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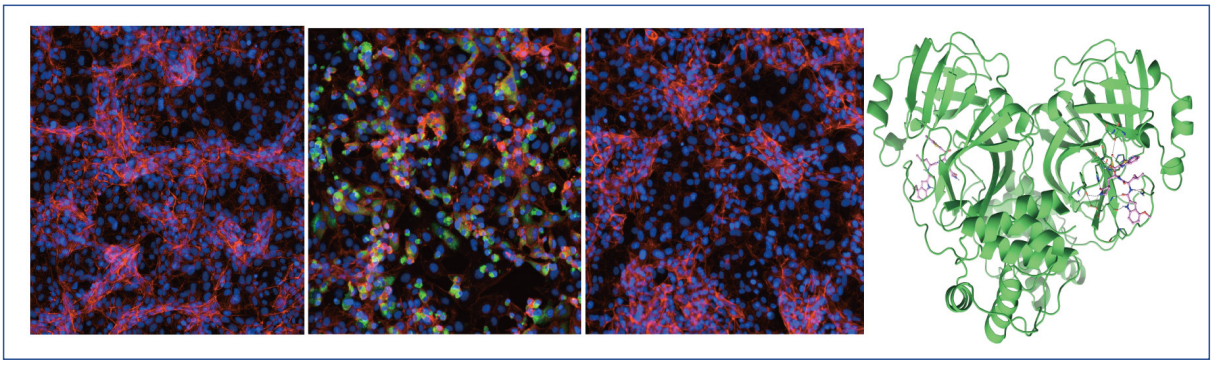

GRL-2420/5h Completely Blocks SARS-CoV-2

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Global Health & Medicine

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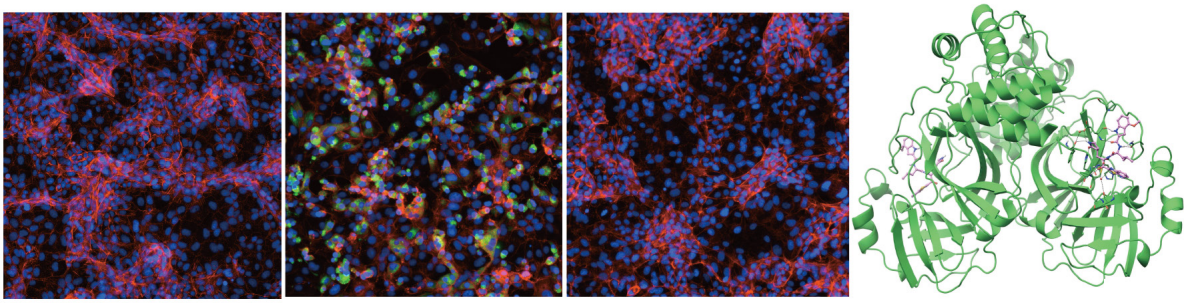
LETTER

CORRIGENDUM

COVER FIGURE OF THIS ISSUE



GRL-2420/5h Completely Blocks the Infectivity and Cytopathic Effect of SARS-CoV-2. When VeroE6 cells that are susceptible to the infectivity and cytopathic effect of SARS-CoV-2 are cultured alone, they stain in red (showing healthy actin filaments of normal cells) and in blue (showing the nuclei of the cells)(leftmost panel). When VeroE6 cells are exposed to SARS-CoV-2, the actin filaments are destroyed and additionally stain in green (showing the presence of viral components)(second panel from left). However, when VeroE6 cells are exposed to SARS-CoV-2 and cultured in the presence of GRL-2420/5h (10-100 μM), the cells are completely protected by GRL-2420/5h from SARS-CoV-2 infection and the cells do not stain in green (third panel from left). The staining method is called immunocytochemistry. The rightmost panel shows the X-ray structure of the main protease (a viral enzyme essential for SARS-CoV-2 replication), in complex with GRL-2420/5h (Hattori S, Higashi-Kuwata N, and Mitsuya H. *Nature Communications 2021*)

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EDITORIAL
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Fight against COVID-19 but avoid disruption of services for other communicable diseases (CDs) and noncommunicable diseases (NCDs)

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Abstract: COVID-19 has been a global and grave public health threat. The number of deaths from COVID-19 has already surpassed by far that of fatalities from the top three communicable diseases (CDs): human immunodeficiency virus type 1 (HIV) infection, tuberculosis, and malaria. The toll from COVID-19 is also inevitably surpassing hepatitis toll by the beginning of 2021. Moreover, it should be noted that COVID-19 has seriously impacted health services for noncommunicable diseases (NCDs), such as diabetes, hypertension, cancers, and cardiovascular diseases. The most common reasons for the disruption of health services are cancellations of scheduled treatments, a paucity in public transport and a lack of staff due to reassignment of a number of health professionals to COVID-19 works. It's an utmost import that scientifically and practically innovative and rational ways and actions are taken, so that deaths due to the simple lack of essential services for various CDs and NCDs are prevented.

***Keywords*:** SARS-CoV-2, COVID-19, communicable diseases (CDs), noncommunicable diseases (NCDs)

The continuing spread of the infection of SARS-CoV-2, which most likely originated in Wuhan or elsewhere in China and causes severe, acute, and often fatal disease (COVID-19), has been a global and grave public health threat. While the World Health Organization (WHO) reports that around 82% of infected individuals present mild symptoms and require little or no treatment and current estimates put the fatality rate of COVID-19 around 2.5% in all inflicted cases, much lower than in SARS, which had a global fatality rate of around 10%. However, such a huge number of people have been infected with highly contagious SARS-CoV-2 and the number of confirmed infected cases has risen to more than 76 million, and consequently, the number of deaths is to reach 1.7 million by the end of December, 2020. The number of deaths from COVID-19 has already surpassed by far that of fatalities from the top three communicable diseases (CDs): human immunodeficiency virus type 1 (HIV) infection, tuberculosis, and malaria (*1,2*) (Figure 1). The toll of hepatitis still continues to rise; however, the toll from COVID-19 is inevitably surpassing hepatitis toll by the beginning of 2021 (*1-4*) (Figure 1). These numbers reveal how grim the emergence of a new hard-to-treat and highly contagious infectious pathogen can be to mankind.

The nature of SARS-CoV-2 and what it causes in human body were virtually unknown and there were no effective vaccines or treatments for the disease at the beginning of the pandemic, which accounts for the high mortality in various cities, regions, and nations early in the pandemic. However, one can say that our learning curve on the virus and its malicious nature has been very steep and with quick accumulation of our knowledge, we have implemented the ways how to avoid infection including setting physical distancing and wearing masks and personal protective equipment. We have also quickly found that a few previously known drugs such as remdesivir and dexamethasone may mitigate the severity of COVID-19. Administration of reportedly effective vaccines has also begun at the time of this writing.

COVID-19 has gravely impacted economics and financial worldwide, but the initial financial stimuli have been effective and appears to have avoided an otherwise greatly catastrophic economic consequences in many regions and nations. However, it should be noted that COVID-19 has also seriously impacted health services for noncommunicable diseases (NCDs). A survey released by WHO in May 2020, in which 155 countries participated, reported the situations of people living with NCDs such as diabetes, hypertension, cancers, and cardiovascular diseases during the beginning of the COVID-19 calamity (*5*). The survey revealed that the impact of COVID-19 has been of a wide spectrum, but also low-income regions and nations have been at much greater risk of severe COVID-19-related sicknesses and deaths. Another main finding of the survey was that essential health services had been greatly disrupted in many countries (Figure 2). Fifty-three percent of

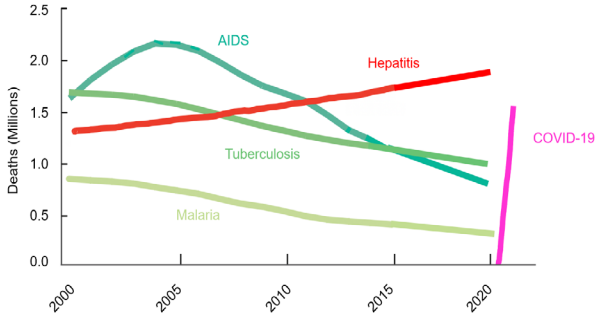

Figure 1. The number of deaths from COVID-19 surpassed by far that of fatalities from the top three communicable diseases (CDs): HIV/AIDS, tuberculosis, and malaria. The death tolls due to HIV/AIDS, tuberculosis, and malaria have been in decline over many years (Data are from WHO: Global health sector strategy on viral hepatitis 2016-2021. Global Burden of Disease and WHO/UNAIDS estimates: *https://ihmeuw.org/3pms*, *http://ihmeuw.org/3pmt*). The number of deaths due to all the viral hepatitis are in rise (*https://ihmeuw.org/3pms*, *http://ihmeuw.org/3pmt*); however, the COVID-19 toll is in a sharp rise and will surpass the hepatitis toll very soon, showing how grim the emergence of SARS-CoV-2 is to mankind (*https://www.who.int/emergencies/diseases/novel-coronavirus-2019*; *https://www.worldlifeexpectancy.com/world-rankings-total-deaths*).

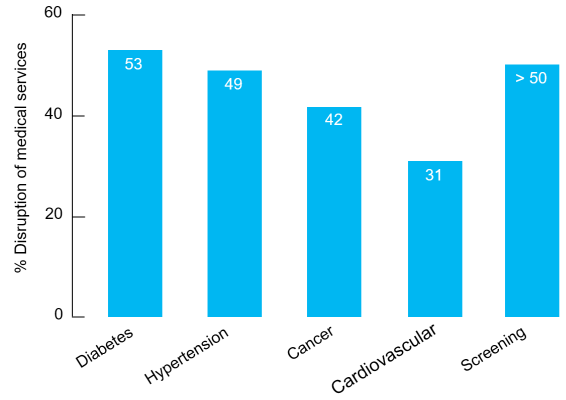

Figure 2. A WHO survey reveals that COVID-19 has greatly disrupted health services for NCDs. A survey by WHO (May 2020), in which 155 countries participated, shows that the COVID-19 pandemic has badly disrupted health services for various NCDs such as diabetes, hypertension, cancers, and cardiovascular diseases. Various screening programs (*e.g.*, for breast and cervical cancers) have also been suspended or postponed in > 50% of the nations (Data are from *https://reliefweb.int/report/world/covid-19-significantly-impacts-health-services-noncommunicable-diseases*).

the nations surveyed reported partial or complete disruption of services for diabetes and diabetes-related complications; 49% for treatment of hypertension; 42% for cancer treatment, and 31% for the response to cardiovascular emergencies. Various screening programs (*e.g.*, for breast and cervical cancers) had also been suspended or postponed in more than 50% of the nations (Figure 2). One of the major reasons for the disruption of such services was a shortage of therapeutics, diagnostics and medical technologies, but the most common reasons for the disruption of services were cancellations of scheduled treatments, a paucity in public transport

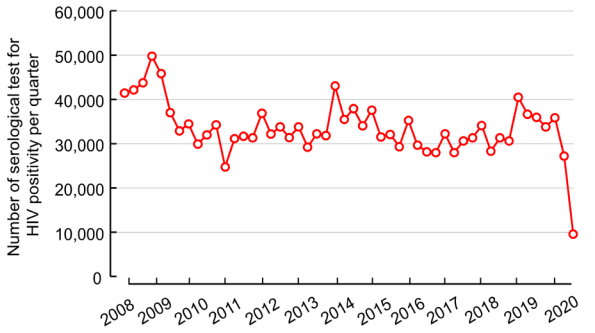

Figure 3. Sudden decrease in the number of serological HIV/AIDS testing in Japan in 2020. The number of serological HIV/AIDS testing had been plateaued counting 30,000 to 40,000 quarterly over the past 12 years; however, that number plunged into only 10,000 in the second quarter of 2020. (Data are from *https://api-net.jfap.or.jp/status/japan/index.html*)

and a lack of staff due to reassignment of a number of health professionals to COVID-19 works. Indeed, the survey indicated that in 94% nations, ministry of health professionals working in the area of NCDs had been partially or fully reassigned to the support of services for COVID-19.

In Japan, we have seen a steep drop (~70%) in the number of voluntary screening test for HIV positivity in 2020 (*6*) (Figure 3). Shin-ichi Oka, Director of AIDS Clinical Center at National Center for Global Health and Medicine, fears that there would be a significant rise in the number of previously healthy people, who did not know their HIV positivity and present frank AIDS, in the upcoming years. Tadao Kakizoe, President of Japan Cancer Society that promotes cancer prevention, guides approximately 11 million cancer screenings, and helps successfully identify as many as 13,000 cancers nationwide every year, warns that the steep decrease by ~30% in the number of cancer screening that began early March 2020 with the following plummet down to virtually zero would result in a failure to find cancers in ~4,000 individuals.

It's an utmost import that scientifically and practically innovative and rational ways and actions are taken, by which deaths due to the simple lack of essential services for various CDs and NCDs are prevented. It is likely that our fight against COVID-19 continues much longer than thought in early 2020. It is hoped that the vaccination, which began toward the end of 2020, would work and effective drugs are developed with our knowledge and skills accumulated through our past and on-going dogfights with other viral infections including HIV, hepatitis B virus, hepatitis C virus, and influenza.

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EDITORIAL

A SARS-CoV-2 antiviral therapy score card

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Abstract: The COVID-19 pandemic has unleashed an unprecedented effort to identify efficacious treatments for persons infected with SARS-CoV-2. As of September 2020, more than 750 completed, ongoing, or planned clinical trials of drugs intended to inhibit SARS-CoV-2 replication have been registered on the ClinicalTrials.gov or WHO International Clinical Trials Platform websites. Most of the treatments studied in these trials are repurposed licensed or investigational drugs targeting viral proteins or cellular pathways required for virus replication. The use of repurposed compounds is understandable because with the exception of monoclonal antibodies, it will be several months before novel SARS-CoV-2-specific drugs will be available for human testing. This editorial describes those compounds that I believe should be prioritized for clinical testing: *i*) viral RNA polymerase inhibitors including GS-441524, its prodrug remdesivir, and EIDD-2801; *ii*) entry inhibitors including monoclonal antibodies, ACE2 molecular decoys, and peptide fusion inhibitors; *iii*) parenteral and inhalational preparations of interferon β and λ; and *iv*) inhibitors of host transmembrane protease serine 2 (TMPRSS2), endosomal trafficking, and pyrimidine synthesis. As SARS-CoV-2 is pandemic and as its most severe consequences result from a dysregulated immunological response to infection, the ideal therapies should be inexpensive and should be able to be administered to non-hospitalized persons at the time of their initial diagnosis.

***Keywords*:** COVID-19, SARS-CoV-2, antiviral therapy

Although a SARS-CoV-2 vaccine will have the greatest impact on ending the COVID-19 pandemic, antiviral drugs are required to treat unvaccinated persons and vaccinated persons who do not develop protective immunity. Antiviral drugs for SARS-CoV-2 may also potentially be effective at treating severe endemic human coronavirus infections, MERS-CoV, and future pandemic coronaviruses. To prioritize licensed drugs and investigational compounds for COVID-19 clinical trials, it is necessary to compare their preclinical data and human pharmacokinetics. Compounds with little or no *in vitro* inhibitory activity will not be clinically efficacious while those with *in vitro* inhibitory activity may be clinically efficacious if their *in vitro* inhibition reflects physiologic conditions, sufficient inhibitory levels can be attained *in vivo*, and they are safe in humans. Regrettably, most clinical trials are studying drugs with minimal inhibitory *in vitro* activity or with a level of inhibitor activity unlikely to be attained with standard dosing. These include the chloroquine analogs, azithromycin, the HIV-1 protease inhibitors ritonavir-boosted lopinavir and darunavir, the anti-influenza drugs favipiravir, oseltamivir, and umifenovir, the antiparasitic drugs ivermectin and nitazoxanide, and the hepatitis C virus inhibitor sofosbuvir. Although there are more than 100 clinical trials of convalescent plasma, few are randomized and/or sufficiently powered to yield meaningful quantitative results particularly as the levels of neutralizing antibodies in convalescent plasma are heterogeneous.

We have created a database to facilitate comparisons between candidate anti-SARS-CoV-2 compounds to help clinical investigators, public health officials, and funding agencies prioritize the most promising candidate drugs and investigational compounds for further development (*https://covdb.stanford.edu*) (*1*). The database classifies compounds according to four broad mechanisms of action: *i*) virus enzyme inhibitors; *ii*) virus entry inhibitors, *iii*) interferons, and *iv*) compounds targeting host processes. In this editorial, I describe promising compounds for the treatment of SARS-CoV-2 according to three main criteria: *i*) they act by a validated direct or indirect antiviral mechanism; *ii*) they display sub-micromolar inhibitor activity *in vitro*; and *iii*) they are likely to be safe and to have favorable pharmacokinetics in human subjects. Most of these compounds are being studied in clinical trials, although the numbers of trials for these compounds are far fewer than those for the less promising compounds described in the previous paragraph.

Viral polymerase inhibitors

Remdesivir is a delayed chain terminator phosphoramidate prodrug of a 1'-cyano-substituted adenine C-nucleoside analogue (GS-441524) with high nanomolar SARS-CoV-2 inhibitory activity *in vitro* (*2*). It reduces viral replication and lung pathology in mice and rhesus macaques when administered shortly after infection (*2,3*). In placebo-controlled randomized clinical trial, its intravenous administration led to a significant reduction in time to recovery from 15 to 11 days ($p < 0.001$) and a non-statistically significant reduction in day 14 mortality of 11.9% *vs*. 7.1% ($p = 0.06$) (*4*). Ongoing trials are examining its safety and efficacy when administered subcutaneously or *via* inhalation. It has been suggested, however, that the parent compound GS-441524 may actually have multiple advantages over remdesivir including the ability to be administered orally, more favorable pharmacokinetics, and a less complicated synthesis (*5*). EIDD-2801 is a nucleoside analog viral mutagen, which like remdesivir has high nanomolar SARS-CoV-2 inhibitory activity (*6*). It reduces SARS-CoV and MERS-CoV replication and lung pathology in a mouse model and is currently being evaluated in two Phase II clinical trials.

Entry inhibitors (monoclonal antibodies [mAbs])

More than thirty research groups have identified mAbs that neutralize virus infection by binding to the SARS-CoV-2 spike protein. These studies characterize neutralizing mAbs according to one or more of the following properties: *i*) the mAb concentrations required for virus neutralization; *ii*) the mAb sequence; *iii*) the 3-dimensional structure of the mAb bound to SARS-CoV-2 spike; and *iv*) the level of protection in animal model challenge studies. One pair of mAbs identified in these studies, REGN10933 and REGN10987 possess sub-nanomolar inhibitor activity and bind to non-overlapping ACE2-competing SARS-CoV-2 receptor binding domain epitopes (*7,8*). The combination also reduces virus replication and lung pathology in Syrian hamsters and rhesus macaques (*9*). The combination of REGN10933 plus REGN10987 and another mAb LY3819253 are in Phase III trials for the prevention and treatment of SARS-CoV-2 infection. Seven other mAbs are in Phase I trials including AZD7442, BRII-196, CT-P59, JS016, SCTA01, STI-1499, and TY027. However, as of early September 2020, there are no publications describing LY3819253 or any of these other mAbs.

Interferons

Interferon-α, interferon-β, and interferon-λ each inhibit SARS-CoV-2 by 90-99% at the relatively low concentrations of approximately 100 international units/mL (*10-13*). Inhalational interferon-α and parenteral interferon-β have been associated with modest reductions in disease severity and/or virus levels in two small open-label randomized clinical trials (*13,14*). An inhaled formulation of interferon-β has been reported in the news to reduce the odds of developing severe disease or death in a blinded randomized control trial of 220 patients, but the study has not yet been published (SNG016; *https://www.isrctn.com/ISRCTN14241621*). There are currently four planned or ongoing Phase II or III placebo-controlled trials of parenteral or inhaled interferon-β and four planned or ongoing Phase II placebo-controlled trials of parenteral interferon-λ.

Host-acting compounds

Camostat and nafamostat are serine protease inhibitors that inhibit human transmembrane protease 2 (TMPRSS2) which appears to be required to cleave the SARS-CoV-2 spike protein thus priming it for host cell fusion (*15-18*). Both drugs are used in Japan for the treatment of pancreatitis while nafamostat is also used as an anticoagulant and for the treatment of disseminated intravascular coagulation. Although nafamostat has > 10-fold greater TMPRSS2 enzymatic and SARS-CoV-2 antiviral inhibitory activity than camostat, it is thought to be associated with greater toxicity. Camostat is being studied in two blinded and two open label randomized controlled trials totaling about 900 patients. Nafamostat is being studied in three small randomized open label trials totaling about 200 patients.

Apilimod has been found in several drug screens to inhibit SARS-CoV-2 with high selectivity at concentrations below 100 nm (*19,20*). It inhibits PIKfyve, an enzyme involved in the formation of a membrane protein required for the endosomal trafficking of SARS-CoV-2 and other viruses (*21,22*). It has been studied in humans in several clinical trials and been found to be safe and well tolerated. A theoretical concern with the use of apilimod for treating viral infections, however, is that it may interfere with T cell antigen presentation (*23*). Apilimod is being studied for the treatment of mild SARS-CoV-2 infections in one randomized placebo-controlled Phase II trial.

PTC299 is an inhibitor of dihydroorotate dehydrogenase (DHODH), a rate limiting enzyme in the pyrimidine biosynthesis pathway (*24*). DHODH inhibitors are therapeutic targets for autoimmune diseases and viral infections (*25,26*). PTC299 has been found to be safe and have favorable pharmacokinetics in more than 300 human subjects. In one study, it demonstrated low nanomolar SARS-CoV-2 inhibitory activity and a high selectivity index (*27*). As both viral replication and cytokine overproduction depend on pyrimidine synthesis, DHODH inhibition may have a dual role in COVID-19 treatment. DHODH inhibitors are expected to be synergistic with viral polymerase inhibitors as both interfere with viral genomic copying

and transcription (*26*). There is one Phase II/III trial of PTC299 for patients with severe COVID-19. Three other DHODH inhibitors have been studied *in vitro* and/or are in COVID-19 clinical trials including leflunomide, brequinar, and IMU-838.

Other compounds

Soluble recombinant human ACE2 has been studied as a treatment for acute respiratory distress syndrome (ARDS) in humans; it has also been reported to protect mice from developing SARS-CoV-1-associated ARDS (*28,29*). It inhibits SARS-CoV-2 spike binding at nanomolar concentrations in several cell lines (*30,31*). There are two ongoing Phase II trials of an intravenous commercial rhACE2 preparation. Recombinant ACE2-IgG is also highly active *in vitro* but has not yet been studied in humans (*31*). Likewise, two highly potent lipopeptide fusion inhibitors have been described – HR2P-EK1C4 (*32*) and IPB03 (*33*) – but are not yet being studied clinically.

Ciclesonide is an inhaled corticosteroid that may interfere with membrane trafficking by binding directly to nsp-3 or nsp-4 or indirectly through a host protein. It is one of the few compounds reported to exert evolutionary pressure on SARS-CoV-2 in that it selects for SARS-CoV-2 mutations during *in vitro* passage (*34*). Although it inhibits SARS-CoV-2 at low micromolar levels, higher inhibitory levels may be attained clinically through the inhalational route. Niclosamide, a licensed anti-parasitic drug with sub-micromolar activity but poor oral bioavailability, is being studied in a Phase I trial in which it will be administered intramuscularly (*35*).

Conclusions

The current paradigm of drug development involves competing research laboratories and companies engaged in compound screening, drug optimization, preclinical studies, pharmacokinetics, and clinical trials. The process is vertically but not horizontally integrated. It is opaque to most stakeholders because it is often difficult to obtain the necessary data to compare different treatment approaches during their development. In this editorial, I've outlined those drugs and compounds that I believe should currently be prioritized pending the development of more targeted SARS-2-specific antivirals. The ability to horizontally integrate the development of new therapeutics is required to expedite their development during a pandemic.

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COVID-19 handling report for pre-case, case (pre-hospital and hospital), and post-case phases in the elderly as vulnerable populations in 6 Asia Pacific countries

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Abstract: In this current COVID-19 pandemic, the elderly (60 years and over) are more vulnerable populations to be infected and become victims. In a disaster cycle, the various parts are usually divided into three stages, consisting of the pre-impact stage, the trans-impact stage, and the post-impact stage. It is necessary to explain how to handle the COVID-19 disaster for the elderly at each step (explain the meaning of pre-case, case (pre-hospital and hospital), and post-case phases, respectively). This paper presents the handling of COVID-19 for elderly in pre-case, case, and post-case phases in six Asia-Pacific countries (Indonesia, Thailand, Singapore, Malaysia, Vietnam, and Japan). The data and information come from COVID-19 official websites of each country, including information from World Health Organization (WHO), United States Centers for Disease Control and Prevention (CDC), mass media, and professional associations. The handling of COVID-19 in the pre-case phase has been done correctly for the elderly, especially in Indonesia, Japan, Thailand, and Singapore. In the case phase (pre-hospital and hospital), only Indonesia, Japan, and Thailand have followed special handling protocols for the elderly, particularly for those who have comorbidities and respiratory diseases. For the post-case phase, all countries have the same treatment protocol for all age groups, with none specific for the elderly.

***Keywords*:** COVID-19, elderly, Asia Pacific, handling, risk

Introduction

COVID-19 is a disease caused by the SARS-CoV-2, with the first case appearing in Wuhan City, China, in December 2019. On Wednesday, 11 March 2020, the World Health Organization (WHO) declared COVID-19 a global pandemic after the virus spread rapidly all over the world. The initial statement about the pandemic was retrieved from the WHO website when COVID-19 had spread to 118 countries and had infected more than 121,564 people with at least 4,373 deaths in Asia, Europe, the Middle East, Africa, and America. As of 31 July 2020, there are over 17,064,064 cases in 215 countries, and 668,073 deaths have been reported from COVID-19 (*1*).

In Indonesia as of 8 August 2020, the fatality rate of COVID-19 in age group of 60 years and above is 18% and it is the highest and above all other age groups (*2*). In other Association of Southeast Asian Nations (ASEAN) countries such as Singapore, it is known as of 8 May 2020 that around 80% of deaths because of COVID-19 are above 60 years old (*3*).

In Malaysia, the incidence rate of COVID-19 is 13.4% for those aged above 60 as of 18 May 2020 (*4*). The fatalities that have been recorded so far show that 62.6% of the deaths are from those aged 60 years and above. Regarding comorbidity factors, it was found that 80.7% of the cases that ended in deaths had underlying chronic diseases, such as diabetes, high blood pressure, kidney disease, heart disease, *etc.* (*5*). In Thailand, data on incidence rates and fatality rates among the elderly is 43% (*6*). According to information provided by the Government Centre for COVID-19, although the elderly accounted for a small proportion of infections,

they comprised the highest number of fatalities (*7*). As of 5 August, 2020, there are 3,328 positive cases in Thailand, with 58 death (*1*).

The prevalence of COVID-19 cases in Japan is similar to that of Thailand. The Asahi Shimbun Digital analyzed the 22,230 infected cases, including 981 death cases up to 15 July 2020. It offered the following observation: 84% of deaths are from those over 70 years old, and 57% of total deaths are from those aged above 80 years. Furthermore, the mortality rate by age groups of the 50s, 60s, 70s, and over 80s is 1.0%, 4.7%, 14.2%, and 28.3% (*8*). Based on these data, we could conclude that the infection rate among senior citizens is not high; however, once infected, the likelihood of mortality in this age group is much higher.

Since the beginning of the COVID-19 pandemic, Vietnam had succeeded in dealing with the spread of the COVID-19. Because there is zero death case of COVID-19, and there are no new cases for 100 days since April 2020. But as of 31 July 2020, there was the first case of death, a man in 70 years old, and following the second death case in a man 63 years old. Per 10 August 2020, the positive of COVID-19 nearly 400 cases, and the number of death case is 10 cases which mostly the victim is an older adult (*9,10*).

Considering the above, it can be assumed that the elderly face higher risks of fatality compared to other age groups (*1-5,7,8*). The high rate of transmission of COVID-19 among the elderly is partly due to a decrease in the function of immune system because of aging and the possibility of the existence of other diseases as comorbidities. It makes the elderly more vulnerable to the COVID-19 pandemic (*9-13*). In a disaster cycle, the various parts are usually divided into three stages, consisting of the pre-impact stage, the trans-impact stage, and the post-impact stage. It is necessary to explain how to handle the COVID-19 disaster for the elderly at each step (explain the meaning of pre-case, case (pre-hospital and hospital), and post-case phases, respectively). Therefore, this paper presents the handling of COVID-19 for elderly in pre-case, case, and post-case phases in six Asia-Pacific countries (Indonesia, Thailand, Singapore, Malaysia, Vietnam, and Japan). An analysis of how each of these countries dealt with the elderly can serve as lessons learned by looking at the weaknesses and strengths of each country.

Literature review

This paper is a report on the handling of COVID-19 in the elderly populations in six Asia-Pacific countries. Considering that there has been so little research on the topic until now, the sources of literature and data for this paper mostly come from the COVID-19 official website of each country, including information from the WHO, CDC, mass media, and professional associations related to the elderly.

For Indonesia, the data and information were collected from the official website for COVID-19 (*covid19.go.id*) of the Ministry of Health, especially the website of the Directorate of Family Health that handles the elderly (*kesga.kemkes.go.id*), professional associations related to the elderly such as the Indonesian Medical Gerontology Association, and mass media.

Data and information for Singapore were collected from the official website for COVID-19 (*https://www.gov.sg/article/taking-care-of-our-seniors-amidst-covid-19*) and senior agency under the Minister of Health (*https://www.aic.sg*). For Thailand, the data and information were collected from the official website for COVID-19 (*https://ddc.moph.go.th*) and Thailand's national website for senior handling of COVID-19 in Thai language. Malaysian data and information were taken from the official website for COVID-19 (*http://covid-19.moh.gov.my*) and the website of the Ministry of Health. Data and information on Vietnam were taken from the national website for COVID-19 in the Vietnamese language. Data and information on Japan were taken from the official website for COVID-19 of the Ministry of Health, Labour, and Welfare (*https://www.mhlw.go.jp/index.html*), which were mostly in Japanese.

The handling of pre-case, case (pre-hospital and hospital), and post-case phases in the elderly in 6 Asia Pacific countries

In a disaster cycle, the various parts are usually divided into three stages, consisting of the pre-impact stage, the trans-impact stage, and the post-impact stage (*14*). Some describe it as the stage of disaster preparedness, the stage of emergency response, and the stage of disaster recovery. Similarly, it is necessary to explain how to handle the COVID-19 disaster for the elderly at each step as the pre-case phase, case phase which is further divided into pre-hospital and hospital stages, and the post-case phase, which is more about the handling of victims who recover or die.

The pre-case stage of the six Asia Pacific countries (Indonesia, Malaysia, Singapore, Thailand, Vietnam, and Japan), which became the scope of this study, found that all countries had provided promotive and preventive programs for COVID-19 for the elderly. The promotions and prevention programs were socialized using posters of guidelines or videos on how to prevent actions by the elderly's family members or caregivers if the elderly had symptoms such as those of COVID-19. Besides that, it was promoted how to conduct online health checks and routine medication taken by the elderly during this pandemic. All countries also have a hotline number for COVID-19. Promotive and preventive efforts are not only by the Ministry of Health or National COVID-19 team but also provided

by non-governmental organizations (NGOs) such as gerontology associations, elderly-friendly communities, and elderly specialized health care clinics.

Whereas in the case stage (pre-hospital and hospital), each country has its own specific set of procedures, but the treatment for all patients is not explicitly represented for the elderly. Only Indonesia, Japan, and Thailand provide particular protocols for the elderly with comorbidities and respiratory diseases, before being treated at the hospital. How treatment at the hospital proceeds has also been addressed by a specific protocol. Whereas in other countries, there is no information about pre-hospital and hospital-specific protocols for the elderly, because of limited published data, and absence of fatality cases due to COVID-19, such as in Vietnam.

The post case stage, is related to how to handle if elderly patients have recovered from COVID-19 or vice versa. The recovery protocol in all countries was the same after two consecutive polymerase chain reaction (PCR) tests had negative results, and the burial protocol for COVID-19 patients was the same in all countries, which continued to avoid direct contact with corpses. However, handling at this stage is not only specific to the elderly, but also applies to all patients. The guidelines and protocols developed for the elderly by each of the countries to deal with the three phases of the disease are represented in Table 1.

The elderly are a vulnerable population group due to a decrease in the body's ability, both physiologically and psychologically. Physiologically, there is a decline in the body's defence system among the elderly due to the ageing process. When a virus enters the body, the immune system should recognize the virus as a foreign object and work to destroy it. In old age, the production of white blood cells in the body is lower; so the ability to fight infections is also lower (*15*).

Previous study shows that if the immune response of older adults to SARS-1 is not successful, it is possible to have the same response to SARS-2 (*16,17*). Due to the ageing process, the ability and speed of the immune system in recognizing the pathogen are slower, less coordinated, and less efficient (*18*).

The immune system in the elderly also cannot distinguish between the infected virus cells and healthy cells. The immune system works uncontrollably so that it can attack even healthy cells; and it is called a cytokine storm (*19*). This condition can cause COVID-19 effects to become worse. In the elderly, antibodies do not work well. Even though the elderly generally produce the antibody to fight the virus, these antibodies do not work as well as they do among the young; and these antibodies are not able to stick to the virus and fight it. This also explains why diseases such as pneumonia or influenza often afflict the elderly and can pose fatal risks.

Psychologically, the elderly are more vulnerable to stress. The elderly undergo significant psychological changes due to the ageing process. This is triggered by decreasing functional capacity and separation from family members, such as children who prefer to stay away from parents often caused by death of one of the spouses. In addition, loneliness becomes a serious problem that triggers the emergence of depression in the elderly. As a result, the elderly are more vulnerable to stress and anxiety. In the atmosphere of the COVID-19 pandemic, many elderly experienced considerable mental stress due to isolation and social distancing (*20*). This condition is exacerbated by situations where the elderly cannot meet their children due to the implementation of social distancing and "lockdown" during the pandemic period.

Apart from having physiological and psychological impairments, the elderly comprise the age group with the highest COVID-19 fatalities due to underlying diseases or comorbidities. As people age, they experience an overall reduction in function due to degenerative processes that cause the emergence of various health problems, such as diabetes, hypertension, heart disease, stroke, and cancer. The data from 2018 notes that the elderly in Indonesia mostly have degenerative diseases and/or chronic health problems, such as diabetes and heart disease (*21*). Thus, the elderly are susceptible to serious complications if they contract the COVID-19. This is evidenced by the high prevalence of COVID-19 with serious complications and high mortality among the elderly (*22*). A study in China showed that people who suffer from one of these diseases will be at high risk for contracting COVID-19 and at risk of experiencing more severe complications (*23*). For example, the elderly with cancer have a weaker immune system, which is a side effect of chemotherapy and is commonly expressed as a form of immune system suppression. Similarly, patients with hypertension and heart disease will experience lung disorders caused by COVID-19, which will cause the heart to work harder to pump blood throughout the body. In the worst conditions, these complications can result in death.

An epidemic is a condition of increasing the number of diseases above normal expectations in a region (*24,25*), while a pandemic is an epidemic occurring throughout the world and in much larger numbers (*24-26*). Therefore, almost all countries that have positive cases of COVID-19 have declared the COVID-19 pandemic as a national disaster. Indonesia made the declaration on 13 April 2020 through the Presidential Decree (Keppres) of the Republic of Indonesia Number 12 of 2020. Japanese Prime Minister Shinzo Abe declared a national emergency in Japan due to soaring COVID-19 cases on 7 April 2020, especially for the cities of Tokyo and Osaka.

From the COVID-19 handling report for six Asia-Pacific countries, the handling of pre-cases has been done correctly for the elderly, especially in Indonesia,

Table 1. Handling report of COVID-19 for elderly patients in six Asia-Pacific countries

No.	Country	Pre-case	Case		Post-case (after discharge hospital)
			Pre-hospital	Hospital	
1	Indonesia (*27*)	The Ministry of Health requires the following: 1. Doing self-quarantine in the house. 2. Not allowed to meet family/relatives, especially those who are sick. 3. Not allowed to gather in the crowd. 4. Doing prayer from home. 5. Report to the nearest health facility if you experience COVID-19 symptoms. 6. Routine medical checkup in hospital replaced by online consultation. 7. Home delivery of drugs for the elderly who are on regular medication. 8. Carry out other provisions according to the protocol of the Ministry of Health.	1. Rapid tests and self-isolation for 14 days for the elderly with the status of people under control (ODP). 2. If the elderly with ODP status are comorbid (have other controlled disease), they will be isolated in COVID-19 Emergency Hospital. 3. Such people must go to COVID-19 Emergency Hospital using a private car/ facility from the nearest health services.	1. The elderly with ODP status who have positive rapid test results will be referred to the COVID-19 Referral Hospital for a swab test using the PCR method for repeated confirmations. 2. Elderly with the status of patient on monitoring (PDP) status are referred to COVID-19 Referral Hospital and swab tested. 3. If the result is positive for COVID-19, treatment will be carried out in the hospital. 4. If the result is negative, self-isolation for ODP will be carried out, but PDP will be isolated in the hospital for 14 days.	If the patient recovers: 1. After two consecutive negative swab tests. 2. The patient is discharged and follows self-isolation for 14 days at home. If the patient dies: 1. The body is wrapped in an airtight bag, and buried for a maximum of 4 hours. 2. Families who want to see are allowed to use complete personal protective equipment (PPE). 3. The medical team instructs the family regarding the rules and regulations that will need to be followed for the last rites.
In Indonesia, pre-case COVID-19 are categorised as follows (*27*): 1. ODP: There are fever (> 38°C) OR symptoms in upper respiratory tract infections; the patient has visited or lived in an area known to be a COVID-19 transmission area, and has had direct contact with a confirmed or probable COVID-19 case. 2. PDP: There are fever (> 38°C) AND symptoms in upper respiratory tract infections; the patient has visited or lived in an area known to be a COVID-19 transmission area, and has had direct contact with a confirmed or probable COVID-19 case.					
2	Japan (*28-30*)	1. The Japanese government declared a state of emergency for initially seven prefectures on 7 April 2020 and extended to all prefecture on 16 April 2020, asking residents to refrain from nonessential outings and some businesses to shut. 2. Initial target prefectures: Tokyo, Kanagawa, Saitama, Chiba, Osaka, Hyogo, Fukuoka. 3. Period: phased termination; until 14 May 2020 for most prefectures and finally until 25 May 2020 for remaining 5 prefectures, including Tokyo. 4. Travel restricted. 5. Schools closed. 6. Public facilities and mass-gathering events closed. 7. Observation of non pharmaceutical interventions: (a) Wearing a mask properly; (b) Cough manner; (c) Frequently washing your hands; (d) Physical Distancing. 8. Various guidelines and guidances for senior citizens, particularly those in long-term care facilities.	1. Anyone who had fever exceeding 37.5 degrees for more than four days with flu-like symptoms. 2. The temperature in the elderly exceeding 37.5 degrees for more than two days with a flu-like syndrome, and underlying comorbidities. 3. Anyone with severe fatigue and/or breathing difficulty. 4. They (Nos. 1, 2, & 3) should contact the Call Centre for assessment of PCR tests initially. The above indications were initially followed by public sectors but in view of accumulation of evidence such as asymptomatic cases, more liberal approach was gradually applied for high risk populations such as senior citizens.	1. All confirmed as the communicable disease control law hospitalizes PCR-positive cases. 2. If the empty beds are saturated, only symptomatic cases (cardiovascular, diabetic, cancer, pulmonary chronic, *etc.*) will be hospitalised. 3. Mild or asymptomatic cases were quarantined at home or designated residential facilities. 4. PCR-positive cases, presenting pneumonia, will be treated intensively: (a) Over 50 years of age with underlying health conditions; (b) Serious respiratory conditions regardless of age. 5. Treatment includes: (a) Respiratory assistance (including the use of ECMO); (b) Treatment with one of the four trial drugs. (with the consent of patients but some declined).	If the patient recovers: 1. When hospital beds are saturated, mild cases may be transferred to hired hotels. 2. Discharge after negative PCR test twice. If the patient death: 1. The body was cremated without family members. 2. This standard procedure was revised and softened.

Table 1. Handling report of COVID-19 for elderly patients in six Asia-Pacific countries (continued)

No.	Country	Pre-case	Case		Post-case (after discharge hospital)
			Pre-hospital	Hospital	
3	Vietnam (*31*)	1. Home self-quarantine instructions to prevent the spread of COVID-19 in the community (with video clip for illustrating). 2. Quarantine subjects (in hospitals or other quarantine places). 3. Persons without COVID-19 symptoms (cough, fever, difficulty breathing) and one of following criteria: (a) Staying in the same house, same area with confirmed case or exposed case (with symptoms of COVID-19); (b) Work with confirmed case or exposed case (with symptoms of COVID-19); (c) Travelling, going on business, entertaining group together with confirmed case or exposed case (with symptoms of COVID-19); (d) Close exposure within 2 metres to confirmed case or exposed case (with symptoms of COVID-19) in any condition; (e) Sitting in the same row or before or behind 2 lines at one car/train/airplane with confirmed case or exposed case; (f) Persons had visited China within 14 days from departure day in Vietnam.	F2: Person who exposed to F1 (a) Wearing face mask; (b) Inform to district health department where accommodating (to get instruction and COVID-19 laboratory test); (c) Ready with personal belongings, follow instruction from health department for quarantining (at the hospital or at home with laboratory test for COVID-19);. (d) Inform F3 persons about personal health conditions. F3: Persons who exposed to F2 (a) Wearing face mask; (b) Inform health department about current address (to get instruction or COVID-19 laboratory test); (c) Ready with personal belongings, follow instructions from health department for quarantining (at the hospital or at home); (d) Inform F4 persons about personal health conditions. F4: Persons exposed to F3 and F5: Persons exposed to F4 (a) Wearing face mask; (b) Self-quarantining at home; (c) Inform health department about current address (to obtain instructions); (d) Probable case or exposed case must update personal conditions of other Fs to health department for suitable treatment (or instructions) immediately; Even those with negative COVID-19 test required to remain in self-quarantine for 14 days.	F0: A confirmed case, person with positive laboratory test of SARS-CoV-2 with symptoms of respiratory diseases: (a) Cure by medical doctor; (b) Quarantine at the hospital; (c) Self-serving for reducing risk to other persons; (d) Inform F1 persons about personal health conditions. F1: Probable case or persons exposed to F0 (a) Wearing face mask; (b) Inform district health department about current address; (c) Ready with personal belongings (for quarantine and treatment at the hospital); (d) Inform F2 persons about personal health conditions.	F0 recovering after 2 consecutive negative COVID-19 test must remain in self-quarantine at home for 14 days.

Table 1. Handling report of COVID-19 for elderly patients in six Asia-Pacific countries (continued)

No.	Country	Pre-case	Case		Post-case (after discharge hospital)
			Pre-hospital	Hospital	
4	Malaysia (*32*)	There is a home sampling programme subject to conditions. The person must not be a patient under investigation (PUI) and should not have had a confirmed contact with an actual patient.	1. If someone experiences symptoms leading to the characteristics of PUI, immediately visit a screening center. 2. If someone is determined to be non-PUI, a screening test is conducted and the results are reported to the Regional Health Officer (PKD) and the person is put under house surveillance for 14 days. 3. If the sample test results are positive, the person is immediately determined as PUI and taken to the hospital. 4. If symptoms develop in test negative patients, they are immediately identified as PUI and taken to the hospital. 5. If after 14 days' home surveillance, there are no symptoms, the person is declared free from supervision, which is proven by a letter.	1. Elders with PUI status were immediately taken to the hospital. 2. If the patient's condition is stable, treatment and sampling are taken. If the sample results are negative, repeat samples are taken within 48 to 72 hours. If negative, patient can go home and remain for 14 days under home surveillance. 3. If the patient is unstable, the patient management procedure is confirmed.	1. If the patient shows recovery as evidenced by the results of the test, they may go home and remain under home surveillance for up to 14 days. 2. If the patient dies, burial is carried out according to protocol (Annex 20). If the patient dies, burial is carried out according to protocol (Annex 20).

Thailand, Japan, and Singapore, whereas the guidelines/ protocols issued by the governments in other countries (Malaysia and Vietnam) were the same as for the other age groups, with no special treatment for the elderly. In the case phase (pre-hospital and hospital), only Indonesia, Japan, and Thailand had particular handling protocols for the elderly, while for the post-case phase, all countries had the same treatment protocol for all age groups.

However, one of the most valuable lessons learned from Vietnam's handling of the pandemic is on how to arrange the tracing of contacts up to the fifth person who has had interactions with positive cases, so that the anticipation of transmission and spread of COVID-19 is reasonable and can be stopped immediately. Usually, tracing of COVID-19 only included other people who had interacted with the confirmed patient for the last 14 days. In a confirmed case, a person with a positive laboratory test of SARS-CoV-2 with symptoms of respiratory diseases (F0), they will find the persons (F1) that could be probable cases or persons exposed to F0. Also in Vietnam, tracing did not stop only at F1 but the tracing continues until the fifth person (F5). It defined that F2 is the person exposed to F1, F3 is the persons exposed to F2, F4 is the persons exposed to F3, and F5 is the persons exposed to F4.

Conclusion

Based on the research findings of this study, the elderly are highly susceptible to death from the COVID-19 pandemic. Therefore, special care is needed starting from the phase before being infected (pre-case), when there are symptoms of COVID-19, examination, and treatment, until returning home from the hospital (case), and after recovering from COVID-19 (post-case). Investigation of the six countries in the Asia-Pacific region, namely Indonesia, Malaysia, Singapore, Thailand, Vietnam, and Japan, revealed different protocols being followed in each of these. The pre-case phase that has been carried out by the six countries was already good. Many promotive and preventive activities for the elderly have been carried out. The guidelines and videos are not only for the elderly themselves but also for family members/caregivers who have a responsibility for them. For case stage (pre-hospital, hospital) not all countries have particular protocol handling COVID-19 specifically for the elderly. There should be a specific protocol starting when the elderly have symptoms of COVID-19 infection, continuing the examination, and how to treat. Then, the protocol should also be special treatment for the elderly with comorbidities and when elderly patients should be treated intensively in the ICU or given a ventilator. So, this is expected to reduce the fatality rate in elderly patients who are infected with COVID-19. The last stage is post case and that needs to have

Table 1. Handling report of COVID-19 for elderly patients in six Asia-Pacific countries (continued)

No.	Country	Pre-case	Case		Post-case (after discharge hospital)
			Pre-hospital	Hospital	
5	Thailand	General advice for elderly in Thailand for prevention of COVID-19 (*33*): 1. Wash hands correctly (picture and poster provided) with soap or alcohol gel or hand sanitiser before eating and after using toilet. 2. Avoid touching face especially eyes, mouth and nose. 3. If sharing food, use individual serving spoons. 4. Promoting health by regular exercise, sleep, rest, and stress reduction through suitable hobby. 5. If coughing or sneezing, use tissue paper to cover nose and mouth, then put it into a bag and close the bag before throwing it into a dustbin, and then wash hands. If there is no tissue paper or there is no time to use one, use arm (sleeve) to cover nose and mouth up to chin, then wash hands with soap or hand sanitiser. 6. Avoid staying close to people who have flu-like symptoms, such as fever, cough and sneeze, and a running nose. 7. Avoid going out of the house, especially in crowded areas. 8. If it is necessary to go out, people must cover nose and mouth with sanitary mask or facial mask. To stay out for the shortest period and keep distance with other people 1-2 metres (social distancing). 9. Avoid hugging, touching, or talking too close to other people. 10. Communicate with others using telephone and social media. 11. The elderly who have chronic diseases such as hypertension and diabetes should stock enough medicines to continue medication. To replenish stock, ask family members to help.	General advice for people who has Flu like symptoms (*34*): 1. Go to see the doctor or call COVID-19 hotline, the ambulance will pick up for an investigation. 2. Stay away from other people. 3. If fever develops, do not use ibuprofen, can use paracetamol. The guideline for patient care and investigation (*35,36*): 1. Separate suspect cases for investigation. 2. During interview, review medical record, physical examination such as chest X-ray and laboratory reports. 3. Collect specimen for SARS-CoV-2 for PCR. (a) Suspect cases with upper respiratoryinfection (URI), middle respiratory problem such as pneumonia, must do nasopharyngeal swab together with throat swab/oro- nasopharyngeal swab (b) If the result is negative and patient does not recover, repeat specimen collection for an investigation within 24 hours. (c) If necessary to admit patients for treatment in hospital for illnesses such as pneumonitis, they must be in a separate room (d) If mild or no symptoms, consider patients for home quarantine while waiting for laboratory results. (e) If patients can do home quarantine, hospital staff to provide information and instructions (f) If it is negative again, provide treatment for OPD (Obstructive Pulmonary Disease) for each symptom and advice patients to self-monitor for 14 days. (g) If the results are positive, admit patients for treatment and quarantine in hospital for every case.	Results positive (*36*): 1. Admit to IPD in single isolation room or cohort ward with only confirmed case by keeping distance between patients of at least 1 metre. 2. For patients in serious condition, consider performing aerosol generating procedure and put to AIIR 3. Provide anti-viral therapy. In case of patients with symptoms or results of film chest X-ray with lung spot and aged more than 60 years, it is a high-risk; together with patients with mild case, they will receive 3 medications for 5 days. Mild case: 1. Hydroxychloroquine or chloroquine; 2. Darunavir + ritonavir or lopinavir/ritonavir; 3. Azithromycin[#] If film chest X-ray worsens, consider adding favipiravir for 5-10 days (depends on clinical sign and symptoms).	In case of death (*37*): 1. Put in zip bag double layer, label with signal and coated with antiseptic outside bag. 2. Send to the post-mortem department as standard. 3. No ceremonials (watering in corpse hand/ bath ceremony) and not allowed to open the bag to see the body. 4. In confirmed cases of COVID-19, it is strictly prohibited to open the bag. In case of cure and discharge from the hospital: 1. Advise patients to wear face mask, practice health promotion and sanitation, and prevent spreading the disease for 30 days. 2. Discharge without repeating swab.

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Table 1. Handling report of COVID-19 for elderly patients in six Asia-Pacific countries (continued)

No.	Country	Pre-case	Case		Post-case (after discharge hospital)
			Pre-hospital	Hospital	
6	Singapore (*38,39*)	We should advise the seniors in our family: 1. Senior citizens should practice safe distancing. 2. They should do social distancing to avoid crowded places as far as possible. 3. Maintaining good personal hygiene: washing their hands frequently and avoiding touching their face, especially the eyes, nose, and mouth. 4. For those of us who are caregivers, or interacting with seniors in any capacity, we should also take extra care with our own personal hygiene. 5. If you are unwell, do avoid interacting with seniors, and only do so when you are better. 6. From 11 March 2020, the government suspended all senior-centric activities organised by government agencies for two weeks, until 24 March 2020; it was extended for another two weeks, until 7 April 2020.	If seniors feel unwell or have respiratory illnesses (*e.g.*, common cold), they can visit any of the Public Health Preparedness Clinics (PHPC). Patient low risk (self isolated at home for 14 days): (a) Age < 30; (b) No chronic comorbidities; (c) Reassuring clinical features (no dyspnoea, respiratory rate ≤ 20 breaths/min, normal SpO2%, not requiring oxygen therapy); (d) Normal chest X-ray; (e) Reassuring laboratory result (CRP ≤ 60 mg/L, LDH ≤ 330 U/L, Lymphocytes ≥ 1×10^9/L, Neutrophils ≤ 3×10^9/L).	The treatment is similar to other patients, there is no special treatment procedure for senior patients. Patient high risk (treatment in hospital): (a) Age > 30, particularly > 50; (b) Chronic comorbidities (chronic lung, heart, or kidney disease, A1c > 7.2%, immunosuppression); (c) Concerning clinical features (dyspnoea, respiratory rate > 20 breaths/min, abnormal SpO2% (< 95%), requiring oxygen therapy), (d) Chest X-ray with pneumonia; (e) Concerning laboratory result (CRP ≥ 60 mg/L, LDH > 330 U/L, Lymphocytes < 1×10^9/L, Neutrophils > 3×10^9/L. Others: rising ferritin level, D-dimer > 1 ug/ml, elevated troponin). Patient severe (treatment in ICU): (a) Dyspnoea; (b) RR > 30 breaths/min; (c) P/F ratio < 300; (d) 50% of lung fields within 24-48 hours; (e) Currently receiving of mechanical, invasive, or non-invasive ventilation; (f) Receiving intravenous vasoactive medications to maintain mean arterial pressure > 65 mmHg and myocarditis/myocardial dysfunction secondary to SARS-CoV-2.	1. The bodies of those infected with COVID-19 will be prepared for cremation or burial by healthcare workers in hospitals as part of a set guidelines issued by the National Environment Agency (NEA). 2. The protocols include double-bagging the bodies before they are placed in airtight coffins. 3. The collecting, casketing, and transporting bodies for cremation or burial will be restricted to companies whose employees have undergone the basic infection control course by the National Centre for Infectious Diseases.

[#]Azithromycin is an antibiotic that fights bacteria. AIIR, Airborne Infection Isolation Rooms; IPD, In Patient Department (Hospital Inpatient Care); PKD, Pejabat Kesihatan Daerah (Regional Health Officer in Malay Language).

special handling of the elderly after being declared cured, to prevent recurring infection. Elderly who have experienced a decrease in the immune system, even though they have recovered from COVID-19, have insufficient immunity and could be infected again.

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Pancreas transplantation for type 1 diabetes in Japan: past, present and future prospects

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Abstract: In Japan, the first pancreas transplantation was performed in 1984 from a brain-dead donor; subsequently, however, the concept of brain death became a social issue. Thereafter, the "Organ Transplant Act", which enables brain-dead transplantation, was enacted in 1997, and then revised in 2010 so that donation after brain death became possible only with the consent of the family. Under the recipient selection and registration system developed after the enactment of the "Organ Transplant Act", more than 400 pancreas transplants have been carried out at facilities certified for brain-dead pancreas transplantation in Japan. Of the 410 total cadaveric pancreas transplants performed by the end of 2019, the patient survival and pancreatic and kidney graft survival rates were considered to be comparable to those in the United States and Europe despite the high frequency of marginal donors. Minimally invasive allogenic islet transplantation came to be covered by national health insurance in 2020 following good outcomes of a recent trial. Furthermore, to overcome the serious donor shortage in Japan, development of xenogeneic islet transplantation and regenerative medicine using stem cells is in progress, with xenotransplantation using porcine islets appearing particularly promising.

***Keywords*:** pancreas transplantation, simultaneous pancreas and kidney transplantation (SPK), pancreas after kidney transplantation (PAK), pancreas transplantation alone (PTA), islet transplantation, xenotransplantation

Introduction

Insulin-depleted patients with type 1 diabetes (T1D), even those receiving intensive insulin therapy, such as multiple daily injections (MDI) and insulin pump (continuous subcutaneous insulin infusion [CSII]), suffer from severe glycemic lability, which frequently causes life-threatening severe hypoglycemia and diabetic ketoacidosis. In addition, these conditions often force patients to undergo emergency transport or hospitalization, resulting in poor quality of life (QOL). Furthermore, complications of diabetes also progress, and renal failure often leads to dialysis treatment. Such patients are candidates for transplantation medicine, and pancreas transplantation or pancreatic islet transplantation is thus considered.

Pancreas transplantation is divided into the following three categories: simultaneous pancreas and kidney transplantation (SPK), pancreas transplantation after kidney transplantation (PAK), and pancreas transplantation alone (PTA). Among these categories, SPK not only improves the QOL due to blood glucose stabilization and insulin withdrawal, but also substantially improves the life prognosis; consequently, more than 80% of Japanese pancreas transplants have been performed as SPK. Allogenic islet transplantation, which is minimally invasive, recently came to be covered by the national health insurance system in Japan based on positive results of a clinical trial.

We herein review the history, current status, and challenges of pancreas transplantation, as well as discuss future prospects concerning diabetes transplantation medicine in Japan.

Brief history of pancreas transplantation in Japan

Since the first pancreas transplant was performed at the University of Minnesota in 1966, more than 50,000 pancreas transplantations have been performed worldwide so far (*1*). In Japan, although the first pancreas transplant was performed in 1984 from a brain-dead donor, the concept of brain death subsequently

became a social issue, and thereafter 14 cases of pancreas transplants were performed using circulatory-death donors. With the introduction of the "Organ Transplant Act", which enables brain-dead transplantation, in October 1997, the Central Coordination Committee of Pancreas Transplantation and the sub-committees were organized in Japan. These organizations comprised three Japanese medical associations: the Japanese societies for Diabetology (the Japan Diabetes Society), Nephrology (the Japanese Society of Nephrology) and Transplantation (the Japan Society for Transplantation and the Japan Society for Pancreas and Islet Transplantation).

These committees operate under the following two policies: participation in an Expert Medical Board of two diabetologists and two nephrologists, set up in the seven local regions of Japan, whose mission was to evaluate pancreas transplantation candidates; and participation in an Expert Surgeon Board, composed of experienced transplantation surgeons, an expert on immunosuppressive therapy, a diabetologist and a nephrologist.

In 2010, to increase the number of brain-dead donors, the "Revised Organ Transplant Act" was enacted, wherein donation after brain death is possible with only consent of the family. Subsequently, a roughly 5-fold increase in the number of brain-dead donors was noted and around 30-40 cases of pancreas transplantation were performed annually (*2*). By the end of 2019, more than 400 pancreas transplants have been carried out at facilities certified for brain-dead pancreas transplantation (currently 18 facilities) since introduction of the "Organ Transplant Act".

Indication and registration system in Japan

Considering the risk of long-term immunosuppression-related adverse events, surgical risk and donor shortage, it has been reported that the traditional indications of pancreas transplantation include T1D patients with end-stage renal failure or nonuremic patients with glycemic lability experiencing problematic hypoglycemia such as severe hypoglycemia (SH) and impaired awareness of hypoglycemia (IAH), despite optimal diabetes management. Correspondingly, in Japan, T1D with renal failure (estimated glomerular filtration rate [eGFR] < 30 ml/min/1.73m^2) is an indication for SPK or PAK; the former has been offered mostly to patients on dialysis therapy and the latter to those who already underwent kidney transplantation and were taking immunosuppressive therapy. In contrast, T1D with severe glycemic lability despite optimal treatment by a diabetologist certified by the Japan Diabetes Society is an indication for PTA. Glycemic lability is evaluated by continuous glucose monitoring (CGM) data as well as self-monitoring of blood glucose values and the incidence of problematic hypoglycemia. Furthermore, in Japan, mainly because of extreme donor shortage, type 2 diabetes (T2D) is never considered an indication for transplant, and patients must be in an insulin-depleted status, defined by a serum C-peptide level ≤ 0.3 ng/mL while fasting and ≤ 0.5 ng/mL when glucagon (or meal)-stimulated (when renal failure is present, ≤ 0.3 ng/mL change in stimulated C-peptide levels from fasting) based on the data of fulminant T1D patients (FT1D). FT1D, originally identified in Japan, is an independent T1D subtype showing a markedly rapid onset of hyperglycemia with ketoacidosis and absence of insulin secretion capacity, even at disease onset (*3*). In practice, however, patients who meet these criteria may be excluded if they have a history of malignant disease, progressive proliferative retinopathy, or a condition that may be aggravated by surgery; of note, while there is no contraindication regarding age, ≤ 60 years old is desirable.

After examination by the Expert Medical Board set up in seven local regions of Japan, all recipient candidates are registered with the Japan Organ Transplant Network (JOTN), and recipient selection is performed based on the following conditions: blood type must be compatible, and the direct crossmatch test must be negative. Recipients on the waiting list are prioritized for selection as follows: *i*) the order of the recipients is arranged based on the number of human leukocyte antigen (HLA) mismatches, with priority given to cases involving fewer HLA mismatches; *ii*) cases are then prioritized in the order of SPK, PAK, and PTA; *iii*) priority is then given according to the length of the waiting period duration; and *iv*) cases are then prioritized in ascending order according to the estimated transport time, with priority given to cases with a shorter estimated transport time (*4*).

Results of pancreas transplantation in Japan

Numbers of pancreas transplantation

The Japan Society for Pancreas and Islet Transplantation has been registering all pancreas transplant cases in Japan since 2006 with the aim of improving pancreas transplant results in Japan. Of the 437 patients who underwent pancreas transplantation by the end of December 2019 since the first case in April 2000 after the introduction of the "Organ Transplant Act", the 410 cadaveric pancreas transplants (407 under brain-death and 3 under circulatory-death) included 344 SPK (83.9%), 48 PAK (11.7%) and 18 PTA cases (4.4%). The remaining 27 cases were living pancreas transplants, which have not been performed since 2014 (Figure 1). The donors' and recipients' background characteristics, immunosuppressive regimen, and outcomes of the above 410 cases of cadaveric pancreas transplantation (*2*) are described as follows.

Donors' background characteristics

The male to female ratio was 234:176, and the median body mass index (BMI) was 21.8 kg/m^2. The median donor age was 43 years old. Figure 2A shows the distribution of the donor age: the majority were in their 40s (27.8%), followed by 50s (22.0%) and 30s (18.3%), and donors ≥ 40 years old accounted for 56.3%. Among the 410 cases, 208 (50.7%) had brain death caused by cerebrovascular accidents, and 190 (46.3%) had episodes of cardiopulmonary arrest during the course. A total of 201 cases (49.0%) were hemodynamically unstable at the time of procurement. The median HbA1c of donors was 5.4%. The total cardiac arrest time was 36 min (range: 2-282). As a result, 291 donors (71.0%) exceeded the Pittsburgh's marginal donor criteria defined as they were *i*) > 45 years of age; *ii*) hemodynamically unstable requiring high dose dopamine (> 10 mg/kg/min) or more than 2 vasopressors; or *iii*) non-heart-beating donors (*5*).

Recipients' background characteristics

The male to female ratio was 161:249, and the median BMI was 20.9 kg/m^2. The median recipient age at transplantation was 44 years old (range: 24-69). Figure 2B shows distribution of recipient age: the majority were in their 40s (46.3%), followed by 30s (26.3%) and 50s (22.0%), and 16 recipients were in their 60s (3.9%). The median pre-operative duration of diabetes was 28 years (range: 2-53), and the median pre-operative dialysis period in SPK patients was 7 years (range: 0-29). The median waiting period was 1,395 days (range: 6-5,740). The median HbA1c level at transplantation was 7.6% (range: 4.8-15.2).

Immunosuppressive regimen

In Japan, tacrolimus (TAC)-based immunosuppression,

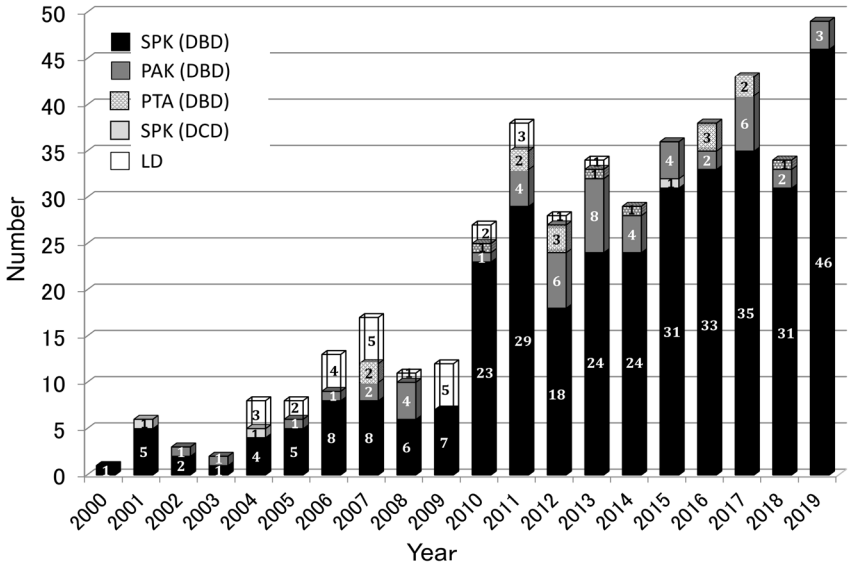

Figure 1. The number of pancreas transplant cases from April 2000 to December 2019 in Japan (*n* = 437) (*2*). DBD, donation after brain-death; DCD, donation after circulatory-death; LD, living donation; PAK, pancreas transplantation after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

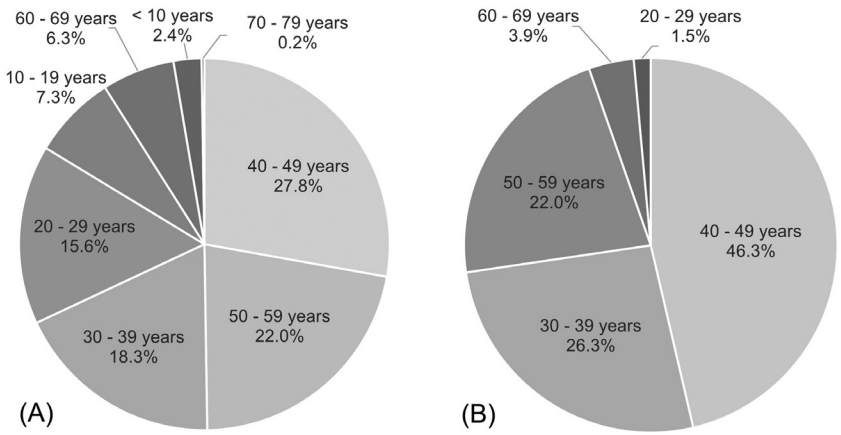

Figure 2. Distribution of the donor age (A) and the recipient age (B) (*n* = 410) (*2*).

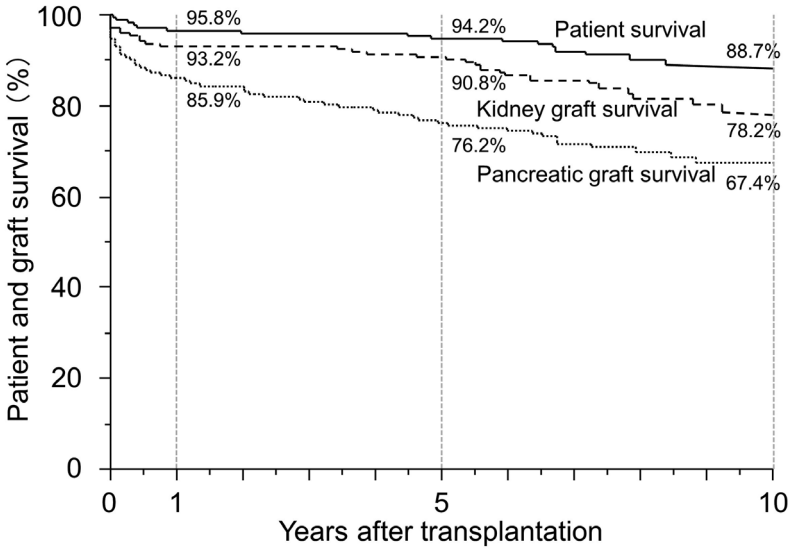

Figure 3. The patient and graft survival after transplantation in Japan (*2*).

in combination with steroids, mycophenolate mofetil (MMF), and anti-IL-2R antibody (basiliximab) was the most frequent regimen, and has been used in 293 cases (71.5%). However, recently, instead of anti-IL-2R antibody, antithymocyte globulin (ATG) has been used in 85 cases (20.7%), and both anti-IL-2R antibody and ATG were used in 6 cases (1.5%). In contrast, a cyclosporine-based combination regimen was only used in 5 cases (1.2%).

The patient survival and pancreas and kidney graft survival

The patient survival and pancreatic and kidney graft survival rates are shown in Figure 3 (pancreatic graft loss was defined as a C-peptide level < 0.3 ng/mL and kidney graft loss as dialysis reintroduction). The patient survival rates at 1, 5, and 10 years after transplantation were 95.8%, 94.2%, and 88.7%, respectively. In addition, the survival rates of pancreas and kidney grafts at 1, 5, and 10 years were 85.9%, 76.2%, and 67.4%, and 93.2%, 90.8%, and 78.2%, respectively. These outcomes were comparable to those observed in other countries (*6*) despite the high frequency of marginal donors as described above. In addition, Ito *et al.* recently reported that the outcomes of pancreas transplantation from ≥ 50-year-old donors were comparable to those from younger donors in their study of 361 cadaveric pancreas transplants in Japan by the end of December 2018 (*4*).

Early and delayed complications of pancreas transplantation

The graft survival rate of pancreata was lower than that of kidneys in every period. Critically, the transplanted pancreas is often abolished early after transplantation. The causes of transplanted pancreas loss were graft thrombosis in 19 cases (5.5%) and patient death in 22 cases (6.4%) among 344 SPK patients; and rejection reaction in 18 cases (27.3%), graft thrombosis in 5 cases (7.6%) among 66 cases of PAK or PTA patients. Since the pancreas is known to be prone to intravascular thrombosis, the high proportion of graft thrombosis may be due in part to the frequent usage of marginal donors. The high frequency of rejection reactions in PAK or PTA may be due to the fact that rejection cannot be monitored by changes in renal function and/or that the current rule does not consider HLA matching in PAK or PTA recipient selection (in SPK, at least one match of HLA-DR is a prerequisite) (*7*). Countermeasures against thrombosis and further improvement in immunosuppressive therapy are therefore imperative. Abolition of the transplanted pancreas due to recurrence of T1D was also observed in 6 (1.5%) of 410 deceased pancreas transplantation patients, another issue that remains to be resolved.

Future Prospects

The comparison with allogenic islet transplantation and allocation of donor pancreata

In Japan, pancreas transplantation has been covered by the national health insurance system under the "Revised Organ Transplant Act", whereas allogenic islet transplantation was recently covered by the national health insurance system, under the "Act on the Safety of Regenerative Medicine". Pancreas transplantation requires major surgery with relatively frequent complications. In contrast, islet transplantation is a minimally invasive procedure involving infusion

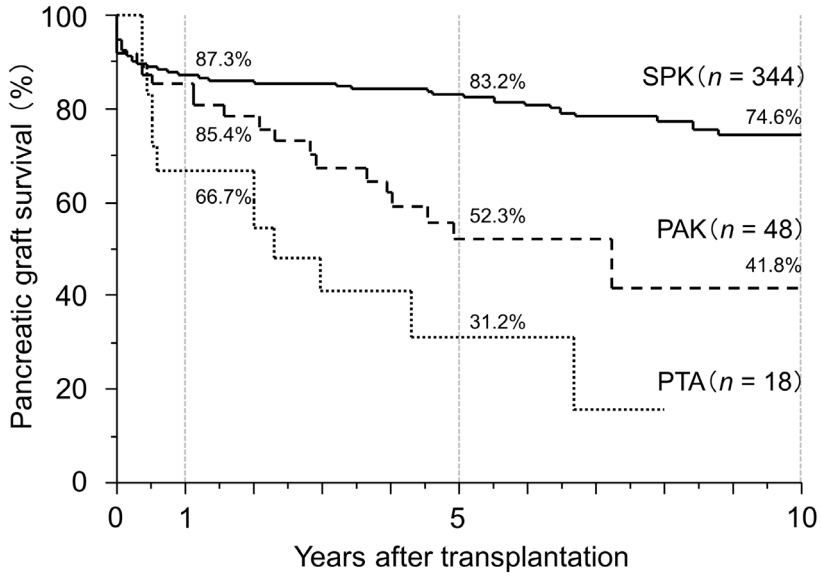

Figure 4. A comparison of the pancreatic graft survival in SPK, PAK and PTA (*2*). PAK, pancreas after kidney transplantation; PTA, pancreas transplantation alone; SPK, simultaneous pancreas and kidney transplantation.

of purified islets *via* the hepatic portal vein with local anesthesia only, although two or more donor organs are usually required to achieve comparable metabolic results to those of pancreas transplantation. Although the number of brain-dead donors has increased, the donor pool remains very small in Japan. With the start of insurance coverage for islet transplantation, the allocation of donor pancreata to pancreas transplantation versus islet transplantation will become an important issue. So far, brain-dead donor pancreata have been used in preference to pancreas transplantation, but the utilization of pancreata for transplantation is approximately 60%, a lower proportion than that of other organs, and this value is decreasing annually (*8*), probably because pancreas transplants from poorly conditioned donors tend to be avoided. An even stronger trend was reported in the United States (*9*). However, a significant percentage of the pancreata that are not used, for reasons such as old age, obesity and a long cardiopulmonary arrest time, may be useful for islet transplantation.

In patients with end-stage renal failure who are indicated for kidney transplantation, since the benefits of SPK are extremely good, pancreas transplantation should be prioritized over islet transplantation. However, in cases of T1D without renal failure or T1D after kidney transplantation, since the long-term pancreas graft survival rate of PAK and PTA is substantially poorer than that of SPK at present (Figure 4) (*2*), islet transplantation may be considered as the first choice, given the degree of invasiveness and safety. Of note, with regard to PAK, it was reported that immunosuppressive therapy using ATG resulted in a lower incidence of complicated graft rejection and better pancreatic graft survival than not using ATG in 39 cases of PAK in Japan (*10*). Further clinical assessment will be necessary to ensure the proper allocation of donor pancreata.

Alternative approaches

To overcome the shortage of available human pancreata, there have been considerable efforts seeking alternative islets sources, such as xenogeneic islets, human embryonic stem cells (hESCs), and induced pluripotent stem cells (iPSCs). Among them, porcine islets are considered the most advanced and promising sources of islets for transplantation based on the long history of clinical trials and accumulated safety and efficacy data, while hESCs-derived β cells have only limited clinical data, and no clinical data are available regarding iPSCs-derived β cell transplantation (*11,12*).

Although porcine islet xenotransplantation for humans has been reported to be less effective than allogeneic islet transplantation (*12*), that has the advantage of providing an unlimited supply of fresh, uniformly quality-controlled islets from medical-grade pigs. Furthermore, porcine insulin differs from human insulin in only a single amino acid residue and was used to treat diabetes in humans for many years before the start of human insulin treatment from the 1980s. Consequently its efficacy and safety are well established. To prevent a xenogeneic immune reaction and instant blood-mediated inflammatory reaction (IBMIR), which also occurs in cases of allotransplantation, without the need for exogenous immunosuppressive therapy, micro- or macro-immune isolation devices are being developed (*9,13*). Indeed, trials of alginate microencapsulated porcine islets (DIABECELL), dubbed "bioartificial islets", are now ongoing.

Conclusion

Insulin pumps and CGM devices are being developed as advanced medical devices for T1D and are gradually becoming popular in Japan. However, given the lag time of both the exogenous insulin effect and the subcutaneous measurement of glucose concentration, it is still an insufficient replacement for pancreatic β-cell function (*9,14*). The superior efficacy of pancreas or islet transplantation is evident with respect to not only the normalization of the blood glucose lability but also IAH and SH avoidance.

In Japan, starting in 2020, allogenic islet transplantation is now covered by the national health insurance system in addition to pancreas transplantation. The continued development of Japanese transplantation medicine, which now enters a new stage 10 years after the introduction of the "Revised Organ Transplant Act", is expected. However, donor shortages remain a serious issue, and only a limited number of patients have been able to benefit from transplantation medicine. As next-generation transplantation medicine, the development of xenogeneic islet transplantation and regenerative medicine using human stem cells (*e.g.* hESCs and iPSCs) has been advancing. In particular, transplantation of "bioartificial islets" using porcine islets appears promising, and clinical translation is expected in the near future.

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Unexpected high prevalence of severe coronary artery stenosis in Japanese hemophiliacs living with HIV-1

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Abstract: To determine the prevalence of coronary artery stenosis (CAS) in Japanese hemophiliacs living with HIV-1 (JHLH), a prospective study at AIDS Clinical Center, Tokyo, which provides care and treatment to nearly 10% of the JHLH was conducted. The study subjects were 76 JHLH who visited our clinic and received coronary computed tomography angiography (CCTA) between January through December 2019. CCTA with radiographic contrast media was used for CAS screening. Coronary artery calcium score (CACS) by CCTA, pulse wave velocity (PWV), electrocardiography, echocardiography, and chest radiography were also included to the screening process. Stenosis of 50% or more by CCTA was defined as moderate to severe CAS. All patients diagnosed with moderate to severe CAS were recommended to undergo coronary angiography (CAG). Among the 76 JHLH, 19 were excluded. Among the enrolled 57 patients, only 5 had complained of chest symptoms. Their median age was 47 years (interquartile range: 44-55 years), prevalence of hypertension 42.1%, diabetes mellitus 14.0%, dyslipidemia 38.6%, and smoking history 52.6%. Moderate to severe CAS was diagnosed in 14 patients by CCTA (24.6% of CCTA tested). Twelve patients agreed to undergo CAG. Seven patients were diagnosed as severe CAS by CAG (12.3% of CCTA received), although only 2 (28.6%) had chest symptoms. PWV and CACS were useful and significant non-invasive markers of moderate to severe CAS ($p = 0.016$, $p < 0.001$, respectively). In conclusions, our study identified high prevalence of severe CAS among JHLH. We recommend screening of all HIV-1-infected hemophiliacs with PWV and CACS, regardless of chest symptoms.

***Keywords*:** coronary artery disease, coronary computed tomography angiography, coronary angiography, coronary artery calcium score, pulse wave velocity

Introduction

Nearly 30% of Japanese with hemophilia and other inherited bleeding disorders were infected with HIV-1 through contaminated non-heated blood products in the early 1980s. As of May 2019, 716 Japanese hemophiliacs infected with HIV-1 were alive (*1*). Thanks to advances of HIV-1 treatment, the prognosis of Japanese hemophiliacs living with HIV-1 (JHLH) has improved dramatically in the past two decades (*2*). The cause of death in JHLH has changed from AIDS before 2000 to other co-morbidities, such as non-AIDS defining malignancies (*2,3*).

Advances in the field of therapeutics, including blood clotting factor concentrates, and in the management of bleeding tendencies have dramatically improved the prognosis of hemophiliacs (*4,5*), resulting in enhancements in life expectancy. Consequently, the proportion of hemophiliacs with coronary risk factors, such as hypertension, diabetes, and dyslipidemia for lifestyle-related diseases increases with age (*6*). In this regard, it is well known that prolonged exposure to HIV infection increases the risk of ischemic heart disease and the use of anti-HIV drugs, particularly protease inhibitors, causes dyslipidemia that increases the risk of coronary artery disease (CAD) (*7,8*). Therefore, JHLH survivors are at high risk of CAD associated with aging, long-term exposure to HIV-1 itself, use of protease inhibitors for HIV-1, and improvement in bleeding tendency.

Coagulation abnormalities are considered less common as the cause of CAD in hemophiliacs (*9,10*). Therefore, physicians have focused on prevention of bleeding, rather than infarction, in these patients. However, in 2018, we encountered a 61-year-old JHLH with subacute myocardial infarction. The diagnosis was difficult and required longer time than usual due to ill-defined and scarce clinical features. The patient had

severe joint deformities related to frequent bleeding, which restricted exercise and limited daily activities, and masked the chest symptoms, and ultimately caused delays in the diagnosis. The case prompted us to screen CAD in the JHLH population.

The purpose of this study was to determine the prevalence of coronary artery stenosis and establish non-invasive screening methods for early detection of CAD in JHLH.

Methods

Patients

This prospective study included all JHLH individuals who visited AIDS Clinical Center (ACC), National Center for Global Health and Medicine (NCGM), Tokyo, and had coronary computed-tomography angiography (CCTA) between January through December 2019.

Data collection

Patients' demographics and CAD risk factors, including age, height, weight, body mass index (BMI), history of hypertension, diabetes mellitus, dyslipidemia, used medications, smoking, alcohol drinking, cardiovascular diseases, and allergy, in addition to family history, were collected. Blood tests included hemoglobin A1c, LDL-cholesterol, HDL-cholesterol, creatinine, hemoglobin, CD4 counts, plasma HIV-RNA, D-dimer, and brain natriuretic peptide (BNP). Furthermore, information on nadir CD4 counts, use of blood products and severity of hemophilia, and period of use of protease inhibitors were collected by the medical records. Electrocardiography, echocardiography, and pulse wave velocity (PWV) (Omron Healthcare, Kyoto, Japan) were also performed in each patient and age-average data of PWV was referred to a Japanese survey (*11*). The presence of pleural effusion and calculated cardio thoracic ratio were checked on the chest X-ray. Coronary artery calcium score (CACS) was weighted by CT value as was the cross-sectional area according to Agatston *et al*. (*12*). In this study, CACS was classified into no calcification (score = 0), minimal risk (score: 1-10), low risk (score: 11-100), moderate risk (score: 101-400), and high risk (score: > 400) (*13,14*). Patients considered to have no severe renal dysfunction or allergy to the contrast agent underwent CCTA with 320-row multidetector computed tomography angiography (Aquilion ONE, Canon Medical System, Otawara, Japan). Based on CCTA image analysis, coronary artery stenosis was classified as mild stenosis (< 50% stenosis in the vessel area, non-CAD group), moderate stenosis (50 to 75% stenosis), and severe stenosis (> 75% stenosis). In this study, the CAD group included patients with moderate to severe CAS. Coronary angiography (CAG) was recommended to all patients with moderate to severe stenosis, as defined by CCTA.

Statistics analysis

The above investigations were used to define the presence or absence of coronary artery stenosis and risks of CAD in the cohort. Differences in categorical variables between the groups were checked using the Pearson's chi-square test, while those in continuous variables were examined by the Mann-Whitney *U* test. Differences in the incidence of moderate to severe stenosis evaluated by coronary CT and absolute values of PWV and CACS were examined by the Mann-Whitney *U* test. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS, SPSS Inc., Chicago, IL).

Ethics statement

The study protocol was reviewed and approved by the human ethics committee of NCGM (#NCGM-G-003086-00) on November 26, 2018. A written informed consent was obtained from all participants at study entry in accordance with the Declaration of Helsinki. This study was registered with the University Hospital Medical Information Network Clinical Trial Registry (Registry number #UMIN000035307).

Results

A total of 76 (10.6%) patients visited ACC out of the 716 registered JHLH. All patients were males, including a single patient with von-Willebrand disease. The patient selection process is outlined in Figure 1. Nineteen patients were excluded from the study for a variety of reasons, including unwillingness to participation (n = 4), ineligibility for participation (*e.g*., coexisting psychiatric diseases, n = 5), renal dysfunction (n = 5), allergy to iodine (n = 3), and past history of CAD (n = 2, one with myocardial infarction, aged 61 years, and another with angina pectoris, aged 44 years). Thus, 57 patients were enrolled in this study and each underwent CCTA during the study period. Among the 57 patients, only 5 had complained of chest symptoms. Table 1 summarizes the patients' characteristics. The median age was 47 years (interquartile range (IQR): 44-55 years). HIV-1 viral load (VL) was suppressed undetectable level in all patients except one whose VL was 51 copies/mL. The median duration of undetectable VL was 16 years (IQR: 12-18 years). Although their nadir CD4 counts were low, the current median CD4 count was 457/μL (IQR: 370-627/μL). Above all, HIV-1 infection was very well controlled in all patients. Most patients (86.0%) had been treated with protease inhibitors for the median period of 10 years (IQR: 4-16 years) and 77.2 % treated with d-drug (any

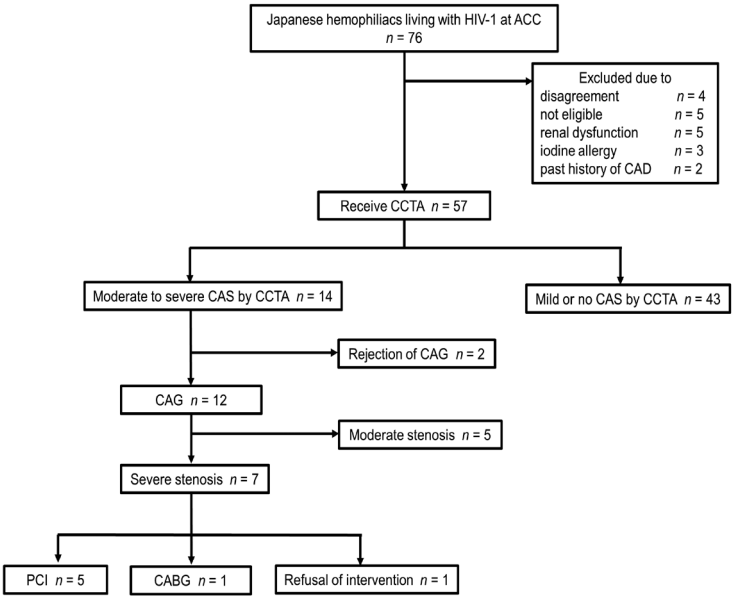

Figure 1. Study protocol and patient selection. Patients with moderate to severe CAS based on CCTA were classified into the CAD group and mild or no CAS as the non-CAD group. ACC, AIDS Clinical Center; CAS, coronary artery stenosis; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CAG, coronary angiography; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 1. Patient demographics and comparison of variables with and without CAD by CCTA

Demographics and variables	All (*n* = 57)	CAD (*n* = 14)	Non-CAD (*n* = 43)	*p*
Age, median year (IQR)	47 (44-55)	55 (47-59)	47 (44-52)	0.089
BMI kg/m^2, median (IQR)	23 (22-25)	22 (20-27)	23 (22-25)	0.204
Hemophilia A, *n* (%)	46 (80.7)	9 (20)	37 (80)	0.073
Hemophilia B, *n* (%)	10 (17.5)	5 (50)	5 (50)	0.044
von Willebrand Disease, *n* (%)	1 (1.8)	-	1	
Nadir CD4/μL, median (IQR)	129 (59-169)	108 (12-177)	130 (69-168)	0.207
Current CD4/μL, median (IQR)	457 (370-627)	452 (370-610)	567 (375-690)	0.305
Duration of undetectable VL, median year (IQR)	16 (12-18)	16 (12-18)	16 (12-18)	0.566
PI use, median year (IQR)	10 (3-17)	14 (3-18)	10 (4-16)	0.362
d-drug use, median year (IQR)	6 (1-9)	5 (1-8)	7 (12-18)	0.074
Smoking history, *n* (%)	30 (52.6)	7 (50.0)	23 (53.5)	0.878
Current smoker, *n* (%)	11 (19.3)	3 (21.4)	8 (18.6)	0.875
Hypertension, *n* (%)	24 (42.1)	7 (50.0)	17 (39.5)	0.491
Diabetes mellitus, *n* (%)	8 (14.0)	4 (28.6)	4 (9.3)	0.071
Dyslipidemia, *n* (%)	22 (38.6)	6 (42.9)	16 (37.2)	0.826
SUITA score, median (IQR)	41 (33-46)	38 (33-44)	44 (40-58)	0.019
PWV cm/sec, median (IQR)	1,527 (1,404-1,657)	1,615 (1,417-1,798)	1,464 (1,336-1,599)	0.016
CACS, median (IQR)	0 (0-27)	111 (29-593)	0 (0-7)	< 0.001

CAD, coronary artery disease; CCTA, coronary computed-tomography angiography; *n*, number of patients; IQR, interquartile range; BMI, body mass index; VL, plasma viral load; PI, protease inhibitor; d-drug, any of ddI, ddC and d4T; PWV, pulse wave velocity; CACS, coronary artery calcium score.

of ddI, ddC and d4T) for the median duration of 6 years (IQR: 1-9 years). The prevalence of hypertension was 42.1%, diabetes mellitus 14.0%, dyslipidemia 38.6%, smoking history 52.6%, and current smoker 19.3%. The median SUITA score that is a predictive score of a 10-year risk of coronary heart disease (CHD) in Japanese (*15*) was 41 (IQR: 33-46).

CCTA showed moderate to severe coronary artery stenosis (CAS) in 14 out of 57 patients (24.6%). The classical risk factors of CAD, including age, smoking history, hypertension, diabetes mellitus, and dyslipidemia, were not significantly different between the CAD and non-CAD groups (Table 1). Although the prevalence of CAD was higher in patients aged more than 40 years (33.3%) than in those less than 40 (18.2%), both age groups included a substantial number of patients with moderate to severe CAS (Figure 2). Electrocardiography, echocardiography, and chest radiography had no diagnostic values in all patients.

The PWV was above that of the age-matched

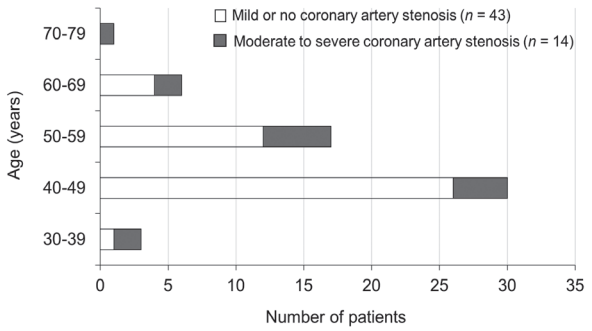

Figure 2. Prevalence of coronary artery stenosis by age. Coronary artery stenosis was diagnosed by coronary computed tomography angiography.

average +1SD and +2SD in 42 (73.7%) and 25 patients (43.9%), respectively (Figure 3). Furthermore, analysis of the CCTA of patients with +2SD PWV (n = 25), showed 10 (40.0%) of these patients had moderate to severe CAS. The finding that the PWV of JHLH was higher than that of the general population in almost all cases was surprising. Furthermore, the absolute values PWV highlighted the presence of significant difference between the CAD and non-CAD groups (p = 0.016). In addition to PWV, the absolute values of CACS were significantly higher in the CAD group than in the non-CAD group (p < 0.001) (Table 1, Figure 4). CACS values were more than 100 in 8 patients and all these patients except one had moderate to severe CAS. In

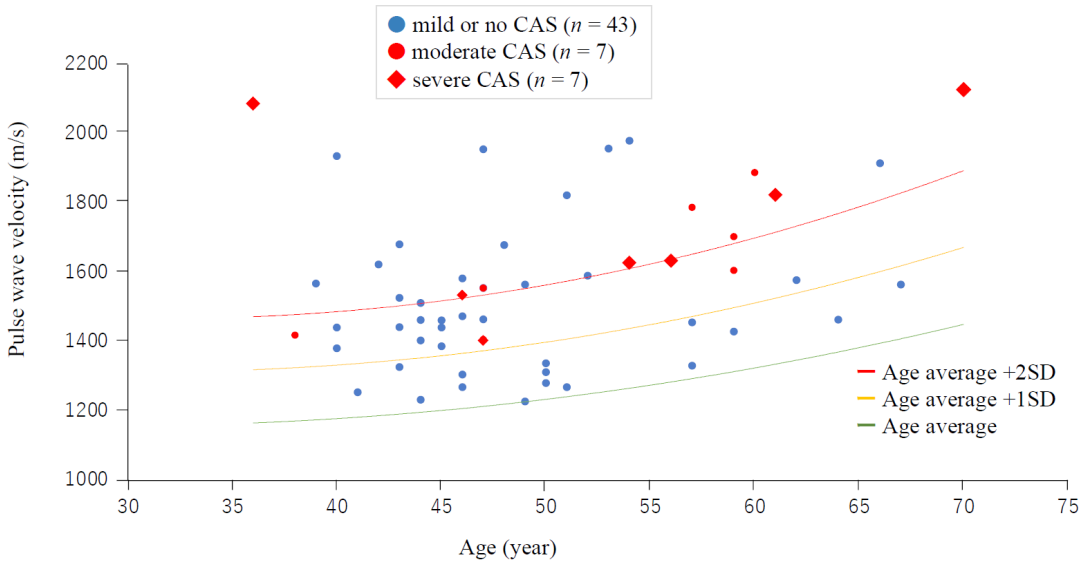

Figure 3. Pulse wave velocity, age, and coronary artery stenosis diagnosed by CCTA. Mild or no stenosis was diagnosed by CCTA. Moderate or severe stenosis was diagnosed by coronary angiography. CAS, coronary artery stenosis; CCTA, coronary computed tomography angiography; CACS, coronary artery calcium score.

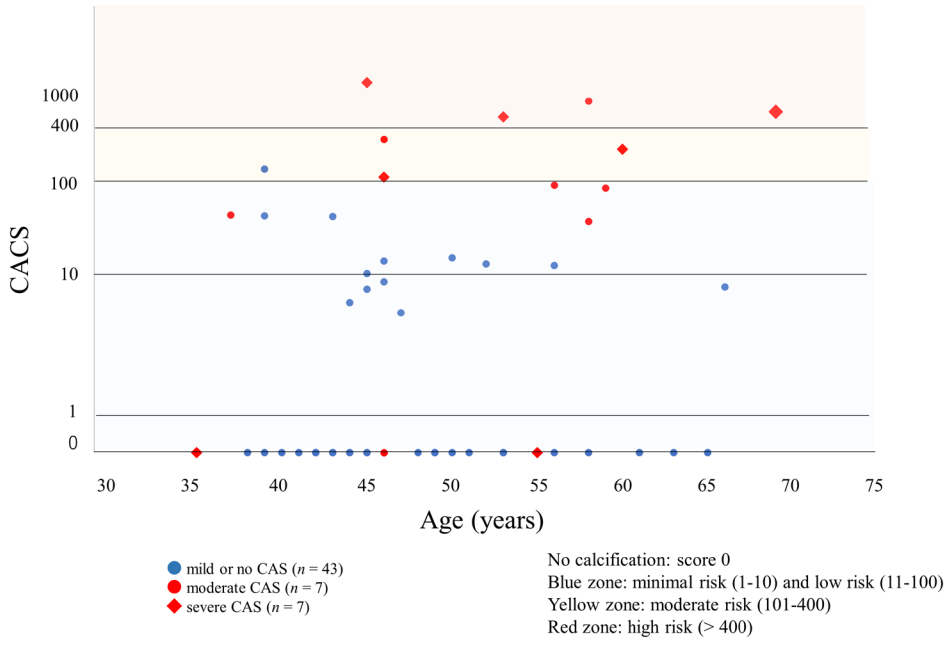

Figure 4. Coronary artery stenosis and risk of ischemic heart disease categorized by CCTA. Mild or no stenosis was diagnosed by CCTA. Moderate or severe stenosis was diagnosed by coronary angiography. (*See Figure 3 for abbreviations*)

these 7 patients with severe coronary artery stenosis, CACS was less than 100 in 3 patients (values: 92, 0, 0). However, the PWV values of these 3 patients were above +2SD. These results indicate that the combination of PWV and CACS can better predict CAD than either parameter alone.

Among the 14 patients diagnosed with moderate to severe CAS based on CCTA, 12 agreed to undergo CAG (Figure 1). CAG confirmed the presence of severe stenosis in 7 patients, requiring multivessel revascularization. Among the 7 patients, only 2 had complained of chest symptoms related to CAD. Of the 7-CAG confirmed patients, 5 subsequently underwent percutaneous coronary intervention (PCI) and one received coronary artery bypass grafting (CABG). The other one patient refused to undergo PCI due to fear of bleeding while under dual antiplatelet therapy and was accordingly treated by medications only.

Discussion

We conducted a prospective screening study for CAD in JHLH and found CAS in almost 25% of the cohort. Moreover, the prevalence of severe CAS confirmed by CAG was 12.3% in those JHLH patients with a median age of 47 years. It is noteworthy that only two patients had experienced chest symptoms, probably due to low physical activity. The prevalence of CAS was unexpectedly higher than in the general population, although the exact CAS prevalence in the general population is difficult to estimate. With regard to the prevalence of myocardial infarction in Japanese men, the available data in the 1990s showed a rate of 100.7 per 100,000 person/year (*16*). In our study, the identified 7 patients required early revascularization due to the severity of CAS.

The current guidelines for the clinical management of hemophiliacs do not mention the prevention of CAD (*17*). Recent years have seen emphasis on the control of cardiovascular risks in these patients (*18*) and establishment of screening methods for CAD is also important. The currently identified classical risk factors of CAD, such as age, smoking history, hypertension, diabetes mellitus, dyslipidemia, and the SUITA score are definitely useful for the prediction of CAD in the general population. However, their importance could not be established in the present study. According to the SUITA score, a 10-year probability of CAD would be only 2% and the score was too low to compare in this patient population. It is possible that other risk factors may override the classical risk factors in this unique population of HIV-1 infection and hemophilia.

In this study, HIV-1 infection of all patients has been very well controlled in terms of CD4 counts and VL for more than the past decade. However, Japanese hemophiliacs were infected with HIV-1 around 1983 (*2*). Before the highly active antiretroviral therapy became available in Japan in 1997, JHLH survivors were exposed for 14 years to high plasma viral loads. The impact of HIV-1 on cardiovascular diseases (CVD) has been documented in a randomized study in which anti-HIV-1 therapy was either interrupted or tailored according to CD4 count (*19*). In this study, patients of the interrupted group had significantly higher CVD events due to high peripheral blood levels of proinflammatory cytokines and endovascular thrombosis (*20*), and the control of plasma viral load reduced markers of endothelial and coagulation activation (*21*). These results indicate the reversibility of hypercoagulability and endovascular reactivity. However, while this is true for short-term endothelial and coagulation dysfunctions, there were no evidence for the same during long-term exposure to high viral load like in the Japanese hemophiliacs. In addition to HIV-1 itself, the 10-year use of protease inhibitors in JHLH patients carried the risk of development of dyslipidemia. In this regard, Friis-Moller *et al*. (*22*) demonstrated that long term use of protease inhibitors increased the risk of myocardial infarction.

We have witnessed lessening of bleeding in hemophiliac patients in this decade thanks to new and improvement in anti-coagulation therapy. The current treatment regimens include regular injections of factor VIII or IX two-to-three times per week. The prophylactic use of coagulation factors has kept the incidence of CVD in hemophiliacs at levels similar to that in the normal population, with lower mortality, according to a report from Sweden (*9*). Wang *et al*. (*23*) studied the prevalence and risk factors of atherothrombotic events in 1,054 hemophiliacs and reported that such events occurred in younger hemophiliacs (mean age 49 years) compared with the general population (55.8 years). The prevalence in hemophiliacs was also comparable to that of the general population in this study. In contrast, Sharathkumar *et al*. (*24*) reported double the CVD rate found in the general population in their hemophiliacs from a single hemophilia center in the United States. Since the pathophysiology of CVD is closely related to hypercoagulability, the effects of long-term use of coagulant factors on atherosclerosis in hemophiliacs need to be analyzed in future studies.

The main finding of this study was the high rate of CAS, which is probably related to atherosclerosis. Evidence indicates that high PWV value is a marker of advanced atherosclerosis. In this study, the majority of JHLH patients had high PWV values. A high PWV value is usually caused by high blood pressure and peripheral artery disease, though neither was detected at the time of PWV measurement in this study. Importantly, atherosclerosis develops earlier in JHLH patients, compared with that in age-matched general population. The importance of high PWV is based on the fact that it correlates with coronary artery calcification (*25,26*) and CVD (*27-29*) in the general population.

Our results showed that the absolute values of PWV

were significantly different between patients of the moderate to severe CAS group and those of the mild to normal coronary artery group. Furthermore, the PWVs of all 14 patients with moderate to severe CAS were higher than those of the age average +1SD (Figure 3). Exercise stress test with ECG monitoring is usually used for assessment of CAD, however, this test is not suitable for at least some hemophiliacs due to the associated joint deformities. For such cases, PWV can be a useful screening test for CAD in JHLH especially as it is a non-invasive test. We also used another index to assess CAD in our patients, the absolute values of CACS were significantly higher in the CAD groups than the non-CAD group (Figure 4). For screening patients for CAD using CACS, it can be calculated on the CT scan without contrast agent. Thus, the use of CACS for CAD in JHLH can be also useful as a screening tool, although score zero does not mean no risk of CAD. In summary, we recommend the combination of PWV and CACS for early detection of CAD in hemophiliacs living with HIV-1 based on their high diagnostic value. Further large-scale studies are needed to establish the diagnostic values of these indexes in JHLH.

In spite of the above strengths, our study has certain limitations. First, the number of participants was not sufficient enough to demonstrate the statistical significance of the classical risk factors of CAD. However, around 10% of the current JHLH were included in this study. A larger study of JHLH should be performed to assess the significance of the classical risk factors. Second, our study demonstrated extremely high prevalence of CAS, high PWV and CACS values in JHLH, but the study did not include a control group. Therefore, the reasons for the high values and the factors that contributed to such high prevalence of CAD remain unclear. Further studies involving hemophiliacs free of HIV-1 infection and non-hemophiliacs who have been on long-term treatment for HIV-1 could provide answers to these questions.

In conclusion, we have demonstrated in the present study a high prevalence of severe CAD in a sample of JHLH community. We strongly recommend screening of hemophiliacs living with HIV-1 for CAD, with the combination of PWV and CACS, regardless of presence or absence of chest symptoms.

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Validation of the Brief Coping Orientation to Problem Experienced (Brief COPE) inventory in people living with HIV/AIDS in Vietnam

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Abstract: The Brief Coping Orientation to Problem Experienced (Brief COPE) inventory is one of the most widely used instruments in coping research; however, no study has evaluated the psychometric properties of the Brief COPE in the Vietnamese population. This study aimed to validate a culturally appropriate Vietnamese version of the Brief COPE for the evaluation of coping strategies in people living with HIV/AIDS in Vietnam. We translated the Brief COPE into Vietnamese, and it was self-administered among 1,164 HIV-infected patients receiving antiretroviral therapy at a large HIV outpatient clinic in Hanoi between January 2019 and March 2020. Data on demographics and HIV-related information, depression and social support were also collected. Confirmatory factor analysis (CFA) and exploratory factor analysis (EFA) were conducted to assess construct validity. Content validity, internal consistency, and convergent validity were also assessed. The CFA of a 14-factor structure of the original Brief COPE revealed acceptable model fitness, but poor internal consistency for some subscales. In the subsequent EFA, we found a revised 26-item version which had a six-factor structure consisting of problem-solving, avoidance, humor, social support, religion, and substance use. The final CFA found that the model fitness of the revised scale with fewer factor structures was comparable to that of the original Brief COPE; the internal consistency of the revised scale was even better than that of the original scale. Furthermore, six factors of the revised scale showed anticipated associations with depression and social support.

***Keywords*:** confirmatory factor analysis, explanatory factor analysis, coping

Introduction

Coping is defined as cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person (*1*). When facing difficult situations, coping strategies available to and employed by an individual determine experience, severity of stress, and pathological consequences (*2*). Thus, different types of coping strategies could have protective or harmful effects on individual health and well-being (*3*).

Approximately 230,000 people in Vietnam are living with HIV/AIDS in 2018 (*4*); the HIV epidemic is concentrated in key populations, including people who inject drugs and sex workers (*5*). Although improved access to antiretroviral therapy (ART) has increased the life expectancy of people living with HIV/AIDS (PLWHA), the chronic course of HIV infection requires patients to cope with various forms of psychosocial stress associated with fear of death, opportunistic infection, and side effects of ART (*6*). In addition, multiple stigmas due to social prejudices against their behavior and their serostatus cause strong discrimination against the HIV population, especially in Vietnam (*6-8*). Given that psychosocial stress is negatively associated with ART adherence, leading to poor treatment outcomes (*9,10*), and that depression is prevalent in PLWHA in Vietnam (*11*), it is important to evaluate their stress coping strategies to reduce stress-related burdens.

The Brief COPE (*12*) is an abbreviated version of the 60-item Coping Orientation to Problems Experienced (COPE) Inventory (*13*) based on Lazarus's transaction model of stress (*1*) and Carver's self-regulation model (*14,15*). Although it is a widely used instrument in coping research among various groups (healthy individuals (*16-18*), ill individuals including those infected with HIV (*19-23*), and caregivers (*19,24*)), no study has evaluated the psychometric properties of the Brief COPE in the Vietnamese population. This multidimensional scale consists of 28 items that measure

14 coping strategies of two items each. However, such a fragmented structure may limit the usefulness of this scale in both clinical and research settings, making statistical interpretation and dissemination of a scientific message difficult. In addition, coping strategies may differ across cultural context. Culture defines stressors, emotional responses, and language used to describe them. Therefore, previous studies explored and suggested structures with fewer factors (*i.e.*, four (*19*), five (*21*), six (*23*), seven (*20*), and eight (*17*)), which may be more sensitive to their sociocultural contexts.

In response to the needs for culturally relevant, validated scales to measure the coping strategies of the HIV population in Vietnam, this study aimed to validate a culturally appropriate Vietnamese version of the Brief COPE for the evaluation of coping strategies in PLWHA in Vietnam.

Material and Methods

Participants

Between January 2019 and March 2020, we conducted a self-administered questionnaire survey using a hospital-based cohort of PLWHA on ART (aged ≥ 18 years). This cohort, the so-called Hanoi cohort, was established in 2007 at the HIV outpatient clinic at the National Hospital for Tropical Diseases (NHTD) in Hanoi, Vietnam. Since then, 1,820 patients have registered for the Hanoi cohort, and 1,287 were still enrolled and underwent follow-up in the study periods. Among those, 1,164 agreed and participated in the survey. The survey for the remaining 123 patients was scheduled in March and April 2020, but it was interrupted due to the epidemic of coronavirus disease 2019 (COVID-19). Since some measurements like depression may be largely affected by the epidemic, we only used data obtained before the epidemic. The semi-structured questionnaire was administered to the participants during their regular consultations. A nurse was assigned to provide appropriate support if the participants encountered difficulties when responding to the questionnaires.

Each participant provided written informed consent. The study was approved by the Human Research Ethics Committee of the National Center for Global Health and Medicine (reference: NCGM-G-002537-00) and NHTD (reference: 15/HDDD-NDTU).

Measurements

Demographics and HIV-related factors

The following data on demographic and HIV-related factors were collected: sex, age, marital status, number of household members, residence, employment, income, educational attainment, social health insurance status, time from HIV diagnosis, route of HIV transmission, and HIV disclosure status.

Brief COPE

The Brief COPE can be used to assess situational coping strategies (ways people cope with a specific stressful event) and dispositional coping strategies (usual ways people cope with stress in everyday life); we assessed the latter ones in this study. The scale measures 14 coping subscales with two items each, which are as follows: self-distraction, active coping, denial, substance use, emotional support, instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame. For each item, respondents indicate whether they use the coping response on a four-point Likert scale (1 = I usually don't do this at all; 2 = I usually do this a little bit; 3 = I usually do this a medium amount; 4 = I usually do this a lot). Cronbach's alpha of original subscales ranged from 0.50 (venting) to 0.90 (substance use).

Center for Epidemiologic Studies Depression Scale (CES-D)

The CES-D is a well-known 20-item self-reporting scale for measuring depression symptoms (*25*). Responses were given on a four-point scale ranging from 0 (rarely or none of the time) to 3 (most or almost all the time), except for four items that were positively worded and scored in reverse. The reliability and validity of the Vietnamese version of the CES-D was confirmed in Vietnam's HIV population, with Cronbach's alpha of 0.81, and sensitivity and specificity of 79.8% and 83.0%, respectively, at the cut-off score of 16 (*26*).

Medical Outcome Study Social Support Survey (MOS-SSS)

The MOS-SSS is a self-administered scale developed to measure perceived availability of social support (*27*). The MOS-SSS consists of 19 items representing four types of social support: emotional/informational support (eight items), tangible support (four items), affectionate support (three items), positive social interaction (three items), and additional item (one item). The score for each item ranges from 0 (rarely or none of the time) to 5 (all of the time), with the higher score indicating more support perceived by respondents. The Vietnamese version of the MOS-SSS was previously validated in HIV outpatients on ART in the Hanoi cohort, with Cronbach's alpha of 0.95 for the overall score and 0.90-0.93 for the four subscales (*11*). This study also validated the structure of an original four-factor model of MOS-SSS with a comparative fit index of 0.96 and adjusted goodness of fit index of 0.89 in the confirmatory factor analysis (CFA).

Analytic approach

The following five steps were taken to validate the Vietnamese version of the Brief COPE: *i*) assessment of content validity, *ii*) translation, *iii*) assessment of

internal consistency and construct validity of the original scale, *iv*) assessment of the factor structure relevant to the HIV population in Vietnam, and *v*) assessment of internal consistency and construct and convergent validities of the revised scale. The contents of assessment in each step are described below.

Assessment of content validity

The content validity of the Brief COPE was determined by an expert panel that was formed by HIV/AIDS specialists, including HIV clinicians, social workers, and a social epidemiologist. The panel reviewed each item to check whether there was any item irrelevant or unsuitable in the Vietnam cultural context.

Translation

The original English version of the Brief COPE was translated into Vietnamese by a Vietnamese research member who is familiar with the HIV population. The instrument was then translated back to English by an independent translator, who has no knowledge of the questionnaire. The above mentioned expert panel determined the conceptual and cultural equivalence between the two versions. Then, five HIV patients in the NHTD were invited to complete the translated instruments for their review, in which respondents were asked to indicate any wording or expressions they did not understand or they found unacceptable or offensive in view of cultural norms. Those who attended the review were excluded from the main survey.

Assessment of internal consistency and construct validity of the original scale

The internal consistency of the original Brief COPE in this sample was assessed by calculating Cronbach's alpha for both overall score and each subscale. Alpha values ≥ 0.70 were indicative of good internal consistency (*28*). A CFA was also performed to assess the construct validity of the original 28-item, 14-factor structure in a sample of Vietnam's HIV population. The root mean square error of approximation (RMSEA), comparative fit index (CFI), normed fit index (NFI), non-normed fit index (NNFI), and goodness of fit index (GFI) were calculated to test the model fit. CFI, NFI, NNFI, and GFI values ≥ 0.9 (*29*) and an RMSEA value ≤ 0.08 was indicative of a good model fit (*30*).

Assessment of the factor structure relevant to the HIV population in Vietnam

To explore a better structure, preferably with fewer factors, an exploratory factor analysis (EFA) of the original Brief COPE was carried out using the maximum-likelihood extraction with varimax rotation on the entire sample. The Kaiser-Meyer-Olkin (KMO) and Bartlett's sphericity tests were used to examine the sampling adequacy of data that were used for the EFA. The number of factors with eigenvalue ≥ 1.0 was retained for the analysis (*31*). The items with factor loading of ≥ 0.4 were also retained. In the case of multiple loading of an item on several factors and of factor loading < 0.4, the conceptual relationship to the factors and the relevance in Vietnam's sociocultural context were considered.

Assessment of internal consistency and construct and convergent validities of the revised scale

The internal consistency of the revised scale was assessed by calculating Cronbach's alpha for both overall score and each subscale. Using the revised scale derived from the steps above, the final CFA was performed. The model fit explained by the fitness indices (*i.e.*, RMSEA, CFI, NFI, NNFI, and GFI) was compared between the original 28-item, 14-factor scale and the revised scale. In addition, given the association between coping and depression (*32,33*) and social support (*34,35*), the convergent validity was examined by evaluating the association of the revised scale with depression measured using CES-D and social support measured using MOS-SSS. The mean scores of each subscale in the revised scale were compared between depressed and not depressed individuals defined by CES-D ≥ 16 or less, and statistical significance was assessed by the *t*-test. Pearson correlation coefficients between each subscale score in the revised scale and the MOS-SSS scores were also calculated.

All analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, USA). Missing data were excluded from the analyses.

Results

Sociodemographic characteristics

The characteristics of the 1,164 participants are described in Table 1. Among all participants, 58.1% were male and 41.9% were female, with median age (interquartile range [IQR]) of 41 (37-45) years, 73.9% were married, and 53.8% were living outside Hanoi. More than 80% of the respondents had been living with HIV for ≥ 7 years, and most of them had disclosed their HIV status to others. Moreover, 19.4% reported injections of drug and/or being a prisoner as their route of HIV transmission.

Content validity

The expert panel did not find any item which is not relevant or suitable to the construct of the coping strategies in the Vietnamese cultural context. Therefore, all 28 items were retained for the analyses. During the translation process, in response to the opinions from the expert panel and from the participants, minor changes were made to the Vietnamese translation of the scale to develop the final version (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=10*).

Table 1. Characteristics of the study participants

Variables	Sample, n = 1,164 n (%)
Sex	
Male	676 (58.1)
Female	488 (41.9)
Age	
Median (IQR)	41 (37, 45)
< 37	272 (23.4)
37-40	275 (23.6)
41-44	281 (24.1)
≥ 45	336 (28.9)
Marital status	
Single (without partner)	78 (6.7)
Married	860 (73.9)
Unmarried with partner	15 (1.3)
Widowed	129 (11.1)
Divorced	82 (7.0)
Number of household members	
1	45 (3.9)
2	143 (12.3)
3	375 (32.2)
≥ 4	601 (51.6)
Residence	
Hanoi	538 (46.2)
Other	626 (53.8)
Employment	
Full-time employment (employee)	441 (37.9)
Part-time employment (employee)	74 (6.4)
Working full-time (self-employed)	278 (23.9)
Working part-time (self-employed)	182 (15.6)
Jobless and not working at all[a]	189 (16.2)
Income (VND/month)[b]	
0-1,499,999	63 (5.4)
1,500,000-4,999,999	324 (27.8)
≥ 5,000,000	686 (58.9)
N/A	91 (7.8)
Educational attainment[c]	
Low	35 (3.0)
Middle	642 (55.2)
High	485 (41.7)
N/A	2 (0.17)
Social health insurance status	
Having an insurance card	1,093 (93.9)
Not having an insurance card	69 (5.9)
Unknown	1 (0.1)
N/A	1 (0.1)
Time from HIV diagnosis	
Median (IQR)	9.3 (7.3, 13.6)
< 7 years	215 (18.47)
7-13 years	672 (57.73)
≥ 14 years	277 (23.8)
Route of HIV transmission	
Men who have sex with men (MSM) or gay or lesbian	22 (1.9)
Sex worker	1 (0.09)
Injecting drug user or prisoner	226 (19.4)
Migrant worker	14 (1.2)
Others	901 (77.4)
HIV disclosure status	
Not having disclosed to anyone	57 (4.9)
Having disclosed to someone	1,107 (95.1)

N/A: Not available. [a]Including retirement. [b]1USD = approximately 23,000 VND; low, < 1,500,000 Vietnamese dong (VND); middle, 1,500,000-4,999,999 VND; high: ≥ 5,000,000 VND. [c]Low, never went to school or primary school; Middle, junior high school or high school; High, vocational school/college or university/graduate university.

Table 2. Model fit indices of the CFA for the original scale and revised scale

Model fit indices	Original scale 28 items, 14 factors	Revised scale 26 items, 6 factors
RMSEA[a]	0.07	0.07
CFI[b]	0.89	0.87
NFI[c]	0.87	0.85
NNFI[d]	0.83	0.85
GFI[e]	0.92	0.90

[a]Root mean square error of approximation. [b]Comparative fit index. [c] Normed fit index. [d]Non-normed fit index. [e]Goodness of fit index.

Construct validity

CFA of the original scale

The CFA of the original Brief COPE with 28 items of 14 factors suggested an acceptable model fit with RMSEA of 0.07 and GFI of 0.92, even though other indices were on the borderline of fitness (CFI = 0.89, NFI = 0.87, and NNFI = 0.83, respectively) (Table 2).

EFA of the original scale

The KMO value was 0.87, and Bartlett's sphericity test results were statistically significant with a p value of < 0.0001, which suggested that data were suitable for the factor analysis. The EFA of the original 28-item Brief COPE with varimax rotation identified a six-factor structure accounting for 46.4% of the total variance (Table 3). Both items from the acceptance and planning subscales and one item from the positive reframing and active coping subscales in the original Brief COPE was loaded on Factor 1 and named "problem-solving". Further, both items from the denial, self-blame, and behavioral disengagement subscales and one item from the self-distraction subscale were loaded on Factor 2 and named "avoidance". Both items from the humor subscale and one item from the self-distraction and positive reframing subscales were loaded on Factor 3 and named "humor". Both items from the use of instrumental support and emotional support subscales were loaded on a single factor (Factor 4) and named "social support". Although one item of the use of instrumental support ("I've been trying to get advice or help from other people about what to do") cross-loaded on Factor 1 and Factor 4, it was assigned to Factor 4 ("social support") as it was conceptually more related to this factor. Two items from the religion subscale and substance use subscale formed individual factors as the same as the original Brief COPE (Factor 5 and Factor 6) and were named "religion" and "substance use", respectively.

In addition, there were two items of venting ("I've been expressing my negative feelings" and "I've been saying things to let my unpleasant feelings escape") and one item from active coping ("I've been concentrating my efforts on doing something about the situation I'm in.") with factor loading < 0.4. Among these, we

Table 3. Factor loading from the explanatory factor analysis of the Brief COPE

Item of Brief COPE	Factors in Brief COPE	Factors					
		F1	F2	F3	F4	F5	F6
25. I've been thinking hard about what steps to take.	Planning	**0.74**	0.02	0.16	0.20	0.11	0.02
12. I've been trying to see it in a different light, to make it seem more positive.	Positive reframing	**0.68**	0.11	0.16	0.17	0.05	-0.01
24. I've been learning to live with it.	Acceptance	**0.66**	0.00	0.20	0.03	0.14	0.04
14. I've been trying to come up with a strategy about what to do.	Planning	**0.64**	0.05	0.13	0.22	0.05	-0.03
7. I've been taking action to try to make the situation better.	Active coping	**0.62**	0.09	0.18	0.23	0.02	-0.02
20. I've been accepting the reality of the fact that it has happened.	Acceptance	**0.58**	-0.02	0.00	0.13	0.19	0.01
2. I've been concentrating my efforts on doing something about the situation I'm in.	Active coping	**0.37**	0.20	0.01	0.02	0.21	0.03
8. I've been refusing to believe that it has happened.	Denial	0.03	**0.67**	0.14	0.01	0.02	0.03
3. I've been saying to myself "this isn't real."	Denial	0.06	**0.63**	0.13	0.01	0.02	0.05
13. I've been criticizing myself.	Self-blame	0.09	**0.54**	0.00	-0.08	-0.02	0.18
26. I've been blaming myself for things that happened.	Self-blame	0.10	**0.51**	0.02	-0.11	0.01	0.20
16. I've been giving up the attempt to cope.	Behavioral disengagement	-0.10	**0.50**	0.04	0.05	0.08	0.04
6. I've been giving up trying to deal with it.	Behavioral disengagement	0.02	**0.46**	0.08	-0.07	0.01	0.06
1. I've been turning to work or other activities to take my mind off things.	Self-distraction	0.14	**0.43**	0.32	-0.11	0.08	0.06
28. I've been making fun of the situation.	Humor	0.25	0.21	**0.75**	0.00	0.03	-0.01
19. I've been doing something to think about it less, such as going to movies, watching TV, reading, daydreaming, sleeping, or shopping.	Self-distraction	0.08	0.20	**0.71**	0.02	0.06	0.01
17. I've been looking for something good in what is happening.	Positive reframing	0.27	0.22	**0.69**	0.12	-0.01	0.03
18. I've been making jokes about it.	Humor	0.10	0.03	**0.59**	0.15	0.12	0.07
10. I've been getting help and advice from other people.	Use of instrumental support	0.38	-0.05	0.11	**0.64**	0.10	-0.04
15. I've been getting comfort and understanding from someone.	Use of emotional support	0.43	-0.09	0.11	**0.60**	0.07	-0.06
5. I've been getting emotional support from others.	Use of emotional support	0.39	-0.09	0.09	**0.60**	0.02	-0.04
23. I've been trying to get advice or help from other people about what to do.	Use of instrumental support	**0.43**	0.04	-0.01	**0.46**	0.34	0.00
22. I've been trying to find comfort in my religion or spiritual beliefs.	Religion	0.26	-0.06	-0.03	0.12	**0.78**	-0.02
27. I've been praying or meditating.	Religion	0.23	0.12	0.16	0.06	**0.64**	-0.05
11. I've been using alcohol or other drugs to help me get through it.	Substance use	-0.01	0.28	0.02	-0.02	0.04	**0.80**
4. I've been using alcohol or other drugs to make myself feel better.	Substance use	0.00	0.26	0.09	-0.06	-0.04	**0.73**
21. I've been expressing my negative feelings.	Venting	0.04	0.24	0.14	0.02	0.29	0.11
9. I've been saying things to let my unpleasant feelings escape.	Venting	0.04	0.40	0.21	0.21	0.10	0.03
Variance (%)		13.18	9.45	8.29	5.98	4.94	4.61

removed the first two items of the venting subscale but retained the last item of the active coping subscale in the "problem-solving", based on a consensus of the expert panel on the relevance in the Vietnamese culture and in the HIV population in this country. Therefore, the revised model identified that the EFA contained 26 items from the original Brief COPE consisting of six subscales.

CFA of the revised scale

The second CFA was conducted to assess the structure of the revised scale. The model fit of the 26-item, 6-factor revised scale was comparable to that of the 28-item, 14-factor original Brief COPE (Table 2).

Internal consistency

The overall Cronbach's alphas of the original and revised scales were 0.86 and 0.85, respectively, indicating a good internal consistency. However, Cronbach's alpha of the original Brief COPE ranged from 0.44 (active coping) to 0.80 (substance use) for each subscale, whereas all the subscales of the revised scale showed good internal consistency with Cronbach's alpha > 0.7 (Table 4).

Convergent validity

The mean scores of each subscale of the revised scale were calculated in the depressed group and in the not depressed group for comparison (Table 5). The mean score of the "avoidance" and "substance use" subscales was significantly higher than that in the depressed group, whereas the mean scores of "problem-solving" and "social support" were significantly higher among those without depression. The Pearson correlation coefficients between the score of each subscale of the revised scale and MOS-SSS are shown in Table 6. The subscales of "problem-solving", "humor", "social support", and "religion" were positively associated with MOS-SSS, whereas the subscales of "avoidance" and "substance use" were negatively associated with MOS-SSS.

Table 4. Cronbach's alpha in the original and revised Brief COPE, overall and by subscale

Original scale 28 items, 14 factors			Revised scale 26 items, 6 factors		
Subscales	No. of items	Cronbach's alpha	Subscales	No. of items	Cronbach's alpha
All	28	0.86	All	26	0.85
Self-distraction	2	0.50	Problem-solving	7	0.82
Active coping	2	0.44	Avoidance	7	0.75
Denial	2	0.72	Humor	4	0.82
Substance use	2	0.80	Social support	4	0.80
Use of emotional support	2	0.73	Religion	2	0.71
Use of instrumental support	2	0.67	Substance use	2	0.80
Behavioral disengagement	2	0.45	-	-	-
Venting	2	0.45	-	-	-
Positive reframing	2	0.50	-	-	-
Planning	2	0.73	-	-	-
Humor	2	0.63	-	-	-
Acceptance	2	0.69	-	-	-
Religion	2	0.71	-	-	-
Self-blame	2	0.74	-	-	-

Table 5. Comparison of the mean score of six subscales in the revised scale by depressed and not depressed group

	Depressed (n = 150)	Not depressed (n = 999)	p value
	CES-D ≥ 16 Mean score ± SD	CES-D < 16 Mean score ± SD	
Problem-solving	14.03 ± 4.58	15.93 ± 4.25	< 0.001[a]
Avoidance	7.71 ± 3.97	3.61 ± 3.88	< 0.001[a]
Humor	6.55 ± 2.83	6.89 ± 3.27	0.18[b]
Social support	6.76 ± 2.95	8.89 ± 2.68	< 0.001[a]
Religion	2.32 ± 2.00	2.14 ± 1.98	0.3[a]
Substance use	0.94 ± 1.43	0.33 ± 0.86	< 0.001[b]

CES-D: Center for Epidemiologic Studies Depression Scale. [a]Student t-test. [b]Welch t-test.

Table 6. Pearson correlation coefficients between the six subscales in the revised scale and MOS-SSS

	Mean (SD)	MOS-SSS
Problem-solving	15.70 (4.35)	0.38**
Avoidance	4.16 (4.13)	-0.21**
Humor	6.86 (3.22)	0.10**
Social support	8.63 (2.81)	0.60**
Religion	2.17 (1.99)	0.22**
Substance use	0.40 (0.97)	-0.12**

**p < 0.01. MOS-SSS, Medical Outcome Study Social Support Survey.

Discussion

In this study, we evaluated the psychometric properties of the Brief COPE among PLWHA receiving ART in one of the biggest HIV clinics in Vietnam. In the EFA, we found a revised 26-item version which had a six-factor structure consisting of "problem-solving", "avoidance", "humor", "social support", "religion", and "substance use". Even with fewer factor structures, the model fitness of the revised scale was comparable to that of the original Brief COPE. Further, the internal consistency of the revised scale was even better than that of the original scale.

We found three items with factor loading < 0.4 in the EFA of the original Brief COPE. Among them, we removed two items which were related to *venting* negative feelings ("I've been expressing my negative feelings" and "I've been saying things to let my unpleasant feelings escape"), assuming a relatively small relevance for these two items in stress coping among Vietnamese HIV patients. Although over 90% of the participants reported that they had disclosed their HIV status to others (Table 1), only 12.4% had disclosed their status to a person outside family (data not shown). Therefore, it may be a fact that HIV patients cannot convey their emotions because of their small social network outside family and/or that they are afraid of their HIV status being disclosed by free expression. Another possible reason for the low factor loading of these two items might reflect a traditional value of self-control in the Vietnamese culture. In Vietnam, emotions are typically kept to oneself, whereas expressions of disagreement that may irritate or offend are avoided. There are also deep cultural restraints against showing "weakness" of the mind (*36*). Such tendencies might discourage their openness and venting negative feelings

to others. On the contrary, another item with factor loading < 0.4, one item of the active coping subscale ("I've been concentrating my efforts on doing something about the situation I'm in."), was retained in the revised scale considering its relevance in the Vietnamese cultural context. It also showed the highest factor loading of 0.37 on the "problem-solving" subscale, which seems to be conceptually rational.

In "problem-solving", both items from the acceptance, planning, and active coping subscales and one item from the positive reframing subscale were grouped together. It was similar to the findings from Carver's original factor analysis, which found that both items from the planning, active coping, and positive reframing subscales and one item from the acceptance subscale were loaded on a single factor. This could be explained by the fact that these subscales are all relevant to problem-focused coping, which explains all active efforts to manage or alter sources of stress.

Lazarus and Folkman presented three coping processes in their transactional model of stress and coping, primary appraisal and secondary appraisal, and coping (*1*). Primary appraisal is the process of perceiving a threat to oneself. Secondary appraisal involves people's evaluation of their resources and options for coping. Coping is the process of executing that response, which includes problem-focused coping and emotional-focused coping. Carver described that acceptance and planning are both related to the cognitive appraisal phase, whereas active coping, which is termed "problem-focused coping" by Lazarus and Folkman, occurs during the coping phase (*13*). According to their assessment, acceptance could occur in both primary and secondary appraisals; people accept a stressor as real in primary appraisal and the current absence of active coping strategies in secondary appraisal while attempting to deal with problems. Planning is defined as thinking about action strategies and how best to handle the problem, which occurs during the secondary appraisal. In addition, they explained that positive reframing intrinsically leads the person to continue active coping actions by construing a stressful transaction in positive terms. Therefore, clustering of the items from the above subscales is theoretically rationalized.

In contrast to "problem-solving", denial, self-blame, behavioral disengagement, and self-distraction were previously categorized in "dysfunctional" or "maladaptive" coping strategies (*24,37*) and loaded on a single factor, named "avoidance", in the EFA in our study. Similar clustering was found in other settings (*19,21,23*) including Carver's original factor analysis in which the items from the self-blame and denial subscales were loaded on a single factor (*12*). One article explained that denial and avoidance could be a common strategy of self-control in the Vietnamese. To avoid being overwhelmed by desperation, they often recognize the stressful situation using a special form of rationalization: "destiny" (*36*). Furthermore, particularly in the HIV population, these coping strategies are often discussed in relation to the HIV-related stigma. For example, multiple stigmas experienced by PLWHA stem in part from the perception of HIV, whose transmission is often perceived to be caused by controllable behaviors that are not sanctioned by societal, religious, and moral codes. Such social stigma affects cognitions, emotions, and behaviors of individual PLWHA (*38*), including blaming themselves for the acquisition of HIV/AIDS (self-blame) (*39*), denial of the HIV status (denial) (*40*), and mental disengagement (self-distraction) (*41*), which might lead to giving up the attempt to attain goals with which the stressor is interfering (behavioral disengagement).

Both items from the humor subscale and one item from the self-distraction and positive reframing subscales were loaded on a single factor, which was named "humor" in this study. The conceptual explanations for the clustering of these items could be provided by published studies. A study suggested that positive humor is closely related to the reappraisal of the situation (*42*), which might help people look on the bright side of the negative event (positive reframing). Another suggested that humor may attenuate negative emotions as a result of cognitive distraction (self-distraction) (*43*). However, cultural rationalization for this factor should be further explored.

The "social support" factor consisted of both items from the use of instrumental support and of emotional support, as had occurred in other studies (*17,21*), including the original analysis of the COPE inventory (*13*) and the Brief COPE (*12*). Although Caver distinguished them as two separate factors considering that they are distinct conceptually (*13*), these two social support functions often co-occur. Similarly, both types of social support have been consistently observed in the HIV population in Vietnam, it promotes disclosure of HIV status to others and mental health in this population (*11,44,45*).

"Religion" and "substance use" formed independent factors, as in the original Brief COPE (*12*) and in other studies (*17,18,21*). Vietnam has many religions, which include folk religion, three main religions of Buddhism, Taoism, and Confucianism (called "tam giáo" in Vietnamese), and Catholicism. The religions provide a strong influence on the beliefs and practices in this country. Indeed, one study in Vietnamese caregivers of patients with dementia found that such a multi-faceted Vietnamese religious system provides a set of cultural resources in which they can manage personal suffering/distress, motivation for caregiving, and understanding the nature of illness itself (*46*). On the contrary, injection of drugs is a major route of HIV transmission in Vietnam (*5*). Accordingly, 19.4% of all participants (32.3% of the male participants) in this study reported a history of using drugs by injection. Substance use, including

injectable drugs, is strongly related to stress.

Our study revealed that "avoidance" and "substance use" known as "maladaptive coping strategies" (*37*) tended to be utilized in the individuals with depression (CES-D ≥ 16) and were negatively associated with the MOS-SSS score. On the contrary, factors known as "adaptive coping strategies" showed the opposite results; "problem-solving" and "social support" tended to be utilized in those without depression (CES-D < 16), and "problem-solving", "social support", "humor", and "religion" were positively associated with the MOS-SSS score. Furthermore, among six factors in the revised scale, "social support" showed the strongest correlation with MOS-SSS. The findings are consistent with evidence from previous studies (*11,27,47-50*) and support the new structure of the revised scale.

HIV-infected individuals need to manage various stresses, which could not only affect individuals' health including mental health and poorer adherence to ART (*9,10*), but also have negative social influences including increase in new infections and medial cost. To reduce the individual and social burden of stress, effective interventions should be developed based on the understanding of coping strategies adapted by HIV patients. With its simplicity, the Brief COPE is a practically useful tool for it. To our knowledge, this is the first study to psychometrically validate the Vietnamese version of the Brief COPE using a large sample of the HIV-infected population. However, this study has several limitations. First, this study was carried out on HIV patients who had been receiving ART for a relatively long time at a large HIV clinic. Their coping strategies may be different from those not receiving ART or those who just started ART. Therefore, the characteristics of the participants may not accurately represent Vietnam's entire HIV population. Second, although Cronbach's alpha of each revised subscale showed good internal consistency, we did not evaluate the other type of reliability, external consistency (*i.e.*, test-retest reliability and alternate form reliability). The reliability of the revised scale should be further investigated in future studies. Finally, a paucity of literature on stress coping in Vietnam may have not allowed us to fully examine the cultural aspects of the revised scale. Different modes of surveys including face-to-face interview may help in understanding better the coping mechanisms and strategies, which are specifically relevant in the HIV population living in Vietnam.

In conclusion, this study provided a revised version of the Brief COPE with a six-factor structure. This new structure was supported both culturally and theoretically for an assessment tool of coping strategies in the HIV population in Vietnam. Further research is needed to add on the psychometric evidence of this new factor structure in PLWHA and other Vietnamese populations.

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Nucleos(t)ide reverse transcriptase inhibitor-sparing regimens in the era of standard 3-drug combination therapies for HIV-1 infection

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Abstract: Nucleos(t)ide reverse transcriptase inhibitor (NRTI)-sparing regimens have often been selected as antiretroviral therapy (ART) for HIV-1 infection recently, but data for characteristics have been lacking. This study aimed to document the current status of NRTI-sparing regimens in the era of standard 3-drug combination therapies. We cross-sectionally compared characteristics of patients treated with NRTI-sparing regimens (NRTI-sparing group) with dolutegravir plus tenofovir alafenamide fumarate/emtricitabine as a standard ART group in 2018. The NRTI-sparing and the standard ART groups included 61 and 469 patients, respectively. The mean (± standard deviation) age and serum creatinine of the NRTI-sparing group were significantly higher than those of the standard ART group (57.6 ± 12.8 years vs 42.8 ± 10.4 years ($p < 0.05$) and 2.09 ± 3.10 mg/dL *vs.* 0.93 ± 0.19 mg/dL ($p < 0.05$), respectively. The percentage of patients with NRTI-sparing regimens increased with age; with less than 5% in their 50s or younger, 8.4% in their 60s, and 14.1% aged ≥ 70 years. The primary reason for switching to the NRTI-sparing regimen was due to reduced renal function. According to the limited data, viral suppression was achieved at week 48 in all patients in the NRTI-sparing group. No patient had treatment failure nor developed drug resistance. The use of NRTI-sparing regimens increased with age. They were more frequently used in patients aged ≥ 60 years and those with decreased renal function.

***Keywords*:** antiretroviral therapy, renal function, aging

Introduction

An antiretroviral regimen for HIV-1 infection generally comprises two nucleos(t)ide reverse transcriptase inhibitors (NRTIs), namely backbone, plus a third drug from the integrase strand transfer inhibitor (INSTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or protease inhibitor (PI) drug classes (*1*), namely key drug. However, in some cases, NRTIs cannot be used because of medication-related adverse effects, accumulated toxicity, or drug resistance. In such situations, NRTI-sparing regimens can be selected. NRTI-sparing regimens are usually composed of two drugs, one each from two of the following three drug classes: INSTI, PI, or NNRTI. Several studies have shown the effectiveness and safety of NRTI-sparing regimens (*2-4*). The U.S. Department of Health and Human Services guidelines recommend darunavir/ritonavir (DRV/r) + raltegravir (RAL) for antiretroviral treatment-naïve patients who cannot use NRTIs (*1*). Although Japanese guidelines stipulate that NRTI-sparing regimens can be used for maintenance treatment in cases with well-controlled viral load, this recommendation is not based on evidence from Japanese patients. Therefore, this study aimed to figure out the status of NRTI-sparing regimens and reasons for regimen change in patients with HIV-1 infection. Efficacy of the NRTI-sparing regimens were also examined in the limited data.

Patients and Methods

There were 2,317 Japanese HIV-1-infected patients who had been treated with any antiretroviral treatment (ART) at AIDS Clinical Center, National Center for Global Health and Medicine as of the date of March 31, 2018. Among them, patients treated with tenofovir alafenamide fumarate/emtricitabine (TAF/FTC) + dolutegravir (DTG) and with NRTI-sparing regimens were included as the standard ART group and the NRTI-sparing group, respectively, and the characteristics why they were selected were analyzed cross-sectionally. The regimen of the standard ART group was chosen because it was the most frequently used one for ART naïve patients in 2018. Comparisons of the two groups were performed using Welch's *t* test and a $p < 0$ .05 was considered statistically significant. EZR (Saitama Medical Center, Jichi Medical

University, Saitama, Japan) was used for analyses.

As to efficacy of the NRTI-sparing group, the plasma HIV-RNA viral load (pVL) at 48 weeks after initiating the NRTI-sparing regimens was evaluated. Treatment success was defined if pVL was suppressed below 50 copies/ml. Patients whose initial pVL were less than 200 copies/ml and those who were lost to follow-up at the 48th week were excluded from the efficacy analysis.

This study was approved by the institutional review board of National Center for Global Health and Medicine (approval number: 3080).

Results

The NRTI-sparing group and the standard ART group included 61 (2.6%) and 469 (20.2%) patients, respectively, among 2,317 patients on ART. All patients of the NRTI-sparing group were switched from standard ART (a key drug + 2 NRTI backbone) except for 3 ART naïve patients. As for the 3 patients, NRTIs needed to be avoided due to renal function: two undergoing dialysis and one low creatinine clearance (CrCl) (< 30 mL/min).

Table 1 shows the patient characteristics. The NRTI-sparing group was significantly older than the standard treatment group (mean age ± standard deviation; 57.6 ± 12.8 years *vs.* 42.8 ± 10.4 years, $p < 0.05$, respectively). The mean serum creatinine (SCr) of the NRTI-sparing group was significantly higher than that of the standard ART group (2.09 ± 3.10 mg/dL *vs.* 0.93 ± 0.19 mg/dL, $p < 0.05$, respectively) and lower estimated glomerular filtration rate (eGFR) (60.7 ± 30.4 mL/min *vs.* 76.2 ± 32.5 mL/min, $p < 0.05$, respectively). The NRTI-sparing group also had a higher mean triglyceride (TG) than the standard ART group (201 ± 143 mg/dL *vs.* 135 ± 113 mg/dL, $p < 0.05$, respectively).

Figure 1 shows details of NRTI-sparing regimens. The most frequently used NRTI-sparing regimen was DTG + rilpivirine (RPV) (n = 28, 45.9%). If regimens were integrated into classes, the combinations were summarized with INSTI + NNRTI in 59% and INSTI + PI in 29.5%, namely almost all regimens included INSTI.

The primary reasons for changing to NRTI-sparing regimens were due to decreased renal function (n = 21, 34.4%), followed by avoidance of side effects (n = 15, 25.9%) or of drug-drug interactions (n = 7, 12.1%), drug resistance (n = 4, 6.9%), and desire to decrease daily pill number (n = 4, 6.9%). Then, we further analyzed status of the NRTI-sparing and the standard groups dividing by SCr levels (Figure 2). As presented, if SCr was elevated over 1.2 mg/dL, the NRTI-sparing regimen was preferentially selected.

Next, we showed connection between age and the NRTI-sparing regimens in Figure 3. As clearly stated, elderly patients were preferably treated with the NRTI-sparing regimens especially over their 60s. In detail, the usage rate was less than 5% among those in their 50s or younger, whereas it increased to 8.4% (19/225) and 14.1% (12/85) among those in their 60s and over 70 years, respectively.

None of the NRTI-sparing group had treatment

Table 1. Patients' demographics

Group *n* (%)	NRTI-sparing 61 (2.6)	Standard ART 469 (20.2)	*p*
Age, mean ± SD years	57.6 ± 12.8	42.8 ± 10.4	< 0.05
Male sex, *n* (%)	58 (95.1%)	445 (94.9%)	-
Infection route, *n*			
MSM	30	397	-
heterosexual	5	39	-
hemophiliacs	11	16	-
unknown	15	17	-
Naïve patients, *n* (%)	3 (4.9%)	33 (7.0%)	-
SCr, mean ± SD mg/dL	2.09 ± 3.10	0.93 ± 0.19	< 0.05
eGFR, mean ± SD ml/min	60.7 ± 30.4	76.2 ± 32.5	< 0.05
AST, mean ± SD IU/L	28.2 ± 24.0	28.9 ± 28.2	0.85
ALT, mean ± SD IU/L	31.6 ± 35.7	41.2 ± 68.7	0.54
LDL, mean ± SD mg/dl	104 ± 34.2	107 ± 31.0	0.51
TG, mean ± SD mg/dl	201 ± 143	135 ± 113	< 0.05
CD4*, mean ± SD /μL	508 ± 201	507 ± 266	0.97
HIV-RNA < 50 copy/mL*, *n* (%)	55 (90.1%)	378 (80.6%)	-

*at initiation of the regimen.

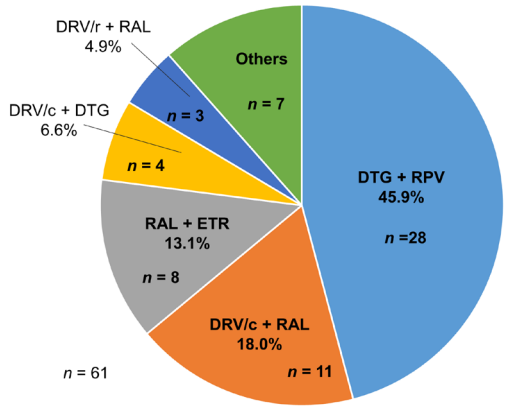

Figure 1. Details of the nucleos(t)ide reverse transcriptase inhibitor-sparing regimens used in this study. NRTI-sparing regimens accounted for only 61 (2.6%) of all (2,317) ART treatments in the study. DTG, dolutegravir; RPV, rilpivirine; DRV, darunavir; r, ritonavir; RAL, raltegravir; ETR, etravirine; c, cobicistat.

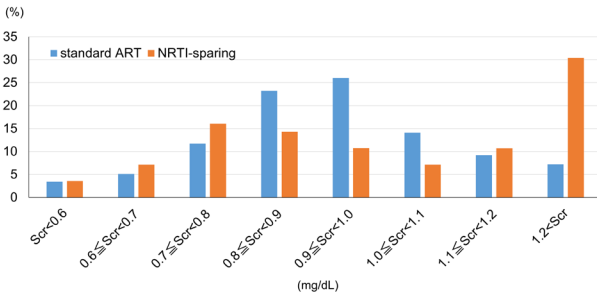

Figure 2. Frequencies of NRTI-sparing and standard ART groups usages in each serum creatinine (SCr) level. Frequencies of each group in each creatinine level were calculated dividing the number of patients in each group in each creatinine level by all NRTI-sparing regimens usage (n = 61) or all the standard ART regimen (n = 469), respectively.

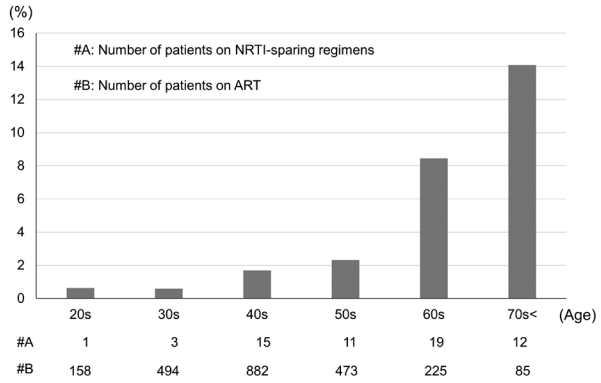

Figure 3. Connection of age and NRTI-sparing regimens. Denominator was number of all patients on ART in each age group.

failure nor developed drug resistance, and all patients exhibited viral suppression at week 48 after initiating the NRTI-sparing regimen.

Discussion

We evaluated characteristics of recent status of NRTI-sparing regimens in Japanese HIV-1-infected patients and found that use of NRTI-sparing regimens increased well with aging. This could be attributed to the age-related physical status decline in HIV-1-infected patients. For example, elderly patients have a decline in their renal function, develop lifestyle-related comorbidities, have increased concomitant drug use and their drug-drug interactions, and their side effects. Actually, renal dysfunction was the main reason for changing to NRTI-sparing regimens in this study. The standard regimens contained tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or abacavir/lamivudine (ABC/3TC) until 2017. However, neither can be used for patients with CrCl < 50 mL/min unless their dose was reduced. For example, if renal function declined to CrCl < 50 mL/min, TDF/FTC must be given every other day. This can lead to poor adherence. Therefore, the NRTI-sparing regimens are reasonable options for elderly patients. In Japan, we tried to demonstrate safety merit of a NRTI-sparing regimen of DRV/r + RAL switching from TDF/FTC + lopinavir/r in a randomized clinical trial (*5*). In this trial, we could not document significant recovery of renal function.

In contrast, drug-drug interactions between NRTIs and other drugs are rare (*6*), and thus changing to another regimen is rarely reported. This could happen in the use of a booster drug such as ritonavir or cobicistat.

Another reason why NRTI-sparing regimens are possible is that recently some drugs such as DRV or DTG have high genetic barriers, suggesting a lower risk of emergence of drug resistance and subsequent treatment failure (*2,3,7,8*). However, for example, even using a combination of DTG + RPV, it should be prescribed carefully with drug resistance of RPV to avoid functional monotherapy with DTG. Otherwise, emergence of DTG resistance will markedly decrease future treatment options.

There are three reasons when we think of NRTI-sparing regimens. One is due to avoidance of side effects caused by NRTIs. Decreased renal function in the elderly is that reason. This type of NRTI-sparing regimen use can be said to be a negative selection. Second one is a neutral reason for long-time safety and simplicity of ART, namely maintenance therapy. Development of a long acting drug makes it possible. Large clinical trials demonstrated safety and efficacy of this type of treatment strategy (*9,10*). The last one is an active reason in the choice of this regimen for ART naïve patients. Development of the strong drug, DTG, is the key. A large, double blind, randomized study documented the non-inferiority between DTG + 3TC and DTG + FTC/TAF (*11*). Although this regimen (DTG + 3TC) contains 3TC, it can be classified as one of the NRTI-sparing regimens and listed in the first line choice in the DHHS Guideline (*1*). This type of choice can be said to be a positive or active selection. According to our data, reasons for our NRTI-sparing regimens have been still limited in negative selection.

This study has some limitations. First, this was a single-center cross-sectional study with a smaller sample size. Therefore, strictly speaking, we cannot evaluate the efficacy of each regimen. However, in our efficacy analysis, all NRTI-sparing regimens achieved virus suppression after 48 weeks, consistent with the results of previous clinical trials (*2-4*). Second, duration of the study was limited. Therefore, we were not able to document the real-world long-term safety and efficacy of the NRTI-sparing regimens. Further and longer analyses could answer these clinical questions. However, it is noteworthy that this study first illustrated the current situation of NRTI-sparing regimens in Japan.

In conclusion, use of NRTI-sparing regimens have increased with age. They were more frequently used in patients aged ≥ 60 years and those with decreased renal function. In our limited data, we did not have treatment failure in patients treated with NRTI-sparing regimens.

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ViiV Healthcare, Merck Sharp & Dohme, Janssen Pharmaceutical K.K., and Torii Pharmaceutical, Co. Other authors declared none.

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BRIEF REPORT
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Cost-effectiveness of bronchial thermoplasty for severe asthmatic patients in Japan

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Abstract: Bronchial thermoplasty (BT) is an interventional endoscopic treatment for severe bronchial asthma. Some studies have shown the clinical efficacy of this intervention, but its cost-effectiveness is unclear. The aim of this study was to evaluate the cost-effectiveness of BT. We collected data from the medical records of 16 Japanese patients who were treated with BT between February 2015 and April 2017, and compared asthma-related medical expenses between the year preceding and the year following BT. Four patients were Global Initiative for Asthma (GINA) treatment step 4, and 12 were step 5. In 8 patients who had a successful response to BT, the annual asthma-related medical expenses decreased because of a reduction in hospitalization and emergency outpatient visits due to asthma attacks, and termination of the use of biologics. Most patients in the non-responder group had increased asthma-related medical costs postoperatively. The main reason for the increase in medical costs was the add-on treatment of biologics. BT was cost-effective in the responder group. If its effects continue for more than 10 years, BT will be a cost-effective treatment. Medical costs will be reduced if those who respond to BT can be identified prior to commencement of treatment.

***Keywords*:** intractable asthma, refractory asthma, bronchial asthma

Introduction

Bronchial thermoplasty (BT) treatment applies thermal energy to smooth muscle of the airway that has been thickened by severe asthma, resulting in a reduction in thickening (*1*). BT has been available in Japan since February 2015 and is covered by medical insurance for patients with severe asthma aged > 18 years in whom asthma symptoms cannot be controlled despite the use of high-dose inhaled corticosteroids (ICSs) and long-acting β2 agonists (LABAs) (*2*). Patients with severe asthma often do not respond to maximal pharmacological treatments with inhaled therapy or even long-term oral corticosteroids (*3*). Several biologics have recently been developed to reduce comorbidity due to systemic steroid use in these patients. However, biologics remain expensive and long-term use is usually inevitable (Table 1). These patients often require emergency room visits and hospitalization due to exacerbation of asthma several times a year. Such frequent exacerbations increase the patient's medical expenses, which is a heavy burden on the medical economy (*4*). Although several previous studies have reported that BT improved asthma-related quality of life and frequency of exacerbation, the cost effectiveness of BT is unclear (*5*). We examined whether BT is an economically useful treatment for severe asthmatic patients in Japan.

Materials and Methods

The study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (NCGM-G-001801-00). Written informed consent was obtained from each participant and the study was conducted according to the principles expressed in the Declaration of Helsinki. Included in the study were 19 patients with severe asthma who underwent BT at our hospital between February 2015 and April 2017. We retrospectively recorded the number of asthma medications, the number of exacerbations, and asthma-related medical expenses incurred in the year prior to and in the year following BT, and compared the pre-and post-treatment expenses. After excluding 2 patients who discontinued treatment after the second of 3 BT treatments and 1 who dropped out during the follow-up period, a total of 16 patients were included in the study. Medical expenses were calculated by aggregating the Japanese prices of asthma-related drugs.

Table 1. Biologics for bronchial asthma available in Japan

biologics	omalizumab	mepolizumab	benralizumab	dupilumab
injection interval	2 or 4 weeks	4 weeks	8 weeks	2 weeks
maintenance dose	75-600 mg	100 mg	30 mg	300 mg
cost per 4 weeks (JPY)	23,556-371,376	178,937	179,023	166,304

Medical expenses for emergency admission due to exacerbation of asthma were estimated at approximately 1,300 Japanese yen (JPY) including bronchodilator nebulizers, systemic steroid use for 5 days, and the examination fee calculated by the medical fee points decided by Ministry of Health Labor and Welfare in Japan. Medical expenses for hospitalization due to exacerbation of asthma were calculated as 143,150 JPY for a 7-day hospitalization, according to the Japanese Diagnosis Procedure Combination system of 2018. The medical cost of a course of 3 BT treatment sessions in Japan is approximately 1,300,000 JPY according to the medical fee points decided by Ministry of Health Labor and Welfare and Japanese Diagnosis Procedure Combination system of 2018. We classified the patients as responders (defined as patients who had a reduction in the number of exacerbations and the amount of asthma-related medication, or an improvement of the asthma symptoms after BT treatment; responder group) or as non-responders (non-responder group). Estimated cost-effectiveness was calculated as the difference of medical costs (one year) × 10 (years) minus BT treatment cost.

Results

Sixteen patients with severe asthma received BT treatment between February 2015 and April 2017 (Figure 1). The median age was 51.5 years and the sex ratio was 1:1. The ratio of smokers *vs.* never smokers was 3:1 and the median number of exacerbations during the preoperative year was 4.5. The GINA treatment step was step 4 in 4 cases and step 5 in 12 cases. The median eosinophil count was 67/μL and the median total-IgE was 154 U/mL. Many of the patients had received preoperative pharmacotherapy such as high dose ICSs and LABAs in addition to long-acting muscarinic antagonists (LAMAs), leukotriene receptor antagonists (LTRAs), and theophylline. Oral steroids were administered in 6 patients and omalizumab in 7 patients (Table 2).

Table 3 lists the asthma-related medical expenses in the year preceding and following BT for responders and non-responders. The total annual asthma-related medical expenses for all 16 patients decreased by a total of about 686,273 JPY after BT. Eight patients had fewer asthma attacks after BT and were classified as responders, and 8 who did not have a reduction in the number of asthma attacks after BT were classified as non-responders. In the responder group, the number of asthma exacerbations per year decreased from a median value of 4 times (range, 0-12) to 0 (range, 0-11), and the annual asthma-related medical costs decreased by a median value of 243,713 JPY (range, 77,341-603,099 JPY). Annual asthma-related medical expenses decreased in all responders because of a decrease in the number of hospitalization and emergency outpatient visits due to asthma attacks, and termination of the use of biologics. Of the non-responders, 4 had unchanged symptoms and 4 patients had worsening symptoms after the BT procedure. There was no change in the number of asthma exacerbations in this group and some patients increased the dose of asthma medications or introduction of biologics after the BT treatment. Accordingly, the annual asthma-related medical costs increased by a median value of 157,534

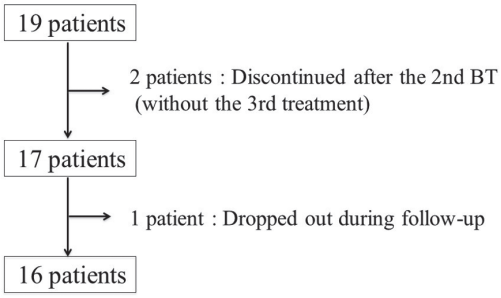

Figure 1. Overview of the study selection process. Patients who underwent BT treatment between February 2015 and April 2017.

Table 2. Patient characteristics

Characteristic	Median (range)
Age (y)	51.5 (33-77)
Gender (male/female), *n*	8/8
Smoking (never/ex), *n*	12/4
Exacerbations per year, *n*	1.5 (0-24)
Exacerbations requiring hospitalization, days	0 (0-27)
GINA step (4/5), *n*	4/12
Eosinophil, /μL	67 (0-616)
Total IgE, U/mL	154 (29-2,318)
Medications	Median (range)
Short-acting β2 agonist	8 (50%)
Long-acting β2 agonist	16 (100%)
Inhaled corticosteroids	16 (100%)
Long-acting muscarinic antagonist	14 (88%)
Leukotriene receptor antagonist	15 (94%)
Theophylline	12 (75%)
Oral corticosteroids	6 (38%)
Omalizumab	7 (44%)

Table 3. Asthma-related medical expenses one year prior to and following BT

Group	No.	Sex	Age (y)	Preoperative medical expenses (JPY)	Postoperative medical expenses (JPY)	Difference (JPY)	Main reason of change of medical expenses	Estimated cost-effectiveness of BT for 10 years (JPY)
Responders	1	M	67	4,353,018	4,159,702	193,316	No hospitalization	633,160
	2	F	71	1,173,150	570,051	603,099	Withdrawal of biologics	4,730,990
	3	F	65	846,508	381,754	464,754	No hospitalization	3,347,540
	4	M	55	848,567	505,355	343,212	No need for frequent SABA inhalation	2,132,120
	5	M	62	556,261	478,920	77,341	No need for intravenous steroid administration	-526,590
	6	M	48	414,241	317,694	96,548	Reduction of ER visits	-334,520
	7	F	77	1,144,055	1,065,650	78,405	Disappearance of asthma attacks	-515,950
	8	M	46	646,140	352,031	294,109	No need for oral steroids	1,641,090
			Sub total	9,981,940	7,831,157	2,150,783		11,107,840
Non-responders	9	F	33	3,798,768	3,756,726	42,042	Frequent asthma attack	-879,580
	10	F	43	326,941	316,631	10,310	Symptoms unchanged	-1,196,900
	11	M	36	2,859,716	3,017,250	-157,534	New biologics use	-2,875,340
	12	F	69	224,402	565,945	-341,543	Frequent asthma attack	-4,715,430
	13	M	47	5,278,305	2,799,666	2,478,639	Switching biologics	23,486,390
	14	M	68	381,846	2,599,006	-2,217,160	New biologics use	-23,471,600
	15	F	35	2,936,701	2,935,568	1,133	New biologics use	-1,288,670
	16	F	40	652,241	1,932,638	-1,280,397	New biologics use	-14,103,970
			Sub total	16,458,920	17,923,430	-1,464,510		-25,045,100
			Total	26,440,860	25,754,587	686,273		-13,937,260

JPY (range, -2,478,639 to 2,217,160 JPY). The main reason for the increase in medical costs was add-on biologic treatments such as omalizumab or mepolizumab. The medical cost decreased significantly in 1 patient, but this was due to a change in biologic from omalizumab to mepolizumab, but there was no significant improvement in symptoms.

The cost-effectiveness of BT was estimated in Table 3 if the effect of BT continues for 10 years. The cost-effectiveness of BT was not observed in the total 16 patients. However, the average cost-effectiveness of BT was observed in BT responders (1,388,479 JPY for 10 years per person).

Discussion

There are 2 types of medical costs: direct costs (hospital consultation costs, drug prices, hospitalization costs) and indirect costs (social costs arising from taking leave from work, *e.g.*, due to asthma attacks). In this study, we investigated and compared only the direct costs; however, we consider that the remission of asthma in the responder group after BT retreatment also reduced the indirect costs, and that if the direct and indirect costs were combined, the treatment would be even more cost-effective. In a previous study that examined the cost-effectiveness of standard therapy, BT, and omalizumab over 5 years in patients with moderate to severe asthma in Canada, BT was cost-effective in > 60% of patients (*6*). A study of the cost-effectiveness of BT and high-dose combination therapy in patients with severe persistent asthma in the USA using quality-adjusted life year (QALY)/incremental cost-effectiveness ratio (ICER) found that BT was cost-effective in about 66% of patients (*7*). In another study in the USA, BT was estimated to be cost-effective in patients with severe uncontrolled asthma who had a high risk of exacerbation (*8*). In contrast, a study that examined the cost-effectiveness of patients with severe asthma in Singapore who received standard therapy alone or standard therapy plus BT showed that BT was not cost-effective (*9*). It is important to note that the results of these previous studies differ slightly because the costs of BT and emergency outpatient consultation differ among these countries. In addition, there is selection bias in patients who received BT, (*e.g.*, severity) in clinical practice in each country. In the present study, 5 patients (31%) had markedly increased asthma-related medical expenses following BT, caused mainly by the introduction of new biologics to treat the unchanged symptoms. The factors that are predictors of response to BT are not yet known. The identification of responders prior to BT treatment would enable a further reduction in medical costs.

A recent study of 192 patients enrolled in Asthma Intervention Research (AIR), AIR2, or Research in Severe Asthma (RISA) trials demonstrated that a reduction in severe exacerbation continued for more than 10 years after BT treatment (median, 12.1 years; range, 10.6-15.8 years) (*10*). Based on the estimated annual reduction in asthma-related medical expenses shown in Table 3, we would expect savings to exceed direct BT treatment costs (approximately 1.3 million JPY) within 10 years after BT in 5 of the responders. So far, there is evidence only that the effects of BT will last for 10 years (*10*); however, if the therapeutic effects continue for more than 10 years, further cost-effectiveness of BT can

be expected.

A recent previous study reported that baseline Asthma Control Questionnaire (ACQ) score and exacerbation frequency were a predictor of BT responders (*11*). In our study, the median number of asthma exacerbations in the responder group during the preoperative year was 4 times (0-12) and the median number of asthma exacerbations in the non-responder group was 0 times. Our results supported the previous study that the number of preoperative asthma exacerbations is one of the factors for predicting BT responders.

There are several limitations in this study. First, the number of patients is small, the study design is retrospective, and it was conducted at a single center. Second, the preoperative annual medical expenses were estimated according to the number of asthma exacerbations. The actual direct expenses for each patient may differ slightly from the estimated expenses. A large prospective multi-center study is required to further elucidate the cost-effectiveness of BT.

In conclusion, in terms of the calculated asthma-related medical expenses after treatment, BT therapy was cost-effective in responders. Identification of BT responders will further increase the cost-effectiveness of BT.

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LETTER
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Telephone consults at the Infectious Disease Outpatient Clinic during the early period of the COVID-19 epidemic

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Abstract: Once novel coronavirus disease 2019 (COVID-19) emerged in Wuhan, China in December 2019 and the first case in Japan was reported the following month, telephone inquiries to the Infectious Disease Outpatient Clinic increased. During the first wave of the epidemic, before medical measures for this emerging infectious disease were in place, the Outpatient Clinic received a significant amount of inquiries, reflecting the prevailing social turmoil. During the second wave, inquiries did not increase because a proper system of medical care was in place in hospitals and communities. Therefore, in the early stages of an emerging infectious disease, relevant information needs to be quickly consolidated and it needs to be linked to measures that are appropriate to the situation.

***Keywords*:** emerging disease, risk assessment, outpatient, foreign patient

The National Center for Global Health and Medicine (NCGM) is a medical facility assigned by the Japanese Government to deal with infectious diseases. The NCGM's Infectious Diseases Outpatient Clinic handles consultations regarding imported and general infectious diseases. Once novel coronavirus disease 2019 (COVID-19) emerged in Wuhan, China in December 2019 and the first case in Japan was reported the following month, telephone inquiries to the Outpatient Clinic increased.

The World Health Organization (WHO) has devised a rapid method of risk assessment for appropriate decision-making in response to a public health crisis (*1*). Information is essential to that process. During this crisis, telephone inquiries have served as a source of information regarding public concerns. Therefore, inquiries received at the Clinic were tracked, and COVID-19-related telephone inquiries during the initial response to the crisis have been reported here.

Nurses and a clerk of the Infectious Disease Outpatient Clinic were tasked with recording all COVID-19-related calls received at the Clinic. Telephone consults in the text refers to nurses or a clerk in the Clinic respond to patients on the advice of infectious disease specialists. From January 30 to August 31, 2020, 1,922 calls were received. The most common inquiry was "A request for a consult and an examination" (1,177), followed by "Other subjects" (476) and "A request for hospitalization or transfer" (97). Many of the inquiries about “Other subjects” related to polymerase chain reaction (PCR) testing. In the first wave of the epidemic, there was a sharp increase in telephone inquiries to the Clinic, and this was presumably linked to an increase in positive cases in Tokyo (Figure 1) (*2,3*). As the early stages of an epidemic often generate uncertainty about the nature and impact of a disease (*4*), a telephone consultation system needs to be enhanced since the number of inquiries (including concerns) increases.

From January to early February when the disease was concentrated in China, the number of inquiries regarding Japanese returning from China increased, such as "I'm worried because my father is returning from China.” There were 131 (6.7%) inquiries from foreign nationals. Foreign inquiries were mainly received from January to April. In late January, the NCGM conducted COVID-19 screening for returnees from Wuhan, and a system for receiving patients, including infection control measures, was established (*5*). At the time, Chinese medical interpreters assisted the Infectious Disease Outpatient Clinic in cooperate with the NCGM's International Health Care Center. On February 3 when the cruise ship Diamond Princess arrived in port, there were 14 inquiries from foreigners, 12 of whom were Chinese; this marked the first peak in the number of inquiries. During this period, people were highly

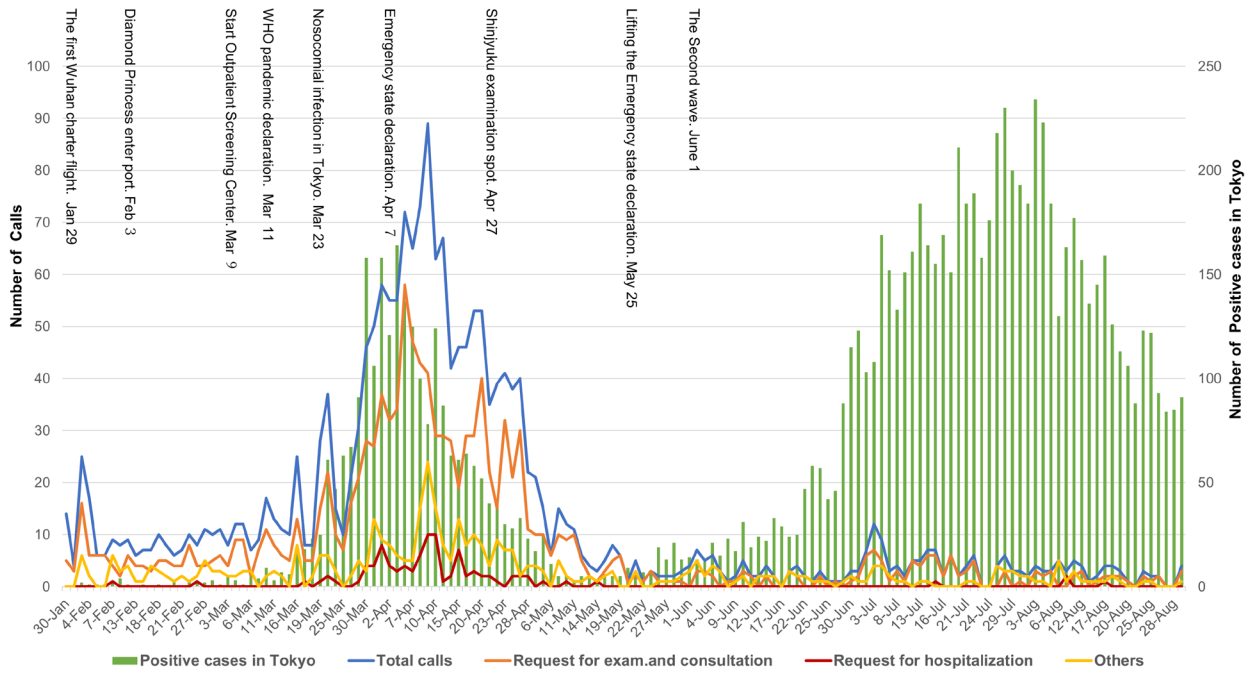

Figure 1. Changes in the number of telephone consults and positive cases in Tokyo. Positive cases in Tokyo: positive number by developed date; data source: *https://stopcovid19.metro.tokyo.lg.jp/cards/positive-number-by-developed-date/*

anxious (*6*).

Additional inquiries were received from Chinese citizens and travelers with a fever and other symptoms who were rejected by medical facilities. Therefore, affiliated medical facilities with Chinese-language capabilities were contacted and asked to treat mild cases of COVID-19. Directing Chinese patients with mild cases of COVID-19 to those affiliated medical facilities reduced the burden on the Outpatient Clinic. The initial development of a consultation system included the preparation of a telephone consultation manual, the assignment of a physician specializing in infectious diseases, and an immediate increase in the number of nurses answering telephones, all of which enabled consistent telephone consults and the collection of information.

In early February, a coherent clinical picture emerged from Wuhan (*7*). When travel restrictions from China were tightened in mid-February, consultations from returnees decreased. Conversely, the number of consults from Japanese people with symptoms began to increase. Responding to these inquiries via administrative procedures alone was difficult, and a testing and medical consultation system run by dedicated staff needed to be established. When reimbursement for PCR testing was included in National Health Insurance, preparations were begun to establish a fever consultation system at a different location than the Infectious Disease Outpatient Clinic, ahead of notification from the Ministry of Health, Labour, and Welfare (MHLW) and the local government.

The number of consultations peaked by April 9, two days after the declaration of a state of emergency, and the number of "requests for hospitalization or transfer" of critically ill patients also peaked. At the end of April, Shinjuku City set up a "Shinjuku Examination Spot" on the premises of this hospital, in collaboration with other medical facilities and laboratories. Since then, the number of phone calls to the Infectious Disease Outpatient Clinic has decreased dramatically, and medical care at the Clinic has returned to normal.

The first wave of inquiries to the Infectious Disease Outpatient Clinic in the early stages of the epidemic reflected the prevalent social turmoil and resulted in a significant number of inquiries to this hospital. The immediate response to these inquiries helped to establish a system of medical care in hospitals and communities. During the second wave of the epidemic, the number of inquiries did not increase because hospitals and communities had adequate systems of medical care.

These experiences indicate that in the early stages of an emerging infectious disease, information needs to be quickly consolidated and it needs to be linked to measures that are appropriate to the situation. The hope is that this description of those experiences will help during similar situations in the future.

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LETTER

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Using flowchart for ophthalmic consultations in hospitalized patients with COVID-19

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Abstract: Ocular complications of coronavirus disease 2019 (COVID-19) do not essentially cause serious visual loss. However, due to the characteristics of this disease, delays in diagnosis and treatment in hospitalized patients may leave them with serious visual impairment. If conjunctivitis is suspected, ophthalmological follow-up is needless because it is expected spontaneous healing. Diplopia is often complicated for extra-ocular neurological findings and need neurological consults. Ophthalmologists should be consulted for ocular surface disease, high intraocular pressure, and ocular inflammation that may cause visual loss if patients complain of blurred vision, visual loss, and ocular pain. The problem is unconscious patients with risk of developing high intraocular pressure or keratitis. An ophthalmologist should be consulted as soon as possible if eye redness or pupil abnormalities appear in these patients. We developed a flowchart for ophthalmic consultations in hospitalized patients with COVID-19, for facilities where an ophthalmologist is not always present, and for third or fourth waves or, a pandemic of another infectious disease.

***Keywords*:** COVID-19, flowchart, ocular complication, ophthalmology, eye

Almost one year has passed since the emergence of the new coronavirus. In addition to conjunctivitis, there have been reports of serious sight-threatening ocular diseases, particularly in hospitalized patients who have been left with impaired vision after recovery from coronavirus disease 2019 (COVID-19). Ideally, an ophthalmologist should be present for all cases of suspected ocular disease. However, not all facilities that accept COVD-19 patients have an ophthalmologist on staff. At the National Center for Global Health and Medicine, the Department of Ophthalmology, Disease Control and Prevention Center, and Department of Intensive Care Medicine staffs have been working together to reduce the risk of infection among ophthalmologists, and minimize the wasteful use of medical materials including PPE, with the primary goal of eliminating visual impairment in COVID-19 patients. Based on previous reports, we developed a flowchart of ophthalmic consultations in hospitalized patients with COVID-19, for use in facilities where an ophthalmologist is not always present, and useful in the event of a third or fourth wave, or a pandemic of another infectious disease.

Conjunctivitis was the first reported ocular manifestation of COVID-19 (*1*). If patients have no consciousness disorder and present mostly bilateral conjunctival hyperemia, chemosis, epiphora, watery discharge, mild eyelid edema without blurred vision or sight-threatening events, Route A in Figure 1 is thought for conjunctivitis, and only follow up would be needed because these findings are heal spontaneously.

Route B and C is thought to be Neuro-Ophthalmological Complications. If patients complain about diplopia with extraocular neurological findings like polyneuritis, Guillain–Barré syndrome, meningitis, encephalomyelitis, and encephalopathy, intracranial disease should be suspected and a neurologist should be consulted first (Route-B) (*2*). Patient complaints about diplopia without other neurological findings are rare cases. When peripheral abducens or oculomotor nerve palsy is suspected in COVID-19 inpatients, ophthalmological examinations should end (Route-C) and careful neurological follow up should be initiated.

The most common ocular complications are ocular surface disorders. When patients complain of blurred vision and irritation or ocular pain, existence of ocular surface disorders, especially infectious keratitis, should be ruled out. In cases of high intraocular pressure (IOP) that leads to blurred vision and deep ocular pain with nausea or vomiting, immediate ocular treatment is necessary to avoid permanent visual loss (Route-D).

If patients complain of blurred vision or visual

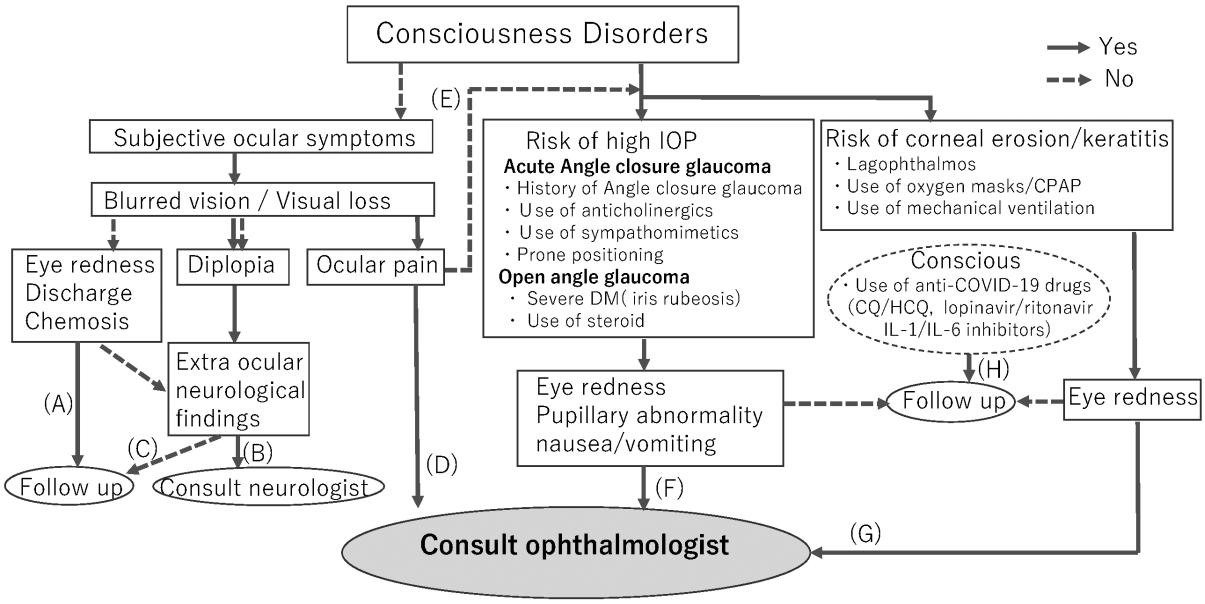

Figure 1. Flowchart for ophthalmic consultations and suspected diseases in hospitalized patients with COVID-19. Route **(A)** conjunctivitis, **(B)** intracranial diseases, **(C)** peripheral abducens or oculomotor nerve palsy, **(D)** ocular surface disorders or high IOP, **(E)** retinal diseases or optic neuritis, **(F)** high IOP, **(G)** infectious keratitis secondary to corneal erosion, **(H)** side effect of medicine for COVID-19. CPAP, continuous positive airway pressure; CQ, Chloroquine; DM, diabetes mellitus; HCQ, hydroxychloroquine; IOP, intraocular pressure.

loss only, retinal diseases or optic neuritis should be considered. COVID-19-associated coagulopathy may predispose patients to a spectrum of thromboembolic events. As for retinal findings, not only subtle cotton-wool spots and microhemorrhages along the retinal arcade (*3*), but isolated central retinal artery occlusion and impending central retinal vein occlusion secondary to COVID-19 has been published (*4,5*). The latter leads to visual loss without ocular pain and extra ocular neurological complications. However, even though macular edema occurs after occlusion, only follow up is required because of the difficulty of ophthalmological treatments like anti-vascular endothelial growth factor (VEGF) vitreous injection. Ischemic or inflammatory optic neuritis, progression of pre-existing diseases, such as diabetic retinopathy or age-related maculopathy, will also contribute to visual loss. However, a full ophthalmological examination is difficult and ocular treatment is limited to hospitalized patients with COVID-19. Therefore, if the risk of high IOP or infectious keratitis due to corneal erosion can be ruled out, these diseases can be followed until a full ophthalmological examination and treatment is available after discharge (Route-E).

For severe COVID-19 patients in Intensive Care Units who could not convey eye problems by consciousness disorder, high IOP is the most notable sight-threatening complication. In general, a history of angle-closure glaucoma, use of anticholinergics (atropine, ipratropium bromide, tricyclic antidepressants, and antihistamine), sympathomimetics (adrenaline, noradrenaline, dopamine, ephedrine, salbutamol, and terbutaline), and other drugs (sulfonamides derivatives and topiramate), are risk factors for acute angle-closure glaucoma. Moreover, prone positioning for improving respiratory outcomes can critically reduce ocular perfusion causing an increase in venous pressure and subsequent increase IOP (*6*). Diabetes mellitus (DM) is one of the factors that can make COVID-19 more severe, and systemic steroids are used for severe patients. Iris rubeosis due to proliferative diabetic retinopathy, and longitudinal use of steroids for steroid responders, these are not angle-closure, sometimes increases IOP. When patients have the fore-mentioned risks, and emerging eye redness, larger pupil size in affected eye, nausea or vomiting; IOP check-up should be done as soon as possible (Route-F).

Infectious keratitis due to corneal erosion should be avoided in patients with consciousness disorder (*7*). Lagophthalmos due to use of muscle relaxants or sedating agents, dry eyes from oxygen masks, continuous positive airway pressure (CPAP), or mechanical ventilation leads to ocular surface disorder. This can develop primarily into infectious keratitis and eventually corneal erosion resulting in irreversible visual loss by corneal opacity (Route-G).

The side effects of COVID-19 medication should be taken into account. Chloroquine (CQ) and its derivative hydroxychloroquine (HCQ) are mainly used to treat malaria, amebiasis, and rheumatologic diseases, while

lopinavir and ritonavir are widely used for the treatment of HIV. The reported toxicity of these drugs include irreversible sight-threatening maculopathy called Bull's eye. Despite the fact that most of the patients treated with CQ and HCQ for COVID-19 receive potentially retinotoxic doses, no reports of retinal toxicity have been described under 2 weeks of CQ or HCQ administration. Moreover ritonavir-associated retinal toxicity has been reported with limited chronic use. Significantly short-term use for these drugs for COVID-19 treatment might be a small concern for retinal toxicity (*8,9*). Interleukin-1 inhibitors (*e.g.*, anakinra) and interleukin-6 inhibitors (*e.g.*, sarilumab, siltuximab, and tocilizumab) under evaluation for the treatment of COVID-19 should be monitored for nystagmus or bilateral retinopathy side effects (Route-H).

At present, telecommunication using smartphones in ophthalmology is rapidly evolving. Anterior segment imaging especially, does not require an ophthalmologist and can be performed by paramedical staff. Some superior quality devices make it possible to provide posterior pole retina and optic disc images without any attachments (*10*). To prevent visual impairment for inpatients with COVID-19, it is important to follow this flowchart, sometimes with use of mentioned devices, for consultation with ophthalmologist at the appropriate time.

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CORRIGENDUM

It has come to the authors' attention that their article entitled "Impact of sex and histology on the therapeutic effects of fluoropyrimidines and oxaliplatin plus bevacizumab for patients with metastatic colorectal cancer in the SOFT trial" (*Global Health & Medicine. 2020; 2(4):240-246. DOI: 10.35772/ghm.2020.01050*) included an error in Table 1. The corrected detailed is published with this corrigendum for your reading.

Table 1. Baseline characteristics of male and female patients

Items	SOX/Bev (*n* = 250)				*P*	FOLFOX/Bev (*n* = 249)				*P*
	Male (*n* = 167)		Female (*n* = 83)			Male (*n* = 156)		Female (*n* = 93)		
	n	%	*n*	%		*n*	%	*n*	%	
Age										
< 70	120	71.9	67	80.7	0.164	116	74.4	69	74.2	1.000
≥ 70	47	28.1	16	19.3		40	25.6	24	25.8	
Primary lesion										
Colon	80	47.9	48	57.8	0.422	76	48.7	47	50.5	0.225
Rectosigmoid	30	18.0	14	16.9		21	13.5	19	20.4	
Rectum	55	32.9	20	24.1		59	37.8	27	29.0	
Others	2	1.2	1	1.2		0		0		
Differentiation assessed by histology										
Well or moderate	148	88.6	67	80.7	0.223	135	86.5	77	82.8	0.331
Poorly	6	3.6	5	6.0		4	2.6	6	6.5	
Other	13	7.8	11	13.3		17	10.9	10	10.8	
Adjuvant chemotherapy for colorectal cancer										
No	142	85.0	72	86.7	0.849	128	82.0	83	89.2	0.147
Yes	25	15.0	11	13.3		28	18.0	10	10.8	
Target lesion										
No	12	7.2	9	10.8	0.340	11	7.0	11	11.8	0.249
Yes	155	92.8	74	89.2		145	93.0	82	88.2	
Liver metastases										
No	45	26.9	38	45.8	0.004	53	34.0	34	36.6	0.683
Yes	122	73.1	45	54.2		103	66.0	59	63.4	
Lung metastases										
No	93	55.7	50	60.2	0.501	87	55.8	47	50.5	0.434
Yes	74	44.3	33	39.8		69	44.2	46	49.5	
Lymph node metastases										
No	123	73.7	66	79.5	0.350	119	76.3	67	72.0	0.456
Yes	44	26.3	17	20.5		37	23.7	26	28.0	
Other metastases										
No	135	80.8	53	63.9	0.005	136	87.2	70	75.3	0.024
Yes	32	19.2	30	36.1		20	12.8	23	24.7	
Metastatic organs										
1	73	43.7	38	45.8	0.788	83	53.2	44	47.3	0.432
≥ 2	94	56.3	45	54.2		73	46.8	49	52.7	

P: Fisher's exact test. Bev, bevacizumab; FOLFOX, 5-FU/*l*-leucovorin plus oxaliplatin; SOX, S-1 plus oxaliplatin.

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Information for Authors

1. Scope of Articles

Global Health & Medicine is (Print ISSN 2434-9186, Online ISSN 2434-9194) 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.

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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
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); ~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.

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The submission to *Global Health & Medicine* should include:

1. Cover letter
2. Main manuscript
3. Figures
4. Supplementary Data, 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

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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. The EndNote Style of *Global Health & Medicine* could be downloaded at Download Center.

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