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## Global Health & Medicine

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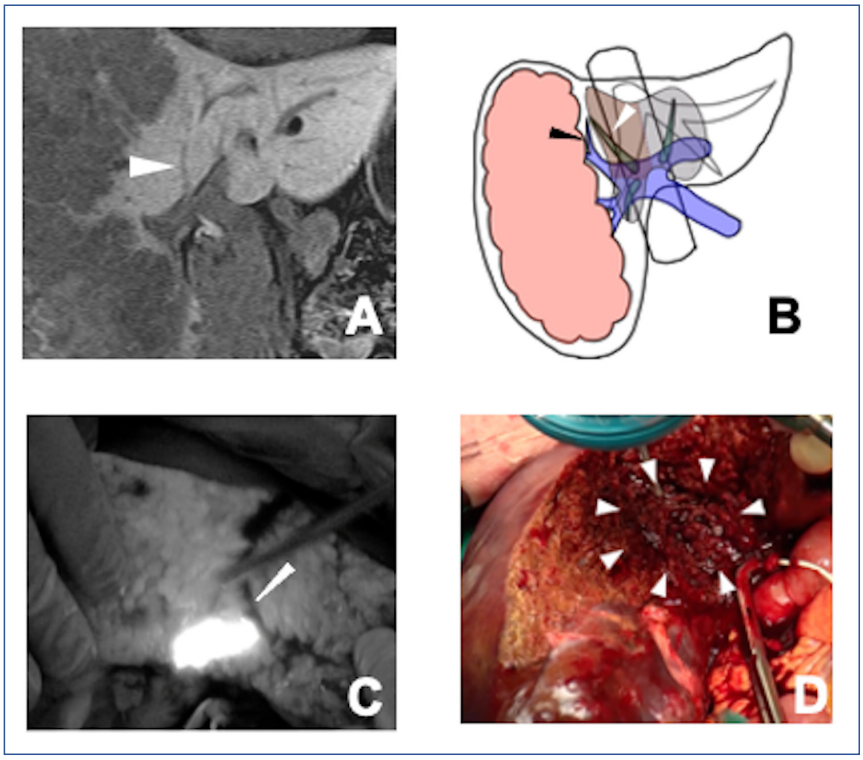


**The fluorescently visible paracaval portion of the caudate lobe (page 378)**

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# Global Health & Medicine

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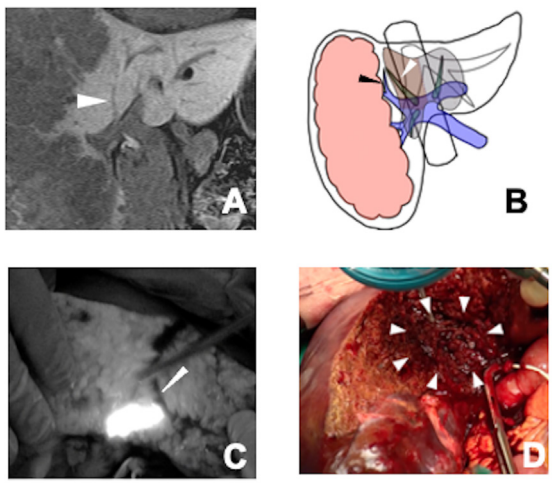


**The fluorescently visible paracaval portion of the caudate lobe. (A)** Preoperative Gd-EOB-DTPA-enhanced magnetic resonance imaging in the hepatobiliary phase. The paracaval (PC) branch (arrowhead) from the hilar bifurcation area is observed in the coronal sectionn. **(B)** Schema of the anatomy of the patient. The PC branch (white arrowhead) corresponds to the PC (brown area) of the caudate lobe. The cranial branch from the anterior portal vein (black arrowhead) corresponds to the cranial region of the anterior sector adjacent to the PC of the caudate lobe. **(C)** Before hepatic transection, the indocyanine green solution was injected into the PC portal branch under intraoperative ultrasonography guidance. During hepatic transection, behind the middle hepatic vein(arrowhead), a small fluorescence area is visualized by a near-infrared imaging system, which corresponds to the stained PC of the caudate lobe. **(D)** PC (arrowhead) existed behind the MHV and above the hepatic hilum in the cut surface. (page 378)

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# Amebiasis as a sexually transmitted infection: A re-emerging health problem in developed countries

Akira Kawashima[1,2,3], Yasuaki Yanagawa[1,2,4], Rieko Shimogawara[2], Kenji Yagita[2], Hiroyuki Gatanaga[1,3], Koji Watanabe[1,2,3,*]

[1] AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Department of Parasitology, National Institute of Infectious Diseases, Tokyo, Japan;
[3] The Joint Research Center for Human Retrovirus Infection Kumamoto University Campus, Kumamoto, Japan;
[4] Department of Microbiology and Immunology, Stanford University School of Medicine, Stanford, CA, USA.

**Abstract:** Amebiasis, which is caused by *Entamoeba histolytica* (*E. histolytica*), is the second leading cause of parasite-related death worldwide. It manifests from asymptomatic carriers to severe clinical conditions, like colitis and liver abscesses. Amebiasis is commonly seen in developing countries, where water and food are easily contaminated by feces because of the poor sanitation. However, a recently challenge in many developed countries is the increase in domestic cases of invasive amebiasis as a sexually transmitted infection (STI amebiasis). In contrast to food-/waterborne transmission of *E. histolytica* in developing countries, transmission of STI amebiasis occurs directly through human-to-human sexual contact (*e.g.*, men who have sex with men and people who engage in oral-anal sex); in this setting, asymptomatic infected individuals are the main reservoir of *E. histolytica*. The Development of screening methods for the early diagnosis of asymptomatic *E. histolytica* infection is the key to epidemiologic control. Moreover, delay in diagnosis of severe cases (*e.g.*, fulminant amebiasis) leads to death even in developed countries. It is also important to increase clinical awareness of domestically transmitted STI amebiasis in the clinical settings. This review considers the changing epidemiology and clinical manifestations of STI amebiasis, and finally discusses the future strategies for the better practice.

***Keywords***: STI amebiasis, *Entamoeba histolytica*, asymptomatic carriers, epidemiological control, high-risk populations, serological screening

## Introduction

Amebiasis is caused by *Entamoeba histolytica* (*E. histolytica*), which is transmitted *via* the fecal-oral route and is the second leading cause of parasite-related death worldwide (*1*). Transmission could occur *via* the oral ingestion of the transmissible cystic form of *E. histolytica*, which is continuously shed in the stool (*2,3*). Therefore, amebiasis was thought to be prevalent only in developing countries due to poor sanitation, but it is increasingly being reported as a sexually transmitted infection (STI amebiasis) in developed nations (*4,5*). Additionally, amebiasis sometimes causes a life-threatening disease called fulminant amebiasis, which presents as an acute abdomen from the perforation of the large intestinal and mimics acute appendicitis (*6-11*). If such cases are not treated with amebicidal drugs and resection of the perforated intestine, they are often critical and result in death. In fact, many cases of fulminant amebiasis are only diagnosed postmortem. This is because clinicians in developed nations may not be fully aware of the increasing risk posed by *E. histolytica* infection.

In this review, we discuss the epidemiology and clinical manifestations of STI amebiasis, as well as the measures required for the epidemiological control of this infection.

## Epidemiology

Amebiasis is a disease caused by the oral ingestion of the transmissible cystic form of *E. histolytica* found in human feces. In developing countries, transmission typically occurs *via* the ingestion of food and water contaminated with feces. It was previously believed that amebiasis only occurred in people who had visited an endemic area, causing imported infections in developed countries. However, it was recently recognized that the pathogen can also be transmitted directly from person to person. Instances of *E. histolytica* strain clustering have been found as a result of sexual contact (*4,5*) or within institutions caring for individuals with cognitive

impairment (*12,13*). Food- or waterborne infections occur in areas with poor sanitation. *E. histolytica* remains a leading cause of parasitic-infection-related mortality and morbidity worldwide (*1*). However, over the past two decades, amebic infection has been increasingly reported as a sexually transmitted infection (STI) in developed countries of East Asia and in Australia (*2,14-21*). One study conducted at a human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) voluntary counseling testing (VCT) center in Taiwan, reported that men who have sex with men (MSM) and people engaging in oral-anal sex, were more likely to be seropositive for *E. histolytica* (*22*). Our group reported that *E. histolytica* seropositivity was over seven times higher than that of HIV-1, and the same as that of syphilis, at a VCT center in Tokyo (*23,24*). The incidence of invasive amebiasis (symptomatic cases) in Japan, based on national surveillance data from 2000 to 2013, is on the rise (*25*). Additionally, the proportion of domestic cases has increased to 85%. Moreover, since 2008, there has been a shift in transmission patterns, with cases associated with heterosexual contact surpassing those derived from homosexual contact (*25*). In addition to the shift in disease epidemiology, the recent rise in the number of amebiasis cases in Japan is thought to be due to an increase in accidentally diagnosed cases by colonoscopy (*25*), highlighting the importance of the active surveillance to reveal the accurate disease prevalence including asymptomatic carriers. Of note, only symptomatic invasive amebiasis cases are currently included in the national surveillance data in Japan.

In addition, genotyping studies of *E. histolytica* clinical isolates have reported that multiple original Japanese genotypes are currently prevalent as STI strains in Japan (*26,27*). Furthermore, whereas older studies from the United States and United Kingdom reported that amebiasis among MSMs arose from nonpathogenic *E. dispar* infection (*28,29*), more recently, specific sexual behaviors among MSM, particularly oral-anal intercourse, have emerged as a key risk factor for amebiasis-related mortality in the United States (*30*). *E. histolytica* infection has also been recently reported to occur as a comorbidity among HIV-infected MSM or as a domestic STI in developed European countries (*5,31-34*). Thus, it is important for primary care physicians to take detailed histories of sexual behavior (*e.g.*, oral-anal sexual contact) as well as travel history, whenever amebiasis is suspected. Furthermore, there are a considerable number of asymptomatic infected people in the high-risk community, which is the main transmission source for STI amebiasis. An effective epidemiological strategy should therefore efficiently identify and treat asymptomatic individuals in high-risk communities to decrease the infection reservoir of STI amebiasis.

**Clinical manifestations of *E. histolytica* infection and the associated disease forms**

Asymptomatic self-limiting infection is the most common form of amebiasis. Up to 80–90% of people exposed to *E. histolytica* cysts have no symptoms or mild symptoms and clear the infection spontaneously. However, asymptomatic infection persists for more than a year in some individuals, who are reported as asymptomatic cyst passers (*2,3*) or as fecal occult blood (FOB)-positive individuals incidentally diagnosed during colonoscopy (*25,35,36*). These asymptomatic infected individuals can be a source of new infections in the community in the poor sanitary condition. Some of these patients develop symptomatic invasive disease, usually within one year of latent infection (*3,37-39*). However, in some cases, *E. histolytica* also causes severe, life-threatening amebiasis.

Amebic colitis and liver abscess are the most common clinical forms of invasive amebiasis. These common disease forms of invasive amebiasis respond well to therapy with tissue-active agents, such as metronidazole. However, in some cases, amebic colitis is complicated by the secondary bacterial peritonitis owing to a fistula or perforation of the large intestine, which leads fulminant amebiasis (*6-8*). The use of immunosuppressive agents, such as corticosteroids, is reported as a risk factor for the development of fulminant amebiasis (*8*). However, because no risk factors can be identified in the majority of fulminant amebiasis cases, this condition is considered to mostly occur in immunocompetent hosts (*8*). Furthermore, fulminant amebiasis presents as an acute abdomen, which often mimics appendicitis; thus, this form of the disease is sometimes called amebic appendicitis (*6,9-11*). It is very difficult for physicians to differentiate between amebic and nonamebic appendicitis using clinical and laboratory findings (*10*). Moreover, amoebic infection is frequently overlooked by routine histological examination (using hematoxylin and eosin [H&E] staining) of the resected intestinal tissue. Instead, immunohistochemistry with a monoclonal antibody against *E. histolytica* or periodic acid–Schiff (PAS) staining are recommended for the identification of *Entamoeba* species. Although PAS non-specifically stains polysaccharides, it can be used to easily distinguish *Entamoeba* species (positive staining) from leukocytes (negative staining) in the resected tissue (Figure 1).

Appendectomy without amebicidal treatment may result in severe postoperative complications, such as abdominal sepsis, gastrointestinal fistula, or hemorrhage (*8-10,40*). The inaccurate diagnosis and treatment of amebic appendicitis result in poor clinical outcomes. Indeed, many cases of amebic appendicitis are only diagnosed at autopsy and the mortality rate for this condition is estimated to be as high as 3.2–33%, even in developed countries (*9,40,41*). Moreover, a systematic review of 174 cases revealed that most patients with amebic appendicitis experienced several months of asymptomatic infection with *E. histolytica* before

developing an acute abdomen, as the time from exposure to symptom onset ranges from months to years (*9*). These findings emphasize the importance of early detection to protect patients from life-threatening invasive disease. Thus, the underestimation of the epidemiology of STI amebiasis cases, as well as the wide range of clinical presentations, pose considerable challenges in primary care settings in developed countries, which need to be overcome.

## Diagnosis of *E. histolytica* infection (Figure 2)

*Diagnosis of invasive "symptomatic" disease*

For symptomatic cases, a combination of antigen detection in the stool and serological testing is currently recommended (*42,43*). When amebic colitis is suspected (owing to diarrhea and/or dysentery), antigen detection and direct microscopic examination are reliable tests, with sensitivities and specificities comparable to those of the polymerase chain reaction (PCR) (*44,45*). Enzyme-linked immunosorbent assay (ELISA) and immunochromatography (IC) antigen detection kits for stool samples are available in many countries. These immunoassays, especially IC, are relatively simple to perform and yield rapid results. Moreover, the most frequently used ELISA (Techlab *E. histolytica* II) and IC (Techlab *E. histolytica* QUIK CHEK) kits can distinguish *E. histolytica* from other *Entamoeba* species because they use antibodies targeting an *E.-histolytica*-specific Gal/GalNAc lectin (*46,47*). PCR (especially real-time PCR) testing of stool or infected abscess/tissue samples is the most sensitive and specific diagnostic method for *E. histolytica* amebiasis. However, PCR protocols, including the need to extract DNA from various clinical samples, remain too technically complex for general dissemination (*43*). In Japan, there is no insurance coverage to be used for the routine clinical diagnosis of *E. histolytica* infection and primarily considered as a research tool. Serum antibody testing is useful in cases when amebic liver abscess is suspected without intestinal symptoms. Antibodies are detectable in over 70% of patients within 5–7 days of acute infection, and in over 90% of patients at 2–3 weeks after infection acquisition. However, patients remain seropositive for years after treatment (*48*). Therefore, although a negative serological result is helpful in ruling out disease, a positive result cannot be used to distinguish between present and past infection.

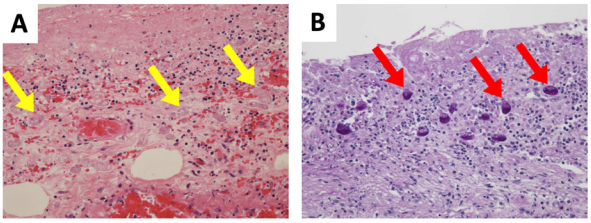


**Figure 1. Representative histopathological images of *Entamoeba*-positive colonic tissue (Original photo from National Center for Global Health and Medicine; magnification, 400×). (A)** In submucosal tissue, the cytoplasm of the invading *Entamoeba* trophozoites (yellow arrows), identified using hematoxylin and eosin (H&E) staining, is very similar to that of leukocytes. **(B)** Periodic acid-Schiff (PAS) staining differentiates PAS-positive *Entamoeba* trophozoites (red arrows) from PAS-negative leukocytes.

| | | Clinical form of amebiasis | | | | Comments for each diagnostic test |
|---|---|---|---|---|---|---|
| | | A. Asymptomatic carrier | B. Amebic colitis | C. Amebic liver abscess | D. Fulminant amebiasis | |
| Pathogen detection tests | Stool, direct microscopy | △ | △ | △ | △ | Not generally recommended because testing accuracy highly depends on the skill and experiences of the examiner. |
| | Stool, antigen test | △ | ◎ | △ | △ | Detection of trophozoite surface antigen. Sensitivity is high for loose stool but low for formed stool. |
| | Histopathology | ○ | △ | × | ◎ | Morphological identification in resected intestinal tissue. Periodic acid Schiff (PAS) staining should be performed. |
| | Nucleic acid detection test (PCR) | ◎ | △ | △ | △ | High sensitivity and specificity; however not widely implemented because of high cost and technical complexity. |
| Blood test | Serological antibody test | ○ | ○ | ◎ | ○ | Highly sensitive in the convalescent phase of infection; however, seropositivity remains for 2–3 years post-infection. |

**Figure 2. Diagnostic methods for different clinical forms of amebiasis. (A)** Asymptomatic carriers can be screened using serology (~90% sensitivity); however, serology can also detect past infections, which had occured within the last 2–3 years. PCR of stool samples or colonoscopy have a high diagnostic value for current *Entamoeba* infection. **(B)** If the patient has diarrhea and/or dysentery, a stool antigen test should be performed for amebic colitis; serology is useful as an adjunct to the diagnosis. **(C)** For amebic liver abscess, a serological test is non-invasive and highly sensitive. A stool antigen test can be performed for patients with diarrhea and/or dysentery. **(D)** For the diagnosis of fulminant amebiasis, *Entamoeba* invasion into the submucosal tissue can be confirmed by histopathology of resected intestinal tissue. Periodic acid-Schiff (PAS) staining should be performed alongside routine hematoxylin and eosin (H&E) staining to differentiate between *Entamoeba* and leukocytes. Marks on the table: ×, cannot be performed; △, generally low diagnostic value or too labor intensive; ○, used alonside other diagnostic tools, ◎, highly recommended.

A diagnosis should be made by combining serological methods with the evaluation of clinical manifestations and the identification of liver abscess using imaging. In patients with diarrhea, antigen testing of stool samples is also a useful method for diagnosing *E. histolytica* infection (*43*). As mentioned above, because *Entamoeba* species have a similar morphology to leukocytes in the resected colonic tissue, routine pathological examination using H&E staining is often ineffective. Thus, if there is even the slightest suspicion of intestinal amebiasis, PAS staining should additionally be performed.

*Diagnosis of noninvasive "asymptomatic" infection*

It is challenging for clinicians to diagnose *E. histolytica* infection in an asymptomatic carrier, as stool antigen tests and direct microscopy have insufficient sensitivities in these individuals (*44,45,49-51*). Although serological testing is highly sensitive, even in asymptomatic carriers (*52,53*), a positive result may indicate past and not necessarily present infection. To distinguish between present and past infections in asymptomatic individuals with positive serological test results, PCR of stool samples is commonly performed. Moreover, colonoscopy has a high diagnostic value (*35,54-57*). In asymptomatic cases, visible infective ulcers can be found but usually limited within the proximal side (from cecum to ascending colon), whereas ulcers are distributed to the multiple sites of large intestine (from cecum to rectum) in symptomatic colitis cases (*58,59*). Interestingly, even in the asymptomatic cases, trophozoites are identified at infection sites whereas cystic forms are commonly detected in the stools (*58,59*). Importantly, these ulcerative lesions are not found in the small intestine (terminal ileum), which helps differentiate amebiasis from other inflammatory diseases, such as Crohn disease, tuberculosis, and cytomegalovirus colitis (*35,60*). In Japan, an increasing number of cases of asymptomatic *E. histolytica* infection have been accidentally diagnosed by colonoscopy in people with positive FOB results who had been referred for colon cancer screening (*25,36*). In another report from a Japanese HIV-1 cohort, amebic colitis was pathologically identified in 11.2% of asymptomatic HIV-1-positive individuals, of whom 87.5% were seropositive for *E. histolytica* (*52*). At present, the diagnosis of *E. histolytica* infection, and especially asymptomatic infection, is often challenging. However, we believe that in high-risk patients, employing a highly sensitive serological antibody test to screen for asymptomatic infection, followed by PCR or colonoscopy and reach a definitive diagnosis, would prove effective.

**Treatment of *E. histolytica* infection**

The recommended treatment regimens differ for the invasive and noninvasive forms of *E. histolytica* infection.

*Treatment of invasive infection*

For invasive infections, such as those leading to amebic colitis and amebic liver abscesses, tissue-active agents should be administered prior to lumen-active agents because the latter are poorly absorbed in the intestine. Metronidazole (Flagyl®) or tinidazole (Tindamax®) are widely used as tissue-active agents; although only metronidazole is approved for use in patients with amebiasis in Japan. Treatment with tissue-active agents should be followed by lumen-active agents because parasites persist in the intestine in up to 40–60% of patients who achieve complete symptom recovery with tissue-active agents (*61*). In addition to tissue-active agents, administration of broad-spectrum antibiotics and/or surgery should be considered in patients with fulminant colitis and amebic appendicitis, as described in detail above (see: Clinical manifestations of *E. histolytica* infection and the associated disease forms). Therapeutic needle aspiration or catheter drainage are not routinely required for uncomplicated liver abscesses (*62*). These interventions are recommended in addition to treatment with medication if the patient experiences clinical deterioration, does not respond to the initial medication, or if alternative diagnoses need to be ruled out. Additionally, some reports suggest that clinicians should consider these interventions in patients with a high risk of abscess rupture, as defined by a cavity with a > 5 cm diameter or by the presence of lesions in the left lobe of the liver; although these criteria have proved inconclusive in case-control studies (*43*).

*Treatment of noninvasive infection*

Noninvasive infections (*i.e.*, those in asymptomatic infected individuals) can be treated using a lumen-active agent and do not require a tissue-active agent (*43*). Paromomycin (Humatin®) is currently recommended because of its high potency in asymptomatic cyst passers (*3*). However, because the criteria of disease severity in amebic colitis have not been clarified, the decision to use a tissue-active agent before a lumen-active agent in such situations has been left to the discretion of the treating clinician. Tissue-active agents, and especially high-dose metronidazole, can cause severe side effects, such as encephalopathy (*63-67*). Older reports published before the era of PCR differentiation of *E. histolytica* from *E. dispar* and *E. moshkovskii* described the efficacy of paromomycin, even for symptomatic amebic colitis (*68-70*). According to recent case reports of endoscopically diagnosed asymptomatic or mild chronic amebic colitis, tissue-active agents are generally used for the initial treatment of infection (*31,71-73*). However, in a case report of two asymptomatic or mildly symptomatic patients with ulcerative lesions, the ulcerative lesions

were completely cured with paromomycin alone, without prior treatment with tissue-active agents (*34*). Although insufficient conclusions have been reached regarding the optimal treatment of endoscopically diagnosed asymptomatic or mild amebic colitis, it may be possible to treat noninvasive infections using only luminal activators. Further investigations will be needed to determine the appropriate treatment for the increasing number of patients with amebic colitis diagnosed *via* colonoscopy, especially in developed countries.

**Monitoring after treatment and disease prevention**

Although routine monitoring after amebiasis treatment is not recommended, reinfection with food-/waterborne and sexually transmitted *E. histolytica* frequently occurs in endemic areas/situations (*27,74-76*). A retrospective study of a Japanese HIV-1 cohort, which investigated the risk factors of invasive amebiasis recurrence (*27*), found that acquiring hepatitis C and syphilis during the follow-up period after the first episode of invasive amebiasis was associated with a higher rate of invasive amebiasis recurrence. This finding suggests that the reacquisition of cysts due to new infections rather than the reactivation of remaining cysts after use of tissue-active agents (in the absence of a lumen-active agent) played a greater role in the recurrence of invasive amebiasis. Thus, primary care physicians working in developed countries should inform their patients of factors and behaviors that will place them at risk of *E. histolytica* cyst acquisition and educate them about how these can be avoided (*e.g.*, avoiding potentially contaminated water or food in developing countries, unsafe homosexual contact, and unsafe oral-anal sexual contact).

**Future directions for the control of STI amebiasis**

*Increasing physician awareness and strengthening epidemiology research programs*

The incidence of ameba-related deaths is increasing worldwide. As mentioned above, amebiasis is no longer only highly prevalent in developing counties but is also re-emerging in many developed nations. Furthermore, an effective vaccine for amebiasis is not currently available. To ensure that patients receive an early diagnosis and appropriate treatment access, it is important to raise awareness and increase knowledge of STI amebiasis among clinicians, especially in developed countries, where this disease may not be well known. Addressing this issue requires the development and dissemination of educational materials and training programs, which should be regularly updated in accordance with the latest research findings. Improving diagnosis and treatment will lead to better patient outcomes. In addition, an effective epidemiological strategy should be implemented. The strategy outlined below underscores the importance of adopting an epidemiological approach for managing STI amebiasis. Continuous monitoring of the epidemiology of *E. histolytica* infection will be necessary to confirm the efficacy of the adopted strategy. This would involve strengthening existing surveillance systems, investing in research to better understand *E. histolytica* biology, and establishing effective infection control measures.

*Proposed epidemiological strategy against STI amebiasis*

In developing countries, contaminated food/water is the main source of *E. histolytica* infection (Figure 3). Therefore, people living in an affected area are at an equally high risk of exposure to this pathogen. In such a scenario, infection control is dependent on the improvement of sanitation and the provision of clean water and food to the community. On the other hand, most residents of developed countries are not at high-risk of *E. histolytica* infection. Thus, in this setting, person to person transmission occurs primarily within a high-risk population/community and often involves asymptomatic infected individuals. Thus, to develop an effective epidemiological strategy to control *E. histolytica* transmission, it is crucial to first identify the population/community at high-risk for amebiasis. Once these individuals are identified, they can be screened of asymptomatic infection and treated to reduce the reservoir of *E. histolytica* in the community. Our previous studies have already identified that MSM and people living with HIV/AIDS (PLWHA) are high-risk populations for STI amebiasis. By contrast, despite the fact that 10–20% of invasive amebiasis cases are reported in women (according to national surveillance program in Japan), the detailed epidemiological data collected from this group are limited. To conduct an effective epidemiological survey, it is important to acknowledge that the majority of the infected individuals are asymptomatic, which leads to the underestimation of STI amebiasis cases. A serological

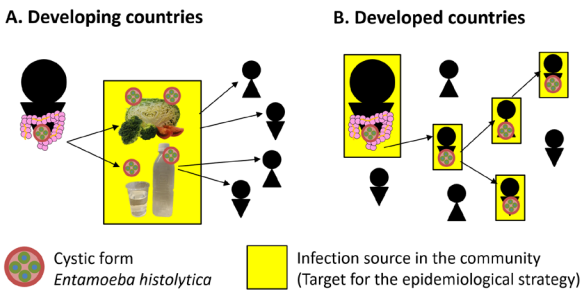


**Figure 3. *Entamoeba histolytica* transmission routes in different settings. (A)** In developing countries, transmission occurs *via* contaminated water and food. Thus, improvement of sanitation and provision of clean water and food is the recommended epidemiological strategy (yellow rectangle). **(B)** In developed countries, person to person transmission through sexual contact is most common. Identification of asymptomatic infected people, followed by treatment initiation, is the recommended epidemiological strategy (yellow rectangle).

survey (or seroprevalence study) is most widely used for the epidemiological assessment of amebiasis. The serological survey has a number of advantages: *i*) It is non-invasive and can be easily performed alongside syphilis and HIV testing; *ii*) Is it highly sensitive, even in asymptomatic infected individuals; *iii*) It can easily be used to compare data generated from multiple cohorts in developing and developed countries; and *iv*) It employs a regression model, which can easily identify risk factors and characteristics. Thus, active surveillance, for example in the form of a seroprevalence study, should be performed to ensure that all high-risk groups are accurately identified.

The next challenge is selecting an appropriate type of examination for individuals at high risk for STI amebiasis. As already described, a significant proportion of *E. histolytica* infections are asymptomatic. Thus, widespread screening of the whole high-risk population should be performed. Because of the large number of individuals requiring screening, the screening methods should ideally be inexpensive, non-invasive, and performable outside the hospital setting (*e.g.*, a VCT). Although PCR of stool samples is the most reliable method for detecting *E. histolytica* infection, it is expensive, time-consuming, and complex; thus, it is not ideal as a widespread screening method. Moreover, the handling of stool samples at VCT centers in developed countries is deemed inconvenient as most STI screening tests at these centers are performed using blood samples. On the other hand, serum antibody testing is a highly sensitive, easy, and inexpensive method for the screening of asymptomatic infection, which can be concurrently performed with other STI screening tests, such as those for HIV and syphilis (*53*). Moreover, in cases of liver abscesses, DNA has been identified in both saliva and serum (*77*). the development of detection methods targeting smaller molecular weight antigens could potentially improve the accuracy of amebiasis screening.

PCR of self-collected rectal swabs is widely used for *Chlamydia trachomatis* and *Neisseria gonorrhea* screening. This type of self-sampling is a highly efficient way of diagnosing current infection in one step, although it has never been evaluated for the diagnostic accuracy of self-collected rectal swab for *E. histoytica*. Thus, individuals with antibodies against *E. histolytica* should be urged to undergo subsequent PCR testing of their stool samples to differentiate between past and present infection; however, the optimal methods of administering the screening test to individuals with asymptomatic infection should be considered in future studies.

## Conclusions

Amebiasis is caused by intestinal infection with the protozoan *E. histolytica*. Although 80–90% of amebiasis cases present with no symptoms or mild symptoms, *E. histolytica* sometimes causes severe, life-threatening disease. To improve the prognosis of patients, it is important to spread awareness of STI amebiasis in developed countries, where knowledge of the disease may be comparatively lower than in developing nations. In addition, efforts should be made to reduce the number of asymptomatic *E. histolytica* infections and limit their spread *via* sexual contact. Moreover, a targeted approach is needed to identify factors that predispose individuals to *E. histolytica* infection in the first place. Although MSM and/or PLWHA (especially men) have been identified as high-risk populations in East Asian countries, data on the female population at risk for STI amebiasis are limited. Of note, although only 10–20% of the reported cases of invasive amebiasis in Japan occur in women, high amebiasis-associated mortality rates are reported among this group. To date, PCR of stool samples is the gold standard for the diagnosis of asymptomatic *E. histolytica* infection. However, because PCR is expensive and technically complex, it is not feasible as a screening test for asymptomatic *E. histolytica* infection. Instead, serological screening followed by PCR of stool samples from seropositive individuals is a potentially feasible epidemiological strategy for targeting asymptomatic carriers. It is possible that more accessible and cost-effective assays will be developed to identify asymptomatic *E. histolytica* carriers in the future. Through these efforts, we can aim to reduce the global burden of amebiasis.

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*Address correspondence to*:
Koji Watanabe, AIDS Clinical Center National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: kwatanab@acc.ncgm.go.jp

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# How did COVID-19 impact development assistance for health? – The trend for country-specific disbursement between 2015 and 2020

Mami Wakabayashi[1,*], Masahiko Hachiya[2], Noriko Fujita[3], Kenichi Komada[2], Hiromi Obara[2], Ikuma Nozaki[2], Sumiyo Okawa[1], Eiko Saito[1], Yasushi Katsuma[1,4,5,6], Hiroyasu Iso[1]

[1] Institute for Global Health Policy Research, Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan;
[3] School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan;
[4] Graduate School of Asia-Pacific Studies, Waseda University, Tokyo, Japan;
[5] Master's Graduate Program in Global Leadership, Vietnam-Japan University, Vietnam National University, Hanoi, Vietnam;
[6] Institute for the Advanced Study of Sustainability, United Nations University, Tokyo, Japan.

**Abstract:** This study aimed to examine the changes that took place between 2015–2019 and 2020 and reveal how the COVID-19 pandemic affected financial contributions from donors. We used the Creditor Reporting System database of the Organization for Economic Cooperation and Development to investigate donor disbursement. Focusing on the Group of Seven (G7) countries and the Bill and Melinda Gates Foundation (BMGF), we analyzed their development assistance for health (DAH) in 2020 and the change in their disbursement between 2015 and 2020. As a result, total disbursements for all sectors increased by 14% for the G7 and the BMGF. In 2020, there was an increase in DAH for the BMGF and the G7 except for the United States. The total disbursement amount for the "COVID-19" category by G7 countries and the BMGF was approximately USD 3 billion in 2020, which was 3 times larger than for Malaria, 8.5 times larger for Tuberculosis, and 60% smaller for STDs including HIV/AIDS for the same year. In 2020 as well, the United States, the United Kingdom, Japan, Italy, and Canada saw their disbursements decline for more than half of 26 sectors. In conclusion, the impact of COVID-19 was observed in the changes in DAH disbursement for three major infectious diseases and other sectors. To consistently address the health needs of low- and middle-income countries, it is important to perform a follow-up analysis of their COVID-19 disbursements and the influence of other DAH areas.

***Keywords*:** development assistance, health finance, COVID-19, low- and middle-income countries, Sustainable Development Goals

## Introduction

When the novel coronavirus infection (COVID-19) caused a global pandemic, the director general of the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern on January 30, 2020 (*1*). In response, donors worldwide increased their development assistance for health (DAH) funding. Early in the pandemic, the WHO and its partners launched a global framework titled "The Access to COVID-19 Tools (ACT) Accelerator" (*2*). Funding for the ACT Accelerator from governments, private sectors, and philanthropic and multilateral contributors collected commitments of USD 23.7 billion between April 2020 and the end of September 2022 (*3*). One study estimated that USD 54.8 billion was disbursed for DAH in 2020, of which USD 13.7 billion was allocated to COVID-19 health response (*4*). Meanwhile, during the pandemic, the donors also experienced economic and social backlash (*5,6*). We anticipate disbursement changes for categories not related to COVID-19 in the health sector or other sectors, but such changes have not been subjected to a data-based review.

Given the rapidly changing patterns of DAH, donors and recipients must capture how much aid is given to evaluate whether the amount is sufficient, addresses needs, and is effective (*7*). The Organization for Economic Cooperation and Development (OECD) registers its official development assistance (ODA) in a database called the Creditor Reporting System (CRS). SEEK Development, a Germany-based consulting group, visualizes ODA data including health, and the US-based Institute for Health Metrics and Evaluation visualizes health financing based on the CRS and their methodology (*8,9*). "Countdown to 2015" and the "Muskoka Initiative" method are concept for estimating the value of aid that

targets reproductive, maternal, newborn, and child health (*10,11*). Those estimations would be helpful in finding the of health disbursements. However, comparing DAH against estimated disbursements in other sectors has been difficult because of the complexity of estimation. Hence, Institute of Global Health Policy Research developed a web-based online database (*12*) that can visualize country-specific disbursements for recipients. This database aims to investigate effective involvement in global health, especially in COVID-19 and the three major infectious diseases (HIV/AIDS, tuberculosis, and malaria), comparing nonhealth sectors or health categories.

DAH is a significant financial support for providing sustainable health services in low- and middle-income countries (LMICs). In 2016, the average estimated proportion of dependence on health financing out of total health spending was 25.4% in low-income counties and 3.2% in LMICs (*13*). Both a stable DAH and adequate DAH contributions based on urgent needs such as COVID-19 response are important components of healthcare financing in LMICs. This study sought to investigate the change in disbursements for DAH and other sectors by comparing 2020 and the previous five years (2015–2019), exploring the annual trend for DAH breakdown from 2015 to 2020, and comparing the disbursements for the three major infectious diseases to distinguish the impact of COVID-19 on DAH.

## Materials and Methods

### *Data source*

Member countries of the OECD's Development Assistance Committee (DAC) register their ODA annually in the CRS, the direct figures of which were used in this study. The governments of all 29 DAC countries submit to the committee their ODA data for the previous three years in a specific form in January. The DAC compiles and validates the data, and detailed information on total resource flows are made available throughout the second half of the year. The open database can be freely accessed to the OECD website (*14*).

### *Target data range*

To identify trends for ODA disbursement by sector in each country and private philanthropy foundation, we combined the databases of DAC member countries and private philanthropy foundations. Similar to the 29 DAC countries, more than 40 private philanthropy foundations, including the Bill and Melinda Gates Foundation (BMGF), have registered their funding data in the CRS since 2009. This study focused on the DAH from the BMGF and the Group of Seven (G7) countries, namely, French Republic (France), the United States (US), the United Kingdom (UK), Federal Republic of Germany (Germany), Japan, Italian republic (Italy), and Canada. This is because disbursements from G7 countries account for approximately 80% of their total ODA, with these countries ranking first to sixth in total ODA among the 29 DAC countries, and BMGF is the largest private philanthropy organization, accounting for more than 46% of total private philanthropic funding (*15*) and focusing its funding on global health compared to other sectors in global development (*16*).

ODA has two channels: bilateral and multilateral aid. This study examines bilateral aid and earmarks multilateral aid through multilateral agencies to determine their recipients and volume in specific sectors. The core funding of multilateral agencies that do not specialize in each aid sector was not included in this study.

This study focuses on 2020, the latest available data as of the end of January 2023, and data from the previous five years (2015–2019) to explore recent trends for DAH and analyze the impact of COVID-19.

### *Measures*

*Sector and program area:* The aid sectors were based on the OECD's purpose codes for sector classification (*17*). The sectors of these purpose codes were grouped into broad three-digit sector categories further classified into five-digit purpose codes. We defined each three-digit series as sector and five-digit category as program area. For example, the 120 series refers to the "Health" sector and consists of 19 program areas categorized into three groups: "Health, general" (CRS code: 121 series), "Basic health" (122 series), and "Noncommunicable diseases (NCDs)" (123 series). The program area "COVID-19" has the CRS purpose code 12264, "Basic health", under the "Health" sector. Details of the DAH program areas are provided in Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=74*), and details of the sector categories are presented in Supplemental Table S2 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=74*) The definition of DAH with CRS purpose codes was defined by sector codes for health (120 series) and population policy and reproductive health (130 series) as well as other studies (*18,19*).

### *Analysis*

First, we analyzed the percentages of disbursement increase or decrease in 26 sectors by comparing 2020 and the average for the previous five years between 2015 and 2019 (Table 1). Supplemental Table S3 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=74*) shows the disbursement data by each sector. Second, we examined the disbursement volume for six health areas from the DAH data from 2015 to 2020 (Figure 1). To show the disbursements for

**Table 1. The percent change in disbursement by sector between 2020 and the average of 2015–2019**

| Sectors | G7 countries | | | | | | | BMGF | Total |
|---|---|---|---|---|---|---|---|---|---|
| | France | US | UK | Germany | Japan | Italy | Canada | | |
| All sectors | 54% | −1% | 3% | 21% | 20% | −39% | 23% | 16% | 14% |
| Education | 27% | −12% | −31% | 38% | 9% | 22% | 26% | 226% | 19% |
| Health | 135% | −6% | 44% | 254% | 180% | 33% | −8% | 31% | 65% |
| Population Policies and Reproductive Health | 18% | −5% | −22% | 2% | −47% | −44% | 45% | −3% | −5% |
| Water Supply and Sanitation | 6% | −19% | −42% | 4% | −43% | 30% | −42% | −20% | −14% |
| Government and Civil Society | 199% | −3% | −14% | 65% | −32% | −42% | 103% | 133% | 31% |
| Other Social Infrastructure and Services | 233% | −37% | −13% | 274% | 49% | −14% | −33% | −54% | 123% |
| Transport and Storage | 34% | −68% | −55% | −4% | 10% | 189% | −38% | | 7% |
| Communications | −16% | 45% | 773% | 73% | −59% | 65% | 30% | −96% | 7% |
| Energy | 8% | 15% | 18% | −3% | −0.4% | 56% | 128% | | 3% |
| Banking and Financial Services | 169% | −20% | −1% | 18% | −5% | −88% | −34% | 2% | 20% |
| Business and Other Services | 332% | 15% | −52% | 51% | 1% | 44% | −16% | −95% | 28% |
| Agriculture, Forestry, Fishing | 101% | −28% | −30% | 64% | 21% | 45% | 49% | −10% | 21% |
| Industry, Mining, Construction | 263% | −80% | 33% | 136% | 102% | 256% | −36% | −100% | 94% |
| Trade Policies and Regulations | −27% | −32% | 7% | −57% | −59% | −28% | −59% | | −42% |
| General Environment Protection | 104% | −33% | −28% | 20% | −70% | −33% | 0.5% | −11% | 10% |
| Other Multisector | 28% | −30% | 0.1% | 57% | 34% | 88% | −13% | −28% | 27% |
| General Budget Support | −59% | 72% | −100% | −100% | 376% | −100% | −13% | | 98% |
| Development Food Assistance | −35% | −34% | 54% | 39% | −2% | −45% | −10% | −100% | −2% |
| Other Commodity Assistance | 138% | | | | −98% | −34% | | | −89% |
| Action Relating to Debt | 205% | 2597% | 10729% | −69% | −100% | −44% | −100% | 7% | 158% |
| Emergency Response | 34% | 19% | 8% | 12% | −43% | −16% | −5% | −55% | 12% |
| Reconstruction Relief and Rehabilitation | −36% | −100% | −17% | −59% | −8% | 55% | −3% | 73% | −49% |
| Disaster Prevention and Preparedness | −39% | 19% | 20% | −24% | −81% | 145% | −77% | −100% | −11% |
| Administrative costs of donors | 19% | 4% | 35% | 43% | 6% | 19% | 31% | | 19% |
| Refugees in Donor Countries | 76% | −13% | 61% | −44% | 11% | −81% | 51% | | −30% |
| Unallocated / Unspecified | 0.4% | 424% | −19% | 14% | −41% | −54% | −53% | 9% | 8% |

"Red" means decreased disbursement in 2020 comparing average disbursement between 2015 and 2019. "Orange" means increased disbursement in 2020 comparing average disbursement between 2015 and 2019 (The increase of below 100%). "Green" means increased disbursement in 2020 comparing average disbursement between 2015 and 2019 (The increase of 100% or more). Blank means no distribution from 2015 to 2019.

the three major infectious diseases, we summed the disbursements for the "Malaria control" (CRS code: 12262), "Tuberculosis control" (12263), and "STDs control including HIV/AIDS" (13040) program areas. Then we subtracted the disbursement volume for these diseases from "Basic health" (122 series) and "Population policies and reproductive health" (130 series). Supplemental Table S4 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=74*) shows the annual DAH disbursements between 2015 and 2020 by G7 countries and the BMGF. Third, we analyzed the rate of increase or decrease by comparing annual disbursements in 2020 and the average disbursement for the previous five years between 2015 and 2019 for health (Figure 2). Supplemental Table S5 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=74*) shows the detailed data for these calculations. Lastly, we examined the annual disbursements for COVID-19 and the three major infectious diseases in G7 countries and the BMGF in 2020 (Table 2).

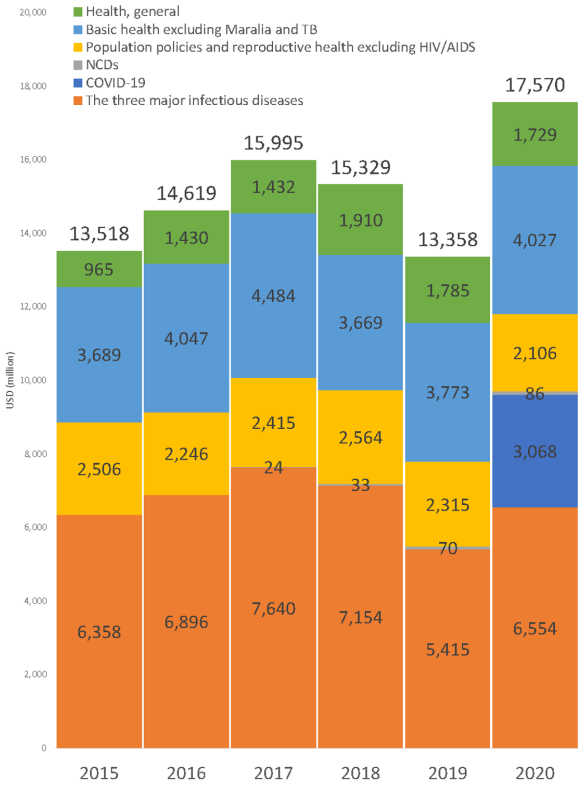


**Figure 1. Development assistance for health of the six health areas between 2015 and 2020.**

## Results

The total ODA of G7 countries and the BMGF increased by 14% in 2020 compared with the previous five years (Table 1). France increased its total ODA by 54%, the highest among the G7 countries, saw its ODA grow in 20 of the 26 sectors, and had more than a 100% increase rate in 10 sectors, including "Health" (CRS code: 120 series), "Government and civil society" (150 series) and "Banking and financial services" (240 series). Meanwhile, the US saw its total ODA in 2020

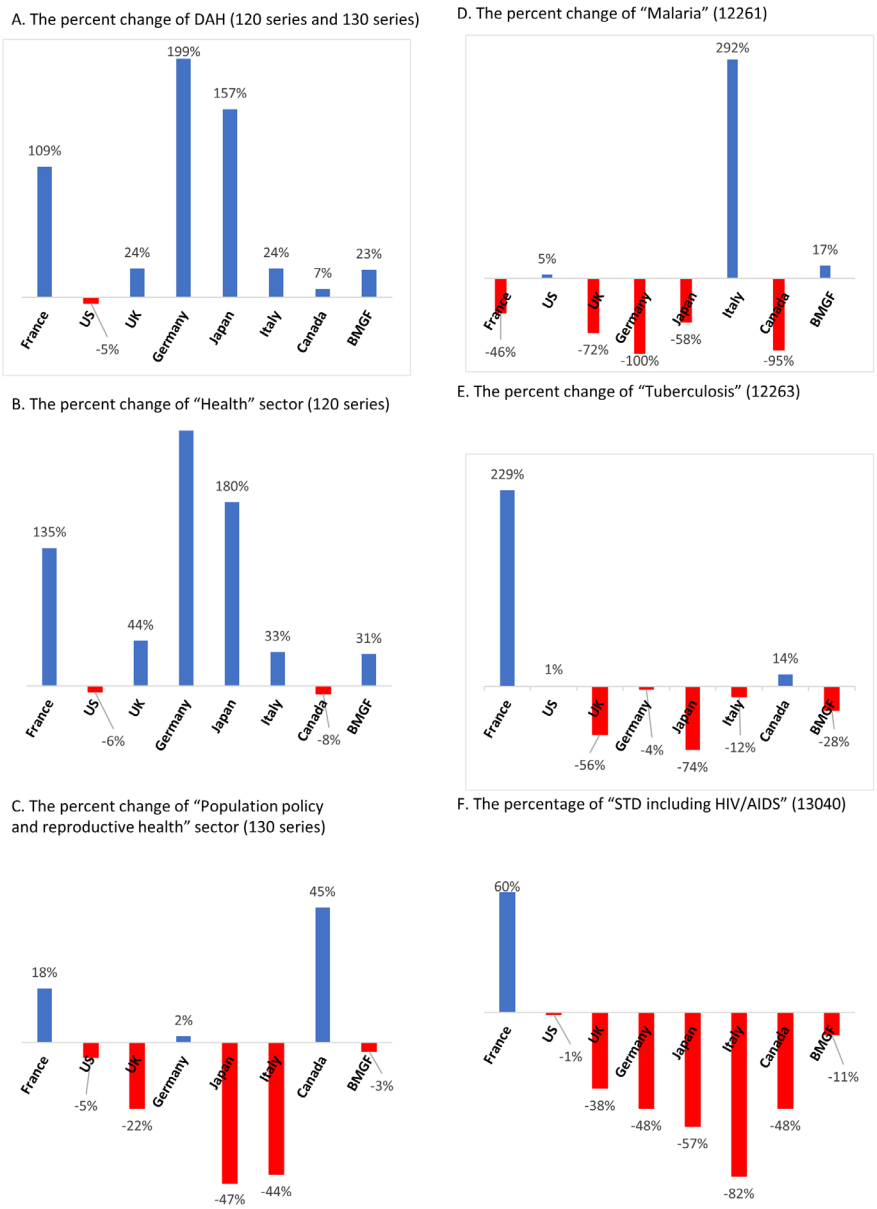


**Figure 2. The percent changes in disbursements between 2020 and the average of 2015–2019 in the international Group of Seven (G7) countries and the Bill and Melinda Gates Foundation (BMGF).**

decrease by 1% from the previous five-year average. In addition, the US, the UK, Japan, Italy, and Canada reduced their disbursements for more than half of the 26 sectors in 2020. For example, disbursements by the US had decreased for 16 sectors including "Education" (110 series), "Health" (120 series), "Population policies and reproductive health" (130 series), "Water supply and sanitation" (140 series), "Government and civil society" (150 series), and "Transport and storage" (210 series). As a health-related sector, "Water supply and sanitation" (140 series) saw lower disbursements from the US, the UK, Japan, Canada, and the BMGF.

Figure 1 shows the DAH disbursement trend for six categories (CRS code: 120 series and 130 series) from 2015 to 2020. In 2020, COVID-19 disbursements accounted for 17% of the total DAH ($17.5 billion). A comparison of the disbursement data for each health area between 2019 and 2020 showed that "Health, general" decreased by 3%, "Basic health excluding malaria and tuberculosis" increased by 7%, "Population policies and reproductive health excluding HIV/AIDS" decreased by 9%, "NCDs" increased by 23%, and "the three major infectious diseases" increased by 21%. The three major infectious diseases accounted for USD 6.4 billion in 2015 (47% of the total DAH), USD 6.9 billion in 2016 (47%), USD 7.6 billion in 2017 (48%), USD 7.2 billion in 2018 (47%), USD 5.4 billion in 2019 (41%), and USD 6.6 billion in 2020 (37%), while NCDs accounted for USD 24 million in 2017 (0.15%), USD 33 million in 2018 (0.21%), USD 70 million in 2019 (0.52%), and USD 86 million in 2020 (0.49%).

The study found that disbursements for "Health" (CRS code: 120 series) had more than a twofold increase in Germany, Japan, and France in 2020 compared with the previous five-year average (Figure 2). The DAH of the BMGF was larger than that of six of the G7 countries in 2020 and the average of the previous five years. In 2020, the BMGF increased its contribution to "Health"

**Table 2. Comparison of annual disbursements (2020) for COVID-19 and for the three major infectious diseases by the international Group of Seven (G7) countries and the Bill and Melinda Gates Foundation (BMGF)**

| Disbursement | G7 countries | | | | | | | BMGF | Total |
|---|---|---|---|---|---|---|---|---|---|
| Disbursements by sector | France | US | UK | Germany | Japan | Italy | Canada | | |
| Annual disbursement for "COVID-19" (USD) | 5,016,701 | 436,301,169 | 418,086,580 | 921,671,539 | 778,702,904 | 28,796,937 | 114,492,987 | 364,579,923 | 3,067,648,740 |
| Annual disbursement for "Malaria" (USD) | 717,283 | 707,740,640 | 23,811,291 | 0 | 1,067,204 | 575,753 | 110,898 | 262,112,950 | 996,136,019 |
| Ratio for "COVID-19" *vs.* "Marilia" | 7.0 | 0.6 | 17.6 | N/A | 729.7 | 50.0 | 1032.4 | 1.4 | 3.1 |
| "Tuberculosis" (USD) | 1,371,364 | 228,961,915 | 3,799,954 | 3,352,671 | 1,228,742 | 634,189 | 12,675,216 | 106,508,581 | 358,532,632 |
| Ratio for "COVID-19" *vs.* "Tuberculosis" | 3.7 | 1.9 | 110.0 | 274.9 | 633.7 | 45.4 | 9.0 | 3.4 | 8.6 |
| Annual disbursement for "STDs including HIV/AIDS" (USD) | 18,272,237 | 4,917,561,729 | 12,172,740 | 18,814,940 | 715,870 | 515,868 | 4,249,145 | 227,127,867 | 5,199,430,396 |
| Ratio for "COVID-19" *vs.* STDs including HIV/AIDS | 0.3 | 0.1 | 34.3 | 49.0 | 1087.8 | 55.8 | 26.9 | 1.6 | 0.6 |
| Annual disbursement for the three major infectious diseases (USD) | 20,360,884 | 5,854,264,284 | 39,783,985 | 22,167,611 | 3,011,816 | 1,725,810 | 17,035,259 | 595,749,398 | 6,554,099,047 |
| Ratio for "COVID-19" *vs.* the total of the three major infectious diseases | 0.2 | 0.1 | 10.5 | 41.6 | 258.5 | 16.7 | 6.7 | 0.6 | 0.5 |

(120 series) and "Population policies and reproductive health" (130 series) compared with the average of the past five years. However, disbursements for "Population policies and reproductive health" declined in the US, the UK, Japan, and Italy from the previous five-year average.

Table 2 compares the annual disbursements for COVID-19 and for the three major infectious diseases in G7 countries and the BMGF in 2020. Disbursements for "COVID-19" (CRS code: 12264) were larger than the total disbursements for the three major infectious diseases in the UK, Germany, Japan, Italy, and Canada in 2020. Among G7 countries and the BMGF, the US accounted for 89% of the total disbursements for the three major infectious diseases and 14% of the total disbursements for COVID-19.

## Discussion

This study illustrated the changing patterns in DAH in 2020, the year the COVID-19 pandemic began. In most of the G7 countries, total ODA increased in 2020 but with an apparent trade-off with disbursements for other sectors. Most countries increased their disbursements for the "Health" sector in relation to their COVID-19 response but reduced their aid for other sectors. Worldwide DAH reached $40.4 billion in 2019 and increased to $54.8 billion in 2020 because of the additional resources necessary for COVID-19 response (*4*). This study found that the total disbursement amount for the "COVID-19" category by G7 countries and the BMGF was approximately USD 3 billion in 2020, which was 3 times larger than for "Malaria", 8.5 times larger for "Tuberculosis", and 60% smaller for "STDs including HIV/AIDS" for the same year. A larger disbursement amount was provided for COVID-19 than for the three major infectious diseases, but it is necessary to further analyze the gap between the actual costs and disbursements to implement COVID-19 response considering the proportion of DAH dependence among LMICs.

Our study revealed the decline in donor contribution in many sectors in 2020 compared with the previous five years. The governments of LMICs have yet to consider health as a high enough priority as evidenced by the proportion of all government spending devoted to the health sector (*20*). Increasing COVID-19 funding may lower the prioritization of domestic health expenditures because the government may reallocate such spending to other sectors; such a phenomenon known as aid fungibility (*21*). In addition, they would expect constant disbursements by donors in sectors besides health and may reallocate their budget for their priority areas because of donors' reduced funding for such areas and higher funding for COVID-19. The year 2020 was an acute phase of the pandemic, and many countries did not have the budget for COVID-19 response. Budget data for COVID-19 in 2021 and 2022 must be collected

to examine the impact of the pandemic. A national-level analysis of changes in budgets for certain sectors in the following years may reveal whether the recipient countries prioritize "health" in their domestic budgets to combat COVID-19 or increase their dependence on DAH.

As a health-related sector, "Water supply and sanitation" (CRS code: 140 series) saw its total disbursements from G7 countries and the BMFG drop by 14% from the previous five years. While "Water supply and sanitation" remains vital for the Sustainable Development Goals, some African countries have already shown a decline in wash services between 2000 and 2015 (*22*). The reduced disbursements for "Water supply and sanitation" in 2020 may help lessen the mobilization of resources toward projects related to the sector.

HIV/AIDS is a health program area that has received the highest contribution since 2004 (*23*). In this study, the largest contributor to HIV/AIDS funding was the US both in 2020 and in terms of the previous five-year average. Compared with the disbursement volume for HIV/AIDS (approximately USD 4.9 billion in 2020), disbursements for COVID-19 in 2020 were much smaller (USD 436 million) in the US. In 2020, the US announced that it would suspend its contributions to the WHO to focus on its COVID-19 response (*24*) and, starting from May 4, 2020, would not host the ACT Accelerator for Coronavirus Global Response (*25*). In 2021, newly elected US president Joe Biden announced the resumption of funding for the WHO (*26*) with a $4 billion contribution to COVAX, a pillar of the ACT Accelerator (*27*). On the other hand, Germany and France proposed WHO reform in 2020 and attempted to strength WHO for pandemic (*28*). These circumstances may reflect disbursements directed toward COVID-19.

Our study observed that most donors reduced their disbursements for each of the three major infectious diseases in 2020, the starting year of the COVID-19 pandemic, compared with the previous five years, although the total disbursement volume for the three major infectious diseases was the largest in DAH. It is also important to evaluate the disbursement trends within program areas in health. NCDs indicated a larger burden of disease defined by death and disability-adjusted life years (*29*), but DAH for NCDs was much smaller than for infectious diseases as one study showed (*4*). This study found that the disbursement volume for NCDs since 2017 was less than one-hundredth of those for COVID-19 and the three major infectious diseases. The large disbursements for infectious diseases including COVID-19 are likely to continue as long as the US, the biggest DAH funder, prioritizes aid for infectious diseases as a matter of global health security (*30*).

This study showed the change in disbursements for DAH and other sectors and compared the disbursements for three major infectious diseases and COVID-19 to investigate the impact of the pandemic. However, there are some limitations. One study that tracked the sectoral allocation of ODA from 2011 to 2018 among 29 DAC countries identified health as the sector with the highest average annual ODA contribution at USD 20.3 billion (*17*). In the previous study, the volume of DAH was larger because the aforementioned study included the estimation for core funding to multilateral agencies. Our study focused on country-specific funding, which consists of bilateral assistance and earmarked contributions through multilateral agencies, but did not include core funding to multilateral agencies. Nevertheless, the DAH in our study had a large distribution volume for other sectors both in 2020 and in terms of the previous five-year average in G7 countries and the BMGF. Our study is presumed to cover approximately 75% of the estimated total DAH, which is based on a study that showed the same figure for country-specific funding (*31*).

## Conclusion

In sum, DAH increased in the BMGF and in the G7 countries except the US in 2020. Disbursements for "Health" including "COVID-19" more than doubled in Germany, Japan, and France in 2020 compared with the average of the previous five years. The disbursement amount for COVID-19 was larger relative to the total disbursements for the major three infectious diseases in 2020 except for France, the US, and the BMGF. This necessitates a follow-up study on COVID-19 disbursements and the influence of other DAH categories to appropriately address health needs in LMICs.

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*Address correspondence to*:
Mami Wakabayashi, Institute for Global Health Policy Research, Bureau of International Health Cooperation, National Center for Global Health and Medicine, 1-21-1, Toyama Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: mwakabayashi@it.ncgm.go.jp

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# The prophylactic role of mitomycin C-based hyperthermic intraperitoneal chemotherapy (MMC-based HIPEC) on peritoneal metastasis of spontaneously ruptured hepatocellular carcinoma (srHCC): A pilot study

Ziqi Hou, Guoteng Qiu, Qingyun Xie, Zhaoxing Jin, Shizheng Mi, Jiwei Huang*

Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, Chengdu, China.

**Abstract:** Hepatocellular carcinoma (HCC) was featured as spontaneous rupture hemorrhage under intratumoral overpressure. Spontaneous rupture hepatocellular carcinoma (srHCC) has a high propensity for peritoneal metastasis (PM). Although HIPEC has become standard treatment for malignancies with PM, it has been poorly described in srHCC. We conducted a single-arm, open-label, single-center, prospective study to explore the prophylactic role of MMC-based HIPEC on PM of srHCC. A total of 7 patients were collected from April 1, 2021 to April 30, 2022. HIPEC was conducted 3 times on the first, third and fifth postoperative days. 15 mg/m$^2$ of MMC was used with 60 minutes perfusion at 43°C. The primary end-point was local peritoneum recurrence free survival (RFS), whereas the secondary end-point was systemic RFS and overall survival (OS). The mean hepatectomy operation time was 232 minutes (SD: 124.08 minutes). The median bleeding loss was 200 mL (range 50–400 mL). The mean hospital stay was 13 days (SD: 3.42 days). Only mild abdominal distension was reported in 4 patients (57%). There were no patients who suffered from life-threatening intra-abdominal and extra-abdominal complications (EAC). At the data cut-off (April 30, 2023), one patient (14%) had died due to cachexia. Local peritoneal recurrence occurred in three patients (43%). Median follow-up was 16.1 months (IQR: 12.8–16.6 months). Median local peritoneum RFS was 12.3 months (95% CI: 7.0–17.5; 4 events) and median overall RFS was 7.5 months (95% CI: 4.2–10.8; 6 events). MMC-based HIPEC was safe and feasible in selected patients of srHCC. It showed a positive tendency in preventing PM, but large-scale research should be continued.

***Keywords*:** hyperthermic intraperitoneal chemotherapy, mitomycin-C, spontaneous rupture hepatocellular carcinoma

## Introduction

Hepatocellular carcinoma (HCC), the most frequently occurring type of primary liver cancer, is the fourth most common cancer and the third most common cancer-related by mortality. The incidence of HCC is higher in East Asia, especially in China (*1*). HCC often develops as a result of chronic liver disease. In the case of cirrhosis and intratumoral overpressure, HCC can have characteristic spontaneous rupture and hemorrhage (*2*). Time has witnessed the increase of ruptured HCC in developing countries in recent years. However, spontaneous rupture HCC (srHCC) possesses higher acute mortality. Although the one-year overall survival rate could reach 57% after transcatheter arterial embolization (TAE) followed by staged surgical resection strategies, the delayed operation could cause postoperative peritoneal metastasis (PM) reached at 34.2% (*2*). In this regard, srHCC is regarded as an independent risk factor for PM of HCC (*3*).

Hyperthermic intraperitoneal chemotherapy (HIPEC) has shown considerable therapeutic efficacy in other tumors with PM, including gastrointestinal tumors, ovarian cancer, and peritoneal malignant tumors (*4*). Different chemotherapeutic drugs can be administrated in HIPEC. Traditionally, mitomycin C (MMC) and oxaliplatin (OX) were the most commonly used drugs in HIPEC. A meta-analysis, compared OX with MMC in HIPEC for PM from colorectal cancer (CRC), showed that MMC possessed comparable survival to OX but lower major complications (*5*). In this regard, could MMC-based HIPEC be applied in HCC? In fact, MMC could be commonly used as a chemotherapeutic agent in conventional transarterial chemoembolization (c-TACE) and hepatic arterial infusion chemotherapy (HAIC) (*6*) for HCC (*7,8*). C-TACE with MMC was effective and safe in a long-term follow-up study (*9*).

Fortunately, an increasing number of previous studies

have demonstrated that cytoreductive surgery (CRS) plus MMC-based HIPEC was a safe and effective approach in cases with PM of HCC (*10-12*). However, srHCC might possess a larger resected surface due to larger tumor size caused larger resection range, compared with PM of HCC. Postoperative HIPEC might increase the risk of hemorrhagic events. Furthermore, the dosage required for prevention purposes is possibly different from the dosage required for treatment purposes. The role of MMC-based HIPEC for srHCC remains unknown. We present cases with srHCC treated with MMC-based HIPEC followed by hepatectomy and evaluate the safety and feasibility of this procedure and the prophylactic role on PM.

## Patients and Methods

This study was a single-arm, open-label, single-center, prospective study conducted with the approval of the Ethics Committee of West China Hospital, Sichuan University (2022-1163). The trial has been registered on *ClinicalTrials.gov* (NCT05544253).

### *Patients*

Data collection was prospective. We selected the candidates at West China Hospital, who were diagnosed with srHCC and received emergency laparotomy or staged hepatectomy between April 1, 2021 and April 30, 2022.

Selections were eligible when meeting the criteria: *i*) Aged from 18–80; *ii*) Clinical diagnoses of srHCC – symptoms: acute abdominal pain and peritonitis; blood routine tests: decreased erythrocyte count; increased leucocyte count, especially the proportion of neutrophils; increased alpha-fetoprotein (AFP) and/or protein induced by vitamin K absence or antagonist-II (PIVKA-II); radiological features: contrast materials extravasation from lesions confirmed by abdominal contrast enhanced computed tomography or gadoxetic acid disodium (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI); intraoperative findings of tumor rupture and postoperative pathology are more confidently conclusive (*13*); *iii*) ECOG score of 0–2 points; *iv*) Child-Pugh class A-B liver function only; and *v*) Received emergency laparotomy or staged hepatectomy.

Exclusion criteria were: *i*) Contraindications of HIPEC, including intra-abdominal adhesions, intestinal obstruction, severe kidney insufficiency, myelosuppression, severe cardiovascular system disease, abdominal infection, bleeding tendency or coagulation dysfunction, severe pulmonary system disease, vital signs are unstable, cachexia; *ii*) Patients who refuse to accept clinical trials.

### *Intervention*

After the written informed consent was given to the candidates, the specific procedures were conducted. All of the candidates have received liver resection and perfusion tubes had been placed at the end of the operation. After the operation, HIPEC was conducted 3 times on the first, third and fifth postoperative day. Intraperitoneal hyperthermic perfusion device (BR-TRG-II$^{TM}$, Bao Rui medical corporation, Guangdong, China) was used for HIPEC. 15 mg/m$^2$ of MMC served as chemotherapeutic agent for HIPEC. MMC possessed the inherent advantages of heat-stability and well-established pharmacokinetics in HIPEC. Furthermore, MMC has proved efficacy in c-TACE and HAIC for HCC. The perfusion volume was 2,000 cm$^3$ of normal saline with 15 mg/m$^2$ MMC. At the beginning of perfusion, it took 5 minutes to reach the target temperature of 43°C (109°F) using this device, and then adjusted the perfusion flow to 400ml/min. The abdominal temperature was maintained at 43°C for the 60 minute perfusion period (Figure 1). The candidate was monitored by electrocardiogram (ECG) and continuous low flow oxygen inhalation.

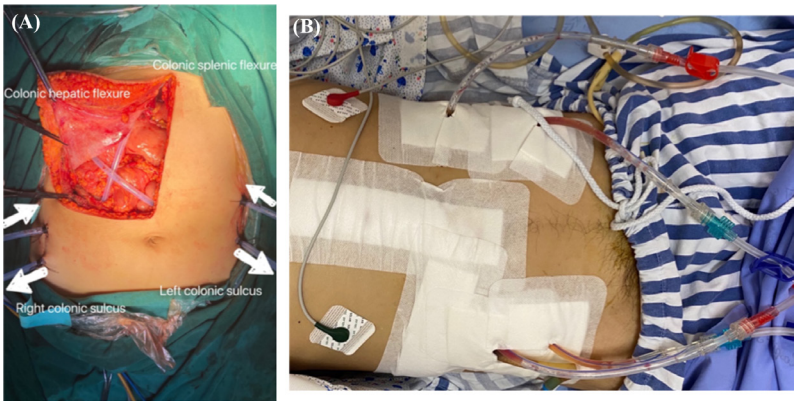


**Figure 1. The position of HIPEC tubes in operation and HIPEC procedure. (A)** Four perfusion drainage tubes were placed and fixed intraoperatively. Among them, 2 tubes were arranged from the left lower colonic sulcus to the right upper colonic hepatic flexure, whereas other 2 tubes were oppositely arranged from the right lower colonic sulcus to the left upper colonic splenic flexure. **(B)** The inflow tubes were connected to the red buttons, and the outflow tubes were connected to the blue buttons.

Simultaneously, the candidate also received balanced solution supplement during the process. HIPEC would be stopped immediately when the candidates were caught in life-threatening adverse events.

*Follow-up and outcomes*

We obtained follow-up data *via* outpatient service and telephone consultation. We followed the selections the first month after the hepatectomy and every 3 months after that. Peripheral blood tests, including routine blood, total biochemical items and tumor biomarkers (AFP and PIVKA-II) and full abdominal contrast-enhanced computed tomography (CECT) or magnetic resonance imaging (MRI) were conducted and administrated at every follow-up. The recurrence and metastasis were mainly assessed from the serum level of tumor markers and imaging evaluation.

The primary efficacy end-point was local peritoneum RFS, whereas the secondary efficacy end-point was systemic RFS and OS. Duration of progression of disease, including local peritoneum progression and systemic recurrence, was calculated from the first administration of MMC-based HIPEC. The definition of OS is the interval between the first administration of HIPEC and death for any reason or the last follow-up in the twelfth month. The censoring date of the present study was April 2023.

Morbidity was regarded as any complication detected during hospitalization or within 30 days after HIPEC. The categorization of postoperative complications were according to the Clavein-Dindo classification (*14*). Grade III or higher were considered as major morbidity (*15*). Specifically, postoperative hemorrhage, bile leakage, hepatic dysfunction, pulmonary infection and reoperation are included in the category of postoperative complications. In addition, National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v.4.03 for adverse events related to mitomycin C of HIPEC were monitored (*14*). Mortality is defined as the death within 30 days after surgery. Safety assessments included monitoring of morbidity and mortality of HIPEC. At a data cut-off of April 30, 2023, 7 patients were recruited to the study.

*Statistics analysis*

The measurement data of normal distribution was represented by mean (SD), the non-normal distribution data was represented by median (IQR), and the enumeration data was represented by frequency (%). Kaplan-Meier method was used to assess overall and progression survival rates and time. Safety was summarized descriptively. All analyses were performed using IBM SPSS statistics ver.26 (IBM, Armonk, NY). $P < 0.05$ was defined as statistically significant in this study.

## Results

*Patient Characteristics*

During the study period, 15 patients underwent hepatectomy due to liver cancer peritoneum related diseases in West China Hospital, Sichuan University between April 1, 2021 and April 30, 2022. All of the selections received postoperative clinical pathological diagnoses. Only 10 of them were diagnosed as spontaneously ruptured hepatocellular carcinoma. At a data cut-off of April 2023, 7 patients were recruited to the study. They received eligibly assessment and received MMC-based HIPEC after hepatectomy. Figure 2 demonstrates patient enrollment.

Baseline characteristics of enrolled patients are shown in Table 1. The mean age of enrolled patients was 51 years and mean BMI was 23.46. Most patients had slightly higher transaminases than normal, but liver

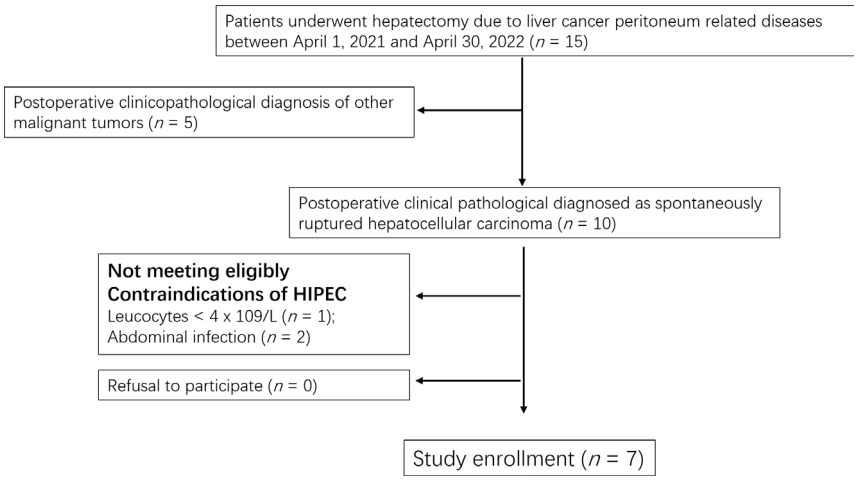


**Figure 2. Flow of study participants.**

**Table 1. Characteristics of enrolled patients**

| Case Number | Age | Sex | BMI | Background Liver Disease | Viral load | PLT 10^9/L | ALT /IU/L | AST /IU/L | TB umol/L | PT /s | INR | Alb/g/L | AFP ng/mL | PIVKA-II mAU/mL |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 38 | M | 24.06 | HBV | <1.00E + 02 | 237 | 324 | 86 | 6.1 | 12.9 | 1.18 | 42.4 | 13,605.0 | 8,051 |
| 2 | 41 | M | 20.76 | HBV | 2.03E + 02 | 209 | 124 | 129 | 21.5 | 12.5 | 1.15 | 39.9 | 8,998.0 | 750,000 |
| 3 | 56 | M | 25.14 | HBV | 1.72E + 05 | 235 | 31 | 34 | 15.5 | 11 | 0.98 | 45.8 | 36.5 | 40,709 |
| 4 | 46 | F | 21.36 | HBV | 6.07E + 05 | 262 | 66 | 50 | 25.2 | 12.5 | 1.11 | 32.2 | 49,334.0 | 4,398 |
| 5 | 75 | F | 27.64 | Primary biliary cirrhosis | - | 46 | 14 | 27 | 21.6 | 12.7 | 1.15 | 33.2 | 43.7 | 74 |
| 6 | 36 | F | 22.76 | HBV | <1.00E + 02 | 97 | 16 | 19 | 6.5 | 11.3 | 1.01 | 37.3 | 10,649 | 1,466 |
| 7 | 68 | M | 21.80 | HBV | <1.00E + 02 | 127 | 37 | 32 | 10.5 | 13.5 | 1.24 | 38.5 | 1,210 | 18,894 |
| Median/Mean (range) | 51 ± 15 | - | 23.36 ± 2.43 | - | - | 173.29 ± 82.84 | 87.43 ± 111.04 | 53.86 ± 39.80 | 15.27 ± 7.76 | 12.34 ± 0.89 | 1.12 ± 0.09 | 38.47 ± 4.83 | 8,998 (43.7–13,605.0) | 8,051 (1,466–40,709) |

M, male; F, female; HBV, hepatitis B virus.

**Table 2. Perioperative Parameters**

| Case Number | Initial Treatment (TAE/Systemic treatment/Emergency Resection/Selective resection) | Duration from initial treatment to resection (month) | Operation time (minutes) | Bleeding loss (mL) | Blood Transfusion (mL) | Hospital Stay (day) | In-hospital costs (dollar) | Perioperative morbidity Clavien-Dindo | Post-operative treatment (TACE/ Huaier Granule/ Targeted agent + immune therapy) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | TAE + Sorafenib | 6 | 290 | 100 | - | 10 | 10,812.64 | II | Huaier Granule + Sorafenib |
| 2 | TAE | 0.25 | 270 | 1400 | - | 17 | 16,345.63 | II | Donafenib |
| 3 | Emergency Resection | - | 360 | 400 | Fresh Frozen Plasma: 400 mL | 9 | 14,564.53 | II | TACE + Donafenib |
| 4 | Emergency Resection | - | 167 | 50 | - | 10 | 14,294.42 | I | Huaier Granule + Sorafenib |
| 5 | Emergency Resection | - | 120 | 20 | - | 17 | 11,581.78 | I | Sorafenib |
| 6 | TAE + Camrelizumab + lenvatinib | 4 | 381 | 200 | - | 15 | 16,181.86 | II | TACE + Camrelizumab + lenvatinib |
| 7 | Emergency Resection | - | 136 | 200 | - | 13 | 9,158.15 | II | TACE + Dnoafenib |
| Median/Mean (range) | - | - | 232.00 ± 124.08 | 200 (50–400) | - | 13.00 ± 3.42 | 13,277.00 ± 2,782.66 | - | - |

function of all enrolled patients conformed to Child-Pugh class A. Except for patient No.5, who suffered from srHCC caused by autoimmune hepatitis, other patients were HBV-related srHCC. Among the patients with HBV-related srHCC, 4 of them (57%) had low viral load, only No.3 and No.4 showed 10^5 higher viral load. The median AFP was 8,998 ng/mL (range: 43.7–13,605.0 ng/mL). The median PIVKA-II was 8,051 mAU/mL (range: 1,466–40,709 mAU/mL). The tumor markers AFP and PIVKA-II in all patients were significantly higher than normal values ($p < 0.05$).

*Perioperative parameters*

Perioperative parameters are shown in Table 2. All of the selections received laparotomy. Figure 3 shows the preoperative CECT images and intraoperative specimens of No.4. Three cases (43%) had initially received emergency transcatheter arterial embolization (TAE) and subsequently staged hepatectomy, and 4 (57%) underwent emergency laparotomy. The mean hepatectomy operation time was 232.00 minutes (SD: 124.08 minutes). The median bleeding loss was 200 mL (range: 50–400 mL). Only 1 (14%) had received intraoperative transfusion of fresh frozen plasma 400 mL. The postoperative complications of surgery of all selections were classified as Clavien-Dindo I-II. Five (71%) were Clavien-Dindo II, whereas the other 2 (29%) were Clavien-Dindo I. Specifically, No.1, 6, and 7 had postoperative fever caused by pulmonary infection, and received total parenteral nutrition for support treatment. No. 2 and No.3 received 2 units of red blood cell suspension. No patients died or underwent reoperations during the perioperative period. The mean hospital stay was 13 days (SD: 3.42 days). The mean hospitalization expenses reached $13,277.00 (SD: 2,782.66). All selections were treated with postoperative targeted therapy, including Sorafenib, Donafenib, and lenvatinib. Patients with microvascular invasion (MVI), one of high-risk factors of recurrence, also received TACE after surgery.

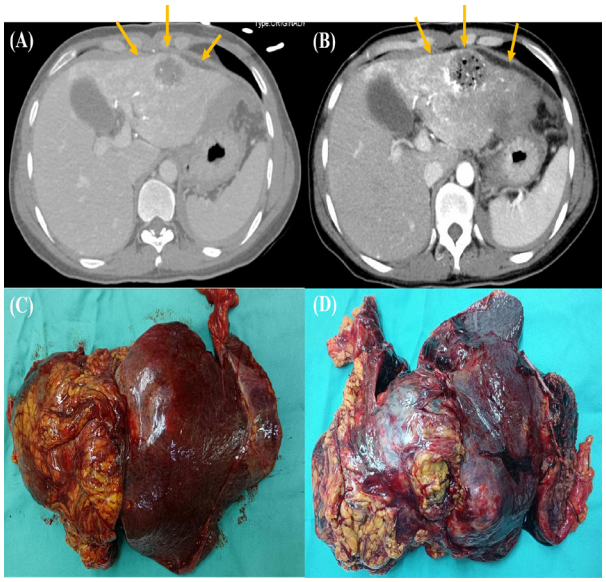


**Figure 3. (A) and (B)** CT image of No.4 patient. The CT image showed the targeted tumor was located in the left hemiliver. **(C) and (D)** the intraoperative specimen of No.4 patient.

*Postoperative clinicopathological characteristics*

All of selections received postoperative pathological examination. The clinicopathological features of 7 patients are shown in Table 3. The median maximum tumor diameter was 11.0 cm (range: 6.0–12.0). All surgical margins reached R0. The mean incisal edge was 1.46 ± 1.26 cm. No satellite lesions were found in all specimens. Three (42,86%) specimens had MVI, but the number is less than or equal to 5, and the distance from the adjacent liver tissue is less than 1cm. Five (71.43%) were medium differentiation, whereas two (28.57%) were medium to low differentiation.

**Table 3. Postoperative clinicopathological characteristics**

| Case number | Maximum tumor diameter (cm) | Incisal Edge (cm) | Satellite lesions | MVI | Degree of Differentiation |
|---|---|---|---|---|---|
| 1 | 10.5 | 1.0 | None | None | Medium to low differentiation |
| 2 | 12.5 | 0.5 | None | None | Medium differentiation |
| 3 | 12.0 | 1.2 | None | Yes, the number is less than or equal to 5, and the distance from the adjacent liver tissue is less than 1 cm | Medium differentiation |
| 4 | 11.8 | 4.0 | None | None | Medium differentiation |
| 5 | 5.0 | 2.0 | None | None | Medium differentiation |
| 6 | 11.0 | 0.2 | None | Yes, the number is less than or equal to 5, and the distance from the adjacent liver tissue is less than 1 cm | Medium to low differentiation |
| 7 | 6.0 | 1.3 | None | Yes, the number is less than or equal to 5, and the distance from the adjacent liver tissue is less than 1 cm | Medium differentiation |
| Median/Mean (range) | 11.0 (6.0–12.0) | 1.46 ± 1.26 | None | - | - |

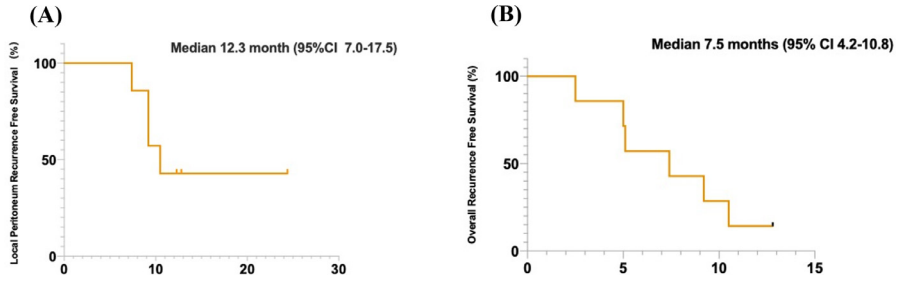


**Figure 4. (A) Local peritoneum RFS and (B) overall RFS for all study patients who underwent postoperative MMC-based HIPEC.** RFS, recurrence free survival; MMC-based HIPEC, mitomycin C-based hyperthermic intraperitoneal chemotherapy.

*Safety and adverse events*

There were no postoperative 30-day mortalities in this study. Postoperative complications of MMC-based HIPEC occurred in 4 patients (57%). Specifically, they developed mild abdominal distension after HIPEC, which could be relieved after symptomatic treatment. There were no patients who suffered from life-threatening intra-abdominal complications (IAC), including anastomotic leakage, abdominal bleeding, and pleural effusion. The previous study showed that MMC had higher incidence of extra-abdominal complications (EAC), including liver function damage, neutropenia, and leucopenia (*16*). Fortunately, no patients developed EAC due to lower MMC dosage.

*Long-term outcomes*

At the data cut-off (April 30, 2023), six patients (86%) still survived, and one patient (14%) had died due to cachexia caused by HCC. Recurrence occurred in six patients (86%). The median follow-up was 16.1 months (IQR: 12.8–16.6). Median local peritoneum RFS was 12.3 months (95% CI: 7.0–17.5; 4 events) and median overall RFS was 7.5 months (95% CI: 4.2–10.8; 6 events). The postoperative 3-month, 6-month, 9-month and 1-year local peritoneum RFS rate was 100%, 100%, 57.1% and 42.9%, respectively (Figure 4A).

The postoperative 3-month, 6-month, 9-month and 1-year RFS rate was 85.7%, 57.1%, 42.9% and 14.3% (Figure 4B). The pattern of recurrence included intrahepatic recurrence, lung, and peritoneal cavity metastasis. Specifically, two patients (29%) suffered from intrahepatic recurrence, four patients (57%) suffered from peritoneum recurrence, and one patient (14%) suffered from lung metastasis. The post-recurrence treatment included targeted strategy plus immune therapy, transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and reoperation according to the HCC treatment guideline of our institution.

## Discussion

Unlike other tumors, hepatocellular carcinoma is featured by spontaneous rupture under intratumoral overpressure (*17*). It has been regarded as a terminal event with a drastically poor prognosis, despite the morbidity of srHCC was low (*17*). Although previous studies demonstrated that standard TAE followed by staged surgical resection strategy improved one-year OS reached at 57% (*3*), the delayed hepatectomy boosted postoperative PM by 34.2% as well (*2*). EVOCAPE-1 (Evolution of Peritoneal Carcinomatosis study 1) elucidated that untreated PM rapidly lead to developed symptoms, including small-bowel obstruction, ascites, tumor-related pain, and malnutrition (*18-20*), which severely impacted survival of patients with liver cancer under chronic liver disease background. However, that did not mean that emergency hepatectomy should be considered predominately to reduce the rate of PM as a result of higher in-hospital mortality rate based on the latest meta-analysis (*21*). Therefore, it is paramount to present a measure to reduce both the risk of perioperative mortality and the risk of peritoneal recurrence.

Sugarbaker *et al.* (*18*) first demonstrated that selected patients with PM could benefit from HIPEC, which provided the foundation (*22-25*). After that, Blake Cady's first-order principle elaborated which tumor types and chemotherapeutic agents were suitable for HIPEC (*18*). Time has witnessed substantial progress of HIPEC in selected patients with PM of colorectal, gastric, appendiceal and ovarian primary tumor. Historically, hepatobiliary organs as part of foregut organs have a high propensity for early metastatic progression. Although they were of the opinion that these tumors subordinated to gastrointestinal tumor have limited response to HIPEC, they showed potential with a condition of valid response to chemotherapeutic agents (*18,26*). Although clinical trials related to application of HIPEC in preventing PM after srHCC were rare, previous researchers were optimistic towards CRS plus HIPEC for PM of HCC (*10,12,27*). A multicenter study conducted by Sanket *et al*. demonstrated that it was a safe and effective approach especially for patients who underwent CCR 0-1 resections. The median OS could reach 46.7 months, whereas the projected RFS could reach more than 3 years (*12*). Tabrizian *et al.* counted CRS with or without HIPEC in patients with PM of HCC (*11*). However, they concluded that the median OS was only 35.6 months even in CCR0-1 group. After that, Hung *et al.* (*10*) also

confirmed the safety and effectiveness of HIPEC. These clinical trials formed the basis of application of HIPEC in HCC. In the present study, we collected candidates with srHCC with high risk of PM. Our findings are also complementary to previous studies. In the 16 months of median follow-up, only one patient died, attributed to cachexia. We highlighted median local peritoneum RFS was 12.3 months. Most studies of srHCC have shown the PM rate from 20–50% (*28,29*). Since our study was small-scale and selected for high risk of PM after srHCC, it showed a modest result in MMC-based HIPEC. As we all know, a small sample size can easily induce type II errors and result in false negative results. However, this study identified the feasibility and safety of MMC-based HIPEC procedure for srHCC, which can potentially be widely adopted in clinical practice. Larger scale research could be sponsored to further explore the real role of MMC-based HIPEC on srHCC.

In addition to the widespread concern of tumor types in the application of HIPEC, rational chemotherapeutic agent selection has been explored as well. Traditional MMC-based HIPEC regiment had proven efficacy in a Netherland's trail (*30*). In addition, OX short time perfusion has also been developed in the PRODIGE 7 trial (*ClinicalTrials.gov* identifier NCT00769405) (*31*). Notably, lower agent activity of OX in the peritoneal cavity was found (*30,32*). Further recent study also highlighted the limitation of OX-based HIPEC and superiority of MMC (*33*). The recent meta-analysis compared the efficacy of OX and MMC-based HIPEC in colorectal cancer (*5*). They concluded that OX and MMC possessed comparable survival, but OX had higher morbidity with major complications (*5*). Furthermore, several publications demonstrated that OX might have a higher risk of postoperative hemorrhage (*15*), which could cause major and even life-threatening complication for major hepatectomy. MMC was time-consuming compared with OX. However, recently, a trial, HIPECT4 (*ClinicalTrials.gov* identifier NCT02614534), will explore the efficacy of 60-minute MMC-based HIPEC in a prophylactic setting (*34*). The previous research showed that complications of HIPEC included anastomotic leakage, abdominal bleeding, pleural effusion, abdominal abscess, and fistula formation (*5*). The process of HIPEC would be disturbed with these complications, leading to limited therapeutic effect. Compared with HIPEC for colorectal tumor, the incidence of complications of HIPEC for srHCC was lower. In the present study, no adverse reactions of Clavien-Dindo Grade III or IV were encountered. On the one hand, absence of intestinal anastomosis operation prevented the incidence of anastomotic leakage, which was the main complication of HIPEC. On the other hand, drug choice of MMC conferred more safety properties. Fortunately, there were no patients with observed abdominal bleeding. Abdominal bleeding was life-threatening for srHCC patients with low levels of hemoglobin, which was thought to be related to the coverage of raw surface (*5*). Hompes *et al.* (*16*) indicated that MMC had a high propensity for EAC, including neutropenia and leucopenia. They showed that up to 39% of patients could suffer from neutropenia (*35*). Melissa *et al*. demonstrated that MMC could also cause interstitial lung disease and acute respiratory distress syndrome (ARDS) (*35*). Fortunately, in the present study, we have not found any adverse reactions related to the above, so far.

MMC, alkylating chemotherapeutic agent, interfered with DNA-synthesis and non-cycle dependent (*36,37*). MMC could reach a high intraperitoneal concentration with low systemic absorption due to large molecular weight (334.3 Da). The cytotoxicity could be amplified by hyperthermia (*38*). In addition, MMC was popular in locoregional treatment of HCC, namely c-TACE and HAIC (*8*). Historically, Gruber-Rouh *et al.* (*39*) and Achenbach *et al*. (*40*) performed TACE using mitomycin and lipiodol. A recent systemic review showed of the 52 articles on TACE, 8% used MMC (*41*). MMC could serve as the most popular component in double and triple chemotherapeutic strategy in TACE. However, some research declared that TAE had comparable efficacy with TACE in 3 recent randomized control trials. Among those, Chang *et al*. used cisplatin (*42*), whereas Kawai *et al.* used doxorubicin (*43*). In this regard, there has been no evidence to prove a limitation of MMC in TACE. Additionally, it has been shown that MMC is preferentially stimulated by hypoxic tumor cells to produce cytotoxic metabolites (*44*).

Of note, as far as we know, it was the first trial focused on MMC-based HIPEC in srHCC. Historically, there was only one retrospective study that highlighted use of HIPEC in srHCC (*45*). However, they concluded negative results. This is possibly caused by 5-fluorouracil administrated in the HIPEC process. 5-FU is a nucleoside metabolism inhibitor and cell cycle specific aimed at S phase (*46,47*). Theoretically, cell cycle-specific agents are modestly suitable to limited duration of HIPEC (30–120 min) (*38,47-49*).

In conclusion, MMC-based HIPEC showed safety and feasibility for srHCCs, although it was limited by the modest result since it's a small-scale sample and the absence of a comparator group. Larger scale research should be continued. Therefore, we would conduct a randomized clinical trial (NCT05544253) highlighted by the prophylactic role of MMC-based HIPEC on PM of srHCCs. We believe that the results of this study could support further investigations.

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

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**Address correspondence to*:
Jiwei Huang, Division of Liver Surgery, Department of General Surgery, West China Hospital, Sichuan University, No. 37 GuoXueXiang Road, Wuhou District, Chengdu 610041, China.
E-mail: huangjiwei@wchscu.cn

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# The role of community nurse in the implementation of health policy for the elderly in Thailand

Kyoko Sudo[1,*], Shinichiro Noda[1], Jun Kobayashi[2], Pongthep Wongwatcharapaiboon[3], Utaiwan Sakolwasan[4], Kenzo Takahashi[5,6]

[1] Bureau of International Health Cooperation, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Graduate School of Health Sciences, University of the Ryukyus, Okinawa, Japan;
[3] Nan hospital, Nan, Thailand;
[4] Nae Fah Luang Hospital, Chiang Rai, Thailand;
[5] Graduate School of Public Health, Teikyo University, Tokyo, Japan;
[6] Department of Pediatrics, Navitas Clinic Kawasaki, Kanagawa, Japan.

**Abstract:** In the implementation of the policy for the elderly, the nurses who have the competency to pull out their potential power to continue living with several stakeholders' support are required to provide care in the community. Community nurse in Thailand has the responsibility to deliver adequate medical care and also social care for the elderly. The study aimed to identify the role of community nurse in the implementation of Thai health policy for the elderly. Codes regarding the role of community nurse in the implementation of Thai health policy for the elderly were extracted from descriptive data interviewed with 15 policy implementors in Thailand. The codes were categorized by similarities using thematic analysis. The role of community nurse was 16 categories and 102 codes out of factors promoting implementation of Thai health policy for the elderly, with 27 categories and 416 codes. The main roles were Coordination, Service delivery, and Monitoring and evaluation, composing seven categories and 45 codes, eight categories and 51 codes, and one category and six codes, respectively. It was conspicuous in coordination mechanisms, especially between the organizations and disciplines in providing Primary Health Care. Both health promotion activities and medical treatment were crucial roles for community nurses. The role of community nurse was one of promoting factors of Thai health policy for the elderly. The community nurse acts as a lubricant between the hospital and the community, which means that the community nurse implements seamless service delivery for the elderly integrating medical care and welfare.

***Keywords*:** community-based integrated care system, Japan, primary health care

## Introduction

By 2050, the elderly population in the world is estimated to be double the current figure (*1*). As a global issue, ageing is not only limited to developed countries but also affects low- and middle-income countries in Asia. Moreover, for achieving universal health coverage (UHC), orienting to the needs of the elderly is essential (*2,3*). World Health Organization (WHO) advocates an approach to prevent disease, slow the decline of physical and mental capacity due to ageing, and maximize the use of existing physical and mental capacity complemented by the residential environment. Integrated Care for Older People (ICOPE) is a system in which health care and long-term care are integrated and service providers share the same goal of providing services to the elderly in the community (*4*), with the primary service provider being nurses (*5*).

Japan is expected to contribute internationally because of its rich experience in the field of health policy for the elderly. In particular, Japan has expressed commitment to achieving UHC in the Asian region and is working to strengthen relations through "Asia Health and Wellbeing Initiative" (*6*). Many Asian countries including Thailand have shown an interest in the Japanese elderly care system and service delivery, and projects transferring Japanese long-term care training skills such as home care, rehabilitation and services in nursing homes to Thailand are being developed (*7*). Thailand is promoting a community-based health policy for the elderly by continuing to provide Primary Health Care (PHC), which has already been revered for its dramatic improvement of health condition (*8*). Our previous study comparing implementation of health policy for the elderly among some Asian countries shows that the effectiveness of service delivery for

the elderly in Thailand has been based on PHC (*9*). PHC is an approach that guarantees community peoples' proactive participation and the right to self-determination, and that encourages them to solve problems equally through their own efforts. Japan's health policy for the elderly, such as the Community-based Integrated Care System focusing on self-help and mutual assistance, is also consistent with the concept of PHC (*10*). Therefore, Thailand's implementation of health policy for the elderly may serve as a reference for Japan.

Japan has developed integrated care for the elderly. In Japan, the municipality represents the insurer of long-term care insurance, and the government requires the local government to take responsibility for implementing the community-based integrated care system successfully in accordance with the unique characteristics of each community. Community General Support Centres, which are central to the system implementation, were established by the Long-Term Care Insurance Act (Act No.123) and their operation is entrusted to the municipality under Japan's Ministry of Health, Labour and Welfare. Community General Support Centres have a predominant role in preventive care management, general consultation, rights advocacy, and comprehensive continuous care support for the elderly and their families (*11*). There are almost 4,300 centres nationwide, of which 30% are managed by municipal offices directly, and the others by the private sector or non-profit organisations (*11*). The Japanese medical care insurance system allows users the freedom to choose the services and service providers based on their personal circumstances and decisions (*12*). Long-term care insurance is based on the same universality as medical care and permits the use of long-term care services, regardless of whether they are public or private. The government is also expanding the economic growth of long-term care services and welcomes companies in the field. To ensure these features in Japan, the essential roles of the Community General Support Centres involve the coordination and integration of diverse stakeholders, including welfare facilities for the elderly, hospitals, home care delivery companies, and municipal health offices. The centres are managed by a public health nurse, the chief "care manager", or a social worker, who are required to strengthen their role (*13*).

Thailand is one of the most aged countries in Southeast Asia, the population aged over 65 years in 2021 is estimated at 15% (*1*). The Thai government formulated the first National Plan for Older Persons (1982–2001) in 1982, influenced by the "Vienna Plan" endorsed by the United Nations General Assembly (*14*). It has been amended into the Second National Plan for Older Persons (2002–2021) (*15*) for advancing a community-based comprehensive care service for the elderly (*14*). The objectives of the plan include involving the community as a support resource (*15*). The plan has been implemented nationally by both local administrative offices and hospitals at the provincial, district, Tambon (subdistrict), and village levels under the supervision of the Ministry of Public Health, Ministry of Social Development and Human Security, Ministry of Interior, and the Ministry of Education (*16*). In Thailand, public hospitals under the Ministry of Public Health deliver medical treatment and easy access to healthcare. Public hospitals also encourage medical care for the elderly and the prevention of non-communicable diseases through home care. Moreover, local governments also aim to financially support community caregivers in providing home care for the elderly. A pilot long-term care programme for the elderly funded solely by taxes has recently begun (*7*). The long-term care programme is not institution-based and focuses on community-based and home care services. Regional and provincial public health offices have a responsibility to train nurses and caregivers, monitor, supervise and evaluate the programme (*17*). In the long-term care scheme, health promoting hospitals, which provide primary care, disease prevention and health promotion as the closest healthcare facilities for community people. They collect health-related data on the elderly, assess their activities of daily living by using the assessment tool based on the Barthel Index standard and classify the elderly into three groups for long-term care planning (*18*).

Health promoting hospitals are not staffed by medical doctors, and 70% of them are staffed by community nurses. Concurrently, the family care team is composed of physician, nurse, physiotherapist, nutritionist, pharmacist, health volunteer for the elderly, village health volunteer and so on, who work at the district hospital, health promoting hospitals and local administration, visit the elderly and their family at home and provide care services including treatment and rehabilitation (*17*). Health volunteers and family caregivers assume the role of key family care team members because they are also community residents expected to provide health care services to the elderly in their own daily-life context. In addition, they have ensured guidance of skills and knowledge of elderly care from community nurses (*17*). Community nurses play the role of gatekeepers making appropriate care decisions and providing treatment for patients who access health care in the community (*18*). Previous studies have clarified that community nurses' role focused more on a disease-oriented approach (*19,20*). Since Thailand's health policy for the elderly is community-based and is designed to focus on supporting their daily living comprehensively, it is significant to clarify the role of community nurses who are the principal responsible for elderly care in the Thai community.

The study aimed to identify community nurse's role in implementing health policy for the elderly in Thailand. Findings from a specific country's attempts

to improve the quality of elderly care might be globally valuable.

## Materials and Methods

### *Study design*

A qualitative descriptive design was used.

### *Interviewers*

Thai and Japanese researchers fluent in English conducted 10 interviews in Thai and English. Both of those were registered nurses, had learned theory and methods in graduate school and already experienced a qualitative research process. The other Thai researcher supported and refined the interview when clarification or explanation was needed.

### *Study sites*

The study sites in Thailand were selected for their active engagement with community-based elderly care services according to the study purpose. The health system in Thailand is the same in all provinces and, in the Bangkok metropolitan is quite different from the others and difficult to generalize in not reflecting on the entire Thai health policy. Therefore, one out of 76 provinces except the Bangkok metropolitan administration was selected based on the Thai researcher's suggestions. The selected province is one of the leaders in providing home care independently and had been awarded for geriatric care. It is located in a mountainous area where residents are primarily engaged in agriculture, and the percentage of elderly residents over 60 years was 17% (*21*).

### *Participants*

Participants were implementers under Thai health policy for the elderly (Table 1), and were selected purposively with advice from a responsible person in each division.

In Thailand, one officer was recruited from the Ministry of Social Development and Human Security at the provincial level, one from the Ministry of Interior at the district level, and two from the Ministry of Social Development and Human Security and the Ministry of Interior at the Tambon level. The officers at each level were responsible to manage and organize, as well as to conduct activities in a non-medical field such as social and welfare. The healthcare providers including a medical doctor, a nurse, and a public health officer conducted direct interpersonal services in medical and disease prevention. Medical doctors only worked for provincial and district hospitals, and were directors of the hospital. Nurses worked at provincial and district hospitals, and health promoting hospitals at the Tambon level. Public health officers, those who had a bachelor's degree in public health, were directors of health promoting hospitals. "Health volunteers" are specific in Thailand, who were community residents and trained as long-term care providers as well. All healthcare facilities provided medical care and long-term care at each level.

### *Data collection*

Semi-structured interviews were conducted in Thailand in October 2017 using the modified Policy Implementation Assessment Tool (*22*), which comprises seven dimensions to evaluate the policy implementation (Table 2). Participants provided informed consent in their native language before being interviewed. All interviews were audio-recorded. The interviews in Thai were transcribed and translated into English simultaneously by a translation company and rechecked the expression in English by Thai researchers. This study was approved by the Ethical Review Committee of the National Center for Global Health and Medicine (NCGM-G-002136-00) and the Provincial Hospital Research Ethics Committee of the study site (COA No.012).

### *Data analysis*

Thematic analysis (*23*) was conducted using the qualitative data analysis software MAXQDA Plus12 (*24*). Transcribed data from Thai interviews were analysed in English with one Thai researcher and three Japanese researchers who were well experienced with thematic analysis including the interviewers. First, codes including factors promoting the implementation of Thai health policy for the elderly were extracted, and then the segments relevant to the role of community nurses were extracted and coded. In this study, community nurses

**Table 1. Participant characteristics**

| Study sites | Officer | Medical doctor | Nurse | Public health officer | Health volunteer | Number of interviews |
|---|---|---|---|---|---|---|
| Thailand $n = 15$ | | | | | | |
| Province | ✓ | ✓ | ✓ | | | 3 |
| District | ✓ | ✓ | ✓✓✓ | | | 3** |
| Tambon 1* | ✓✓ | | | ✓ | ✓✓ | 2*** |
| Tambon 2* | | | ✓ | ✓ | | 2 |

Note: *Tambon 1 was administrated under the assigned district in the province, and Tambon 2 was administrated under another district in the same province. **Conducted two individual interviews with a district officer and a medical doctor and a group interview with three nurses. *** Conducted two group interviews, the first with two officers and a public health officer, and the second with two health volunteers.

**Table 2. Sample questions**

| Theme | Questions |
|---|---|
| 1. The policy, its formulation, and dissemination | • To what extent do you think the goals and objectives address issues for the elderly?<br>• Are the goal and objectives achievable within the timeframe set out in the policy??<br>• How well was the policy disseminated to various implementing agencies? |
| 2. Social, political, and economic context | • What are (Social, Political, Economic) factors facilitate/hinder the process of implementing this policy? |
| 3. Leadership for policy implementation | • Is there support/opposition among opinion leaders or influential institutions for implementing this policy? Which? How? |
| 4. Stakeholder involvement in policy implementation | • To what extent are you involved in different departments within your office or other stakeholders?<br>• To what extent is your organization implementing the policy or involved in its implementation?<br>• Which organization could be involved to improve implementation of the policy? |
| 5. Implementation planning and resource mobilisation | • What document is guiding in implementing activities under the policy? How helpful?<br>• How would you describe the changes that this policy requires of your organization? How well is your organization adopting to the changes? |
| 6. Operations and services | • How effective is the coordination among organizations to achieve the policy's goal.<br>• Have there been positive changes/ barriers related to service delivery? What? |
| 7. Feedback on progress and results | • What institution is monitoring the implementation of this policy? What methodology? What indicators? |

are defined as nurses assigned as community nurses by the hospital, who provide care both in the hospital and in the community at each level, regardless of possessing community nurse practitioner certification. Seven dimensions of the Policy Implementation Assessment Tool were used as themes due to its well-structured questions to cover all policy implementation areas. The codes were generated regardless of each theme. Categories were defined and named based on the codes' similarity. Interpretation in the context and validity of results were confirmed over repeated discussions with analysis team members in the process.

## Results

### *The role of community nurses in health policy for the elderly in Thailand*

In total, 102 codes regarding the role of community nurses were extracted from descriptive data interviewed with 15 policy implementers, those out of promoting factors in the implementation of Thai health policy for the elderly, with 27 categories and 416 codes (Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=72*). The codes were categorized into 16 including, 1) Being a bridge to the hospital and community, health and quality of life, 2) Coordinating between the Ministry of Health and the other ministries, 3) Coordinating between hospitals and other organizations to support elderly care, 4) Following the guideline to conduct activities for the elderly, 5) Engaging the community activity negotiating with a community leader to involve the elderly, 6) Coordinating between hospitals, including health promotion hospitals, district hospitals and provincial hospital, vertically, 7) Coordinating between departments within the hospital, 8) Collaborating with Health Volunteers to obtain information of the elderly fast, easily and properly and conduct activities fit for individual health and environmental condition, 9) Conducting activities based on the elderly needs as a community member coordinating resources in the community, 10) Conducting activities for health promotion and preventive medicine, 11) Providing medical treatment focusing on the individual characteristics of the elderly, 12) Providing integrated care including treatment, rehabilitation, and health education to maintain their remaining functions after discharge from the hospital, 13) Supporting caregivers as a member of a health care team for the elderly in the community teaching skills and knowledge of care to provide necessary care at home, 14) Training the health promotion group and providing health education to the elderly group in the community not only inside the hospital to strengthen mutual support, 15) Allocating and utilizing budget for the elderly care activities, 16) Monitoring and evaluation of provided care and activities to understand the achievement and give feedback to build forward better (Table 3).

The categories showed three main roles; Coordination, Service delivery and Monitoring and evaluation. Coordination includes categories 1) to 7), Service delivery includes categories 8) to 15) and Monitoring and evaluation includes category 16). These codes were not extracted following the themes, however, community nurses' roles were revealed conspicuously in "Stakeholder involvement in policy implementation" and "Operations and services" based on themes of the Policy Implementation Assessment Tool (Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=72*.

### *The role of community nurses: Coordination*

Coordination consisted of seven categories and 45 codes.

**Table 3. The role of community nurse in Health policy for the elderly in Thailand**

| Category | # of Codes ($n$ = 102) | Representative code |
|---|---|---|
| 1) Being a bridge to the hospital and community, health and quality of life | 6 | • Disseminate health information that nurses have and interpret it to the elderly for better understanding. |
| 2) Coordinating between the Ministry of Health and the other ministries | 4 | • Coordinate to incorporate among ministries and departments focusing on both health and the quality of life |
| 3) Coordinating between hospitals and other organizations to support elderly care | 17 | • Support the elderly club receiving financial and physical support from the private organization |
| 4) Following the guideline to conduct activities for the elderly | 2 | • Arrange the activities to fit in a community context following the guideline |
| 5) Engaging the community activity negotiating with a community leader to involve the elderly | 5 | • Ask the village leader to invite the elderly who has no social contact and negative participation in the activities to the group |
| 6) Coordinating between hospitals, including health promotion hospitals, district hospitals and provincial hospital, vertically | 4 | • Provide care for complicated and difficult cases with the team to utilize the elderly's data transferring from the provincial hospital where he/she was hospitalized |
| 7) Coordinating between departments within the hospital | 7 | • Conduct regular meetings in the hospital to connect the nursing department and patient care team such as orthopaedics, psychiatrist, obstetrics, surgery |
| 8) Collaborating with health volunteers to obtain information of the elderly fast, easily and properly and conduct activities fit for individual health and environmental condition | 4 | • Have a meeting with health volunteer to discuss the case assigned and share information about elderly needed care in the community |
| 9) Conducting activities based on the elderly needs as a community member coordinating resources in the community | 10 | • Utilize retirees for vocational training in the elderly club in the community |
| 10) Conducting activities for health promotion and preventive medicine | 16 | • Focus on prevention of non-communicable diseases which are the main cause of health problems for the elderly utilizing the linkage between the outpatient department and community medicine department including home visit |
| 11) Providing medical treatment focusing on the individual characteristics of the elderly | 7 | • Prepare medical equipment such as oxygen, suction and so on for the bedridden elderly patient at home in the health promoting hospital |
| 12) Providing integrated care including treatment, rehabilitation, and health education to maintain their remaining functions after discharge from the hospital | 4 | • Make a discharge plan together with the elderly him/herself, nurses, doctors, physiotherapists and family caregivers by a hospital nurse |
| 13) Supporting caregivers as a member of a health care team for the elderly in the community teaching skills and knowledge of care to provide necessary care at home | 5 | • Teach caregivers how to support activities for daily living such as cleaning up the body, aiding in eating and taking medicine |
| 14) Training the health promotion group and providing health education to the elderly group in the community not only inside the hospital to strengthen mutual support | 2 | • Train the health promotion group in the community to decrease the number of elderly with chronic diseases |
| 15) Allocating and utilizing budget for the elderly care activities | | • Consider additional financial support to improve the environment |
| 16) Monitoring and evaluation of provided care and activities to understand the achievement and give feedback to build forward better | 3<br>6 | • Evaluate the result using data, the prevalence rate of hypertension and diabetes, the incidence of aspiration pneumonia and fall accidents after hospital discharge |

Several coordination types included inter-ministries, hospital-other organizations, in the community, inter-hospitals and inter-department within the hospital.

Community nurses make it so the elderly could receive services in both the hospital and community and make it easy to use local communication. They try to develop one community to minimize the personal burden and to have a quality of life for the elderly. They provide information when the elderly in the community do not recognize what they need. "We are a nurse. Ageing is a part of their life. We are going to coordinate with the hospital to do what you can contact. We use health information that we have in hand so that we can talk with them". *(Nurse, District hospital)*

Community nurses have recognized who is the community leader and have a dialogue with them utilizing the opportunity when they come to the health promoting hospital. Dialogue between community nurse and community leader has been conducted closely and cultivates the community culture through health promotion activities for the elderly. "We have three community leaders and recognize who is the leader in the community. I sometimes feel close to the residents". *(Nurse, Health promoting hospital, Tambon)*

Community nurses working in the hospital, to conduct continuous care in the community, are involved in the hospital community care team, and consult and have discussions regularly with specialists inside the hospital. Provincial/district hospital and health promoting hospital share the health status information of elderly residents to provide needed care in the community. "We conducted collaboration with the psychiatric doctor, orthopaedics-surgery, physiotherapist, nutrition, and nursing using a meeting once or twice a month". *(Nurse, Provincial hospital)*

Simultaneously, community nurses work with other local organizations and private sectors as well not only to enhance service delivery but also to solve facing barriers

to service delivery. "In the case of the poor, I asked to support him to NGO and collaborated with other organizations to take a rehabilitation, then I bought a bed for nursing care". *(Nurse, Health promoting hospital, Tambon)*

*The role of community nurses: Service delivery*

Service delivery consisted of eight categories and 51 codes. Service included both prevention and health promotion, and medical treatmen. Moreover, resources of service delivery were health professionals, health volunteers, caregivers and the elderly themselves as human resources and budget.

Community nurses conduct a regular meeting with health volunteers to share information about mainly health condition of the elderly. Moreover, community nurses pay close attention to cultivating health volunteers according to the community needs.

Community nurses intentionally make an elderly group in the community to have more social connection. They involve community leaders in the elderly club to have more chances to participate in the community group such as teaching school for the younger generation, disabled elderly support and prevention of depression. They coordinate financial support to the community group from the local administration office.

Conducting activities for health promotion and preventive medicine were 16 codes, that focus on more elderly's independent life in the community. Based on three categorized health conditions evaluated by community nurses, they conduct adequate health promotion activities for each condition. "Our goal is to promote quality of life (for the elderly) and promote our profession as well. There is a life (of the elderly) in society. We think that the activities will give them a good quality of life on all sides". *(Nurse, Health promoting hospital, Tambon)*

Community nurses always try to make the elderly go out of the house conducting activities such as exercise, health lectures, craft work and so on. There is a side purpose to check and observe health conditions of the elderly through the activities when community nurses conduct health promotion activities. "Most of our elderly will stay home, they will not go out and work at home. For synthetic information (about the elderly), we have to take him/her out of the house". *(Nurse, Health promoting hospital, Tambon)*

Some hospitals conduct a special outpatient department for the older person. Community nurses also connect to health promotion groups in the community and ask them to support maintaining the medical treatment of the patient, such as medication compliance for non-communicable diseases and remind them of an appointment to see a doctor. Community nurses provide services as team members of community care after discharge from the hospital, it is mainly community nurses in district and provincial hospitals. "… cardiovascular disease patient hospitalized today, and maybe one week improve and discharge. Before discharge, we conduct a discharge plan with nurses and other department specialists. Then, we send the discharge plan to the lower level hospital through the system". *(Medical doctor, Provincial hospital, Province)*

Community nurses support caregivers, the majority of those are family caregivers, and train them to provide better care to the elderly at home as well. "Caregiver training …… in the matter of long-term care. We give the knowledge to the caregiver on how to treat their family bedridden". *(Nurse, Health promoting hospital, Tambon)*. "Bedridden elderly at home get better care with caregivers, who help us to take care of the elderly. But first, we did not provide services as maximum encouragement. With the caregiver, nurses can go to see him getting better". *(Public Health Officer, Health promoting hospital, Tambon)*

The budget is the incentive to conduct activities for community nurses. Community nurses arrange funding and its allocation because the budget from the government's long-term care scheme is a small amount. They sometimes use their own hospital budget to improve the environment for the elderly.

*The role of community nurses: Monitoring and evaluation*

Monitoring and evaluation consisted of one category and six codes. Community nurses monitor and evaluate input, output, outcome and impact of their activities qualitatively and quantitatively. "As a result of last year, the number of new cases of hypertension and diabetes patients was zero, Bedridden elderly had neither bedsore nor aspiration pneumonia, and there is no fall accident of elderly in the community". *(Nurse, Provincial hospital, Province)*

**Discussion**

The purpose of this study was to identify the role of community nurses in health policy for the elderly in Thailand through semi-structured interviews with policy implementors at several administrative levels. The first finding of this study was that the role of community nurses was the promoting factor in implementing Thai health policy for the elderly. There were three main roles extracted from the interviews, and the coordination mechanism between the organizations and disciplines was conspicuous.

In this study, the Policy Implementation Assessment Tool was used. This aims to assess the extent and nature of policy implementation, to identify facilitators for and barriers to policy implementation, and to inspire dialogue and renewed commitment on the way forward (*22*). Among 416 facilitators extracted from Thai health

policy for the elderly, 102 codes were relevant in the role of community nurses, showing a nonnegligible number. This means that community nurses are one of the principal implementors of Thai health policy for the elderly. According to the dimensions that influence policy implementation, it could be said that community nurses implement their role in multiple dimensions comprehensively, whereas the appearance of community nurses' role in the dimensions was unbalanced, thereby suggesting the weight of community nurses' role in elderly care.

The three main roles – Coordination, Service delivery, and Monitoring and evaluation –extracted in this study were shown in the competency of Family and Community Nurse (FCN) in US and Europe (*25,26*), in which FCNs collaborate closely with other health workers, provide care based on evidence, conduct activities for health promotion and disease prevention such as screening, health behaviour change and medical recommendations for managing chronic diseases. This study indicated that these roles of community nurses contribute to PHC settings in the Asian context.

Through the entire data, the interviewee as a policy implementor described consistently not only health but also the quality of life of the elderly. It means that health is necessary for life but not all of life. Therefore, coordination was highlighted as a community nurse's role in policy implementation. "*Being a bridge to the hospital and community, health and quality of life*" and "*Engaging the community activity negotiating with a community leader to involve the elderly*" were direct linkages between the provider and the elderly as a recipient, and other coordination linked to the elderly indirectly. Moreover, "*Following the guideline to conduct activities for the elderly*" would be a part of accountability for the policy, passing a message of elderly care policy to the community. Community nurse's role is the most important to involve sectors except the health field in community-based elderly care. Opinion leaders and influencers are always both facilitator and hinderer of policy implementation. Community nurses were focused on the group more than the individual to strengthen community cohesion. In the Thai context, that is high respect for the dignity of older people and one's virtues as social norms, there is no opposition to health policy for the elderly. Community nurses make the best use of this. It is necessary to keep in mind many more difficulties in the multi-ministerial approach although Thai health policy for the elderly is implemented under a multisectoral approach with the Ministry of Public Health, Ministry of Social Development and Human Security, Ministry of Interior, and Ministry of Education. However, without these coordination mechanisms, satisfactory care for the elderly could not be achieved. In addition, the multidisciplinary team care approach in institutions has been significant in some areas (*27,28*). Elderly care is fit for multidisciplinary care due to the variety of symptoms and comorbidities, individual differences and consideration of physical, psychological and social support. Even inside the hospital, a multisectoral approach beyond the department is not easy.

Service delivery could be explained by types, ways and targets. The first was "*Conducting activities for health promotion and preventive medicine*". PHC is based on community needs and focuses on health promotion and interventions from prevention to treatment (*29*). Community nurse's role in Thailand was reconfirmed focusing on health promotion based on the PHC concept. "*Conducting activities based on the elderly needs as a community member coordinating resources in the community*" was also reflected in PHC, which is rooted in solidarity and participation (*30*). Community nurses support conducting their own PHC.

The second type was "*Providing medical treatment focusing on the individual characteristics of the elderly*". Community nurses, who have the knowledge, skills, and competencies to tailor care to individual needs, are required to provide evidence-based care (*30*). That is why community nurses should be health professionals to give proper medication and assessment including checking vital signs, physical and psychological changes, as well as the surroundings of the elderly, such as family members, friends, the living environment and so on. From another point of view, focusing on the way of providing treatment, it was important that "*Providing integrated care including treatment, rehabilitation, and health education to maintain their remaining functions after discharge from the hospital*". It means continuous care and observation, such as compliance with medication and health assessment. Because it tends to struggle to deliver continuous care after discharge from the hospital, the role of community nurses working between the hospital and the community is crucial. In Japan, a special unit arranged to support life in the community and continuing care after discharge has been prepared in the hospital, which assigns the nurse as a manager (*31*). Community nurses had a similar role to these nurses in Japan's system.

Next, the targets supported by community nurses in service delivery, who were mainly health volunteer and caregiver, were extracted. For the elderly especially those suffering from diseases, multiple barriers are faced in the process of returning to community life. Community nurses had the role of *"Supporting caregivers as a member of a health care team for the elderly in the community teaching skills and knowledge of care to provide necessary care at home*". Informal caregivers such as family members are the main stakeholders of elderly care at home in many countries. In Japan, the care burden of family caregivers and long hospitalization periods for respite purposes had been a social issue by 2000, when long-term care insurance was introduced (*32*). Currently, there is significant

evidence for supporting caregivers in elderly care (*33,34*). It is a featuring point that the caregivers could also be objects of service delivery, not only direct care for the elderly, in the role of community nurses. In addition, "*Collaborating with Health Volunteers to obtain information of the elderly fast, easily and properly and conduct activities fit for individual health and environmental condition*" is also a part of the multidisciplinary team care approach. Health volunteers have a role in conducting a very close connection between the community and the hospital because they are community residents. On the other hand, issues in implementation except for health professionals have been raised, for instance, in the delegation of medication administration from registered nurses to non-registered support workers within community settings (*35*). This type of collaboration, in short, hospital-community collaboration, could be actively applicable in Japan's system considering regulatory factors.

"*Allocating and utilizing budget for the elderly care activities*" was also the basis of service delivery. Budgeting is supposed to be complicated although this study did not clarify its mechanism. However, community nurses are required to manage the budget for effective activities, which is not only for the elderly, when they are responsible for the health promoting hospital.

The last main role was Monitoring and evaluation, "*Monitoring and evaluation of provided care and activities to understand the achievement and give feedback to build forward better*". It pointed out evidence-based community nurses' activities that are required. Community nurse practitioner is required to analyse the situation, design a nursing programme, strengthen family management, improve the ability to work with the community, teach skills, develop information systems and digital technology, lead organizations and systems, have morals and ethics, encourage analytical thinking, improve health conditions and evaluate health outcomes (*36*). Community nurses utilize collected data and monitor it to find an approach point and to show the value of their activities as well.

The limitation of this study was that the results were collected in one province and district even though the health system in Thailand is the same in all provinces. This study was conducted in the selected province, which engages actively with community-based elderly care services according to the research purpose. When research in a whole country is conducted, the data could be more robust due to including the diversity of experiences in Thailand.

In conclusion, the role of community nurse in Thailand was one of the promoting factors of Thai health policy for the elderly. Community nurse is acting as a lubricant between the hospital and the community. Community nurse implements seamless service delivery for the elderly integrating medical care and welfare. This finding indicated that coordination with different disciplines and beyond the organizations is needed more for healthcare service delivery for the elderly.

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**Address correspondence to*:
Kyoko Sudo, Bureau of International Health Cooperation, National Center for Global Health and Medicine, 1-21-1, Toyama, Shinjuku-ku, Tokyo, 162-8655, Japan
E-mail: ksudo@it.ncgm.go.jp

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# Development of an educational program for healthcare professionals who provide appearance care for patients with cancer: Feasibility study of an e-learning program

Keiko Iino[1,*], Namiko Nagaoka[1], Shigeaki Watanuki[2], Chikako Shimizu[3], Keiko Nozawa[4], Shoko Toma[5], Ayako Mori[6], Taeko Shimazu[7], Tomoko Sato[8]

[1] Division of Adult Nursing, National College of Nursing, Japan, Tokyo, Japan;
[2] Division of Gerontic Nursing, National College of Nursing, Japan, Tokyo, Japan;
[3] Department of Breast and Medical Oncology, National Center for Global Health and Medicine, Tokyo, Japan;
[4] Faculty of Nursing, Mejiro University, Saitama, Japan;
[5] Appearance Support Center, National Cancer Center Hospital, Tokyo, Japan;;
[6] Department of Nursing, National Cancer Center Hospital, Tokyo, Japan;
[7] Graduate School of Health and Welfare Sciences, International University of Health and Welfare, Tokyo, Japan;
[8] Department of Nursing, National Center for Global Health and Medicine, Tokyo, Japan.

**Abstract:** This study aimed to evaluate the feasibility and utility of an e-learning training program to improve healthcare professionals' knowledge about providing appearance care to patients with cancer. Healthcare professionals who provide appearance support were invited to participate voluntarily and complete a survey before and after the program. Participation request letters were distributed to 133 individuals, including 75 from four facilities invited via professional connections, and agreed to participate in the study and 58 participated in the National Cancer Center's appearance care training and indicated an interest in participating in the study. The 100 participants (75.2%) included 96 females, with an average age of 40.5 years. The participants reported high levels of satisfaction with the program, where more than 90% responded "satisfied" or "somewhat satisfied" and eager to use the content they learned in the program when they returned to their workplaces. However, the participants identified several barriers to applying their newly acquired knowledge including lack of knowledge (about 80%). Participant knowledge scores about appearance support were significantly higher after program participation. The survey results indicated the high feasibility of the e-learning program through improved knowledge about appearance care and high satisfaction with the program. The program needs further improvements for its practical utility.

***Keywords*:** appearance care, cancer therapy, e-learning, pretest-posttest design

## Introduction

Patients undergoing cancer treatment experience a variety of appearance changes, and these appearance changes are among the most painful symptoms of adverse events for patients (*1*). Appearance care was identified as one of the issues to be addressed in the Third Basic Plan for the Promotion of Cancer Control (*2*), as "build a society in which people can live with dignity and peace of mind".

Since 2012, we have been holding training sessions for medical staff at designated cancer care hospitals in order to improve their skills in appearance care, and we are constantly improving the content of these sessions.

In order to obtain basic data regarding the establishment of an appearance care training program, this research group conducted a survey to clarify the actual conditions and issues of appearance care (*3,4*). The results indicated that medical care providers implement various types of appearance care, and that although they feel the need for support, they are not confident in their support.

Furthermore, as requests for training in appearance care, the participants expressed a desire for more training opportunities and locations, such as "more training opportunities" and "training sessions should be held in rural areas", "training should be provided to multiple professions" in order to take on the role in team medicine, and "hope for an e-learning format" that is easy for male medical professionals to learn, since most of the participants in transportation, repetitive learning, and training sessions are women.

This research group has conducted face-to-face

training sessions in the past, but in light of the background of the spread of e-learning training development as a form of learning to improve professional competence, we have been considering the establishment of an e-learning training program to expand learning opportunities.

Prior studies have reported that e-learning provides learning opportunities, convenience and economy, a change to a learner-centered learning style, and high levels of learner motivation and satisfaction (*5-8*) as advantages, although the effectiveness of e-learning has not been fully verified.

The primary objective of this study was to assess the feasibility of an e-learning program developed by the research group to improve the abilities of healthcare professionals who provide appearance care to cancer patients. As a secondary objective, we further examined the participants' satisfaction and perceived usefulness of the program.

The results will be used as the basis for building an e-learning program, and will be used to develop a full-scale national-level training program in the future.

## Materials and Methods

*Definition of terms*

Appearance support: Support from healthcare professionals for patients with changes in appearance (nails, skin disorders, hair loss, *etc*.) associated with cancer treatment.

*Research subjects*

This study is a feasibility study of an e-learning program on appearance care. The survey period is from September 2019 to December 2019.

The eligibility criteria for the study subjects were as follows: *i*) nurses, physicians, and pharmacists who provide appearance care from the four designated cancer care hospitals; *ii*) participants of the appearance care training organized by the Appearance Center of the National Cancer Center Hospital.

*Subject registration*

The method of enrolling the subjects was to request the selection of research candidates to each department where nurses, physicians, and pharmacists belonged at the base hospital for cancer treatment. In total, request letters were sent to 50 nurses, 10 physicians, and 20 pharmacists. Request letters were given to 58 nurses participating in the Appearance Support Workshop (leadership training), and they were asked to participate on a voluntary basis. The total number of participants was 133.

The request letter included the URL and two-dimensional bar code for access to the e-learning site linked to the workshop's website, as well as a login ID and password, which were made available to participants who voluntarily agreed to view the site.

*Sample size*

The number of subjects was assumed to be evaluated by repeated measures for each of the above three selected optional topic groups.

Generally, a sample size of $n$ =12 or more cases per group is recommended for studies to reduce variability and increase precision about the mean and variance (*9*). The acceptance rate was estimated to be about 60%, and the attrition rate about 10%, for a total of at least 75 participants (25 per group).

*Development of contents of e-learning materials about appearance care* (Table 1)

Based on the literature review (*3,4,10-12*), the items and contents of the educational materials were drafted by the research team (nurses, psychologists, cosmetic specialists, and physicians) and revised based on feedback from cancer survivors (one male and two females in their 30s to 50s).

The process of creating educational materials was as follows: PowerPoint materials were created, narration was recorded and converted to video, and the video was made available to the target audience in a limited public format on YouTube.

The content of the structure included general discussion and care (prevention, care along the course of the disease, care of characteristic symptoms, *etc.*). The course was divided into Step I, which is general-purpose, Step II, which is highly specialized, and Step III, which is related to medical procedures and the use of cosmetic products, respectively. The required "Concept of Appearance Care Step I" was followed by a format in which students must select at least one of "Drug Therapy (Hair Loss) (Skin and Nail Disorders)" and "Radiation Therapy Step I". Other than that, Step II/III and surgical therapy, which can be studied in more detail, were designated as "recommended optional viewing" (Figure 1).

It is recommended that the viewing time for each video in the program be broken down by detailed content, as it is said that an adult can only concentrate on learning for 10-15 minutes (*13*) and can listen to a story while retaining memory for about 20 minutes (*14*). Therefore, the videos in this program were planned to be basically divided into 15-minute increments on each topic. The required items were to be taken first, and after that, the participants were free to choose any of them, and the program could be interrupted at any time and split up during the course period.

The e-learning site was created using Google Sites, with links to the YouTube-converted video and survey questionnaire. The survey form was created in Google

**Table 1. Contents of e-learning about appearance care**

| Training content of Appearance Care [Running time for each step] |
|---|
| Concept of Appearance Care<br>[Step I = 22 min 04 sec; Step II = 24 min 40 sec; Step III = 30 min 19 sec)<br>●What is appearance care by medical professionals<br>●Types and processes of major appearance changes associated with cancer treatment<br>●Steps in appearance care |
| Drug therapy (hair loss)<br>[Step I: 10 min 04 sec; Step II: 19 min 51 sec, Step III: 9 min 47 sec]<br>●High risk of hair loss, areas and processes of hair loss<br>●Psychological characteristics of patients associated with hair loss and their life, work, and relationships |
| Drug therapy (skin and nail disorders)<br>[Step I: 19 min 27 sec, Step II: 25 min 07 sec, Step III: 14 min 25 sec]<br>●High risk of skin and nail disorders, process of change<br>●Characteristics of patients with skin and nail disorders and their life, work, relationships, *etc*.<br>●Appearance care provided by healthcare professionals for skin and nail disorders |
| Radiation therapy<br>[Step I: 15 min 43 sec, Step II: 21 min 36 sec]<br>●Hair loss and skin types associated with radiation, high risk, process of change<br>●Effects of radiation-induced changes in appearance on life, work, and relationships<br>●Appearance care by healthcare professionals for radiation-induced hair loss and skin disorders |

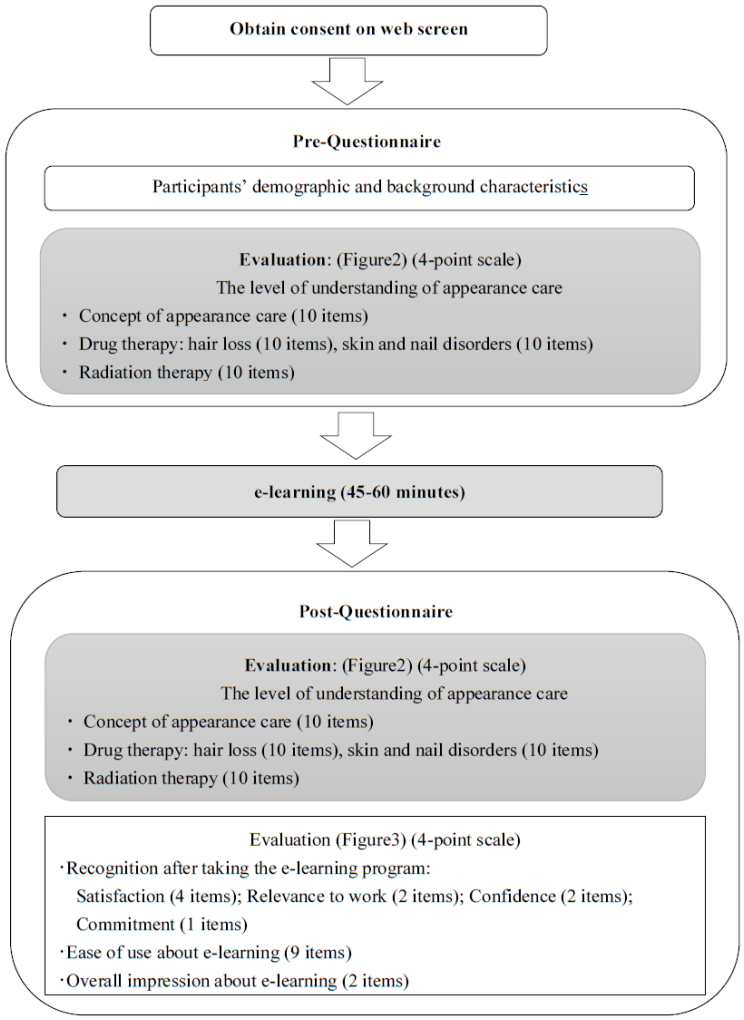


**Figure 1. Flowchart of the study process: Items and timing of evaluation regarding the e-learning program for appearance care training**

Forms, and the data was saved in Google Spread Sheet and downloaded in Excel format.

*Survey questionnaire*

The items included in the survey questionnaire were as follows:

(1) Participants' demographic and background characteristics

The participants were asked to respond to the questions regarding gender, age, and *etc.* by filling in the actual numbers or by choosing one of the options.

(2) Evaluation of the feasibility of the e-learning program

The feasibility of the e-learning program was evaluated by the level of participation, the perceived usefulness and satisfaction of e-learning, and increased levels of understanding about appearance care.

*i*) *Evaluation of e-learning participation*

In order to evaluate the feasibility, satisfaction and usefulness of the e-learning, the research team created an evaluation form for up to the second of the four stages, referring to Kirkpatrick's "4-stage evaluation method for training" (*15,16*).

Level 1: "Reaction" consisted of 4 items of "satisfaction" and 2 items of "relevance to work", with a 4-point scale: 1 for "Disagree", 2 for "Somewhat disagree", 3 for "Somewhat agree", and 4 for "Agree".

The confidence and commitment (willingness to use in clinical practice) questions were 2 items of "confidence" and 1 item of "commitment", and the response format was the same 4-point scale as above.

For commitment, respondents other than "agree" were asked to respond on the same four-point scale as above to the reasons for "lack of sufficient knowledge", "lack of a department to implement what has been learned", "too busy with other work to utilize what has been learned", and "lack of surrounding support to utilize what has been learned.

*ii*) *Evaluation of the usability of e-learning materials*

The questions, which were developed with reference to the literature (*15*), were 1 item for "likability", 2 items for "reliability", 2 items for "ease of operation", 1 item for "clarity of organization", 2 items for "ease of viewing", and 1 item for "responsiveness". The response format was the same as above, with four-point scale. The "Other" category asked respondents to provide a free-writing response on points that need improvement.

*iii*) *Evaluation of the levels of understanding about appearance care*

The e-learning program consisted of: concept of appearance care (10 items); drug therapy (hair loss, 10 items; skin and nail disorders, 10 items); radiation therapy (10 items). Each item of the level of understanding ("I can explain about…") was rated on a 4-point scale: 1 for "I cannot", 2 for "I cannot, to some extent", 3 for "I can, to some extent", and 4 for "I can".

(3) Overall impressions

The response format was the same as above, with a four-point scale. The feasibility of the e-learning program was evaluated by the "degree of participation" in the e-learning program, using the number of video views, number of viewers, average viewing time, average viewing rate (viewer retention rate), and number of respondents to the questionnaire.

The evaluation of usefulness included: Level 1 "satisfaction" and "relevance to work" as an evaluation of the e-learning course; Level 2 "learning achievement" and "confidence and commitment" about appearance care; an evaluation of the easy use of the e-learning materials; and overall impressions.

The content validity of the questions was checked among the researchers. The "Perceived Comprehension" section consisted of 10 questions for each of the e-learning contents: overview, hair loss, skin/nail disorders, and radiation therapy, and their reliability was checked using Cronbach's alpha coefficient. Alpha coefficients were as high as 0.959 for overview, 0.963 for cancer drug therapy (hair loss), 0.960 for cancer drug therapy (skin nail disorders), 0.954 for radiation therapy, and 0.875 for surgical therapy.

*Analysis method*

Descriptive statistics were calculated, and pre- and post-course comparisons of perceived understanding of the content were made using the Wilcoxon signed rank sum test for the total score for each of the concepts, drug therapy (hair loss)/(skin and nail disorders), and radiation therapy. The statistical significance level was set at 5%. The main statements were extracted and analyzed based on similarities and differences.

*Ethical considerations*

This survey was conducted with the approval of the Ethics Review Committee of the National Center for Global Health and Medicine (NCGM-G-003297-00).

The survey was conducted on the web, and responses were voluntary and unsigned. As a way to ensure that individuals could not be identified, a form with an optional ID and password was enclosed with each individual package of the request letter, and respondents were asked to enter their ID and password and respond to the web-based survey. No personally identifiable information was collected as personal attributes.

## Results

*Participant characteristics*

There were 100 participants with a 75.2% response rate, including 71 (71.0%) who selected hair loss (drug therapy), 61 (61.0%) who selected skin and nail disorders (drug therapy), and 57 (57.0%) who selected radiation therapy. They selected at least one of these topics for viewing and evaluation, indicating that there were more than the expected number of participants who selected multiple topics for viewing and evaluation.

Overall participants included 4 males and 80 females with a mean (SD) age of 40.5 (16.7) years. The participants' qualifications as healthcare professionals were 80 nurses, 2 physicians, 2 pharmacists, with 16

unknown qualifications (no response).

Of the nursing staff, 38 were Certified Nurses, including 22 in cancer chemotherapy, 11 in breast cancer, 2 in cancer pain control, 1 each in palliative care, radiation oncology, and wound, ostomy and continence, and 2 were Certified Nurse Specialists. Affiliated departments included 33 in the hospital wards, 22 in the outpatient treatment centers, and 12 in the outpatient medical department (Table 2).

*Number of views and viewing time of e-learning programs*

The degree of participation was evaluated by the number of times each instructional video was played, the number of people who viewed it, and the number of people who responded to the questionnaire. The number of times each e-learning video was played and viewed by 115 times and 100 persons, respectively, for the compulsory "Introduction" and 120 times and 100 persons for the "Concept of Appearance Care Step I". Of the three optional topics, Step I had 83–95 views and 69–82 viewers, and Step II and III, the recommended optional viewing, had 29–63 views and 27–56 viewers. The average playback rate was generally in the 70% range, although some were in the 60% range, and some were in the 80% range. In all videos, there was no significant decrease in the average playback rate over time.

*The level of understanding of e-learning: pre- and post-change* (Figure 2)

**Table 2. Participants' demographic and background characteristics ($n$ = 100)**

| | $n$ | (%) | Mean ± SD |
|---|---|---|---|
| Gender* | | | |
| Male | 4 | (4.8) | |
| Female | 80 | (95.2) | |
| Age (years)* | | | 40.5±16.7 |
| Qualifications* | | | |
| Nurse | 80 | (95.2) | |
| Physician | 2 | (2.4) | |
| Pharmacist | 2 | (2.4) | |
| Total years of practice experience (years)* | | | 16.7±10.7 |
| Certified Nurse qualification* | | | |
| Certified Nurse (Details) | 38 | (45.2) | |
| Cancer chemotherapy | 22 | (26.2) | |
| Breast cancer | 11 | (13.1) | |
| Cancer pain control | 2 | (2.4) | |
| Palliative care | 1 | (1.2) | |
| Radiation oncology | 1 | (1.2) | |
| Wound, Ostomy and Continence | 1 | (1.2) | |
| Certified Nurse Specialist | | | |
| Oncology Nursing | 2 | (2.4) | |
| Department* | | | |
| Hospital ward | 33 | (39.3) | |
| Outpatient Treatment Center | 22 | (26.2) | |
| Outpatient Medical Department | 12 | (14.3) | |
| Others | 13 | (15.5) | |

*The valid responses for those variables are smaller ($n$ = 84) due to missing data.

Comparisons were made for those who responded to the pre- and post-surveys in each e-learning content. 68 (68.0%) responded to the overview, 71 (71.0%) responded to the drug therapy (hair loss), 61 (61.0%) responded to the drug therapy (skin and nail disorders), and 57 (57.0%) responded to the radiation therapy.

(1) Concept of appearance care

Sixty-eight respondents responded to both the pre- and post-answers; the median (interquartile range) pre/post for the total of 10 questions was 26 (21–31)/34.5 (29–38.75) points, higher for the post-answers ($p < 0.001$).

(2) Drug therapy (hair loss)

Seventy-one respondents answered both pre- and post-question; the median (interquartile range) pre/post for the 10-question total was 29 (22–35)/38 (32–40) points higher for the post ($p < 0.001$).

(3) Drug therapy (skin and nail disorders)

Sixty-one respondents answered both pre and post. The median (interquartile range) pre/post for the total of 10 questions was 27 (21–31)/40 (33–40) points, higher for the post ($p < 0.001$).

(4) Radiation therapy

Fifty-seven respondents answered both pre and post. The median (interquartile range) pre/post for the total of 10 questions was 25 (21–30)/36 (30.5–39) points, with the post being higher ($p < 0.001$).

*E-learning satisfaction, relevance to work, confidence, and commitment rating* (Figure 3)

(1) Satisfaction with the program and relevance to work

The majority responded positively to both satisfaction and relevance to work, with more than 70% responding positively to both.

(2) Relevance to work, confidence, and commitment

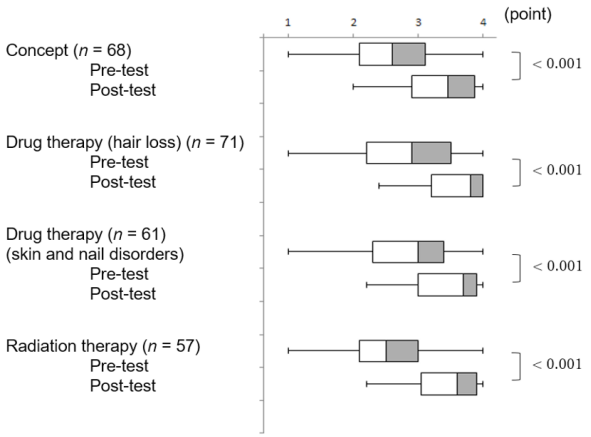


**Figure 2. The level of understanding of appearance care: pre- and post- change.** Each item ("I can explain about…") was rated on a 4-point scale: 1 for "I cannot", 2 for "I cannot, to some extent", 3 for "I can, to some extent", and 4 for "I can".

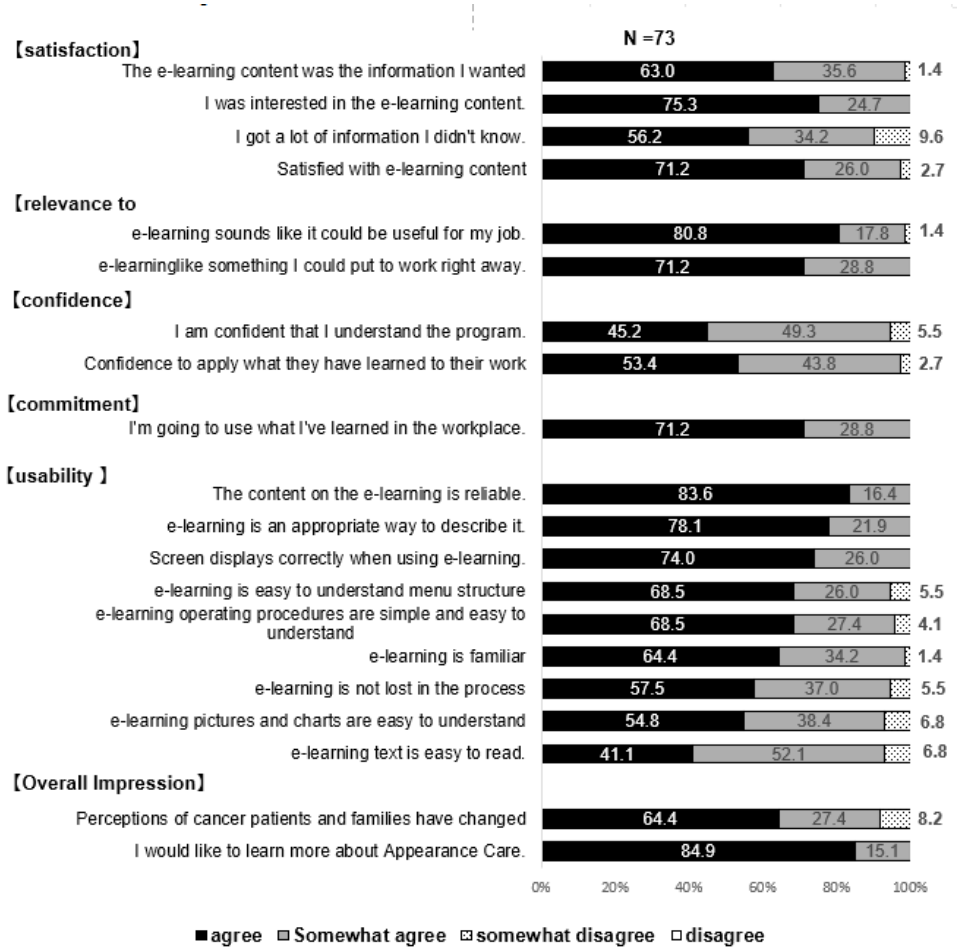


**Figure 3. Evaluation on satisfaction and utility of the e-learning appearance care (*n* = 73)**

About half of the respondents answered positively for confidence, and the majority answered positively for commitment. 21 respondents answered other than "Yes" for the use of the knowledge in the workplace, 13 (76.5%) for "Insufficient knowledge," 8 (47.0%) for "Too busy with other duties to use what I have learned," and 8 (47.0%) for "Lack of support from others to use what I have learned. 8 respondents (47.0%) answered that they "do not have enough knowledge," and 8 respondents (47.0%) answered that they "do not have the support from others to use what I have learned".

*Evaluation of the usability of e-learning materials, overall evaluation*

About 84% of the respondents answered "Yes" to the question "The content in this program is reliable".

The free comments were diverse, including: easy to understand overall, requests for improvement of the screen (font size, font style) and narration (speed, sound clutter), requests for distribution of materials, and limited Wi-fi data traffic as a viewing environment. Some of the comments included: "I would like to know more specific care", "It is easy to understand as it is linked to the number of pages in major books", "It was useful as I am often asked questions in clinical practice", and "Some contents were not helpful as they are different from the care methods used at my institution".

## Discussion

This survey was conducted as a prospective observational study among healthcare professionals already practicing in this field in order to evaluate the feasibility, satisfaction and usefulness of the e-learning program that was constructed based on the results of the previously conducted training sessions and research findings. This e-learning program was evaluated as feasible because the survey results indicated the participants' increased knowledge, enhanced perception related to their clinical relevance, and high level of satisfaction after taking the e-learning program. However, since the majority of respondents were nurses, the results of the analysis need to be interpreted in light of this when generalizing the results.

The number of participants was 100, and the response rate was high at 75.2%. The survey was conducted after confirming the number of participants with the permission of department managers, and it is assumed that many of them were interested in this field.

The following section discusses the results of the survey in terms of participation, satisfaction,

comprehension, and ease of use.

*Number of views and viewing time of e-learning programs*

The number of viewers of the e-learning videos indicated that all 100 participants viewed the required "Introduction" and "Concept of Appearance Care Step I" videos. The number of views was slightly higher than the number of viewers, indicating that some participants viewed the videos more than once, and the number of viewers was slightly higher than the number of survey respondents, indicating that some participants viewed videos other than those on the selected topics that required responses in the survey.

The average playback rate was around 70% and showed almost no decline over time, indicating that around 70% of the participants watched the material almost to the end once they started watching it. Although we had initially expected at least 25 participants for each selected theme, the number of participants for some themes far exceeded that number. Since this was an e-learning program on appearance, it can be assumed that viewers had a wide range of interests in participating in the course.

In this study, since Google Sites and YouTube were combined as a simple e-learning system, only the number of times the videos were viewed, the number of viewers, and the average playback rate were tabulated. In the future, by introducing a dedicated e-learning system (learning management system), it will be possible to grasp and evaluate individual viewing and learning situations and reflect on them in instructional planning.

*Evaluation of the e-learning program (satisfaction and comprehension)*

In terms of evaluation of the program content, the usefulness of the program was indicated by high scores for "satisfaction", "degree of participation", and "relevance to work" at "Level 1" and "confidence" at "Level 2", as well as high recognition of "commitment" in "willingness to use what was learned in the workplace".

As a training evaluation, Kirkpatrick has added a new content that is important for "Level 1", which is interest, and for "Level 2", which is knowledge, skills, and attitude change, as well as confidence and commitment, *i.e.*, "whether the trainee is confident/willing to utilize the training content" (*14,16*). The new content has been added to the current version of the training evaluation. This indicates that the importance of these factors is not only knowledge and skills, but also confidence and commitment, which are meaningless unless the trainee has the confidence and commitment and can appropriately utilize them in clinical practice. The high level of confidence, commitment, *etc.* in this study, including confidence and willingness to utilize the program in clinical practice, is a valuable finding that demonstrates the high usefulness of the clinical application of this program.

On the other hand, about 80% of the respondents answered that they "do not have sufficient knowledge", and about 50% answered that they "are too busy with other duties to use what they have learned" and "lack support from others to use what they have learned", indicating the need to acquire reliable knowledge, work environment, and support from others to apply what they have learned in the workplace. In the future, it is necessary to develop more practical programs that include not only the acquisition of knowledge, but also its application and dissemination in the workplace.

Ten questions were set for each of the following areas of understanding of the program: overview, hair loss, skin/nail disorders, and radiation therapy. However, the fact that the participants in this study were medical professionals involved in this field at a designated cancer care hospital for cancer treatment and the high participation rate in this program suggest that they were a group with a high level of interest in this field from the beginning.

*Evaluation of the usability of e-learning materials*

Many respondents answered "strongly agree" to the item "The content in this program is reliable". Considering the convenience for trainees and the possibility of continuing training during an infectious disease pandemic, the usefulness of e-learning, which can be conducted remotely, is expected to further increase in the future. While a small number of respondents stated that the course was easy to understand, there were also various opinions regarding improvements to the presentation of the text and the sound. The materials need to be revised based on these opinions.

Regarding the communication environment of the participants, there were opinions regarding the communication capacity of Wi-Fi. In addition, according to the results of our survey of designated cancer care hospital (*3*), it was reported that there were some who wanted to learn about support for appearance care but were not comfortable with e-learning, so we believe that consideration should be given to simplifying the operation method.

The viewing time for each video material ranged from 10 to 22 minutes. In previous studies (*13,14*), it was estimated that it takes 10 to 15 minutes to concentrate on learning and 20 minutes to listen to a story while retaining memory. Although this study employed a split program, some e-learning contents were of somewhat longer duration. In particular, although not included in the current evaluation items, Step II resulted in a wide range of video viewing time settings, from 6 to 30 minutes. Although the program can be interrupted at any time and can be divided into separate courses during the course period, we believe that there is room for further

consideration regarding time settings.

## Conclusions

The results of this feasibility study indicated the following, including the level of understanding about appearance care, satisfaction and usefulness of the e-learning training program that was developed by this research group in order to improve the competence of healthcare professionals who support cancer patients' appearance: *i*) The number of times participants replayed the e-learning program and the response rate to pre- and post-questionnaire surveys were high, indicating the high feasibility of the program. Further refinement of content and methods is needed in the future; *ii*) The scores for satisfaction with the training content, relevance to work, confidence, and intention to use the training in clinical practice were all high, indicating its usefulness in clinical practice; *iii)* While many participants responded with positive comments about the ease of use of e-learning, several participants had diverse opinions about the contents and methods of the program. It is necessary to develop a more practical program that includes not only the acquisition of knowledge, but also the application and dissemination of knowledge in the workplace; and *iv*) The mean comprehension scores after viewing were significantly higher than before viewing for all of the concepts, hair loss, skin/nail disorders, and radiation injury, indicating that knowledge was gained through program viewing.

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**Address correspondence to*:
Keiko Iino, National College of Nursing, Japan, 1-2-1 Umezono, Kiyose-City, Tokyo 204-8575, Japan.
E-mail: iinok@adm.ncn.ac.jp

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BRIEF REPORT
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# Clinical features and treatment outcomes of Fournier's gangrene in a single tertiary emergency hospital: Simplified Fournier's Gangrene Severity Index score is a predictor for death

Taichi Shiratori[1], Masaki Nakamura[2,*], Akihiro Naito[1], Masahiro Yamamoto[1], Yoshihiro Okura[3], Jun Yamakawa[3], Haruki Kume[4], Motofumi Suzuki[1]

[1] Department of Urology, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan;
[2] Department of Urology, NTT Medical Center Tokyo, Tokyo, Japan;
[3] Tertiary Emergency Medical Center, Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan;
[4] Department of Urology, The University of Tokyo Hospital, Tokyo, Japan.

**Abstract:** To assess the predictive reliability of the Simplified Fournier's Gangrene Severity Index Score (SFGSI) for mortality in Japanese patients with Fournier's gangrene (FG), we compared the clinical features and outcomes of a patient sample with the SFGSI. The medical records of 36 patients diagnosed with FG at our hospital between October 2007 and September 2022 were reviewed retrospectively. Clinical and laboratory variables, including SFGSI, were evaluated and predictive factors for fatality were investigated using multivariate logistic regression analysis. The median age and body mass index were 65 and 24.2, respectively. Eight patients had cooccurring chronic kidney disease and 23 had diabetes. None were taking sodium-glucose co-transporter-2 (SGLT-2) inhibitors. The causative organisms were diverse, and no specific trends in causative organisms were observed. 26 patients underwent debridement of necrotic tissue including eight colostomies, two orchiectomies, and one cystectomy. Multivariate logistic regression analysis revealed that SFGSI alone was an independent predictor of case fatality, with an odds ratio of 20.167 (95% CI: 1.66–245.53). In conclusion, the fatality rate was 19.4%, which was comparable to that reported in other studies. The SFGSI was an independent predictor of mortality in this study.

***Keywords*:** debridement, Fournier gangrene, necrotizing fasciitis, orchiectomy, scrotum

## Introduction

Fournier's gangrene (FG) is an acute bacterial necrotizing fasciitis originating from the scrotum, external genitalia, and perineum (*1,2*). FG morbidity is reported to occur in 1.6 out of 100,000 males in the United States (3). Although FG is rare, the fatality rate is around 20% and requires multidisciplinary intensive care. Importantly, multidisciplinary intervention under government-led health care system decreased mortality in FG (*4*). Administration of broad-spectrum antibiotics followed by appropriate debridement of necrotic tissue is essential for the treatment of FG. Delayed debridement of the affected tissue leads to poor outcomes and high mortality (*5*).

Risk factors for FG include diabetes, obesity, alcohol abuse disorders, kidney failure, immunocompromised state, *etc*. (*2*). Besides these factors, several scoring systems for predicting the fatality of patients with FG have been reported (*6-9*). Among these scoring systems, Fournier's Gangrene Severity Index (FGSI) and Uludag Fournier's Gangrene Severity Index (UFGSI) are the most commonly used (*10-12*). The problem in clinical use, however, is the complicated and multiple parameters involved in these scoring systems. The Simplified FGSI (SFGSI) consists of three parameters that are extracted from the SFGSI: serum potassium, serum creatinine, and hematocrit (*13,14*). Although it is a convenient tool, there are no reports from Japan on the usefulness of this scoring system. We have performed literature search on the PubMed database with "Fournier's gangrene", "Fournier gangrene", "simplified Fournier's gangrene severity index" and did not find any report from Japanese institutes.

Herein, we report the clinical features and treatment outcomes of 36 FG patients in our tertiary referral center. We also investigated the predictive ability of the SFGSI for fatality.

## Patients and Methods

### *Patients*

The medical records of 36 consecutive patients diagnosed

**Table 1. Simplified Fournier's Gangrene Severity Index**

| Variables | + 4 | + 3 | + 2 | + 1 | 0 | + 1 | + 2 | + 3 | + 4 |
|---|---|---|---|---|---|---|---|---|---|
| Serum potassium (mmol/L) | > 7 | 6–6.9 | - | 5.5–5.9 | 3.5–5.4 | 3–3.4 | 2.5–2.9 | - | < 2.5 |
| Serum creatinine (mg/100 mL)* | > 3.5 | 2–3.4 | 1.5–1.9 | - | 0.6–1.4 | - | < 0.6 | - | - |
| Hematocrit (%) | > 60 | - | 50–59 | 46–49 | 30–45 | - | 20–29 | - | < 20 |

* ×2 for acute renal failure

with FG based on EAU guidelines on Urological Infections (*15*) at our hospital between October 2007 and September 2022 were reviewed retrospectively. Informed consent was obtained in the form of an opt-out on a website. Exclusion criteria were patients who did not consent to participate in this study.

*Simplified Fournier's Gangrene Severity Index*

SFGSI consists of three variables extracted from the original FGSI: serum potassium, serum creatinine, and hematocrit. The SFGSI scoring system is presented in Table 1. Based on previous reports, we set the threshold at SFGSI > 2 (*13,16*).

*Statement of ethics*

This study was approved by the Ethics Committee of Tokyo Metropolitan Bokutoh Hospital (ID: 04-058). Informed consent was obtained in the form of an opt-out on a website. Patients who were rejected were excluded. This study was conducted in accordance with the Declaration of Helsinki (revised in 2013).

*Statistical analysis*

Fisher's chi-squared test was used to analyze categorical variables. Multivariate logistic regression analysis was performed to identify the predictors of fatality. Sex, age, number of days from onset to debridement, total number of debridements, and SFGSI were included in the logistic regression analysis. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 24.

**Results and Discussion**

The patient characteristics are described in Table 2. Of the 36 patients, 26 were male and 21 lived alone. The median age and median body mass index were 65 and 24.2, respectively. Eight patients had chronic kidney disease, and 23 patients had diabetes mellitus. Although a meta-analysis failed to clarify the relationship between sodium-glucose cotransporter-2 (SGLT-2) inhibitor and FG, there exist several reports on FG caused by SGLT-2 inhibitor (*17,18*). Importantly, no patient was prescribed a SGLT-2inhibitor inhibitor in this study.

The median time from FG onset to hospitalization was five days (interquartile range, 1–6 days). The causative bacteria were diverse, including Escherichia coli, Klebsiella pneumoniae, and proteus. Of the 36 patients with FG in our study, 34 underwent debridement. One did not because the infection foci in the scrotum had already self-destructed and opened, while the other did not due to advanced rectal cancer and multiple liver metastases. Additionally, of those who underwent debridement, there were also eight colostomies, two orchiectomies, and one cystostomy (Table 3). Among our sample, seven patients died of FG. The fatality rate in our study was 19.4% (7/36 cases). There was no difference in fatalities between the early and late intervention groups (21.7% and 15.4%, $p = 0.644$).

**Table 2. Patients' characteristics**

| Characteristics | Cases |
|---|---|
| No. patients | 36 |
| Sex (%) | |
| Male | 26 (72.2) |
| Female | 10 (27.8) |
| Median age (IQR) | 65 (51–75) |
| Median BMI (IQR) | 24.2 (21.0–29.0) |
| Type of residence | |
| Home | 33 (91.7) |
| Hospital | 2 (5.6) |
| Nursing home | 1 (2.8) |
| Living alone, *n* (%) | |
| Yes | 21 (58.3) |
| No | 14 (41.7) |
| Comorbidity, *n* (%) | |
| CKD | 8 (22.2) |
| Diabetes mellitus | 23 (63.9) |
| Dyslipidemia | 6 (16.7) |
| Medication, *n* (%) | |
| Insulin injection | 9 (25.0) |
| STLG-2 inhibitor | 0 (0) |

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; IQR interquartile range; STLG-2, sodium-glucose cotransporter-2.

The results of univariate analysis are presented in Table 4. Amongst the variables, only SFGSI was a predictor for case fatality with an odds ratio of 6.563 (95% confidence interval (CI): 1.05–40.95) For patients with SFGSI > 2, the fatality rate was 38.5%. Furthermore, multivariate logistic regression analysis revealed that only SFGSI was an independent predictor of case fatality, with an odds ratio of 20.167 (95% CI: 1.66–245.53) (Table 5).

Despite advances in treatment, FG is still a life-threatening disorder with a fatality rate of 20–40%

(*3*). The fatality rate was 19.4% in this study, which was comparable with other reports. Owing to the rapid progress of FG, immediate debridement and broad — spectrum antibiotics are mandatory, as delay in intervention leads to poor prognosis (*5*). In the current study, among 34 patients who required debridement, 33 (97%) underwent debridement within two days of hospitalization. Hence, we did not detect any difference in fatalities between the early and late intervention groups.

Several prognostic tools have been developed to predict the fatality of FG and help with clinical decision-making. FGSI consists of nine components, including temperature, heart rate, respiratory rate, serum potassium, serum sodium, serum creatinine, hematocrit, white blood count, and serum bicarbonate (*10,11*). UFGSI is an extension of FGSI, with the addition of age and dissemination of disease score (*19,20*). The sensitivity and specificity for FGSI and UFGSI are reported to be 65–88% and 70–100%, respectively (*6,8,13,16,21*). The UFGSI was developed using data from 80 FG patients, and the area under the receiver operator characteristics curve was larger than that of FGSI (0.947 *vs.* 0.843). As we did not measure serum bicarbonate routinely, the FGSI and UFGSI were calculated in only 13 patients. As also reported by others, the limitation of FGSI and UFGSI is the complexity of the variables (*13,16*).

The SFGSI, consisting of parameters of creatinine, hematocrit, and potassium, has been reported to be comparable to FGSI in predicting the prognosis of FG (*13,16*). The sensitivity and specificity of the SFGSI were 87% and 77%, respectively (*15*). In the current study, the SFGSI was the only predictor of FG-related fatality (Table 5). In patients with SFGSI > 2, 5 of 13 patients died of disease (38.5%), while in patients with SFGSI ≤ 2, 2 of 23 patients died (8.7%). The sensitivity and specificity for SFGSI were 71% and 72%, respectively. Considering its easier applicability, the SFGSI may greatly contribute to the assessment of fatality in patients with FG.

The limitations of this study are its retrospective nature and the relatively small number of patients enrolled.

In conclusion, we retrospectively analyzed the clinical data of 36 patients with FG and found SFGSI to be an independent predictor of disease fatality. Large-scale prospective studies are needed to further validate the utility of SFGSI and to establish appropriate treatments for FG.

*Funding*: None.

**Table 3. Treatment outcome**

| Characteristics | Cases |
|---|---|
| No. patients | 36 |
| Days from onset to hospitalization, median (IQR) | 5 (1–6) |
| Surgical treatment, *n* (%) | |
| Debridement | 34 (94.4) |
| Colostomy | 8 (22.2) |
| Orchiectomy | 2 (7.7% of men) |
| Cystostomy | 1 (2.7) |
| Penectomy | 0 (0) |
| Number of debridement, *n* (%) | |
| Once | 26 (72.2) |
| Twice or more | 10 (27.8) |
| Causative bacteria, *n* (%) | |
| Aerobic | 16 (44.5) |
| Anaerobic | 20 (55.5) |
| Escherichia coli | 6 (16.7) |
| Klebsiella pneumoniae | 3 (8.3) |
| Proteus | 2 (5.6) |
| Catecholamine use on admission, *n* (%) | |
| Yes | 9 (25.0) |
| No | 27 (75.0) |
| Outcome | |
| Cure | 29 (80.6) |
| Death | 7 (19.4) |

Abbreviations: IQR, interquartile range

**Table 5. Multivariate logistic regression analysis of case fatality**

| Characteristics | OR | 95% CI | *$p$ value |
|---|---|---|---|
| Female (ref. male) | 0.89 | 0.08–9.65 | 0.925 |
| Age ≥ 60 (ref. < 60) | 1.09 | 0.09–13.04 | 0.946 |
| Days onset to debridement > 5 (ref. ≤ 5) | 0.37 | 0.04–3.32 | 0.372 |
| Number of debridement ≥ 2 (ref. <2) | 0.69 | 0.07–6.98 | 0.749 |
| SFGSI > 2 (ref. ≤ 2) | 20.17 | 1.66–245.55 | 0.019 |

Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference; SFGSI simplified Fournier's Gangrene Severity Index.

**Table 4. Univariate analysis of case fatality rates**

| Characteristics | Case fatality rate, % | OR | 95% CI | *$p$ value |
|---|---|---|---|---|
| Overall | 19.4 | | | |
| Female (ref. male) | 20.0 | 1.014 | 0.603–1.705 | 0.645 |
| Age ≥ 60 (ref. < 60) | 21.7 | 1.528 | 0.252–9.272 | 0.501 |
| Diabetes mellitus | 17.4 | 0.702 | 0.131–3.771 | 0.499 |
| Days onset to hospitalization > 5 (ref. ≤ 5) | 16.7 | 0.7 | 0.132–3.699 | 0.5 |
| Days onset to debridement > 5 (ref. ≤ 5) | 15.4 | 0.818 | 0.128–5.233 | 0.608 |
| Number of debridement ≥ 2 (ref. < 2) | 20.0 | 1.05 | 0.168–6.551 | 0.645 |
| SFGSI > 2 (ref. ≤ 2) | 38.5 | 6.563 | 1.052–40.946 | 0.044 |

Abbreviations: CI, confidence interval; OR, odds ratio; ref, reference; SFGSI, simplified Fournier's Gangrene Severity Index. *Fisher's chi-square test.

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**Address correspondence to*:
Masaki Nakamura, Department of Urology, NTT Medical Center Tokyo, 5-9-22, Higashigotanda, Shinagawa-ku, Tokyo 141-8625, Japan.
E-mail: masakin64@gmail.com

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BRIEF REPORT
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# A novel protocol for de-isolating moderately and severely immunocompromised COVID-19 patients

Kohei Kamegai[1,*], Noriko Iwamoto[1], Masahiro Ishikane[1], Kei Yamamoto[1], Kumi Horii[2], Shiho Kubota[2], Akira Hangaishi[3], Hiroshi Shimazu[3], Tomiteru Togano[3], Hiroyuki Yamashita[4], Yasuhide Yamada[5], Norio Ohmagari[1]

[1] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Infection Control Office, National Center for Global Health and Medicine, Tokyo, Japan;
[3] Department of Hematology, National Center for Global Health and Medicine, Tokyo, Japan;
[4] Division of Rheumatic Diseases, National Center for Global Health and Medicine, Tokyo, Japan;
[5] Comprehensive Cancer Center, National Center for Global Health and Medicine, Tokyo, Japan.

**Abstract:** Immunocompromised coronavirus disease 2019 patients are at a higher risk of prolonged viral shedding than immunocompetent patients. However, as of August 2023, there is no clear international standard for de-isolating vulnerable patients. A comprehensive assessment is advisable based on various information, such as the increase in immune escape of specific mutant strains as well as the patient's innate immunity and vaccination status; therefore, consultation with an infectious disease specialist is recommended. The patient population defined as moderately or severely immunocompromised by the Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control is significantly broad. A boundary between the two remains to be delineated, and the existing protocols allow the release of patients based on their symptoms alone. This may lead to an unnecessary extension or premature termination of isolation. In this study, we searched for studies, particularly those that used real-world data, discussed the results with experts in our hospital, and proposed new isolation criteria based on both testing and clinical symptoms. We classified patients into three groups namely severely, moderately, and mildly immunocompromised, defined by their background and the administration of immunosuppressive drugs. A separate flowchart for ending isolation is indicated for each group. This standard may be a useful support material, especially for non-specialists. Nevertheless, our criteria must be revised and added continuously; accumulating real-world data to support revision of and addition to the list is becoming increasingly important.

***Keywords*:** prolonged viral shedding, SARS-CoV-2, anti-CD20 therapy, hematological malignancy, solid tumor

## Introduction

Effective isolation of coronavirus disease 2019 (COVID-19) patients is essential to prevent outbreaks in hospitals (*1*). As of August 2023, no established criteria exist to de-isolate these immunosuppressed populations at risk of prolonged viral shedding in Japan. This situation may consequently result in suboptimal strategies such as insufficient or unnecessarily extended isolation.

Herein, we propose a novel strategy to de-isolate patients at risk of prolonged viral shedding in medical facilities.

## Materials and Methods

This protocol was developed based on current evidence and discussions with various experts last February 2023. Our authors include four certified infectious disease specialists (Iwamoto N, Ishikane M, Yamamoto K, and Ohmagari N), two certified nurses in infection prevention and control (Horii K, Kubota S), three experts in hematology (Hangaishi A, Shimazu H, Togano T), one expert (Yamashita H) in autoimmune disease, and one expert in solid tumor (Yamada Y).

Also, we performed a scoping review of searched the latest English-written articles on PubMed describing the real-world data. We searched using words including "COVID-19", "SARS-CoV-2", "immunocompromised", "seroconversion rate", "vaccination", and some specific immunosuppressive conditions like "B-cell depletion therapy", "chemotherapy", "hematologic malignancy", and "malignancy".

We initially decided to propose a flowchart and a detailed list of immunosuppressive drugs. We roughly divided the list into three categories based on the magnitude of immunosuppressive effect of the drug: mild, moderate, and severe. For the mild category,

we enlisted drugs with no evidence of prolongation or patients' seroconversion rates after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) messenger ribonucleic acid (mRNA) vaccine was approximately > 90%. For the moderate category, we enlisted drugs with evidence of prolongation or patients' seroconversion rates after the SARS-CoV-2 mRNA vaccine was approximately 70–90%. For the severe category, drugs with profound immunosuppressive effects or clear evidence of extended viral shedding were included.

Our novel strategy has passed strict peer reviews by our authors and the cancer board in our hospital, which consists of 21 physicians with expertise in malignancy.

## Results and Discussion

We introduce a novel protocol to de-isolate COVID-19 patients with sustained contagiousness (Figure 1 and Table 1). Our flowchart shows the isolation of moderately or severely immunocompromised patients for at least 20 days. This strategy is based on the current guidelines of the Centers for Disease Control and Prevention (CDC) (*2*). However, for example, patients evaluated as severely immunocompromised will likely be long shedders, trespassing the 20-day border (*3*). Therefore, according to our criteria, a negative PCR test is required to de-isolate this special population. If the cycle threshold (Ct) value is measurable, it should be > 35, which is generally considered the cut-off for recovering SARS-CoV-2 in the culture of the upper airway sample (*4*). We rejected testing twice 24 hours apart as polymerase chain reaction (PCR) testing has excellent sensitivity and specificity, and we may be able to ignore the small risk of false negatives. In addition, although there is a risk of COVID-19 relapse in these populations, it will not occur within a day.

*Severely immunocompromised patients*

Multiple studies have attributed the prolongation of viral shedding to severely impaired B-cell function, which minimizes the humoral response. B-cell depletion is profound when patients receive B-cell depletion therapy (BCDT), such as the anti-cluster of differentiation (CD) 20 therapy drug (*5*). CD20 is an antigen widely expressed on the surface of B cells that plays a critical role in developing plasma cells from naïve B cells to the terminal phase. Thus, the blockade of CD20 hinders the development of B-cells from the beginning (*6*).

In addition, other BCDT, such as anti-CD19 therapy (*7*), and lymphopenic hematological malignancy receiving active chemotherapy, will likely create the same situation.

Bruton tyrosine kinase (BTK) is an enzyme that regulates B-cell proliferation and activation by stimulating B-cell receptor signaling (*8*). BTK inhibitors have a tremendous negative impact on B-cell function among individuals receiving these drugs whose seroconversion rate is substantially low (*9*).

Other potent factors that have profound adverse effects on immunogenicity include X-linked agammaglobulinemia (*10*), hematopoietic transplantation, chimeric antigen receptor-T cell therapy, lymphoma, B-cell related malignancy, solid tumor transplant, T-cell depletion therapy, and primary and acquired immunodeficiency (*11*).

The Ministry of Health, Labour and Welfare in Japan regulates the criteria for administering tixagevimab/cilgavimab (TIX/CIL) to severely immunocompromised patients (*12*). TIX/CIL is a monoclonal antibody combination consisting of two neutralizing antibodies against SARS-CoV-2 and is effective in preventing COVID-19. Owing to its limited distribution in

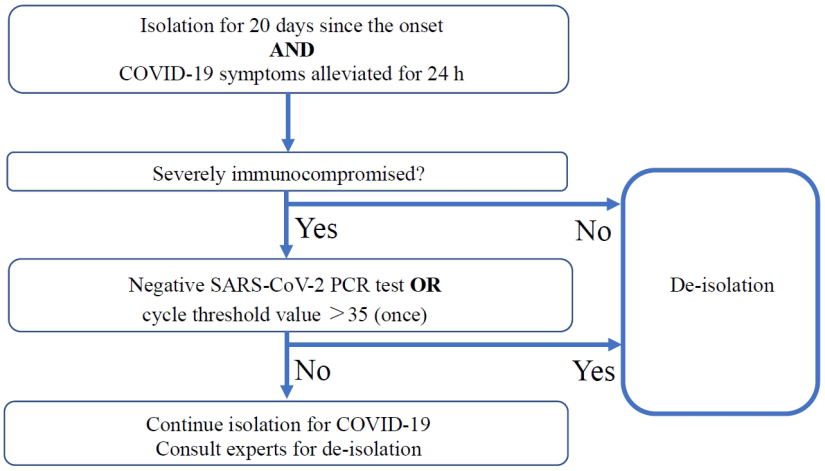


**Figure 1. A flowchart for de-isolating moderately or severely immunocompromised patients.** Patients categorized as "severely immunocompromised" are as follows: *i*) Primary immunodeficiency with antibody production failure or complex immunodeficiency, *ii*) Patients within 1 year of receiving B-cell depletion therapy, *iii*) Patients receiving Bruton's tyrosine kinase inhibitors, *iv*) Chimeric antigen receptor (CAR) recipients, *v*) Patients receiving immunosuppressive drugs for chronic graft-versus-host disease, *vi*) Recipients for hematopoietic cell transplantation, *vii*) Patients with hematologic malignancies undergoing aggressive therapy, *viii*) Lung transplant recipient, *ix*) Within 1 year of solid organ transplant, other than lung transplant, *x*) Solid organ transplant recipients recently treated with cell-depleting agents for acute rejection; *xi*) HIV patients with CD4 < 50/mm$^3$.

**Table 1. Criteria of the drugs classified by degree of immunosuppression**

| Degree | Large category | Category | Examples of the drugs |
|---|---|---|---|
| Mild | Steroids | Steroids | Equivalent to prednisolone < PSL 20 mg/d or < 2 weeks |
| | Immune checkpoint inhibitors | CTLA-4 inhibitors | Ipilimumab |
| | | PD-1 inhibitors | Nivolumab, pembrolizumab |
| | | PD-L1 inhibitors | Avelumab, atezolizumab, durvalumab |
| | Tyrosine kinase inhibitors | ALK inhibitors | Crizotinib, ceritinib, alectinib, brigatinib |
| | | BCR-Abl inhibitors | Imatinib, nilotinib, dasatinib, bosutinib |
| | | EGFR inhibitors | Cetuximab, panitumumab, vandetanib, lapatinib, gefitinib, erlotinib, lenvatinib, afatinib, osimertinib |
| | | HER2 inhibitors | Trastuzumab, pertuzumab |
| | | PDGFR α/β inhibitors | Gefitinib, imatinib, lenvatinib, nintedanib, pazopanib, regorafenib, sorafenib, sunitinib |
| | | VEGFR inhibitors | Ramucirumab, bevacizumab, lenvatinib, nintedanib, regorafenib, pazopanib, sorafenib, sunitinib |
| | Serine/threonine kinase inhibitors | BRAF inhibitors | Vemurafenib, dabrafenib |
| | | CDK 4/6 inhibitors | Palbociclib, sorafenib, ribociclib |
| | Hormonal therapies | Hormonal therapies | Tamoxifen |
| | Cytotoxic drugs | DNA synthesis inhibitors | Methotrexate(< 20 mg/week) |
| | | Folic acid synthesis inhibitors | Azathioprine(< 3 mg/kg/day), mercaptopurine(< 1.5 mg/kg/day), |
| | Interleukin inhibitors | IL-4/13 inhibitors | Dupilumab |
| | | IL-12/23 inhibitors | Ustekinumab |
| | | IL-17 inhibitors | Ixekizumab, secukinumab |
| | DMARDs | DMARDs | Hydroxychloroquine, salazosulfapyridine, igratimod, bucillamine, leflunomid |
| | Gut-specific integrins | Anti-α4β7integrin | Vedolizumab, natalizumab |
| | Others | Drugs associated with multiple sclerosis | Dimetyl fumarate, fingolimod, glateramer acetate, interferon-β 1a |
| Moderate | Steroids | Steroids | Equivalent to prednisolone ≥ PSL 20 mg/d and ≥ 2 weeks |
| | DMARDs | DNA synthesis inhibitors | Mercaptopurine(≥ 1.5 mg/kg/day), azathioprine(≥ 3 mg/kg/day), mycophenolate mofetil, mizoribine |
| | Cytotoxic drugs | Alkylating drugs | Temozolomide, ranimustine, melphalan, ifosphamide, cyclophosphamide |
| | | Antibiotics | Doxorubicin, epirubicin, idarubicin, aclarubicin, amrubicin, daunorubicin, bleomycin, mitomycin C, actinomycin D, |
| | | Antimetabolites | Fluorouracil/tegafur, gemcitabine, capecitabine, cytarabine |
| | | Calcineurin inhibitors | Tacrolimus, cyclosporin A |
| | | Folic acid synthesis inhibitors | Methotrexate(≥ 20 mg/week) |
| | | Microtubule inhibitors | Paclitaxel, docetaxel |
| | | Platinum-based drugs | Cisplatin, carboplatin, nedaplatin |
| | | Proteasome inhibitors | Bortezomib |
| | | Topoisomerase inhibitors | Irinotecan, nogitecan |
| | Immunomodulators | CTLA-4 | Abatacept |
| | | IL-2 inhibitors | Basiliximab |
| | | IL-6 inhibitors | Tocilizumab, sarilumab |
| | Tyrosine kinase inhibitors | JAK inhibitors | Baricitinib, peficitinib, tofacitinib, ruxolitinib |
| | Molecular-targeted drugs | mTOR inhibitors | Everolimus, sirolimus, rapalimus |
| | | TNF-α inhibitors | Etanercept, certolizumab, golimumab, adalimumab, infliximab |
| Severe | B-cell depleting therapies | Anti-CD19 inhibitors | Inebilizumab |
| | | Anti-CD20 inhibitors | Rituximab, obinutuzumab, ofatumumab |
| | | Anti-CD38 inhibitors | Daratumumab |
| | | Anti-CD52 inhibitors | Alemtuzumab |
| | Tyrosine kinase inhibitors | Bruton kinase inhibitors | Iburutinib, acalabrutinib, tirabrutinib |

Japan, TIX/CIL is approved only for the pre-exposure prevention of COVID-19. As the criteria cover our drug list sufficiently, we diverted the TIX/CIL criteria to de-isolation standards as severely immunocompromised patients.

*Moderately immunocompromised patients*

We defined moderately immunocompromised patients by extracting severely immunocompromised patients from the CDC and European Centre for Disease Prevention and Control (ECDC) criteria (*13,14*). Individuals with solid malignant tumors receiving active chemotherapy can have more sustained viral shedding than healthy patients but are mostly not more extended than patients with hematological malignancies (*15*). Cytotoxic agents such as alkylating agents, antimetabolites, microtubule inhibitors, topoisomerase inhibitors, rapamycin analogs and mechanistic targets of rapamycin (mTOR) (*16*); DNA synthesis inhibitors and folic acid synthesis agents (*17*) have a negative effect. We categorized mercaptopurine > 1.5 mg/kg/day, methotrexate > 20 mg/week, and corticosteroids equivalent to 20 mg/day for more than two weeks, referencing a guideline from the

Infectious Diseases Society of America (*18*).

Biologic agents for autoimmune diseases, Janus kinase inhibitors, DNA synthesis inhibitors, calcineurin blockers, B-cell activating factor inhibitors, methotrexate; corticosteroids (70–90%); and cytotoxic T-lymphocyte-associated protein 4 (< 70%) induce relatively low vaccination response rate, and thus put patients at risk for sustained viral shedding (*17*). Another data showed a reduced seroconversion rate in breast cancer patients receiving cyclin-dependent kinase 4/6 inhibitors (*19*). In a prospective cohort study, the seroconversion rate was reduced two months after receiving the last mechanistic target of rapamycin (mTOR), topoisomerase inhibitors. Additionally, antimetabolites, and alkylating drugs induce a low seroconversion rate (*16*).

Conversely, real-world data have shown an excellent (> 90%) vaccine response rate among patients with autoimmune diseases receiving interleukin (IL)-6 inhibitors tocilizumab and tumor necrosis factor (TNF)-alpha inhibitors (*17*). However, some autoimmune diseases such as rheumatic arthritis are risk factors for viral shedding prolongation, and immunosuppressive drugs are likely to be combined; patients with autoimmune disease are likely to have cumulative immunosuppression (*20*).

*Drugs with minimal effect on humoral response*

Not all cancer patients undergoing treatment should be categorized as moderate. Immune checkpoint inhibitors, such as programmed death-1 (PD-1) and programmed death ligand-1 inhibitors, have minimal impact on vaccine response based on real-world data (*21*).

A prospective cohort study showed that the seroconversion rate of tyrosine kinase inhibitors (TKIs) recipients two months after the second mRNA was not significantly different from the control group (*16*). However, real-world data for each kind of TKIs have been scarce. Another real-world data showed that hormonal therapy for breast cancer patients did not affect the seroconversion rate (*17*).

Immunomodulators, hydroxychloroquine, and salazosulfapyridine are described in this section. Methotrexate (< 20 mg/week), mercaptopurine (< 1.5 mg/kg), and azathioprine (3 mg/kg) should be put into this category (*15,16*).

The IL-4/13, IL-12/23 and IL-17a inhibitors have minimal effect on the seroconversion rate, and are thought to not interfere with T-cell and B-cell responses to vaccination (*15,22*).

Among the drugs used to treat patients with multiple sclerosis, leflunomide, teriflunomide, fingolimod, interferon-beta, glatiramer acetate, dimethyl fumarate, and natalizumab had minimal effect on immunodepleting phase (*17,23*).

*Discussion on the prolongation mechanism*

The prolongation mechanism is complex and is determined by multiple factors such as disease severity, duration, clinical stability, complications, host immunity, vaccination status, variant of the virus (the Omicron variant has spread nationwide since November 2021(*24*)), and immunosuppressive treatment (*20*). Immunologically, T and B cells play a prominent role in the immune response. The acquisition of immunity starts after immunization, previous history of infection, or the receipt of antibody treatment, as dendritic cells regulate the proliferation of $CD4^+$ T-cells into a variety of helper T cells, including Th1, Th2, Th17, T follicular helper cells ($T_{FH}$ cells), and T regulatory cells (*5,20*). The $T_{FH}$ cells help mature naïve B cells as well as in the development of antibodies and memory B cells during germinal center formation (*20*). In this mechanism, drugs can prolong viral shedding by affecting T cells, B-cells, or antibody responses.

The severity of immunosuppression can also be extrapolated from the vaccination effectiveness rate. In a landmark study by Barrière *et al*., antibody titers were measured in four groups after a series of SARS-CoV-2 mRNA vaccinations; all patients in the anti-CD20 therapy group had no immunological response, and most patients in the active hematological malignancy group had low or no response (*25*). Almost half of those receiving active treatment for solid tumors did not achieve an acceptable response rate, while only one had a good response in the healthy group.

*Major criteria issued regarding COVID-19 isolation*

As of August 2023, two major criteria have been issued regarding COVID-19 isolation. The CDC suggests lifting isolation after 20 days when the patient defervesces and is free from other symptoms, provided that the patient is negative from two consecutive SARS-CoV-2 antigen or polymerase chain reaction (PCR) tests, obtained 24 hours apart (*13*). Meanwhile, ECDC suggests a de-isolation when the patient defervesces and is free from other symptoms, provided that SARS-CoV-2 antigen or PCR tests obtained 24 hours apart are negative, or that it has been 20 days after the onset (*14*). CDC recommendations are categorized as fully test-based, whereas ECDC advocates a half-test and half-clinical-based strategy.

However, these criteria are insufficient for several reasons. First, no clear-cut border exists between moderately and severely immunocompromised patients, and each group should have their corresponding isolation policy. Second, the moderately and severely immunocompromised category corresponds to a large number of patients, which may lead to unnecessary isolation of immunocompetent patients. For example, the criteria refer to recipients of active treatment for solid tumors; however, some chemotherapies, such as immune checkpoint inhibitors, have minimal effect on immunosuppression, and

the extension of viral shedding may not occur (*21*). Third, severely immunocompromised patients who shed active SARS-CoV-2 for more than 20 days can discontinue isolation without testing following the ECDC criteria. This loophole may result in an outbreak in the hospital ward (*3*).

*Protocol for de-isolating immunosuppressed COVID-19 patients proposed by this study*

We proposed an original and straightforward protocol for de-isolating immunosuppressed COVID-19 patients. This protocol may help reduce the chance of in-ward outbreaks and the variation of infection control practices among the personnel in charge. To date, after implementing the novel protocol in our hospital in February 2023, there has never been any nosocomial outbreak whose index case is de-isolated immunocompromised patients. To cite another example to support the safety of this protocol, national cancer centers in Japan, where the de-isolating strategies are similar to ours, no outbreaks have occurred yet during the observation period (*26*).

However, several limitations are still yet to be solved. First, the isolation period cannot be determined by only the type of immunosuppressor used. Increased immune escape of specific variants, the patients' innate immunity, and vaccination have a significant role in their immune status. In general, the immunosuppressive effect of drugs is dose-dependent. Therefore, when drugs are combined, their immunosuppressive effects may accumulate. A combination of drugs in the mild category can cause extended viral shedding, which may then be categorized as moderate. Second, as the mechanism of viral shedding prolongation is complex, quantification of the immune status of the patient is unfeasible. Therefore, bias cannot be entirely removed when allocating those immunosuppressive drugs into each category. The list should be modified as real-world data for each drug is collected in the future; however, the process may take time. Third, it is unknown when the immune system recovers after using immunosuppressors. For example, anti-CD20 therapy profoundly reduces both B-cell and T-cell function; however, the recovery mechanism of the patients remains uncertain. Moreover, BCDT recipients may be prone to relapse. Even after de-isolation, these populations may need to be re-isolated if they become symptomatic again. The optimal strategy for these special populations, and the magnitude of impact of COVID-19 relapse remains unknown. Fourth, not all immunosuppressive drugs are included in our list as we could not find credible evidence for some drugs. Since we are exploiting a new frontier in an uncertain area, supporting evidence is scarce, which can be our major limitation.

When evaluating unfamiliar immunosuppressive drugs, it is vital to consider the lymphopenic effect of the drug or investigate whether it can affect the B-cell/T-cell cascade. A report from China described a significantly lower response rate after the second dose of SARS-CoV-2 vaccination among those with lymphocytopenia ($< 1{,}000/mm^3$). The included population received inactivated and not mRNA vaccines. Nevertheless, profound lymphocytopenia may be an indication of poor responders (*27*).

## Conclusion

Despite all the limitations, we firmly believe that our novel de-isolating strategy for the immunocompromised population is meaningful as it is simple enough to follow, particularly for non-experts. In addition, we hope that our work will be evaluated because we optimized de-isolation strategies for "moderate and severe immunocompromised patients. However, these criteria alone cannot decide when to lift isolation; therefore, expert consultation may still be needed. These criteria may need to be modified based on an analysis of real-world data using clinical and virological information.

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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, Tokyo 162-8655, Japan.
E-mail: kkamegai@hosp.ncgm.go.jp

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# Epidemiological trends of traveler's diarrhea in Japan: An analysis of imported infectious disease registry data from 2017–2022

Taketomo Maruki[1], Kei Yamamoto[1,*], Masaya Yamato[2], Toshinori Sahara[3], Michinori Shirano[4], Naoya Sakamoto[5], Ryota Hase[6], Koh Shinohara[7,8], Yukihiro Yoshimura[9], Natsuko Imakita[10], Fumihiro Kodama[11], Yoshihiro Yamamoto[12], Kyoko Yokota[13], Yusuke Yoshimi[14], Chihiro Hasegawa[15], Satoshi Kutsuna[1,16], Norio Ohmagari[1]

[1] Disease Control and Prevention Center, National Center for Global Health and Medicine, Tokyo, Japan;
[2] Rinku General Medical Center, Osaka, Japan;
[3] Tokyo Metropolitan Ebara Hospital, Tokyo, Japan;
[4] Osaka City General Hospital, Osaka, Japan;
[5] Tokyo Metropolitan Bokutoh Hospital, Tokyo, Japan;
[6] Japanese Red Cross Narita Hospital, Chiba, Japan;
[7] Kyoto City Hospital, Kyoto, Japan;
[8] Department of Clinical Laboratory Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan;
[9] Yokohama Municipal Citizen's Hospital, Kanagawa, Japan;
[10] Nara Medical University Hospital, Nara, Japan;
[11] Sapporo City General Hospital, Hokkaido, Japan;
[12] Toyama University Hospital, Toyama, Japan;
[13] Kagawa Prefectural Central Hospital, Kagawa, Japan;
[14] Japanese Red Cross Nagoya Daini Hospital, Aichi, Japan;
[15] Nagoya City University East Medical Center, Aichi, Japan;
[16] Graduate School of Medicine Faculty of Medicine, Osaka University, Osaka, Japan.

**Abstract:** Traveler's diarrhea (TD) is a global problem, and identifying the causative organisms of TD is important for adequate treatment. Therefore, this study retrospectively analyzed TD cases in patients who returned to Japan after traveling abroad to determine the causative organisms by travel region. We included patients with a final diagnosis of TD registered in the Japan Registry for Infectious Diseases from Abroad database from September 25, 2017, to September 1, 2022, from 14 medical institutions. A total of 919 patients were analyzed; the causative TD pathogen was identified in 188 cases (20%), of which 154 were caused by diarrheagenic bacteria, the most common being *Campylobacter* spp. (64%). A 2.2 mg/dL C-reactive protein concentration cutoff value had some predictive ability for bacterial TD (negative predictive value, 89%). Therefore, the C-reactive protein level may help rule out bacterial diarrhea and prevent unnecessary antimicrobial administration when patients cannot provide a stool specimen.

***Keywords*:** traveler's diarrhea, epidemiology, travel diseases, C-reactive protein

## Introduction

Despite improved hygiene, traveler's diarrhea (TD) is a continuing global issue with frequent occurrence and many potential adverse consequences, including lost time and opportunities, itinerary changes, overseas medical encounters, and hospitalization (*1*). For certain destinations, the TD incidence rate is 20–60% within a two-week period (*2,3*). In Japan, the frequency of TD is estimated to be higher owing to the large number of travelers visiting Asia, which has a high TD risk. Therefore, this study analyzed TD cases diagnosed in Japan.

## Study design and data collection

The Japan Registry for Infectious Diseases from Abroad (J-RIDA) was established to clarify the status of imported infectious diseases in Japan (*4*), with 14 Japanese medical institutions contributing to the database. The registry collects information about the patient's age, sex, nationality, travel history, country of residence, departure, return, consultation, onset dates, whether a visit was made to a travel clinic before travel, the prophylactic antimicrobials administered, the final diagnosis, blood collection (yes/no), the TD causative organisms, antimicrobial therapy (yes/no), and outcomes.

Thus, we retrospectively collected data from the J-RIDA database from September 25, 2017, to September 1, 2022, for our analyses.

We included patients with a final diagnosis of TD registered in the J-RIDA database. Patients who developed TD during the trip were included, but those who developed TD more than six days after returning to Japan were excluded because they were likely unrelated to the trip. Similarly, foreign visitors to Japan were included if they were abroad at the time of onset. The destination country was defined as that where the patient stayed at the time of TD onset. However, for patients who developed the disease after returning to Japan, the destination country was defined as the last country the patient traveled to before returning to Japan. Moreover, we analyzed the diagnostic ability of the C-reactive protein (CRP) level for bacterial enteritis. *Campylobacter, Salmonella* spp*., Shigella* spp*., Vibrio parahaemolyticus, V. cholerae,* Enterotoxigenic *Escherichia coli,* Enteroinvasive *E. coli,* Enteropathogenic *E. coli,* Enterohaemorrhagic *E. coli,* and *Plesiomonas shigelloides* were considered causative agents of bacterial enteritis.

Continuous variables were compared by the Mann–Whitney *U* test. A two-sided *p*-value of $< 0.05$ was considered statistically significant. Cutoff values were assessed by receiver operating characteristic curve analyses based on the area under the curve (AUC) and Youden's index. All statistical analyses were performed using EZR software version 1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is based on R and R Command (R Foundation for Statistical Computing, Vienna, Austria).

This publication was exempt from Institution Review Board (IRB) approval (NCGM-G-002328). The patients' data were anonymized before analysis, and the requirement of individual informed consent was waived by providing an opt-out opportunity because of the study's retrospective design. The study was conducted in accordance with the principles of the Declaration of Helsinki.

**Epidemiological trends of TD in Japan**

We included 919 patients (average age, 34.3 years; men, 512 [56%]). Furthermore, 870 patients (95%) and 876 (95%) were Japanese and residents of Japan, respectively. Notably, most cases were attributed to destination areas in Southeast Asia ($n = 498$; 54%). By country, most cases were from Thailand ($n = 99$; 11%). Moreover, before traveling, 138 (15%) patients visited a travel clinic, and three patients were prescribed antimicrobial prophylaxis, a standby treatment for TD. Additionally, 815 (89%), 71 (8%), and 33 (4%) patients were treated as outpatients, in a hospital, and had unknown outcomes, respectively. Concurrently, blood tests and antimicrobial prescriptions were administered to 485 (53%) and 129 (14%) patients, respectively (Table 1). Overall, 731 cases (80%) were of unknown origin, and the causative organism was identified in 188 cases (Table 2); of these, most were caused by *Campylobacter* spp. ($n = 93$; 52%).

We obtained the CRP level from 486 patients. The causative organism was bacterial in 102 cases and "other" in 384 cases (including 378 cases where the causative organism was unknown). The bacterial group had a significantly higher CRP level than did the "other" group (median: 3.85 mg/dL [interquartile range: 1.93–7.24] *vs.* 1.36 mg/dL [0.30–3.99], $p < 0.001$) (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=75*). Furthermore, the CRP level had a high AUC (0.67) (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=75*). Thus, several CRP cutoff values were tested for their diagnostic accuracy to distinguish bacterial causative agents from other agents. The optimal cutoff value stood at 2.2 mg/dL, exhibiting a sensitivity, specificity, positive predictive value, and negative predictive value of 73.0% (95% CI: 3.2–81.4%), 60.2% (95% CI: 55.0–65.2%), 33.0% (95% CI: 29.3–37.0%), and 89.2% (95% CI: 85.6–92.1%), respectively. In this study, 72 patients with TD of a non-bacterial cause received antimicrobial prescriptions, and 40 underwent blood testing. Of these, 25 patients had a 2.2 mg/dL or lower CRP level.

Reports indicate that 16.1% of travelers experience TD in Southeast Asia (*5*), and bacterial pathogens are detected in only about 60% of TD cases (*6*). In this study, we found that most TD cases in Japan occurred after traveling to Southeast Asian countries; however, there were more cases with unknown etiologic agents than those previously reported. Importantly, it is unclear whether stool tests were performed in patients with unknown causative organisms, which may explain this result. Many mild TD cases are treated without antibiotics; therefore, stool tests are not conducted, which increases the number of cases with unknown causative agents. We found that 33/188 patients (18%) with confirmed causative organisms required hospitalization, whereas only 38/731 patients (5%) with unknown causative organisms did so, suggesting that cases with unknown causative organisms are less severe. Often, many less severe TD cases only require follow-up observations and no stool test, potentially explaining our results.

In this study, only 3 patients received antimicrobial prophylaxis for TD. Notably, antimicrobial prophylaxis treatment is not routinely recommended for TD (*7*) because it does not protect against non-bacterial pathogens and can harm normal, protective microflora in the bowel, increasing the risk of infection by resistant bacterial pathogens (*8*).

Our analysis suggested that in patients with TD and a CRP level of 2.2 mg/dL or lower, bacteria were likely not the causative agents; thus, the utility of antimicrobial agents appeared to be minimal. Consequently, this

**Table 1. Study population characteristics**

| Characteristics | Total (*n* = 919) | % | Bacterial causative agent (*n* = 154) | % | Other (*n* = 765) | % |
|---|---|---|---|---|---|---|
| Age (median), years | 31 | | 27 | | 31 | |
| Male | 512 | 56 | 87 | 56 | 423 | 55 |
| Nationality | | | | | | |
| Japanese | 870 | 95 | 150 | 97 | 720 | 94 |
| Other | 49 | 5 | 4 | 3 | 45 | 6 |
| Country of residence | | | | | | |
| Japan | 876 | 95 | 152 | 99 | 724 | 95 |
| Other | 43 | 5 | 2 | 1 | 41 | 5 |
| Destination area | | | | | | |
| Southeast Asia | 498 | 54 | 104 | 68 | 394 | 52 |
| South Asia | 128 | 14 | 17 | 11 | 111 | 15 |
| Africa | 120 | 13 | 8 | 5 | 112 | 15 |
| East Asia | 75 | 8 | 13 | 8 | 62 | 8 |
| Central and South America | 26 | 3 | 2 | 1 | 24 | 3 |
| Central and West Asia | 20 | 2 | 4 | 3 | 16 | 2 |
| Oceania | 19 | 2 | 4 | 3 | 15 | 2 |
| Europe | 17 | 2 | 1 | 1 | 16 | 2 |
| North America | 16 | 2 | 1 | 1 | 15 | 2 |
| Destination country | | | | | | |
| Thailand | 99 | 11 | 25 | 16 | 74 | 10 |
| Indonesia | 98 | 11 | 24 | 16 | 74 | 10 |
| India | 92 | 10 | 15 | 10 | 77 | 10 |
| Philippines | 88 | 10 | 16 | 10 | 72 | 9 |
| Vietnam | 76 | 8 | 10 | 6 | 66 | 9 |
| Cambodia | 51 | 6 | 7 | 5 | 44 | 6 |
| China | 34 | 4 | 5 | 3 | 29 | 4 |
| Myanmar | 30 | 3 | 7 | 5 | 23 | 3 |
| Malaysia | 24 | 3 | 7 | 5 | 17 | 2 |
| Singapore | 19 | 2 | 6 | 4 | 13 | 2 |
| Visited a travel clinic before traveling | | | | | | |
| Yes | 138 | 15 | 13 | 8 | 125 | 16 |
| No | 781 | 85 | 141 | 92 | 640 | 84 |
| Antimicrobial prophylaxis | | | | | | |
| Yes | 3 | 0.3 | 0 | 0 | 3 | 0.4 |
| No | 916 | 99 | 154 | 100 | 762 | 99 |
| Outcome | | | | | | |
| Outpatient | 815 | 89 | 115 | 75 | 700 | 92 |
| Hospitalization | 71 | 8 | 31 | 20 | 40 | 5 |
| Unknown | 33 | 4 | 8 | 5 | 25 | 3 |
| Blood collection | | | | | | |
| Yes | 486 | 53 | 102 | 66 | 384 | 50 |
| No | 433 | 47 | 52 | 34 | 381 | 50 |
| Prescribed antimicrobials | | | | | | |
| Yes | 129 | 14 | 57 | 37 | 72 | 9 |
| No | 790 | 86 | 97 | 63 | 693 | 91 |

indicator could help reduce the inappropriate use of antimicrobial agents. Furthermore, the relatively high negative predictive value supports the conclusion that the CRP level can rule out bacterial diarrhea, which accounted for approximately 20% of cases in this study. Therefore, unnecessary antimicrobial administration could be avoided in at least 25/72 patients (34.7%) with TD of unknown origin.

Most of the cases in this study pertain to the pre-Coronavirus disease 2019 (COVID-19) era, given that COVID-19 was globally detected in January 2020 (*9*). The COVID-19 epidemic has resulted in significant changes in international travel patterns. Notably, only 51 patients (5.5%) were enrolled in the study subsequent to 2020. Among these, 45% (23/51), 78% (40/51), and 13% (7/51) were attributed to destination areas in Southeast Asia, had an unknown etiological agent, and were caused by *Campylobacter* spp., respectively. Although simple comparisons are difficult due to the small number of post-COVID-19 participants, these data appear to align broadly with the overall study findings.

Our study had some limitations. First, there was considerable bias in the number of TD reports from the medical facilities; thus, reporting bias is possible. In Japan, unlike other travel-related infectious diseases, such as dengue fever and malaria, TD does not have to be reported to public health centers. Additionally, many mild TD cases may not be registered in the J-RIDA database even if encountered in routine medical care. Finally, mild TD cases often do not present in large hospitals with specialized departments and may not be reported.

**Table 2. Organisms that caused diarrhea and corresponding travel regions**

| Organisms | Southeast Asia | South Asia | Africa | East Asia | Central and South America | Central and West Asia | Oceania | Europe | North America |
|---|---|---|---|---|---|---|---|---|---|
| Case Numbers | 498 | 128 | 120 | 75 | 26 | 20 | 19 | 17 | 16 |
| Pathogenic organism unknown | 377 (76%) | 102 (80%) | 106 (88%) | 61 (81%) | 24 (92%) | 16 (80%) | 15 (79%) | 15 (88%) | 15 (94%) |
| Bacteria (total cases) | 105 | 17 | 9 | 13 | 2 | 4 | 4 | 1 | 1 |
| Enterotoxigenic *Escherichia coli* | 3 | 5 | 2 | 1 | 0 | 1 | 1 | 0 | 0 |
| Enteroinvasive *E. coli* | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enteropathogenic *E. coli* | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Enterohaemorrhagic *E. coli* | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Plesiomonas shigelloides* | 2 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Vibrio parahaemolyticus* | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Vibrio cholerae* | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Salmonella* spp. | 11 | 0 | 0 | 5 | 0 | 0 | 1 | 0 | 0 |
| *Shigella* spp. | 13 | 0 | 1 | 0 | 2 | 0 | 0 | 0 | 1 |
| *Campylobacter* spp. | 70 | 10 | 5 | 7 | 0 | 3 | 2 | 1 | 0 |
| Viruses (total cases) | 2 | 3 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Norovirus | 0 | 2 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Rotavirus | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Protoza (total cases) | 14 | 6 | 4 | 0 | 0 | 0 | 0 | 1 | 0 |
| *Cryptosporidium* spp. | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| *Giardia lamblia* | 5 | 6 | 1 | 0 | 0 | 0 | 0 | 1 | 0 |
| *Entamoeba histolytica* | 8 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 |

Second, the low causative organism detection rate may be due to in-hospital testing differences. For instance, polymerase chain reaction methods, such as the FilmArray Gastrointestinal Panel (BioFire Diagnostics, Salt Lake City, UT, USA), may be more sensitive for detecting pathogens than conventional stool cultures (*10*). In the present study, only two facilities reported positive results for viruses. Thus, we suspect that identifying the causative organisms is easier in facilities with such capabilities, whereas facilities with less advanced testing capabilities report a higher percentage of cases with unknown causative organisms. Moreover, patients with unknown organisms included those with stool culture tests that did not reveal diarrheagenic organisms and those who did not undergo stool culture tests. Possibly, most patients for whom stool cultures were not performed may have visited hospitals after their diarrhea had improved, suggesting that they could have surpassed the inflammatory extreme stage. Therefore, CRP levels might be lower in this study's group of patients with unknown bacteria. Importantly, the association between CRP and bacterial enteritis is the same as that previously reported (*11*). These factors may have influenced the study results, and we believe that it is necessary to improve the registry studies in the future to accurately determine the contents and severity of the tests performed.

Third, statistics on the antimicrobial use type and duration were lacking in this study. Thus, collecting antimicrobial therapy data would be beneficial as it could encourage the reduction of unnecessary antibiotic administration in the future, suppressing resistant bacterial strains. Generally, TD is self-limiting without antimicrobial therapy (*1*). In this study, 58/731 patients (8%) with unknown causative organisms were prescribed antimicrobial drugs. Thus, investigating whether antimicrobial therapy is essential may prevent unnecessary prescription of antibacterial drugs. Consequently, in future J-RIDA registry studies, we would like to include the antimicrobial administration type and duration, as well as treatment and prognosis factors.

In conclusion, this study retrospectively analyzed TD cases in patients who returned to Japan after traveling abroad to determine the causative organisms by travel region. The CRP level may help rule out bacterial diarrhea and prevent unnecessary antimicrobial administration when patients cannot provide a stool specimen.

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

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# Right hemihepatectomy preserving the fluorescently visible paracaval portion of the caudate lobe

Masaharu Kogure[1], Masamitsu Kumon[2], Ryota Matsuki[1], Yutaka Suzuki[1], Yoshihiro Sakamoto[1,*]

[1] Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, Tokyo, Japan;
[2] Noichi Central Hospital, Kochi, Japan.

**Abstract:** The paracaval portion (PC) of the caudate lobe is a small area of the liver located in front of the inferior vena cava. Conventional right hemihepatectomy (RH) along the Rex–Cantlie line involves resection of not only the anterior and posterior sections but also the PC behind the middle hepatic vein (MHV). However, to preserve the future liver remnant volume as much as possible, PC-preserving RH may be beneficial in selected patients. We injected an indocyanine green (ICG) solution in the PC portal branch under intraoperative ultrasonography (IOUS) guidance and performed an RH preserving the fluorescently visible PC in a patient with liver metastasis. The patient was a 47-year-old male with a 24 ×10 cm metastatic hepatic tumor from sigmoid colon cancer. CT volumetry revealed that the left hemiliver excluding the caudate lobe was 55%, and the caudate lobe was 5.3%. Before hepatic transection, the ICG solution was injected into the PC portal branch under IOUS guidance. During hepatic transection, the PC was identified as a fluorescent area behind the MHV using a near-infrared imaging system. Thus, the anatomical right-side boundary of the caudate lobe was clearly found. Following RH, the PC was preserved as a fluorescently visible area. The patient had an uneventful recovery. RH preserving the fluorescently visible PC of the liver is a feasible procedure.

***Keywords*:** caudate lobe, colorectal liver metastasis, indocyanine green, paracaval portion, right hemihepatectomy

## Introduction

Right hemihepatectomy (RH) of the liver is a standard procedure to remove an anatomically right-sided hemiliver. In 1949, Honjo performed the first RH (*1,2*) followed by Lotart–Jacob in 1951 (*3*), where the right hemiliver was resected concomitant with the right hepatic artery, portal vein, and hepatic veins regardless of the preservation of the middle hepatic vein (MHV). Conventional standard RH along the Rex–Cantlie line exposing the MHV on the transection plane (*4*) has been first presented by Hasegawa (*5,6*). According to Kumon's classification, the dorsal area of the MHV corresponds to the paracaval portion (PC) of the caudate lobe (*7,8*), and the conventional RH involves resection of the PC of the caudate lobe. Recently, Kumon *et al*. described the right-side boundary of the caudate lobe based on portal segmentation using liver casts (*9*). However, visualizing the right-side boundary of the caudate lobe during parenchymal transection has been considered challenging.

This is the first report of intraoperative identification and preservation of the fluorescently visible PC of the caudate lobe during RH.

## Case characteristics

The patient was a 47-year-old man with a 24 × 10 cm synchronous liver metastasis occupying the right lobe of the liver from sigmoid colon cancer (Figure 1A). Although the colon cancer was a circumferential type 2 lesion, the patency of the bowel was well preserved. Therefore, considering the rapid progression of the hepatic tumor, the liver-first approach was performed. Preoperative CT volumetry revealed that the left hemiliver (S2–4) and the total caudate lobe were 55% and 5.3% of the total liver volume, respectively. The indocyanine green (ICG) retention rate at 15 min was 5.8%, suggesting normal liver function. On gadolinium–ethoxybenzyl–diethylenetriamine pentaacetic acid (Gd–EOB–DTPA)-enhanced magnetic resonance imaging, a thick PC branch occupying a small lesion behind the MHV was noted in accordance with cranial branches from the anterior and posterior portal veins (Figure 1B–1E). These findings suggested that if the right-side boundary of the PC could be identified during liver resection, PC-preserving RH may be feasible to preserve the liver parenchyma as much as possible.

## Surgical technique

Liver mobilization was performed after laparotomy with thoracotomy. Following right hepatic artery ligation,

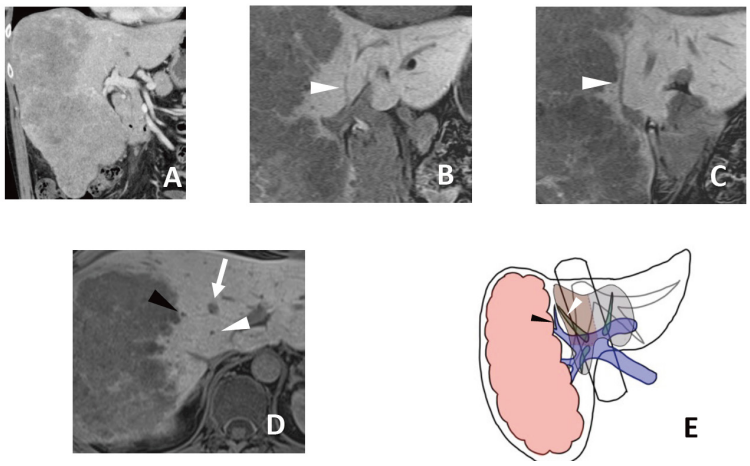


**Figure 1. Radiological findings. (A)** Preoperative contrast-enhanced CT imaging in the coronal section. The tumor occupies the right lobe. **(B)** Preoperative Gd–EOB–DTPA-enhanced magnetic resonance imaging in the hepatobiliary phase. The PC branch (arrowhead) from the hilar bifurcation area is observed in the coronal section. **(C)** Cranial branch from the anterior portal vein (arrowhead) is observed in the coronal section. **(D)** PC branch (white arrowhead), cranial branch from the anterior portal vein (black arrowhead), and MHV (arrow) are observed in the axial section. **(E)** Schema of the anatomy of the patient. The PC branch (white arrowhead) corresponds to the PC (brown area) of the caudate lobe. The cranial branch from the anterior portal vein (black arrowhead) corresponds to the cranial region of the anterior sector adjacent to the PC of the caudate lobe. Gd–EOB–DTPA, gadolinium–ethoxybenzyl–diethylenetriamine pentaacetic acid; PC, paracaval; MHV, middle hepatic vein.

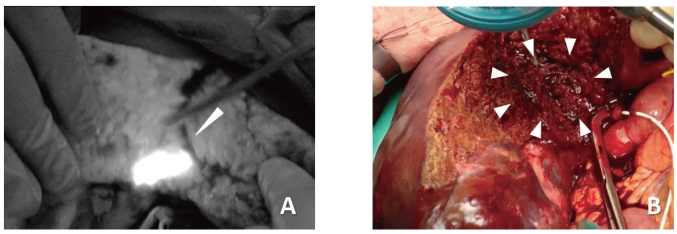


**Figure 2. Operative findings. (A)** Behind the MHV (arrowhead), a small fluorescence area is visualized, which corresponds to the stained PC of the caudate lobe. **(B)** PC (arrowhead) existed behind the MHV and above the hepatic hilum in the cut surface. MHV, middle hepatic vein; PC, paracaval.

the right portal vein was ligated and divided on the distal side of the PC portal branch bifurcation, which was confirmed using intraoperative ultrasonography (IOUS). An indigo carmine plus ICG solution (0.25-mg ICG and 5-mg indigo carmine) was injected into the PC portal branch under IOUS guidance. However, no fluorescence area except for fluorescing tumor due to preoperative venous ICG injection for liver function test was observed on the liver surface using a near-infrared image system (PDE NEO; Hamamatsu Photonics, Hamamatsu, Japan). The right hepatic duct was divided following intraoperative cholangiography.

Hepatic transection was performed along the Rex–Cantlie line using the clamp crushing method under Pringle's maneuver. The main trunk of the MHV was exposed to the cut surface and preserved in the left hemiliver. Behind the MHV, a small fluorescence area was visualized, which corresponded to the stained PC of the caudate lobe (Figure 2A and 2B). The fluorescently visible PC was preserved with the left hemiliver, and RH was completed.

The operative time was 6 h and 45 min, and the estimated blood loss was 140 mL. On day 7, a self-expandable metallic stent (Niti-S stent, Taewoong Medical, Seoul, Korea) was placed in the sigmoid colon to treat circumferential colon cancer-associated obstructive colitis. On day 16, the patient was discharged without any significant morbidity. Laparoscopic sigmoidectomy was successfully performed 36 days following hepatectomy. The patient received systemic chemotherapy for the treatment of multiple liver metastases detected 7 months following hepatectomy.

## Discussion

By injecting dye into the PC portal branch under IOUS guidance, it was possible to identify the right-side boundary of the PC and preserve the PC of the liver.

In 1949, Honjo first performed RH. In 1950, he described his RH in Japanese (*1*) and in 1955 in English. He did not intentionally expose the MHV to avoid bleeding (*2*). In 1951, Lotart–Jacob performed RH combined with MHV resection and published it in 1952 (*3*). In 1982, Bismuth described RH with a middle division of the MHV (*10*). In 1975, published in Japanese, Hasegawa proposed RH exposing the MHV along the intersegmental plane between the right and left hemilivers (*5*). In 1980, his idea was introduced as the

"cherry fruits theory" or "banana theory" in French (*6*). Since then, RH exposing the MHV on the cut surface to its root has been considered an anatomically precise RH; however, there have been no arguments regarding right caudate lobe resection during RH. To preserve the future liver remnant volume and minimize the risks of posthepatectomy liver failure, it may be acceptable to preserve the whole caudate lobe during RH.

The anatomical boundary of the caudate lobe has been controversial. Couinaud defined the caudate lobe as a dorsal liver based on the spatial position against the major hepatic veins and inferior vena cava. He classified the caudate lobe into segments I and IX or other variations (*11-13*), however, in 2000, he finally abandoned his idea (*14*) and accepted the definition proposed by Kumon (*8*). Kumon defined the caudate branches as dorsal branches ramified from the first-order branch or main trunk of the portal vein (*8,15*). Regarding the right-side boundary of the caudate process, using a cadaver liver, Kogure proposed that the hepatic vein of the caudate process can be the landmark between the right liver and caudate lobe (*16*). Maki *et al*. reported that the PC branches reached the right subphrenic surface of the liver in one-third of cases (*17*). In this case, the PC area could not be fluorescently visualized before hepatic transection. In a clinical setting, the right-side boundary of the PC will be important for determining the hepatic transection line during caudate lobectomy; RH; anatomical resection of the anterior section and segments 6, 7, and 8; or extended left hemihepatectomy with caudate resection for perihilar cancer.

Takayama determined the right-side boundary of the caudate lobe using the counter-staining technique by injecting dye into the posterior portal vein before isolated caudate lobectomy (*18*), which is similar to the negative staining technique during recent laparoscopic anatomical hepatectomy using ICG fluorescence imaging (*19*). However, in negative staining, the caudate lobe may be overestimated, because some branches may present at the root of the posterior portal vein, and the area supplied by these branches will be recognized as the caudate lobe. In the present case, we directly inject dyes into the PC to stain the PC and right-side boundary of the caudate lobe. We must concede that the PC branch may be excessively thin to precisely inject the dye solution at all times. Preoperative identification of the PC branch by imaging study will be important. This technique may be used to identify the anatomical area of PC during caudate lobectomy; RH; anatomical resection of the anterior section and segments 6, 7, and 8; or extended left hemihepatectomy with caudate resection for perihilar cancer.

In conclusion, RH preserving the PC of the liver is a feasible procedure by identifying the PC using ICG fluorescence imaging. This technique can be applied in other anatomical hepatectomy procedures to identify the caudate lobe boundary.

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

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*Address correspondence to*:
Yoshihiro Sakamoto, Department of Hepato-Biliary-Pancreatic Surgery, Kyorin University Hospital, 6-20-2 Shinkawa, Mitaka-City, Tokyo 181-8611, Japan.
E-mail: yosakamo@ks.kyorin-u.ac.jp

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# Prevention of cuff injury of the intubation tube by blunt window opening in tracheostomy

Kenshiro Taniguchi*, Katsuhiro Tsutsumiuchi, Yukiko Sagara, Niro Tayama

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

**Abstract:** One of the intraoperative complications of tracheostomy under general anesthesia is cuff injury of the intubation tube. In the present study, we investigated whether a blunt tracheal opening is a useful method to avoid cuff injury. A retrospective cohort study was conducted to examine patients who underwent tracheostomy under general anesthesia at a single institution from January 1, 2017 to July 31, 2021. Electrocautery was used to thin the connective tissue between the tracheal rings, and bluntly open the trachea with mosquito forceps or similar instruments. Primary outcomes included cuff injury rate, number of surgeons involved, and career as otolaryngologist at the time of surgery. The secondary outcome was perioperative complications. Of the 64 cases, 3 had cuff injuries. 2 of the 3 had cuff injuries during the creation of an anteriorly based flap. 16 surgeons were involved ranging from the first to sixth year as an otolaryngologist, with the third year of otolaryngologist being the most common. The median physician year for instructors was 18 years. The most common postoperative complication was granulation in 9 cases. There were no cases of incorrect cannula insertion or difficulty in cannula insertion. A blunt tracheal opening was considered useful as a method to prevent cuff injury.

***Keywords*:** tracheostomy, cuff injury, blunt window opening, aerosol's generation

## Introduction

Tracheostomy is one of the oldest and most commonly performed procedures in respiratory critically sick patients. Tracheostomy is the process of creating an opening in the anterior wall of the trachea. Surgical tracheostomy refers to placement of a tracheostomy cannula under direct vision after dissection of pretracheal tissues and incision of the tracheal wall. When opening the trachea, incisions with scalpels are generally known. Premature intubation tube cuff injury, which can occasionally occur during tracheostomy, can result in failure of ventilation and poor visualization (*1*).

In this study, we describe a simple change from the method of cutting the trachea with a scalpel to the method of bluntly opening the trachea in order to reduce the probability of cuff injury and thus prevent ventilation difficulties and aerosol generation.

We also examined whether this technique can be performed by anyone as a standard procedure. Furthermore, by examining the perioperative complications, we examined whether this is a safe method of tracheostomy. We will demonstrate the method and its effectiveness so that the surgeon who reads this paper can immediately put it into practice.

## Patients and definitions

The present, retrospective cohort study was performed at National Center for Global Health and Medicine from January 2017 to August 2021 and enrolled patients who underwent tracheostomy in the Department of Otolaryngology under general anesthesia. Tracheostomy cases associated with other surgeries, such as facial bone fracture surgery, were excluded. Cases that were not anesthetized by an anesthesiologist were excluded. Tracheostomy is only surgical tracheostomy and does not include percutaneous dilatational tracheostomy. All patients underwent tracheostomy because of the prospect of long-term intubation. The tracheostomy procedure performed in our department consists of tracheal fenestration, which is suturing the tracheal window with surrounding skin. This is to prevent accidental cannula insertion to the outside of the trachea.

The study protocol was approved by the ethics committee at National Center for Global Health and Medicine (approval no. NCGM-S-004370-00).

## Study design

The patients' demographic and baseline data were

collected from the electronic medical records at National Center for Global Health and Medicine. Age at surgery, gender, height, weight, BMI, and co-morbidities were collected. The use of antithrombotic and anticoagulant drugs was examined. Outcome of hospitalization and duration of hospitalization were also examined. Perioperative records were investigated for operative time, anesthesia time, blood loss, cuff injury, tube movement before tracheostomy, cuff position during tracheostomy, and disturbance of EtCo2. The number of surgeons involved in our tracheostomy and the number of years as an otolaryngologist were also examined. Postoperative complications included postoperative bleeding, postoperative infection, tube occlusion, tracheal granulation, incorrect insertion of the cannula, and difficulty in cannula exchange.

The primary outcome was the presence of cuff damage, referring to surgical and anesthesia records and changes in EtCo2. The number of cases in which the cuff was directly underneath the tracheostomy window was also examined. We also examined whether the intubation tube was moved caudally to shift the position of the cuff caudally before opening the trachea. In addition, the number and year of the surgeons and instructors involved in tracheostomy in our hospital were examined to determine its validity as a standard procedure that does not require special skills that only expert surgeons can perform. The goal is to show that this surgical procedure is effective in preventing cuff damage and does not require special skills.

As secondary outcomes, we evaluated the safety of tracheostomy performed in our department by assessing postoperative complications.

**Surgical tracheostomy techniques**

There is no special procedure until the anterior tracheal wall is exposed. The tracheotomy is usually carried out in the 2nd or 3rd tracheal rings. The power of the electrocautery is set at 25 watts. When cauterizing the peritracheal area, the oxygen concentration is kept close to room air to ensure that no high concentrations of oxygen are delivered.

Electrocautery was used to gradually thin the connective tissue between the tracheal rings (Figure 1A). The tracheal mucosa is cauterized until only a thin layer is left (Figure 1B), and bluntly open the trachea with mosquito forceps or similar instruments (Figure 1C). If the cuff is visible (Figure 1D), the intubation tube is pushed caudally by the anesthesiologist. An anteriorly based flap is then created with surgical scissors and the skin and flap are sutured. In our hospital, for patients who are expected to be intubated for a long period of time, the tracheal window and skin are sutured together (Figure 1E). Even when long-term cannula placement is not anticipated, the four corners of the tracheal foramen are sutured to the surrounding skin to prevent stenosis and facilitate cannula replacement. As the cuff is not injured, the suturing procedure can be fully performed.

**Baseline characteristics and primary outcome**

Sixty-four patients met the inclusion criteria. The patients' demographic and perioperative baseline data are shown in Table 1. Median operation and anesthesia time were 44 and 84 minutes. Median amount of bleeding was low.

Primary outcome is also shown in Table 1. The cuff was injured in three (4.7%) cases. Disturbance of EtCo2 was also observed in the same cases. In two of the three cases, the cuff was injured when creating the anteriorly based flap, not when opening the trachea. When the trachea was opened, the cuff was found directly below the opening in 28 (43.8%) cases. In five cases, the intubation tube was moved caudally before opening the trachea. However, in one of the five cases, the cuff was found just below the tracheal opening. 16 otolaryngologists were performing the procedure. The median experience of the surgeon as an otolaryngologist was 3 years. The median physician year for instructors was 18 years.

**Preventing cuff technique**

A well-known method of preventing cuff injury is to move the cuff caudally before opening the trachea, which

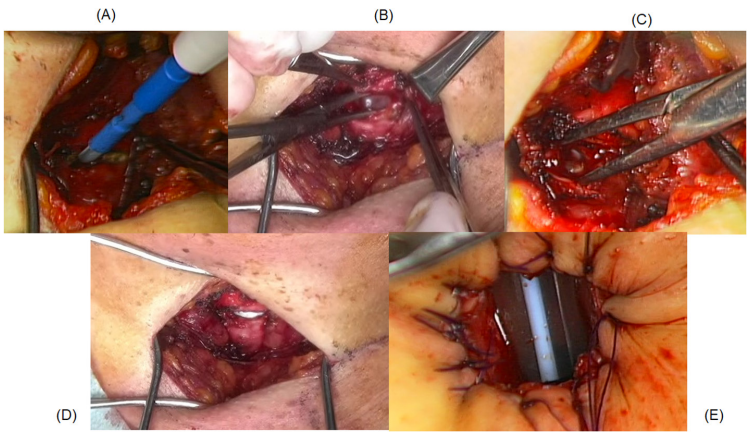


**Figure 1. Surgical technique. (A)** electrocautery was used to gradually thin the connective tissue between the tracheal rings, **(B)** the tracheal mucosa is cauterized until only a thin layer is left, and **(C)** bluntly opening the trachea with mosquito forceps or similar instruments. **(D)** If the cuff is visible, the intubation tube is pushed caudally by the anesthesiologist. **(E)** For patients who are expected to be intubated for a long period of time, the tracheal window and skin are sutured together.

**Table 1. The patients' demographic and perioperative baseline data and primary outcome**

| *The patients' demographic and perioperative baseline data* | | |
|---|---|---|
| The number of patients | 64 | |
| median Age | 70 (60–77) | |
| Male | 44 (69%) | |
| Female | 20(31%) | |
| median Height(cm) | 163 | |
| median Weight(kg) | 59.3 | |
| BMI(median) | 22.8 | |
| median Operation time(min) | 44 (39–54) | |
| median Anesthesia time(min) | 84 (72–93) | |
| median Amount of Bleeding | few | |
| *Primary Outcome* | | |
| ① Cases of the cuff injury | | |
| Cuff injury | 3/64 | 4.68(%) |
| Changes in EtCo2 | 3/64 | |
| ② Positioning of the cuff | | |
| Cuff directly under the tracheal opening | 28*/64 | 43.8(%) |
| Cuff located cephalad to the tracheal opening | 1/64 | |
| ③ Moving of the cuff | | |
| Caudal move of intubation tube before tracheostomy | 5/64 | |
| ④ Surgeons included | | |
| Total number of surgeon | 16 | |
| Median years of practicing otolaryngologist | 3 | |
| Median number of years of instructing physician | 18 | |

The cuff was injured in three (4.7%) cases. In two of the three cases, the cuff was injured when creating the anteriorly based flap, not when opening the trachea. The cuff was found directly under the opening in 28 (43.8%) cases. Sixteen otolaryngologists performed the procedure and the median experience of the surgeons as an otolaryngologist was 3 years. *In one case, the cuff was found just below the window opening even though the intubation tube was moved caudally.

was reported to have prevented cuff injury in 123 of 129 cases (*2*). However, there are cases in which the tube was not moved caudally properly. In our study, there was one case in which the cuff was found directly under the tracheal opening even after the tube was actually moved, and one case in which the cuff was located cephalad to the opening when the trachea was opened. When opening the trachea, incisions with scalpels are generally known, but a blunt opening is rarely seen. With this technique, theoretically, the possibility of cuff injury can be reduced to almost zero because the trachea is opened bluntly. In two of the three cases where the cuff was injured, the injury occurred when the flap was made, not when the trachea was opened. In this study, there were 28 cases (43.8%) in which the cuff was directly under the tracheal opening, suggesting that there is a high risk of cuff injury if no precautions are taken. If the cuff is directly under the tracheal opening, there is always a possibility of injuring the cuff as long as the trachea is opened sharply with a scalpel, no matter how carefully it is done.

**Establish the standardization of surgery**

Tracheostomy is a basic surgical technique for the airway, and it is likely that many young otolaryngologists will be the primary surgeons. In particular, tracheostomies for non-urgent, intubated patients under general anesthesia are likely to be performed by younger surgeons. If the cuff is injured during tracheal opening, ventilatory management becomes unstable (*1*), and it is difficult to perform the settled surgery. It is very important to ensure a settled operation in order to reduce patient burden and to allow young surgeons to complete the operation. A total of 16 otolaryngologists with less than 6 years of experience in otolaryngology were involved in the tracheostomy at our hospital. With standard surgical skills, this procedure is considered practicable.

**Secondary outcome**

Postoperative complications, including minor ones, were observed in 19 cases. The most common complication was granulation in 9 cases, but none of them resulted in airway stenosis, only small granulation around the trachea that did not affect the airway or cannula exchange. Granulation is considered to be generated by stimulation of cannula insertion, and it is assumed that suturing the tracheal opening to the surrounding skin prevented the formation of a large granulation. Accidental decannulation was observed in 6 patients, but there was no stenosis of the tracheal canal in all cases, so there was no case of difficulty in cannula insertion. Difficulty in reinserting the cannula after decannulation would be a serious problem, but the stable tracheal opening led to the avoidance of cannula insertion difficulties. In one case, minor bleeding from the airway was observed 2 months after surgery, but no specific cause could be identified. Other cases were 2 cases of recurrent aspiration, 1 case of infection, 1 case of subcutaneous emphysema, and 1 case of tube obstruction.

Antithrombotic and anticoagulant drugs were used in 14 cases. However, none of them had a problem with perioperative bleeding. The process of thinning the trachea with electrocautery is also advantageous in that it reduces bleeding when the trachea is opened.

As for the outcome of hospitalization, 28 patients were discharged dead, 31 patients were transferred, and 5 patients were discharged home.

**Complications of tracheostomy**

Complications of tracheostomy can be divided into intraoperative, early, and late. Intraoperative complications include hemorrhage; pneumomediastinum, pneumothorax, and recurrent laryngeal nerve injury; and cuff rupture of the intubation tube. Early complications include hemorrhage, tracheitis, mucous plugging, accidental decannulation, subcutaneous emphysema, and swallowing problems (*3*). Late complications can include tracheal stenosis from excessive granulation tissue, tracheomalacia, tracheoesophageal fistula, tracheoinnominate artery fistula, and recurrent aspiration (*4*).

Tracheostomies are generally considered safe

procedures, but can result in untoward complications. In a recent survey of American Academy of Otolaryngology–Head and Neck Surgery members, it was calculated that 55% of otolaryngologists cared for at least 1 patient who underwent tracheostomy that resulted in a catastrophic complication (*5*). In particular, the overall incidence of tracheostomy complications has been suggested to be 3.2% (*6*). In proposing a new surgical method in the present study, the trachea was opened bluntly, and there seemed to be no significant complications compared to the common complications of tracheostomy.

**Tracheal fenestration**

The development of granulation causes difficulty in replacing the tracheostomy tube, and may delay decannulation and interfere with the function of the tracheostomy. Obstruction related to granulation tissue has been cited as the cause of death in several patients (*7*). Using a surgical technique that mobilizes cervical skin flaps to create a circumferential mucocutaneous junction at the window has been suggested as a method to decrease development of granulation tissue. This technique has been suggested for patients who are thought to need a "permanent" or long-term tracheostomy (*7,8*).

In order to facilitate cannula management without the need for an otolaryngologist who is experienced in airway management, we perform tracheotomy with tracheal fenestration, in which the tracheal window and skin are fixed in a circumferential fashion.

In order to perform tracheal fenestration, it is necessary to open the trachea without injuring the cuff and then allow time for suturing the tracheal window to the skin.

**Prevention of Aerosol generation**

Many societies have recommended that Aerosol-Generating Procedures be avoided as much as possible and tracheostomy is said to be an Aerosol-Generating Procedure (*9*). In general, tracheostomy is associated with an increased production of aerosols and a higher risk of viral transmission to healthcare personnel (*10*). Injury of the cuff during tracheostomy increases the risk of infection from some virus from the patient to the surgeon.

Avoidance of Aerosol-Generating Procedures will continue to be important not only for new coronaviruses but also for general infection control. Therefore, it is strongly recommended that this technique, which bluntly opens the trachea to prevent cuff tube injury, be used as the standard procedure to prevent aerosol generation.

In conclusion, compared to sharp opening, blunt opening of the trachea is a very useful method in establishing a safe tracheostomy, because it requires no special skills and prevents damage to the cuff of the intubation tube.

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**Address correspondence to*:
Kenshiro Taniguchi, Department of Otolaryngology, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku, Tokyo 162-8655, Japan.
E-mail: ktani2020office@gmail.com

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**Abstract**: ~250 words (Original Articles, Brief Reports, Reviews, Policy Forum); ~150 words (Communications, Editorials, Letters, and News).
***Keywords***: 3~6 words

**Brief Reports** definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references. Brief Reports should be structured as follows: Title page, Abstract, Introduction, Materials and Methods, Results and Discussion, Acknowledgments, References, Figures and/or Tables; and Supplementary Data, if appropriate.

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

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

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

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

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

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

## 3. Formatting Guidelines

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

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

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

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

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

For manuscript samples, please visit *https://www.globalhealthmedicine.com/site/download.html* (Download Center).

Please provide all figures as separate files in an acceptable format (TIFF

or JPEG). Supplementary Data should also be submitted as a single separate file in Microsoft Word format.

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

**4. Manuscript Preparation**

**Title page:** The title page must include 1) the title of the paper (Please note the title should be short, informative, and contain the major key words); 2) full name(s) and affiliation(s) of the author(s), 3) abbreviated names of the author(s), 4) full name, mailing address, telephone/fax numbers, and e-mail address of the corresponding author; and 5) conflicts of interest (if you have an actual or potential conflict of interest to disclose, it must be included as a footnote on the title page of the manuscript; if no conflict of interest exists for each author, please state "There is no conflict of interest to disclose").

**Abstract:** The abstract should briefly state the purpose of the study, methods, main findings, and conclusions. For articles that are Original Articles, Brief Reports, Reviews, or Policy Forum articles, a one-paragraph abstract consisting of no more than 250 words must be included in the manuscript. For Communications, Editorials, Letters, and News, a one-paragraph brief summary of the main content in 150 words or less should be included in the manuscript. Abbreviations must be kept to a minimum and non-standard abbreviations should be explained in brackets at first mention. References should be avoided in the abstract. Three to six key words or phrases that do not occur in the title should be included on the Abstract page.

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

**Materials/Patients and Methods:** The description should be brief but with sufficient detail to enable others to reproduce the experiments. Procedures that have been published previously should not be described in detail but appropriate references should simply be cited. Only new and significant modifications of previously published procedures require complete description. Names of products and manufacturers with their locations (city and state/country) should be given and sources of animals and cell lines should always be indicated. All clinical investigations must have been conducted in accordance with the Declaration of Helsinki (as revised in 2013, *https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki*). All human and animal studies must have been approved by the appropriate institutional review board(s) and a specific declaration of approval must be made within this section.

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

**Acknowledgments:** All funding sources should be credited in the Acknowledgments section. In addition, people who contributed to the work but who do not meet the criteria for authors should be listed along with their contributions.

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

Examples are given below:

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Kokudo N, Hara T. "History, Tradition, and Progress": The ceremony of 150th Anniversary of the National Center for Global Health and Medicine held in Tokyo, Japan. BioSci Trends. 2019; 13:105-106.

*Example 2 (Sample journal reference with more than 15 authors)*:
Darby S, Hill D, Auvinen A, *et al*. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005; 330:223.

*Example 3 (Sample book reference)*:
Shalev AY. Post-traumatic stress disorder: Diagnosis, history and life course. In: Post-traumatic Stress Disorder, Diagnosis, Management and Treatment (Nutt DJ, Davidson JR, Zohar J, eds.). Martin Dunitz, London, UK, 2000; pp. 1-15.

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World Health Organization. The World Health Report 2008 – primary health care: Now more than ever. *http://www.who.int/whr/2008/whr08_en.pdf* (accessed March 20, 2022).

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

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

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

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