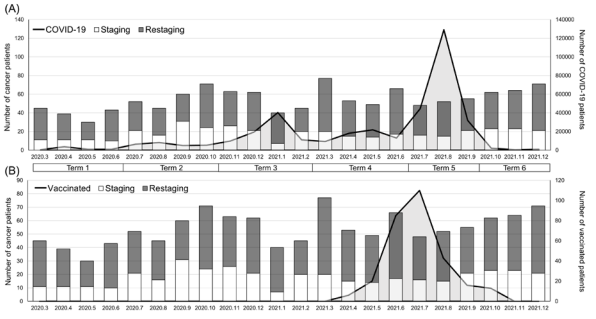

Figure 1. The trend of COVID-19 patients, cancer patients undergone FDG-PET/CT and status of COVID-19 vaccination. (A) the trend of COVID-19 patients in Tokyo and cancer patients undergone FDG-PET/CT; **(B)** COVID-19 vaccination status and cancer patients undergone FDG-PET/CT.

pandemic, 5 waves of COVID-19 occurred in Tokyo. We defined six PANS terms according to outbreak wave number as follows: Term 1 (related to the 1st wave), 11 March 2020 to 30 June 2020; Term 2 (related to 2nd wave), 1 July 2020 to 31 October 2020; Term 3 (related to the 3rd wave), 1 November 2020 to 28 February 2021; Term 4 (related to the 4th wave), 1 March 2021 to 30 June 2021; Term 5 (related to the 5th wave), 1 July 2021 to 30 September 2021; and Term 6 (sharp decline in the number of COVID-19 cases after the 5th wave), 1 October 2021 to 28 December 2021.

COVID-19 vaccination

From 1 June 2021, we interviewed the vaccination status from all patients who underwent FDG-PET/CT examination in our department (date of 1st and 2nd vaccinations and side of arm for injection) because COVID-19 vaccination can affect specific findings of FDG uptake and thus influence image interpretation (*18*). For this reason, we advised physicians and patients of the recommendation to wait at least six weeks after vaccination before having FDG-PET/CT examination, but scheduling of FDG-PET/CT was ultimately decided based on the disease status of the patient. COVID-19 vaccination status according to type of malignancy in patients who underwent FDG-PET/CT is shown in Figure 1B.

Results

Cancer patients who underwent FDG-PET/CT and COVID-19 patients in Tokyo

The number of cancer patients who visited our hospital for receiving FDG-PET/CT decreased during each peak of COVID-19 cases in Tokyo (May 2020, August 2020, January to February 2021, July to September 2021) and increased when the case numbers dropped (June 2020, September to October 2020, March 2021, October to December 2021). The number of patients who received FDG-PET/CT for initial staging of cancer increased between the peaks of Terms 2 and 3 and became constant during Terms 4 to 6. The number of patients who received FDG-PET/CT for restaging of cancer increased temporarily when the case numbers dropped and became almost constant during other periods (Figure 1A).

Cancer patients receiving FDG-PET/CT and vaccination status

Among the present patient cohort, vaccination against COVID-19 began in March 2021 and peaked in July 2021 (Figure 1B). Of patients who underwent FDG-PET/CT in March 2021 to December 2021, 47.3% (243/514) had been vaccinated at least one time: 44.1% (82/186) of those for initial staging and 49.1% (161/328) of those for restaging. The duration between the last vaccination and FDG-PET/CT showed several peaks in patient numbers for restaging, but there was no remarkable peak in those for initial staging (Table 1 and Figure 2). Although recommended to avoid FDG-PET/CT for at least 6 weeks after vaccination, it was apparent that patient status had been given priority in the decision whether or not to perform FDG-PET/CT.

Table 1. Duration between FDG-PET/CT and last COVID-19 vaccination

Duration (days)	Staging (n = 82)	Restaging (n = 161)	All (n = 243)
Average (± SD)	84 ± 57	75 ± 57	78 ± 57
Range	2 - 204	4 - 243	2 - 243
Median	83.5	63	69

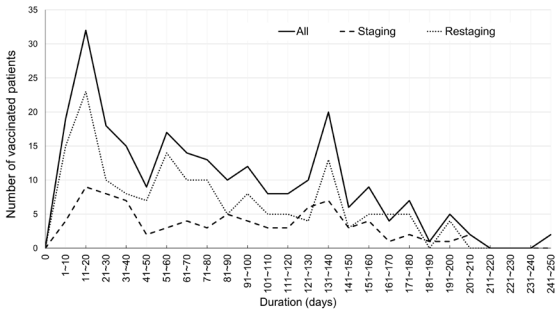

Figure 2. Duration between FDG-PET/CT examination and COVID-19 vaccination.

Malignant lymphoma

The average age of patients with ML who underwent FDG-PET/CT showed no change between pPANS (65 ± 15) and PANS (66 ± 14). The number of patients receiving FDG-PET/CT examinations per month was higher in PANS (20.7 patients/month) than in pPANS (11.7 patients/month) in these patients (Table 2). The number of FDG-PET/CT examinations per month was slightly higher in Terms 4-6 (21.2 patients/month) than in Terms 1-3 (20.3 patients/month) and dropped temporarily in Term 5 (Table 2, Figure 3A). The ratio of purpose for FDG-PET/CT examination was shifted from initial staging to restaging in PANS (pPANS: staging 23.3%, restaging 76.7%, PANS: staging 19.2%, restaging 80.8%) (Table 2). The rates of Stage I and Stage IV disease was higher in PANS (Stage I: 32.6%, Stage IV: 37.2%) than in pPANS (Stage I: 27.8%, Stage IV: 25.0%), and the initial cancer stage was more advanced in Terms 4-6 (Stage I: 28.6%, II: 11.9%, III: 19.0%, IV: 40.5%) than in Terms 1-3 (Stage I: 36.4%, II: 11.3%, III: 18.2%, IV: 34.1%). No specific trend in cancer stage was observed in patients with ML, but Stage IV disease was constantly diagnosed in PANS (Figure 4A).

Table 2. Characteristics of patients with malignant lymphoma receiving FDG-PET/CT

Variables	PANS			pPANS		
Role of examination	Number	Ratio (%)		Number	Ratio (%)	
Staging	86 (44/42)	19.2 (18.6/19.8)		72	23.3	
Restaging	363 (193/170)	80.8 (81.4/80.2)		237	76.7	
Total	449 (237/212)			309		
Number per month	20.7 (20.3/21.2)			11.7		
Cancer stage	Number	Ratio (%)		Number	Ratio (%)	
1	28 (16/12)	32.6 (36.4/28.6)		20	27.8	
2	10 (5/5)	11.6 (11.3/11.9)		15	20.8	
3	16 (8/8)	18.6 (18.2/19.0)		19	26.4	
4	32 (15/17)	37.2 (34.1/40.5)		18	25.0	
Age	Staging	Restaging	All	Staging	Restaging	All
Average (± SD)	66 ± 16	66 ± 14	66 ± 14	66 ± 16	64 ± 15	65 ± 15
Range	30 - 93	20 - 93	20 - 92	20 - 86	20 - 91	20 - 91
Median	70.5	69	69	68.5	68	68

Data in parenthesis represent the situation of Term 1-3/Term 4-6.

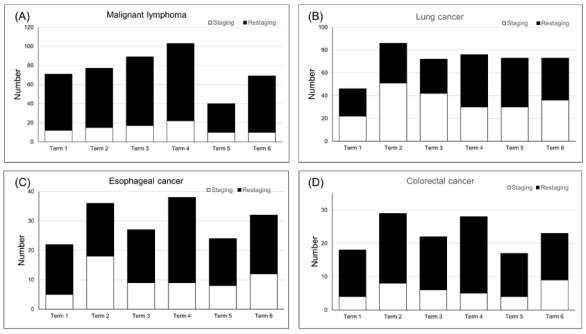

Figure 3. The number of cancer patients undergone FDG-PET/CT for staging and restaging in 4 types of cancers in each term. (A) malignant lymphoma, **(B)** lung cancer, **(C)** esophageal cancer, **(D)** colorectal cancer.

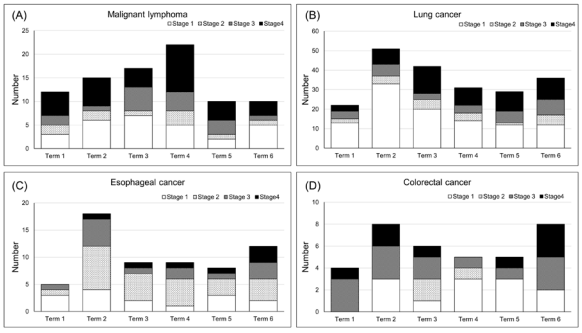

Figure 4. Cancer staging by FDG-PET/CT in 4 types of cancers in each term. (A) malignant lymphoma, **(B)** lung cancer, **(C)** esophageal cancer, **(D)** colorectal cancer.

Lung cancer

There was no change between pPANS (70 ± 11) and PANS (72 ± 11) in terms of average age in the patients with lung cancer, and the number of FDG-PET/CT examinations per month was almost the same between pPANS (19.4 patients/month) and PANS (19.6 patients/month). The number of FDG-PET/CT examinations per month was higher in Terms 4-6 (22.2 patients/month) than in Terms 1-3 (17.4 patients/month). The ratio of purpose for FDG-PET/CT was almost the same between pPANS and PANS (pPANS: staging 50.7%, restaging 49.3%, PANS: staging 49.5%, restaging 50.5%). Compared with Terms 1-3, more patients underwent FDG-PET/CT for restaging than for initial staging in Terms 4-6 (Table 3, Figure 3B). In PANS, cancer stage shifted to an earlier stage, but the rates of Stage I to Stage IV disease did not change. Cancer stage was more advanced in Terms 4-6 (Stage I: 39.6%, II: 10.4%, III: 18.8%, IV: 31.3%) than in Terms 1-3 (Stage I: 57.4%, II: 9.6%, III: 11.3%, IV: 21.4%). The number of Stage I cancers increased temporarily in Term 2, and advanced cancer stage was more common in later terms (Figure 4B). With referring to the result on contrast-enhanced brain MRI, FDG-PET/CT could not identify 9 cases of brain metastases in pPANS and 10 cases of them in PANS. Based on this result, stage IV cancer was underestimated in two cases (both stage III by FDG-PET/CT) in PANS, but no case in pPANS.

Esophageal cancer

Mean age of the patients with esophageal cancer was slightly higher in PANS (70 ± 9) than in pPANS (68 ± 10). The number of FDG-PET/CT examinations per month was slightly lower in PANS (pPANS, 8.9 patients/month; PANS, 8.3 patients/month), and the number of patients was higher in Terms 4-6 (9.5 patients/month) than in Terms 1-3 (7.3 patients/month) (Table 4). The number of FDG-PET/CT examinations performed for initial staging was greatest in Term 2, followed by Term 6 (Figure 3C). The ratio of purpose of FDG-PET/CT were similar between pPANS and PANS (pPANS: staging 30.5%, restaging 69.5%, PANS: staging 33.9%,

Table 3. Characteristics of patients with lung cancer receiving FDG-PET/CT

Variables	PANS			pPANS		
Role of examination	Number	Ratio (%)		Number	Ratio (%)	
Staging	211 (115/96)	49.5 (56.4/43.2)		259	50.7	
Restaging	215 (89/126)	50.5 (43.6/56.8)		252	49.3	
Total	426 (204/222)			511		
Number per month	19.6 (17.4/22.2)			19.4		
Cancer stage	Number	Ratio (%)		Number	Ratio (%)	
1	104 (66/38)	49.3 (57.4/39.6)		116	44.8	
2	21 (11/10)	10.0 (9.6/10.4)		33	12.7	
3	31 (13/18)	14.7 (11.3/18.8)		45	17.4	
4	55 (25/30)	26.1 (21.4/31.3)		65	25.1	
Age	Staging	Restaging	All	Staging	Restaging	All
Average (± SD)	72 ± 11	71 ± 11	72 ± 11	71 ± 11	70 ± 11	70 ± 11
Range	38 - 94	34 - 95	34 - 95	31 - 92	37 - 90	31 - 92
Median	74	72	73	72	71	71

Data in parenthesis represent the situation of Term 1-3/Term 4-6.

Table 4. Characteristics of patients with esophagus cancer receiving FDG-PET/CT

Variables	PANS			pPANS		
Role of examination	Number	Ratio (%)		Number	Ratio (%)	
Staging	61 (32/29)	33.9 (37.6/30.9)		71	30.5	
Restaging	118 (53/65)	66.1 (62.4/69.1)		162	69.5	
Total	180 (85/94)			233		
Number per month	8.3 (7.3/9.5)			8.9		
Cancer stage	Number	Ratio (%)		Number	Ratio (%)	
1	15 (9/6)	24.6 (28.1/20.7)		20	28.2	
2	26 (14/12)	42.6 (43.8/41.4)		23	32.4	
3	13 (7/6)	21.3 (21.9/20.7)		14	19.7	
4	7 (2/5)	11.5 (6.3/17.2)		14	19.7	
Age	Staging	Restaging	All	Staging	Restaging	All
Average (± SD)	72 ± 8	69 ± 9	70 ± 9	68 ± 10	67 ± 10	68 ± 10
Range	56 - 91	43 - 92	43 - 92	31 - 88	38 - 87	31 - 88
Median	73	70	71	70	68.5	69

Data in parenthesis represent the situation of Term 1-3/Term 4-6.

restaging 66.1%), but compared with Terms 1-3 (staging 37.6%, restaging 62.4%), there was a slight shift from initial staging to restaging in Terms 4-6 (staging 30.9%, restaging 69.1%). The rates of Stage I and IV cancer were lower and that of Stage II cancer was higher in PANS (Stage I: 24.6%, II: 42.6%, III: 21.3%, IV: 11.5%) than in pPANS (Stage I: 28.2%, II: 32.4%, III: 19.7%, IV: 19.7%) (Table 4). Compared with Terms 1-3 (Stage I: 28.1%, II: 43.8%, III: 21.3%, IV: 6.3%), cancer stage was more advanced in Terms 4-6 (Stage I: 20.7%, II: 41.4%, III: 20.7%, IV: 17.2%) (Figure 4C). In Terms 4-6, the rate of Stage IV cancer (0.50 patients/month) was higher than in Terms 1-3 (0.17 patients/month) and almost equal to that in pPANS (0.53 patients/month).

Colorectal cancer

The average age of patients with colorectal cancer who underwent FDG-PET/CT showed no change between pPANS (63 ± 13) and PANS (62 ± 14). In these patients, the number of FDG-PET/CT examinations per month was slightly higher in PANS than in pPANS (pPANS, 5.8 patients/month; PANS, 6.3 patients/month), and was higher in Terms 4-6 (6.8 patients/month) than in Terms 1-3 (5.9 patients/month) (Table 5). The number of FDG-PET/CT examinations performed for initial staging was greatest in Term 6, followed by Term 2 (Figure 3D). Compared with pPANS, more examinations were performed for the purpose of initial staging in PANS (pPANS: staging 20.4%, restaging 79.6%, PANS: staging 26.9%, restaging 73.1%), and there was no difference between Terms 4-6 (staging 26.5%, restaging 73.5) and Terms 1-3 (staging 26.1%, restaging 73.9) (Table 5, Figure 3D). The stage of colorectal cancer shifted to an earlier stage in PANS (pPANS; Stage I: 16.1%, II: 6.5%, III: 41.9%, IV: 35.5%, PANS; Stage I: 33.3%, II: 8.3%,

Table 5. Characteristics of patients with colorectal cancer receiving FDG-PET/CT

Variables	PANS			pPANS		
Role of examination	Number	Ratio (%)		Number	Ratio (%)	
Staging	36 (18/18)	26.9 (26.1/26.5)		31	20.4	
Restaging	101 (51/50)	73.1 (73.9/73.5)		121	79.6	
Total	137 (69/68)			152		
Number per month	6.3 (5.9/6.8)			5.8		
Cancer stage	Number	Ratio (%)		Number	Ratio (%)	
1	12 (4/8)	33.3 (22.2/44.4)		5	16.1	
2	3 (2/1)	8.3 (11.1/5.6)		2	6.5	
3	13 (8/5)	36.1 (44.4/27.8)		13	41.9	
4	8 (4/4)	22.2 (22.2/22.2)		11	35.5	
Age	Staging	Restaging	All	Staging	Restaging	All
Average (± SD)	65 ± 14	61 ± 14	62 ± 14	59 ± 14	65 ± 13	63 ± 13
Range	39 - 88	29 - 88	29 - 88	29 - 79	29 - 89	29 - 89
Median	68.5	62	63	60	66	65

Data in parenthesis represent the situation of Term 1-3/Term 4-6.

III: 36.1%, IV: 22.2%). Cancer stage shifted to an earlier stage in Terms 4-6 (Stage I: 44.4%, II: 5.6%, III: 27.8%, IV: 22.2%) compared with Terms 1-3 (Stage I: 22.2%, II: 11.1%, III: 44.4%, IV: 22.2%), but the highest number of advanced stage cancers were in Term 6 (Figure 4D).

Discussion

This study evaluated change in cancer diagnosis by FDG-PET/CT during the COVID-19 pandemic compared with the pre-pandemic status. The number of patients who underwent FDG-PET/CT was influenced by the COVID-19 epidemic in Tokyo. There was a prominent decrease in cancer patients underwent FDG-PET/CT in Terms 1-3 but the numbers recovered in Terms 4-6. Our results showed no significant difference between PANS and pPANS regarding the number of examinations performed for initial cancer staging, but the rates of Stage IV disease of ML and Stage II of esophageal cancer were increased in PANS. The initial stage of ML, lung cancer, and esophageal cancer shifted to a more advanced stage in Terms 4-6 compared with Terms 1-3.

In patients who underwent FDG-PET/CT for initial staging, COVID-19 had a greater effect in Terms 1-3 than in Terms 4-6. The number of patients who underwent FDG-PET/CT for restaging showed a temporary increase after the peak of COVID-19 had passed. This finding indicates that the COVID-19 epidemic did indeed impact cancer patients, but to a lesser degree in Terms 4-6, when one year had passed after declaration of the COVID-19 pandemic. It is noteworthy that the number of patients who underwent FDG-PET/CT gradually kept increased in the time of the large peak in COVID-19 cases in August 2021. When the peak vaccination rate in July 2021 is taken into account, it is possible that vaccination may have influenced patients' psychological condition. Although the average period between vaccination and FDG-PET/CT was approximately 80 days, the peak timing was 11-20 days after vaccination. Our department recommended waiting at least 6 weeks after vaccination before scheduling an FDG-PET/CT examination (*18*), but the patient's condition and treatment planning was given priority. However, over half of the patients were not vaccinated at the time of the FDG-PET/CT examination. Patients with cancer and cardiovascular disease are at high risk for worse clinical outcomes in COVID-19 infection (*19*), and vaccination against COVID-19 helps prevent serious complications (*20*). The attitude of the present patients toward vaccination is unclear, and the recommendation timing of vaccination in cancer patients appears to be an ongoing issue.

In Japan, the diagnosis of five types of cancer (gastric, colon, lung, breast, and cervical cancer) were 9.2% lower in 2020 than in 2019 (*8*). In 2020, the number of newly diagnosed cancers was reduced by 13.4% in gastric cancer, 10.2% in colon cancer, 8.2% in breast cancer, 6.4% in lung cancer and 4.8% in cervical cancer, compared with those diagnosed in 2019 (*8*). In US and the UK, a significant decline in the number of encounters with cancer had been reported for April 2020 compared with 2019. Lung (-39.1%), colorectal (-39.9%), and hematologic (-39.1%) cancer cohorts showed smaller decreases in size compared with decreases in cohort size for breast cancer (-47.7%), prostate cancer (-49.1%), and melanoma (-51.8%) (*21*), which suggests that the impact of the COVID-19 pandemic might have differed according to the type of cancer.

In the present study, the number of FDG-PET/CT examinations increased between Terms 1 and 4 in ML patients, but this trend was not observed in the other three cancer types. There is no specific screening program for ML and patients are generally referred to the hospital after the emergence of clinical symptoms such as continuous fever and lymph node swelling. As

early diagnosis and treatment is essential in patients with aggressive disease, hospitals should consider retaining capacity to accept these patients and reflect it to BCP. The other three types of cancer have specific screening programs: low-dose chest CT for lung cancer screening, upper endoscopy for esophageal cancer, and lower endoscopy and fecal occult blood testing for colorectal cancer. Many major cancer organizations have recommended delaying screening studies such as screening mammograms, colonoscopy, and surveillance for lung cancer during the COVID-19 pandemic (*22,23*). However, delay in the diagnosis of rapidly growing malignancies such as breast and lung cancer carry the risk of causing adverse outcomes (*24,25*), whereas suspension of screening for slow-growing malignancies such as prostate cancer and cervical cancer are considered to have a minimal effect on outcomes. (*25,26*).

According to the Japan Cancer Society, 30.5% fewer people underwent cancer screening for five types of cancer in 2020 compared with 2019 (*27*). The screening rate had recovered by the first half of 2021, but was still 17.4% lower than in 2019 (*28*). Therefore, it is possible that the number of FDG-PET/CT examinations performed for initial cancer staging could have been affected by the reduction in cancer screenings, which decreased the opportunity to detect cancer in the early stages.

Maringe *et al*. estimated the impact of delays in diagnosis on cancer survival outcomes in breast, colorectal, esophageal, and lung cancer. Compared with the pre-pandemic status, the estimated increase of deaths in the pandemic status was 7.9-9.6% for breast cancer, 15.3-16.6% for colorectal cancer, 4.8-5.3% for lung cancer, and 5.8-6.0% for esophageal cancer, up to year 5 after diagnosis (*29*). It is known that delays in therapy for cancer have a significant impact on survival (*30*). Delays of 3 or 6 months in surgery for incident cancers have been shown to reduce life-years gained by 19% and 43%, respectively (*31*). As another critical issue, even a 3-month delay in diagnosis and initiation of treatment due to the COVID-19 pandemic was shown to result in excess healthcare costs (*32*).

The present results showed no significant difference between PANS and pPANS in terms of the number of FDG-PET/CT examinations performed for initial staging, however the rate of detection of Stage IV disease in ML and Stage II disease in esophageal cancer were higher in PANS than in pPANS.

The initial stage of ML, lung cancer, and esophageal cancers shifted to a more advanced stage in Terms 4-6 compared with Terms 1-3. These results may indicate that the shift to a more advanced stage first began in 2021, and occurred earlier in ML due to the aggressiveness of the disease. This trend should be monitored to understand of the actual impact of the COVID-19 pandemic on patients with cancer.

It is known that FDG-PET/CT has limitations in assessment of lesions that have high background physiologic FDG uptake, which led to brain metastasis being missed by FDG-PET/CT in several of the present cases, and have caused underestimation of cancer staging. Small lesions (< 10 mm) can be missed by FDG-PET/CT due to the limited resolution of PET. FDG-PET/CT has limitations in detecting bone marrow invasion in ML, which might have caused underestimation of staging in ML.

The limitations of this study include its retrospective design and that it was conducted at a single institution. Seasonal variations in the number cancer patients underwent FDG-PET/CT were not taken into account. Hospitals in Japan have played different roles during the COVID-19 pandemic, and the trends in cancer patients may differ among hospitals. To understand the influence of the COVID-19 pandemic on cancer patients, a large multicenter study is warranted.

Acknowledgements

We thank all the staff in National Center for Global Health and Medicine who struggled with COVID-19. We also thank Kaori Saito, Kiyoyuki Kodama, Daisuke Horikawa, Masashi Hayano, Fumio Sunaoka, Megumi Fujii, Keiichi Kurihara, Yui Yamada, Hisayoshi Mizunuma, Kazuhiko Nakajima, Kahori Miyake, Hironori Kajiwara and Futoshi Matsunaga for contributing to this study.

Funding: None.

Conflicts of interest: The authors have no conflicts of interest to disclose.

References

1. Zhu N, Zhang D, Wang W, *et al*. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020; 382:727-733.
2. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. *https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020* (accessed March 7, 2022).
3. Kokudo N, Sugiyama H. Hospital capacity during the COVID-19 pandemic, Glob Health Med. 2021; 3:56-59.
4. The Lancet Oncology. COVID-19 and cancer: 1 year on. Lancet Oncol. 2021; 22:411.
5. Cancer Research UK. Almost half of people with possible cancer symptoms didn't see GP in first wave of pandemic. *https://news.cancerresearchuk.org/2021/02/25/almost-half-of-people-with-possible-cancer-symptoms-didnt-see-gp-in-first-wave-of-pandemic/* (accessed March 7, 2022).
6. Rodriguez GM, Ferguson JM, Kurian A, Bondy M, Patel MI. The Impact of COVID-19 on patients with cancer: A national study of patient experiences. Am J Clin Oncol. 2021; 44:580-587.
7. Cancer Council Victoria. More than 2,500 cancer

diagnoses slip through the COVID-19 pandemic cracks in Victoria, sparking fears of a possible 'cancer spike' to come. *https://www.cancervic.org.au/about/media-releases/2021-media-releases/march-2021/more-cancer-diagnoses-slip-through-the-covid-19-cracks.html* (accessed March 7, 2022).
8. Japan Cancer Society. *https://www.jcancer.jp/news/12418* (accessed March 7, 2022). (in Japanese)
9. The Japan Lung Cancer Society. *https://www.haigan.gr.jp/modules/english/index.php?content_id=1* (accessed March 7, 2022).
10. National Cancer Center Japan. *https://www.ncc.go.jp/jp/information/pr_release/2021/1126/index.html* (accessed March 7, 2022). (in Japanese)
11. Gambhir SS. Molecular imaging of cancer with positron emission tomography. Nat Rev Cancer. 2002; 2:683-693.
12. Minamimoto R, Senda M, Jinnouchi S, *et al*. The current status of an FDG-PET cancer screening program in Japan, based on a 4-year (2006-2009) nationwide survey. Ann Nucl Med. 2013; 27:46-57.
13. Paez D, Gnanasegaran G, Fanti S, *et al*. COVID-19 pandemic: Guidance for nuclear medicine departments. Eur J Nucl Med Mol Imaging. 2020; 47:1615-1619.
14. Saito K, Horikawa D, Takeuchi T, Mizunuma H, Yamada Y, Hironaka S, Kajiwara H, Hotta M, Matsunaga F, Minamimoto R. An Experience of PET/CT Examination in the Patient with a Recent History of COVID-19 Infection. Nihon Hoshasen Gijutsu Gakkai Zasshi. 2020; 76:761-767. (in Japanese)
15. Amin MB, Edge S, Greene F, *et al*., editors. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017.
16. Cheson BD, Fisher RI, Barrington SF, *et al*. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014; 32: 3059-3068.
17. Updates on COVID-19 in Tokyo. *https://stopcovid19.metro.tokyo.lg.jp/en* (accessed March 7, 2022).
18. Minamimoto R, Kiyomatsu T. Effects of COVID-19 vaccination on FDG-PET/CT imaging: A literature review. Glob Health Med. 2021; 3:129-133.
19. Dai M, Liu D, Liu M, *et al*. Patients with cancer appear more vulnerable to SARS-CoV-2: A multicenter study during the COVID-19 outbreak. Cancer Discov. 2020; 10:783-791.
20. American Cancer Society. COVID-19 vaccines in people with cancer. *https://www.cancer.org/treatment/treatments-and-side-effects/physical-side-effects/low-blood-counts/infections/covid-19-vaccines-in-people-with-cancer.html#shouldcancerpatientsandsurvivorsgetthevaccine* (accessed March 7, 2022).
21. London JW, Fazio-Eynullayeva E, Palchuk MB, Sankey P, McNair C. Effects of the COVID-19 pandemic on cancer-related patient encounters. JCO Clin Cancer Inform. 2020; 4:657-665.
22. Waterhouse DM, Harvey RD, Hurley P, Levit LA, Kim ES, Klepin HD, Mileham KF, Nowakowski G, Schenkel C, Davis C, Bruinooge SS, Schilsky RL. Early impact of COVID-19 on the conduct of oncology clinical trials and long-term opportunities for transformation: Findings from an American Society of Clinical Oncology Survey. JCO Oncol Pract 2020; 16:417-421.
23. Rubin GD, Ryerson CJ, Haramati LB, *et al*. The role of chest imaging in patient management during the COVID-19 pandemic: A multinational consensus statement from the Fleischner Society. Radiology 2020; 296:172-180.
24. Yousaf-Khan U, van der Aalst C, de Jong PA, Heuvelmans M, Scholten E, Lammers JW, van Ooijen P, Nackaerts K, Weenink C, Groen H, Vliegenthart R, Ten Haaf K, Oudkerk M, de Koning H. Final screening round of the NELSON lung cancer screening trial: the effect of a 2.5-year screening interval. Thorax. 2017; 72:48-56.
25. Boettcher AN, Hammoud DA, Weinberg JB, Agarwal P, Mendiratta-Lala M, Luker GD. Cancer imaging and patient care during the COVID-19 pandemic. Radiol Imaging Cancer. 2020; 2:e200058.
26. Perri T, Issakov G, Ben-Baruch G, Felder S, Beiner ME, Helpman L, Hogen L, Jakobson-Setton A, Korach J. Effect of treatment delay on survival in patients with cervical cancer: a historical cohort study. Int J Gynecol Cancer. 2014; 24:1326-1332.
27. The Japan Lung Cancer Society. 30% decrease in the number of people receiving medical examinations in 2020, and approximately 2,100 cancers may go undetected - survey by 32 chapters of the Japan Cancer Society *https://www.jcancer.jp/news/11952* (accessed March 7, 2022). (in Japanese)
28. The Japan Lung Cancer Society. Cancer screening visits in the first half of 2021 doubled from the same period last year, but down 17% from before the new coronary (Japan Cancer Society branch survey). *https://www.jcancer.jp/news/12360* (accessed March 7, 2022). (in Japanese)
29. Maringe C, Spicer J, Morris M, Purushotham A, Nolte E, Sullivan R, Rachet B, Aggarwal A. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. Lancet Oncol. 2020; 21:1023-1034.
30. Sharpless NE. COVID-19 and cancer. Science. 2020; 368:1290.
31. Sud A, Jones ME, Broggio J, *et al*. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. Ann Oncol. 2020; 31:1065-1074.
32. Degeling K, Baxter NN, Emery J, Jenkins MA, Franchini F, Gibbs P, Mann GB, McArthur G, Solomon BJ, IJzerman MJ. An inverse stage-shift model to estimate the excess mortality and health economic impact of delayed access to cancer services due to the COVID-19 pandemic. Asia Pac J Clin Oncol. 2021; 17:359-367.

Received March 9, 2020; Revised March 22, 2022; Accepted March 28, 2022.

Released online in J-STAGE as advance publication March 31, 2022.

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Global Health & Medicine. 2022; 4(2):116-121.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2021.01114

Trends in endotracheal intubation for patients with COVID-19 by emergency physicians

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Abstract: Emergency physicians perform endotracheal intubations for patients with COVID-19. However, the trends in the intubation for COVID-19 patients in terms of success rate, complications, personal protective equipment (PPE) information, barrier enclosure use, and its transition have not been established. We conducted a retrospective study of COVID-19 cases that required tracheal intubation at four hospitals in the Tokyo metropolitan area between January 2020 and August 2021. The overall intubation success rate, operator experience, and infection control methods were investigated. We then compared the early and late phases of the pandemic for a period of 8 months each. A total of 211 cases met the inclusion criteria, and 133 were eligible for analysis. The intubation success rate increased from 85% to 94% from early to late phase, although the percentage of intubations performed by emergency medicine residents increased significantly in the late phase ($p = 0.03$). The percentage of light PPE use significantly increased from 65% to 91% from early to late phase ($p < 0.01$), whereas the percentage of barrier enclosure use significantly decreased from 26% to 0% ($p < 0.01$). Furthermore, the infection prevention methods during intubation became more simplified from early to late phase.

***Keywords*:** COVID-19, emergency physician, endotracheal intubation, Japan

Introduction

Patients with coronavirus disease 2019 (COVID-19) sometimes require emergency intubation for mechanical ventilation (*1-3*). Several observational studies have assessed emergency tracheal intubations for patients with COVID-19 mainly performed by anesthesiologists in China (*4,5*), the UK (*6*), the United States (*7*), Canada (*8*), and one international cohort study (*9*). The intubation success rate, complications, method of endotracheal intubation, types of personal protective equipment (PPE), and operator safety have not been described.

In the arduous fight against COVID-19 over the past year and a half, method of endotracheal intubation and types of PPE have been changed for various reasons (*10,11*), and their trends have not been examined at all. Considering those trends may contribute to the preparedness for the next pandemic, as well as to the current clinical practice. For example, a retrospective study in Brazil examined 112 COVID-19 cases with emergency intubations; however, only patients in the early phase of COVID-19 were included (*12*).

In the present study, we aim to describe the trends in the endotracheal intubations performed by emergency physicians for COVID-19 cases in terms of the success rate, complications, intubation method (including video laryngoscopy), types of PPE, and operator safety.

Materials and Methods

Study design and patients

This retrospective study includes data for adult patients with COVID-19 who underwent endotracheal intubation performed by emergency physicians at four hospitals (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=44*) in the Tokyo metropolitan area between January 2020 and August 2021. The emergency departments of these four hospitals meet once a month to discuss issues to be solved in daily medical care. Data from medical records obtained from the four hospitals were collected, organized into datasets, and analyzed. The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the local ethics committee (Approval Number 20-

R044). This observational study was conducted in compliance with the Strengthening the Reporting of Observational Studies in Epidemiology or STROBE statement (*13*).

Data collection

The following parameters were recorded: age, sex, body mass index (BMI), laryngoscopy method (McGrath video laryngoscope (Aircraft Medical Ltd., Edinburgh, UK), Macintosh direct laryngoscope (Teleflex, Morrisville, NC), or change from Macintosh to McGrath), barrier enclosure use, operator experience, pre-intubation analgesia (fentanyl or none), pre-intubation sedative use (propofol, midazolam, or propofol and midazolam combined), pre-intubation neuromuscular blockade (rocuronium) use, intubation success rate on the first attempt, reasons for failed tracheal intubation, complications, confirmation after intubation, PPE combinations, patient outcomes (discharge, transfer to another hospital, in-hospital death, or still in hospital), and whether the operator contracted COVID-19.

Operator experience was recorded as emergency medicine resident (postgraduate year 1-6), attending physician, or change of operator from resident to attending physician. Reasons for intubation failure/difficulty were difficulty to confirm the glottis, closure of the glottis, inability to ventilate, damage to the cuff, and poor visibility due to protective glasses. Complications during intubation included oxygen desaturation (SpO_2 < 90%), systolic hypotension (< 90 mmHg), intubation of the main bronchus, and arrhythmia (atrial fibrillation and sinus bradycardia). The following PPE combinations were considered (Figure 1): Type A comprised an N95 mask, plastic gown, and eye shield; Type B comprised an N95 mask, surgical gown, and eye shield; Type C comprised an N95 mask, a Tyvek suit, and a powered air-purifying respirator; and Type D comprised an N95 mask, a Tyvek suit, and eyewear. Confirmation after intubation was performed by one of four approaches: stethoscope, capnometer, and portable X-ray; capnometer and portable X-ray; stethoscope and portable X-ray; or portable X-ray only.

Definitions

The diagnosis of COVID-19 was dependent on a positive reverse transcription-polymerase chain reaction test confirming the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a nasal swab, pharyngeal swab, or sputum sample (*12*). Emergency physicians in Japan have a 3 to 4 year residency training program which has been established with a curriculum similar to that of the US program (*14*). But some emergency physicians working in the designated tertiary emergency hospitals usually have training in one additional specialty, such as Trauma Surgery and Critical Care (*15*). Therefore, Japanese emergency physicians have a high level of competence in dealing with hospitalized acutely injured and ill patients, and are sometimes required to provide in-patient care (*16*). Emergency tracheal intubation was performed by personnel authorized by the in-charge doctor at the time. If an operator had a confirmed COVID-19 infection up to 30 days after intubation, it was considered "operator infection". The target period was divided into two 8-month periods: early phase from January 1, 2020, to August 31, 2020 (first and second waves), and late phase from September 1, 2020, to April 31, 2021 (third and fourth waves).

Study endpoints

The primary focus of this study is to describe the

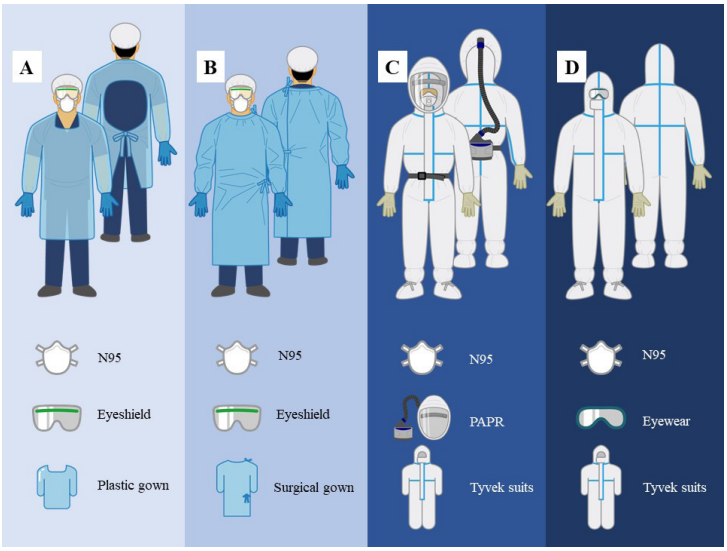

Figure 1. Types of personal protective equipment used during intubation.

overall success rate of emergency tracheal intubation, operator experience, and infection control methods, in patients with COVID-19. A secondary objective is to compare the early (initial 8 month) and late (the subsequent 8 month) phases of the study period.

Data analysis

Statistical analysis was performed using JMP version 11 (SAS, Cary, NC, USA). Patient characteristics, intubation-related factors, and outcomes were compared between the early and late phases using the Mann-Whitney *U* or Fisher exact tests for categorical variables, as appropriate. Two-tailed *p*-values < 0.05 were considered statistically significant. Imputation of missing values was not performed.

Results

Baseline characteristics

In total, 211 COVID-19 cases with intubation were retrieved. The data are shown in Table 1. The excluded cases consisted of 76 cases intubated by a non-emergency doctor (intensivist: 42 cases; respiratory physician: 27 cases; infectious disease physician: 5 cases and anesthesiologist: 2 cases,) and 2 cases in which the operator was changed (from emergency doctor to intensive care doctor, and from infectious disease physician to emergency doctor). A final total of 133 cases were thus included in further analyses (Figure 2). The median age was 66 years (range, 26 to 96 years), and the mean BMI was 24.8 kg/m^2 (range, 15.6 to 53.3 kg/m^2) (Table 1). Overall, 42 intubations (31.6%) were performed in the emergency department, and 91.0% were successful on the first attempt. Most intubations were performed by emergency medicine residents (66.9%; n = 89), followed by attending physicians (30.8%; n = 41). The percentages of Macintosh glass and Macintosh direct laryngoscopes used were the same (48.8%; n = 65). Neuromuscular blockade was used in 122 cases (91.7%). Desaturation was observed in 25 cases (18.8%) and hypotension in 29 (21.8%). In-hospital mortality was 21.1%, and none of the operators became infected with SARS-CoV-2.

Comparison of early and late phase outcomes

The 133 patients were divided between the early and late phases, based on when they were intubated. In both phases, about 30% of the intubations were performed in the emergency department, and 70% in the intensive care unit (ICU) and general ward. The use of the McGrath video laryngoscope decreased from early to late phase (58.7% to 43.7%), whereas that of the Macintosh direct laryngoscope increased correspondingly (37.0% to 55.2%). Of the 87 cases in the late phase, none were intubated using a barrier enclosure, significantly reducing the rate of use (p < 0.01) (Figure 3A). A significant increase was observed in intubation cases by emergency medicine residents (p = 0.03). The percentage of first-attempt intubation success rose from 84.8% to 94.3%. Difficulty to confirm the glottis and inability to ventilate were the common reasons for failed or difficult intubation in both phases. The rate of SpO_2 decrease was significantly reduced in the late phase (p < 0.01). Confirmation after intubation was mostly with the stethoscope, capnometer, and portable X-ray, which was significantly increased in the late phase compared with the early phase (p < 0.01). The proportion of light PPE types A and B increased significantly from early to late phase, whereas those of heavy PPE types C and D decreased (p < 0.01) (Figure 3B).

Discussion

The success rate of first-attempt intubation for the entire study period was high at 91% and the success rate increased from 85% to 94% in the early to late phase. All tracheal intubations in the previous studies were performed in the early phase (Table 2). This success rate was almost equal to the success rate performed by anesthesiologists (*4-6*) and higher than the success rates of emergency physicians in other studies (*7,12*). Patient BMI and years of operator experience were not comparable between the two phases.

Hypoxia and hypotension each occurred in approximately 20% of cases, which was clinically relevant. The percentage of hypoxia occurrence decreased significantly from the early to late phase (from 27.8% to 17.2%; p < 0.01), as well as that of hypotension, although not significantly (from 27.3 to 19.5%; p = 0.09). Although no significant difference was observed, propofol was used as a sedative in 72.4% of cases in which hypotension occurred, and midazolam, which is less likely to affect circulatory dynamics, was used in 17.2% (p = 0.36).

In this study, the overall percentage of emergency resident operators who performed intubations was as high as 67%, rising to about 75% in the late phase, a significant increase when compared with the early phase (p = 0.03). Thus, the most skilled operator available should perform endotracheal intubation in patients with COVID-19 (*17*). Several factors contribute to the difficulty of intubation, not least of which is the lack of familiarity with PPE (*18*), the risk of acquiring infection, and the presence of severe hypoxemia (*19*). Failure to implement the said recommendation in the current study likely reflects a unique problem of physician availability in the emergency department. However, the success rate increased significantly from the early phase to the late phase. This may be due to the fact that the operators, especially the emergency residents, improved as they gained intubation experience.

Table 1. Patient characteristics

Characteristic	Total (n = 133)	Early phase (n = 46)	Late phase (n = 87)	p
Age	66 (26-96)	63.5 (26-85)	68 (36-96)	
Sex (Male)	106 (79.7)	38 (82.6)	68 (78.2)	0.65
BMI	24.8 (15.6-53.3)	25.4 (16.8-35.4)	24.6 (15.6-53.3)	
Intubation location				0.85
Emergency department	42 (31.6)	15 (32.6)	27 (31.0)	
Intensive Care Unit/general ward	91 (68.4)	31 (67.4)	60 (69.0)	
Laryngoscopy method				0.09
McGrath video laryngoscope	65 (48.8)	27 (58.7)	38 (43.7)	
Macintosh direct laryngoscope	65 (48.8)	17 (37.0)	48 (55.2)	
Macintosh → McGrath	3 (2.3)	2 (4.3)	1 (1.2)	
Barrier Enclosure				< 0.01
Used	12 (9.0)	12 (26.1)	0 (0.0)	
Operator experience				0.03
Emergency medicine resident	89 (66.9)	24 (52.2)	65 (74.7)	
Attending physician	41 (30.8)	20 (43.5)	21 (24.1)	
Resident → Attending physician	3 (22.6)	2 (4.3)	1 (1.2)	
Analgesia before intubation				0.02
Fentanyl	129 (97.0)	42 (91.3)	87 (100)	
None	2 (1.5)	2 (2.9)	0 (0.0)	
Sedative before intubation				0.16
Propofol	113 (85.0)	36 (78.3)	77 (88.5)	
Midazolam	15 (15.2)	7 (15.2)	8 (9.2)	
Propofol + Midazolam	3 (2.3)	1 (2.2)	2 (2.3)	
Neuromuscular blockade before intubation				0.11
Rocuronium	122 (91.7)	40 (87.0)	82 (94.3)	
None	9 (6.8)	4 (8.7)	5 (5.8)	
Success/failure of tracheal intubation				0.11
First-attempt intubation success	121 (91.0)	39 (84.8)	82 (94.3)	
> 2 intubation attempts	12 (9.0)	7 (15.2)	5 (5.8)	
Reasons for failed tracheal intubation				
Difficult to confirm the glottis	6 (4.5)	5 (10.9)	1 (1.2)	0.02
Closure of the glottis	2 (1.5)	0 (0.0)	2 (2.3)	0.54
Inability to ventilate	2 (1.5)	1 (2.2)	1 (1.2)	1.00
Damage to the cuff	1 (0.8)	0 (0.0)	1 (1.2)	1.00
Poor visibility due to protective glasses	1 (0.8)	1 (2.2)	0 (0.0)	0.36
Complications				
SpO_2 < 90%	25 (18.8)	10 (27.8)	15 (17.2)	< 0.01
Systolic blood pressure < 90 mmHg	29 (21.8)	12 (27.3)	17 (19.5)	0.09
Intubation of the main bronchus	1 (0.8)	0 (0.0)	1 (1.2)	1.00
atrial fibrillation	1 (0.8)	0 (0.0)	1 (1.2)	1.00
sinus bradycardia	1 (0.8)	0 (0.0)	1 (1.2)	1.00
Confirmation after intubation				< 0.01
Stethoscope + Capnometer + Portable X-ray	99 (74.4)	19 (41.3)	80 (92.0)	
Capnometer + Portable X-ray	30 (22.6)	23 (50.0)	7 (8.1)	
Stethoscope + Portable X-ray	3 (2.3)	3 (6.5)	0 (0.0)	
Portable X-ray only	1 (0.8)	1 (2.2)	0 (0.0)	
PPE type				< 0.01
N95 + Plastic gown + Eye shield	39 (29.3)	13 (28.3)	26 (30.0)	
N95 + Surgical gown + Eye shield	70 (52.6)	17 (37.0)	53 (61.0)	
N95 + Tyvek suits + PAPR	20 (15.4)	12 (26.1)	8 (9.2)	
N95 + Tyvek suits + Eyewear	4 (3.0)	4 (8.7)	0 (0.0)	
Patient outcome				0.36
Discharged home	66 (50.0)	26 (56.5)	40 (46.5)	
Transfer	37 (28.0)	9 (19.6)	28 (32.6)	
Death	28 (21.1)	11 (23.9)	17 (19.8)	
In the hospital	1 (0.8)	0 (0.0)	1 (1.2)	
Operator infection	0 (0.0)	0 (0.0)	0 (0.0)	

Data are presented as median (interquartile range) for continuous variables and n (%) for categorical variables. Emergency medicine residents are those in postgraduate years 1-6. Missing data: Analgesia before intubation = 2; sedative before intubation = 2; neuromuscular blockade before intubation = 2; SpO_2 < 90% = 6; and systolic blood pressure < 90 mmHg = 2. BMI; body mass index, PAPR; powered air purifying respirator.

Not only that, the simplification of PPE used from the early to the late phase (Figure 3B) and the significant decrease in the rate of hypoxia also support this result.

The barrier enclosure ("aerosol box") was introduced in the early phase to prevent droplet exposure during tracheal intubation in patients with COVID-19 or

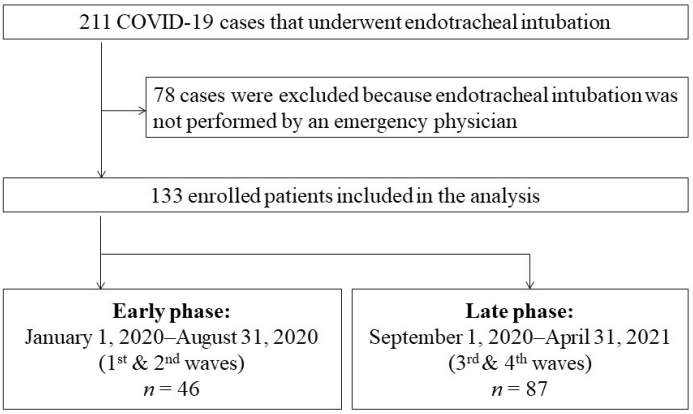

Figure 2. Flow diagram of the selection of COVID-19 cases with endotracheal intubation.

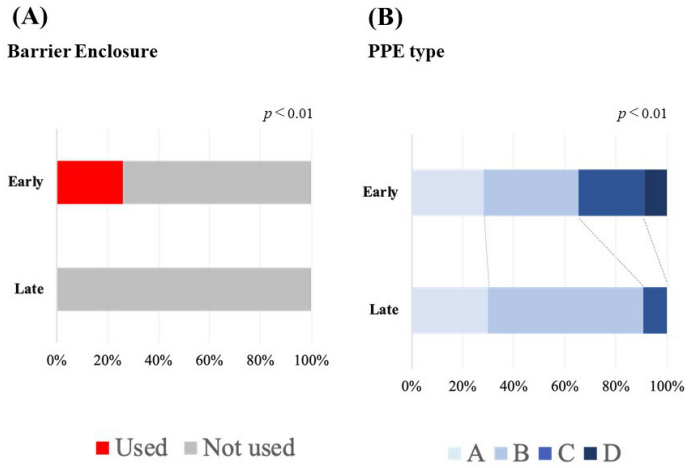

Figure 3. Comparison between the early and late phases of the COVID-19 pandemic on (A) barrier enclosure used and (B) percentage of each PPE type used.

Table 2. First-attempt intubation success, neuromuscular blockade use, and video laryngoscope use reported studies in the literature

Study and included patients (*Ref.*)	Total number of intubations	Proportion of emergency physicians	First-attempt intubation success	Neuromuscular blockade use	Video laryngoscope
Wuhan, China (*4*)	20	0	100	100	100
Wuhan, China (*5*)	202	0	89.1	99.0	89.6
London, United Kingdom (*6*)	150	0	88.0	N/A	91.3
Boston, United States (*7*)	123	22.8	89.4	100	91.7
	28		63.6	100	36.4
Vancouver, Canada (*8*)	227	41.4	85.9	N/A	83.7
	94		N/A	N/A	N/A
503 hospitals in 17 countries (*9*)	1,718	1.6	N/A	N/A	76.1
	28		N/A	N/A	N/A
Sao Paulo, Brazil (*12*)	112	100	82.0	100	62.0
Tokyo, Japan	133	100	91.0	91.7	48.8

The first three studies (*4-6*) all involved tracheal intubation by an anesthesiologist.

suspected COVID-19 (*11*). Barrier enclosure was not used in any of the cases in the late phase semester, which was a significant decrease ($p < 0.01$) (Figure 3A).

Several limitations of this study should be addressed. First, because of the retrospective nature, the details of all complications were possibly not obtained. Second, no specific protocols for intubation were used. Therefore, the selection of the drug administered at the time of intubation, the laryngoscopy method, and the confirmation after intubation were made based on the

operator and the doctor-in-charge's judgment. Third, the number of included patients was relatively small, increasing the risk of beta error.

Conclusions

The current study showed a high success rate in emergency endotracheal intubation in patients with COVID-19 by emergency physicians using laryngoscopy and simple PPE. Furthermore, the success rate increased and complications became fewer toward the late phase with increased operator experience. With the rapid spread of COVID-19 infection, emergency tracheal intubation has become necessary even in facilities where it was not previously needed. Thus, the results of the current study will be highly relevant to the ongoing efforts to manage the COVID-19 pandemic in terms of improving the intubation success rate while lessening the occurrence of complications.

Acknowledgments

We thank all the members who participated in this study.

Funding: This study was supported by the Daiwa Securities Health Foundation.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Grasselli G, Zangrillo A, Zanella A, *et al.* Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA. 2020; 323:1574-1581.
2. Richardson S, Hirsch JS, Narasimhan M, *et al.* Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020; 323:2052-2059.
3. Guan WJ, Ni ZY, Hu Y, *et al.* Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020; 382:1708-1720.
4. Zhang L, Li J, Zhou M, Chen Z. Summary of 20 tracheal intubation by anesthesiologists for patients with severe COVID-19 pneumonia: retrospective case series. J Anesth. 2020; 34:599-606.
5. Yao W, Wang T, Jiang B, *et al.* Emergency tracheal intubation in 202 patients with COVID-19 in Wuhan, China: lessons learnt and international expert recommendations. Br J Anaesth. 2020; 125:e28-e37.
6. Ahmad I, Jeyarajah J, Nair G, Ragbourne SC, Vowles B, Wong DJN, El-Boghdadly K. A Prospective, Observational, cohort study of airway management of patients with COVID-19 by specialist tracheal intubation teams. Can J Anaesth. 2021; 68:196-203.
7. Hawkins A, Stapleton S, Rodriguez G, Gonzalez RM, Baker WE. Emergency tracheal intubation in patients with COVID-19: a single-center, retrospective cohort study. West J Emerg Med. 2021; 22:678-686.
8. Dullemond K, Renschler C, Trojanowski J, Scheuermeyer F, Stenstrom R, Griesdale D, MacRedmond R, Nattrass E, Farina L, Yoo J. Success and complications of endotracheal intubation in critical care settings under COVID-19 protocols. CJEM. 2021; 23:512-517.
9. El-Boghdadly K, Wong DJN, Owen R, *et al.* Risks to healthcare workers following tracheal intubation of patients with COVID-19: a prospective international multicentre cohort study. Anaesthesia. 2020;75:1437-1447.
10. Shrestha GS, Shrestha N, Lamsal R, Pradhan S, Shrestha A, Canelli R, Ortega R. Emergency intubation in Covid-19. N Engl J Med. 2021;384:e20.
11. Canelli R, Connor CW, Gonzalez M, Nozari A, Ortega R. Barrier enclosure during endotracheal intubation. N Engl J Med. 2020; 382:1957-1958.
12. de Alencar JCG, Marques B, Marchini JFM, *et al.* First-attempt intubation success and complications in patients with COVID-19 undergoing emergency intubation. J Am Coll Emerg Physicians Open. 2020; 1:699-705.
13. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, STROBE Initiative. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008; 61:344-349.
14. Shingo Hori. Emergency medicine in Japan. Keio J Med. 2010; 59:131-139
15. Kentaro Shimizu, Seikei Hibino, Michelle H. Biros, Taro Irisawa, Takeshi Shimazu. Emergency medicine in Japan: past, present, and future. Int J Emerg Med. 2021; 14:2
16. O'Malley RN, O'Malley GF, Ochi G. Emergency medicine in Japan. Ann Emerg Med. 2001; 38:441-446
17. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med. 2020; 383:2451-2460.
18. Greenland KB, Tsui D, Goodyear P, Irwin MG. Personal protection equipment for biological hazards: does it affect tracheal intubation performance? Resuscitation. 2007; 74:119-126.
19. Gandhi A, Sokhi J, Lockie C, Ward PA. Emergency tracheal intubation in patients with COVID-19: experience from a UK centre. Anesthesiol Res Pract. 2020; 2020:8816729.

Received November 10, 2021; Revised December 15, 2021; Accepted January 7, 2022.

Released online in J-STAGE as advance publication January 17, 2022.

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Global Health & Medicine. 2022; 4(2):122-128.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2021.01121

Poor prognosis of patients with severe COVID-19 admitted to an infectious disease intensive care unit during the pandemic caused by the Delta variant in Japan

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Abstract: During the surge of coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) delta variant, our institution operated an intensive care unit (ICU) for patients with severe COVID-19. The study aim was to determine the survival rate and treatment outcomes of patients with severe COVID-19 treated in the ICU during the surge. A total of 23 consecutive patients with severe COVID-19 were admitted to the ICU between August 5 and October 6, 2021. Patients received multidrug therapy consisting of remdesivir, tocilizumab, heparin, and methylprednisolone. The patients were divided into two groups based on the ordinal scale (OS): a non-invasive oxygen therapy (OS-6) group, and an invasive oxygen therapy (OS-7) group. There were 13 (57%) and 10 (43%) patients in the OS-7 and OS-6 groups, respectively. All patients were unvaccinated. Sixteen patients (70%) were male. The median age was 53 years; the median body mass index (BMI) was 30.3 kg/m^2; and the median P/F ratio on admission was 96. The 30-day survival rate was 69% and was significantly poorer in the OS-7 group (54%) than in the OS-6 group (89%; $p = 0.05$). The prevalence of obesity ($p = 0.05$) and the Sequential Organ Failure Assessment (SOFA) score on admission ($p < 0.01$) were significantly higher in the OS-7 group. Seven patients in the OS-7 group (54%) developed bacteremia. A low P/F ratio on admission was a significant unfavorable prognostic factor (hazard ratio: 10.9; $p = 0.03$). The survival rate was poor, especially in patients requiring invasive oxygen therapy. More measures are needed to improve the treatment outcomes of patients with severe COVID 19.

***Keywords*:** SARS-CoV-2 infection, mortality, mechanical ventilation, secondary hospital-acquired infection

Introduction

The number of cases of coronavirus disease (COVID-19) due to the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection continues to increase worldwide (*1-3*). The severity of the disease varies widely, ranging from asymptomatic to fatal cases. In Japan, the overall number of patients exceeds 1,700,000, and there have been more than 18,000 COVID-19-related deaths (*4*). Coronaviruses are prone to mutation, resulting in changes in infectivity and virulence. The delta variant is extremely infectious and has spread worldwide (*5*). In Japan, the delta variant was prevalent in the summer of 2021 (*6*), and the number of newly diagnosed cases exceeded 5,000 per day (*4*).

Some patients with COVID-19 may present with respiratory failure and require intubation and mechanical ventilation. The effectiveness of extracorporeal membrane oxygenation (ECMO) for severe respiratory failure has already been demonstrated for H1N1 influenza (*7*). ECMO is also recommended for eligible patients with SARS-CoV-2 (*8,9*). The appropriate use of invasive oxygen therapy, and technology such as artificial respirators and ECMO, can be life-saving in patients with severe COVID-19.

However, due to the rapid increase in the number of infected patients, the public health center ordered individuals with mild disease to stay at home. Some patients deteriorated while staying at home, and some died without being admitted to hospital. Securing an infectious disease ward to accommodate patients with

COVID-19 was a national problem because the number of intensive care units (ICUs) with available artificial respirators and ECMO were limited. Our institution reconstructed the high care unit, which was usually used for postoperative management, and converted it into an ICU for patients with severe COVID-19.

Few studies have reported the survival rate of patients with severe COVID-19 during the surge in the COVID-19 pandemic in Japan caused by the delta variant of SARS CoV 2, and the survival rate of patients who require ICU admission is unknown. Our clinical impression of the pandemic caused by the delta variant is different from the previous pandemics. There is an increased number of patients, the age of patients is younger, the incidence of obesity is higher, and it is more difficult to save lives. In this study, we examine the survival rate of patients with severe COVID-19 treated in the infectious disease ICU at our hospital in order to improve the quality of intensive care and future treatment outcomes.

Patients and Methods

Study design and patients

Patients with severe COVID-19 who were admitted to the infectious ICU of the National Center for Global Health and Medicine in Tokyo between August 5 and October 6, 2021 were included in the analysis. The admission and discharge criteria for the ICU are described below. Patients were provided with oxygen using nasal high flow therapy (NHF; Optiflow™, Fisher and Paykel), non-invasive positive pressure ventilation (NPPV; V60 ventilator™ produced by PHILIPS), an artificial respirator (Puritan Bennett™ 840, Medtronic), or ECMO (MERA centrifugal blood pump system HCS-CFP™ produced by MERA). The severity of COVID-19 was evaluated according to the National Institute of Allergy and Infectious Disease ordinal scale (OS), depending on the method of oxygen therapy. We divided the patients into two groups based on OS. The OS-6 group received non-invasive oxygen therapy using NHF or NPPV and the OS-7 group received invasive oxygen therapy using an artificial respirator or ECMO. The diagnosis of COVID-19 was confirmed by detection of SARS-CoV-2 RNA using polymerase chain reaction tests. Samples were checked for genetic mutations of SARS-CoV-2. The P/F ratio was calculated as the ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO2). According to the Extracorporeal Life Support Organization guidelines for COVID-19 (*10*), ECMO was considered for patients with a P/F ratio < 150. The hemoglobin A1c (HbA1c) level was examined in patients with a history of diabetes mellitus (DM) and patients who were hyperglycemic at the time of ICU admission. Blood, sputum, and urine samples were cultured at least once per week. Additional cultures were performed as needed, based on clinical findings, including fever and inflammatory.

This study was approved by the National Center for Global Health and Medicine institutional review board (approval number: 004411), and the need to obtain written informed consent was waived by posting a release of information document that enabled patients to opt out of the study.

Intensive care unit admission and discharge criteria

The criteria for ICU admission were as follows: *i*) patients requiring invasive oxygen therapy (OS-7) using an artificial respirator or ECMO; *ii*) patients requiring non-invasive oxygen therapy (OS-6; NHF or NPPV) with a P/F ratio of < 200; and *iii*) patients with COVID-19 with complications such as convulsions, heart failure, or diabetic ketoacidosis. The criteria of discharge from the ICU were as follows: *i*) stable respiratory function after extubation; *ii*) improvement of the P/F ratio; or *iii*) a stable general clinical condition and a stable P/F ratio < 150, enabling the patient to be treated in the general infectious disease wards.

Treatment strategy

Patients received multidrug therapy as follows: *i*) A 5-day course of remdesivir, 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 4 days of treatment if patients had a creatinine clearance > 30 mL/min and serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels less than five times the upper limit of normal (*11-13*). *ii*) Tocilizumab 8 mg/kg body weight was administered intravenously, up to a dose of 800 mg on day 1. Patients with a recent history of treatment with biologic agents or immunosuppressive therapy were excluded (*14,15*). *iii*) Heparin sodium 10,000 U/day was administered intravenously during the ICU stay (*16*) provided that the activated partial thromboplastin time was < 60 s. Heparin sodium was also administered intravenously to patients on ECMO therapy, using activated clotting time (ACT) as an index, with a target of 180-200 s. *iv*) Methylprednisolone (2 mg/kg/day) was infused intravenously over 60 min, and tapered by half dosage every 5 days. Methylprednisolone treatment was discontinued in any patient who developed severe elevations in blood pressure or blood sugar (*17*).

Statistical analyses

Differences in categorical variables were analyzed using Fisher's exact test. Univariate analysis of overall survival was performed to identify prognostic factors using Cox proportional hazards regression. Cumulative survival was estimated using the Kaplan-Meier method, and

differences between groups were evaluated using the log-rank test. The overall survival was defined as the time from the date of admission to the date of death from any cause or the date of the last follow-up. All *p*-values were two-sided, and the statistical significance level was set at $p < 0.05$. All statistical analyses were performed with R for Windows GUI front-end version 3.0.2 (R Development Core Team 2013, A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria. *http://www.r-project.org*).

Results

Clinical characteristics of patients

A total of 23 patients were admitted to the ICU with severe COVID-19 between August 5 and October 6, 2021. The clinical course and terms of ICU stay of each patient are shown in Figure 1. The median length of ICU stay was 11 days. The clinical characteristics of patients with severe COVID-19 are shown in Table 1. Sixteen of the 23 patients (70%) were male and the median age was 53 years (range: 28-78 years). The median body mass index (BMI) was 30.3 kg/m^2 (range: 18.7-52.2 kg/m^2) and the prevalence of obesity (BMI ≥ 25 kg/m^2) was 70%. Seven patients (30%) had hypertension, and 14 patients (60%) had diabetes mellitus (DM). Eight patients (35%) had a smoking history. Among the patients with a smoking history, the median Brinkman index (the number of cigarettes smoked per day multiplied by the number of years of smoking) was 575 (range: 320-880). The median interval from onset to admission was 9 days (range: 3-43 days). One patient was transferred to our hospital from another hospital 43 days after onset. The median P/F ratios on admission and discharge were 96 (range: 62-283) and 129 (range: 36-550), respectively. The median

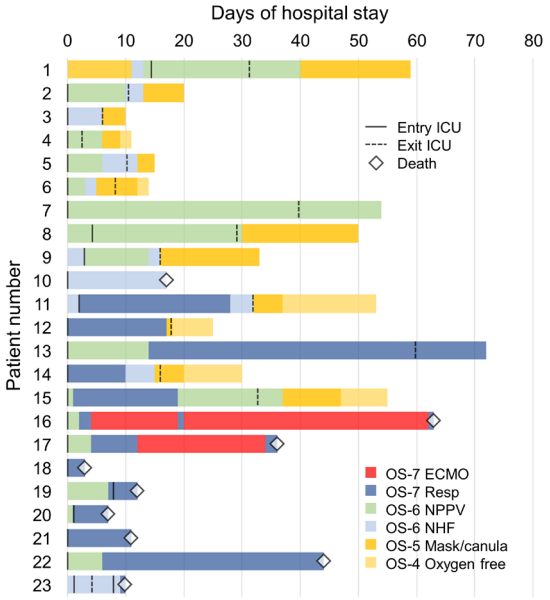

Figure 1. Clinical course of each patient. ECMO: extracorporeal membranous oxygenation; ICU: intensive care unit; Resp: artificial respirator; NHF: nasal high flow; NPPV: non-invasive positive pressure ventilation.

Table 1. Patient characteristics (*n* = 23)

Variables		All patients (*n* = 23)
Age (median, range)		53 (28-78)
Sex (*n*, %)	Male	16 (70)
BMI (median, range)		30.3 (18.7-52.2)
Obesity (*n*, %)		17 (74)
Hypertension (*n*, %)		7 (30)
Diabetes mellitus (*n*, %)		14 (60)
HbA1c (median, range)		7.7 (6.6-10.9)
Rheumatoid arthritis (*n*, %)		2 (9)
Smoking history (*n*, %)		8 (35)
Brinkman index (median, range)		575 (320-880)
Days from onset to admission		9 (3-43)
P/F ratio (median, range)	Admission	96 (62-283)
	Discharge	129 (36-550)
SOFA score (median, range)	Admission	6 (3-10)
	Discharge	4 (1-12)
SARS-CoV-2 variant (*n*, %)	L452R	18 (78)
	N501Y	2 (9)
	Unknown	3 (13)
Laboratory test results (median, range)	WBC (cells/uL)	7,290 (4,710-23,340)
	CRP (mg/dL)	11.54 (0.39-26.1)
	LDH (U/L)	654 (233-1,521)
	KL-6 (U/mL)	1,168 (295-4,396)
	D-dimer (ug/mL)	3.4 (0.5-89.5)

BMI: body mass index; CRP: C-reactive protein; FiO_2: fraction of inspired oxygen; HbA1c: hemoglobin A1c; KL-6: Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO_2: partial pressure of arterial oxygen; P/F ratio: ratio of PaO_2 to FiO_2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOFA: Sequential Organ Failure Assessment; WBC: white blood cells.

Sequential Organ Failure Assessment (SOFA) scores on admission and discharge were 6 (range: 3-10) and 4 (range: 1-12), respectively. The L452R mutation was detected in 18 patients (78%) and the N501Y mutation was detected in 2 patients (9%). The SARS CoV 2 strain could not be determined in 2 patients because the RNA could not be amplified, and one patient who was transferred from another hospital was not tested for the SARS-CoV-2 strain. The majority of patients had elevated levels of C-reactive protein (CRP) (median: 11.54 mg/dL, upper limit of normal: 0.14 mg/dL), lactate dehydrogenase (LDH) (median: 654 U/L, upper limit of normal: 222 U/L), Krebs von den Lungen-6 (KL-6) (median: 1,168 U/L, upper limit of normal: 450 U/L), and D-dimer (median: 3.4 μg/mL, upper limit of normal 1.0 μg/mL). Two patients received immunosuppressive therapy for rheumatoid arthritis.

Invasive oxygenation was required by 13 (57%) of the 23 patients. The clinical characteristics of the OS-7 and OS-6 groups are shown in Table 2. In the OS-7 group, 8 patients (62%) were male, and the median age was 56 years (range: 28-68 years). Although there was no significant difference in BMI in the OS-7 group and OS-6 group (30.0 *vs.* 25.0; $p = 0.12$), the prevalence of obesity was significantly higher in the OS-7 group than the OS-6 group (92% *vs.* 50%; $p = 0.05$). There was no significant difference between the OS-7 and OS-6 groups in the prevalence of hypertension (38% *vs.* 20%; $p = 0.41$), DM (54% *vs.* 70%; $p = 0.67$), or smoking history (23% *vs.* 50%; $p = 0.22$). In addition, there was no significant difference in the interval from onset to admission, P/F ratio, or the laboratory test results between groups. The SOFA score on admission was significantly higher in the OS-7 group than the OS-6 group (median: 7 *vs.* 4; $p < 0.01$).

Secondary infections during the intensive care unit stay

Seven patients in the OS-7 group (54%) and no patients in the OS-6 group developed bacteremia ($p < 0.01$). The causative agents were *Klebsiella pneumoniae* in three patients, methicillin-susceptible *Staphylococcus aureus* (MSSA) in two patients, *Staphylococcus hominis* in one patient, and *Staphylococcus pneumoniae* in another patient. One patient with MSSA bacteremia developed infectious endocarditis and severe aortic regurgitation and required surgery for the aortic regurgitation. Another patient with bacteremia caused by *Klebsiella pneumoniae* died and was discovered to have had a second infection with *Pseudomonas aeruginosa* after her death. No fungal infections were detected in any patients.

Survival and prognostic factors

The median follow-up period was 33 days. Nine (39%) of the 23 patients died during the follow-up period (patient numbers #10 and #16 to #23 in Figure 1). The overall mortality rates were 10% (1/10) and 62% (8/13) in the OS-6 and OS-7 groups, respectively. The cause of death was respiratory failure due to COVID-19 in

Table 2. Patient characteristics according to disease severity

Variables		Patients with OS-7 disease ($n = 13$)	Patients with OS-6 disease ($n = 10$)	p value
Age (median, range)		56 (28-68)	52 (37-78)	0.93
Sex (n, %)	Male	8 (62)	8 (80)	0.41
BMI (median, range)		30.0 (21.2-52.2)	25.0 (18.7-40.0)	0.12
Obesity (n, %)		12 (92)	5 (50)	0.05
Hypertension (n, %)		5 (38)	2 (20)	0.41
Diabetes mellitus (n, %)		7 (54)	7 (70)	0.67
HbA1c (median, range)		8.0 (6.6-10.9)	7.4 (6.6-9.5)	-
Rheumatoid arthritis (n, %)		0 (0)	2 (20)	0.18
Smoking history (n, %)		3 (23)	5 (50)	0.22
Brinkman index (median, range)		660 (330-780)	550 (320-880)	-
Days from onset to admission (median, range)		8 (4-17)	9 (3-43)	0.27
P/F ratio (median, range)	Admission	96 (62-283)	92 (64-263)	0.94
	Discharge	86 (44-550)	138 (36-292)	0.70
SOFA score (median, range)	Admission	7 (4-10)	4 (3-7)	< 0.01
	Discharge	8 (1-12)	3 (1-7)	0.02
SARS-CoV-2 variant	L452R	10 (77)	8 (80)	> 0.99
	N501Y	1 (8)	1 (10)	-
	Unknown	2 (15)	1 (10)	-
Laboratory test results (median, range)	WBC (cells/uL)	9,210 (4,710-23,340)	6,540 (5,230-17,330)	0.29
	CRP (mg/dL)	12.0 (0.65-26.1)	9.0 (0.39-22.2)	0.76
	LDH (U/L)	781 (233-1,344)	615 (360-1,521)	0.95
	KL-6 (U/mL)	931 (295-2,617)	1,604 (697-4,396)	0.17
	D-dimer (ug/mL)	6.0 (0.5-89.5)	3.0 (1.1-23.3)	0.15

BMI: body mass index; CRP: C-reactive protein; FiO_2: fraction of inspired oxygen; HbA1c: hemoglobin A1c; KL-6: Krebs von den Lungen-6; LDH, lactate dehydrogenase; PaO_2: partial pressure of arterial oxygen; P/F ratio: ratio of PaO_2 to FiO_2; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SOFA: Sequential Organ Failure Assessment; WBC: white blood cells.

all fatal cases. The 30-day survival rate of all patients was 69% (Figure 2A). The 30-day survival rate of the OS-7 group was significantly lower than that of the OS-6 group (54% *vs.* 89%, respectively; $p = 0.05$; Figure 2B). Table 3 shows the results of the univariate analyses of prognostic factors for overall survival for the study cohort. The only factor associated with a significantly worse prognosis was severe respiratory failure on admission (Hazard ratio [HR] 10.9; $p = 0.03$). Older age (HR: 1.99; $p = 0.40$), males (HR: 0.57; $p = 0.57$), hypertension (HR: 1.68; $p = 0.44$), DM (HR: 3.21; $p = 0.15$), obesity (HR: 2.75; $p = 0.35$), and invasive oxygenation (HR: 6.27; $p = 0.09$) were not significantly associated with prognosis.

Discussion

All patients included in the analysis had severe COVID-19, with a median P/F ratio of 96 on admission. Despite their relatively young age, the 30-day survival rate was poor (69%), particularly in the OS-7 group (54%).

In Japan, surges of COVID-19 infection rate occurred sixth times: from April to June in 2020 ("first wave"), from August to October in 2020 ("second wave"), from December in 2020 to March in 2021 ("third wave"), from April to July in 2021 ("fourth wave"), from August to October 2021 ("fifth wave"), and from January 2022 ("sixth wave" is still continuing presently). In our institution, the median age of patients who needed invasive oxygen therapy (the definition was the same as the OS-7 group) was 67, 74, 70, 60, for each of the first four waves respectively. The incidence of obesity was 18%, 56%, 27%, 60%, respectively. The mortality was 29%, 22%, 45%, 20% respectively (unpublished data). In the current wave in the OS-7 group, the median age was 56, the rate of obesity was 92%, and the mortality was 62%. This data supported our clinical impression described in the introduction.

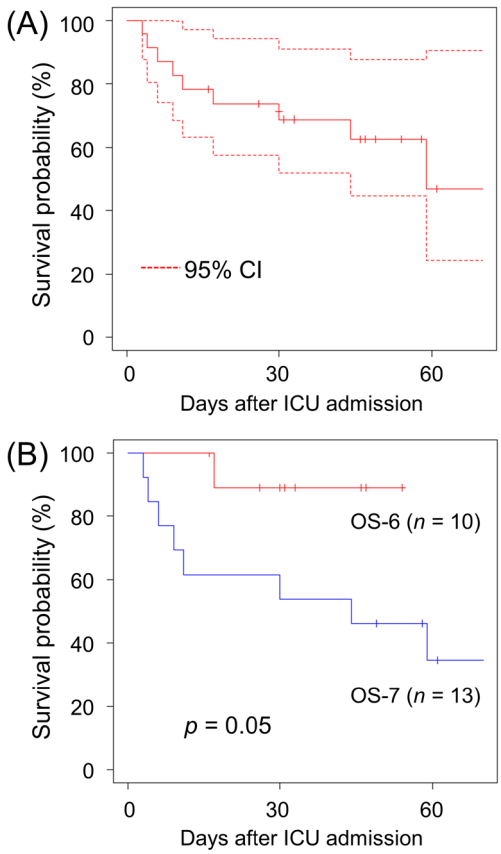

Figure 2. Patient overall survival according to time since admission to the intensive care unit. (A) Survival in all patients, **(B)** Survival according to the OS group. CI: confidence interval, OS: US National Institute of Allergy and Infectious Diseases ordinal scale of disease severity.

The delta strain is highly virulent and highly contagious and has spread worldwide (*5*). It has spread extensively in Asia (*18,19*) and caused the "fifth wave" of COVID-19 in Japan in the summer of 2021 (*4*). In this study, the L452R mutation, which is a spike protein mutation of the delta variant, was detected in approximately 80% of patients (*20*). Vaccines have been found to be highly efficacious in preventing symptomatic disease, as shown by clinical trials (*21-23*). The rapid development and deployment of vaccines has been the single greatest achievement for prevention during the COVID-19 pandemic in the United Kingdom (*24*). In Japan, COVID-19 vaccination was started in people aged 65 years or older. In our study, the patients were relatively young with a median age of 53 years and all were unvaccinated.

Treatment for COVID-19 included remdesivir, tocilizumab, heparin, and methylprednisolone, each of which has been shown to be effective in clinical trials (*11-17*). Remdesivir is less effective in severe cases, and its usefulness in patients with severe disease has not been confirmed (*13*). However, steroids and heparin

Table 3. Results of the univariate Cox proportional hazards regression analysis of risk factors for death ($n = 23$)

Variables		*n*	Hazard ratio	*p* value
Age (years)	< 50	7	*ref*	
	≥ 50	16	1.99 (0.41-9.64)	0.40
Sex	Female	7	*ref*	
	Male	16	0.68 (0.18-2.67)	0.57
Obesity	Absent	6	*ref*	
	Present	17	2.75 (0.34-22.5)	0.35
Hypertension	Absent	16	*ref*	
	Present	7	1.68 (0.45-6.32)	0.44
Diabetes mellitus	Absent	9	*ref*	
	Present	14	3.21 (0.64-16.1)	0.15
Smoking history	Absent	15	*ref*	
	Present	8	0.23 (0.03-1.81)	0.16
NIAID Ordinal Scale	OS-6	10	*ref*	
	OS-7	13	6.27 (0.77-51.2)	0.09
P/F ratio	≥ 100	11	*ref*	
	< 100	12	10.9 (0.09-13.3)	0.03

FiO_2: fraction of inspired oxygen; PaO_2: partial pressure of arterial; NIAID: US National Institute of Allergy and Infectious Diseases; P/F ratio: ratio of PaO_2 to FiO_2; ref: reference.

have been reported to be highly effective in severe cases (*13,16*). Patients with poor response to the regimen for mild/moderate disease, worsening oxygenation, and no improvement in their condition were admitted to the infectious disease ICU. The median P/F ratio on admission was 96, indicating severe respiratory failure, which has been reported to be associated with a mortality rate of over 80% (*10*).

Despite the patients being relatively young, the 30-day survival rate was 69%, which was extremely poor even with intensive care using ECMO. The prognosis was significantly worse when the patient was intubated. Although univariate analysis did not reveal that invasive oxygenation was a prognostic factor, the P/F ratio on admission was associated with significantly poorer prognosis. A previous report has shown that the timing of invasive oxygen therapy does not affect mortality (*25*). Thus, our data demonstrated the possibility that mortality reflects respiratory function due to the progression of COVID-19. Another reason for the poor prognosis of our patients was complications. The SOFA score on admission was significantly higher in the OS-7 group than the OS-6 group due to factors such as impaired consciousness due to diabetic ketoacidosis and catecholamine activation due to low cardiac function.

In intubated patients, there is a risk of ventilator-associated pneumonia (*26,27*). In addition, the increase in the number of catheters, such as the central venous lines and ureteral catheters, and the use of immunosuppressive drugs, increases the risk of secondary healthcare-associated infections (*28*). In our study, two patients developed bacteremia that was difficult to treat. The incidence of secondary healthcare-associated infections has been reported to be approximately 10-15/1,000 days of catheter exposure (*29-31*). In our study, the OS-7 group, of whom 54% had bacteremia, had a high risk of secondary infection. The incidence of bacteremia has increased during the COVID-19 pandemic (*32*), posing an important challenge for ICU management.

Although immunosuppressive agents have been reported to be effective in suppressing cytokine storms, excessive immunosuppression increases the risk of secondary infection. There is a concern that new mutant strains may become more prevalent in the future. The increasingly large number of clinical trials and research studies with various combinations of drugs has made it difficult to establish appropriate treatment (*24*). A treatment regimen for patients with severe COVID-19 with a mechanism of action other than immunosuppression is needed.

There were some limitations to our study. First, the number of cases was small because the study was a single-center retrospective study carried out over a two-month period. However, the ICU was a temporary ICU that operated only during the fifth wave of the pandemic, and it made an important contribution to treating 23 patients with the most severe COVID-19 in just 2 months. Second, there were clear criteria for admission, but because it was an emergency situation, the criteria for discharge were unclear, and some patients who were not well enough to be discharged from the ICU under normal circumstances were discharged early. Third, although there was a clear association between a poor P/F ratio and death, we were unable to perform a multivariable analysis of the risk factors for death.

Few studies have been published on the survival rate of patients with severe COVID-19 admitted to ICUs. Many challenges were attributable to the emergency situation during the pandemic. This study provides an understanding of the current situation regarding the outcomes in patients with severe COVID-19 due to the delta variant. In conclusion, the survival rate was poor, especially in patients requiring invasive oxygen therapy. Since all patients were unvaccinated, it underlines the need for widespread vaccinations in the community. And the quality of intensive care needs to be improved in order to improve future treatment outcomes.

Funding: This work was supported in part by Grants-in-Aid for Research from the National Center for Global Health and Medicine (20A-3002).

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Adachi T, Chong JM, Nakajima N, *et al.* Clinicopathologic and immunohistochemical findings from autopsy of patient with COVID-19, Japan. Emerg Infect Dis. 2020; 26:2157-2161.
2. Martines RB, Ritter JM, Matkovic E, *et al.* Pathology and pathogenesis of SARS-CoV-2 associated with fatal coronavirus disease, United States. Emerg Infect Dis. 2020; 26:2005-2015.
3. Okudela K, Hayashi H, Yoshimura Y, Sasaki H, Horiuchi H, Miyata N, Tachikawa N, Tsuchiya Y, Mitsui H, Ohashi K. A Japanese case of COVID-19: An autopsy report. Pathol Int. 2020; 70:820-824.
4. Japanese Ministry of Health, Labour and Welfare. COVID-19 in Japan. *https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html* (accessed November 16, 2021). (in Japanese)
5. Twohig KA, Nyberg T, Zaidi A, *et al.* Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. Lancet Infect Dis. 2022; 22:35-42.
6. Ito K, Piantham C, Nishiura H. Predicted dominance of variant Delta of SARS-CoV-2 before Tokyo Olympic Games, Japan, July 2021. Euro Surveill. 2021; 26:2100570.
7. Chow FC, Edlow BL, Frosch MP, Copen WA, Greer DM. Outcome in patients with H1N1 influenza and cerebrovascular injury treated with extracorporeal membrane oxygenation. Neurocrit Care. 2011; 15:156-160.
8. Badulak J, Antonini MV, Stead CM, *et al.* Extracorporeal membrane oxygenation for COVID-19: Updated

2021 Guidelines from the Extracorporeal Life Support Organization. ASAOI J. 2021; 67:485-495.
9. Ramanathan K, Antognini D, Combes A, Paden M, Zakhary B, Ogino M, MacLaren G, Brodie D, Shekar K. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. Lancet Respir Med. 2020; 8:518-526.
10. Bartlett RH, Ogino MT, Brodie D, McMullan DM, Lorusso R, MacLaren G, Stead CM, Rycus P, Fraser JF, Belohlavek J, Salazar L, Mehta Y, Raman L, Paden ML. Initial ELSO Guidance Document: ECMO for COVID-19 patients with severe cardiopulmonary failure. ASAOI J. 2020; 66:472-474.
11. Goldman JD, Lye DCB, Hui DS, *et al.* Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med. 2020; 383:1827-1837.
12. Beigel JH, Tomashek KM, Dodd LE, *et al.* Remdesivir for the treatment of Covid-19 – final report. N Engl J Med. 2020; 383:1813-1826.
13. Grein J, Ohmagari N, Shin D, *et al.* Compassionate use of Remdesivir for patients with severe Covid-19. N Engl J Med. 2020; 382:2327-2336.
14. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021; 397:1637-1645.
15. Stone JH, Frigault MJ, Serling-Boyd NJ, *et al.* Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020; 383:2333-2344.
16. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020; 18:1094-1099.
17. Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarirad R, Erfani A, Khodamoradi Z, Gholampoor Saadi MH. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. BMC Infect Dis. 2021; 21:337.
18. Dyer O. Covid-19: Indonesia becomes Asia's new pandemic epicentre as delta variant spreads. BMJ. 2021; 374:n1815.
19. Novelli G, Colona VL, Pandolfi PP. A focus on the spread of the delta variant of SARS-CoV-2 in India. Indian J Med Res. 2021; 153:537-541.
20. Mor O, Mandelboim M, Fleishon S, Bucris E, Bar-Ilan D, Linial M, Nemet I, Kliker L, Lustig Y, Israel National Consortium For Sars-Co VS, Mendelson ES, Zuckerman NS. The rise and fall of a local SARS-CoV-2 variant with the spike protein mutation L452R. Vaccines (Basel). 2021; 9:937.
21. Baden LR, El Sahly HM, Essink B, *et al.* Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021; 384:403-416.
22. Skowronski DM, De Serres G. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2021; 384:1576-1577.
23. Voysey M, Clemens SAC, Madhi SA, *et al.* Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021; 397:99-111.
24. Angus DC, Gordon AC, Bauchner H. Emerging Lessons From COVID-19 for the US Clinical Research Enterprise. JAMA. 2021; 325:1159-1161.
25. Papoutsi E, Giannakoulis VG, Xourgia E, Routsi C, Kotanidou A, Siempos II. Effect of timing of intubation on clinical outcomes of critically ill patients with COVID-19: a systematic review and meta-analysis of non-randomized cohort studies. Crit Care. 2021; 25:121.
26. National Healthcare Safety Network. Ventilator-associated (VAP) and non- ventilator-associated Pneumonia (PNEU) Event. 2021. *https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf* (accessed November16, 2021).
27. National Healthcare Safety Network. Ventilator-Associated Event (VAE). 2021. *https://www.cdc.gov/nhsn/pdfs/pscmanual/6pscvapcurrent.pdf* (accessed November 16, 2021).
28. Allegranzi B, Bagheri Nejad S, Combescure C, Graafmans W, Attar H, Donaldson L, Pittet D. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. Lancet. 2011; 377:228-241.
29. Buetti N, Timsit JF. Management and prevention of central venous catheter-related infections in the ICU. Semin Respir Crit Care Med. 2019; 40:508-523.
30. Rosenthal VD, Bat-Erdene I, Gupta D, *et al.* International Nosocomial Infection Control Consortium (INICC) report, data summary of 45 countries for 2012-2017: Device-associated module. Am J Infect Control. 2020; 48:423-432.
31. Stevens V, Geiger K, Concannon C, Nelson RE, Brown J, Dumyati G. Inpatient costs, mortality and 30-day re-admission in patients with central-line-associated bloodstream infections. Clin Microbiol Infect. 2014; 20:O318-324.
32. Pérez-Granda MJ, Carrillo CS, Rabadán PM, Valerio M, Olmedo M, Muñoz P, Bouza E. Increase in the frequency of catheter-related bloodstream infections during the COVID-19 pandemic: a plea for control. J Hosp Infect. 2022; 119:149-154.

Received December 13, 2021; Revised February 22, 2022; Accepted February 26, 2022.

Released online in J-STAGE as advance publication March 5, 2022.

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Global Health & Medicine. 2022; 4(2):129-132.
BRIEF REPORT
DOI: 10.35772/ghm.2022.01015

Impact of prioritized vaccinations for the elderly on the COVID-19 pandemic in Japan

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Abstract: The Japanese government implemented a large-scale vaccination policy against the coronavirus disease 2019 (COVID-19) pandemic, primarily using messenger RNA vaccines in 2021. Its hallmark was prioritized vaccination for the elderly after healthcare workers in a short period of time. Vaccination for the elderly, vulnerable to infection and severe disease, was carried out rapidly in approximately 4 months since April 2021. We evaluated the impact of Japan's vaccination policy against COVID-19 during the pandemic, with a particular focus on how prioritized vaccination for the elderly affected the pandemic. We observed a remarkable decrease in the number of infections, cluster events in long-term care facilities, and severe disease among the elderly during the fifth wave (August 2021) despite rising incidence of infections in the overall population. In conclusion, we think that prioritized vaccination for the elderly was efficacious in preventing infections and severe COVID-19 among the elderly during the fifth wave in Japan.

***Keywords*:** vaccination policy, pandemic, messenger RNA vaccines

Introduction

Coronavirus disease 2019 (COVID-19) has caused a pandemic since its emergence at the end of 2019, with Japan experienced five endemic waves during 2020 and 2021. No treatment was known for this infectious disease until various protocols were developed, including vaccination. In 2021, the Japanese government implemented a large-scale vaccination policy using messenger RNA (mRNA) vaccines (*1*). The highest priority group for vaccination included healthcare workers who provide medical care for patients with COVID-19, followed by the elderly aged ≥ 65 years. Japan rapidly achieved approximately 80% coverage with two-dose vaccinations among the elderly from April to the end of July in 2021 (*2*), which was completed in the early stage of the fifth wave. With limited medical resources (*3*), it is important to review how this vaccination strategy helped control the spread of infection. However, there is a paucity of reports on the impact of prioritized vaccination on the COVID-19 pandemic in Japan.

In this study, we aimed to discuss the impact of the prioritized vaccination policy against COVID-19 during the pandemic in Japan, with a particular focus on how prioritized vaccination for the elderly affected the situation.

Materials and Methods

W'e analyzed open data on COVID-19 published by the Ministry of Health, Labor and Welfare, including the number of new infections, severe cases, and cluster events (*4*). We determined the number of infections using the Vaccination Record System data published by the Digital Agency of the Japanese government (*5*). We also used the latest population estimates published by the Statistics Bureau of Japan to estimate vaccination rates (*6*).

Based on the age categories in these data sources, for new infections and severe cases, patients aged ≥ 70 years were regarded as the elderly, whereas for vaccination rate, patients aged ≥ 65 years were regarded as the elderly. Regarding the epidemic curves of COVID-19 in Japan in 2021, we defined the third, fourth, and fifth waves as substantial increases in the number of infections, occurring primarily in January, May, and August, respectively (*7*).

The need for ethical approval was waived in accordance with the guidelines of the National Center for Global Health and Medicine Ethics Committee.

Results and Discussion

The Japanese government started a vaccination program

for healthcare workers on February 17, and a prioritized large-scale vaccination program for approximately 36 million elderly people started on April 12, 2021.

Figure 1 illustrates the vaccination rate in the elderly and the overall population from April 12 to December 31, 2021. The two-dose vaccination rate among the elderly was 79.1% on July 31, whereas the rate for overall population was 28.3%. Finally, two-dose vaccination rate for the elderly was 91.1% by the end of December.

Figure 2 shows a comparison of weekly counts of newly confirmed patients over time between patients aged ≥ 70 years and all patients. In the middle of the third wave, the proportion of weekly new infections in patients aged ≥ 70 years reached 25.4%. However, it decreased sharply from June with a minimum of 2.5% in the fifth wave. This trend continued until the late stage of the fifth wave, when the overall number of infections radically decreased.

Figure 3 shows the change in weekly severe cases of COVID-19 in patients aged ≥ 70 years and in all patients. Despite the increase in the number of severe cases in all patients since mid-September 2021, the proportion of severe cases in patients aged ≥ 70 years declined from 46.6% in mid-September to 18.7% in early-October.

Figure 4 presents the number of outbreaks by facility type in 2021. In the third and fourth waves of January and May 2021, long-term care facilities (LTCFs) for the elderly were facilities with the highest proportion of cluster events. In contrast, during the fifth wave in August, schools and offices had the highest number of cluster events, whereas there were relatively few cluster events in LTCFs for the elderly.

In Japan, vaccination of the elderly, who are

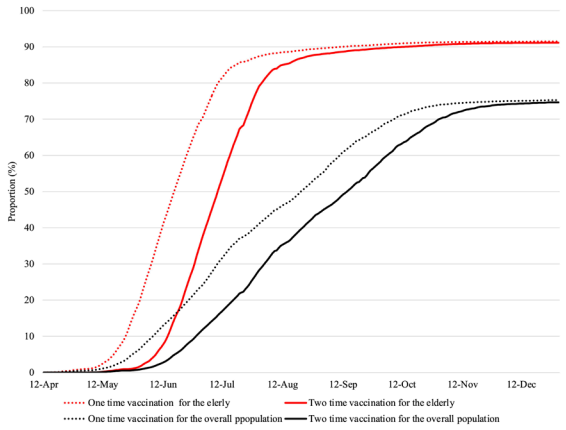

Figure 1. Changes in vaccination rate for COVID-19 over time in 2021. The red dotted and solid lines represent one-and two-dose vaccination rates for the elderly, respectively. The black dotted and solid lines represent the one-and two-dose vaccination rates for the overall population, respectively.

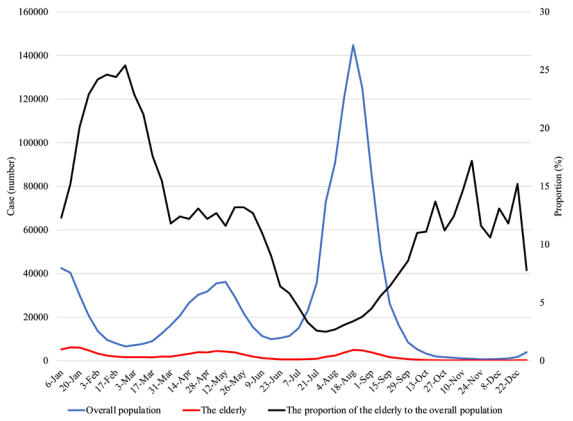

Figure 2. Number of newly confirmed COVID-19 patients over time in 2021. The blue and red lines represent the number of infections in the overall population and those aged ≥ 70 years, respectively. The black line represents the proportion of elderly patients among all patients.

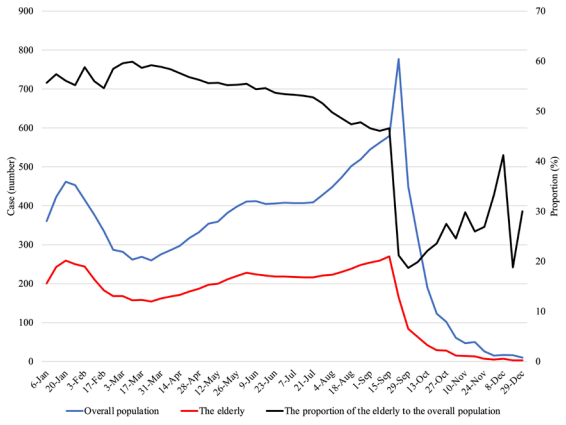

Figure 3. Number of severe diseases of COVID-19 over time in 2021. The blue and red lines represent the number of severe COVID-19 cases among the overall population and those aged ≥ 70 years, respectively. The black line represents the proportion of elderly patients among all patients. Patients with severe COVID-19 were defined as those who were on a ventilator or on extracorporeal membrane oxygenation or were treated in an ICU.

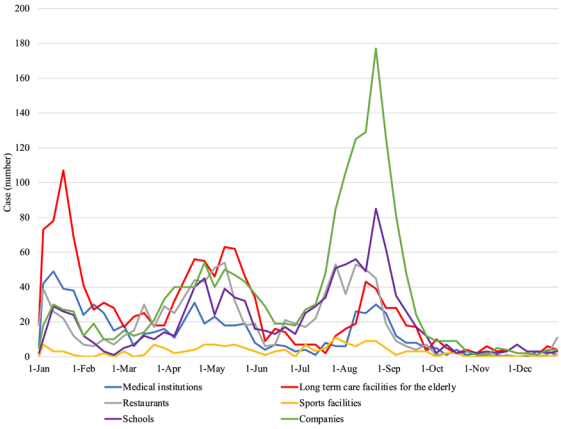

Figure 4. Number of cluster events by different types of facilities over time in 2021. The red, blue, violet, gray, yellow, and green lines represent cluster events in the long-term care facilities for the elderly, medical institutions, schools, restaurants, sports facilities, and companies, respectively.

vulnerable to infection, was accomplished in approximately 4 months. In the subsequent fifth wave, large differences were noted in immunization coverage among generations. The proportion of the elderly among the newly confirmed patients and patients with severe disease was low and the number of cluster events in LTCFs was small. On the other hand, increased spread of infection was noted among the younger populations. Based on these disparities in epidemics among generations in the fifth wave and comparison of the fifth wave to previous waves in terms of infections among the elderly, we believe that prioritized vaccination for the elderly is largely responsible for the decline in the incidence of infection in the elderly.

Japan's Pharmaceuticals and Medical Devices Agency reviews new drugs, and the Minister of Health, Labor, and Welfare grants final approval. The Pfizer-BioNTech mRNA vaccine was approved on February 14, 2021, and both the Moderna mRNA vaccine and the Oxford/Astra Zeneca vaccines were approved on May 21, 2021 (*8*). Subsequently, the Japanese government made mRNA vaccines the mainstay of large-scale vaccination.

Healthcare workers who provide medical care for COVID-19 were given the highest vaccination priority. Next, the elderly (people aged ≥ 65 years) were regarded as the second-priority group for vaccination. Large-scale vaccination centers were established in each area to prepare for mass vaccination within a short period of time (*9*). In addition, LTCFs for the elderly were registered as satellite facilities for vaccine administration.

Older age is a risk factor for severe COVID-19, and various comorbidities in the elderly are associated with severe disease. A high incidence of severe disease in patients aged ≥ 65 years was reported in the first and second waves in Japan (*10*). Our previous study, which used multicenter registry data that included patients up to the third wave, showed that the proportion of severe disease and death increased with age among the elderly (*11*). Additionally, the number and size of clusters in LTCFs were associated with increased mortality due to COVID-19 (*12*). Japan is a country with a super-aged population. The average life expectancy in 2019 ranked highly worldwide: 87.4 years for women; and 81.4 years for men (*13*). The proportion of the elderly population is the highest worldwide, at 28.7%. Additionally, 950,000 people received services from LTCFs in 2019 (*14*). Therefore, reducing the risk of infection and severe COVID-19 in the elderly has become a critical issue in Japan.

Given the unprecedented COVID-19 pandemic, prioritizing limited vaccine resources was a major issue. A variety of ethical aspects must be considered in vaccine prioritization (*15*). Vaccines can not only prevent the direct health problems associated with diseases but also reduce the accompanying socioeconomic losses. Equity for different groups of people should also be considered. However, prioritizing vaccine distribution to protect more disadvantaged groups is a fundamental issue. In the United States, the Advisory Committee on Immunization Practices (ACIP) advised the Centers for Disease Control and Prevention to prioritize COVID-19 vaccines. The ACIP recommended that healthcare personnel and residents of LTCFs be offered vaccination in the initial phase 1a of the COVID-19 vaccination program (*16*). Elderly populations and people with underlying diseases were given second priority for phases 1b and 1c. The strategy for prioritizing vaccination against COVID-19 in Japan was determined through discussions within the Committee on Vaccination Basic Policy of the Inoculation and Vaccination Working Group of the Health Science Council at the Ministry of Health, Labor, and Welfare (*17*). Its main purpose is to reduce the risk of severe diseases and maintain the healthcare delivery system. Japan decided that the elderly would be the second priority for vaccination after medical personnel.

Despite the largest increase in the number of infections in the fifth wave, we observed a sharp decrease in the proportion of newly confirmed cases and severe cases among the elderly in that wave after initiating prioritized vaccination. This radical change in the epidemic curve indicates that prioritizing vaccination for more vulnerable populations in a short period, and achieving high vaccine coverage, was efficacious in handling the outbreak with limited medical resources. The proportion of newly confirmed patients among the elderly began to decline relatively early in June, along with an increase in vaccine coverage among the elderly. Additionally, the proportion of patients with severe disease among the elderly began to decline in mid-September, with a time lag of approximately 3 months. This time interval suggests that intensive vaccination over a short period can effectively control the transmission of infection. Meanwhile, it might take time to prevent severe disease, possibly due to the difficulty in treating COVID-19 in the elderly and the prolonged care needed for various complications during the clinical course.

In conclusion, prioritizing the elderly for vaccination against COVID-19 seems efficacious in reducing the number of new infection cases, severe disease, and cluster events in LTCFs among the elderly during the pandemic in Japan. This contributed to reducing the burden on healthcare facilities and making effective use of limited healthcare resources during the COVID-19 pandemic. Future strategies should include administration of appropriate booster shots to cope with attenuated vaccine efficacy and novel variant strains with immune escape from currently available vaccines.

Funding: This research was supported by the NCGM COVID-19 Gift Fund.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. NIKKEI Asia. Japan starts COVID vaccination drive: five things to know. *https://asia.nikkei.com/Spotlight/Coronavirus/Japan-starts-COVID-vaccination-drive-five-things-to-know* (accessed January 28, 2022).
2. Prime Minister's Office of Japan. Ministerial Meeting on the Progress in Countermeasures against the Novel Coronavirus Disease. *https://www.kantei.go.jp/jp/99_suga/actions/202108/04corona.html* (accessed January 28, 2022). (in Japanese)
3. Kokudo N, Sugiyama H. Hospital capacity during the COVID-19 pandemic. Glob Health Med. 2021; 3:56-59.
4. Ministry of Health, Labour and Welfare. Visualizing the data: information on COVID-19 infections. *https://covid19.mhlw.go.jp/en/* (accessed January 28, 2022).
5. Digital Agency. Vaccination Record System: Vaccination status of novel corona virus. *https://info.vrs.digital.go.jp/dashboard* (accessed January 28, 2022). (in Japanese)
6. Statistics of Japan. Population Estimates by Age (Five-Year Groups) and Sex - September 1, 2021 (Final estimates), February 1, 2022 (Provisional estimates). *https://www.e-stat.go.jp/en/stat-search/files?page=1&layout=datalist&toukei=00200524&tstat=000000090001&cycle=1&year=20220&month=11010302&tclass1=000001011678&tclass2val=0* (accessed January 28, 2022).
7. Song P, Karako T. The strategy behind Japan's response to COVID-19 from 2020-2021 and future challenges posed by the uncertainty of the Omicron variant in 2022. Biosci Trends. 2022; 15:350-352.
8. Novel Coronavirus Response Headquarters. Basic policy for countermeasures against novel coronavirus infections. *https://www.kantei.go.jp/jp/singi/novel_coronavirus/th_siryou/kihon_r_040218.pdf* (accessed January 28, 2022). (in Japanese)
9. Ministry of Defense. SDF large-scale vaccination centers in Tokyo and Osaka. *https://www.mod.go.jp/en/article/2021/05/d767c5209c1b9599a7b77d877b44b226d435fd9c.html* (accessed January 28, 2021).
10. Saito S, Asai Y, Matsunaga N, Hayakawa K, Terada M, Ohtsu H, Tsuzuki S, Ohmagari N. First and second COVID-19 waves in Japan: A comparison of disease severity and characteristics. J Infect. 2021; 82:84-123.
11. Asai Y, Nomoto H, Hayakawa K, Matsunaga N, Tsuzuki S, Terada M, Ohtsu H, Kitajima K, Suzuki K, Suzuki T, Nakamura K, Morioka S, Saito S, Saito F, Ohmagari N. Comorbidities as risk factors for severe disease in hospitalized elderly COVID-19 patients by different age-groups in Japan. Gerontology. 2022; 1-11. doi: 10.1159/000521000.
12. Iritani O, Okuno T, Hama D, Kane A, Kodera K, Morigaki K, Terai T, Maeno N, Morimoto S. Clusters of COVID-19 in long-term care hospitals and facilities in Japan from 16 January to 9 May 2020. Geriatr Gerontol Int. 2020; 20:715-719.
13. Ministry of Health, Labor and Welfare. Life expectancies at birth in some countries. *https://www.mhlw.go.jp/english/database/db-hw/lifetb19/dl/lifetb19-03.pdf* (accessed January 28, 2022). (in Japanese)
14. Report on Long-Term Care Insurance Operation (2021). *https://www.mhlw.go.jp/topics/kaigo/osirase/jigyo/19/dl/r01_point.pdf* (accessed January 28, 2022). (in Japanese)
15. Persad G, Peek ME, Emanuel EJ. Fairly prioritizing groups for access to COVID-19 Vaccines. JAMA. 2020; 324:1601-1602.
16. Dooling K, Marin M, Wallace M, McClung N, Chamberland M, Lee GM, Talbot HK, Romero JR, Bell BP, Oliver SE. The Advisory Committee on Immunization Practices' Updated Interim Recommendation for Allocation of COVID-19 Vaccine - United States, December 2020. MMWR Morb Mortal Wkly Rep. 2021; 69:1657-1660.
17. Committee on Vaccination Basic Policy of the Inoculation and Vaccination Working Group of the Health Science Council. The 45th meeting. *https://www.mhlw.go.jp/stf/shingi/shingi-kousei_127714.html* (accessed January 28, 2022). (in Japanese)

Received March 9, 2022; Revised March 25, 2022; Accepted April 2, 2022.

Released online in J-STAGE as advance publication April 9, 2022.

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Global Health & Medicine. 2022; 4(2):133-136.
COMMUNICATION
DOI: 10.35772/ghm.2021.01124

The first eleven cases of SARS-CoV-2 Omicron variant infection in Japan: A focus on viral dynamics

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Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Omicron variant has spread rapidly worldwide. We report the clinical characteristics and threshold cycle (Ct) values of the first 11 patients infected with the SARS-CoV-2 Omicron variant in Japan. All patients were younger returnees from abroad; 10 patients had received two doses of vaccine. Estimated Ct values for the 11 patients were 6.0 (95% confidence interval [CI] 4.2-7.3) days for > 30, 10.6 (95% CI 9.5-11.9) days for > 35, 15.1 (95% CI 13.6-17.6) days for > 40, and 19.7 (95% CI 17.3-23.7) days for > 45. Our results provide important insights for indicators of infection control.

***Keywords*:** COVID-19, B.1.1.529, threshold cycle, characteristics

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) B.1.1.529 variant, subsequently named Omicron, was first identified in South Africa on 24 November 2021 (*1*). It has spread rapidly, with 11,148 confirmed cases worldwide as of 18 December 2021 (*2*). In Japan, the first case of SARS-CoV-2 Omicron variant infection was reported on 30 November 2021 in a man returning from Namibia (*3*). Although there is increasing information concerning the genetic and molecular characteristics of the Omicron variant, there remains limited information regarding its clinical characteristics and viral dynamics. Here, we describe the clinical characteristics and threshold cycle (Ct) values of the first 11 cases of SARS-CoV-2 Omicron variant infection reported in Japan.

Setting and patients

This study was approved by the ethics committee of the National Center for Global Health and Medicine (NCGM) (Approval no. NCGM-G-003472-02). Written consent for participation in the study was obtained from all patients. This retrospective cohort study of patients with SARS-CoV-2 Omicron variant was conducted between November and December 2021 at the NCGM (Tokyo, Japan), an infectious disease reference centre with approximately 780 hospital beds.

Demographic and clinical characteristics

The following information was collected from medical charts: characteristics and comorbidities; risky behaviour including travel history; vaccination; symptoms at admission, body temperature, supplementary oxygen, and treatment; and imaging findings.

In total, 11 patients with SARS-CoV-2 Omicron variant infection were examined in this study. The median (range) age was 39 (1-64) years; 10 patients (90.9%) were male. All patients had been diagnosed after travelling abroad; eight (72.7%) were from Africa, while one (9.1%) each was from Europe, North America, and Latin America. All but one paediatric patient had received two doses of vaccine: seven had received mRNA-1273 (Moderna) and three had received BNT162b2 (Pfizer-BioNTech). Three patients (27.3%) had comorbidities: two had hypertension (18.2%), and one (9.1%) each had hyperlipidaemia and diabetes mellitus. The most common symptoms were fever and sore throat (n = 5, 45.5%), followed by cough (n = 4, 36.4%) and fatigue (n = 1, 9.1%). No patients exhibited pneumonia or required supplementary oxygen (Table 1).

Table 1. Characteristics of 11 cases of SARS-CoV-2 Omicron variant infection

Characteristics	Values
Age	39 [1-64][a]
Male sex	10 (90.9)[b]
Body mass index	23.8 [22.0-26.4][c]
Smoking	0 (0, two ex-smokers)
Travel history	11 (100)
	Africa 8 (72.7)
	Europe 1 (9.1)
	North America 1 (9.1)
	Latin America 1 (9.1)
Risky behaviour within 14 days before symptom onset	
Close contact	3 (27.3)
Eating with other people	0 (0)
No avoidance of three Cs[d]	0 (0)
Asymptomatic infection	3 (27.3)
Days from onset to admission	2 [2-3]
Past history of COVID-19	0 (0)
Vaccination	
None	1 (9.1)
1 dose	0 (0)
2 doses	10 (90.9)
	Moderna 7 (70.0)
	Pfizer 3 (30.0)
Comorbidities	
Hypertension	2 (18.2)
Hyperlipidaemia	1 (9.1)
Diabetes mellitus	1 (9.1)
Maximum body temperature	37.0 [36.5-37.9]
Supplementary oxygen required	0 (0)
Pneumonia	0 (0)
Symptoms during admission	
Fever (≥ 37.5°C)	5 (45.5)
Cough	4 (36.4)
Sore throat	5 (45.5)
Headache	0 (0)
Fatigue	1 (9.1)
Difficulty breathing	0 (0)
Myalgia	0 (0)
Treatment during admission[e]	
Antivirals	0 (0)
Biologics	1 (9.1)
	Sotrovimab 1 (100)
Steroids	0 (0)

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019. [a]Numbers here are median [range]. [b]Categorical variables are presented as absolute number (percentage).[c]Continuous variables are presented as median [interquartile range]. [d]Closed spaces with poor ventilation, Crowded places with many people nearby, and Close-contact setting (*e.g.*, close-range conversations). [e]Based on the clinical record until 18th December 2021. Eight of 11 patients remain hospitalised.

Laboratory analysis

Samples for mutational analysis were sent to the National Institute of Infectious Diseases for viral genome sequencing and confirmed to contain the Omicron variant (GISAID Accession 64 ID: EPI_ISL_6913953, 6914908, 7194610, 7860178, 7889643, 7889642, 7860189, 7860190, 7860188, 7860185, 7860184). All specimens used for the analysis of Ct values were collected by clinical staff with nasopharyngeal swabs after admission. Ct values were measured for the nucleocapsid N2 gene using Xpert® Xpress SARS-CoV-2 (Cepheid, Sunnyvale, CA, USA) (*4*). Associations of Ct values with days from symptom onset or diagnosis were examined by linear regression analysis. Fifty-seven polymerase chain reaction (PCR) test results from 11 patients were included in the analysis. The Ct values were positively correlated with days from symptom onset or diagnosis (Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=41*). An interval of 6.0 (95% confidence interval [CI] 4.2-7.3) days was needed for the Ct value to become greater than 30; additional intervals were 10.6 (95% CI 9.5-11.9) days for > 35, 15.1 (95% CI 13.6-17.6) days for > 40, and 19.7 (95% CI 17.3-23.7) days for > 45 (Figure 1, Figure S1, and S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=41*).

Discussion

The viral dynamics of SARS-CoV-2 vary according to variant type and patient vaccination status. For example, the Delta variant exhibits significantly lower Ct values at symptom onset and a slower decay rate, compared with the Alpha variant (*5*). To our knowledge, there are no reports concerning the trends of Ct values for SARS-CoV-2 Omicron variant. In this study, we investigated the changes in Ct values from the time of symptom onset or test positivity when reverse transcriptase (RT)-PCR was performed on nasopharyngeal swab specimens.

All 11 patients were diagnosed with SARS-CoV-2 infection during post-travel quarantine; eight of them were returnees from Africa. This quarantine is a component of the increased screening required by the Japanese government in the context of the Omicron variant. None of the patients were elderly; only three had comorbidities. This would be related the fact that all patients were overseas travellers. All but one patient (a 1-year-old child) had received two doses of vaccine (none received booster shots); thus, these 10 patients exhibited breakthrough infections. All patients were asymptomatic or had mild disease; however, they were hospitalised because Japanese Infectious Disease Control Act tentatively requires all patients with Omicron variant to be hospitalised and isolated. Although clinical outcomes have not been followed until discharge in eight patients, no patient has developed a severe respiratory condition or died. The clinical characteristics of the patients with SARS-CoV-2 Omicron variant infection in this study are consistent with the characteristics of such patients in the United States (most are younger, have been vaccinated, and exhibit mild disease) (*6*).

In this study, the estimated Ct values were > 30 at 6.0 (95% CI 4.2-7.3) days, > 35 at 10.6 (95% CI 9.5-11.9) days, > 40 at 15.1 (95% CI 13.6-17.6) days, and > 45 at 19.7 (95% CI 17.3-23.7) days. A study from England reported that in patients with coronavirus disease 2019 (COVID-19), Ct values gradually decrease during the first 10 days, then reach a plateau and remain positive (*7*). Additionally, a report from Italy regarding hospitalised patients with COVID-19 indicated that the time to PCR-

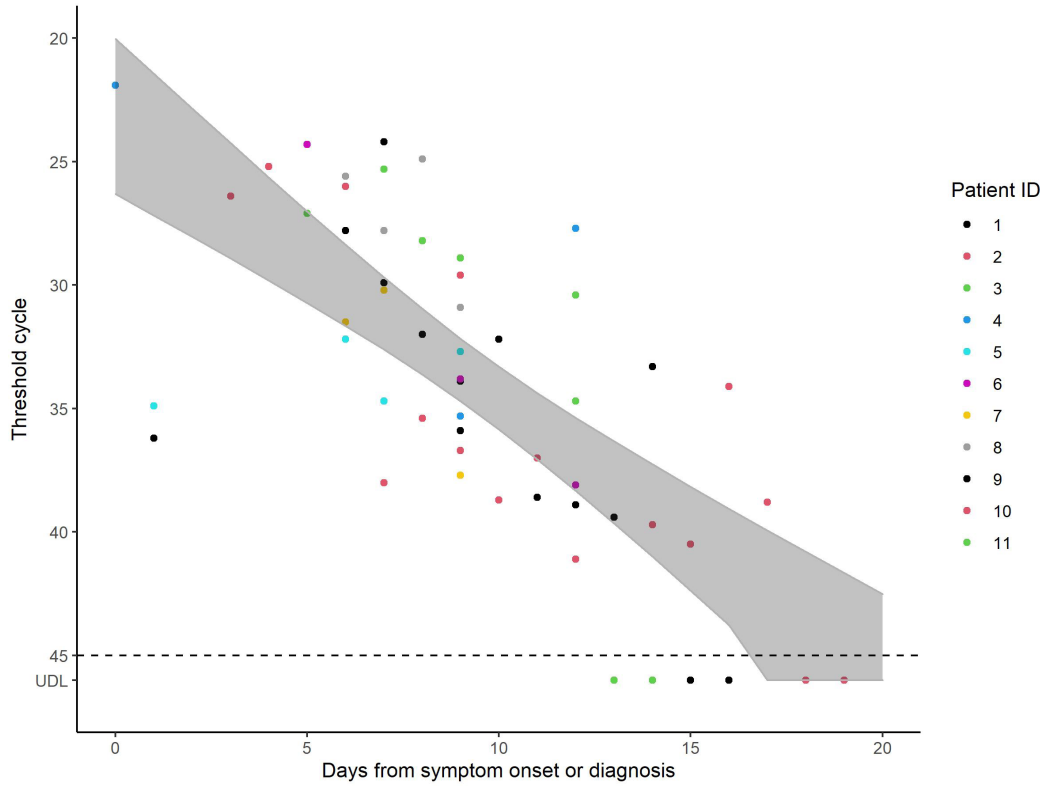

Figure 1. Detection of SARS-CoV-2 by RT-PCR targeting the nucleocapsid N2 gene. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; RT-PCR: reverse transcription polymerase chain reaction; UDL: under detection limit; ID: identification. Shaded area represents 95% confidence interval of the predicted value of the liner model. Threshold cycle values > 45 were regarded as 45 because of the detection sensitivity limit. Threshold cycle values were measured for the nucleocapsid N2 gene using Xpert® Xpress SARS-CoV-2.

negativity was approximately 30 days (*8*). These studies were performed in patients infected with the original SARS-CoV-2 strain, before the introduction of the vaccine. In a French study of patients with COVID-19 (mainly caused by the SARS-CoV-2 Delta variant), regression analysis predicted that RT-PCR test results would remain positive for > 20 days for the Delta variant (*5*). In our analysis, 19.7 days were needed for the Ct value to become > 45. Although our analysis did not investigate the influences of factors other than the time from symptom onset or diagnosis, it might be valuable information for public health authority. Most patients had completed two doses of vaccinations, suggesting that the Omicron variant causes long-term virus excretion, despite full vaccination.

Because we did not attempt to isolate the virus, we could not evaluate its viability or infectivity. However, some studies have revealed relationships between Ct value and culture positivity findings. In separate studies by French, Canadian, and Japanese investigators, no cultures were obtained from samples with Ct ≥ 34, Ct > 24, and Ct > 30, respectively (*9-11*). Another study in England revealed the estimated probability of viral recovery from samples with Ct > 35 was 8.3% (*7*). Considering that samples with Ct values > 35 are unlikely to contain viable virus, our finding of Ct values > 35 in 10.6 (95% CI 9.5-11.9) days might be useful as an indicator for infection control.

Conclusions

In our investigation of the first 11 patients with Omicron variant infection in Japan, all were asymptomatic or had mild disease after travelling abroad. Assuming a linear association between Ct values and the days from symptom onset or diagnosis (with no other influencing factors), the estimated Ct values were > 30 at 6.0 (95% CI 4.2-7.3) days, > 35 at 10.6 (95% CI 9.5-11.9) days, > 40 at 15.1 (95% CI 13.6-17.6) days, and > 45 at 19.7 (95% CI 17.3-23.7) days. Our results provide important insights for indicators of infection control; further analysis of the relationships between Ct values and viral load will enable more robust control measures for the Omicron variant.

Acknowledgements

We thank Ms. Michiyo Suzuki for data entry, Dr. Masumichi Saito, Ms. Naomi Nojiri, Ms. Hazuka Yoshida, Dr. Nozomu Hanaoka, Dr. Tsuguto Fujimoto and Dr. Kenichiro Takahashi for technical support with respect to SARS-CoV-2 viral RNA genome sequencing, and all staff members for the provision of care to patients with COVID-19.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. Classification of Omicron (B1.1.529): SARS-CoV-2 Variant of Concern. *https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern* (accessed December 12, 2021).
2. Global Initiative on Sharing Avian Influenza Data. Tracking of Variants. *https://www.gisaid.org/hcov19-variants/* (accessed December 18, 2021).
3. Ministry of Health, Labour and Welfare. Asymptomatic carriers of a SARS-CoV-2 infection (mutant variant) (Airport Quarantine) in Japan. November 30, 2021. *https://www.mhlw.go.jp/stf/newpage_22507.html* (accessed December 18, 2021). (in Japamese)
4. Cepheid. Xpert® Xpress SARS-CoV-2 Test: Package Insert, 2020. *https://www.fda.gov/media/136315/download* (accessed December 18, 2021).
5. Blanquart F, Abad C, Ambroise J, Bernard M, Cosentino G, Giannoli JM, Débarre F. Characterisation of vaccine breakthrough infections of SARS-CoV-2 Delta and Alpha variants and within-host viral load dynamics in the community, France, June to July 2021. Euro Surveill. 2021; 26:2100824.
6. Centers for Disease Control and Prevention COVID-19 Response Team. SARS-CoV-2 B.1.1.529 (Omicron) Variant-United States, December 1-8, 2021. MMWR Morb Mortal Wkly Rep. 2021;70 (Early Release). *https://www.cdc.gov/mmwr/volumes/70/wr/mm7050e1.htm* (accessed December 18, 2021).
7. Singanayagam A, Patel M, Charlett A, Bernal JL, Saliba V, Ellis J, Ladhani S, Zambon M, Gopal R. Duration of infectiousness and correlation with RT-PCR cycle threshold values in cases of COVID-19, England, January to May 2020. Euro Surveill. 2020; 25:2001483.
8. Mancuso P, Venturelli F, Vicentini M, Perilli C, Larosa E, Bisaccia E, Bedeschi E, Zerbini A, Rossi PG. Temporal profile and determinants of viral shedding and of viral clearance confirmation on nasopharyngeal swabs from SARS-CoV-2-positive subjects: A population-based prospective cohort study in Reggio Emilia, Italy. BMJ Open. 2020; 10:e040380.
9. Bullard J, Dust K, Funk D, Strong JE, Alexander D, Garnett L, Boodman C, Bello A, Hedley A, Schiffman Z, Doan K, Bastien N, Li Y, Van Caeseele PG, Poliquin G. Predicting infectious severe acute respiratory syndrome coronavirus 2 from diagnostic samples. Clin Infect Dis. 2020; 71:2663-2666.
10. la Scola B, le Bideau M, Andreani J, Hoang VT, Grimaldier C, Colson P, Gautret P, Raoult D. Viral RNA load as determined by cell culture as a management tool for discharge of SARS-CoV-2 patients from infectious disease wards. Eur J Clin Microbiol Infect Dis. 2020; 39:1059-1061.
11. Yamayoshi S, Sakai-Tagawa Y, Koga M, *et al*. Comparison of rapid antigen tests for covid-19. Viruses. 2020; 12:1420.

Received December 23, 2021; Revised December 28, 2021; Accepted December 29, 2021.

Released online in J-STAGE as advance publication December 30, 2021.

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Global Health & Medicine. 2022; 4(2):137-140.

CORRESPONDENCE

DOI: 10.35772/ghm.2022.01024

Promotion of proper use of anti-SARS-CoV-2 drugs and SARS-CoV-2 vaccines by hospital pharmacists and establishment of an adverse drug reaction reporting system

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Abstract: Newly developed anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) drugs are being rapidly approved in countries worldwide. These new drugs are being approved after testing with a limited number of cases, and in real-world clinical practice, unknown and potentially serious adverse events that could not be detected in clinical trials may emerge. Accordingly, in the event of an adverse drug reaction for which a causal relationship with these new drugs cannot be ruled out, it is vital to promptly report the details of the case to the regulatory authorities. To date, through close cooperation between physicians and pharmacists, we have reported four cases of adverse drug reactions for which a causal relationship to anti-SARS-CoV-2 drugs cannot be ruled out. Herein, we introduce safety measures taken by pharmacists when using these new drugs in the hospital, and a system for reporting to the regulatory authorities when adverse events occur.

***Keywords*:** regulatory authorities, safety, adverse events, Japan

Introduction

New developments in the drugs to treat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are occurring daily. In Japan, drugs confirmed to be effective for SARS-CoV-2, including vaccines, have thus far been approved under the Special Approval system and these have been used in numerous cases in real-world clinical settings. Moreover, due to the characteristics of the SARS-CoV-2 virus, new variants are expected to emerge in the future, and many additional drugs capable of treating them are expected to become available. However, from a safety perspective, most of these new drugs are tested in pre-approval clinical trials with a limited number of cases, and in actual clinical settings they may be administered in cases in which the patient background does not match the eligibility criteria of the clinical trial. As such, there may be unknown adverse events that were not detected when the drug was approved or known adverse events that become more severe. Therefore, it is critical to collect and evaluate safety information on medical and pharmaceutical products licensed under Special Approval, and extremely careful monitoring is essential in the months immediately following approval.

In Japan, hospital medical staffs are obligated to make a report to the Pharmaceuticals and Medical Devices Agency (PMDA) if they become aware of a death or event suspected to be an adverse drug reaction (side effect). This is necessary to prevent the occurrence or spread of a health or hygiene hazard (*1*). It is crucial to establish a system at medical institutions to track the condition of patients to whom such drugs have been administered. When an adverse event occurs, it is important to refer the Risk Management Plan (RMP) and the clinical trial data from the time of the approval of the application, and make a report as soon as possible in order to prevent adverse drug reactions from becoming widespread. Herein, we introduce the system for safe usage of new anti-SARS-CoV-2 drugs and SARS-CoV-2 vaccines in use at the Department of Pharmacy, Center hospital of the National Center for Global Health and Medicine (NCGM), and provide examples of adverse event reports created through prompt information gathering and collaboration with physicians.

Current anti-SARS-CoV-2 drugs and vaccines

In Japan, five anti-SARS-CoV-2 drugs Remdesivir (7 May 2020), Baricitinib (23 April 2021), Casirivimab/Imdevimab (19 July 2021), Sotrovimab (27 September 2021), and Molnupiravir (24 December 2021) and three SARS-CoV-2 vaccines COMIRNATY® (14 February 2021), Spikevax® (21 May 2021), and Vaxzebria® (21 May 2021) have been approved under the Special Approval system (as of 4 February 2022).

Special Approval in Japan is a system that allows for the post-approval submission of materials other than the clinical trial documents typically required for application if a drug satisfies the following conditions: *i*) urgent use is necessary in the prevention of the spread of disease, *ii*) no proper method is available except the use of such drug, and *iii*) such drug is authorized for sale in a foreign country (*2*).

The therapeutic effects and safety of the drugs specially approved in Japan have largely been based on data from overseas Phase III trials. These data are Remdesivir (approximately 1,000 subjects) (*3*), Baricitinib (approximately 1,000 subjects) (*4*), Casirivimab/Imdevimab (approximately 5,600 subjects) (*5*), Sotrovimab (approximately 1,000 subjects) (*6*), Molnupiravir (approximately 1,900 subjects) (*7*), COMIRNATY® (approximately 44,000 subjects) (*8*), Spikevax® (approximately 30,000 subjects) (*9*), and Vaxzebria® (approximately 24,000 subjects) (*10*).

In addition to these data, evaluations are made based on data from domestic Phase I and II trials with tens to hundreds of subjects, or from the small number of Japanese patients participating in overseas Phase III trials. Thus, the amount of data from Japanese patients is extremely limited immediately after the approval.

Establishment of a system for introducing anti-SARS-CoV-2 drugs in the hospital

Each time a new anti-SARS-CoV-2 drug receives Special Approval, we create a checklist to confirm patient eligibility for the drug's administration. When the drug is prescribed, it is dispensed only after reviewing the checklist, prescription, and medical chart, and confirming that the eligibility criteria are met. In addition, physicians need to provide a number of instructions for the proper use of the drug when ordering a prescription, such as dosage, flow rate, amount of infusion to be diluted, and administration schedule. Therefore, as a measure to prevent medical errors, we set prescription orders on the electronic medical record system so that physicians can easily and accurately place these orders, enabling all physicians to place the appropriate orders as prescribed in advance.

At the NCGM, clinical pharmacists are assigned to each ward to check the dosage, flow rate, and clinical laboratory values to be monitored to ensure the proper use of drugs, not just specially approved drugs. These pharmacists have a range of roles, for example, checking the details of concomitant medications, adherence, and interactions. When injectable drugs are used, the pharmacists confirm the route of administration to avoid incompatibilities with other drugs, instruct nurses on how to prepare the drugs, and provide information on whether a filter is required for administration. In addition, they monitor for the occurrence of adverse drug reactions. When an adverse drug reaction is suspected, the clinical pharmacists share the information with physicians and the pharmacists of the Drug Information service.

At the NCGM, As shown in Figure 1, physicians and pharmacists work together smoothly to establish a system for prompt reporting of adverse drug reactions, which enables prompt reporting of adverse drug reactions to the PMDA.

The adverse drug reactions reporting system at the NCGM

When the pharmacists of the Drug Information service obtain information on a patient with a suspected adverse

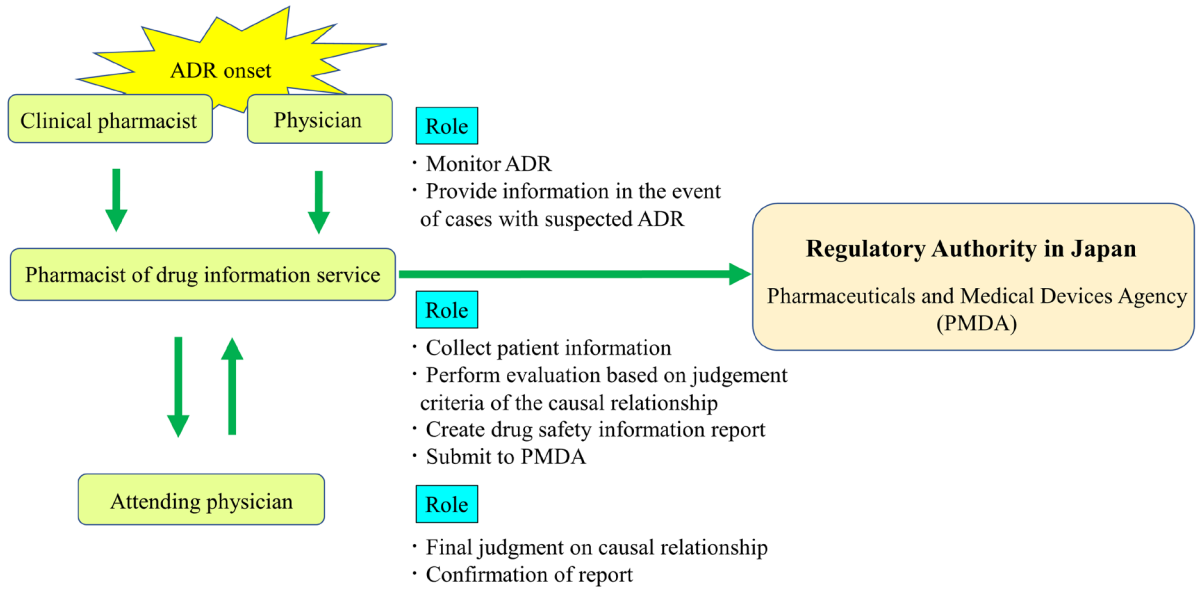

Figure 1. Procedure for reporting suspected adverse drug reactions (ADR) to Pharmaceuticals and Medical Devices Agency (PMDA).

Table 1. Cases of reported adverse drug reactions (ADR) to SARS-CoV-2 drugs or vaccines

Case No.	Sex	Age	Brand name (manufacturer)	Adverse drug reaction	No. of days from ADR onset to PMDA report
1	Male	50s	Remdesivir (GILEAD)	Rash	23
2	Female	60s	COMIRNATY® (Pfizer)	Hypertension and headache	21
3	Female	70s	COMIRNATY® (Pfizer)	Myocardial infraction	21
4	Male	10s	Spikevax® (TAKEDA)	Myocarditis	56

drug reaction from physicians or clinical pharmacists, they collect data on the patient's background (medical history, comorbidities), clinical laboratory values, history of administration of drugs including concomitant drugs, timing and course of the reaction, and severity. Furthermore, after collecting data on adverse events of the suspected drug that have been reported so far, the causal relationship between the suspected drug and the adverse event in the patient is comprehensively verified, and a Drug Safety Information Report (hereafter, DSIR) is prepared. There are several proposed methods for evaluating the degree of association between a suspected drug and an adverse event, but the NCGM evaluates causal relationships based on the criteria proposed in the report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI (*11*) and the Naranjo Scale (*12*). As there are minimal existing data on adverse events for specially approved drugs, causal relationships are carefully investigated based on the chronological clinical course, and the DSIRs are created with special emphasis on the temporal association between the period of drug administration and the onset of the adverse event. DSIRs are submitted to the PMDA after confirming with the physicians responsible for treatment that the final decision of the DSIR is consistent with their opinion.

So far, we have submitted 53 DSIRs in the last three years. For the twelve DSIRs from the past year, the median time to report was 49 days (range 14 to 157 days) from the date the adverse event occurred.

We have submitted the DSIRs to the PMDA for the four cases of adverse events to anti-SARS-CoV-2 drugs or SARS-CoV-2 vaccines specially approved after January 2021 (Table 1). Pharmacists in the drug information service submitted the DSIRs to the PMDA within 21 days of obtaining information in all the cases. In one of the four cases, adverse event information was obtained more than 30 days after the occurrence and as a result, the DSIR was submitted 56 days after onset. DSIRs were completed within 30 days of occurrence in the other three cases.

Case 1 (50s, male)

The second day after Remdesivir administration, an itching sensation was observed on the patients' arms and back, followed by itchiness of the face, trunk, and thighs, and a swollen, red rash which spread across the whole body. The rash disappeared with antihistamine and steroid administration. The Remdesivir was believed to be the cause, and its administration was discontinued thereafter. Afterwards, the patient's fever and pneumonia improved, and the discharge criteria were met, allowing him to be discharged seven days after symptom onset. A DSIR was made because this was a serious case in which a causal relationship between the symptom onset and Remdesivir could not be ruled out.

Case 2 (60s, female)

After receiving her second dose of COMIRNATY® at a different clinic, the patient reported dizziness and her systolic blood pressure was found to be elevated to around 180 mmHg. After this, the patient reported headache in the left temporal region and underwent a head CT scan. This indicated subarachnoid hemorrhage, and the patient was transferred to the NCGM. CT and MRI performed at the NCGM showed no evidence of subarachnoid hemorrhage, and the blood pressure stabilized at 100-120 mmHg with continuous administration of intravenous nicardipine. Subsequently, the symptoms abated, and the patient was discharged five days after symptom onset. Although headache has been reported to occur in 39% of patients ≥ 55 years following the second dose of COMIRNATY® (8), a DSIR was made in this case because there was blood pressure elevation and severe headache requiring hospitalization.

Case 3 (70s, female)

The patient experienced neck pain, nausea, weakness, and cold sweats after receiving her second dose of COMIRNATY®. Her symptoms did not improve after returning home, and she was brought to the NCGM by ambulance where she was diagnosed with myocardial infarction. After hospitalization, percutaneous coronary intervention (PCI) was performed, and she was discharged after eleven days. In addition to hypertension and dyslipidemia, the patient had untreated diabetes, and was thus at high risk for myocardial infarction, but a DSIR was made in this case because the heart attack occurred immediately after vaccination, and the possibility that vaccination triggered the onset of symptoms cannot be ruled out.

Case 4 (10s, male)

Three days after administration of Spikevax®, the

patient reported chest pain and was examined at the NCGM emergency room. Blood test results showed elevation of troponin I and the electrocardiogram showed ST elevation. Based on his clinical course the patient was admitted to the hospital on suspicion of vaccine-associated myocarditis. Over time, the chest pain improved, troponin I dropped to within normal limits, and the ST elevation on the electrocardiogram disappeared, so the patient was discharged after seven days. There are more frequent reports of myocarditis and pericarditis after Spikevax® administration compared to COMIRNATY®, and the Ministry of Health, Labour and Welfare website reports that these cases are often males between 10 to under 30 years of age within about four days of vaccination (*13*).

These findings were not known immediately after Spikevax® was approved, but have become clear as a result of extensive collection and evaluation of cases suspected of adverse events by medical institutions both in Japan and abroad. Although this is a known adverse event, we chose to make a DSIR because these findings may serve as reference data for vaccine selection for male patients in their teens and 20s who plan to get a SARS-CoV-2 vaccine in the future.

Conclusion

Pharmacists can contribute to the proper use of specially approved drugs by confirming the eligibility of patients when dispensing prescriptions and monitoring the drug effects and safety after administration. However, there are cases in which adverse events occur even when drugs are used appropriately.

As specially approved drugs are approved with a limited number of cases, obtaining information on adverse events at an early stage, collaboration between physicians and pharmacists, and prompt and detailed reporting of information on adverse drug reactions will prevent the spread of harm caused by adverse drug reactions and identify previously unknown events and contribute to building evidence and disseminating new information of benefit to patients.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Act No. 145 of 1960, Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Article 68-10, paragraph (2). *https://www.japaneselawtranslation.go.jp/en/laws/view/3213* (accessed February 28, 2022).
2. Act No. 145 of 1960, Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, Article 14-3, paragraph (1) *https://www.japaneselawtranslation.go.jp/en/laws/view/3213* (accessed February 28, 2022).
3. Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the treatment of Covid-19 – Final report. N Engl J Med. 2020; 383:1813-1826.
4. Kalil AC, Patterson TF, Mehta AK, *et al*. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med. 2021; 384:795-807.
5. Weinreich DM, Sivapalasingam S, Norton T, *et al*. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. N Engl J Med. 2020; 385:e81.
6. Gupta A, Gonzalez-Rojas Y, Juarez E, *et al*. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med. 2021; 385:1941-1950.
7. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, *et al*. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. N Engl J Med. 2022; 386:509-520.
8. Polack FP, Thomas SJ, Kitchin N, *et al*. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020; 383:2603-2615.
9. Baden LR, El Sahly HM, Essink B, *et al*. Efficacy and safety of the mRNA-1273 SARS-Cov-2 vaccine. N Engl J Med. 2021; 384:403-416.
10. Voysey M, Costa Clemens SA, Madhi SA, *et al*. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK. Lancet. 2021; 397:99-111
11. Report of CIOMS Working Group VI. Management of Safety Information from Clinical Trials, 2005. *https://cioms.ch/publications/product/management-of-safety-information-from-clinical-trials-report-of-cioms-working-group-vi/* (accessed February 28, 2022).
12. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts E A, Janecek E, Domecq C, Greenblatt D J. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981; 30:239-245.
13. Ministry of Health, Labour and Welfare. SARS-CoV-2 vaccines Q and A *https://www.cov19-vaccine.mhlw.go.jp/qa/0079.html* (accessed January 18, 2022). (in Japanese)

Received March 1, 2022; Revised March 28, 2022; Accepted April 4, 2022.

Released online in J-STAGE as advance publication April 9, 2022.

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Global Health & Medicine. 2022; 4(2):141-143.
LETTER
DOI: 10.35772/ghm.2021.01125

Adverse reactions and attitudes toward vaccines among young populations one month after receiving a second dose of mRNA-1273 in Japan

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Abstract: To investigate adverse reactions and attitudes toward the vaccine during the first month after mRNA-1273 vaccination in a larger sample including younger men and women in Japan, we distributed a 1-month post-vaccination questionnaire using a Google form to 8,566 people who received a second dose of mRNA-1273 at Okayama University. The response rate was about 40.2% (3,447 responses), the sex ratio was about the same, and 73.3 % (2,528 respondents) were students in their twenties or younger. Poisson regression with robust variance was performed to calculate the prevalence ratio of each symptom by different attributes. The most common adverse reactions after the second vaccine dose were local pain (80.4%), fever (85.1%), malaise (82.0%), headache (64.0%), and chills (57.4%). Approximately 99% of respondents reported that their adverse reactions resolved within 1 week. Over 80% of respondents were satisfied with their vaccination (87.2%), expressed interest in receiving the third vaccination (83.3%), and would recommend vaccination to their loved ones (80.2%). However, among them, 22.0% (757 respondents) would recommend and 28.4% (980 respondents) also stated that they would consider the type of vaccine in these decisions.

***Keywords*:** COVID-19, mRNA, adverse events, safety

An outbreak of a novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) began in Wuhan, China in 2019 and subsequently developed into a worldwide pandemic. To bring the pandemic under control, various efficacious vaccines have been developed and introduced, starting with the approval of BNT162b2 in December 2020 and now including mRNA-1273 and AZD1222. These vaccines have contributed significantly to reducing coronavirus disease 2019 (COVID-19) severity and mortality rates (*1,2*).

Although a sufficient proportion of the population needs to be vaccinated to fully benefit from the effects of vaccination (*3*), some individuals remain vaccine-hesitant (*4*). Vaccine hesitancy is partially attributed to concerns regarding medium- to long-term adverse events following administration of new types of vaccines such as mRNA vaccines. There have been reports of medium-term adverse reactions following vaccination in clinical trials conducted overseas (*5*). However, no reports of medium-term adverse reactions following COVID-19 vaccination in Japanese subjects are available. A post-vaccination health status survey conducted by the Ministry of Health, Labour, and Welfare of Japan made no mention of residual adverse reactions 1-month post-vaccination (*6*). In the mRNA-1273 post-vaccination survey, most of the respondents were Japan Self-Defense Forces personnel (more than 65% were aged 30-49 and 95% were male). Therefore, to provide information on actual adverse reactions to both men and women among young people who may hesitate to be vaccinated, it would be desirable to investigate early and medium-term adverse reactions to mRNA-1273 vaccination in a larger study population that includes younger individuals of both sexes.

We distributed a self-administered questionnaire survey to collect information on adverse reactions 1-month post-mRNA-1273 vaccination as well as respondents' thoughts regarding vaccination. Following informed consent, the questionnaire was distributed using a Google form in Japanese or English to 8,566 students and faculty members who received a second dose of mRNA-1273 between August 6 and September 15, 2021, at Okayama University. The questionnaire period was

Table 1. Adverse reactions after a second dose of mRNA-1273 vaccine (*n* = 3,447)

Adverse reactions	N/A (%)	Within 3 days (%)	Within 1 week (%)	Within 2 weeks (%)	Within 1 month (%)	Ongoing (%)
Local adverse reactions						
Pain	19.61	67.42	11.87	0.67	0.26	0.17
Swelling	46.82	42.30	9.81	0.93	0.12	0.03
Redness	60.40	29.39	8.67	1.25	0.26	0.03
Pruritus	70.09	18.86	8.70	1.83	0.46	0.06
Swollen lymph nodes	90.08	7.25	2.32	0.20	0.12	0.03
Systemic adverse reactions						
Fever ≥ 37.5°C	14.91	81.98	2.99	0.06	0.06	0.00
Headache	36.15	57.12	6.06	0.32	0.23	0.12
Malaise	18.02	72.99	7.63	0.75	0.41	0.20
Chills	42.65	55.90	1.39	0.03	0.03	0.00
Nausea and vomiting	89.61	9.49	0.58	0.23	0.09	0.00
Diarrhea	92.98	6.09	0.73	0.12	0.06	0.03
Myalgia	35.94	55.76	7.83	0.32	0.09	0.06
Joint pain	58.08	39.02	2.70	0.15	0.06	0.00
Rash	93.99	4.24	1.28	0.32	0.09	0.09
Chest pain	94.08	4.55	0.90	0.35	0.12	0.00

N/A, not applicable.

from September 27 to October 25, 2021. Descriptive analyses were conducted to assess adverse reactions during the first month after the second vaccine dose as well as respondents' thoughts concerning vaccination. We performed Poisson regression with robust variance to calculate the prevalence ratio of each symptom by different attributes. Stata version 17 (StataCorp LLC, College Station, TX, USA) was used for all analyses. The study was approved by the Institutional Review Board of Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (No. 2110-025). Online informed consent was obtained from all participants following full disclosure and explanation of the study's purpose and procedures.

The response rate was about 40.2% (*n* = 3,447 responses). In the submitted surveys, there were no missing values because all questions were set as mandatory in Google forms. The proportions of male and female respondents were similar, and because this was a survey of university-based vaccination, about three-quarters of respondents were students in their twenties or younger. Most respondents were Japanese citizens. Only 6.1% of respondents (210 respondents) had underlying diseases while 44.2% (1,525 respondents) had a history of allergy, including pollen or food allergy (Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=46*). The most common adverse reactions after the second vaccine dose were local pain (80.4%), fever (85.1%), malaise (82.0%), headache (64.0%), and chills (57.4%). The majority of respondents (approximately 99%) reported that their adverse reactions resolved within 1 week (Table 1). However, a small number of patients complained of persisting discomfort 1-month post-vaccination. Fever was more common in those in their forties or younger than in those in their fifties or older and was slightly more common in those with a history of allergies (Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=46*). There was no difference in the frequency of fever by sex; the frequency of fever was slightly lower in those with underlying diseases. Even though 84.9% of respondents reported that the adverse reactions of mRNA-1273 vaccination were more severe than those of influenza vaccination and 43.3% of respondents reported that adverse events were more severe than they expected, over 80% of respondents were satisfied with their vaccination (87.2%), expressed interest in receiving a third vaccine dose (83.3%), and stated that they would recommend vaccination to their loved ones (80.2%) (Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=46*). However, among them, 22.0% (757 respondents) would recommend and 28.4% (980 respondents) also stated that they would consider the type of vaccine in these decisions.

A survey conducted by the Ministry of Health, Labour, and Welfare of Japan summarized adverse reactions after 10 days of vaccination (*6*). However, comparatively little is known regarding medium-to long-term adverse reactions in Japanese individuals over the first month after vaccination. While many respondents in our study indicated that their adverse reactions disappeared within 1-week post-vaccination and had positive opinions regarding vaccination, a small minority of individuals complained of medium-term discomfort. Although a causal relationship could not be established, the persisting symptoms of these individuals reminded us of the importance of longer-term follow-up. The intensity of adverse reactions to mRNA-1273 vaccination seemed to be widely known among respondents, and approximately one-quarter of respondents said that they would consider the type of vaccine for future vaccinations. The data from this

study may inform the direction of future vaccination strategies.

Acknowledgements

We thank Yasutomo Nasu, Chikara Miyaji, Yuta Mori, Yoko Oka, and Saori Irie for their valuable support in data collection.

Funding: The present study was supported by donations to the Okayama University Academic Capital Foundation (support for research related to COVID-19) and a grant from Okayama City (No. 7402100053) for COVID-19 research. The sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, and approval of the manuscript; or in the decision to submit the manuscript for publication.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. Vasileiou E, Simpson CR, Shi T, *et al*. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet. 2021; 397:1646-1657.
2. Fiolet T, Kherabi Y, MacDonald CJ, Ghosn J, Peiffer-Smadja N. Comparing COVID-19 vaccines for their characteristics, efficacy and effectiveness against SARS-CoV-2 and variants of concern: A narrative review. Clin Microbiol Infect. 2022; 28:202-221.
3. Randolph HE, Barreiro LB. Herd immunity: Understanding COVID-19. Immunity. 2020; 52:737-741.
4. Okubo R, Yoshioka T, Ohfuji S, Matsuo T, Tabuchi T. COVID-19 vaccine hesitancy and its associated factors in Japan. Vaccines (Basel). 2021; 9:662.
5. Baden LR, El Sahly HM, Essink B, *et al*. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021; 384:403-416.
6. Ito S, Kusunoki S, Tsuchida N, Kaneko Y, Tobita M. Intensive survey in the early phase of the administration of the new corona vaccine (cohort survey) Interim report on the health observation diary (17). *https://www.mhlw.go.jp/content/10601000/000862143.pdf* (accessed February 14, 2022). (in Japanese)

Received December 23, 2021; Revised February 15, 2022; Accepted February 22, 2022.

Released online in J-STAGE as advance publication March 5, 2022.

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Global Health & Medicine. 2022; 4(2):144-145.
LETTER
DOI: 10.35772/ghm.2022.01023

Establishment of an emergency regulatory approval system in Japan in response to the COVID-19 pandemic and challenges in developing domestically produced vaccines

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Abstract: Although ten vaccines against novel coronavirus infection (COVID-19) have been placed on the World Health Organization (WHO)'s emergency use list, no vaccine has been developed by Japanese pharmaceutical companies. As of March 2022, 10 billion doses of vaccines have been administered worldwide 2 years after the infection was declared a pandemic by the WHO. Japan lacks a system for approval of pharmaceuticals at the stage of presumed efficacy in emergencies, such as the COVID-19 pandemic. The absence of such an emergency approval mechanism is believed to have been a stumbling block to the rapid availability of urgently needed drugs. Further promotion of vaccine development in Japan will require comprehensive improvement of investment in the vaccine field, which is critically lacking from a long-term perspective.

***Keywords*:** vaccine development, Japan, COVID-19 pandemic, emergency approval system

Two years have passed since March 11, 2020, when the Director-General of the World Health Organization (WHO) declared the novel coronavirus infection (COVID-19) a pandemic (*1*). Many vaccines and therapeutics are now available; however, regional inequality in access to medicines is a global problem. Ten vaccines have already been placed on the WHO's emergency use list. As of January 2022, 1 billion doses of vaccines had been supplied to low- and middle-income countries through the COVID-19 Vaccines Global Access (COVAX). In addition, more than 10 billion doses of vaccines have been administered worldwide as of March 2022 (*2*). Nevertheless, no COVID-19 vaccine has been developed by Japanese pharmaceutical companies, and the only vaccine in Phase III clinical trials is a recombinant protein vaccine (S-268019) developed by Shionogi Inc (*3*).

In Japan, the manufacture and sale of pharmaceuticals and medical devices are approved under the Pharmaceuticals and Medical Devices (PMD) Act. In emergencies, such as the COVID-19 pandemic, there is no system for approval of pharmaceuticals at the stage of presumed efficacy in Japan, as is the case with the Emergency Use Authorization (EUA) system in the United States. Currently, newly developed drugs have been approved under the framework of "special approval". This system is applicable only when the following three conditions are met: *i*) The drug is urgently needed to prevent the spread of a disease that may seriously affect the lives and health of the Japanese people; *ii*) There are no other alternative measures available; and *iii*) The quality of the drug is systematically guaranteed on a par with that in Japan.

The product must already be approved for manufacture and sale in a foreign country. In the current outbreak, foreign countries in this condition were defined as the United States, the United Kingdom, Canada, Germany, and France. The absence of such an emergency approval mechanism is believed to have been a stumbling block to the rapid availability of urgently needed drugs (*4*). Pfizer's COVID-19 vaccine was approved for emergency use in the United States on December 11, 2020, but was granted special exception approval in Japan on February 14, 2021. In light of this, a draft amendment to the PMD Act to allow for emergency regulatory approvals was submitted to the Diet on March 1, 2022, for deliberation (*5*). The outline of the revised law is as follows: *i*) The drug must be used urgently to prevent the spread of a disease or other health hazard that may seriously affect the lives and health of the public; *ii*) No other alternative means exist. However, a time limit is given for approval, and confirmation of efficacy is required within the time limit, or the approval will be revoked. Reports of adverse reactions are collected under the existing reporting system and compensated under the Adverse Reaction Relief System.

If this emergency approval legislation is enacted, it will allow for more rapid use of drugs with

presumable efficacy under the system. However vaccine development challenges remains a response to the COVID-19 pandemic. First, since several vaccines and therapeutics have already been approved under the notable exception, alternative methods being established would not meet the requirements for emergency approval. Second, the evaluation of efficacy based on presumption would need to be executed with considerable caution. If efficacy is not confirmed after emergency approval, the effort in making the drug widely available would have been wasted, and the issue of adverse reactions may be brought into greater focus. There is also a risk that this could lead to a loss of confidence in the regulatory system and science, adversely affecting the credibility of drugs approved under other standard systems.

In the strategy for strengthening vaccine development and production systems approved by the Cabinet last June (*6*), it was noted that there was a critical lack of investment in the vaccine sector, as a long-term, ongoing national strategy to be implemented by the government as a whole. In addition, the goal is to ensure that the necessary financial resources are secured on a continuous and stable basis in regular times, including flexible and rapid funding in times of emergency, arrangements on how funds are allocated, research and development expenses, equipment maintenance expenses, and the purchase of vaccines in development. In these ways, measures are being taken to address the delay in vaccine development in Japan experienced during the COVID-19 pandemic against the next pandemic that is sure to occur in the future. Continuous monitoring is required to ensure that the stakeholders in vaccine development can steadily implement improvements based on the plan.

Funding: None.

Conflict of Interest: The author has no conflicts of interest to disclose.

References

1. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020, 2020. *https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020* (accessed March 14, 2022)
2. World Health Organization. COVID-19 vaccines WHO EUL issued, 2022. *https://extranet.who.int/pqweb/vaccines/vaccinescovid-19-vaccine-eul-issued* (accessed March 14, 2022)
3. ClinicalTrials.gov [Internet]. National Library of Medicine (US). Identifier NCT05212948, A Study of S-268019 for the Prevention of COVID-19. *https://clinicaltrials.gov/ct2/show/NCT05212948* (accessed March 14, 2022)
4. Ministry of Health, Labour and Welfare. Enforcement of the Cabinet Order for Partial Revision of the PMD Act Implementation Order, Notice of May 2, 2020. *https://www.mhlw.go.jp/content/000627465.pdf* (accessed March 14, 2022) (in Japanese)
5. Ministry of Health, Labour and Welfare. The 208th Congress of Japan Presenting Legal Cases. *https://www.mhlw.go.jp/stf/topics/bukyoku/soumu/houritu/208.html* (accessed March 14, 2022) (in Japanese)
6. Prime Minister of Japan and the Cabinet. Strategy to strengthen vaccine development and production system, 2021. *https://www.kantei.go.jp/jp/singi/kenkouiryou/tyousakai/dai28/siryou1-2.pdf* (accessed March 14, 2022) (in Japanese)

Received March 17, 2022; Revised April 4, 2022; Accepted April 6, 2022.

Released online in J-STAGE as advance publication April 9, 2022.

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(*As of January 2022*)

Global Health & Medicine
National Center for Global Health and Medicine,
1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan
URL: *www.globalhealthmedicine.com*
E-mail: *office@globalhealthmedicine.com*

Print ISSN: 2434-9186 Online ISSN: 2434-9194

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Global Health & Medicine

Volume 1, Number 1
October, 2019

www.globalhealthmedicine.com