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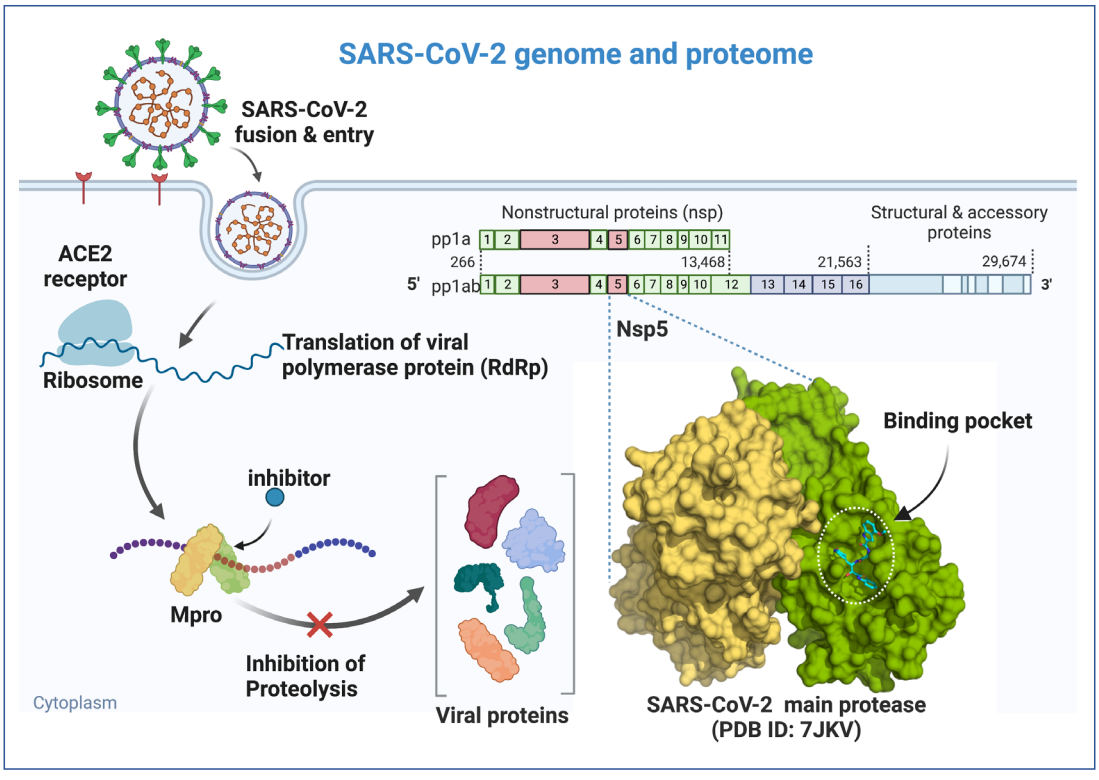

Schematic representation of the SARS-CoV-2 docking onto human ACE2 receptor, entry into the cell, and proteolytic cleavage of viral polypeptides by M^{pro} (page. 297)

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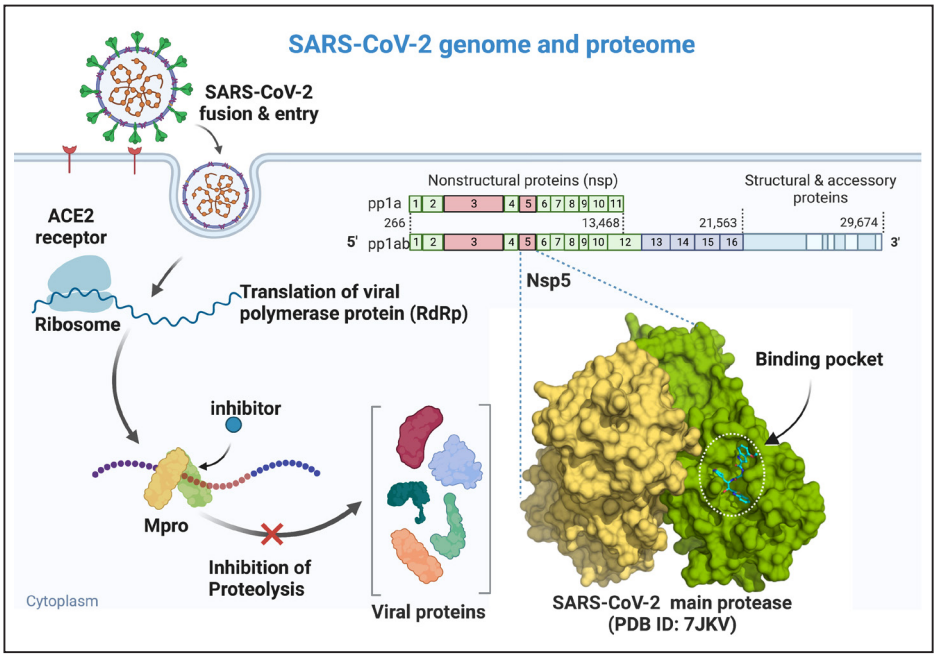

Schematic representation of the SARS-CoV-2 docking onto human ACE2 receptor and entry into the cell. Inside the cell, SARS-CoV-2 replicates its RNA genome in order to manufacture numerous viral proteins using host ribosomes. The proteome of SARS-CoV-2 consists of two non-structural polyproteins pp1a (490 kDa), pp1ab (794 kDa), and additional structural & accessory proteins (pale cyan) such as spike, envelope, membrane, and nucleocapsid. Protomers of M^{pro} is shown in green and yellow, breaking polypeptides into functional viral proteins. Inhibition of M^{pro} with small compound blocks this essential step in viral life cycle. Figure created using Biorender (*https://biorender.com*). (page. 297)

Global Health & Medicine. 2022; 4(6):296-300.
MINI-REVIEW
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Drug development targeting SARS-CoV-2 main protease

Haydar Bulut*

The Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA.

Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its variants are responsible for the devastating coronavirus disease 2019 (COVID-19) pandemic with more than 6.5 million deaths since 2019. Although a number of vaccines significantly reduced the mortality rate, a large number of the world population is yet being infected with highly contagious omicron variants/subvarints. Additional therapeutic interventions are needed to reduce hospitalization and curb the ongoing pandemic. The activity of the SARS-CoV-2 enzyme; chymotrypsin-like main protease (M^{pro}) is essential for the cleavage of viral nonstructural polypeptides into individual functional proteins and therefore M^{pro} is an attractive drug target. The aim of this review is to summarize recent progress toward the development of therapeutic drugs against M^{pro} protease.

***Keywords*:** COVID-19, SARS-CoV-2, main protease, drug development

Introduction

The ongoing COVID-19 pandemic initially started with SARS-CoV-2 infection in China, and since then it has evolved to more contagious mutant variants such as delta, and omicron (*1*). The original SARS-CoV2 originated in Wuhan, China has disappeared in the meantime. Many vaccines, including the most effective ones based on novel mRNA technology, cannot fully stop infections (*2,3*). In addition, high mutation rates of coronavirus decreased the vaccine efficacy (*4*).

The genome of SARS-CoV-2 consists of single-stranded positive-sense RNA, which encodes two non-structural polyproteins and several structural & accessory proteins (Figure 1). Non-structural proteins are initially produced in two segments, the shorter polypeptide pp1a contains around 11 proteins, and the larger pp1ab consists of 16 different proteins. Those polypeptide chains need to be processed into single functional units to assemble into new viruses (Figure 1). SARS-CoV-2 contains two different enzymes responsible for the proteolysis of the non-structural polypeptides into single functional proteins. While papain-like protease (PL^{pro}) cleaves the polyproteins at three different sites, SARS-CoV-2 chymotrypsin-like main protease (M^{pro}) cleavage reaction takes place at eleven sites. Inhibition of those viral protease enzymes effectively interrupts the formation of functional viral proteins required for the viral life cycle (*1*).

M^{pro} is one of the most heavily studied drug target in terms of therapeutic development for treating COVID-19, and so far more than 2,700 structures of the M^{pro} have been submitted to protein data bank (PDB) mostly in complex with drug candidates & fragments. Actually, drug development targeting M^{pro} started with emerging SARS-CoV-1 and MERS coronavirus infections prior to SARS-CoV-2 (*5*). Some of the lead compounds had already been designed for the M^{pro} of SARS-CoV-1.

Enzymatic activity and Substrate recognition M^{pro}

M^{pro} functions as a dimer, consisting of 3 domains for each protomer. While two catalytic domains consist of beta sheets forming a substrate binding cleft, the C-terminal domain consists of entirely alpha helices that function as dimerization platforms by interacting with N-terminal residues from the second protomer. Mutations or truncations of N-terminal residues result in a dramatic reduction in enzyme activity, based on this observation several attempts have been made to design dimerization inhibitors that mimic the N-terminal residues, however, this approach has shown limited success so far (*6*).

Natural cleavage sites of M^{pro} have been analyzed in molecular detail in recent studies (*7,8*). Except for the fully conserved glutamine residue at P1 position, the eleven cleavage sites show little conservation. Interestingly, the P1' position within the nsp8-nsp9 sequence is uniquely conserved among the various coronaviruses. In contrast to other cleavage sites, which are occupied by rather small residues of Ser or Ala at P1' position, the nsp8-nsp9 sequence is substituted with

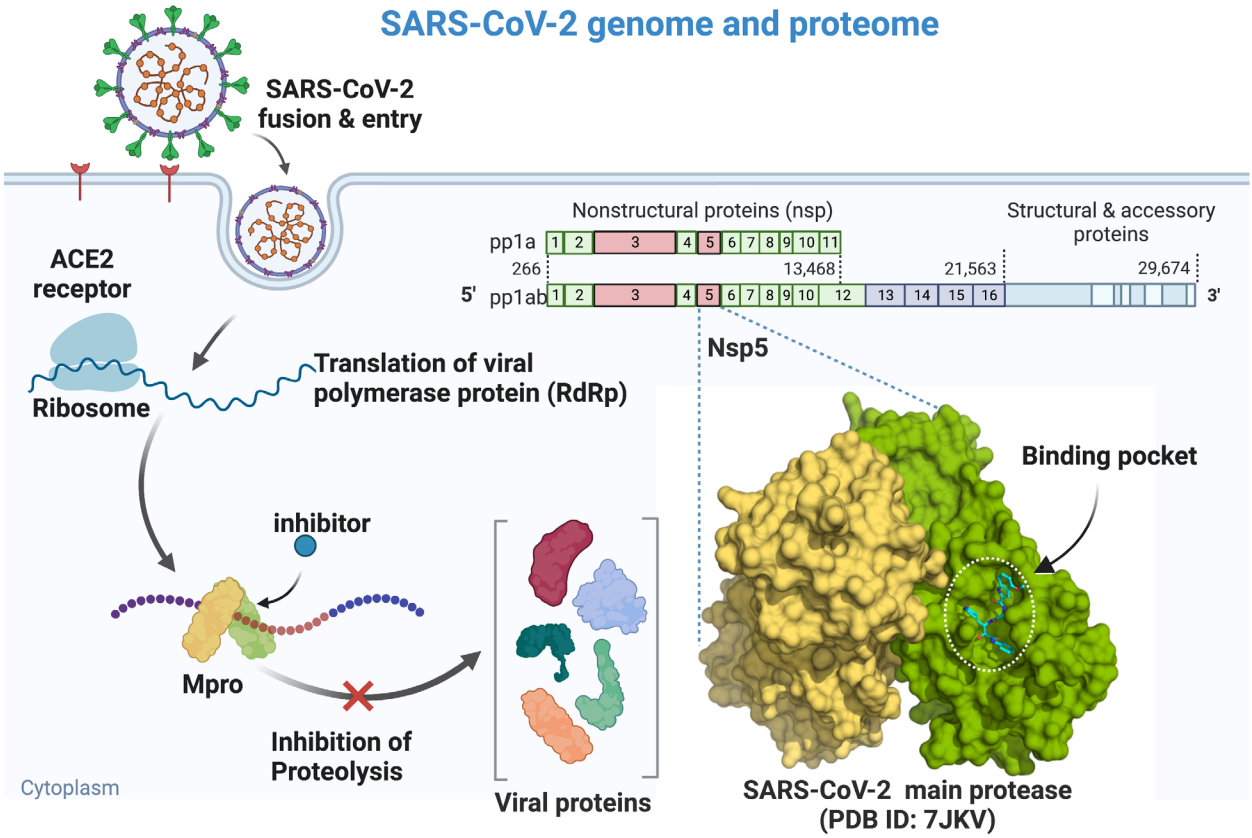

Figure 1. Schematic representation of the SARS-CoV-2 docking onto human ACE2 receptor and entry into the cell. Inside the cell, SARS-CoV-2 replicates its RNA genome in order to manufacture numerous viral proteins using host ribosomes. The proteome of SARS-CoV-2 consists of two non-structural polyproteins pp1a (490 kDa), pp1ab (794 kDa), and additional structural & accessory proteins (pale cyan) such as spike, envelope, membrane, and nucleocapsid. Protomers of M^{pro} is shown in green and yellow, breaking polypeptides into functional viral proteins. Inhibition of M^{pro} with small compound blocks this essential step in viral life cycle. Figure created using Biorender (*https://biorender.com*).

Asn residue at P1' position (Figure 2). Structural and biochemical studies reveal that the presence of Asn of nsp8/9 at P1' position actually reduces the speed of catalytic reaction about 36-fold compared to P1' Ser of nsp4/5 (*9*).

M^{pro} active site contains a cysteine-histidine catalytic dyad (C145 and H41). Key steps of the catalytic cycle are depicted in Figure 3 as the formation of the "thiohemiketal" group, intermediate acyl-enzyme complex, and the final stage cleavage of Gln-(Ser/Ala/Asn) peptide bond with the action of a catalytic water molecule (*10*).

Molecular details of M^{pro}-Inhibitor interactions

As the COVID-19 pandemic emerged scientists around the world accelerated drug development efforts. One of the first M^{pro} inhibitors redesigned for M^{pro} was the so-called compound N3, which was based on α, β-unsaturated carbonyl groups that form a covalent bond with a catalytic cysteine residue (Cys145) inside the active site (*11*). The chemical composition of the inhibitor resembles the natural substrate of M^{pro} (Figure 4a, 4b). The γ-lactam

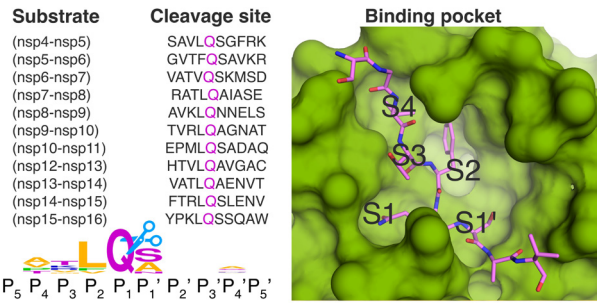

Figure 2. The left 10 amino acid length of M^{pro} cleavage sites within pp1ab is illustrated. The logo was generated using WEBLOGO (*http://weblogo.threeplusone.com*) with the recognition sequences of M^{pro} ranging from the P5 to P5' positions. Schematic diagram of subsite binding pockets with site-specific residues is indicated on the right. While the S1 subsite only recognizes Gln at this position, the S2 site recognizes hydrophobic residues such as L, F or V, and other subsites tolerate more variation in peptide sequences.

ring as P1 moiety engages in bifurcated hydrogen bonds as Gln forms at this position. In addition, a larger lactam ring increased productive var der walls interactions (*7,12,13*). Since then, the γ-lactam ring has

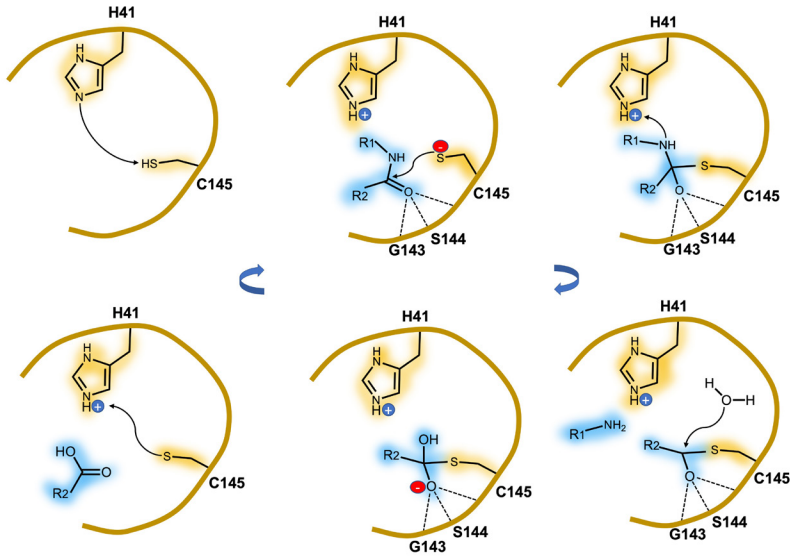

Figure 3. Catalytic mechanism of the proteolysis by M^{pro}. The active site of M^{pro} with the catalytic dyad is highlighted in yellow and the substrate peptide is highlighted in blue. In the free state, imidazole of H41 deprotonates the thiol of C145. The proteolysis reaction starts with the nucleophilic attack by the deprotonated C145 sulfur on the peptide carbonyl carbon. During the transition state, an oxyanion hole forms between the negatively charged oxygen atom and backbone amides of C145, S144, and G143 (dashed triple lines) in order to stabilize the substrate. The part of the peptide (R1-NH) bond breaks down and is released due to the nucleophilic attack by the water molecule onto carboxyl-moiety, and H41 becomes protonated again.

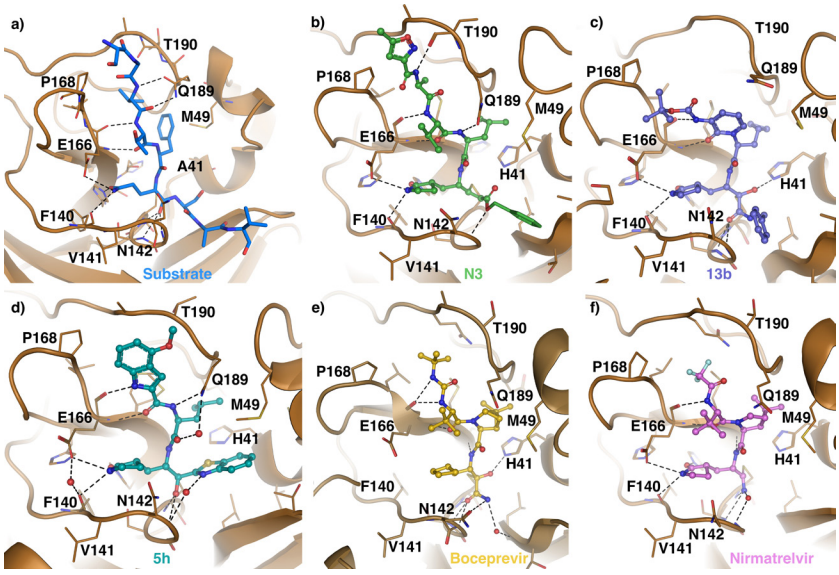

Figure 4. Comparison of the binding modes of substrate and five M^{pro} inhibitors. M^{pros} are shown as cartoons in brown and the inhibitors are shown as stick and ball mode. The binding pocket in complex with nsp5|6 peptidyl substrate (**a**, PDB: 7DVW, blue), N3 (**b**, PDB: 6LU7, green), 13b (**c**, PDB: 6Y2G, purple), 5h (**d**, PDB: 7JKV, aqua-cyan), boceprevir (**e**, PDB: 7BRP, yellow) and nirmatrelvir (**f**, PDB: 7VLQ, pink) are shown. All inhibitors contain P1 gamma lactam in the chemical structure as a common feature except boceprevir. Nirmatrelvir lacks any P1' to occupy S1 subsites.

been essentially kept as a Gln surrogate in the design of most of the M^{pro} inhibitors (*14*). The M^{pro}-N3 complexed structure revealed a strong hydrogen bonding network in a similar fashion to the original substrate, the inhibition of N3 was determined using SARS-CoV-2-infected Vero cells required 10 μM concentration of N3.

Soon later Hilgenfeld's research group designed a new lead compound based on the α-ketoamide group. Initial compound 11r was further optimized by substituting moieties engaging at three subsites resulting in 13b (IC_{50} = 0.67 ± 0.18 μM). The center part of the molecule is built on a pyridine scaffold, which significantly improved drug properties such as plasma half-life and kinetic plasma solubility (Figure 4c). The P2 phenyl group of 11r was substituted with a smaller cyclopropyl methyl moiety, which is deeply embedded in the S2 pocket of M^{pro}. Lead compound 13b was tested on mice with no adverse effects (*15*). Another interesting M^{pro} inhibitor reported 6 months after the pandemic's start was compound 5h comprised of an indole moiety as P4 moiety (*16*). Although the indole group is relatively larger than the substrate peptide at S4 subsite, the M^{pro}-5h-complexed structure revealed a well-fit of the inhibitor inside the binding pocket (Figure 4d). *In vitro* assay performed with VeroE6 cells exposed to SARS-CoVWK-52 resulted in the IC_{50} of 4.2 ± 0.7 μM antiviral activity, which was further boosted with synergistic use of remdesivir (*16*). Recently, 5h was also co-crystallized with MERS and SAR-CoV-1 main proteases revealing similar binding modes with some differences in adaptation of the benzothiazole group inside S1' subsite (*17*). The potency of 5h further increased with the substation of two fluorine atoms (*18*).

So far only one M^{pro}-specific inhibitor "nirmatrelvir" was approved by the FDA to use against COVD-19 (*19*). The oral form of nirmatrelvir/ritonavir is the most effective therapeutic option against SARS-CoV-2 infection reducing hospitalization or death by 89%

(*20*). Nirmatrelvir was developed by Pfizer utilizing the nitrile group as a warhead, which forms covalent bond to the catalytic residue C145. Inside the S2 subsite, the 6,6-dimethyl-3-azabicyclo[3.1.0]hexane group functions well as Leu mimic, and the trifluoro acetyl group inside the S4 subsite engaged in multiple fluorine-based halogen interactions (Figure 4f). Interestingly, nirmatrelvir resembles similar chemical features of hepatitis C virus (HCV) protease inhibitor boceprevir (*21*). Studies show that boceprevir also binds the M^{pro} substrate pocket in a similar conformation (Figure 4e).

Conclusions and future directions

Coronaviruses mutate randomly and active site residues that contact the inhibitor can mutate without affecting the substrate recognition to confer resistance. Inhibitors that optimally occupy the substrate envelope as the natural substrates are less likely to be affected by those mutations. The inhibitors we presented in this review form several hydrogen bonds with protein backbone atoms including oxyanion hole residues through backbone amides, these interactions are likely retained in the active sites of mutant proteases.

Recent studies reported a combination of mutations (L50F and E166V) in the M^{pro} sequence reduces the potency of nirmatrelvir about 80-fold (*22*). Since the P1-γ-lactam ring forms hydrogen bonds with His-163 and Asp-166 side chains, mutation at this P1 site dramatically reduces the inhibitor potency. This possibility of those mutations may emerge in infected people is raising concerns, it may practically end the use of nirmatrelvir.

Previously protease inhibitors have been successfully employed against HIV and HCV proteases and other viral enzymes (*23*). So far about ten HIV protease inhibitors are approved and most of the regiments are given in cocktails to avoid the emergence of new resistant viruses (*23*). The success of anti-HIV-1 protease therapy took a continuous improvement in the potency of inhibitors that are classified in three generations, suggests that anti-M^{pro} drug development is at the initial stage and more potent inhibitors are to arrive, however, more precise understanding of the mechanism of SARS-CoV-2 resistance to M^{pro} inhibitors is required.

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

Note: The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

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**Address correspondence to*:
Haydar Bulut, The Experimental Retrovirology Section, HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.
E-mail: haydar.bulut@nih.gov

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ORIGINAL ARTICLE
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Association between increased peripheral blood CD86-positive plasmacytoid dendritic cells and immune-related adverse events in patients with non-small cell lung cancer

Masato Karayama[1,2,*], Yukihiro Mizoguchi[3], Yusuke Inoue[1], Hironao Hozumi[1], Yuzo Suzuki[1], Kazuki Furuhashi[1], Tomoyuki Fujisawa[1], Noriyuki Enomoto[1], Yutaro Nakamura[1], Naoki Inui[4], Takafumi Suda[1], Shigehisa Kitano[5], Kazunori Aoki[3], Yasuhide Yamada[2]

[1] Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, Hamamatsu, Japan;
[2] Department of Medical Oncology, Hamamatsu University School of Medicine, Hamamatsu, Japan;
[3] Department of Immune Medicine, National Cancer Center Research Institute, Tokyo, Japan;
[4] Department of Clinical Pharmacology and Therapeutics, Hamamatsu University School of Medicine, Hamamatsu, Japan;
[5] Division of Cancer Immunotherapy Development, Advanced Medical Development Center, The Cancer Institute Hospital of JFCR, Tokyo, Japan.

Abstract: The occurrence of immune-related adverse events (irAEs) after immune checkpoint inhibitors (ICIs) is unpredictable. Profiles of peripheral blood mononuclear cells (PBMCs) represent the host immune system and have the potential to predict irAEs. We analyzed PBMC subsets using multicolor flow cytometry before and at weeks 2 and 8 after the start of ICIs in patients with non-small cell lung cancer. Sixteen eligible patients were evaluated. The irAEs occurred in 6 patients (37.5%): diarrhea in 2, diarrhea and a rash in 1, pituitary dysfunction in 1, cholangitis in 1, and pneumonitis in 1. Patients experiencing irAEs had higher levels of $CD86^+$plasmacytoid dendritic cells (pDCs) at the baseline and weeks 2 and 8 after the ICIs than those not experiencing irAEs (p = 0.005, 0.038, and 0.050, respectively). In patients experiencing irAEs, the levels of $CD86^+$pDCs significantly decreased at weeks 2 and 8 compared to the baseline (p = 0 .034 and 0.025, respectively) but did not change in those not experiencing irAEs. The levels of other PBMC subsets were not significantly associated with irAEs. Higher levels of natural killer (NK) cells were significantly associated with an overall objective response (p = 0.024). In conclusion, higher levels of $CD86^+$pDCs at the baseline and a reduction in those levels 2 and 8 weeks after ICIs were associated with the occurrence of irAEs. Higher levels of NK cells were associated with an objective response to ICIs. Evaluation of PBMCs may help to predict the efficacy and safety of ICIs.

***Keywords*:** immunotherapy, immune-related adverse events (irAEs), immune checkpoint inhibitors (ICIs), peripheral blood mononuclear cells (PBMCs), $CD86^+$plasmacytoid dendritic cells (pDCs)

Introduction

Immune checkpoint inhibitors (ICIs) are an important part of cancer therapy. Conventional chemotherapy has direct toxicity to tumor cells, but ICIs activate anti-tumor immune responses that provide unprecedented clinical benefits. Treatment of patients with ICIs may result in immune-related adverse events (irAEs), which are defined as a spectrum of side effects that mimic autoimmune diseases (*1*). ICI treatment can cause irAEs in any organ at any time, hampering the prediction of their occurrence in clinical practice (*2*).

Assessment of host–tumor interactions and tumor characteristics is essential to understanding the modulatory effects of ICIs on the immune system of cancer patients. Research has increasingly revealed that the host immune status, assessed using peripheral blood mononuclear cell (PBMC) profiles, is associated with the clinical efficacy of ICIs. For example, higher levels of active natural killer (NK) cells and programmed death-1 (PD-1) positive $CD8^+$T cells in peripheral blood are associated with the clinical response to nivolumab, an anti-PD-1 antibody (*3*). Moreover, increased NK cells and decreased myeloid-derived suppressor cells are associated with the clinical response to nivolumab (*4*).

Little is known about the association between irAEs and PBMCs. The occurrence of irAEs after ICI treatment is likely caused by an activated immune system. A positive relationship exists between the efficacy of ICIs and the development of irAEs, which suggests common underlying mechanisms (*5,6*). Since irAEs may represent enhanced immune function, assessment

of PBMC profiles may provide useful information for understanding the mechanisms for development of irAEs. Using advanced multicolor flow cytometric analysis, this exploratory study comprehensively assessed PBMC profiles before and after ICI therapy and it analyzed the association between immune cell subsets and irAEs in patients with advanced non-small cell lung cancer (NSCLC).

Materials and Methods

Study design

This was an exploratory, prospective observational study conducted in accordance with the ethical standards of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Hamamatsu University School of Medicine (No. 16-080). Each patient provided written informed consent. The study was registered with the University Hospital Medical Information Network Clinical Trial Registry (000026140).

Patient eligibility

Patients were included in this study if they presented with inoperable stage IIIB or IV NSCLC, had an Eastern Cooperative Oncology Group performance status (ECOG-PS) of 0–2, and were scheduled for anti-PD-1 therapy. Patients who had a history of ICI therapy were excluded. The choice of anti-PD-1 therapy depended on the treating physician, and therapy was administered intravenously as follows: nivolumab at a dose of 3 mg/kg every 2 weeks or pembrolizumab at a dose of 200 mg every 3 weeks.

Treatment and evaluation schedule

Blood samples were collected before and at weeks 2 and 8 after the initiation of anti-PD-1 therapy. Chest computed tomography was performed before and 4 and 8 weeks after the initiation of anti-PD-1 therapy and repeated every 8 weeks until the cessation of ICI therapy. The expression of PD-L1 was assessed using the Dako 22C3 pharmDx (Agilent Technologies Santa Clara, CA, USA). Adverse events were graded using the Common Terminology Criteria for Adverse Events, version 5.0. Radiological response was evaluated according to the Response Evaluation Criteria in Solid Tumors, version 1.1.

Measurements of PBMCs

A total of 16 mL of peripheral blood samples was collected using two preparation tubes (8mL for each) containing sodium heparin (BD Vacutainer CPT; Becton, Dickinson and Company, Franklin Lakes, NJ, USA). The collection tubes were gently inverted 8 to 10 times to mix the anticoagulant with blood. After centrifugation at 1500 × g for 15 min at room temperature, PBMCs were present in a whitish layer just under the plasma layer. The PBMCs were collected with Pasteur pipettes, cryopreserved immediately in CellBanker 1® medium (Takara Bio Inc., Tokyo, Japan), and stored at −80°C. Aliquots of the frozen PBMCs were suspended in 50 μL phosphate buffered saline (PBS). Then, 50 μL of fluorescent labeled-surface marker antibody (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=57*) with Brilliant Stain Buffer (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) was combined with PBMCs to constitute 100 μL of cell solution, and the solution was incubated for 20 min at 4°C. PBMCs were immediately washed once with 2.0 mL of PBS, and after washing, samples were fixed using BD CellFIX (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). At least 50,000 live events were detected using an LSRFortessa™ X-20 flow cytometer with FACSDiva™ software (BD Biosciences, San Jose, CA, USA). For analysis of the immune cell profile, at the beginning of the gating strategy, the discrimination of single cells from doublets was performed using a forward scatter-area (FSC-A) versus forward scatter-height (FSC-H) bivariate plot, followed by use of a side scatter-area (SSC-A) versus side scatter-height (SSC-H) bivariate plot. Then, dead cells were removed using Fixable Viability Dye. All flow cytometric analyses were performed using FlowJo (BD Biosciences). Details of the FCM panel and gating strategy are described in Supplementary Figure S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=57*).

Different immune cell populations were analyzed as follows: $CD4^+$T cells, $CD8^+$T cells, B cells, monocytes, proinflammatory monocytes, monocytic myeloid derived suppressor cells (mMDSCs), myeloid dendritic cells (mDCs), $CD141^+$ dendritic cells (DCs), plasmacytoid dendritic cells (pDC), basophils, natural killer (NK) cells, minor NK cells, and NK T cells (NKT). To evaluate the activation status, the expression of CD80, CD86, CD274 (PD-L1), and CD273 (PD-L2) was analyzed for each immune cell type. The definitions of immune cell types are described in Supplementary Tables S1 and S2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=57*). Immune cell populations were expressed as a percentage of PBMCs, and the activation status of each immune cell type was expressed as a percentage of the corresponding immune cell population.

Statistical analyses

The Wilcoxon rank sum test was used to compare $CD86^+$plasmacytoid dendritic cell (pDC) levels between the patients experiencing and not experiencing irAEs. A *p*

value < 0.05 (two-sided) was considered significant. All values were analyzed using the software JMP, version 13.0.0 (SAS Institute Japan, Tokyo, Japan).

Results

Patient characteristics

From September 2016 to December 2018, 23 patients were enrolled in this study. Of those, 7 patients were excluded from analysis because of rapid disease progression, which caused early withdrawal from ICI therapy (n = 3), and insufficient PBMC availability (n = 4). As a result, 16 patients had evaluable blood samples before ICI treatment and were available for analysis (Table 1). In addition to the baseline samples, 14 and 9 patients had evaluable blood samples at weeks 2 and 8, respectively, after the initiation of anti-PD-1 therapy. Only 1 patient (case 12) had a mutation in the epidermal growth factor receptor gene; the other patients had no oncogenic driver mutations. Eleven patients (68.8%) had positive PD-L1 expression with tumor proportion scores (TPS) ≥ 1%, 8 (50.0%) of whom had TPS ≥ 50%. No patients had a history of autoimmune disease or received systemic steroid therapy or immunosuppressive agents.

Delivery of ICI therapy

Nivolumab was administered to 10 patients (62.5%) as second line or later therapy, and pembrolizumab was administered to 6 patients (37.5%) as first line therapy. An objective response was observed in 9 patients (56.3%); 3 (18.8%) had stable disease and 4 (25.0%) had progressive disease. The median duration of anti-PD-1 treatment was 3.9 months (range: 1.0–18.5 months), and the median observation time was 12.3 months (range: 3.1–24.6 months).

Occurrence of irAEs

The occurrence of irAEs was observed in 6 patients (37.5%) (Table 2). The median time to an irAE was 44 days (range: 7–133 days). Systemic steroid therapies were administered to 3 patients, and the patient with pituitary dysfunction received a low-dose mineralocorticoid supplementation. Patient 1

Table 1. Characteristics of the patients in this study who presented with non-small cell lung cancer

Case	Group	Age, years	Sex	ECOG-PS	Stage	Pathology	PD-L1: TPS, %	Treatment line of ICI	ICI therapy	Best response
1	irAE	79	Female	1	IV	Ad	Unknown	2nd	Nivolumab	PD
2	irAE	73	Male	1	IV	Ad	≥ 50	1st	Pembrolizumab	PR
3	irAE	77	Female	1	IV	Ad	≥ 50	1st	Pembrolizumab	SD
4	irAE	81	Male	0	IV	Ad	≥ 50	1st	Pembrolizumab	PR
5	irAE	70	Male	1	IV	Sq	0	4th	Nivolumab	CR
6	irAE	56	Male	0	IV	Ad	≥ 50	3rd	Nivolumab	CR
7	Non-irAE	69	Male	1	IIIB	Ad	≥ 50	2nd	Nivolumab	PR
8	Non-irAE	67	Male	1	IV	Ad	0	2nd	Nivolumab	PD
9	Non-irAE	48	Male	0	IV	Others	1–49	2nd	Nivolumab	PD
10	Non-irAE	66	Male	0	IV	Ad	1–49	3rd	Nivolumab	PD
11	Non-irAE	41	Male	1	IV	Others	1–49	2nd	Nivolumab	PR
12	Non-irAE	73	Male	1	IV	Ad	0	7th	Nivolumab	SD
13	Non-irAE	69	Male	1	IV	Ad	≥ 50	1st	Pembrolizumab	PR
14	Non-irAE	77	Male	0	IV	Sq	≥ 50	1st	Pembrolizumab	CR
15	Non-irAE	65	Male	0	IV	Ad	≥ 50	1st	Pembrolizumab	CR
16	Non-irAE	58	Female	0	IV	Ad	0	3rd	Nivolumab	SD

Ad, adenocarcinoma; CR, complete response; ECOG-PS, Eastern Cooperative Oncology Group-performance status; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; Sq, squamous cell carcinoma; TPS, tumor proportion score.

Table 2. The clinical courses of six patients with non-small cell lung cancer who developed immune-related adverse events

Case	irAE	Grade	Time to an irAE, days	ICI therapy	Treatment for irAE	Outcomes of irAE
1	Diarrhea	1	7	Continued	Antidiarrheal	Not alleviated
	Rash	1	28		Steroid ointment	
2	Diarrhea	2	84	Discontinued	Antidiarrheal	Alleviated
3	Diarrhea	3	23	Discontinued	Antidiarrheal and oral steroid	Alleviated
4	Pneumonitis	2	119	Discontinued	Oral steroid	Alleviated
5	Pituitary dysfunction	3	133	Discontinued	Mineralocorticoid supplementation	Not alleviated
6	Cholangitis	5	57	Discontinued	Intravenous steroid and immunosuppressant	Not alleviated/died

ICI, immune checkpoint inhibitor; irAE, immune-related adverse event.

developed grade 1 diarrhea and a rash at 7 and 28 days, respectively, which was alleviated by antidiarrheal and steroid ointment without systemic steroid therapy. Patient 3 developed grade 3 diarrhea 23 days after the start of ICI therapy; however, an antidiarrheal was administered first and then oral steroids were initiated 63 days after the start of ICI therapy (40 days after the development of diarrhea). Thus, no patient received systemic steroids or immunosuppressive agents during the 8 weeks of the period studied. The occurrence of irAEs was not significantly associated with age, sex, or ECOG-PS.

Association between CD86$^+$pDCs and the occurrence of irAEs

Compared to 10 patients not experiencing irAEs, the 6 patients who experienced irAEs had significantly higher CD86$^+$pDC levels at the baseline (a median of 3.15% *vs.* 15.0%, p = 0.005) (Figure 1A). CD86$^+$myeloid dendritic cells (mDCs) and the other analyzed PBMC subsets were not significantly associated with the occurrence of irAEs (Figure 1B, Supplementary Table S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=57*). CD86$^+$pDCs levels in patients experiencing irAEs decreased significantly weeks 2 and 8 after ICI therapy compared to the baseline values for those patients (p = 0.034 and 0.025, respectively); however, the levels did not change from the baseline in patients not experiencing irAEs (Figure

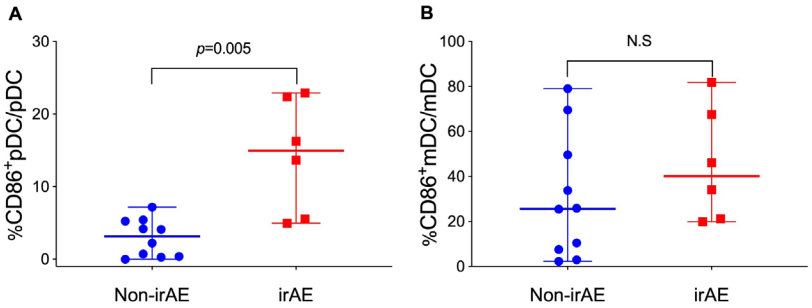

Figure 1. Association between circulating dendritic cells at the baseline and the occurrence of immune-related adverse events. Levels of circulating **(A)** CD86$^+$plasmacytoid dendritic cells (pDCs) and **(B)** CD86$^+$myeloid dendritic cells (mDCs) at the baseline. Patients experiencing and not experiencing immune-related adverse events (irAEs) are indicated in red and blue, respectively. Horizontal lines and error bars represent the median and the minimum and maximum, respectively. Activation status is expressed as a percentage of each corresponding immune cell type.

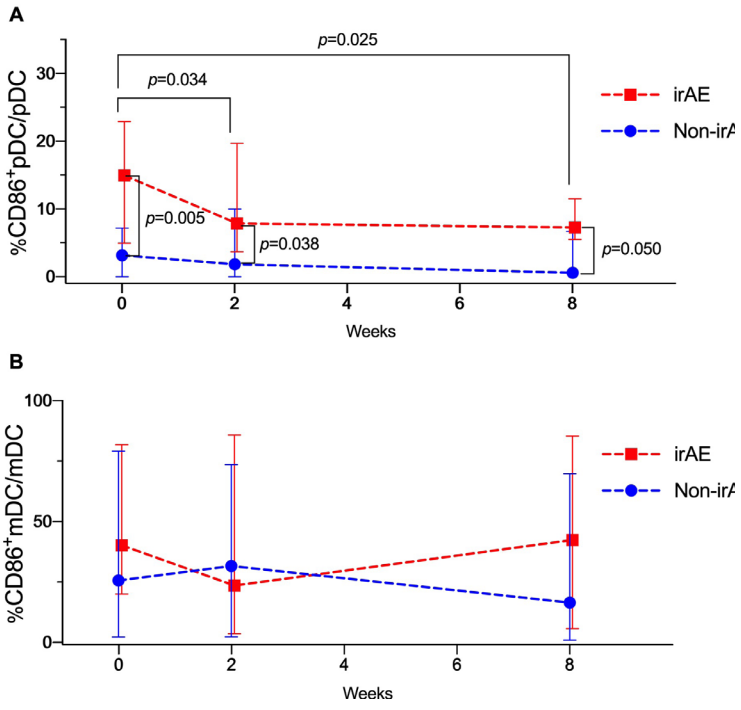

Figure 2. Changes in circulating dendritic cells after treatment with immune checkpoint inhibitors in patients experiencing and not experiencing immune-related adverse events. Changes in circulating **(A)** CD86$^+$plasmacytoid dendritic cells (pDCs) and **(B)** CD86$^+$myeloid dendritic cells (mDCs) at weeks 2 and 8 during treatment with immune checkpoint inhibitors (ICIs). Patients experiencing and not experiencing immune-related adverse events (irAEs) are displayed in red and blue, respectively. Horizontal lines and error bars represent the median and the minimum and maximum, respectively. Activation status is expressed as a percentage of each corresponding immune cell type.

2A). Even with decreased levels after ICI treatment, the patients experiencing irAEs still had significantly higher CD86$^+$pDC levels at 2 weeks (p = 0.038) and tended to have higher levels at 8 weeks (p = 0.050) compared to those not experiencing irAEs (Figure 2A). A decreased proportion of CD86$^+$pDC after ICI therapy was observed in all patients experiencing irAEs (except Patient 3, who did not have evaluable samples 2 and 8 weeks after ICI therapy). The time course of CD86$^+$pDC in individual patients is shown in Supplementary Figure S2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=57*). The representative flow cytometric data for CD86$^+$pDCs in patients experiencing and not experiencing irAEs are shown in Figure 3. The levels of CD86$^+$mDCs and other PBMC subsets did not change 2 and 8 weeks after the initiation of ICI therapy (Figure 2B). CD86$^+$pDC levels were not closely associated with the grade of or time to an irAE (Supplementary Figure S3-S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=57*). An increased proportion of NK cells in PBMCs was significantly associated with the objective response rate (ORR, p = 0.024), whereas the other PBMC subsets and activation status, including that of CD4$^+$T cells, CD8$^+$T cells, B cells, CD86$^+$pDCs, and CD86$^+$mDCs, were not associated with the ORR (Figure 4A–F). CD86$^+$pDC levels were not significantly associated with age, sex, or ECOG-PS.

Discussion

This prospective exploratory study comprehensively assessed multiple PBMC subsets in patients with NSCLC who were receiving ICI therapy. The patients who experienced irAEs had increased CD86$^+$pDC levels at the baseline compared to patients who did not experience irAEs. Moreover, CD86$^+$pDC levels in patients experiencing irAEs decreased significantly weeks 2 and 8 after initiation of anti-PD-1 therapy. The CD86$^+$mDC levels were not associated with irAEs. In addition, an increased proportion of NK cells in PBMCs was associated with the efficacy of ICI. Results indicate that the assessment of PBMC subsets may aid in predicting the efficacy and safety of ICI therapy.

DCs are a group of antigen-presenting cells that stimulate T cells *via* co-stimulatory factors, including CD86 (also known as B7-2) (*7,8*). Among several subsets of DCs, pDCs produce type I interferons (IFN-I) in response to viruses, unlike mDCs, which mainly act as conventional antigen-presenting cells (*9*). Although pDCs constitute only 0.2%–0.8% of PBMCs, emerging evidence suggests that pDCs contribute to the pathogenesis of autoimmune diseases including systemic lupus erythematosus (SLE), systemic sclerosis, psoriasis, autoimmune thyroid diseases, type I diabetes, autoimmune pancreatitis, and inflammatory bowel diseases (IBDs), as well as having a role in immune responses to infectious diseases (*10-16*). For example, antibody-mediated depletion of pDCs reduced type I interferon responses and disease activity in patients with cutaneous lupus (*10*). In patients with IBDs, increased numbers of pDCs were observed in inflamed mucosa, and increased levels of peripheral CD86$^+$pDCs were associated with disease activity (*14*). Moreover, patients with type I diabetes had significantly higher pDC levels in their peripheral blood than healthy individuals (*17*). Interestingly, autoimmune thyroid disease, IBDs, and

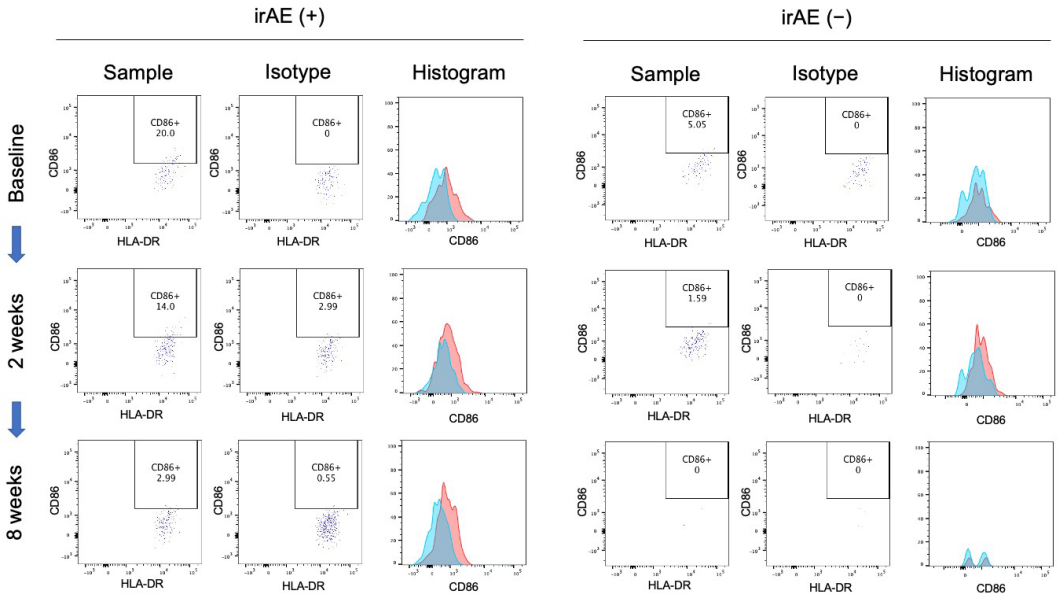

Figure 3. Representative flow cytometric data for CD86$^+$pDCs. Levels of circulating CD86$^+$ plasmacytoid dendritic cells (pDCs) in patients experiencing and not experiencing immune-related adverse events (irAEs) at the baseline and 2 and 8 weeks after immune checkpoint inhibitor therapy.

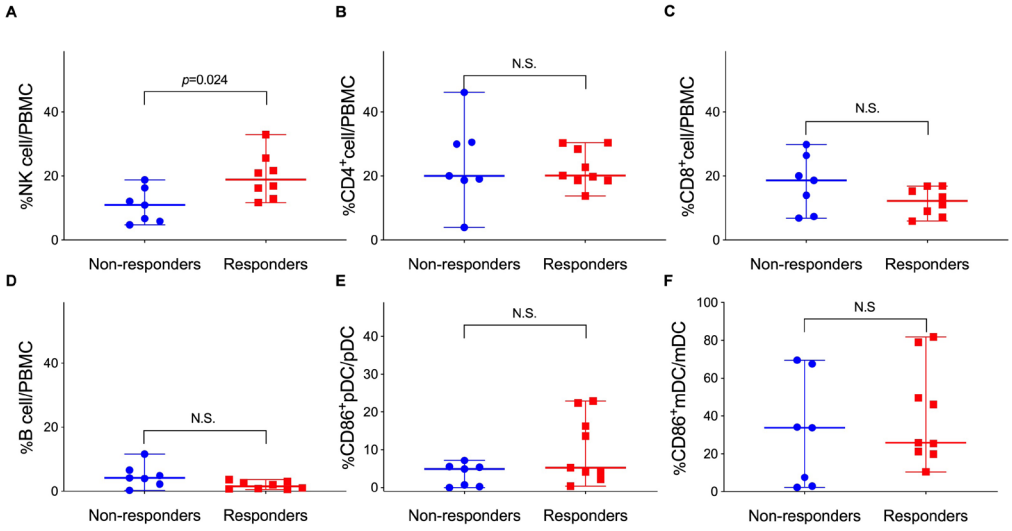

Figure 4. Association between circulating immune cells and the efficacy of immune checkpoint inhibitor therapy. Circulating **(A)** natural killer cells (NK cells), **(B)** $CD4^+$T cells, **(C)** $CD8^+$T cells, **(D)** B cells, **(E)** $CD86^+$plasmacytoid dendritic cells (pDCs), and **(F)** $CD86^+$myeloid dendritic cells (mDCs) at the baseline. Patients in whom an objective response was achieved (responders) and those in whom such a response was not achieved (non-responders) are displayed in red and blue, respectively. Horizontal lines and error bars represent the median and the minimum and the maximum, respectively. Data are expressed as a percentage of peripheral blood mononuclear cells (PBMCs) (A–D) or each immune cell type (E, F).

type I diabetes are known to develop after ICI therapy. Given the autoimmune nature of irAEs, one can reasonably deduce that an increase in activated pDCs at the baseline may affect the occurrence of irAEs.

The decrease in $CD86^+$pDC levels after ICI therapy in patients experiencing irAEs displayed another interesting similarity to autoimmune diseases. In patients with type I diabetes, the increased number of peripheral blood pDCs at diagnosis tended to decrease after 2 years whereas the number of peripheral pDCs was stable over 2 years in controls (*17*). In patients with SLE, psoriasis, and autoimmune thyroid diseases, pDC levels decreased in peripheral blood instead of increasing (*13,15,18*). This seemingly paradoxical behavior is thought to be due to an accumulation of pDCs in tissue lesions. In fact, increased pDCs have been observed in involved organs (such as the skin, lymph nodes, kidneys, or thyroid) in patients with SLE, psoriasis, or autoimmune thyroid diseases (*13,15,19*). The decrease in circulating $CD86^+$pDCs after ICI therapy may reflect the recruitment of these cells from the peripheral blood to specific organs.

The accumulation of pDCs in lesional tissues is a common characteristic in several autoimmune diseases; however, controversy exists regarding the levels of circulating pDCs. Those levels increased in type I diabetes and IBDs and decreased in SLE, psoriasis, or autoimmune thyroid diseases (*13-15,17,19*). Although the precise mechanisms involved are unknown, the timing of the evaluation during the course of disease (at diagnosis or after progression) or the specific organs involved may be associated with differences in circulating pDCs among autoimmune diseases.

The pathogenesis of irAEs and differences in that pathogenesis among different irAEs are largely unknown. Shared antigens between tumors and organs, inflammation generated by cytokines and activated immune cells, or pre-existing organ inflammation (*i.e.* autoimmune diseases) might be potential mechanisms (*5*). irAEs occur in a wide variety of organs, and therefore, organ-specific mechanisms may exist for each irAE. However, some common mechanisms might also be involved because all of the irAEs were caused by autoimmunity triggered by ICIs. As well as having a role in innate immunity by producing IFN-I, pDCs promote the differentiation and maintenance of autoreactive B cells (*20,21*). Given their multiple roles in innate and adaptive immunity, pDCs might be involved in various irAEs. However, there were no obvious differences in the baseline levels of $CD86^+$pDCs among the different types of irAEs. Moreover, a decreased proportion of $CD86^+$pDCs was observed after ICI therapy regardless of the type of irAE. These results indicate that pDCs were associated with a common mechanism across irAEs. However, the current study evaluated a limited number and type of irAEs. The organ-specific roles of pDCs should be investigated further.

The association between increased peripheral blood NK cell levels and ICI efficacy has previously been reported and was also observed in the current study (*3,22*). In animal models, depletion of NK cells attenuated the anti-tumor effects of a PD-1/PD-L1 blockade. In addition, PD-1/PD-L1 signaling resulted in reduced anti-tumor activity of NK cells, which was restored after a PD-1/PD-L1 blockade (*23*). The underlying mechanisms are largely unknown; however, these results indicate the considerable importance of NK cells in ICI therapy as a predictor of efficacy or delivery to the therapeutic target.

The current study had four main limitations. First,

this was an exploratory study with a limited number of subjects. Multiple surface markers were evaluated on immune cells, and this may have led to false positives. Moreover, PBMCs contained a small fraction of pDCs, and therefore, the results of this study should be interpreted with caution. To validate the utility of $CD86^+$pDC levels in predicting irAEs, further studies need to be conducted with larger cohorts. Second, the association between $CD86^+$pDC levels and the severity of or time to onset of irAEs was not evaluated because of the limited number of the patients. Moreover, irAEs are considered to be the result of complex immune responses. Although the current findings suggest that $CD86^+$pDCs play an important role in the occurrence of irAEs, other unknown factors may be associated with the severity of or time to onset of irAEs. The differences in pDC function among the organs involved in the irAEs are also unknown. ICI-induced irAEs are a heterogeneous group of conditions that occur in various organs, and the roles of pDCs may differ depending on the irAE phenotype. Third, differences in the distribution of immune cells between peripheral blood and organs were not determined. Although circulating $CD86^+$pDC levels were not associated with the efficacy of ICI treatment, tumor-infiltrating pDCs likely play an essential role in cancer immunity. In animal models, tumor-infiltrating pDCs induced antitumor immunity by activating NK cells, conventional DCs, and $CD8^+$T cells (*24*). In the tumor microenvironment, anti-tumor activity by tumor-infiltrating pDCs is attenuated by tumor-derived soluble factors, including transforming growth factor-β, which results in immune tolerance to the tumor (*25*). Fourth, the current study only evaluated anti-PD-1 therapy. Several single or combinatorial ICI therapeutic strategies exist, including anti-PD-ligand(L)1 or anti-cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody therapy, combinations of ICI with chemotherapy, and combinations of ICI antibody therapies. Immune status may differ depending on the type of immunotherapy used. In fact, the combination of anti-PD-1 and anti-CTLA-4 therapeutics results in frequent irAEs (*26,27*). CTLA-4 suppresses T cell activity by binding to CD86; therefore, $CD86^+$pDC behavior during anti-CTLA-4 therapy is of interest. Immunotherapies will become more diversified in the near future as new immunomodulating agents emerge. The association between host immune status and immunotherapy efficacy and safety should be investigated further.

In conclusion, NSCLC patients who experienced irAEs had increased $CD86^+$pDC levels in their peripheral blood at the baseline. These $CD86^+$pDC levels decreased after ICI treatment. Assessment of host immune status by profiling PBMCs may help to predict the efficacy and safety of ICI treatment.

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**Address correspondence to*:
Masato Karayama, Second Division, Department of Internal Medicine, Hamamatsu University School of Medicine, 1-20-1 Handayama, Hamamatsu, Japan 431-3192.
E-mail: karayama@hama-med.ac.jp

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Outcomes following cholecystectomy in human immunodeficiency virus-positive patients treated with antiretroviral therapy: A retrospective cohort study

Kenta Aso[1], Kyoji Ito[1], Nobuyuki Takemura[1,*], Kunihisa Tsukada[2], Fuyuki Inagaki[1], Fuminori Mihara[1], Shinichi Oka[2], Norihiro Kokudo[1]

[1] Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, National Center for Global Health and Medicine, Tokyo, Japan;
[2] AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: The number of the human immunodeficiency virus (HIV)-positive patients are increasing worldwide, and more HIV-positive patients are undergoing urgent or elective cholecystectomy. There is still insufficient evidence on the relationship between surgical complications of cholecystectomy and antiviral status in HIV-positive patients. The purpose of the present study is to evaluate surgical outcomes after cholecystectomy in HIV-positive patients. Records of consecutive HIV-positive patients who underwent cholecystectomy between January 2010 and December 2020 were reviewed retrospectively. Patients were divided into urgent and elective surgery groups. Urgent surgery was defined as surgery within 48 hours of admission. Postoperative complications were evaluated according to the Clavien-Dindo classification. A total of 30 HIV-positive patients underwent urgent (n = 7) or elective (n = 23) cholecystectomy. Four complications (13.3%) occurred, and the rate was significantly higher in the urgent group than in the elective group (p = 0.008). However, all complications were minor (3 cases of grade I and one case of grade II), and there were no severe postoperative complications. There was no significant difference in CD4+ lymphocyte status in all patients and between the 2 groups before and after surgery (p = 0.133). No cases of postoperative deterioration in the control of HIV infection were observed. In conclusion, cholecystectomy in HIV-positive patients with controlled HIV under recent antiretroviral therapy may be performed safely even in an emergency situation.

***Keywords*:** cholecystectomy, human immunodeficiency virus, surgical outcome

Introduction

Globally, approximately 38 million people live with human immunodeficiency virus (HIV) (*1*). Advances in antiretroviral therapy (ART) have greatly improved the prognosis of HIV-positive patients (*2*). As a result, surgical interventions are being commonly applied in HIV-positive patients (*3*), and the number of surgeries performed for such patients is expected to increase. As HIV affects the host's immune system, there is concern about increased incidence of postoperative complications in HIV-positive patients (*4*).

Cholecystectomy is a common surgical procedure for cholelithiasis or gallbladder polyps, and is often performed urgently for acute cholecystitis (*5,6*). From the perspective of postoperative complications, urgent cholecystectomy, which is often performed for severe acute cholecystitis, has been reported to be associated with higher overall morbidity, surgical site infections, and serious morbidities such as bleeding requiring transfusion, sepsis, and other severe systemic dysfunctions compared to elective cholecystectomy for symptomatic cholelithiasis and gallbladder polyps. With the increase in HIV-positive patients, the number of urgent cholecystectomies is also expected to increase. However, there are few reports on the postoperative outcomes of urgent and elective cholecystectomy in HIV-positive patients and its impact on subsequent HIV infection treatment after surgery.

The aim of the present single center's retrospective study was to evaluate surgical outcomes after cholecystectomy in HIV-positive patients, with special reference to the impact of surgery on HIV control and treatment.

Patients and Methods

Patients

Records of consecutive HIV-positive patients who underwent cholecystectomy between January 2010 and December 2020 were reviewed retrospectively at the

National Center for Global Health and Medicine, which has been designated as a clinical center for acquired immunodeficiency syndrome (AIDS) treatment. We performed a retrospective review of the medical records of these patients. Data were retrieved from prospectively maintained databases and included baseline patient characteristics (demographic data, preoperative risk factors, and comorbidities), type of antiretroviral drug being used, operative characteristics, and postoperative outcomes. All operations were performed after obtaining informed consent from each patient. This study was conducted in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The present study was approved by and satisfied the consensus of the National Center for Global Health and Medicine Research Ethics Committee/Institutional Review Board (ID: NCGM-G-004099-00).

Study variables

We defined comorbidity as follows: chronic kidney disease was defined as decreased kidney function as evidenced by a glomerular filtration rate of less than 60 mL/min/1.73 m^2, markers of kidney damage such as increased urine albumin-to-creatinine ratio or both of at least three months duration, regardless of the underlying cause (*7*). Diabetes mellitus, hypertension, hemophilia A, hepatitis B virus infection, and hepatitis C virus infection were already diagnosed at the time of admission and treated as appropriate. Alcohol use was defined as consuming more than 14 units of alcohol per week. One unit was defined as 10 mL or 8 g of pure alcohol (*8*). Smoking status was defined in patients who smoked before admission; past smokers were not included in the smoking group. Postoperative morbidity was graded based on the Clavien-Dindo classification (*9*). According to this grading, grade III, IV, and V complications were defined as "major complications"; grade I and II complications were described as "minor complications".

Patients were divided into the urgent surgery group and the elective surgery group. Urgent surgery was defined as surgery within 48 hours of admission. Urgent cholecystectomy was conducted for acute cholecystitis according to the Tokyo Guidelines 2018 (*10*). According to these guidelines, urgent cholecystectomy was indicated in the following conditions: severity grade I or higher, no negative predictive factors, favorable organ system failure conditions, and good performance status. The variables described above were compared between the groups.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and were compared using the Student's *t*-test. Categorical variables were described as numbers (%) and were compared using the Pearson's chi-squared test. A paired *t*-test was applied to the corresponding results that changed between before and after surgery. Statistical significance was set at $p < 0.05$. Statistical analysis was performed using JMP software (version 15.1.0; SAS Institute Inc., Cary, NC, USA).

Results

Patient demographics

A total of 30 HIV-positive patients were enrolled in this study. The patient characteristics are shown in Table 1. This study included cholecystectomy for cholecystolithiasis (16/30, 53.3%), cholecystitis (13/30, 43.3%), and gallbladder polyps (1/30, 3.3%) in HIV-positive patients. In 13 acute cholecystitis cases, 9 cases were calculous cholecystitis, and 4 cases were acalculous cholecystitis. Their mean age was 47.3 ± 8.7 years. Of the 30 cases, 7 were urgent surgeries and 23 were elective surgeries. HIV transmission routes were homosexual contact (21/28, 75.0%), heterosexual contact (4/28, 14.2%), bisexual contact (2/28, 7.1%), and blood transfusion for hemophilia A (1/28, 3.5%); 2 patients were not analyzed in this regard. HIV RNA in serum was examined in 28 patients before surgery, and 14 patients showed detectable HIV RNA as follows: < 20 copies/mL, 7/28 (25%); 20-40 copies/mL, 5/28 (17.8%); and > 40 copies/mL, 2/28 (7.1%). The mean preoperative CD4+ lymphocyte count of all patients was 551.0 ± 253.1 cells/μL, indicating that HIV infection in the patients included in this study was well controlled. None of the patients developed AIDS-related complexes at the time of surgery.

Baseline characteristics were compared between the urgent and elective surgery groups. Bivariate analysis revealed a significant difference in smoking status between the urgent and elective groups ($p = 0.047$). However, other preoperative variables including HIV RNA and CD4+ lymphocyte status were not significantly different between the groups.

The preoperative laboratory examination results are summarized in Supplementary Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=59*). Bivariate analysis showed a significant difference in white blood cell count between the urgent and elective surgery groups ($p < 0.001$).

Risk factors for postoperative complications

The intraoperative and postoperative outcomes are summarized in Table 2. The mean operation time and intraoperative bleeding volume were 127.0 ± 58.5 minutes and 8.0 ± 19.8 mL, respectively. Open cholecystectomy was performed in only 3 cases (3/30; 10.0%), all of which required urgent surgery. The mean postoperative CD4+ lymphocyte count of all the patients was 532.5 ± 235.5 cells/μL. 4 complications occurred

Table 1. Comparison of patient characteristics between the study groups before surgery

Variables	All (n = 30) n (%) or mean ± SD	Urgent surgery (n = 7) n (%) or mean ± SD	Elective surgery (n = 23) n (%) or mean ± SD	p value
Patient characteristics				
Age, years	47.3 ± 8.7	49.4 ± 9.2	46.7 ± 8.8	0.062
Sex				
Male/Female	28/2	7/0	21/2	0.419
BMI, kg/m^2	27.1 ± 3.93	25.8 ± 3.6	27.5 ± 4.0	0.297
Diagnosis				
Cholecystolithiasis	16 (53.3)	0 (0.0)	16 (53.3)	0.001
Cholecystitis	13 (43.3)	7 (23.3)	6 (20.0)	0.0005
Gallbladder polyps	1 (3.3)	0 (0.0)	1 (4.3)	0.574
Comorbidities				
CKD	3 (10.0)	2 (28.5)	1 (4.3)	0.061
Diabetes	3 (10.0)	0 (0.0)	3 (13.0)	0.313
Hypertension	3 (10.0)	2 (28.5)	1 (4.3)	0.061
Hemophilia A	1 (3.3)	1 (14.2)	0 (0.0)	0.065
HBV	1 (3.3)	0 (0.0)	1 (4.3)	0.574
HCV	3 (10.0)	1 (14.2)	2 (8.7)	0.666
Alcohol use	2 (6.8)	0 (0.0)	2 (9.0)	0.408
Smoking status	9 (30)	0 (0.0)	9 (39.1)	0.047
Previous abdominal surgery	3 (10.3)	0 (0.0)	3 (13.6)	0.302
HIV RNA, copies/mL				0.197
Not detectable	14 (50.0)	2 (7.1)	12 (42.8)	
< 20	7 (25.0)	3 (10.7)	4 (14.2)	
20–40	5 (17.8)	0 (0.0)	5 (17.8)	
> 40	2 (7.1)	1 (3.5)	1 (3.5)	
N/D	2 (7.1)	1 (3.5)	1 (3.5)	
CD4+ lymphocyte status				
Number, cells/μL	551.0 ± 253.1	468.3 ± 269.8	573.5 ± 250.1	0.416
Percentage, %	27.2 ± 9.3	27.2 ± 11.7	27.2 ± 8.8	0.996

Abbreviations: BMI, body mass index; CKD, Chronic kidney disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, Human immunodeficiency virus; N/D, no data; SD, standard deviation.

Table 2. Surgical outcomes

Variables	All (n = 30) n (%) or mean ± SD	Urgent surgery (n = 7) n (%) or mean ± SD	Elective surgery (n = 23) n (%) or mean ± SD	p value
Operation time, min	127.0 ± 58.5	110.8 ± 45.2	132.4 ± 62.0	0.331
Intraoperative bleeding, mL	8.0 ± 19.8	27.4 ± 30.6	2.1 ± 10.4	0.073
Open cholecystectomy	3 (10.0)	3 (42.8)	0 (0.0)	< 0.001
CD4+ lymphocyte status around POD 30				
Number, cells/μL	532.5 ± 235.5	523.1 ± 287.0	511.2 ± 251.7	0.929
Percentage, %	25.9 ± 8.8	26.1 ± 8.2	25.8 ± 9.2	0.935
Complications				
Major	0	0	0	-
Minor	4 (13.3)	3 (42.8)	1 (4.3)	0.008
PO hospital stay, days	5.7 ± 2.8	9.8 ± 2.4	4.5 ± 1.5	< 0.001

Abbreviations: PO, postoperative.; POD, postoperative day; SD, standard deviation.

(4/30; 13.3%), 3 complications in the urgent surgery group, and one in the elective surgery group. The chest pain and fever were nonspecific, and the cause was never clearly determined. The overall mean duration of postoperative hospital stay was 5.7 ± 2.8 days; 9.8 ± 2.4 days in the urgent surgery group compared with 4.5 ± 1.5 days in the elective surgery group. Results of the bivariate analysis showed that for patients with cholecystectomy, complication rates were significantly higher in the urgent surgery group than in the elective surgery group (p = 0.008). Furthermore, open cholecystectomy and postoperative hospital stay duration were significantly associated with urgent surgery (p < 0.001). The types of complications are listed in Table 3. Of the 4 complications, 3 were grade I, and one was grade II; all complications were minor. Only grade II complications occurred in the urgent surgery group. No major complications occurred in either the urgent or the elective surgery group. In addition, there were no significant differences between the open cholecystectomy

group and the laparoscopic cholecystectomy group in the postoperative complication rates ($p = 0.341$).

Effect on HIV treatment

All patients included in this study were treated with antiretroviral drugs at the time of surgery, and HIV infection in all patients was well controlled. Furthermore, all patients were restarted on oral antiretroviral drugs in the early postoperative period. No patients used other medications, such as intravenous infusions for HIV infection treatment. The antiretroviral drugs used for patients in this study are summarized in Supplementary Table S2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=59*). The details of perioperative HIV infection status in the 4 patients who had postoperative complications are summarized in Table 4. All 4 patients had well-controlled HIV infections before surgery and no postoperative deterioration in HIV infection control. Bivariate analysis showed no significant difference in CD4+ lymphocyte status in all patients and between the urgent and elective groups before and after surgery ($p = 0.133$, paired t-test). Furthermore, there were no significant differences between the open cholecystectomy group and the laparoscopic cholecystectomy group in postoperative CD4+ lymphocyte status ($p = 0.952$).

Discussion

In the present study, the postoperative outcomes of cholecystectomy were investigated in HIV-positive patients. The incidence of postoperative complications after cholecystectomy in HIV-positive patients was significantly higher in the urgent surgery group than in the elective surgery group. We also demonstrated that there was no significant difference in CD4+ lymphocyte status between the urgent and elective groups before and after surgery. A systematic literature search was conducted using the PubMed database on May 22, 2022, to identify published reports of cholecystectomy for HIV-positive patients. A combination of the following search terms was used: "cholecystectomy" AND "HIV". The literature search revealed 5 reports, including the surgical outcome of cholecystectomy for HIV-positive patients in the English-language medical literature (*11-15*). To the best of our knowledge, this is the first retrospective cohort study to analyze postoperative outcomes of cholecystectomy performed in HIV-positive patients divided into urgent and elective procedures.

The surgical outcomes for HIV-positive patients have changed over time. HIV infection was initially thought to be a fatal disease, and some reports revealed that the rate of postoperative complications was higher in HIV-positive patients than in HIV-negative patients (*11,14,16-19*). However, with advancements in ART, HIV infection is now becoming a controllable chronic disease (*20,21*). Some recent studies revealed that postoperative complication rates in patients with well-controlled HIV infections were comparable to those in HIV-negative patients (*15,22-26*). CD4+ lymphocyte status is one of the indicators of HIV infection status (*27,28*), and various reports have revealed that a low CD4+ lymphocyte count (especially < 200 cells/μL) was associated with a significant increase in postoperative complications (*12,29,30*). Furthermore, Foschi *et al.* demonstrated that highly active antiretroviral therapy, low HIV RNA load (< 5,000 copies/ml), and a high CD4+ lymphocyte count (> 200 cells/μL) were associated with a significantly lower complication rate in cholecystectomy with HIV-positive patients (*13*). In the present study, postoperative complications were not common in either the elective or the urgent groups. The most likely explanation for this finding is that all patients in this study were treated with ART and had well-controlled HIV infections, which is consistent with previously reported results. Furthermore, bivariate analysis showed no significant difference in CD4+ lymphocyte status in all patients and between the

Table 3. Postoperative complications classified according to the Clavien-Dindo classification

Complication	Urgent surgery ($n = 7$)	Elective surgery ($n = 23$)	Grade
Ascites	1 (14.3)	0 (0.0)	I
Chest pain	0 (0.0)	1 (4.3)	I
Fever	1 (14.3)	0 (0.0)	I
Hemorrhage	1 (14.3)	0 (0.0)	II

Table 4. The details of perioperative HIV infection status in the cases with postoperative complications

Case No.	HIV treatment	Complications	CD4+ lymphocyte status				HIV RNA	
			Pre op.		Post op.		Pre op. (copies/mL)	Post op. (copies/mL)
			Number (cells/μL)	Percentage (%)	Number (cells/μL)	Percentage (%)		
1	TAF/FTC, DTG	Ascites	370	23.9	362	25.3	N.D.	N.D.
2	ABC/3TC, DRV/r	Chest pain	344	30.8	532	30.0	< 20	39
3	ABC/3TC, DRV/r	Fever	300	20.0	329	21.7	N.D.	N.D.
4	ABC/3TC, DTG	Hemorrhage	566	32.3	518	25.0	N.D.	< 20

Abbreviations: ABC, abacavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; FTC, emtricitabine; N.D, not detectable; pre op, preoperation; post op, postoperarion; TAF, tenofovir alafenamide; 3TC, lamivudine; HIV, human immunodeficiency virus.

urgent and elective groups before and after surgery. This theory is supported by recent reports revealing that major emergency abdominal surgery had no significant effect on CD4+ T cell counts (*31*). Thus, our study suggests that cholecystectomy may be performed safely in HIV-positive patients without deterioration of HIV control, provided that HIV is well controlled.

It has been reported that urgent and emergency surgery is associated with a higher morbidity and mortality rate than elective surgery in the field of abdominal surgery (*32*). From the perspective of cholecystectomy, Rice *et al.* demonstrated that the overall rate of complications after urgent cholecystectomy for acute cholecystitis in the general population was significantly higher than that after elective cholecystectomy (16.8% *vs.* 6.2%) (*33*). In laparoscopic surgery, the most common complications of urgent cholecystectomy were "minor complications" such as wound infection, port site hernia, chest infection, and urinary tract infection (*34,35*). In addition to these minor complications, bile leaks and bile duct injury were the two common serious complications of laparoscopic cholecystectomy, with a risk rate of 2.2% (*36*). On the other hand, urgent open cholecystectomy, which is often performed for severe cholecystitis, is known to be associated with serious morbidities such as bleeding requiring transfusion, sepsis, and other systemic severe dysfunctions (*35*). In contrast, elective cholecystectomy is a safe and well-established procedure. In laparoscopic cholecystectomy, which is performed in most elective surgeries, the incidence of serious postoperative complications involving bile leakage and postoperative hemorrhage was reported to be 0.59% (*37*). In the present study, the rate of postoperative complications in the urgent surgery group was 42.8% and that in the elective surgery group was 4.3%, with a significant difference between the groups. All complications in this study were minor, and there were no major complications. These results are compatible with previous reports on cholecystectomy in HIV-negative patients.

This study has some limitations. First, the retrospective nature of the study and the relatively small number of included patients could have weakened the analyses. Prospective studies with large cohorts are needed to analyze the actual surgical outcomes in HIV-positive patients. Furthermore, the current study does not include a cohort of individuals not affected by HIV to serve as a control group and help validate the surgical outcome. Further large-scale studies are required to validate the surgical outcomes in both HIV-positive and HIV-negative patients.

In conclusion, cholecystectomy in HIV-positive patients with controlled HIV under recent ART may be performed safely even in an emergency situation.

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

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**Address correspondence to*:
Nobuyuki Takemura, Hepato-Biliary Pancreatic Surgery Division, Department of Surgery, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: ntakemura@hosp.ncgm.go.jp

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BRIEF REPORT
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Short- and long-term efficacy of bronchial artery embolization using a gelatin sponge for the treatment of cryptogenic hemoptysis

Naoko Nagano[1,2], Manabu Suzuki[1,*], Shota Yamamoto[1,3], Konomi Kobayashi[1], Motoyasu Iikura[1], Shinyu Izumi[1], Masayuki Hojo[1], Haruhito Sugiyama[1]

[1] Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Department of Respiratory Medicine, The University of Tokyo, Tokyo, Japan;
[3] Department of Radiology, Tokai University Hachioji Hospital, Tokai University School of Medicine, Tokyo, Japan.

Abstract: Bronchial artery embolization (BAE) is the first choice treatment for hemoptysis. With advances in endovascular treatment, various embolic materials have become available. However, the optimal embolic material for the treatment of cryptogenic hemoptysis has not been determined. This study aimed to investigate the short- and long-term efficacy of BAE using a gelatin sponge in the treatment of patients with cryptogenic hemoptysis. The clinical characteristics, angiographic findings, and short- and long-term outcomes of BAE were retrospectively analyzed in 22 consecutive patients who underwent BAE for control of cryptogenic hemoptysis between January 2010 and September 2018. Selective angiography and super-selective BAE were successfully performed for all patients. A gelatin sponge was used in all patients. Further, polyvinyl alcohol was mixed with the gelatin sponge in 11 patients (50%). Angiography showed that the bronchial artery was responsible for hemoptysis in all patients, along with the intercostal artery in one patient (4.5%) and the inferior phrenic artery in one patient (4.5%). Immediate hemostasis was achieved in all patients. The recurrence-free rate was 100% for 1 month, 94.1% for 3 months, 94.1% for 12 months, and 87.4% for 24 months. Of two patients with recurrent hemoptysis, one underwent bronchoscopic hemoptysis and the other received intravenous hemostatic agents. No patient underwent BAE for recurrence. No severe complications occurred. In conclusion, BAE using a gelatin sponge has short- and long-term hemostatic efficacy for treating cryptogenic hemoptysis without any severe complications. A gelatin sponge is a suitable embolic material for patients with cryptogenic hemoptysis.

***Keywords*:** angiography, bronchial arterial embolization, emergency treatment, treatment outcome

Introduction

Hemoptysis is a common but occasionally life-threatening symptom in a wide variety of diseases such as lung cancer, tuberculosis, and aspergillosis. However, a small number of patients presenting with this symptom have no specific causative disease; this presentation is known as "cryptogenic hemoptysis". This group accounts for 7–22% of all hemoptysis cases (*1-4*).

Since its initial application in 1973 (*5*), bronchial artery embolization (BAE) has been the mainstay treatment for hemoptysis. BAE is less invasive than other treatments, and is applicable to patients who are ineligible for surgery or those with bilateral lung disease (*6-8*). Contrast-enhanced chest computed tomography (CT) and subsequent BAE are recommended for massive or life-threatening hemoptysis (*9*). The utilization of BAE for non-massive hemoptysis is also increasing (*9*). As endovascular treatment has achieved popularity for control of bleeding, various embolic materials have been developed. In general, coils and polyvinyl alcohol (PVA) permanently embolize target vessels, while embolization with a gelatin sponge (GS) is essentially temporary (*10,11*). Embolization with a GS can result in recanalization within several weeks to months (*12*). Although many retrospective studies have compared the efficacy of individual embolic materials, the optimal embolic material for BAE has not been fully elucidated. Moreover, as mentioned above, because hemoptysis incorporates various causative diseases, the optimal material may differ according to the underlying disease. Under these circumstances, the embolic materials for BAE are selected based on their characteristics and local availability.

Few studies have investigated the efficacy of BAE for cryptogenic hemoptysis to date (*4,9-15*). The prognosis for cryptogenic hemoptysis after BAE

is thought to be favorable (*9-15*), but the optimal embolizing material for cryptogenic hemoptysis remains unclear. Assuming that the rebleeding rate of cryptogenic hemoptysis is relatively low (*13*,*15*), BAE with transient embolic materials, but not with permanent materials, may be sufficient and suitable for these patients. Further, we previously reported favorable outcomes in patients who underwent BAE with a GS (*16*). In the current study, we aimed to investigate the short- and long-term efficacy of BAE using a GS in the treatment of patients with cryptogenic hemoptysis.

Materials and Methods

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board for clinical research of National Center for Global Health and Medicine (NCMG-G-003639-00) and registered on the UMIN Clinical Trials Registry (UMIN000042050). Informed consent was obtained from patients.

Study population

We retrospectively reviewed the medical records of 120 consecutive patients who underwent BAE for hemoptysis between January 2010 and September 2018 at the National Center for Global Health and Medicine, Department of Respiratory Medicine, and identified patients with cryptogenic hemoptysis. Cryptogenic hemoptysis was defined as follows: *i*) no history of respiratory comorbidities causing hemoptysis and *ii*) no indications of the etiological cause based on laboratory and radiological results. Whether these inclusion criteria were met was independently confirmed by at least one young pulmonary physician and one well-experienced pulmonary physician. All patients underwent BAE during hospitalization and received standard therapy, such as the administration of oxygen and homeostatic materials, including tranexamic acid and/or carbazochrome sodium sulfonate hydrate. The degree of hemoptysis was defined as follows: massive, > 400 mL/24 h; moderate, 30–400 mL/24 h; and mild, < 30 mL/24 h (*17*).

Imaging studies and analysis

All patients underwent contrast-enhanced CT of the chest before BAE to determine the responsible arteries, diameter of the bronchial artery on the lesion side, and presence or absence of bronchial arterial dilatation. Bronchial arterial dilatation was defined as a bronchial artery diameter of > 2 mm (*18*) or when the bronchial artery was traceable from its origin to the ipsilateral hilum (*19*). The imaging studies were independently reviewed by at least one diagnostic radiologist and at least two pulmonary physicians.

Angiography and embolization

All BAE procedures were performed by radiologists or with the collaboration of radiologists and respiratory physicians. We performed BAE *via* a transfemoral approach with the placement of a long vascular sheath (25 cm). All possible responsible arteries identified by CT were super-selectively evaluated using arteriography with 4-Fr guiding catheter and 2.8-Fr microcatheter systems with 0.014-inch guide wires during the session. When vascular abnormalities such as bronchial arterial hypertrophy, aneurysms, hypervascularity, and systemic-pulmonary shunting were observed, the arteries were super-selectively embolized using the 2.8-Fr microcatheter system. Embolization was performed on the responsible arteries with a GS or a combination of a GS and PVA particle. The GS was cut into 1 × 1 to 2 × 2 mm pieces in advance and was prepared as a slurry by mixing with contrast medium. We injected the embolic materials into the responsible arteries until the proliferation of peripheral blood vessels had disappeared on angiography. Bronchial aneurysm was defined as localized arterial dilation ≥ 1.3-fold larger than the proximal and distal vessels on CT or angiography. The bleeding site was identified by the greatest degree of diffuse ground-glass opacities on CT and/or coagulation on bronchoscopy. The angiography findings were retrospectively reviewed by at least one radiologist and one well-experienced pulmonary physician.

Outcome analysis

Technical success was defined as the successful embolization of responsible arteries. Short-term efficacy was defined as the cessation of hemoptysis associated with an improved clinical course during hospitalization (*13*). Long-term efficacy was defined as the absence of rebleeding for more than three months from the day of BAE. Recurrence was defined as either a new episode of hemoptysis of > 200 mL/24 h or the need for interventional therapies such as intravenous administration of hemostatic agents, bronchoscopy, or BAE. Complications resulting from additional treatment, permanent or significant disability, or death, were retrospectively reviewed.

Statistical analysis

Continuous variables were expressed as median and range. The bleeding recurrence-free rate was analyzed using the Kaplan–Meier method and was presented in a Kaplan–Meier curve. Statistical analyses were preformed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

Results and Discussion

Of the 120 patients who underwent BAE for hemoptysis during the study period, 22 patients with cryptogenic hemoptysis were identified. The clinical characteristics of the subjects are summarized in Table 1.

Of the 22 patients who underwent BAE for cryptogenic hemoptysis, 4 (18.2%) presented with massive hemoptysis, 15 (68.2%) with moderate hemoptysis, and 1 (4.5%) with mild hemoptysis. The degree of bleeding was not available in two (9.1%) patients because the data were missing. The bleeding region determined by CT and bronchoscopy was as follows: nine (40.9%) in the right upper lobe, two (9.1%) in the right middle lobe, three (13.6%) in the right lower lobe, seven (31.8%) in the left upper lobe, and one (4.5%) in the left lower lobe. All patients exhibited bronchial arterial dilatation on chest CT, and the median diameter was 2.4 mm (range 1.1–4.8 mm) at the origin of the bronchial artery on the affected side.

Technical success was achieved in all patients. All 22 patients exhibited hypervascularity and bronchial arterial hypertrophy on angiography. Four patients (18.2%) experienced aneurysms and six (27.2%) experienced systemic-pulmonary shunting. The number of embolized arteries was one in eight patients (36.4%), two in eight patients (36.4%), three in five patients (22.7%), and four in one patient (4.5%). The bronchial artery was responsible in all patients. The intercostal artery and inferior phrenic artery were also targeted in one patient each (each 4.5%). The intercostobronchial trunk (ICBT) was found in 12 patients (54.5%). In such patients, BAE was performed on the distal side to the branch of the intercostal arteries (Figure 1). The angiographic findings are summarized in Table 2. The median procedure time was 86 min (range 40–142 min). A GS was used as the embolic material in all patients (100%). The GS and PVA combination was used in 11 patients (50.0%).

Short-term efficacy was achieved in all patients after BAE. Nineteen patients were followed-up for

Table 1. Clinical characteristics of patients with cryptogenic hemoptysis (*n* = 22)

Clinical characteristics	Patients, *n* (%)
Male	14 (63.6)
Ever-smokers	16 (72.7)
Current smokers	9 (40.9)
Respiratory comorbidity	7 (31.7)
COPD	5 (22.7)
Asthma	1 (4.5)
Interstitial pneumonia	1 (4.5)
Cardiovascular comorbidity	13 (59.1)
Hypertension	6 (27.2)
Atrial fibrillation	3 (13.6)
Valvuloplasty	3 (13.6)
Deep venous thrombosis	1 (4.5)
Liver cirrhosis	1 (4.5)
Chronic renal failure	2 (9.1)
Use of antiplatelet/anticoagulant medications	5 (22.7)

COPD, chronic obstructive pulmonary disease

Table 2. Summary of angiographic findings (*n* = 22)

Angiographic findings	Patients, *n* (%)
Bronchial artery hypertrophy	22 (100)
Hypervascularity	22 (100)
Bronchial aneurysm	4 (18.2)
Systemic-pulmonary shunting	6 (27.2)
No. of embolized arteries	
1	8 (36.4)
2	8 (36.4)
3	5 (22.7)
4	1 (4.5)
Responsible artery	
Bronchial artery	22 (100)
Intercostal artery	1 (4.5)
Inferior phrenic artery	1 (4.5)
Intercostobronchial trunk	12 (54.5)

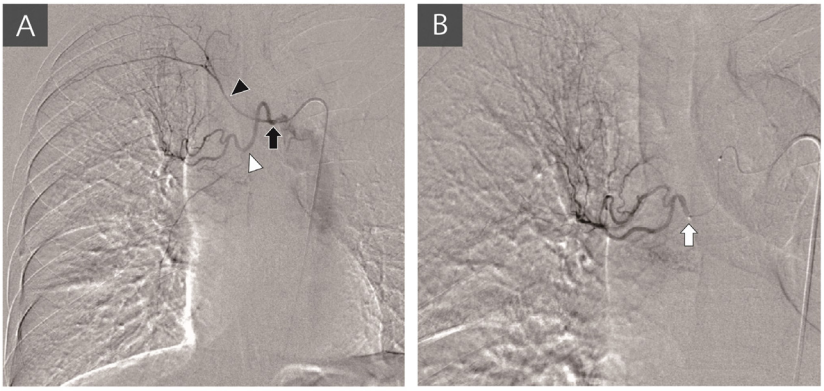

Figure 1. Selective angiography and super-selective bronchial artery embolization in a 68-year-old male patient. (A) Hypervascularity was observed during selective angiography of the intercostobronchial trunk (black arrow) with the right third and fourth intercostal arteries (black arrowhead) and a right bronchial artery (white arrowhead). The bronchial artery diameter was 1.2 mm. **(B)** Super-selective bronchial artery embolization performed on a right bronchial artery. The embolization was performed on a right bronchial artery after placing the microcatheter (white arrow) distal to the bronchial artery branch.

> 1 month, and the median follow-up period was 17 months (range 1–69 months). The recurrence-free rate was 100% for 1 month, 94.1% for 3 months, 94.1% for 12 months, 87.4% for 24 months, and 87.4% for >24 months (Figure 2). Rebleeding was observed in two patients, and only one patient required a bronchoscopic hemostasis procedure in addition to the administration of homeostatic materials. No patient underwent BAE for rebleeding. Table 3 summarizes the characteristics of patients who experienced rebleeding. No patient experienced severe complications such as spinal cord ischemia that resulted in prolonged hospitalization for additional treatment, permanent or significant disability, or death.

This study aimed to investigate the short- and long-term efficacy of BAE using a GS in the treatment of patients with cryptogenic hemoptysis. We found that BAE with a GS can terminate bleeding and suppress severe rebleeding with minimal complications in patients with cryptogenic hemoptysis. After conducting a literature research in PubMed and Ichushi-Web, we believe that this is the first study to investigate the efficacy of BAE with a GS in the treatment of cryptogenic hemoptysis in > 20 patients.

A GS is a widely used BAE material. In Japan, a national database study showed that 79% of BAE for cryptogenic hemoptysis used a GS (*20*). The advantages include its low cost; wide availability; and accumulated years of clinical use, which indicates its safety (*10,11*). In addition, as it is absorbed within several weeks after embolization (*12*), a second BAE procedure can target the same artery in case of rebleeding. One of the concerns regarding BAE with

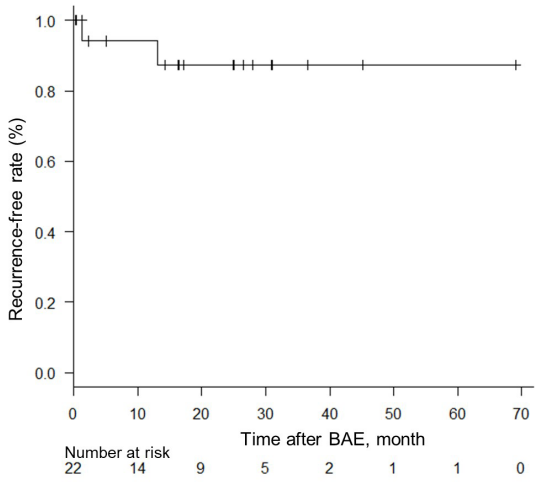

Figure 2. Cumulative recurrence-free rate curve of patients who underwent bronchial artery embolization (BAE). The recurrence-free rate was 100% for 1 month, 94.1% for 3 months, 94.1% for 12 months, 87.4% for 24 months, and 87.4% for > 24 months.

Table 3. Summary of patients with recurrent bleeding (n = 2)

Case no.	Recurrence-free duration	Age (years)	Sex	Smoking	Bronchial artery dilation	Hypervascularity	Aneurysm	Shunting	Bleeding site at time of BAE	Bleeding site at time of recurrence	Treatment for rebleeding	Recanalization on CT
1	15	67	M	Ex	Yes	Yes	No	No	RML	RLL	Bronchoscopic hemostasis, hemostatic materials	Yes
2	1	78	M	Ex	Yes	Yes	No	No	RUL	RUL	Hemostatic materials	No

M, male; BAE, bronchial artery embolization; RML, right middle lobe; RLL, right lower lobe; RUL, right upper lobe; CT, computed tomography

a GS is recanalization that leads to another episode of hemoptysis. A previous study found that the recurrence rate was higher in a group of patients treated with gelfoam particle than in those treated with PVA (*21*). However, in light of its low risk of rebleeding (*13*,*15*), we hypothesized that BAE with a GS, a transient but inexpensive and widely used embolic material, is as effective as other permanent embolic materials for cryptogenic hemoptysis. Our results showed that BAE with a GS was sufficient and effective for treating cryptogenic hemoptysis. The recurrence-free rate remained as high as 87.4% during the 2-year follow-up period, and no life-threatening hemoptysis occurred at recurrence. Previous studies on cryptogenic hemoptysis also reported favorable prognoses after BAE (*13,22-25*). These studies used detachable coils (*13*), N-butyl cyanoacrylate (*22*), or PVA (*24*) as permanent embolic materials. Our outcome was comparable to these previous findings. Notably, no patients required a second BAE procedure for recurrence. Based on our results, we consider that the temporary effect of GS embolization is sufficient for treating cryptogenic hemoptysis, which has no underlying abnormality that can cause repetitive hemoptysis. The low cost, wide availability, and abundant clinical use are additional major advantages of the GS. Therefore, the GS should be considered an appropriate embolic material for the treatment of cryptogenic hemoptysis.

The representative complications associated with BAE include fever, local chest pain and allergic reaction to gelatin. Among such complications, the most severe complication is spinal cord ischemia caused by occlusion of the spinal artery, particularly of the great anterior radiculomedullary artery (the artery of Adamkiewicz, AKA). In this study, no cases of spinal cord ischemia were observed. To avoid AKA occlusion, BAE should be selectively performed on the exact responsible artery through precise angiography. Super-selective BAE has decreased the occurrence of spinal cord ischemia. The prevalence of spinal cord ischemia was reported to be as low as 0.19% in a recent report from Japan (*20*). This occurrence rate was quite low compared to previous studies, who reported rates between 1.4% and 6.5% (*26*). In addition, the accurate anatomical analysis of the AKA and bronchial artery has contributed to the decrease in spinal cord ischemia. The bronchial artery is the responsible artery in cryptogenic hemoptysis in most cases. In this study, 20 (90.9%) patients underwent BAE only in the bronchial artery. This finding is in line with previous studies (*13,22-24*). Uotani *et al.* (*27*) reported that the AKA originated from the intercostal or lumber artery at the Th7–12 or L1–3 level. Another study demonstrated that the spinal arterial supply directly from the bronchial artery was absent (*28*). Based on these data, BAE with a GS for cryptogenic hemoptysis targeting the bronchial artery can be performed safely without any concern for spinal cord ischemia. Moreover, the one concern regarding embolization of the bronchial artery is the presence of an ICBT. The intercostal artery can be a culprit in cryptogenic hemoptysis in a small population of patients. Due to the continuity between the intercostal arteries and the AKAs, extra attention should be paid to neurological complications in such cases. In our cohort, 12 patients (54.5%) had an ICBT. In such cases, GS embolization should be performed in the distal area posterior to the branching intercostal artery. One patient with intercostal artery embolization in this study underwent embolization after confirming no depiction of the AKAs by super-selective angiography for the intercostal artery.

Angiographic findings revealed the hypervascularity and hypertrophy of the bronchial artery in patients with cryptogenic hemoptysis, which is comparable with the findings of previous studies (*4,13,22-25*). In contrast, the prevalence of systemic-pulmonary shunting differs among studies. Most previous studies reported a low frequency of shunting in cryptogenic patients (*4,13,24,29*), but one study investigating cryptogenic hemoptysis in smokers noted shunting in 80% of patients (*23*). In the current study, systemic-pulmonary shunting was found in 27.2% of patients. This relatively high rate of shunting can be explained by the fact that our cohort included patients with a history of thoracic surgery such as cardiac valve replacement and mediastinal tumor resection. Inflammatory adhesion after surgery could induce shunting (*30*).

This study has several limitations. First, this was a single-arm retrospective analysis conducted in a single hospital. To generalize the results, we have begun a new prospective study regarding GS BAE. The results of the present study will aid the interpretation of more generalized studies in the future. Second, cryptogenic hemoptysis is essentially a diagnosis by exclusion and is thus heterogenous. Previous studies defined cryptogenic hemoptysis as no signs of underlying diseases on clinical investigation. As the precise definition differs slightly among studies, the validity of study comparisons is questionable. Finally, screening for asymptomatic cerebral infarction after BAE was not performed in this study.

In conclusion, GS BAE for cryptogenic hemoptysis yields short- and long-term hemostatic efficacy without severe complications. GS is a leading candidate for the optimal embolic material for patients with cryptogenic hemoptysis.

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Address correspondence to:
Manabu Suzuki, Department of Respiratory Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: manabu@nms.ac.jp

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Long-term sequelae of different COVID-19 variants: The original strain versus the Omicron variant

Xuejiao Liao[1,§], Yuan Guan[1,2,§], Qibin Liao[1,§], Zhenghua Ma[1], Liping Zhang[1], Jingke Dong[1], Xiaojuan Lai[1], Guoqin Zheng[1], Sumei Yang[1,3], Cheng Wang[1,3], Zhonghui Liao[1,3], Shuo Song[1], Hongyang Yi[1], Hongzhou Lu[1,*]

[1] Institute for Hepatology, Bio-therapeutic Center, National Clinical Research Center for Infectious Disease, Shenzhen Third People's Hospital; The Second Hospital Affiliated with the School of Medicine, Southern University of Science and Technology, Shenzhen, Guangdong, China;
[2] Department of Epidemiology, School of Public Health, Fudan University, Shanghai, China;
[3] Bengbu Medical College, Bengbu, Anhui, China.

Abstract: Although Omicron appears to cause less severe acute illness than the original strain, the potential for large numbers of patients to experience long COVID is a major concern. Little is known about the recovery phase in cases of Omicron, highlighting the importance of dynamically monitor long COVID in those patients. Subjects of the current study were patients available for a three-month follow-up who were admitted from January 13 to May 22, 2020 (period of the original strain) and from January 1 to May 30, 2022 (period of Omicron). Twenty-eight-point-four percent of patients infected with the original strain had long-term symptoms of COVID-19 and 5.63% of those infected with the Omicron strain had such symptoms. The most common symptom was a cough (18.5%), followed by tightness in the chest (6.5%), in patients infected with the original strain. Fatigue (2.4%) and dyspnea (1.7%) were the most commonly reported symptoms in patients infected with the Omicron strain. The respiratory system is the primary target of SARSCoV-2. Supportive treatment is the basis for the treatment of respiratory symptoms in patients with COVID-19. Quality sleep and good nutrition may alleviate fatigue and mental issues. Further knowledge about a long-term syndrome due to Omicron needs to be discussed and assembled so that healthcare and workforce planners can rapidly obtain information to appropriately allocate resources.

Keywords: SARS-CoV-2, Omicron variant, long COVID, long-term sequelae

The outbreak of Coronavirus Disease 2019 (COVID-19) remains a major public health emergency of international concern, resulting in a significant global disease burden. By September 1, 2022, there have been more than 600 million confirmed cases of COVID-19, and more than 6.4 million people globally have died following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (*1*). The Omicron variant of SARS-CoV-2 spread rapidly across the world, out-competing former variants soon after it was first detected in November 2021 (*2*).

As the patients recovering from COVID-19 continue to increase, long-term symptoms of COVID-19 (long COVID) after discharge from hospital have been widely reported (*3-7*). Long COVID is defined as the presence of signs and symptoms that develop during or after an infection consistent with COVID-19 and that continue for more than 12 weeks (*8*). These symptoms include fatigue, a cough, myalgia, shortness of breath, loss of taste or smell, headaches, and dyspnea and they affect the neurological, nervous, respiratory, cardiovascular, and digestive systems (*3,5,9,10*). One early study found that of patients who had recovered from acute COVID-19, 87.4% reported persistence of at least one symptom, and fatigue and dyspnea in particular, at 1 month follow-up after discharge (*9*). As follow-up studies continue to report, there are significant differences in the prevalence of long-term symptoms among patients with COVID-19 after discharge (*7,11-14*) (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=61*). The main reason may be that new variants appear to cause less severe acute illness than previous strains (*2*). However, the potential for large numbers of patients experiencing long COVID is a major concern, and healthcare and workforce planners rapidly need information to appropriately allocate resources.

At the peak of the first wave of the outbreak in Shenzhen in 2022, a large number of asymptomatic and mild cases involving Omicron emerged. As described here, a cohort study based on a telephone interview collected data on the sequelae of an Omicron infection at 3 months. Results were compared to a follow-up

of cases involving the original strain in Shenzhen in 2020 to explore the characteristics of sequelae after recovering from an infection with different viral variants.

Subjects were patients with confirmed COVID-19 who were admitted to Shenzhen Third People's Hospital from January 13 to May 22, 2020 (period of the original strain) and from January 1 to May 30, 2022 (period of Omicron). In accordance with the Guidelines for Clinical Diagnosis and Treatment of COVID-19 (9th edition) (*15*), potential subjects were over the age of 6, and they were excluded if they had a documented neurological or psychiatric disease. The categorization of COVID-19 disease severity was in accordance with the World Health Organization's interim guidance (*16*).

Subjected were contacted by phone and asked about their symptoms. A follow-up was conducted *via* phone on an outpatient basis, and subjects who have COVID-19 sequelae were recalled to the outpatient clinic for symptom-related laboratory testing until July 30, 2022. The recovery phase was defined as the period after discharge and more than 3 months after the diagnosis of COVID-19. Data on patient sociodemographic and clinical characteristics were obtained from an electronic medical record system. COVID-19 sequelae, which were defined as new and persistent symptoms and more severe symptoms than at the onset of COVID-19, were investigated by a well-trained nurse or doctor. Written informed consent was obtained from all patients or their guardians before participation in this study. The study protocol was approved by the Ethics Committee of Shenzhen Third People's Hospital (approval No.2022-074-02).

Baseline demographic and clinical characteristics of the two groups of patients are summarized in Table 1. The patients infected with the original strain included 303 patients with COVID-19 who were admitted to Shenzhen Third People's Hospital between January 13 and May 22, 2020. Eighty-six (28.4%) had one or more long-term symptoms of COVID-19. The median age of patients infected with the original strain was 47 years of age (IQR: 35-59 years) and the median duration of hospitalization was 21 days. Disease severity was ordinary in 81.8% of patients, mild in 3.6%, and severe in 14.0%. Sixty-seven patients (21.8%) infected with the original strain had comorbidities, and the most common was hypertension. A total of 1,829 patients who were admitted during the period of Omicron were also available for a 3-month follow-up. A total of 103 patients (5.63%) infected with the Omicron strain had

Table 1. Demographic and clinical characteristics of cases involving the original strain or Omicron strain by sequelae 3 months after discharge

Variables	Original strain				Omicron			
	Non-sequelae (*n* = 222)	Sequelae (*n* = 86)	Total patients (*n* = 308)	*p* value	Non-sequelae (*n* = 1,726)	Sequelae (*n* = 103)	Total patients (*n* = 1,829)	*p* value
Age (years), median (IQR)	47 (35-60)	46 (36-56)	47 (35-59)	0.82	34 (25-47)	37 (29-44)	34 (26-47)	0.32
Age group, *n* (%)				0.05				< 0.01
6-18	16 (7.2)	1 (1.2)	17 (5.5)		255 (14.8)	2 (1.9)	257 (14.1)	
18-30	23 (10.4)	7 (8.1)	30 (9.7)		347 (20.1)	25 (24.3)	372 (20.3)	
31-60	123 (55.4)	62 (72.1)	185 (60.1)		996 (57.7)	70 (68.0)	1066 (58.3)	
60-	60 (27.0)	16 (18.6)	76 (24.7)		128 (7.4)	6 (5.8)	134 (7.3)	
Sex				0.89				0.86
Male	100 (45.0)	38 (44.2)	138 (44.8)		904 (52.4)	53 (51.5)	957 (52.3)	
Female	122 (55.0)	48 (55.8)	170 (55.2)		822 (47.6)	50 (48.5)	872 (47.7)	
Disease severity				0.50				0.53
Asymptomatic	2 (0.9)	0 (0.0)	2 (0.6)		516 (29.9)	29 (28.2)	545 (29.8)	
Mild	9 (4.1)	2 (2.3)	11 (3.6)		1,064 (61.6)	62 (60.2)	1126 (61.6)	
Ordinary	183 (82.4)	69 (80.2)	252 (81.8)		146 (8.5)	12 (11.7)	158 (8.6)	
Critical	28 (12.6)	15 (17.4)	43 (14.0)		0 (0.0)	0 (0.0)	0 (0.0)	
Comorbidities	51 (23.0)	16 (18.6)	67 (21.8)	0.40	313 (18.1)	31 (31.1)	344 (18.9)	< 0.01
Hypertension	21 (9.8)	10 (11.6)	31 (10.1)		98 (5.7)	6 (5.9)	104 (5.7)	
Diabetes	13 (5.9)	1 (1.3)	14 (4.5)		52 (3.0)	2 (1.9)	54 (3.0)	
Chronic kidney disease	0 (0.0)	0 (0.0)	0 (0.0)		33 (1.9)	4 (3.9)	37 (2.0)	
Cardiovascular disease	5 (2.3)	2 (2.3)	7 (2.3)		14 (0.8)	1 (1.0)	15 (0.8)	
Chronic obstructive pulmonary disease	5 (2.3)	2 (2.3)	7 (2.3)		33 (1.9)	4 (3.9)	37 (2.0)	
Virus infection	6 (2.7)	1 (1.2)	7 (2.3)		38 (2.2)	4 (3.9)	42 (2.3)	
Rounds of COVID-19 vaccination								
Zero	--	--	--		98 (5.7)	2 (1.9)	100 (5.5)	0.11
One	--	--	--		14 (0.8)	0 (0.0)	14 (0.8)	0.36
Two	--	--	--		467 (27.1)	31 (30.1)	498 (27.2)	0.50
Three or more	--	--	--		422 (24.4)	28 (27.2)	450 (24.6)	0.53
Unknown	--	--	--		724 (41.9)	40 (38.8)	764 (41.8)	0.53
Length of hospitalization (days)	20 (16-24)	21 (15-26)	21 (16-25)	0.48	16 (12-20)	16 (13-20)	16 (12-20)	0.24

IQR: interquartile range.

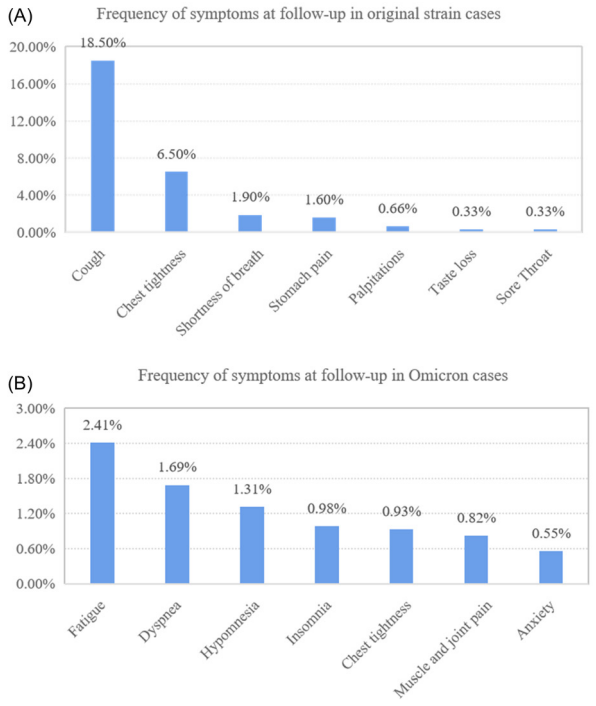

Figure 1. Characteristics and prevalence of the long-term (more than 3 months after diagnosis) clinical sequelae of COVID-19. (A) The prevalence of specific sequelae in cases involving the original strain. **(B)** The frequency of specific sequelae in cases involving omicron.

one or more long-term symptoms of COVID-19. The median age of patients infected with the Omicron strain was 34 years of age (IQR: 26-47 years), and 957 (52.3%) were male. Disease severity was categorized as non-severe in all of those patients; disease severity was asymptomatic in 29.8%, mild in 61.6%, and ordinary in 8.6%.

The characteristics and prevalence of long-term clinical sequelae of COVID-19 are shown in Figure 1. The prevalence of long-term symptoms of COVID-19 was 28.4% in patients infected with the original strain and 5.63% in those infected with the Omicron strain. The most common respiratory symptom was a cough (18.5%), followed by tightness of the chest (6.5%) and shortness of breath (1.9%) in patients infected with the original strain. The prevalence of stomach pain was 1.6% and that of palpitations was 0.66%. Among the clinical sequelae in patients infected with the Omicron strain, fatigue was the most common general symptom (2.41%, 44/1,829). The prevalence of dyspnea was 1.69% (31/1,829) and that of tightness of the chest was 0.93% (17/1,829). Hypomnesia (1.31%, 24/1,829) was the most reported neurological and psychological symptom, followed by insomnia and anxiety.

Several studies have found that 59.4% of severely ill patients had symptoms that persisted for more than 30 days after discharge, whereas 14.3% of patients with a mild to asymptomatic infection had such symptoms (*5,7*). A cohort study found that severely ill patients who were hospitalization had an increased risk of diminished lung diffusion capacity, radiographic abnormalities, and muscle or limb pain than those with less severe symptoms (*6*). These results strongly suggested a correlation between the severity of the infection and the development of long-term complications. In the current study, 5.6% of patients infected with Omicron suffered from persistence of at least one symptom after a 3-month follow-up; this was a significant reduction from 28% in patients infected with the original strain. An analysis of the proportion of disease severity in the two groups also supported the contention that the severity of the infection affected long COVID.

Among the clinical sequelae included in the current study, respiratory symptoms like a cough, tightness of the chest, and shortness of breath were most commonly reported in patients infected with the original strain, and dyspnea was also the second most frequent in patients infected with Omicron. The respiratory system is the primary target of SARS-CoV-2. Many patients who have recovered from COVID-19 still suffered from coughing and shortness of breath, and some patients with severe COVID-19 even developed extensive pulmonary fibrosis (*17*). Some subjects complained of dyspnea and an increased respiratory rate following light or moderate activity, even though the lung lesions had resolved completely according to high-resolution CT of the lungs, which indicated that COVID-19 can cause persistent damage. The pulmonary effects of SARS-CoV-1 were described in a 2-year follow-up, highlighting a marked diminishing of exercise capacity, respiratory function, and tolerance of exertion (*18*). In patients infected with the Omicron strain, fatigue was the most commonly reported symptom. To date, there is no pathophysiological explanation for fatigue in literature. One possible cause could be the prolonged hospitalization of patients, with consequent loss of muscle strength and tone mostly followed by an incomplete recovery (*9*). However, the patients infected with Omicron in the current study included those with a mild to moderate infection who were unlikely to have been bedridden for long periods of time, and the cause needs to be further explored.

Neuropsychiatric sequelae caused by viral pathogens have always garnered attention when discussing long-term complications and persisting symptoms in patients who recovered from COVID-19. Approximately 2.7% of the patients infected with Omicron complained about experiencing neurological and psychological symptoms. Hypomnesia and anxiety are also commonly seen in other viral illnesses, and both psychical and psychological sequelae have been noted in MERS and SARS (*7,9,19*).

There are several limitations to the current study. This study was underpowered and thus unable to identify the factors that are directly correlation with the development of long-term sequelae in recovered

patients. That said, results did reveal the prevalence of long COVID and the most common persistent symptoms with different viral variants after 3 months. This study relied on a semi-structured phone interview, and symptoms were self-assessed instead of being measured by a validated scale. Accordingly, the results may have underestimated the health consequences of Omicron.

As we continue to accrue experience, our understanding of the long-term complications of infection with SARS-CoV-2 continues to increase. Previously, long COVID, and especially fatigue, a cough, dyspnea, and psychological symptoms, was a frequent long-term complication of COVID-19. The common persistent symptoms of long COVID-19 in Omicron cases were similar to those in previous studies, but the overall incidence of long COVID was significantly lower. Supportive treatment is the basis for the treatment of respiratory symptoms in patients with COVID-19. Patients need to be allowed to rest in bed and to receive good nutrition since this could alleviate fatigue, tightness of the chest, and other serious symptoms. Considering the current high number of Omicron cases worldwide, healthcare professionals should not ignore its importance even though the incidence of sequelae is declining. Communities need to establish follow-up clinics for COVID-19 sequelae, including the provision of appropriate medical care and psychological counseling.

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[§]*These authors contributed equally to this work*.
**Address correspondence to*:
Hongzhou Lu, Institute for Hepatology, Bio-therapeutic Center, National Clinical Research Center for Infectious Disease, Shenzhen Third People's Hospital; The Second Hospital Affiliated with the School of Medicine, Southern University of Science and Technology, No. 29 Bulan Road, Long Gang District, Shenzhen, Guangdong 518112, China.
E-mail: luhongzhou@fudan.edu.cn

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Towards the light at the end of the tunnel: Changes in clinical settings and political measures regarding COVID-19 from 2021, and future perspectives in Japan

Kohei Kamegai*, Kayoko Hayakawa

Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Japan has faced seven waves of the COVID-19 pandemic since 2020. Due to the less severe Omicron variant and the high rate of vaccination nationwide, the death rate has declined compared to that due to previous variants. In early 2022, current Prime Minister Fumio Kishida devised a new concept entitled "Living with COVID-19", encouraging a new lifestyle of living with SARS-CoV-2. Although treatment and prevention options have increased, the Omicron variant still causes deaths among the most vulnerable population. Before accepting life with SARS-CoV-2, challenges remain, especially with regard to communication, the healthcare system, and vaccination. A society-wide strategy involving multiple stakeholders should be adopted to mitigate the damage and achieve a true world where we are "Living with COVID-19".

***Keywords*:** Omicron variant, living with COVID-19, communication, healthcare system, vaccination

The world has been suffering from the COVID-19 pandemic since the end of 2019, and Japan is no exception. Drastic changes have occurred in epidemiology, virology, public health, and the medical response to COVID-19 (*e.g.*, prevention, diagnosis, and treatment). From a clinician's perspective, this work outlines the changes in and evolution of measures against COVID-19 in Japan from the outbreak of the Delta variant (the 5th wave) to the present outbreak due to the Omicron variant (the 7th wave) (from August 2021 to November 2022).

A summary of changes in public health and political measures

Countries have adopted different policies and philosophies with respect to the pandemic. In the United Kingdom, for example, the government aimed to overcome the pandemic early, and all restrictions regarding COVID-19 were lifted in March 2022 (*1*). In contrast, the Chinese Government has implemented strict regulations known as the "Zero-COVID policy" (*2*). Unlike either of these approaches, Japan has implemented multiple mitigation measures but it has not lifted most COVID-19 restrictions (Figure 1).

Since the time of former Prime Minister Shinzo Abe, Japan has developed a vaccination program as one of its main strategies against the pandemic.

In May 2021, after former Prime Minister Yoshihide Suga initiated the "one million vaccinations per day" campaign during the 4th wave, the number of COVID-19 cases and deaths consequently fell (*3*). Japan faced the 5th wave (late July - early October 2021) during the Tokyo Olympic Games (23rd July - 8th August 2021) due to the Delta variant. The Delta variant was notorious for its high virulence; even young patients occasionally succumbed to severe disease (*4*). Hospitals kept being overwhelmed with many COVID-19 patients, especially patients who were unvaccinated (*5*). The Japanese Government declared a 4th state of emergency (12th Jul 2021-30th Sep 2021) and semi-emergency measures (known as "Man-bo" in Japanese) to reduce the number of cases and severe cases.

Japan is currently facing waves of the Omicron variant, with the 6th in mid-January- early June 2022 and the 7th in early July - early October 2022. The Omicron variant has a higher transmissibility than any previous Variants of Concern (VOCs) (*6*).

In early 2022, under the current Prime Minister Fumio Kishida, the government devised a new concept, "Living with COVID-19", to live with SARS-CoV-2 instead of suppressing it. The decline in mortality among patients with COVID-19 compared to that during the early stages of the pandemic corroborated this approach (*7*).

The government shortened the quarantine period for people who had close contact with COVID-19 patients (July 2022), it subsequently shortened the quarantine

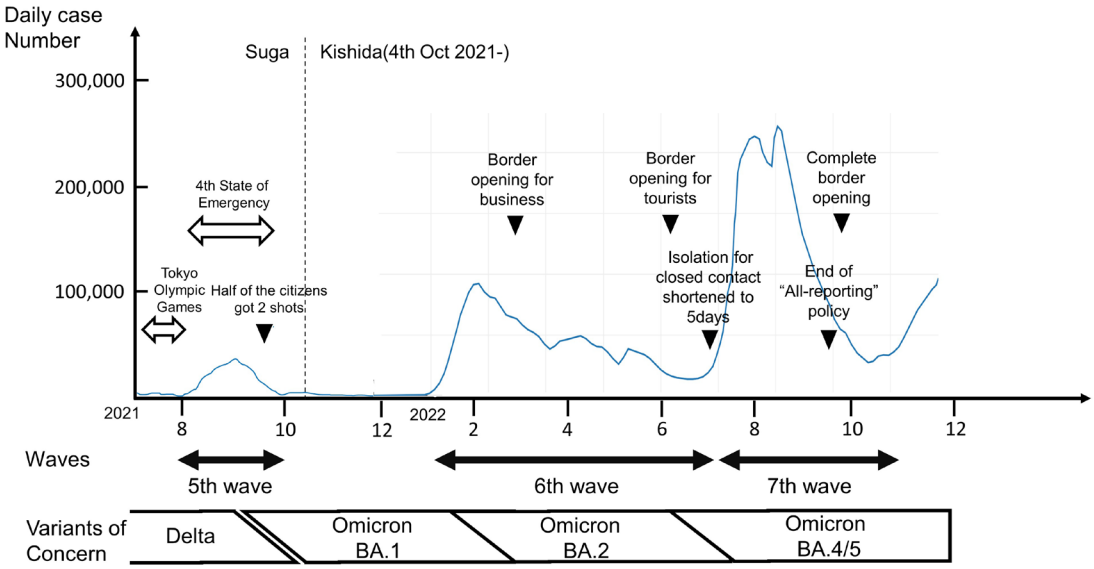

Figure 1. A graph of the daily number of cases from August 2021 to the present. During this period, Japan faced the 5th wave due to the Delta variant and the 6th and 7th waves due to the Omicron variant. The number peaked in August during the 7th wave, preventive measures were gradually implemented. The 8th wave began at the end of November 2022.

period for patients with COVID-19 (September 2022), and it eased restrictions to an extent. In August 2022, Japan's weekly number of newly diagnosed COVID-19 patients was the highest worldwide for four weeks. This is probably a misleading figure because Japan still conducted notifiable disease surveillance to actively diagnose and report cases, whereas other countries reduced the rounds of testing.

In September 2022, the government changed the "all reporting policy" of notifiable disease surveillance of COVID-19 and Japan opened its borders to the outside, shifting toward a world where we are "Living with COVID-19".

Clinical issues

Changes in clinical epidemiology

During the 5th wave, the proportion of severe cases was high mainly because the virulent Delta variant was dominant. Most patients who needed immediate hospitalization were unvaccinated or had an underlying illness. Overloaded hospitals had difficulty promptly receiving patients with severe COVID-19 or who were at high risk of becoming severely ill.

During the 6th and 7th waves, when Omicron was the main variant, the disease was less severe than that due to the Delta variant. The Omicron variant is less virulent than conventional strains and may be less deadly than seasonal influenza (*8*). Patients in critical condition who needed specialized urgent care, such as intubation and extracorporeal membrane oxygenation, were seldom seen (*5*).

However, the number of COVID-19 patients increased more than before, mainly because of the enhanced transmissibility of the Omicron variant. A review indicated that the Omicron variant has a mean primary reproduction number of 8.2, 3.8 times higher than that of the Delta variant (*6*). Most admitted patients are senior citizens, and young patients with mild disease are advised to stay home, even if unvaccinated.

Outside large hospitals, calls for on-site clinics, remote medical interviews, and at-home medical care increased.

The causes of death have also been changed as a consequence. According to a brief report from a national hospital in Tokyo, the leading cause of death during the days of Omicron was exacerbation of pre-hospitalization complications (46%; 11 out of 24 deaths), followed by respiratory failure due to pneumonia (29%; 7/24 deaths.), which was far lower than that during the days of Delta (80%; 16 out of 20 deaths) (*9*)

The aforementioned report implies that succumbing to COVID-19 is less likely but that the virus still causes death among the most vulnerable. Thus, COVID-19 is still a serious threat that cannot be ignored.

Treatment

Emerging evidence has revealed that the pillars for the treatment of COVID-19 include early antiviral therapy, steroids such as dexamethasone for patients needing oxygen, and appropriate anticoagulation (*10*).

For patients in dire need of oxygen, adjunctive immunomodulators such as tocilizumab and baricitinib are also available. Monoclonal antibodies such as

casirivimab/imdevimab and sotrovimab were approved in July 2021 and September 2021, respectively. However, there is a concern that the efficacy of these drugs may decrease with the Omicron subvariants (B1.1.529/BA.2, BA.4, and BA.5.strains) (*11,12*), so these drugs are currently withheld in clinical practice. Available antivirals in Japan are similar to those in the US, such as remdesivir, molnupiravir, and nirmatrelvir/ritonavir, with indicated use for patients with risk factors for severe disease. All of these antivirals and monoclonal antibodies were controlled by the Ministry of Health, Labor, and Welfare when they were first approved, and remdesivir and molnupiravir are now in general distribution. Ensitrelvir is the first-ever Japanese-made oral antiviral granted approval for emergency use in November 2022. The current recommendation is to consider using it for patients with clinical symptoms such as a high fever, bad cough, and severe sore throat (*13*). Further considerations regarding the population to receive this drug should be based on the results of future clinical trials.

Vaccine and pre-exposure prophylaxis

Encouraging vaccines is the most reliable way to prevent severe disease and infection. To date, approved vaccines in Japan include those from Pfizer-BioNTech (approved on February 14, 2021), AstraZeneca (May 21, 2021), Takeda/Moderna (May 21, 2021), and Johnson & Johnson (May 24, 2021). As of November 2022, only the Pfizer-BioNTech and Moderna/Takeda vaccines are publicly used. Omicron-targeting bivalent vaccines, such as the BA.1-targeting bivalent vaccines by Pfizer and Moderna and BA.4/5-targeting bivalent vaccine by Pfizer, were approved by October 2022.

A study has noted the effectiveness of COVID-19 vaccines against symptomatic SARS-CoV-2 infection during periods when Delta and Omicron prevailed in Japan (*14*). Both BA.1- and BA.4/5-targeting vaccines have similar effectiveness against the current dominant subvariant (BA.4/5 (*15*)), so the government, local authorities, and healthcare workers should encourage vulnerable people to receive either instead of waiting for a BA.4/5-targeting vaccine.

Tixagevimab/cilgavimab, a combination of two different monoclonal antibodies, was approved on September 7, 2022 for pre-exposure prophylaxis and treatment of severely immunocompromised patients. Currently, it is not generally distributed and available only for pre-exposure prophylaxis.

Prospects for the future

We discussed what has already been done thus far in Japan. Our philosophy is that every political measure, form of medical care, and public health effort has to target vulnerable people in various ways. Here, from a physician's perspective, is a 3-pronged approach to coping with this pandemic involving communication, the healthcare system, and vaccination.

Communication

Providing citizens with evidence-based information is crucial. Some may believe misinformation without evidence, increasing their mistrust of evidence-based medicine. Mass media such as TV channels, social media, and movie streaming sites are responsible for spreading information. Former President of the United States Donald Trump publicly supported the antimalarial drug hydroxychloroquine, and former President of Brazil Jair Bolsonaro advocated chloroquine, both of which have not proven effective against COVID-19. The government, local authorities, and scientific experts must collaborate to establish an effective and clear message and to proactively combat fake news.

Within the bounds of free speech, every communication must be evidence-based and unbiased. Every disseminator of information should be aware of its responsibility and its possible impact on society. Severe adverse reactions to vaccines should be acknowledged as a fact, but messages should nonetheless support mass vaccination programs because they are absolutely essential to alleviating a pandemic's effects on society.

Various challenges to Japan's healthcare system remain

First, some facilities and clinics still do not accept COVID-19 patients or people with suspected symptoms of COVID-19. Patients in a particular condition (such as pregnant women, newborns, and people who need specialized care) often have difficulty promptly accessing medical care. This is presumably because of a lack of knowledge and experience. Since we face a pandemic, the entire healthcare system must tackle this public enemy.

Most patients infected with Omicron have mild disease, so stratification of healthcare facilities may be effective; clinics and doctors providing at-home care could take on risk-free patients with mild symptoms while referring patients in serious condition to larger hospitals. Testing should be prioritized for vulnerable people to optimize the workforce. The over-the-counter self-antigen test should be encouraged for people without risk of severe disease to reduce unnecessary doctor visits.

Second, the role of surveillance is likely to be affected because notifiable disease surveillance changed dramatically after September 26, 2022. Nowadays, only patients with the following conditions are to be reported: those who are *i*) older than 65 years of age, *ii*) hospitalized, *iii*) with severe disease risk factors and receiving COVID-specific treatment, or *iv*) pregnant. As a result, follow-up with patients who do not fall into these categories through surveillance will be difficult. In medicine, a close eye has to be kept on the unusual

clinical course of unreported cases. Periodic studies of particular populations, such as children, might need to be conducted. In addition, precautions are required for racial and ethnic minorities who are at a greater risk of COVID-19 exposure (*16*). The low severity of the disease and its impact on daily life may cause people to forego testing. As a result, the number of people with undiagnosed "hidden COVID-19" may increase as the infection spreads. "Hidden COVID-19" may trigger an outbreak of varying size in various settings. Therefore, a preemptive policy on preventing infection might be necessary for certain circumstances, and especially where a vulnerable population is involved.

As the government opens the borders, new variants will enter into Japan. In November 2022, there were signs of other outbreaks of BQ.1, BQ1.1, and XBB (recombinants of the BJ.1 and BM1.1.1 lineages) that may negatively affect vaccine effectiveness (*17*). Genetic mutations appear one after another, so quality surveillance should be maintained by enhancing genomic surveillance.

Third, in some medical settings such as nursing homes or remote areas, essential public health supplies to protect healthcare workers tend to run short. The World Health Organization guidelines recommend using droplet and contact precautions (medical masks, gowns, gloves, and eye protection) for all healthcare workers when caring for patients with suspected or confirmed COVID-19 (*18*). The pandemic has revealed longstanding vulnerabilities in the supply chain for essential items. Remedies such as enhancing domestic manufacturing and use of digital technology should soon be implemented.

Fourth, effective antivirals that reduce the proportion of severe cases have been distributed disproportionately. In medically underserved areas such as mountain regions and remote islands, oral antivirals may play a more crucial role than in urban areas, since there may be minimal or no hospital beds. The government and local authorities have to tackle this problem soon to prevent greater disparities in accessing treatment.

Vaccination

Vaccine hesitancy is a significant challenge to ending this pandemic. Multifaceted problems contribute to it, including socioeconomic status, low trust in government, fake news, rumors spread by influential people, and incorrect advice from primary care doctors. Vaccination should be increasingly encouraged since it offers the most robust protection one can have, and especially when preceded by previous infections (i.e., hybrid immunity) (*19*).

Conclusion

We have discussed 3 prongs of a possible approach to end this pandemic. A society-wide strategy involving multiple stakeholders should be adopted to mitigate the damage and achieve a world where we are "Living with COVID-19".

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**Address correspondence to*:
Kohei Kamegai, Disease Control and Prevention Center, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: kkamegai@hosp.ncgm.go.jp

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Infection control of COVID-19 in operating theaters in a designated hospital for specified infectious diseases in Japan

Kazuhiko Yamada[1,2,*], Tetsuo Hara[1], Kazue Sato[1], Yuki Koyama[1], Daiki Kato[2], Kyoko Nohara[2], Naoki Enomoto[2], Syusuke Yagi[2], Dai Kitagawa[2], Nobuyuki Takemura[2], Satoshi Nagasaka[3], Tomomichi Kiyomatsu[2], Norihiro Kokudo[2]

[1] Division of Operating Theaters, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Department of Surgery, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Department of Thoracic Surgery, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: At the beginning of the COVID-19 pandemic in 2020, many hospitals around the world recommended stopping elective surgery as a precaution to stop the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The number of elective surgeries was reduced in Japan due to several waves of the pandemic. This work describes the management of COVID-19 and actual polymerase chain reaction (PCR) screening in operating theaters at the National Center for Global Health and Medicine (NCGM), a designated hospital for specified infectious diseases in Japan. The following three steps for COVID-19 infection control were taken to maintain the operating theater: *i*) Do not bring COVID-19 into the operating theater, *ii*) Infection control for all medical staff, and *iii*) Surgical management of surgical patients with COVID-19. We introduced checklists for surgical patients, simulations of surgery on infected patients, screening PCR tests for all surgical patients, and use of a negative pressure room for infective or suspected cases. We determined the flow and timing of surgery for patients with COVID-19. However, many aspects of COVID-19 infection control measures in the operating theater are still unclear. Therefore, infection control measures require further advances in the future to manage new infections.

***Keywords*:** COVID-19, surgery, PCR screening, operating theater

Introduction

At the beginning of the COVID-19 pandemic in 2020, most governments and academic institutions worldwide recommended stopping elective surgery to stop the spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This action was key to freeing up hospital beds, obtaining a supply of personal protective equipment (PPE), and protecting patients and medical staff (*1-6*).

In Japan, the number of surgeries has been reduced because of several waves of the pandemic. The number of surgeries was restricted, and the total number of surgeries was about 80-90% of that in 2019.

For surgeons, the spread of COVID-19 has required surgeries to be reduced to protect patients and staff through infection control. At first, there was no evidence of the effectiveness of measures to prevent COVID-19, and various measures had to be taken. The current work reports on COVID-19 infection control for staff in operating theaters at the National Center for Global Health and Medicine Hospital (NCGM), a designated hospital for specified infectious diseases in Japan.

Infection control in the operating theater

The following three steps for COVID-19 infection control were taken to maintain the operating theater: *i*) Do not bring COVID-19 into the operating theater, *ii*) Infection control for all medical staff; and *iii*) Surgical management of surgical patients with COVID-19.

When COVID-19 is found in the operating theater, medical staff are isolated and surgery is postponed, and the damage to the hospital is immeasurable. In operating theaters at the NCGM, various steps have been taken and polymerase chain reaction (PCR) screening has been implemented based on infection status. PCR screening has been performed on all surgical patients two to seven days before surgery.

Fortunately, an unexpected case of COVID-19 did not occur in the operating theater between April 2000 and December 2021. In addition, surgery on COVID-19-positive patients was simulated and then performed if necessary. The current authors previously reported on

management of COVID-19 in operating theaters at the NCGM (Figure 1) (*7-9*).

COVID-19 management in the operating theater

COVID-19 management in the operating theater is shown in Supplementary Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=62*). When the first wave of the pandemic hit Japan in April 2020, we discussed steps to deal with a preoperative fever and respiratory symptoms. We created a medical checklist to enter the operating theater. The decision to perform surgery was not made by the attending physician alone, and an operating room checklist was created so that it could be confirmed by multiple personnel such as ward nurses, doctors in charge, operating rooms, and anesthesiologists (Supplementary Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=62*). The checklists are still being created and are being used for treatment endoscopy and angiography. Body temperature in particular is recorded on the morning of the day of surgery so that people are aware of a fever before entering the operating theater.

PCR screening for surgery

The most common technique for molecular diagnosis of COVID-19 is PCR testing (*10*). We have introduced PCR screening for surgical patients after meeting with relevant departments (the operating room, the testing department, the infection control team, the nursing department, and the administrative office). Initially, PCR tests were performed on patients suspected of having COVID-19 based on clinical findings, but some COVID-19-positive patients may be asymptomatic due to prolonged infection. Since PCR results are not available on the day of surgery, rapid tests (an antigen test and film array) were introduced for emergency surgery, but the number of reagents was limited. However, the test reagents have been gradually replenished, and rapid tests mainly in the form of film arrays can now be performed (*7*).

At the beginning of April 2020, infections were identified based on clinical findings and checklists. Due to the further spread of COVID-19, PCR screening was performed on all patients undergoing elective surgery. Since August 2020, some patients that appear unlikely to have COVID-19 have tested positive, and all results are presented before entering the operating room, except for emergency surgery (bleeding events, trauma, *etc.*). PCR screening for elective surgery should be performed within one week of surgery. The risk of infection may indeed increase because a patient has ventured out unnecessarily after the test, and patients are instructed to refrain from going out after the test. Moreover, rapid tests (film array) were introduced for emergency cases, and the results improved: results can now be obtained in a short amount of time (about 1–2 hour). However, rapid tests are more costly than normal PCR screening.

By the end of October 2022, infection was not noted in operating staff. PCR screening revealed that 78 out of 14,043 cases (0.5%) were positive, but fortunately almost of them were identified preoperatively and no positive patients were brought in. No new cases of infection were noted after surgery. Surgeons wore a powered air purifying respirator (PAPR) and performed surgery on 23 COVID-19-positive patients under general, spinal, or local anesthesia within four weeks of developing COVID-19. In the first half in 2020, infection could not be ruled out in eight patients undergoing emergency surgery. The results of the rapid test were not known, but the patients were able to return to the general hospital ward after they were confirmed to be negative during surgery.

Timing of elective surgery for patients with COVID-19

In April 2020, surgery on a patient with COVID-19 was high-risk. Little information was known about surgical practices and postoperative complications in the initial phase of the COVID-19 pandemic. After that, numerous studies reported on COVID-19 and the timing of elective surgery (*11-15*). In 2022, Deng *et al.* reported that elective surgery within 4 weeks after the development of COVID-19 was associated with an increased risk of postoperative complications (*16*). At 4 to 8 weeks, elective surgery was associated with an increased risk of postoperative pneumonia. We performed elective surgery on infected patients (Figure 2). Within 4 weeks, we performed emergency surgery (a caesarean section, perforation of the gastrointestinal tract, open bone fracture, brain hemorrhage, *etc.*) and temporary surgery (advanced cancer surgery) while wearing a PAPR and using a negative pressure room. Four weeks after the development of COVID-19, we determined elective surgery depending on the patient's COVID-19 status and the presence of systemic complications (diabetes mellitus, immunodeficiency *etc.*). Fortunately, by October 2022, post-operative infections did not worsen and medical staff dealing with surgical patients with COVID-19 were not infected.

Surgery for COVID-19-positive patients

We are prepared to perform surgery on COVID-19-positive patients. Moreover, we can perform emergency surgery on COVID-19-positive patients and also treat previously infected patients. The flow for surgery on patients with COVID-19 is shown in Figure 2. We have amassed considerable experience performing surgery on infected patients: *i*) The flow needs to be organized (staff flow, time zone, entrance/exit), *ii*) Changing clothing such as gowns is difficult, *iii*) More nurses are needed

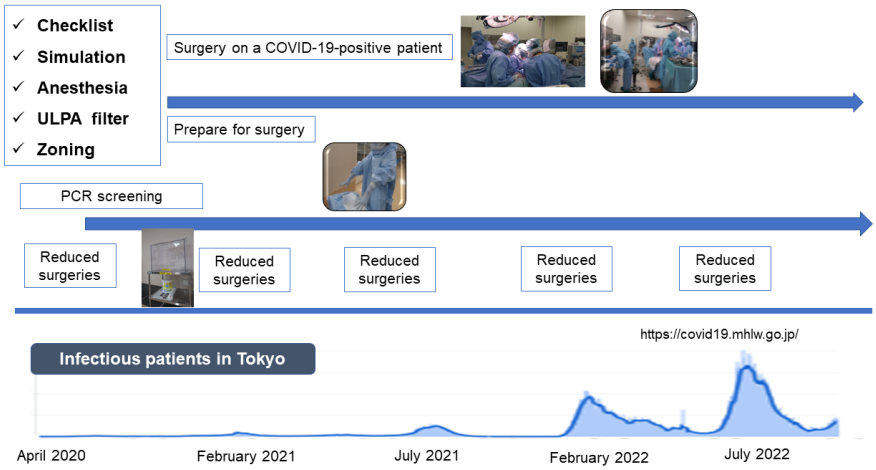

Figure 1. Infection control in operating theaters at the NCGM. Total management in operating theaters from April 2020 to October 2022. PCR, polymerase chain reaction; UPLA filter, ultra-low penetration air filter.

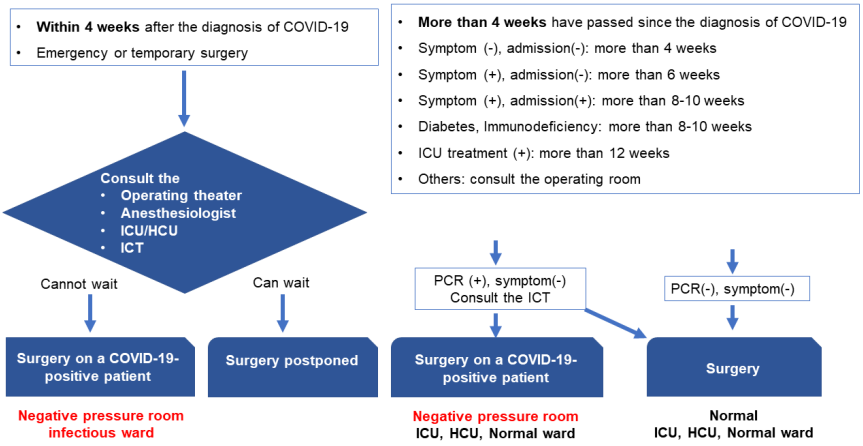

Figure 2. Therapeutic strategy for patients with COVID-19. PCR, polymerase chain reaction; ICU, intensive care unit; HCU, high-risk care unit; ICT, infection control team.

for surgery on patients with COVID-19, *iv*) Protracted surgery is more tiring than expected, and *v*) Regular simulation of surgery on infected patients is required.

Due to the COVID-19 pandemic, the number of surgeries was restricted. The number of surgeries was about 80% of the number in 2019 (Figure 1). The acceptance of emergency patients at hospitals in Tokyo has become stricter, and emergency surgeries have increased.

In conclusion, this work has reported on the status of COVID-19 in operating theaters at the NCGM. Actual PCR screening was also described. Many aspects of COVID-19 infection control in the operating theater are still unclear, and we are searching for answers. PCR screening was performed by multiple medical professionals and individual judgments were not made. Central management of the entire hospital was possible. In addition, the number of surgical patients has not increased, and financial issues remain. Infection control measures, including those dealing with new infectious diseases, need to be advanced further in the future.

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**Address correspondence to*:
Kazuhiko Yamada, Department of Surgery, National Center for Global Health and Medicine, 1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan.
Email: kayamada@hosp.ncgm.go.jp

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Glycemic control using intermittently scanned continuous glucose monitoring in patients with diabetes requiring methylprednisolone therapy for severe COVID-19

Masaki Uchihara[1], Noriko Kodani[1,*], Ryotaro Bouchi[1,2], Sho Saito[3], Yusuke Miyazato[3], Hirofumi Sugimoto[1], Kotaro Umamoto[1], Michi Kobayashi[1], Noriko Ihana-Sugiyama[1,2], Mitsuru Ohsugi[1,2], Akiyo Tanabe[1], Kohjiro Ueki[1,4], Jin Takasaki[3,5], Masayuki Hojo[5], Hiroshi Kajio[1]

[1] Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Diabetes and Metabolism Information Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan;
[4] Department of Molecular Diabetic Medicine, Diabetes Research Center, Research Institute, National Center for Global Health and Medicine, Tokyo, Japan;
[5] Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: In patients with severe coronavirus disease 2019 (COVID-19) with diabetes, glycemic control is essential for a better outcome, however, we face difficulty controlling hyperglycemia induced by high-dose glucocorticoids. We report five cases of severe COVID-19 patients with diabetes, whose glycemic control was managed using an intermittently scanned continuous glucose monitoring (isCGM) system during methylprednisolone therapy. Patients using isCGM showed significantly lower average blood glucose levels and significantly higher total daily insulin dose during the methylprednisolone therapy, compared to patients under regular blood glucose monitoring. The use of isCGM enables remote glucose monitoring, and this can reduce the risks of healthcare workers who have frequent contact with the patients. Thus, we suggest that using isCGM should be considered in hospitalized patients with diabetes under the COVID-19 pandemic to achieve better glycemic control and to minimize the possible risks of healthcare workers.

***Keywords*:** COVID-19, hyperglycemia, isCGM

Introduction

For patients with diabetes who are infected by the coronavirus disease 2019 (COVID-19), recent data have shown the importance of good glycemic control for better outcomes (*1*). Methylprednisolone therapy is effective in reducing mortality for patients with severe COVID-19 (*2*). However, in patients who are comorbid with COVID-19 and diabetes, hyperglycemia induced by methylprednisolone therapy is often difficult to control, and there is no well-established insulin regimen to manage this hyperglycemia.

To adjust the appropriate insulin dosage for controlling blood glucose levels that fluctuate with diet and glucocorticoid treatment, timely monitoring by point-of-care (POC) blood glucose testing is recommended (*3*). However, during a pandemic with limited medical resources, performing frequent blood glucose testing is a challenging task because it can increase the risk of infection for the medical staff, and there is a need for sufficient personal protective equipment (PPE) to manage the task.

Previous studies have shown that in hospitalized patients with severe COVID-19, the use of continuous glucose monitoring in combination with POC testing significantly reduced the frequency of POC testing (*4,5*). Intermittently scanned CGM (isCGM; FreeStyle Libre Flash glucose monitoring system, Abbott Laboratories, Chicago, IL) is an easy handling device, and the glycemic data can be remotely monitored by healthcare professionals when a patient scans the sensor with his/her smartphone. The use of isCGM for inpatient glycemic control is still not widespread in Japan due to insurance coverage matters (Supplementary document 1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*).

However, considering the COVID-19 pandemic, isCGM is effective for obtaining better glycemic control and can be a safe device for healthcare workers to minimize the frequency of patient contact. Therefore,

isCGM was used in some patients who were capable of scanning their sensor with their smartphone, which enabled healthcare professionals to remotely and continuously monitor patients' glycemic data. Thus, utilizing isCGM to assess trends in blood glucose levels allows timely and adequate adjustment of the insulin dose.

In our hospital, patients with severe COVID-19 were treated with methylprednisolone from the early stages of infection according to the dosing regimen used for acute respiratory distress syndrome and severe pneumonia (*6*). Glycemic control under COVID-19 infection and steroid use has been a major issue in patient management. Therefore, this observation aimed to examine the efficacy and safety of isCGM in controlling hyperglycemia induced by methylprednisolone therapy in patients with diabetes who were infected with severe COVID-19.

Patient characteristics

We studied adult patients with diabetes and severe COVID-19 who required methylprednisolone therapy and were hospitalized at CHNCGM between April 1 and August 18, 2021 (Supplementary document 2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*). Intermittently scanned CGM (isCGM) was used in 5 patients, and the rest of the 21 patients were controlled by regular blood glucose monitoring (BGM). Since isCGM requires self-scanning of glucose data, intubated patients and/or older patients who have difficulties managing the device were excluded. Therefore, intubated patients and patients aged over 65 was excluded from analysis, leaving 14 patients controlled by BGM. Patient characteristics on admission are shown in Supplementary Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*).

There were no significant differences in age, sex, body mass index (BMI), systolic blood pressure, body temperature, oxygen saturation, and comorbidities between the two groups. According to the laboratory data, there were no significant differences in the levels of plasma glucose, HbA1c, serum albumin, aminotransferase, alanine aminotransferase, lactate dehydrogenase, serum creatinine, C-reactive protein, D-dimer, and neutrophil count. The lymphocyte count was significantly higher in the isCGM group than in the BGM group.

The severity of COVID-19 infection, treatment regimen, and outcomes are shown in Supplementary Table S2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*). Regarding COVID-19 severity, critical cases were two (40.0%) and nine (64.3%) in the isCGM and BGM groups, respectively. The treatment regime for COVID-19 did not differ significantly between the two groups. There were no deaths among patients in either group.

Glycemic control and insulin dose

The blood glucose data during the first week after hospitalization are shown in Figure 1 and Supplementary Table S3 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*). The 4-point glucose data (before each meal and bedtime) using BGM were used to compare the glycemic control between isCGM and BGM (Supplement "Materials and methods"). Although the methylprednisolone therapy regimen and severity of COVID-19 did not significantly differ between the isCGM and BGM groups, the mean blood glucose levels during the 7 days were significantly lower in the isCGM group than in the BGM group. The mean blood glucose levels were high on days 1–3 in both groups; however, after day 4, the blood glucose levels were significantly lower in the isCGM group than in the BGM group. In the isCGM group, more than 70% of glucose measurements were in the range of 70–180 mg/dL (3.9–10.0 mmol/L) after the sixth day while it was only 40.9 % in the BGM group. In patients using BGM, marked hyperglycemia (blood glucose level > 250 mg/dL) was observed in 59.9% during the first 3 days, with persisting hyperglycemia (blood glucose level > 180 mg/dL). No hypoglycemia was observed in the isCGM group, but hypoglycemia was observed in a few patients in the BGM group.

The total daily insulin doses during the first week after admission are shown in Figure 2 and Supplementary Table S4 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=58*). In patients using isCGM, the insulin dose significantly increased after methylprednisolone therapy was started, leading to better glycemic control in the isCGM group than in the BGM group. Patients using isCGM were treated with > 110 units/day (1.19 units/kg/day) of insulin on the third and fourth days after admission; however, hypoglycemia was not observed. The basal and bolus insulin levels increased, and the bolus insulin requirement was particularly prominent.

The use of isCGM improves glycemic management under methylprednisolone therapy

This is exploratory research showing that although it is difficult to control hyperglycemia in patients with diabetes receiving methylprednisolone therapy for severe COVID-19, using isCGM enables better glycemic control through timely and adequate increases in the insulin dose without causing hypoglycemia.

Intravenous insulin is recommended for glycemic control in critically ill patients (*7*). However, frequent patient contact is required to monitor blood glucose levels. There is a need for alternative methods of glycemic control, particularly during a pandemic with limited resources for intensive care unit beds and PPE, to reduce the risk of exposure for healthcare

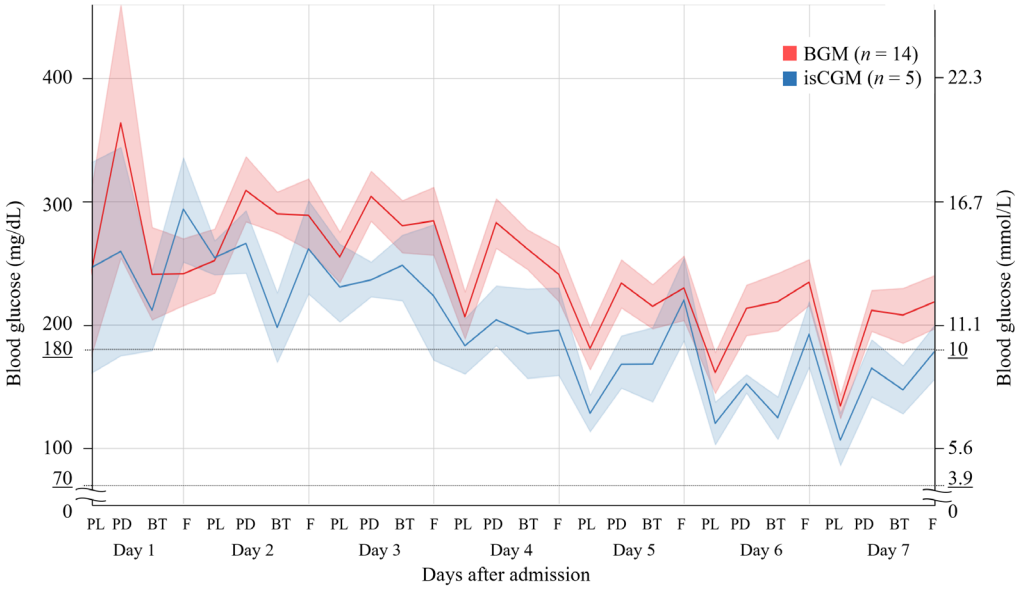

Figure 1. Dynamic trajectories of median blood glucose levels during the first week of hospitalization in patients using intermittently scanned continuous glucose monitoring (isCGM) or blood glucose monitoring (BGM) (red). Point-of-care glucose levels were assessed at fasting (F), pre-lunch (PL), pre-dinner (PD), and at bedtime. The target range of the blood glucose level is between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) (underlined). The interquartile ranges for median blood glucose levels are presented as shaded regions.

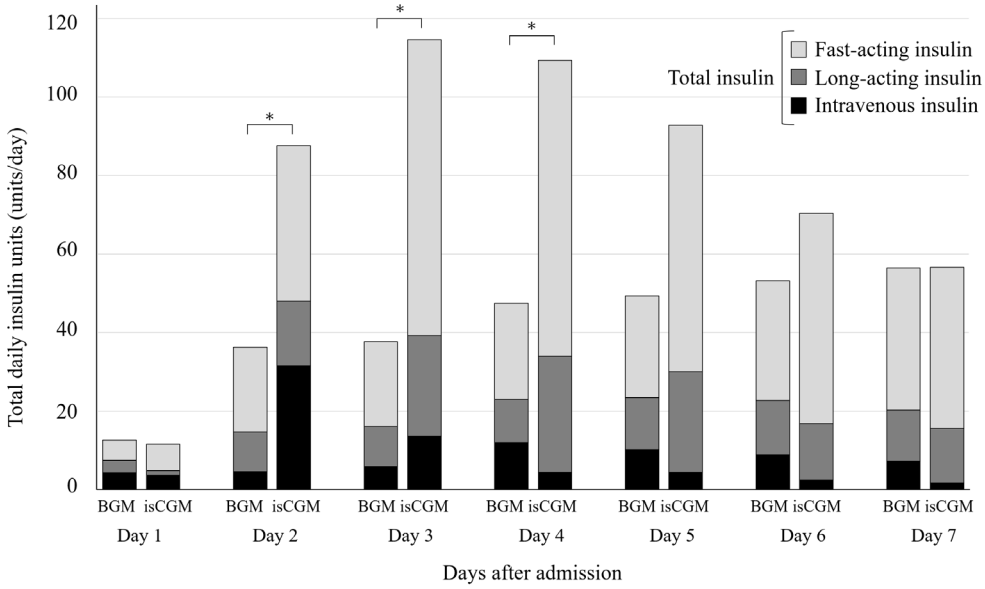

Figure 2. Bar graph showing the mean total daily insulin dose (TDI) in the blood glucose monitoring (BGM) group and intermittently scanned continuous glucose monitoring (isCGM) group during the first week of hospitalization. TDI includes subcutaneous injection of fast-acting insulin (shown in light gray), long-acting insulin (shown in dark gray), and intravenous insulin injection (shown in black). $^{*}p < 0.05$ according to the Student *t*-test.

workers caring for patients with COVID-19 (*8*). Use of CGM devices are recommended for these purposes (*9*). Several reports have shown that patients with severe COVID-19 require higher than usual insulin requirements, and glucocorticoids may significantly affect insulin requirements (*8,10*). Methylprednisolone, which is an intermediate-acting glucocorticoid, imparts a hyperglycemic effect 4 hours after administration, which peaks at 8 hours and decreases at 12–16 hours. This effect disappears by the following day. Therefore, methylprednisolone therapy causes drastic fluctuations in blood glucose levels throughout the day, whereas dexamethasone (a long-acting glucocorticoid) has a slow-acting hyperglycemic effect that continues to the next day (*11*). Thus, insulin delivery that enables rapid adaptation to dramatic changes in blood glucose levels

is required. In our study, elevated blood glucose levels caused by meals and intravenous methylprednisolone were continuously monitored in patients using isCGM. This enabled timely and adequate adjustment of insulin doses. Our observation indicates that using CGM is an effective way to attain good and safe glycemic control, especially in patients with severe COVID-19.

COVID-19 infection increases insulin resistance through the activation of inflammatory cells, which affect insulin-sensitive organs such as skeletal muscle and liver. Further, the induced cytokine storm blocks insulin signaling (*12*). With this background in patients with COVID-19, the use of glucocorticoids further reduces peripheral insulin sensitivity, increases hepatic gluconeogenesis, and inhibits pancreatic insulin production and secretion (*13-15*). Thus, in patients with diabetes who require glucocorticoid therapy for severe COVID-19, an adequate amount of insulin needs to be used to avoid severe hyperglycemia.

In our observation, insulin requirements began to decrease after the fourth day of hospitalization. Since insulin requirements may change daily due to the patient's clinical conditions and methylprednisolone doses change in patients with severe COVID-19 with diabetes (*16*), careful attention should be paid to the appropriate timing of insulin dose adjustment. Although methylprednisolone therapy initially causes hyperglycemia, it also blocks the cytokine storm and can improve insulin resistance (*17*). Furthermore, a recent study showed that tocilizumab used in patients with severe COVID-19 improves insulin resistance by targeting the interleukin-6 pathway (*18*). This may also be true in patients with diabetes, however, further studies are required. Tocilizumab is less effective when administered under hyperglycemic conditions (*19*), therefore, achieving good glycemic control during the initial hospitalization stage of COVID-19 infection is extremely important.

Four of the five patients using isCGM scanned the sensor with their smartphones, allowing their diabetologists to remotely monitor their trends of blood glucose levels through the cloud system. One patient in the present study did not possess a smartphone, and a reader device was provided to the patient to scan the sensor. Since changes in blood glucose levels can be monitored without increasing the frequency of POC testing, isCGM is beneficial in reducing the exposure of healthcare staff to infected patients (*5*). In April 2020, the Food and Drug Administration stated that it would not object to the use of CGM devices in the inpatient setting during the pandemic (*20*). We strongly emphasize the need for CGM, including isCGM, to be implemented in the hospital setting for effective and safe glycemic control during hospitalization, especially in patients with diabetes who require glucocorticoid therapy or those who require strict glycemic control.

This study has some limitations. First, the sample size was small, and only five patients used isCGM. Nevertheless, we believe that these five cases can provide important information in the situation of the COVID-19 pandemic. Second, the selection of patients using isCGM was left to the decision of the diabetologist in charge, and there were no definite criteria. Thus, there may be bias to consider, although there were no apparent differences in the history of diabetes control, severity of COVID-19 infection, and treatment regimen between the two groups. Therefore, we believe that our results warrant attention.

Conclusion

We show that despite the extreme difficulty of controlling hyperglycemia in severely ill patients with COVID-19 receiving methylprednisolone therapy, isCGM can be safely and effectively used to achieve better glycemic control and minimize the possible risks to healthcare workers during the COVID-19 pandemic. The use of isCGM will lead to good glycemic control with decreased time in hyperglycemia and hypoglycemia in patients with severe infectious diseases. Our next task will be to build a structured system, including staff education and technical support, for the safe implementation of isCGM for inpatient glycemic control.

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Address correspondence to:
Noriko Kodani, Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine, Toyama 1-21-1, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: nkodani@hosp.ncgm.go.jp

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Challenges and the potential of promoting remote medical interpreting during COVID-19

Soichiro Saeki[1,*], Mizuki Iwata[1], Rie Tomizawa[2], Kaori Minamitani[3,4]

[1] Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan;
[2] Department of Nursing, Graduate School of Nursing, Osaka Metropolitan University, Osaka, Japan;
[3] Department of International Medical Care, Rinku General Medical Center, Osaka, Japan;
[4] Department of Public Health, Graduate School of Medicine, Osaka University, Osaka, Japan.

Abstract: Language barriers negatively affect patient outcomes, and linguistic assistance is essential for adequate healthcare. The adoption of face-to-face medical interpretating is believed to have been rendered more challenging by the implementation of hospital admission restrictions following the outbreak of novel coronavirus disease (COVID-19). On the other hand, remote interpretating can be implemented using merely equipment, enabling it to be introduced without being impacted by the transmission of illness, and its use may have spread globally. To comprehend how COVID-19 has impacted remote interpreting utilization and what issues have arisen, we conducted a systematic review of two databases, PubMed and Ichushi-web (Japanese medical literature) with "remote interpreting" and "COVID-19" as keywords in June, 2022. Five references were included in the review. The research supported an increase in remote interpreting during COVID-19 to limit the risk of infection. This change in the trend of medical interpreting has the potential of promoting remote medical interpreting for places lacking sufficient linguistically skilled human resources, regardless of the pandemic status. There have also been accounts of novel methods of remote medical interpretation in which neither the healthcare professional nor the interpreter was face-to-face with the patient, and difficulty was acknowledged by both the healthcare professional and the patient with remote interpreting. To fully take advantage of the possibilities of remote interpreting, additional training and support would be required. Further studies are also required to determine the best way to employ this technology.

***Keywords*:** medical interpreters, healthcare interpreting, foreign patients, emigrants and immigrants, migrant health, minority health

Introduction

Language barriers negatively affect patient outcomes, and linguistic assistance is essential when providing adequate healthcare (*1*). However, the number of hospitals that provide daily medical interpreting services are still a minority even in countries which uses a minor language as a mother tongue, such as Japan (*2*).

This problem may be solved with the utilization of remote (mobile) medical interpreting, by connecting with medical interpreters over telephone or video calls (*3*). This enables hospitals to deal with patients with linguistic barriers, even for hospitals that hire medical interpreters on site, for the medical facilities that lack such resources (*4,5*). Utilization of such resources is the key, initial step in providing necessary preparations to deal with the rising need for medical services for non-Japanese patients.

In addition, mobile technology, including remote medical interpreting services is currently gaining attention, as they do not require face-to-face interpreters on-site. During the novel coronavirus disease (COVID-19) pandemic, hospitals limited the entrance of people, including patients and their families (*6*). Medical staff were not an exception, including medical trainees (*7,8*) and interpreters. Although travel restrictions hindered foreign tourists to visit other countries, medical care for foreign residents (*9*) who have linguistic barriers are still necessary.

Prior to the pandemic, however, the preference for remote interpreting has been inconsistent throughout the world (*10-12*). Thus, we hypothesized that the changes during the pandemic would increase the necessity to use mobile technologies such as remote medical interpreting as a source of linguistic assistance, and change the perception of patients and medical professionals towards it.

In order to systematically identify the trends of remote medical interpreting throughout the COVID-19

pandemic, and to clarify the current obstacles to distribute remote medical interpreting throughout the medical system, we conducted a search of current literature.

Literature search strategies and methods

On June 26, 2022, PubMed and Ichushi (Ichushi-web: Japanese medical literature) was searched in accordance with the strategy implemented in a previous literature review (*4*) (Supplementary Tables S1 and S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=60*). As this review focused on technology that did not require human interpreters, we added keywords such as "remote interpreting" and "COVID-19" to the search strategy. The search was limited to manuscripts in English and the Japanese language, published from January 1, 2020 to June 25, 2022, in an effort to catch manuscripts that were relevant to the COVID-19 pandemic. Manuscripts reporting in-person, telephone, or video interpretation in a healthcare setting were included. Studies that did not evaluate remote interpreting services in medical facilities, such as studies with their scope limited to telemedicine only (without interpreters) or only using mobile translation applications were excluded from the study.

Two authors independently evaluated the titles and abstracts of the identified papers for inclusion and exclusion based on the established criteria. Conflicts were resolved upon discussion of the authors. Using the Rayyan platform (*13*), full-text publications were obtained after preliminary inclusion and read to establish final research inclusion. From the full-text articles presented, one author culled pertinent data. The following information was extracted from each study: country of study, languages interpreted, implication for COVID-19, study population, and key findings. Each emergent theme was subjected to narrative evidence synthesis.

Figure 1 shows the inclusion and exclusion process. 39 citations were found after searching the database. Upon initial title and abstract screening, seven papers in total satisfied the inclusion criteria implying the usage of remote healthcare interpretation during the COVID-19 pandemic. Following a full-text review, two studies were excluded because one was completed prior to the outbreak and the other was ongoing research with no study implications. Five manuscripts were evaluated qualitatively.

Trends in literature during COVID-19

Table 1 shows a summary of the results. Of the five studies, three were published in 2021 (*14-16*), while the rest were each published in 2020 (*17*) and 2022 (*18*). Two studies were conducted in Japan (*14,15*) and the United States of America (USA) (*17,18*), and one study came from the United Kingdom (UK) (*16*). Studies that were conducted in Japan were published in the Japanese language. Three were research manuscripts, with one longitudinal study, qualitative study, and a multimodal study of a consultation using remote

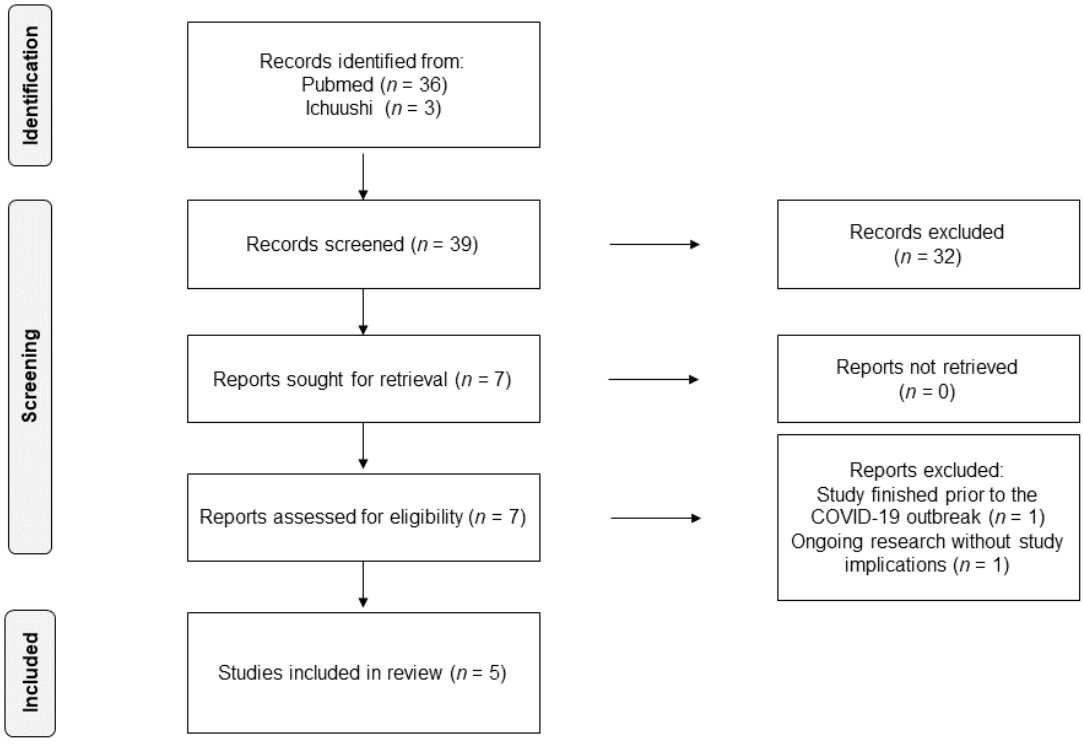

Figure 1. Extraction and Identification of studies. Identification was conducted along with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, and screening was conducted by two blinded authors.

Table 1. Summary of the studies included in the review

Authors (*Ref.*)	Country	Implications for COVID-19	Language	Population	Findings
Lee S, *et al.,* 2021 (*14*)	Japan	Increase	Japanese - unspecified	Medical interpreters in Japanese medical facilities	Medical interpreters who had received infectious disease training were more likely to be willing to participate in in-person interpreting, but they were also more likely to feel anxious in such situations. Many medical interpreters expressed a desire for opportunities for training on infection control, the use of a remote interpretation system, and the development of a secure working environment and support network for medical interpreters.
Hara H, *et al.,* 2021 (*15*)	Japan	NA	Japanese - unspecified	Foreigners participating in the annual health checkup in Shizuoka, Japan	Preparing social resources such as WiFi connection would be helpful for patients.
Knights F, *et al.,* 2021 (*16*)	UK	Increase	English - unspecified	Sixty-four primary care physicians and administrative staff, and 17 recently-arrived migrants	Physicians feel anxiety towards the new technology used for remote medical interpreting systems. Translations in the language of patients are essential for dissemination of accurate data during pandemics.
Le Neveu M, *et al.,* 2020 (*17*)	USA	Increase	NA	Patients in obstetrics	In clinical settings, universal masking is an additional physical barrier to relationship building and clear communication, which may be especially significant across language barriers due to the importance of facial expression. There are some situations where remote methods are preferable, but many patients, interpreters, and providers prefer in-person encounters. During the COVID-19 pandemic and beyond, high-risk clinical encounters on labor and delivery may warrant the use of an in-person interpreter.
Tan-McGrory A, *et al.,* 2022 (*18*)	USA	Increase	English- 127 anguages (Top 3: Spanish, Portuguise, Arabic)	Patients in obstetrics Massachusetts General Hospital	Privacy policy for patients were reenforced for online platforms. New technical platforms were created for third-party members such as medical interpreters could join online consultations.

NA, not available; USA, United States of America; UK, United Kingdom; COVID-19, novel coronavirus disease.

medical interpretation. The rest were field reports and a perspective article.

Four manuscripts stated unequivocally that they saw or surmised an increase in the use of remote medical interpreting systems during COVID-19. The languages used for translations varied and were not always specified in manuscripts.

Three implications emerged from the literature review.

i) Pros and cons compared to on-site (person-to-person) medical interpretation

In the COVID-19 pandemic, all studies recognized the benefits of remote medical interpretation; as it does not involve the interpreter having direct contact with patients or medical staff, the risk of infection is essentially eliminated. However, there were also reports of communication issues as compared to face-to-face interpreters. Building a connection with the patient is challenging while interpreting remotely. There might not be established mutual eye contact, and universal masking might make it challenging to hear the dialogue properly or read their facial expressions over the webcam (*17*).

ii) Support needed to promote the utilization of remote medical interpretation

The challenges of setting up a remote medical interpreting service were mentioned in several articles. First, all parties, including healthcare professionals, patients, and interpreters, experienced technical issues. The technology needed for remote interpretation was challenging for some medical staff to adopt (*16*), and managing the integration of a third party into the hospital system presented challenges (*18*). Patients were more susceptible to these problems because they couldn't use the systems or follow directions unless they were given in a language they could comprehend (*18*). Additionally, patients who needed interpretation were more likely to lack the required technology, such as internet access or communication devices (*15,18*). In order for patients to have access to the required systems for remote translating services, one institution strengthened its privacy policy (*18*).

iii) With, and beyond COVID-19

As previously stated, all research acknowledged the relevance of remote medical interpretation during the COVID-19 pandemic. Remote medical interpreting would also be a practical choice in remote locations, small-town settings, or for languages with few native speakers, where it would be difficult to find an interpreter in person (*14*).

One study in Japan (*14*) looked into the perspectives of interpreters during the pandemic. Lee *et al.* performed a countrywide survey of medical interpreters and discovered that medical interpreters who had received infectious disease training were more likely to be willing to participate in in-person interpretation, but they were also more likely to feel apprehensive in such settings. Many medical interpreters also stated a wish for possibilities for training on infection control, the use of a remote interpretation system, the creation of a safe working environment, and the creation of a support system for medical interpreters.

Current and future challenges in utilizing remote interpreting

The influence of COVID-19 towards remote medical interpreting outlined in the current literature generally recognized remote medical interpreting as an effective technique for providing language support in medical settings. However, other papers have emphasized the drawbacks of remote medical interpretation, raising fresh issues that must be addressed to improve patient care.

As we predicted, the rise in the use of remote medical interpretation was motivated by the need to prevent infection. In the instance of COVID-19, this occurred in hospitals that turned away patients who were not the most "essential" during the fight against the epidemic. However, this can also be considered as a valuable tool for giving language aid in situations lacking human resources. But even without the pandemic, there are some regions of the world where it is difficult to find people with sufficient linguistic skills (*4,5*). In these places, the tendency we discovered in the recent literature might prompt us to think about implementing remote interpretation.

The challenges that patients, medical professionals, and interpreters encounter when performing medical interpreting, however, have also been brought to light. Remote interpreters would need more training and expertise than on-site interpreters since communication across a camera, microphone, and screen is more challenging than live interactions (*17*). This may provide a contradiction since, while remote interpreting should make linguistic aid in medicine more accessible, the quality of that assistance may differ depending on the interpreter assigned to the particular clinical environment. Prior to its use, detailed instructions should be given to both patients and medical professionals that employ remote medical interpreting. This might have happened as a result of the fact that many nations had a stake in controlling the pandemic (*19*), platforms were set up in a hassle during the COVID-19 outbreak, and no one had the time to become used to a system of remote medical interpretation. More training for all parties is required, and further testing in the usage of remote medical interpreting should be conducted in the near future.

Indications for future studies

Nonetheless, further research on this topic is needed on an ongoing basis. Our review included very few studies,

and we are currently awaiting additional studies from around the globe to better grasp the state of remote medical interpreting. We acknowledge that obtaining data from patients who speak a foreign language can be a great difficulty, especially when obtaining patient consent (*20*). However, further studies that focus on the actual benefits of remote medical interpreting, both in a qualitative and quantitative manner would be needed. In addition, our literature is limited to English and Japanese literature. As remote interpreting focuses on a variety of languages, there may be more papers published worldwide that did not meet our inclusion criteria. Finally, studies focusing on the long-term use of remote medical interpreting should also be considered. As remote medical interpreting requires an on-demand interpreter, a different interpreter may be assigned when the connection is terminated, even during the same visit. Patients and healthcare workers may feel anxious while waiting for a medical interpreter to be assigned following the request. We hope that further studies will be published soon to comprehensively analyze the situation posed during this pandemic.

Conclusion

The COVID-19 pandemic encouraged an increase in the use of remote medical interpretation. However, the rising usage of remote medical interpretation has brought to light a number of challenges to its most effective application. Efforts to conduct studies, as well as promoting the best practices within the use of linguistic assistance in general must be widely promoted in Japan, and elsewhere. We must strive to build a better platform to fully utilize the potential of remote medical interpretation.

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Address correspondence to:
Soichiro Saeki, Center Hospital of the National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku, Tokyo, 162-8655, Japan.
E-mail: sosaeki@hosp.ncgm.go.jp

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LETTER

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Gastrointestinal endoscopy trends in a designated hospital for specified infectious diseases in Japan during the dawn of the "living with COVID-19" era

Chizu Yokoi*, Yuka Yanai, Keigo Suzuki, Naok Akazawa, Natsuyo Yamamoto, Junichi Akiyama

Department of Gastroenterology, National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: January 2020 marked the very early period of SARS-CoV-2's arrival in Japan. At the time, we immediately and strictly adopted the use of enhanced PPE, including a N95, gown, gloves, eye protection, and an apron, during every endoscopic procedure for every patient, with or without COVID-19. One reason why we use enhanced PPE for every patient is because all endoscopic procedures should be considered aerosol-generating procedures, and another reason is that asymptomatic patients with COVID-19 cannot be identified during a pandemic. The volume of endoscopic screening/surveillance endoscopies decreased markedly, but therapeutic endoscopies did not decrease. In contrast, urgent endoscopic hemostasis has increased more than ever. The most common reason for the increase might be that the lack of protective equipment and the need for medical staff to deal with an unknown virus, creating a pandemic panic in emergency medicine.

***Keywords*:** COVID-19, GI endoscopy, hemostasis, acceptance of emergency patients

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), referred to as COVID-19, has become a global pandemic. Globally, as of October 21, 2022, there have been 623,893,894 confirmed cases of COVID-19, including 6,553,936 deaths, reported to the WHO (*1*). Since the outbreak of COVID-19 in Japan in January 2020, the pandemic has struck in 7 waves. Lockdowns cannot be instituted in Japan due to legal constraints. A "state of emergency" has been declared four times and "priority preventive measures" were declared twice by the national government in Tokyo. After that, the Omicron strain became the main strain, and the rate of severe cases decreased although the number of temporarily infected people increased. In addition, a vaccine was developed and made widely available, and now the fourth round of vaccination is in progress. Recently, COVID-19 measures have been lifted in various situations, and endoscopic medicine is returning to its normal state while always remaining mindful of the risk of infection. As of October 22, 2022, 21,960,404 people had been infected, including 46,230 deaths, and 20,468,671 people were discharged from the hospital or released from medical treatment (*2*).

The National Center for Global Health and Medicine (NCGM) in Shinjuku is one of six National Centers in Japan, and it is the only one with a general hospital. Our mission is to function as a general hospital both as an emergency and critical care facility and as a regional site for cancer treatment; we also serve as a designated hospital for local and global outbreaks of infectious diseases. In light of these missions, the NCGM accepted the first patient with COVID-19 in Japan from a charter flight returning from Wuhan in January 2020. As COVID-19 spread rapidly around the country, a major concern has been the ability of hospitals to accept, admit, and care for patients with or without COVID-19.

The number of endoscopic procedures at the NCGM deceased each time a "state of emergency" was declared or "priority preventive measures" were instituted (Figure 1). Given the global shortage of protective equipment and insufficient information about SARS-CoV-2 and COVID-19 during the 1st wave of the pandemic, postponement or cancellation of endoscopies was strongly recommended except for emergency procedures (*3-5*) to prevent the spread of infection and protect healthcare workers. Reflecting that context, and especially during the first "state of emergency," about 80% fewer upper and lower gastrointestinal (GI) endoscopic procedures were performed at the NCGM compared to the same period in 2019. The number recovered somewhat the day after the first "state of emergency" was lifted, but every time a state was declared or measures were instituted, endoscopic procedures had to be curtailed to allocate medical supplies (manpower and beds) to COVID-19 patients instead of other patients. The number has repeatedly

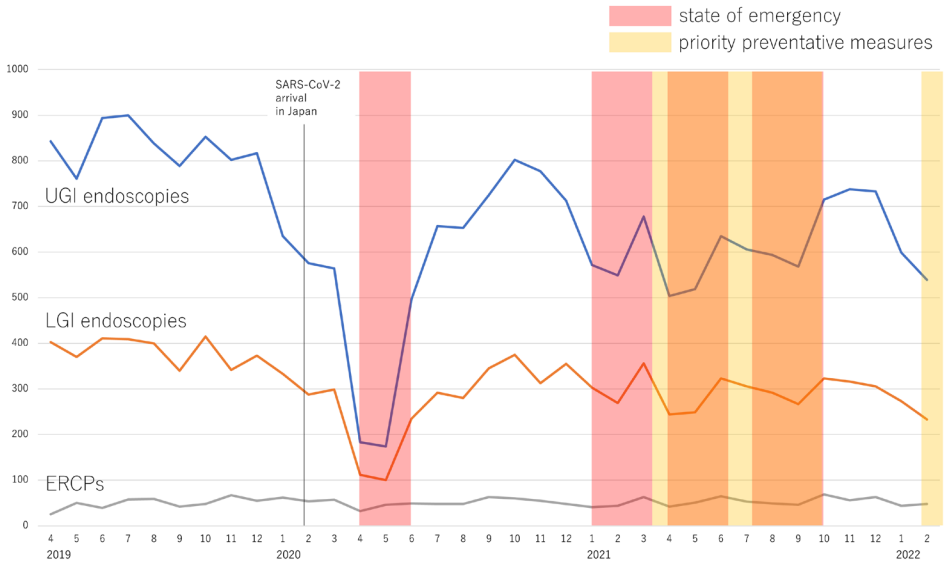

Figure 1. The number of GI endoscopies at the National Center for Global Health and Medicine (NCGM) during the COVID-19 pandemic.

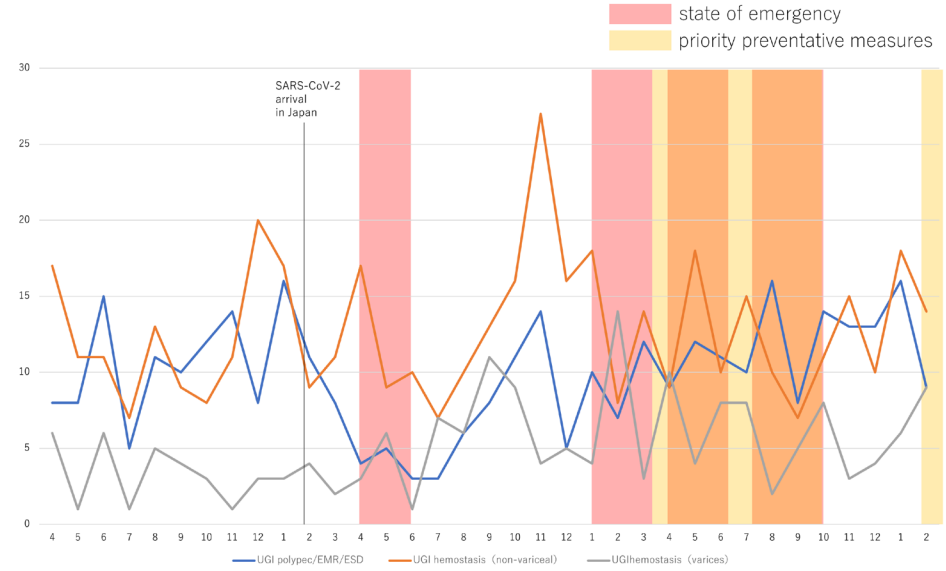

Figure 2. Trends in UGI procedures at the National Center for Global Health and Medicine (NCGM) during the COVID-19 pandemic.

increased and decreased, and the monthly average has remained low despite recovering. In contrast, the number of endoscopic retrograde cholangiopancreatography (ERCP) procedures has maintained at a certain level, probably because the procedure is often unavoidable to save the patient's life. The number of GI endoscopic procedures for screening/surveillance decreased most; the common reasons for the decreased number were the number of outpatients, cancellations by patients, and adherence to the guidelines of academic societies.

We investigated trends in therapeutic upper GI endoscopies such as endoscopic surgery for esophageal and gastric neoplasms (endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)), hemostasis (for varices and non-variceal GI bleeding), and other conditions (such as removal of foreign matter, dilation, stent placement, and gastrostomy). Urgent endoscopic hemostasis has increased more than ever (Figure 2). There are more than 15 tertiary hospitals (most of which are University Hospitals) in the Tokyo metropolitan area, and the NCGM has traditionally had the highest acceptance of emergency patients with severe GI bleeding (such as in 2019, before the dawn of the "living with COVID-19" era). In 2020, the dawn of the "living with COVID-19" era, the NCGM accepted the largest number of emergency patients with

severe GI bleeding alongside St. Luke's International Hospital. The 2021 rankings have not been published, but the NCGM accepted 50 patients more than it did in 2020. The COVID-19 pandemic has highlighted the problem of ambulance "re-routing" in Japan. When a hospital is not willing to accept a patient, that patient is referred to as a "refused emergency patient;" in such instances, "the ambulance crew may contact 4 or more medical facilities" and "await acceptance for 30 minutes or longer." Since the dawn of the "living with COVID-19" era, the NCGM has received more requests for acceptance of "refused emergency patients" than ever, and especially during the 1st wave of the pandemic. Several hospitals in Tokyo had to closed due to infection clusters and perhaps because of inadequate PPE supplies. Urgent endoscopies have increased significantly.

We also investigated urgent and semi-urgent GI endoscopies undergone by patients with COVID-19. Since January 2020, 17 patients with COVID-19 (ages 7-95) have required GI endoscopy, and a total of 27 endoscopic procedures have been performed. Despite the high risk of infection, urgent endoscopy in a negative pressure room was required for 6 patients with life-threatening GI bleeding (2 patients with a variceal rupture due to alcoholic liver cirrhosis, 3 patients with an acute hemorrhagic gastroduodenal ulcer, and 1 patient with overt obscure GI bleeding (OGIB)). Five of the 6 patients with life-threatening GI bleeding were rescued by endoscopic hemostasis, but one patient died of massive bleeding from a gastric variceal rupture. Once the specified quarantine period had passed, 11 patients with active but non-life-threatening GI bleeding received semi-urgent endoscopy after receiving prioritizing proton pomp inhibitors. No one has died of GI bleeding, but 3 patients died of COVID-19. Nineteen physicians were exposed to SARS-CoV-2 as endoscopists or assistants, but no one was infected. During outbreaks in Tokyo (and especially the 3rd and 4th waves of the pandemic), some patients who had received outpatient endoscopy contacted us one or two days later to inform us that they had an asymptomatic SARS-CoV-2 infection. Thanks to impeccable hand hygiene and enhanced PPE, none of the medical staff, including the reception staff, cleaners, and porters, was infected, either.

The COVID-19 pandemic has posed several medical challenges to human beings. Now is the time to reconsider how to cooperate and transcend the boundaries of departments, hospitals, people, and countries to survive this new era. As Dr. Kokudo, who is the president of the NCGM, says, "We stand on the side of people". We will continue to work as a team to complete our mission and go forward.

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

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**Address correspondence to*:
Chizu Yokoi, Department of Gastroenterology, National Center for Global Health and Medicine,
Toyama 1-21-1, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: cyokoi@hosp.ncgm.go.jp

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Communications	~2,000	~2	~20
Perspectives			
Comments			
Correspondence			
Editorials	~1,000	~1	~10
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3. Main Text
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5. References
6. Tables
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(*As of November 2022*)

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