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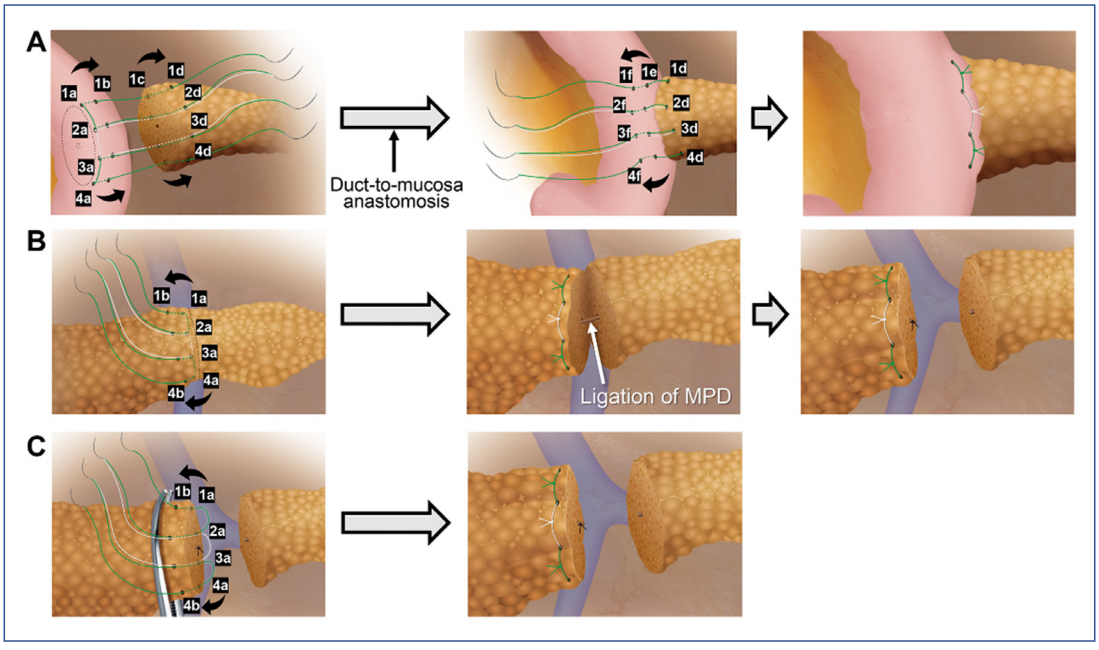

The four-needle three-loop suture device in pancreaticoduodenectomy and distal pancreatectomy.
(Page 227)

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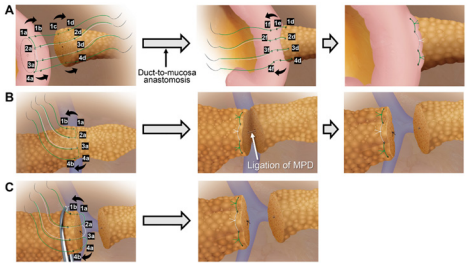

Methods of using the four-needle three-loop suture device in PD and DP. (A): In pancreatojejunostomy during PD, the first needle is used to suture the seromuscular layer on the posterior jejunal wall (1a to 1b) and then the pancreatic stump from the posterior to ventral aspects (1c to 1d). The remaining needles are respectively used in a similar manner (2a to 2d, 3a to 3d, and 4a to 4d). Following duct-to-mucosa anastomosis of the MPD, the seromuscular layer of the anterior jejunal wall is sutured with the first needle (1e to 1f), followed by caudal anastomoses with use of the remaining three needles. Finally, the needles are detached and the three loop threads are respectively ligated. **(B)**: In DP, the future pancreatic remnant is sutured from the dorsal to ventral aspects using the four needles respectively (1a to 1b, 2a to 2b, 3a to 3b, and 4a to 4b), usually from the cranial side and caudal side. After gentle ligation of the three loops, the pancreatic parenchyma is transected to identify and ligate the MPD independently. **(C)**: Another use of the three-loop suture device in DP. This device can also be used to reinforce the pancreatic stump after parenchymal transection by suturing the pancreas, usually from the dorsal to ventral aspects, with the four needles. PD, pancreaticoduodenectomy; DP, distal pancreatectomy; MPD, main pancreatic duct. (Page 227).

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Evaluation of the representativeness of data in the COVID-19 Registry Japan during the first six waves of the epidemic

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Abstract: The COVID-19 Registry Japan (COVIREGI-JP), a registry of patients hospitalized with coronavirus disease (COVID-19), contains the largest national COVID-19 inpatient population. Since COVIREGI-JP invites voluntary participation by facilities, selection bias is inevitable. The current study examined the representativeness of COVIREGI-JP data in comparison to open-source national data. The number of infections and deaths among hospitalized COVID-19 patients in COVIREGI-JP were compared to those in national data recorded during the six waves of the COVID-19 epidemic until March 6, 2022. During the period studied, patients in COVIREGI-JP represented 1% of the total COVID-19 cases according to national data; the proportion was high during the first wave (32.7%) and tended to decrease, especially after the fourth wave. The overall proportion of patients from each region varied from 0.8% to 2.5%, but case fatality rates in COVIREGI-JP tended to be higher than those in the national data, with the exception of a few waves, in several regions. The difference was smallest during the first wave. Although COVIREGI-JP consistently registered cases from all regions of the country, the proportion tended to decline after the beginning of the epidemic. Given the epidemiological persistence and the ever-changing epidemiology of COVID-19, continued case registration and data utilization in COVIREGI-JP is desirable, although selection bias in COVIREGI-JP registration of cases should be carefully interpreted.

***Keywords*:** COVIREGI-JP, epidemiology of COVID-19, pandemic, selection bias

Introduction

The number of cumulative cases and hospitalizations due to coronavirus disease (COVID-19) continues to increase in Japan (*1,2*). The COVID-19 Registry Japan (COVIREGI-JP), a registry of hospitalized COVID-19 patients, was started on March 2, 2020 and has, with the cooperation of various facilities, accumulated detailed information on hospitalized COVID-19 patients in Japan since the beginning of the COVID-19 pandemic (*3*). Detailed clinical information (clinical epidemiology, comorbidities, vital signs, pharmacotherapy and supportive care, complications, detailed prognosis, laboratory findings, *etc*.) that is unavailable in publicly accessible government-reported data is available in COVIREGI-JP and has been utilized in various studies as well as for public policy formulation and implementation (*4-6*). Moreover, some of the published data have been used to formulate the national COVID-19 treatment guidelines (*7-9*).

The fact that COVIREGI-JP contains the largest COVID-19 inpatient population in the country is a major advantage. However, various limitations of COVIREGI-JP data have previously been discussed (*10*), and especially the inevitable selection bias, because COVIREGI-JP is a voluntary registry that involves the participation of many facilities. One needs to understand the biases the affect COVIREGI-JP data before interpreting and utilizing the data from this registry. This review has examined the representativeness of COVIREGI-JP data in comparison to open-source national data.

Study design

Data sets

This retrospective study used data aggregated in COVIREGI-JP and the national open database (*2*). To determine the extent to which the COVIREGI data are nationally representative of Japan, the number of infections and deaths among hospitalized patients

registered in COVIREGI-JP were compared to those in Japan (*i.e*., national data). Moreover, the total number of hospitals (*11*) and the facilities participating in COVIREGI-JP were summarized. For region-wise comparisons, 10 categories were obtained from the existing classifications. In this study, Tokyo and Osaka were not included in each regional category, but rather, were separately accounted for in 12 regions (*12*).

The details of COVIREGI-JP have been described previously (*3,10*). To ascertain the number of patients and deaths, data on patients for whom major items, including outcome at discharge, had been entered and finalized (*i.e.*, these items were finalized and the facility was unable to make any further modifications) by March 6, 2022 were used. National data were the data released by the Ministry of Health, Labour, and Welfare (MHLW) of Japan prior to March 7, 2022.

Waves of the COVID-19 epidemic

The waves of the COVID-19 epidemic were defined as follows using the admission date: *i*) first wave (Wave 1), January 1–May 31, 2020; *ii*) second wave (Wave 2), June 1–October 31, 2020; *iii*) third wave (Wave 3), November 1, 2020–March 31, 2021; *iv*) fourth wave (Wave 4), April 1–June 30, 2021; *v*) fifth wave (Wave 5), July 1–November 30, 2021; and *vi*) sixth wave (Wave 6), November 1, 2021-March 6, 2022.

For cases where the date of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) test was later than the date of admission (*e.g.*, in hospital-acquired COVID-19 cases), the test date was used instead of the admission date.

Statistical analysis

Data were analyzed descriptively and calculated for proportions, differences, and ratios. Differences in the mortality between the national and regional data were determined in two data sets (national data on total infections and COVIREGI-JP data). In the national data, the total value for each area did not match the national value due to a problem with the original data source. All statistical analyses were performed using R, version 3.5.1 (R Core Team, Vienna, Austria) and Microsoft Excel (2019).

Statistical analysis

Ethical review was considered unnecessary for this study because only aggregate data were used.

Characteristics, regional divisions, and the region-wise proportion of patients in COVIREGI-JP

Figure 1 separately shows the epi-curves of the number of infections reported nationwide and those of COVIREGI-JP registrations. Data in COVIREGI-JP were consistently registered although fewer data tended to be registered after the fourth wave, and the number of registrations during the sixth wave of the epidemic was lower than that during other waves.

Figure 2 shows a map of the regional divisions and the region-wise proportion of patients (the number of COVIREGI-JP registrants/number of persons infected with SARS-CoV-2- according to national data). Patients registered in COVIREGI-JP accounted for 1% of the number of total SARS-CoV-2 infections according to national data during the period studied; this figure was initially high during the first wave (32.7%) and then tended to decrease.

The overall proportion of patients in each region varied from 0.8% (Tokyo, Kanto, Osaka) to 2.5% (Tohoku) but followed almost the same trend as the waves of the epidemic progressed. In Shikoku, an increase in the proportion of patients was noted during the third wave compared to the second wave.

Number of COVID-19 cases and deaths according to national data and COVIREGI-JP

Table 1a (Online Data, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=50*) shows the number of cases and deaths according to national data and COVIREGI-JP data. The national data included 5,273,350 infections and 24,927 deaths; COVIREGI-JP included 54,350 cases and 2,512 deaths. In the national data, the largest number of cases was in Kanto (n = 1,354,178; 25.7% of all cases), followed by Tokyo (n = 1,056,983; 20.0%) and Osaka (n = 677,489; 12.8%). The Kanto region accounted for the largest number of deaths (5,398, or 21.7% of the total), followed by Osaka with 4,105 deaths (16.5%) and Tokyo with 3,809 deaths (15.3%).

In COVIREGI-JP data, the largest number of registrations were from the Kanto region (n = 10,941; 20.1% of all COVIREGI-JPs), followed by Tokyo (n = 8,659; 15.9%) and Kinki (n = 6,714; 12.4%). Analysis of COVIREGI-JP data indicated that the largest number of deaths occurred in Kanto (n = 575; 22.9%), followed by Tokyo (n = 395; 15.7%) and Osaka (n = 361; 14.4%).

Table 1b (Online Data, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=50*) shows the ratio of case fatality rates for COVIREGI-JP data compared to that in national data. Overall, case fatality rates in COVIREGI-JP tended to be higher (overall, 1.4 times higher) than those in the national data, and the difference was smallest during the first wave. However, the case fatality rate in the national data was higher than that in COVIREGI-JP in Hokkaido, Tokai, and Osaka during the first wave and in Hokuriku during the fifth wave.

Table 1c (Online Data, *https://www.*

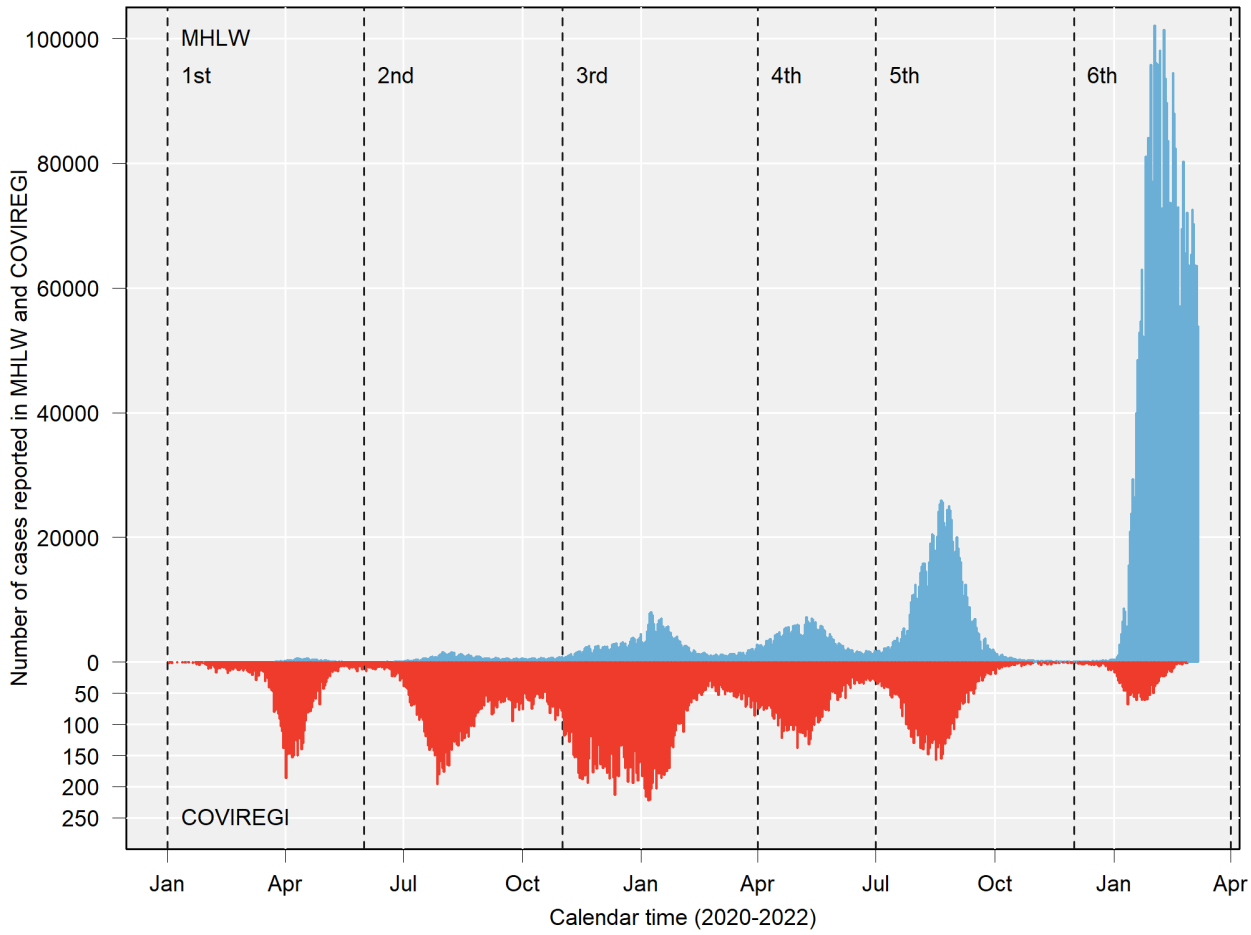

Figure 1. Epi-curves of the number of infections nationwide and the number of COVIREGI registrations.

globalhealthmedicine.com/site/supplementaldata.html?ID=50) shows the difference in the national and regional case fatality rates between the national data and COVIREGI-JP data. Positive values indicate that the case fatality rate in the region is higher than the national rate, whereas negative values indicate a lower rate. In most regions, the direction of the positive and negative values was consistent for both national and COVIREGI-JP data; however, there was a divergence in the overall rates in the Kanto, Kinki, and Kyushu regions when all waves were evaluated together. Moreover, there are some areas that diverged during each wave, and, there were five regions that diverged from each other during Wave 3.

Number of facilities that registered cases during the six waves and the number of patients from facilities that continued to register cases

Table 2 (Online Data, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=50*) shows the number of facilities that registered cases during each wave and the number of patients from facilities that continued to register cases throughout the six waves. However, the number of facilities decreased significantly after the fourth wave. The percentage of patients registered by the 33 facilities that continuously registered cases during the six waves was minimal during the first wave and gradually increased, especially after the fourth wave.

The representativeness of COVIREGI-JP in regions and the six waves of the epidemic

This review summarizes the representativeness of COVIREGI-JP from two perspectives: the region and each wave of the epidemic. Although the representativeness of COVIREGI-JP up to the third wave has previously been examined (*13*), this is the first time that the representativeness of COVIREGI-JP up to Wave 6 has been examined.

Patients were consistently registered in COVIREGI-JP, although a decrease was noted after the fourth wave. In waves with a large number of cases, such as waves 5 or 6, the proportion of patients decreased significantly. There were few COVIREGI-JP registrations during the sixth wave because the epidemic was still in progress, and the number of cases itself increased steeply, leading to a large decline in the proportion of patients. COVIREGI-JP commenced registrations on March 2, 2020, and permitted retrospective data entry. One

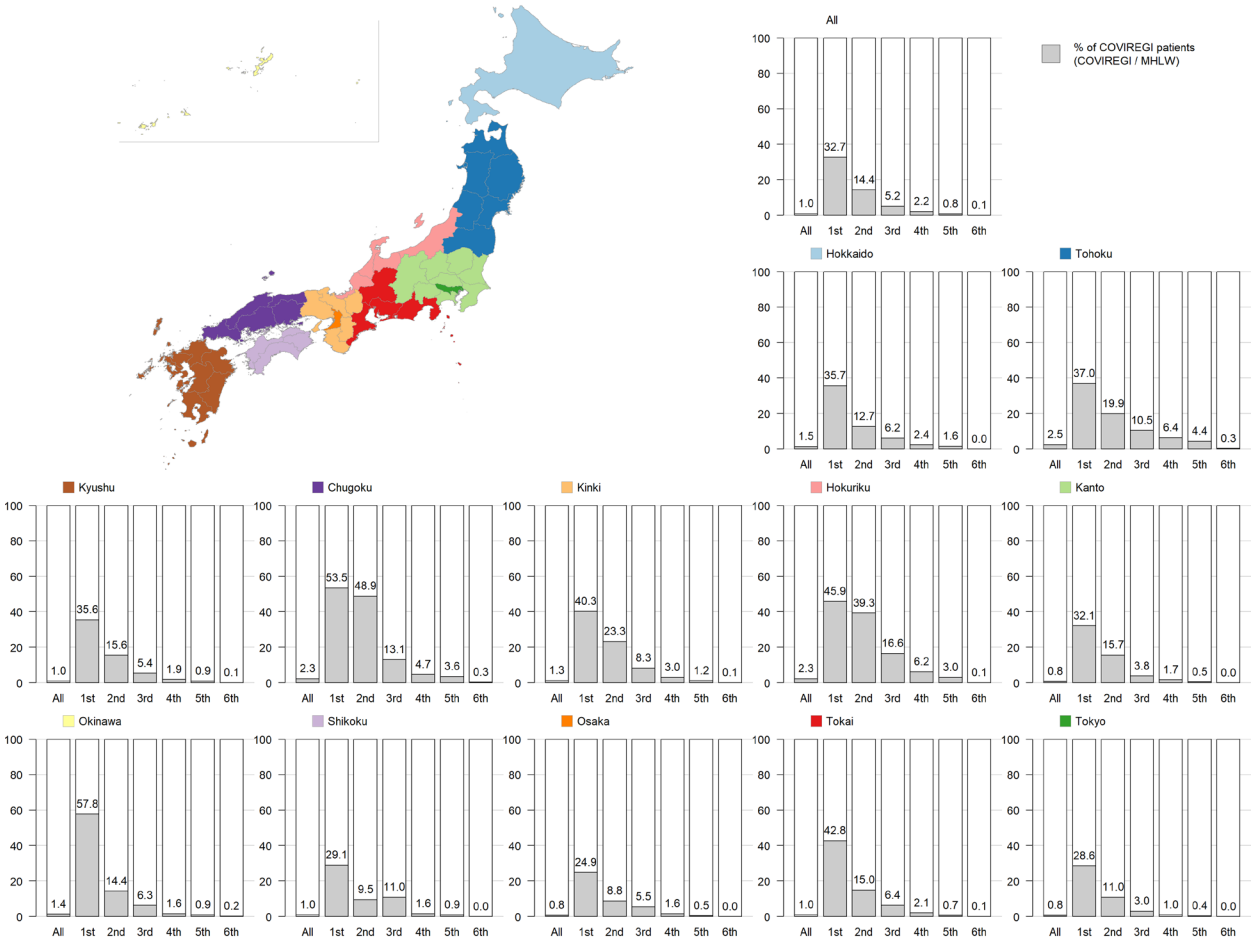

Figure 2. Map of the regional divisions and the region-wise proportion of patients. Proportion of patients = Number of COVIREGI-JP registrants / Number of COVID-19 cases according to national data).

factor that could have affected the number of cases was the reduction in the funding to each participating facility for each patient registered after November 28, 2020 as well as the termination of funding on April 1, 2021. The aforementioned factors were likely to have reduced the number of cases registered after the fourth wave. In addition, medical facilities were encouraged to participate in COVIREGI-JP when they contacted the MHLW to requisition favipiravir, and this may have facilitated case registration. The MHLW provision for the use of favipiravir for COVID-19 ended on December 28, 2021.The current benefits of case registration in COVIREGI-JP by participating facilities include the return of institutional data, the ability to propose and conduct research using multicenter data (if a certain number of patients are registered by the facility), and the contribution to COVID-19 research and to public health through the use as public data. Nonetheless, registration of cases is a manual process and places a heavy burden on facilities.

The importance of and challenges with continuous data registration

Although a registry system for emerging infectious diseases is essential for the accumulation of real-world data and clinico-epidemiological national evaluation outside of fully controlled conditions, such as in interventional studies, the role of such registries is likely to change over time after the beginning of an epidemic. For example, studies to understand the clinico-epidemiological characteristics and to prioritize the measures of an epidemic should be conducted as soon as possible in the early stages of the epidemic. In contrast, more detailed studies along the lines of research questions are often considered in the later stages as the epidemic continues. As in the case of COVID-19, continuous data registration is important in a situation where various conditions are continually changing, such as vaccine coverage, the prevalence of variants, advances in treatment, and policy changes. Case report forms need to be revised to ascertain these changes while maintaining a balance with data continuity. Some facilities have continued to register cases after the termination of funding for case registration, and such data are very valuable to reducing selection bias during each wave in terms of continuity at the same facility. For the continuity of the registry, financial support commensurate with the registration effort, automated entry, at least partially, to reduce

registration effort, and resources for quality control are important not just in the early stages of the epidemic.

One of the reasons for evaluating the representativeness of COVIREGI-JP data using the approaches in this study is that the cumulative number of hospitalized patients is not publicly available in Japan. Although the number of cases requiring hospitalization is publicly available, this number actually includes patients who were treated at home. Moreover, the number of cases requiring hospitalization includes diverse factors besides disease severity and the patient's underlying condition (*e.g.,* occupancy of beds by patients with COVID-19 and municipal policies) and is not uniform. Therefore, this study used the number of infected patients and the number of deaths, which are less susceptible to such factors, for comparison.

COVIREGI-JP registered cases from all regions, but the regions with a low proportion of patients (Tokyo, Kanto, and Osaka) had the highest number of infected cases. An inversion in the ratio of the case fatality rate (the case fatality rate of the entire infected population was higher than the case fatality rate in COVIREGI-JP) was noted, and especially during Wave 1, when hospitalization was basically recommended for all cases, including mild ones (*14*). This may have contributed, at least partially, to the fact that registration by participating facilities was biased toward milder cases within each region. The overall case fatality rate ratio of COVIREGI-JP to that of the infected patients nationwide was lowest during this period.

In the analysis of the differences in case fatality rates between the national and regional data in the national data and COVIREGI-JP data sources, there were several regions where the results from COVIREGI-JP and national data diverged. The direction of the discrepancies varied and was not consistent, possibly reflecting the selection bias of COVIREGI-JP in these regions. Despite the decrease in the proportion of patients after Wave 4, divergence did not tend to increase. In addition, although Tokyo, Osaka, and other areas had a large number of infected cases, no divergence was noted. In the regions where the results diverged, that phenomenon was thought to reflect the lack of parallelism in terms of disease severity among the overall infected population and among patients registered in COVIREGI-JP.

A limitation of this study is that the data from Wave 6 were included to provide the most up-to-date data. However, because the epidemic is ongoing and the fact that data entry was incomplete, the analysis in this study may have missed more than a few cases from Wave 6. Therefore, the results of this analysis do not adequately represent the trends during Wave 6. Moreover, the prefecture in the national data and the prefecture in COVIREGI-JP may not match in some cases (*e.g.*, when the patient was admitted to a medical facility far from his or her place of residence). The number of hospitals is based on published data (*11*), but it may not indicate the current number. Due to differences in the timing of data download and regional classifications, there are minor discrepancies in the data from a previous study (*13*) up to the third wave that were included in the current study.

Conclusion

The current study reviewed the representativeness of COVIREGI-JP data; although COVIREGI-JP consistently registered cases from all regions of the country, the proportion of patients tended to decline compared to the beginning of the epidemic. In light of the epidemic's persistence and the ever-changing epidemiology of COVID-19, continued case registration and data utilization in COVIREGI-JP is desirable, although selection bias in COVIREGI-JP registration of cases should be carefully interpreted.

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Conflict of Interest: There is no conflict of interest to disclose.

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The patient-centered diabetes management during the COVID-19 pandemic

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Abstract: Since December 2019, in the fight against the coronavirus disease 2019 (COVID-19) pandemic, we observed that glycemic control in people with diabetes is easily affected by lifestyle changes. To maintain a good health condition, a patient-centered approach with mental support and close monitoring is required. For these, telemedicine and online continuous glucose monitoring (CGM), are effective systems. Therefore, based on our experience during the two-year period, we reviewed the literature for appropriate actions required for the management of diabetes to prevent COVID-19 infection and avoid unfavorable outcomes in COVID-19 cases. Once infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there is a high risk of a poor prognosis in patients with diabetes. Glucocorticoid therapy in severe COVID-19 cases leads to further hyperglycemia. Since good glycemic control has been shown to improve outcomes, strict glycemic control using CGM is recommended. Using CGM data, insulin can be adequately titrated without causing hypoglycemia, and remote data monitoring can reduce the risk of infection for health care professionals, by reducing the frequency of patient contact. Among patients with COVID-19, some are found to have newly-diagnosed diabetes at admission. Those newly diagnosed patients present with a higher risk of poor prognosis compared to those with pre-existing diabetes. Therefore, glycemic status should be evaluated in all patients with COVID-19 admitted to hospitals.

Keywords: glycemic control, lifestyle change, prognosis, insulin, continuous glucose monitoring (CGM)

Introduction

During the COVID-19 pandemic, the management of diabetes has become a challenging task in some patients partly due to lifestyle changes imposed by the pandemic. Studies have shown that patients with diabetes in general present with excess mortality due to infectious diseases and their complications (*1*). In patients with COVID-19 and diabetes, if their glycemic control is worsened, they may have a poor prognosis and high mortality. Based on the reports thus far, diabetes does not appear to increase the risk of contracting SARS-CoV; however, when infected, the risk of hospitalization, intensive care unit (ICU) admission, and mortality increase (*2,3*). When patients with diabetes are managed with good glycemic control for a long period, the risk of developing severe COVID-19 is reduced (*4*).

In this review, based on our experience of the last two years and literature search, we describe the management of diabetes, to prevent COVID-19 infection and avoid unfavorable outcomes in COVID-19 cases.

Diabetes management taking into consideration the lifestyle changes during the COVID-19 pandemic

Since the onset of COVID-19 in 2019, the pandemic has caused changes in lifestyle, with people experiencing lockdown and teleworking. Changes in behavioral patterns had a significant impact on the self-management of diabetes. Due to lifestyle restrictions, body weight gain, reduced physical activity, and changes in eating habits affected glycemic control (*5-9*). Table 1 summarizes the results of past studies conducted to monitor changes in hemoglobin A1c (HbA1c) and body weight before and during the COVID-19 pandemic.

The effects of lifestyle changes on glycemic control during the COVID-19 pandemic in patients with diabetes (n = 321) were studied at our institution (*5*). The overall HbA1c levels showed no significant difference before and during the COVID-19 pandemic. However, although the number was small, there were patients with extreme deterioration in HbA1c level (median [interquartile range]; 0.1 [-0.30, 0.37]) who required adjustment and intensification of their diabetes management. Remote working was associated with an increase in HbA1c levels, accompanied by reduced physical activity and exercise. Notably, people living with companion animals such as dogs, who had unchanged regular walking habits, maintained their glycemic control.

Table 1. Effect of lifestyle changes before and during the COVID-19 pandemic

			Before COVID-19 pandemic		During COVID-19 pandemic	
Terakawa A, *et al*., J Diabetes Investig. 2022 (*5*)			Mean	SD	Mean	SD
n = 321	HbA1c (%)		7.13	0.98	7.18	0.98
	BW (kg)		69.2	14.9	68.9	14.9
	BMI (kg/m^2)		25.6	4.5	25.4	4.5
			Before declaration of state of emergency		After declaration of state of emergency	
Tanaka N, *et al*., J Diabetes Investig. 2021 (*6*)			Median	IQR	Median	IQR
n = 463	HbA1c (%)		7.5	1.3	7.3	1.3
	BW (kg)		68.7	18.9	68.5	18.4
			Before lockdown		During lockdown	
Ruissen MM, *et al*., BMJ Open Diabetes Res Care. 2021 (*8*)			Mean	SD	Mean	SD
n = 435[#]	HbA1c (%)		7.68	1.2	7.52	1.1
			Pre-lockdown		Post-lockdown	
Sanker P, *et al*., Diabetes Metab Syndr. 2020 (*10*)			Mean	SD	Mean	SD
n = 110	HbA1c (%)		8.2	1.3	8.12	1.6
	BW (kg)		71.5	14.8	71.8	13.6
			Pre-lockdown		Post-lockdown	
Khare J, *et al*., Prim Care Diabetes. 2021 (*9*)			Mean	Range	Mean	Range
n = 307	HbA1c (%)	M	7.85	6.1-13.0	8.37[*]	6.0-15.0
		F	8.03	6.3-15.0	8.52[*]	6.6-15.0
	BW (kg)	M	76.8	55-108	77.5	55-106
		F	68.9	54-110	70.1	57-111

BMI, body mass index; BW, body weight; COVID-19, coronavirus diseases 2019; IQR, interquartile range; SD, standard deviation; M, male; F, female. [#]Analysis was conducted in patients with type 1 diabetes. [*]$p < 0.05$.

In another study on Japanese patients with diabetes (*n* = 463), glycemic control was compared before and after the state of emergency declared by the Japanese government in the Spring of 2020 (*6*). Similar to the previous study, there were no changes in the median HbA1c level; however, the study showed that body weight gain was associated with HbA1c increase. In younger adults (< 65 years), changes in eating habits increased body weight and aggravated HbA1c levels. In older adults (≥ 65 years), reduced daily activity was associated with decreased body weight indicating loss of muscle mass.

In a study conducted in the Netherlands (*n* = 435), lockdown measures during the COVID-19 pandemic resulted in body weight gain, reduced exercise, and increased stress and anxiety in patients with diabetes (*8*). Despite these changes, no deterioration in overall glycemic control was observed. The study emphasized that increased stress is associated with difficulty in glycemic control. In another study conducted in South India on patients with type 2 diabetes (*n* = 110), the lockdown did not cause changes in glycemic control and body weight; however, increased psychosocial stress was observed, especially in women and older adults (*10*).

Psychological well-being in people with diabetes has been increasingly recognized as an important factor in maintaining better glycemic control (*11,12*). Psychological stress can simultaneously be a risk factor for the onset of metabolic disorder and a prognostic factor in diabetes. Although there are recommendations for the management of diabetes during the COVID-19 pandemic in terms of glycemic control targets and maintaining healthy lifestyles (*13,14*), they are not focused on psychological issues. The healthcare professionals need to design an approach to reduce psychosocial stress during pandemics, as well as manage diabetic conditions.

In the previous studies, there were no prominent changes in glycemic control during the COVID-19 pandemic; however, other reports have shown an increase in HbA1c levels (*9,15*). The setting of each study, including the duration of lockdown, medical conditions during the pandemic, and ethnicity, need to be considered when comparing theses contrasting

Table 2. Glycemic control and clinical outcomes in patient with COVID-19 and diabetes

Zhu L, *et al*., Cell Metab, 2020 (*20*)	Well controlled (*n* = 282) BG 70-180 mg/dL	Poorly controlled (*n* = 528) BG >180 mg/dL[1)]	*p* value
BG (IQR) (mg/dL)	115 (94-135)	196 (137-257)	< 0.001
In-hospital management			
Systemic corticosteroids, *n* (%)	57 (20.2%)	184 (34.9%)	< 0.001
Invasive ventilation, *n* (%)	0 (0.0%)	22 (4.2 %)	0.001
Well controlled *vs.* Poorly controlled	HR (95% CI)[2)]		
All-cause mortality	0.13 (0.04, 0.44)		< 0.001

Bode B, *et al*., J Diabetes Sci Technol, 2020 (*22*)	Diabetes and/or uncontrolled hyperglycemia[3)] (*n* = 184)	No diabetes and/or uncontrolled hyperglycemia (*n* = 386)	*p* value
Mean HbA1c (%)	8.5 ± 2.3	5.9 ± 0.51	< 0.001
Mean glucose (mg/dL)	178 ± 72.9	110.9 ± 22.6	< 0.001
Died in hospital	53 (28.8%)	24 (6.2%)	< 0.001
	Diabetes by HbA1c criteria (*n* = 88)	Uncontrolled hyperglycemia[3)] by BG (*n* = 96)	
Mean HbA1c (%)	9.1 ± 2.3	5.9 ± 0.4	< 0.001
Mean glucose (mg/dL)	177.8 ± 64.5	178.5 ± 78.9	0.704
Died in hospital	13 (14.8%)	40 (41.7%)	< 0.001

[1)]2 hr postprandial BG. [2)]Adjusted variables included age, gender, severity of COVID-19 and comorbidities. [3)]Uncontrolled hyperglycemia, defined as two or more BG measurements > 180 mg/dL in a 24-hour period with an HbA1c < 6.5% or no HbA1c available. BG, blood glucose; IQR, interquartile range; CI, confidence interval; HR, hazard ratio.

results. One study showed that the duration of lockdown was directly proportional to the worsening of glycemic control and diabetes-related complications (*15*). Healthcare professionals should be aware of certain high-risk cases, particularly patients with diabetes who require close monitoring, due to lifestyle changes that resulted in body weight increase, reduced exercise, and psychological stress, to prevent aggravation of the glycemic states. Telemedicine is a good strategy for maintaining communication with patients, for close follow-up, especially during stay-at-home periods. Recently, blood glucose monitoring (BGM) and continuous glucose monitoring (CGM) data can be stored on the web-based server, enabling remote monitoring of glycemic control. We need a patient-centered approach by a multidisciplinary medical team using these remote monitoring systems whenever necessary, to maintain healthy lifestyle practices and mental health under the restrictions of the COVID-19 pandemic.

Diabetes management under COVID-19 infection

As reported, there is a higher proportion of patients with diabetes among severe and ICU-admitted cases of COVID-19 than in mild cases (*16-18*). The cause of the poor prognosis can be multifactorial. In addition to hyperglycemia, older age, obesity, hypertension, cardiovascular disease, renal dysfunction, and pro-inflammatory and pro-coagulative states are considered to contribute to increased mortality and morbidity due to COVID-19 (*19*). In patients with diabetes comorbidity, any of these factors should be considered to reduce the risk of COVID-19.

Hyperglycemia is one of the main causes of poor prognosis and high mortality rate due to COVID-19 (*20-22*). Although diabetes is a risk factor, a recent study showed that when hyperglycemia is well-controlled, the risk for worse outcome can be reduced (Table 2) (*20*). A retrospective study conducted in China showed that the mortality rate was significantly lower in patients with well-controlled blood glucose levels (within 70-180 mg/dL) than in those with poorly-controlled blood glucose levels during hospitalization, (adjusted hazard ratio [HR] 0.14). This result suggests that even under diabetic conditions, well-controlled blood glucose levels may improve outcomes in patients with COVID-19.

Another retrospective study conducted in the U.S. showed that in-hospital mortality was significantly higher in people with diabetes and/or with uncontrolled hyperglycemia than in people without diabetes (Table 2) (*22*). Uncontrolled hyperglycemia is defined as two or more blood glucose measurements above 180 mg/dL in a 24-hour period, with a HbA1c less than 6.5%. In a subset analysis, patients with uncontrolled hyperglycemia had a particularly high mortality rate. This raises the important question of whether acute hyperglycemia can be a risk factor for poor outcomes in patients with COVID-19. The data show that better glycemic management will improve the outcome; therefore, close monitoring of blood glucose levels is essential in all patients with

COVID-19, regardless of their diabetes status.

These results provide us with important insights that must not be overlooked. In the COVID-19 ward, provision of care is challenging, with limited numbers of carers and protective equipment. Contact carers and healthcare professionals with patients need to be minimized. Under these constrained conditions, patients with no history of diabetes may not have their glucose levels frequently monitored. In the treatment of COVID-19, glucocorticoids are used in severe cases, which frequently causes acute hyperglycemia even in non-diabetic subjects. The results of previous studies strongly suggest that good glycemic control, below 180 mg/dL whenever possible, should be aimed to attain a better outcome in all patients.

In order to achieve this goal, CGM is an effective tool. Recent CGM can be remotely monitored, and frequent visits to patients and frequent point-of-care glucose testing can be safely minimized (*23*). In our institution, intermittently scanned CGM (isCGM) is used for severe COVID-19 patients with diabetes who require methylprednisolone therapy. The insulin dose was titrated as appropriate, without causing hypoglycemia, and better glycemic control was achieved (unpublished data). The daily glucose trend was remotely monitored by health care professionals, enabling a reduced frequency of patient contact. However, the use of the CGM system in COVID-19 wards is still limited to certain institutions and has not yet become widespread. Thus, there is an urgent need to develop a system in which any institution can easily introduce the CGM system to patients under this COVID-19 pandemic.

New-onset diabetes in COVID-19 patients

During the COVID-19 pandemic, a large number of COVID-19 patients developed diabetic ketoacidosis (DKA), ketosis, or hyperglycemic hyperosmolar syndrome (HHS). Data shows that DKA and combined DKA/HHS in patients with COVID-19 present with poor prognosis and high mortality rate (*24*). These metabolic disturbances may be caused by severe insulin resistance under viral infection combined with decreased insulin secretion due to b-cell dysfunction. Many reports have suggested a link between COVID-19 and diabetes (*13,25,26*).

The potential mechanism of metabolic disturbances in COVID-19 have been postulated. The major pathogenic mechanisms are systemic inflammation and immunological dysregulation induced by SARS-CoV-2 infection, which induces acute respiratory distress syndrome (ARDS), insulin resistance, hyperglycemia, vascular endothelial damage, thromboembolism, cardiovascular events, and disseminated intravascular coagulopathy (DIC) (*25*). In regard to metabolic disorder, renin-angiotensin system (RAS) is considered to play an important role in pancreatic b-cell dysfunction (*27*). In the diabetic state, the RAS is activated in the pancreas, and angiotensin II (AngII), downstream of the RAS, is strongly associated with islet dysfunction in experimental models. Angiotensin-converting enzyme 2 (ACE2) promotes the degradation of AngII into angiotensin (1-7) [Ang(1-7)] (*8,9*), and Ang(1-7) acts through the G protein-coupled receptor Mas and opposes many of the actions of AngII (*28,29*). The ACE2/Ang(1-7)/Mas axis serves as a protective and negative regulator of RAS (*30*). In COVID-19, ACE2 functions as an entry receptor for SARS-CoV-2 (*31*), and the infection breaks down the function of the ACE2/Ang(1-7)/Mas axis as a negative regulator of the RAS. However, whether this causes direct impact on pancreatic islets is still not clear and evidence is scant (*32,33*). There are discussions that this may not be the central pathogenic feature of COVID-19, and further study is awaited.

The direct effect of SARS-CoV-2 on b-cell function not only causes the deterioration of metabolic control in people with diabetes, but it is also speculated to lead to the development of new-onset diabetes (*19*). In a survey conducted at our institution, among the 62 patients with COVID-19 and diabetes, 19 (30.6 %) were newly-diagnosed at admission (*34*). It must be noted that in these patients with newly-diagnosed diabetes, plasma blood glucose levels were significantly higher three days after admission, and the severity of COVID-19 was significantly higher than that in patients with pre-existing diabetes. In another study of 102 patients with COVID-19 and diabetes, 21 (20.6%) were newly diagnosed with diabetes on admission (*35*). In a meta-analysis of eight studies, more than 3700 patients with COVID-19 and diabetes were included, and 14.4% were newly-diagnosed diabetes cases (*36*). In both studies, patients with newly diagnosed diabetes had higher blood glucose levels. These results strongly suggests that patients with COVID-19 need to be monitored for the presence of hyperglycemia and diabetes at admission, and newly diagnosed diabetes should be managed closely to prevent hyperglycemia and resultant worse outcomes.

Conclusion

We emphasize that patients with diabetes are vulnerable to lifestyle changes, which were observed during the current COVID-19 pandemic. A patient-centered approach is essential. Mental support, telemedicine, and the use of CGM to remotely monitor glycemic changes can be an effective tool to maintain healthy life styles and better glycemic control. Although diabetes is a risk factor for poor prognosis in patients with COVID-19, good glycemic management will lead to better outcomes. In the COVID-19 ward, CGM system is an effective and safe measure to maintain a balance between close glucose monitoring and adequate patient contact frequencies. Lastly, we must be aware that COVID-19 can deteriorate the metabolic system, and some cases

of newly-diagnosed diabetes occur in patients with COVID-19. Blood glucose levels should be examined and the state of diabetes should be carefully evaluated in all patients with COVID-19 at admission, so that treatment for hyperglycemia can be started without unnecessary delay.

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No increased risk of hepatocellular carcinoma after eradication of hepatitis C virus by direct-acting antivirals, compared with interferon-based therapy

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Abstract: It is well-known that sustained virological response (SVR) by interferon (IFN)-based therapy against hepatitis C virus (HCV) infection reduced the incidence of hepatocellular carcinoma (HCC). However, whether IFN-free direct-acting antivirals reduce the risk of HCC is controversial. Therefore, this study aims to compare the incidence of HCC after the achievement of SVR between sofosbuvir combined with ledipasvir (SOF/LDV) and simeprevir with pegylated interferon plus ribavirin (Sim+IFN). Japanese patients with HCV infection (genotype 1) who achieved SVR between January 2013 and December 2014 by SOF/LDV (NCT01975675, n = 320) or Sim+IFN (000015933, n = 289) therapy in two nationwide, multicenter, phase III studies were prospectively monitored for the development of HCC by ultrasonography for 5 years after the end of treatment (EOT). No HCC was detected before the treatment. HCC was detected in 9 and 7 patients in the SOF/LDV and the Sim+IFN group in 5 years, respectively. The cumulative incidences of HCC rates 1, 3, and 5 years after EOT were similar between the two groups (1.5%, 2.7%, and 3.2% for the SOF/LDV and 1.8%, 2.8%, and 3.0% for the Sim+IFN group, respectively). No HCC was developed 3.5 years after EOT. Interestingly, a retrospective careful review of imaging taken before therapy revealed hepatic nodules in 50% of HCC patients, suggesting HCC was pre-existed before therapy. In conclusion, we could not find any differences in the incidence of HCC after the HCV eradication between the two therapeutic regimens, suggesting no enhancement of HCC development by DAA.

***Keywords*:** hepatitis C virus, direct-acting antivirals, interferon

Introduction

Hepatitis C virus (HCV) infection is a leading cause of cirrhosis, liver failure, and hepatocellular carcinoma (HCC) (*1,2*). Particularly among cirrhotic patients with HCV infection, the annual incidence of HCC is 3% to 7% (*3,4*). Therefore, one of the goals for the treatment is the eradication of HCV and the prevention of HCC. Interferon (IFN) has long been used for anti-HCV therapy, and achievement of sustained virological response (SVR) by IFN-based therapy such as IFN monotherapy (*5-7*) or pegylated-interferon plus ribavirin (Peg-IFN/RBV) therapy (*8*) significantly reduced the incidence of HCC in patients with chronic HCV infection.

Direct-acting antivirals (DAA) that selectively inhibit HCV proteins such as nonstructural protein (NS) 3/4A protease, NS5A, and NS5B polymerase, have been approved for the treatment of chronic hepatitis C. In Japan, a protease inhibitor with Peg-IFN/RBV regimen has been firstly introduced for patients with chronic hepatitis C in 2013 and its SVR rate in the IFN-naïve patients was about 80-90% (*9*). However, there are no reports on whether a protease inhibitor with Peg-IFN/RBV reduced the long-term risk of HCC development.

Meanwhile, an IFN-free DAA regimen such as sofosbuvir combined with ledipasvir (SOF/LDV) was approved for the treatment of genotype 1 HCV infection in 2015 in Japan, which showed a tremendous high SVR rate (*10*). However, concerns were raised from two studies that reported the increased rates of *de novo* HCC occurrence and high rates of recurrence in patients who eradicated HCV by IFN-free DAA therapy (*11,12*). Recent large prospective studies showed a reduction in the incidence of HCC after SVR in patients treated with IFN-free DAA therapy (*13-15*), but these observation periods were not long enough to evaluate the long-term risk of HCC. A similar risk of HCC development after HCV eradication has been reported between IFN-free DAA and Peg-IFN/RBV therapy, but the observation periods of IFN-free DAA therapy was not long enough to evaluate the long-term risk of HCC as well (*16,17*).

Therefore, we extended two different nationwide, multicenter prospective cohort studies after the end of treatments (EOT) and compared the long-term incidence of HCC after SVR.

Materials and Methods

Study design and patient population

We have two nationwide, multicenter, phase III prospective studies for HCV treatment such as simeprevir with Peg-IFN/RBV (Sim+IFN, 000015933) and SOF/LDV (*clinicaltrials.gov* identifier NCT01975675) (*10*) in Japanese patients with HCV infection. In these two studies, eligible patients had been 20 years of age or higher with genotype 1 HCV infection with serum HCV RNA levels of 5 log10 IU/mL or higher and creatinine clearance levels of 1.0 mL/s or higher (Cockcroft-Gault equation). Patients with hepatic decompensation (as shown by the presence of ascites, encephalopathy, or a history of variceal hemorrhage), bodyweight less than 40 kg, or coinfection with hepatitis B virus or human immunodeficiency virus had been excluded. The standard treatment of Sim+IFN was as follows: Simeprevir (Sovriad®, 100 mg, once-daily, Janssen Tokyo, Japan) was co-administered with RBV (Copegasys®, 400–600 mg, twice a day, Chugai, Tokyo, Japan), and Peg-IFNα-2a (Pegasys®, 180 μg, Chugai, Tokyo, Japan) was injected weekly for 12 weeks, followed by additional Peg-IFN/RBV treatment for 12 weeks. The SOF/LDV group received SOF/LDV once a day (Harvony®, Gilead Sciences, Tokyo, Japan) for 12 weeks. No participants had used DAA before this cohort.

We extended the above-mentioned two prospective studies to monitor the incidence of HCC after EOT. Then, we retrospectively reviewed 653 consecutive patients with genotype 1 HCV infection who achieved SVR by SOF/LDV (n = 338) or Sim+IFN (n = 315) at 19 hospitals between January 2013 and December 2014. Among them, 18 and 26 patients in the SOF/LDV and the Sim+IFN group, respectively, rejected participation in this follow-up study and we excluded them from this cohort (Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=54*). Therefore, 320 and 289 patients in the SOF/LDV and the Sim+IFN group, respectively, were prospectively monitored for HCC development after EOT by ultrasonography (US) at least every 3 months, and the incidence of HCC between the two groups was compared. Contrast-enhanced computed tomography (CT), or gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (EOB-MRI) was used on demand.

Written informed consent was obtained from each participant. This study was conducted under provisions of the 1975 Declaration of Helsinki and approved by the Institutional Ethics Committee of the National Center for Global Health and Medicine (NCGM-A-001649) and each hospital participating in the studies.

Clinical and laboratory assessments

Clinical and laboratory assessments were performed before treatment. Alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) were used as tumor markers of HCC. Serum HCV RNA levels were measured using a COBAS 135 TaqMan HCV test (Roche Diagnostics, Tokyo, Japan). Its detection limit was 1.2 log IU/mL. HCV genotype was determined by sequence determination of the 5' non-structural region of the HCV genome, followed by phylogenetic analysis. Fibrosis-4 (FIB-4) index was used as a surrogate

marker for liver fibrosis. A formula of FIB-4 index was age (years) × aspartate aminotransferase (AST) [IU/L] / (platelet count [10^9/L] × (alanine aminotransferase, ALT [IU/L])1/2). A liver biopsy was done if necessary. We considered a FIB-4 index ≥ 3.25 and/or FibroScan® score ≥ 12.5 kPa, and/or fibrosis staging ≥ F3 as advanced fibrosis.

The presence of type 2 diabetes mellitus (T2DM) was determined based on fasting blood glucose levels > 126 mg/dL, hemoglobin A1c (HbA1c) > 6.5%, or by the use of anti-diabetic agents. The presence of steatosis was recognized as a marked increase in hepatic echogenicity, poor penetration of the posterior segment of the right lobe of the liver, and poor or no visualization of the hepatic vessels and diaphragm by the US. Patients with a hepatic injury who consumed more than 60 g of alcohol per day were classified as having alcoholic liver disease.

HCC surveillance

HCC surveillance was done using the combination of tumor markers (AFP and DCP) and the US at least every 3 months after EOT for 5 years in all participants. CT and/or EOB-MRI were used at the discretion of the attending physician. The diagnosis of HCC was based on the hypervascular staining pattern of the arterial phase and the hypovascular staining pattern of the portal phase and was confirmed by dynamic CT, EOB-MRI, or target biopsy if necessary.

Statistical analysis

Continuous variables were analyzed using the Mann-Whitney *U*-test. Categorical variables were compared using the chi-square or Fisher exact test. The incidence of HCC was calculated by the Kaplan-Meier method, and differences between the groups were assessed by the log-rank test. A p-value < 0.05 was considered statistically significant.

Results

Patients characteristics

The clinical characteristics of the 609 patients before anti-viral therapy are shown in Table 1. Serum AFP levels in the SOF/LDV group were significantly higher than those in the Sim+IFN group (11.9 and 7.4 ng/mL, p = 0.0045). Serum creatinine levels (average 0.74 *vs.* 0.68 mg/dL) and serum HCV RNA levels (average 6.6 *vs.* 6.3 mg/dL) were significantly lower in the Sim+IFN group. However, there were no differences in their ages, genders, body mass index (BMI), prior anti-viral therapies, hepatic biochemical data, or the FIB-4 index before therapy between the two groups. The presence of T2DM, fatty liver, or alcohol inhabit was similarly observed. A total of 30.5% of patients showed a FIB-4 index value > 3.25, indicating advanced fibrosis at baseline (31% for the SOF/LDV and 34% for the Sim+IFN groups, respectively). Before starting anti-viral therapy, all patients have performed the abdominal US, but 89 patients (14.6%) have performed CT and/or EOB-MRI within 4 months before the treatments (16% for the SOF/LDV and 14% for the Sim+IFN groups, respectively).

Follow-up and tumor development

The median observation periods of the SOF/LDV and Sim+IFN were 56.1 (6-60) and 52.3 (6-60) months, respectively. The follow-up rates were similar between the two groups 1, 3, and 5 years after EOT (Figure 1, 98%, 92%, and 89% for the SOF/LDV and 96%, 85%, and 81% for the Sim+IFN group, respectively). HCC was developed in 9 and 7 patients in the SOF/LDV and the Sim+IFN groups, respectively. There were no differences in the cumulative rates of HCC development between the two groups (Figure 1, 1, 3, and 5 years after EOT: 1.5%, 2.7%, and 3.2% for the SOF/LDV and 1.8%, 2.8%, and 3.0% for the Sim+IFN group, respectively.).

Propensity score matching analysis

To overcome the bias due to differences in the

Table 1. Comparison of clinical characteristics in different therapeutic groups before anti-viral therapy

Characteristics	SOF/LDV	Sim+IFN	p value
Number of patients	320	289	N.S.
Age, mean (range)	59.4 (28-80)	60.1 (20-78)	N.S.
Age ≥ 65 year, *n* (%)	108 (33)	107 (37)	N.S.
Male, *n* (%)	132 (41)	134 (46)	N.S.
BMI, kg/m^2 mean (range)	23.3 (16-36)	23.0 (17-34)	N.S.
Treatment for Naïve, *n* (%)	165 (52)	141 (49)	N.S.
Albumin g/dL mean (SD)	4.2 (0.3)	4.1 (0.4)	N.S.
AST, IU/L mean (SD)	55 (37)	51 (37)	N.S.
ALT, IU/L mean (SD)	59 (45)	57 (50)	N.S.
γ-GTP, IU/L mean (SD)	47 (46)	44 (45)	N.S.
Creatinine mg/dL (SD)	0.74 (0.15)	0.68 (0.17)	< 0.001
WBC, (×10^2/mm^3) (SD)	45.8 (14.0)	44.7 (18.2)	N.S.
Hb, (g/dL) (SD)	14.0 (1.3)	13.9 (1.3)	N.S.
Platelet, ×10^4/μL mean (SD)	17.6 (6.3)	16.7 (5.6)	N.S.
HCV *RNA*, logIU/L mean (SD)	6.6 (0.5)	6.3 (1.0)	< 0.001
FIB-4 index, mean (SD)	2.90 (2.00)	2.90 (1.80)	N.S.
FIB-4 index > 3.25, *n* (%)	99 (31)	97 (34)	N.S.
AFP, ng/mL mean (SD)	11.9 (22.0)	7.4 (14.0)	0.0045
Diabetes, *n* (%)	26 (8)	33 (11)	N.S.
Alcohol (> 60 g/day), *n* (%)	40 (12)	43 (15)	N.S.
Fatty liver, *n* (%)	45 (14)	38 (13)	N.S.
Image (US/CT/MRI)	320/35/15	289/27/12	N.S.

SOF/LDV, sofosbuvir combined with ledipasvir; Sim-IFN, simeprevir with pegylated interferon plus rivabirin; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma glutamyltransferase; WBC, white blood cell counts; Hb, hemoglobin concentration; HCV, hepatitis C virus; AFP, alpha-fetoprotein; US, ultrasonography; CT, contrast-enhanced computed tomography; MRI, Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging; N.S., not significant.

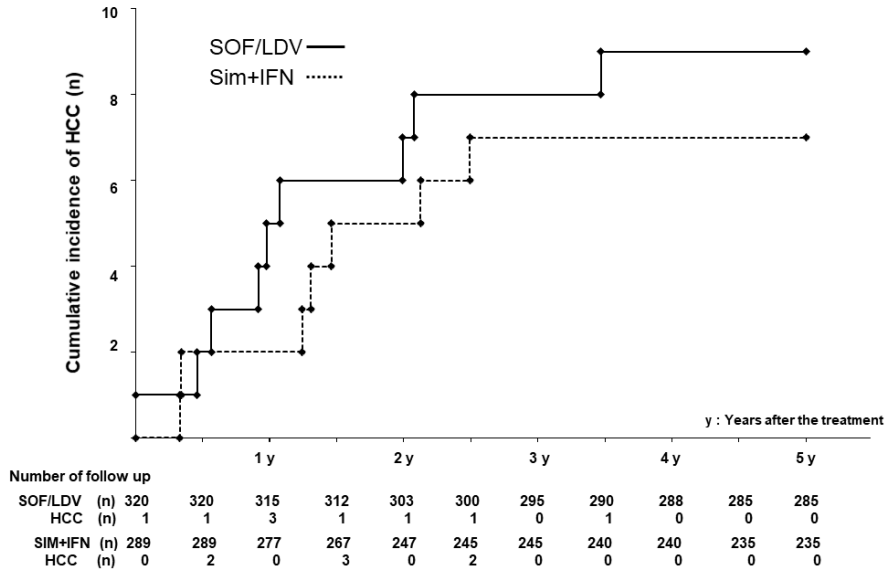

Figure 1. Kaplan-Meier curves of cumulative incidence of hepatocellular carcinoma after eradication of HCV according to the different therapies. SOF/LDV, sofosbuvir combined with ledipasvir; Sim+IFN, simeprevir with pegylated-interferon plus ribavirin.

distributions of covariates between the two groups, one-to-one matches were created using propensity score analysis. Variables entered in the propensity model included their ages, genders, BMI, prior treatments, serum albumin, ALT, AST, γ-glutamyl transpeptidase (γ-GTP), HCV-RNA, AFP levels, white blood cell counts, hemoglobulin levels, platelet counts, FIB-4 index, the presence of T2DM, alcohol habits and fatty liver. The model was used to obtain a one-to-one match by using the nearest-neighbor matching method in 206 patients with SOF/LDV and 206 patients with Sim-IFN therapies, resulting in a sample size of more than 70% patients per cohort (Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=54*). Propensity score matching analysis did not find any differences in the incidence of HCC ($n = 3$ each) between the two groups.

Risk factors before anti-viral therapy for the development of HCC in patients treated with SOF/LDV and Sim+IFN

In the SOF/LDV group, older ages, male gender, lower platelet counts, higher FIB-4 index, and higher serum AFP level were observed in patients who developed HCC, compared with those who did not ($p < 0.001$, Table 2). Meanwhile, in the Sim+IFN group, older ages were the only factors that were significantly observed in patients with HCC, compared with those without HCC ($p < 0.05$, Table 3). There were no differences in the clinical characteristics of patients who developed HCC in different treatment regimens before anti-viral therapy (Table 4).

Table 2. Comparison of clinical characteristics in patients who developed HCC or not in the SOF/LDV group before anti-viral therapy

Characteristics	Non-HCC	HCC	*p* value
Number of patients	311	9	N.S.
Age, mean (range)	59 (28-80)	66 (57-75)	< 0.05
Age ≥ 65 year, *n* (%)	98 (31)	4 (44)	N.S.
Male, *n* (%)	124 (39)	8 (89)	< 0.001
BMI, kg/m^2 mean (range)	23.2 (16-36)	23.7 (22-27)	N.S.
Treatment for Naïve, *n* (%)	161 (52)	4 (44)	N.S.
Albumin g/dL mean (SD)	4.2 (0.4)	4.1 (0.2)	N.S.
AST, IU/L mean (SD)	55 (37)	64 (32)	N.S.
ALT, IU/L mean (SD)	59 (45)	61 (43)	N.S.
γ-GTP, IU/L mean (SD)	44 (45)	68 (31)	N.S.
Platelet, ×10^4/μL mean (SD)	17.8 (6.3)	10.2 (2.7)	< 0.001
FIB-4 index, mean (SD)	2.83 (1.90)	5.90 (2.35)	< 0.001
FIB-4 index > 3.25, *n* (%)	91 (29)	8 (89)	< 0.001
AFP, ng/mL mean (SD)	11.3 (21.0)	34.0 (38.0)	< 0.001
Diabetes, *n* (%)	25 (8)	1 (11)	N.S.
Alcohol (> 60 g/day), *n* (%)	37 (12)	2 (22)	N.S.
Fatty liver, *n* (%)	43 (14)	2 (22)	N.S.

SOF/LDV, sofosbuvir combined with ledipasvir; HCC, hepatocellular carcinoma; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma glutamyltransferase; AFP, alpha-fetoprotein; N.S., not significant.

Clinical characteristics of HCC patients in each therapeutic group

Clinical background before anti-viral therapy and the detailed information on HCC at detection are shown in Table 5 and Table 6, respectively. All patients who developed HCC in the SOF/LDV group ($n = 9$) had advanced fibrosis (FibroScan ≥ 12.5 kPa and/or FIB-4 index ≥ 3.25 and/or fibrosis staging ≥ 3). Meanwhile,

Table 3. Comparison of clinical characteristics in patients who developed HCC or not in the Sim+IFN group before anti-viral therapy

Characteristics	Non-HCC	HCC	*p* value
Number of patients	282	7	N.S.
Age, mean (range)	60 (20-78)	68 (58-75)	< 0.05
Age ≥ 65 year, *n* (%)	101 (36)	5 (71)	< 0.05
Male, *n* (%)	133 (47)	3 (42)	N.S.
BMI, kg/m^2 mean (range)	23.0 (17-34)	22.9 (20-27)	N.S.
Treatment for Naïve, *n* (%)	133 (47)	5 (71)	N.S.
Albumin g/dL mean (SD)	4.1 (0.4)	4.2 (0.2)	N.S.
AST, IU/L mean (SD)	51 (38)	62 (32)	N.S.
ALT, IU/L mean (SD)	57 (50)	64 (38)	N.S.
γ-GTP, IU/L mean (SD)	44 (46)	36 (17)	N.S.
Platelet, ×10^4/μL mean (SD)	16.7 (5.6)	14.3 (4.5)	N.S.
FIB-4 index, mean (SD)	2.86 (1.80)	4.13 (2.10)	N.S.
FIB-4 index > 3.25, *n* (%)	93 (33)	4 (57)	N.S.
AFP, ng/mL mean (SD)	7.3 (14.0)	10.1 (9.7)	N.S.
Diabetes, *n* (%)	32 (11)	1 (14)	N.S.
Alcohol (> 60 g/day), *n* (%)	42 (15)	1 (14)	N.S.
Fatty liver, *n* (%)	45 (16)	0 (0)	N.S.

Sim+IFN, simeprevir with pegylated interferon plus ribavirin; HCC, hepatocellular carcinoma; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma glutamyltransferase; AFP, alpha-fetoprotein; N.S., not significant.

Table 4. Comparison of clinical characteristics in patients who developed HCC in the different therapeutic groups before anti-viral therapy

Characteristics	SOF/LDV	Sim+IFN	*p* value
Number of patients	9	7	N.S.
Age, mean (range)	66 (57-75)	68 (58-75)	N.S.
Age ≥ 65 year, *n* (%)	4 (44)	5 (71)	N.S.
Male, *n* (%)	8 (89)	3 (42)	N.S.
BMI, kg/m^2 mean (range)	23.7 (22-27)	22.9 (20-27)	N.S.
Treatment for Naïve, *n* (%)	4 (44)	5 (71)	N.S.
Albumin g/dL mean (SD)	4.1 (0.2)	4.2 (0.2)	N.S.
AST, IU/L mean (SD)	64 (32)	62 (32)	N.S.
ALT, IU/L mean (SD)	61 (43)	64 (38)	N.S.
γ-GTP, IU/L mean (SD)	68 (31)	36 (17)	N.S.
Platelet, ×10^4/μL mean (SD)	10.2 (2.7)	14.3 (4.5)	N.S.
FIB-4 index, mean (SD)	5.90 (2.35)	4.13 (2.10)	N.S.
FIB-4 index > 3.25, *n* (%)	8 (89)	4 (57)	N.S.
AFP, ng/mL mean (SD)	34.0 (38.0)	10.1 (9.7)	N.S.
Diabetes, *n* (%)	1 (11)	1 (14)	N.S.
Alcohol (> 60 g/day), *n* (%)	2 (22)	1 (14)	N.S.
Fatty liver, *n* (%)	2 (22)	0 (0)	N.S.

SOF/LDV, sofosbuvir combined with ledipasvir; Sim+IFN, simeprevir with pegylated interferon plus rivabirin; HCC, hepatocellular carcinoma: BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, gamma glutamyltransferase; AFP, alpha-fetoprotein; *N.S.*, not significant.

5 out of 7 patients in the Sim+IFN group had advanced fibrosis, but the other two (Sim+IFN-2 and Sim+IFN-7) showed high BMI and/or DM and alcohol habits (Table 5). Fourteen (88%, except for SOF/LDV-9 and Sim+IFN-7) patients developed HCC within 2.5 years after EOT while no one developed HCC 3.5 years after EOT (Table 6).

Therapeutic regimens and prognosis of HCC

All patients who developed HCC were successfully treated and survived during follow-up (Table 6). No recurrences of HCC were observed in patients whose HCC was detected at a very early stage (BCLC 0, *n* = 11), regardless of HCC therapeutic strategies. Meanwhile, all patients in the SOF/LDV group whose HCC was detected at BCLC A (*n* = 4) underwent radiofrequency ablation (RFA), in all of whom HCC recurred within 1 year after RFA, but were successfully treated by further RFA. The Sim+IFN-5 (75-year-old male) who was detected HCC at BCLC B despite repeated US every 3 months was treated by transcatheter arterial chemoembolization, which needed further treatment for HCC recurrence.

Discussion

This study compared the relative long-term risk of HCC developments after eradication of HCV between the SOF/LDV and the Sim+IFN groups. We found no differences in the cumulative incidence of HCC between the two groups for at least 5 years.

The achievement of SVR by IFN-based therapy was associated with a significant reduction in HCC development (*5-7*). HCV proteins exert a direct carcinogenic effect by deregulating the host cell cycle checkpoints and increasing the immune-mediated oxidative stress, which leads to DNA mutations frequently in the liver cells (*18*). Necro-inflammatory activity and its process is a contributor to a wide variety of neoplasm (*19*). Thus, HCV clearance by DAA should theoretically reduce the risk of HCC development as seen in IFN-based therapy (*5-7*). Indeed, DAA contributed to a significant reduction of HCC incidence as well as improved the SVR rate, compared with patients with non-SVR (*13-15*,*20*).

However, unexpected data suggest the potential increased risk of *de novo* and recurrent HCC after DAA therapy (*11,12*). Cases with the rapid growth of HCC were observed during DAA (*21*), which raised the question of whether DAA could enhance hepatic carcinogenesis. The mechanism underlying this association has been hypothesized that abrupt hepatic downregulation of type II and III IFN by HCV clearance might hurt immune cancer control (*22*). An experimental study has shown that double-stranded DNA breaks induced by chronic inflammation lead to genomic instability, which accelerates carcinogenesis by liver regeneration (*23*). Therefore, whether DAA enhances hepatic carcinogenesis or not has been controversial.

Kanwal recently reported the relative long-term incidence of HCC in patients who eradicated HCV by DAA, which revealed that the cumulative rate of 1 and 3 year risks of HCC were 1.1% and 2.8%, respectively, in a nationwide, prospective cohort (*24*). Meanwhile, Nahon P, *et al.* (*14*) and Innes H, *et al.*

Table 5. Clinical characteristics of patients who developed HCC in the SOF/LDV (*n* = 9) and the Sim+IFN group (*n* = 7) before anti-viral therapy

Groups	Age	Sex	Prior treatment	BMI (kg/m2)	LSM (kPa) or Staging	FIB-4 index	ALT (IU/L)	DM	Alcohol	Fatty liver
SOF/LDV-1	70	M	Naïve	23.7	12.5	7.18	34	-	-	-
SOF/LDV-2	75	M	Naïve	23.5	24.5	5.79	42	+	-	+
SOF/LDV-3	71	M	PegIFN/RBV	25.3	26.7	5.81	160	-	-	-
SOF/LDV-4	63	M	PegIFN/RBV	27.1	38.6	4.12	41	-	-	+
SOF/LDV-5	63	M	PegIFN/RBV	22.2	F3	8.26	77	-	+	-
SOF/LDV-6	57	F	PegIFN/RBV	22.3	22.3	10.05	75	-	-	-
SOF/LDV-7	62	M	PegIFN/RBV	25.3	28.4	5.64	25	-	-	-
SOF/LDV-8	73	M	Naïve	23.7	11.8	3.75	40	-	-	-
SOF/LDV-9	59	M	PegIFN/RBV	23.0	F3	2.46	40	-	+	-
Sim+IFN-1	68	F	Naïve	22.7	F3	5.76	74	-	-	-
Sim+IFN-2	74	F	PegIFN/RBV	26.4	6.5	2.69	21	-	-	-
Sim+IFN-3	73	F	Naïve	21.3	F2	4.48	25	-	-	-
Sim+IFN-4	64	F	PegIFN/RBV	23.4	F3	7.80	104	-	-	-
Sim+IFN-5	75	M	Naïve	20.0	F1	3.76	106	-	-	-
Sim+IFN-6	66	M	Naïve	20.2	F3	2.78	108	-	-	-
Sim+IFN-7	58	M	Naïve	26.6	F1	1.66	30	+	+	-

SOF/LDV, sofosbuvir combined with ledipasvir; Sim-IFN, Simeprevir with pegylated interferon plus rivabirin; M, male; F, female; PegIFN/RBV, pegylated interferon plus ribavirin; BMI, body mass index; LSM, liver stiffness measurement; Staging, fibrosis staging by liver biopsy; ALT, alanine aminotransferase; DM, diabetes mellitus.

Table 6. Clinical characteristics at detection of patients who developed HCC in the SOF/LDV (*n* = 9) and the Sim+IFN groups (*n* = 7)

Groups	Detection from EOT (days)	US	CT	MRI	AFP (ng/mL)	AFP-L3 (%)	DCP (mAU/mL)	BCLC stage	CPT score	Therapy	Recurrence	Alive at 5 years after EOT
SOF/LDV-1	0	○	–	○	41.1	3.2	13	0	A	RFA	No	Yes
SOF/LDV-2	168	○	○	○	4.7	< 0.5	19	0	A	Surgery	No	Yes
SOF/LDV-3	207	○	○	–	14.1	20.7	17	A	A	RFA	Yes	Yes
SOF/LDV-4	334	○	○	○	4.1	< 0.5	17	A	A	RFA	Yes	Yes
SOF/LDV-5	357	○	○	○	4.1	< 0.5	14	0	A	Surgery	No	Yes
SOF/LDV-6	393	○	○	○	375.0	2.4	57	A	A	RFA	Yes	Yes
SOF/LDV-7	727	○	–	○	3.6	< 0.5	23	A	A	RFA	Yes	Yes
SOF/LDV-8	759	○	–	○	4.0	< 0.5	< 10	0	A	RFA	No	Yes
SOF/LDV-9	1,267	×	○	○	2.9	< 0.5	12	0	A	Surgery	No	Yes
Sim+IFN-1	121	○	–	○	7.0	< 0.5	23	0	A	RFA	No	Yes
Sim+IFN-2	125	○	○	○	3.7	< 0.5	66	0	A	RFA	No	Yes
Sim+IFN-3	454	○	○	–	2.0	< 0.5	20	0	A	Surgery	No	Yes
Sim+IFN-4	478	○	○	○	25.6	24.1	353	0	A	Surgery	No	Yes
Sim+IFN-5	533	○	○	○	59.2	75.9	754	B	A	TACE	Yes	Yes
Sim+IFN-6	776	○	–	○	3.8	43.9	47	0	A	Surgery	No	Yes
Sim+IFN-7	943	×	○	○	2.5	< 0.5	14	0	A	Surgery	No	Yes

SOF/LDV, sofosbuvir combined with ledipasvir; Sim+IFN, simeprevir with pegylated interferon plus rivabirin; EOT, end of treatments; BCLC, Barcelona Clinic Liver Cancer Score; CPT, Child-Pugh score; –, not tested; ○, detected; ×, not detected; US, ultrasonography; CT: contrast-enhanced computed tomography; MRI: Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced magnetic resonance imaging; AFP, alpha-fetoprotein; DCP, des-γ-carboxy prothrombin, RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization.

(*25*) showed a higher incidence of HCC following SVR by DAA therapy, compared with IFN-based therapy, but these were dependent on the baseline characteristics of patients such as their ages and liver function. Comparison between DAA and IFN-based therapy in HCC incidence after HCV eradication was reported to be similar (*16,17*). However, the median observation periods of these two reports were 23 (4-78) and 21.6 (1.2–92.4) months, respectively, which were not long enough to evaluate the long-term risk of HCC occurrence. Therefore, we conducted the current study. Indeed, the median observation period of our SOF/LDV group was significantly longer (56.1 months) than those previous reports and we found no differences in the risk of HCC between the SOF/LDV group and the Sim+IFN group (1, 3, and 5 years risks of HCC were 1.5%, 2.7%, and 3.2% for the SOF/LDV, and 1.8%, 2.8% and 3.0% for the Sim+IFN, respectively), which were the similar incidence of HCC as Kanwal F, *et al.* reported (*23*). These accumulating pieces of evidence suggest that

the HCC risk after SVR might be similar regardless of treatment regimens although higher SVR rates, fewer side effects, and higher costs are observed in the DAA therapy (*10,26*) than those in the IFN monotherapy (*5-7*) or the Sim+IFN therapy (*9*).

In this cohort, 88% (14/16) of patients developed HCC within 2.5 years after EOT. Therefore, we hypothesized that pre-existing HCC before DAA therapy could develop during therapy or after EOT although all patients were confirmed to be no HCC by pre-treatment screening. To confirm this hypothesis, we retrospectively reviewed the abdominal imaging of patients who developed HCC (n = 16), which were taken before anti-viral therapy. Surprisingly, a retrospective review with location information of HCC was able to recognize hepatic nodules in eight patients (50%) by at least one imaging of US, CT, or EOB-MRI (Table S2, Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=54*) although no imaging showed typical characteristics of HCC such as early enhancement or washout at the portal phase. These results partially support the notion that DAA did not induce hepatic carcinogenesis, but HCC was pre-existing before therapy (*27*). Mariño Z, *et al.* (*28*) reported the presence of non-characterized nodules before DAA was associated with a 3 times greater risk of HCC development. Therefore, screening of the early stage of HCC by other imaging modalities such as EOB-MRI before therapy could reduce the incidence of HCC after SVR since no lesions were detected by the US alone at baseline in our study and EOB-MRI is superior to detecting early HCC (*29,30*).

It is well known that advanced fibrosis is one of the risk factors for HCC after the achievement of SVR (*18*), but no differences in the FIB-4 index were observed between the DAA group and the Sim+IFN group (Table 1). However, all patients who developed HCC in the DAA group showed advanced liver fibrosis before anti-viral therapy (Tables 3). Meanwhile, several other factors such as older age, male gender, high serum AFP levels, and presence of T2DM, obesity, steatosis, and alcohol abuse were associated with long-term risk of HCC after SVR by DAA (*12,16*). Indeed, in the current study, two patients without advanced fibrosis (Sim+IFN-2 and Sim+IFN-7) had metabolic disorders. Therefore, environmental factors, as well as liver fibrosis, should be considered for a careful HCC survey. In general, higher AFP levels represent the presence of severer inflammation in the liver, which suggested that patients with a higher risk of HCC development were included in the DAA group. Alternatively, to our knowledge, we cannot find any reports regarding serum creatine levels and HCC development in patients with chronic hepatitis C. Therefore, the significant differences in the serum creatine levels between the DAA and the Sim+IFN group may not affect our results. HCV genotype 1 is one of the well-known risk factors for HCC (*31*). Since all enrolled patients had genotype 1b, the conclusion from this study should be limited to patients with genotype 1.

Results from our study must be interpreted in light of other limitations. First, this is not a randomized study. However, these two studies were prospectively done in similar periods. Therefore, the bias between the two groups might be small. Second, the sample size was relatively small and the follow-up periods were not long enough for HCC surveillance. We had planned to follow these patients longer but lost patients during follow-up partially because of COVID-2019. Third, there were many missing data, especially after EOT. If not, we could show predictive factors for HCC development from laboratory data. Forth, enhanced CT and/or EOB-MRI for the pre-treatment screening were done in only 15% of patients. If not, we could clearly show no pre-existing HCC before therapy. Fifth, the majority of included patients did not have advanced fibrosis, which may result in a low incidence of HCC in this cohort. Similar incidence of HCC in the two therapeutic regimens could be shown more clearly when we used more patients with advanced fibrosis. The conclusion of this study should be mainly limited to chronic hepatitis without severe fibrosis.

In conclusion, we could not find any differences in the incidences of HCC after eradication of HCV between the SOF/LDV and the Sim+IFN therapy by two nationwide, prospective, multicenter studies. However, we should remind that HCC develops from undetectable pre-existing nodules before therapy. Therefore, we should follow the patients after EOT for at least 3.5 years until useful clinical predictive markers for HCC would be settled in the future.

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BRIEF REPORT
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Closure and anastomosis of the pancreas using a four-needle three-loop suture device

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Abstract: Pancreatic juice can leak not only from the main pancreatic duct but also from unclosed ductal branches appearing on the pancreatic stump. We have developed a suture device consisting of three loops of suture attached to four small-curvature needles with the aim to maximize the area of pancreatic parenchyma to be ligated and reduce the number of punctures made on the pancreas during pancreatic closure or anastomosis. In pancreatojejunostomy, the dorsal wall of the jejunum and then the pancreatic parenchyma are sutured using the four needles. Following duct-to-mucosa anastomosis, the ventral jejunal wall is sutured, and the three threads are finally tied sequentially to complete the reconstruction following the Blumgart method. In distal pancreatectomy, the pancreatic stump is sutured from the dorsal aspect sequentially using the four needles, before or after the pancreatic transection. The three threads are then respectively tied on the ventral surface of the pancreas. This device was used in six pancreatoduodenectomies (including two minimally invasive procedures) and five distal pancreatectomies. A postoperative pancreatic fistula requiring additional drainage or repositioning of abdominal drains developed in two patients. No adverse events associated with this device were encountered. The four-needle three-loop suture device can be an alternative to conventional staplers or sutures for closure and anastomosis of the pancreatic stump.

***Keywords*:** distal pancreatectomy, pancreatic fistula, pancreatic leak, pancreatic reconstruction, suture device, pancreaticoduodenectomy

Introduction

Despite advances in suturing techniques and surgical devices, there is no single method for closing and anastomosing the pancreatic stump to prevent development of postoperative pancreatic fistula (POPF). Among a variety of surgical techniques, Blumgart anastomosis (*1*) has become widely used as a safe and effective method of pancreatojejunostomy during pancreaticoduodenectomy (PD) (*2*). In distal pancreatectomy (DP), staple closure is the most common technique, especially in the minimally invasive setting. Hand-sewn suture closure can also be used to ensure adequate management of the pancreatic stump with closure of the main pancreatic duct (MPD) in complicated surgical procedures (*3*).

In our previous studies, fluorescence imaging using a chymotrypsin-activated probe showed that pancreatic juice could leak not only from the MPD stump but also from unclosed ductal branches located in the whole pancreatic raw surface and pinholes made by surgical instruments (*4,5*). These findings suggested that it would be reasonable to extend areas of pancreatic parenchyma to be ligated while minimizing injuries on the pancreas, leading to development of a new suturing device consisting of three loops of suture connected to four small-curvature needles (three-loop suture device). The methods for using the three-loop suture device in PD and DP are herein detailed with operative outcomes.

Materials and Methods

This study protocol was reviewed and approved by the Institutional Ethics Review Board of The University of Tokyo (approval number: 2021194NI) and performed in accordance with the guidelines of the Declaration of Helsinki. Informed consent was obtained from all patients.

Concept and design of the suture device

Previous studies aiming to develop intraoperative fluorescence imaging of pancreatic juice using a chymotrypsin-specific probe demonstrated that pancreatic juice could leak not only from the MPD stump but also from orifices of unclosed branches located widely on the pancreatic raw surface and/or pinholes made by suturing or stapler devices (Figure

1A, 1B). These findings inspired the author (T.I.) to design a new four-needle three-loop suturing device that maximizes areas of the pancreatic stump to be ligated with a minimum number of punctures on the pancreas (Figure 1C).

A prototype of this device was manufactured and clinically used in 2016. The updated version used in the present study consisted of three nonabsorbable threads (PTFE-coated polyester, U.S.P. 4-0 and 70 cm in length) and four small-curvature needles (1/5 circle and 3.0 cm in length). The ends of the first and second threads were attached to the second needle and those of the second and third threads were connected to the third needle, making three loops in a row (Figure 1D). The first and third threads were blue and the second thread was white, making it easy to differentiate the ends of each thread when ligated.

Use of three-loop suturing device in PD and DP

In pancreatojejunostomy during PD, the dorsal wall (seromuscular layer) of the elevated jejunum and then the pancreatic parenchyma (from dorsal to ventral aspects) are sutured, usually from the cranial to caudal side, using the four needles of the above-described suturing device in a sequential manner. Following duct-to-mucosa anastomosis of the MPD, the ventral seromuscular layer of the jejunum is sutured in sequence, the needles are removed by cutting the threads at their roots, and the three threads are then respectively tied to complete the anastomosis following the Blumgart method (Figure 2A). The above procedures can be followed in either laparoscopic or robot-assisted surgery.

In DP, the pancreatic stump is sutured from the dorsal to ventral aspects using the four needles in a sequential fashion, usually from the cranial to caudal side, before (Figure 2B) or after (Figure 2C) pancreatic transection. The three threads are then respectively

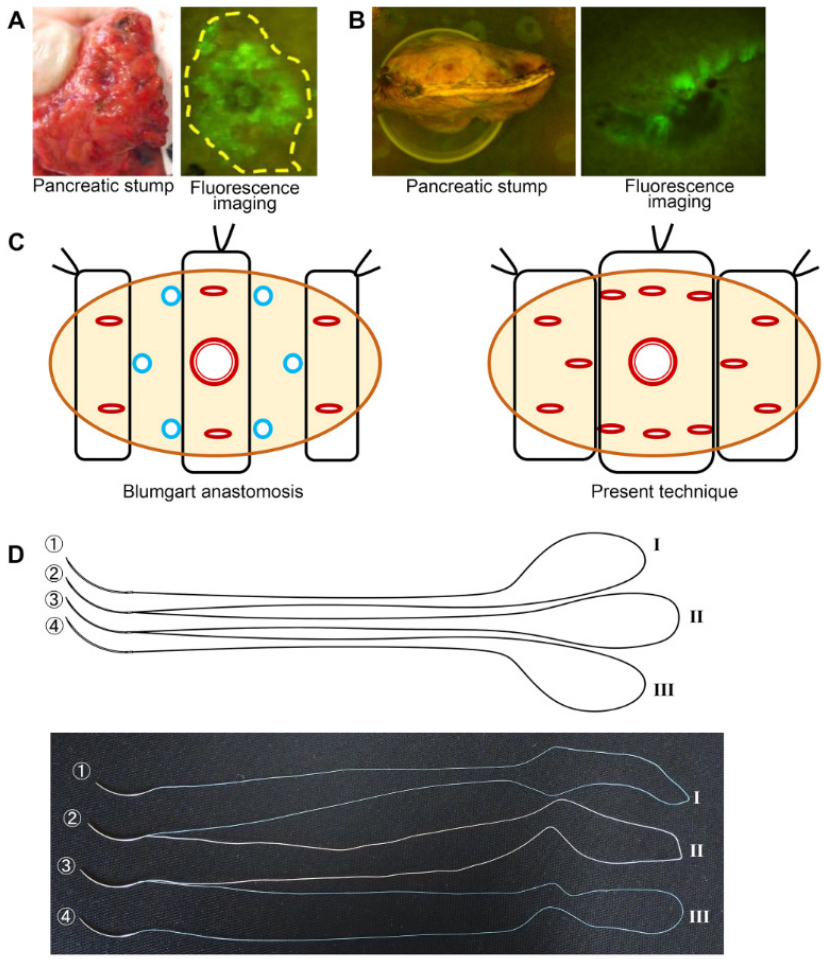

Figure 1. Design of the four-needle three-loop suture device based on fluorescence imaging of pancreatic juice. (A, B): Fluorescence imaging using a chymotrypsin-activated probe facilitates visualization of pancreatic juice leaking from **(A)** the whole raw surface of the pancreatic stump and **(B)** pinholes made by staples. **(C)**: Device concept. In the conventional Blumgart anastomosis (left), pancreatic ductal branches located in the parenchyma between the ligations may remain unclosed (blue circles), and they can be closed with use of the three-loop suture device by maximizing the extent of ligations (right). **(D)**: A drawing (above) and picture (below) of the four-needle three-loop suture device, which consists of four needles (1/5 curvature, φ0.45 mm for the needles "1" and "4" and φ0.6 mm for the needles "2" and "3") and three nonabsorbable threads (U.S.P. 4-0, I-III). Threads I (blue) and II (white) and threads II and III (green) are attached to needle "2" and "3", respectively, making three loops in a row.

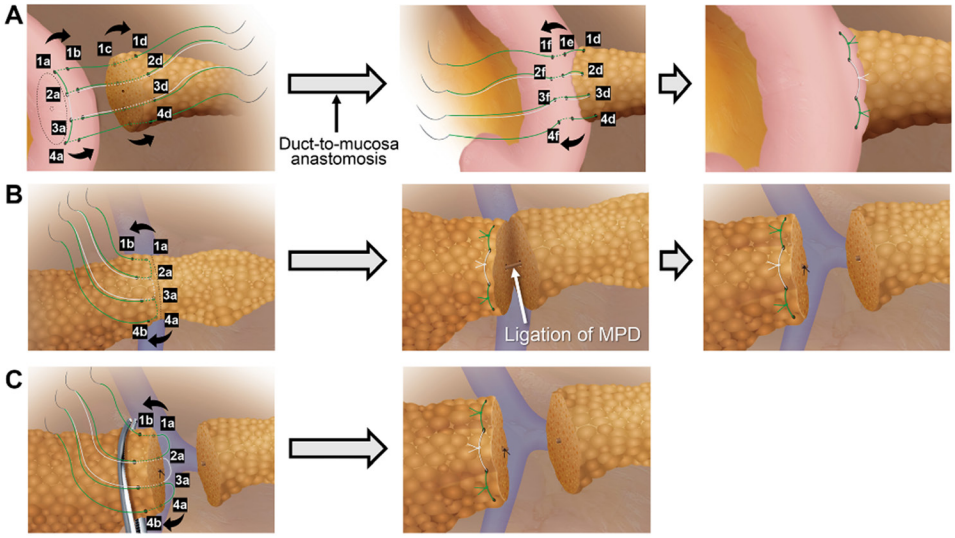

Figure 2. Methods of using the four-needle three-loop suture device in PD and DP. (A): In pancreatojejunostomy during PD, the first needle is used to suture the seromuscular layer on the posterior jejunal wall (1a to 1b) and then the pancreatic stump from the posterior to ventral aspects (1c to 1d). The remaining needles are respectively used in a similar manner (2a to 2d, 3a to 3d, and 4a to 4d). Following duct-to-mucosa anastomosis of the MPD, the seromuscular layer of the anterior jejunal wall is sutured with the first needle (1e to 1f), followed by caudal anastomoses with use of the remaining three needles. Finally, the needles are detached and the three loop threads are respectively ligated. **(B)**: In DP, the future pancreatic remnant is sutured from the dorsal to ventral aspects using the four needles respectively (1a to 1b, 2a to 2b, 3a to 3b, and 4a to 4b), usually from the cranial side and caudal side. After gentle ligation of the three loops, the pancreatic parenchyma is transected to identify and ligate the MPD independently. **(C)**: Another use of the three-loop suture device in DP. This device can also be used to reinforce the pancreatic stump after parenchymal transection by suturing the pancreas, usually from the dorsal to ventral aspects, with the four needles. PD, pancreaticoduodenectomy; DP, distal pancreatectomy; MPD, main pancreatic duct.

tied on the ventral surface of the pancreas. During the pancreatic transection, the MPD can be identified and ligated independently.

Results and Discussion

During November 2018 and March 2021, the four-needle three-loop suture device was used in six PDs (including one laparoscopy-assisted and one robot-assisted procedure) and five open DPs with no additional resections on the remnant pancreas. The patients' demographic background characteristics and operative outcomes are summarized in Table 1. Seven patients had a normal soft pancreas without diabetes mellitus or obstruction of the MPD.

The amylase concentration in the drained abdominal fluids on postoperative day 3 ranged from 22 to 17,000 IU/L (median, 2,448 IU/L). International Study Group on Pancreatic Surgery (ISGPS) grade B POPF (*6*) developed in two (18%) patients (additional percutaneous puncture of abdominal fluid in one patient and drain repositioning for symptomatic fluid collection in one patient). No adverse events associated with use of the three-loop suture device were encountered.

The concept of the four-needle three-loop suture device is application of uniform pressure on the whole area of the pancreatic stump by making three ligations following four punctures on the pancreas. In the present series consisting of 11 pancreatic resections, this device could be used as designed with an acceptable incidence of POPF (18%, ISGPS grade B) and no device-associated adverse events, albeit the efficacy of this technique in preventing POPF should be fully evaluated by further comparative studies. The key factor for successful utilization of the three-loop suture device is to tie the threads gently with adequate force, feeling the texture of the pancreas and intestines. Too-tight ligations may cause ischemia of the pancreatic remnant, whereas too-lax threads (especially on the dorsal aspect of the pancreas) will lead to leakage of pancreatic juice.

Closure of the pancreas in DP using the four-needle three-loop suture device has potential advantages over stapler-based techniques in that this procedure can be used in a wider range of surgical situations; *e.g.*, when there is limited space for stapler insertion, a thick/irregular pancreatic shape and fragile texture, a proximal transection around the pancreatic head, and the need to obtain intact specimens of the pancreatic stump for precise evaluation of surgical margins. Using this device for ligation of the future pancreatic remnant prior to parenchymal division makes the transection plane bloodless and ensures identification and ligation of the MPD, which may lead to decreasing risk of POPF in some particular conditions (*7*). The present technique can also be applied to coverage of the pancreas by suturing the pancreatic stump with mesh (*8,9*), the round ligament (*10*), or the seromuscular layer of the jejunum (*11*). According to a recent meta-analysis focusing on DP, patch closure using the round ligament led to the lowest incidence of clinically relevant POPF (*12*).

Table 1. Patients' demographic background characteristics and operative outcomes

No.	Age (y) / Sex	Preoperative diagnosis	DM or MPD obstruction	Surgical procedure	Maximum amylase level in abdominal drainage on POD3 (IU/L)	POPF (ISGPS grade)	Other complications	Postoperative hospital stay (days)
1	29/F	Mucinous cystic neoplasm		Open DP	2,448	B*		19
2	73/F	Metastatic tumor	DM	Open DP	10,938			12
3	63/F	Neuroendocrine tumor		Laparoscopy-assisted PD	4,949			14
4	74/M	Pancreatic adenocarcinoma	DM	Open DP	349			9
5	73/F	Serous cystic tumor		Open DP	16,000			10
6	74/M	Pancreatic adenocarcinoma		Open DP with gastric wall resection	2,255		DGE	22
7	57/F	Pancreatic adenocarcinoma		Open PD with portal vein resection	135		DGE, epileptic seizure	34
8	83/M	Distal bile duct cancer		Open PD	7,027			28
9	75/M	Ampullary cancer		Open PD	205			23
10	46/F	Pancreatic adenocarcinoma		Open PD	22			18
11	61/M	Intraductal papillary mucinous neoplasm	MPD obstruction	Robot-assisted PD	17,000	B*		15

F, female; M, male; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; DM, diabetes mellitus; MPD, main pancreatic duct; POD, postoperative day; POPF, postoperative pancreatic fistula; ISGPS, International Study Group on Pancreatic Surgery; DGE, delayed gastric emptying. *Additional abdominal drainage or adjustment of abdominal drains under X-ray fluoroscopy.

A meta-analysis focusing on PD demonstrated that Blumgart anastomosis was associated with a decreased risk of grade B/C POPF (*2*). Use of the three-loop suture device for Blumgart anastomosis is reasonable because it reduces the number of pancreatic punctures used in conventional techniques from six to four, thus decreasing the risk of bleeding and pancreatic juice leakage due to needle trauma. The reduction of pancreatic punctures enabled by this device would also be beneficial in Blumgart anastomosis during laparoscopic and robot-assisted PD (*13,14*), although the current thread length (70 cm) should be shortened to 20 to 30 cm to facilitate manipulation during minimally invasive procedures. Furthermore, the three-loop suture device may be useful in pancreaticogastrostomy using matless sutures (*15*).

The four-needle three-loop suture device recently became commercially available in Japan (PANC LOOP, KONO SEISAKUSHO Co., Ltd., Chiba, Japan). This device has potential to be widely used for closure and anastomosis of the pancreatic stump as a safe and effective alternative to conventional staplers or sutures.

In conclusion, the four-needle three-loop suture device can be an alternative to conventional staplers or sutures for closure and anastomosis of the pancreatic stump.

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Conflict of Interest: T.I. has served as a consultant to SONY Corporation and KONO SEISAKUSHO Co., Ltd., Chiba, Japan. None of the other authors have actual or potential conflicts of interest regarding the submission of this article. A part of this study was presented at the 32nd Meeting of Japanese Society of Hepato-Biliary-Pancreatic Surgery (24 February 2021).

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Actual situation of handling Tokyo 2020 Games-related patients at a designated hospital during COVID-19 pandemic

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Abstract: In preparation for the Tokyo 2020 Olympic and Paralympic Games, our hospital was responsible for accepting mainly media representatives, marketing partners, and other Games staff. Given that restricting our regular capacity to treat certain groups of patients could potentially result in social losses, to avoid this we made rigorous preparations for the entire hospital to accept Games-related patients. It was rational to set up a single 24-h contact point at the Emergency Department for making the decision on whether to accept the patient or not and for coordinating the patient's medical care. With respect to language support, International Health Care Center staffs were made available as interpreters on weekdays. Multilingual support was available all day *via* an application run on tablet devices. During a 67-day period, the hospital accepted 31 Games-related patients (mean age 43.4 years, male: female ratio 25:6). Eighteen patients were from Europe, 4 patients each were from North America and Asia, 2 each were from Central America, South America, and Africa, and 1 was from Oceania. The most common cause of visits was COVID-19, but none were severe cases. Other causes were diverse and included moderate and severe conditions. We summarized the challenges and experiences in handling Tokyo 2020 Games-related patients at a designated hospital during the COVID-19 pandemic.

***Keywords*:** Olympics and Paralympics, pandemic, COVID-19

Introduction

In preparation for the Tokyo 2020 Olympic and Paralympic Games, several hospitals were designated to provide health care services to athletes, team officials, international sports organization officials, Olympic and Paralympic families, media representatives, marketing partners, and other Games staff. Each of the 8 designated hospitals in Tokyo were allocated categories of the aforementioned groups to accept during the Games. Five of these hospitals, including ours, were responsible for accepting mainly media representatives, marketing partners, and other Games staff. In the remaining 3 hospitals, 1 was responsible for accepting athletes and team officials and 2 for accepting Olympic and Paralympic families.

After the World Health Organization announced the global pandemic of COVID-19, the Tokyo 2020 Games were postponed for 1 year. However, the situation continued longer than expected and the Games ended up being held in summer 2021 amid the ongoing pandemic (*1*). Designated hospitals were therefore given the additional responsibility of accepting Games-related patients with COVID-19 (*2*).

Our hospital is a general hospital with approximately 700 beds, located in a busy district of Tokyo (9.9 km from the Olympic and Paralympic Village). We regularly accept emergent cases brought by ambulance. Our hospital is also a designated medical institution for infectious diseases and plays a pivotal role in providing clinical care for patients with infectious diseases. We have therefore also been accepting many patients with COVID-19. Given that restricting our regular capacity to treat certain groups of patients could potentially result in social losses, to avoid this we made rigorous preparations for the entire hospital to accept Games-related patients.

Establishing a system to accept Tokyo 2020 Games-related patients

With our Emergency Department and the administrative division, the International Health Care Center of National Center for Global Health and Medicine (NCGM) led efforts to establish a system to accept Games-related

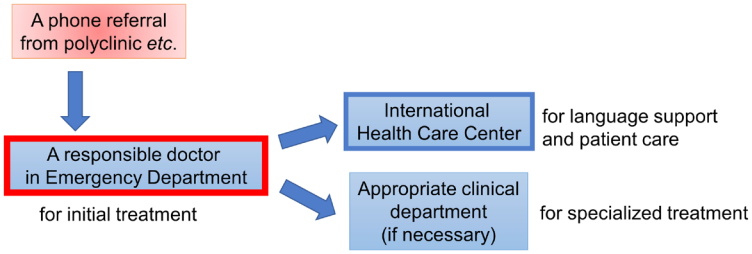

Figure 1. Flow chart for accepting patients of the Olympic and Paralympic officials. All necessary information on patients were collected by a responsible doctor in Emergency Department. If patients were suspected or apparently had COVID-19, they were treated in a negative pressure room in the emergency department. There were no restrictions on the acceptance of COVID-19 patients.

patients. The Center routinely coordinates the acceptance of international patients. The hospital was supposed to accept patients upon prior request, except in highly urgent cases, so it was rational to set up a single 24-h contact point (the responsible person in the Emergency Department with a designated mobile phone) for making the decision on whether to accept the patient or not and for coordinating the patient's medical care. Because it was likely that patients would be referred to the relevant department after the first consultation at the polyclinic of International Olympic Committee (IOC), each hospital department at our hospital was duly notified about the system before the Games started (Figure 1).

Our hospital was not designated to accept athletes in the first line, but was expected to accept them when the designated hospital responsible for their treatment could not accept them. To account for this possibility, selected staff (mainly from the Pharmacy Department and Emergency Department) received training on doping and an emergency physician must be accompanied by a pharmacist if we needed to treat an athlete. Actually, our hospital accepted patients from the test competitions held immediately before the Games started, which was a good simulation exercise.

Measures against COVID-19 outbreaks continued to be crucial, and special attention was required for personnel who had just arrived in Japan. Irrespective of their specific symptoms (*e.g.*, fever), they needed to be managed in the same way as patients with COVID-19 until they completed the 2-week isolation imposed by the government. They also needed to be separated from general patients, and coordination of the reception and consultation areas had to be set up for each case.

With respect to health insurance claims, patients with insurance arranged by the Committee of the Tokyo 2020 Games were simply discharged, while those insured by other means were asked to pay their expenses by themselves and consult with their insurance providers later. The hospital was expected to make best efforts to avoid uncollected medical bills, but if they occurred, the Committee of the Tokyo 2020 Games promised to cover them.

With respect to language support, International Health Care Center staff were made available as interpreters (*e.g.*, in English and Chinese) during working hours on weekdays. Multilingual support was available all day *via* an application run on tablet devices.

Clinical practice in handling Tokyo 2020 Games-related patients

During a 67-day period that included the pre- and post-Game periods (July 7-September 11, 2021), the hospital accepted 31 Games-related patients (mean age 43.4 years, male: female ratio 25:6). Seven of the 31 patients visited the hospital twice. Nine patients were hospitalized but all were discharged within 10 days.

Seventeen patients visited our hospital between 08:00 and 16:00, 10 visited between 16:00 and 24:00, and 4 visited between 00:00 and 08:00. Despite the need for prior request, 3 patients arrived without it. Ten patients arrived by ambulance.

Among the 28 patients who visited out hospital with prior request, referrals were from the IOC polyclinic or by the Committee of the Tokyo 2020 Games in 18 cases, from insurance companies in 7 cases, from other hospitals in 2 cases, and from an accompanying doctor in 1 case. Eighteen patients were from Europe, 4 patients each were from North America and Asia, 2 each were from Central America, South America, and Africa, and 1 was from Oceania. Among the allocated categories of Games-related patients we accepted, 16 patients were media representatives and 10 were Games staff; we also accepted 5 athletes when the need arose.

The most common cause of visits was COVID-19 (8 patients, 5 of whom were hospitalized), but none were severe cases. Other causes were diverse and included moderate and severe conditions (*e.g.*, diaphragmatic hernia requiring operative repair, pancreatitis, status epilepticus, and angina pectoris, humeral shaft fracture, malaria (*Plasmodium falciparum*), optic neuropathy, urolithiasis, inner ear vertigo, and earwax plug).

Eleven patients were covered by insurance arranged by the Committee of the Tokyo 2020 Games, while 20 were insured by general insurance companies. All medical expenses were collected. Patient identification

was confirmed by the Games accreditation card (AD card), although 3 patients visited our hospital without it.

Challenges and experiences in handling Tokyo 2020 Games-related patients at a designated hospital during COVID-19 pandemic

The Tokyo 2020 Games were held under a state of emergency due to the COVID-19 pandemic, amid a serious surge in COVID-19 infections in Japan. At that time, almost all hospitals needed to limit routine clinical practice, and our hospital additionally needed to accept Game-related patients. Fortunately, the number of COVID-19 patients in Japan peaked during the window of time between the Olympic Games and Paralympic Games and we rarely accepted Games-related patients at that time. We accepted 37 patients in total during the 67-day period, averaging 0.55 patients per day. We had held several training events and completed preparations to deal with potential mass casualties such as from a terrorist attack or heat stroke event. At the last minute, spectators were largely barred from Games and no such incidents occurred.

Regarding SARS-CoV-2 screening, 55 cases with COVID-19 were confirmed among 54,250 tests at the airport for those who came to Japan from overseas to participate in the Tokyo 2020 Games; 299 cases were confirmed among 1,014,170 tests conducted during the Olympics and Paralympics (*3*). Our hospital was designated to accept Games-related patients with COVID-19, and actually accepted 8 such patients, 5 of whom were hospitalized. Many of those with COVID-19 were cared for at designated hotels, which likely avoided placing a substantial burden on the designated hospitals. One of the reasons for this is that COVID-19 infection was well controlled in the Olympic Village.

Language support (interpretation in English) was provided mainly from 08:00 to 16:00 and 16:00 to 24:00 for night shift which coincided with many of the patients' visits, thus we rarely encountered language-related difficulties.

In conclusion, our hospital fulfilled its responsibilities as a designated hospital for the Tokyo 2020 Olympic and Paralympic Games during the 5th wave of the COVID-19 pandemic in Japan, in the situation where the hospital had placed restrictions on routine clinical practice. We could offer best possible medical care to various patients, including those with COVID-19, without substantial confusion.

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A novel anticoagulation treatment protocol using unfractionated heparin for coronavirus disease 2019 patients in Japan, 2022

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Abstract: Hypercoagulability, which can be induced by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) plays an important role in the pathogenesis of coronavirus disease 2019 (COVID-19). Although anticoagulation therapy is expected to decrease the incidence of thrombosis and mortality in COVID-19 patients, the optimal use of anticoagulation therapy has not been established, especially using unfractionated heparin (UFH). Herein, we suggest a new anticoagulation treatment protocol for the use of UFH in Japanese COVID-19 patients. This protocol considers the safety regarding UFH usage, to lower major bleeding events, and reflects the latest evidence and the current situation regarding anticoagulation therapy in Japan.

***Keywords*:** SARS-CoV-2, hypercoagulability, thrombosis

Introduction

Systemic and microvascular thrombosis induced by hypercoagulability are important complications of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. At the beginning of the coronavirus disease 2019 (COVID-19) pandemic, several reports showed a high prevalence of venous thromboembolism (VTE) in COVID-19 patients (*1,2*). Although some reports have suggested the indication and efficacy of anticoagulation therapy to treat COVID-19 patients (*3,4*), the optimal use of anticoagulation therapy remains unclear. Regarding drug approval in Japan, we previously reported an anticoagulation protocol using unfractionated heparin (UFH) to treat moderate-to-severe COVID-19 patients in Japan in early 2020 (*5*). Here, we report an updated anticoagulation protocol for COVID-19 patients, which reflects the latest evidence and current situation of anticoagulation therapy for COVID-19 in Japan.

Latest worldwide evidence regarding anticoagulation therapy for COVID-19 treatment

A meta-analysis showed that the prevalence of VTE in COVID-19 patients is approximately 7–8 times higher than that for other respiratory infections, and the incidence of VTE is lowered by anticoagulation therapy (*6*). Moreover, several open-label randomized controlled trials evaluated the efficacy of anticoagulation therapy in reducing mortality of COVID-19 patients. Two trials, which enrolled COVID-19 patients with elevated d-dimer level and hypoxemia showed that therapeutic-dose anticoagulation could reduce all-cause mortality (*7,8*). The most comprehensive study was a multiplatform randomized controlled trial of anticoagulation therapy for COVID-19 patients, which was conducted mainly in Western countries and Brazil. It showed that therapeutic-dose anticoagulation, compared to the usual prophylactic-dose anticoagulation, decreased in-hospital mortalities and protracted organ support-free days in patients with moderate disease. This benefit was observed regardless of the baseline D-dimer level (*9*). This trial also showed that patients with severe COVID-19 who required organ support (including high-flow nasal cannula, noninvasive or invasive mechanical ventilation, extracorporeal life support, and vasopressors or inotropes) did not benefit from therapeutic-dose anticoagulation over the prophylactic dose (*10*). Instead, patients who received therapeutic-dose anticoagulation experienced more major bleeding events than did those who received prophylactic anticoagulation therapy (*9,10*).

Consequently, the National Institutes of Health (NIH) recommends therapeutic-doses of heparin for COVID-19 patients who require low-flow oxygen and prophylactic-doses of heparin for COVID-19 patients who require intensive care unit (ICU)-level care (including high-flow

oxygen) (*11*). These recommendations are based on the results of the aforementioned open-label randomized controlled trials (*7-10*). Meanwhile, the World Health Organization has recommended prophylactic-dose anticoagulation in all hospitalized COVID-19 patients, on the grounds of low certainty of evidence (*12*).

Anticoagulation treatment strategy for COVID-19 patients in Japan

Several important points must be considered when using the latest worldwide evidence to determine anticoagulation therapy protocols for COVID-19 patients in Japan. First, in the aforementioned multiplatform randomized controlled trial, the majority of patients received anticoagulation therapy with low-molecular-weight heparin (LMWH), while UFH use is preferred in Japan, where LMWH has not been approved for thrombotic diseases. A Japanese questionnaire-based survey showed that UFH was used in 67.6% of COVID-19 patients who received anticoagulation therapy, while LMWH was used in only 12.8% of patients (*13*).

UFH mainly inhibits thrombin and factor Xa, while LMWH inhibits factor Xa more specifically than UFH (*14*). Because the biological half-life of UFH is 45-60 minutes with usual intravenous doses, intravenous infusion is necessary to maintain the therapeutic range (*15*). Since the bioavailability of UFH is unstable, which is because UFH also binds endothelial cells, platelet factor 4, and platelets, frequent monitoring of the activated partial thromboplastin time (aPTT) is necessary (*14*). In contrast, the biological half-life of LMWH is 2 hours for intravenous infusion and 4 hours for subcutaneous infusion, and the bioavailability of LMWH is 90-100% after subcutaneous infusion. Therefore, the therapeutic range can be easily maintained with subcutaneous infusion of fixed dose LMWH. Dose adjustment of LMWH is necessary when creatinine clearance is less than 30mL/min, while UFH is not affected by renal function. LMWH is associated with a lower risk of heparin induced thrombocytopenia and bleeding complications compared to UFH (*15*). Additionally, a systematic review using the Cochrane database revealed that prophylactic-dose LMWH is more effective than UFH in reducing the risk of deep vein thrombosis in acutely ill medical patients, also exhibiting a lower bleeding risk (*16*). For these reasons, there is a concern that therapeutic-dose anticoagulation therapy with UFH may increase the incidence of major bleeding events compared with LMWH.

Second, whether ethnic differences affect the incidence of thrombosis in COVID-19 patients should be considered. The reported prevalence of thromboembolic events in COVID-19 patients in Japan is 1.9-2.9% among all hospitalized patients, and 7.5-13.5% among patients who require ICU-level care (*13,17*). A systematic review of the incidence of VTE in COVID-19 patients, which included 17 studies from Europe and the USA and three studies from China, showed that the pooled incidence of VTE was 21% among all hospitalized patients and 27% among ICU patients (*18*). Even though systematic screening of VTE was not routinely performed in Japanese studies, the prevalence of VTE in COVID-19 patients may possibly be lower in Japan than in Western countries. Indeed, induced endothelial dysfunction and hypercoagulability may differ generally according to ethnicity; however, a firm conclusion has not been attained due to insufficient data. Besides, Asian populations are considered to be more prone to bleeding complication due to anticoagulation therapy than other ethnicities. Although, the data for ethnic disparity of bleeding complications with UFH and LMWH is insufficient so far (*19*).

For these reasons, considering the therapeutic-dose of UFH for all COVID-19 patients requiring low-flow oxygen – based on the NIH recommendation – may not be reasonable in the Japanese population when considering the bleeding risk and expected benefit.

Suggestion for a new anticoagulation protocol, using UFH for COVID-19 treatment in Japan

We suggest a new anticoagulation protocol for COVID-19 treatment that reflects the latest evidence and considers the concerns regarding anticoagulation therapy for COVID-19 treatment in Japan (Figure 1). In this new anticoagulation protocol, we recommend a prophylactic-dose of UFH for patients who need oxygenation regardless of the method of administration (from nasal cannula to mechanical ventilation), unless there is a contraindication for UFH. If thrombosis is clinically suspected, we recommend diagnostic imaging before initiating therapeutic-dose UFH. If the diagnosis of thrombosis is confirmed or the imaging test is unavailable, but clinicians strongly suspect thrombosis, therapeutic-dose UFH should be initiated. To minimize the risk of bleeding, aPTT should be routinely monitored. Protamine can be administered for neutralizing UFH when excessive prolongation of aPTT or major bleeding events occur. Because of rapid drug clearance, the advantage of UFH for LMWH is flexibility of discontinuation when clinically indicated. Moreover, UFH can be neutralized by protamine more effectively than LMWH (*15*).

In conclusion, because the efficacy and safety of UFH for COVID-19 treatment is uncertain, we developed a new protocol for its safe usage and to reduce the risk of major bleeding events. A multiplatform randomized controlled trial showed that therapeutic-doses of LMWH lowers the mortality and number of organ support-free days in COVID-19 patients requiring low-flow oxygen. Although there are limited data of the usefulness of UFH use in Japanese patients with COVID-19, for example,

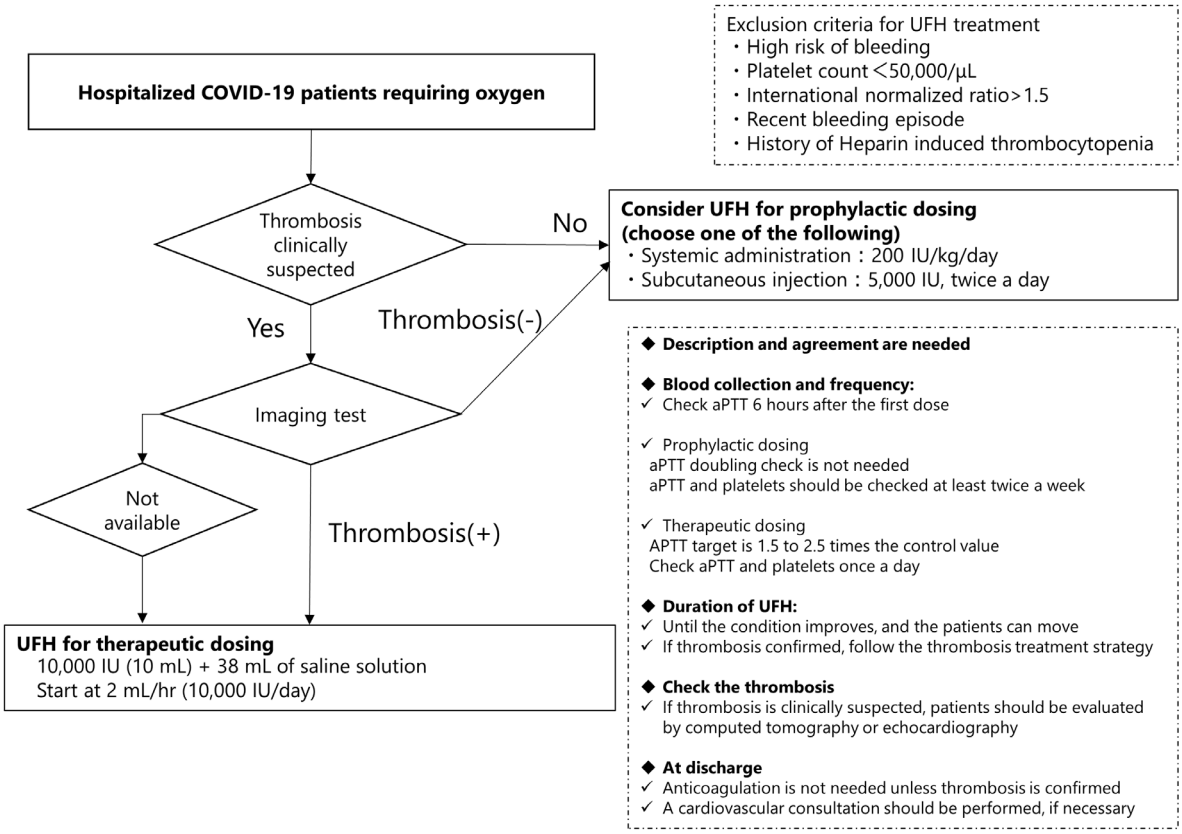

Figure 1. New anticoagulation protocol for the use of unfractionated heparin (UFH) in coronavirus disease 2019 (COVID-19) patients in Japan. This figure shows the new anticoagulation treatment protocol for the use of UFH in COVID-19 patients who require oxygen support.

in young patients without underlying diseases, the risk of bleeding is low, and therefore, UFH with a therapeutic dose may be acceptable. UFH may be considered for therapeutic doses if new studies clarify that UFH has a low risk of bleeding if used appropriately. Thus, it will be necessary to further investigate the usefulness of UFH use in Japanese patients with COVID-19 based on the latest evidence and the situation in Japan when new evidence emerges.

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The role of radiologic technologists during the COVID-19 pandemic

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Abstract: During the pandemic, stress of coronavirus disease 2019 (COVID-19) on a radiology department has caused major change in the workflow and protocol, which can inflame unnecessary anxiety among the staff. We have adapted and responded quickly however, to the volatile clinical situations owing to a close consultant in infection control. Our repeatedly revised procedures since the 2014 Ebola outbreak possess the expertise and were very useful. In-house training sessions have been held and updated accordingly. In-house networking service has now become more common in our department instead of the emergency contact network relaying the message to the person on the phone tree. Up until January 2022, we examined 10,861 chest X-rays with no in-hospital infection. We sincerely hope our chest X-ray strategies comply with infection prevention and control standards and minimize use of personal protective equipment will be embraced as a positive initiative by frontline radiologic technologists and relieve their anxiety.

***Keywords*:** coronavirus disease 2019 (COVID-19), chest X-ray, sustainable operation, personal protective equipment (PPE), pandemic, staff management

Introduction

The first case of coronavirus disease 2019 (COVID-19) in Japan was reported on 16 January 2020. The total number of infected reached 8,876,504 and the number of deaths reached 30,659 as of June 1, 2022. The main symptoms of COVID-19 are fever and respiratory symptoms (*1*). Despite the absence of dyspnea, some patients with COVID-19 may have markedly reduced oxygen saturation. In Japan, every time there was a major COVID-19 wave, the medical facilities became overwhelmed.

The decision to image patients who are positive for COVID-19 or are suspected of having COVID-19 is based on how the imaging will impact patient care. Although we do not routinely use imaging for COVID-19 screening, imaging is performed in patients positive for or suspected of having COVID-19 to rule out other diagnoses that can be treated. Chest X-ray (CXR) and computed tomography (CT) are the most commonly used imaging techniques for the management (diagnosis, hospitalization, and follow-up) of patients with COVID-19 (*2,3*), and several authors have found that both modalities are useful predictors of patient outcome (*4-10*).

In this scenario, the radiologic technologists accepted their crucial roles in the management of infected and non-infected patients. They need to work safely to limit the spread of the virus to decrease morbidity and mortality rate, which may result from delayed diagnosis and treatment of the infected patients.

Another important consideration is conserving PPE by avoiding excessive precaution and resource utilization. These stresses of COVID-19 on a radiology department have caused major changes in the workflow and protocol, which can vary among institutions and inflame unnecessary anxiety among the staff.

Ever since the 2014 Ebola outbreak, we have employed and revised procedures and held in-house training sessions repeatedly. From the first acceptance of a COVID-19 case in January 2020, our radiology department has worked safely up to January 2022 (10,861 chest X-rays and 3,985 CT cases).

The purpose of this article is to describe and suggest our procedures to assist in combating not only this pandemic but also another one, which may emerge in the future.

Approach

Following hospital policy, close contacts of people infected with coronavirus are to stay at home and self-isolate while they are suspected of being infected with the coronavirus, including their family members. With the exception that employees exposed to COVID-19 who are asymptomatic are required to return to work, to attest to their health daily, and to self-monitor for symptoms before the time they leave home. We worked

on an assignment of minimizing close contacts with COVID-19 so as to maintain the state.

Our approaches to COVID-19 cases are summarized in Table 1 and below:

Staff management for sustainable radiology operation

Our existing radiology management structure was too large to effectively respond to the rapid scenario changes. In order to reduce risk from outbreak of clusters happening and to have multiple backups in case of a cluster, we broke up all radiologic technologists into four hybrid groups and operated as individual organizational structures dealing with daily routine. Each group was equally composed of experts in X-ray, CT, Magnet Resonance Imaging, Interventional Radiology, Nuclear Medicine, and Radiation Therapy. Every member had restricted access to the others outside his or her group members. Meetings were conducted online to avoid congregation. Staff were encouraged to maintain social distancing and encouraged to stay home if exhibiting cold-like symptoms or fever (37.0℃ and over). The unit supervisor kept health status records of every staff member and reported with them and consulted with our Infection Control Team when necessary.

Monitor and respond to rapid changes in the COVID-19 pandemic

The same trend that was seen for the number of patients with severe symptoms in Tokyo reported on Tokyo Metropolitan Government COVID-19 Information Website was also seen for the number of CXR for COVID-19 cases at NCGM between September 2020 and November 2021 (Figure 1). The website served as a good indicator to predict waves of COVID-19 and to allocate more radiologic technologists and resources for CXR to cope with the sharp increase in infections.

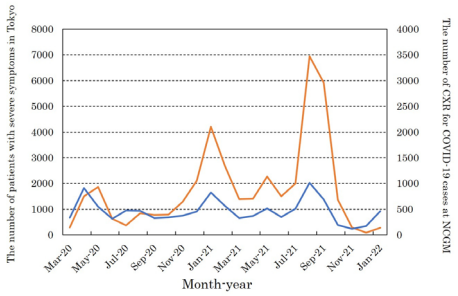

Figure 1. Patients with severe symptoms in Tokyo Metropolitan Government Website and CXR cases for COVID-19 at NCGM. This figure nicely illustrates the website served as a good indicator of allocation of radiologic technologists for CXR. The same trend that is seen for the number of patients with severe symptoms in Tokyo reported on Tokyo Metropolitan Government COVID-19Information Website (orange line) is also seen for the number of CXR for COVID-19 cases at NCGM (blue line) between September 2020 and November 2021.

Table 1. Summary of the standard approach and procedure during the pandemic

Approach	Procedure
1) Staff management for sustainable radiology operation	● Breaking up radiologic technologists into four hybrid groups. ● Restricting access to only his or her group members. ● Conducting meetings online. ● Maintaining social distancing and encouraging members to stay home if exhibiting cold-like symptoms or fever (37.0 oC and over). ● Keeping health status records of every staff member.
2) Monitor and respond to rapid changes in the COVID-19 pandemic	Using the website as an indicator to predict waves of COVID-19 and to allocate radiologic technologists and resources to cope with the sharp increase in infections.
3) Education	● Discontinuing the existing training program and not accepting external students and trainers. ● Training all staff regularly for donning and doffing of personal protective equipment (PPE), hand hygiene and infection prevention protocols. ● Composing an infectious disease clinical team in radiology department.
4) General environment	● Setting up a waiting area to keep social distancing and temperature checks before entering the hospital. ● Scheduling suspected and confirmed COVID-19 patients at the end of morning work and at the end of clinic day. ● Informing suspected or confirmed patients in radiology information system prior to imaging.
5) COVID-19 chest X-ray	● Designating and covering mobile X-ray equipment and flat panel detectors (FPDs) with plastic bags. ● Working in pairs to promote the contract/non-contract technique. ● Keeping track of all staff involved in scanning.
6) COVID-19 CXR Procedure	● Identifying patients in the clean area. ● Covering the FPD with a plastic bag and touching and manipulating the mobile X-ray only on the designated landmarks. ● After imaging, carrying out the PPE to avoid self-contamination. ● Cleaning all visible surfaces of the room with approved disinfecting agents, if necessary.

Education

We discontinued the existing training program and did not to accept external students and trainers for the time being at this stage. All staff were trained regularly for donning and doffing of PPE, hand hygiene and infection prevention protocols. Radiology department selected and composed an infectious disease clinical team to fulfill the key role of infection control. The team actively disseminated useful information and provided guidance to all staff members electronically.

General environment

We set up a designated waiting area for patients keeping social distancing and submitted all out-patients and visitors to temperature checks and inquiries before entering the hospital. We extended time between exams for cleaning and disinfecting equipment and scheduled suspected and confirmed COVID-19 patients at the end of morning work and at the end of clinic day. We informed suspected or confirmed patients in radiology information system prior to imaging.

Preparing COVID-19 CXR

Mobile X-rays are the mainstay imaging tool for emergency department and inpatient settings. We designated and covered mobile X-ray equipment and flat panel detectors (FPDs) with plastic bags to reduce transmission risk. We worked in pairs to promote the contract/non-contract technique; one radiologic technologist positioned the X-ray tube and made the exposure and another positions the patient and set the covered FPD. We cleaned and disinfected the imaging equipment after each procedure. We kept track of all the staff involved in scanning.

Following are our standard procedures:

i) Landmarks for touch of the equipment We designated some landmarks as red circles on the equipment for touching to operate. These reduced number of contact points not only economized time and labor to sanitize the equipment but limited the spread of the virus (Figure 2).

ii) Suggested personal protective equipment (PPE) set Body protection: long-sleeved water-resistant gown; Head protection: cap; Respiratory protection: particulate respirator type N95 mask (N95); Eye protection: face shield or goggles; Hand protection: inner and outer gloves.

iii) Protective equipment for indirect transmission Plastic cover for operator console and FPD

iv) Wearing (donning) the PPE

Before wearing the PPE, proper hand hygiene should be performed following international recommendations (*11*). This is a critical aspect in this setting and should be performed using an alcohol-based solution in accordance with the manufacturer's instructions.

Figure 2. Landmarks (red circles) for touch on the X-ray tube. These landmarks served not only to limit the spread of the virus but also to economize time and labor to sanitize the X-ray tube.

The first PPE to be worn is the gown. When using a gown with back closure, a second operator assisted in buttoning up the back.

After wearing the gown, it is suggested to proceed with the respirator (N95) that protects from the inhalation of droplets and particles. It is important to perform a fitting test after the respirator has been put on, following the manufacturer's instructions. The metal nose clip needs to be adjusted and the straps have to be tightened to have a firm fit. Once the respirator has been properly positioned, put on the face shield or goggles for eye protection. Position the face shield or goggles properly and ensure it fits well.

After the goggles, wearing gloves is next. It is important to extend the glove to cover the wrist over the gown's cuffs. For individuals allergic to latex gloves, an alternative option, for example nitrile gloves, should be available.

COVID-19 CXR procedure

i)Patient identification Patients should be identified not in the contaminated but in the clean area. We employed the modality work list passing a barcode scanner in a Digital Imaging and Communications in Medicine (DICOM) process for this purpose.

ii) Patient positioning and imaging We moved the mobile X-ray to the contaminated area and covered the FPD with a plastic bag. The mobile X-ray should be touched and manipulated only on the designated landmarks to prevent the spread of infection in the hospital. After imaging, we removed the plastic bag carefully and disposed of it in a designated infectious waste container.

iii) Removing (doffing) the contaminated outer gloves After disposing of the plastic bag, we removed the PPE; the PPE should by now be contaminated and this is an important step to be carefully carried out to avoid self-

contamination. The outer gloves were removed first because they are considered heavily contaminated. Alcohol-based hand disinfectant was done before removing the outer gloves. We disposed of the removed gloves in a biohazard bin.

iv) Imaging equipment cleaning Mobile X-rays and other devices including FPDs and barcode scanners were sanitized with sodium hypochlorite solution focusing on the predetermined contact points. Then adequate ventilation was ensured.

v) Room cleaning With approved disinfecting agents following a clockwise, linear, from top to bottom pattern of cleaning all visible surfaces was done, if necessary.

vi) Removing Gowns and inner gloves After disinfection of the equipment and room, the inner gloves were disinfected with an alcoholic solution. The gown and inner gloves were removed by grabbing the back of the gown and pulling it away from the body, keeping the contaminated front part inside the gown.

vii) Removing eye protection After the gown, either the goggles or face-shields were removed. When removing face-shields, hand disinfection was performed, and care was taken not to touch the surface of the mask. In order to remove the goggles, a finger was placed under the textile elastic strap in the back of the head and the goggles were taken off. Touching the front part of the googles, which can be contaminated, should be avoided.

viii) Removing cap Hand disinfection was performed before removing the cap, and the cap was removed from the inside so that the outside of the cap should not touch hair or face.

ix) Removing respirator In order to remove the respirator, a finger or thumb was placed under the straps in the back and the respirator to be taken off. The respirator was disposed of after removal. It is important to avoid touching the respirator with hands during its removal. After glove removal, hand hygiene was performed.

Outcomes

During the COVID-19 pandemic, the clinical environment has been constantly changing. Constantly updated Tokyo Metropolitan Government COVID-19 Information Website and research on COVID-19 have been valuable sources of information reflecting the latest status. We have adapted and responded quickly to the volatile clinical situations owing to a close consultant in infection control. Since employing procedures during the 2014 Ebola outbreak, those manuals have been revised and enlarged repeatedly. In-house training sessions have been held and updated accordingly. The number of face-to-face meetings has been minimized, while that of online meetings has been proven fast and effective means of communication among the staff. In-house networking service has now become more common in our department instead of the emergency contact network relaying the message to the person on the phone tree.

Up until January 2022, we examined 10,861 CXRs with no in-hospital infection. In this article, we described our chest X-ray strategies to comply with infection prevention and control standards and to minimize use of personal protective equipment: patient identification, patient positioning and imaging, removing the contaminated outer gloves, imaging equipment cleaning, room cleaning, removing gowns and inner gloves, removing eye protection, removing cap, and removing respirator. We sincerely hope this technique will be embraced as a positive initiative by frontline radiologic technologists and relieve their anxiety.

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Adapting pediatric health care responses to the COVID-19 pandemic in Japan: A clinical perspective

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Abstract: The COVID-19 pandemic required our pediatric health care staff to adjust to many irregularities and solve serious issues in our routine clinical practice. In outpatient clinics, many children exhibited common cold symptoms that mimic COVID-19, thus we initially screened patients *via* an interview form, then later *via* SARS-CoV-2 antigen test. Cluster infections were entirely avoided by following systematic, everyday precautions. Patients'quality of life has been difficult to maintain during the pandemic, due to social and staffing restrictions. Other unexpected repercussions – such as an unexpected lack of seasonal virus infections, then a respiratory syncytial (RS) virus outbreak – required agile management of hospital resources. While we must continue to adapt our treatment programs in response to the evolving COVID-19 crisis, it remains essential to support the well-being of children through regular health check-ups, mental health support, educational opportunities, proper socialization, and close communication with parents and families.

***Keywords*:** COVID-19, pandemic, child, health care delivery, clinical application

Introduction

In late 2019, novel coronavirus (severe acute respiratory syndrome coronavirus 2: SARS-CoV-2) infection (COVID-19) was first reported from Wuhan, China (*1*) and subsequently spread worldwide. As in other countries, Japan experienced several waves of COVID-19 (Figure 1) that forced its pediatric healthcare providers to quickly adapt to multiple issues. In this communications report, we offer our perspectives on key issues that we as Japanese pediatricians experienced during the pandemic and offer insights into how we continually adapted our treatment programs in response to the ongoing crisis.

A brief chronology of the COVID-19 pandemic and Japan's official response

Near the very start of the pandemic, we at the National Center for Global Health and Medicine (NCGM) assisted with charter flights evacuating Japanese citizens, including children, from Hubei, China (*2*). Shortly thereafter, the first wave reached Japan (Figure 1) and the government declared a state of emergency (similar to a lockdown) in which all residents were urged to avoid public contact.

While the number of COVID-19 pediatric patients did not spike like that of adults, each subsequent wave brought renewed social restrictions. Schools were closed and social activity was restricted, resulting in prolonged lifestyle changes. For children, these closures had a significant impact on their well-being – particularly on socialization and mental health (*3*). We learned from the first wave that it is essential for children to continue to have proper conditions for learning and fostering social relationships *via* group activities. As such, in subsequent waves, schools tended to avoid closing, instead implementing measures such as online classes and staggered attendance. During the onset of the 6th wave (the omicron variant outbreak), however, pediatric COVID-19 patient numbers increased drastically, such that schools and nursery schools had no choice but to temporarily close due to cluster infections.

COVID-19 in children is mostly transmitted *via* family contact (*4,5*). While infected children normally exhibit only light symptoms or asymptomaticity (*4-6*), during the 6th wave children exhibited more pronounced symptoms such as fever, sore throat, nasal discharge, increased cough, and even febrile convulsions in some younger children While most children with COVID-19 show mild symptoms, for younger children and those

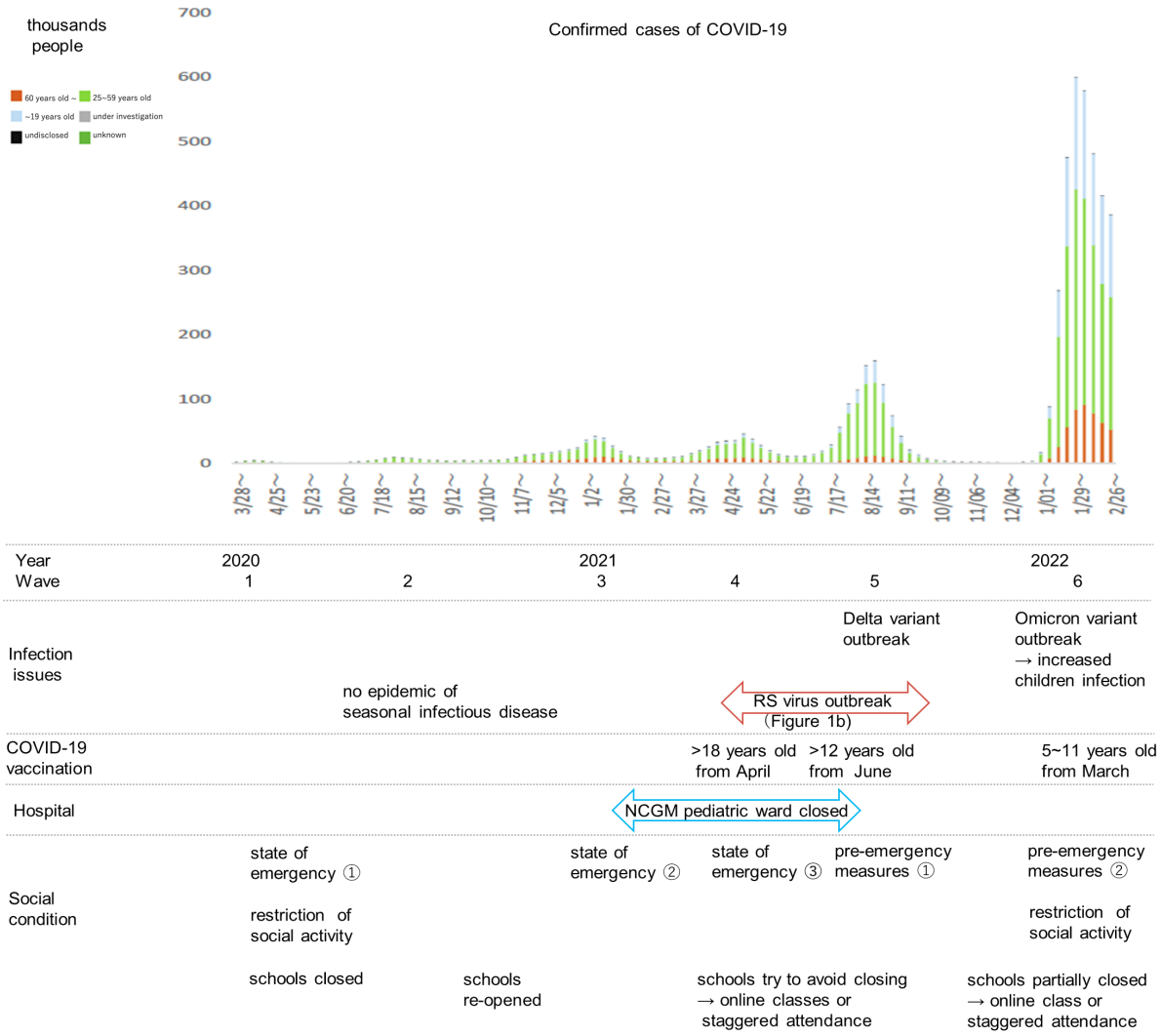

Figure 1. The COVID-19 pandemic and its impact in pediatric field in Japan. Data source: Ministry of Health, Labour and Welfare. 76th COVID19 infection control advisory board distributed data (published March15, 2022). *https://www.mhlw.go.jp/content/10900000/000913201.pdf*

with underlying disease, caregivers and parents need to be aware of the risk of severeness (*7,8*). Japan began vaccinating children 12 years old and over in June 2021 and 5–11 years old starting March 2022.

Prolonged quarantine has often been imposed on adults (including health care workers) who have been in close contact with infected children of family members. This has led to health care worker shortages, prompting the Japanese government to shorten the length of quarantine in order to help ease the situation.

Management of outpatient clinics

In the early stages of the pandemic, we had little information about the clinical features of pediatric patients with COVID-19; early reports suggested that children were mostly contracting COVID-19 from family members (*4,5*). Many children visit hospitals with common cold symptoms, such as fever and respiratory symptoms, which mimic COVID-19 symptoms. As it is often initially difficult to distinguish between the common cold and COVID-19, we began requiring patients to fill out an interview form (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=51*). The form asks not only about the patient's condition, but also their family's condition, whether they have been in crowed places, or had any contact with SARS-CoV-2-infected people. Patients who report having contact with the infected or suspected infected are then asked to enter an isolation room for examination by staff wearing appropriate personal protective equipment.

This interview form proved very effective until the 5th wave. However, starting from the 6th wave it became difficult to initially screen COVID-19 cases using just the form. Therefore, we began administering SARS-CoV-2 antigen tests to any patients showing a fever or respiratory symptoms. Suspected infected were given the antigen test in the infection division's isolated room before visiting the pediatric outpatient clinic. These

antigen tests revealed many patients with COVID-19, including asymptomatic cases. As such, we wore N95 masks and eye shields whenever we performed physical examinations.

We focused on keeping the outpatient clinic environment regularly and thoroughly sanitized, as it is difficult to get younger patients to wear masks properly. We installed several circulators in the outpatient clinic and used negative-air-pressure rooms for examining suspected COVID-19 positive patients. In cases of asthma attacks, we avoided nebulizer therapy (which increases the risk of COVID-19 transmission *via* aerosol) without first giving a SARS-CoV-2 antigen test. As of this writing, we have not experienced any COVID-19 cluster infections in our division; we believe this is owing to the everyday infection control precautions systematically taken by all of our staff.

Management of hospitalized patients

Children with COVID-19 were hospitalized in our infectious disease ward, instead of the pediatric ward. Most of our child patients displayed slight-to-moderate symptoms, and merely needed supportive care (*6*). We do not yet have enough evidence of the effectiveness and safety of antivirals nor antibody therapies for children; as such, such treatments are used sparingly. We experienced one case of novel disease state multisystem inflammatory syndrome in children (MIS-C), in which the patient showed gastrointestinal symptoms, cardiovascular dysfunction, and multisystem inflammation, including Kawasaki disease-like features after SARS-CoV-2 infection (*9*).

In terms of general care of inpatients, it was difficult to maintain the same quality of life as we had done before the pandemic. It proved problematic to confine quarantined COVID-19 children to their room for the full prescribed term; some even tried to escape. Normally, nursery staff and child life specialists would perform various support activities, however these activities were scuttled to prevent further infections. By the 3rd wave, we had fewer hospitalized children, which eventually led to our pediatric ward being temporarily closed for more than half a year. During this time of closure, many healthcare professionals from our pediatric division were reassigned to support COVID-19 patients elsewhere in the hospital, leaving gaps in patient care. Existing pediatric inpatients were redistributed to beds in various other wards and were not able to use the playroom in the pediatric ward. Visits by family members were generally not allowed. For patients who absolutely needed family attendance, one of the parents, after taking a PCR test for SARS-CoV-2, would occasionally obtain approval to stay with their children at hospital. For family members who were not allowed to visit the hospital, we made efforts to contact them regularly *via* phone and explain their child's condition; still, many families expressed their anxiousness. Overall, quality of life of inpatients and their families was very negatively impacted.

Regarding newborn babies delivered by COVID-19 infected mothers, we began quarantining them immediately after birth. It has been reported that vertical transmission is rare and that the major cause of COVID-19 transmission from mother to neonate is contact and airborne infection after birth (*10*). During the early stages of the pandemic we had little information on best practices, so we quarantined newborns for two weeks. Recently however, it is recommended to conduct a neonatal PCR test twice: at 24 hours and at 48 hours after birth; if both tests are negative, the newborn is confirmed to be uninfected with SARS-CoV-2 and is released from quarantine (*11*).

Impact of the COVID-19 pandemic on the pediatric field as a whole

The pandemic is likely to have an impact on other infectious diseases. Initially, after the first and second wave, seasonal viral infections specific to children (such as respiratory syncytial (RS) virus or Influenza virus) dramatically decreased (*12,13*). We assume that this was due to infection prevention controls such as hand sanitizing or wearing masks, although there were reports that other respiratory virus infections such as rhinovirus infection were increasing (*14*). We saw similar trends in detecting other respiratory pathogens from multiplex real-time PCR tests (Filmarray®) before hospitalization with respiratory symptoms. In the summer of 2021, an RS virus infection outbreak occurred (Figure 2). The RS virus usually causes cold-like symptoms (such as fever and a severe cough); as such, we needed to conduct differential diagnoses to screen for COVID-19, especially in infants with bronchiolitis and pneumonia complications. We believe that seasonal viral infections are contributing to the development and acquisition of infant immunity. Previous reports from 2020 suggest that many infants were not able to develop immunity to the RS virus and thus were infected during the 2021 outbreak (*13*). Furthermore, in April 2022, the World Health Organization reported that severe acute hepatitis of unknown etiology was increasing among children in several countries (*15*). We should expect the pandemic to have unexpected repercussions (*i.e.* influence on other pathogens) on pediatric disease control.

Another potential impact of COVID-19 is the delay or avoidance of medical care. During the initial waves of COVID-19, many parents were wary of bringing their children to hospital for routine checkups, vaccinations, and follow-ups. We grew increasingly concerned about such avoidance of routine care. Many clinics, including ours, set aside special hours for outpatient clinics so that non-infected children could visit the hospital safely and get appropriate treatment

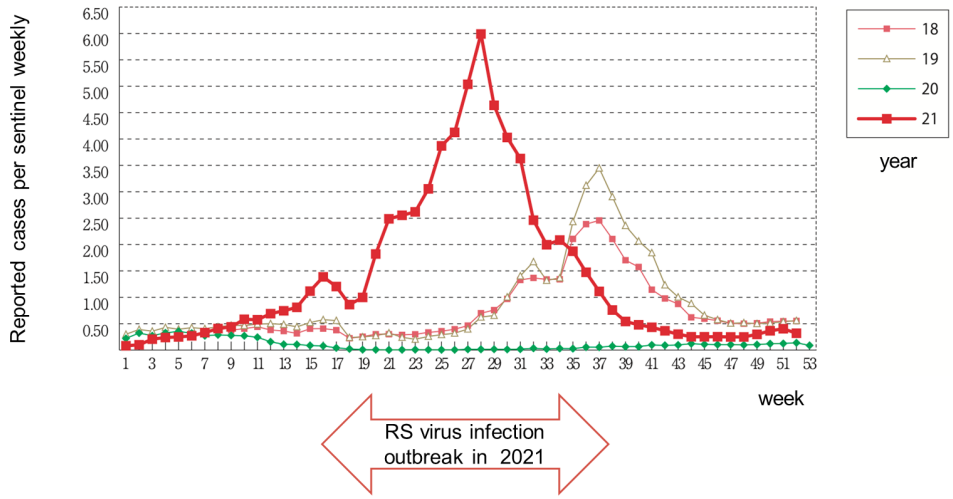

Figure 2. RS virus infection cases reported per sentinel weekly. RS, respiratory syncytial. Data source: Ministry of Health, Labour and Welfare/National Institute of Infectious Diseases Infectious diseases weekly report (published January 17, 2022). *https://www.niid.go.jp/niid/images/idsc/idwr/IDWR2021/idwr2021-51-52.pdf*

or preventive care. We also implemented telephone consultations and follow-ups. During the 5th and 6th waves, patients with COVID-19-like symptoms might have found it difficult to get an appointment at the overwhelmed outpatient clinic. We grew concerned about infants with issues such as bacterial infections who might not attain proper treatment, so we made every effort to not refuse consultations.

A third impact on pediatric care that we have witnessed is the disruption of daily routines. During the first wave of the pandemic, most schools were closed and children had to stay at home. Many faced mental health issues due to this radical change of lifestyle (*2*). Unable to go to school, meet friends, play outside, nor engage in physical activity, many children suffered physiological stress (*16*). After schools re-opened, some children struggled to catch up on missed schoolwork, and some even refused to go back to school altogether. Autonomic imbalances and/or mental illnesses such as depression and anorexia have increased; many children visited our hospital with these symptoms during the pandemic. This continued stress on families stuck at home has brought concerns of increased incidence of domestic violence and/or child abuse (*17*).

Conclusion

The COVID-19 pandemic required pediatric health care staff to adjust to many irregularities and solve serious issues in our routine clinical practice. Children and their families confronted profound difficulties in adjusting to major disruptions to their educational and social activities. In any circumstance it is essential to support the well-being of children through regular health check-ups, mental health support, educational opportunities, and proper socialization, all while maintaining regular communication with their families. Restrictions on social contact – while effective for limiting SARS-CoV-2 infections – are greatly stressful for hospitalized children and their families. Despite the ongoing emergence of new variants, we expect that vaccinating a wider age range – together with maintenance of standard infection controls and precautions – will bring the pandemic under control so that we may protect the rights and general welfare of hospitalized children.

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Boosting multiregional clinical trials (MRCT) in Asia through the establishment of the Japan-led network for clinical research, the ARO alliance for ASEAN & East Asia (ARISE)

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Abstract: There is an increasing demand for clinical research, and this demand has particularly increased during the novel coronavirus infection (COVID-19) pandemic. In the light of these events, fostering international cooperation has become essential. The ARO Alliance for ASEAN & East Asia (ARISE) is a Japan-led international network for clinical research in Asia that was established to encourage and facilitate multiregional clinical trials. The Department of International Trials of the National Center for Global Health and Medicine (NCGM) launched ARISE in December 2021 to pursue efficacious, high-quality clinical research and ensure rapid responses to health emergencies, with the timely provision of new medicinal products to patients in Asia.

***Keywords*:** clinical research, clinical trial, global health, Asia

To respond to rapidly growing demands for clinical research at the local level, it is important to build robust research infrastructure in low- and middle-income countries. The 2014–2015 Ebola outbreak in West Africa revealed the lack of infrastructure, expertise, and regulations in the face of an urgent need for clinical trials at the local level during public health crises (*1*). The number and complexity of clinical trials have increased significantly in recent years. According to ClinicalTrials.gov, a registry of clinical studies conducted worldwide in 220 countries, the number of registered clinical studies is rising from 325,773 in 2019–2020 to 362,505 in 2020–2021 (2). The complexity of clinical trials has also increased, particularly since the novel coronavirus infection (COVID-19) pandemic. Consequently, the demand for clinical research professionals exceeds availability, and global efforts to increase the clinical research workforce are underway (*3*).

International cooperation in clinical research is essential for addressing common global health issues and enabling the provision of evidence-based solutions to patients and health professionals in a timely manner. In the face of the COVID-19 pandemic, the need for global cooperation in clinical research to overcome unprecedented health challenges has been reaffirmed. However, multinational research is complex due to differences in regulatory and ethical requirements, medical systems, health priorities, and cultures between countries. These barriers affect the scope of research and reduce its potential impact on healthcare industries, health economies, and societies.

To tackle this problem, the Asian Health and Welfare Initiative (AHWIN), created in 2019 by the Japanese government, has promoted establishing a clinical research network to improve the infrastructure and development capacity of clinical research in Asia (*4*). Undertaking these missions as one of the national centers for Advanced and Specialized Medical Research under Japan's Ministry of Health, Labour, and Welfare, the National Center for Global Health and Medicine (NCGM) launched the ARO Alliance for ASEAN & East Asia (ARISE) in December 2021. ARISE is a network of major academic research organizations (AROs) that promotes and facilitates multiregional clinical trials (MRCTs) in Asia. ARO denotes "an academic and non-profit institution that performs one or more functions in the conduct of clinical trials" (*5*). The NCGM established this ARO network with the support of the Japan Agency for Medical Research and Development (AMED) to enable the rapid and low-cost development of pharmaceuticals and medical devices. ARISE is headed by the President of the NCGM, and its secretariat office is within the Department of International Trials of the Center for Clinical Sciences. There are currently ten member AROs from Indonesia, Japan, the Philippines, Thailand, and Vietnam, and membership is expected to grow in the future.

On December 9, 2021, the ARISE kick-off meeting

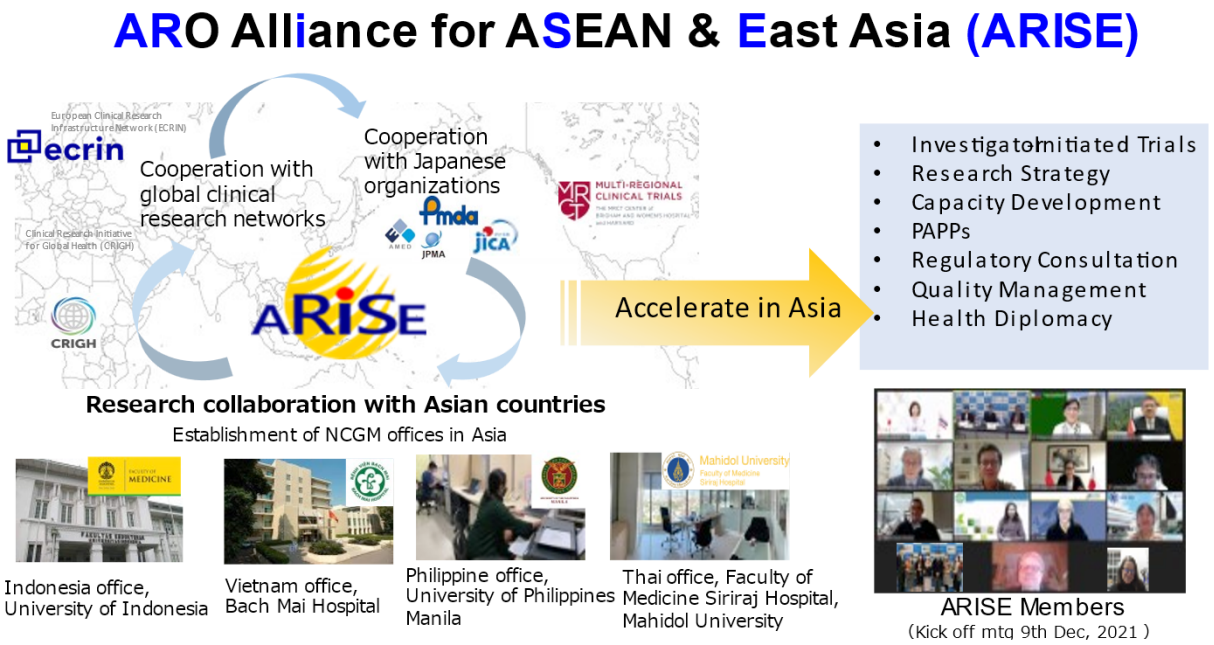

Figure 1. ARISE's strategic framework for partnership and collaborative relationships to accelerate clinical research in Asia.

was held online, with approximately 70 participants from both Asian and international medical institutions. During the meeting, the concept of ARISE (Figure 1) was elucidated and members introduced their organizations. Representatives from the Clinical Research Initiative for Global Health (CRIGH), European Clinical Research Infrastructure Network (ECRIN), MRCT Center of Brigham and Women's Hospital, and Harvard (MRCT Center) shared their experiences of international collaborative clinical research networks in Europe, the USA, and the world.

As an Asian clinical research network responsible for global health, ARISE aims to promote health and reduce illness and disability by creating a network of Asian AROs. Through the efficient and effective collaboration of member organizations and stakeholders, it strives to achieve the following objectives: *i*) Promote the integrity, safety, ethics, and quality of clinical research; *ii*) Contribute to the development of innovative medical products that address unmet health needs and significant diseases in Asia; *iii*) Improve the resources and capacity of Asian clinical study sites; *iv*) Accelerate clinical research and authorization processes; *v*) Promote public-academic-private-partnerships in Asia; *vi*) Bridge the gap between scientific research and health policies.

Since its inception, ARISE members have conducted several activities to develop clinical research capacity, including introducing core competencies for clinical research professionals and training in member countries. We also have undertaken international studies to evaluate the safety and efficacy of antiviral drugs for COVID-19 treatment and drug susceptibility measurement of gram-negative bacteria. In the future, we plan to increase the number of global clinical research further and conduct thematic working groups to address specific needs and common issues relevant to clinical studies.

To advance clinical research activities, member organizations will share their experiences and resources and work closely with the governments and regulatory authorities of the concerned countries. We will also ensure value to commercial and academic partners through sustainable and expeditious research development. Finally, we will advance regional collaborations with the instigation of international medical research cooperation, which will enable us to deliver valuable medical products to people in need.

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

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LETTER
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International technical cooperation to low- and middle-income countries during the COVID-19 pandemic

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Abstract: This paper reports on the current status of international technical cooperation, reflecting the views of the Bureau of International Health Cooperation of the National Center for Global Health and Medicine (NCGM) during the COVID-19 pandemic. To appropriately respond to the pandemic, the need for assistance to low- and middle-income countries has increased. Since 2020, there has been a shift from on-site to online international technical cooperation to avoid human contact. While online solutions increased the number of participants in international conferences and training, business travel costs and time were reduced. However, it became necessary to consider not only effective labor-management practices to enable participation in meetings held in different time zones but also quicker ways to develop online training materials, which took a long time. In the future, a hybrid format combining offline and online international technical cooperation will become mainstream.

***Keywords*:** COVID-19, global health, international technical cooperation, low- and middle-income countries, online training

The Bureau of International Health Cooperation (BIHC) of the National Center for Global Health and Medicine (NCGM) has been engaged in global health issues since 1986 in collaboration with many domestic and international organizations (*1*). It plays several roles, including dispatching Japanese experts who provide technical support mainly to low- and middle-income countries, conducting interventions at international conferences as members of the Japanese government delegation to set global health norms, generating evidence from field experiences, developing human resources both in low- and middle-income countries and Japan, and promoting Japan's healthcare technology and services in low- and middle-income countries.

Owing to the recent increase in international mobility, infectious diseases such as COVID-19 can quickly spread worldwide. This provides an opportunity to reaffirm the importance of international technical cooperation. COVID-19 has plunged the world into a health crisis. However, this crisis has caused us to recognize the importance of international technical cooperation (*2*). The COVID-19 pandemic has forced us to recognize the necessity of understanding and solving the problems of all people globally without being bound by the framework of international technical cooperation implemented between low- and middle-income countries and high-income countries. The European Union has claimed that this health crisis is transforming the international system and regional order (*3*). Thus, the COVID-19 pandemic has provided an opportunity to reconsider the relationship of economic cooperation between countries.

According to the World Health Organization (WHO), as of 27th July 2022, there were 486.1 million confirmed cases of COVID-19 in high to upper middle-income countries compared to 81.2 million cases in lower middle- and low-income countries (*4*). Clinical and public health responses to COVID-19 in high and upper middle-income countries, such as avoiding enclosed spaces, crowded people, and close person-to-person contact, *etc*., could serve as valuable experiences for low- and middle-income countries (*5-7*). Despite high-income countries also being affected by COVID-19, BIHC is continuing its international technical cooperation.

In the past, BIHC's international technical cooperation was mainly based on fieldwork. In 2019, we dispatched 347 experts for technical assistance and 53 attendees in international conferences, all of which were conducted on-site. Training for health personnel in low- and middle-income countries has generally been conducted through visits by trainees from low- and middle-income countries to Japan or dispatchments of Japanese trainers to low- and middle-income countries. A total of 332 trainees from low- and middle-income countries participated in the trainings conducted by BIHC in 2019 (Figure 1).

However, the COVID-19 pandemic has made such trainings difficult due to the restrictions enforced to avoid human contact. In response to these challenges,

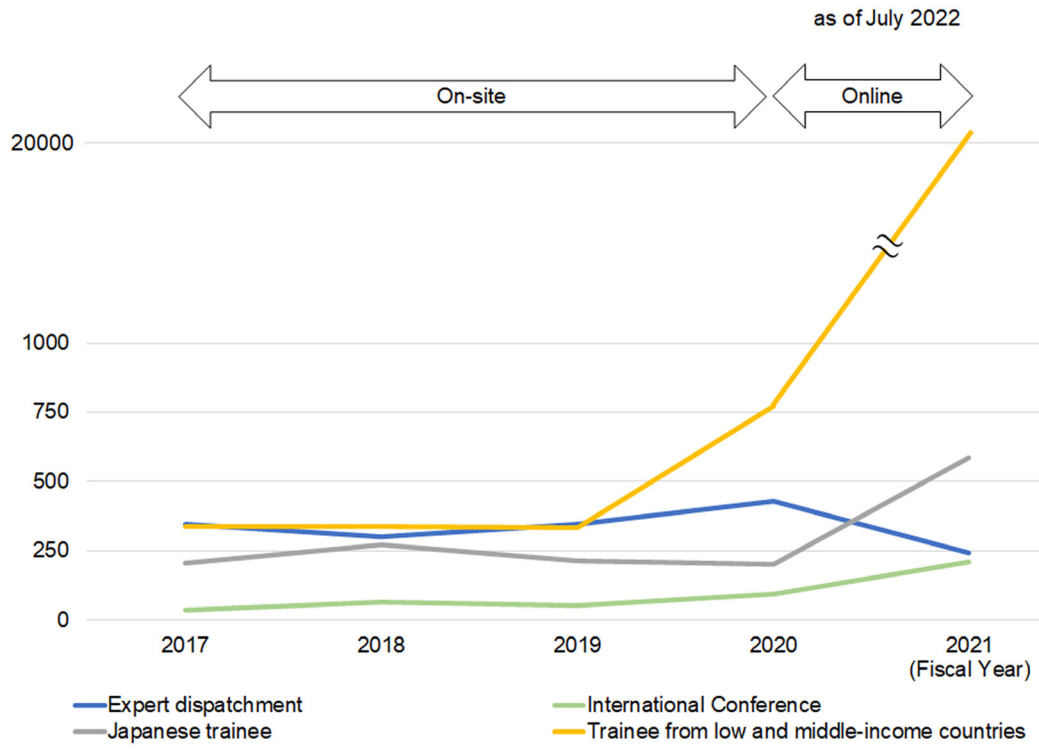

Figure 1. Number of participants involved in international technical cooperation conducted by BIHC during 2017-2021.

information and communications technology, such as online meetings, conferences, and training, has advanced rapidly around the world, with the BIHC also adopting such technology. After the outbreak of the COVID-19 pandemic, 428 and 241 Japanese experts provided technical assistance for thirteen countries, namely Democratic Republic of the Congo, Independent State of Papua New Guinea, Kingdom of Cambodia, Lao People's Democratic Republic, Malaysia, Mongolia, People's Republic of China, Republic of Indonesia, Republic of Senegal, Republic of the Philippines, Republic of the Union of Myanmar, Republic of Zambia and Socialist Republic of Viet Nam in 2020 and 2021, respectively, and 94 and 211 experts participated in international conferences in 2020 and 2021, respectively, all of which were conducted online (Figure 1). The ability to easily participate in online meetings has resulted in an increase in the number of participants in international conferences. This strategy emerged as the most accessible means of participating in the meeting (*8,9*). We were also able to reduce the amount of time and expenses we spend on international business trips. However, the opportunity to contribute by offering technical assistance and participating in international conferences, which were held at midnight Japan standard time due to different time zones, created an unprecedented challenge related to the labor-management of BIHC members.

Prior to COVID-19, our institute received a maximum of 433 trainees from low- and middle-income countries annually, which increased to 773 and 20,236 in 2020 and 2021, respectively, when we shifted to online training. The number of Japanese participants who aspire to be involved in international technical cooperation also increased from approximately 230 to 585 in 2021 (Figure 1). Online training enabled us to increase the number of trainees significantly. However, creating materials for online training was time-consuming. Hameed *et al*. and Kim *et al*. highlighted the importance of considering factors related to learners and educators, content and resources, educator-learner interactions, quality of operational strategies, and learning environment (*8,9*). Given this worldwide trend, we face the challenge of developing effective online training methodologies and assessment tools that can find application in global health.

In the future, certain activities should be conducted offline. However, a hybrid format combining offline and online meetings, conferences, and training for international technical cooperation is likely to become mainstream, especially since online cooperation can yield results while greatly reducing the time and expense of international business trips.

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