

Print ISSN: 2436-293X Online ISSN: 2436-2956



# GHM Open

**Global Health & Medicine Open**

Volume 1, Number 1  
August, 2021

[www.ghmopen.com](http://www.ghmopen.com)



## GHM Open

*GHM Open* (Print ISSN 2436-293X, Online ISSN 2436-2956) is an international, open-access, peer-reviewed journal, published by the National Center for Global Health and Medicine (NCGM), which is a national research and development agency in Japan that covers advanced general medicine, basic science, clinical science, and international medical collaboration. It is published by NCGM and supported by the International Research and Cooperation Association for Bio & Socio-Sciences Advancement (IRCA-BSSA).

### 1. Mission and Scope

*GHM Open* is dedicated to publishing high-quality original research that contributes to advancing global health and medicine, with the goal of creating a global information network for global health, basic science as well as clinical science oriented for clinical application.

The articles cover the fields of global health, public health, and health care delivery as well as the seminal and latest research on the intersection of biomedical science and clinical practice in order to encourage cooperation and exchange among scientists and healthcare professionals in the world.

### 2. Manuscript Types

*GHM Open* publishes Original Articles, Brief Reports, Reviews, Policy Forum articles, Study Protocols, Case Reports, Communication, Editorials, Letters, and News.

### 3. Editorial Policies

*GHM Open* will perform an especially prompt review to encourage submissions of innovative work. All original research manuscripts are to be subjected to an expeditious but rigorous standard of peer review, and are to be edited by experienced copy editors to the highest standards.

We aspire to identify, attract, and publish original research that supports advances of knowledge in critical areas of global health and medicine.

#### Editor-in-Chief

Norihiro Kokudo, M.D., Ph.D.  
President,  
National Center for Global Health and Medicine;  
Professor Emeritus,  
The University of Tokyo.

#### Editorial and Head Office

*GHM Open*  
National Center for Global Health and Medicine,  
1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan  
URL: [www.ghmopen.com](http://www.ghmopen.com)  
E-mail: [office@ghmopen.com](mailto:office@ghmopen.com)

### Associate Editors

Masayuki Hojo  
*Tokyo*

Tatsuya Kanto  
*Tokyo*

Hong-Zhou Lu  
*Shenzhen*

Wataru Sugiura  
*Tokyo*

Yukihito Ishizaka  
*Tokyo*

Takashi Karako  
*Tokyo*

Tetsuro Matano  
*Tokyo*

Guido Torzilli  
*Milan*

### Office Director & Executive Editor

Peipei Song  
*Tokyo*

### Editorial Board

Daniele Del Fabbro  
*Milan*

Yukio Hiroi  
*Tokyo*

Norio Ohmagari  
*Tokyo*

Yasuhide Yamada  
*Tokyo*

Nermin Halkic  
*Lausanne*

Takeshi Inagaki  
*Tokyo*

Shinichi Oka  
*Tokyo*

Hidekatsu Yanai  
*Chiba*

Kiyoshi Hasegawa  
*Tokyo*

Akio Kimura  
*Tokyo*

Fabio Procopio  
*Milan*

Kojiro Ueki  
*Tokyo*

Hiroshi Obara  
*Tokyo*

Nobuyuki Takemura  
*Tokyo*

### Advisory Board

Nobuyoshi Aoyanagi  
*Tokyo*

Hiroaki Mitsuya  
*Tokyo*

Haruhito Sugiyama  
*Tokyo*

(As of August 2021)

## EDITORIAL

- 1-2 ***GHM Open* – A new journal dedicated to advancing global health and medicine.**  
*Norihiro Kokudo*

## STUDY PROTOCOL

- 3-11 **Prevention of Worsening Diabetes through Behavioral Changes by an IoT-based Self-Monitoring System in Japan (PRISM-J): Study design and rationale for a multicenter, open-label, randomized parallelgroup trial.**  
*Ryotaro Bouchi, Kazuo Izumi, Hiroshi Ohtsu, Kengo Miyo, Shigeho Tanaka, Noriko Satoh-Asahara, Kazuo Hara, Masato Odawara, Yoshiki Kusunoki, Hidenori Koyama, Takeshi Onoue, Hiroshi Arima, Kazuyo Tsushita, Hirotaka Watada, Takashi Kadowaki, Kohjiro Ueki*

## REVIEW

- 12-19 **Effects of COVID-19 on vital organs in patients infected with SARS-CoV-2.**  
*M. Ibrahim Hossain, Esha Binte Shahriar, Anamika Sarker, Nafisa Lubna, Mehjabeen Haque, Md. Ibrahim Khalil*

## BRIEF REPORT

- 20-27 **Survey of motor function and activities of daily living in hemophilia patients with HIV.**  
*Kazuko Kikuchi, Toshiharu Komachi, Yoshinori Honma, Tomoyuki Endo, Keiko Watabe, Yoshiyuki Yokomaku, Chieko Hashiba, Masahiro Yamamoto, Yukiko Nagayo, Toshihiro Ito, Junji Imamura, Tomoko Suzuki, Junko Fujitani*

## COMMUNICATION

- 28-30 **Trends in prostate cancer diagnosis during the COVID-19 crisis: A report from one high-volume Japanese center.**  
*Daisuke Yamada, Taketo Kawai, Yusuke Sato, Yuta Yamada, Yoshiyuki Akiyama, Jimpei Miyakawa, Sayuri Takahashi, Haruki Kume*
- 31-35 **Development of active learning materials and use of those materials to educate nursing students primarily in respiratory nursing and to train new nurses.**  
*Fumino Sugiyama, Tomoko Inoue, Kimikazu Kashiwagi, Mitsumi Masuda, Namiko Nagaoka, Ayako Narita*

## LETTER

- 36-37 **Japan's first online media seminar on antimicrobial resistance.**  
*Yoshiaki Gu, Yumiko Fujitomo, Rie Takahashi, Norio Ohmagari*
- 38-39 **Home-visit services for the families with newborns during the COVID-19 pandemic.**  
*Yukari Isaka, Ai Hori, Takahiro Tabuchi, Sumiyo Okawa, Masao Ichikawa*

- 40-42      **Seroprevalence of antibodies against SARS-CoV-2 among workers in a national research institute and hospital in Central Japan.**

*Akihiko Nishikimi, Masayo Kojima, Ken Watanabe, Atsushi Watanabe, Mikako Yasuoka,  
Hironori Oshima, Haruhiko Tokuda, Shumpei Niida*

# ***GHM Open* — A new journal dedicated to advancing global health and medicine**

Norihiro Kokudo\*

National Center for Global Health and Medicine, Tokyo, Japan.

**Abstract:** To generate high-quality evidence and serve as a platform for interdisciplinary communication regarding challenging issues in global health and medicine, we are launching a new open-access multispecialty journal — *GHM Open* ([www.ghmopen.com](http://www.ghmopen.com)) – with the goal of creating a network to share global health information and findings from basic science and clinical science for use in practice. *GHM Open* will be an inclusive and global journal; the diversity of our editorial board, authors, and reviewers will allow us to showcase rich and wide-ranging content, making it ever more relevant to researchers and clinicians around the world. The journal prioritizes specialized research with wider general relevance that will influence clinical care, global health, public health, medical education, and the direction of future research. We aim to be relevant, accessible, and enjoyable, not only to researchers but also to global health and medical care providers. We sincerely look forward to having you join us as a reader, author, reviewer, or editorial board member to address challenging issues in global health and medicine.

**Keywords:** global health, medicine, health care, basic science, clinical science

Academic journals are responsible for facilitating the rapid dissemination of reliable information. This has become even more true amidst the challenges and unprecedented situations created by the COVID-19 pandemic. The sharing of data and global collaboration is leading to various solutions, including prediction of outbreaks, virus tracking, diagnosis and treatment, vaccine development, and drug research. Moreover, the rapid sharing of scientific information is an effective way to reduce public panic given the need for timely and reliable medical information during the COVID-19 pandemic (1,2).

The COVID-19 pandemic has been accompanied by an explosion in scientific discourse in peer-reviewed journals as research data and relevant findings are rapidly shared and highlighted to support the global response to this threat (3,4). Our first journal – *Global Health & Medicine* ([www.globalhealthmedicine.com](http://www.globalhealthmedicine.com)) – is an academic journal that actively disseminates reliable information and that has published a large number of articles since the outbreak, including two special issues on COVID-19 (5,6), in the hopes of contributing to the global fight against COVID-19 in any way possible.

The COVID-19 pandemic has reinforced the importance of robust journal processes in advancing knowledge and managing information. What is more, the dissemination of scientific information on other communicable diseases (CDs) and non-communicable

diseases (NCDs) is also important to advancing global health and medicine (7).

To generate high-quality evidence and serve as a platform for interdisciplinary communication regarding these challenging issues in global health and medicine, we are launching a new open-access multispecialty journal – *GHM Open* ([www.ghmopen.com](http://www.ghmopen.com)) – with the goal of creating a network to share global health information and findings from basic science and clinical science for use in practice.

*GHM Open* (Print ISSN 2436-293X, Online ISSN 2436-2956) is an international, open-access, peer-reviewed journal published by the National Center for Global Health and Medicine (NCGM), which is a national research and development institute in Japan that covers advanced general medicine, basic science, clinical science, and international medical collaboration. Closely aligned with *Global Health & Medicine*, *GHM Open* will provide an important forum for high-quality multidisciplinary communication targeting a broad international readership, and it will adopt the evaluation criteria, editorial standards, and author service being applied by *Global Health & Medicine*.

*GHM Open* is dedicated to publishing high-quality original research that helps to advance global health and medicine. Articles will cover the fields of global health, public health, and health care delivery as well as seminal research and the latest research on the intersection of biomedical science and clinical practice

in order to encourage interaction and collaboration among scientists and healthcare professionals around the world.

*GHM Open* will be an inclusive and global journal; the diversity of our editorial board, authors, and reviewers will allow us to showcase rich and wide-ranging content, making it ever more relevant to researchers and clinicians around the world. The journal prioritizes specialized research with wider general relevance that will influence clinical care, global health, public health, medical education, and the direction of future research. We aim to be relevant, accessible, and enjoyable, not only to researchers but also to global health and medical care providers. The first issue of *GHM Open* contains a delightfully diverse selection of research articles. The topics include global health, type 2 diabetes, hemophilia, antimicrobial resistance, and COVID-19.

*GHM Open* seeks to work closely with the international academic community to ensure that the research we publish is novel, high-quality, diverse in content, and timely. We sincerely look forward to having you join us as a reader, author, reviewer, or editorial board member to address challenging issues in global health and medicine. And we are always happy to receive suggestions regarding new ways and means of communicating important research findings.

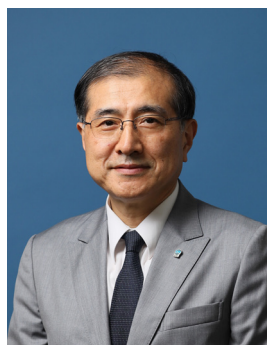
*Funding:* None.

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

## References

1. The Lancet. COVID-19: Fighting panic with information. *Lancet*. 2020; 395:537.
2. The World Health Organization. Mental health and psychosocial considerations during the COVID-19 outbreak. <https://www.who.int/docs/default-source/coronaviruse/mental-health-considerations.pdf> (accessed August 10, 2021).
3. Mitsuya H, Kokudo N. Sustaining containment of COVID-19: Global sharing for pandemic response. *Glob Health Med*. 2020; 2:53-55.
4. Kokudo N, Sugiyama H. Hospital capacity during the COVID-19 pandemic. *Glob Health Med*. 2021; 3:56-59.
5. *Global Health & Medicine*. Volume 2, Number 2, 2020. Special Topic: COVID-19. [https://globalhealthmedicine.com/files/GHM\\_2020Vol2No2\\_pp53\\_150.pdf](https://globalhealthmedicine.com/files/GHM_2020Vol2No2_pp53_150.pdf) (accessed August 10, 2021).
6. *Global Health & Medicine*. Volume 3, Number 2, 2021. Special Topic: COVID-19. [http://globalhealthmedicine.com/files/GHM\\_2021Vol3No2\\_pp56\\_124.pdf](http://globalhealthmedicine.com/files/GHM_2021Vol3No2_pp56_124.pdf) (accessed August 10, 2021).
7. Mitsuya H. Fight against COVID-19 but avoid disruption of services for other communicable diseases (CDs) and noncommunicable diseases (NCDs). *Glob Health Med*. 2020; 2:343-345.

----  
Received August 10, 2021; Accepted August 17, 2021.



Norihiro Kokudo  
MD, PhD, FACS, FRCS  
Editor-in-Chief, *GHM Open*

President, National Center for Global Health and Medicine  
Professor Emeritus, The University of Tokyo  
President (2012 - 2016), Japan Surgical Society  
President (2015 - 2017), Asian-Pacific Hepato-Pancreato-Biliary Association  
President (2020 ~), International Hepato-Pancreato-Biliary Association  
President-elect (2021 ~), Asia-Pacific Primary Liver Cancer Expert Association



# Prevention of Worsening Diabetes through Behavioral Changes by an IoT-based Self-Monitoring System in Japan (PRISM-J): Study design and rationale for a multicenter, open-label, randomized parallel-group trial

Ryotaro Bouchi<sup>1,2</sup>, Kazuo Izumi<sup>3</sup>, Hiroshi Ohtsu<sup>4</sup>, Kengo Miyo<sup>5</sup>, Shigeho Tanaka<sup>6,7</sup>, Noriko Satoh-Asahara<sup>8</sup>, Kazuo Hara<sup>9</sup>, Masato Odawara<sup>10</sup>, Yoshiki Kusunoki<sup>11</sup>, Hidenori Koyama<sup>11</sup>, Takeshi Onoue<sup>12</sup>, Hiroshi Arima<sup>12</sup>, Kazuyo Tsushita<sup>6,13</sup>, Hirotaka Watada<sup>14</sup>, Takashi Kadowaki<sup>15</sup>, Kohjiro Ueki<sup>2,16,\*</sup>

<sup>1</sup>Diabetes and Metabolism Information Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan;

<sup>2</sup>Department of Diabetes and Endocrinology and Metabolism, Center Hospital, National Center for Global Health and Medicine, Tokyo, Japan;

<sup>3</sup>Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan;

<sup>4</sup>Department of Clinical Study and Informatics, Clinical Epidemiology Section/JCRAC Data Center, Center for Clinical Sciences, National Center for Global Health and Medicine, Tokyo, Japan;

<sup>5</sup>Center for Medical Informatics Intelligence, National Center for Global Health and Medicine, Tokyo, Japan;

<sup>6</sup>Faculty of Nutrition, Kagawa Nutrition University, Saitama, Japan;

<sup>7</sup>Department of Nutrition and Metabolism, National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition, Tokyo, Japan;

<sup>8</sup>Department of Endocrinology, Metabolism, and Hypertension Research, Clinical Research Institute, National Hospital Organization Kyoto Medical Center, Kyoto, Japan;

<sup>9</sup>Department of Endocrinology and Metabolism, Saitama Medical Center, Jichi Medical University, Saitama, Japan;

<sup>10</sup>Department of Diabetology, Metabolism, and Endocrinology, Tokyo Medical University Hospital, Tokyo, Japan;

<sup>11</sup>Department of Diabetes, Endocrinology and Clinical Immunology, Hyogo College of Medicine, Hyogo, Japan;

<sup>12</sup>Departments of Endocrinology and Diabetes, Nagoya University Graduate School of Medicine, Nagoya, Japan;

<sup>13</sup>Comprehensive Health Science Center, Aichi Health Promotion Foundation, Higashiura-cho, Aichi, Japan;

<sup>14</sup>Department of Metabolism and Endocrinology, Juntendo University Graduate School of Medicine, Tokyo, Japan;

<sup>15</sup>Toranomon Hospital, Tokyo, Japan;

<sup>16</sup>Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan.

**Abstract:** The use of the Internet-of-Things has improved glycemic control in individuals with diabetes in several small-scale studies with a short follow-up period. This large-scale randomized controlled trial investigates whether a smartphone-based self-management support system prevents the worsening of glycemic control in individuals with type 2 diabetes. Individuals with type 2 diabetes (age range 20-74 years;  $n = 2,000$ ) will be recruited, enrolled, and randomly assigned to two groups: the intensive therapy group and the conventional therapy group. Participants in the intensive therapy group will be supervised to use an automated Internet-of-Things system that demonstrates a summary of lifelogging data (e.g., weight, blood pressure, and daily activities) obtained from each measurement device and will receive feedback messages *via* smartphone applications to encourage them to increase their physical activity and to monitor weight and blood pressure. Participants in the conventional therapy group are allowed to use the same measurement devices as part of the routine diabetes care but without the Internet-of-Things system. The primary endpoint is the between-group difference in HbA1c levels from baseline to 52 weeks. This randomized controlled study will test the hypothesis that an Internet-of-Things-based self-monitoring system could effectively prevent the worsening of diabetes in individuals with type 2 diabetes. The expected results of the study should facilitate the development of novel strategies for both diabetes treatment and social health.

**Keywords:** behaviour modification, application, glycemic control, type 2 diabetes

## Introduction

Individuals with diabetes who have inadequate glycemic control develop diabetes-related microvascular

complications, including retinopathy and nephropathy, and have a 2- to 3-fold increased risk of incident cardiovascular disease (CVD) (1,2). Early detection of diabetes and its complications and ensuring adequate

glycemic, blood pressure, and lipid control by using pharmacotherapy is necessary to reduce the risk of both micro- and macrovascular diabetes-related complications (3-6). Moreover, regular medical check-ups are effective for diabetes prevention and to prevent or delay the worsening of diabetes-related complications. In Japan, healthcare activities for "specific medical check-up" and "specific health guidance" have been carried out since April 2008 (7). Specific health check-ups are available to people aged 40-74 years, and specific healthcare guidance is provided to those with increased abdominal circumference, blood glucose, blood pressure, and lipid levels. However, approximately 50% have never availed specific medical check-ups because individuals with early-stage non-communicable diseases, such as type 2 diabetes, are mostly asymptomatic. People who were newly diagnosed with diabetes during a medical check-up had a low persistence rate for regular visits for diabetes management (8). Accordingly, hurdles persist for the early detection of and initiation of interventions for diabetes; thus, novel strategies are necessary to overcome these challenges.

Behavioral change plays an important role in the efficacy of diabetes treatment and patient education. Meta-analyses of type 2 diabetes found that psychological interventions significantly improve glycemic control (9). Telephonic or web-based counselling and education by medical staff are effective for diabetes management (10,11). Multifaceted behavioral interventions, including lifestyle advice by telephone, can significantly reduce the dropout rate for regular visits and improve the quality of diabetes care in people with type 2 diabetes in primary-care settings (12). However, evidence-based lifestyle interventions are expensive and require extensive use of human resources (13). Therefore, an effective and low-cost self-management tool needs to be developed. With the technological advent of the Internet-of-Things (IoT), several studies have shown that IoT-based activation of self-monitoring can accelerate behavioral changes and improve glycemic control in people with diabetes (14-19). Given the limitations of small study samples or short follow-up period in these studies, their preliminary results need to be validated in larger randomized controlled trials (RCTs) with long follow-up durations. Therefore, this large-scale randomized controlled trial will investigate whether a smartphone-based self-management support system prevents the worsening of glycemic control in individuals with type 2 diabetes.

## Methods

### Study design

The Prevention of Worsening Diabetes through Behavioral Changes by an IoT-based Self-Monitoring

System in Japan (PRISM-J) is a multicenter, open-label, parallel-group, RCT to investigate whether both behavioral changes and glycemic control could be improved by interventions *via* messages that are automatically generated from health-related information obtained from wearable devices in people with type 2 diabetes.

### Organization and funding

This study is supported by the Japan Agency for Medical Research and Development (AMED), Research Program for Health Behavior Modification by using IoT during fiscal years 2017-2019.

### Eligibility

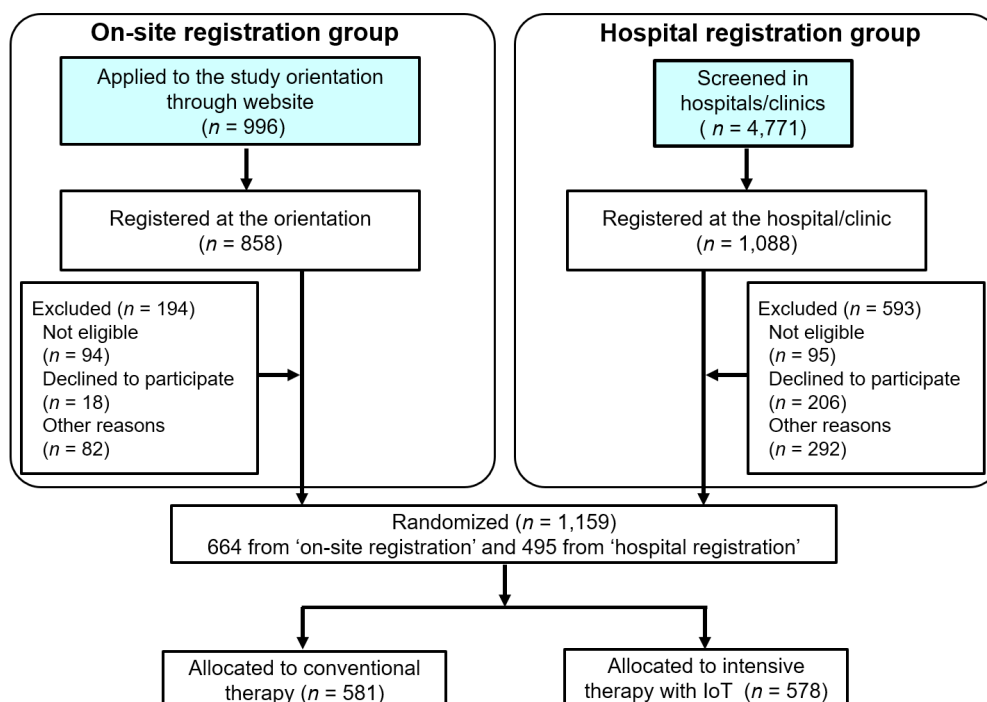
The PRISM-J inclusion and exclusion criteria are presented in Table S1 (<https://www.ghmopen.com/site/supplementaldata.html?ID=22>). We initially planned to include patients who were receiving up to two oral antidiabetic agents; however, in April 2018, we modified the protocol to promote the recruitment of patients who were being treated with up to three oral antidiabetic agents. Patients who were treated with insulin or glucagon-like peptide-1 agonist were excluded in this study.

### Screening and enrolment

Screening was performed through: *i*) regular medical check-ups provided by health insurance societies (Table S2, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>) and *ii*) chart review of medical records of outpatients who regularly visited the participating hospitals/clinics of PRISM-J (Table S3, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>). Eligible participants were recruited from January 1, 2018 to December 31, 2018.

### Participation model for collaborators

This study comprises two participation models (Figure 1). One is a "Hospital registration group" wherein physicians in each hospital/clinic recruit candidates; obtain informed consent for study participation; register, allocate and educate the participants on diabetes management and IoT devices; and follow-up with them during the entire study period. The other model is an "On-site registration group" that research staff at National Center for Global Health and Medicine (NCGM) host for the orientation for participants who are introduced through collaborators, including health insurance societies (Table S2, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>) and hospitals/clinics (Table S3, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>); the staff also obtain informed consent and register, allocate, and



**Figure 1. Flowchart of study processes and participant disposition.**

educate participants on diabetes management and IoT devices. Thereafter, the participating medical institutions will follow up on the participants. For participants who were newly diagnosed with type 2 diabetes and did not have a primary care physician, PRISM-J indicated medical institutions where they could be introduced (Table S3, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>).

#### *Informed consent, registration, and random allocation*

All participants provided written informed consent before participation. Participants were randomized to either the conventional therapy group (CTG) or the IoT group (ITG) with an allocation ratio of 1:1 using a stratified blocked randomization (block size set to 10) based on age ( $\geq 50$  or  $< 50$  years), sex (male/female), body mass index (BMI;  $\geq 25$  or  $< 25$  kg/m<sup>2</sup>) and glycated hemoglobin (HbA1c;  $\geq 8.0$  [64 mmol/mol],  $< 8.0\%$ ). Based on the eligibility information, registration forms were sent on website or faxed to the Data Center (JCRAC Data Center of NCGM, Tokyo, Japan) for registration and randomization. The registration codes and the assigned treatment groups were emailed or faxed to the attending medical staff on the same day.

#### *Interventions*

All participants were lent free IoT devices, including a weight and body composition monitor (HBF-255T, Omron Healthcare, Kyoto, Japan), blood pressure monitor (HEM-7271T, Omron Healthcare, Kyoto,

Japan) and activity monitor (HJA-405T, Omron Healthcare, Kyoto, Japan). This activity monitor has been proven to provide valid estimation of total and physical activity-related energy expenditure (20). All devices could transmit measurement data over a wireless network to a cloud server *via* a Bluetooth connection (Figure S1, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>). Participants were instructed to measure weight once a day at approximately the same time. Home blood pressure was measured according to the Japanese Society of Hypertension guidelines for the management of hypertension 2014 (21). Participants were instructed to wear the activity monitor from the time they woke up until they went to bed every day for the assessment of daily physical activity. In both groups, participants are treated in accordance with the "Treatment Guide for Diabetes 2016-2017" edited by the Japan Diabetes Society (JDS) (22), and physicians were, at their discretion, allowed to select and adjust the medications for diabetes, hypertension, and dyslipidemia for the optimal control of these diseases. Investigators recommended practical ways to reduce or maintain weight with careful consideration of the participants' lifestyles and physical activity.

After randomization, participants in the ITG download the "Omron connect App", which allows them to transfer measurements to their smartphone. Data are displayed in clear and insightful graphs that can help participants see their health trends. In addition to the "Omron connect App", participants in the ITG download the "Shichifukujin" application (SFJA),

which has been described elsewhere (23). *Shichifukujin* means "The Seven Deities of Good Luck" (Figure S1, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>); each god has a specific role for the patient's self-monitoring and gives feedback messages for lifestyle modification to the patient twice a week based on data obtained from the "Omron connect App". All the ITG participants are provided printed support materials that describe the use of both applications. Every four weeks, participants in the ITG received summary messages, including the number of days that the participants used the devices and the changes and means of weight, blood pressure, and physical activity. The SFJA automatically sends reminder messages when the participants do not access the SFJA or they do not use the devices for 3 and 7 consecutive days (Table S4, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>). These messages are generated automatically, according to the 'Treatment Guide for Diabetes 2016-2017' edited by the JDS (22), "JSH Guideline for the Management of Hypertension 2014" (21), 'Treatment Guideline for Obesity Disease 2016' edited by the Japan Society for the Study of Obesity (24), the Exercise and Physical Activity Reference for Health Promotion 2013 (25), and the Japanese official physical activity guidelines for health promotion (26). Primary care physicians can access patient data *via* the *Shichifukujin* cloud that regularly connects to the device database (Omron Cloud); check/confirm the summary of the measurement data, graphs and lifestyle habits; and use them appropriately as supportive data/documents for medical treatment and guidance based on the participant's lifelogging records (Figure S1, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>).

### Observation and evaluation schedule

The data collection schedule is summarized in Table 1 and Figure S2 (<https://www.ghmopen.com/site/supplementaldata.html?ID=22>). Participants regularly visited their outpatient clinic at least once every 12 weeks. At 52 weeks or later, participants in the ITG continue to use the IoT system until the end of the study whereas participants in the CTG receive education and instructions related to IoT, similar to that in the ITG, and the period during which IoT can be used will be specified as a maximum of 52 weeks before study termination (until December 31, 2019). Therefore, the maximum study participation period of the study participants is presumed to be 104 weeks (~2 years).

The lifestyle questionnaire included medical history, family history, and behavioral modification stages related to diet and exercise (Table S5, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>). Treatment satisfaction and quality of life (QOL) were assessed using the Diabetes Therapy-Related QOL (DTR-QOL) (27). Food intake was estimated using a Brief-type Self-administered Diet History Questionnaire (BDHQ) that was developed for the assessment of Japanese diets (28). Information obtained *via* connected devices are listed in Table 2.

The method used for providing data in this study is unique in that participants take pictures of laboratory data and of the forms of their weight and blood pressure measurements, which are measured at clinics/hospitals and of prescription information, and upload them to a portal site. After anonymization, data are sent to the Data Center. To promote participant retention and complete follow-up, the Research Support Center will contact

**Table 1. Schedule of data collection**

	Baseline	12 weeks	24 weeks	36 weeks	52 weeks	Study end
Physical examination						
Height	○					
Weight	○	○	○	○	○	○
Blood pressure	○	○	○	○	○	○
Laboratory examination						
HbA1c	○	○	○	○	○	○
Glucose	○	○	○	○	○	○
Total cholesterol	○	○	○	○	○	○
HDLC	○	○	○	○	○	○
ALT	○	○	○	○	○	○
Creatinine	○	○	○	○	○	○
Urinary protein	○	○	○	○	○	○
Health assessment questionnaire						
Lifestyle questionnaire	○	○	○	○	○	○
DTR-QOL	○	○	○	○	○	○
BDHQ	○	○	○	○	○	○
Information on medication	○	○	○	○	○	○

ALT, alanine transaminase; BDHQ, Brief-type Self-administered Diet History Questionnaire; DTR-QOL, diabetes therapy-related quality of life; HDLC, high-density lipoprotein cholesterol.

**Table 2. Information obtained via connected devices**


---

Weight and body composition monitor (HBF-255T)
Weight
Body fat percent level
Percent body fat
Basal metabolic rate
Body mass index
Physical age
Visceral fat level
Impedance
Fat-free mass
Blood pressure monitor (HEM-7271T)
Systolic blood pressure
Diastolic blood pressure
Pulse
Posture
Room temperature
Flag related to irregular pulse wave
Flag related to the detection of body motion
Frequency of artefact detection
Frequency of irregular pulse wave detection
Activity monitor (HJA-405T)
Steps
Exercise steps
Brisk steps
Stair steps
Calories related to activity
Calories related to moderate- to high-strength activity
Total calorie consumption
Calories related to walking
Distance
Fitting flag
Unrecorded flag
Fat combustion amount
Exercise amount
Exercise (walking) amount
Basal metabolic rate
Sedentary time
Activity time related to low-intensity exercise
Activity time related to moderate-intensity exercise
Activity time related to high-intensity exercise

---

participants by email or phone if they do not send the data.

## Outcomes

The study endpoints are shown in Table 3.

### Sample size

In this study, the difference between the effects of HbA1c was set at 0.2, assuming a 1-year intervention throughout Japan. Furthermore, it is assumed that the variations of other data would be widened. Due to the study design, participants are expected to be recruited from both primary-care settings and clinics/hospitals specializing in diabetes care. To estimate the SD of HbA1c in patients with type 2 diabetes in clinics/hospitals specializing in diabetes care in Japan, we calculated the SD of people with type 2 diabetes who were enrolled in the Japan Diabetes CompREhensive database project based on an Advanced Electronic Medical record System (J-DREAMS) (29), met the inclusion criteria of this

study and whose HbA1c values were available in 2017. The HbA1c was  $7.05 \pm 0.67\%$  in 8,416 people with type 2 diabetes (unpublished data). Most patients in the registry are enrolled from facilities designated by the JDS as educational facilities; thus, the data are considered representative of patients in clinics/hospitals specializing in diabetes care in Japan. Therefore, we initially estimated SD of HbA1c as 0.6, but it was finally confirmed as 1.2 because of the multicenter study design and evidence that HbA1c levels were  $7.4 \pm 1.2\%$  in 2,199 Japanese patients with type 2 diabetes in primary care (30). Based on these facts, when the power was set to 0.8 or 0.9, the required number of cases was calculated to be 567 or 758, respectively (SAS Ver 9.4 [SAS Institute Inc., Cary, NC, USA]) in this study to prevent loss. As the dropout rate is assumed to be 20%, 680 to 910 people are required in each group. Therefore, the total number of patients in each group was 1,000. To recruit a sufficient number of participants, we extended the registration period from 6 to 9 months in February 2018 and, subsequently, to 12 months in September 2018.

### Safety

Serious adverse events (SAEs) include those that: *i*) result in death, *ii*) are life-threatening, *iii*) require inpatient hospitalization or prolongation of existing hospitalization, *iv*) result in persistent or significant disability or incapacity, or *v*) cause a congenital anomaly or birth defect in the offspring. Serious hypoglycemia, defined as hypoglycemia necessitating someone else's assistance and/or hospitalization, was included as an SAE in this study. The safety assessment committee oversees the evolving safety profile by reviewing cumulative SAEs.

### Discontinuance and dropout

The criteria for discontinuance in this study were: *i*) refusal to participate in the study, *ii*) participants were judged as unsuitable for the study participation by physicians, *iii*) treatment continuation would be difficult due to the worsening of diabetes and its complications or other adverse events, *iv*) pregnancy confirmation, *v*) aborting of the study, and *vi*) investigators determine that the discontinuance of the study is appropriate for reasons other than those mentioned above. Even in the case of discontinuance, a patient who consented to participate can be followed up until the end of the study. Dropout in this study was defined as participants with whom the study team had lost contact or those who had revoked consent during the follow-up after discontinuing the study.

### Ethical principles

This study is to be conducted in accordance with the

**Table 3. Study endpoints**

## Primary endpoint

- Intergroup differences in HbA1c levels from baseline to 52 weeks

## Secondary endpoints

- Intergroup differences in HbA1c levels from baseline to 12, 24, and 36 weeks and the end of the study
- Intergroup differences in plasma glucose, total cholesterol, HDLC, ALT, creatinine, weight, systolic and diastolic blood pressures, and total number of antidiabetic agents for the following 12, 24, 36, and 52 weeks from the baseline.
- Intragroup changes in scores obtained from the BDHQ from baseline to 52 weeks and the DTR-QOL from baseline to 24 and 52 weeks and the end of the study

## Explanatory endpoints

- Self-measurement (sphygmomanometer, scale and activity monitor)  
The transition from the start date is illustrated for each group.  
Information from the day closest to 12, 24, 36, and 52 weeks from the start of the study is extracted, and repeated-measures analysis of variance is performed.
- Stages in dietary and exercise-related behavioral change  
Create a contingency table for each time point and repeat the entire test for intergroup comparison. Comparison between time points is performed for reference.
- Prescription information  
Total number of prescriptions at each time (except for oral antidiabetic agents)

ALT, alanine transaminase; BDHQ, Brief-type Self-administered Diet History Questionnaire; DTR-QOL, diabetes therapy-related quality of life; HDLC, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin.

principles of Declaration of Helsinki, as well as the "Ethical Guidelines for the Conduct of Clinical Studies" and the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" both of which are established by the Ministry of Health, Labour and Welfare in Japan. This study was approved by the Ethical Committee of NCGM (NCGM-G-002373) and by the Institutional Review Board/Ethics Committee at each study site in a hospital registration group and in the facilities of the executive committee members (Table S6, <https://www.ghmopen.com/site/supplementaldata.html?ID=22>). Primary care physicians who intend to access the administrator section in the SFJA would need to be ethically reviewed. Following approval by the ethical committee, the protocol of this study and its revisions are to be reviewed and approved by the ethics committee of each institution for their feasibility as well as their ethical and scientific validity. For collaborators who do not have a local Institutional Review Board/Ethics Committee, the ethical committee of the NCGM assumes ethical review. This study was registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) before the first participant was enrolled (UMIN 000030823).

*Data management*

Data obtained from the weight and body composition, blood pressure, and activity monitors were captured electronically and stored on a server. Laboratory and QOL data were reported through the patient portal or through the healthcare institutions. The JCRAC Data Center oversees data management.

*Statistical analyses*

All analyses will be based on an intention-to-treat principal and will be performed with two-sided *P*-values

which are considered significant when they are below 0.05. For the missing values, there are no plans at this time to supplement them with the last observation carried forward method or with other methods. Furthermore, given the difficulty in defining non-compliance with this study's protocol, a per-protocol analysis will be performed to check the agreement of the analysis. For a detailed analysis, the statistician will make a statistical analysis plan before the data lock, as indicated below:

*i) Primary endpoint:*

- Difference in HbA1c levels from baseline to 52 weeks

Calculate the difference 1 year after the baseline and compare the two groups.

*ii) Secondary endpoint:*

- HbA1c, plasma casual glucose, total cholesterol, high-density lipoprotein cholesterol, alanine transaminase, and creatinine levels; weight; systolic and diastolic blood pressures; and total number of antidiabetic agents

Repeated data for the 12, 24, 36, and 52 weeks from the baseline for between-group comparisons (except for HbA1c levels at 52 weeks).

- BDHQ

Analyse the change for each subgroup based on the values surveyed at baseline and at 52 weeks.

- DTR-QOL

We analysed the change for each subgroup based on the values surveyed at baseline, at 24 and 52 weeks and at the end of the study.

*iii) Planned other analyses*

- Self-measurement (sphygmomanometer, scale, activity monitor)

The transition from the start date is illustrated for each group.

- Blood pressure and weight

Information from the day closest to 12, 24, 36, and 52 weeks from the study initiation was extracted, and a repeated-measures analysis of variance was performed.

- The dietary and exercise-related behavioral change stages

Create a contingency table for each time point and repeat the entire test to ascertain the between-group differences. Moreover, a comparison between time points is performed for reference.

- Prescription information

The total number of prescriptions at each time (except for antidiabetic agents).

*iv) Safety*

Based on the adverse event surveys conducted individually, the reported cases are added using the reported cases as the denominator. The chi-squared test is performed because it depends on the report, but it is used as a reference value.

For SAEs (*e.g.*, death, hospitalization), events reported individually to the secretariat are to be tabulated.

The PRISM-J clinical investigators are not allowed to access data on outcome measurements until the end of this study, when the primary endpoint data analysis is completed.

#### *History of modifications of the protocol*

Modifications in the protocol, including those on the inclusion criteria and registration period, have been approved by the Ethical Committee of NCGM as stated earlier.

## **Discussion**

We have presented the study design of and rationale for the PRISM-J study. This is the first large-scale RCT to investigate the efficacy of an IoT-based self-monitoring system on behavioral changes and glycemic control in individuals with type 2 diabetes. This study aimed to obtain daily physical activity and behavioral changes, both in exercise and diet, over 1 year in more than 1,000 people with type 2 diabetes. We recognize that this study may face challenge in terms of participant adaptation to the IoT system and retention for long term follow up, however, due to strengths in the large sample size, we will be able to descriptively determine the types of food and exercise behaviors that could be associated with the improvement of glycemic control, which could presumably lead to the development of customized exercise and diet therapies. We believe that the expected results of the PRISM-J trial will provide novel strategies for both diabetes treatment and social health.

## **Acknowledgements**

We acknowledge the contributions of Eri Nomura and Maki Iwatake (Comprehensive Health Science Center,

Aichi Health Promotion Foundation) in providing training and guidance to staff on the IoT systems; Yumi Maeda, Yuko Takano, Yuka Ikeda, and Yoko Hirata (Mitsubishi Research Institute, Inc., Tokyo) for providing support in project management; Kohei Higuchi, Masato Yamashin, Kazuhiko Ikebe, and Takaaki Matsuda (Omron Healthcare Co., Ltd. Kyoto) for the construction of the IoT system and technical operational assistance; Yasuhiro Igarashi (ABeam Consulting Ltd., Tokyo) and Kengo Ozeki (2nd Factory, Tokyo) for the construction of the intervention system and operation service; Toyotaka Mori (IROM CS Co., Ltd., Tokyo) for the support service at the participation facility; and Shibuki Iimori, Kazumi Kimura, Azusa Mizuma, and Naohide Nomi (IBERICA Co., Ltd., Fukuoka) for support at the research office. We would like to thank the members of the Project Office of PRISM-J (Mikiko Uwano, Tomoko Ogawa, and Minoru Matsuda) and of the JCRAC Data Center (Chiyoko Toyama, Keiko Momose, Misuzu Yoshida, and Mariko Tateo).

*Funding:* This study was supported by the Japan Agency for Medical Research and Development (AMED) and the Research Program for Health Behaviour Modification by using IoT during fiscal years 2017-2019. The AMED does not/will not have any role in the study design, management, data analysis and interpretation, writing of the report or the decision to submit the report.

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

## **Additional Statement**

### *Authors' contributions*

RB designed the protocol, guided the study, enrolled participants, managed onsite registration, researched the data, and wrote the manuscript. KI designed the protocol, guided the study, and researched the data. HO designed the protocol, generated the allocation sequence, assigned participants to interventions, and guided the study as a biostatistician. KM guided the study as an expert of medical information. ST designed the protocol and guided the study as an expert in exercise physiology. NSA, KH, MO, YK, HK, TO, and HA guided the study, enrolled participants, and researched the data. KT designed the protocol, guided the study, and researched the data. HW and TK supervised the study. UK designed the protocol, guided the study, researched the data, and reviewed and edited the manuscript and, as the guarantor of this work, takes responsibility for the integrity of the data and the accuracy of the data analysis.

### *Steering Committee*

Ryotaro Bouchi (National Center for Global Health and Medicine, Tokyo), Kazuo Izumi (National Center for Global Health and Medicine, Tokyo), Hiroshi Ohtsu

(National Center for Global Health and Medicine, Tokyo), Kengo Miyo (National Center for Global Health and Medicine, Tokyo) and Kohjiro Ueki\* (National Center for Global Health and Medicine, Tokyo).

\*Principal investigator

#### *Safety Assessment Committee*

Hiroshi Sakura\* (Tokyo Women's Medical University Medical Center East, Tokyo) \*Chief

#### *Data Center*

Hiroshi Ohtsu\* (JCRAC Data Center, Tokyo) \*Chief  
Koji Kitajima (JCRAC Data Center, Tokyo)

#### *Statistical Team and Allocation*

Hiroshi Ohtsu\* (National Center for Global Health and Medicine, Tokyo) \*Chief

#### *Data Monitoring*

Shinji Inagaki\* (ACCERISE, Inc., Tokyo, Japan) \*Chief

#### *Audit*

Natsue Matsumoto (ACCERISE, Inc., Tokyo, Japan), and Otoji Mori\* (ACCERISE, Inc., Tokyo, Japan) \*Chief  
Auditing will be conducted at four sites, including Nagoya University, Hyogo Medical University, ACCERISE, and IBERICA, which are independent of the investigators and the sponsor.

#### *Collaborators*

The PRISM-J Study Group.

#### **Ethics and Dissemination**

*Patient consent:* Obtained prior to study participation.

*Ethics approval:* NCGM-G-002373-13.

*Dissemination policy:* The researchers plan to present their findings to the participants, healthcare professionals, the public, and other relevant groups *via* publications and conference presentations.

*Provenance and peer review:* Not commissioned; externally peer reviewed.

*Data sharing statement:* No additional data are available.

*Compliance with Ethical Standards:* This study is to be conducted in accordance with the ethical standards of the responsible committee on human experimentation (Ethical Committee of NCGM/September 29, 2017/NCGM-G-002373-13) and with the Helsinki Declaration of 1964 and later versions. No potential conflicts of interest relevant to this article were reported. Informed consent is to be obtained from all patients for being included in the study.

*Trial registration number:* University Hospital Medical Information Network Clinical Trials Registry (ref: UMIN000030823).

*Protocol Version:* Ver 13.0 (Approval date: July 10, 2020).

#### **References**

1. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979; 241:2035-2038.
2. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998; 339:229-234.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352:837-853.
4. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998; 317:703-713.
5. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003; 348:383-393.
6. Ueki K, Sasako T, Okazaki Y, *et al.* Effect of an intensified multifactorial intervention on cardiovascular outcomes and mortality in type 2 diabetes (J-DOIT3): an open-label, randomised controlled trial. Lancet Diabetes Endocrinol. 2017; 5:951-964.
7. Kohro T, Furui Y, Mitsutake N, Fujii R, Morita H, Oku S, Ohe K, Nagai R. The Japanese national health screening and intervention program aimed at preventing worsening of the metabolic syndrome. Int Heart J. 2008; 49:193-203.
8. Ministry of Health, Labor, and Welfare. Ministerial Notification No. 430 of the Ministry of Health, Labour and Welfare. 2012. <https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000047330.pdf> (accessed January 22, 2021).
9. Ismail K, Winkley K, Rabe-Hesketh S. Systematic review and meta-analysis of randomised controlled trials of psychological interventions to improve glycaemic control in patients with type 2 diabetes. Lancet. 2004; 363:1589-1597.
10. Piette JD, Weinberger M, McPhee SJ, Mah CA, Kraemer FB, Crapo LM. Do automated calls with nurse follow-up improve self-care and glycemic control among vulnerable patients with diabetes? Am J Med. 2000; 108:20-27.
11. Phillips LS, Ziemer DC, Doyle JP, *et al.* An endocrinologist-supported intervention aimed at providers improves diabetes management in a primary care site: improving primary care of African Americans with diabetes (IPCAAD) 7. Diabetes Care. 2005; 28:2352-2360.
12. Noda M, Hayashino Y, Yamazaki K, Suzuki H, Goto A, Kato M, Izumi K, Kobayashi M. A cluster-randomized trial of the effectiveness of a triple-faceted intervention promoting adherence to primary care physician visits by



- diabetes patients. *Sci Rep.* 2020; 10: 2842.
13. Diabetes Prevention Program Research Group. The 10-year cost-effectiveness of lifestyle intervention or metformin for diabetes prevention: an intent-to-treat analysis of the DPP/DPPOS. *Diabetes Care.* 2012; 35:723-730.
  14. McMahon GT, Gomes HE, Hickson Hohne S, Hu TM, Levine BA, Conlin PR. Web-based care management in patients with poorly controlled diabetes. *Diabetes Care.* 2005; 28:1624-1629.
  15. Quinn CC, Clough SS, Minor JM, Lender D, Okafor MC, Gruber-Baldini A. WellDoc mobile diabetes management randomized controlled trial: change in clinical and behavioral outcomes and patient and physician satisfaction. *Diabetes Technol Ther.* 2008; 10:160-168.
  16. Ryan EA, Holland J, Stroulia E, Bazelli B, Babwik SA, Li H, Senior P, Greiner R. Improved A1C levels in type 1 diabetes with smartphone app use. *Can J Diabetes.* 2017; 41:33-40.
  17. Waki K, Fujita H, Uchimura Y, Omae K, Aramaki E, Kato S, Lee H, Kobayashi H, Kadowaki T, Ohe K. Dialbetics: a novel smartphone-based self-management support system for type 2 diabetes patients. *J Diabetes Sci Technol.* 2014; 8:209-215.
  18. Cho JH, Kim HS, Yoo SH, Jung CH, Lee WJ, Park CY, Yang HK, Park JY, Park SW, Yoon KH. An Internet-based health gateway device for interactive communication and automatic data uploading: clinical efficacy for type 2 diabetes in a multi-centre trial. *J Telemed Telecare.* 2017; 23:595-604.
  19. Onoue T, Goto M, Kobayashi T, Tominaga T, Ando M, Honda H, Yoshida Y, Tosaki T, Yokoi H, Kato S, Maruyama S, Arima H. Randomized controlled trial for assessment of Internet of Things system to guide intensive glucose control in diabetes outpatients: Nagoya health navigator study protocol. *Nagoya J Med Sci.* 2017; 79:323-329.
  20. Murakami H, Kawakami R, Nakae S, Nakata Y, Ishikawa-Takata K, Tanaka S, Miyachi M. Accuracy of wearable devices for estimating total energy expenditure: comparison with metabolic chamber and doubly labeled water method. *JAMA Intern Med.* 2016; 176:702-703.
  21. Shimamoto K, Ando K, Fujita T, *et al.* The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). *Hypertens Res.* 2014; 37:253-392.
  22. The Japan Diabetes Society. Treatment Guide for Diabetes 2016-2017. [http://www.jds.or.jp/modules/en/index.php?content\\_id=1](http://www.jds.or.jp/modules/en/index.php?content_id=1) (accessed January 22, 2021).
  23. Kobayashi T, Tsushita K, Nomura E, Muramoto A, Kato A, Eguchi Y, Onoue T, Goto M, Muto S, Yatsuya H, Arima H. Automated feedback messages with shiffukujin characteristics using IoT system-improved glycemic control in people with diabetes: a prospective multicenter randomized controlled trial. *J Diabetes Sci Technol.* 2019; 13:796-798.
  24. Japan Society for the Study of Obesity. Guidelines for the management of obesity disease 2016, Life Science Publishing Co., Ltd., Tokyo, Japan.
  25. Miyachi M, Tripette J, Kawakami R, Murakami H. "+10 min of physical activity per day": Japan is looking for efficient but feasible recommendations for its population. *J Nutr Sci Vitaminol (Tokyo).* 2015; 61 Suppl:S7-S9.
  26. Ministry of Health, Labor, and Welfare. ActiveGuide. <http://www.nibiohn.go.jp/eiken/info/pdf/active2013-e.pdf> (accessed January 22, 2021).
  27. Ishii H. Development and psychometric validation of the diabetes therapy-related QOL questionnaire. *J Med Econ* 2012; 15:556-563.
  28. Kobayashi S, Murakami K, Sasaki S, Okubo H, Hirota N, Notsu A, Fukui M, Date C. Comparison of relative validity of food group intakes estimated by comprehensive and brief-type self-administered diet history questionnaires against 16 d dietary records in Japanese adults. *Public Health Nutr.* 2011; 14:1200-1211.
  29. Sugiyama T, Miyo K, Tsujimoto T, Kominami R, Ohtsu H, Ohsugi M, Waki K, Noguchi T, Ohe K, Kadowaki T, Kasuga M, Ueki K, Kajio H. Design of and rationale for the Japan diabetes CompREhensive database project based on an advanced electronic medical record system (J-DREAMS). *Diabetol Int.* 2017; 8: 375-382.
  30. Hayashino Y, Suzuki H, Yamazaki K, Goto A, Izumi K, Noda M. A cluster randomized trial on the effect of a multifaceted intervention improved the technical quality of diabetes care by primary care physicians: The Japan diabetes outcome intervention trial-2 (J-DOIT2). *Diabet Med.* 2016; 33: 599-608.
- 
- Received April 14, 2021; Revised May 17, 2021; Accepted May 19, 2021.
- \*Address correspondence to:*  
 Kohjiro Ueki, National Center for Global Health and Medicine,  
 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.  
 E-mail: uekik@ri.ncgm.go.jp

# Effects of COVID-19 on vital organs in patients infected with SARS-CoV-2

M. Ibrahim Hossain\*, Esha Binte Shahriar, Anamika Sarker, Nafisa Lubna, Mehjabeen Haque, Md. Ibrahim Khalil

Laboratory of Preventive and Integrative Biomedicine, Department of Biochemistry and Molecular Biology, Faculty of Biological Sciences, Jahangirnagar University, Savar, Bangladesh.

**Abstract:** The world is now facing one of the most devastating public health concern where the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is spreading all over the world initiating from Wuhan, China, started from December, 2019. The World Health Organization (WHO) already announced the situation as pandemic all over the world. According to the webpage of WHO, this SARS-CoV-2 has been spreading all over the world (223 countries, areas or territories) with 126,890,643 confirmed cases of coronavirus disease 2019 (COVID-19) and 2,778,619 confirmed deaths (as of March 30, 2021). Accumulated published documents indicate that the SARS-CoV-2 virus primarily affects the lungs causing hypoxia, which is the leading cause of death. There are many reports describing that with the progress of this disease, many other organs (such as heart, kidney, liver, brain) of the affected person start to malfunction. Though SARS-CoV-2 uses the cell surface receptor angiotensin-converting enzyme 2 (ACE-2) expressed by lungs, cardiovascular system, and kidneys but it is still not clear except for lungs that all these other organs are directly affected by this virus or not. Therefore, the aim of this review is to gather informations about affected/damaged organs or tissues and consequences of this damage in COVID-19 patients.

**Keywords:** SARS-CoV-2, COVID-19, ACE-2, multi-organ failure, ARDS

## Introduction

Coronaviruses are a family of related viruses that cause diseases, ranging from mild to lethal, in mammals and birds. In humans such types of coronavirus cause deadly pneumonia with other life threatening diseases. The first coronavirus was reported in 1931 but the first human coronavirus (HCoV-229E) was isolated from humans in 1965 (1). However, five coronaviruses have been reported at different times during this century: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 (2,3), human coronavirus (HCoV-NL63) in 2003 (4), coronavirus HKU1 (CoV-HKU1) in 2004 (5), Middle-East respiratory syndrome coronavirus (MERS-CoV) in 2012 (6) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in 2019 (7,8). Among them SARS-CoV-2 (also called the 2019 novel coronavirus, 2019-nCoV) is the coronavirus strain that causes the deadly respiratory illness, severe pneumonia, along with other severe health problems and is known as coronavirus disease 2019 (COVID-19).

Since December 2019 starting from Wuhan, China, this SARS-CoV-2 has been spreading all over the world (223 countries, areas or territories) with 126,890,643 confirmed cases and 2,778,619 confirmed deaths (as of March 30, 2021) (9). This situation in the current World

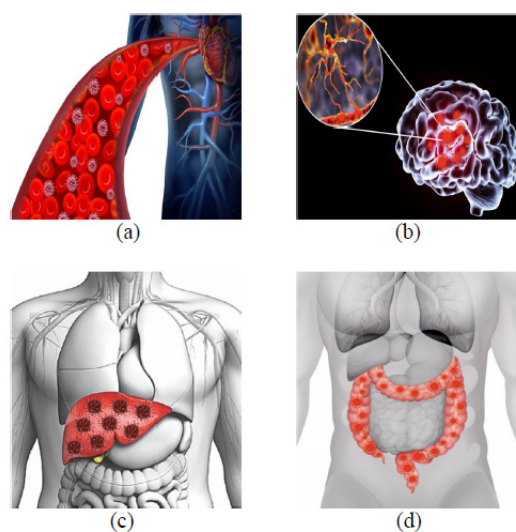
is declared as the most serious crisis situation since World War 2 by World Health Organization (WHO). Though currently some vaccines are approved by WHO and these vaccines are used in different countries all over the world, in many countries where vaccines are inadequate, treatment of COVID-19 largely depends on the usual treatment of pneumonia and the experience of the clinicians (10).

Therefore, the aim of this current review is to gather information about the complications of patients infected with this novel virus, SARS-CoV-2.

## Clinical features

Persons infected with SARS-CoV-2 showed similar symptoms of normal flu. But the most important clinical feature is the occurrence of severe pneumonia. Within February 2020, three major case studies reported pneumonia as a major clinical feature of patients infected with SARS-CoV-2 in Wuhan, China (7,11,12). One study about the clinical manifestations of COVID-19 patients infected with SARS-CoV-2 had been reported. The study reported about 278 COVID-19 patients where all of them were suffering from severe pneumonia. All the patients were older than 18 years and about 61.9% ( $n = 172$ ) were males.

Fever was the most common symptom (92.8%;  $n = 258$ ), followed by cough (69.8%;  $n = 194$ ), dyspnoea (34.5%;  $n = 96$ ), myalgia (27.7%;  $n = 77$ ), headache (7.2%;  $n = 20$ ) and diarrhoea (6.1%;  $n = 17$ ) (13). However, symptoms of COVID-19 can vary from mild features to a critical state. In addition to those that were mentioned earlier, the patients may show muscle aches, confusion, headache, sore throat, rhinorrhoea, chest pain, sputum production, nausea and vomiting and many others (7,11,12). Following such types of symptoms acute respiratory distress syndrome (ARDS) and multiple-organ failure occurred rapidly, resulting in death within a short period of time (14). Patients with underlying conditions like hypertension, cancer, kidney disease, diabetes and many other comorbidities are more prone to severe respiratory conditions and death than normal patients (11,12,14). However, as the virus is spreading all over the world, newer symptoms might occur depending on the changed nature of this virus, physiological status of patients as well as the region of the world.



**Figure 1. Distribution of SARS-CoV-2 in the COVID-19 patients.** In COVID-19 patients, the SARS-CoV-2 is mainly found in the lungs. Beside lungs, so far reported, this virus is found in the cardiovascular system (a), in the brain (b), in the liver but at low levels (c) and in the gastrointestinal system (d).

The reason behind the occurrence of severe pneumonia (inflammation of the air sacs of lungs) in the SARS-CoV-2 infected persons is that the virus uses the surface protein called angiotensin-converting enzyme 2 (ACE-2) (15) and cells of the lungs express ACE-2 surface receptors (16). This ACE-2 cell surface receptor is also expressed by some other cell types such as cells of the gastrointestinal system (17), arterial and venous endothelial cells, smooth muscle cells (16), cells of heart, kidney and testes (18). Structural studies showed that the SARS-CoV-2 binds 10 to 20 times more strongly with the human ACE-2 than the SARS-CoV predecessor (19). This might be the reason why this new SARS-CoV-2 is more infectious or contagious than its 2002 predecessor, SARS-CoV. Since a variety of tissues express ACE-2 in their cells, these tissues or organs might be affected first and due to the malfunctions of one organ others are affected and as a result the person dies (Figure 1). In the following section, we will try to summarize information found in different articles affecting various vital organs of COVID-19 patients (Table 1).

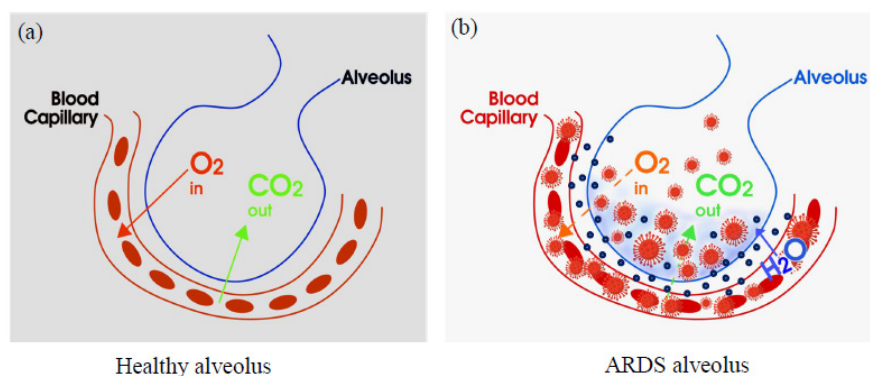
### Lungs

As the name suggests, SARS-CoV-2, this virus primarily/mainly affects the respiratory system with severe infection in the lungs. There are a large number of reports of severe pneumonia in COVID-19 patients (7,8,20,21). Although much is known about the rate of mortality in COVID-19 patients, less is known about the pathophysiology of this virus. However, accumulating evidences suggest a general mechanism causing pneumonia (22) (Figure 2). According to this article the mechanism starts with binding of virus to epithelial cells in the nasal cavity and starts replicating. This virus uses the cell surface receptor ACE-2 to bind to the cell (23). In the next few days, the virus starts to migrate down the respiratory tract. During this time the body responds by activating the innate immune response by producing interferons. One of the interferons that is produced during early phase of infection of SARS is interferon-inducible protein-10, CXCL-10. For this reason CXCL-10 has been reported

**Table 1. Summary of the effects of organs/tissues with their corresponding symptoms in the COVID-19 patients all over the Globe**

Name of the organ/tissue	Expression of ACE-2	Symptoms of COVID-19 patients	Ref.
Lungs (alveolus)	yes, high	ARDS, pneumonia	(7,8,16,20,21)
Gastrointestinal system (intestine)	yes, high	diarrhea	(17,20,34)
Blood vessels (endothelial cells)	yes, high	blood coagulation	(16,40,41,42)
Heart (myocardium)	yes, high	arrhythmia, myocardial damage	(7,18,44,45)
Kidney (nephron)	yes, high	chronic kidney disease	(18,48,49)
Liver (hepatocytes)	no (yes* low)	liver injury, abnormal functions	(51,52)
Brain (neuron, glia)	no (yes**)	anosmia, ageusia	(62-64)

Footnote: \* non-conclusive; \*\* highly non-conclusive.



**Figure 2. Probable mechanism of the formation of ARDS in COVID-19 patients.** (a) The alveolus of a healthy person shows frequent exchange of gases between  $O_2$  and  $CO_2$  ( $O_2$  goes into the blood for use by different types of cells and  $CO_2$  goes into alveolus to be expelled out from the body). (b) The alveolus of COVID-19 patient shows due to infection by SARS-CoV-2, the infected alveolus secreted various cytokines and chemokines (shown as blue dots) causing damage of pulmonary microvascular and alveolar epithelial cell barriers. As a result  $H_2O$  enters into the alveolus from blood capillaries causing pulmonary edema or ARDS. Therefore exchange of gases is hampered causing breathing difficulties.

as a disease marker for SARS patients (24). Within the next few days, the virus reaches the basic structure of the lungs, the alveolus. With the help of this basic structure, the lungs perform its main function, which is the exchange of gases ( $O_2$  and  $CO_2$ ). Probably, like SARS-CoV, SARS-CoV-2 infects type-II alveolar cells (25). Influenza virus also infects the same alveolar cells of the lungs (26). Type-II alveolar cells constitute 60% of lung alveolar cells and produce phospholipid rich materials known as surfactant, which reduces the surface tension between the two wet surfaces of the alveolus (27). As a result the alveolus fails to reinflate causing ARDS with the body's excessive defense mechanism. One of the major causes of ARDS and multiple-organ failure is the cytokine storm (28).

The cytokine storm contains a large number of different types of soluble mediators like pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8, granulocyte-macrophage colony stimulating factor and ROS) and chemokines (CCL2, CCL3, CCL5, IFN $\gamma$ -induced protein 10) that all contribute to the occurrence of ARDS (29,30). Viral replication into the cell causes these pro-inflammatory cytokines or chemokines to release and as a response to this there is induction of apoptosis in lung epithelial and endothelial cells involving mechanisms like Fas-Fas ligand (FasL) or TRAIL-death receptor 5 (DR5) (31,32). Death of lung epithelial cells and endothelial cells causes damage to pulmonary microvascular and alveolar epithelial cell barriers leading to formation of alveolar edema ultimately causing hypoxia in the body. Therefore, probably, the cytokine storm is the cause of ARDS in COVID-19 patients infected with SARS-CoV-2.

#### Gastrointestinal system

Initially diarrhea or gastrointestinal problems was considered as a minor symptom of this virus compared

with pneumonia or problems with respiratory systems but with the increasing number of infection cases the incidence of diarrhea is also increasing (33). Now, diarrhea is one of the frequent symptoms in COVID-19 infection as it was detected in up to 30% of patients with MERS-CoV and 10.6% of patients with SARS-CoV-2 (20,34). In addition to use the receptor protein ACE-2 expressed on the cell surface, SARS-CoV also uses cellular serine proteases (TMPRSS2) to get entry inside the cell. The entry process into the cell involves priming by TMPRSS2, which allows spike protein cleavage and regulation of the entire mechanism (23). But the major role of entry is by the surface protein ACE-2, which first mediates the attachment of the virus with the host cell membrane and then TMPRSS2 favors the fusion of the two (one is the virus and other one is the host cell) cell membranes (23). Therefore, the virus entry into the host cell or infectivity mainly depends on binding with the ACE-2 surface receptor (35) and the ACE-2 surface receptor is also greatly expressed by gastrointestinal epithelial cells (17,36). Analyses of COVID-19 patients also confirmed the presence of SARS-CoV-2 RNA in anal or rectal swabs (37,38) as well as in stool specimens (39). Even after clearance of the virus in the upper respiratory system, SARS-CoV-2 RNA is still found in anal or rectal swabs (37,38). All of this evidence indicates that diarrhea or gastrointestinal abnormalities should be considered as a major symptom of SARS-CoV-2 infections and absence of SARS-CoV-2 RNA in anal or rectal swabs or in stool specimens should be taken into account before declaring an infected person to be a healthy person.

#### Blood endothelial cells

ACE-2 surface receptors are expressed in the endothelial cells of blood vessels (16). Therefore, the consequences of infected endothelial cells of blood

vessels have not yet been addressed. However, there is evidence that some COVID-19 patients have prominent changes in blood coagulation (40). For example, the values of D-dimer, fibrin/fibrinogen degradation products (FDP), and fibrinogen (FIB) in all SARS-CoV-2 cases are substantially higher than those in healthy controls and values of D-dimer and FDP are higher in severe COVID-19 patients than milder patients. And the prothrombin time activity (PT-act) is lower in SARS-CoV-2 patients (40). In another article, it was also reported that in the late stages of pneumonia caused by SARS-CoV-2, fibrin-related markers (e.g. D-dimer) are markedly elevated suggesting coagulation activation and start of secondary hyperfibrinolysis, which may be induced following severe COVID-19 infection (41). When some ( $n = 99$ ) severe COVID-19 patients, who had markedly elevated D-dimer, received heparin as anticoagulant therapy for 7 days or longer they had better prognosis of the disease with a decreased rate of mortality of about 20% (42). Therefore, changes in blood coagulation is a prominent feature of severe infection with SARS-CoV-2 and it was suggested that monitoring D-dimer and FDP values may be helpful for early identification of severe cases (40).

#### *Heart and cardiovascular system*

Since myocardium or cardiac muscle cells express ACE-2 surface receptor (18), SARS-CoV-2 might attack the heart as well though there is no report about the presence of virus in the heart (43). In a case study of 138 COVID-19 patients admitted into the hospital, 16.7% developed arrhythmia and 7.2% presented acute cardiac injury (12). In another report, acute cardiac injury was reported in 5 among the first 41 humans infected with SARS-CoV-2 in Wuhan, China, with an increased level of high-sensitivity cardiac troponin I, cTnI (7). Another acute cardiac injury marker brain-type natriuretic peptide (BNP) was also found to be elevated among patients admitted into a hospital ICU in Washington (44). There is a report of 150 COVID-19 patients from Wuhan, China, where 68 (45%) died. Among the 68 patients, 29 (40%) patients died exclusively due to myocardial damage or in combination with myocardial damage and circulatory failure (45). COVID-19 patients with these comorbidities are more likely to die than regular patients. According to the New York State Health Department, among these comorbidities hypertension is number one in terms of patient's severity. Because hypertensive patients have to use ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and usage of these drugs can increase ACE-2 expression. Since ACE-2 surface receptors are used by SARS-CoV-2, usage of these anti-hypertensive drugs can be life threatening for a person who has both hypertension and COVID-19 (46). However, Tignanelli *et al.* claimed that no evidence is available

to support routine discontinuation of ACEIs or ARBs in COVID-19 patients since the role of renin-angiotensin system (RAS) inhibition in COVID-19 is controversial (47). Therefore, they suggest an urgent investigation in multicenter trials to test this hypothesis in patients with COVID-19 before the medical community makes recommendations for patients to withhold potentially life-saving drugs (47).

All of these data indicate that myocardium of infected persons is somehow involved in the mortality rate of COVID-19 patients. Though the mechanisms of such acute cardiac injury in COVID-19 patients are not well understood, however, Akhmerov and Marban proposed one mechanism which likely involves increased cardiac stress due to respiratory failure and hypoxemia, direct myocardial infection by SARS-CoV-2, indirect injury from the systemic inflammatory response, or a combination of all three factors (43).

#### *Kidneys*

Though kidneys express ACE-2, there are no reports yet about the presence of SARS-CoV-2 into the kidney like heart. Chronic kidney disease (CKD) is a frequently encountered disease in the general population of a country. During the first two months of the current outbreak in China, CKD was re-reported in 4.3% of the Chinese patients infected with COVID-19 who had severe presentation (48,49). End-stage kidney disease patients are a highly susceptible group with an infection rate of 16%, which exceeds that observed in other populations (49). Persons infected with SARS-CoV-2 with this co-morbidity are at high risk of mortality. And various kidney diseases are a vital candidate of this comorbidity. One article concludes that the prevalence of kidney disease on admission and the development of acute kidney disease (AKI) during hospitalization in patients with COVID-19 is high and is associated with in-hospital mortality (50). Hence, clinicians should increase their awareness of kidney disease in patients with severe COVID-19 (50).

#### *Liver*

There are few reports concerning liver dysfunction in COVID-19 patients. Though there are no reports yet that hepatocytes express ACE-2 surface receptors, although one article reported that bile duct epithelial cells may express ACE-2 receptors more than hepatocytes (51). In a study of 417 COVID-19 patients, 318 (76.3%) had abnormal liver test results and 90 (21.5%) had liver injury during hospitalization. These abnormal liver tests became more pronounced in the next 2 weeks where all the essential liver enzymes (ALT, AST, total bilirubin and  $\gamma$ -GT) were elevated to more than 3 times of the upper limits indicating abnormal liver tests had higher risks of progressing to severe

disease in SARS-CoV-2 infection (52). In another study of 99 COVID-19 patients in China, 43% of patients had differing degrees of liver function abnormalities with ALT and AST with an upper range of ALT 7,590 U/L and AST 1,445 U/L (55). An opposing state of arguments was also reported concerning liver damage in COVID-19 patients. According to the report the derangement of liver function is mild and when liver function tests for patients with different durations of symptoms are examined, there is no evidence that later presentation is associated with greater liver function derangement (53).

Therefore, whether SARS-CoV-2 has direct adverse effects on liver function is currently not known due to unavailable data on the expression of viral receptor ACE-2 in hepatocytes. But according to Guan *et al.* hepatocytes do express ACE-2 receptors but at very low concentrations. They also proposed a mechanism of how hepatocytes are infected by SARS-CoV-2. They reported that upon SARS-CoV-2 infection, the upregulation of ACE-2 in liver tissue is caused by compensatory proliferation of hepatocytes derived from bile duct epithelial cells, which express ACE-2 at higher levels than hepatocytes and this might play a role in liver damage in COVID-19 patients (51).

### Brain

Though the invasions of molecules or particles are strictly regulated into the brain by the blood-brain barrier (BBB), many viruses (from human immunodeficiency virus type 1 to togaviruses) can escape the BBB by different mechanisms and enter into the brain (54). The neuroinvasive nature of coronaviruses has been documented for different members of the betacoronaviruses such as SARS-CoV (55), MERS-CoV (56), HCoV-229E (57), HCoV-OC43 (58), and mouse hepatitis virus (MHV) (59). Since coronaviruses use the cell surface receptor protein ACE-2, now the question arises do cells of the brain express the ACE-2 receptor? Well, the answer is not known clearly yet but mice transgenic (Tg) for the expression of human ACE-2 (*hACE-2*), called K18-*hACE2* mice, were shown to be extremely susceptible to SARS-CoV with infection of the lungs and brain in all the experimental mice which were infected with intranasal inoculation (60). Later it was reported that SARS-CoV causes neural death in the brain of K18-*hACE2* mice even in the absence of encephalitis (61). There is another report shown to have SARS-CoV RNA polymerase gene in neurons of an infected person (62) indicating neurons might have the viral receptor ACE-2 but more studies are required to make sure of the existence of SARS-CoV in neurons.

Several other recent reports described COVID-19 patients experienced anosmia and ageusia, which might be due to an invasion of this virus into the brain causing olfactory and gustatory dysfunction (63-65). In one study of 417 mild to moderate COVID-19 patients

with general symptoms like cough, myalgia and loss of appetite, about 85.6% and 88% of patients suffered from olfactory and gustatory dysfunctions, respectively (63). In another study of 72 COVID-19 patients in Italy, 60 cases had a variable degree of hyposmia with 2 cases of anosmia and 33 cases of hypogeusia and 1 case of ageusia (66) suggesting anosmia and ageusia as initial or unique symptoms after SARS-COV-2 virus infection (64,65). Since neither the olfactory neurons nor the other brain cells express the surface receptor ACE-2 for viral entry, further research is urgently needed to solve this issue of how the olfactory or gustatory related neurons are affected due to SARS-COV-2 virus infection.

There is an alternative way of SARS-CoV-2 invasion into the brain of COVID-19 patients described by Kabbani and Olds (67). According to them, if brain is susceptible to SARS-CoV-2 infection then persons will be at high risk if they have a habit of smoking. Functional interactions between nicotine exposure and ACE2 expression in lungs and other organ systems such as heart and kidneys, as well as nicotine and other components of the renin-angiotensin system (RAS) suggest that smoking can promote COVID-19 cellular entry through nicotinic acetylcholine receptor (nAChR) signaling. Kabbani and Olds suggest that regions, which are known to express various types of nAChRs, are putative sites for primary infection with COVID-19 in the human brain. Interactions between nAChRs and ACE2 have been studied in several of these regions including the ventrolateral medulla and smoking may lead to enhanced viral infection through the ability of nicotine to upregulate nAChRs in regions such as the lungs. In this case, upregulation of nAChRs in either/both neurons and astrocytes could promote greater viral entry and replication through augmented ACE2 expression in the cell (67). Supporting the notion that smokers are at high risk for SARS-CoV infection, there is another report which demonstrated that ACE-2 expression are increased in the small airway epithelia of smokers (68). Dealing with all of these, SARS-CoV might infect brain tissue and smokers are at high risk.

### Conclusion

In conclusion, we may say COVID-19 patients might die due to lack of oxygen as lungs are suffering from ARDS. But as the infection progresses within the body, various other organs are being affected. But it is not yet known, whether other organs are affected due to the direct attack of this virus or as a consequence of lack of oxygen since lungs are not working properly or any other unknown underlying reasons. More extensive research is required to further rule out these possibilities.

### Acknowledgements

We thank department of Biochemistry and Molecular

Biology, Jahangirnagar University, for their effort to complete this study.

*Funding:* None.

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

## References

- Stephen NJK, Gert U. van Zyl, Louise N, Monique IA, Wolfgang P. Human coronaviruses. Virology, Churchill Livingstone, 2012; pp. 94.
- Drosten C, Günther S, Preiser W, *et al.* Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med.* 2003; 348:1967-1976.
- Ksiazek TG, Erdman D, Goldsmith CS, *et al.* A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med.* 2003; 348:1953-1966.
- van der Hoek L, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJ, Wolthers KC, Wertheim-van Dillen PM, Kaandorp J, Spaargaren J, Berkhout B. Identification of a new human coronavirus. *Nat Med.* 2004; 10:368-373.
- Woo PC, Lau SK, Chu CM, Chan KH, Tsoi HW, Huang Y, Wong BH, Poon RW, Cai JJ, Luk WK, Poon LL, Wong SS, Guan Y, Peiris JS, Yuen KY. Characterization and complete genome sequence of a novel coronavirus, coronavirus HKU1, from patients with pneumonia. *J Virol.* 2005; 79:884-895.
- Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med.* 2012; 367:1814-1820.
- Huang C, Wang Y, Li X, *et al.* Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet.* 2020; 395:497-506.
- Zhu N, Zhang D, Wang W, *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med.* 2020; 382:727-733.
- World Health Organization. Coronavirus disease (COVID-19) pandemic. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019> (accessed March 30, 2021).
- Li H, Zhou Y, Zhang M, Wang H, Zhao Q, Liu J. Updated approaches against SARS-CoV-2. *Antimicrob Agents Chemother.* 2020; 64:e00483-20.
- Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet.* 2020; 395:507-513.
- Wang D, Hu B, Hu C, hu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA.* 2020; 323:1061-1069.
- Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents.* 2020; 55:105924.
- Goh KJ, Choong MC, Cheong EH, Kalimuddin S, Duu Wen S, Phua GC, Chan KS, Haja Mohideen S. Rapid progression to acute respiratory distress syndrome: review of current understanding of critical illness from COVID-19 infection. *Ann Acad Med Singapore.* 2020; 49:108-118.
- Zhou P, Yang XL, Wang XG, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature.* 2020; 579:270-273.
- Hamming I, Timens W, Bultuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *J Pathol.* 2004; 203:631-637.
- Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. *FEBS Lett.* 2002; 532:107-110.
- Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res.* 2000; 87:E1-9.
- Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science.* 2020; 367:1260-1263.
- Chan JF, Yuan S, Kok KH, *et al.* A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020; 395:514-523.
- Pan F, Ye T, Sun P, Gui S, Liang B, Li L, Zheng D, Wang J, Hesketh RL, Yang L, Zheng C. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology.* 2020; 295:715-721.
- Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *Eur Respir J.* 2020; 55:2000607.
- Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and is Blocked by a Clinically Proven Protease Inhibitor. *Cell.* 2020; 181:271-280.
- Tang NL, Chan PK, Wong CK, To KF, Wu AK, Sung YM, Hui DS, Sung JJ, Lam CW. Early enhanced expression of interferon-inducible protein-10 (CXCL-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. *Clin Chem.* 2005; 51:2333-2340.
- Mossel EC, Wang J, Jeffers S, Edeen KE, Wang S, Cosgrove GP, Funk CJ, Manzer R, Miura TA, Pearson LD, Holmes KV, Mason RJ. SARS-CoV replicates in primary human alveolar type II cell cultures but not in type I-like cells. *Virology.* 2008; 372:127-135.
- Weinheimer VK, Becher A, Tönnies M, *et al.* Influenza A viruses target type II pneumocytes in the human lung. *J Infect Dis.* 2012; 206:1685-1694.
- Mason RJ. Biology of alveolar type II cells. *Respirology.* 2006; 11 Suppl:S12-S15.
- Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. *Semin Immunopathol.* 2017; 39:517-528.
- Reghunathan R, Jayapal M, Hsu LY, Chng HH, Tai D, Leung BP, Melendez AJ. Expression profile of immune response genes in patients with severe acute respiratory syndrome. *BMC Immunol.* 2005; 6:2.
- Cameron MJ, Bermejo-Martin JF, Danesh A, Muller MP,

- Kelvin DJ. Human immunopathogenesis of severe acute respiratory syndrome (SARS). *Virus Res.* 2008; 133:13-19.
31. Herold S, Steinmueller M, von Wulffen W, Cakarova L, Pinto R, Pleschka S, Mack M, Kuziel WA, Corazza N, Brunner T, Seeger W, Lohmeyer J. Lung epithelial apoptosis in influenza virus pneumonia: the role of macrophage-expressed TNF-related apoptosis-inducing ligand. *J Exp Med.* 2008; 205:3065-3077.
  32. Högner K, Wolff T, Pleschka S, Plog S, Gruber AD, Kalinke U, Walmrath HD, Bodner J, Gattenlöhner S, Lewe-Schlosser P, Matrosovich M, Seeger W, Lohmeyer J, Herold S. Macrophage-expressed IFN- $\beta$  contributes to apoptotic alveolar epithelial cell injury in severe influenza virus pneumonia. *PLoS Pathog.* 2013; 9:e1003188.
  33. Pan L, Mu M, Yang P, *et al.* Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China: a descriptive, cross-sectional, multicenter study. *Am J Gastroenterol.* 2020; 115:766-773.
  34. D'Amico F, Baumgart DC, Danese S, Peyrin-Biroulet L. Diarrhea during COVID-19 infection: pathogenesis, epidemiology, prevention and management. *Clin Gastroenterol Hepatol.* 2020; 18:1663-1672.
  35. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol.* 2020; 94:e00127-20.
  36. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology.* 2020; 158:1831-1833.
  37. Wu F, Zhao S, Yu B, *et al.* A new coronavirus associated with human respiratory disease in China. *Nature.* 2020; 579:265-269.
  38. Lu R, Zhao X, Li J, *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet.* 2020; 395:565-574.
  39. Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. *Gastroenterology.* 2020; 158:1518-1519.
  40. Han H, Yang L, Liu R, Liu F, Wu KL, Li J, Liu XH, Zhu CL. Prominent changes in blood coagulation of patients with SARS-CoV-2 infection. *Clin Chem Lab Med.* 2020; 58:1116-1120.
  41. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost.* 2020; 18:844-847.
  42. Tang N, Bai H, Chen X, Gong J, Li D, Sun Z. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost.* 2020; 18:1094-1099.
  43. Akhmerov A, Marban E. COVID-19 and the Heart. *Circ Res.* 2020; 126:1443-1455.
  44. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M, Lee M. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA.* 2020; 323:1612-1614.
  45. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med.* 2020; 46:846-848.
  46. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med.* 2020; 8:e21.
  47. Tignanelli CJ, Ingraham, Sparks MA, Reilkoff R, Bezdicek T, Benson B, Schacker T, Chipman JG, Puskarich MA. Antihypertensive drugs and risk of COVID-19? *Lancet Respir Med.* 2020; 8:e30-e31.
  48. Guan WJ, Ni ZY, Hu Y, *et al.* Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med.* 2020; 382:1708-1720.
  49. Izzedine H, Jhaveri KD, Perazella MA. COVID-19 therapeutic options for patients with kidney disease. *Kidney Int.* 2020; 97:1297-1298.
  50. Cheng Y, Luo R, Wang K, Zhang M, Wang Z, Dong L, Li J, Yao Y, Ge S, Xu G. Kidney disease is associated with in-hospital death of patients with COVID-19. *Kidney Int.* 2020; 97:829-838.
  51. Guan GW, Gao L, Wang JW, Wen XJ, Mao TH, Peng SW, Zhang T, Chen XM, Lu FM. Exploring the mechanism of liver enzyme abnormalities in patients with novel coronavirus-infected pneumonia. *Zhonghua Gan Zang Bing Za Zhi.* 2020; 28:100-106.
  52. Cai Q, Huang D, Yu H, *et al.* COVID-19: Abnormal liver function tests. *J Hepatol.* 2020; 73:566-574.
  53. Bangash MN, Patel J, Parekh D. COVID-19 and the liver: little cause for concern. *Lancet Gastroenterol Hepatol.* 2020; 5:529-530.
  54. Michalicová A, Bhide K, Bhide M, Kováč A. How viruses infiltrate the central nervous system. *Acta Virol.* 2017; 61:393-400.
  55. Glass WG, Subbarao K, Murphy B, Murphy PM. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *J Immunol.* 2004; 173:4030-4039.
  56. Li K, Wohlford-Lenane C, Perlman S, Zhao J, Jewell AK, Reznikov LR, Gibson-Corley KN, Meyerholz DK, McCray PB Jr. Middle east respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J Infect Dis.* 2016; 213:712-722.
  57. Talbot PJ, Ekané S, Cashmn NR, Mounir S, Stewart JN. Neurotropism of human coronavirus 229E. *Adv Exp Med Biol.* 1993; 342:339-346.
  58. Dubé M, Le Coupance A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal Transport Enables Neuron-to-Neuron Propagation of Human Coronavirus OC43. *J Virol.* 2018; 92:e00404-18.
  59. Zhou X, Huang F, Xu L, *et al.* Hepatitis E virus infects neurons and brains. *J Infect Dis.* 2017; 215:1197-1206.
  60. McCray PB Jr, Pewe L, Wohlford-Lenane C, Hickey M, Manzel L, Shi L, Netland J, Jia HP, Halabi C, Sigmund CD, Meyerholz DK, Kirby P, Look DC, Perlman S. Lethal infection of K18-hACE2 mice infected with severe acute respiratory syndrome coronavirus. *J Virol.* 2007; 81:813-821.
  61. Netland J, Meyerholz DK, Moore S, Cassell M, Perlman S. Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J Virol.* 2008; 82:7264-7275.
  62. Zhang QL, Ding YQ, Hou JL, *et al.* Detection of severe acute respiratory syndrome (SARS)-associated coronavirus RNA in autopsy tissues with in situ hybridization. *Di Yi Jun Yi Da Xue Xue Bao.* 2003; 23:1125-1127. (in Chinese)
  63. Lechien JR, Chiesa-Estomba CM, De Siati DR, *et al.* Olfactory and gustatory dysfunctions as a clinical



- presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol.* 2020; 277:2251-2261.
64. Moein ST, Hashemian SMR, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty RL. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol.* 2020; 10:944-950.
65. Lee Y, Min P, Lee S, Kim SW. Prevalence and Duration of Acute Loss of Smell or Taste in COVID-19 Patients. *J Korean Med Sci.* 2020; 35:e174.
66. Vaira LA, Deiana G, Fois AG, Pirina P, Madeddu G, De Vito A, Babudieri S, Petrocelli M, Serra A, Bussu F, Ligas E, Salzano G, De Riu G. Objective evaluation of anosmia and ageusia in COVID-19 patients: a single-center experience on 72 cases. *Head Neck.* 2020; 42:1252-1258.
67. Kabbani N, Olds JL. Does COVID19 infect the brain? If so, smokers might be at a higher risk. *Mol Pharmacol.* 2020; 97:351-353.
68. Leung JM, Yang CX, Tam A, Shaipanich T, Hackett TL, Singhera GK, Dorscheid DR, Sin DD. ACE-2 Expression in the Small Airway Epithelia of Smokers and COPD Patients: Implications for COVID-19. *Eur Respir J.* 2020; 55:2000688.
- 
- Received May 13, 2021; Revised June 13, 2021; Accepted June 22, 2021.
- \*Address correspondence to:*  
M. Ibrahim Hossain, Department of Biochemistry and Molecular Biology, Faculty of Biological Sciences, Jahangirnagar University, Savar, Dhaka-1342, Bangladesh.  
E-mail: ibrahim\_bmb@juniv.edu

# Survey of motor function and activities of daily living in hemophilia patients with HIV

Kazuko Kikuchi<sup>1,2</sup>, Toshiharu Komachi<sup>2</sup>, Yoshinori Honma<sup>2</sup>, Tomoyuki Endo<sup>3</sup>, Keiko Watabe<sup>4</sup>, Yoshiyuki Yokomaku<sup>5</sup>, Chieko Hashiba<sup>6</sup>, Masahiro Yamamoto<sup>7</sup>, Yukiko Nagayo<sup>8</sup>, Toshihiro Ito<sup>9</sup>, Junji Imamura<sup>9</sup>, Tomoko Suzuki<sup>10</sup>, Junko Fujitani<sup>2,\*</sup>

<sup>1</sup> Japan Foundation for AIDS Prevention, Tokyo, Japan;

<sup>2</sup> Department of Rehabilitation Medicine, National Center for Global Health and Medicine, Tokyo, Japan;

<sup>3</sup> Department of Hematology, Hokkaido University Hospital, Sapporo, Japan;

<sup>4</sup> Department of HIV Infection Medical Support Center of Hokkaido University Hospital, Hokkaido, Japan;

<sup>5</sup> Clinical Research Center, National Hospital Organization Nagoya Medical Center, Aichi, Japan;

<sup>6</sup> Department of HIV Infection Medical Support Center of National Hospital Organization Nagoya Medical Center, Aichi, Japan;

<sup>7</sup> Internal Medicine, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan;

<sup>8</sup> Department of HIV Infection Medical Support Center of National Hospital Organization Kyushu Medical Center, Fukuoka, Japan;

<sup>9</sup> Department of Hematology, Sendai Medical Center, National Hospital Organization, Miyagi, Japan;

<sup>10</sup> HIV/AIDS Comprehensive Medical Center of Sendai Medical Center, Miyagi, Japan.

**Abstract:** This study aimed to clarify the current status of motor function, activities of daily living (ADL), and instrumental ADL (IADL) in hemophilia patients with HIV infection due to treatment with non-heat-treated blood products as they now enter middle and old age. Participants were 70 such patients (mean age, 52.1 years), and their range of motion (ROM), muscle strength, extremity circumference, walking speed, ADL, and IADL were evaluated at checkups of motor function, ADL, and IADL that were held during patients' association meetings. Results showed that ROM was limited in all joints. Ankle dorsiflexion, hip abduction, and shoulder abduction were particularly restricted. Decreased muscle strength was most frequent in ankle plantarflexion, followed by hip extension. The proportion of patients with walking speed and grip strength below reference values increased with age. Walking speed was 73.9-110.9% of reference values. Factors affecting walking speed were knee flexion, ankle dorsiflexion, and hip extension muscle strength. Grip strength was 58.0-83.5% of reference values. Thigh girth most greatly differed between the patients and healthy individuals. Among the ADL items, "standing up from the floor" was reported as "difficult"/"cannot do" by 45.7% of the patients. The most common IADL problem was "putting away futons", which 17.2% responded was "difficult"/"cannot do". Parents were the most common helpers with household tasks (12.9%). "Decreased muscle strength/limited ROM" was the most frequently reported troublesome problem (35.7%). These results reveal the current status of motor function, ADL, and IADL limitations in hemophilia patients with HIV.

**Keywords:** hemophilia patients with HIV, aging, ADL, IADL, motor function, multicenter study

## Introduction

In Japan mostly between 1982 and 1985, about 2,000 hemophilia patients, or about 40% of these patients, were infected with human immunodeficiency virus (HIV) due to treatment with non-heat-treated blood products (1). Since the 1980s, advances in blood coagulation factor products and home self-injection therapy have dramatically improved the prognosis and quality of life (QOL) of hemophilia patients, and the average age of death has become almost the same as that of the general male population (2-4). With longer

life expectancy, hemophilia patients are now entering middle to old age for the first time. At the same time, advances in the treatment of HIV infection have dramatically improved its prognosis and life expectancy (5). On average, hemophilia patients with HIV infection caused by non-heat-treated blood coagulation factor products are entering their fifties (6).

Although some previous studies have investigated motor dysfunction and ADL in hemophilia patients entering middle and old age, there have been no multicenter studies. Moreover, no report has specifically focused on patients affected by adverse events due to

blood products. Therefore, for the first time in Japan, in this study we investigated the current status of motor function, activities of daily living (ADL), and instrumental ADL (IADL) in hemophilia patients with HIV infection due to contaminated blood products as they enter middle and old age, by performing checkups of motor function, ADL, and IADL during patients' association meetings that were held in Hokkaido, Sendai, Tokyo, Nagoya and Beppu between August and December 2019.

## Patients and Methods

Participants in this multicenter study were 70 hemophilia patients with HIV infection due to contaminated blood products who were members of a patients' association and who provided written informed consent.

### *Basic attributes*

Sex and age of the patients were examined.

### *Joint range of motion (ROM)*

Bilateral passive shoulder flexion/abduction, elbow flexion/extension, forearm pronation/supination, hip flexion/abduction/extension, knee flexion/extension, and ankle dorsiflexion/plantarflexion were evaluated.

### *Muscle strength*

The manual muscle test (MMT) was evaluated for bilateral passive shoulder flexion/abduction, elbow flexion/extension, forearm pronation/supination, hip flexion/abduction/extension, knee flexion/extension, and ankle dorsiflexion/plantarflexion, while considering the burden on the joints.

### *Grip strength*

Grip strength was measured twice on each side while the patient was seated with the elbow extended, with an approximately 30-s rest between measurements.

### *Walking*

Patients were instructed to walk quickly for 10 m, which was timed and analyzed.

### *Girth measurements*

The girth of the bilateral upper and lower extremities was measured using a tape measure in a sitting position at the end of an examination table and in the supine position. The maximum girth of the upper arm and forearm in elbow extension and the maximum girth of

the lower leg and the thigh at 10 cm proximal from the upper edge of the patella were measured.

### *ADL*

ADL was evaluated in a one-on-one semi-structured interview using questions from an interview guide with the scale developed by Goto *et al.* (7).

### *IADL*

IADL was evaluated in a one-on-one interview. Patients were asked about self-injection therapy for hemophilia, in addition to putting away futons, laundry, cooking, moving furniture, cleaning, shopping, and using a phone, with reference to the Frenchay Activities Index developed by Holbrook *et al.* (8). The response options for each question were "can do without problems", "difficult", and "cannot do".

### *Interview survey on the person who mainly performs household tasks*

We asked who mainly performs household tasks.

### *Interview survey on things that are troublesome*

Patients were asked to list up to three things that they currently find troublesome.

### *Analysis*

The mean and standard deviation were calculated for joint range of motion. Muscle strength was measured using the MMT, and the proportions of the patients with each score from 1 to 5 were obtained. The individual means of the right and left grip strengths were calculated and the proportion of patients with grip strength below age-group reference values (9) was determined. The proportion of patients with walking speed below age-group reference values (10) was also determined. To investigate the factors affecting walking speed, we performed multiple regression analysis with walking speed as the objective variable and joint ROM, muscle strength of the lower extremities, and grip strength as explanatory variables. Patients were divided into 10-year age groups, and the mean girth measurements were compared with those of healthy individuals. Ratios relative to standard values were determined for grip strength, walking speed, and girth measurements. The answers for the ADL and IADL items were divided into three groups according to response ("can do without problems", "difficult", and "cannot do") and the proportion of patients in each group was determined for each question. A simple tabulation was performed for the answers to "things that are troublesome" and "the person who mainly performs

household tasks". SPSS version 26 (IBM Corp., Armonk, NY) was used for analysis. The significance level was set at 5%.

*Ethical considerations*

This study was approved by central review at the Ethics Review Committee of the National Center for Global Health and Medicine (approval number, NCGM-G-003242-00), and appropriate ethics procedures were followed at each participating facility.

**Results and Discussion**

*Basic attributes*

Patients were all male, with a mean age of 52.1 (standard deviation, 9.08) years.

*Joint ROM*

Table 1 shows the results for joint ROM. Patients' mean

ROM values were below the reference values for all joints evaluated. Ankle dorsiflexion, hip abduction, and shoulder abduction showed especially restricted ROM.

*Muscle strength*

Table 2 shows the muscle strength results. Muscle strength was most frequently decreased in ankle plantarflexion, with MMT scores of 3 and 2 in 8.5% and 27.1% of the patients, respectively. Hip extension was the second most frequently decreased, with MMT scores of 3 and 2 each in 5.3% of the patients, followed by hip abduction, with MMT scores of 3 and 2 in 3.0% and 3.7% of the patients, respectively.

*Grip strength*

Table 3 shows the results for grip strength. Compared with healthy individuals by age group, the proportions of patients with grip strength below the reference values were 75.0% for patients in their 30s and 96.4% for those in their 40s. All patients in their 50s and 60s

**Table 1. Range of motion in the study population of 70 hemophilia patients with HIV infection from contaminated blood products**

Motion	n	Mean (deg)	SD (deg)	Ratio relative to the reference value (%)
Shoulder flexion	138	147.2	20.6	81.8
Shoulder abduction	138	143.3	30.5	79.6
Elbow flexion	138	125.6	19.6	86.6
Elbow extension	138	-22.4	22.3	87.2
Elbow pronation	138	73.2	18.2	81.3
Elbow supination	138	79.4	24.9	88.2
Hip flexion	138	105.8	18.2	84.6
Hip extension	138	14.4	13.5	96.0
Hip abduction	138	32.6	13.4	72.5
Knee flexion	138	116.1	31.5	89.3
Knee extension	138	-8.5	13.3	95.3
Ankle dorsiflexion	138	2.1	11.0	10.4
Ankle plantarflexion	138	35.1	11.6	78.0

Values are the percentage of the target joints. Ratio relative to the reference value (%) = [(mean measurement value of the target joint)/(reference ROM of the target joint)] × 100. SD, standard deviation.

**Table 2. Muscle strength measurements**

Muscle strength (MMT)	n	5	4	3	2	1
Motion						
Shoulder flexion	140	90.7%	7.9%	1.4%	0.0%	0.0%
Shoulder abduction	138	88.4%	9.4%	2.2%	0.0%	0.0%
Elbow flexion	138	91.3%	8.0%	0.7%	0.0%	0.0%
Elbow extension	126	85.7%	13.5%	0.8%	0.0%	0.0%
Forearm pronation	138	84.1%	15.9%	0.0%	0.0%	0.0%
Forearm supination	140	82.9%	16.4%	0.7%	0.0%	0.0%
Hip flexion	137	76.6%	21.2%	2.2%	0.0%	0.0%
Hip abduction	134	73.9%	19.4%	3.0%	3.7%	0.0%
Hip extension	133	66.2%	23.3%	5.3%	5.3%	0.0%
Knee extension	133	85.0%	12.8%	2.3%	0.0%	0.0%
Ankle dorsiflexion	135	85.9%	11.9%	2.2%	0.0%	0.0%
Ankle plantarflexion	118	44.1%	20.3%	8.5%	27.1%	0.0%

Values are the percentage of target joints. MMT, manual muscle test.

**Table 3. Grip strength and walking speed**

Age	Grip strength				Fast walking speed			
	n	Mean (kg)	Ratio relative to the reference value (%)	Patients below the reference value (%)	n	Mean (m/min)	Ratio relative to the reference value (%)	Patients below the reference value (%)
30s	4	39.6	83.5	75.0	4	133.1	110.9	25.0
40s	28	30.7	65.6	96.4	27	102.6	85.5	77.8
50s	23	28.3	62.3	100.0	21	89.9	78.2	90.5
60s	14	24.2	58.0	100.0	13	85	73.9	100.0

Grip strength ratio relative to the reference value (%) = [(mean grip strength of all patients)/(reference value)] × 100. Fast walking speed ratio relative to the reference value (%) = [(mean fast walking speed of all patients)/(reference value)] × 100.

**Table 4. Girth measurements**

Age	Upper arm		Forearm		Thigh		Lower leg								
	Right (cm)	Left (cm)	Ratio relative to the reference value	Upper arm reference value (cm)	Right (cm)	Left (cm)	Ratio relative to the reference value	Thigh reference value (cm)	Right (cm)	Left (cm)	Ratio relative to the reference value	Lower leg reference value (cm)			
30s	Mean	29.5	28.8	—	—	27.0	25.8	47.8	47.3	—	—	36.5	37.3	—	—
n = 2	SD	0.50	0.25	—	—	0.50	0.75	2.25	0.25	—	—	1.50	0.75	—	—
40s	Mean	25.9	26.5	90.3%	29.0	25.1	24.7	42.4	41.3	84.5%	49.6	33.5	32.8	89.7%	36.9
n = 13	SD	3.59	4.19	—	2.6	2.10	2.16	8.46	7.25	—	3.80	4.81	4.75	—	2.70
50s	Mean	25.8	26.7	90.8%	28.9	23.9	24.4	38.0	39.0	78.7%	48.9	30.8	32.0	84.8%	37.0
n = 9	SD	3.82	4.19	—	2.4	2.96	2.26	5.27	4.52	—	3.80	2.69	3.54	—	2.70
60s	Mean	24.8	24.8	79.4%	28.1	23.6	23.5	38.2	36.3	88.3%	46.9	31.2	30.4	86.6%	35.6
n = 5	SD	4.32	5.27	—	2.2	1.98	1.84	3.23	4.46	—	3.50	3.80	4.17	—	2.60

Upper arm girth was measured in elbow extension. We were unable to obtain a reference value for patients in their 30s. Reference values for patients in their 40s, 50s, and 60s were taken from reference 11. Ratio relative to the reference value (%) = [(mean value of the target site of all patients)/(reference value of the target site)] × 100. Ratios relative to the reference values (%) were obtained for the mean of the left and right sides. SD, standard deviation.

had grip strength below the reference values. Muscle strength relative to the reference values was 83.5%, 65.6%, 62.3%, and 58.0% for patients in their 30s, 40s, 50s, and 60s, respectively.

*Walking speed*

Table 3 shows the results for walking speed. Walking speeds by age group were below reference values of healthy individuals for 25% of patients in their 30s, 77.8% of those in their 40s, 90.5% of those in their 50s, and all patients in their 60s. Measured values of the patients in their 30s were above the reference value with a ratio relative to the reference value of 110.9%, while the ratios were 85.5%, 78.2%, and 73.9% for patients in their 40s, 50s, and 60s, respectively.

Factors contributing to walking speed were knee flexion ROM (standardized coefficient, 0.446), hip extension ROM (0.418), and ankle dorsiflexion ROM (0.216).

*Girth measurements*

Table 4 shows the results for the four girth

measurements taken. Mean values were highest for patients in their 30s at all measurement sites and tended to decline with age. Compared with reference values of healthy individuals in their 40s and 60s (11), the measured values were below the reference values at all sites in all age groups. In particular, the difference was the largest for thigh girth, at 84.5% of the reference value for patients in their 40s, 78.7% in their 50s, and 77.4% in their 60s.

*ADL*

Table 5 shows the ADL results. The most frequent difficulty in ADL was "standing up from the floor", which 64.3% of the patients reported as "difficult" or "cannot do". The second most common difficulty in ADL was "squatting", which 62.9% reported was "difficult" or "cannot do". This was followed by "climbing up and down stairs", which was either "difficult" or "cannot do" for 54.3% of the patients.

*IADL*

Table 5 shows the results for IADL. In terms of

**Table 5. ADL and IADL**

	<i>n</i>	Can do without problem	Difficult	Cannot do	Difficult/cannot do
<b>ADL</b>					
Standing up from the floor	70	35.7%	45.7%	18.6%	64.3%
Squatting	70	28.6%	22.9%	40.0%	62.9%
Climbing up and down stairs	70	41.4%	51.4%	2.9%	54.3%
Sitting on the floor	70	38.6%	24.3%	21.4%	45.7%
Walking on a slope	70	47.1%	40.0%	2.9%	42.9%
Clipping toenails	70	64.3%	28.6%	5.7%	34.3%
Washing face with both hands	70	72.9%	12.9%	12.9%	25.7%
Buttoning and unbuttoning top button	70	74.3%	22.9%	2.9%	25.7%
Washing body	70	74.3%	24.3%	2.9%	25.7%
Putting on and taking off socks	70	74.3%	18.6%	1.4%	25.7%
Walking without a cane	70	75.7%	10.0%	2.9%	21.4%
Sitting on a chair	70	88.6%	10.0%	0.0%	10.0%
<b>IADL</b>					
Putting away futons	70	55.7%	5.7%	22.9%	28.6%
Laundry	70	74.3%	12.9%	8.6%	21.4%
Cooking	70	74.3%	10.0%	11.4%	21.4%
Moving furniture	70	78.6%	5.7%	8.6%	14.3%
Self-injection	70	82.9%	2.9%	11.4%	14.3%
Cleaning	70	88.6%	5.7%	4.3%	10.0%
Shopping	70	90.0%	4.3%	5.7%	10.0%
Using a phone	70	97.1%	1.4%	0.0%	1.4%

Values are the percentage of patients. ADL, activities of daily living; IADL, instrumental activities of daily living.

difficulties in IADL, 5.7% of the patients responded that "putting away futons" was either "difficult" or "cannot do". Next was "laundry", with 12.9% and 8.6% responding "difficult" or "cannot do", and then "cooking" at 10% and 11.4%, respectively.

#### *Persons who mainly perform household tasks*

The persons who mainly performed household tasks were the patients themselves (38.6%), followed by their spouses (25.7%), parents (12.9%), both patients and spouse (8.6%), both patients and parents (4.3%), siblings (2.9%), and parents- or siblings-in-law (1.4%).

#### *Things that are troublesome*

The most frequent responses for things that are troublesome were "physical changes (decline in muscle strength and limited joint ROM)" (35.7%), followed by "pain" (31.4%), "parents" (20%), and then "limitations of ADL/IADL" and "difficulty moving" (both 18.6%). Only 1 patient listed bleeding.

#### *Discussion*

Hemophilia patients in middle and old age, who have experienced the time when there was no regular replacement therapy to suppress bleeding as can be done with current therapy, often have limited ROM, joint instability, joint contracture, muscle atrophy, and synovitis (3). This is the first multicenter study to investigate motor function and ADL in hemophilia patients with HIV infection. As of May 31, 2019,

there are 6,596 hemophilia patients in Japan, 706 of whom are living with HIV infection due to receiving contaminated blood products (6). This study involved 70 patients, representing 10% of this population.

In a multicenter study, Siboni *et al.* investigated the elbow, knee, and ankle joint function of 39 middle aged and older hemophilia patients (mean age, 68 years; range, 65-78 years) (12) and found hemophilic arthropathy in 37 of the patients. Goto *et al.* also investigated joint function in 31 hemophilia patients (mean age, 38.3 years; range, 16-61 years) targeting the elbow, knee, and ankle joints and found end-stage arthropathy in 60.2% (13). Our study, which also included the shoulder and hip joints, showed that these joints and the elbow, knee, and ankle joints all had limited ROM. In particular, ankle dorsiflexion showed severely limited ROM at 10.4% of the reference value. The next most severely affected joint motions were hip abduction at 72.5% of the reference value and then shoulder abduction at 79.6%. Our study is the first to reveal limited ROM in the hip and shoulder joints.

Some previous studies have investigated muscle strength in patients with hemophilia (13-15) but were limited to the knee joint. The present study investigated muscle strength around the shoulder, elbow, hip, knee, and ankle joints, finding that decreased muscle strength was most frequently seen in ankle plantarflexion, followed by hip extension and hip abduction. The decline in muscle strength around the ankle joints was attributed to immobility of the joints caused by intra-articular bleeding (pain and swelling), given the severely limited ROM relative to the reference values of ankle dorsiflexion (10.4%) and plantarflexion (78.0%).

The decrease in hip joint ROM was attributed to pain and immobility caused by arthropathy, given that the flexion and extension ROM were 84.6% and 96.0% of the reference values, respectively.

Because bleeding is less common in the wrist joint compared with other joints in hemophilia (16), we did not include it in the evaluation of ROM or muscle strength in this study. However, grip strength is an index of muscle strength and is also correlated with cardiopulmonary function (17); thus, we evaluated grip strength as an index of general physical function in this study. The result showed that grip strength of the patients in their 30s was 83.5% of the reference value, which decreased with age. The grip strength of those in their 60s was 58.0% of the reference value, indicating deterioration of physical function with age. In a study by Goto *et al.* measuring grip strength, the mean value was 31.9 kg in patients with mean age of 38.3 years (15), which is lower than the mean grip strength of our patients in their 30s of 39.6 kg. The reason for the higher value of grip strength in our study is thought to be selection bias. The patients in the study by Goto *et al.* were outpatients, whereas our patients participated in the motor function, ADL, and IADL checkups that were held at patients' association meetings and thus could be presumed to have better motor function and to more actively exercise.

No conventional cross-sectional study of hemophilia patients has examined walking speed. Given that studies of healthy individuals and stroke patients have demonstrated the importance of being able to walk quickly to being able to walk practically (18,19), we evaluated fast walking. We found the proportions of patients in their 40s, 50, and 60s who could walk quickly were 85.5%, 78.2%, and 73.9% of the reference values, respectively. These data indicate practical walking ability may decrease with age in these patients. Knee flexion ROM, ankle dorsiflexion ROM, and hip extension muscle strength were identified as factors affecting walking speed. The hip extensor muscles play a role in supporting body weight from initial ground contact to mid-stance (20). Hip extensor muscle weakness was frequently seen in the patients in this study, suggesting that it may have also affected the walking speed.

Siboni *et al.* (13) and Stephensen *et al.* (21) have reported that muscular atrophy is present in hemophilia patients. However, no study has reported the four girth measurements that we examined in these patients, and both Canaro *et al.* (2) and Stephensen *et al.* (22) have pointed out that there has been no quantitative study of muscle atrophy. Here, we measured the girth of the upper arm, forearm, and lower leg and thigh, and compared the values with those of healthy individuals in 10-year age groups (11). The values were smaller in our patients than in healthy individuals at all measurement sites, and the difference was largest in the

thigh. In addition, a notable finding was that the mean girth of the thigh in patients in their 50s and 60s was 38.5 cm and 37.2 cm, respectively, which was about the same as the standard values of healthy individuals.

Siboni *et al.* also evaluated ADL in a multicenter study (13) but did not evaluate items related to Japanese lifestyle. Therefore, we used a scale developed by Goto *et al.* (7). Many patients responded that movements requiring deep flexion or heavy loading of the lower limbs, such as "standing up from the floor", "squatting", "climbing up and down stairs", "sitting on the floor", and "walking on a slope" were either "difficult" or "cannot do", consistent with the results of Goto *et al.* (14) and Iwata *et al.* (22). More than 60% of the patients in the present study responded that the movements of "standing up from the floor" and "squatting" were "difficult" or "cannot do". The mean age of patients of this study was 52 years, which means that aspects of the Japanese lifestyle are difficult for these patients although they are only in their 50s.

Siboni *et al.* (12) examined IADL in patients with hemophilia, but their study was conducted outside Japan. In the present study, "putting away futons" was found to be the most difficult activity, revealing difficulty in Japanese lifestyle, as with ADL. Moreover, "laundry" and "cooking" were listed as difficult activities, showing that patients have difficulties in activities related to food, clothing, and housing, which are necessities of life.

In this study, we also included "self-injection", which is necessary for treatment, as an IADL item. The result showed that 14.3% of the patients answered that "self-injection" was "difficult" or "cannot do". As this patient population ages, it can be expected that ROM will worsen and presbyopia will develop, so the number of patients who have difficulties in "self-injection" may increase further in the future.

The results revealed that a "decrease in muscle strength and limitation of ROM" was the most frequent response, at 35.7%, for the most troublesome problem, followed by "pain" (31.4%). On the other hand, only 1 patient listed "bleeding". These results reflect that the problem of bleeding itself is being solved with advances in treatment methods, but that joint dysfunction and pain are issues that remain to be addressed.

The study showed that the person who mainly performs household tasks is someone other than the patient in more than half of the cases. Notably, for 12.9% of these patients, the primary helper was their parents. Given that "pain", "parents", and "limitation in ADL/IADL" were some of the most common problems, we can surmise that many patients have pain and rely on their parents for ADL/IADL.

#### Limitations

Some limitations of this study include that we are

unable to determine whether the decline in motor function revealed in this study was due to hemophilia or HIV infection. The reason for this is that the previous studies referred to in this report also included some hemophilia patients with HIV infection, ranging from 3.0% (13) to 38.7% (14), and it is not possible to compare our results with those of the previous studies with respect to the presence or absence of HIV infection. In addition, because the patients in this study voluntarily participated in patients' meetings where motor function, ADL, and IADL checkups were offered, our study population may have been biased toward patients with relatively good motor function and those who are proactive in maintaining or improving motor function. The patients in this study accounted for about 10% of hemophilia patients with HIV infection due to contaminated blood products in Japan. A study including all of these patients might show even greater impairment of motor function and ADL. Based on the above, it is necessary in the future to survey more patients with hemophilia and compare those with and those without HIV infection to accurately understand the condition of motor function and ADL/IADL in these patients.

## Conclusion

Evaluation of hemophilia patients with HIV infection due to contaminated blood products who participated in checkups of motor function, ADL, and IADL that were held during patients' association meetings revealed that they had locomotor disorders, impairment in functions required for ADL, and pain even though they were fairly young, at a mean age of 52 years, and that they were in the worrying situation that maintenance of daily life may become difficult in the future depending on their parents' condition.

## Acknowledgements

We thank all the staff members who participated and contributed to the patients' meetings.

**Funding:** This study was supported by a Ministry of Health, Labour and Welfare Policy Research Grant and the AIDS Policy Research Project (H30-AIDS-Designated-002).

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

## References

- Kimura S. Analyses and resolution of challenges to which HIV-infected hemophiliacs are facing, by a group study with participaton of patients. *Antibiot Chemother.* 2014; 30:130-138. (in Japanese)
- Canaro M, Goranova-Marinova V, Berntorp E. The ageing patient with haemophilia. *Eur J Haematol.* 2015; 94 Suppl 77:17-22.
- Angelini D, Sood SL. Managing older patients with hemophilia. *Hematology Am Soc Hematol Educ Program.* 2015; 2015:41-47.
- Shapiro S, Makris M. Haemophilia and ageing. *Br J Haematol.* 2019; 184:712-720.
- Nasi M, De Biasi S, Gibellini L, Bianchini E, Pecorini S, Bacca V, Guaraldi G, Mussini C, Pinti M, Cossarizza A. Ageing and inflammation in patients with HIV infection. *Clin Exp Immunol.* 2017; 187:44-52.
- Ministry of Health, Labour and Welfare. Nationwide Survey on Coagulation Disorders 2019. Japan Foundation for AIDS Prevention, Tokyo, Japan, 2020; pp 3-4. (in Japanese)
- Goto M, Takedani H, Kawama K, Nitta O. Development of an activity scale for patients with hemophilia. *J Jpn Academ Health Sci.* 2014; 16:184-189. (in Japanese)
- Holbrook M, Skilbeck CE. An activities index for use with stroke patients. *Age Ageing.* 1983; 12:166-170.
- e-Stat. Physical fitness and athletic ability survey FY 2017. <https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00402102&tstat=000001088875&cycle=0&tclass1=000001119456> (accessed October 27, 2020). (in Japanese)
- Ministry of Health, Labour and Welfare. Exercise guidelines for health promotion 2006. ~To prevent lifestyle-related disease~ Exercise guide 2006 (Draft). <https://www.mhlw.go.jp/shingi/2006/07/dl/s0719-3c.pdf> (accessed October 27, 2020). (in Japanese)
- National Institute for Longevity Sciences. Longitudinal study of aging. <https://www.ncgg.go.jp/cgss/department/ep/monograph7thj/index.html> (accessed October 27, 2020). (in Japanese)
- Siboni SM, Mannucci PM, Gringeri A, Franchini M, Tagliaferri A, Ferretti M, Tradati FC, Santagostino E, von Mackensen S; Italian Association of Haemophilia Centres (AICE). Health status and quality of life of elderly persons with severe hemophilia born before the advent of modern replacement therapy. *J Thromb Haemost.* 2009; 7:780-786.
- Goto M, Takedani H, Nitta O, Kawama K. Associations between joint function, activities of daily living, and health-related quality of life in patients with hemophilia. *Rigakuryoho Kagaku Sci.* 2015; 30:413-419. (in Japanese)
- Fearn M, Hill K, Williams S, Mudge L, Walsh C, McCarthy P, Walsh M, Street A. Balance dysfunction in adults with haemophilia. *Haemophilia.* 2010; 16:606-614.
- Goto M, Takedani H, Nitta O, Kawama K. Joint function and arthropathy severity in patients with hemophilia. *J Jpn Physic Ther Assoc.* 2015; 18:15-22.
- Srivastava A, Brewer AK, Mauser-Bunschoten EP, Key NS, Kitchen S, Llinas A, Ludlam CA, Mahlangu JN, Mulder K, Poon MC, Street A; Treatment Guidelines Working Group on Behalf of The World Federation of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia.* 2013; 19:e1-e47.
- Wu ZY, Han YX, Niu ME, Chen Y, Zhang XQ, Qian HY. Handgrip strength is associated with dyspnoea and functional exercise capacity in male patients with stable COPD. *Int J Tuberc Lung Dis.* 2019; 23:428-432.
- Schmid A, Duncan PW, Studenski S, Lai SM, Richards L, Perera S, Wu SS. Improvements in speed-based gait classifications are meaningful. *Stroke.* 2007; 38:2096-



- 2100.
19. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: Reference values and determinants. *Age Ageing*. 1997; 26:15-19.
  20. Sano K, Iida T, Ebisu S, Takahashi Y, Ito M, Kado N. Physical therapy using a weight-transfer exercise for a patient with femoral neck fracture: A case report. *J Kansai Phys Ther*. 2017; 17:127-131. (in Japanese)
  21. Stephensen D, Rodriguez-Merchan EC. Orthopaedic comorbidities in the elderly haemophilia population: A review. *Haemophilia*. 2013; 19:166-173.
  22. Iwata N, Hachisuka K, Tanaka S, Naka Y, Ogata H.

Measuring activities of daily living among haemophiliacs. *Disabil Rehabil*. 1996; 18:217-223.

----

Received April 28, 2021; Revised June 4, 2021; Accepted June 14, 2021.

*\*Address correspondence to:*

Junko Fujitani, Department of Rehabilitation Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.  
E-mail: jufujita@hosp.ncgm.go.jp

# Trends in prostate cancer diagnosis during the COVID-19 crisis: A report from one high-volume Japanese center

Daisuke Yamada<sup>1,\*</sup>, Taketo Kawai<sup>1</sup>, Yusuke Sato<sup>1</sup>, Yuta Yamada<sup>1</sup>, Yoshiyuki Akiyama<sup>1</sup>, Jimpei Miyakawa<sup>1</sup>, Sayuri Takahashi<sup>2</sup>, Haruki Kume<sup>1</sup>

<sup>1</sup> Department of Urology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan;

<sup>2</sup> Department of Urology, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan.

**Abstract:** Self-isolation to prevent the spread of the novel coronavirus SARS-CoV-2 began in April 2020. As a result, the number of prostate needle biopsies taken at our hospital for suspicion of prostate cancer decreased by 30.5%, from 403 in 2019 to 280 in 2020. The number of diagnoses of prostate cancer decreased by 35.4% from 189 to 122. High-risk and intermediate-risk prostate cancers were 36.5% and 49.7%, respectively, in 2019. Assuming that this situation in our hospital reflects events nationwide, approximately 32,575 (high-risk; 11,890, intermediate risk; 16,189) patients annually would be suffering delays in diagnosis. Furthermore, > 90% of the decrease are curable cases in their 60s and 70s, with prostate specific antigen levels of 30 ng/mL or less, with stage T2, and N0M0. Widely aware that more than 30,000 prostate cancers might be overlooked nationwide in 2020, we recommend establishing a health checkup system with infection control and undergoing early testing.

**Keywords:** coronavirus, biopsy, SARS-CoV-2, stage, prostate-specific antigen (PSA), age

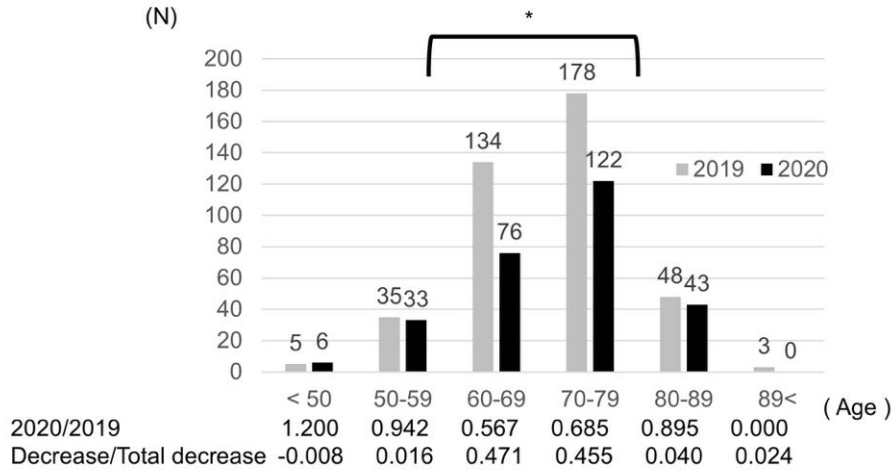
A state of emergency was declared in Japan on April 7, 2020, due to the rapid nationwide spread of the novel coronavirus SARS-CoV-2. Leaving home for unnecessary or non-urgent purposes was restricted. Employees teleworked from home, and schools adopted online lessons. Accordingly, the number of outpatients at our hospital decreased by 14.4%, from 683,275 in 2019 to 585,187 in 2020; the number of outpatients in our Department also decreased by 13.4%, from 24,896 to 21,567. Except for symptomatic cases, those with extremely high prostate-specific antigen (PSA), and those with multiple metastases, patients solely with high PSA tended to avoid medical consultation due to the stay-at-home rules. Furthermore, non-urgent prostate biopsy was not prioritized, because of the restriction of hospital medical service capacity under pandemic conditions. Here, we analyze the number and breakdown of prostate needle biopsy cases in 2019 and 2020, in order to provide an estimate of the indirect influence of the novel coronavirus SARS-CoV-2 crisis nationwide on the clinical management of prostate cancer.

Patients who underwent prostate needle biopsy between January 1, 2019, and December 31, 2020 were reviewed. Biopsies for known prostate cancer cases (*i.e.*, protocol biopsy on active surveillance) were excluded from this analysis. Written informed consent was obtained for the use of patients' medical information (Ethics Committee, Faculty of Medicine, University of

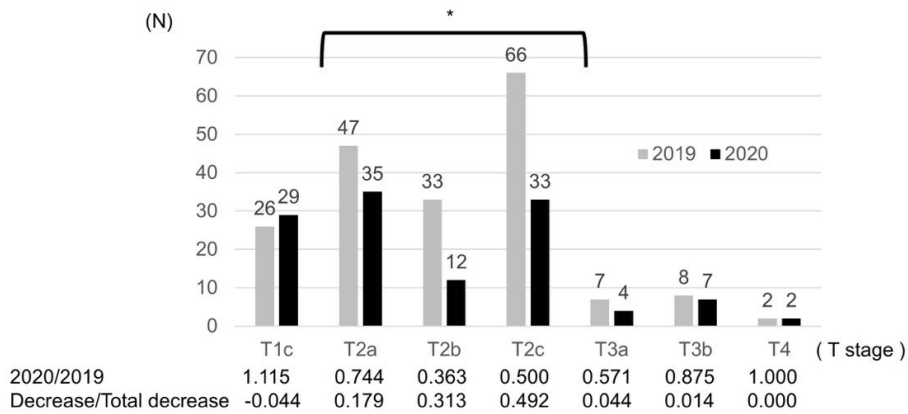
Tokyo; #3124). The pre-biopsy PSA value was set as the highest value within the six months prior to biopsy. T staging was performed based on magnetic resonance imaging, digital examination, and needle prostate biopsy results according to the Union for International Cancer Control TNM classification of malignant tumors 8th edition (1). Computed tomography and bone scintigraphy were used for detecting regional lymph node metastasis and distant metastasis. Statistical analysis was performed using JMP pro ver.15.2.1, and Fisher's exact test was used for stratified analysis.

We identified a total of 683 prostate needle biopsies taken on suspicion of prostate cancer, 403 cases in 2019 and 280 cases in 2020, representing a decrease of 123 cases (30.5%). The number of patients in their 60s and 70s decreased by 36.5%, from 312 cases to 198 cases, accounting for 92.6% of the total decrease and significantly less in 2020 compared to 2019 ( $p = 0.0296$ , Figure 1). The median (interquartile range) pre-biopsy PSA level (ng/mL) increased from 6.9 (5.1-11.1) in 2019 to 7.1 (5.3-11.1) in 2020. The number of cases with a pre-biopsy PSA level (ng/mL) of 30.0 or less decreased by 31.7% from 384 to 262, accounting for 99.1% of the total decrease (Figure S1, <https://www.ghmopen.com/site/supplementaldata.html?ID=24>). In contrast the number of cases with PSA higher than 30.0 ng/mL was similar, 19 in 2019 and 18 in 2020 (not significant,  $p = 0.210$ ).

The number of diagnoses of prostate cancer



**Figure 1. Numbers of prostate needle biopsies by age.** The number of patients in their 60's and 70's decreased by 58 and 56, accounting for 92.6% of the total decrease. \*Significantly less in 2020 compared to 2019 ( $p = 0.0296$ ).



**Figure 2. Numbers of prostate cancer diagnoses by T stage.** Cases at T2a, T2b, and T2c decreased by 12, 21, and 33 cases, accounting for 98.5% of the total decrease. \*Significantly less in 2020 compared to 2019 ( $p = 0.0172$ ).

decreased by 35.4% from 189 to 122. Cases at T2 stage decreased by 45.2%, from 146 to 80, whereas T3 and T4 cases slightly decreased from 17 to 13 (Figure 2). The total number of patients at T2 stage decreased by 66, accounting for 98.5% of the total decrease and significantly less in 2020 than 2019 ( $p = 0.0172$ ). Finally, the number of patients with N0 and M0 disease decreased by 36.9% from 175 to 111, accounting for 95.5% of the total decrease, but this was not significant ( $p = 0.379$ , Figure S2, <https://www.ghmopen.com/site/supplementaldata.html?ID=24>).

In 2020, the number of biopsies taken decreased by 30.5% compared to 2019, with > 90% of the decrease accounted for by patients in their 60's and 70's and with pre-biopsy PSA levels of 30 ng/mL or less. The number of prostate cancer diagnoses decreased by 35.4%, more than 90% of which were T2 and N0M0. In contrast, there were few changes in advanced cases including those with PSA over 30 ng/mL, with stages T3 or more, or with

nodal and/or distant metastasis. These cases might be symptomatic, or might have had to have a biopsy, even during the coronavirus crisis. In our Department, the number of all outpatients in their 60's and 70's decreased by 13.0%, similar to the decrease of 13.4% across all ages, while the number of patients at this age undergoing prostate needle biopsy decreased greatly.

One Italian study on colorectal cancer screening reported that the number of tests during lockdown due to the pandemic was reduced by a quarter, but the probability of finding cancer increased from 1% to 8% (2). In that study, many of the cases examined during lockdown were high-risk, including those with subjective symptoms such as bloody stools and those with a family history. In contrast, the cancer detection rate in our report was similar before and after lockdown at 46.8% in 2019 and 43.5% in 2020. This might result from the lower accuracy of prostate biopsy compared with colonoscopy.

According to the National Cancer Center Institute

in Japan, the annual number of cases of prostate cancer is 92,021 in 2018 (3). Prostate cancer diagnoses at our hospital decreased by 35.4% from 2019 to 2020. Assuming that this rate is the same across the nation, the number of patients with a delayed diagnosis of prostate cancer will reach 32,575. The number of high-risk (Gleason Score 8 and above) and intermediate-risk cases (Gleason Score 7) was 69 (36.5%) and 94 (49.7%), respectively, of prostate cancer diagnoses at our hospital in 2019. Assuming that this rate is the same across the nation, 11,890 are likely to be in the high-risk group and 16,189 in the intermediate-risk group. Several studies have reported that the time patients can wait for treatment of prostate cancer should be 2.5-6 months in the high-risk group and 9-24 months in the intermediate-risk group (4-11).

Delays in diagnosis occurred worldwide. De Vincentiis *et al.* (12) reported that prostate cancer and bladder cancer diagnoses fell in 2020 by 75% and 66%, respectively, compared with the average number recorded in 2018 and 2019. There is also a concern that cases of more advanced prostate cancer will increase because health examinations and medical institutional consultations were postponed due to the coronavirus crisis.

One limitation of this research is that it is not necessarily applicable to Japan as a whole, and the world in general, because it involved only a single facility, a small number of cases, and was a retrospective study. No prospective study reports have been found on treatment delays, and bias is unavoidable.

In conclusion, the number of prostate diagnoses in 2020 was 35.4% lower than in 2019. More than 90% of the decrease was accounted for by patients in their 60's and 70's that would have been curable, with PSA of 30 or less, and at stage T2, N0M0. There is a concern that because of delayed diagnosis the relative proportion of more advanced prostate cancer cases will increase and some of them will no longer be curable. Widely aware that more than 30,000 prostate cancers might be overlooked nationwide in 2020, we recommend establishing a health checkup system with infection control and undergoing early testing.

*Funding:* None.

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

## References

- Gospodarowicz MK, Mason M. Prostate cancer: Urological Tumors. In: UICC TNM classification of malignant tumours. Eighth ed (Brierley JD, Gospodarowicz MK, Wittekind C, eds.). Wiley-Blackwell; Hoboken, NJ, USA, 2017; pp. 187-190.
- D'Ovidio V, Lucidi C, Bruno G, Lisi D, Miglioresi L,

- Bazuro ME. Impact of COVID-19 pandemic on colorectal cancer screening program. *Clin Colorectal Cancer*. 2021; 20:e5-e11.
- Cancer Information Service, National Cancer Center, Japan (National Cancer Registry, Ministry of Health, Labour and Welfare). Cancer Statistics. [https://ganjoho.jp/reg\\_stat/statistics/data/dl/index.html](https://ganjoho.jp/reg_stat/statistics/data/dl/index.html) (accessed July 15, 2021). (in Japanese)
- Abern MR, Aronson WJ, Terris MK, Kane CJ, Presti JC Jr, Amling CL, Freedland SJ. Delayed radical prostatectomy for intermediate-risk prostate cancer is associated with biochemical recurrence: possible implications for active surveillance from the SEARCH database. *Prostate*. 2013; 73:409-417.
- Khan MA, Mangold LA, Epstein JI, Boitnott JK, Walsh PC, Partin AW. Impact of surgical delay on long-term cancer control for clinically localized prostate cancer. *J Urol*. 2004; 172:1835-1839.
- Nam RK, Jewett MA, Krahn MD, Robinette MA, Tsihlias J, Toi A, Ho M, Evans A, Sweet J, Trachtenberg J. Delay in surgical therapy for clinically localized prostate cancer and biochemical recurrence after radical prostatectomy. *Can J Urol*. 2003; 10:1891-1898.
- Nguyen PL, Whittington R, Koo S, Schultz D, Cote KB, Loffredo M, McMahon E, Renshaw AA, Tomaszewski JE, D'Amico AV. The impact of a delay in initiating radiation therapy on prostate-specific antigen outcome for patients with clinically localized prostate carcinoma. *Cancer*. 2005; 103:2053-2059.
- O'Brien D, Loeb S, Carvalhal GF, McGuire BB, Kan D, Hofer MD, Casey JT, Helfand BT, Catalona WJ. Delay of surgery in men with low risk prostate cancer. *J Urol*. 2011; 185:2143-2147.
- Loeb S, Folkvaljon Y, Robinson D, Makarov DV, Bratt O, Garmo H, Stattin P. Immediate versus delayed prostatectomy: Nationwide population-based study. *Scand J Urol*. 2016; 50:246-254.
- Westerman ME, Sharma V, Bailey GC, Boorjian SA, Frank I, Gettman MT, Thompson RH, Tollefson MK, Karnes RJ. Impact of time from biopsy to surgery on complications, functional and oncologic outcomes following radical prostatectomy. *Int Braz J Urol*. 2019; 45:468-477.
- Zanaty M, Alnazari M, Ajib K, Lawson K, Azizi M, Rajih E, Alenizi A, Hueber PA, Tolmier C, Meskawi M, Saad F, Pompe RS, Karakiewicz PI, El-Hakim A, Zorn KC. Does surgical delay for radical prostatectomy affect biochemical recurrence? A retrospective analysis from a Canadian cohort. *World J Urol*. 2018; 36:1-6.
- De Vincentiis L, Carr RA, Mariani MP, Ferrara G. Cancer diagnostic rates during the 2020 'lockdown', due to COVID-19 pandemic, compared with 2018-2019: an audit study from cellular pathology. *J Clin Pathol*. 2021; 74: 187-189.

Received June 25, 2021; Revised July 17, 2021; Accepted July 28, 2021.

*\*Address correspondence to:*

Daisuke Yamada, Department of Urology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.  
E-mail: dyamada-ky@umin.net

# Development of active learning materials and use of those materials to educate nursing students primarily in respiratory nursing and to train new nurses

Fumino Sugiyama<sup>1\*</sup>, Tomoko Inoue<sup>1</sup>, Kimikazu Kashiwagi<sup>1</sup>, Mitsumi Masuda<sup>2</sup>, Namiko Nagaoka<sup>1</sup>, Ayako Narita<sup>3</sup>

<sup>1</sup>National College of Nursing, Japan;

<sup>2</sup>Nagoya City University, Nagoya, Japan;

<sup>3</sup>National Cancer Center Hospital East, Tokyo, Japan.

**Abstract:** The current study examined the effectiveness of using e-learning to teach respiratory nursing to students and provide continuing education to new nurses. An e-learning system was developed for pre-learning activities in combination with simulations. Ten new nurses were interviewed about nursing practices to identify learning tasks that were appropriate for new nurses. Based on those interviews, the current authors developed teaching materials for the core program. The e-learning system used was a web-based platform that conforms to global standards (TAO, Infosign Inc., Tokyo). The e-learning system was tested with students in their third and fourth years of nursing school at two universities in January and February of 2017. A follow-up indicated that third- and fourth-year nursing students who participated in clinical learning found the e-learning system (which was developed based on the experiences of new nurses) useful.

**Keywords:** active learning, e-learning, new nurse, nursing student, respiratory nursing

Clinical learning is essential to reach a stage where knowledge gained in the classroom can be put into practice (1). However, the skills acquired during practical training depend on the condition of patients and the nursing students themselves. The skills required of a new nurse depend on the role of the facility where the nurse will be working (2). The role differentiation of medical facilities presumably contributes to a discrepancy between the skills acquired in nursing school and the practical skills required of new nurses.

E-learning and simulation-based learning have been used in place of clinical learning to educate nursing students (3,4). Members of the nursing profession require continuing education, and they must think independently. This type of human resource development necessitates a shift from traditional classroom-based knowledge transfer to active learning, in which students identify problems and find solutions independently (5-7).

Goal-based scenarios are an instructional design theory consisting of the following seven elements: mission, cover story, role, learning goals, scenario operations, feedback, and resources (8). Although pre-learning usually takes place in lectures, combining goal-based scenarios with e-learning should improve the understanding of learners. In addition, the effectiveness

of an e-learning course can be evaluated by surveying learners regarding their level of interest, the relevance of content, and their level of confidence and satisfaction after completing the course (9).

From this perspective, the current study developed an e-learning system for nursing students in order to establish the clinical competencies required of new nurses. This study focused on the continuity of education in respiratory nursing for nursing students as they became new nurses and it evaluated the effectiveness of that education.

This study was conducted in two stages: *i*) an assessment of learning needs and development of e-learning materials, and *ii*) an assessment of the e-learning system's effectiveness.

## First stage: Assessment of learning needs

### Subjects

Subjects were 10 new nurses who had worked in one of four wards: internal medicine, surgery, internal medicine and surgery combined, or intensive care. The nurses worked in three large general hospitals in metropolitan areas, each with more than 500 beds. A new nurse was defined as a nurse with less than one year of experience.

*Assessment*

Between October 2015 and February 2016, semi-structured interviews were conducted with the ten new nurses regarding their observations, judgments, performance, and difficulties they experienced due to differences between their nursing school training and actual practice.

*Development of the e-learning system*

Qualitative data were obtained from transcripts of the recorded interviews. The disease-related specializations of the new nurses and situations in which they had experienced difficulties were noted. The seven elements of the goal-based scenario were identified based on their correspondence to the qualitative data.

Based on these elements, an e-learning system was developed in which a nursing student would play the role of a nurse. The Question and Test Interoperability/Learning Tools Interoperability of TAO (Infosign Inc., Tokyo), a web-based testing system that complies with international standards, was used for this study.

*Ethical considerations*

This study was conducted in compliance with the ethical guidelines of the Japanese Ministry of Health, Labor, and Welfare for medical and health research involving human subjects. Approval was obtained from the Ethical Review Board of St. Luke's International

Hospital (15-042) before conducting interviews.

*Outcomes*

*Overview of nursing practice*

Nine of the 10 new nurses were women. Most of the patients under the care of the new nurses had lung cancer. The remaining patients had pneumonia or pneumothorax. The new nurses worked together with senior nurses who were in charge of educating them. The new nurses had difficulties with several of the tasks, e.g. collecting all of the necessary information at one time, sputum suction, supporting patients with dyspnea, and clinically assessing patient results. Although they used viscous fluids to practice sputum suction in school, they still had difficulty performing sputum suction with real patients, as they had to synchronize their actions with the patients' cough reflex. New nurses were unable to interact properly with patients exhibiting dyspnea due to distress in those emergency situations.

*Components of the e-learning system*

The e-learning system included two scenarios: *i*) ambulatory support for patients after surgery for lung cancer, and *ii*) support for patients with chronic obstructive pulmonary disease (COPD) and dyspnea. Each program consisted of three parts: collection of information, provision of care, and reporting (Table 1).

In the lung cancer scenario, the mission of the new nurse was to provide ambulatory support for a

**Table 1. Elements of the goal-based scenarios**

A case of a patient after right lower lobectomy for lung cancer	
Scenario context	
Learner's mission	The learner is to provide proper care and report to the lead nurse to help treat the patient.
Cover story	The cover story is that the learner observes the patient and then reports to the lead nurse. At the beginning, the learner observes and evaluates the patient and predicts possible changes in the patient's condition. Then, the learner provides necessary care. Finally, the learner reports on the patient's condition and care to the lead nurse.
Learner's role	After receiving detailed information on the patient's surgery, the learner (A) observes and evaluates the patient, (B) provides care and evaluates the patient's condition, and (C) reports the care provided and the patient's condition to the lead nurse.
Learning goals	(1) Procedural knowledge Using what the learner has observed, judged, performed, and evaluated as information, the learner will be able to develop the skills to prepare a report that will facilitate the patient's treatment. (2) Declarative knowledge Based on a case of lung cancer, the learner will be able to understand postoperative complications and impacts of invasive surgery on the patient's body and learn how to manage drains. Based on a case of COPD, the learner will be able to understand hypoxemia and hypercapnia and learn how to assist the patient in performing pursed-lip breathing.
Scenario operations	To promote nursing practice, questions are prepared on (A) observation and evaluation, (B) care and evaluation, and (C) reporting. When the learner fails to give the correct answer, the correct answer is provided before the learner proceeds to the next section.
Scenario framework	
Feedback	The learner can receive feedback after answering each question. After completing all of the questions, the learner can watch a video that explains the two cases.
Resources	Information that serves as the basis for the answer is available whenever the learner wants it.

patient one day after surgery. The learning goals were to acquire the ability to observe patients to prevent postoperative complications and to provide necessary support. Learners were allowed to comment freely in their responses using the Situation, Background, Assessment, and Recommendations (SBAR) method.

The mission of the new nurse in the COPD scenario was to provide care to a patient complaining of dyspnea after walking to the bathroom. The learning goals were to acquire the ability to observe a patient with COPD and to provide the requisite support. Learners were allowed to comment freely using the SBAR method to answer questions for their report.

When the learner clicked on the answer button, the correct answer was displayed as feedback. A video explaining the two scenarios was viewed at the end of the program.

### **Second stage: Assessing the effectiveness of the e-learning system**

#### *Subjects*

Subjects were third- and fourth-year nursing students from two schools.

#### *Assessment*

Assessment was performed in January and February of 2017. Subjects were asked to use the e-learning system and fill out a follow-up questionnaire, which was generated using TAO. The questionnaire was used to evaluate interest, relevance, confidence, and satisfaction on a four-point scale and also included an open-ended question about the e-learning system.

#### *Methods of analysis*

Descriptive statistics were calculated based on the answers to questions about the e-learning materials, and the responses to the open-ended question were analyzed qualitatively.

#### *Ethical considerations*

The study was conducted in compliance with the ethical guidelines of the Japanese Ministry of Health, Labor, and Welfare for medical and health research involving human subjects. Approval was obtained from the Ethical Review Boards of the National Center for Global Health and Medicine (NCGM-G-002354-00) and Nagoya City University (172026-2) before this stage of the study.

#### *Outcomes*

##### *Overview of the subjects*

Responses from 43 nursing students who answered two or more of the questions were analyzed. All but one of the students were using the e-learning system for the first time. Of the 33 respondents, 27 (82%) were female students. Eighteen (56%) of thirty-two respondents were fourth-year students.

#### *Ambulatory support for patients after surgery for lung cancer*

When asked about the most common complications observed one day after surgery, 21% (9/43) of the nursing students responded correctly. Fifty-three percent (20/38) provided the correct answer regarding methods of identifying subcutaneous emphysema. Sixty-five percent (24/37) correctly identified the location of the fourth rib on the midclavicular line for auscultation. The location of the spinous process on the back of the seventh cervical vertebra was correctly identified by 73% (21/35) of the nursing students. Eight-one percent (35/43) of the nursing students responded to questions about the provision of care was 81% (35/43), and the correct answer rate was 60% (21/35). Forty percent (17/43) of the nursing students responded to questions about reporting, and 82% (14/17) of the correct answers were based on the SBAR method.

#### *Support for patients with COPD and dyspnea*

Seventy-seven percent (33/43) of the nursing students responded to questions in the section on information collection. The correct answer rate for causes of dyspnea was 76% (25/33). Twenty-four percent (8/33) of the nursing students correctly identified the causes of hypoxemia and hypercapnia. Nine percent (3/34) answered correctly regarding methods of identification. Seventy-nine percent (34/43) of the nursing students responded to the section on providing, and 79% (27/34) of the respondents answered correctly. Forty-four (19/43) of the nursing students responded to the section on reporting, and 79% (15/19) of the answers were based on the SBAR method.

#### *Motivation to learn using the e-learning system*

Questions regarding interest, relevance, confidence, and satisfaction had a response rate of 76% (33/43). Responses were rated on a four-point scale. The mean score for interest, or avoiding boredom, was 3.3. The mean score for relevance was 3.1. The mean score for confidence was 2.1 and that for satisfaction was 1.5.

Comments in the open-ended answer portion included the following: "The materials allowed learners to more fully understand what they had previously understood superficially" and "It would be nice if there were scenarios for other diseases." Students learned that information should be collected with a purpose.

### **The necessity of a learning program that encourages continuous learning**

The students had not practiced the nursing techniques required for new nurses in a clinical setting. Many of the new nurses had not cared for patients with lung cancer or COPD as nursing students, and they had never practiced suction. Even in Japan, where lung cancer and pneumonia are the leading causes of death (10), nursing students having difficulty acquiring the requisite skills to become professional nurses through practical training.

Suction is an essential technique for regulating breathing, but the resulting damage to the airway mucosa and coughing are painful for the patient. Synchronizing the patient's coughing with the timing of aspiration allows the patient to be aspirated painlessly. However, new nurses are forced to learn techniques that may require patient cooperation in the field. This indicates that new nurses lack certain skills, and this can lead to patient harm (11). While aspiration skills are important for new nurses in respiratory facilities, different skills are required for nurses who begin employment in other types of facilities. Based on these facts, the specific clinical skills that will be required of new nurses in different facilities need to be considered. Creating tailored programs with the most appropriate learning tasks for nursing students will help them respond to changes in medicine and the workplace and facilitate reemployment.

### Providing learners with opportunities for safe and repeated training through e-learning

The combination of pre-learning in nursing school, the freedom of e-learning, and repeated on-site care training will contribute to the development of knowledge, critical thinking, and problem-solving skills in the nursing profession. Nursing students who use Information and Communication Technology (ICT) are reported to have a stronger sense of self-efficacy than nurses (12). Incorporating ICT into primary nursing education and its use after graduation will showcase the strengths of nursing students. Self-managed e-learning is also more effective than being taught by others (13,14).

The results of the current study highlight the need for repeated learning opportunities in realistic situations, which will enable new nurses to practice in a clinical setting without experiencing anxiety. This is evinced by higher rates of anxiety and restlessness after nurses care for patients, so they benefit more by learning in a simulator (15). Therefore, learners need to be given the opportunity to learn repeatedly and safely via e-learning, and care-based training needs to be combined with improved reproducibility in the field.

### Limitations and challenges for the future

E-learning and evaluations were performed only in the context of pre-learning in this study. In the future,

simulation-based learning for nursing students will need to be investigated and changes in the practical skills of new nurses will need to be assessed. The opportunity to learn repeatedly and safely through e-learning must be available to learners.

### Acknowledgements

The authors would like to thank everyone who helped with this study. The process used to identify learning tasks was described at the Asia-Pacific Meeting on Simulation in Healthcare. A review of the literature on clinical decision-making was also announced at the International Meeting on Simulation in Healthcare. A study on the effectiveness of e-learning materials was presented at the Annual Meeting of the Japanese Society of National Medical Services.

*Funding:* This work was supported by the KAKENHI program of the JSPS (grant no. 15K15837).

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

### References

1. World Health Organization. (2006). Global Standards for the Initial Education of Professional Nurses and Midwives. Nursing and Midwifery-Human Resources for Health. 1-36. [https://www.who.int/hrh/nursing\\_midwifery/hrh\\_global\\_standards\\_education.pdf](https://www.who.int/hrh/nursing_midwifery/hrh_global_standards_education.pdf) (accessed on June 7, 2021).
2. Sugiyama F, Inoue T. A survey of learning needs about oral care for intubated patients among new nursing staff. *Open J Nurs.* 2020; 10:462-472.
3. Hayden JK. Use of simulation in nursing education: National survey results. *J Nurs Regul.* 2010; 1:52-57.
4. Hayden JK, Smiley RA, Alexander M, Kardong-Edgren S, Jeffries PR. The NCSBN National Simulation Study: A longitudinal, randomized, controlled study replacing clinical hours with simulation in prelicensure nursing education. *J Nurs Regul.* 2014; 5:C1-S64.
5. Felder RM, Brent R. Active learning: An introduction. *ASQ Higher Education Brief.* 2009; 2: 1-5.
6. The Central Council for Education, Ministry of Education, Culture, Sports, Science, and Technology, Japan. (2012). A qualitative shift in university education to build a new tomorrow: Universities that offer lifelong learning and that foster independent thinking. [https://www.mext.go.jp/component/b\\_menu/shingi/toushin/\\_icsFiles/afieldfile/2012/10/04/1325048\\_1.pdf](https://www.mext.go.jp/component/b_menu/shingi/toushin/_icsFiles/afieldfile/2012/10/04/1325048_1.pdf) (accessed March 2, 2019). (in Japanese)
7. Smart D, Ross K, Carollo S, Williams-Gilbert W. Contextualizing instructional technology to the demands of nursing education. *Comput Inform Nurs.* 2020; 38:18-27.
8. Nemoto J, Suzuki K. Application of Goal-based Scenario (GBS) theory to develop a fitness checklist' would be appropriate. *Educational Studies in Japan.* 2005; 29, 309-318. (in Japanese)
9. Suzuki K. Training Design Manual-Instructional Design



- for Human Resource Development. Kitaoji Shobo, Kyoto, Japan. (in Japanese)
10. Cancer Information Service, National Cancer Center, Japan. Cancer Registry and Statistics. [https://ganjoho.jp/reg\\_stat/statistics/stat/summary.html](https://ganjoho.jp/reg_stat/statistics/stat/summary.html) (accessed July 4, 2019). (in Japanese)
  11. Hezaveh MS, Rafii F, Seyedfatemi N. Novice nurses' experiences of unpreparedness at the beginning of the work. *Glob J Health Sci.* 2013; 6:215-22.
  12. Warshawski S, Itzhaki M, Barnoy S. Nurse and nurse student attitudes and perceived self-efficacy in use of information and communication technologies: Professional and cultural differences. *Comput Inform Nurs.* 2019; 37:20-28.
  13. Chipman JG, Beilman GJ, Schmitz CC, Seatter SC. Development and pilot testing of an OSCE for difficult conversations in surgical intensive care. *J Surg Educ.* 2007; 64:79-87.
  14. Alfaro-LeFevre R. *Critical Thinking, Clinical Reasoning, and Clinical Judgement: A Practical Approach* (7th Edition). Elsevier Health Sciences. 2019; pp.55-74.
  15. Günay İsmailoğlu E, Zaybak A. Comparison of the effectiveness of a virtual simulator with a plastic arm model in teaching intravenous catheter insertion skills. *Comput Inform Nurs.* 2018; 36:98-105.
- Received May 9, 2021; Revised June 8, 2021; Accepted June 14, 2021.
- \*Address correspondence to:*  
 Fumino Sugiyama, National College of Nursing, Japan, 1-2-1 Umezono, Kiyose-shi, Tokyo 204-8575, Japan.  
 E-mail: sugiyamaf@adm.ncn.ac.jp

## Japan's first online media seminar on antimicrobial resistance

Yoshiaki Gu<sup>1,2,\*</sup>, Yumiko Fujitomo<sup>1</sup>, Rie Takahashi<sup>1</sup>, Norio Ohmagari<sup>1,3</sup>

<sup>1</sup> AMR Clinical Reference Center, National Center for Global Health and Medicine Hospital, Tokyo, Japan;

<sup>2</sup> Department of Infectious Diseases, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan;

<sup>3</sup> Department of Infectious Diseases, Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan.

**Abstract:** According to the National Action Plan on Antimicrobial Resistance, published in 2016, various measures have been implemented to combat antimicrobial resistance (AMR) in Japan. Subsequently, promoting public education is important, as the Japanese public does not have sufficient knowledge about antimicrobials and AMR. The AMR Clinical Reference Center (AMRCRC) of the National Center for Global Health and Medicine conducts seminars for the media once a year as part of information and education services. In 2020, the AMRCRC conducted the first online seminar since it was unable to conduct face-to-face seminars due to the novel coronaviral disease 2019 (COVID-19) pandemic. An online seminar was considered effective in promoting education and awareness through the media. Twenty-four media representatives (from 19 companies) participated in the online seminar. Media articles related to the activities of AMRCRC were similar to those of the previous years despite the impact of COVID-19.

**Keywords:** antimicrobial resistance, online seminar, awareness, media coverage

Combating antimicrobial resistance (AMR) is a global challenge that is being tackled with the help of the Global Action Plan on AMR (2015) (1). In Japan, various measures are being implemented in accordance with the National Action Plan on Antimicrobial Resistance (NAP-AMR) (2016) (2). In both the action plans, the emphasis is on promoting public education. The first agenda (Strategy 1.1) in NAP-AMR is to promote awareness and education of AMR among the public, as the Japanese people have insufficient knowledge about antimicrobials, AMR, and infectious diseases in general (3). Although antimicrobial agents are prescription drugs in Japan, many physicians believe that misconceptions among the general public is one of the barriers to the proper use of antimicrobials (4). Patients may ask for prescriptions for antimicrobials even when they are not needed or may interrupt the use of prescribed antimicrobials to take them later at their own discretion.

The AMR Clinical Reference Center (AMRCRC) of the National Center for Global Health and Medicine was established in 2017 as a commissioned project of Japan's Ministry of Health, Labour and Welfare. The AMRCRC conducts information and education services along with clinical epidemiology services. Such educational and awareness-raising campaigns are aimed at both healthcare professionals and the general public. For the public, we are working on circulating necessary

information through our website and by conducting events. Seminars for the media, however, are held in the fall along with press releases with the expectation that it will be reported in November, the month for campaigning on AMR.

In 2020, it was impossible to conduct face-to-face seminars due to the novel coronaviral disease 2019 (COVID-19) pandemic. However, since we were concerned that media coverage would decrease, we decided to proactively provide information to the media. Therefore, we conducted the first online seminar on October 6. The program consisted of a 20-minute presentation each by the director of the AMRCRC and the chiefs of the three divisions: Information and Education Division, Pharmacoepidemiology Division and Clinical Epidemiology Division.

Twenty-four media representatives (from 19 companies) participated in the seminars. The participants were mainly journalists from the medical media and medical beats of mass media and news services. The number of participants was the highest ever. Dr. Yoshiaki Gu, the chief of the Information and Education Division explained the results of an awareness survey conducted on the public in August 2020. Dr. Yoshiki Kusama, the chief of the Pharmacoepidemiology Division focused on the results of the latest survey on antimicrobial usage. Dr. Nobuaki Matsunaga, the chief of the Clinical Epidemiology Division introduced websites that compile

**Table 1. Summary of media seminars by AMRCRC**

Items	2017	2018	2019	2020
Date of Media Seminar	8 November (face to face)	30 October (face to face)	24 September (face to face)	6 October (Online)
Number of companies (persons) participated	9 (11)	15 (21)	16 (22)	19 (24)
Number of media reports related to AMRCRC in November				
TV programs	2	4	2	0
Newspapers and Magazines	14	20	32	24
Web articles	148	79	46	70
Total	164	103	80	94

data from hospitals and all over Japan and the process of utilizing them. Finally, Dr. Norio Ohmagari, the Director of the AMRCRC explained the progress made since the NAP-AMR was launched as well as future challenges. This was followed by an enthusiastic interaction session lasting over 30 minutes.

A total of 94 media reports related to the activities of AMRCRC were published from November 1 to 30, including 24 newspaper and magazine reports and 70 web articles (Table 1). Although no television coverage has been reported, the media coverage was no less than the previous years.

The media plays an important role in disseminating appropriate information to the public. Despite the widespread use of social networking services (SNS), mass media still has a great impact. The AMRCRC is continuously working to provide accurate information about AMR to the public through media. Since the public receives abundant information from the media, awareness campaigns through the media can significantly increase their knowledge (5). The media also has a critical influence on SNS (6). However, the media should ensure dispersion of scientifically accurate information to avoid misinformation (7).

Media seminars by AMRCRC provide a good opportunity to present data on AMR that can be used as media coverages and deepen understanding through interaction session. It is also an excellent opportunity for experts to understand the importance of explaining things in a more lucid manner through media interaction. While COVID-19 coverage dominated in 2020, media coverage of the activities of AMRCRC was about the same as in the previous years. It was thought that conducting media seminars online would have the same effect as face-to-face seminars. Online seminars for media can be used in the future to educate and raise awareness about AMR.

**Funding:** This study was supported by a Ministry of Health, Labour and Welfare (MHLW) research grant of Japan (H29-shinkougouseishitei-005).

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

## References

1. World Health Organization. Global action plan on antimicrobial resistance. <http://www.who.int/antimicrobial-resistance/publications/global-action-plan/en> (accessed January 14, 2021)
2. The Government of Japan. National action plan on antimicrobial resistance (AMR), 2016-2020. <https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/0000138942.pdf> (accessed January 14, 2021)
3. Kamata K, Tokuda Y, Gu Y, Ohmagari N, Yanagihara K. Public knowledge and perception about antimicrobials and antimicrobial resistance in Japan: A national questionnaire survey in 2017. *PloS One*. 2018; 13:e0207017.
4. Gu Y, Fujitomo Y, Soeda H, Nakahama C, Hasegawa N, Maesaki S, Maeda M, Matsumoto T, Miyairi I, Ohmagari N. A nationwide questionnaire survey of clinic doctors on antimicrobial stewardship in Japan. *J Infect Chemother*. 2020; 26:149-156.
5. Robert A, Nguyen Y, Bajolet O, Vuillemin B, Defoin B, Vernet-Garnier V, Drame M, Bani-Sadr F. Knowledge of antibiotics and antibiotic resistance in patients followed by family physicians. *Med Mal Infect*. 2017; 47:142-151.
6. Andersen B, Hair L, Groshek J, Krishna A, Walker D. Understanding and diagnosing antimicrobial resistance on social media: a yearlong overview of data and analytics. *Health Commun*. 2019; 34:248-258.
7. Davis M, Whittaker A, Lindgren M, Djerf-Pierre M, Manderson L, Flowers P. Understanding media publics and the antimicrobial resistance crisis. *Glob Public Health*. 2018; 13:1158-1168.

----

Received April 15, 2021; Revised May 14, 2021; Accepted May 18, 2021.

*\*Address correspondence to:*

Yoshiaki Gu, Department of Infectious Diseases, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan.

E-mail: [yogu.cid@tmd.ac.jp](mailto:yogu.cid@tmd.ac.jp)

# Home-visit services for the families with newborns during the COVID-19 pandemic

Yukari Isaka<sup>1\*</sup>, Ai Hori<sup>2</sup>, Takahiro Tabuchi<sup>3</sup>, Sumiyo Okawa<sup>3,4</sup>, Masao Ichikawa<sup>2</sup>

<sup>1</sup> Doctoral Program in Human Care Science, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan;

<sup>2</sup> Department of Global Public Health, Faculty of Medicine, University of Tsukuba, Ibaraki, Japan;

<sup>3</sup> Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan;

<sup>4</sup> Institute for Global Health Policy Research, Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan.

**Abstract:** Home-visit services are provided to families with newborns as means of parenting support. These services potentially are playing major roles during the coronavirus disease 2019 (COVID-19) pandemic, where people have been socially isolated. However, the pandemic has deterred the use of this service to some extent. From the Japan "COVID-19 and Society" Internet Survey, we identified that 15% of the survey respondents who delivered between January 2020 and October 2020 refused home visit services. The proportion of the services used during the pandemic (85%) was lower than those used before the pandemic (95%). Home-visit services provide a unique opportunity for public health nurses to assess the risk of postpartum depression and child maltreatment in the family; thus, families with newborns should be instructed to receive home-visit services as well as child immunization and health checkups, despite the continuation of the pandemic.

**Keywords:** SARS-CoV-2, maternal-child health service, social welfare

During the coronavirus disease 2019 (COVID-19) pandemic, care for children's mental health is of growing importance because their well-being has been affected by the continued restriction of daily activities and the loss of social connectivity due to a state of emergency and temporary school closures as of July 2021 (1). The same can be said for mothers with newborns. It is noted that they are at risk of postpartum depression, and the risk may have enhanced during the pandemic.

In Japan, given the high incidence of postpartum depression (10-15%) (2) affecting maternal well-being and increasing the risk of child maltreatment, home-visit services have been provided to families with newborns by a legislated welfare program called "Konnichiwa Akachan Jigyo". The program aims at providing information on parenting support through home-visits by public health nurses or midwives within four months of birth (3).

Home-visit services, which can play a greater role when people are more socially isolated than usual, are continuing during the pandemic. However, the pandemic might have deterred families from receiving services for fear of COVID-19 infection. Thus, we examined whether home-visit services have decreased during the pandemic, using the Japan "COVID-19 and Society" Internet Survey (JACSIS) data targeting pregnant and postpartum

women (4).

The survey participants included 1,000 pregnant and parturient women. The participants were recruited from an online panel of approximately 2.2 million individuals managed by Rakuten Insight from October 15, 2020 to October 25, 2020, and were asked to fill out online questionnaires that included questions regarding whether they received home-visit services. Home visit services are usually availed within 4 months of delivery but the appointment for such services is made shortly after delivery. Thus, we assumed that the decision to receive home-visit services was affected by the pandemic situation around the delivery time. The study protocol was approved by the Research Ethics Committee of the Osaka International Cancer Institute on June 19, 2020 (approval number 20084).

Of the 479 women who delivered between January 2020 and October 2020, 409 (85%) received the service (*i.e.*, 15% of women refused home visit services). Table 1 shows the proportion of service recipients by month of delivery. Although caution should be exercised with the small denominator, the proportion was lower (*i.e.*, 77-78% from March to May), just before and during the first state of emergency compared to other months.

Before the pandemic, families with newborns were more likely to receive home-visit services: 95% of

**Table 1. Number and proportion of 479 families with newborns receiving home-visit services by month of delivery in 2020<sup>a</sup>**

Month	Home-visit services	
	Number <sup>b</sup>	Percentage (%)
January	31/33	94
February	29/34	85
March	17/22	77
April	75/97	77
May	79/101	78
June	35/36	97
July	37/42	88
August	32/34	94
September	19/22	86
October	55/58	95
Total	409/479	85

<sup>a</sup>Japan's first state of emergency lasted from April 7 to May 25, 2020.

<sup>b</sup>Number of families with newborns receiving home-visit services/total number of families with newborns.

927,816 families availing home-visit services received it between April 2017 and March 2018 (5). Therefore, the pandemic might have interrupted service use. To respond to fear of COVID-19 infection in service use, the Ministry of Health, Labour and Welfare advised local governments to provide telephone or online consultation if home-visit is not accepted (6). The survey did not investigate to what extent telephone or online consultation has been used by families with newborns, and it is uncertain that such consultation is useful for public health nurses to identify families at risk of postpartum depression and child maltreatment. It should be worth examining the usefulness of telephone and online consultation for emergency preparedness. Moreover, since our study investigated service use in the online panel up to October 2020, further investigation is warranted with a representative sample over a prolonged period as the pandemic continues.

Home-visit services provide a unique opportunity for public health nurses or midwives to contact families with newborns at home, helping them assess the risk of postpartum depression and child maltreatment in the family. Families with newborns should be instructed to receive home-visit services as well as child immunization and health checkups despite the prevailing pandemic.

*Funding:* This study was funded by the Japan Society

for the Promotion of Science (JSPS) KAKENHI Grants (grant numbers 18H03062 and 21H04856), Research Support Program to Apply the Wisdom of the University to tackle COVID-19 Related Emergency Problems, University of Tsukuba. The findings and conclusions of this article are the sole responsibility of the authors and do not represent the official views of the research funders.

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

## References

1. Usami M, Sasaki S, Sunakawa H, *et al.* Care for children's mental health during the COVID-19 pandemic in Japan. *Glob Health Med.* 2021; 3:119-121.
2. Tokumitsu K, Sugawara N, Maruo K, Suzuki T, Shimoda K, Yasui-Furukori N. Prevalence of perinatal depression among Japanese women: a meta-analysis. *Ann Gen Psychiatry.* 2020; 19:41.
3. Ministry of Health, Labour, and Welfare. Outline of home-visit services for the families with newborns. <https://www.mhlw.go.jp/bunya/kodomo/kosodate12/01.html> (accessed June 28, 2021). (in Japanese)
4. Miyawaki A, Tabuchi T, Tomata Y, Tsugawa Y. Association between participation in the government subsidy programme for domestic travel and symptoms indicative of COVID-19 infection in Japan: cross-sectional study. *BMJ Open.* 2021; 11:e049069.
5. Ministry of Health, Labour, and Welfare. Survey on home-visit services for the families with newborns. <https://www.mhlw.go.jp/content/11900000/000680041.pdf> (accessed June 28, 2021). (in Japanese)
6. Ministry of Health, Labour, and Welfare. Response to the maternal and child health services on COVID-19. <https://www.mhlw.go.jp/content/11920000/000636735.pdf> (accessed July 14, 2021). (in Japanese)

----

Received July 1, 2021; Revised July 19, 2021; Accepted July 27, 2021.

*\*Address correspondence to:*

Yukari Isaka, Doctoral Program in Human Care Science, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8577, Japan.

E-mail: s1530359@u.tsukuba.ac.jp

# Seroprevalence of antibodies against SARS-CoV-2 among workers in a national research institute and hospital in Central Japan

Akihiko Nishikimi<sup>1</sup>, Masayo Kojima<sup>2,\*</sup>, Ken Watanabe<sup>3</sup>, Atsushi Watanabe<sup>4</sup>, Mikako Yasuoka<sup>2</sup>, Hironori Oshima<sup>5</sup>, Haruhiko Tokuda<sup>3,5</sup>, Shumpei Niida<sup>6</sup>

<sup>1</sup> Biosafety Division, Research Institute, National Center for Geriatrics and Gerontology, Aichi, Japan;

<sup>2</sup> Department of Frailty Research, Research Institute, National Center for Geriatrics and Gerontology, Aichi, Japan;

<sup>3</sup> Bioresource Division, Research Institute, National Center for Geriatrics and Gerontology, Aichi, Japan;

<sup>4</sup> Research Advancement Division, Research Institute, National Center for Geriatrics and Gerontology, Aichi, Japan;

<sup>5</sup> Department of Clinical Laboratory, Hospital, National Center for Geriatrics and Gerontology, Aichi, Japan;

<sup>6</sup> Research Institute, National Center for Geriatrics and Gerontology, Aichi, Japan.

**Abstract:** To achieve effective prevention and control strategies for COVID-19, regular survey of seroprevalence of antibodies against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is essential. Using four serological tests, we examined the residual sera collected in an annual medical checkup of the staff members of the National Center for Geriatrics and Gerontology in Aichi Prefecture, Central Japan in June 2020. Of the 631 samples, two were positive for anti-SARS-CoV-2 antibodies in at least two tests, showing a seroprevalence of 0.32%. Four subjects showed positive results in only one test. All individuals were asymptomatic and had not been in close contact with patients diagnosed with COVID-19. Multiple antibody tests could be used to assess the prevalence of SARS-CoV-2 infection including individuals without COVID-19 symptoms.

**Keywords:** SARS-CoV-2, COVID-19, seroprevalence

The spread of SARS-CoV-2 had various impacts on social activities. Since the first case of coronavirus disease 2019 (COVID-19) was identified in January 2020, more than 813000 cases and 15000 deaths have occurred in Japan so far. Just before the opening of the Olympics, the number of new cases has been again increasing in Tokyo. Although the vaccination rollout started in mid-February, only 29.6% of the population has completed at least once in Japan and the pandemic has still not ended. As a considerable number of individuals have only mild or no symptoms, the extent of infection has been evaluated by seroepidemiological studies (1). The seroprevalence in the Japanese general populations was 0.03-0.17 in June 2020 and 0.14-0.91 in December 2020 (2,3). To achieve effective prevention and control strategies for COVID-19, regular survey of seroprevalence is essential.

The National Center for Geriatrics and Gerontology (NCGG), which comprises a hospital and research institute, is one of the national centers for advanced and specialized medicine located in Aichi Prefecture, a central region of Japan. To investigate the seroprevalence of SARS-CoV-2 among NCGG workers over time, we designed a repeated cross-sectional study and reported the results of the first survey using the sera collected at

annual health checkups in June 2020.

Of the 743 NCGG employees invited, 632 agreed to participate in the survey (participation rate: 85.0%). However, one was excluded because of insufficient serum volume. Thus, 631 samples were tested for anti-SARS-CoV-2 antibody levels. In January 2021, the participants were asked to answer an electronic questionnaire on sociographic and COVID-19-related factors. All participants provided written informed consent, and the Institutional Review Board of the ethics and conflicts of interest committee approved this study (No: 1481).

At the inhouse laboratory, serum anti-SARS-CoV-2 antibodies were measured using clinical diagnostic systems manufactured by Sysmex, Abbott, and Roche. We performed Sysmex SARS-CoV-2 N-IgG and SARS-CoV-2 S-IgG assays that detect immunoglobulin G against viral nucleoprotein and spike protein antigens, respectively. In addition, we performed Abbott SARS-CoV-2 assay that detects IgG against nucleocapsid protein. Further, we performed the Roche Elecsys Anti-SARS-CoV-2 RUO assay that detects total antibodies, including IgG against nucleocapsid protein. Samples with positive results in two or more tests were considered antibody positive. To compare the distribution of values,

**Table 1. Individual index values of each test in samples that were tested positive in at least one test**

Participants	Age Range	Gender	Tests (positive threshold value)			
			Abbott (1.4)	Sysmex-S (10)	Sysmex-N (10)	Roche (1.0)
A	≥ 50	female	<b>2.58</b>	<b>13.9</b>	<b>43.8</b>	<b>2.220</b>
B	30-39	male	<b>1.61</b>	0.0	<b>22.8</b>	0.071
C	40-49	male	<b>1.52</b>	0.0	0.2	0.204
D	30-39	female	0.01	0.0	0.6	<b>1.340</b>
E	40-49	female	0.01	0.0	0.8	<b>1.500</b>
F	≥ 50	female	<b>1.56</b>	0.0	0.0	0.070

Positive values are indicated in bold letters.

logarithmic transformation of the index value +1 was used.

Table S1 (<https://www.ghmopen.com/site/supplementaldata.html?ID=25>) summarizes the participant characteristics. The proportions of participants in their 20s, 30s, 40s, and older than 50 years were 22.1%, 23.1%, 31.5%, and 23.3%, respectively, and 63.6% were female. The healthcare workers including doctors, nurses, and allied healthcare professionals accounted for 65.0%, whereas the others were engaged in basic research and investigation, general office duties, and other nonclinical work. A total of 104 (16.5%) participants were reported to have engaged in work activities with high infection risks.

As shown in Table 1, among 631 participants, only two were positive in two or more tests, indicating a seroprevalence of 0.32% (95% confidence interval: 0.04–1.14). One participant was positive in all tests, with indices of 2.58, 13.9, 43.8, and 2.220 in the Abbott, Sysmex-N, Sysmex-S, and Roche tests, respectively. Another participant was positive in Abbott test (index: 1.61) and Sysmex-N test (index: 22.8). Both individuals were nonclinical workers. Meanwhile, four participants were positive in one of the tests, two in the Abbott test (indices: 1.52 and 1.56) and two in the Roche test (indices: 1.340 and 1.500). No participant had a history of PCR testing or close contact with patients diagnosed with SARS-CoV-2. In addition, they claimed absence of any symptom implying infection between January and June 2020.

The Ministry of Health, Labor, and Welfare of Japan conducted a survey of the general population; the results showed that the seroprevalences in Tokyo, Osaka, and Miyagi were 0.10%, 0.17%, and 0.03%, respectively, in June 2020 (2). During the same period, SoftBank Group Corp. reported that 0.20% of their employees in Aichi Prefecture, where NCGG is located, were positive in the anti-SARS-CoV-2 antibody test (4). Furthermore, 2.1% of the healthcare workers in Kanagawa Prefecture (near Tokyo) (5) and 0.16% of those in the National Center for Global Medicine in Tokyo were antibody positive (6). The antibody prevalence in the present study is similar to that reported in these surveys, suggesting that the residual serum of medical examinations can be used for the rough estimation of seroprevalence.

In this study, discordant assay results were obtained in five cases. Such discrepancies were observed in samples presumably with low antibody levels (7,8). When the normalized values were compared between assays, the Sysmex tests (both S and N) showed a clear distinction between positive and negative values (Figure S1, <https://www.ghmopen.com/site/supplementaldata.html?ID=25>). The discordance among the tests may have resulted from the difference in assay characteristics. Antibodies reportedly cross-react with some SARS-CoV-2 epitopes detected in the serum from individuals without SARS-CoV-2 infection or those with seasonally spreading human coronaviruses (HCoV), possibly because the cross-reactivity persisted from earlier HCoV infection (9). Cross-immunity is possible in cases that show positivity in a single assay. Therefore, multiple assays are needed to identify individuals with prior SARS-CoV-2 infection.

#### Acknowledgments

The authors thank Megumi Banno, Mayumi Taguchi, Risa Nishijima, Koto Kamiji, Keiko Funatsu, and Yukari Kido for their technical assistance.

*Funding:* This work was supported by the Japan Health Research Promotion Bureau Research Fund (2020-B-09).

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

#### References

- Heymann DL, Shindo N, WHO Scientific and Technical Advisory Group for Infectious Hazards. COVID-19: what is next for public. *Lancet* 2020, 395:542-545.
- Ministry of Health, Labour and Welfare of Japan. About antibody prevalence survey. <https://www.mhlw.go.jp/content/10906000/000640184.pdf> (accessed June 19, 2021) (in Japanese).
- Ministry of Health, Labour and Welfare of Japan. About antibody prevalence survey. <https://www.mhlw.go.jp/content/000734482.pdf> (accessed July 12, 2021) (in Japanese).
- SoftBank Group Corp. About preliminary estimates of antibody test results. <https://group.softbank/system/>

- files/pdf/antibodytest.pdf* (accessed June 19, 2021) (in Japanese).
5. Tanaka A, Yamamoto S, Miyo K, Mizoue T, Maeda K, Sugiura W, Mitsuya, H, Sugiyama H, Ohmagari N. Seroprevalence of antibodies against SARS-CoV-2 in a large national hospital and affiliated facility in Tokyo, Japan. *J Infect.* 2021; 82:e1-e3.
  6. Matsuba, I, Hatori N, Koido N, Watanabe Y, Ebara F, Matsuzawa, Nishikawa T, Kunishima T, Degawa H, Nishikawa M, Ono Y, Kanamori A. Survey of the current status of subclinical coronavirus disease 2019 (COVID-19). *J Infect Chemother.* 2020; 26:1294-1300.
  7. The National SARS-CoV-2 Serology Assay Evaluation Group. Performance characteristics of five immunoassays for SARS-CoV-2: A head-to-head benchmark comparison. *Lancet Infect Dis.* 2020; 20:1390-1400.
  8. Manthei DM, Whalen JF, Schroede LF, Sinay AM, Li SH, Valdez R, Giacherio DA, Gherasim C. Differences in performance characteristics among four high-Throughput assays for the detection of antibodies against SARS-CoV-2 using a common set of patient samples. *Am J Clin Pathol.* 2021; 155:267-279.
  9. Ng KW, Faulkner N, Cornish GH, Rosa A, Harvey R, Hussain S, Ulferts R, Earl C, Wrobel AG, Benton DJ, Roustan C. Preexisting and de novo humoral immunity to SARS-CoV-2 in humans. *Science.* 2020; 370:1339-1343.
- Received June 29, 2021; Revised July 20, 2021; Accepted July 27, 2021.
- \*Address correspondence to:*  
Masayo Kojima, Department of Frailty Research, Research Institute, National Center for Geriatrics and Gerontology, 7-430 Morioka Obu Aichi 474-8511, Japan.  
E-mail: masayok@ncgg.go.jp





## Information for Authors

### 1. Scope of Articles

*GHM Open* (Print ISSN 2436-293X, Online ISSN 2436-2956) is an international, open-access, peer-reviewed journal dedicated to publishing high-quality original research that contributes to advancing global health and medicine, with the goal of creating a global information network for global health, basic science as well as clinical science oriented for clinical application.

We encourage submission of original research findings in the fields of global health, public health, and health care delivery as well as the seminal and latest research on the intersection of biomedical science and clinical practice.

### 2. Types of Articles

Types of Articles	Words in length (excluding references)	Figures and/or Tables	References
Original Articles	~5,000	~10	~50
Brief Reports	~3,000	~5	~30
Reviews	~8,000	~10	~100
Mini reviews	~4,000	~5	~50
Policy Forum articles	~3,000	~5	~30
Study Protocols	~5,000	~10	~50
Case Reports	~3,000	~5	~30
Communications	~2,000	~2	~20
Perspectives			
Comments			
Correspondence			
Editorials	~1,000	~1	~10
Letters	~1,000	~1	~10
News	~800	~1	~5

**Abstract:** ~250 words (Original Articles, Brief Reports, Reviews, Policy Forum, Study Protocols, Case Reports); ~150 words (Communications, Editorials, Letters, and News)

**Keywords:** 3-6 words

**Original Articles** should be well-documented, novel, and significant to the field as a whole. They should include an abstract and be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate. Original articles should not exceed 5,000 words in length (excluding references) and should be limited to a maximum of 50 references. Articles may contain a maximum of 10 figures and/or tables. Supplementary Data are permitted but should be limited to information that is not essential to the general understanding of the research presented in the main text, such as unaltered blots and source data as well as other file types.

**Brief Reports** definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a

maximum of 5 figures and/or tables and 30 references. Brief Reports should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results and Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate.

**Reviews** should present a full and up-to-date account of recent developments within an area of research. Normally, reviews should not exceed 8,000 words in length (excluding references) and should be limited to a maximum of 100 references and up to 10 figures and/or tables. Mini reviews are also accepted, which should not exceed 4,000 words in length (excluding references), have no more than 50 references, and have up to 5 figures and/or tables.

**Policy Forum** articles discuss research and policy issues in areas related to global health and medicine, such as public health, medical care, and social science that may address governmental issues at district, national, and international levels of discourse. Policy Forum articles should not exceed 3,000 words in length (excluding references), have no more than 30 references, and have up to 5 figures and/or tables.

**Study Protocols** should be the manuscripts report proposed or ongoing prospective research. Preference will be given to submissions describing long-term studies and those likely to generate a considerable amount of outcome data. Trial registration details should be stated in the manuscript, if appropriate. Study Protocols should not exceed 5,000 words in length (excluding references) and should be limited to a maximum of 10 figures and/or tables and 50 references.

**Case Reports** should be detailed reports of the symptoms, signs, diagnosis, treatment, and follow-up of an individual patient. Case reports may contain a demographic profile of the patient but usually describe an unusual or novel occurrence. Unreported or unusual side effects or adverse interactions involving medications will also be considered. Case Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references.

**Communications** are short, timely pieces that spotlight new research findings or policy issues of interest to the field of global health and medical practice that are of immediate importance. Depending on their content, Communications will be published as "Perspectives", "Comments", or "Correspondence". Communications should not exceed 2,000 words in length (excluding references), have no more than 20 references, and have up to 2 figures and/or tables.

**Editorials** are short, invited opinion pieces that discuss an issue of immediate importance to the fields of global health, medical practice, and basic science oriented for clinical application. Editorials should not exceed 1,000 words in length (excluding references), have no more than 10 references, and have one figure or table.

**Letters** are articles that provide readers with an opportunity to respond to an article published in *GHM Open* within the previous two months or to raise issues of general interest to our readers. Letters should provide new information or insights. If appropriate, letters are sent to the authors of the article in question for a response. Letters should not exceed 1,000 words in length (excluding references), have no more than 10 references, and have one figure or table.

**News** articles should report the latest events in health sciences and medical research from around the world. News should not exceed 800 words in length (excluding references), have no more than 5 references, and have one figure or table.

### 3. Formatting Guidelines

Manuscripts should be written in clear, grammatically correct English and submitted as a Microsoft Word file in a single-column format. Manuscripts must be paginated and typed in 12-point Times New Roman font with 24-point line spacing. Please do not embed figures in the text. Technical terms should be defined. Abbreviations should be used as little as possible and should be explained at first mention unless the term is a well-known abbreviation (e.g. DNA). Single words should not be abbreviated. Please include page numbers in your submitted file. We also encourage use of line numbers.

#### The submission to *GHM Open* should include:

1. Cover letter
2. Submission Checklist
3. Main Manuscript (including Tables)
4. Figures
5. Supplementary Data (e.g. Supplementary Tables/Figures), if appropriate

#### The main manuscripts should be assembled in the following order:

1. Title page
2. Abstract
3. Main Text
4. Acknowledgments
5. References
6. Tables
7. Figure Legend
8. List of Supplementary Data, if appropriate

For manuscript samples, please visit <https://www.ghmopen.com/site/download.html> (Download Center).

Please provide all figures as separate files in an acceptable format (TIFF or JPEG). Supplementary Data should also be submitted as a single separate file in Microsoft Word format.

An abstract is necessary for all types of articles. An Original Article should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate. A Brief Report contains the same sections as an Original Article, but the Results and Discussion sections should be combined. For manuscripts that are Reviews, Policy Forum, Study Protocols, Case Reports, Communication, Editorials, Letters, or News, subheadings should be used for increased clarity.

### 4. Manuscript Preparation

**Title page:** The title page must include 1) the title of the paper (Please note the title should be short, informative, and contain the major key words); 2) full name(s) and affiliation(s) of the author(s), 3) abbreviated names of the author(s), 4) full name, mailing address, telephone/fax numbers, and e-mail address of the corresponding author.

**Abstract:** The abstract should briefly state the purpose of the study, methods, main findings, and conclusions. For articles that are Original Articles, Brief Reports, Reviews, Policy Forum, Study Protocols, or Case Reports, a one-paragraph abstract consisting of no more than 250 words must be included in the manuscript. For Communications, Editorials, Letters, and News, a one-paragraph brief summary of the main content in 150 words or less should be included in the manuscript. Abbreviations must be kept to a minimum and non-standard abbreviations should be explained in brackets

at first mention. References should be avoided in the abstract. Three to six key words or phrases that do not occur in the title should be included on the Abstract page.

**Introduction:** The introduction should provide sufficient background information to make the article intelligible to readers in other disciplines and sufficient context clarifying the significance of the experimental findings.

**Materials and Methods:** The description should be brief but with sufficient detail to enable others to reproduce the experiments. Procedures that have been published previously should not be described in detail but appropriate references should simply be cited. Only new and significant modifications of previously published procedures require complete description. Names of products and manufacturers with their locations (city and state/country) should be given and sources of animals and cell lines should always be indicated. All clinical investigations must have been conducted in accordance with Declaration of Helsinki principles. All human and animal studies must have been approved by the appropriate institutional review board(s) and a specific declaration of approval must be made within this section.

**Results:** The description of the experimental results should be succinct but in sufficient detail to allow the experiments to be analyzed and interpreted by an independent reader. If necessary, subheadings may be used for an orderly presentation. Two levels of subheadings may be used if warranted, please distinguish them clearly. All Figures and Tables should be cited in order, including those in the Supplementary Data.

**Discussion:** The data should be interpreted concisely without repeating material already presented in the Results section. Speculation is permissible, but it must be well-founded, and discussion of the wider implications of the findings is encouraged. Conclusions derived from the study should be included in this section.

**Acknowledgments:** People who contributed to the work but do not meet the criteria for authors should be listed along with their contributions in the Acknowledgments section.

**Funding:** All funding sources should be credited in the Funding section. If no funding sources need be credited, please state "None".

**Conflict of Interest:** If you have an actual or potential conflict of interest to disclose, it must be listed; if no conflict of interest exists for each author, please state "The authors have no conflicts of interest to disclose".

**References:** References should be numbered in the order in which they appear in the text. Two references are cited separated by a comma, with no space, for example (1,2). Three or more consecutive references are given as a range with an en rule, for example (1-3). Citing of unpublished results, personal communications, conference abstracts, and theses in the reference list is not recommended but these sources may be mentioned in the text. In the reference list, cite the names of all authors when there are fifteen or fewer authors; if there are sixteen or more authors, list the first three followed by *et al.* Names of journals should be abbreviated in the style used in PubMed. Authors are responsible for the accuracy of the references.

Examples are given below:

*Example 1 (Sample journal reference):*

Mitsuya H, Kokudo N. Focusing on global health and medicine. *Glob Health Med.* 2019; 1:1-2.

*Example 2 (Sample journal reference with more than 15 authors):*

Hayakawa K, Kutsuna S, Kawamata T, *et al.* SARS-CoV-2 infection among returnees on charter flights to Japan from Hubei, China: a report from National Center for Global Health and Medicine. *Glob Health Med.* 2020; 2:107-111.

*Example 3 (Sample book reference):*

Shalev AY. Post-traumatic stress disorder: Diagnosis, history and life course. In: *Post-traumatic Stress Disorder, Diagnosis, Management and Treatment* (Nutt DJ, Davidson JR, Zohar J, eds.). Martin Dunitz, London, UK, 2000; pp. 1-15.

*Example 4 (Sample web page reference):*

World Health Organization. The World Health Report 2008 – primary health care: Now more than ever. [http://www.who.int/whr/2008/whr08\\_en.pdf](http://www.who.int/whr/2008/whr08_en.pdf) (accessed March 20, 2021).

**Tables:** All tables should be prepared in Microsoft Word and should be arranged at the end of the manuscript after the References section. Please note that tables should not be in image format. All tables should have a concise title and should be numbered consecutively with Arabic numerals. Every vertical column should have a heading, consisting of a title with the unit of measure in parentheses. If necessary, additional information should be given below the table.

**Figure Legend:** The figure legend should be typed on a separate page of the main manuscript and should include a short title and explanation. The legend should be concise but comprehensive and should be understood without referring to the text. Symbols used in figures must be explained. Any individually labeled figure parts or panels (A, B, *etc.*) should be specifically described by part name within the legend.

**Figure Preparation:** All figures should be clear and cited in numerical order in the text. Figures must fit in a one- or two-column format on the journal page: 8.3 cm (3.3 in.) wide for a single column, 17.3 cm (6.8 in.) wide for a double column; maximum height: 24.0 cm (9.5 in.). Please make sure that the symbols and numbers appearing in the figures are clear. Please make sure that artwork files are in an acceptable format (TIFF or JPEG) at minimum resolution (600 dpi for illustrations, graphs, and annotated artwork, and 300 dpi for micrographs and photographs). Please provide all figures as separate files. Please note that low-resolution images are one of the leading causes of article resubmission and scheduling delays.

**Units and Symbols:** Units and symbols conforming to the International System of Units (SI) should be used for physicochemical quantities. Solidus notation (*e.g.* mg/kg, mg/mL, mol/mm<sup>2</sup>/min) should be used. Please refer to the SI Guide [www.bipm.org/en/si/](http://www.bipm.org/en/si/) for standard units.

**Supplemental Data:** Supplemental data might help to support and enhance your manuscript. *GHM Open* accepts the submission of these materials, which will be only published online alongside the electronic version of your article. Supplemental files (figures, tables, and other text materials) should be prepared according to the above guidelines, numbered in Arabic numerals (*e.g.*, Figure S1, Figure S2, and Table S1, Table S2), and referred to in the text. All figures and tables should have titles and legends. All figure legends, tables and supplemental text materials should be placed at the end of the paper. Please note all of these supplemental data should be provided at the time of initial submission and note that the editors reserve the right to limit the size and length of Supplemental Data.

## 5. Cover Letter

The manuscript must be accompanied by a cover letter prepared by the corresponding author on behalf of all authors. The letter should indicate the basic findings of the work and their significance. The letter should also include a statement affirming that all authors concur with the submission and that the material submitted for publication has not been published previously or is not under consideration for publication elsewhere. For example of Cover Letter, please visit: Download Centre. (<https://www.ghmopen.com/site/download.html>).

## 6. Submission Checklist

The Submission Checklist will be useful during the final checking of a manuscript prior to sending it to *GHM Open* for review. Please visit Download Centre and download the Submission Checklist file.

## 7. Online Submission

Manuscripts should be submitted to *GHM Open* online at <https://www.ghmopen.com/site/login.html>. If for any reason you are unable to submit a file online, please contact the Editorial Office by e-mail at [office@ghmopen.com](mailto:office@ghmopen.com)

## 8. Editorial Policies

For publishing and ethical standards, *GHM Open* follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (<http://www.icmje.org/recommendations>) issued by the International Committee of Medical Journal Editors (ICMJE), and the Principles of Transparency and Best Practice in Scholarly Publishing (<https://doaj.org/bestpractice>) jointly issued by the Committee on Publication Ethics (COPE), the Directory of Open Access Journals (DOAJ), the Open Access Scholarly Publishers Association (OASPA), and the World Association of Medical Editors (WAME).

*GHM Open* will perform an especially prompt review to encourage innovative work. All original research will be subjected to a rigorous standard of peer review and will be edited by experienced copy editors to the highest standards.

The publishing is supported by the International Research and Cooperation Association for Bio & Socio-Sciences Advancement (IRCA-BSSA) Group Journals. The editorial office comprises a range of experienced individuals, including managing editor, editorial associates, software specialists, and administrative coordinators to provide a smooth service for authors and reviewers.

**Ethics:** *GHM Open* requires that authors of studies involving humans or animals to indicate that those studies were formally approved by a relevant ethics committee or review board. For research involving human experiments, a statement that the participants gave informed consent before taking part (or a statement that it was not required and why) should be indicated. Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

**Conflict of Interest:** All authors are required to disclose any actual or potential conflict of interest, including financial interests or relationships with other people or organizations that might raise questions of bias in the work reported. If no conflict of interest exists for each author, please state "The

authors have no conflicts of interest to disclose".

**Submission Declaration:** When a manuscript is considered for submission to *GHM Open*, the authors should confirm that 1) no part of this manuscript is currently under consideration for publication elsewhere; 2) this manuscript does not contain the same information in whole or in part in manuscripts that have been published, accepted, or are under review elsewhere, except in the form of an abstract, a letter to the editor, or part of a published lecture or academic thesis; 3) authorization for publication has been obtained from the authors' employer or institution; and 4) all contributing authors have agreed to submit this manuscript.

**Copyright:** Before a manuscript is accepted for publication in *GHM Open*, the transfer of copyright is necessary. A JOURNAL PUBLISHING AGREEMENT (JPA) form will be e-mailed to the authors by the Editorial Office and must be returned by the authors by mail, fax, or as a scan. Only forms with a hand-written signature from the corresponding author are accepted. This copyright will ensure the widest possible dissemination of information. Please note that the manuscript will not proceed to the next step in publication until the JPA Form is received. In addition, if excerpts from other copyrighted works are included, the author(s) must obtain written permission from the copyright owners and credit the source(s) in the article.

**Peer review:** *GHM Open* uses single-blind peer review, which means that reviewers know the names of the authors, but the authors do not know who reviewed their manuscript. The external peer review is performed for research articles by at least two reviewers, and sometimes the opinions of more reviewers are sought. Peer reviewers are selected based on their expertise and ability to provide high quality, constructive, and fair reviews. For research manuscripts, the editors may, in addition, seek the opinion of a statistical reviewer. Consideration for publication is based on the article's originality, novelty, and scientific soundness, and the appropriateness of its analysis.

**Suggested Reviewers:** A list of up to 3 reviewers who are qualified to assess the scientific merit of the study is welcomed. Reviewer information including names, affiliations, addresses, and e-mail addresses should be provided at the same time the manuscript is submitted online. Please do not suggest reviewers with known conflicts of interest, including participants or anyone with a stake in the proposed research; anyone from the same institution; former students, advisors, or research collaborators (within the last three years); or close personal contacts. Please note that the Editor-in-Chief may accept one or more of the proposed reviewers or request a review by other qualified persons.

**Language Editing:** Manuscripts prepared by authors whose native language is not English should have their work

proofread by a native English speaker before submission. If not, this might delay the publication of your manuscript in *GHM Open*.

The Editorial Office can also provide English proofreading services to authors who want to publish in *GHM Open*. Please contact the Editorial Office by e-mail ([office@ghmopen.com](mailto:office@ghmopen.com)) for details such as expenses.

## 9. Accepted Manuscripts

**Proofs:** Galley proofs in PDF format will be e-mailed to the corresponding author. Corrections must be returned to the editor ([office@ghmopen.com](mailto:office@ghmopen.com)) within 3 working days.

**Offprints:** Authors will be provided with electronic offprints of their article. Paper offprints can be ordered at prices quoted on the order form that accompanies the proofs.

**Article-processing Charges:** The open-access policy of *GHM Open* will allow all readers from the medical and scientific community to freely utilize material published in the journal. To achieve open access, article-processing charges (\$150 per page for black & white pages, \$300 per page for color pages) will be levied for manuscripts accepted for publication in *GHM Open*. In exceptional circumstances, the author(s) may apply to the editorial office for a waiver of the publication charges at the time of submission. All invited articles are free of charge.

Article-processing charges pay for: Immediate, worldwide open access to the full article text; Preparation in various formats for print & online publication; Inclusion in global important platforms, enabling electronic citation in other journals that are available electronically.

**Misconduct:** *GHM Open* takes seriously all allegations of potential misconduct and adheres to the ICMJE Guideline (<http://www.icmje.org/recommendations>) and COPE Guideline ([http://publicationethics.org/files/Code\\_of\\_conduct\\_for\\_journal\\_editors.pdf](http://publicationethics.org/files/Code_of_conduct_for_journal_editors.pdf)). In cases of suspected research or publication misconduct, it may be necessary for the Editor or Publisher to contact and share submission details with third parties including authors' institutions and ethics committees. The corrections, retractions, or editorial expressions of concern will be performed in line with above guidelines.

(As of August 2021)

## GHM Open

National Center for Global Health and Medicine,  
1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan  
URL: [www.ghmopen.com](http://www.ghmopen.com)  
E-mail: [office@ghmopen.com](mailto:office@ghmopen.com)



Print ISSN: 2436-293X Online ISSN: 2436-2956



# GHM Open

**Global Health & Medicine Open**

Volume 1, Number 1  
August, 2021



[www.ghmopen.com](http://www.ghmopen.com)