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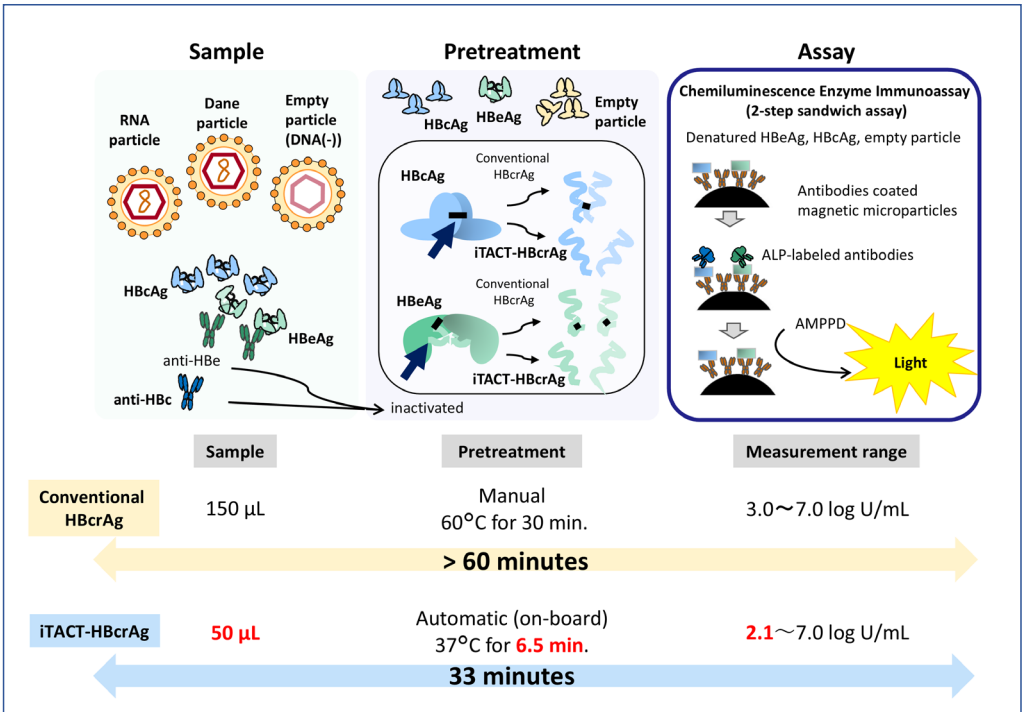


Comparison of the conventional and highly sensitive HBcrAg assays (Page 68)

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Global Health & Medicine

# Global Health & Medicine

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# Global Health & Medicine

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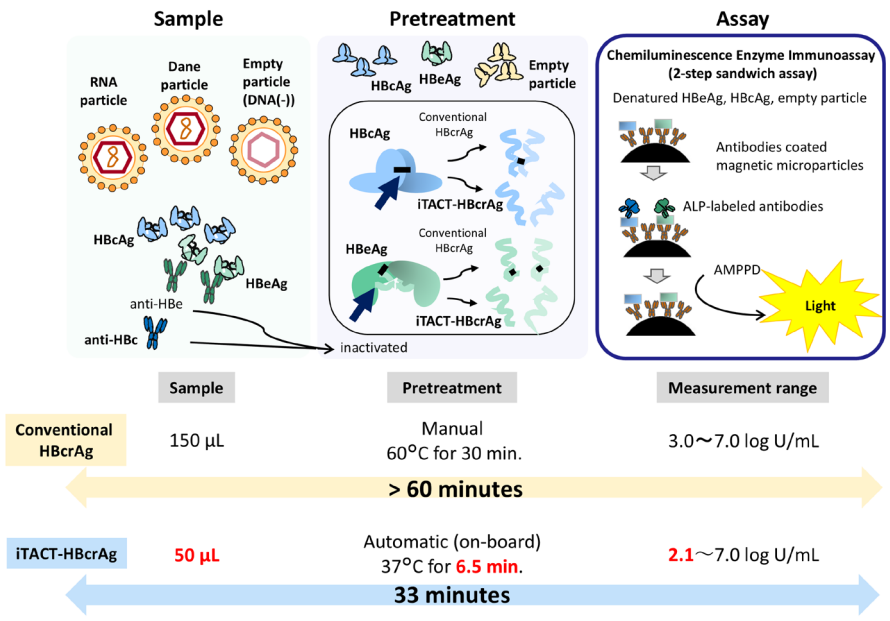


**Comparison of the conventional and highly sensitive HBcrAg assays.** The figure compares the iTACT-HBcrAg assay with a conventional assay, divided into sample, pretreatment, and assay sections. The illustration at the top of the figure shows a schematic of the iTACT-HBcrAg measurement system. The bottom of the figure contrasts these two assays in terms of sample amount required for measurement, measurement time, and measurement range (sensitivity). (Page 68)

Global Health & Medicine. 2025; 7(1):1-12. REVIEW
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# A review of epidemiology, diagnosis, and management of Mpox: The role of One Health

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**Abstract:** Human monkeypox (Mpox) is an emerging zoonotic disease. Its clinical features are similar to but less severe than those of smallpox. The etiology of this disease is the monkeypox virus. This virus is a double-stranded DNA virus that is classified into the genus *Orthopoxvirus* and the family *Poxviridae*. Human monkeypox was first identified in 1970 and mainly occurred in Central and Western Africa. In 2022, outbreaks of Mpox virus infection occurred in several non-endemic countries and caused a potential threat to humans. It is urgent to take immediate action to control and prevent the outbreak of the Mpox virus infection. This paper summarizes the current status of Mpox and generated strategies for managing the Mpox epidemic. Although progress in the diagnostic methods and treatment of Mpox produces better knowledge, we argue that the sensitive surveillance for animal and human Mpox virus infection and evidence-based response and management of Mpox outbreaks is critical. This study highlights the need for further research on preventive and control strategies for Mpox disease approached through the One Health concept.

***Keywords*:** Mpox, epidemiology, diagnosis, treatment, One Health

## Introduction

Monkeypox (Mpox) is an emerging zoonosis caused by the monkeypox virus (Mpoxv), which is classified into the genus Orthopoxvirus member, and family *Poxviridae*. Four species, including smallpox or *variola virus*, *cowpox virus*, *vaccinia virus*, and Mpox, can cause human infection in the family *Poxviridae* (*1*). Poxviruses are large double-stranded DNA viruses that replicate within the host cell cytoplasm of various vertebrates and invertebrates (*2*). Mpoxv is categorized into Clade I and II, with Clade II further divided into Clade IIa and IIb (*3,4*). The two genetic subtypes of Mpoxv are associated with disease patterns in Central and West Africa. The Central African Mpox viruses are often linked to more severe health outcomes, higher mortality rates, and an increased risk of human-to-human transmission compared to their West African counterparts (*3,4*). The natural reservoirs of the virus in endemic areas are not known. Before the Mpox outbreaks in 2022, many Mpox cases occurred in Central and West Africa. However, since May 2022, the emergence of the Mpox epidemic has occurred in non-endemic countries and has become a significant threat to human health (*5-9*). Investigating the spatial distribution characteristics and risk factors associated with Mpoxv infections is essential to prevent its global spread effectively (*10,11*). In addition, the One Health approach has been proposed as an optimal strategy for preventing and controlling zoonotic infectious diseases (*12,13*). This review provides an overview of the epidemiology, transmission, and management of Mpox disease, offering strategic recommendations for managing and preventing its outbreaks.

## Biology and genetics of Mpoxv

Mature poxvirus particles measure approximately 200 nm in diameter and 300 nm in length, exhibiting an ovoid or brick-like shape (*1*). They feature surface tubules and possess a distinctive dumbbell-shaped nucleoprotein core that houses the viral genome (*1,2*). Mpoxv produces three distinct infectious viral particles: the intracellular mature virus, the cell-associated enveloped virus, and the extracellular virus (*2*). As illustrated in Figure 1, the replication cycle begins with the virus attaching to host cells, leading to the fusion of viral and cellular membranes, releasing the viral core into the cytoplasm

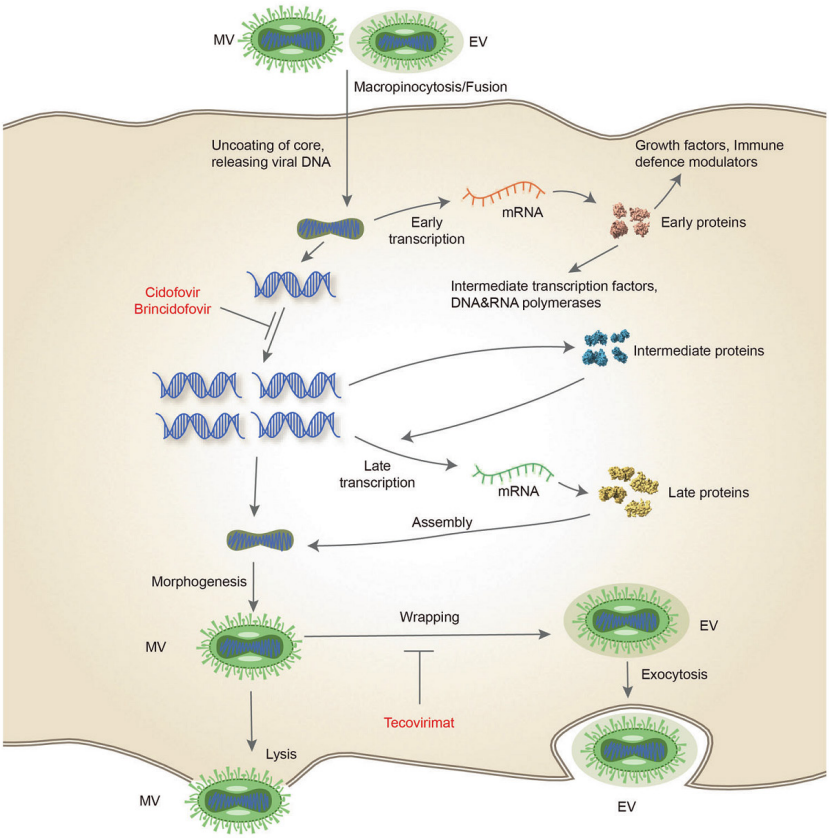


**Figure 1. Mpox virus life cycle.** This diagram depicts the life cycle of the Mpox virus inside a human cell. Notably, the replication cycle of the Mpox virus occurs in the host cell's cytoplasm. MV, mature virus; EV, enveloped virus. (We have obtained permission to use this figure from the journal's editor, and the photograph is courtesy of Huang Y *et al.* (*13*)).

(*13,14*). Notably, poxviruses have a unique characteristic of generating two types of infectious particles: the extracellular virus and mature virions (MVs), each possessing distinct surface epitopes (*14*). Depending on their infectious forms, poxviruses enter host cells through various mechanisms. Mature virions (MVs) possess a single outer membrane, while enveloped virions (EVs) have additional membranes and exhibit different protein compositions (*15*).

Within the viral core, transcription activation takes place, resulting in the synthesis of 118 early messenger RNAs (mRNAs) from the vaccinia virus (*16*). These mRNAs encode enzymes essential for genome replication in the cytoplasm, as well as intermediate-stage transcription factors and immune defense proteins (*13,16*). Following genome replication, 93 mRNAs are transcribed from intermediate and late genes assembled into mature virions (*15,16*). The Mpoxv evolution rate is estimated at 2 × 10^-6, significantly lower than that of SARS-CoV-2, which ranges from 0.8 to 2.38 × 10^-3 (*16*). *In vitro* studies indicate transient gene duplications may occur before further mutational events in orthopoxviruses, potentially facilitating accelerated adaptation to host antiviral defenses (*1,16*).

**Epidemiological characteristics of Mpoxv infection**

In 1958, the virus was first reported among monkeys transported from Africa to an animal facility in Denmark (*17*). Mpoxv has been detected in various wild animals (*17,18*). However, the first human case of Mpoxv infection was diagnosed in a patient aged 9 years old who lived in the Democratic Republic of Congo in August 1970 (*19*). The disease has become endemic in Central and Western Africa since the discovery of the Mpox case; some sporadic cases of infection by local wildlife have been reported among humans (*20,21*). The first outbreak of Mpoxv infection outside the African regions was reported in the United States in 2003 (*22,23*). The attack involved 47 people in five states in the United States and was associated with marmots imported from Ghana, Africa (*23*). Subsequently, imported cases of Mpox have been found in Israel (*24*), the United Kingdom (*25*), and Singapore (*26*).

Twenty cases of Mpoxv infection were first reported in England in May 2022, then the number of Mpox cases rapidly rose worldwide (*27*). It is noted that the first patient with Mpoxv infection in the United Kingdom in 2022 had a history of visiting Nigeria before he was diagnosed. Therefore, all the other confirmed patients would have experienced visiting Nigeria or Africa (*28,29*). This result indicated

that Mpoxv had developed a pattern of community transmission (*28*). The subsequent occurrence of the Mpox epidemic became known worldwide, and it has been proposed that the Mpox epidemic is a potential threat to whole human populations (*30-34*). The Mpox outbreak of 2022 constituted a Public Health Emergency of International Concern, which the WHO declared on 23 July 2022 (*26,27*). On 28 November 2022, the WHO suggested using the word "Mpox" as a replacement for "monkeypox". Both terms will be used for one year, and "monkeypox" is being phased out (*35*).

Figure 2 illustrates the global distribution of Mpox cases reported by the WHO in 2024 (*35*). Since 1 January 2022, Mpox cases have been reported to the WHO by 121 member states across all six WHO regions. As of 31 July 2024, 103,038 laboratory-confirmed cases and 186 probable cases, including 53 fatalities, were reported to the WHO (*35,36*). The ten most affected countries from 1 January 2022 are the United States (*n* = 33,556), Brazil (*n* = 11,841), Spain (*n* = 8,104), the Democratic Republic of the Congo (*n* = 4,385), France (*n* = 4,283), Colombia (*n* = 4,256), Mexico (*n* = 4,132), the United Kingdom (*n* = 4,018), Peru (*n* = 3,939), and Germany (*n* = 3,886). Collectively, these countries account for 80.0% of the global cases reported. In 2024, as of 1 September 2024, 15 countries have reported 3,891 confirmed cases, including 32 deaths. The three countries with the highest number of cases in 2024 are the Democratic Republic of the Congo (*n* = 3,361), Burundi (*n* = 328), and Nigeria (*n* = 48) (*35*).

According to their molecular characteristics, cases of Mpoxv infection reported from Central Africa and West Africa are classified into the Congo Basin (Clade I) and West Africa (Clades IIa and IIb) groups (*3,4*). Previous studies showed that the diseases caused by Clades IIa and IIb most closely resemble the cases in 2022, which occurred in non-endemic countries (*37,38*). It was reported that the fatality rate of the cases caused by Clade IIa and IIb was only approximately 1% (*39*). In contrast, the disease caused by the Clade I virus had a more severe condition, with a case fatality rate of 10% (*37,38*). The evolutionary changes of the viruses in the current outbreak are possibly activated by apolipoprotein B messenger RNA (*40,41*).

Mpox disease has been present in Central and Western Africa since its discovery. The emergence of the Mpox epidemic in 2022 in non-endemic countries has triggered widespread panic globally, raising concerns about a significant threat to human health (*42*). The ongoing Mpox pandemic is attributed to the same viral strain (Clade IIb) that caused outbreaks in Nigeria in 2017 and 2018. The factors contributing to the current Mpox outbreak remain unclear, suggesting that mutations in viral proteins may be affecting phenotype and pathogenesis (*43*). Several risk factors, including climate change, increased international travel, human behavior, and deforestation, are influencing the recent epidemiological trends of Mpox in Africa, where cases are now being reported in non-endemic countries (*44-46*). Given the limited understanding of the epidemiological characteristics of the current outbreak, it is crucial to conduct further detailed epidemiological studies, serosurveys, and continuous surveillance using

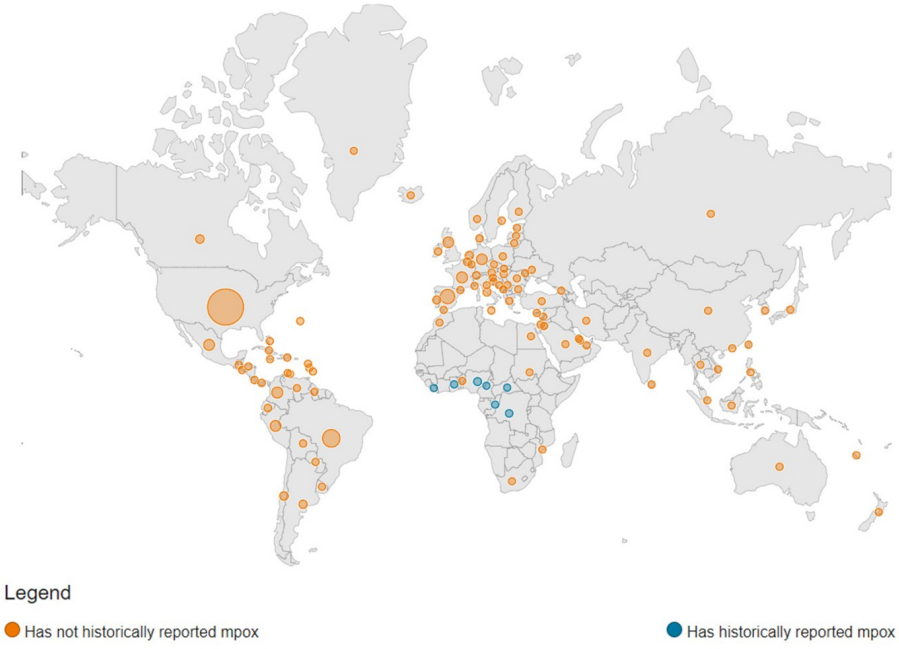


**Figure 2. Distribution Of Mpox Cases by Country between January 2022 and December 2023**. The circle size reflects the number of cases in each country. (The figure is free to use, and the photograph is courtesy of the World Health Organization (*35*)).

the One Health approach to monitor new cases.

**Transmission**

While the definitive host reservoir for Mpoxv is not yet fully established, it is believed that the transmission of Mpoxv to humans is facilitated by wild animals such as squirrels, sooty mangabeys (Cerocebus atys), and Gambian rats, which play significant roles in this process (*47-49*). Figure 3 depicts the potential modes of Mpoxv transmission. Humans can become infected with Mpoxv through animal interactions and person-to-person contact (*47,48*). In endemic countries, Mpox transmission primarily occurs from animals to humans through direct contact with infected animals, often during activities such as hunting, capturing, and processing these animals or their bodily fluids (*5*). This contact can involve scratches, bites, injuries sustained while preparing bushmeat, and direct or indirect exposure to bodily fluids or lesion material (*50*). The virus has been isolated from various species, including the rope squirrel, sooty mangabey, prairie dog, pouched rat, African dormouse, African giant pouched rats, and the elephant shrew (*51*). However, the precise mechanisms by which humans are exposed to infectious sources from these animals remain unclear (*52,53*).

Human-to-human transmission of Mpoxv has been observed in Nigeria and West Africa (*53*). This transmission can occur through several routes, including respiratory droplets, direct contact, vertical transmission, percutaneous transmission, and fomites (*11,50*). Factors recognized as risk factors for infection — including living in the same household, sharing dishes with an infected individual, close contact with skin lesions, and exposure to large respiratory droplets — can elevate the risk of infection to as high as 9% (*11,37,53*). However, during the 2022 outbreak, household transmission was relatively rare, accounting for less than 3% of cases (*9*). This finding suggests that Mpoxv infection is not transmitted through casual contact; instead, it likely requires extended or repeated contact with lesions from individuals infected with Mpoxv.

Additionally, it has been established that contact with contaminated materials, such as sex toys, can facilitate the transmission of Mpoxv infection (*54*). The 2022 Mpox outbreak demonstrated that 73% of individuals in the cohort presented with lesions in the anogenital region, indicating that close contact with infectious sores or lesions on mucous membranes may serve as a primary route of transmission (*9,39,55*). Table 1 shows the demographic characteristics of persons with Mpox infection; the highest risk age group is 31-40 years (39.7%), followed by 21-30 years (29.3%), 41-50 (18.9%); homosexuals, bisexuals, and men who have sex with men (MSM) are the main targets of Mpoxv infection (Table 1) (*9,36*). In endemic countries, children, pregnant women, and immunocompromised subjects are high-risk groups for Mpoxv infection; however, during an outbreak of Mpox in 2022, few children, adolescents, and pregnant women were infected (*9,11,36*).

While some studies have detected Mpoxv in semen (*55,56*), it remains unclear whether Mpox

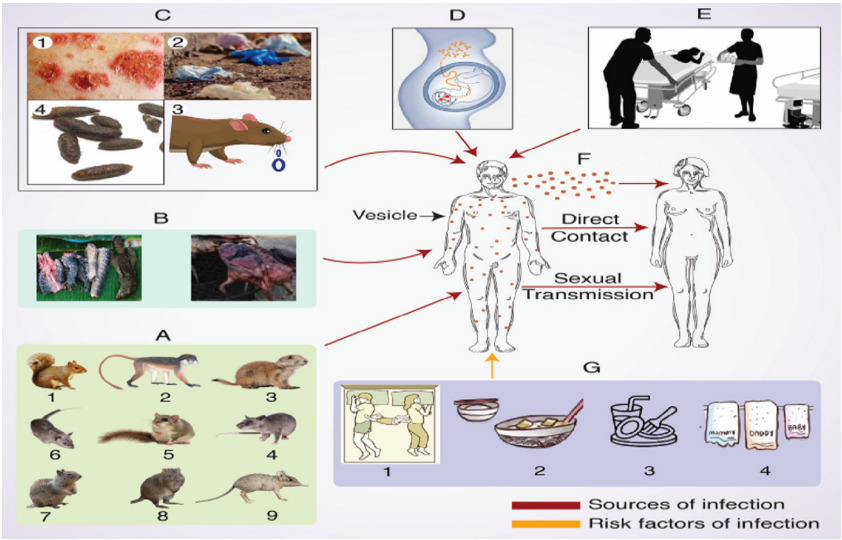


**Figure 3. Transmission of Mpox virus. This schematic illustration shows the different transmission routes. (A)** The number corresponds to the following animals: 1. rope squirrel; 2. sooty mangabey; 3. prairie dog; 4. Gambian pouched rat; 5. African dormice rodent; 6. African giant pouched rat; 7. sun squirrel; 8. rufous-nosed rat; and 9. elephant shrew. **(B)** Represents bush meat consumption as a potential route of transmission. **(C)** The number corresponds to the following: 1. Skin crust; 2. Patients' used materials; 3. Contaminated saliva; 4. Fecal material. **(D)** Illustrates trans-placental transmission, indicating the possibility of the virus passing from mother to fetus. **(E)** Highlights nosocomial infections, which are acquired in healthcare settings. **(F)** Depicts transmission through respiratory droplets and direct contact between individuals. **(G)** Represents scenarios involving sharing personal items such as beds, food, glasses, utensils, and hand towels. (We have obtained permission to use this figure from the authors and the photograph courtesy of Zinnah MA *et al*. (*51*)).

can be transmitted through genital, vaginal, or other bodily secretions (*56,57*). Additionally, it is uncertain if Mpoxv can infect individuals who do not have skin lesions or the extent of the infection risk associated with sexual contact, regardless of sexual orientation or gender identity. Nonetheless, those in close contact with individuals infected with Mpoxv, as well as workers in animal breeding facilities, laborers involved in the slaughter of wild animals, and pet owners, are considered high-risk groups for contracting Mpoxv infection (*36*).

Controlling Mpox will not be feasible without understanding the relationship between the biological characteristics of Mpoxv and human immunity. The rise in reported cases across various countries suggests that specific genomic changes in Mpoxv may have resulted in more efficient transmission and dispersal mechanisms, potentially facilitating sexual transmission (*58*). However, further research is necessary to corroborate this hypothesis.

**Table 1. Demographic characteristics of persons with monkeypox in the United States, 17 May 2022 – 15 March 2023**

| Variables | Number (%) |
|---|---|
| Total | 29,894 (100) |
| Age group (years) | |
| ≤ 10 | 46 (0.2) |
| 11-20 | 692 (2.3) |
| 21-30 | 8,771 (29.3) |
| 31-40 | 11,861 (39.7) |
| 41-50 | 5,641 (18.9) |
| ≥ 51 | 2,883 (9.6) |
| Gender identity | |
| Man | 28,441 (95.1) |
| Transgender man | 67 (0.2) |
| Woman | 879 (2.9) |
| Transgender woman | 272 (0.9) |
| Undetermined | 235 (0.8) |

Data collected from Centers for Disease Control and Prevention and workout this table. (Source: Centers for Disease Control and Prevention (*36*).

## Diagnosis

### *Clinical characteristics of Mpoxv infection*

Mpox is generally considered a mild and self-limiting disease, with a mean incubation period of approximately 7.6 days (95% CI: 6.2-9.7) (*36,48*). The primary classic symptoms of Mpox include fever, malaise, headache, and fatigue, followed by the appearance of bumps, skin lesions, and eventual scarring after scabs have formed (Figure 4) (*5,48,59,60*). Skin lesions are primarily localized on the face, palms, soles, oral mucosa, genitals, and conjunctiva. These lesions evolve and typically resolve in 2 to 4 weeks, transitioning from plaques to pimples to blisters, pimples, and scabs before shedding (*5,61,62*). Skin lesions may appear on the body in quantities ranging from a few to several thousand (*17*). These lesions tend to be uniform in stage and size. While pain associated with the lesions can be significant, it is not universally experienced (*63*). Patients may also exhibit lymphadenopathy or face complications such as secondary bacterial infections (*17,64*). The case fatality rate associated with Mpox ranges from 1% to 10% in the general population. Children and individuals with specific underlying immunodeficiency conditions are at a higher risk for severe complications, including pneumonia, encephalitis, and eye infections, as well as increased mortality (*39*). In contrast to the classic symptoms of Mpoxv infections, common symptoms in the outbreak in 2022 are present with skin rashes or

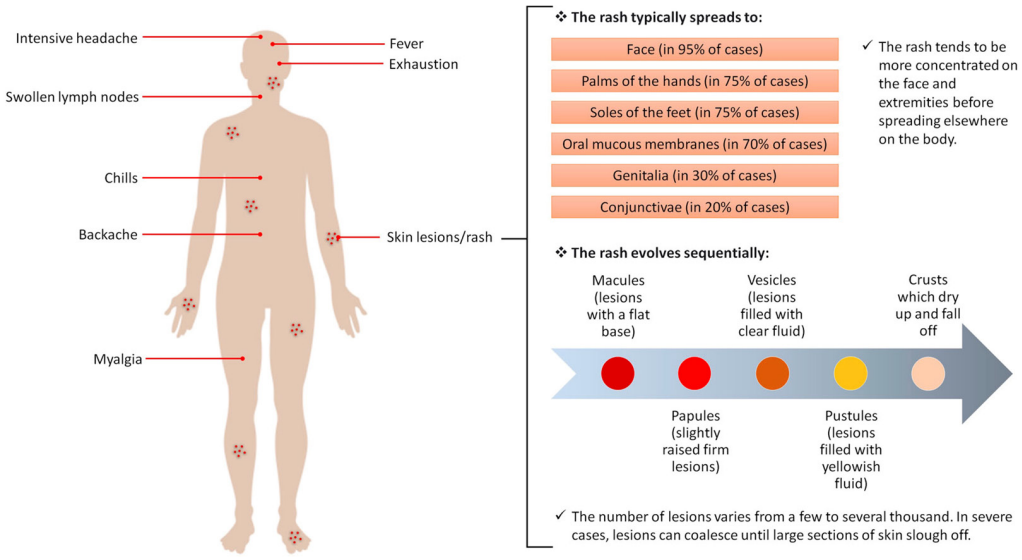


**Figure 4. The main symptoms occur following exposure to the Mpox virus.** (We have obtained permission to use this figure from the authors, and the photograph is courtesy of Hatmal MM *et al.* (*60*)).

lesions (95%), mainly located on the anogenital and perioral mucosal area (*6,9,36,65*). Other symptoms, including fever (58%), lymphadenopathy (53%), lethargy (39%), myalgia (31%), and headache (30%), have also been described in previous studies but do not always precede skin lesions (*8,9,61*). The earlier research, including 528 patients across 16 countries, showed that the most common anatomical sites of skin ulcerations occurred on the anogenital region (73%), body, upper or lower extremities (55%), face (25%), and palms and soles (10%); a majority of persons (90%) presented with multiple skin ulcerations, and approximately 10% of persons had only one single lesion in the genital area (*9*). These findings suggest the relationship between lesions' location and vaccination sites.

*Laboratory tests for Mpoxv*

Mpoxv infection presents as a smallpox-like disease, making it challenging to distinguish Mpox from other conditions that exhibit similar skin lesions at various stages of development. These conditions include herpes simplex virus, varicella-zoster virus, molluscum contagiosum, enterovirus infections, measles, scabies, syphilis, bacterial skin infections, rickettsialpox, drug allergies, papillomaviruses, and other related disorders (*66*). Therefore, laboratory tests are essential for accurately confirming Mpoxv infection (*67,68*). Various laboratory tests are available to diagnose Mpoxv infection. Nucleic acid amplification testing (NAAT), which includes both real-time and conventional polymerase chain reaction (PCR), is used to confirm Mpoxv infection (*69-71*). PCR plays a critical role in distinguishing between viral clades — effectively differentiating the Congo Basin strain (Clade I) from the West African strain (Clade II) — whether used alone or in combination with sequencing methods (*70,71*). PCR tests are the standard method for confirming a diagnosis of Mpox. Patients exhibiting skin lesions associated with Mpoxv infection should undergo further laboratory investigation. However, PCR tests are often expensive and difficult to obtain, particularly in underdeveloped countries. There is a pressing need for more affordable and easily accessible commercial tests to facilitate the detection of Mpox cases.

*Other tests for diagnosis*

Serological testing for Mpoxv can aid in diagnosing Mpox, mainly when NAAT testing is not feasible (*72*). The detection of IgM antibodies in acutely ill patients (within 4 to 56 days after rash onset) or the identification of IgG antibodies in paired serum samples — collected at least 21 days apart, with the first sample obtained during the first week of illness — can contribute to the diagnosis (*11*). However, the effectiveness of Mpoxv-specific serological tests may be compromised by the potential for cross-reactivity with antibodies against other orthopoxviruses and with those generated by recent or historical vaccination (*72,73*). Consequently, it is recommended that serological testing be conducted only in reference laboratories until further evidence supports the use of serological or antibody-detecting point-of-care (POC) tests in other settings (*73*). This approach highlights the complex role of serology within the diagnostic framework, emphasizing its potential usefulness in certain conditions and noting the necessity for rigorous validation and adherence to application standards.

Electron microscopy offers a technique for visually identifying potential poxviruses within specimens (*74*). However, due to the need for specific technical expertise, requisite facilities, and the proliferation of more accessible molecular assays, its application in Mpoxv diagnosis is not widespread (*74*). Consequently, electron microscopy is infrequently utilized in the routine diagnostic assessment of poxviruses.

Virus isolation and culture are long-established techniques for diagnosing viral diseases, including Mpoxv (*17*). This process is essential for comprehensive characterization through sequencing, which facilitates antiviral testing, vaccine development, and the formulation of clinical applications and research methodologies (*22*). Isolating viruses from critical cases is vital for outbreak investigation and containment efforts, as it allows for identifying the virus's origin, detecting mutations, and reconstructing transmission chains through genomic and phenotypic comparisons among isolates. Mpoxv exhibits strong growth in various mammalian cell lines, including HeLa, Vero, BSC-1, and RK-13, as well as in chicken embryos, which are particularly susceptible to poxviruses (*24*). The virus induces cytopathic effects in chicken embryos' chorioallantoic membranes (CAMs), observable 1 to 4 days post-inoculation. These effects include cell rounding, granulation, cytoplasmic bridging, and syncytium formation (*75*). Conversely, when cultured in Vero cells, typical rounded and detached cells become noticeable within approximately 24 hours, enabling the identification of virus particles using immunofluorescence and specific antibodies (*24,75*). Although this method is precise, its lengthy detection timeframe, the necessity for high-level biosafety laboratories (Biosafety Level 3 or higher), the requirement for experienced personnel, and the inherent risk of infection — even with complete personal protective equipment — significantly limit its widespread application.

Whole-genome sequencing (WGS), a leading technology in next-generation sequencing, enables the complete sequencing of an organism's genome. It is the most accurate method for distinguishing the Mpoxv from orthopoxviruses (OPVs), providing broader pathogen coverage than other molecular

diagnostics (*76*). Genome sequencing of the Mpoxv responsible for the 2022 outbreak has been conducted, and whole-genome sequencing is regarded as the gold standard for differentiating Mpoxv infections from other orthopoxvirus diseases (*77,78*). WGS supports comprehensive bioinformatic analyses, advancing virological research and facilitating the development of related immunoassays. This technique is particularly effective in identifying specific strains and genetic variants, which can help trace the origins of outbreaks, especially in instances where transmission chains are unknown (*79*).

Skin tissue biopsies are additional clinical samples that may be considered for diagnostic testing when clinically warranted (*11*). The histological characteristics of Mpox are similar to those of smallpox, vaccinia, and cowpox, which can assist in distinguishing it from other infections, such as herpes simplex (*11*).

In summary, Mpox represents a significant public health concern. Early diagnosis and prompt management are essential for preventing the spread of Mpoxv infection. Physicians must maintain high vigilance in suspecting Mpoxv infection and be aware of the atypical presentations observed in 2022. There should be a heightened clinical suspicion of Mpox in patients displaying isolated lesions, particularly among high-risk groups (*65*). Diagnosing Mpox requires a comprehensive assessment that includes clinical symptoms, epidemiological information, and laboratory tests (*6*). Additionally, a detailed travel and sexual history, along with any close contact with known Mpox cases, should be thoroughly investigated.

## Treatment

No specific antiviral drug exists to treat patients with Mpoxv infection; the most common therapies are symptomatic and supportive care (*80*). Treatment is only recommended for high-risk groups, including young children, persons with immunocompromised conditions, and those with complications. Several antivirals (tecovirimat, cidofovir, and brincidofovir) are supposed to be effective in treating Mpoxv infections, but the efficacy of these drugs has yet to be thoroughly determined (*6*). Tecovirimat (TPOXX or ST-246) is the first antiviral drug to treat smallpox based on data from animal studies (*81-85*). Mpox and smallpox belong to the *Orthopoxvirus* genus in the family *Poxiviridae*. Therefore, while no drug is approved for Mpox, tecovirimat is used to treat Mpox through the procedures of an expanded-access Investigation New Drug (IND) protocol (*84,85*). Tecovirimat is a virus inhibitor that inhibits the envelope protein VP37 of *Orthopoxvirus*, thus blocking the virus's growth within an infected host (*86*). However, the efficacy of tecovirimat against Mpox in humans has not been identified.

Although tecovirimat is available for treating Mpox and might rapidly improve Mpox clinical symptoms/signs and outcomes, the safety and efficacy of tecovirimat in humans have yet to be proven. The efficacy data of tecovirimat studied in animals only sometimes translates directly into effectiveness in the human population (*81,87*). Additionally, the current worldwide outbreak involves a different strain of Mpoxv than that which generally causes Mpoxv infection in Africa, and some of the clinical presentations of the epidemic in 2022 and affected populations differ from those in countries where Mpox is endemic (*9*). Therefore, further study of the safety and effectiveness of antiviral drugs against Mpoxv infection is needed.

### *Alternative plant-based therapies*

Despite Mpox occurring endemic in Africa for years, efficacy studies of drugs or vaccines for treating Mpox have yet to be completed. Microtubules provide scaffolding for cells, facilitate cellular long-distance traffic, and serve as essential components of multiple biological processes (*88*). The virus often interacts with the cytoskeleton and requires an intact microtubule network. Pharmacological modulation of microtubules has been proposed to interfere with virus replications and spread, indicating their potential as broad-spectrum antivirals. Therefore, studying the molecular mechanism underlying these plant-based therapies and identifying their pharmacological effects on treating Mpoxv infection is crucial.

## Preventive measures

### *Vaccine development*

Currently, there is no specific commercial vaccine available for Mpoxv infection. However, previous studies suggest that individuals vaccinated with the smallpox vaccine may experience a protective effect against Mpoxv infection and a reduction in the severity of clinical symptoms associated with the infection (*89,90*). One study indicated that the effectiveness of smallpox vaccination with the vaccinia virus in preventing Mpox was approximately 85% (*91*). Two vaccines are currently available for preventing smallpox and Mpox among those at risk of exposure: ACAM2000 and JYNNEOS (also known as IMVAMUNE, IMVANEX, or MVA-BN) (*32,87,92*).

JYNNEOS is a replication-deficient Vaccinia virus vaccine and is an attenuated live virus vaccine produced from the third-generation modified vaccinia Ankara-Bavarian Nordic (MVA-BN) (*36,83*). Replication-deficient Vaccinia virus vaccines do not cause clinical infection because they do not develop infectious viruses in humans (*93,94*). The U.S. Food and Drug Administration (FDA) approved this vaccine as an alternative to ACAM2000 to prevent infection with the

smallpox virus and Mpox disease in people aged 18 years or older, a high-risk infection group with Orthopoxvirus infection (*36,93,94*). The European Medicine Agency (EMA) has approved this vaccine to prevent smallpox (*94*). JYNNEOS is vaccinated subcutaneously using a 2-dose series (0.5 mL per dose), 28 days apart; on 9 August 2022, an emergency use authorization was issued by US FDA for dose-sparing intradermal administration of JYNNEOS as a 2-dose series (0.1 mL per dose, 4-weeks apart); no significant cutaneous or systemic reactions are expected because JYNNEOS is a replication-deficient virus vaccine; JYNNEOS boosters are recommended every two years; JYNNEOS does not produce a lesion at the vaccine site, which is often recognized as a sign of successful vaccination with replication-competent vaccines (*93-96*). A case-control study using data from the Epic Cosmos platform indicated the estimated vaccine effectiveness was 66.0% (95% CI: 47.4-78.1) for patients with 2-dose vaccination, and 35.8% (95% CI: 22.1-47.1) for patients with one-dose immunization (*95*). In contrast to the ACAM2000 vaccine, the JYNNEOS vaccine can be administered to patients with atopic dermatitis and immunocompromised people (*97*).

ACAM2000 is a replication-competent live vaccinia vaccine used against orthopoxvirus infection to eradicate smallpox (*94*). Because the replication-competent poxvirus strain can produce an infectious virus in humans, there is a risk of causing severe adverse reactions (*81,94*). The FDA approves ACAM2000 for vaccination in persons at high risk for smallpox infection; the CDC can authorize the emergency use of ACAM2000 for MPOXV infection (*36*). In 2003, during the outbreak of Mpoxv infection in the United States, ACAM2000 was found to reduce the severity of Mpoxv infection (*92*). Still, side effects occurred in patients with atopic dermatitis and individuals with immunodeficiency. ACAM2000 is vaccinated percutaneously *via* a multiple punctures (scarification) technique using a stainless-steel bifurcated needle (*94*). ACAM2000 is applied in one dose of the vaccine, and boosters are recommended every three years; the peak vaccine protection occurs within 28 days; after successfully administering the vaccine, a skin lesion is produced, which contains the infectious vaccinia virus, which causes close contact infection (*94,97*).

Aventis Pasteur Smallpox Vaccine (APSV) is a replication-competent vaccina vaccine that may be used under an IND or Emergency Use Authorization (EUA) to prevent smallpox if licensed vaccines are available or contraindicated (*83,98*). However, it is unknown if this vaccine could be used for Mpox.

Vaccinating ACAM2000 or JYNNEOS in the general population is not recommended. Data must still be collected to convince us that smallpox vaccines could effectively prevent Mpoxv infection in endemic areas (*64,99*). More research is needed to study the efficacy and safety of the Mpox vaccine in humans.

Recently, a study indicated that mRNA-A-LNP and mRNA-B-LNP appear to be safe and effective vaccine candidates against Mpox epidemics and outbreaks caused by other orthopoxviruses, including the smallpox virus (*100,101*).

*Surveillance strategies through One Health approach*

Mpox is a viral zoonosis characterized by symptoms similar to those in smallpox patients. The global outbreaks of Mpox have significantly impacted public health, highlighting the urgent need for comprehensive preventive measures to strengthen the resilience of healthcare systems (*102*). For timely alerts for potential Mpox outbreaks, it is essential to develop more advanced surveillance systems that facilitate early detection and investigation of the causes behind Mpox epidemics (*103*).

As an infectious disease that affects both animals and humans, Mpox warrants a One Health approach to surveillance, which enhances collaboration between human and veterinary health services. This approach is cost-effective for monitoring human and animal health (*104-106*). Implementing preventive strategies aligned with the One Health framework can yield multiple benefits in controlling and preventing wildlife-associated Mpox zoonoses. It enables monitoring wild animals for signs of Mpox within their confined environments or the regions from which they originate (*104*). Overall, this approach effectively addresses shared health threats at the intersection of human, animal, and environmental health.

*Education program*

Raising awareness and educating the public about the risk factors associated with Mpoxv infection are crucial preventive strategies to reduce exposure to the virus (*36,60*). The risk of contracting Mpoxv in healthcare settings is low, primarily due to healthcare workers' stringent use of personal protective equipment (PPE) (*59*). The CDC recommends that healthcare workers wear gowns, gloves, eye protection, and masks while on duty. Patients diagnosed with Mpoxv infection should wear masks and be isolated in individual rooms. Those with suspected Mpox skin rashes should refrain from close contact with others until their skin rashes have entirely healed (*36*). It remains unclear whether individuals who recover from Mpoxv infection are protected against future infections; however, those who have received smallpox vaccinations appear to have some protection.

Findings from laboratory studies, field surveys, and natural experiments indicate that various animals can be infected with Mpoxv and may be capable of transmitting the virus to humans. In many regions of Africa where Mpox is prevalent, protein supplementation from wild animal sources is crucial. For instance, in rural areas of

the Democratic Republic of the Congo (DRC), residents living near forests frequently encounter the carcasses of rodents, primates, and other animals (*107*). This situation underscores the need for Mpox education campaigns to prioritize reducing human contact with potentially infected animals, particularly those commonly utilized as protein sources, such as primates and larger rodents (*108*).

Observations from the current Mpox outbreak have revealed distinct characteristics of at-risk groups and highlighted the inadequacies of existing sexual health infrastructure. This new Mpox pandemic has indicated that men who have sex with men (MSM) and transgender individuals are among the highest-risk populations (*13,20*). Consequently, there is an urgent need to develop a robust sexual health infrastructure and enhance genomic surveillance (*109,110*). Sexual health clinics play a critical role in controlling Mpox, and it is essential to establish an effective sexually transmitted infection (STI) surveillance framework within public health systems. Active measures for monitoring Mpox cases are also necessary (*111*).

## Conclusions

Since May 2022, the outbreak of Mpoxv infection has affected more than 116 countries (*35*), drawing global attention. Although Mpox has been endemic in Africa for years, comprehensive efficacy studies on drugs or vaccines for its treatment have yet to be completed. The 2022 outbreaks outside Africa's endemic regions underscore the urgent need for global investigation into Mpox disease. This current epidemic highlights the critical importance of not neglecting Global Health. Furthermore, it is essential to bolster foundational research on both animal and human poxvirus diseases, including the epidemiology of Mpox, the development of diagnostic tools (*e.g.*, laboratory tests), formulation of preventive strategies (*e.g.*, effective surveillance systems), and the creation of preventive measures (*e.g.,* vaccines and treatments). Education programs will also be vital. Additionally, enhancing international cooperation through the One Health concept is crucial for reducing the risk of Mpoxv infection.

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# Postoperative adjuvant chemotherapy in patients with gastric cancer based on the Nationwide Gastric Cancer Registry in Japan

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**Abstract:** The nationwide registry of the Japanese Gastric Cancer Association contains data related to the efficacy of adjuvant chemotherapy and prognostic factors across this patient population; elderly patients with advanced resectable gastric cancer are especially prevalent. Here, we analyzed data from 34,931 patients, who were treated between 2011 and 2013 at 421 hospitals in Japan. Although adjuvant chemotherapy was effective overall, 75 years or older elderly patients had a worse prognosis compared to younger patients. The most administered adjuvant chemotherapy was S-1 monotherapy. Adjuvant S-1 monotherapy was also effective for patients with pT1N2, pT1N3, and pT3N0 stage II tumors, as well as patients with other stage II and III malignancies. Independent prognostic factors for poor overall and relapse-free survival in patients at both stage II and stage III were age 75 or older, male, preoperative Eastern Cooperative Oncology Group performance status (ECOG-PS) 1 or more, preoperative renal dysfunction, undifferentiated adenocarcinoma, undergoing total gastrectomy, open laparotomy, no adjuvant chemotherapy, D1 lymphadenectomy, residual tumor R1 or R2, and Clavien-Dindo classification grade II or higher. Age 75 or older, renal dysfunction, ECOG-PS 1 and total gastrectomy were also significant risk factors for postoperative complications and lower compliance with adjuvant chemotherapy. Our analysis also revealed that adjuvant chemotherapy after resection of cancer of gastric remnant and postoperative chemotherapy against CY1 gastric cancer were also effective. We conclude that adjuvant chemotherapy is effective for all stage II and III patients including age 75 or older gastric cancer patients, in addition to distal gastrectomy, proximal gastrectomy, and pylorus-preserving surgery to avoid total gastrectomy may improve surgical outcomes and quality of life for elderly patients.

***Keywords*:** stomach cancer, lavage cytology, elderly patient, S-1, surgical site infection, postoperative complication, Clavien-Dindo

## Introduction

Gastric cancer, a significant global health burden, remains the fifth most common malignancy worldwide, accounting for the fifth leading cause of cancer-related deaths (*1*). In 2022, the global incidence of gastric cancer reached 968,000 cases, with 660,000 individuals succumbing to the disease. Notably, Eastern Asian regions, including China, Japan, and Korea, exhibit disproportionately high incidence rates, with Mongolia recording the most cases per capita. Eastern Europe and South America also experience elevated rates, while Africa demonstrates the lowest incidence. Gastric cancer represents a leading cause of cancer mortality in some Central Asian countries. The etiological role of *Helicobacter pylori* infection in non-cardiac gastric cancer is well-established (*2*).

Gastrectomy with D2 lymphadenectomy has been the standard surgical approach for resectable gastric cancer in Japan. A paradigm shift has emerged, with a surgery-first approach followed by postoperative adjuvant chemotherapy using S-1 for stage II and a combination of S-1 and docetaxel or fluoropyrimidines and oxaliplatin for stage III gaining prominence (*3-14*). This shift was sustained by the findings of the JCOG0501 clinical trial, which demonstrated that preoperative chemotherapy with S-1 plus cisplatin did not confer a survival advantage for type 4 or large type 3 gastric cancer (*15*). The ACTS-GC trial, The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer, which compared postoperative S-1 monotherapy with surgery alone (*3,4*), included pStage II and III patients. It did not include patients with pT1N2, pT1N3, and pT3N0 tumors, because the Japanese Classification of Gastric Carcinoma, the 13$^{th}$ edition (*16*), did not include T1N2, T1N3, and T3N0 as Stage II in the Japanese Classification after the 14$^{th}$ edition (*17*). Therefore, the Gastric Cancer Treatment Guidelines 2021 of the Japanese Gastric Cancer Association (JGCA) (*18*) did not recommend adjuvant chemotherapy for such individuals yet. The surgical approach for advanced cancer of gastric remnant aligns with that of primary gastric cancer, which includes lymph node dissection (*19*). On the other hand, perioperative or postoperative chemotherapy has been the standard treatment paradigm for resectable advanced gastric cancer in China, Korea, and Western nations.

Regional variations in the efficacy of perioperative chemotherapy are attributable to differences in surgical techniques, medical infrastructure, and patient characteristics, such as obesity and comorbidities (*14,15,20-23*). Several factors have been identified as risk predictors for surgical site infection following gastrectomy, including male gender, age 60 or older, smoking, diabetes, anemia, preoperative obstruction, advanced TNM stage, hypoproteinemia, prolonged operative time, laparotomy, and blood transfusion (*24*). Postoperative infectious complications, which are more prevalent after D2 lymphadenectomy and in older patients, have been linked to poor adherence to adjuvant S-1 chemotherapy for gastric cancer (*25*).

To fully evaluate the efficacy of adjuvant chemotherapy in stage II and III primary gastric cancer, elderly patients, cancer of gastric remnant, and stage IV disease with positive lavage cytology without any other distant metastases, and identify prognostic factors across a diverse population, predictive factors of postoperative complication and compliance of postoperative adjuvant chemotherapy, we conducted a comprehensive analysis of data from the nationwide registry maintained by the JGCA.

## Patients and Methods

### *Patients*

Patients diagnosed with gastric cancer between January 1, 2011 and December 31, 2013 and registered with the JCGA nationwide registry of gastric cancer patients were enrolled in this study. Eligibility requirements were that patients had undergone surgery for gastric cancer at stage II and III, or that their cytology lavage result was positive according to the Japanese Classification of Gastric Carcinoma, the 14$^{th}$ edition (*17*), and UICC, Union for International Cancer Control, TNM classification, the 7$^{th}$ edition (*26*). The cases with cancer of gastric remnant were excluded from the analyses of primary gastric cancer. Patients who survived more than 8 weeks were analyzed in this study. Patients who received preoperative chemotherapy were excluded. This study was approved by the Ethics Review Committee of the National Center for Global Health and Medicine and opt-out informed consent was obtained.

### *Statistical analysis*

Overall survival (OS) and relapse-free survival (RFS) were estimated using the Kaplan-Meier method, and confidence intervals (CI) were calculated based on the Greenwood formula. To address potential confounding factors in comparing the survival curves of two groups, 1:1 propensity score matching with the nearest neighbor method was implemented using logistic regression. The following binary variables were used to estimate propensity scores: age, sex, The American Society of Anesthesiologists classification of physical status (ASA-PS), Eastern Cooperative Oncology Group performance status (ECOG-PS), histology, operative approach, lymphadenectomy, residual tumor, methods of gastrectomy, and Clavien-Dindo (C-D) classification. To avoid issues with estimation, variables where the proportion of patients in one category was less than 10% were excluded from the covariates. The *glm* function from the *statsmodels* package was employed to conduct the propensity score matching process with a

caliper width of 0.1, ensuring closer matching between treatment and control units and improving covariate balance. Cases with missing data in any of the variables used for propensity score estimation were excluded from the analysis. To evaluate the quality of the matching, we compared the standardized mean differences of covariates between the two groups after matching. Our analysis confirmed that the standardized mean differences for all covariates were below 0.1, indicating a good balance. Hazard ratios (HR) for OS and RFS were obtained using Cox regression models. Possible prognostic factors were adjusted in multivariable analyses as appropriate. A two-sided $p$-value <0.05 was deemed significant. Moreover, propensity score matching was conducted to evaluate adjusted OS and PFS, where the propensity score was calculated by fitting the logistic regression model with the same prognostic factors as the Cox regression model. Logistic regression was used for determining the risk factors for postoperative complication and compliance with S-1 treatment in the adjuvant setting. Python version 3.9.7 with the *lifelines* package was used for all statistical analyses.

## Results

Data from 34,931 patients with gastric cancer treated between 2011 and 2013 at 421 hospitals in Japan were collected. Among these, 15,848 patients had stage II and III disease, and 2,052 patients had stage IV disease that their cytology lavage result was positive (CY1) without any other distant metastases (Figure 1). Patient characteristics are described in Table 1 and Supplemental Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*). Pylorus-preserving gastrectomy was performed in only 0.5% of patients, proximal gastrectomy in 1.9%, and both segmental gastrectomy and local resection in 0.1% of overall patients each, while total gastrectomy was performed in 39.0% of all patients and in 37.5% of those who were 75 or older. Cisplatin combination chemotherapy comprised either S-1 or capecitabine. Other combination chemotherapies included capecitabine plus oxaliplatin, S-1 plus oxaliplatin, and S-1 plus docetaxel. The survival rates of elderly patients were at least 10 points lower than those of the total population (Figure 2).

### *Efficacy of postoperative chemotherapy in Stage II and III, the elderly, cancer of gastric remnant, and CY1*

The efficacy of postoperative chemotherapy for stage II and III gastric cancer in terms of OS and RFS is shown in Figure 3 and Supplemental Figure S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*). Our analysis of this large dataset also revealed that adjuvant S-1 monotherapy for gastric cancer patients after surgical resection was effective in OS (Stage II, HR: 0.61, 95% CI: 0.54-0.69, $p < 0.001$; Stage III, HR: 0.54, 95% CI: 0.50-0.59, $p < 0.001$). Adjuvant S-1

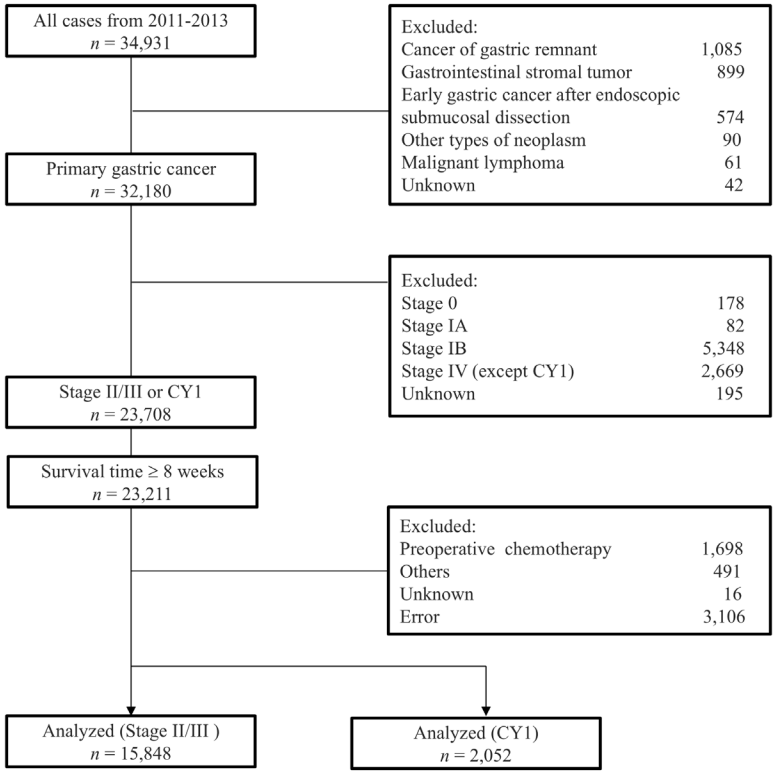



**Figure 1. Flow diagram of the patient selection process.** The cases with cancer of gastric remnant were excluded from the analyses of primary gastric cancer. Patients who survived more than 8 weeks were analyzed in this study. Patients who received preoperative chemotherapy were excluded. CY1, cancer cells on peritoneal cytology.

**Table 1. Patient characteristics**

| Characteristics | Primary gastric cancer (*n* = 15,848) | 75 or older, primary gastric cancer (*n* = 5,781) | Cancer of gastric remnant (*n* = 463) | CY1, gastric cancer (*n* = 2,052) |
|---|---|---|---|---|
| Age, median (range) | 71.0 (38-88) | 80.0 (75-88) | 74.0 (40-88) | 72.0 (38-88) |
| Sex | | | | |
| Male | 10,777 (68.0%) | 3,828 (66.2%) | 375 (81.0%) | 1,366 (66.6%) |
| Female | 5,071 (32.0%) | 1,953 (33.8%) | 88 (19.0%) | 686 (33.4%) |
| ASA-PS | | | | |
| 1 | 3,385 (21.4%) | 621 (10.7%) | 69 (14.9%) | 373 (18.2%) |
| 2 | 9,497 (59.9%) | 3,694 (63.9%) | 317 (68.5%) | 1,268 (61.8%) |
| ≥ 3 | 1,957 (12.3%) | 1,129 (19.5%) | 51 (11.0%) | 305 (14.9%) |
| ECOG-PS | | | | |
| 0 | 8,642 (54.5%) | 2,491 (43.1%) | 250 (54.0%) | 943 (46.0%) |
| 1 | 3,587 (22.6%) | 1,694 (29.3%) | 119 (25.7%) | 551 (26.9%) |
| ≥ 2 | 1,309 (8.3%) | 791 (13.7%) | 24 (5.2%) | 238 (11.6%) |
| Creatinine clearance, median (mL/min) | 67.3 | 51.5 | 60.8 | 62.4 |
| Normal | 7,180 (45.3%) | 865 (15.0%) | 160 (34.6%) | 756 (36.8%) |
| Abnormal | 7,779 (49.1%) | 4,745 (82.1%) | 284 (61.3%) | 1,171 (57.1%) |
| Macroscopic morphology | | | | |
| Type 0 | 2,242 (14.1%) | 616 (10.7%) | 60 (13.0%) | 50 (2.4%) |
| Type 1 | 848 (5.4%) | 401 (6.9%) | 43 (9.3%) | 40 (1.9%) |
| Type 2 | 5,028 (31.7%) | 2,055 (35.5%) | 114 (24.6%) | 285 (13.9%) |
| Type 3 | 5,675 (35.8%) | 1,990 (34.4%) | 131 (28.3%) | 876 (42.7%) |
| Type 4 | 1,244 (7.8%) | 411 (7.1%) | 59 (12.7%) | 683 (33.3%) |
| Type 5 | 751 (4.7%) | 283 (4.9%) | 52 (11.2%) | 111 (5.4%) |
| Location | | | | |
| U, fundus | 4,834 (30.5%) | 1,755 (30.4%) | 215 (46.4%) | 839 (40.9%) |
| M, corpus | 7,351 (46.4%) | 2,449 (42.4%) | 184 (39.7%) | 1,145 (55.8%) |
| L, antrum and pylorus | 7,462 (47.1%) | 2,991 (51.7%) | 42 (9.1%) | 1,294 (63.1%) |
| T, total stomach | 96 (0.6%) | 45 (0.8%) | 13 (2.8%) | 54 (2.6%) |
| D, invasion to duodenum | 499 (3.1%) | 227 (3.9%) | 7 (1.5%) | 94 (4.6%) |
| E, invasion to esophagus | 655 (4.1%) | 255 (4.4%) | 19 (4.1%) | 111 (5.4%) |
| Histological type | | | | |
| Differentiated adenocarcinoma | | | | |
| pap | 482 (3.0%) | 208 (3.6%) | 19 (4.1%) | 34 (1.7%) |
| tub1 | 1,734 (10.9%) | 699 (12.1%) | 52 (11.2%) | 142 (6.9%) |
| tub2 | 5,003 (31.6%) | 2,065 (35.7%) | 139 (30.0%) | 481 (23.4%) |
| Undifferentiated adenocarcinoma | | | | |
| por1 | 2,528 (16.0%) | 1,046 (18.1%) | 72 (15.6%) | 243 (11.8%) |
| por2 | 4,442 (28.0%) | 1,240 (21.4%) | 123 (26.6%) | 887 (43.2%) |
| sig | 841 (5.3%) | 189 (3.3%) | 29 (6.3%) | 134 (6.5%) |
| muc | 484 (3.1%) | 199 (3.4%) | 17 (3.7%) | 107 (5.2%) |
| Others | 322 (2.0%) | 128 (2.2%) | 11 (2.4%) | 21 (1.0%) |
| Gastrectomy | | | | |
| Total gastrectomy | 6,174 (39.0%) | 2,168 (37.5%) | 435 (94.0%) | 1,134 (55.3%) |
| Distal gastrectomy | 9,263 (58.4%) | 3,440 (59.5%) | 19 (4.1%) | 901 (43.9%) |
| Pylorus-preserving gastrectomy | 75 (0.5%) | 15 (0.3%) | 0 (0%) | 3 (0.1%) |
| Proximal gastrectomy | 300 (1.9%) | 139 (2.4%) | 0 (0%) | 12 (0.6%) |
| Segmental gastrectomy | 13 (0.1%) | 7 (0.1%) | 3 (0.6%) | 2 (0.1%) |
| Local resection | 23 (0.1%) | 12 (0.2%) | 6 (1.3%) | 0 (0.0%) |
| Reconstruction | | | | |
| B-I | 4,493 (28.4%) | 1,597 (27.6%) | 4 (0.9%) | 260 (12.7%) |
| B-II | 718 (4.5%) | 354 (6.1%) | 7 (1.5%) | 133 (6.5%) |
| DT | 91 (0.6%) | 29 (0.5%) | 1 (0.2%) | 10 (0.5%) |
| EG | 185 (1.2%) | 85 (1.5%) | 0 (0%) | 10 (0.5%) |
| IP | 53 (0.3%) | 29 (0.5%) | 0 (0%) | 2 (0.1%) |
| PP | 67 (0.4%) | 12 (0.2%) | 0 (0%) | 3 (0.1%) |
| RY | 10,080 (63.6%) | 3,603 (62.3%) | 438 (94.6%) | 1,619 (78.9%) |
| Others | 74 (0.5%) | 39 (0.7%) | 6 (1.3%) | 5 (0.2%) |
| NR | 26 (0.2%) | 9 (0.2%) | 2 (0.4%) | 0 (0.0%) |

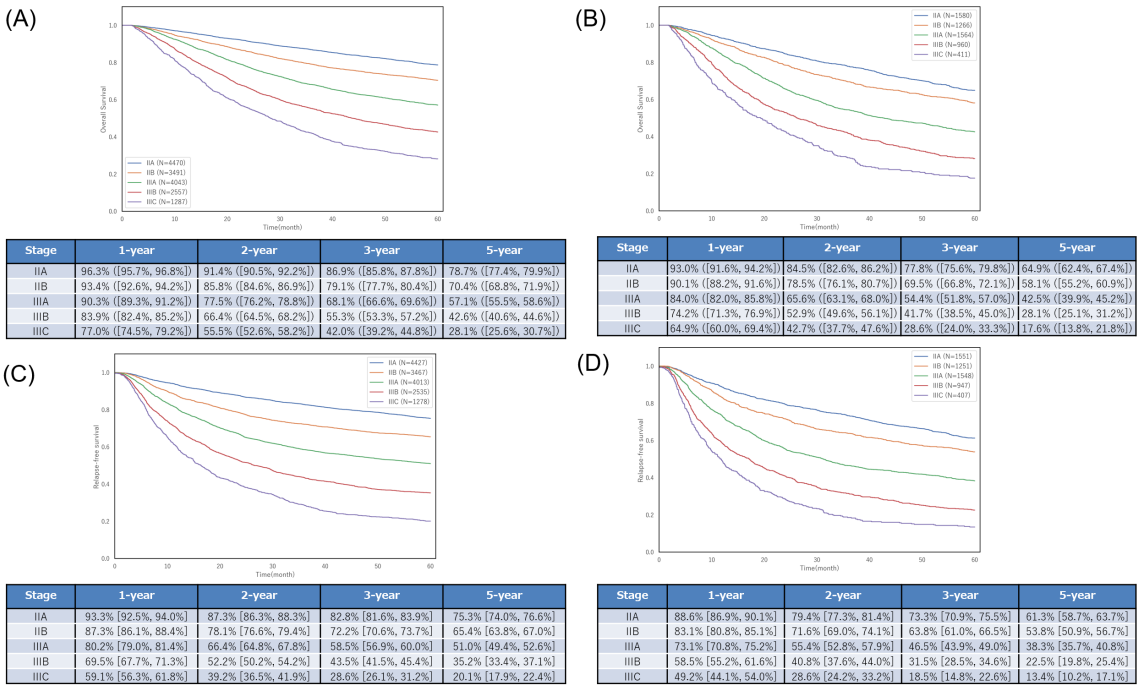
*Abbreviations*: ASA-PS, American Society of Anesthesiologists - physical status; B-I, Billroth I gastroduodenostomy; B-II, Billroth II gastrojejunostomy; Cap, capecitabine; CY1, cancer cells on peritoneal cytology; D0, no lymphadenectomy; D1, D1 lymphadenectomy; D2, D2 lymphadenectomy; DM, distal margin; DT, Double-tract method; ECOG-PS, Eastern Cooperative Oncology Group - performance status; EG, Esophagogastrostomy; IP, Jejunal interposition; muc, mucinous adenocarcinoma; NR, Non-resectional surgery; pap, papillary adenocarcinoma; PM, proximal margin; por1, solid type poorly differentiated adenocarcinoma; por2, non-solid type poorly differentiated adenocarcinoma; PP, Pylorus-preserving gastrectomy; R, residual tumor; RY, Roux-en-Y esophagojejunostomy or Roux-en-Y gastrojejunostomy; sig, signet-ring cell adenocarcinoma; tub1, well differentiated tubular adenocarcinoma; tub2, moderately differentiated adenocarcinoma.

**Table 1. Patient characteristics (continued)**

| Characteristics | Primary gastric cancer (*n* = 15,848) | 75 or older, primary gastric cancer (*n* = 5,781) | Cancer of gastric remnant (*n* = 463) | CY1, gastric cancer (*n* = 2,052) |
|---|---|---|---|---|
| Lymph node dissection | | | | |
| D0 | 244 (1.5%) | 128 (2.2%) | 55 (11.9%) | 217 (10.6%) |
| D1 | 1,197 (7.6%) | 700 (12.1%) | 100 (21.6%) | 491 (23.9%) |
| D1+ | 3,223 (20.3%) | 1,418 (24.5%) | 91 (19.7%) | 354 (17.3%) |
| D2 | 10,489 (66.2%) | 3,323 (57.5%) | 149 (32.2%) | 889 (43.3%) |
| D2+ | 533 (3.4%) | 143 (2.5%) | 5 (1.1%) | 70 (3.4%) |
| Approach | | | | |
| Laparoscopic | 2,828 (17.8%) | 866 (15.0%) | 23 (5.0%) | 122 (5.9%) |
| Open | 12,846 (81.1%) | 4,850 (83.9%) | 434 (93.7%) | 1,914 (93.3%) |
| Others | 174 (1.1%) | 65 (1.1%) | 6 (1.3%) | 16 (0.8%) |
| pT-Depth of tumor invasion | | | | |
| pT1a | 72 (0.5%) | 11 (0.2%) | 2 (0.4%) | 2 (0.1%) |
| pT1b | 688 (4.3%) | 232 (4.0%) | 7 (1.5%) | 13 (0.6%) |
| pT2 | 2,118 (13.4%) | 725 (12.5%) | 32 (6.9%) | 17 (0.8%) |
| pT3 | 7,023 (44.3%) | 2,554 (44.2%) | 221 (47.7%) | 173 (8.4%) |
| pT4a | 5,448 (34.4%) | 2,055 (35.5%) | 131 (28.3%) | 1,621 (79.0%) |
| pT4b | 499 (3.1%) | 204 (3.5%) | 70 (15.1%) | 223 (10.9%) |
| pN-Extent of lymph node metastasis | | | | |
| pN0 | 3,920 (24.7%) | 1,405 (24.3%) | 232 (50.1%) | 106 (5.2%) |
| pN1 | 3,850 (24.3%) | 1,480 (25.6%) | 106 (22.9%) | 148 (7.2%) |
| pN2 | 4,050 (25.6%) | 1,491 (25.8%) | 79 (17.1%) | 320 (15.6%) |
| pN3a | 2,778 (17.5%) | 1,018 (17.6%) | 39 (8.4%) | 625 (30.5%) |
| pN3b | 1,250 (7.9%) | 387 (6.7%) | 7 (1.5%) | 834 (40.6%) |
| pStage | | | | |
| IIA | 4,470 (28.2%) | 1,580 (27.3%) | 172 (37.1%) | - |
| IIB | 3,491 (22.0%) | 1,266 (21.9%) | 118 (25.5%) | - |
| IIIA | 4,043 (25.5%) | 1,564 (27.1%) | 97 (21.0%) | - |
| IIIB | 2,557 (16.1%) | 960 (16.6%) | 58 (12.5%) | - |
| IIIC | 1,287 (8.1%) | 411 (7.1%) | 18 (3.9%) | - |
| Proximal margin and distal margin | | | | |
| PM0 and DM0 | 15,406 (97.2%) | 5,564 (96.2%) | 431 (93.1%) | 1,758 (85.7%) |
| Others | 368 (2.3%) | 180 (3.1%) | 27 (5.8%) | 270 (13.2%) |
| Residual tumor | | | | |
| R0 | 15,036 (94.9%) | 5,406 (93.5%) | 419 (90.5%) | 326 (15.9%) |
| Others | 763 (4.8%) | 355 (6.1%) | 44 (9.5%) | 1,713 (83.5%) |
| Clavien-Dindo classification | | | | |
| Grade I or none | 13,089 (82.6%) | 4,543 (78.6%) | 345 (74.5%) | 1,656 (80.7%) |
| Grade II | 1,885 (11.9%) | 820 (14.2%) | 76 (16.4%) | 249 (12.1%) |
| Grade III or higher | 874 (5.5%) | 418 (7.2%) | 42 (9.1%) | 147 (7.2%) |
| Postoperative chemotherapy | 8,485 (53.5%) | 1,645 (28.5%) | 185 (40.0%) | 974 (47.5%) |
| None | 7,363 (46.5%) | 4,136 (71.5%) | 278 (60.0%) | 1,078 (52.5%) |
| S-1 monotherapy | 7,925 (50.0%) | 1,597 (27.6%) | 173 (37.4%) | 616 (30.0%) |
| S-1 plus oxaliplatin | 43 (0.3%) | 9 (0.2%) | 0 (0.0%) | 3 (0.1%) |
| S-1 plus cisplatin | 346 (2.2%) | 20 (0.3%) | 9 (1.9%) | 295 (14.4%) |
| S-1 plus docetaxel | 108 (0.7%) | 15 (0.3%) | 1 (0.2%) | 50 (2.4%) |
| Cap plus oxaliplatin | 59 (0.4%) | 4 (0.1%) | 2 (0.4%) | 1 (0.0%) |
| Cap plus cisplatin | 4 (0.0%) | 0 (0.0%) | 0 (0.0%) | 9 (0.4%) |

*Abbreviations*: ASA-PS, American Society of Anesthesiologists - physical status; B-I, Billroth I gastroduodenostomy; B-II, Billroth II gastrojejunostomy; Cap, capecitabine; CY1, cancer cells on peritoneal cytology; D0, no lymphadenectomy; D1, D1 lymphadenectomy; D2, D2 lymphadenectomy; DM, distal margin; DT, Double-tract method; ECOG-PS, Eastern Cooperative Oncology Group - performance status; EG, Esophagogastrostomy; IP, Jejunal interposition; muc, mucinous adenocarcinoma; NR, Non-resectional surgery; pap, papillary adenocarcinoma; PM, proximal margin; por1, solid type poorly differentiated adenocarcinoma; por2, non-solid type poorly differentiated adenocarcinoma; PP, Pylorus-preserving gastrectomy; R, residual tumor; RY, Roux-en-Y esophagojejunostomy or Roux-en-Y gastrojejunostomy; sig, signet-ring cell adenocarcinoma; tub1, well differentiated tubular adenocarcinoma; tub2, moderately differentiated adenocarcinoma.

monotherapy was also effective in patients with pT1N2, pT1N3, and pT3N0 stage II tumors, as well as in those with other stage II and III malignancies (Supplemental Figure S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*). The matched 5-year OS rates of pT1N2 and pT1N3 patients were 85.6% (95% CI: 79.6%-90.0%) in any adjuvant chemotherapy group and 73.7% (95% CI: 66.7%-79.5%) in surgery alone group ($p$ = 0.004). The matched 5-year OS rates of pT3N0 patients were 88.1% (95% CI: 84.9%-90.6%) in any adjuvant chemotherapy group and 82.3% (95% CI: 78.7%-85.4%) in surgery alone group ($p$ = 0.012). Compared to S-1 monotherapy, the efficacy of oxaliplatin combination therapy or S-1 plus docetaxel




(A)

| Stage | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| IIA | 96.3% ([95.7%, 96.8%]) | 91.4% ([90.5%, 92.2%]) | 86.9% ([85.8%, 87.8%]) | 78.7% ([77.4%, 79.9%]) |
| IIB | 93.4% ([92.6%, 94.2%]) | 85.8% ([84.6%, 86.9%]) | 79.1% ([77.7%, 80.4%]) | 70.4% ([68.8%, 71.9%]) |
| IIIA | 90.3% ([89.3%, 91.2%]) | 77.5% ([76.2%, 78.8%]) | 68.1% ([66.6%, 69.6%]) | 57.1% ([55.5%, 58.6%]) |
| IIIB | 83.9% ([82.4%, 85.2%]) | 66.4% ([64.5%, 68.2%]) | 55.3% ([53.3%, 57.2%]) | 42.6% ([40.6%, 44.6%]) |
| IIIC | 77.0% ([74.5%, 79.2%]) | 55.5% ([52.6%, 58.2%]) | 42.0% ([39.2%, 44.8%]) | 28.1% ([25.6%, 30.7%]) |

(B)

| Stage | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| IIA | 93.0% ([91.6%, 94.2%]) | 84.5% ([82.6%, 86.2%]) | 77.8% ([75.6%, 79.8%]) | 64.9% ([62.4%, 67.4%]) |
| IIB | 90.1% ([88.2%, 91.6%]) | 78.5% ([76.1%, 80.7%]) | 69.5% ([66.8%, 72.1%]) | 58.1% ([55.2%, 60.9%]) |
| IIIA | 84.0% ([82.0%, 85.8%]) | 65.6% ([63.1%, 68.0%]) | 54.4% ([51.8%, 57.0%]) | 42.5% ([39.9%, 45.2%]) |
| IIIB | 74.2% ([71.3%, 76.9%]) | 52.9% ([49.6%, 56.1%]) | 41.7% ([38.5%, 45.0%]) | 28.1% ([25.1%, 31.2%]) |
| IIIC | 64.9% ([60.0%, 69.4%]) | 42.7% ([37.7%, 47.6%]) | 28.6% ([24.0%, 33.3%]) | 17.6% ([13.8%, 21.8%]) |

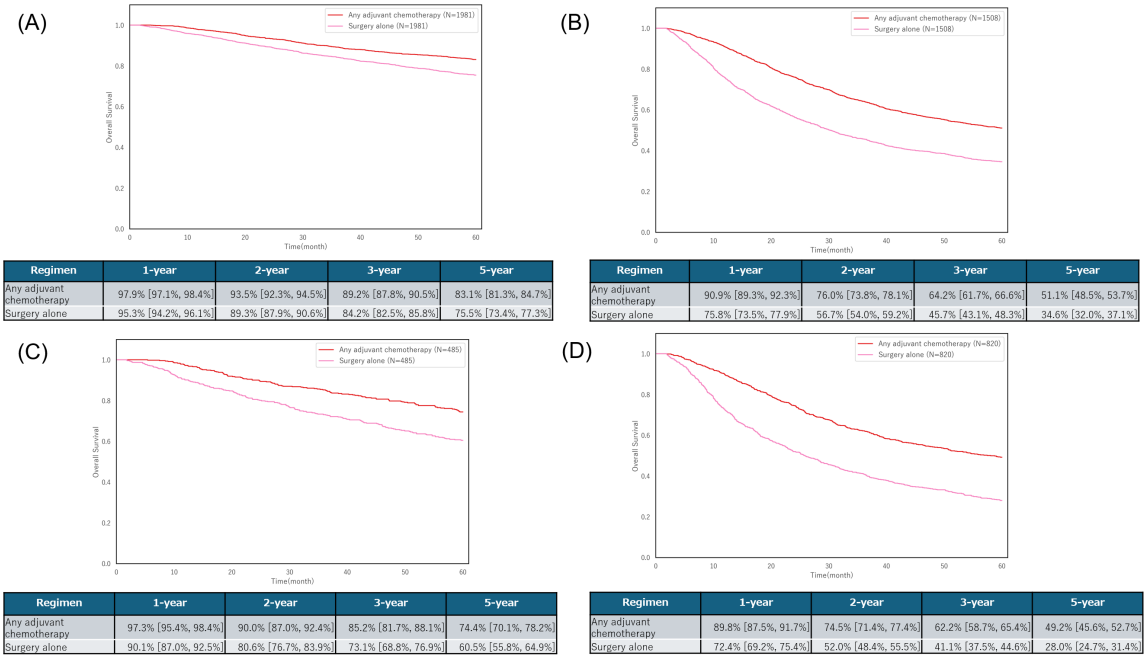
(C)

| Stage | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| IIA | 93.3% [92.5%, 94.0%] | 87.3% [86.3%, 88.3%] | 82.8% [81.6%, 83.9%] | 75.3% [74.0%, 76.6%] |
| IIB | 87.3% [86.1%, 88.4%] | 78.1% [76.6%, 79.4%] | 72.2% [70.6%, 73.7%] | 65.4% [63.8%, 67.0%] |
| IIIA | 80.2% [79.0%, 81.4%] | 66.4% [64.8%, 67.8%] | 58.5% [56.9%, 60.0%] | 51.0% [49.4%, 52.6%] |
| IIIB | 69.5% [67.7%, 71.3%] | 52.2% [50.2%, 54.2%] | 43.5% [41.5%, 45.4%] | 35.2% [33.4%, 37.1%] |
| IIIC | 59.1% [56.3%, 61.8%] | 39.2% [36.5%, 41.9%] | 28.6% [26.1%, 31.2%] | 20.1% [17.9%, 22.4%] |

(D)

| Stage | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| IIA | 88.6% [86.9%, 90.1%] | 79.4% [77.3%, 81.4%] | 73.3% [70.9%, 75.5%] | 61.3% [58.7%, 63.7%] |
| IIB | 83.1% [80.8%, 85.1%] | 71.6% [69.0%, 74.1%] | 63.8% [61.0%, 66.5%] | 53.8% [50.9%, 56.7%] |
| IIIA | 73.1% [70.8%, 75.2%] | 55.4% [52.8%, 57.9%] | 46.5% [43.9%, 49.0%] | 38.3% [35.7%, 40.8%] |
| IIIB | 58.5% [55.2%, 61.6%] | 40.8% [37.6%, 44.0%] | 31.5% [28.5%, 34.6%] | 22.5% [19.8%, 25.4%] |
| IIIC | 49.2% [44.1%, 54.0%] | 28.6% [24.2%, 33.2%] | 18.5% [14.8%, 22.6%] | 13.4% [10.2%, 17.1%] |

**Figure 2. Overall and relapse-free survival of all stage II and III patients, and those age 75 or older. (A)** Overall survival of all patients by stage, **(B)** Overall survival of age 75 or older patients by stage, **(C)** Relapse-free survival of all patients by stage, **(D)** Relapse-free survival of age 75 or older patients by stage.




(A)

| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 97.9% [97.1%, 98.4%] | 93.5% [92.3%, 94.5%] | 89.2% [87.8%, 90.5%] | 83.1% [81.3%, 84.7%] |
| Surgery alone | 95.3% [94.2%, 96.1%] | 89.3% [87.9%, 90.6%] | 84.2% [82.5%, 85.8%] | 75.5% [73.4%, 77.3%] |

(B)

| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 90.9% [89.3%, 92.3%] | 76.0% [73.8%, 78.1%] | 64.2% [61.7%, 66.6%] | 51.1% [48.5%, 53.7%] |
| Surgery alone | 75.8% [73.5%, 77.9%] | 56.7% [54.0%, 59.2%] | 45.7% [43.1%, 48.3%] | 34.6% [32.0%, 37.1%] |

(C)

| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 97.3% [95.4%, 98.4%] | 90.0% [87.0%, 92.4%] | 85.2% [81.7%, 88.1%] | 74.4% [70.1%, 78.2%] |
| Surgery alone | 90.1% [87.0%, 92.5%] | 80.6% [76.7%, 83.9%] | 73.1% [68.8%, 76.9%] | 60.5% [55.8%, 64.9%] |

(D)

| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 89.8% [87.5%, 91.7%] | 74.5% [71.4%, 77.4%] | 62.2% [58.7%, 65.4%] | 49.2% [45.6%, 52.7%] |
| Surgery alone | 72.4% [69.2%, 75.4%] | 52.0% [48.4%, 55.5%] | 41.1% [37.5%, 44.6%] | 28.0% [24.7%, 31.4%] |

**Figure 3. Matched analysis of overall survival for all patients and those age 75 or older patients with or without adjuvant chemotherapy at stage II and III. (A)** Overall survival of matched patients at stage II, **(B)** Overall survival of matched patients at stage III, **(C)** Overall survival of matched age 75 or older patients at stage II, **(D)** Overall survival of matched age 75 or older patients by stage III. Age, sex, American Society of Anesthesiologists classification of physical status, Eastern Cooperative Oncology Group performance status, histology, operative approach, lymphadenectomy, residual tumor, methods of gastrectomy, and Clavien-Dindo classification were adjusted for propensity score matching.

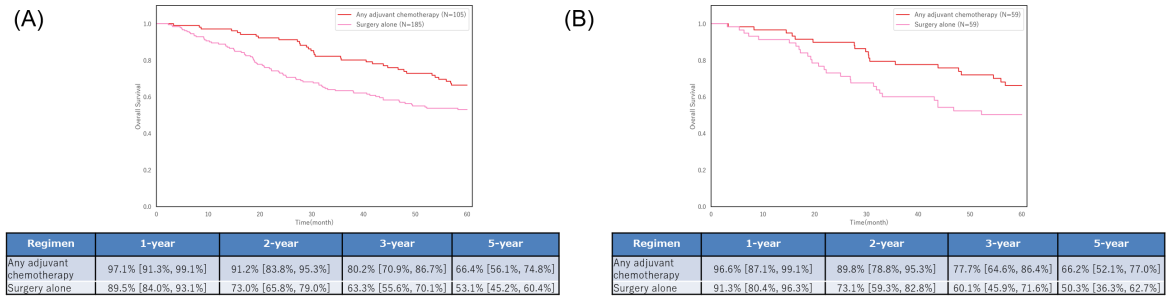
therapy was similar for stage II (HR: 0.75, 95% CI: 0.24-0.36, $p = 0.629$) and superior for stage III (HR: 0.66, 95% CI: 0.48-0.89, $p = 0.007$) (Supplemental Figure S3 and S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*) The OS of patients treated with cisplatin was inferior to those who received S-1 monotherapy (Stage II, HR: 2.00, 95% CI: 1.01-3.94, $p = 0.047$; Stage III, HR: 1.31, 95% CI: 1.09-1.57, $p = 0.004$). Across the whole population, some form of adjuvant chemotherapy was given to 45.2% and 63.0%

of stage II and stage III patients, respectively; for patients over age 75 years these figures were 20.9% and 35.8%. The most administered adjuvant chemotherapy was S-1 monotherapy. Adjuvant chemotherapy after resection of cancer of gastric remnant (Figure 4; Supplemental Figure S5, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*) and post-operative chemotherapy against CY1 gastric cancer were also effective (Figure 5).

*Prognostic factors of stage II and III gastric cancer*

Independent prognostic factors for poor OS and RFS in patients with both stage II and stage III disease were: age 75 or older, male, preoperative ECOG-PS ≥ 1, preoperative renal dysfunction, total gastrectomy, D1 lymphadenectomy, open laparotomy, residual tumor R1 or R2, and C-D classification grade II or higher, no adjuvant chemotherapy (Table 2 and Table 3). Preoperative ASA-PS was not a statistically significant prognostic factor for OS and RFS at stage III but stage II. Undifferentiated carcinoma, which consisted of solid and non-solid types of poorly differentiated adenocarcinoma and signet ring cell carcinoma, was an independent prognostic factor for OS in both stage II and III disease. In the total population, the incidence rates of C-D grade II or more in patients with stage II and III disease were 10.5% (183/1,735) in those who underwent D1 lymphadenectomy and 13.2% (874/6,630) in those who underwent D2 lymphadenectomy. The HR for OS in D2 versus D1 lymphadenectomy was 0.78 ($p < 0.001$) for stage II patients and 0.81 ($p < 0.001$) for stage III patients (Table 2). In patients age 75 or older, these rates were 14.7% (46/436) for D1 and 14.8% for D2 lymphadenectomy. For laparoscopic surgery versus open surgery, multivariate analyses yielded a HR of 0.83 (95% CI: 0.72-0.95, $p = 0.006$) for stage II patients and 0.85 (95% CI: 0.75-0.96, $p = 0.007$) for stage III patients. Thus, laparoscopic surgery is an independent favorable prognostic factor for OS.

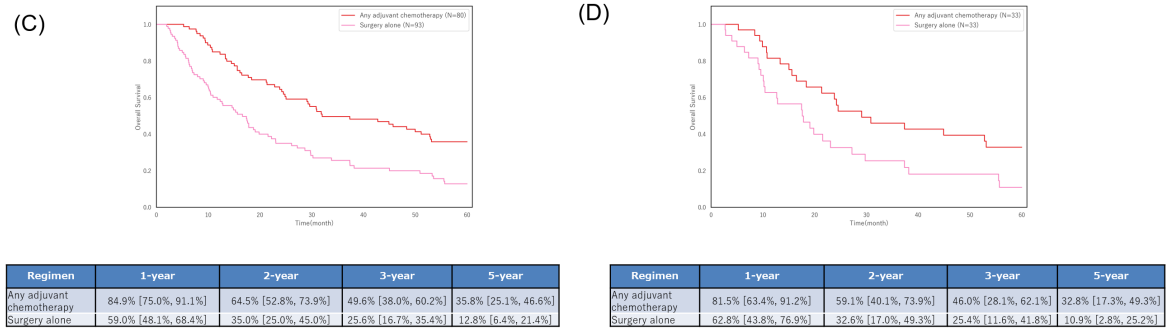
The OS of patients with postoperative complications classified as C-D grade II or higher was shorter than that of patients without complications or with C-D grade I (Figure 6; Supplemental Figure S6, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=96*). Logistic regression showed that age 75 or older, male, renal dysfunction, ECOG-PS or more 1, and total gastrectomy were all correlated significantly with a higher incidence of C-D grade II or more disease ($p < 0.01$) (Table 4). In age 75 or older patients, male, ECOG-PS 1 or more, total gastrectomy were correlated significantly with a higher incidence of C-D grade II or more disease. Age 75 or older, renal dysfunction, ECOG-PS 1 or more, total gastrectomy, stage III disease, and C-D grade II or higher all correlated with a lower compliance with adjuvant S-1 chemotherapy ($p < 0.01$).




| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 97.1% [91.3%, 99.1%] | 91.2% [83.8%, 95.3%] | 80.2% [70.9%, 86.7%] | 66.4% [56.1%, 74.8%] |
| Surgery alone | 89.5% [84.0%, 93.1%] | 73.0% [65.8%, 79.0%] | 63.3% [55.6%, 70.1%] | 53.1% [45.2%, 60.4%] |




| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 96.6% [87.1%, 99.1%] | 89.8% [78.8%, 95.3%] | 77.7% [64.6%, 86.4%] | 66.2% [52.1%, 77.0%] |
| Surgery alone | 91.3% [80.4%, 96.3%] | 73.1% [59.3%, 82.8%] | 60.1% [45.9%, 71.6%] | 50.3% [36.3%, 62.7%] |

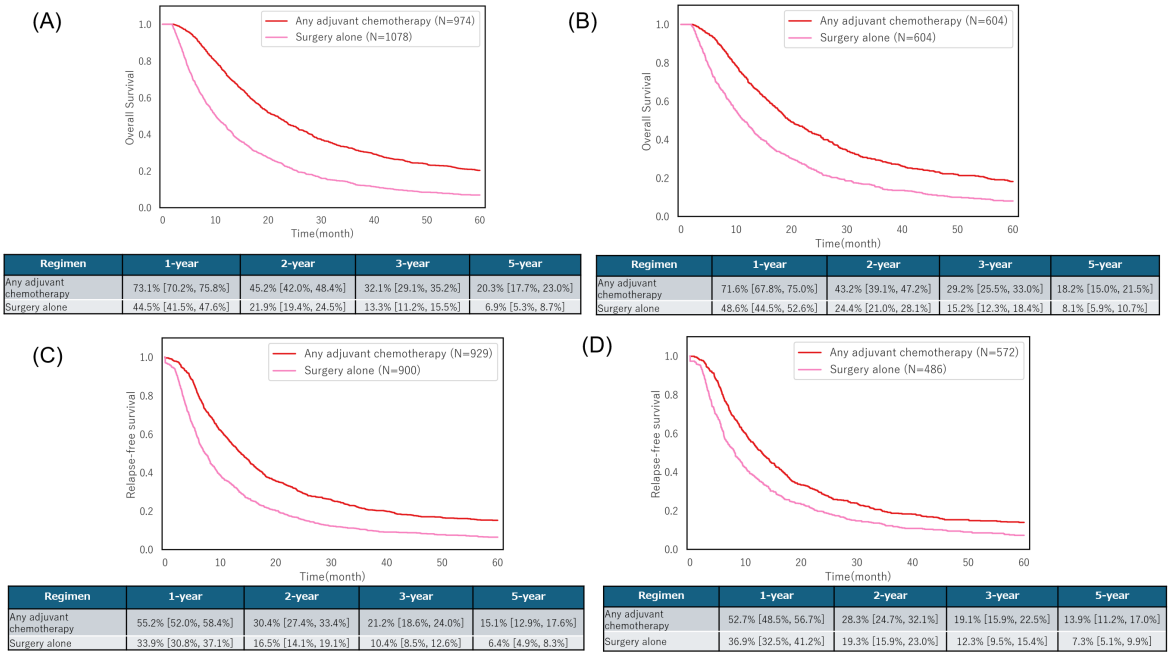



| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 84.9% [75.0%, 91.1%] | 64.5% [52.8%, 73.9%] | 49.6% [38.0%, 60.2%] | 35.8% [25.1%, 46.6%] |
| Surgery alone | 59.0% [48.1%, 68.4%] | 35.0% [25.0%, 45.0%] | 25.6% [16.7%, 35.4%] | 12.8% [6.4%, 21.4%] |




| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 81.5% [63.4%, 91.2%] | 59.1% [40.1%, 73.9%] | 46.0% [28.1%, 62.1%] | 32.8% [17.3%, 49.3%] |
| Surgery alone | 62.8% [43.8%, 76.9%] | 32.6% [17.0%, 49.3%] | 25.4% [11.6%, 41.8%] | 10.9% [2.8%, 25.2%] |

**Figure 4. Overall survival of pre-matched and matched patients with cancer of gastric remnant with or without adjuvant chemotherapy. (A)** Overall survival of pre-matched patients who have equivalent depth of tumor invasion and extent of lymph node metastasis to stage II, **(B)** Overall survival of matched patients equivalent to stage II, **(C)** Overall survival of pre-matched patients equivalent to stage II, **(D)** Overall survival of matched patients equivalent to stage III. Age, sex, American Society of Anesthesiologists classification of physical status, Eastern Cooperative Oncology Group performance status, histology, operative approach, lymphadenectomy, residual tumor, methods of gastrectomy, and Clavien-Dindo classification were adjusted for propensity score matching.




| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 73.1% [70.2%, 75.8%] | 45.2% [42.0%, 48.4%] | 32.1% [29.1%, 35.2%] | 20.3% [17.7%, 23.0%] |
| Surgery alone | 44.5% [41.5%, 47.6%] | 21.9% [19.4%, 24.5%] | 13.3% [11.2%, 15.5%] | 6.9% [5.3%, 8.7%] |

| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 71.6% [67.8%, 75.0%] | 43.2% [39.1%, 47.2%] | 29.2% [25.5%, 33.0%] | 18.2% [15.0%, 21.5%] |
| Surgery alone | 48.6% [44.5%, 52.6%] | 24.4% [21.0%, 28.1%] | 15.2% [12.3%, 18.4%] | 8.1% [5.9%, 10.7%] |

| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 55.2% [52.0%, 58.4%] | 30.4% [27.4%, 33.4%] | 21.2% [18.6%, 24.0%] | 15.1% [12.9%, 17.6%] |
| Surgery alone | 33.9% [30.8%, 37.1%] | 16.5% [14.1%, 19.1%] | 10.4% [8.5%, 12.6%] | 6.4% [4.9%, 8.3%] |

| Regimen | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|
| Any adjuvant chemotherapy | 52.7% [48.5%, 56.7%] | 28.3% [24.7%, 32.1%] | 19.1% [15.9%, 22.5%] | 13.9% [11.2%, 17.0%] |
| Surgery alone | 36.9% [32.5%, 41.2%] | 19.3% [15.9%, 23.0%] | 12.3% [9.5%, 15.4%] | 7.3% [5.1%, 9.9%] |

**Figure 5. Postoperative systemic chemotherapy in pre-matched and matched CY1 gastric cancer patients. (A)** Overall survival of pre-matched CY1 gastric cancer patients, **(B)** Overall survival of matched CY1 gastric cancer patients, **(C)** Relapse-free survival of pre-matched CY1 patients, **(D)** Relapse-free survival of matched CY1 patients. Age, sex, American Society of Anesthesiologists classification of physical status, Eastern Cooperative Oncology Group performance status, histology, operative approach, lymphadenectomy, residual tumor, methods of gastrectomy, and Clavien-Dindo classification were adjusted for propensity score matching.

## Discussion

Our real-world analysis of the large JGCA dataset reveals that postoperative chemotherapy is effective for age 75 or older patients as well as less than 75 with advanced stage II and III resectable primary gastric cancer without C-D II or more complications, cancer of gastric remnant, and stage IV disease with CY1 without any other distant metastases.

Because we found that adjuvant chemotherapy was effective in patients with pT1N2, pT1N3, and pT3N0 in the current retrospective study, we suggest that adjuvant chemotherapy should be also recommended for these individuals although it is difficult to conduct clinical trials to compare adjuvant chemotherapy with surgery alone for these limited cases with pT1N2, pT1N3, and pT3N0 with the similar risk of recurrence for the other stage II. Until the 13$^{th}$ edition of the Japanese Classification of Gastric Carcinoma, lymph nodes were classified based on the anatomical location of the primary tumor within the stomach. This anatomical classification was used to determine the extent of lymph node metastasis, N1-N3, M1 and staging, as well as to define the extent of lymph node dissection, D1-D3. Although this method was rational, based on extensive data accumulation and detailed analysis over many years, it was complex and difficult for general surgeons and overseas specialists to fully understand. Additionally, the determination of the primary tumor location and metastatic lymph node sites sometimes lacked objectivity. In the 14$^{th}$ edition of the Japanese Classification of Gastric Carcinoma, this anatomical N classification was abolished, and an N classification based on the number of metastatic lymph nodes, linked to the TNM classification, was adopted. This change was made because studies both domestically and internationally have shown that classification based on the number of metastatic lymph nodes better reflects prognosis than anatomical classification, and to emphasize international universality and objectivity (*18*).

Age 75 or older, male, preoperative ECOG-PS 1 or more, preoperative renal dysfunction, total gastrectomy, D1 lymph node dissection, open laparotomy, residual tumor R1 or R2, undifferentiated carcinoma, and C-D classification grade II or higher, and no adjuvant chemotherapy were the independent prognostic factors for poor OS in patients with both stage II and stage III disease. The predictive factors of C-D II or higher which is one of the worse prognostic factors were 75 or older age, male, preoperative renal dysfunction, preoperative ECOG-PS 1 or more, total gastrectomy, except lymphadenectomy. A few of earlier randomized controlled trials where the risk of recurrence after curative resection was not significantly different for patients who underwent D1 or D2 lymphadenectomy due to high mortality of D2, lack of quality control of surgical skills, or inadequate lymph node dissection in obese patients (*23,27*). Additionally, patients who underwent D2 lymphadenectomy reportedly have significantly higher postoperative morbidity compared with those who underwent a D1 procedure (*23,28-32*). Hemorrhage,

**Table 2. Prognostic factors of overall survival in patients with primary gastric cancer at stage II and III by univariate and multivariate analyses**

| Factors | | Univariate analysis | | | | | Multivariate analysis | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Covariate | *n* | HR | 95% CI (lower) | 95% CI (upper) | *p*-value | *n* | HR | 95% CI (lower) | 95% CI (upper) | *p*-value |
| **Stage II** | | | | | | | | | | |
| Age (≥ 75 *vs.* < 75) | 7,738 | 2.57 | 2.34 | 2.82 | < 0.001 | 6,223 | 1.69 | 1.49 | 1.93 | < 0.001 |
| Sex (male *vs.* female) | 7,961 | 1.39 | 1.26 | 1.54 | < 0.001 | 6,223 | 1.44 | 1.28 | 1.63 | < 0.001 |
| Preoperative_ASA-PS (1 *vs.* 2 or more) | 7,423 | 0.43 | 0.38 | 0.50 | < 0.001 | 6,223 | 0.68 | 0.58 | 0.80 | < 0.001 |
| Preoperative_ECOG-PS (0 *vs.*1or more) | 6,770 | 0.57 | 0.51 | 0.63 | < 0.001 | 6,223 | 0.77 | 0.69 | 0.86 | < 0.001 |
| Preoperative_CCr (more than the upper limit *vs.* normal) | 7,533 | 2.30 | 2.08 | 2.54 | < 0.001 | 6,223 | 1.31 | 1.16 | 1.49 | < 0.001 |
| Macroscopic morphology (type 4 *vs.* others) | 7,927 | 1.93 | 1.60 | 2.32 | < 0.001 | | | | | |
| Location (UML *vs.* others) | 7,961 | 2.72 | 1.41 | 5.23 | 0.003 | | | | | |
| Histology (differentiated *vs.* undifferentiated) | 7,773 | 1.15 | 1.05 | 1.26 | 0.003 | 6,223 | 0.89 | 0.80 | 0.99 | 0.026 |
| Method of resection (total gastrectomy *vs.* others) | 7,961 | 1.29 | 1.18 | 1.42 | < 0.001 | 6,223 | 1.29 | 1.16 | 1.44 | < 0.001 |
| Lymphadenectomy (D2 *vs.* D1) | 7,887 | 0.63 | 0.58 | 0.69 | < 0.001 | 6,223 | 0.78 | 0.70 | 0.87 | < 0.001 |
| Approach (laparoscope *vs.* others) | 7,961 | 0.75 | 0.67 | 0.84 | < 0.001 | 6,223 | 0.83 | 0.72 | 0.95 | 0.006 |
| Depth of tumor invasion (pT4 *vs.* pT1-T3) | 7,961 | 1.48 | 1.31 | 1.67 | < 0.001 | | | | | |
| Extent of lymph node metastasis (pN0/N1 *vs.* pN2/N3) | 7,961 | 1.11 | 0.98 | 1.26 | 0.087 | | | | | |
| Proximal margin and distal margin (PM0 and DM0 *vs.* others) | 7,928 | 0.32 | 0.24 | 0.43 | < 0.001 | | | | | |
| Residual tumor (R0 *vs.* others) | 7,930 | 0.35 | 0.27 | 0.45 | < 0.001 | 6,223 | 0.35 | 0.27 | 0.47 | < 0.001 |
| Clavien-Dindo classification (Grade II or more *vs.* others) | 7,961 | 1.64 | 1.47 | 1.83 | < 0.001 | 6,223 | 1.29 | 1.13 | 1.46 | < 0.001 |
| Adjuvant chemotherapy (any chemotherapy except cisplatin *vs.* surgery alone) | 7,928 | 0.42 | 0.38 | 0.47 | < 0.001 | 6,223 | 0.63 | 0.56 | 0.71 | < 0.001 |
| **Stage III** | | | | | | | | | | |
| Age (≥ 75 *vs.* < 75) | 7,643 | 1.96 | 1.84 | 2.10 | < 0.001 | 5,981 | 1.34 | 1.22 | 1.46 | < 0.001 |
| Sex (male *vs.* female) | 7,887 | 1.20 | 1.12 | 1.29 | < 0.001 | 5,981 | 1.26 | 1.16 | 1.37 | < 0.001 |
| Preoperative_ASA-PS (1 *vs.*2 or more) | 7,416 | 0.68 | 0.63 | 0.74 | < 0.001 | 5,981 | 0.92 | 0.83 | 1.02 | 0.098 |
| Preoperative_ECOG-PS (0 *vs.*1or more) | 6,768 | 0.65 | 0.61 | 0.70 | < 0.001 | 5,981 | 0.82 | 0.76 | 0.89 | < 0.001 |
| Preoperative_CCr (more than the upper limit *vs.* normal) | 7,426 | 1.69 | 1.58 | 1.80 | < 0.001 | 5,981 | 1.14 | 1.05 | 1.25 | 0.002 |
| Macroscopic morphology (type 4 *vs.* others) | 7,861 | 1.78 | 1.64 | 1.94 | < 0.001 | | | | | |
| Location (UML *vs.* Other) | 7,887 | 1.68 | 1.27 | 2.23 | < 0.001 | | | | | |
| Histology (differentiated *vs.* undifferentiated) | 7,741 | 0.88 | 0.82 | 0.94 | < 0.001 | 5,981 | 0.78 | 0.72 | 0.84 | < 0.001 |
| Method of resection (total gastrectomy *vs.* others) | 7,887 | 1.28 | 1.20 | 1.37 | < 0.001 | 5,981 | 1.27 | 1.18 | 1.37 | < 0.001 |
| Lymphadenectomy (D2 *vs.* D1) | 7,799 | 0.60 | 0.56 | 0.64 | < 0.001 | 5,981 | 0.81 | 0.74 | 0.88 | < 0.001 |
| Approach (laparoscope *vs.* others) | 7,887 | 0.77 | 0.69 | 0.85 | < 0.001 | 5,981 | 0.85 | 0.75 | 0.96 | 0.007 |
| Depth of tumor invasion (pT4 *vs.* pT1-T3) | 7,887 | 1.49 | 1.40 | 1.60 | < 0.001 | | | | | |
| Extent of lymph node metastasis (pN1 *vs.* pN2/N3) | 7,887 | 0.74 | 0.67 | 0.81 | < 0.001 | | | | | |
| Proximal margin and distal margin (PM0 and DM0 *vs.* others) | 7,846 | 0.40 | 0.35 | 0.46 | < 0.001 | | | | | |
| Residual tumor (R0 *vs.* others) | 7,798 | 0.40 | 0.37 | 0.45 | < 0.001 | 5,981 | 0.48 | 0.42 | 0.54 | < 0.001 |
| Clavien-Dindo classification (Grade II or more *vs.* others) | 7,887 | 1.47 | 1.36 | 1.59 | < 0.001 | 5,981 | 1.21 | 1.11 | 1.33 | < 0.001 |
| Adjuvant chemotherapy (any chemotherapy except cisplatin *vs.* surgery alone) | 7,570 | 0.40 | 0.37 | 0.42 | < 0.001 | 5,981 | 0.53 | 0.49 | 0.58 | < 0.001 |

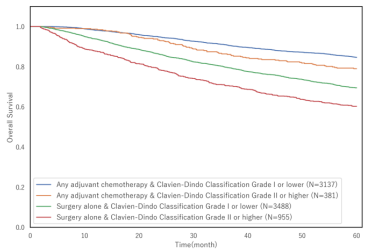
*Abbreviations:* 95% CI, 95% confidence interval; ASA-PS, American Society of Anesthesiologists - physical status; CCr, creatinine clearance; D1, D1 lymphadenectomy; D2, D2 lymphadenectomy; differentiated, differentiated carcinoma which consists of papillary adenocarcinoma, well differentiated tubular adenocarcinoma, and moderately differentiated adenocarcinoma; DM, distal margin, ECOG-PS, Eastern Cooperative Oncology Group - performance status; HR, hazard ratio; PM, proximal margin; R, residual tumor; UML, Fundus, Corpus, and Antrum and pylorus; undifferentiated, undifferentiated carcinoma which consists of solid type poorly differentiated adenocarcinoma, non-solid type poorly differentiated adenocarcinoma, signet-ring cell adenocarcinoma, and mucinous adenocarcinoma.

**Table 3. Prognostic factors of relapse-free survival in patients with primary gastric cancer at stage II and III by univariate and multivariate analyses**

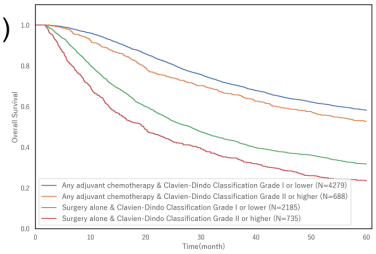
| Factors | Univariate analysis | | | | | Multivariate analysis | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Covariate | *n* | HR | 95% CI (lower) | 95% CI (upper) | *p*-value | *n* | HR | 95% CI (lower) | 95% CI (upper) | *p*-value |
| **Stage II** | | | | | | | | | | |
| Age (≥ 75 *vs*. <75) | 7,674 | 2.26 | 2.07 | 2.46 | < 0.001 | 6,171 | 1.65 | 1.47 | 1.86 | < 0.001 |
| Sex (male *vs*. female) | 7,894 | 1.36 | 1.24 | 1.50 | < 0.001 | 6,171 | 1.39 | 1.24 | 1.55 | < 0.001 |
| Preoperative_ASA-PS (1 *vs*. 2 or more) | 7,361 | 0.49 | 0.44 | 0.56 | < 0.001 | 6,171 | 0.73 | 0.64 | 0.85 | < 0.001 |
| Preoperative_ECOG-PS (0 *vs*. 1 or more) | 6,715 | 0.60 | 0.55 | 0.65 | < 0.001 | 6,171 | 0.77 | 0.70 | 0.85 | < 0.001 |
| Preoperative_CCr (more than the upper limit *vs*. normal) | 7,475 | 1.97 | 1.80 | 2.15 | < 0.001 | 6,171 | 1.17 | 1.04 | 1.32 | 0.007 |
| Macroscopic morphology (type 4 *vs*. others) | 7,860 | 1.95 | 1.65 | 2.31 | < 0.001 | | | | | |
| Location (UML *vs*. others) | 7,894 | 2.79 | 1.55 | 5.05 | < 0.001 | | | | | |
| Histology (differentiated *vs*. undifferentiated) | 7,707 | 1.20 | 1.10 | 1.30 | < 0.001 | 6,171 | 0.96 | 0.87 | 1.05 | 0.361 |
| Method of resection (total gastrectomy *vs*. others) | 7,894 | 1.31 | 1.20 | 1.42 | < 0.001 | 6,171 | 1.28 | 1.16 | 1.41 | < 0.001 |
| Lymphadenectomy (D2 *vs*. D1) | 7,820 | 0.68 | 0.62 | 0.74 | < 0.001 | 6,171 | 0.81 | 0.73 | 0.90 | < 0.001 |
| Approach (laparoscope *vs*. others) | 7,894 | 0.74 | 0.67 | 0.83 | < 0.001 | 6,171 | 0.82 | 0.72 | 0.92 | 0.001 |
| Depth of tumor invasion (pT4 *vs*. pT1-T3) | 7,894 | 1.50 | 1.34 | 1.67 | < 0.001 | | | | | |
| Extent of lymph node metastasis (pN0/N1 *vs*. pN2/N3) | 7,894 | 1.08 | 0.97 | 1.21 | 0.181 | | | | | |
| Proximal margin and distal margin (PM0 and DM0 *vs*. others) | 7,862 | 0.33 | 0.25 | 0.44 | < 0.001 | | | | | |
| Residual tumor (R0 *vs*. others) | 7,863 | 0.35 | 0.27 | 0.44 | < 0.001 | 6,171 | 0.34 | 0.26 | 0.44 | < 0.001 |
| Clavien-Dindo classification (Grade II or more *vs*. others) | 7,894 | 1.54 | 1.39 | 1.70 | < 0.001 | 6,171 | 1.24 | 1.10 | 1.40 | < 0.001 |
| Adjuvant chemotherapy (any chemotherapy except cisplatin *vs*. surgery alone) | 7,861 | 0.51 | 0.47 | 0.56 | < 0.001 | 6,171 | 0.72 | 0.65 | 0.81 | < 0.001 |
| **Stage III** | | | | | | | | | | |
| Age (≥ 75 *vs*. <75) | 7,586 | 1.70 | 1.60 | 1.81 | < 0.001 | 5,939 | 1.22 | 1.12 | 1.33 | < 0.001 |
| Sex (male *vs*. female) | 7,826 | 1.19 | 1.11 | 1.27 | < 0.001 | 5,939 | 1.20 | 1.12 | 1.30 | < 0.001 |
| Preoperative_ASA-PS (1 *vs*. 2 or more) | 7,361 | 0.72 | 0.67 | 0.78 | < 0.001 | 5,939 | 0.92 | 0.84 | 1.01 | 0.077 |
| Preoperative_ECOG-PS (0 *vs*. 1 or more) | 6,721 | 0.70 | 0.65 | 0.74 | < 0.001 | 5,939 | 0.86 | 0.80 | 0.92 | < 0.001 |
| Preoperative_CCr (more than the upper limit *vs*. normal) | 7,372 | 1.54 | 1.45 | 1.64 | < 0.001 | 5,939 | 1.16 | 1.07 | 1.25 | < 0.001 |
| Macroscopic morphology (type 4 *vs*. others) | 7,801 | 1.72 | 1.59 | 1.87 | < 0.001 | | | | | |
| Location (UML *vs*. Other) | 7,826 | 1.64 | 1.26 | 2.14 | < 0.001 | | | | | |
| Histology (differentiated *vs*. undifferentiated) | 7,680 | 0.95 | 0.89 | 1.01 | 0.084 | 5,939 | 0.86 | 0.80 | 0.93 | < 0.001 |
| Method of resection (total gastrectomy *vs*. others) | 7,826 | 1.26 | 1.19 | 1.33 | < 0.001 | 5,939 | 1.24 | 1.16 | 1.33 | < 0.001 |
| Lymphadenectomy (D2 *vs*. D1) | 7,739 | 0.65 | 0.61 | 0.69 | < 0.001 | 5,939 | 0.85 | 0.78 | 0.92 | < 0.001 |
| Approach (laparoscope *vs*. others) | 7,826 | 0.79 | 0.72 | 0.87 | < 0.001 | 5,939 | 0.86 | 0.77 | 0.96 | 0.006 |
| Depth of tumor invasion (pT4 *vs*. T1-T3) | 7,826 | 1.43 | 1.34 | 1.52 | < 0.001 | | | | | |
| Extent of lymph node metastasis (pN0/N1 *vs*. N2/N3) | 7,826 | 0.71 | 0.65 | 0.77 | < 0.001 | | | | | |
| Proximal margin and distal margin (PM0 and DM0 *vs*. others) | 7,785 | 0.43 | 0.37 | 0.49 | < 0.001 | | | | | |
| Residual tumor (R0 *vs*. others) | 7,738 | 0.43 | 0.39 | 0.48 | < 0.001 | 5,939 | 0.50 | 0.45 | 0.56 | < 0.001 |
| Clavien-Dindo classification (Grade II or more *vs*. others) | 7,826 | 1.40 | 1.31 | 1.51 | < 0.001 | 5,939 | 1.20 | 1.10 | 1.30 | < 0.001 |
| Adjuvant chemotherapy (any chemotherapy except cisplatin *vs*. surgery alone) | 7,511 | 0.47 | 0.44 | 0.5 | < 0.001 | 5,939 | 0.61 | 0.56 | 0.66 | < 0.001 |

*Abbreviations:* 95% CI, 95% confidence interval; ASA-PS, American Society of Anesthesiologists- physical status; CCr, creatinine clearance; D1, D1 lymphadenectomy; D2, D2 lymphadenectomy; differentiated, differentiated carcinoma which consists of papillary adenocarcinoma, well differentiated tubular adenocarcinoma, and moderately differentiated adenocarcinoma; DM, distal margin, ECOG-PS, Eastern Cooperative Oncology Group-performance status; HR, hazard ratio; PM, proximal margin; R, residual tumor; UML, Fundus, Corpus, and Antrum and pylorus; undifferentiated, undifferentiated carcinoma which consists of solid type poorly differentiated adenocarcinoma, non-solid type poorly differentiated adenocarcinoma, signet-ring cell adenocarcinoma, and mucinous adenocarcinoma.

(A)

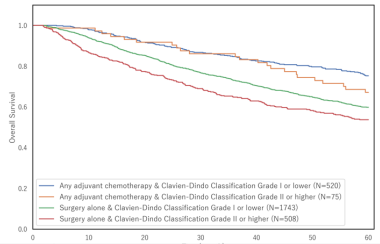



(B)

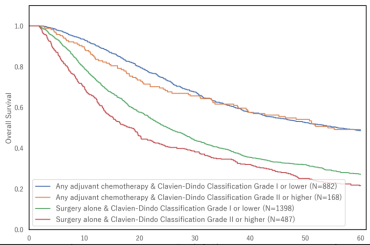



| Subpopulation | Regimen & Clavien-Dindo Classification Grade | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|---|
| Stage II | Any adjuvant chemotherapy & Clavien-Dindo Classification Grade I or lower | 98.1% [97.6%, 98.6%] | 94.7% [93.9%, 95.4%] | 90.9% [89.9%, 91.9%] | 84.7% [83.3%, 85.9%] |
| | Any adjuvant chemotherapy & Clavien-Dindo Classification Grade II or higher | 98.7% [96.8%, 99.4%] | 93.0% [89.8%, 95.2%] | 86.3% [82.4%, 89.5%] | 79.0% [74.4%, 82.9%] |
| | Surgery alone & Clavien-Dindo Classification Grade I or lower | 93.8% [93.0%, 94.6%] | 86.0% [84.8%, 87.2%] | 79.7% [78.3%, 81.1%] | 69.5% [67.8%, 71.0%] |
| | Surgery alone & Clavien-Dindo Classification Grade II or higher | 87.7% [85.4%, 89.7%] | 78.3% [75.5%, 80.8%] | 70.5% [67.4%, 73.4%] | 60.3% [56.9%, 63.5%] |
| Stage III | Any adjuvant chemotherapy & Clavien-Dindo Classification Grade I or lower | 94.3% [93.5%, 94.9%] | 81.5% [80.3%, 82.7%] | 70.6% [69.2%, 72.0%] | 58.2% [56.7%, 59.7%] |
| | Any adjuvant chemotherapy & Clavien-Dindo Classification Grade II or higher | 89.6% [87.0%, 91.7%] | 74.7% [71.2%, 77.8%] | 65.9% [62.1%, 69.3%] | 52.7% [48.8%, 56.5%] |
| | Surgery alone & Clavien-Dindo Classification Grade I or lower | 75.3% [73.4%, 77.1%] | 54.4% [52.2%, 56.5%] | 43.1% [40.9%, 45.3%] | 31.7% [29.6%, 33.9%] |
| | Surgery alone & Clavien-Dindo Classification Grade II or higher | 64.5% [60.8%, 67.9%] | 44.2% [40.4%, 47.9%] | 34.7% [31.1%, 38.4%] | 23.6% [20.4%, 27.0%] |

(C)




(D)




| Subpopulation | Regimen & Clavien-Dindo Classification Grade | 1-year | 2-year | 3-year | 5-year |
|---|---|---|---|---|---|
| Stage II | Any adjuvant chemotherapy & Clavien-Dindo Classification Grade I or lower | 96.5% [94.5%, 97.8%] | 89.5% [86.5%, 91.9%] | 84.7% [81.2%, 87.5%] | 75.3% [71.2%, 78.9%] |
| | Any adjuvant chemotherapy & Clavien-Dindo Classification Grade II or higher | 97.3% [89.6%, 99.3%] | 91.7% [82.5%, 96.2%] | 86.1% [75.7%, 92.3%] | 67.1% [54.8%, 76.8%] |
| | Surgery alone & Clavien-Dindo Classification Grade I or lower | 92.0% [90.6%, 93.2%] | 81.3% [79.4%, 83.1%] | 73.0% [70.8%, 75.1%] | 59.8% [57.3%, 62.2%] |
| | Surgery alone & Clavien-Dindo Classification Grade II or higher | 84.5% [81.0%, 87.4%] | 73.9% [69.7%, 77.6%] | 64.8% [60.3%, 69.0%] | 53.7% [48.9%, 58.3%] |
| Stage III | Any adjuvant chemotherapy & Clavien-Dindo Classification Grade I or lower | 90.6% [88.5%, 92.4%] | 74.7% [71.7%, 77.5%] | 61.1% [57.7%, 64.3%] | 48.6% [45.1%, 52.0%] |
| | Any adjuvant chemotherapy & Clavien-Dindo Classification Grade II or higher | 84.2% [77.6%, 88.9%] | 69.5% [61.8%, 76.0%] | 61.6% [53.5%, 68.7%] | 49.2% [41.0%, 56.8%] |
| | Surgery alone & Clavien-Dindo Classification Grade I or lower | 73.9% [71.4%, 76.1%] | 51.5% [48.7%, 54.2%] | 39.3% [36.5%, 42.0%] | 27.1% [24.6%, 29.7%] |
| | Surgery alone & Clavien-Dindo Classification Grade II or higher | 64.7% [60.1%, 68.8%] | 41.8% [37.1%, 46.3%] | 34.6% [30.1%, 39.1%] | 21.6% [17.7%, 25.7%] |

**Figure 6. Overall survival of all and age 75 or older patients at stage II or III by Clavien-Dindo classification and adjuvant chemotherapy. (A)** Overall survival of all patients at stage II by Clavien-Dindo classification and adjuvant chemotherapy, **(B)** Overall survival of all patients at stage III by Clavien-Dindo classification and adjuvant chemotherapy, **(C)** Overall survival of age 75 or older patients at stage II by Clavien-Dindo classification and adjuvant chemotherapy, **(D)** Overall survival of age 75 or older patients at stage III by Clavien-Dindo classification and adjuvant chemotherapy.

anastomotic leakage, and intra-abdominal infection were other frequent complications. We recommend D2 lymphadenectomy as the standard surgical approach for patients with resectable gastric cancer because it is associated with a lower relapse rate and similar morbidity (*30-35*). Males are generally more susceptible than females to bacterial infections, and surgical site infection was also a risk factor for loss of lean body mass (*36,37*), which would decrease the compliance with S-1 treatment in the adjuvant setting after D2 lymphadenectomy (*36*). There was no difference in the incidence of postoperative complications between D1 and D2 in this retrospective study, although postoperative weight was not recorded in this registry. Laparoscopic surgery, which was an independent favorable prognostic factor compared with open surgery in this study, should be considered for elderly patients to improve their prognosis (*38*).

S-1 is an oral fluorouracil antitumor drug that combines tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP, which inhibits dihydropyrimidine dehydrogenase), and potassium oxonate (Oxo). CDHP clearance is delayed in patients with renal dysfunction, leading to a high AUC of 5-FU (*39*). Patients with creatinine clearance less than 60 mL/min are at significant risk of discontinuing S-1 in an adjuvant setting (*40*). Food intake affects the pharmacokinetics of Oxo but not of FT, CDHP, and 5-FU. Oxo exposure, which protects against gastrointestinal toxicity, is reduced under fed conditions compared to fasting conditions. Insufficient oral intake after gastrectomy leads to reduced levels of plasma Oxo, which in turn can engender diarrhea due to mucosal injury (*41-43*). Total gastrectomy significantly increased the maximum concentration and the area under the curve of plasma 5-FU and CDHP, which caused delayed clearance (*44*). Consistent with a previous study (*45*), we also found that patients who underwent total gastrectomy or those with a low creatinine clearance level tended to require dose reduction. The compliance of adjuvant chemotherapy was significantly worse in aged 75 or older, abnormal renal function, preoperative ECOG-PS 1 or more, total gastrectomy, stage III, and C-D II or more in this study. In age 75 or older patients, the compliance of adjuvant chemotherapy was significantly better in patients with normal renal function, preoperative ECOG-PS 0, D2 lymphadenectomy, except total gastrectomy, stage II in this study. Proximal gastrectomy, pylorus-preserving gastrectomy, or other ways to avoid total gastrectomy should be considered for some patients age 75 or more, as this could avert problems associated with reduced food intake and increased plasma 5-FU concentration.

The Maruyama Index (MI), an algorithm calculated

**Table 4. Predictive factors of postoperative complication and compliance of adjuvant chemotherapy**

| Factors | Objective variant | *n* | Variant | Coefficient | 95% CI (lower) | 95% CI (upper) | *p*-value |
|---|---|---|---|---|---|---|---|
| **Postoperative complication** | | | | | | | |
| Overall patients | Clavien-Dindo classification | 13,051 | Constant | -2.07 | -2.23 | -1.92 | < 0.001 |
| | (Grade II or more *vs.* others) | 13,051 | Age ≥ 75 (*vs.* <75) | 0.33 | 0.22 | 0.43 | < 0.001 |
| | | 13,051 | Male (*vs.* female) | 0.44 | 0.34 | 0.55 | < 0.001 |
| | | 13,051 | Abnormal CCr (*vs.* Normal CCr) | 0.15 | 0.04 | 0.26 | 0.006 |
| | | 13,051 | ECOG-PS 0 (*vs.* 1 or more) | -0.39 | -0.48 | -0.29 | < 0.001 |
| | | 13,051 | D2 lymphadenectomy (*vs.* D1) | 0.01 | -0.09 | 0.11 | 0.844 |
| | | 13,051 | Total gastrectomy (*vs.* others) | 0.45 | 0.36 | 0.55 | < 0.001 |
| | | 13,051 | pStage III (*vs.* pStage II) | 0.07 | -0.02 | 0.16 | 0.123 |
| Age ≥ 75 | Clavien-Dindo classification | 4,936 | Constant | -1.52 | -1.76 | -1.29 | < 0.001 |
| | (Grade II or more *vs.* others) | 4,936 | Male (*vs.* female) | 0.45 | 0.29 | 0.60 | < 0.001 |
| | | 4,936 | Abnormal CCr (*vs.* Normal CCr) | 0 | -0.18 | 0.18 | 0.982 |
| | | 4,936 | ECOG-PS 0 (*vs.* 1 or more) | -0.39 | -0.53 | -0.25 | < 0.001 |
| | | 4,936 | D2 lymphadenectomy (*vs.* D1) | -0.08 | -0.22 | 0.06 | 0.236 |
| | | 4,936 | Total gastrectomy (*vs.* others) | 0.28 | 0.14 | 0.42 | < 0.001 |
| | | 4,936 | pStage III (*vs.* pStage II) | 0.12 | -0.02 | 0.26 | 0.091 |
| **Compliance of adjuvant chemotherapy** | | | | | | | |
| Overall patients | Adjuvant chemotherapy | 6,757 | Constant | 0.98 | 0.80 | 1.16 | < 0.001 |
| | (Completion *vs.* others) | 6,757 | Age ≥ 75 (*vs.* <75) | -0.42 | -0.56 | -0.29 | < 0.001 |
| | | 6,757 | Male (*vs.* female) | -0.05 | -0.16 | 0.06 | 0.359 |
| | | 6,757 | Abnormal CCr (*vs.* Normal CCr) | -0.53 | -0.64 | -0.42 | < 0.001 |
| | | 6,757 | ECOG-PS 0 (*vs.* 1 or more) | 0.23 | 0.11 | 0.34 | < 0.001 |
| | | 6,757 | D2 lymphadenectomy (*vs.* D1) | 0.10 | -0.03 | 0.23 | 0.118 |
| | | 6,757 | Total gastrectomy (*vs.* others) | -0.42 | -0.53 | -0.32 | < 0.001 |
| | | 6,757 | pStage III (*vs.* pStage II) | -0.36 | -0.46 | -0.25 | < 0.001 |
| | | 6,757 | Clavien-Dindo classification Grade II or more (*vs.* others) | -0.21 | -0.36 | -0.06 | 0.007 |
| Age ≥ 75 | Adjuvant chemotherapy | 1,298 | Constant | 0.51 | 0.12 | 0.90 | 0.010 |
| | (Completion *vs.* others) | 1,298 | Male (*vs.* female) | -0.02 | -0.26 | 0.22 | 0.899 |
| | | 1,298 | Abnormal CCr (*vs.* Normal CCr) | -0.58 | -0.84 | -0.32 | < 0.001 |
| | | 1,298 | ECOG-PS 0 (*vs.* 1 or more) | 0.31 | 0.08 | 0.53 | 0.009 |
| | | 1,298 | D2 lymphadenectomy (*vs.* D1) | 0.28 | 0.02 | 0.54 | 0.032 |
| | | 1,298 | Total gastrectomy (*vs.* others) | -0.51 | -0.75 | -0.28 | < 0.001 |
| | | 1,298 | pStage III (*vs.* pStage II) | -0.50 | -0.73 | -0.26 | < 0.001 |
| | | 1,298 | Clavien-Dindo classification Grade II or more (*vs.* others) | -0.20 | -0.52 | 0.12 | 0.210 |

*Abbreviations:* CCr, creatinine clearance; D1, D1 lymphadenectomy; ECOG-PS, Eastern Cooperative Oncology Group - performance status.

using preoperative patient characteristics such as age, sex, Borrmann type, presumed depth of the primary tumor, tumor location, maximum tumor diameter, and histologic type, estimates nodal metastatic status preoperatively to optimize lymphadenectomy. The MI was an independent predictor of both OS and disease-specific survival in a Dutch trial (*46-48*). Additionally, surgery in patients with a low MI was associated with enhanced regional control and survival, but did not alter the incidence of isolated distant metastases. We suggest that artificial intelligence that incorporates measurements such as the MI, pre-operative patient status and expected operative methods could facilitate personalized treatments including postoperative chemotherapy.

We observed that CY1 was associated with significantly reduced OS. Although S-1 monotherapy is recommended for CY1 gastric cancer after gastrectomy in Japanese Guidelines (*18,49*), its efficacy is questionable. Negative cytology following neoadjuvant chemotherapy has previously been associated with significantly improved OS in previous meta-analysis (*50*). Postoperative chemotherapy was clearly effective for CY1-positive gastric cancer cases in this study as well as adjuvant and metastatic setting, and we therefore strongly recommend this treatment for these patients.

There was no comparable previous big data analysis worldwide to analyze postoperative chemotherapy of gastric cancer. All patients underwent gastrectomy in Japanese hospitals and the most administered drug postoperatively was S-1 monotherapy as Japanese standard treatment in this retrospective study. Potential biases would not be excluded completely by the adjustment of considerable prognostic factors of the propensity score matching.

## Conclusion

We found that although adjuvant chemotherapy was effective in elderly patients, they did tend to have a worse prognosis than younger patients. One of the main modifiable predictors of postoperative complications and lower compliance with adjuvant chemotherapy was total gastrectomy. Subtotal gastrectomy and total gastrectomy are recommended mainly as the standard procedure for resectable gastric cancer at stage II and III by the Japanese Gastric Cancer Treatment Guidelines. Through shared decision making among patients, doctors, and medical staff, proximal gastrectomy and pylorus-preserving surgery in addition to distal gastrectomy should therefore be considered to improve survival and quality of life for elderly patients. Additionally, segmental gastrectomy or local resection instead of total gastrectomy should be evaluated in clinical trials. Particular attention should be paid to proximal and distal margins in this case, because a poor post-surgery outcome cannot be rectified by adjuvant chemotherapy.

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# Advantages of short-term antimicrobial treatment for pneumonia and aspiration pneumonia in older patients aged over 65: A nationwide inpatient database study

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**Abstract:** The duration of antimicrobial therapy required to treat community-acquired pneumonia is often longer than expected, likely because of the high number of such inpatients in developed countries with aging populations. In this study, we evaluated the effects of short-term treatments for both pneumonia and aspiration pneumonia in older Japanese adults using the nation's inpatient database. Inpatients aged ≥ 65 years who were admitted to the hospital for pneumonia or aspiration pneumonia between April 1, 2018, and October 31, 2018, were included. We compared patients treated *via* intravenous antibiotics for 3-7 days to control patients treated with a similar regimen for 8-28 days, using inverse probability of treatment-weighted Cox regression. The primary outcome was relapse or readmission for pneumonia and death within 30 days after completing antimicrobial therapy. The secondary outcomes were average treatment effect for *Clostridioides difficile* infection (CDI), chest drainage, and length of hospital stay. The total number of eligible patients was 72,294. The hazard ratio for the primary outcome was 1.04 (95% confidence interval: 0.99-1.10). The mean length of hospital stay was shortened to 9.74 days (range, 9.34-10.1) in the short-term treatment group. The prevalence rates of CDI and chest drainage did not differ significantly between the short- and long-term treatment groups. We observed no statistically significant difference in clinical outcomes between the older adults with pneumonia including aspiration pneumonia who received short- *vs* long-term antimicrobial therapy.

***Keywords*:** aspiration pneumonia, short-term antimicrobial therapy, national inpatient database, older adults, antimicrobial administration

## Introduction

Studies on the duration of antimicrobial treatment for various infectious diseases have been conducted recent years, and pneumonia is one of the most commonly studied infectious diseases. In a randomized controlled trial (RCT) of non-severe pneumonia, no significant difference was observed in the rate of re-hospitalization or mortality up to 30 days after treatment between the 3-day and 7-day antimicrobial treatment groups (*1*). In a cohort study of severe community-acquired pneumonia, no difference in mortality or re-hospitalization rate was observed between 7-day and 10-day or longer antimicrobial treatment, using propensity-score matching (*2*). Similarly to these studies, a meta-analysis of severe community-acquired pneumonia showed that there was no difference in the rate of re-hospitalization or mortality between treatment with antibiotics for < 7 days and treatment with antibiotics for 10 days or longer (*3*). Short-term antimicrobial therapy for community-acquired pneumonia may also contribute to controlling the spread of antimicrobial resistance. The guidelines of the Infectious Diseases Society/Respiratory Society of America recommend a minimum antimicrobial therapy duration of 5 days if there is a trend toward improvement within 2 days (*4*). However, in real-world settings, the median duration of treatment for community-acquired pneumonia ranges from 9.5 days in the United States (*5*) to 14 days in Japan (*6*). Moreover, the participants in previous RCTs were relatively young, in their 60s and 70s, and those with aspiration pneumonia (AP) were excluded (*1,2*). However, the median age of patients with moderate or severe community-acquired pneumonia in Japan is 80-85 years (*6*), meaning that physicians in the country may be reluctant to shift to short-term regimens.

Furthermore, there are no data regarding AP from Japan, although it is frequently diagnosed in older patients and may be useful as a reference to justify

shortening antibiotic treatment durations. Although some guidelines state that the duration of treatment for community-acquired AP should be 5-7 days (*7*), Japanese guidelines and manuals on antimicrobial use recommend 7-10 days (*8,9*). We used data from the Diagnosis Procedure Combination (DPC) database, which includes almost all of the acute-care beds and > 50% of all hospital beds in Japan, along with payment claims data for all inpatients from >1,500 participating hospitals (*10*), to determine the outcomes of short-term antimicrobial therapy for pneumonia, including AP, in older patients.

## Patients and Methods

### *Study design and participants*

This multicenter, retrospective, observational study used DPC data between April 1 and October 31, 2018. We excluded data after 2020, when the COVID-19 pandemic began, because the COVID-19 would affect the diagnosis of respiratory infections including pneumonia, and there were no major changes in the treatment policy for pneumonia after 2018. In order to avoid any modification due to viral diseases that spread on a large scale in winter, such as influenza, data analysis was conducted using data from April to October. We included patients aged ≥ 65 years who were hospitalized for the first time for pneumonia or AP, as coded by the International Classification of Diseases, 10th revision (ICD-10; Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*).

We excluded patients with pyothorax, pulmonary pyogenic disease, or bacteremia at the time of admission (as noted by ICD-10; Supplemental Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*); those who had not begun taking antimicrobial agents within 2 days of admission to the hospital; those whose initial antimicrobial treatments were administered for < 3 or > 28 days; those who were discharged from the hospital before the end of antimicrobial therapy with a 2-day antimicrobial-free period (including cases of death); and those with scheduled hospital admissions.

### *Extracted information*

The following information was extracted from the database: age, sex, body mass index (BMI), Japan Coma Scale score at admission, activities of daily living (ADL) assessment scores according to the Barthel index at admission (*11*), comorbidities at admission, length of hospitalization, discharge outcome, ambulance use, medications, procedures, and hospitalization-related piecework medical expenses. Information regarding underlying diseases was extracted if the following ICD-10 codes were present: diseases included in the Charlson comorbidity index (CCI) (*12*), diseases associated with dysphagia, and *Clostridioides difficile* infection (CDI).

The extracted information concerning medications included catecholamines taken within 3 days of admission and antimicrobials to treat pneumonia or AP at admission. Information was extracted for the following drugs if they were prescribed within 6 months following admission and up to 1 week prior to discharge: immunosuppressive agents, corticosteroids, molecular-targeted agents, antitumor agents, angiotensin-converting enzyme inhibitors, cilostazol, *Hange-koboku-to* (Kampo), antihistamines, antiemetic drugs (metoclopramide and domperidone), antipsychotic drugs included in the Screening Tool for Older Person's appropriate Prescriptions in Japanese (*13*), hypnotic sedatives, anxiolytics, antidepressants, and sulpiride.

The inpatient procedures included tabulated receipt processing codes for hemodialysis and nasal nutrition on prior hospitalization within 6 months. Data regarding oxygen administration, high-flow therapy, and ventilator use were collected at administration (Figure 1).

### *Definitions*

The following diseases were defined as being associated with dysphagia: cerebrovascular disease, dementia, Parkinson's disease, Parkinson's syndrome, myofascial junction diseases, cranial nerve palsy, brainstem encephalitis, hyperthyroidism, systemic amyloidosis, Wilson's disease, Arnold-Chiari malformation, esophageal stenosis, esophageal achalasia, dysphagia, and vocal cord paralysis. State of consciousness was assessed in the order of 0, 1, 2, 3, 10, 20, 30, 100, 200, and 300 on the Japan Coma Scale (*14*). Each order was then replaced by 0-9, respectively. The short-term treatment group included patients who received antimicrobial agents for 3-7 days, whereas the longer treatment group included those who received antimicrobial agents for 8-28 days. Antimicrobials were divided according to the antimicrobial spectrum into anti-anaerobic, antipseudomonal, anti-methicillin-resistant *Staphylococcus aureus,* and other antimicrobial agents. Treatment duration was defined by the end of treatment, with 2 consecutive days where no antimicrobial agents were administered.

### *Outcomes*

The primary outcome was relapse or death within 30 days after the completion of antimicrobial therapy. Relapse was defined as oxygen administration on the day when antimicrobials were resumed or readmission to the hospital for pneumonia or AP.

The secondary outcomes were hospitalization duration, rate of chest drainage implementation, and

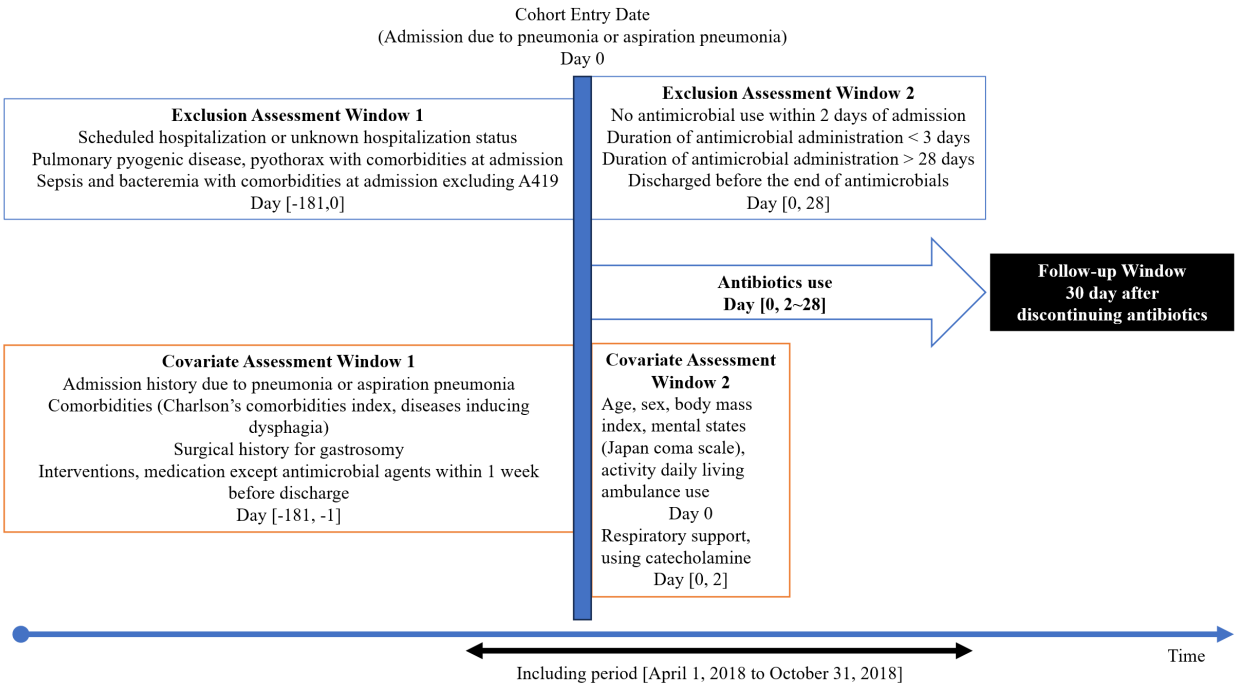


**Figure 1. Schematic representation of patient cohort recruitment and covariate sampling processes.**

rate of CDI complications following the termination of antimicrobial therapy. Cases were considered complicated by CDI if oral vancomycin, fidaxomicin, or bezlotoxumab were used after the initial antibiotic therapy course was completed or if metronidazole was used after the end of the initial antibiotic regimen and CDI has been noted as a comorbidity.

*Statistical analysis*

Assuming random missing values, a propensity score for the treatment was calculated after processing the missing values using multiple imputations with chained equations. Following imputation, the primary outcome was subjected to Cox regression after inverse probability of treatment weighting (IPTW). The average treatment effect (ATE) was calculated for each secondary outcome. Propensity score estimates were calculated using a logistic regression model with the following covariates: age, sex, BMI, state of consciousness, ambulance use, ADL assessment score, CCI, comorbidities involving dysphagia, hemodialysis, use of medications that may affect swallowing, use of medications associated with immune suppression, initial antimicrobial agents and combination antimicrobial therapy, nasal tube feeding, surgical history of gastrostomy, admission history for pneumonia or AP, use of advanced respiratory support therapy (*e.g.*, oxygen administration, high-flow therapy, or the use of a ventilator), and the administration of catecholamines within 3 days of admission. To balance the evaluation, absolute standardized mean difference (ASD) values of $< 0.10$ were considered evaluable. Subgroup analysis was performed according to age group (< 75, 75-89, and ≥ 90 years), oral antibiotics during initial therapy, oral antibiotics on the final prescription, and discharge to another hospital. A *p*-value less than 0.05 was considered statistically significant.

Sensitivity analyses were performed as follows: *i*) the primary outcome was changed to restarting antimicrobials without the use of an oxygen supply, and *ii*) the hazard ratio (HR) was calculated using IPTW Cox regression analysis with death within 30 days of admission as the outcome — including patients who were excluded from the main analysis because their completion of antimicrobial therapy was not confirmed. All statistical analyses were performed using R version 4.3.0 (R Core Team 2023, Vienna, Austria). Multiple imputations *via* chained equations were performed for 20 imputed datasets with 15 iterations through classification and regression tree approaches using the R package "mice". IPTW was performed using the R package "weightthem". A Kaplan–Meier survival curve was created using the "adjustedCurves" R package.

*Ethics approval statement*

The study was conducted in accordance with the principles of the Declaration of Helsinki, and was approved by the Institutional Review Board of Tokyo Medical and Dental University (M2000-788-23; March 2021). The requirement for informed consent was waived owing to the use of anonymized retrospective data.

**Results**

Of the 119,564 initially eligible patients, 47,270 met the exclusion criteria, resulting in 72,294 eligible patients across 1,795 institutions. Only 141 facilities treated > 50% of their patients with short-term antibiotic courses (Supplemental Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*). From these facilities, 22,569 patients were included in the short-term treatment group, and 49,725 were included in the long-term treatment group (Figure 2). The mean duration of antimicrobial therapy was 10.3 ± 4.6 days, with values of 5.9 ± 1.2 and 12.2 ± 4.2 in the short- and long-term treatment groups, respectively. The mean patient age was 84.0 ± 8.0 years, and 46.4% were female (Table 1). The mean Charlson's comorbidity index was 1.57 ± 1.59, and the underlying disease had an ASD < 0.1 in both treatment groups (Table 1). The level of respiratory support within 3 days of hospitalization was higher in the long-term treatment group vs the short-term one. The initial use of antipseudomonal antibiotics was slightly higher in the long-term treatment group than in the short-term one. The average length of stay after discontinuing antimicrobial agents was longer for the long-term group (20.8 days) than for the short-term one (16.2 days). The overall crude number of primary outcomes (*i.e.*, relapse and death) was 10,356 (14.3%), which was higher in the long-term treatment group (15.5%) than in the short-term one (11.6%; Table 2). The HR of the primary outcome within 30 days following the completion of antimicrobial therapy without IPTW was 1.11 (95% confidence interval [CI]: 1.06-1.16), and the Kaplan–Meier survival curve indicated a worse prognosis in the long-term treatment group (Figure 3A). A log-log plot of the proportional hazard is shown in Supplemental Figure S2A (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*). The average cost per hospitalization was 1,059,773 ± 861,678 JPY, which was significantly higher in the long-term treatment group (1,177,023 JPY) than in the short-term one (801,441 JPY).

After multiple imputations, the convergence and distribution of the assignments were confirmed (Supplemental Figure S3, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*). After IPTW, the balance assessment showed that the ASD values were <0.1 for all covariates (Figure 4; Supplemental Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*). The HR of the primary outcome within 30 days following antimicrobial therapy completion was 0.99 (95% CI: 0.95-1.04), and the Kaplan–Meier survival curve indicated a similar prognosis between the short- and long-term treatment groups (Figure 3B). Regarding ATE, we found no significant differences in the proportion of chest drainage implementations and CDI complications between the two groups at 0.01% (95% CI: –0.06 to 0.07) and 0.07% (95% CI: –0.03 to 0.17), respectively. No significant differences were observed in the HRs for death and relapse (Table 2). Regarding length of hospital stay, the ATE for short-term treatment was –9.65 days (95% CI: –10.05 to –9.25). In our subgroup analysis, the primary outcome

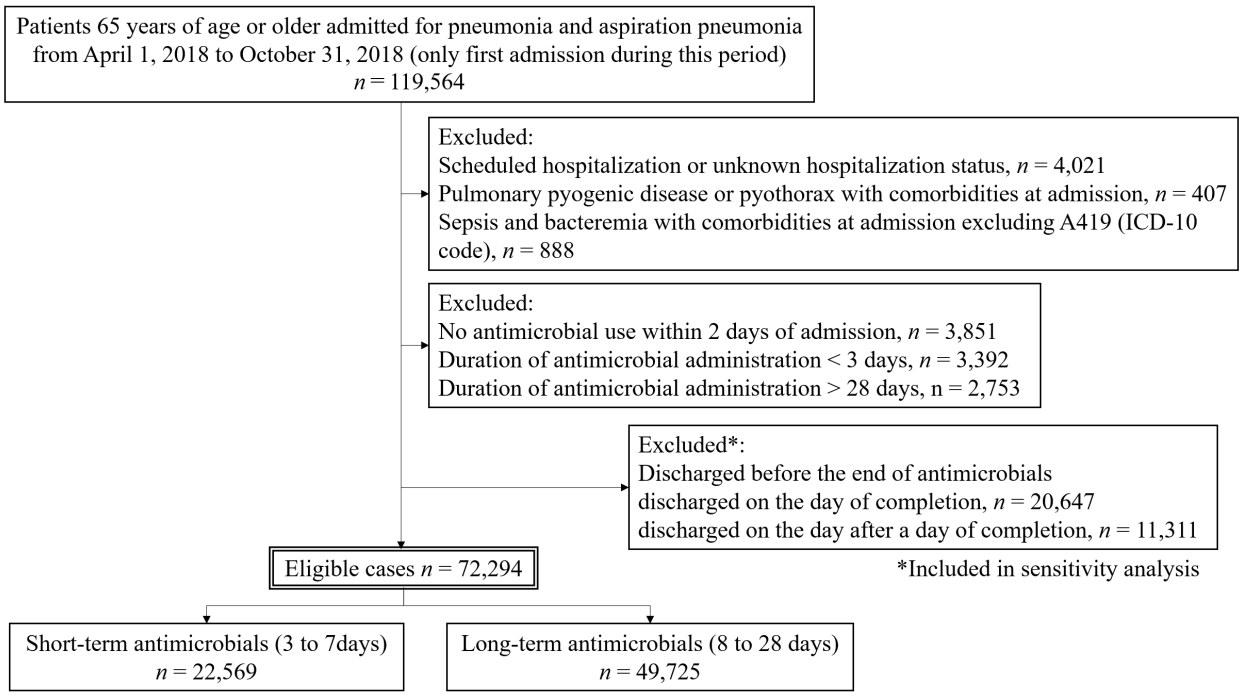


**Figure 2. Flowchart of the study procedure.**

**Table 1. Characteristics of patients admitted with pneumonia and aspiration pneumonia**

| Characteristics | All | Short-term treatment | Long-term treatment | ASD |
|---|---|---|---|---|
| *n* | 72,294 | 22,569 | 49,725 | |
| Age, years (mean [SD]) | 83.97 (7.96) | 83.89 (8.03) | 84.01 (7.93) | 0.015 |
| Sex, female (%) | 33,570 (46.4) | 11,323 (50.2) | 22,247 (44.7) | 0.109 |
| Body mass index (mean [SD]) | 19.90 (3.92) | 20.12 (3.98) | 19.80 (3.89) | 0.08 |
| Missing value | 8,151 (11.2) | 2,439 (10.8) | 5,712 (11.5) | |
| Japan coma scale (mean [SD])* | 1.11 (1.82) | 1.02 (1.73) | 1.15 (1.86) | 0.069 |
| ADL assessment score | | | | |
| Feeding (%) | | | | 0.12 |
| unable | 32,359 (44.8) | 9,353 (41.4) | 23,006 (46.3) | |
| needs help cutting, spreading butter, *etc.*, or requires modified diet | 15,396 (21.3) | 5,060 (22.4) | 10,336 (20.8) | |
| independent | 20,994 (29.0) | 7,198 (31.9) | 13,796 (27.7) | |
| missing value | 3,545 (4.9) | 958 (4.2) | 2,587 (5.2) | |
| Transfers (bed to chair and back) (%) | | | | 0.122 |
| unable, no sitting balance | 37,655 (52.1) | 10,888 (48.2) | 26,767 (53.8) | |
| major help (one or two people, physical), can sit | 5,747 (7.9) | 1,806 (8.0) | 3,941 (7.9) | |
| minor help (verbal or physical) | 14,972 (20.7) | 5,084 (22.5) | 9,888 (19.9) | |
| independent | 12,584 (17.4) | 4,401 (19.5) | 8,183 (16.5) | |
| missing value | 1,336 (1.8) | 390 (1.7) | 946 (1.9) | |
| Grooming (%) | | | | 0.084 |
| needs to help with personal care | 52,835 (73.1) | 16,006 (70.9) | 36,829 (74.1) | |
| independent face/hair/teeth/shaving (implements provided) | 17,203 (23.8) | 5,923 (26.2) | 11,280 (22.7) | |
| missing value | 2,256 (3.1) | 640 (2.8) | 1,616 (3.2) | |
| Getting on and off toilet (%) | | | | 0.118 |
| dependent | 42,044 (58.2) | 12,260 (54.3) | 29,784 (59.9) | |
| needs some help, but can do something alone | 14,282 (19.8) | 4,830 (21.4) | 9,452 (19.0) | |
| independent (on and off, dressing, wiping) | 14,416 (19.9) | 5,021 (22.2) | 9,395 (18.9) | |
| missing value | 1,552 (2.1) | 458 (2.0) | 1,094 (2.2) | |
| Bathing self (%) | | | | 0.076 |
| dependent | 54,610 (75.5) | 16,796 (74.4) | 37,814 (76.0) | |
| independent (or in shower) | 12,198 (16.9) | 4,220 (18.7) | 7,978 (16.0) | |
| missing value | 5,486 (7.6) | 1,553 (6.9) | 3,933 (7.9) | |
| Walking on level surface (%) | | | | 0.116 |
| immobile or < 50 yards | 42,957 (59.4) | 12,686 (56.2) | 30,271 (60.9) | |
| wheelchair independent, including corners, > 50 yards | 4,498 (6.2) | 1,525 (6.8) | 2,973 (6.0) | |
| walks with help of one person (verbal or physical) > 50 yards | 8,213 (11.4) | 2,816 (12.5) | 5,397 (10.9) | |
| independent (but may use any aid; for example, stick) > 50 yards | 12,672 (17.5) | 4,432 (19.6) | 8,240 (16.6) | |
| missing value | 3,954 (5.5) | 1,110 (4.9) | 2,844 (5.7) | |
| Ascend and descend stairs (%) | | | | 0.094 |
| unable | 45,913 (63.5) | 13,825 (61.3) | 32,088 (64.5) | |
| needs help (verbal, physical, carrying aid) | 7,843 (10.8) | 2,705 (12.0) | 5,138 (10.3) | |
| independent | 11,168 (15.4) | 3,876 (17.2) | 7,292 (14.7) | |
| missing value | 7,370 (10.2) | 2,163 (9.6) | 5,207 (10.5) | |
| Dressing (%) | | | | 0.109 |
| dependent | 42,765 (59.2) | 12,562 (55.7) | 30,203 (60.7) | |
| needs help but can do about half unaided | 14,927 (20.6) | 5,022 (22.3) | 9,905 (19.9) | |
| independent (including doing buttons, zips, laces, *etc*.) | 13,106 (18.1) | 4,548 (20.2) | 8,558 (17.2) | |
| missing value | 1,496 (2.1) | 437 (1.9) | 1,059 (2.1) | |
| Controlling bowels (%) | | | | 0.114 |
| incontinent (or needs to be given enemas) | 40,262 (55.7) | 11,778 (52.2) | 28,484 (57.3) | |
| occasional accident | 9,803 (13.6) | 3,191 (14.1) | 6,612 (13.3) | |
| continent | 20,221 (28.0) | 7,027 (31.1) | 13,194 (26.5) | |
| missing value | 2,008 (2.8) | 573 (2.5) | 1,435 (2.9) | |
| Controlling bladder (%) | | | | 0.114 |
| incontinent, or catheterized and unable to manage alone | 40,483 (56.0) | 11,842 (52.5) | 28,641 (57.6) | |
| occasional accident | 10,114 (14.0) | 3,311 (14.7) | 6,803 (13.7) | |
| continent | 19,817 (27.4) | 6,882 (30.5) | 12,935 (26.0) | |
| missing value | 1,880 (2.6) | 534 (2.4) | 1,346 (2.7) | |
| Underlying diseases and medications for daily use | | | | |
| Charlson comorbidity index (mean (SD)) | 1.57 (1.59) | 1.55 (1.59) | 1.58 (1.58) | 0.016 |
| Admission history of aspiration pneumonia (%) | 3,368 (4.7) | 894 (4.0) | 2,028 (4.1) | 0.006 |
| Admission history of pneumonia (%) | 2,922 (4.0) | 999 (4.4) | 2,369 (4.8) | 0.016 |

*The state of consciousness is assessed in the order 0, 1, 2, 3, 10, 20, 30, 100, 200, and 300, whereas each of these in turn was replaced from 0 to 9. ASD, absolute standardized mean difference; SD, standard deviation; ADL, active daily living; MRSA, methicillin-resistant *Staphylococcus aureus*.

**Table 1. Characteristics of patients admitted with pneumonia and aspiration pneumonia (continued)**

| Characteristics | All | Short-term treatment | Long-term treatment | ASD |
|---|---|---|---|---|
| Diseases with dysphagia (%) | 31,661 (43.8) | 9,771 (43.3) | 21,890 (44.0) | 0.015 |
| Surgical history of gastrostomy (%) | 342 (0.5) | 99 (0.4) | 243 (0.5) | 0.007 |
| Nasal tube feeding (%) | 425 (0.6) | 113 (0.5) | 312 (0.6) | 0.017 |
| Hemodialysis (%) | 30 (0.0) | 7 (0.0) | 23 (0.0) | 0.008 |
| Medications associated with immune suppression | | | | |
| corticosteroid (%) | 638 (0.9) | 208 (0.9) | 430 (0.9) | 0.006 |
| antitumor agents (%) | 3 (0.0) | 2 (0.0) | 1 (0.0) | 0.009 |
| immunosuppressants (%) | 8 (0.0) | 2 (0.0) | 6 (0.0) | 0.003 |
| Medications involved in swallowing | | | | |
| angiotensin-converting enzyme inhibitors (%) | 212 (0.3) | 53 (0.2) | 159 (0.3) | 0.016 |
| cilostazol (%) | 6 (0.0) | 3 (0.0) | 3 (0.0) | 0.007 |
| antiemetic agents (metoclopramide and domperidone) (%) | 8 (0.0) | 4 (0.0) | 4 (0.0) | 0.009 |
| psychiatric agents (%) | 50 (0.1) | 14 (0.1) | 36 (0.1) | 0.004 |
| Hange-koboku-to (Kampo) (%) | 3 (0.0) | 0 (0.0) | 3 (0.0) | 0.011 |
| About admission of pneumonia | | | | |
| Aspiration pneumonia (%) | 31,112 (43.0) | 9,504 (42.1) | 21,608 (43.5) | 0.027 |
| Ambulance use (%) | 32,313 (44.7) | 9,566 (42.4) | 22,747 (45.7) | 0.068 |
| Most advanced respiratory support therapy within three days of admission (%) | | | | 0.246 |
| none | 26,113 (36.1) | 9,887 (43.8) | 16,226 (32.6) | |
| oxygen administration by oxygen canula or mask | 43,794 (60.6) | 12,229 (54.2) | 31,565 (63.5) | |
| high-flow therapy | 440 (0.6) | 73 (0.3) | 367 (0.7) | |
| mechanical ventilator support | 1,947 (2.7) | 380 (1.7) | 1,567 (3.2) | |
| Catecholamine use within 3 days of admission(%) | 1,524 (2.1) | 264 (1.2) | 1,260 (2.5) | 0.101 |
| Combination antimicrobial therapy (%) | 6,971 (9.6) | 1,859 (8.2) | 5,112 (10.3) | 0.071 |
| Initial antimicrobial agents | | | | |
| anti-pseudomonal agents (%) | 19,648 (27.2) | 5,067 (22.5) | 14,581 (29.3) | 0.157 |
| anti-anaerobic agents (%) | 50,782 (70.2) | 14,796 (65.6) | 35,986 (72.4) | 0.148 |
| anti-MRSA agents(%) | 236 (0.3) | 43 (0.2) | 193 (0.4) | 0.037 |
| oral antibiotics (%) | 11,001 (15.2) | 1,147 (5.1) | 2,374 (4.8) | 0.014 |
| Oral antibiotics for final administration (%) | 3,521 (4.9) | 3,050 (13.5) | 7,951 (16.0) | 0.07 |
| Length of hospital stay, days (mean, [SD]) | 29.6 (28.8) | 22.1 (23.4) | 33.1 (30.3) | 0.404 |

*The state of consciousness is assessed in the order 0, 1, 2, 3, 10, 20, 30, 100, 200, and 300, whereas each of these in turn was replaced from 0 to 9. ASD, absolute standardized mean difference; SD, standard deviation; ADL, active daily living; MRSA, methicillin-resistant *Staphylococcus aureus*.

**Table 2. Outcomes associated with treatment duration for pneumonia by using inverse probability of treatment weighting Cox regression**

| Characteristics | Overall | Short-term treatment | Long-term treatment | Unadjusted HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|---|---|
| a) Relapse as resumption of antimicrobial therapy and oxygen supply | | | | | |
| primary outcome (%) | 10,356 (14.3) | 2,626 (11.6) | 7,730 (15.5) | 1.11 (1.06 to 1.16) | 0.99 (0.95 to 1.04) |
| relapse during hospitalization (%) | 4,877 (6.7) | 1,085 (4.8) | 3,792 (7.6) | 1.07 (1.01 to 1.13) | 0.97 (0.92 to 1.03) |
| readmission due to pneumonia or aspiration pneumonia (%) | 2,202 (3.0) | 754 (3.3) | 1,448 (2.9) | | |
| death during hospitalization (%) | 3,080 (4.3) | 717 (3.2) | 2,363 (4.8) | 1.21 (1.12 to 1.32) | 1.03 (0.95 to 1.12) |
| death during re-hospitalization (%) | 197 (0.3) | 70 (0.3) | 127 (0.3) | | |
| b) Relapse as resumption of antimicrobial therapy | | | | | |
| primary outcome (%) | 15,343 (21.2) | 3,801 (16.8) | 11,542 (23.2) | 1.17 (1.13 to 1.22) | 1.08 (1.04 to 1.12) |
| relapse during hospitalization (%) | 10,127 (14.0) | 2,316 (10.3) | 7,811 (15.7) | 1.16 (1.12 to 1.21) | 1.09 (1.05 to 1.14) |
| readmission due to pneumonia or aspiration pneumonia (%) | 2,152 (3.0) | 738 (3.3) | 1,414 (2.8) | | |
| death during hospitalization (%) | 2,872 (4.0) | 679 (3.0) | 2,193 (4.4) | 1.21 (1.12 to 1.32) | 1.02 (0.94 to 1.11) |
| death during re-hospitalization (%) | 192 (0.3) | 68 (0.3) | 124 (0.2) | | |

"Unadjusted HR" was calculated without inverse probability of treatment weighting, and "Adjusted HR" was calculated after inverse probability of treatment weighting. HR, hazard ratio; CI, confidence interval.

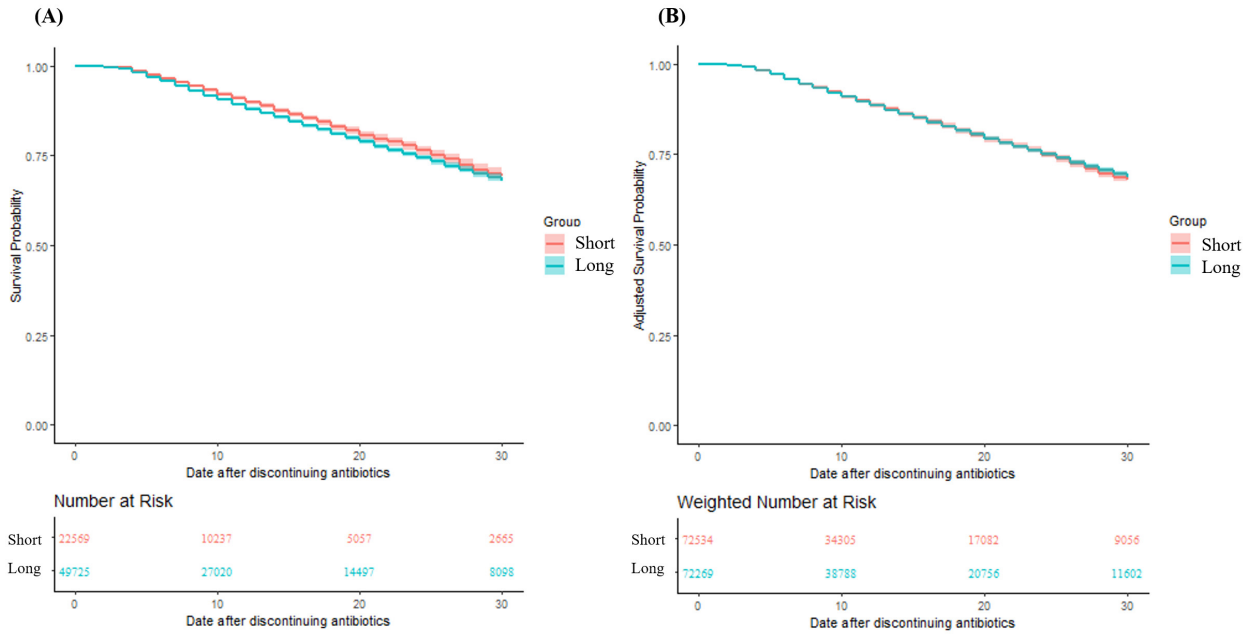


**Figure 3. Kaplan–Meier survival curve for relapse and death. (A)** Analysis after multiple imputations; **(B)** Analysis after multiple imputation and inverse probability of treatment weighting.

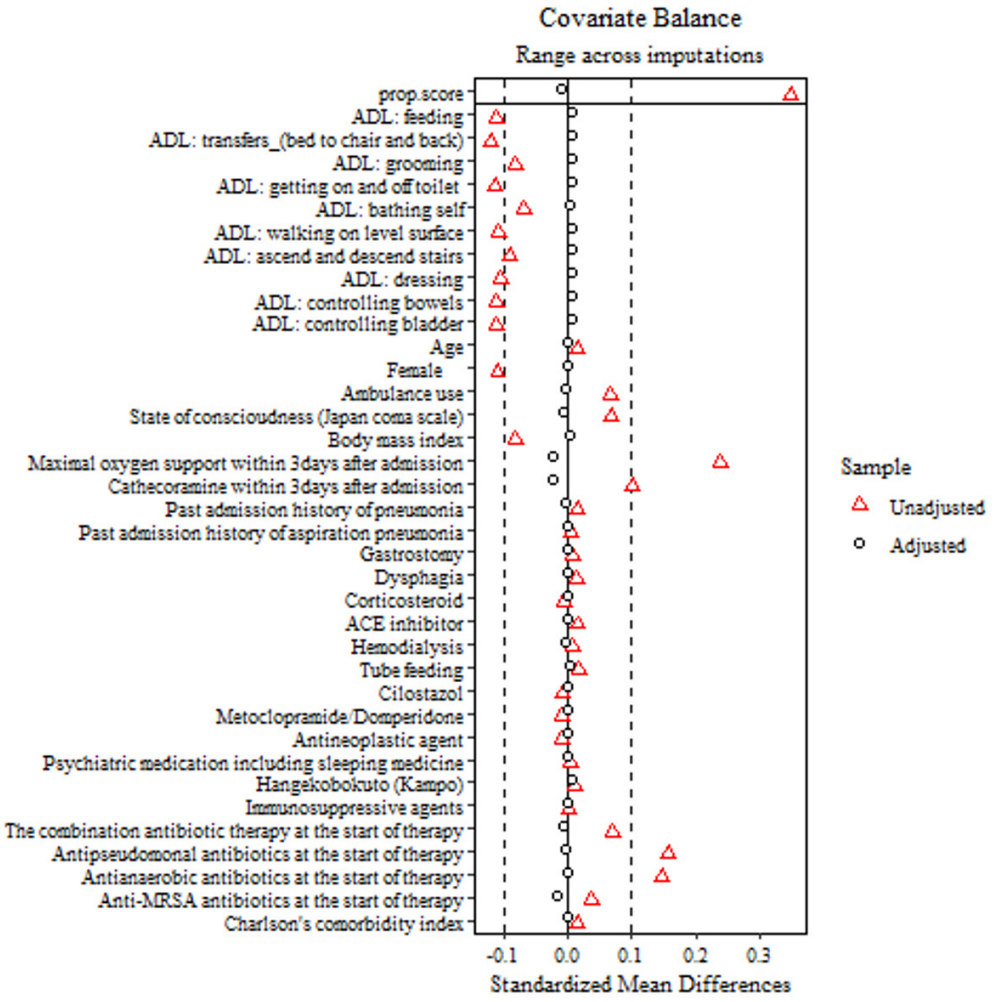


**Figure 4. Balance evaluation after the inverse probability of treatment weighting.** After multiple imputations for each covariate, standard mean differences are plotted before (red triangles) and after (white circles) inverse probability of treatment weighting. Values of < 0 indicate covariates that were more common in the control group, while those with values > 0 were more common in the short-term treatment group.

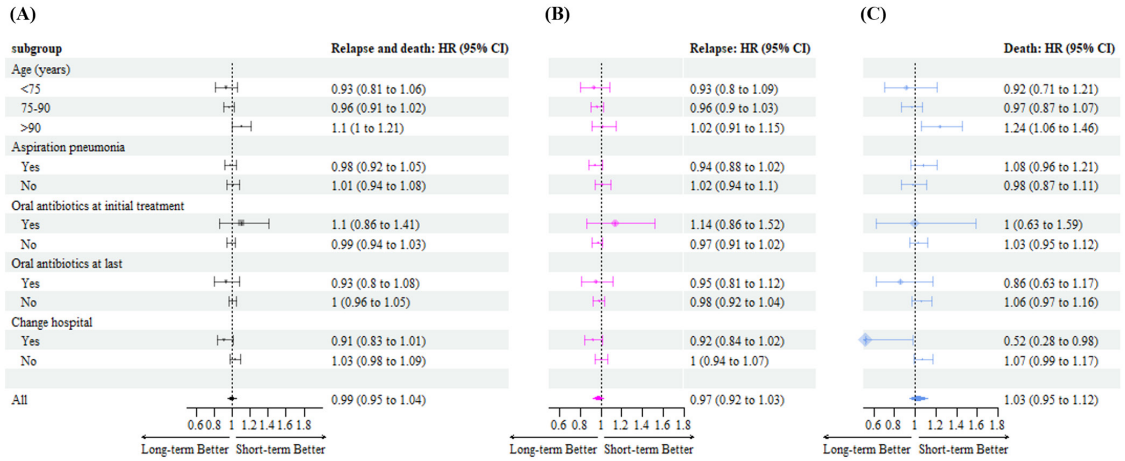


**Figure 5. Subgroup analysis. (A)** Primary outcome; **(B)** Relapse; **(C)** Death. Hazard ratios for outcomes after the inverse probability of treatment weighting in each subgroup are shown; whisker ends indicate 95% confidence intervals.

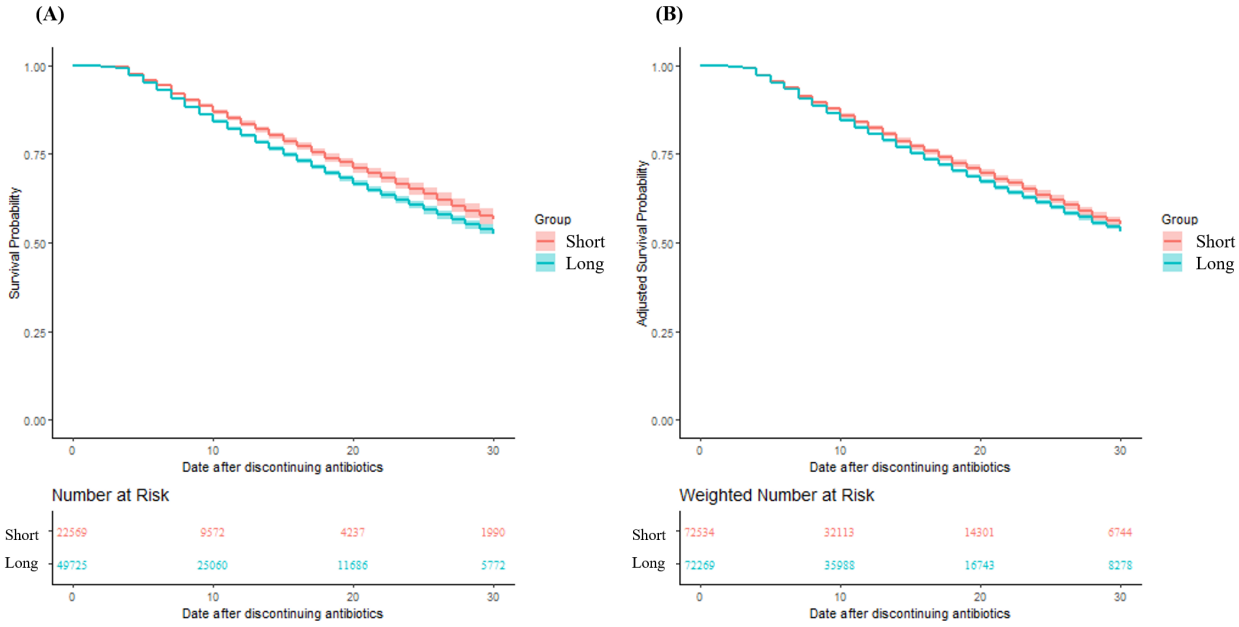


**Figure 6. Kaplan–Meier survival curve for death and relapse (defined as resumption of antimicrobial therapy).**

was slightly more common in the long-term treatment group for patients who initially received anti-anaerobic antimicrobials. No significant difference was observed in the prevalence of AP between the groups (Figure 5).

*Sensitivity analysis*

Our analysis with in-hospital pneumonia relapse, defined as all cases where antimicrobial agents were restarted, showed significant differences in the HRs for the primary outcome and relapse, at 1.08 (95% CI: 1.04-1.12) and 1.09 (95% CI: 1.05-1.14), respectively, but showed no significant difference for death (Table 2, Figure 6; Supplemental Figure S2B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*).

To compare the duration of antimicrobial therapy, we had initially excluded > 30,000 patients for whom completion of antimicrobial therapy was not confirmed (Figure 2). We performed a second survival analysis with death at 30 days following admission as the outcome, with these patients re-included. Although the covariates were balanced *via* the same approach used in the main analysis (Supplemental Figure S4A, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*), the HR for death was 0.42 (95% CI: 0.40-0.43) — indicating a higher mortality rate in the short-term treatment group. The Kaplan–Meier survival curve showed that the occurrence of death within 7 days was higher in the short-term treatment group (Supplemental

Figure S4B, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=98*).

**Discussion**

Short-term antimicrobial treatment did not increase the risk of relapse or death at 30 days following completion of initial antibiotic therapy for pneumonia, including AP, in older Japanese patients aged ≥ 65 years who were indexed in the DPC database between April 1 and October 31, 2018. Many RCTs have focused on reducing the duration of antimicrobial therapy for various infectious diseases, including pneumonia. Our results were consistent with theirs; however, many of these studies included relatively younger patients (*i.e.*, aged between 40 and 79) (*1-3*). Few such studies have focused exclusively on older adults (*15*). The mean patient age in this study was 80 years, which is appropriate for pneumonia treatment in a country such as Japan with an aging population. Although the median duration of antimicrobial treatment was shorter than what was reported in a previous related study (*6*), it was nevertheless relatively long (≥ 10 days). A few centers in Japan still actively provide short-term antimicrobial treatments. Although short-term antimicrobial treatment did not decrease the occurrence of CDI in this study, it shortened the length of hospital stay. Before adjustment, there was an average difference of ~300,000 JPY between our treatment groups regarding medical costs related to hospitalization. Although the cost difference is expected to be smaller when illness severity and other factors are accounted for, shortening the duration of antimicrobial treatment may reduce medical costs, as has been previously reported (*3*).

In this study, because the timing of pneumonia relapse could not be determined from the data, re-administration of antimicrobials and oxygenation was defined as relapse. Because hypoxemia was found in 90% of the patients with AP who required hospitalization (*16*) and in ~60% of those with healthcare-associated pneumonia (*17*), we considered the need for re-administration of antimicrobials and oxygen to represent a more appropriate indicator of relapse than antimicrobial re-administration alone. Our sensitivity analysis examining only the re-initiation of antimicrobials determined that relapse was more frequent in the long-term treatment group. This group also had a longer average hospital stay and was at a higher risk of developing common nosocomial infections such as urinary tract infections (UTIs), surgical site infections, and catheter-related bloodstream infections (*18*). Bacteremic UTI is occasionally associated with respiratory symptoms, which can be difficult to distinguish from pneumonia in ~10% of cases (*19*). These infectious diseases can be difficult to distinguish from pneumonia using this definition.

In one multicenter cohort study conducted in Japan, 625 of 677 (92%) patients with pneumonia and AP were hospitalized for treatment (*20*). Therefore, the results of our present study are likely representative of most older patients with these conditions. Cases of pneumonia that are treated using oral antimicrobial agents, without hospitalization, are typically milder than those requiring hospitalization, meaning that our present results may also be generalizable to outpatients. However, it remains unclear whether such a generalization is possible for patients with pneumonia or AP that occurs under similar conditions to healthcare-associated pneumonia (*17*), which has higher rates of both mortality and detection of antibiotic-resistant bacteria. Our results may nevertheless be generalizable to healthcare-associated AP because previous RCTs were not limited by administering short-term antibiotic treatments in cases of severe healthcare-associated pneumonia (*e.g.*, ventilator-associated pneumonia) (*21*).

This study has several key limitations. First, although we could not obtain information about race of patients, this study included older adults who were almost certainly Japanese. Therefore, it had limited generalizability for other races or in other health systems. Moreover, it was limited to a time when the effects of seasonal influenza and COVID-19, which are epidemic respiratory viral diseases, could be avoided, so it may be difficult to generalize to the current situation where sporadic outbreaks of COVID-19 occur or during the winter flu season.

Second, information regarding predictors of severity, such as vital signs and laboratory tests (*22*), was not available in the DPC database. Given that such determinants of severity were more prevalent in the long-term treatment group, the pneumonia severity determinant was considered an unmeasured confounder that could undermine the causal relationship. For example, elevated C-reactive protein level predicts complex pneumonia (such as pyothorax and pulmonary pyogenic disease), for which long-term antimicrobial therapy is preferred (*23,24*). Further, although hyponatremia, thrombocytopenia, alcohol abuse, and hypoalbuminemia have been reported to be associated with complex pneumonia (*25*), it was difficult to adjust such factors using DPC data. However, death and chest drainage — which is often performed in cases of complex pneumonia — were not more prevalent in the long-term treatment group. Given the absence of information regarding microbiological tests, the organisms responsible for the assessed pneumonia cases were unknown. *Pseudomonas aeruginosa* is known to represent a common cause of recurrent pneumonia (*3,26*); however, pneumonia and AP in older adults are typically caused by mixed infections of oral commensal bacteria, thereby excluding *P. aeruginosa* as a main causative organism (9.7%) (*27*). It was difficult to determine whether the type of antimicrobial agent selected and the dosage of the antimicrobial agent

were appropriate because the causative pathogens of pneumonia and accurate kidney function could not be acquired due to the limitations of the DPC data. It seems unlikely that the antimicrobial spectrum was less consistent in the long-term treatment group, as antimicrobials with activity against *Pseudomonas aeruginosa* and obligate anaerobes tended to be selected more frequently in the long-term treatment group, but this was not measured in the data. Therefore, their influence as unmeasured confounders in this study was considered negligible.

Third, antimicrobials administered before hospitalization were not adjusted for. Community-acquired pneumonia in Japan is administered to ~18% of patients before hospitalization (*20*). However, this information could not be captured in this study.

Fourth, this is a problem with the validation of the diagnosis (ICD-10). Although, in this study, the diagnosis is the disease that led to the patient being admitted to the hospital, a recent diagnostic validation study of pneumonia and AP using the DPC database revealed that AP had low sensitivity and positive predictive value (*28*). However, that study had a small sample size in AP and the sample was difficult to assess. The sensitivity and positive predictive value reported by the study for pneumonia were 63.0% and 73.0%, respectively (*28*), which is comparable to what has been reported in other similar database studies (*29*). Although there was no significant difference in the adjusted hazard ratio for AP and pneumonia in the stratified analysis, this was a limitation because the diagnosis of AP was included in many cases.

Finally, the indicators for assessing the patients' responses to pneumonia treatment, which typically determine treatment durations in general situations or clinical trials (*4*), could not be tracked using this database. The duration of antibiotic treatment may have been prolonged because of poor clinical progress in a few of the patients who received short-term treatment and vice-versa. However, after adjusting for propensity scores, in-hospital mortality showed no bias toward the long-term treatment group, so we concluded that our adjustment was likely adequate.

In conclusion, although the effect of unadjusted confounding cannot be excluded, short-term antimicrobial therapy for older adults with pneumonia—including AP—did not increase the risk of pneumonia relapse or death in our cohort of older Japanese patients as in past reports of short-term treatments for pneumonia. Although it should be needed to re-evaluate this conclusion in future randomized prospective studies, short-term antibiotic therapy may be suitable for patients with complicated and severe pneumonia in real-world clinical practice if considered carefully.

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# Psychological support for people with hemophilia and HIV who suffer from cancer: A first national survey

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**Abstract:** Psychological support is necessary for people with hemophilia and HIV (PHH) who suffer from cancers. Most PHH are infected with not only HIV but also hepatitis C virus due to non-heat-treated blood coagulation factor products. PHH have a high risk of carcinogenesis, including liver cancer. Furthermore, many PHH present psychological problems, due to the great stress resulting from carcinogenesis and which impedes their cancer treatment. This study aimed to assess the psychological support system through a nationwide survey of healthcare workers caring for PHH at HIV care hospitals in Japan. The response rate was 49.1% (194/395), with a coverage rate of 74% (516/697) for PHH. Our findings indicated that psychologists were the most likely to be "coordinated" or "expected to coordinate" when PHH suffered from cancer (74%, multiple responses allowed). The most common reason for rating the adequacy of psychological support as "very good" or "good" was "easy collaboration with various professionals and medical teams". The number of HIV coordinator nurses and clinical psychologists per facility was 1.06 and 2.56, respectively. Our findings indicated more psychological support systems should be established in Japan, including reimbursement for psychological support for PHH.

***Keywords*:** HIV, hemophilia, cancers, psychologists, psychological support

## Introduction

In the early 1980s, there were reported outbreaks of human immunodeficiency virus (HIV) infection among patients with hemophilia due to imported unheated blood coagulation products (*1-3*). There are currently estimated to be 697 people with HIV and hemophilia (PHH) in Japan (*2*). Improvements in antiretroviral therapy and dissemination of knowledge have dramatically decreased the incidence of acquired immune deficiency syndrome (AIDS) (*3-5*). As a result, however, there has been an increasing incidence of non-AIDS-defining malignancy (NADM) among patients with HIV, which may occur approximately 40 years after infection (*4,6*). Moreover, approximately 99% of PHH have co-infections with hepatitis B and C viruses and are at high risk of developing liver cancer (*4,6*). Among these patients, the standardized cancer incidence ratio (SCIR) is 2.08 (95% confidence interval [CI]: 1.48-2.90) for all malignancies, with liver cancer accounting for most NADMs (43%, SCIR: 23.09 [95% CI: 13.92-38.30]) (*6*).

The HIV medical care system in Japan was established in 1993 at the request of PHH members and is described in Hazardous AIDS Trial History (*7*). It is based on the notification from the Director-General of the Health and Medical Service Bureau of the Ministry of Health and Welfare, "Development of Regional Block Core Hospitals for AIDS Treatment", and is centered at the AIDS Clinical Center (ACC) established at the National Center for Global Health and Medicine (*7*). There are 14 block core hospitals in eight regional blocks, 54 core base hospitals representing each prefecture, and designated independent support medical institutions (the immune system outpatient care) throughout the country (*8*). The main support staff in those hospitals are HIV coordinator nurses (HIVCNs) who care for patients through a team approach in the comprehensive medical system; furthermore, they coordinate between departments as well as provide advice for the patient's understanding (*8*). "Senjuu Nurses" are those who spend at least 80% of their working hours engaged in HIV medical treatment. "Sennin Nurses" are those qualified to oversee both HIV and other medical treatment and spend at least 50% of their working time engaged in HIV treatment.

Generally, patients with cancers have a relatively high prevalence of depression and anxiety (*9,10*). Even

without meeting the diagnostic criteria for depression, the process of psychological acceptance of a cancer diagnosis involves gradual psychological distress, including denial, anger, bargaining, depression, and acceptance (*11*). Cognitive-behavioral formulations are useful tools for understanding the thoughts, feelings, and behaviors that can cause or maintain symptoms of depression or anxiety in patients such as treatment refusal, avoidance behavior, or excessive reassurance seeking (*10*). In Japan, some centers have recently established psycho-oncology teams that consist of psychiatrists, palliative care physicians, oncology nurses, and oncology pharmacists. Additionally, starting in 2022, the occupation of a certified public psychologist was updated with the calculation of guidance and management fees for patients with cancer; as such, they are very much expected to provide psychological care to these patients (*12*).

It is apparent that PHH have higher levels of psychological distress than people with hemophilia without HIV (*1,13*), indicating that many PHH may present mental health problems. A recent study showed that compared with people with HIV without hemophilia, PHH had a significantly lower prevalence of tension–anxiety and a significantly higher prevalence of low vigor (*14*). PHH who are suffering from cancer may experience further stress and significant psychological reactions. Additionally, their physical health may be affected by refusal to seek medical treatment due to reduced motivation. Counseling interventions by psychologists have been reported to help PHH gain self-awareness (*15*) and are of critical importance in major events such as cancer complications. However, such psycho-oncological interventions, treatments, or support systems for PHH have not been established. Additionally, there remain challenges in ensuring medical cooperation between hemophilia/HIV care professionals and cancer care professionals.

Accordingly, this study aimed to conduct a nationwide questionnaire survey among core hospitals providing HIV treatment to ascertain the status of their psychological support systems for PHH, especially those suffering from cancers.

## Materials and Methods

### *Study design*

A nationwide questionnaire survey was conducted in June 2023 among 395 HIV core hospitals and clinics providing HIV care (Table 1). The questionnaire included items regarding the number of PHH who visited each facility between January 1 and December 31, 2022, the number of cancer cases among them, the number of workers within each profession who cared for PHH, the degree of "psychological support" for PHH who were suffering from cancer, and the level of "mental care representing psychological support" at their facilities. Regarding "psychological support", we also included free-answer items, followed by after-coding using keywords and similar content. The questions regarding "psychological support" (Questions 3 and 4) were targeted to healthcare professionals at

**Table 1. Questionnaire items**

| |
|---|
| Question 1<br>How many people with hemophilia and HIV (PHH) visited the hospitals between January 1 and December 31, 2022?<br>How many PHH were newly diagnosed with cancer? |
| Question 2<br>Tell us about the medical service system for people with hemophilia and HIV (PHH).<br>Number of workers of each profession and employment status (number of full-time and part-time workers).<br>HIV/AIDS practitioner, Board-certified member of the Japanese Society for AIDS Research, The Japanese Society of Psychosomatic Medicine specialist physician, The Japanese Society of Psychiatry and Neurology specialist physician, Board-certified consultation-liaison psychiatrist by the Japanese Society of General Hospital Psychiatry,<br>Board-certified member of the Japan Psycho-Oncology Society,<br>HIV coordinator nurse, Certified HIV infection nurse of the Japanese Society for AIDS Research, Clinical psychologist, Certified public psychologist, Other counselors, Certified social worker, and Mental health social worker. "Number of HIV coordinator nurses" is the total number of full-time nurses including Senjyuu or Sennin.<br>For questions 3-5, there are some notes as follows:<br>No answer is required if no PHH visits your facility. The respondent should be a medical professional who is involved in PHH treatment. |
| Question 3<br>If PHH are affected with cancer, what worker profession do you coordinate (or expect to coordinate) with in your facility on "mental care (psychological support)"? Please select the profession below (multiple answers allowed):<br>(a) Certified nurse in palliative care (b) Oncology-certified nurse specialist (c) Certified nurse in cancer-related nursing (d) Certified social worker (e) Mental health social worker (f) Psychiatrist (g) Psychologist (h) Others (free description) |
| Question 4<br>Please assess the fulfillment level of the "mental care (psychological support)" system for PLWHH affected with cancer. Please select one and give the reason in free description.<br>(a) Very good (b) Good (c) Neither good nor bad (d) Bad (e) Very bad |

medical institutions attended by PHH.

*Analysis*

Fisher's exact test was used to assess the significance of the level of "psychological support" and the employment status of psychologists. A *p*-value of less than 0.05 was considered statistically significant.

*Ethical considerations*

The study protocol was approved by the Ethics Board of the Institute of Medical Science, University of Tokyo (approval no. 2021-71-1216) and adhered to the principles of the Declaration of Helsinki. The requirement for consent to participate was waived by the Institutional Review Board of the Institute of Medical Science, University of Tokyo, following national regulations.

**Results**

*Questionnaire collection rate and coverage rate of people with hemophilia and HIV*

Among 395 facilities that received questionnaires, 194 facilities responded (response rate 49.1%), of which 59 (30.4%) were medical facilities attended by PHH. The total number of PHH attending these hospitals was 516, representing a capture rate of 74.0% (516/697). Among them, 228 were attending ACCs and block core hospitals (22.8 PHH/facility, 44.2% [228/516], 10 facilities), 158 were attending core hospitals (6.07 PHH/facility, 30.6% [158/516], 26 facilities), and 130 were attending other medical institutions (5.65 PHH/facility, 25.2% [130/516], 23 facilities) (Figure 1). Moreover, eight PHH had been newly diagnosed with cancer in 2022 (1.6%, 8/516).

*Medical service system for people with hemophilia and HIV*

Table 2 shows the total number of healthcare workers involved in caring for PHH, their employment status, and the total and average number of workers per medical facility. The average number of HIV practitioners per facility was 4.63 persons, with 1.66 persons/facility being board-certified members of the Japanese Society for AIDS Research (JSAR), 4.11 persons/facility being specialists of the Japanese Society of Psychiatry and Neurology (JSPN), 2.56 persons/facility being Clinical psychologists, 2.38 persons/facility being certified public psychologists, 4.88 persons/facility being social workers, 1.06 persons/facility being HIVCNs, and 0.78 persons/facility being a certified HIV infection nurse of JSAR. HIVCNs were very few, and certified HIV infection nurses of JSAR were even fewer, with approximately three nurses assigned to four facilities. Among HIV clinicians, 35.3% (66/187, 47 valid responses) were certified by JSAR.

Regarding full-time workers, the average number of HIV practitioners per facility was 3.85 persons, with 2.79 persons/facility being specialists of JSPN,

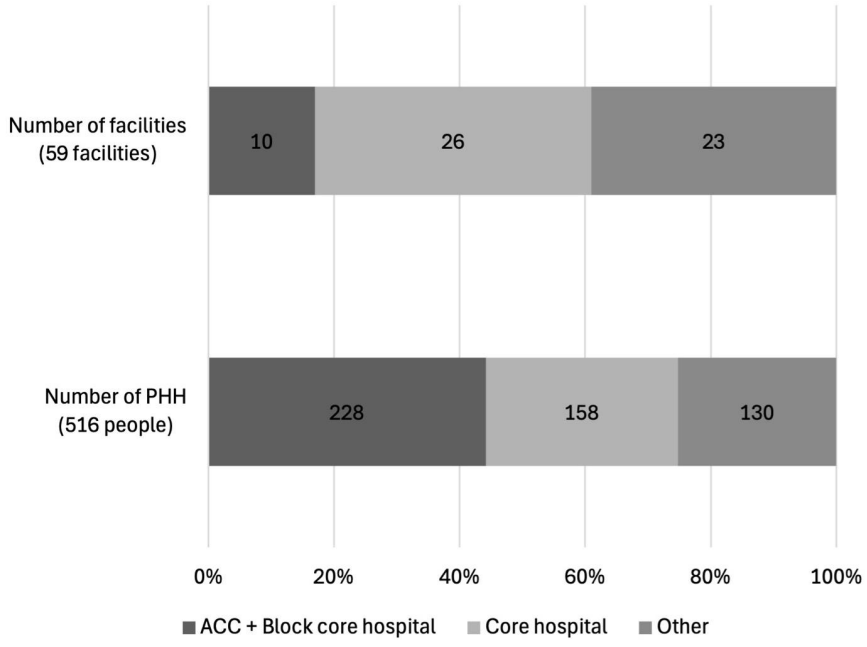


**Figure 1. Number of facilities with valid responses and the number of outpatient PHH.** ACC, AIDS Clinical Center; PHH, people with hemophilia and HIV.

**Table 2. Medical service system for people with haemophilia and HIV**

| Professions | Number of facilities with valid responses | Number of full-time workers (person) | Number of part-time workers (person) | Average number of full-time workers (person/facility) | Average number of part-time workers (person/facility) | Average number of workers (person/facility) | Full-time work rate (%) |
|---|---|---|---|---|---|---|---|
| HIV practitioner | 54 | 208 | 42 | 3.85 | 0.78 | 4.63 | 83.2 |
| Board-certified member of the Japanese Society for AIDS Research | 47 | 66 | 12 | 1.40 | 0.26 | 1.66 | 84.6 |
| The Japanese Society of Psychosomatic Medicine specialist physician | 35 | 1 | 1 | 0.03 | 0.03 | 0.06 | 50.0 |
| The Japanese Society of Psychiatry and Neurology specialist physician | 38 | 106 | 50 | 2.79 | 1.32 | 4.11 | 67.9 |
| Board-certified psychiatrist by the Japanese Society of General Hospital Psychiatry | 38 | 18 | 1 | 0.47 | 0.03 | 0.50 | 94.7 |
| Board-certified member of the Japan Psycho-Oncology Society | 35 | 3 | 0 | 0.09 | 0.00 | 0.09 | 100.0 |
| Clinical psychologist | 52 | 73 | 60 | 1.40 | 1.15 | 2.56 | 54.9 |
| Certified public psychologist | 47 | 60 | 52 | 1.28 | 1.11 | 2.38 | 53.6 |
| Other counselor | 36 | 8 | 20 | 0.22 | 0.56 | 0.78 | 28.6 |
| Certified social worker | 48 | 216 | 18 | 4.50 | 0.38 | 4.88 | 92.3 |
| Mental health social worker | 40 | 95 | 9 | 2.38 | 0.23 | 2.60 | 91.3 |

| Professions | Number of facilities with valid responses | Number of Senjyuu HIVCNs (person) | Number of Sennin HIVCNs (person) | Average number of Senjyuu HIVCNs per facility (person/facility) | Average number of Sennin HIVCNs per facility (person/facility) | Average number of total Senjyuu and Sennin HIVCNs per facility (person/facility) | Senjyuu work rate (%) |
|---|---|---|---|---|---|---|---|
| HIV coordinator nurse | 48 | 30 | 21 | 0.63 | 0.44 | 1.06 | 58.8 |
| Certified HIV infection nurse of the Japanese Society for AIDS Research | 48 | 16 | 21 | 0.33 | 0.44 | 0.78 | 43.2 |

*Abbreviations:* HIVCNs, HIV coordinator nurses.

1.40 persons/facility being clinical psychologists, 1.28 persons/facility being certified public psychologists, and 4.50 persons/facility being certified social workers. Regarding the percentage of full-time workers (full-time work rate), 83.2% were HIV clinicians, 67.9% were specialists of JSPN, 54.9% were clinical psychologists, and 92.3% were certified social workers. Comparing the number of full-time workers per facility, it was found that the number of HIVCNs and clinical or public psychologists was less than one-third of the number of certified social workers.

As shown in Figure 1, the total number of PHH attending facilities differed across facilities; therefore, the average number of HIV practitioners, JSPN specialists, clinical psychologists, certified social workers, and HIVCNs working per facility was calculated separately for each medical facility category (Figure 2). The average number of JSPN specialists (3.13-4.64) and certified social workers (4.73-5.22) working per facility did not significantly differ among the three facility categories. However, HIV practitioners and HIVCNs working per facility were relatively higher in ACCs and block core hospitals (7.50 HIV practitioners and 4.63 HIVCNs) than in core hospitals (4.26 HIV practitioners and 0.57 HIVCNs) and other medical institutions (4.00 HIV practitioners and 0.11 HIVCNs). The average number of clinical psychologists (2.40-3.00) working per facility did not significantly

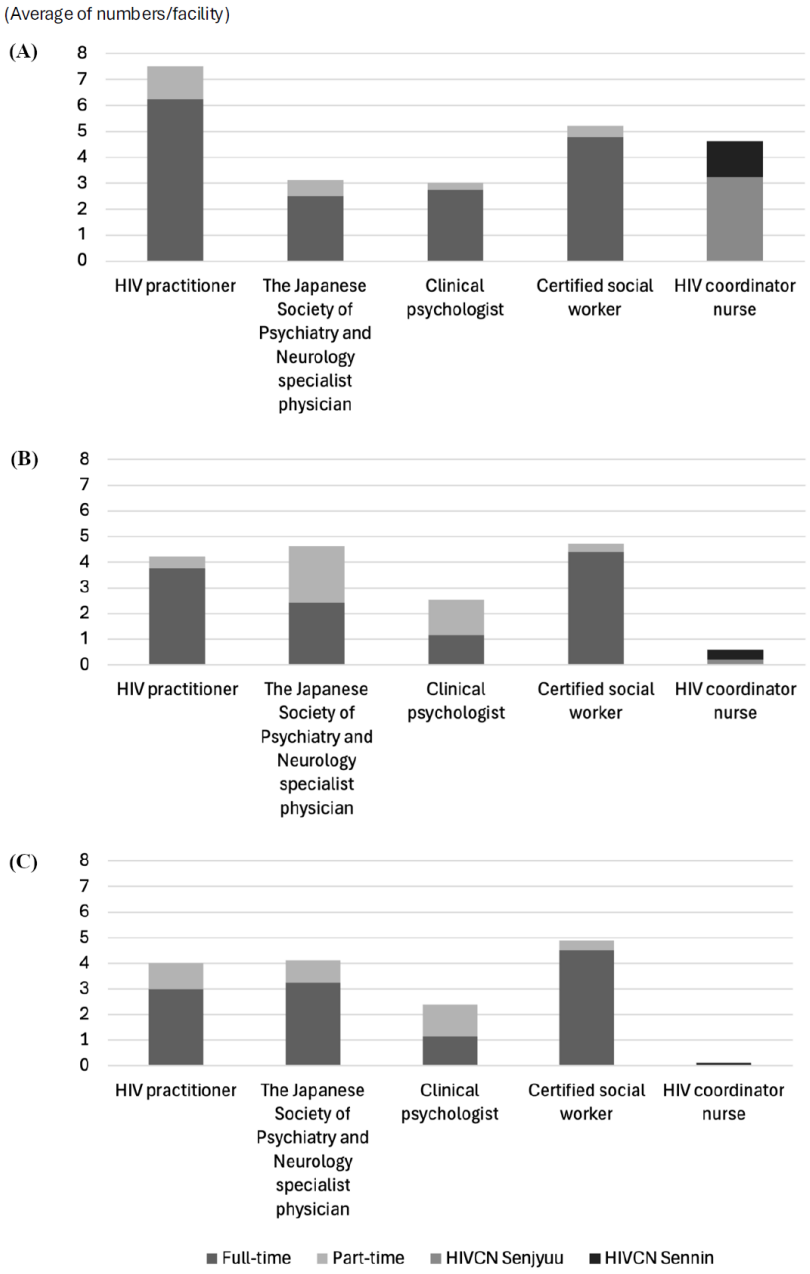


**Figure 2. The average number of specialist workers.** (**A**) ACC and nine block core hospitals, (**B**) Twenty-six core hospitals, **(C)** Twenty other hospitals. ACC, AIDS Clinical Center; HIVCNs, HIV coordinator nurse.

differ among the three categories; however, there were fewer full-time clinical psychologists in core hospitals and other medical institutions than in ACCs and block core hospitals.

*System of coordination between professions in "psychological support" and the level of satisfaction at their own facilities*

According to the responses, in cases of PHH with cancers, the most common occupations who coordinated (or expected to coordinate) in "psychological support" were psychologists (74.0%, 37/50), certified social workers (64.0%, 32/50), oncology-certified nurse specialists (58.0%, 29/50), certified nurses in palliative care (58.0%, 29/50), psychiatrists (52.0%, 26/50), certified nurses in cancer-related nursing (40.0%, 20/50), and "mental health social workers" (20.0%, 26/50) (Figure 3A). Only one medical facility listed the occupation as HIVCN. Despite the low average number of psychologists working per facility (2.56 for clinical psychologists, 2.38 for certified public psychologists, and 0.78 for other counselors), 74% of the facilities indicated psychologists as the profession with which they worked or expected to work with.

Figure 3B shows the level of "psychological support" for PHH with cancers at each facility. "Physiological support" was rated as "very good", "good", "Neither good nor bad", and "poor" in 7 (12%), 20 (34%), 21 (36%), and 2 (3%) facilities, respectively. Among institutions that rated "psychological support" as "very good", the most frequent reason for this rating was "Easy to cooperate with other professionals and medical teams" (42.9%, 3/7), followed by "Well-staffed for psychological support" (28.6%, 2/7). In institutions that responded as "Neither good nor bad", the most common reason was "Lack of experience" (23.8%, 5/21), followed by "Due to part-time psychologists" and "Difficulty in responding to sudden needs", both at 14.2% (3/21). There was one institution that cited, "We believe that support can be provided through the existing cancer patient support system, and there is no specialized system for PHH". The institutions that rated "psychological support" as "poor" tended

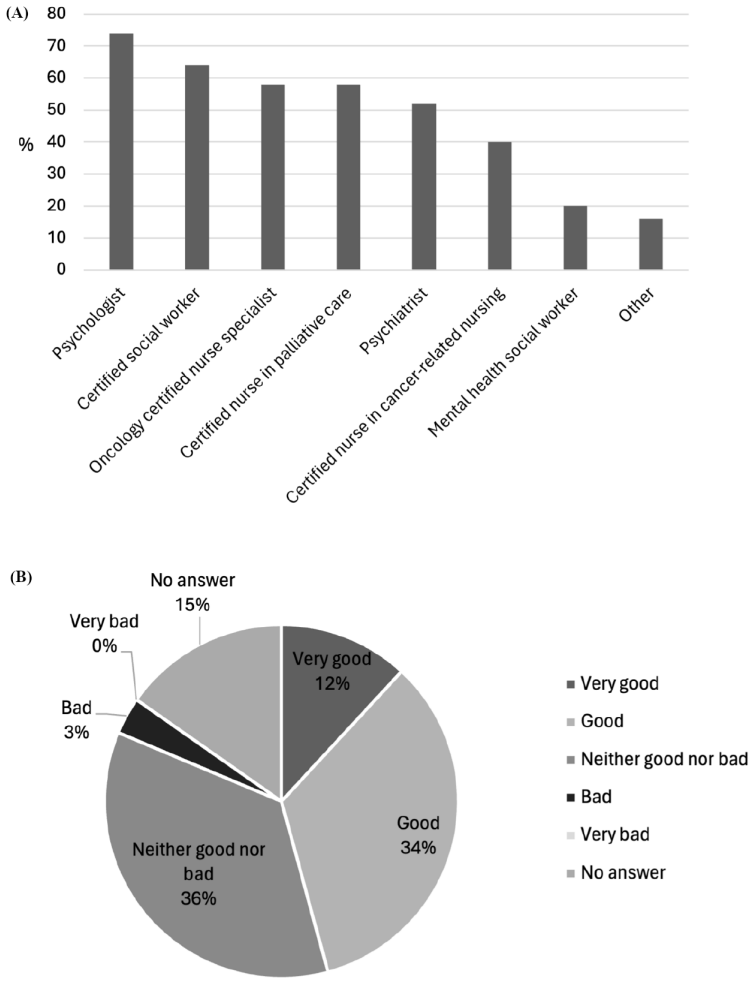


**Figure 3. System of coordination among healthcare professionals working within an institution when PHH are affected by cancer. (A)** Profession that coordinates with your facility (or expects to coordinate), multiple answers were allowed; 50 hospitals responded. **(B)** Fulfillment level of psychological care (psychological support).

to have "no access to counselors" and "no system for PHH". Moreover, institutions that rated "psychological support" as "very good" tended to have more full-time psychologists than the "undecided" institutions. Still, this difference was not significant ($p = 0.19$).

## Discussion

This is the first national questionnaire survey regarding the psychological support system in medical institutions handling PHH affected by cancer. In our survey, the capture rate for PHH was 74%, suggesting a high level of interest among healthcare professionals involved in the psychological care of PHH patients with malignancy. Additionally, psychologists were the most common profession (74%) that medical workers would coordinate with in cases of PHH affected by cancer, suggesting that healthcare professionals treating PHH trust and expect psychologists to provide "psychological support".

In the 1990s, countries such as France, Germany, Switzerland, Canada, Italy and the USA established reimbursement programs for PHH (*16*). Sulser emphasized the need for physicians, government agencies, and industry to complement policy decisions with considerations of medical ethics, psychosocial factors, and quality of life. He also stressed that vigilance regarding the safety of therapy for PHH must be maintained (*17*). In the Netherlands, the treatment of hemophilia became increasingly centralized from the early 2000s. By 2013, standard criteria were introduced in hemophilia treatment centers, treatment guidelines were revised, and in 2014, all patients infected with HCV were treated with direct-acting antiviral drugs, achieving complete eradication of the virus (*18*). However, many countries have yet to identify all PHH. Moreover, no country has reported successfully implementing comprehensive psychological support for PHH. It has been suggested that Japan faces similar challenges, where not all PHH are adequately identified or treated uniformly. Psychological support, particularly for aging PHH who may develop malignancies, is likely a global concern but has not been thoroughly investigated or reported.

As mentioned above, HIV care is provided by three medical systems in Japan (*7,8*). In our study, the largest proportion of PHH attended ACCs and block core hospitals (44.2%), followed by core hospitals (30.6%) and other medical hospitals (25.2%). This could be assumed to represent the current situation regarding hospital attendance by PHH throughout Japan. The average number of staff working per facility was very low for HIVCNs (1.06 people/facility) compared with those for HIV practitioners (4.63 people/facility) and JSAR-certified doctors (1.66 people/facility). This also indicates that 64.7% of HIV practitioners at each facility were not JSAR-certified doctors (Table 2). HIV practitioners and HIVCNs working per facility were relatively higher in ACCs and block core hospitals (7.50 HIV practitioners and 4.63 HIVCNs) than in core hospitals (4.23 HIV practitioners and 0.57 HIVCNs) and other medical institutions (4.00 HIV practitioners and 0.11 HIVCNs) (Figure 2). These results suggest that the burden on HIVCNs and HIV practitioners at facilities other than ACCs and block core hospitals was relatively high. However, it should be noted that there are differences in the number of PHH attendees at different facilities. Even considering these factors, our findings may indicate an extremely low number of assigned HIVCNs, especially in core hospitals and other medical hospitals.

As earlier mentioned, mental health issues are more prevalent among PHH than in the general population. It has been estimated that approximately 50% of PHH have neurocognitive dysfunction (*19*). Moreover, Komatsu *et al.* reported a high prevalence of "low vigor" among PHH, leading to impaired executive and social functioning. Therefore, healthcare professionals should pay attention to the vigor, executive functioning, and social functioning in PHH (*14*). Moreover, in addition to HIV infection, many PHH have suffered from other chronic complications such as type 2 diabetes and cardiovascular disease. Generally, depression is correlated with chronic illness and affects treatment adherence, so that patients with depression are three times more likely to be non-compliant to treatment than patients without depression (*20*). Psychological support of patients with chronic illness requires the intervention.

In our study, psychologists were the most common profession (74%) that workers would coordinate with in cases of PHH affected by cancer. Further, medical institutions with "very good" psychological care tended to have full-time psychologists; however, there was no significant difference compared with institutions with "neither good nor poor" psychological support. In facilities with "very good" psychological care, this is attributed to the relative ease of coordination between the various professionals and healthcare teams. The National Institute for Health and Clinical Excellence practice guidelines in the UK include a recommended "stepped care model" (*21*). This is a useful model for depression and palliative care in patients with cancer. In the beginning, a liaison team of psychologists, psychiatrists, and psychiatric liaison nurses provide support through supervision, while doctors and nurses in each department provide screening and preventive intervention. The model shows the hierarchy of the level of intervention required; for example, psychologists and other professionals coordinate to intervene when depression becomes apparent. As mentioned earlier, facilities with "very good" psychological have relatively easy coordination among the various professionals and healthcare teams, thus these facilities may be capable of

establishing such a system.

Moreover, PHH affected by cancer often receive care and treatment in a department and medical facility different from the previously attended ones. Since childhood, PHH have suffered from fatal congenital diseases, endured HIV and HCV infections, and have faced life-threatening illnesses multiple times. Even though many of their peers have passed away, numerous PHH who are battling malignancies sometimes hesitate to seek treatment for these conditions. Accordingly, it is important to address how to maintain continuity of psychological support in such cases. Psychologists who understand the history of PHH, the mental health characteristics of PHH, and the characteristics of patients with chronic illness can provide "psychological support" throughout this transfer across departments/facilities for PHH with cancer.

Currently, certified public psychologists contribute to team medicine as treatment advisors for patients with chronic diseases, including obesity and heart failure (*22,23*). Certified public psychologists are included in the reimbursement of the cancer patient management fee, but not in the calculation of the medical fee (viral disease guidance and management fee) for ordinary medical treatment of PHH. This should be considered in future policy formulations. Taken together, it is important to develop a system for the stable placement of psychologists to allow continuous psychological support for PHH, even with the occurrence of cancer.

Further studies are strongly recommended. This study highlights that only a limited number of psychologists are currently engaged in this field. Therefore, we anticipate that more psychological professionals will enter this area, facilitated by measures such as reimbursement programs. However, prior to the implementation of a comprehensive medical system that includes reimbursement, alternative psychological support systems should be activated using the limited resources available. For instance, group psychotherapies such as mindfulness-based stress reduction and mindfulness-based cognitive therapy, which were originally developed as group interventions, could be employed (*24,25*). Additionally, in response to the challenges posed by COVID-19, various forms of psychotherapy have been successfully adapted for remote delivery through methods such as telephone and internet-based platforms (*26-29*). Furthermore, novel therapies like acceptance and commitment therapy (ACT) have emerged, aiming to enhance an individual's psychological flexibility in addressing difficult thoughts and feelings related to their physical condition. ACT operates through six core processes collectively known as the "ACT Hexaflex": acceptance, cognitive defusion, contact with the present moment, self-as-context, value-driven behavior, and commitment to value-driven behaviors (*30*). Given its adaptability, ACT may represent an ideal strategy for PHH, particularly in institutions where access to psychologists is limited.

This study has several limitations. First, the coverage rate of PHH in our survey was 74%; accordingly, we did not include approximately 200 PHH nationwide. Second, we could not determine the status of "psychological care (psychological support)" in medical institutions that did not respond. Although it can be assumed that "psychological support" may be enhanced by increasing the number of psychologists engaged, further studies are warranted to determine the extent to which the number of psychologists needs to be increased. Third, these issues are somewhat specific to Japanese PHH. Therefore, the psychological care findings from this study might not be generalized to other countries or regions. Finally, the respondents to the questions regarding "psychological support" were healthcare professionals, and it may be important to consider the opinions and needs from the perspective of PHH. Finally, the respondents to the "psychological support" questions were healthcare professionals, so it may be important to explore the opinions and broader needs of PHH themselves for a more comprehensive perspective and better healthcare management.

In conclusion, this is the first nationwide survey of the psychological support system for PHH with cancer. The coverage rate for PHH was 74%, indicating a high level of interest among healthcare workers. The average number of HIVCNs and JSAR-certified doctors per medical facility was low; further, the number of HIVCNs and HIV practitioners was especially low in core base hospitals and other medical facilities compared to ACCs and block core hospitals. Psychologists were the most common profession (74%) that workers would coordinate with in cases of PHH affected by cancer. Psychological support for PHH, many of whom may have psychological problems including stress, should be provided on a regular basis and continued in the event of a cancer.

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# Analysis of the toxic and lethal doses of one over-the-counter drug product in humans and the ingredients that may be abused: Building a drug database to prevent drug overdoses

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**Abstract:** Pharmacists who provide medication to patients immediately before they overdose should intervene appropriately; however, little information exists on the types and amounts of over-the-counter (OTC) drugs that are dangerous. This study investigated the toxicity and characteristics of overdosing on a single package of commercially available OTC drugs in humans. We researched 14,107 OTC drugs. The number of products that could contain a lethal dose if taken as a single package was 1,223 (8.7%) and a toxic dose was 2,982 (21.1%). A single product containing a lethal dose to humans by therapeutic category included skin drugs ($n$ = 672, 25.0%), psychotropic drugs ($n$ = 288, 17.9%), and public health drugs ($n$ = 92, 26.1%) in descending order. Comparing before and after April 2023, the number of OTC pharmaceuticals that contained ingredients that may be abused, significantly increased: psychotropic drugs (44.9% increase), respiratory drugs (8.2% increase), and urogenital and anal organs drugs (3.5% increase) ($p <$ 0.05). These products had not been previously designated as hazardous despite their potential for abuse. The registrants in the "Drug Database for Overdose Prevention" that made these public included 199 pharmacists, registered sellers, and doctors as of July 31, 2024. The city with the most users was Osaka (377 users) and an average engagement time of 41.8 seconds, followed by Sapporo, Fukuoka, and Nagoya. These areas were consistent with urban centers and high numbers of emergency transports due to overdose. Our findings provide important pharmaceutical information that pharmacists can use for their gatekeeper activities.

***Keywords*:** database, overdose, over-the-counter drug, lethal dose, toxic dose, pharmacist

## Introduction

Overdoses have increased in recent years, particularly for the use of over-the-counter (OTC) drugs (*1,2*). There have been reports in Japan and other countries of OTC drugs being used for self-harm and suicide (*3*). Japanese OTC drugs contain multiple ingredients and have some characteristics that are not present in overseas OTC drugs; however, there is little information on what types and amount of OTC drugs are dangerous. This valuable information can be used as a gatekeeper to prevent overdose.

Individuals who play a role in preventing overdose and suicide by "noticing" and "listening" are considered "gatekeepers." The Japanese Ministry of Health, Labor, and Welfare stated that "pharmacists who have many opportunities to come into contact with information about residents' health conditions through dispensing medicines and selling pharmaceuticals" as examples of gatekeepers (*4*). In contrast, according to a survey of pharmacists and registered sellers, when acting as a gatekeeper, the percentage of individuals who answered "There is no information or measures to prevent overdosing" and "There is no specific information on dosage regarding overdosing" was 52% and 53.4%, respectively (*5*). Furthermore, in response to the question of what type of information would be useful for taking measures against overdoses, the percentage of individuals who wanted "information on the names of dangerous drugs in the event of an overdose" and "information on drugs used in current overdoses" was 72.8% and 76.2%, respectively (*5*). Thus, it is evident that there is a lack of information available that would enable measures to be taken to prevent overdose in clinical settings, such as pharmacies and drugstores. Furthermore, in a previous report by the author, "workplace measures" were identified as a factor in the ability to intervene as a gatekeeper with subjects by both pharmacists and registered sellers. Thus, it is important to introduce tools to combat overdose (*5*).

In a recent report, 65.9% of drugs used in overdoses

were obtained from brick-and-mortar stores, whereas only 9.3% were purchased online (*6*). Therefore, pharmacists and registered distributors who may hand over medication to a patient just before they overdose should be aware of the toxicity of the product itself and intervene where appropriate. However, there have been no reports examining the toxicity to humans caused by overdosing on a single package of OTC drug products currently on the market. In this study, we characterized the toxicity to humans of overdosing on a single package of OTC drugs that are currently in circulation. In addition, we examined the characteristics of products that contain ingredients that may be abused. The scope of these ingredients has been expanded as of April 2023, as specified by the Minister of Health, Labor, and Welfare.

## Materials and Methods

*Survey of OTC drugs and their toxicity to human*

This study covered the ingredients of OTC drugs listed in the Japan Pharmaceutical Information Center (JAPIC) over-the-counter drug collection (July 2021 edition). The amount of each ingredient contained in the entire product was calculated. We also surveyed the dosage that is considered dangerous in the event of an overdose using the Japanese Society for Clinical Toxicology's Guide to Standard Clinical Practice for Acute Poisoning (*7*), Clinical Toxicology (*8*), the pharmaceutical package insert, and the literature (*9-15*). Next, we built a centralized database that could be used to gather all of the information. In addition, we focused on ingredients that the Minister of Health, Labor, and Welfare has warned of potential abuse. Thus, a database was established that provides an assessment of toxicity for a particular dose. For risk classification, we examined Class 1 drugs, Class 2 drugs, Designated class 2 drugs, Class 3 drugs, and Quasi drugs. We also evaluated drugs by 18 therapeutic categories, which included psychotropic drugs, digestive tract drugs, cardiovascular and hematological drugs, respiratory drugs, urogenital and anal organ drugs, tonic health drugs, women's drugs, allergy drugs, skin drugs, ophthalmic drugs, otorhinolaryngological drugs, dental and oral cavity drugs, smoking cessation agents, Kampo preparations, herbal preparations (preparations not belonging to other therapeutic classes), public health drugs, general test kits, and others (preparations not belonging to any therapeutic category). These classifications were registered in the JAPIC over-the-counter drug collection.

*OTC drugs that contain ingredients that may be abused as designated by the Minister of Health, Labor, and Welfare*

We examined the number of products that contain ingredients for which the Minister of Health, Labor, and Welfare has warned about the risk of misuse. The specific ingredients included ephedrine, codeine, dihydrocodeine, bromovalerylurea, pseudoephedrine, and methylephedrine. We compared the products containing these designated ingredients up until March 2023 with those containing the designated ingredients after the April 2023 additions, based on the therapeutic category (*16*). We also determined the toxic and lethal doses of these substances in humans based on the literature (*7-15*).

*Building a drug database to prevent drug overdoses*

For the server, XServer was used (PHP 7.4, MySQL 5.7, Apache version 2.4). WordPress 6.3 was used as the Contents Management System (CMS). Data on the drugs was gathered as described in the previous section, and the basic data was constructed. The drug data was exported in Comma Separated Values (CSV) format and imported in bulk using the WordPress plugin WP All Import. A drug search function was created using WordPress.

*Number of people registered with and access to the "Drug Database for Overdose Prevention"*

The database was made public on the Internet and linked to Google Analytics. We examined changes in access to the homepage and the characteristics of the search results. The survey period was from April 1, 2023, to June 25, 2024, and the number of registered users were as of July 31, 2024.

*Statistical analysis*

Chi-square test was conducted using JMP Pro 18 software (SAS Institute Inc., NC, USA). The significance level was set to 0.05.

*Ethical statement*

This study was reviewed and approved by the Institutional Review Board of the Graduate School of Pharmaceutical Sciences, Chiba University (No. R054).

## Results

*OTC drugs surveyed and their toxicity to humans per product*

We determined whether each OTC drug product constituted a toxic or lethal dose in humans. The survey covered 10,773 different products, and 14,107 products when multiple contents were considered. The number of products that could contain a lethal dose if one package were to be taken as an overdose was 1,223 (8.7%), whereas the number of products that could contain a toxic dose was 2,982 (21.1%) (Table 1). With respect to a therapeutic category, the most common products with

lethal doses to humans were dermatological drugs (672, 25.0%), followed by psychoneurological drugs (288, 17.9%), and public health drugs (92, 26.1%).

*Relationship between risk categories of surveyed OTC drugs and toxic or lethal doses in humans*

We determined the relationship between the risk classification of OTC drugs and the toxic or lethal dose in humans. The number of products that fell into this risk category by therapeutic category is listed in Table 2. A comparison of risk categories (Class 1 drugs, *etc.*) and drugs whose total content in one package corresponds to a lethal or toxic dose for humans (Table 1) indicated that they do not necessarily match.

*Ingredients that are toxic or lethal to humans in one product*

To determine which ingredients per product could pose toxic or lethal doses to humans, the data were examined by therapeutic category. Specific ingredients included caffeine, acetaminophen, diphenhydramine, ethanol, menthol, salicylic acid, and aspirin. There were also cases in which the entire content of one package contained a lethal dose to humans (Table 3). For public health drugs, there were examples in which the entire amount of a single package of characteristic ingredients, such as N, N-Diethyl-meta-toluamide (DEET), dichlorvos, fenitrothion, sodium hypochlorite, trichlorfon, and cresol, was sufficient to be lethal to humans.

*Changes in regulations regarding OTC drugs containing ingredients that may be abused as designated by the Minister of Health, Labor, and Welfare*

To determine the regulatory status of each ingredient, we evaluated products that contain ingredients designated by the Minister of Health, Labor, and Welfare as likely to be abused. Until March 31, 2023, the Minister of Health, Labour, and Welfare determined that the products containing ingredients that may be the subject of abuse were respiratory organ drugs (188, 35.9%), followed by psychotropic drugs (131, 8.2%) and otorhinolaryngological drugs (92, 27.2%), in order of efficacy. Next, we examined the increase in the number of products resulting from the addition of new designations after April 1, 2023, according to the therapeutic category. A significant increase was observed ($p < 0.05$) for psychotropic drugs (44.9% increase), respiratory drugs (8.2% increase), and urogenital and anal organ drugs (3.5% increase), with additional products in other therapeutic categories (Table 4). These products had not previously been designated as hazardous despite their potential for abuse.

**Table 1. The number of OTC drugs surveyed and risk of being abused or have lethal and toxic doses**

| Therapeutic Category[a] | Number of target products (JAPIC OTC drugs, July 2021 edition) *n* | Number of products surveyed: multiple contents *n* | When taking 1 product (1 box/1 bottle) | |
|---|---|---|---|---|
| | | | Number of products with toxic doses for human[b] *n* (%) | Number of products with lethal doses for human[c] *n* (%) |
| Psychotropic drugs | 1,188 | 1,607 | 255 (15.9) | 288 (17.9) |
| Digestive tract drugs | 1,094 | 1,730 | 136 (7.9) | 0 (0) |
| Cardiovascular and Hematological Drugs | 246 | 407 | 12 (2.9) | 0 (0) |
| Respiratory drugs | 407 | 524 | 45 (8.6) | 65 (12.4) |
| Urogenital and anal organs drugs | 167 | 230 | 153 (66.5) | 0 (0) |
| Tonic health drugs | 1,609 | 2,236 | 80 (3.6) | 3 (0.1) |
| Women's drugs | 101 | 151 | 61 (40.4) | 0 (0) |
| Allergy drugs | 26 | 34 | 4 (11.8) | 2 (5.9) |
| Skin drugs | 2,305 | 2,684 | 253 (9.4) | 672 (25.0) |
| Ophthalmic drugs | 478 | 482 | 33 (6.8) | 2 (0.4) |
| Otorhinolaryngological drugs | 272 | 338 | 116 (34.3) | 79 (23.4) |
| Dental and oral cavity drugs | 258 | 305 | 0 (0) | 0 (0) |
| smoking cessation agents | 11 | 27 | 0 (0) | 20 (74.1) |
| Kampo preparation | 2,120 | 2,697 | 1,726 (64.0) | 0 (0) |
| Herbal preparation (Preparations not belonging to other therapeutic classes) | 226 | 280 | 108 (38.6) | 0 (0) |
| Public health drugs | 244 | 352 | 0 (0) | 92 (26.1) |
| General test kits | 17 | 17 | 0 (0) | 0 (0) |
| Others (preparations not belonging to any therapeutic category) | 4 | 6 | 0 (0) | 0 (0) |
| Total | 10,773 | 14,107 | 2,982 (21.1) | 1,223 (8.7) |

[a]Classifications registered with JAPIC. [b,c]Total number. The denominator of the percentage was the number of products in the multiple contents survey.

**Table 2. Risk classification of surveyed OTC drugs**

| Therapeutic Category[a] | Number of products surveyed: multiple contents *n* | Risk classification | | | | |
|---|---|---|---|---|---|---|
| | | Class 1 drugs, *n* (%) | Class 2 drugs, *n* (%) | Designated class 2 drugs, *n* (%) | Class 3 drugs, *n* (%) | Quasi drugs, *n* (%) |
| Psychotropic drugs | 1,607 | 18 (1.1) | 236 (14.7) | 1,323 (82.3) | 25 (1.6) | 5 (0.3) |
| Digestive tract drugs | 1,730 | 19 (1.1) | 789 (45.6) | 308 (17.8) | 536 (31.0) | 78 (4.5) |
| Cardiovascular and Hematological Drugs | 407 | 3 (0.7) | 287 (70.5) | 8 (2.0) | 109 (26.8) | 0 (0) |
| Respiratory drugs | 524 | 2 (0.4) | 82 (15.6) | 268 (51.1) | 135 (25.8) | 37 (7.1) |
| Urogenital and anal organs drugs | 230 | 18 (7.8) | 62 (27.0) | 146 (63.5) | 0 (0) | 4 (1.7) |
| Tonic health drugs | 2,236 | 2 (0.1) | 645 (28.8) | 38 (1.7) | 1,258 (56.3) | 293 (13.1) |
| Women's drugs | 151 | 9 (6.0) | 63 (41.7) | 11 (7.3) | 64 (42.4) | 4 (2.6) |
| Allergy drugs | 34 | 0 (0) | 31 (91.2) | 3 (8.8) | 0 (0) | 0 (0) |
| Skin drugs | 2,684 | 43 (1.6) | 996 (37.1) | 465 (17.3) | 1,041 (38.8) | 139 (5.2) |
| Ophthalmic drugs | 482 | 0 (0) | 239 (49.6) | 0 (0) | 238 (49.4) | 5 (1.0) |
| Otorhinolaryngological drugs | 338 | 1 (0.3) | 214 (63.3) | 120 (35.5) | 0 (0) | 3 (0.9) |
| Dental and oral cavity drugs | 305 | 0 (0) | 25 (8.2) | 19 (6.2) | 164 (53.8) | 97 (31.8) |
| Smoking cessation agents | 27 | 6 (22.2) | 0 (0) | 21 (77.8) | 0 (0) | 0 (0) |
| Kampo preparation | 2,697 | 0 (0) | 2,675 (99.2) | 18 (0.7) | 4 (0.1) | 0 (0) |
| Herbal preparation (Preparations not belonging to other therapeutic classes) | 280 | 0 (0) | 194 (69.3) | 36 (12.9) | 49 (17.5) | 1 (0.4) |
| Public health drugs | 352 | 16 (4.5) | 324 (92.0) | 0 (0) | 10 (2.8) | 2 (0.6) |
| General test kits | 17 | 7 (41.2) | 10 (58.8) | 0 (0) | 0 (0) | 0 (0) |
| Others (preparations not belonging to any therapeutic category) | 6 | 1 (16.7) | 0 (0) | 0 (0) | 5 (83.3) | 0 (0) |

[a]Classifications registered with JAPIC. The denominator of the percentage was the number of products in the multiple contents survey.

**Table 3. Ingredients in surveyed OTC drugs that are at lethal or toxic doses to humans**

| Therapeutic Category[a] | 1 product (1 box/1 bottle): Human toxic dose ingredient name (example) | 1 product (1 box/1 bottle): Human lethal dose ingredient name (example) |
|---|---|---|
| Psychotropic drugs | bromovalerylurea, caffeine, ibuprofen, liquorice, Cyperus rhizome, acetaminophen, diphenhydramine | bromovalerylurea, caffeine, methylephedrine, acetaminophen, aspirin, dihydrocodeine |
| Digestive tract drugs | liquorice, Cyperus rhizome | not applicable |
| Cardiovascular and Hematological Drugs | liquorice, caffeine | not applicable |
| Respiratory drugs | liquorice, theophylline, caffeine, diphenhydramine | methylephedrine, dihydrocodeine, caffeine, menthol |
| Urogenital and anal organs drugs | lidocaine, liquorice | not applicable |
| Tonic health drugs | caffeine, liquorice, Cyperus rhizome | caffeine |
| Women's drugs | caffeine, liquorice, Cyperus rhizome | not applicable |
| Allergy drugs | liquorice, diphenhydramine | diphenhydramine, methylephedrine |
| Skin drugs | liquorice, diphenhydramine, menthol, naphazoline, isopropanol, lidocaine | diphenhydramine, menthol, ethanol, isopropanol, benzalkonium chloride, salicylic acid, ammonia solution |
| Ophthalmic drugs | naphazoline, boric acid | boric acid |
| Otorhinolaryngological drugs | naphazoline, fexofenadine, caffeine, loratadine | ephedrine |
| Dental and oral cavity drugs | not applicable | not applicable |
| smoking cessation agents | not applicable | nicotine |
| Kampo preparation | liquorice, Cyperus rhizome, Scutellaria root, rhubarb | not applicable |
| Herbal preparation (Preparations not belonging to other therapeutic classes) | liquorice, Cyperus rhizome, Scutellaria root | not applicable |
| Public health drugs | not applicable | DEET, dichlorvos, fenitrothion, sodium hypochlorite, trichlorfon, saponated cresol solution, ethanol, diazinon |
| General test kits | not applicable | not applicable |
| Others (preparations not belonging to any therapeutic category) | not applicable | not applicable |

[a]Classifications registered with JAPIC.

*Publication and access status of the "Drug Database for Overdose Prevention"*

For safety reasons, the constructed database was made available on the Internet with registration and permission (*https://overdose-med.com*). The database also makes public the specific product names of the OTC drugs as well as the literature and package insert information.

To determine how the published website was being used, Figure 1A shows the change in user engagement over time since publication on the Internet. We also determined the regions and countries from which the homepages were accessed (Figure 1B). In terms of access, Japan had the highest interaction at 5,290, followed by the United States of America with 125, and Taiwan R.O.C. with 99 (Figure 1B). Access was detected not only from Japan and Asia, but also from North America and Europe. A total of 199 people were registered with the website, including 187 pharmacists (94.0%), 7 registered sellers (3.5%), and 5 others (2.5%), including doctors (Figure 1C). We also identified the top 15 regions by city/town/village based on the number of users in Japan, excluding the not set, which did not register a region (1,620 users, average engagement time 29.6 s) (Figure 1D). The city with the most users was Osaka at 377 users and an average engagement time of 41.8 s, followed by Sapporo, Fukuoka, Nagoya, Chiyoda city, and Yokohama (Figure 1D). These areas are urban and corresponded to a high number of people being taken to emergency facilities for drug overdoses.

## Discussion

Of the OTC drugs included in this study, 1,223 products contained a lethal dose if taken in one package, whereas 2,982 contained a toxic dose. Overall, the fatal and toxic dose rates were 8.7% and 21.1%, respectively. The specific ingredients found in lethal doses from a single package included methylephedrine, caffeine, diphenhydramine, and ethanol, which are present in OTC drugs across multiple therapeutic categories. In addition, characteristic public health drugs were listed, including DEET, dichlorvos, and fenitrothion. Furthermore, the risk classification of OTC drugs (Class 1 drugs, *etc*.) did not always match the number of drugs that were considered lethal or toxic to humans in one full package. Therefore, pharmacists and other individuals with specialized knowledge should provide appropriate warnings, manage the distribution of OTC medicines, and provide guidance on how to properly use them. The risk classification is currently under review by the Drug Sales System Review Committee of the Ministry of Health, Labor, and Welfare. As of February 2024, two categories of medicines remain under discussion: medicines sold by pharmacists and medicines sold by pharmacists or registered sellers. It will be necessary to monitor these for future regulatory changes.

**Table 4. Number of OTC drugs surveyed that are at risk of being abused or lethal or toxic**

| Therapeutic Category[a] | Number of products surveyed: multiple contents *n* | Number of over-the-counter drugs containing ingredients designated by the Minister of Health, Labour and Welfare as "drugs that may be abused, *etc*." | | | *p* |
|---|---|---|---|---|---|
| | | Total, *n* (%) | Number of products till March 31, 2023 *n* (%) | Number of additional products from April 1, 2023 *n* (%) | |
| Psychotropic drugs | 1607 | 852 (53.0) | 131 (8.2) | 721 (44.9) | < 0.01* |
| Digestive tract drugs | 1730 | 0 (0) | 0 (0) | 0 (0) | - |
| Cardiovascular and Hematological Drugs | 407 | 0 (0) | 0 (0) | 0 (0) | - |
| Respiratory drugs | 524 | 231 (44.1) | 188 (35.9) | 43 (8.2) | < 0.01* |
| Urogenital and anal organs drugs | 230 | 11 (4.8) | 3 (1.3) | 8 (3.5) | 0.03* |
| Tonic health drugs | 2236 | 0 (0) | 0 (0) | 0 (0) | - |
| Women's drugs | 151 | 0 (0) | 0 (0) | 0 (0) | - |
| Allergy drugs | 34 | 2 (5.9) | 0 (0) | 2 (5.9) | - |
| Skin drugs | 2684 | 2 (0.1) | 0 (0) | 2 (0.1) | - |
| Ophthalmic drugs | 482 | 1 (0.2) | 1 (0.2) | 0 (0) | - |
| Otorhinolaryngological drugs | 338 | 108 (32.0) | 92 (27.2) | 16 (4.7) | 0.18 |
| Dental and oral cavity drugs | 305 | 0 (0) | 0 (0) | 0 (0) | - |
| smoking cessation agents | 27 | 0 (0) | 0 (0) | 0 (0) | - |
| Kampo preparation | 2697 | 0 (0) | 0 (0) | 0 (0) | - |
| Herbal preparation (Preparations not belonging to other therapeutic classes) | 280 | 0 (0) | 0 (0) | 0 (0) | - |
| Public health drugs | 352 | 0 (0) | 0 (0) | 0 (0) | - |
| General test kits | 17 | 0 (0) | 0 (0) | 0 (0) | - |
| Others (preparations not belonging to any therapeutic category) | 6 | 0 (0) | 0 (0) | 0 (0) | - |

[a]Classifications registered with JAPIC. *p*-value indicate number of products till March 31, 2023 *vs.* Total Chi-square test; *$p < 0.05$.

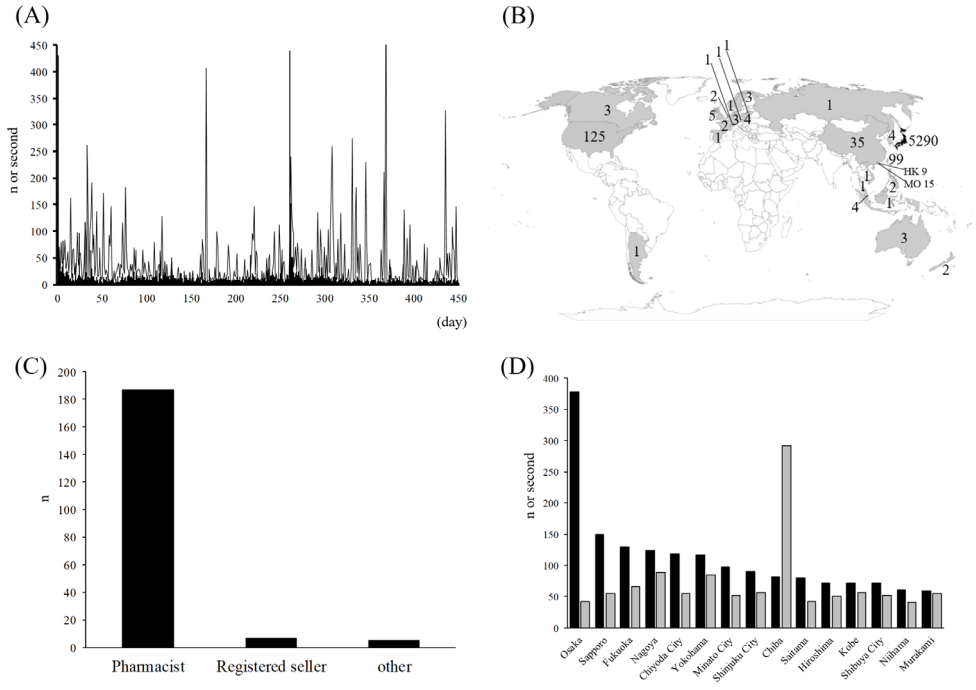


**Figure 1. Data on the "Drug Database for Overdose Prevention" website. (A)** Users and average engagement time over time since publication on the Internet. Black bar graph: Users (*n*), Solid black line: average engagement time (seconds). **(B)** Number of website accesses from each region and country. April 1, 2023, to June 25, 2024. **(C)** Database registrants; as of July 31, 2024 (*n*). **(D)** Top 15 users by region in Japan and the average engagement time (seconds). Black bar graph: Users by region (*n*), grey bars: Average engagement time (seconds). Users of "not set" were not included.

Although there are no legal restrictions, such as the designation of ingredients as potentially misused, there have been reports of ingredients being abused. As an example, surveys of young people and medical professionals have shown an increase in caffeine abuse (*17,18*). Similarly, studies among USA adolescents indicate the increased abuse of diphenhydramine (*19*). These ingredients are toxic and dangerous. A retrospective study of emergency care facilities in Japan reported that caffeine overdose can cause symptoms such as tachypnea, tachycardia, hypokalemia, and hyperlactatemia, and can even result in death (*20*). Diphenhydramine also has no antidote and because it acts directly on the vascular system as well as the autonomic and somatic central nervous systems, it may cause multiple serious side effects, including death (*21,22*). Pesticides and insecticides, such as DEET and organophosphates, which are classified as public health drugs, are also likely to be used for suicide (*13,23*). Thus, for these ingredients, measures must be taken by pharmacists with specialized pharmaceutical knowledge when the product is sold. Moreover, children and individuals with cognitive impairment may unintentionally misuse OTC drugs, leading to poisoning and death (*23*). According to the data on lethal doses of OTC drugs in humans surveyed in the present study, it was considered necessary to actively listen to the circumstances of the purchasers and to alert parents and caregivers to the importance of managing medications at home.

Similar poisoning information databases, such as POISINDEX® (TECHNOMICS, INC.), are available under contract, however, these do not cover Japanese OTC drug products; therefore, the database that we established is novel in this respect. In contrast, because many OTC drugs in Japan contain multiple ingredients, toxicity resulting from drug-drug interactions is an issue to be considered. Thus, it is necessary to clarify toxicity due to drug-drug interactions. Analysis of the logs revealed that most users were from urban areas of Japan, where there are many incidents of drug overdose. This suggests that the database is being used effectively in these areas, although a more detailed analysis is needed. In addition, access to the published website from other countries was detected; thus, it is necessary to make the database available in English in the future.

The newly published Comprehensive Suicide Prevention Principles (Ministry of Health, Labor, and Welfare), which was approved by the Cabinet in October 2022 (*4*), continues to place expectations on pharmacists to act as gatekeepers. The database established in this study is expected to be used as one of the tools for gatekeepers to prevent overdose and suicide. Currently, 94% of the registered users are pharmacists. In a recent report, 65.9% of drugs used in overdoses were obtained from brick-and-mortar stores, whereas only 9.3% were purchased online (*6*). This suggests that local pharmacists are likely to play an active role as gatekeepers in the prevention of

medication overdose. In contrast, overdoses can occur repeatedly (*24,25*). Therefore, pharmacists at hospitals where the patients are transported or examined should provide information to local pharmacies and other professionals, including doctors. Thus, there is a need to strengthen cooperation between hospitals and pharmacies.

One limitation of this study is that there is limited information on the toxic or fatal doses of certain drugs in humans. Based on the literature (*7-15*), we evaluated the toxic and lethal doses for humans. The usual amount of drug used is the amount in which safety has been confirmed, which is listed on the package insert; however, the effects on humans in the event of an overdose must be based on post-marketing reports. Therefore, it is important to note that there are compounds whose effects in some cases of overdose are unknown. In conclusion, the database established in this study is expected to be useful as a tool for gatekeepers to prevent overdose and suicide associated with OTC drugs.

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BRIEF REPORT
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# Relationship between ego depletion and health promotion behaviors in older adults with diabetes: A cross-sectional study in Shanghai, China

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**Abstract:** In recent years, the prevalence of diabetes in the elderly has risen sharply, and diabetes and its related complications seriously affect the physical and mental health of patients. Health promotion behaviors are extremely important in preventing the onset and development of diabetes. Ego depletion is a common negative psychological experience among most patients with chronic disease, which affects their performance of health-promoting behaviors. However, the relationship between ego depletion and health-promoting behaviors in elderly patients with diabetes is unclear. We assessed the relationship between ego depletion and health-promoting behaviors in older people with diabetes, and the factors influencing health-promoting behaviors. The 751 participants had an ego depletion score of 44.55 ± 6.62 and a health-promoting behavior score of 77.61 ± 18.72, with a significant negative correlation between ego depletion and health-promoting behavior ($r$ = -0.320, $p < 0.001$). The level of health promotion behaviors was higher in patients with a high school level of education and above ($p < 0.001$), living with a spouse and children ($p = 0.010$) and having received diabetes-related health education ($p < 0.001$), and the cognitive ($p < 0.001$), emotional ($p < 0.001$) and behavioral control dimensions of ego depletion ($p = 0.016$) were significant predictors of health promotion behaviors. Nursing staff should provide personalized care for patients with a low level education, who are living alone, and who have not received health education to prevent or respond to patient ego depletion and to improve patients' health promotion behaviors.

***Keywords*:** ego depletion, health promotion behaviors, diabetes, the elderly, influencing factors

## Introduction

In recent years amidst increasing urbanization, further aging of the population, and lifestyle changes, the prevalence of diabetes mellitus (DM) and the number of people suffering from the disease have been proliferating at an alarming rate, making it another major challenge in the field of chronic diseases globally, after cancer and cardiovascular and cerebrovascular diseases (*1*). According to the global diabetes map published by the International Diabetes Federation (*2*), about 537 million adults (20-75 years old) worldwide have diabetes, accounting for 11.30% of the total. The number of older adults with diabetes ages 65 years and above is up to 136 million, accounting for 19.9%. China has the most significant number of diabetes patients, the prevalence of diabetes among the elderly (≥ 60 years old) is 30.49%, the number of patients totals 78.13 million, and the elderly have become the main population suffering from diabetes in China (*3*). The bodily functions of elderly patients decline with age, and the disease is more protracted. Long-term abnormalities of glucose metabolism and lipid metabolism increase the incidence of complications such as peripheral neuropathy, vasculopathy, and podiatry and even lead to amputation (toes) or death of the patient, causing grave harm to the patient and his/her family (*4*). Therefore, preventing and controlling the development of diabetes is imperative.

Pender *et al.* integrated nursing and behavioral medicine in the concept of health-promoting behavior, stating that health-promoting behavior is a multidimensional model of behavior that encompasses cognitive, emotional, and behavioral components and is a series of actions that an individual actively undertakes in order to maintain and promote health (*5*). Health-promoting behaviors are recognized as key to treating chronic diseases such as coronary heart disease and diabetes (*6*). At least 80% of chronic diseases, including

diabetes, can be managed through the implementation of health-promoting behaviors such as exercise adherence and medication compliance (*7,8*), and adherence to these behaviors and lifestyle changes can be effective in mitigating the progression of the disease and reducing the cost of health care (*9,10*). Studies have shown that sustaining health-promoting behaviors provides additional health benefits for people with diabetes, improves their quality of life, and reduces the risk of disability or death (*11*), and it also delays the onset of diabetes in people at high risk of diabetes and reduces the overall incidence of diabetes over 10 years (*12*).

DM is characterized by a prolonged and recurrent course, many complications, and complexity. To effectively prevent the disease, patients must engage in long-term health-promoting behaviors such as dietary control, exercise, insulin injections, and glucose-lowering medication. Baumeister *et al.* (*13*) suggested that individual self-management is embodied in self-control and that performing self-control can cause energy depletion in an organism. When this energy depletion reaches a certain amount, the individual is in a state of low control, *i.e.*, ego depletion. When patients are in a state of ego depletion, it affects the activities that they need to control themselves afterward, and they experience a decrease in their ability or willingness to control cognitive, emotional, and behavioral aspects, which can lead to barriers to the management of the patient's health (*14*). Previous studies (*15,16*) have shown that ego depletion is a common negative psychological experience for most chronic disease patients. Patients have to suffer from the pain caused by the disease as well as regulate the anxiety and depression caused by the disease, which rapidly depletes their self-control resources, resulting in patients not having sufficient self-control resources to manage their health and not being able to demonstrate better health-promoting behaviors (*17*).

Previous studies (*18,19*) have focused on ego depletion and health-promoting behaviors in diabetics, but they have focused on adult diabetics, and older diabetics have unique physiopathological characteristics due to metabolic disorders and multiorgan dysfunction. Therefore, the ego depletion and health promotion behaviors of elderly diabetics need to be determined and the health promotion behaviors of different patients and their association with ego depletion need to be explored to assist medical personnel in implementing interventions and enhancing patients' health promotion behaviors.

## Patients and Methods

*Study setting and participants*

Patients were recruited from five community health hospitals in Shanghai, China. Inclusion criteria for elderly diabetics: *i*) age ≥ 60 years; *ii*) meeting the 2006 (WHO) diagnostic criteria for DM; *iii*) being able to communicate and voluntarily participating in this study. Patients with severe mental disorders, cognitive dysfunction, physical activity limitations due to complications or comorbidities, and severe cardiac, pulmonary, and cerebral diseases were excluded.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of the Huadong Hospital Affiliated with Fudan University(20240065). All participants gave informed consent.

*Research instruments*

*General information questionnaire*

Demographic characteristics included sex, age, education, residence, and mean monthly income. Disease information included disease duration, diabetes health education, smoking status, and comorbidities.

*Self-Regulation Fatigue Scale (SRF-S)*

First developed in 2013 by Nes *et al.* (*20*), the SRF-S is mainly used to measure the degree of ego depletion of an individual and consists of a total of 18 entries in 3 dimensions, with a total scale Cronbach's alpha of 0.81. Chinese researchers (*21*) revised the scale in 2016 to consist of 16 items, which were cognitive (6 items), behavioral (5 items), and emotional (5 items). Each item was rated on a 5-point Likert scale, with the options ranging from "very poorly" to "very well," and 5 of the items were reverse-scored. The scale score ranges from 16 to 80, with a higher score indicating more significant ego depletion. This scale is reliable and valid and has been used by several researchers to study Chinese patients with chronic diseases (*22,23*). In the current study, the Cronbach's alpha for this scale was 0.747.

*Type 2 Diabetes and Health Promotion Scale (T2DHPS)*

Developed by Chen *et al.* (*24*) in Taiwan in 2013, the T2DHPS specifically assesses the level of health promotion behaviors among diabetics, and its reliability and validity were later re-tested by Cao *et al.* (*25*) based on a mainland population. The Cronbach's alpha for the total scale was 0.943, and the Cronbach's coefficient for the dimensions ranged from 0.819 to 0.931. The scale consists of 28 items, including 6 dimensions of exercise (7 items), risk avoidance (7 items), stress management (5 items), health responsibility (3 items), healthy eating (3 items), and life appreciation (3 items). Each entry was scored on a 5-point Likert scale, with scores of 1, 2, 3, 4, and 5 representing never (0-10%), occasionally (11-30%), about half (31-50%), often (51-80%), and always (81-100%), respectively. The total scale score was 28-140, with a higher score indicating a higher level of a patient's health-promoting behaviors. In the current study, Cronbach's alpha was 0.97, with dimension coefficients of 0.907, 0.832, 0.840, 0.894, 0.800, and

0.855, respectively.

*Data collection methods*

A researcher explained the purpose, significance, and content of filling out the questionnaire to the respondents and answered the patients' questions as they filled out the questionnaire to ensure that the patients understood what was being asked. If the respondent who could not answer the questionnaire by himself or herself or had a low level of education, the researcher repeated the questions one by one, filled in the questionnaire on behalf of the respondents according to their answers, and verified it again. The questionnaire was filled out anonymously and collected on the spot after completion. Eight hundred questionnaires were distributed in this study, and 751 valid questionnaires were received, with a validity rate of 93.88%.

*Statistical analysis*

Socio-demographic and disease variables of the study population and the main study variables (ego depletion and health-promoting behaviors) were described using descriptive statistical analysis based on the type of variables and normality assessment. One-way ANOVA, a *t*-test, and Pearson correlation analyses were used to assess the relationship between dependent and independent variables. Multiple linear stepwise regression analysis was used to analyze the predictors of health promotion behaviors among elderly diabetics. Data were analyzed using SPSS 26.0, and all statistical tests were two-tailed, with $p < 0.05$ indicating a statistically significant difference.

**Results and Discussion**

*Characteristics of participants*

A total of 751 patients were included in this study, 320 (42.61%) of whom were male, and 431 (57.39%) of whom were female; their ages ranged from 60 to 94 (69.97 ± 7.04) years; 40.6% of them had a junior high school education, 28.0% had a high school or secondary school education, and 11.3% had a college education. In addition, 47.6% of the patients lived with their spouses, 20.5% lived with their children, and a few patients (13.1%) lived alone. Other general information is shown in Table 1.

*Scale means for ego depletion and health promotion behaviors*

The ego depletion score for 751 patients was 44.55 ± 6.62, with the highest score of 3.12 ± 0.51 in the cognitive dimension. The health-promoting behavior score was 77.61 ± 18.72. The mean scores for the entries in each dimension were, in descending order: appreciation of life (3.20 ± 0.98), healthy eating (3.12 ± 0.92), responsibility for health (3.02 ± 0.93), stress management (2.87 ± 0.83), risk avoidance (2.63 ± 0.75), and exercise (2.40 ± 0.78) (Table 2).

Findings showed that the degree of ego depletion among elderly diabetics is at a high level, which is consistent with findings of Wang *et al.* (*18*). DM is characterized by a disease with a long duration and difficulty recovering completely, requiring patients take medications over a long period and make lifestyle changes to prevent complications. These long-term stressors constantly deplete patients' self-control resources. According to the ego depletion theory, an individual's self-regulation resources are limited. Long-term self-control, such as suppressing eating impulses and engaging in physical exercise, as well as the accompanying prolongation of disease and deterioration and the painful experience brought by the symptoms, continue to wear down the patient's self-control resources, which makes them physically and mentally exhausted (*13*). Notably, the highest score in this study was for the cognitive control dimension, meaning that older diabetics had the highest level of depletion in cognitive control. This differs from the findings of Gao *et al*. (*26*). The difference may be due to the fact that the subjects of the current study were elderly patients who have a reduced ability to understand and acquire information about the disease and deep-rooted cognitive perceptions. Implementing the process of cognitive control requires a significant number of psychological resources, which results in the highest attrition of cognitive control in patients. That said, individuals' thoughts and emotions gradually stabilized with age; they can control their emotions and behaviors better, and impulsive behaviors subsequently decrease. Therefore, healthcare professionals should pay more attention to identifying and intervening in the cognitive control depletion of elderly diabetics, helping patients to improve their misperceptions of the disease and practice health-promoting behaviors.

This study showed that the health promotion behavior score for elderly diabetics was 77.61 ± 18.72, with a score of 55.44%, which was lower than the results reported by Du *et al.* (*27*). This may be because the subjects of this study were elderly diabetics, most of whom suffer from comorbidities, who may have multifunctional disorders, and who may be taking multiple medications compared to younger patients (*28*). In elderly diabetics, disease management is more complex, leading to a decrease in tolerance and self-care awareness, which in turn results in a low level of health-promoting behaviors among patients. A point worth noting is that elderly diabetics in this study had the lowest scores on the risk avoidance dimension, which disagreed with the findings of Du *et al.* (*27*). A single item analysis revealed that the possible reason

**Table 1. Impact of different characteristics on health promotion behaviors of older adults with DM**

| Variables | *n* (%) | Mean ± SD | F/t | *p* |
|---|---|---|---|---|
| Age | | | 6.294 | 0.002 |
| 60-70 | 471 (62.7) | 79.14 ± 18.41 | | |
| 71-80 | 221 (29.4) | 76.21 ± 19.36 | | |
| > 80 | 59 (7.9) | 70.61 ± 18.72 | | |
| Sex | | | 1.939 | 0.164 |
| Male | 320 (42.6) | 76.51 ± 18.17 | | |
| Women | 432 (57.4) | 78.43 ± 19.10 | | |
| Level of education | | | 20.575 | < 0.001 |
| Primary school and below | 151 (20.1) | 70.53 ± 19.13 | | |
| Junior high school | 305 (40.6) | 76.35 ± 16.72 | | |
| High school or Junior college | 210 (28.0) | 79.96 ± 17.55 | | |
| College and above | 85 (11.3) | 88.91 ± 21.42 | | |
| Monthly income (RMB) | | | 6.052 | < 0.001 |
| < 3,000 | 53 (7.1) | 78.57 ± 16.27 | | |
| 3,000-5,999 | 121 (16.1) | 74.69 ± 18.63 | | |
| 6,000-8,999 | 357 (47.5) | 75.83 ± 18.71 | | |
| ≥ 9,000 | 220 (29.3) | 81.89 ± 18.69 | | |
| Residential status | | | 6.410 | < 0.001 |
| Live alone | 99 (13.1) | 74.27 ± 22.37 | | |
| With a spouse | 358 (47.6) | 79.37 ± 17.54 | | |
| With children | 154 (20.5) | 73.05 ± 20.25 | | |
| With children and spouse | 140 (18.6) | 80.51 ± 15.77 | | |
| Smoking | | | 0.924 | 0.337 |
| Smoking | 128 (17.0) | 76.16 ± 17.90 | | |
| Never | 623 (87.0) | 77.91 ± 18.88 | | |
| Course of the disease (years) | | | 2.569 | 0.037 |
| ≤ 1 | 38 (5.1) | 76.18 ± 21.57 | | |
| 1-5 | 232 (30.9) | 80.68 ± 17.64 | | |
| 6-10 | 268 (35.7) | 76.37 ± 17.88 | | |
| 11-20 | 131 (17.4) | 76.53 ± 19.36 | | |
| ≥ 20 | 82 (10.9) | 74.22 ± 21.10 | | |
| Health education on diabetes | | | 10.611 | < 0.001 |
| Yes | 569 (75.8) | 78.86 ± 18.82 | | |
| No | 182 (24.2) | 73.70 ± 17.90 | | |
| Comorbidities | | | 4.018 | 0.018 |
| No | 242 (32.2) | 79.53 ± 18.45 | | |
| 1-2 | 363 (48.3) | 77.78 ± 18.40 | | |
| ≥ 3 | 146 (19.5) | 74.01 ± 19.55 | | |

**Table 2. Distribution of mean scores for patients' ego depletion and health promotion behaviors**

| Variables | Domain Mean ± SD | Item Mean ± SD | Rank |
|---|---|---|---|
| Ego depletion, total | 44.55 ± 6.62 | | |
| Cognitive control | 18.75 ± 3.05 | 3.12 ± 0.51 | 1 |
| Emotional control | 13.64 ± 2.50 | 2.72 ± 0.50 | 2 |
| Behavioral control | 12.16 ± 3.36 | 2.43 ± 0.67 | 3 |
| Health-promoting behaviors, total | 77.61 ± 18.72 | | |
| Risk aversion | 18.44 ± 5.22 | 2.63 ± 0.75 | 5 |
| Movement | 16.82 ± 5.49 | 2.40 ± 0.78 | 6 |
| Stress management | 14.34 ± 4.17 | 2.87 ± 0.83 | 4 |
| Life appreciation | 9.60 ± 2.94 | 3.20 ± 0.98 | 1 |
| Healthy eating | 9.37 ± 2.77 | 3.12 ± 0.92 | 2 |
| Health responsibility | 9.05 ± 2.78 | 3.02 ± 0.93 | 3 |

for this was that most of the patients in this study were not well-educated, had a reduced ability to understand and perceive the information about the disease and its associated complications, and were not aware of the importance of foot care and healthy eating. The exercise dimension scores were similarly low in the current study, which is consistent with the findings of Hernandez *et al.* (*29*). This may be related to the poor understanding of exercise among older patients, who believe that doing housework, farming, and casual activities are all that is required to maintain regular exercise. In elderly patients, physiological functions gradually decline, and physical activity is also limited due to long-term illness, fear of falling, and other psychological factors. Given this situation, how to provide appropriate exercise guidance to elderly diabetics and devise an exercise plan that meets the needs of the patients has become the focus of instructing them on how to improve their health promotion behaviors.

*Factors influencing health promotion behaviors in elderly patients with DM*

Results showed that age, level of education, monthly income, residential status, diabetes health education, and

number of comorbidities were factors influencing the health promotion behaviors of elderly diabetics, and the difference was significant ($p < 0.05$), as shown in Table 1.

Pearson's correlation coefficient analysis showed that scores on the SRF-S were negatively correlated with scores on the T2DHPS in elderly diabetics ($r$ = -0.320, $p < 0.001$), with the cognitive dimension being the most significant variable ($r$ = -0.415, $p < 0.001$). Correlations between behavior and exercise ($r$ = 0.071, $p$ = 0.052), risk aversion ($r$ = 0.053, $p$ = 0.143), stress management ($r$ = -0.051, $p$ = 0.162) and health behavior ($r$ = -0.04, $p$ = 0.278) were not significant, but the correlations between the remaining variables were negative ($r$ = -0.415 to -0.118, $p < 0.001$) (Table 3).

Pearson's correlation analysis showed that ego depletion was negatively correlated with health promotion behaviors and all dimensions, which means that when patients' level of ego depletion increases, their health promotion behaviors decrease (*19*). This may be related to the fact that the higher the patient's degree of ego depletion, the more his or her psychological resources or energy are depleted. However, the individual's resources or energy are limited, and once they are not replenished promptly, the patient's subsequent control behaviors will be biased or even fail. They will be prone to engage in behaviors detrimental to their health (*17*). Therefore, healthcare professionals should promptly assess the degree of ego depletion in elderly diabetics, provide patients with strategies to cope with ego depletion, help patients establish a correct knowledge of the disease, reduce patients' ego depletion, and improve patients' health-promoting behaviors.

Multiple linear stepwise regression analyses incorporated significant variables for differences in health promotion behaviors among older people with diabetes in both univariate and correlational analyses, and all variance inflation factors were close to 1 and less than 10, indicating no multicollinearity in the data. As shown in Table 4, level of education, living with a spouse and children, having received diabetes health education, and behavioral dimensions were positive predictors of health promotion behaviors; cognitive and emotional dimensions were negative predictors of health promotion behaviors, explaining 25.0% of the total variance ($F$ = 35.668, $p < 0.001$).

The current results indicated that level of education, residential status, and diabetes health education independently influenced the health promotion behaviors of elderly diabetics. This is consistent with a previous study (*30*), which stated that the higher the level of education of the patients, the higher the level of their health promotion behaviors. People with a high level of education perceive a greater need to be healthy and will use more ways to acquire knowledge related to health behaviors; at the same time, people with a high level of education perceive a greater need to accept and understand, and they are more apt to adopt positive coping styles to establish health behaviors, which is more conducive to the performance of health behaviors by the patients (*31*). The current results showed that patients who lived with their children and spouses exhibited better health promotion behaviors compared to patients who lived alone. A meta-analysis (*32*) showed that patients living alone, lacking the companionship and care of their loved ones, are more likely to experience self-abandonment, depression, and other psychological aspects, which in turn affects their performance of health-promoting behaviors while patients living with their spouses and children are able to receive more support in terms of life, emotional, and economic aspects. This

**Table 3. Correlations between ego depletion and health promotion behaviors**

| Variables | Ego depletion | Cognitive | Emotion | Behavior |
|---|---|---|---|---|
| Health-promoting behaviors | -0.320* | -0.415* | -0.04 | -0.286* |
| Risk aversion | -0.187* | -0.371* | 0.071 | -0.139* |
| Movement | -0.180* | -0.313* | 0.053 | -0.166* |
| Stress management | -0.329* | -0.424* | -0.051 | -0.284* |
| Life appreciation | -0.405* | -0.387* | -0.161* | -0.384* |
| Healthy eating | -0.224* | -0.190* | -0.118* | -0.204* |
| Health responsibility | -0.300* | -0.243* | -0.143* | -0.307* |

*$p < 0.001$.

**Table 4. Multiple linear stepwise regression analysis of factors influencing health promotion behaviors in elderly patients with DM**

| Variables | B | SE | β | $t$ | $p$ | $R^2$ |
|---|---|---|---|---|---|---|
| constant | 124.667 | 4.626 | | 26.951 | < 0.001 | 25.0 |
| Level of education (ref. Primary school and below) | | | | | | |
| High school and junior college | 3.241 | 1.405 | 0.078 | 2.307 | 0.021 | |
| College and above | 7.608 | 1.922 | 0.129 | 3.958 | < 0.001 | |
| Residential status (ref. Living alone) | | | | | | |
| Living with a spouse and children | 3.988 | 1.538 | 0.083 | 2.593 | 0.010 | |
| Diabetes health education | | | | | | |
| Yes | 4.870 | 1.398 | 0.112 | 3.484 | < 0.001 | |
| Ego depletion | | | | | | |
| Cognitive control | -1.838 | 0.231 | -0.299 | -7.967 | < 0.001 | |
| Emotional control | -1.528 | 0.360 | -0.204 | -4.243 | < 0.001 | |
| Behavioral control | 0.590 | 0.245 | 0.106 | 2.406 | 0.016 | |

facilitates the management of their condition, promotes patients' independent learning of relevant knowledge, and improves the level of patients' health-promoting behaviors (*33*). In addition, the current study showed that health promotion behaviors were higher in patients who had received diabetes health education than in those who had not. This finding may be related to the patient's basic knowledge of diabetes, as lack of knowledge about the disease often leads to a blind response to the disease, and the more patients know about diabetes-related complications, the more they will pay more attention to self-health management and practice health-promoting behaviors (*34*). Given this, healthcare professionals should provide diabetes health education and support to every patient (*35*).

Multiple linear stepwise regression analyses showed that cognitive control, behavioral control, and emotional control of ego depletion were significant predictors of health-promoting behaviors. Cognitive control and emotional control were negative predictors of health promotion behaviors, which was similar to the findings of a previous study (*36*), which showed that negative emotions and abnormal cognitions caused by an imbalance of ego depletion in elderly diabetics reduced the patients' subjective initiative to practice health promotion behaviors. This had a detrimental effect on health promotion behaviors.

This study had several limitations. It was conducted only in community hospitals in Shanghai, with limited sample representativeness, and future studies could be expanded to conduct related surveys in other regions. In addition, this study only used a cross-sectional research methodology, which is less able to establish causality, and further research could be conducted using longitudinal or qualitative studies.

In conclusion, this study explored the factors influencing health promotion behavior and the relationship between ego depletion and health promotion behavior. Level of education, residential status, and diabetes health education were the individual-level factors influencing health promotion behaviors among older adults with DM. Results suggested that healthcare personnel should pay more attention to the health promotion behaviors of patients with a low level of education, who are living alone, and who have not received diabetes health education. In addition, ego depletion is prevalent and is a significant predictor of health promotion behaviors among elderly patients with diabetes. Healthcare personnel should provide personalized care to prevent or cope with patients' ego depletion and enhance their health promotion behaviors.

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# Clinical potential of SAG-524: A novel HBV RNA destabilizer with a unique mechanism of action

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**Abstract:** SAG-524 is a novel, oral HBV RNA destabilizer developed to address the limitations of treatment with nucleos(t)ide analogues (NAs), which are effective against HBV DNA but show limited efficacy in reducing hepatitis B surface antigen (HBsAg) levels. SAG-524 exerts its effect by destabilizing HBV RNA by shortening the poly(A) tail, which leads to a significant reduction of both pgRNA and PreS/S mRNA. This destabilization seems to be specific for HBV RNA molecules. The mechanism involves the recruitment of PAPD5/7 by ZCCHC14 to the HBV RNA, where guanine is incorporated into the poly(A) tail to protect against degradation. SAG-524 disrupts this process by directly targeting PAPD5, thus destabilizing HBV RNA. In preclinical trials, oral administration of SAG-524 reduced serum HBsAg levels in HBV-infected PXB mice. When combined with NAs or capsid assembly modulators (CAMs), significant reductions in HBsAg, HBV DNA, and intrahepatic covalently closed circular DNA were observed. Safety studies conducted over 13 weeks in mice and monkeys revealed no significant toxicity, demonstrating the drug demonstrated a favorable safety profile. In conclusion, the novel mechanism of action, high oral bioavailability, and strong suppression of HBsAg make SAG-524 a promising candidate for future therapeutic use. The potential for combination therapy with NAs or CAMs underscores its capacity to contribute to achieving a functional cure for chronic HBV infection.

***Keywords*:** HBV, SAG-524, combination therapy

## Introduction

Currently, nucleos(t)ide analogues (NAs) and pegylated interferon are used to treat chronic hepatitis caused by persistent hepatitis B virus (HBV) infection. However, NAs, the most commonly used treatment, do not significantly reduce serum hepatitis B surface antigen (HBsAg) levels, which limits their potential for achieving a functional cure (HBsAg loss). Despite the antiviral efficacy of NAs in controlling HBV replication, their ability to clear HBsAg remains minimal, with low seroclearance rates observed over extended treatment periods. As a result, the likelihood of achieving a functional cure with current therapies is considered low. Therefore, there is an ongoing effort to develop new therapeutic agents aimed at achieving a functional cure for HBV infection (*1*).

One class of direct-acting antiviral agents, HBV RNA inhibitors, has shown promising results in suppressing viral protein expression and genome replication. This article outlines the possible mechanisms of action of HBV RNA inhibitors and highlights new therapeutic agents currently under development and in clinical trials.

## What are HBV RNA inhibitors?

The HBV genome exists as a covalently closed circular DNA (cccDNA) in the nuclei of hepatocytes. Several mRNAs are transcribed from the cccDNA, including a 3.5 kb mRNA that functions as pregenomic RNA, and 2.4 kb and 2.1 kb mRNAs encoding the various forms of HBsAg. RNA inhibitors target these RNAs and include small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs); examples of both are currently undergoing clinical trials. Additionally, a new class of drugs, known as RNA-binding protein inhibitors, is under development. These agents aim to suppress HBsAg production and contribute to the restoration of the host immune response, thereby achieving a functional cure (Figure 1).

## Antisense oligonucleotides

ASOs are short, single-stranded DNA or RNA sequences, typically fewer than 20 nucleotides in length,

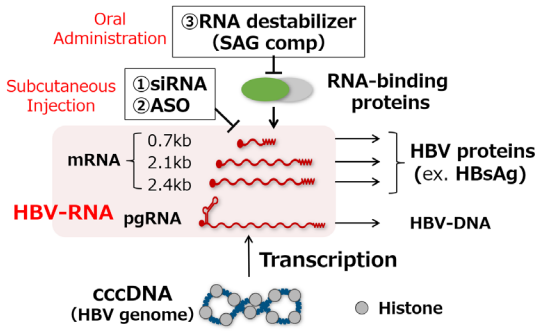


**Figure 1. Targeting HBV replication: RNA inhibitors as a strategy for suppressing HBs antigen production.** The HBV genome exists as cccDNA in hepatocyte nuclei, where it transcribes various RNAs for viral replication. RNA inhibitors like ①siRNA, ②antisense oligonucleotides (ASO), and our newly developed ③RNA-binding protein inhibitors target HBV-RNA to block its replication. These inhibitors can effectively suppress HBs antigen production.

that are complementary to a specific target sequence. By binding to RNA molecules in a complementary manner, ASOs regulate their function. Antisense DNA binds to complementary RNA and the RNA component of the DNA/RNA hybrid is quickly degraded by ribonuclease H (RNaseH1). ASOs can be designed with various combinations of DNA and modified nucleic acids to target entire RNAs or act on specific mRNA precursors or microRNAs (miRNAs), resulting in diverse mechanisms of action (*2,3*). Furthermore, ASOs can be modified to target functional sites on RNA, allowing them to exert a range of effects, such as inhibiting or enhancing RNA function. This versatility suggests the potential for their development as drugs tailored to specific disease mechanisms. ASOs designed for anti-HBV therapy specifically target the degradation of viral RNA to block the expression of viral proteins. With modified DNA strands that resist degradation by nucleases, ASOs bind to HBV RNA transcribed from cccDNA, in the nucleus and cytoplasm, and enable its cleavage by RNaseH1, thereby inhibiting viral protein translation and generating antiviral activity. Notably, these ASOs inhibit not only pregenomic RNA (pgRNA) but also the synthesis of HBsAg, which cannot be targeted by nucleoside analogues. Therefore, they are promising agents that may reduce HBsAg levels and potentially induce a functional cure for HBV infection.

A phase III trial of GSK3228836 (bepirovirsen), which lacks asialoglycoprotein modification, is currently ongoing. In this trial, subcutaneous injections are administered initially twice weekly, then once per week from the third week onwards (*4*). This treatment regimen results in a significant reduction of serum HBsAg. In particular, the HBsAg clearance rate (< 0.05 IU/mL) in the 300 mg dose group was 9% in the subjects receiving NAs and 10% in the subjects without combination therapy. Notably, among patients with baseline HBsAg levels below 1,000 IU/mL, a functional cure was achieved in 16% of the NA combination group and 25% of the non-combination group (*5*). Interestingly, in the cases where the HBsAg levels decreased, an elevation in ALT levels was observed during the course of treatment, suggesting the potential induction of HBV-specific immune responses.

## RNA-binding protein inhibitors (HBV RNA destabilizers)

A new class of drugs known as RNA-binding protein inhibitors has been developed. RG-7834, a novel, oral HBV agent, belongs to the dihydroquinolizinone (DHQ) class and functions by inhibiting PAPD5/7, RNA-binding proteins that stabilize HBV RNA. By inhibiting these proteins, RG-7834 acts as an RNA destabilizer, promoting the degradation of HBV RNA (*6*).

Recently, from a library of approximately 30,000 compounds, we identified a new hit compound, SAG-524, with strong anti-HBV activity (*7*). This report outlines the developmental status of SAG-524. First, we analyzed the mechanism of action using the BRIC assay, a method for measuring intracellular RNA degradation rates. By incorporating bromouridine during RNA synthesis and conducting a time-chase experiment, we found that SAG treatment specifically degraded HBV RNA without significantly affecting GAPDH or albumin RNA, showing that SAG selectively degrades HBV RNA. Further analysis revealed that treatment with SAG significantly reduced the intracellular levels of pgRNA and PreS/S mRNA, leading to a shortening of the poly(A) tail on HBV RNA, which suggests destabilization of the RNA. PAPD5 is known as a poly(A) polymerase that stabilizes mRNA by incorporating random guanines, which confer resistance to deadenylation, and recent reports have identified PAPD5 as a key factor in HBV RNA stabilization. We also investigated the interaction between SAG compounds and PAPD5. In thermal shift assays, we observed that PAPD5 was degraded at 52°C but, when treated with SAG, it remained stable at higher temperatures, indicating that SAG interacts with PAPD5. However, there was little interaction with PAPD7. Additionally, in HepG2.2.15 cells, SAG treatment reduced HBsAg concentrations in the culture supernatant, but this effect was negated when siPAPD5 was introduced. These results suggest that SAG compounds specifically and significantly destabilize HBV RNA through interaction with PAPD5 (Figure 2).

Next, we investigated combination therapy of SAG-524 with a NA (Entecavir, ETV), which is expected to be used in clinical settings, using HBV-infected chimeric mice. While ETV monotherapy significantly reduced HBV DNA levels, it did not result in a noticeable reduction in HBsAg. However, the addition of orally administered SAG-524 led to a marked reduction in both serum HBsAg and HBV DNA levels,

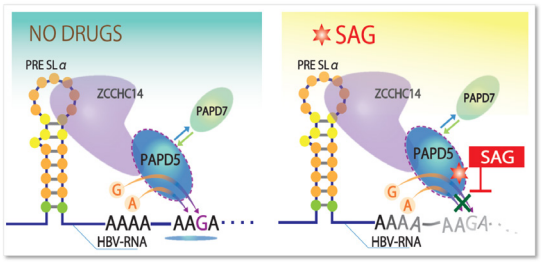


**Figure 2. Summary of the mechanism of action of SAG compounds**. The HBV RNA stem-loop recruits ZCCHC14 as a scaffold to form a complex with PAPD5. SAG-525 reduces HBsAg levels by acting through PAPD5.

and also decreased intrahepatic cccDNA. Additionally, we evaluated the safety of the drug in animal models. Cynomolgus monkeys, a large animal species, were administered a high dose of 1000 mg/kg of SAG-524 daily for 13 consecutive weeks. No significant abnormalities were observed. Furthermore, pathological examination of the liver, kidneys, brain, nervous system, and other tissues in high-dose treated monkeys revealed no signs of toxicological abnormalities.

In summary: *i*) Combination therapy of orally administrable SAG-524, which destabilizes HBV RNA and strongly suppresses HBsAg, together with a nucleos(t)ide analogue, reduced HBsAg, HBcrAg, and HBV DNA in serum, and intrahepatic cccDNA, in HBV-infected chimeric mice. This suggests the potential for achieving a functional cure; *ii*) Safety tests using large animal models showed no significant toxicity, demonstrating good tolerability. Clinical application is now being pursued.

## Conclusion

Prolonged exposure to high levels of viral antigens may lead to exhaustion of the host's immune response, contributing to persistence of HBV infection. Therefore, HBV RNA inhibitors, which aim to reduce HBsAg levels, are considered as an effective therapeutic strategy for controlling HBV infection (*8*). However, some investigators have reported HBsAg rebound after the cessation of RNA inhibitor therapy. In clinical practice, careful attention must be given to the sustainability of the therapeutic response. To enhance the durability of treatment effects, combination therapies that utilize other mechanisms, such as immunotherapy, may be necessary to efficiently achieve a functional cure. The addition of immune-enhancing treatments could provide further support by reactivating the immune system and preventing viral rebound, which is crucial for the long-term control of HBV.

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# Current global applications of HBcrAg assays in the management of chronic hepatitis B

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**Abstract:** Hepatitis B core-related antigen (HBcrAg) is a vital marker for monitoring chronic hepatitis B (CHB) as it correlates with hepatitis B (HBV) DNA and covalently closed circular DNA (cccDNA). The iTACT-HBcrAg assay, approved in Japan, provides highly sensitive and automated testing, reducing patient burden by requiring smaller specimen volumes and offering shorter processing times. Crucial for managing HBV reactivation and predicting hepatocellular carcinoma, it delivers consistent and reliable results. In resource-limited regions, the HBcrAg-rapid diagnostic test (HBcrAg-RDT) facilitates early HBV detection and management. This point-of-care testing (POCT) tool requires no specialized equipment and provides results within 30 minutes, making it invaluable in areas lacking HBV DNA quantification. Trials in West Africa, Asia, and other developing regions demonstrate its sensitivity and specificity. Together, these advancements in iTACT-HBcrAg and HBcrAg-RDT assays enhance CHB patient care and contribute significantly to the global effort to eliminate HBV as a public health threat.

***Keywords*:** hepatitis B virus (HBV), covalently closed circular DNA (cccDNA), point-of-care testing (POCT)

## Introduction

Hepatitis B virus (HBV) integrates into host liver cell nuclei as covalently closed circular DNA (cccDNA), playing a crucial role in chronic hepatitis B (CHB) progression (*1*). Current anti-HBV treatments using nucleos(t)ide analogues (NAs) or pegylated interferons inhibit HBV replication but cannot eliminate HBV from hepatocytes. The progression and prognosis of CHB are closely associated with the amount and activity of cccDNA (*2*).

HBV reactivation is commonly seen in patients receiving systemic chemotherapy for hematological malignancies or in hematopoietic stem cell transplantation recipients (*3*). Measuring serum HBV DNA is essential for preventing and diagnosing HBV reactivation. Novel biomarkers, such as high-sensitive HBsAg and hepatitis B core-related antigen (HBcrAg), help in early diagnosis of HBV reactivation. HBcrAg, correlating well with traditional HBV biomarkers, is valuable for screening and diagnosing HBV reactivation, especially in hepatitis B core antigen (HBeAg)-negative patients, even when HBV DNA is suppressed by NAs (*4*). A highly sensitive and automated HBcrAg assay iTACT-HBcrAg was approved in Japan in June 2022 (*5*). iTACT stands for Immunoassay for Total Antigen including Complex *via* pretreatment, and is an assay that analyzes the different molecular modalities present in the specimen (*6*).

Regions such as sub-Saharan Africa, Asia, and the Western Pacific are high-risk areas for HBV infections (*7*). The World Health Organization (WHO) recommends peripartum antiviral prophylaxis for HBV-infected pregnant women with high HBV DNA levels (> 200,000 IU/mL) to prevent mother-to-child transmission (*8-10*). Despite the importance of measuring HBV DNA, over 95% of HBV-infected individuals live in areas where HBV DNA quantification is not readily available (*11*). In these settings, a rapid and simple HBcrAg assay is effective as point-of-care testing (POCT) (*12*).

Currently, there are two main needs for HBV biomarkers: highly sensitive automated assays and systems suitable for POCT in resource-limited settings. This communication highlights the clinical application of the new HBcrAg marker in CHB and HBV reactivation treatment, focusing on the iTACT-HBcrAg assay and a novel HBV prevention strategy based on POCT.

## Development of a fully automated highly sensitive HBcrAg assay

*Characteristics of iTACT-HBcrAg*

We have developed a new sensitive HBcrAg assay called iTACT-HBcrAg. This assay measures HBcrAg, which consists of hepatitis B core antigen, HBeAg, and empty particles (*13,14*). The iTACT-HBcrAg assay contains a reducing agent in the pretreatment solution that alters the molecular structure of HBcrAg and facilitates its measurement. iTACT-HBcrAg achieves a sensitivity about 10 times greater than the conventional assay and improves analytical performance at low concentrations compared to a conventional assay. Additionally, the sensitivity of iTACT-HBcrAg was improved by increasing the number of solid-phase antibodies and optimizing the reagent assay (Figure 1).

Another significant advantage of the high-sensitivity iTACT-HBcrAg assay is the fully automated sample preparation, which saves assay time. Previously, about 30 minutes of manual sample preparation was required, but iTACT-HBcrAg automates this process, reducing the assay time to only 6.5 minutes. The new assay provides results in just 33 minutes. Furthermore, automation eliminates the variability inherent in manual processes, ensuring consistent and reliable results, which is especially important for longitudinal studies and CHB monitoring. Furthermore, iTACT-HBcrAg can reduce the required specimen amount for measurement by one-third, thereby reducing the burden on patients (*5,6*).

*Basic performance evaluation of iTACT-HBcrAg*

Our initial report highlighted the analytical performance of iTACT-HBcrAg. Compared to a conventional assay, iTACT-HBcrAg accurately measures low-concentration areas below 2.7 log U/mL. The cutoff values are 2.1 log U/mL (limit of quantification: 1.8 log U/mL) for iTACT-HBcrAg and 2.8 log U/mL for a conventional assay (*5*). Serial sera from 161 HBeAg-negative patients with CHB and persistently undetectable HBV DNA were measured using iTACT-HBcrAg and a conventional HBcrAg assay. HBcrAg was detectable in the sera of 97.5% (157/161) of these patients by iTACT-HBcrAg, with 75.2% (121/161) having > 2.8 log U/mL HBcrAg and 22.4% (36/161) having 2.1–2.8 log U/mL HBcrAg, which was undetectable by a conventional assay (*5*). Furthermore, correlation studies with samples from 389 HBeAg-positive or negative patients show that iTACT-HBcrAg correlates well with conventional HBcrAg values ranging from 2.8 log U/mL to 7 log U/mL (*5*).

In summary, iTACT-HBcrAg detects HBcrAg levels between 2.1 log U/mL and 2.8 log U/mL that are undetectable using a conventional HBcrAg assay. Performance evaluation studies have demonstrated that iTACT-HBcrAg has excellent specificity and reproducibility, making it a reliable tool for clinical use. This enhanced detection capability improves the ability to monitor and manage CHB more effectively (*5*).

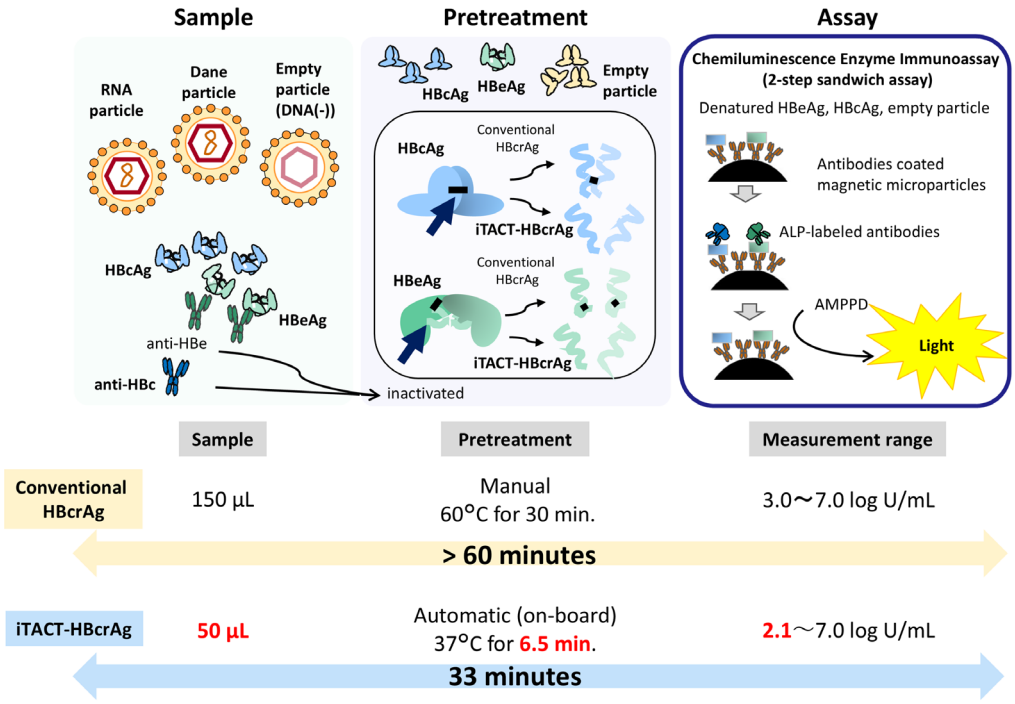


**Figure 1. Comparison of the conventional and highly sensitive HBcrAg assays.** The figure compares the iTACT-HBcrAg assay with a conventional assay, divided into sample, pretreatment, and assay sections. The illustration at the top of the figure shows a schematic of the iTACT-HBcrAg measurement system. The bottom of the figure contrasts these two assays in terms of sample amount required for measurement, measurement time, and measurement range (sensitivity). *Abbreviations:* HBcrAg, hepatitis B core-related antigen; HBcAg, hepatitis B core antigen; HBeAg, hepatitis B e antigen; anti-HBc, hepatitis B core antibody; anti-HBe, hepatitis B e antibody; ALP, alkaline phosphatase; AMPPO, 3-(2'-spiroadamantane)4-methoxy-4-(3"-phosphoryloxy)phenyl-1,2-dioxetane.

**Clinical utility of iTACT-HBcrAg in the diagnosis of HBV reactivation**

In our initial studies comparing serum HBcrAg and HBV DNA from samples of 13 patients diagnosed with HBV reactivation, iTACT-HBcrAg detected HBV reactivation earlier than HBV DNA in 9 of the 13 patients. Furthermore, a comparison between HBcrAg and high-sensitivity hepatitis B surface antigen (HBsAg) showed that iTACT-HBcrAg detected serum HBcrAg earlier than HBsAg in 7 cases, highlighting its superior sensitivity in early HBV reactivation detection (*5*).

Analysis of serum from one patient using the OptiPrep density gradient ultracentrifugation method revealed that during the early stages of HBV reactivation, HBcrAg primarily detects empty particles derived from cccDNA. In serum samples taken before HBV DNA detection, HBcrAg levels increased, indicating HBeAg presence due to HBV reactivation. The serum analysis after HBV DNA detection showed further increases in HBcrAg, demonstrating the clinical utility of iTACT-HBcrAg in early HBV reactivation diagnosis (*5*).

iTACT-HBcrAg and HBV DNA quantification results show that iTACT-HBcrAg detection could serve as markers for initiating NA treatment in HBV reactivation (Figure 2). We categorized 44 HBV reactivation cases based on serum HBV DNA levels, with 27 cases quantifiable and 17 cases non-quantifiable. HBcrAg was detectable by iTACT-HBcrAg before HBV DNA was quantifiable in 15 of the 27 patients. Of the 11 patients with HBV reactivation and undetectable HBcrAg by iTACT-HBcrAg at HBV reactivation and/or thereafter, 10 had unquantifiable HBV DNA and none developed hepatitis (*15*).

In another of our papers, among 25 HBV reactivation patients, iTACT-HBcrAg became negative in 68% (17/25) after NA treatment. Eight patients who achieved iTACT-HBcrAg loss or anti-HBs seropositivity had no recurrence of HBV reactivation after NA discontinuation, except for one patient who did not have anti-HBs after allogeneic transplantation (*16*).

Detecting HBV reactivation in its early phase and safely discontinuing treatment in patients with post-reactivation is crucial to prevent disease progression and improve patient outcomes. The ability of iTACT-HBcrAg to detect HBV reactivation enables clinicians to start treatment sooner, potentially preventing complications and improve the overall prognosis for CHB patients.

**Clinical utility of the HBcrAg assay in resource-limited regions**

In 2016, WHO called for the elimination of viral hepatitis by 2030 (*17*). The WHO published guidelines in March 2024 outlining NA therapy indications for pregnant women with CHB. In areas where measuring HBV DNA or HBeAg is challenging, all HBsAg-positive pregnant women are eligible for NA therapy, even if they are HBeAg-negative, which may lead to overtreatment.

The HBcrAg-rapid diagnostic test (HBcrAg-RDT),

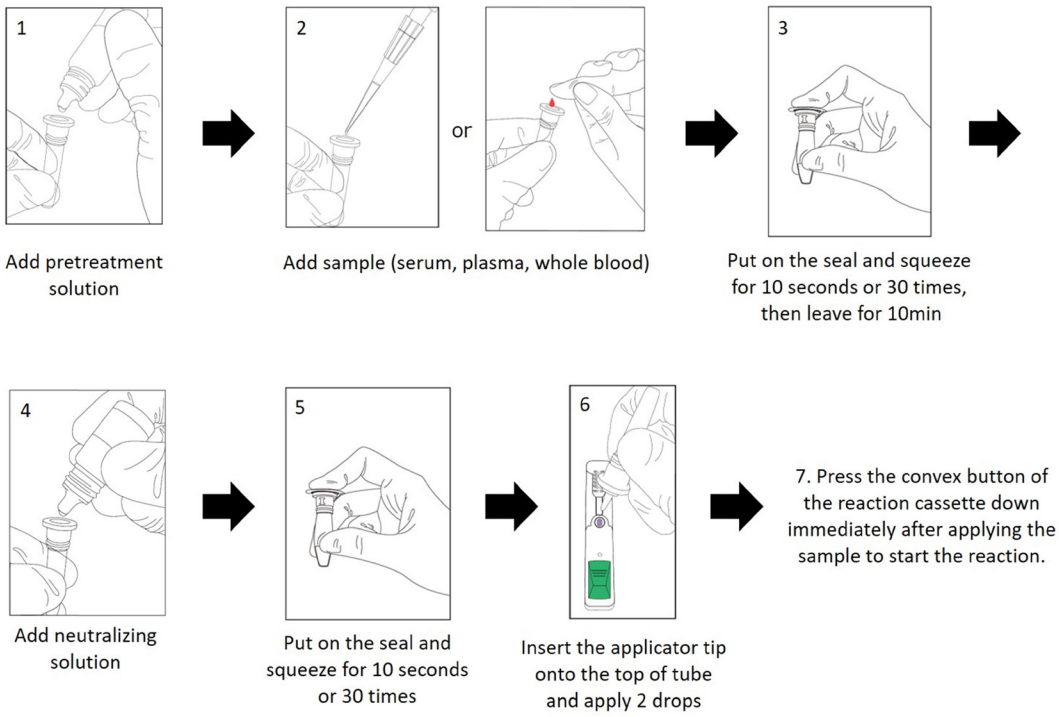


**Figure 2. HBcrAg detection procedure by HBcrAg-RDT.** The measurement process using HBcrAg-RDT is shown in a simplified diagram. HBcrAg-RDT is for the detection of HBcrAg in serum, plasma, whole blood or dried blood spots. This figure is based on Figure 4 in "Fundamental performance and clinical utilities of LumipulsePresto® iTACT® HBcrAg, a novel highly sensitive immunoassay for hepatitis B core-related antigen" by Yagi (*6*). *Abbreviations:* HBcrAg, hepatitis B core-related antigen; HBcrAg-RDT, HBcrAg rapid diagnostic test.

based on immunochromatography, is being developed to quickly identify HBeAg-positive cases. This easy-to-use kit requires no specialized equipment and delivers results within 30 minutes (*18*). Priced at under $15 per assay, HBcrAg provides a cost-effective alternative for diagnosing clinically significant HBV DNA thresholds (≥ 2,000, ≥ 20,000, and ≥ 200,000 IU/mL). Thus, HBcrAg represents an accurate, simple, and inexpensive substitute for HBV DNA quantification in resource-limited settings (*19*). Its low cost, minimal preparation requirements, lack of need for specialized equipment, and rapid turnaround time make it particularly suited for use in these regions (*20*).

Trials conducted in West Africa, Asia, and other developing regions have demonstrated that HBcrAg-RDT is sufficiently sensitive and specific, supporting effective CHB management (*19*). The implementation of HBcrAg-RDT in resource-limited regions facilitates early detection, monitoring, and management of HBV infections, improving patient outcomes. Its cost-effectiveness ensures broader accessibility, increasing public health impact. The success of the HBcrAg assay highlights its potential as a vital tool in the global effort to combat HBV.

## Conclusion

The iTACT-HBcrAg assay is a highly sensitive, fully automated HBcrAg test suitable for outpatient pre-consultation screening. Offering approximately ten times the sensitivity of traditional methods, it has proven effective in managing HBV reactivation cases. The HBcrAg-RDT, in contrast, offers rapid diagnostic capabilities in resource-limited regions, facilitating the prompt identification of cases requiring treatment. The development and implementation of these assays mark significant advancements in the management and prevention of HBV, particularly in settings with limited healthcare resources.

Current HBcrAg assays not only enhance the accuracy and efficiency of HBV diagnosis but also have the potential to significantly impact public health by facilitating early detection and timely intervention. As these advanced diagnostic tools become more widely adopted across regions, the global burden of HBV can be substantially reduced.

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# The process of post-traumatic growth for the main caregivers of patients with Alzheimer's disease

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**Abstract:** Family members caring for individuals with Alzheimer's disease (AD) often experience significant psychological distress, which can lead to mental health issues such as severe depression, post-traumatic stress disorder, and anxiety. We conducted a study to explore the experiences of 18 primary caregivers of AD patients through semi-structured in-depth interviews. The study identified four key stages of post-traumatic growth (PTG): *i*) the pain period, *ii*) the struggle period, *iii*) the recovery period, and *iv*) the period of positive growth. Additionally, factors that contribute to PTG among caregivers include *i*) strong social support, *ii*) active coping strategies, *iii*) reflection on and understanding of their caregiving experience, and *iv*) future planning. Healthcare professionals should incorporate strategies to promote PTG in clinical practice to effectively support caregivers.

***Keywords*:** post-traumatic growth, Alzheimer's disease, primary caregiver

Alzheimer's disease (AD) is a debilitating condition that leads to a gradual decline in cognitive function and the ability to perform daily activities, ultimately imposing a significant burden on society and the economy (*1*). Family members who care for individuals with AD often experience substantial psychological strain, resulting in mental health issues such as severe depression, post-traumatic stress disorder, and anxiety (*2,3*). Post-traumatic growth (PTG) refers to the positive changes that can occur following a traumatic event (*4*). Previous studies have shown that caregivers of AD patients face significant mental, physical, and financial challenges (*2,3,5*). As AD progresses, patients lose their ability to care for themselves, which can deeply affect the physical and emotional well-being of their caregivers and ultimately influence the quality of care provided. Given the increasing number of AD patients and the associated disease burden, study of the PTG experienced by primary caregivers is crucial to enhancing the quality of care.

A study was conducted from a positive psychology perspective to explore the process of PTG and the experiences of primary caregivers of patients with AD in order to provide insights on how to effectively harness caregivers' PTG experiences to improve the quality of care provided to patients. Participants were 18 primary caregivers of AD patients at five medical facilities in Sichuan Province, China who were identified using purposive sampling from March 2020 to May 2021.

The inclusion criteria were as follows: *i*) the primary caregiver of an AD patient, responsible for the majority of caregiving tasks, which could include the patient's children, spouse, friends, or other relatives; *ii*) age ≥ 18 years; *iii*) daily caregiving time ≥ 4 hours, with at least 3 months of direct care experience; *iv*) living with the patient; *v*) alert and oriented, able to communicate, and able to understand this study; *vi*) informed consent and voluntary participation. Exclusion criteria included: *i*) caregivers of patients with other serious diseases and *ii*) paid caregivers, such as nannies.

**Four major themes and their key characteristics**

The process of PTG for primary caregivers of AD patients was explored through semi-structured in-depth interviews. Findings revealed the following four major themes and their key characteristics:

*i*) *Period of Pain*: Upon learning of the diagnosis, caregivers often experience an emotional period of pain, where their beliefs and worldviews are shaken. They struggle with feelings of helplessness and guilt, especially in managing the patient's condition and coping with the emotional toll. Common challenges include handling medications, dealing with patients' refusal to accept their condition, and the financial strain of long-term care. As one caregiver shared, "It's very stressful...

there is another family member with the same condition, and I have to take care of both of them". Guilt and self-blame were also prevalent, as caregivers questioned whether they could have prevented or better managed the illness.

*ii*) *Period of Struggle*: In this stage, caregivers begin to accept the reality of the disease. Despite the challenges, many increase their caregiving role and reflect on their experiences, finding strength in adversity. Caregivers often seek professional help or focus on non-drug interventions, such as diet and exercise, for the patient. Spiritual comfort also becomes a key source of motivation during difficult times.

*iii*) *Period of Recovery*: During the recovery phase, caregivers reflect on their lives and develop a deeper sense of purpose in their caregiving role. They begin to focus on the present moment. As one caregiver explained, "When he passes away one day, our lives will lose a huge part of their meaning". Social support is crucial, with caregivers who received help from family or friends feeling more confident and motivated. As one caregiver shared, "My brothers provide financial assistance and visit him during major holidays". Caregivers also prioritize their physical health, recognizing that their well-being is vital to providing quality care. As one caregiver said, "I can't be the first to go down – who will she rely on in the future?"

*iv*) *Period of Positive Growth*: In this stage, caregivers demonstrate resilience with a more active and positive attitude, reflecting on their growth as they manage caregiving responsibilities. They develop a deeper understanding of humanity and life. Caregivers are also willing to offer support and share their experiences with others facing similar challenges. Focused on providing the best care for patients, they actively seek opportunities to enhance their caregiving skills through training and education.

**Factors facilitating PTG**

*i*) *Social Support*: Higher levels of social support reduce negative emotions and increase the likelihood of adopting positive coping strategies, leading to a better quality of life and a greater appreciation of caregiving (*6,7*).

*ii*) *Active Coping*: Active coping enhances immunity and helps caregivers shift their perspectives, improve their cognitive function, and alleviate their caregiving stress (*8,9*).

*iii*) Reflection on Caregiving: Reflecting on caregiving experiences allows caregivers to gain new perspectives, reduce feelings of helplessness and foster personal growth.

*iv*) *Planning for the Future*: Caregivers who set goals, such as improving caregiving skills or seeking professional support, demonstrate greater adaptability in managing caregiving challenges.

Despite immense challenges, caregivers can experience positive psychological changes that enhance their resilience and caregiving abilities. Healthcare professionals should integrate strategies to foster PTG in clinical practice, ensuring caregivers receive the support necessary to improve their well-being and the quality of care they provide to AD patients.

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LETTER

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# Post-COVID-19 era trends in foreigners undergoing a complete medical examination in Japan: A single-center analysis of inbound medical care

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**Abstract:** In the post-COVID-19 era, inbound medical care in Japan adapted to the growing demand for high-quality and precise healthcare. One form of this care is a complete medical examination, which has gained significant popularity among foreign residents of Japan and foreign visitors to Japan. From 2021 to 2024, 787 individuals from 27 countries underwent a complete medical examination at our facility. The annual growth rate in foreign residents undergoing a complete medical examination was 64% (2022 *vs*. 2021), 22% (2023 *vs*. 2022), and 10% (2024 *vs*. 2023); a notable proportion of those individuals were originally from China. These findings underscore the need for Japan's medical care to evolve in response to the diverse needs of an international clientele, highlighting the importance of tailored healthcare solutions in a globalized context.

***Keywords*:** complete medical examination, foreign residents, inbound medical care, comprehensive checkup, post-COVID-19 era

A complete medical examination (in Japanese called Ningen Dock) (*1*) is a comprehensive checkup (*2*) that is performed in Japan to detect diseases early and maintain health. Our facility (Medical Examination Center, Hospital of the National Center for Global Health and Medicine) seeks to become an international facility for complete medical examinations. To achieve this goal, our facility needs to continue to engage in three efforts.

First, the concept of a complete medical examination needs to be spread around the world through papers and academic conferences. Second, our facility needs to interact with foreigners. Third, our facility needs to accept foreign residents of Japan for a complete medical examination (foreign residents) and inbound visitors undergoing such an examination (inbound visitors).

In accordance with that philosophy, we regularly publish papers (*3-5*) on the tests and examinations that comprise a comprehensive checkup. Moreover, we continually welcome and accommodate visiting delegations from overseas and conduct facility tours. In order to broaden our international appeal, we need to inform foreigners about the concept of a complete medical examination and explain how Japan can meet those healthcare needs of foreigners.

Before the COVID-19 pandemic, our facility accepted many inbound visitors wishing to undergo a complete medical examination; at the time, we were too busy dealing with inbound visitors, so we were unable to keep statistics on foreign residents of Japan who wished to undergo such an examination. Therefore, we started to keep statistics on foreign residents wishing to undergo a complete medical examination as inbound visitors decreased due to COVID-19.

In order for a complete medical examination to spread internationally, trends in foreign resident undergoing a complete medical examination at our facility are as important as trends in inbound visitors undergoing a complete medical examination. Here, we have compared the data from 2021, 2022, 2023, and 2024. In total, 787 people from 27 countries visited our facility (Figure 1).

Since 2021, the annual rate of the increase in all individuals undergoing a complete medical examination has been 14% (2022 compared to 2021), 21% (2023 compared to 2022), and 2% (2024 compared to 2023), while the increase in the rate of foreign residents undergoing such an examination has been 64% (2022 compared to 2021), 22% (2023 compared to 2022), and 10% (2024 compared to 2023). As is evident, there has been a notable increase in foreign residents undergoing a complete medical examination. This is believed to be due to our facility's active acceptance of foreigners. The increase in foreign residents undergoing a complete medical examination mainly involves Chinese, with a rate of increase of 93% (2022 compared to 2021), 26%

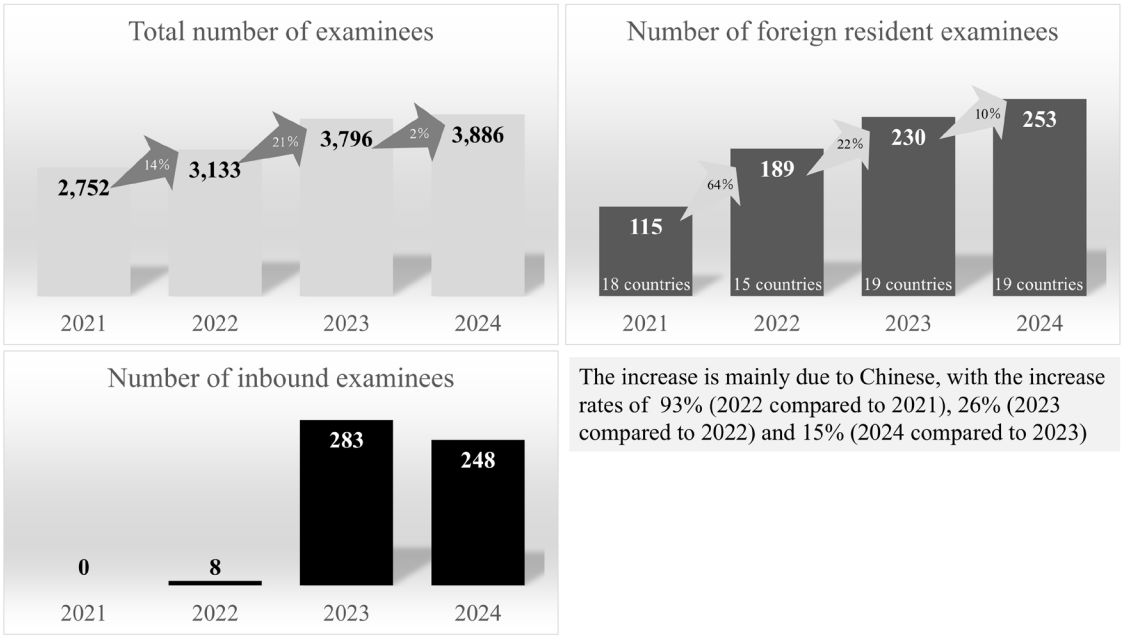


**Figure 1. The number of individuals undergoing a complete medical examination at the Medical Examination Center, Center Hospital of the National Center for Global Health and Medicine, and the annual rate of the increase in individuals undergoing such an examination from 2021 to 2024.** The arrow indicates the annual rate of the increase.

(2023 compared to 2022), and 15% (2024 compared to 2023). This is presumably due in part to the outflow of Chinese to foreign countries. By year and country, foreigners from 18 countries visited our facility for complete medical examination in 2021, foreigners from 15 countries did so in 2022, foreigners from 19 countries did so in 2023, and foreigners from 19 countries did so in 2024. About 30% of the foreigners living in Japan required language assistance. The number of foreigners is expected to increase in Japan, so language assistance in medical settings is also a challenge for the future. The annual rate of the increase (%) = (number this year - number last year) / number last year.

Next, let's look at the characteristics of foreign residents of Japan who underwent a complete medical examination. Forty-one percent of Japanese females underwent a complete medical examination; in comparison, 48% of female foreign residents underwent a complete medical examination. In general, females are more health-conscious, so the percentage of Japanese females undergoing a complete medical examination would be on par with that percentage or slightly higher. In fact, however, more Japanese males underwent a complete medical examination.

Foreign residents who underwent a complete medical examination were younger, on average, than Japanese who did (46.8 *vs*. 55.1, T.TEST: $p < 0.01$). Moreover, about 40% of foreign residents underwent repeated examinations (about 65% of Japanese did so). Only in the last few years has the concept of "a complete medical examination" gained popularity among foreigners in Japan. If the current health-conscious younger generation continues to undergo a complete medical examination in the future, the average age gap between Japanese and foreigners may decrease. The rate of repeated examinations (%) = number of individuals undergoing a complete medical examination at our facility multiple times during a specific period / total number of individuals undergoing a complete medical examination during that period.

Finally, let us look at inbound visitors undergoing a complete medical examination. Inbound visits for a complete medical examination were temporarily suspended due to the COVID-19 pandemic but resumed in January 2023. The tests and examinations performed were also adjusted for inbound visitors, and the most preferred option consisted of a medical examination over two days that comprehensively screened for stomach, colon, lung, breast, and gynecological cancer and metabolic diseases such as diabetes, lipid disorder, and hypertension.

As a result, 521 inbound visitors underwent a complete medical examination at our facility between January 2023 and December 2024. Of these, 394 were Chinese and 127 were Vietnamese. By month, there were fewer inbound visitors in January and February than in other months, which is presumably due to the Lunar New Year holiday. By country, Chinese visitors remain the majority, but the proportion of Vietnamese has increased from before.

As mentioned earlier, we seek to become an international facility for complete medical examinations,

and we would like to continue our worldwide efforts to help maintain health and detect diseases early based on the experience we have gained thus far in dealing with foreigners.

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

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Global Health & Medicine

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*Global Health & Medicine* is (Print ISSN 2434-9186, Online ISSN 2434-9194) is an international, open-access, peer-reviewed journal dedicated to publishing high-quality original research that contributes to advancing global health and medicine, with the goal of creating a global information network for global health, basic science as well as clinical science oriented for clinical application.

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

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

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|---|---|---|---|
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| Reviews | ~8,000 | ~10 | ~100 |
| Mini reviews | ~4,000 | ~5 | ~50 |
| Policy Forum articles | ~3,000 | ~5 | ~30 |
| Communications | ~2,000 | ~2 | ~20 |
| Perspectives | | | |
| Comments | | | |
| Correspondence | | | |
| Editorials | ~1,000 | ~1 | ~10 |
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**Abstract**: ~250 words (Original Articles, Brief Reports, Reviews, Policy Forum); ~150 words (Communications, Editorials, Letters, and News).
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2. Main manuscript
3. Figures
4. Supplementary Data, if appropriate

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2. Abstract
3. Main Text
4. Acknowledgments
5. References
6. Tables
7. Figure Legend
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