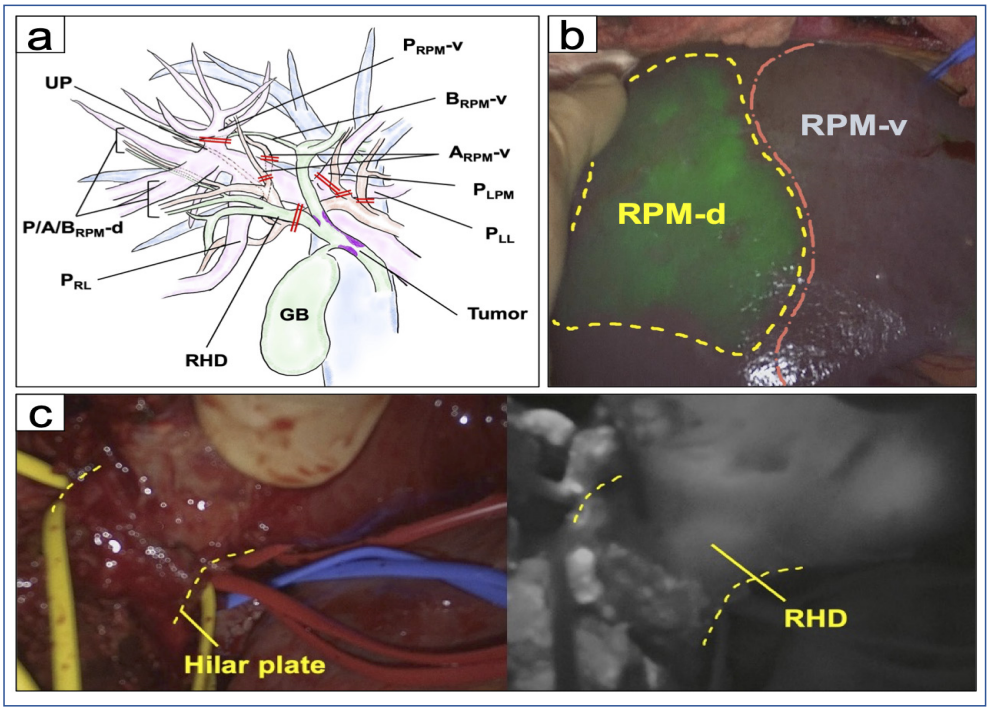
Print ISSN: 2434-9186 Online ISSN: 2434-9194

Global Health & Medicine

Volume 8, Number 4
August 2026



Indocyanine green fluorescence-guided left hepatopancreatoduodenectomy for cholangiocarcinoma with right-sided ligamentum teres (Page 316)

Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English

Global Health & Medicine

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Global Health & Medicine (Print ISSN 2434-9186, Online ISSN 2434-9194) is an international, open-access, peer-reviewed journal, published by the Japan Institute for Health Security (JIHS), which is a national research and development agency in Japan that covers advanced general medicine, basic science, clinical science, and international medical collaboration.

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Editorial and Head Office:

Global Health & Medicine
Japan Institute for Health Security,
1-21-1 Toyama Shinjuku-ku,
Tokyo 162-8655, Japan
URL: www.globalhealthmedicine.com
E-mail: office@globalhealthmedicine.com

Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
Language: English

Global Health & Medicine

CONTENTS

Volume 8, Number 4, 2026

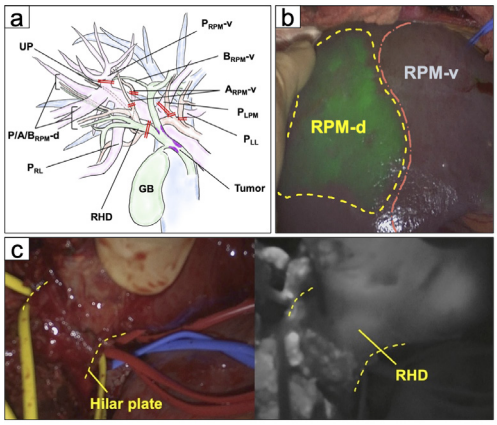
POLICY FORUM

REVIEW

ORIGINAL ARTICLE

CONTENTS (Continued)

COVER FIGURE



Indocyanine green fluorescence-guided left hepatopancreatoduodenectomy for cholangiocarcinoma with right-sided ligamentum teres. (a) Preoperative schematic shows planned resection line (double red line). Right-sided ligamentum teres originates from the right portal branch, with the gallbladder located on its left side. Additionally, the bile duct of the ventral region of the right paramedian sector (RPM) drains into the left hepatic duct, while the portal vein of this region drains into the right-sided umbilical portion. **(b)** Positive staining is performed for the dorsal region of the RPM, and indocyanine green (ICG) fluorescence is observed in the dorsal region of the RPM (dotted yellow line). Liver transection line (orange point-and-line representation) is delineated along boundary between ventral and dorsal regions of the RPM. **(c)** ICG fluorescence imaging in Monochromatic display mode shows right hepatic duct within the hilar plate (dotted yellow line), visualized 95 minutes after intravenous injection of 2.5 mg of ICG. *Abbreviations*: UP, umbilical portion; P/A/BRPM-d, dorsal branch of the right paramedian portal vein/hepatic artery/bile duct; PRPM-v, ventral branch of the right paramedian portal vein; BRPM-v, ventral branch of the right paramedian bile duct; ARPM-v, ventral branch of the right paramedian hepatic artery; PLPM, left paramedian portal vein; PLL, left lateral portal vein; PRL, right lateral portal vein; RHD, right hepatic duct; GB, gallbladder; RPM-d, dorsal region of the right paramedian sector; RPM-v, ventral region of the right paramedian sector. (Page 316)

Global Health & Medicine. 2026; 8(4):233-240.
POLICY FORUM
DOI: 10.35772/ghm.2026.01029

Current status and actions needed for disseminating medical information to the public at National Centers in Japan

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Abstract: Providing reliable medical information *via* the Internet is a pivotal mission for the National Centers (NCs) in Japan. This paper reports on the current state of medical information dissemination *via* the Internet and the management systems at eight departments across six NCs, and explores strategies for optimizing their services of information delivery. We investigated these departments' establishment backgrounds, website content, quality control measures, and dissemination challenges. The rationale for establishing the departments and the types of medical information disseminated varied across the NCs. Regarding information quality control, most departments relied on reference materials with robust supporting evidence, with medical professionals-such as physicians, pharmacists, nurses, and individuals with PhDs—playing a central role in content preparation. However, only three departments had established editorial policies, and just one had a system for incorporating public peer review. The key factors in effective information dissemination, as perceived by practitioners, include identifying the public's needs and fostering accessible information environments. Challenges identified included a shortage of human resources for information development and difficulties adapting to the increasing diversification of information dissemination platforms, such as social media. Although all NCs leverage their specialized expertise to provide information, there is a lack of standardization in the quality control processes. To improve the reliability and accessibility of medical information, it is essential to establish standardized quality control processes, integrate public perspectives into content creation, secure dedicated personnel, and strengthen cross-NC collaboration, particularly in the era of social media and generative AI.

***Keywords*:** information dissemination, quality control, internet, public health communication, national center

1. Introduction

Japan has established the Japan Institute for Health Security (JIHS) and five National Centers for Advanced and Specialized Medical Care and Health Security. National Centers (NCs) include the National Cancer Center Japan (NCCJ), National Cerebral and Cardiovascular Center (NCVC), National Center of Neurology and Psychiatry (NCNP), National Center for Child Health and Development (NCCHD), and National Center for Geriatrics and Gerontology (NCGG). Together, these six institutions, collectively referred to as the six NCs (*1*), address specific disease areas aligned with national health policies and play a crucial role in advancing public health through research, medical technology development, specialized medical care, training for healthcare professionals (*2,3*) and the dissemination of evidence-based medical information

to the public (*4*). In particular, the role of the NCs in disseminating reliable medical information has become increasingly important in shaping public understanding and health-related decision-making, and each NC has independently engaged in information provision, primarily through its website.

With the rapid expansion of the internet and the advent of generative artificial intelligence, the overwhelming volume of online information has become a pressing societal concern. Medical information warrants particular attention, as it significantly influences health-related decisions and treatment choices (*5*). In the United States, fewer than 40% of individuals report accessing health information without frustration (*6*), and in Japan, fewer than half consider themselves capable of assessing its reliability (*7*). The general public, lacking medical expertise, often has difficulty evaluating the quality of this vast amount of information, determining its accuracy, and applying it effectively. To address these concerns, the information dissemination departments of the six NCs have been holding liaison meetings since 2021 to share their experiences in disseminating information to the public and to facilitate dialogue. Through these discussions, a consensus has emerged on the urgent need to enhance the infrastructure for delivering accurate medical information to the public and promoting its appropriate use.

Assessing each center's independent information dissemination efforts is essential for establishing a collaborative foundation for cross-specialty medical information dissemination among Japan's NCs; however, systematic data on these activities are currently lacking. This paper reports on the current status of medical information dissemination to the public *via* the Internet, examines the organizational structures of NCs responsible for these activities, and explores optimal strategies for improving information provision while addressing key challenges faced by the NCs. In this paper, the term 'NCs' is used to refer to these six institutions. Although JIHS transitioned out of the traditional NC system in April 2025, we use the term 'NCs' in a broader definition that emphasizes their unified role in national health security (*1*) and the organizational framework at the time of our survey.

2. Data collection and analysis

In April 2024, we conducted an email-based questionnaire survey of eight medical information dissemination departments across the six NCs. The survey aimed to assess the content and quality control measures of the medical information provided through their websites, identify key priorities for information dissemination, and explore perceived challenges.

We analyzed the collected responses using qualitative content analysis to summarize the background of each NC's medical information dissemination department, the types of medical information disseminated to the public, the processes for creating content, editorial policies, and quality control. In addition, we categorized responses regarding the challenges of information dissemination and identified key issues to optimize these activities.

Ethical approval was not required because this survey collected institutional-level information provided by designated representatives of each organization and did not involve patient data or identifiable personal information.

3. Establishment backgrounds of the medical information dissemination departments and overview of public information provision

The rationales for establishing medical information dissemination departments in the NCs varied. We classified them into four categories: (A) departments established in response to the enactment of action plans, or other regulatory measures; (B) those developed as a fusion of national initiatives and the NCs' own initiatives (not directly stemming from policy measures); (C) those created in the wake of disasters; and (D) those developed as unique NC initiatives.

The duration of information provision varied from 7 to 20 years, depending on factors such as the timing of regulatory implementation, the occurrence of disasters, and the independent implementation of measures (Figure 1). This section summarizes the backgrounds of the establishment of medical information dissemination departments at each center. The purpose and overview of providing information to the public, as well as the number of page views based on the established background, are shown in Table 1.

3.1. Established in response to action plans by the Ministry of Health, Labour, and Welfare

This category includes the NCCJ's Cancer Information Service (*8*), the JIHS's Hepatitis Information Center (*9*), the JIHS's Diabetes and Metabolism Information Center (*10*), and the JIHS's Antimicrobial Resistance (AMR) Clinical Reference Center (*11*).

NCCJ: Cancer Information Service

In 2005, the Ministry of Health, Labour, and Welfare (MHLW) developed the Cancer Control Headquarter in order to promote multidisciplinary activity for comprehensive cancer control, and launched the Action Plan 2005 for Promotion of Cancer Control (*12,13*). This indicated the need to provide information to patients and their families, leading to the establishment of the Cancer Control Information Center (now the Institute for Cancer Control). In October 2006, the "Cancer Information Service" website began providing information on cancer and its treatment to patients and their families.

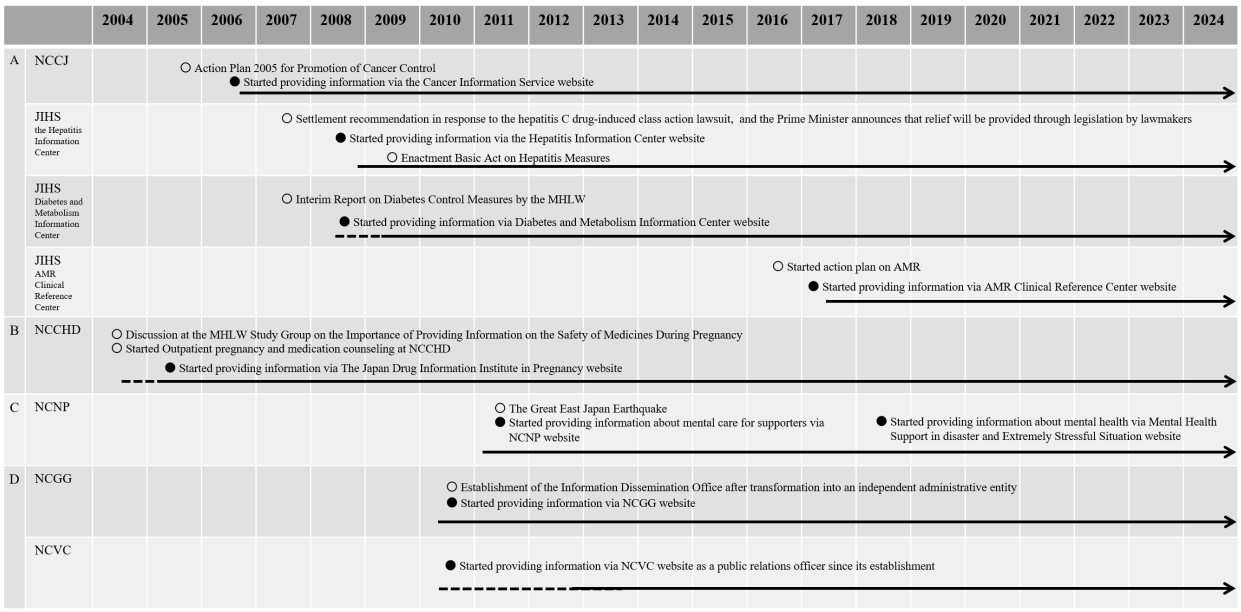

Figure 1. History of the establishment of the Medical Information Dissemination Department. *Notes*: ○: Events that are the trigger or basis for the information. ●: When to start providing information. *Abbreviations*: AMR, Antimicrobial Resistance; JIHS, Japan Institute for Health Security; MHLW, the Ministry of Health, Labour, and Welfare; NC, National Center; NCCJ, National Cancer Center Japan; NCCHD, National Center for Child Health and Development; NCGG, National Center for Geriatrics and Gerontology; NCNP, National Center of Neurology and Psychiatry; NCVC, National Cerebral and Cardiovascular Center.

JIHS: Hepatitis Information Center

The Hepatitis Information Center was established in 2008 to promote the standardization of hepatitis care and to further improve the medical standard nationwide. The Center collaborates with a total of 72 Regional core centers in 47 prefectures throughout Japan. The Center is in charge of accomplishing three important missions: *i*) to provide information on hepatitis care, *ii*) to facilitate information sharing among the regional core centers, and *iii*) to train medical staff, hepatitis medical care coordinators, and counselors who are involved in hepatitis care. The main mission of the center had been reviewed in 2016 to work closely with the regional core centers, strengthen the full network for liver disease care, and make recommendations regarding hepatitis care based on their activities.

JIHS: Diabetes and Metabolism Information Center

In 2007, MHLW issued the "Interim Report on Diabetes Countermeasures", which emphasized information dissemination. In 2008, the Diabetes Information Center was established within the JIHS to provide information on diabetes pathology, diagnosis, and treatment.

JIHS: AMR Clinical Reference Center

In 2016, the Japanese government formulated a national action plan for AMR. In April 2017, the AMR Clinical Reference Center was established within the JIHS to provide information. In September 2017, a public information website was launched, providing information on infectious diseases and drug-resistant organisms.

3.2. Developed from a combination of MHLW initiatives and NC initiatives

NCCHD: The Japan Drug Information Institute in Pregnancy

The Japan Drug Information Institute in Pregnancy (*14*), part of the NCCHD, is classified in this category. In 2005, the MHLW discussed the importance of providing drug safety information during pregnancy. Although the NCCHD had already started an outpatient pregnancy and drug counseling service in 2003, its efforts coincided with the MHLW's initiative, leading to the establishment of the institute in October 2005. Since then, the NCCHD has provided information on medications administered during pregnancy and lactation.

3.3. Developed in the wake of disasters

NCNP: Mental Health Support during Disasters and Extremely Stressful Situations

Mental Health Support during disasters and Extremely Stressful Situations at the NCNP (*15*) falls into this category. Between March and November 2011, following the Great East Japan Earthquake, the NCNP launched and maintained the Tohoku Mental Health Information page on its website. This platform provided guidelines, manuals, activity tools, brochures, and links to related websites to support mental health care providers. In

Table 1. The purpose and outline of information provided by National Centers

Category/NC	Purpose of providing information/ outline of information provided	PV/month
A		
NCCJ	<Purpose> To provide the public with reliable, easy-to-understand, and useful cancer information to support better decision-making by encouraging patients, families, and others to seek further information and take the following actions. <Outline> Different types of cancer, treatment, daily life, medical care, hospitals, cancer statistics, and local cancer-related activities.	4,000,000
JIHS the Hepatitis Information Center	<Purpose> To widely disseminate accurate information to further promote the equalization of hepatitis treatment and the improvement of medical standards nationwide, as the role of the Hepatitis Information Center in accordance with the Basic Act on Hepatitis Measures and the Basic Guidelines. <Outline> Liver diseases, hepatitis viruses, various subsidy programs, information on medical institutions that commission hepatitis virus tests and medical specialists.	390,000
JIHS Diabetes and Metabolism Information Center	<Purpose> To provide evidence-based information to the public and healthcare professionals in order to prevent the development of diabetes and its complications. <Outline> Diabetes, lifestyle and medical care, medical institutions, and statistics.	400,000
JIHS AMR Clinical Reference Center	<Purpose> To provide the public with information on drug resistance, its countermeasures, and the proper use of antimicrobial agents in accordance with the Action Plan for Counteracting Drug Resistance (AMR) formulated by the government. <Outline> Basic knowledge about drug resistance, the difference between bacteria and viruses and antimicrobial agents, efforts based on the Action Plan for AMR Countermeasures (introducing examples of efforts in various parts of Japan), and the publication and provision of educational materials.	110,000
B		
NCCHD	<Purpose> To provide information on the procedures for consultation with the Japan Drug Information Institute, as well as information on lactation and medications. <Outline> Since most of the specific information on pregnancy and medications is sensitive, the content provided is very brief and the website serves as an entry point for consultation.	180,000
C		
NCNP	<Purpose> To provide mental health care, research, training, and support in the context of disasters. <Outline> About mental health care, research, training, and support related to disasters, a website was created to disseminate information and provide guidelines, manuals, activity tools, brochures, and other information related to mental health care for support.	6,000*
D		
NCGG	<Purpose> • Dementia Portal: To provide information to the public by consolidating dementia-related information disseminated by the NCGG. • Health and Longevity Navigator: To provide easy-to-understand explanations of the symptoms that are of concern as aging. • The Integrative Medicine Information Site: To provide information on the safety and efficacy of various therapies that can be combined with modern Western medicine, whether effective or not, and that are currently available. <Outline> • Dementia Portal: A collection of frequently asked questions about dementia and points to consider when caring for a person with dementia, *etc*. • Health and Longevity Navigator: Symptoms that are of concern as aging. • The Integrative Medicine Information Site: About evidence-based information to help people consider how to approach and use complementary and alternative therapies, including folk remedies	670,000**
NCVC	<Purpose> To provide the public with easy-to-understand explanatory information on major diseases related to cardiovascular diseases, their causes, and treatments, as part of efforts to overcome cardiovascular diseases. <Outline> The causes and treatments of major diseases related to the circulatory system, how to respond to certain golden symptoms and test results, and information on nutrition, diet, and therapeutic drugs.	220,000

Notes: *PV increase when a disaster occurs; at the time of the Noto Peninsula earthquake in January 2024, the number of monthly PV was 20,000. **Combined PV of other NCGG sites for medical professionals and researchers. *Abbreviations*:AMR, Antimicrobial Resistance; JIHS, Japan Institute for Health Security; NC, National Center; NCCJ, National Cancer Center Japan; NCCHD, National Center for Child Health and Development; NCGG, National Center for Geriatrics and Gerontology; NCNP, National Center of Neurology and Psychiatry; NCVC, National Cerebral and Cardiovascular Center; PV, Page Views.

December 2011, the NCNP established the "Disaster Mental Health Information and Support Center" as a project commissioned by the MHLW to provide mental health care measures, conduct research, provide training, and offer disaster-related support. Upon completing the commission in 2018, the center was renamed the "Stress and Disaster Mental Health Information and Support Center". The center has since expanded its scope to include various traumas and severe stressors beyond disasters and continues to provide valuable information.

3.4. Developed as a unique NC initiative

The NCGG and NCVC fit into this category, in which information dissemination was primarily the responsibility of the public relations department rather than a dedicated information dissemination department.

NCGG: Dementia Portal, the Healthy Longevity Navi, and the Integrative Medicine Information Site.

Following the establishment of the information dissemination office after its transformation into an independent administrative entity in 2010, the NCGG has continued to disseminate information through the Dementia Information Portal (*16*), the Healthy Longevity Navi (*17*), and the Integrated Medicine Information Site (*18*).

NCVC: Learn about Cardiovascular Disease

At its establishment, the NCVC operated a Learn about Cardiovascular Disease website (*19*) as the public relations section of the general affairs department for information dissemination. Since 2022, it has been providing information as the planning and management department's public relations and planning office.

4. Variability in organizational structure, editorial policies, and quality control systems across NCs

The organizational structure for creating medical information varies across the departments within the NCs. Some departments have no full-time staff, while others have staff with concurrent appointments. Regarding professional qualifications, seven departments were staffed by individuals licensed as physicians, nurses, or pharmacists, while one department had staff without such licenses. In terms of academic backgrounds, five departments had staff with doctoral or master's degrees.

Concerning editorial policy and quality control in the preparation of information, three institutions reported having an editorial policy or equivalent, while two institutions have an editorial board. Three institutions have standards for reference materials used in content creation, while four institutions have a system for peer review of manuscripts by experts. One institution has a system for patient/public review of manuscripts, while six institutions respond to inquiries (Table 2).

In the information dissemination departments of each NC, information is prepared by staff with medical certifications and degrees using evidence-based reference materials. However, some departments lack a clearly defined policy for information preparation and may not have a peer review system. The content, target audience, and context in which the information is needed vary according to each NC's area of expertise.

5. Key challenges in medical information dissemination by NCs

The challenges identified by NCs can be grouped into three domains: staffing shortages and limited specialized expertise; funding restrictions and sustainability; and accessibility, dissemination channels, and evaluation of effectiveness.

5.1. Staffing shortages and limited specialized expertise

Regarding staffing shortages, respondents noted a lack of specialists, with few staff members possessing expertise in information dissemination and behavioral economics. In addition, there are staff shortages relative to the volume and scope of work. For example, some departments lack full-time staff, and while clinical staff experience is important for creating content that meets the needs of patients and families, their demanding clinical workload prevents them from spending sufficient time on information dissemination.

5.2. Funding restrictions and sustainability

Concerning financial resources, respondents noted that a dedicated budget is not always available. The allocation of funds remains unclear, and even when a budget for information dissemination exists, it may not be utilized to hire staff for this purpose. To ensure the dissemination of accurate medical information, it is crucial to first determine the minimum required expertise, staffing levels, and budget necessary to support these roles.

5.3. Accessibility, dissemination channels, and evaluation of effectiveness

Regarding access to information, it has been emphasized that diversifying information delivery methods is essential. Incorporating universal design principles is vital to ensure that public information is accessible through a variety of channels. To achieve this, NC information dissemination departments must adapt to rapidly evolving information access methods and implement flexible, prompt measures. For instance, leveraging social media, which is widely used across generations, to disseminate information requires timely and flexible responses. In addition, practical strategies for directing visitors to websites and methods for measuring and evaluating the effectiveness of information dissemination are needed.

6. Policy implications and future directions for public medical information dissemination from Japan's NCs

This paper highlights critical challenges in public medical information dissemination in Japan, drawing on questionnaire responses from staff at the NCs'

Table 2. Structure, editorial policy, and quality control in the production of medical information at National Centers

NC	Number of staff[1]	Number of people who have medical license				Staff degrees[2]			Availability of editorial policy and editorial board		Criteria for reference	Manuscript peer review system/user feedback		
		MD	RN	Ph	No license	Ph.D.	Master	Others	Policy	Editorial board		Expert	Patient/Public	Inquiry response
NCCJ	12	1	4	1	6	2	5	5	●	●	●	●	●	●
JIHS the Hepatitis Information Center	6	4	0	0	2	4	0	0						●
JIHS Diabetes and Metabolism Information Center	8	3	3	1	1	2	1	4	●	●	●	●		●
JIHS AMR Clinical Reference Center	5	2	0	0	3	0	0	0			●	○		●
NCCHD	12.5	6	0	1.5	5	3	N/A	N/A	○			●		●
NCNP	6	4	0	0	2	N/A	N/A	N/A						
NCGG	5	0	0	0	5	0	0	5						●
NCVC	5	1	0	0	4	1	0	4						

Notes: [1]Listed as indicated in the answer or by adding the number of persons listed in the qualifications held by the staff. [2]Listed as indicated in response. Includes concurrent appointments. Qualifications and degrees are duplicated. ●: Available. ○: Some internal standards exist, but there are no explicit requirements.. *Abbreviations*: AMR, Antimicrobial Resistance; JIHS, Japan Institute for Health Security; MD, Medical Doctor; N/A, Not applicable; NC, National Center; NCCJ, National Cancer Center Japan; NCCHD, National Center for Child Health and Development; NCGG, National Center for Geriatrics and Gerontology; NCNP, National Center of Neurology and Psychiatry; NCVC, National Cardiovascular Center; Ph, Pharmacist; Ph.D., Doctor of Philosophy; RN, Registered Nurse.

information dissemination departments. We identified significant structural barriers, including the absence of established content creation protocols, funding constraints, human resource shortages, and difficulties in adapting to rapidly evolving technologies. While the NCs have made progress in providing information on key diseases related to healthcare policies (Table 1), challenges remain in meeting the dynamic needs of users and society. Consequently, these findings suggest that disseminating medical information to the public should be viewed not merely as an institutional communication activity, but as a foundational element of health policy. Providing medical information to the public requires translating specialized knowledge into plain language and formats understandable to non-experts while reflecting the perspectives of intended audiences. This, in turn, calls for collaboration across disciplines, including disease specialists, medical information creators, and behavioral science experts. In addition, the diversification of information channels demands that NCs remain responsive to evolving information environments. Given the limits of any single NC, cross-NC collaboration is needed to develop a system that supports diverse populations and situations.

6.1. Establishing shared quality standards and sustainable governance

To address these challenges, we propose three strategic priorities. First, NCs should strengthen content quality and consistency by establishing shared quality control standards comparable to the Healthy People 2020 web quality benchmarks (*20*) and National Health Service (NHS) guidance (*21*). Japan currently lacks a unified national framework comparable to established content governance standards and guidance used in other settings, such as NHS guidance, for quality control of public medical information. To improve the quality of medical information provided to the public in Japan, NCs should consider developing national-level quality control standards for medical information in line with international discussions on online health information quality and content governance (*e.g.*, clear editorial policies, transparent citation of evidence sources and update dates, and defined expert and patient/public review procedures) and promote their adoption across NCs.

Second, NCs should establish a structured mechanism to incorporate public perspectives into content development (*e.g.*, patient/public review panels and user feedback loops). Meaningful public engagement across different levels of healthcare has been recognized as a promising pathway toward improving the quality of care (*22*). Public involvement in developing health information can help ensure that materials reflect users' needs, questions, and perspectives, thereby improving their relevance, understandability, and usability for

intended audiences (*23*). This approach aligns with World Health Organization's concept of health-literate systems that support and strengthen individual health literacy (*24*), as well as NHS guidance emphasizing user needs (*21*). This approach would emphasize accessible, evidence-based, clinically safe, and user-centered medical information. Such mechanisms may also help NCs respond effectively to emerging dissemination channels, including social media.

Third, NCs should strengthen sustainable capacity by securing dedicated human and financial resources. Furthermore, they must foster multidisciplinary collaboration to translate specialized knowledge into understandable, user-centered information, drawing on expertise from disease specialists, medical information creators, and behavioral science. Such collaboration is essential to address the complex, interconnected nature of stakeholders in health literacy (*24*). Given the limits of what any single NC can provide, cross-NC collaboration may be particularly valuable—not only for sharing knowledge and best practices, but also for jointly building a sustainable system for the dissemination of public medical information. Currently, the medical information dissemination departments of each NC in Japan independently produce and disseminate medical information. By first establishing a collaborative framework among these NCs to share medical information across disease categories and then organizing interdisciplinary teams that include experts in communications and behavioral science, the quality of public medical information in Japan can be expected to improve. Future consideration could be given to mechanisms such as pooled funding, shared communication specialists, and common platforms for developing, disseminating, evaluating, and updating public medical information across NCs.

6.2. Sustaining trusted medical information in the age of generative AI: The role of NCs

Generative AI may intensify health misinformation by producing content that appears fluent, professional, and evidence-based, even when it is inaccurate or insufficiently grounded. Generative AI can increase the volume, speed, and perceived credibility of health misinformation, while responses to such risks are still evolving (*25*). In this context, authoritative sources of public medical information are increasingly important. Public trust has been identified as central to mitigating health misinformation, particularly for health authorities and governmental institutions that must build such trust systematically (*26*). Although NCs cannot directly control all AI-generated outputs, they can serve as trusted public medical information infrastructures and reference sources in the era of AI. NCs provide accessible, evidence-based public medical information with transparent documentation of authorship, evidence sources, review processes, update dates, and references. In addition, public guidance regarding how to evaluate AI-generated medical information and verify it against trusted institutional sources could support more informed health-related decisions. Cross-center standards for quality assurance, timely updates, expert review, accessibility, and AI-era health information literacy will be essential for sustaining a trustworthy public health information ecosystem.

7. Conclusions

To enhance NC-based public medical information dissemination and contribute to public health, it is imperative to address shortages in human and financial resources, maintain agility to adapt to an evolving information environment, and establish a collaborative foundation across NCs. Strengthening these elements will help ensure that reliable public medical information functions as a foundational element of health policy. In the era of social media and generative AI, such efforts are increasingly important for maintaining a trustworthy public medical information ecosystem.

Acknowledgements

The findings reported in this manuscript were previously presented at The 83rd Annual Meeting of Japanese Society of Public Health. The authors are grateful to Ms. A. Ishikawa, Dr. Y. Saito, Dr. S. Ogata for their collaboration and advice.

Funding: This work was supported by research projects supported by JH 2024 (National Center for Medical Information Dissemination Infrastructure Development Project) and research projects supported by JH for younger researchers 2024 (Exploratory research for contributing to the creation of an environment for the dissemination of medical information that takes into account the health literacy of the public).

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

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Received March 19, 2026; Revised May 27, 2026; Accepted June 8, 2026.

Released online in J-STAGE as advance publication July 8, 2026.

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Global Health & Medicine. 2026; 8(4):241-247.
DOI: 10.35772/ghm.2026.01049

Rethinking responses to over-the-counter drug overdose among young people in Japan: Toward a low-threshold support architecture

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Abstract: Over-the-counter (OTC) drug misuse and overdose among young people in Japan should be understood not only as a medication-safety issue but also as a public health and youth support issue situated at the intersection of psychological distress, self-harm, suicidality, help-seeking difficulties, digital environments, and fragmented care systems. Current responses, including emergency treatment for acute intoxication, psychiatric assessment, consultation services, school-based prevention, and retail regulation, remain important but often operate after crisis escalation or depend on young people's ability to present themselves through institutionally recognizable forms of help-seeking. In this Policy Forum article, we argue that Japan's response to OTC overdose should be redesigned as a low-threshold support architecture that connects early relational entry points with professional assessment, crisis escalation pathways, interagency collaboration, and safeguards for supporters. We also caution that peer support, while potentially valuable as an accessible first point of contact, should not be treated as a stand-alone intervention. Potential risks, including contagion-related concerns, exposure to distressing self-harm narratives, blurred role expectations, over-reliance on a single supporter, and safety-management failures, require explicit training, supervision, boundaries, and safeguarding protocols. We propose a three-zone framework comprising low-threshold entry points (Zone A), professional medical and interagency backup (Zone B), and sustainability infrastructure for supporters (Zone C). Rather than replacing clinical or regulatory responses, this architecture is intended to connect them with youth-accessible forms of support and to generate testable implementation models for future research.

***Keywords*:** help-seeking, interagency collaboration, continuity of care, community support, self-harm, public health

1. Introduction

Suicide prevention among children, adolescents, and young adults remains a major policy priority in Japan. The Japanese government's annual White Paper on Suicide Countermeasures reported 529 suicides among elementary, junior high, and high school students in 2024, the highest number since national record-keeping began in 1980 (*1*). Against this background, over-the-counter (OTC) drug misuse and overdose have become increasingly visible as problems that intersect with youth distress, self-harm, and difficulty accessing support.

This Policy Forum article uses the term OTC drug misuse to refer broadly to the use of OTC medicines outside their intended dosage, purpose, or pattern of use. OTC drug overdose refers more specifically to ingestion of quantities that may cause physical or psychological harm, whether or not suicidal intent is present. Intentional overdose, self-harm, and suicidality overlap with, but are not identical to, OTC misuse or overdose. We therefore avoid treating OTC overdose as synonymous with attempted suicide, while recognizing that it may occur in a context of self-harm, suicidal ideation, or acute psychological distress.

OTC overdose differs from illicit drug use because it relies on medicines embedded in ordinary daily life. The Ministry of Health, Labour and Welfare identifies cold medicines and cough suppressants as common OTC products misused by young people for psychoactive effects and discussed through social media. Clinical and epidemiological studies describe a broader range of products involved in overdose presentations (*2*-*5*). Their familiarity and legality may lower the psychological barrier to first use, and misuse can remain hidden from family members, schools, and professionals. Kyan *et al*. reported that emergency patients with OTC overdose in Japan were disproportionately young and female (*2*). Shimane *et al*. found that 1.5% of high school students had engaged in OTC drug abuse in the previous year, with school dissatisfaction, long periods without parents at home, and pandemic-related environmental

stress as associated factors (*3*). Digital environments are also part of this ecology: online question-and-answer platforms include inquiries about product choice, dosage, expected effects, anxiety, and withdrawal in relation to OTC overdose (*4*).

The purpose of this Policy Forum article is to integrate available epidemiological, clinical, help-seeking, regulatory, and practice-oriented evidence in order to clarify policy and practice directions for Japan. We ask why OTC overdose cannot be understood as medication management alone, where current responses have made progress and where they remain limited, and how low-threshold support, peer support, professional care, and retail regulation can be connected within a safer support architecture.

2. Why OTC drug misuse and overdose require a broader lens

OTC misuse among young people has four interrelated features. First, OTC drugs are legal, familiar, and readily available, which can make them seem less deviant and safer than illicit substances (*3*). Second, overdose behavior does not always represent a straightforward suicide attempt. It may reflect a wish to regulate overwhelming affect, reduce emotional pain, obtain sedation or sleep, numb affect, escape reality, communicate distress, or make suffering visible to others (*4,6*). These motives may overlap, and even when physical toxicity is limited, the behavior should not be trivialized as merely accidental or experimental. Third, digital environments can amplify both information access and social normalization. People with overdose intent may use online platforms to ask about drug selection, dosage, anticipated effects, and withdrawal (*4*). Such spaces are not simply information sources; they are social contexts in which distress may be recognized, shared, amplified, or normalized. Fourth, OTC overdose is linked with difficulty seeking help. Reviews of youth help-seeking show that shame, fear of judgment, uncertainty about whether one's suffering is serious enough, difficulty identifying where to go, and distrust of adults or services inhibit access to care (*7-10*). Thus, OTC overdose should be understood not only as a pharmacological event, but also as an expression of distress that emerges when words, relationships, and service access have failed.

3. Current responses in Japan: Progress, but uneven reach

Japan has made progress in recognizing OTC misuse and overdose. Emergency medicine has begun to identify OTC overdose as an important clinical issue, with multicenter evidence making the problem visible at a national clinical level (*2*). Prevention research has also shown that OTC drug abuse is a measurable risk among high school students, with implications for drug and mental health education (*3*). National suicide policy has moved toward broadening entry points for young people, including telephone and social media consultation and understandable support information (*1*). Support resources also exist outside formal medical settings, including municipal consultation services, schools, private support organizations, telephone and online services, and youth drop-in spaces. The problem is therefore not that resources are absent, but that they are scattered and unevenly connected. The main achievement of current responses may be visibility rather than early reach: the problem is becoming easier to recognize after overdose has occurred, but remains difficult to address before crisis escalation.

4. Where the current system falls short

The first limitation is concentration on the acute phase. Emergency treatment is essential, but management of intoxication alone cannot adequately address loneliness, trauma, family adversity, suicidal ideation, or repeated self-harm. Stabilization of the body is necessary, but it is not sufficient. The second limitation is fragmentation across systems. OTC overdose intersects with mental health, school health, family support, welfare, and community services. When medical care, schools, municipalities, welfare agencies, pharmacies, and community organizations operate in parallel rather than in connection, support becomes discontinuous in complex cases. Barriers to help-seeking for self-harm should be understood within a broader system rather than as individual reluctance alone (*8*). The third limitation is that many services assume institutionally legible help-seeking. Existing systems often expect young people to present themselves using recognizable language such as "I want help" or "I want treatment". Yet young people may struggle to describe their own state, feel ashamed of asking for support, or endure alone until crisis deepens (*7,9,10*). A system that waits for clear disclosure will miss many of those most in need.

The fourth limitation lies in structural access to OTC drugs. Japan's drugstore environment has expanded substantially, with more than 20,000 stores nationwide and OTC drug sales reaching 1,040,057 million yen in 2025 (*11*). These figures do not demonstrate causality between OTC availability and overdose or suicide. They indicate that OTC products are embedded in a large retail environment that should be considered when designing prevention policies. Responses should therefore examine the access environment shaped by health policy, distribution structures, and retail practices.

The fifth limitation is that disclosure of self-harm or overdose may paradoxically narrow support. A recent Japanese practice-oriented study suggests that when

overdose or self-harm becomes known, some support settings become more hesitant to accept the young person rather than less (*12*). This is critical: the point at which support should expand is sometimes the point at which it contracts.

5. Regulatory and retail-environment dimensions

Policy responses to OTC overdose should include regulatory and retail-environment dimensions as well as psychosocial support. Possible measures include restrictions on quantities sold per purchase, smaller package sizes, blister packaging that slows impulsive ingestion, age-sensitive sales procedures, pharmacist or registered-seller engagement at point of sale, and monitoring of repeated or suspicious purchases across online and in-person channels (*5,13-15*). These measures should not be framed as punitive restrictions on young people, but as environmental safeguards that reduce immediate access to large quantities during short-lived crises.

International examples show that packaging and sales regulation can be part of overdose-prevention policy, although effects vary across settings. In the United Kingdom, legislation restricted pack sizes for paracetamol and aspirin, and subsequent research reported reductions in deaths and liver-transplant registrations related to paracetamol overdose, while also noting the need for cautious interpretation (*13,14*). In Australia, new paracetamol restrictions introduced from February 2025 reduced general-sale pack sizes, reduced unsupervised pharmacy pack sizes, and required larger packs to involve pharmacist supervision (*15*). These examples do not provide a simple template for Japan, where products, retail systems, and misuse patterns differ, but they show that product availability, packaging, and retail workflow are legitimate prevention targets.

In Japan, pharmacists and registered sellers are increasingly expected to play a gatekeeping role (*5*), yet this role is operationally difficult. Brief questioning at point of sale may be ineffective if young people fear reprimand, purchase from multiple retailers, use online channels, or present with ordinary symptoms. Gatekeeping requires more than refusing sales. It should include youth-sensitive communication, non-stigmatizing risk information, clear criteria for pharmacist consultation, mechanisms for repeated purchases, and pathways to low-threshold support when concern arises. Retail regulation and relational support should operate as complementary layers rather than competing approaches.

6. Why low-threshold support matters

In OTC overdose, low-threshold support is important because current systems often require too much from young people at first contact. In this paper, it means support that does not require self-disclosure, formal help-seeking language, or readiness for treatment. It includes outreach, social media consultation, youth-friendly drop-in support, school-adjacent contact, non-stigmatizing pharmacy contact, and relational approaches that begin with connection rather than assessment.

Its significance lies not only in ease of use but in relational safety. For many young people, the first question is not what to say but whether it is safe to stay. Being able to enter a space without being judged, lectured, diagnosed, or immediately disciplined may make further engagement possible. Online help may be valued because it is private, less stigmatizing, and easier to access than conventional services (*10*). Thus, the key issue is not only what support contains but how support begins. Needing support and being able to walk into a formal system are not the same thing.

7. Peer support: Potential contributions, risks, and safeguards

Peer support has been conceptualized as support grounded in mutuality, equality, and shared experience (*16*). In youth mental health settings, it may foster connection, hope, and engagement, although implementation models and organizational supports vary considerably (*17-19*). Its relevance to OTC overdose should therefore be framed as a plausible and practice-informed contribution, not as a proven stand-alone intervention for preventing repeated overdose or suicide.

A Japanese practice-oriented study describes how peer supporters involved in street outreach, social media consultation, and youth place-making deliberately reduce the institutional tone of "consultation" or "support" (*12*). Their strategies include using everyday language, aligning with youth culture through topics such as makeup or nails, avoiding excessive formality, and not pressing immediately for disclosure of overdose. The aim is not to deny risk but to create a relationship in which the young person can remain without feeling judged. These practices show that low-threshold support is not only about where support is offered, but how it is embodied.

At the same time, the evidence base remains limited. Much of the literature on peer support for self-harm and youth mental health is qualitative, heterogeneous, practice-oriented, or indirect. It would therefore be inappropriate to conclude that peer support by itself improves clinical outcomes, prevents suicide, or reduces repeated overdose. A more cautious interpretation is that peer support may facilitate earlier engagement and relational continuity when embedded within supervised systems that provide clinical assessment, crisis intervention, and sustained aftercare.

Potential harms must also be addressed. Peer support around self-harm and overdose may create risks such as contagion-related concerns when methods or experiences are shared without boundaries; exposure to distressing self-harm narratives; blurred role expectations when supporters are treated as clinicians, friends, or crisis responders; over-reliance on a single peer relationship; and delayed professional escalation when supporters hesitate to involve professionals out of fear of damaging trust (*20,21*). These risks do not negate peer support, but they make governance indispensable.

Safeguards should include role descriptions, training in suicide and self-harm risk recognition, protocols for acute intoxication and suicidal escalation, supervision by mental health or public health professionals, documentation rules, privacy and information-sharing procedures, debriefing after high-risk contacts, and explicit limits on availability (*17,20,21*). Confidentiality should be relationally important but not absolute: when there is imminent danger, acute intoxication, abuse, or serious safeguarding concern, supporters need agreed procedures for involving emergency, clinical, welfare, or child-protection services. Peer support is safest when young people know both that they will not be judged and that risk will not be held by one unsupported person.

8. Toward system redesign: A policy and practice framework

What is needed is not separation of low-threshold support, professional care, and retail regulation, but their reconstruction as one connected support architecture. Figure 1 presents a proposed policy and practice framework rather than an evidence-summary diagram. It builds conceptually on the authors' previously published practice-oriented study (*12*),

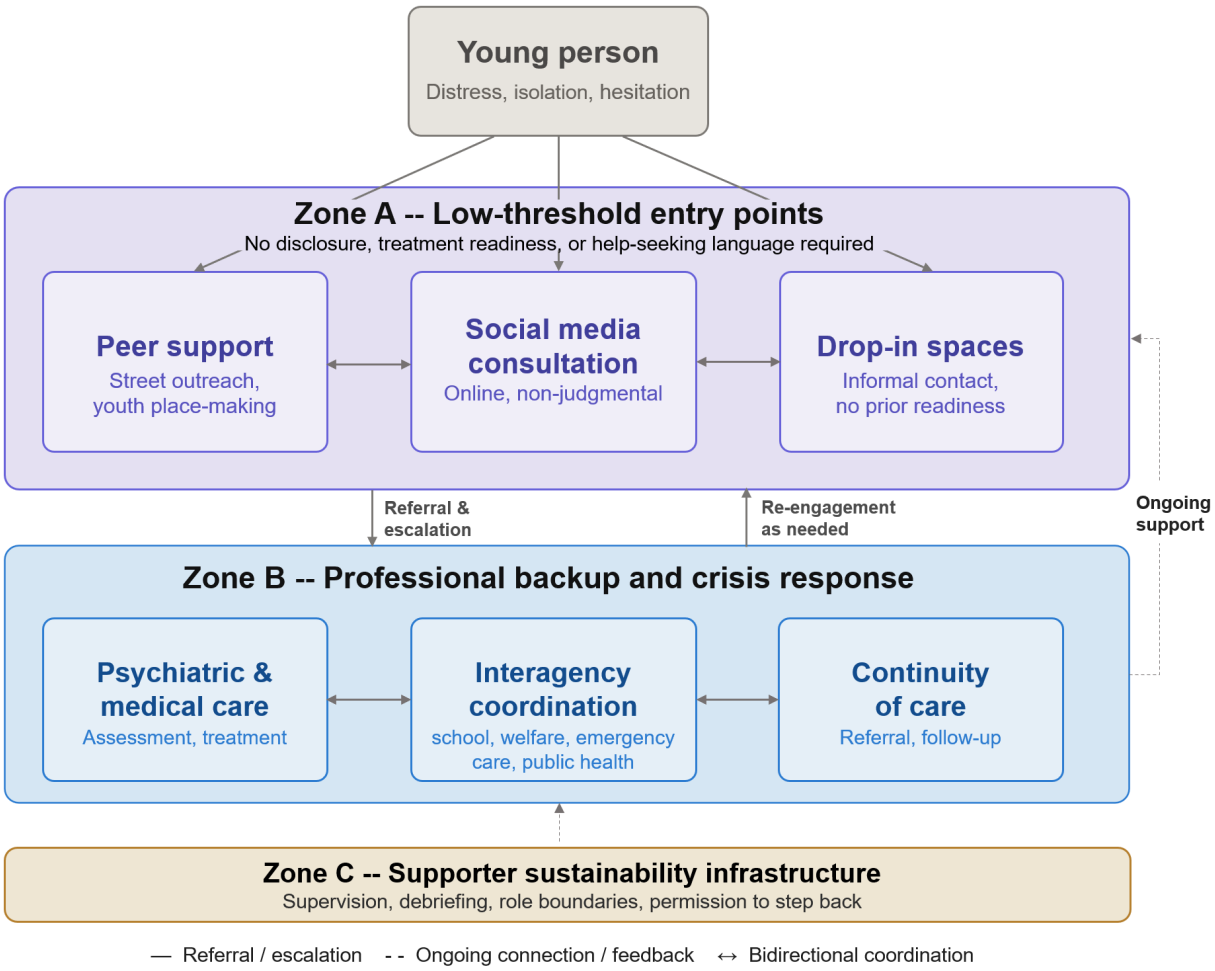

Figure 1. Proposed connected support architecture for OTC overdose among young people. Zone A represents low-threshold entry points focusing on relational safety and early contact, including social media consultation, outreach, youth drop-in spaces, school-adjacent support, and non-stigmatizing pharmacy or retail contact. Zone B represents professional medical and interagency backup, including emergency care, psychiatry, school health, public health, welfare, and child and family services. Zone C represents sustainability infrastructure for supporters, including training, supervision, debriefing, role boundaries, funding, and organizational accountability. Solid arrows indicate referral and escalation pathways when risk increases; dashed and bidirectional arrows indicate continuing coordination, return pathways after crisis care, and feedback for system improvement.

while extending those findings into a broader policy and practice architecture. It is organized into three functional zones.

Zone A comprises low-threshold entry points that should be delivered primarily by non-governmental organizations, private support groups, community-based youth services, and other non-clinical actors: social media consultation, street outreach, school-adjacent counseling, youth drop-in spaces, community organizations, and non-stigmatizing pharmacy or drugstore contact. In Zone A, the main tasks are relational safety, recognition of concern, and maintenance of contact. Zone B encompasses professional medical and interagency backup, including emergency departments, psychiatry, primary care, school health staff, public health nurses, municipal welfare services, child and family services, and addiction or youth mental health services. Escalation should occur when there are signs of acute intoxication, rapidly intensifying suicidal ideation, loss of consciousness or medical danger, repeated overdose in a short period, abuse or exploitation, or inability to maintain safety in the current setting. These thresholds should be written into protocols rather than left to individual intuition.

Zone C represents sustainability infrastructure: training, reflective supervision, case conferences, debriefing, workload limits, role boundaries, funding, and organizational accountability. Supporters should not be expected to absorb repeated exposure to self-harm narratives, online abuse, or life-threatening crises without institutional protection. Movement between Zones A, B, and C should be bidirectional rather than linear. A young person may first encounter support through an SNS message or pharmacy contact in Zone A, require same-day medical assessment through Zone B after an overdose, and later return to a drop-in space or online peer contact in Zone A while professional follow-up continues. Zone C supports this movement by ensuring supervision, lawful and proportionate information-sharing, and organizational learning from repeated breakdowns in care. The goal is not to transfer the young person from one sector to another and end contact, but to prevent every transition from becoming another rupture. Interagency collaboration must therefore be operational rather than aspirational. Emergency departments, psychiatry, schools, public health, welfare services, pharmacies, and community organizations may all act in good faith, but without agreed pathways for communication, role allocation, and information-sharing. Young people can move between services without ever becoming securely connected to any of them.

9. Implications for policy, practice, and research

The policy implication is that OTC overdose among young people should be positioned within broader frameworks of youth suicide prevention, mental health, isolation, school health, and retail safety, not only drug misuse. The direction already signaled in national suicide policy should be more explicitly connected to overdose-responsive pathways (*1*). The practice implication is that some young people need a relationship before they can tolerate assessment. Delayed or hesitant help-seeking should not be read simply as resistance or immaturity. It may reflect shame, distrust, difficulty putting distress into words, or prior traumatic experiences. Risk work has to be embedded within acceptable human contact.

The regulatory implication is that access controls should be designed with young people's help-seeking realities in mind. Smaller package sizes, quantity limits, pharmacist involvement, and online-sales safeguards may reduce immediate access to large quantities, but they will be incomplete if they only block purchase without opening a route to support. A young person prevented from buying a large quantity of OTC medicines still needs somewhere to go, someone to contact, and a system that does not punish disclosure.

The research implication is that the field should move beyond asking whether OTC overdose exists. Epidemiological studies have established its presence, clinical studies have shown its relevance, and practice-oriented work has begun to describe both possibilities and fragilities (*2,3,12*). Systematic reviews suggest that youth peer support may enhance connection, engagement, and hope when implemented with role clarity and organizational support, while peer support and self-help approaches for self-harm require attention to safety, boundaries, and unintended harms (*17-21*). Broader review evidence indicates that self-harm among young people is shaped by interacting risk and protective factors and that engagement with web-based support depends on accessibility and perceived relevance (*22,23*). A recent Japanese case series of vulnerable runaway girls transported to emergency care, often following OTC overdose, further underscores the intersection of repeated self-harm, school absenteeism, and insufficient support systems (*24*).

The next task is to evaluate implementation models that connect low-threshold support with professional care and retail safeguards. Outcomes should include earlier help-seeking, linkage to care, continuity after emergency presentation, repeated overdose, suicidal ideation, young people's perceived safety, and supporter burden. Studies should also examine feasibility, fidelity, cost, training requirements, and unintended harms. Until such evidence accumulates, the proposed architecture should be understood as a policy and practice framework for implementation and evaluation, not as an already validated intervention.

10. Conclusions

OTC drug misuse and overdose among young people

in Japan cannot be explained by availability alone. They emerge at the intersection of isolation, distress, difficulty seeking help, online environments, retail access, and weakly connected support systems. Current responses have improved visibility, but they have not yet become fully reachable, durable, or non-excluding for the young people most at risk. The task ahead is to connect relational strengths of low-threshold support with safety, accountability, and continuity of professional care and preventive potential of retail-environment safeguards. Peer support matters in this architecture not because it can do everything, but because it may become the first place where a young person is able to remain, speak, and be linked onward. Policy and practice must ensure that this first contact becomes a connected path toward support, not another break in care.

Funding: None.

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

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Received April 29, 2026; Revised May 12, 2026; Accepted June 9, 2026.

Released online in J-STAGE as advance publication June 23, 2026.

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Global Health & Medicine. 2026; 8(4):248-252.
POLICY FORUM
DOI: 10.35772/ghm.2026.01075

Late release of World Health Organization governing body documents: Trends in documentation timing at the World Health Assembly and Executive Board and considerations for Member State engagement

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Abstract: Timely access to documentation is essential for meaningful participation in global health governance. At the World Health Organization (WHO), governing body documents for the World Health Assembly (WHA) and the Executive Board (EB) provide the basis on which Member States assess agenda items, consult domestically, and prepare their negotiating positions. In this sense, the timing of document release directly affects transparency, accountability, and quality of decision-making. This study examines trends in documentation timing between 2016 and 2026 using data from the WHO governing body documentation portal. The findings show a clear and sustained shortening of the interval between document release and opening of WHA sessions since 2021, reaching the lowest level observed during the study period. By contrast, timelines for the EB, which were affected during the COVID-19 period, have largely recovered, suggesting that earlier circulation remains feasible in practice. Although this analysis does not directly measure downstream effects, shorter preparation periods may constrain Member States' ability to review materials carefully, coordinate across institutions, and develop negotiation strategies. These constraints may be felt most strongly by countries with limited participation capacities, potentially widening existing disparities in participation. A recent case further illustrates how late document release can affect not only meeting procedures but also depth and coherence of discussions. Despite ongoing WHO governance reforms, the timeliness of documentation has received limited attention. Ensuring earlier circulation and closer adherence to existing timelines would be a practical step toward strengthening transparency, equity, and effectiveness in global health governance.

***Keywords*:** global health governance, global health diplomacy, WHO governance reform, decision-making process, quality of deliberation

1. Introduction

Within the World Health Organization (WHO), governing body documents for the World Health Assembly (WHA) and the Executive Board (EB) form a central part of the decision-making process. They allow Member States to understand agenda items, consult relevant ministries and experts at the national level, and prepare their negotiating positions. WHO plays a distinctive role in the global health architecture, with responsibilities such as norm-setting, international coordination, and responses to public health emergencies. In this setting, documentation is not simply procedural. It shapes how Member States engage in discussions and, ultimately, how decisions are made.

The importance of timing in document circulation is explicitly recognized in WHO rules of procedure, which state that, as a general rule, reports and other documents should be made available at least six weeks before the opening of a session (*1,2*). This is intended to give delegations sufficient time to prepare and to support informed and inclusive deliberations. Timely documentation therefore represents an important operational condition for transparency and accountability in governance (*3*).

In recent years, however, documents have increasingly been issued shortly before meetings. This raises concerns about whether Member States

have adequate time to review materials, coordinate domestically, and engage fully in intergovernmental discussions. This paper examines trends in documentation timing between 2016 and 2026 and considers their implications for governance within WHO, with particular attention to how changing timelines may shape Member State engagement.

2. Empirical trends in documentation timing, 2016–2026

This analysis draws on data from the WHO governing body documentation portal (*4*) to assess timing of governing body documents for WHA and EB sessions between 2016 and 2026. Document release dates were obtained from dates displayed on document webpages within the portal, using the English-language version as reference when multiple language versions were available. To ensure comparability, only even-numbered EB sessions were included because odd-numbered EB sessions, which were held immediately after WHA, typically contain substantially fewer agenda items and associated documents. WHA73 (2020), which was conducted in a virtual and split format due to the COVID-19 pandemic, was also excluded.

Analysis focused on substantive policy documents available to Member States in relation to each governing body session. Excluded document categories included agenda documents, Director-General's addresses, sessional committee reports and other procedural documents, Programme, Budget and Administration Committee (PBAC) reports, draft resolutions and draft decisions, including associated financial and administrative implication documents, and corrigenda. These document types primarily reflect procedural matters, committee deliberations, negotiation outcomes, or administrative processes rather than substantive policy content intended for advance consideration by Member States. Revised documents issued after session opening were excluded because the original version may already have been available before the session, making timing of document availability difficult to assess consistently. Revised documents issued before session opening were included using the publication date of the revised version. Documents without identifiable publication dates were also excluded. After applying these criteria, a total of 1009 documents across 21 meetings were included in the analysis.

The findings indicate a clear shift in documentation timing for the WHA. Between 2016 and 2019, documents were typically issued around one month prior to sessions (Table 1). Since 2021, however, this interval has shortened considerably (Figure 1). The six-week benchmark specified in WHO rules of procedure corresponds to 42 days before opening of a session. Since 2021, WHA documents have been released substantially closer to session opening than this, with

Table 1. Average number of days between document release and the opening of the World Health Assembly (WHA) and the even-numbered sessions of the WHO Executive Board (EB), 2016–2026

Year	World Health Assembly (WHA)				Executive Board (EB)			
	Session	No. of documents*	Mean days before opening	95% CI	Session	No. of documents*	Mean days before opening	95% CI
2016	WHA69	67	30.75	24.52–36.97	EB138	58	34.45	28.73–40.17
2017	WHA70	59	27.98	22.84–33.12	EB140	49	39.43	33.24–45.62
2018	WHA71	42	41.48	35.06–47.89	EB142	35	31.91	25.46–38.37
2019	WHA72	54	33.11	27.93–38.29	EB144	45	43.73	40.35–47.12
2020	WHA73		excluded**		EB146	51	52.31	48.60–56.03
2021	WHA74	51	18.76	15.08–22.45	EB148	46	12.30	9.50–15.11
2022	WHA75	56	17.11	13.40–20.81	EB150	47	29.72	25.04–34.40
2023	WHA76	44	15.95	11.66–20.25	EB152	52	39.63	35.72–43.55
2024	WHA77	30	28.50	22.73–34.27	EB154	52	31.71	27.72–35.70
2025	WHA78	37	13.27	9.33–17.21	EB156	48	27.81	23.04–32.59
2026	WHA79	33	10.91	8.18–13.64	EB158	53	45.15	40.85–49.46

*Analysis was restricted to substantive policy documents and excluded procedural, negotiation-derived, and administrative documents, as detailed in the main text. **WHA73 (2020) was excluded because it was conducted in a virtual and split format during the COVID-19 pandemic.

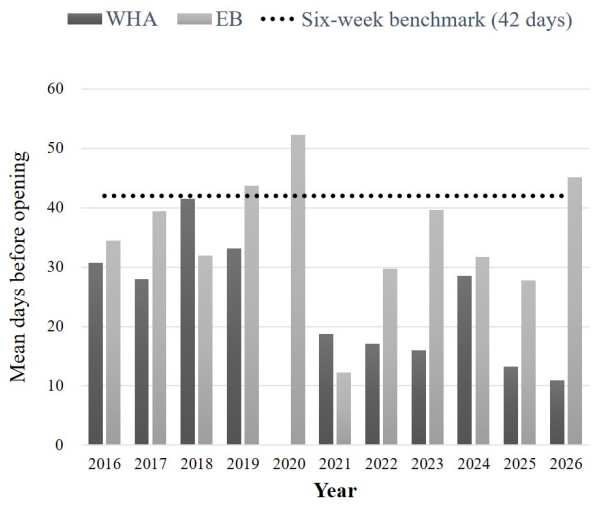

Figure 1. Trend in the average number of days between document release and opening of the World Health Assembly (WHA) and even-numbered Executive Board (EB) sessions, 2016–2026. WHA73 (2020) was excluded due to its virtual and split format during the COVID-19 pandemic. Only even-numbered EB sessions were included because odd-numbered sessions typically contain substantially fewer documents and are therefore less comparable. Analysis was restricted to substantive policy documents and excluded procedural, negotiation-derived, and administrative documents as detailed in the main text. The dotted horizontal line indicates six-week documentation benchmark (42 days) specified in the WHO Rules of Procedure.

lead times falling to 18.76 days for WHA74 (2021) and reaching 10.91 days for WHA79 (2026)—the lowest level observed during the study period.

In contrast, EB documentation shows a different trajectory. Although timelines declined during the COVID-19 period, they have since recovered, reaching approximately 45 days before EB158 (2026). This suggests that timely circulation remains operationally feasible but is not consistently implemented across governing bodies. Divergence in documentation timelines between the WHA and the EB may reflect differences not only in institutional function but also in processes through which consensus is formed. In particular, issues that remain unresolved at the EB level may require additional negotiation among Member States in the lead-up to the WHA, potentially delaying finalization and release of documentation. Conversely, documents prepared for the EB may in some cases be circulated at an earlier stage of policy development, prior to extensive Member State negotiation. While present analysis does not directly test these mechanisms, these observations suggest that institutional and political factors may contribute to differences in documentation timing and warrant further empirical investigation.

3. Implications for Member State engagement

Delays in documentation represent more than an operational issue; they affect how Member States engage in decision-making. National policymaking typically involves multiple stages, including inter-ministerial coordination, expert review, and consultation with domestic stakeholders. These processes take time, and compressed timelines can disrupt them. Implications are also visible in negotiation dynamics. Effective participation depends on the ability to anticipate alternative scenarios and prepare negotiation strategies in advance. Late release of documents constrains such preparation and may increase reliance on Secretariat framing, as effective participation in global health diplomacy depends on advance preparation and strategic positioning (*5*).

These effects are not evenly distributed. Countries with more constrained participation capacities, or smaller delegations are more vulnerable to shortened preparation periods, potentially reinforcing existing asymmetries in influence during negotiations (*6*). This raises concerns not only about efficiency, but also about equity in global governance. The issue has also been raised by Member States in recent WHO governing body discussions, underscoring importance of timely documentation for effective participation.

Recent cases illustrate how implications of delayed documentation can vary depending on context. For example, document A79/8 on the Open-ended Intergovernmental Working Group on the WHO Pandemic Agreement (*7*) was issued five days before the session, following intensive negotiations among Member States. In such cases, where Member States are directly involved in ongoing negotiation processes, later document circulation may be difficult to avoid and does not necessarily undermine participation, as substantive engagement occurs through other channels.

By contrast, document A79/24 on reform of the global health architecture and the UN80 Initiative (*8*) was issued eleven days before the WHA. Given that it was also scheduled for consideration by PBAC, this effectively left only six days for preparation from the perspective of PBAC participants. When travel time to Geneva and practical constraints of delegation coordination are taken into account, this timeframe is, in practice, highly constrained for adequate preparation. For an agenda item of such institutional significance, these conditions may have limited both substantive review and domestic coordination. A further example illustrates related concerns. The "Financing, Implementation and Performance Framework for the Programme Budget 2026–2027" (A79/15) (*9*) was released only two days before the relevant PBAC session. Given its central role in guiding decisions on financing and performance, this short timeframe may have limited detailed analysis and coordination.

Taken together, these examples suggest that delays in documentation can have different implications depending on nature of the agenda item and extent of prior Member State engagement. However, where late release occurs

in absence of sustained negotiation processes, it is more likely to affect depth and coherence of deliberation. These concerns are heightened in the current global context, where ongoing WHO governance reforms, broader UN system discussions, and increasing financial constraints make informed and timely decision-making ever more critical.

4. Documentation delays and WHO governance reform

Documentation timeliness remains a relatively under-addressed issue within ongoing WHO governance reform. While recent efforts have focused on financial sustainability and accountability, operational dimensions such as documentation practices have received comparatively less attention (*10-12*). At the same time, the policy environment has become more complex, with parallel processes such as revision of the International Health Regulations and negotiations on a pandemic agreement placing additional demands on documentation systems (*13,14*).

Institutional responses have begun to emerge. A decision adopted by the EB allows for deferral of agenda items when documentation is not made available in a timely manner (*15*). However, the practical impact of such measures has been limited, particularly in WHA sessions, suggesting a gap between formal rules and operational practice.

Transparency and accountability depend not only on availability of information but also on its usability (*3*). Timely documentation should therefore be understood as a structural element of governance, consistent with WHO's constitutional framework (*16*). More fundamentally, timely documentation is not merely an administrative requirement but a prerequisite for meaningful Member State participation in WHO decision-making processes. Evidence from global health treaty implementation further underscores the role of institutional design in shaping outcomes (*17*).

Addressing documentation delays will require practical measures, including earlier circulation of draft materials to facilitate preliminary review, stricter adherence to existing timelines to ensure predictability, and more consistent application of deferral mechanisms when deadlines are not met. Additional options could include routine public reporting of documentation timeliness and explanatory reporting for substantial delays, helping to strengthen transparency and accountability in documentation practices.

5. Limitations

This analysis has several limitations. First, it evaluates documentation timing rather than direct measures of Member State preparation, negotiation behaviour, or quality of deliberation. Consequently, the effects discussed in this paper should be interpreted as plausible implications rather than empirically demonstrated outcomes. Second, the analysis does not assess differences in participation capacity across Member States and therefore cannot determine how documentation timing may affect countries differently. Third, the analysis focused on substantive policy documents circulated prior to opening of governing body sessions, consistent with the study's aim of examining documentation timing. As a result, procedural documents, negotiation-derived materials, and other excluded categories were not assessed. Finally, this analysis does not investigate underlying causes of documentation delays, which may reflect a combination of Secretariat processes, intergovernmental negotiations, and other factors involved in document development. Further work exploring both causes and consequences of documentation delays could help strengthen the evidence base for governance reform.

6. Conclusions

This analysis shows that the interval between document release and session opening has shortened significantly over the past decade, particularly for the WHA, and that this trend persists. Timely documentation is not merely a procedural concern but a prerequisite for effective, equitable, and legitimate decision-making. Ensuring that Member States have adequate time to review and engage with key documents is essential for maintaining transparency, accountability, and meaningful participation in global health governance. As WHO reforms continue, improving timeliness of documentation should be recognized as a practical and immediate priority for strengthening governance in practice.

Funding: This study was funded by the Health, Labour and Welfare (MHLW) Sciences Research Grant (research project: Study on Strengthening Governance of the World Health Organization; Principal Investigator: Hiroki Nakatani, summary to be published in the MHLW Research Grant Database (in Japanese), Project ID: 25BA2001) (*18*).

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

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Received June 16, 2026; Revised July 23, 2026; Accepted August 6, 2026.

Released online in J-STAGE as advance publication August 8, 2026.

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Global Health & Medicine. 2026; 8(4):253-264. REVIEW
DOI: 10.35772/ghm.2026.01008

Effectiveness of human induced pluripotent stem cell-derived β-like cell/islet transplantation in animal models of diabetes: A meta-analysis of preclinical studies

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Abstract: Emerging approaches in regenerative medicine for the treatment of diabetes have attracted attention. This meta-analysis aimed to evaluate the effectiveness of human induced pluripotent stem cell (hiPSC)-derived β-like cell/islet transplantation in animal models of diabetes. Studies using strictly controlled designs to assess hiPSC-derived β-like cell/islet transplantation were included. A reduction in blood glucose (BG) levels and improvement on the glucose tolerance test (GTT) served as indices to assess effectiveness. Twelve studies published between January 1, 2016 and December 31, 2025 were included. Pooled evidence indicates that transplantation of hiPSC-derived β-like cells/islets is associated with significant reductions in BG levels from four weeks to two months post-transplantation, with hypoglycemic effectiveness tending to increase over time. Improvements in glucose tolerance were also consistently observed. Overall, this meta-analysis synthesizes current preclinical evidence and identifies key areas where further research is needed to clarify translational and potential clinical applications.

***Keywords*:** diabetes, hiPSC derived β-like cells, islet, hypoglycemic effects, regenerative medicine

1. Introduction

Diabetes, and particularly type 2 diabetes (T2D), is a major public health concern that must be faced by governments worldwide as lifestyles change and populations age (*1*). Although hypoglycemic therapy or administration of exogenous insulin can effectively control blood glucose (BG) and improve the quality of life in patients, thus far there is still no specific treatment that can cure diabetes. The core problem lies in restoring islet function, which ensures that enough β cells generate sufficient endogenous insulin. Islet transplantation is a plausible treatment option. However, it cannot be widely used because of several well-known ethical and technological problems. Accordingly, emerging approaches in regenerative medicine are considered a beacon of hope for diabetes treatment.

The conventional approach involves the transplantation of pancreatic progenitor cells or islet organoids induced from human pluripotent stem cells (hPSCs). Technology for differentiating hPSCs into pancreatic progenitors and β-like cells is becoming increasingly mature. Our previous study provided a robust approach to induce vascularized pancreatic organoids from hPSCs by modulating WNT signaling with CHIR99021 in mTeSR1 and incorporating VEGFA (*2*). Although the effectiveness of transplantation of hPSC-derived β-like cells has been demonstrated in both animal and human studies (*3*), potential risks, such as technological difficulties (complicated differentiation processes, cancerization, and allograft rejection) and ethical risks (source of stem cells), cannot be ignored. Human induced pluripotent stem cells (hiPSCs) derived from somatic cells are a next-generation approach in regenerative medicine. Previous studies have focused on inducing β-like cells using somatic cells *in vitro* (*4,5*). Subsequent studies have evaluated the effectiveness of β-like cell transplantation in animal models (*6-10*). Recently, with the development of the concept of "organoids" researchers have attempted to "produce" islet organoids from hiPSCs *in vitro* and then transplant

them into animal models (*11,12*). A handful of reports on human patients are available (*3,13*). Although these reports documented the satisfactory effectiveness of transplanting islet-like organoids, they commonly suffer from small sample sizes, which precludes the obtaining of more convincing evidence. Due to the limitations of human studies, more useful information, such as the transplantation dose/site, approach, adverse events, and long-term effects, cannot be collected. Nevertheless, the massive demand for cellular therapy research on the bench and at the bedside mean that these issues are at the forefront during clinical use and experiments. Thus, animal studies are being considered because the available literature is far more extensive than that for human studies, offering more in-depth exploration. In addition, our previous studies focused on regenerative medicine using hPSCs (*2,14*) and hiPSCs (*15-17*) to generate a variety of functional cells and organoids, such as pancreatic progenitors and β-like cells (*2*), functional hepatobiliary organoids (*14,15,17*), and cardiomyocytes (*16*). Based on our experience using hPSCs and hiPSCs, along with our insights in this field, we believe that a meta-analysis that comprehensively investigates the effectiveness of hiPSC-based transplantation in diabetes is needed and timely.

Accordingly, we designed the current meta-analysis in compliance with the PRISMA guidelines (*18*) to investigate the effectiveness of transplantation of hiPSC-derived β-like cells/islets in treating diabetes. Due to the limited number of human studies, the current study focused on available animal studies.

2. Literature search strategies and analytical approach

2.1. Literature search strategy

A comprehensive electronic search was conducted using eight medical search engines (the PubMed, Cochrane Library, ISI Web of Science, Embase, CNKI, SinoMed, Wanfang, and Weipu databases). This study was not registered in any public database. Articles in English from January 1, 2016 to December 31, 2025 were included in the review. The following terms were used for the search: ("Induced Pluripotent Stem Cells"[MeSH] OR "hiPSC"[Title/Abstract] OR "iPS cells"[Title/Abstract] OR "induced pluripotent stem cell*"[Title/Abstract]) AND ("Islets of Langerhans"[Mesh] OR "pancreatic islet*"[Title/Abstract] OR "islet cell*"[Title/Abstract] OR "beta cell*"[Title/Abstract] OR "β cell*"[Title/Abstract] OR "insulin-producing cell*"[Title/Abstract]) AND ("Diabetes Mellitus"[MeSH] OR "diabetes *"[Title/Abstract]). The references of important studies were also manually reviewed to identify more potentially relevant studies. Inclusion and exclusion criteria were established based on the PICOS criteria, all the included studies used data of animal experiments (Table 1).

2.2. Data extraction and evaluation of study quality

First, two authors (RC and JX) searched the databases and performed primary screening by reading the titles and abstracts of the articles obtained. Subsequently, a third author (XS) read the full texts and recommended potentially eligible studies. Finally, these studies were cross-checked by senior authors (TA and FW), and the final eligible studies were determined. Two independent authors (JK and GW) extracted data from the eligible studies for further investigation. Information including authors, title, publication time, experimental design (subjects, sample size, setting of treatment/control groups, randomization, blinding, intervention, and outcome measures), and results was acquired. In line with the aim of this study, changes in BG levels and improvement on the glucose tolerance test (GTT) served as indices to assess the effectiveness of transplantation. The software Getdata Graph Digitizer (V2.26.0, *http://getdata-graph-digitizer.com*) was used to assist in data acquisition. In this study, the time points for BG monitoring (weeks 1, 2, 3, and 4) and oral glucose tolerance test (OGTT; 30, 60, 90, and 120 min) were standardized as evaluation nodes. Since the raw data were primarily extracted from the original figures using digitalization software, this standardization was performed to minimize data heterogeneity and ensure comparability across studies, thereby meeting the statistical requirements for meta-analysis. Discussions were conducted weekly to reach a consensus. Finally, a third-party author (NL) checked all data before they were submitted for meta-analysis.

Study quality was assessed using the SYRCLE Risk of Bias Tool (*19*). This tool included 10 entries, including selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Egger's test (*20*)

Table 1. PICOS criteria for inclusion and exclusion of studies in the current study

Parameters	Inclusion criteria	Exclusion criteria
Population	Animal models of diabetes	Non-animal models of diabetes
Intervention	Treatment using hiPSC-derived β cells	Treatment not using hiPSC-derived β cells
Comparison	hiPSC-derived β cells *vs.* Blank control or Sham group	Without using parallel control
Outcome	BG levels, GTT outcomes	BG levels and GTT outcomes were not reported

Abbreviations: BG, blood glucose; GTT, glucose tolerance test; hiPSC, human induced pluripotent stem cells.

was used to analyze publication bias. The potential for publication bias regarding BG levels and GTT outcomes was initially assessed *via* visual inspection of funnel plots. Publication bias was further evaluated using Egger's linear regression test. W4 for BG levels and 90 min on the GTT were selected for Egger's test because these two time points were included in the largest number of studies. Two authors (RC and TA) conducted the assessments of all included articles.

2.3. Statistical analysis

This study was designed and performed in accordance with the Cochrane Handbook (*21*) and PRISMA guidelines (*22*). The software Stata SE 16 (StataCorp LLC, TX, USA) was used for meta-analysis. Weighted mean differences (WMDs) with 95% confidence intervals (CIs) were calculated for continuous data. WMDs were selected rather than standard mean differences (SMDs) for the following reasons: *i*) all indices (BG levels and GTT outcomes) were expressed in mg/dL; *ii*) the magnitude of improvement in all indices was the most important parameter in this study, and WMD can provide quantitative data; *iii*) the heterogeneity of included studies was not caused by the method of measurement (such as measuring BG levels); and *iv*) we performed subgroup and sensitivity analyses to explore the causes of heterogeneity. The I^2 index was used to evaluate heterogeneity among the studies. If the p-value was ≥ 0.1 and I^2 was $\leq 50\%$, the study was considered homogeneous, and a fixed-effects model was used. If $p < 0.1$ and $I^2 > 50\%$, the study was considered heterogeneous, and a random-effects model was used. Statistical significance was set at $p < 0.05$. The software RevMan (V5.4; Cochrane, London, UK) was also used to evaluate the quality of the studies.

2.4. Subgroup analysis and sensitivity analysis

Subgroup analyses were performed to identify potential sources of inconsistency and to evaluate the robustness of the pooled estimates. The predefined grouping criteria for BG levels included cell source (β cells *vs.* organoid-derived β-like cells), cell infusion dose (low dose $< 5.0\times10^6$ *vs.* high-dose $\geq 5.0 \times 10^6$), and mouse strain (NOD-SCID *vs.* SCID-Beige). The predefined grouping criteria for the GTT included an OGTT *vs.* an intraperitoneal GTT (IPGTT). To assess the stability of the pooled estimates of BG levels, a leave-one-out sensitivity analysis was performed for each time point. BG levels and GTT parameters at each time point were statistically analyzed. These analyses aimed to determine whether experimental variations significantly influenced therapeutic outcomes and contributed to overall statistical diversity.

3. Key research findings

3.1. Characteristics of the included studies

As shown in Figure 1, 12 studies published after 2016 were included in this study. Table 2 shows the characteristics of the included studies. All 12 studies (published between 2016 and 2025) were in English and involved transplantation of iPSC-derived β-cells (studies were published between 2016 and 2022) (*6-10,18,23*) or iPSC-derived islet organoids (studies were published between 2022 and 2025) (*3,11-13,24*). All studies used data of animal studies and no human studies were included in the review, despite two studies (*3,13*) included human data. Streptozotocin-induced diabetic mice were used in these studies. Of the 12 studies, seven used NOD-SCID mice (*6-10,12,24*), whereas five used SCID-Beige mice (*3,11,13,18,23*). Most studies implanted cells/islet organoids surrounding the kidney capsule (*3,6-8,10-13,18,23*), whereas one study used intraperitoneal and subcutaneous transplantation (*9*), and one study transplanted islet organoids at the dorsal subcutaneous site (*24*). The main outcome measures included BG levels and improvement on the GTT (intraperitoneal or oral). The detailed characteristics of the included studies are listed in Table 2.

3.2. Quality assessment of included studies

The quality of the included studies was assessed using the

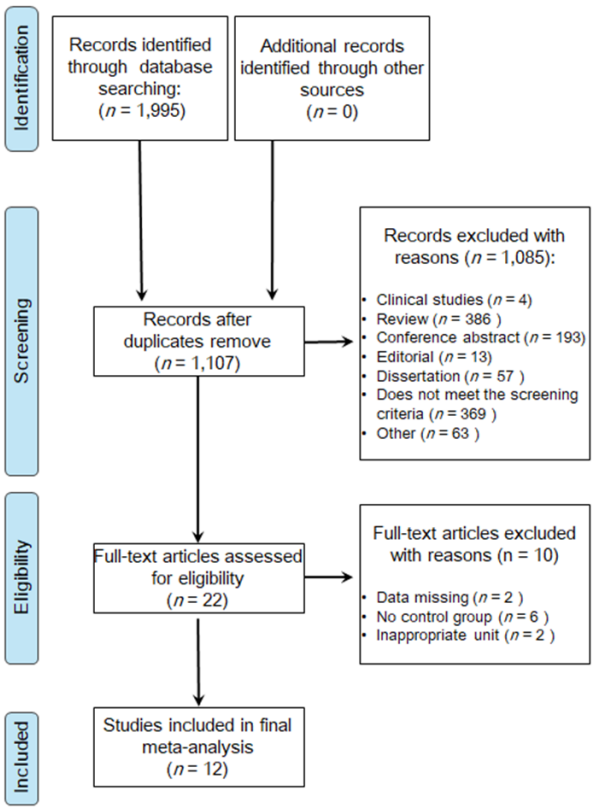

Figure 1. Flow chart for the search strategy and selection of studies.

Table 2. Characteristics of the included studies

Study (*Ref.*)	Sample size	Animal	Number of hiPSC-derived cells	Transplantation site	Endpoints
hiPSC-derived β-like cells					
Yoshihara 2016 (*6*)	13	NOD-SCID mice	1.0×10^7	Kidney capsule	BG levels, Human C-peptide levels
Kondo 2017 (*7*)	3/3	NOD-SCID mice	2.0×10^6	Renal subcapsules	BG levels
Yabe 2017 (*8*)	20	NOD-SCID mice	4.0×10^6	Kidney capsules	BG levels, OGTT outcomes, Human C-Peptide
Fukuda 2019 (*9*)	4/4	NOD-SCID mice	1.2×10^7	Intraperitoneal and subcutaneous administration	OGTT outcomes
Yabe 2019 (*10*)	7	NOD-SCID mice	6.0×10^6	Left kidney capsule	BG levels, OGTT outcomes, Human C-peptide levels
Yang 2020 (*23*)	8/8	SCID-Beige mice	1.0×10^7	Left renal capsule	BG levels, OGTT outcomes
Du 2022 (*18*)	17	SCID-Beige mice	3.0×10^6	Kidney capsules	IPGTT outcomes, Human C-peptide levels
hiPSC-derived islets					
Takaichi 2022 (*24*)	4/4	NOD-SCID mice	7.68×10^5	Dorsal subcutaneous site	BG levels, IPGTT outcomes
Wang 2024 (*13*)	20	SCID-Beige mice	3.0×10^6	Kidney capsule	IPGTT outcomes
Wu 2024 (*3*)	5	SCID-Beige mice	0.6 or 3×10^4	Kidney capsule	BG levels
Chen 2025 (*12*)	8/5/9	NOD-SCID mice	5.0×10^6	Renal peritoneum	BG levels, IPGTT outcomes, Body
Dadheech 2025 (*11*)	15	SCID-Beige mice	1.5×10^6	Renal sub capsule	BG levels, IPGTT outcomes, Human C-peptide levels

Abbreviations: BG, blood glucose; GTT, glucose tolerance test; IPGTT, intraperitoneal glucose tolerance test; hiPSC, human induced pluripotent stem cells; OGTT, oral glucose tolerance test.

SYRCLE Risk of Bias Tool. Figure 2 was prepared based on the results of the SYRCLE-based quality assessments. Detailed information on each article is provided in the Supplementary Material. As shown in Figure 2, two studies adopted a randomization design (*23,24*), whereas two studies did not perform randomization (*7,11*). The randomization status of the other eight studies was also unclear. Information regarding concealment and blinding of the researchers was unclear (Figure 2A). Since these studies involved only animals and all indices were objective, blinding of the animals was acceptable (*25*). Attrition and reporting biases were judged to be low risk because the experimental protocols were available in all of the studies. In addition, all of the studies reported homogeneity of the baseline data between the treatment and control groups (Figure 2B). Other biases defined by the SYRCLE Risk of Bias Tool were identified as low risk.

Figure 3 shows the results of Egger's test. The funnel plot for BG levels (Figure 3A) revealed that most study coordinates were clustered to the left of the mean effect size (negative WMD region), suggesting a general consensus on the effectiveness of the intervention at lowering glucose. However, pronounced asymmetry was observed; data points in the right-hand region (WMD ≥ 0) were sparse, and particularly among small-sample studies with larger standard errors. This void suggests a potential risk of publication bias, in which studies yielding negative or non-significant results may remain unpublished. Egger's linear regression test yielded a regression intercept (bias) of 1.248 with a *p*-value of 0.637 ($p > 0.05$) (Figure 3B), indicating no statistically significant small study effects. These results suggest that any observed asymmetry in the funnel plot was due to genuine inter-study heterogeneity or other factors rather than systematic publication bias. The funnel plot for GTT outcomes (Figure 3C) exhibited a markedly asymmetrical distribution. Most of the studies were concentrated in the negative effect size region, with a conspicuous absence of corresponding studies in the right-hand (positive effect size) quadrant. This pattern further indicates the potential omission of small-sample studies with negative outcomes. Egger's linear regression test yielded a bias of 1.48, with a *p*-value of 0.169 ($p > 0.05$) (Figure 3D). Since the *p*-values for both primary outcomes exceeded the 0.05 threshold, one can conclude that there was no evidence of significant publication bias in this meta-analysis.

3.3. Outcome measures

3.3.1. BG levels

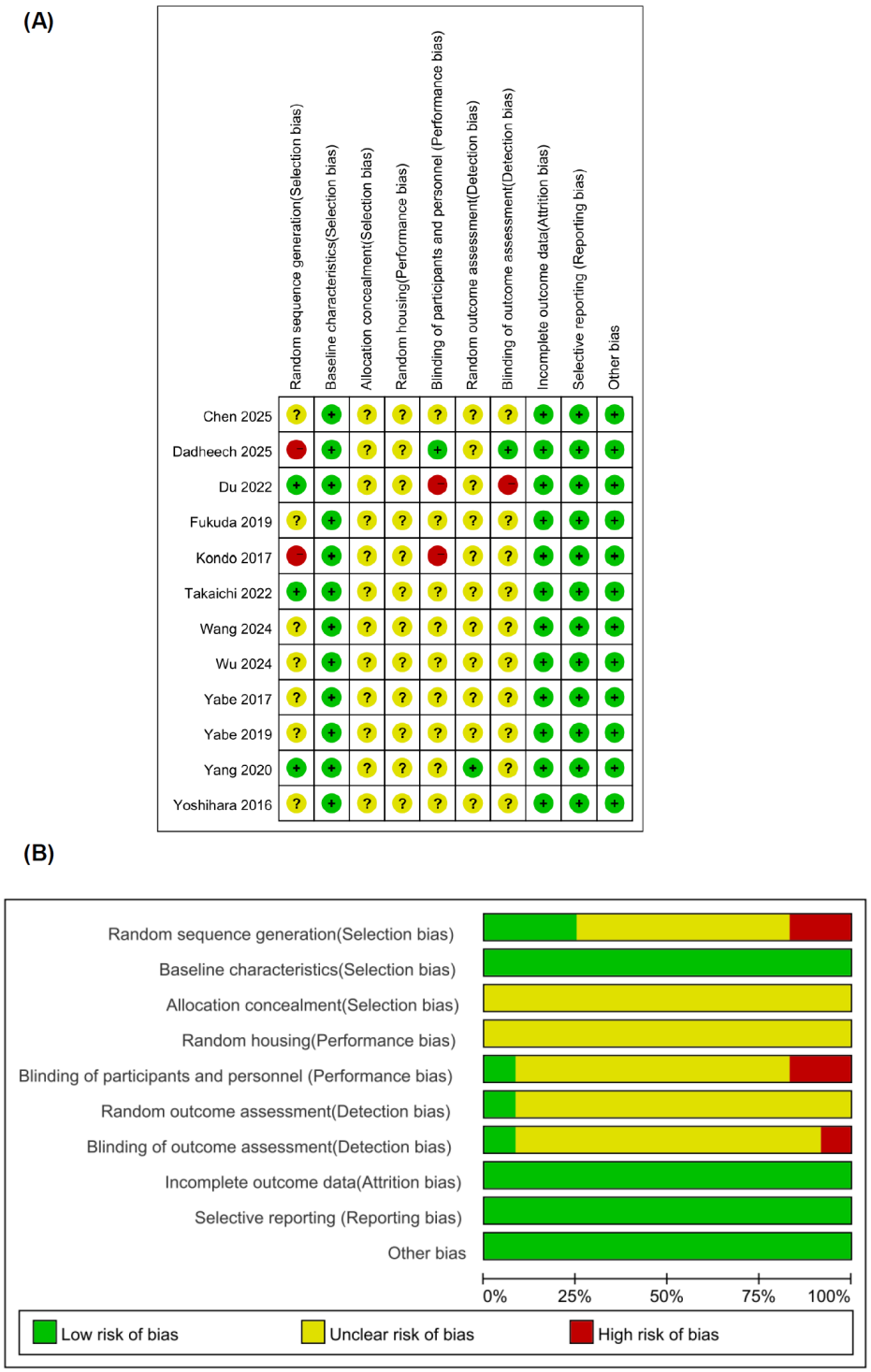

Figure 2. Potential risk of bias in the current study. (A) Risk of bias in the included studies; **(B)** Summary of the risk of bias in the included studies.

Figure 4 shows the decrease in BG levels after transplantation of hiPSC-derived β-cells or islets (treatment *vs.* control). All results indicated that transplantation of hiPSC-derived β-cells or islets led to a decrease in BG levels from one week (W1) to two months after treatment. After transplantation in W1, BG levels began to decrease. Such changes in BG levels were significant (n = 97, WMD = -134.39, 95% CI [-182.10 – -86.68], $p < 0.001$). The homogeneity test (X^2 = 289.05, p = 0.00, I^2 = 97.22%) indicated a high level of heterogeneity among the studies (Figure 4A). After transplantation in W2, BG levels also significantly decreased (n = 97, WMD = -131.45, 95% CI [-194.34 – -68.54], $p < 0.001$). The homogeneity test (X^2 = 442.03, p = 0.00, I^2 = 97.78%) indicated a high level of heterogeneity among these studies (Figure 4B). After

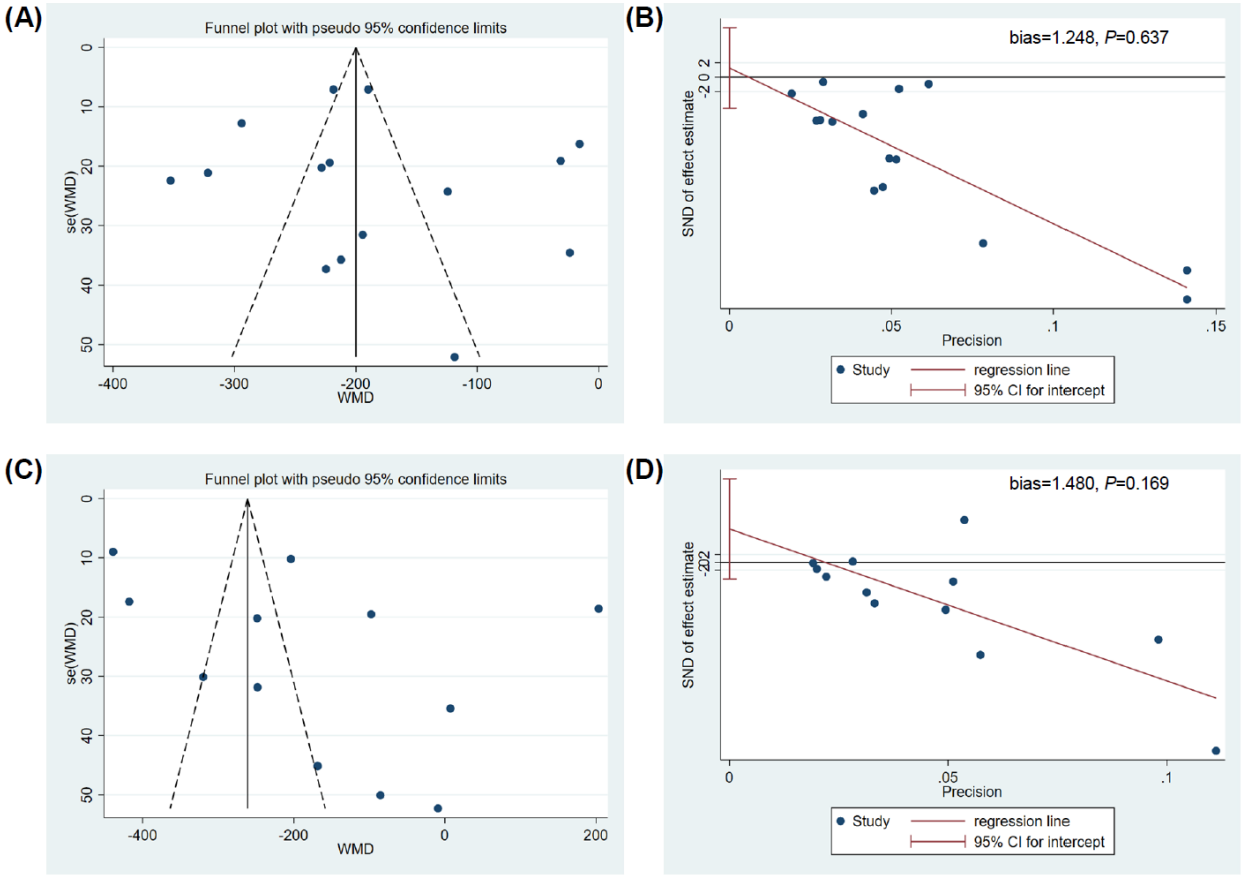

Figure 3. Results of Egger's test. (A) Funnel plot of the standard error by WMD for blood glucose BG levels; **(B)** Egger's linear regression test for publication bias in BG levels; **(C)** Funnel plot of the standard error by WMD for GTT outcomes; **(D)** Egger's linear regression test for publication bias for GTT outcomes.

transplantation in W3, BG levels also significantly decreased (n = 96, WMD = -170.46, 95% CI [-223.96 – -116.95], p < 0.001). The homogeneity test (X^2 = 444.20, p = 0.00, I^2 = 97.70%) indicated a high level of heterogeneity among these studies (Figure 4C). After transplantation in W4, BG levels decreased significantly (n = 95, WMD = -185.97, 95%CI [-228.58 – -133.36], p < 0.001). The homogeneity test (X^2 = 391.23, p = 0.00, I^2 = 97.51%) indicated a high level of heterogeneity among these studies (Figure 4D). Four studies (*6,10-12*) conducted long-term (two months after treatment) observations, and BG levels significantly decreased further (n = 40, WMD = -317.23, 95% CI [-362.41 – -272.05], p < 0.001). The homogeneity test (X^2 = 5.40, p = 0.15, I^2 = 66.59%) indicated a relatively low level of heterogeneity among the studies (Figure 4E). The data imply that the effect of lowering BG levels tends to become stronger and that the heterogeneity among studies tends to decrease over time after transplantation.

3.3.2. Results on the GTT

Figure 5 shows the reduction in BG levels after the GTT (treatment *vs.* control). Thirty min after glucose administration, BG levels decreased significantly (n = 93, WMD = -192.89, 95% CI [-273.28 – -112.50], p < 0.001). The homogeneity test (X^2 = 1526.58, p = 0.00, I^2 = 98.64%) indicated a high level of heterogeneity among these studies (Figure 5A). Sixty min after glucose administration, BG levels decreased significantly (n = 93, WMD = -238.71, 95% CI [-324.68 – -152.74], p < 0.001). The homogeneity test (X^2 = 1161.37, p = 0.00, I^2 = 98.55%) indicated a high level of heterogeneity among these studies (Figure 5B). Ninety min after glucose administration, BG levels decreased significantly (n = 88, WMD = -206.52, 95% CI [-287.86 – -125.18], p < 0.001). The homogeneity test (X^2 = 643.47, p = 0.00, I^2 = 98.12%) indicated a high level of heterogeneity among these studies (Figure 5C). One hundred and twenty min after glucose administration, BG levels decreased significantly (n = 75, WMD = -229.35, 95% CI [-325.10 – -133.59], p < 0.001). The homogeneity test (X^2 = 409.73, p = 0.00, I^2 = 97.99%) indicated a high level of heterogeneity among these studies (Figure 5D). Accordingly, improvement on the GTT was evaluated in this study.

3.4. Subgroup analysis and sensitivity analysis

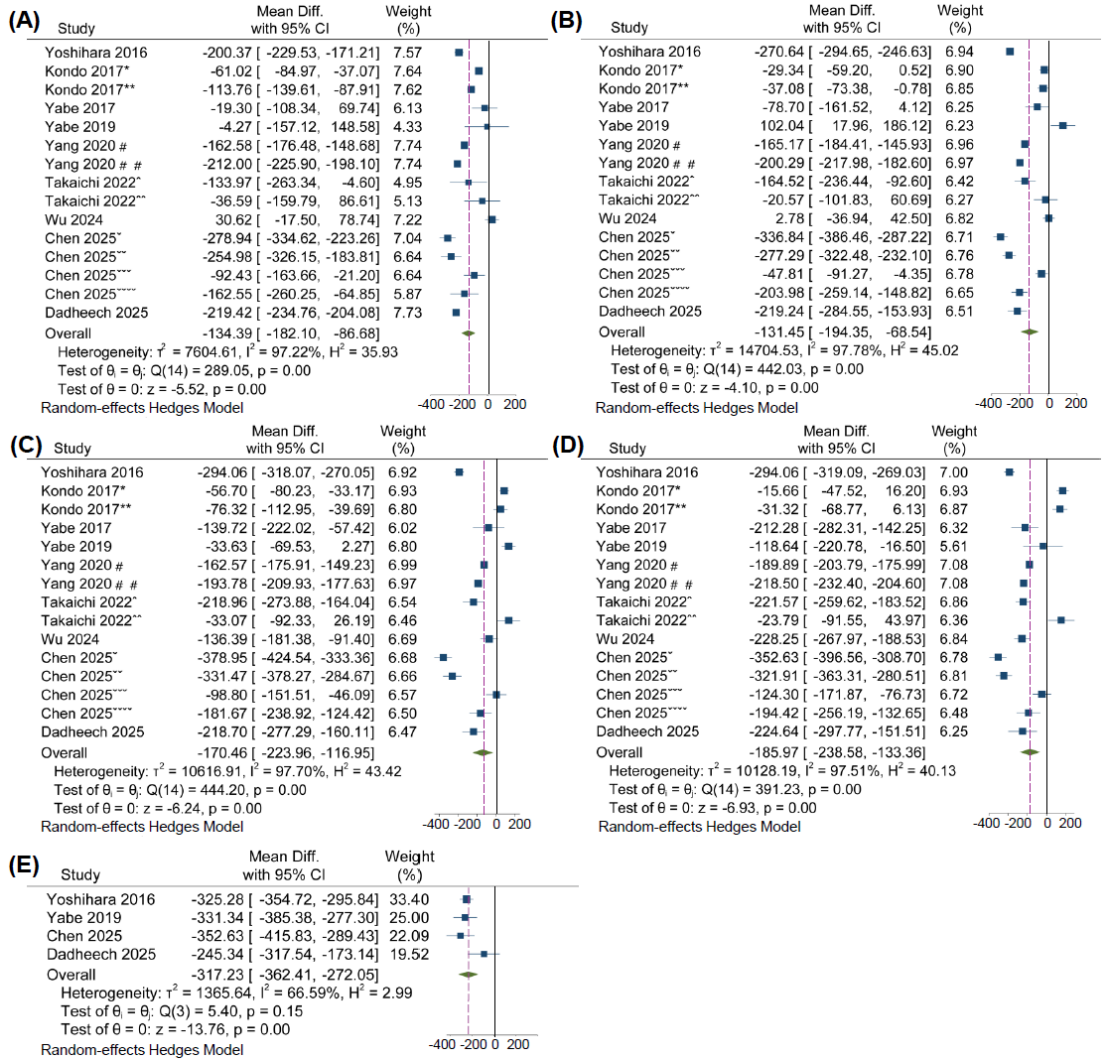

Figure 4. The effectiveness of hiPSC-derived-β cell/islet transplantation at reducing BG. (A) Forest plot of reduction in BG 1 week (W1) after transplantation; **(B)** Forest plot of reduction in BG W2 after transplantation; **(C)** Forest plot of reduction in BG W3 after transplantation; **(D)** Forest plot of reduction in BG W4 after transplantation; **(E)** Forest plot of reduction in BG 2 months after transplantation. *Abbreviations*: BG, blood tolerance. List of symbols in the figures (The different symbols represent the attributes of the intervention): *INS+-hiPSCs-4Fs, **INS+-hiPSCs-4Fs + SCG, #IPCs-scrambled-shRNA, ##IPC-shRNA-LSD1-927, ^vascularized hiPS β-cell spheroid tissue, ^^non-vascularized hiPS β-cell spheroid tissue, ˇβ cell-hiPSCs, ˇˇMVF-vascularized islets, ˇˇˇHUVEC-vascularized islets, ˇˇˇˇun-vascularized islets.

3.4.1. Subgroup analysis of BG levels

Table 3 shows the results of the subgroup analysis (primary β cells *vs.* organoid-derived β-like cells). The heterogeneity test revealed that the I^2 values for all indices remained substantially high and did not decrease significantly within the subgroups (Table 3). These findings suggest that the observed inter-study heterogeneity was not primarily attributable to the β-cell source, indicating that the origin of the cells did not significantly moderate the pooled treatment effects in this study.

When a low dose was compared to a high dose, the heterogeneity of BG levels tended to decrease in week 2 (I^2 = 86.7%, $p < 0.001$). To further isolate the sources of inconsistency, a sensitivity analysis was performed while excluding one study (Dadheech 2025) that utilized a different mouse strain. Once it was excluded, the heterogeneity of the outcome significantly decreased further to I^2 = 68.8% (p = 0.012). These findings suggest that the substantial heterogeneity observed in the primary analysis is likely attributable to variations in cell dosage and animal strains.

Results for the mouse strain indicated a marked decrease in the heterogeneity of BG levels within the SCID-beige subgroup in both week 3 (I^2 = 77.8%, p = 0.004) and week 4 (I^2 = 69.1%, p = 0.021) compared to the overall pooled analysis. These findings indicate that the inherent biological variations between different immunodeficient mouse strains are likely the primary driver of the high level of heterogeneity observed in this study.

3.4.2. Subgroup analysis of GTT outcomes

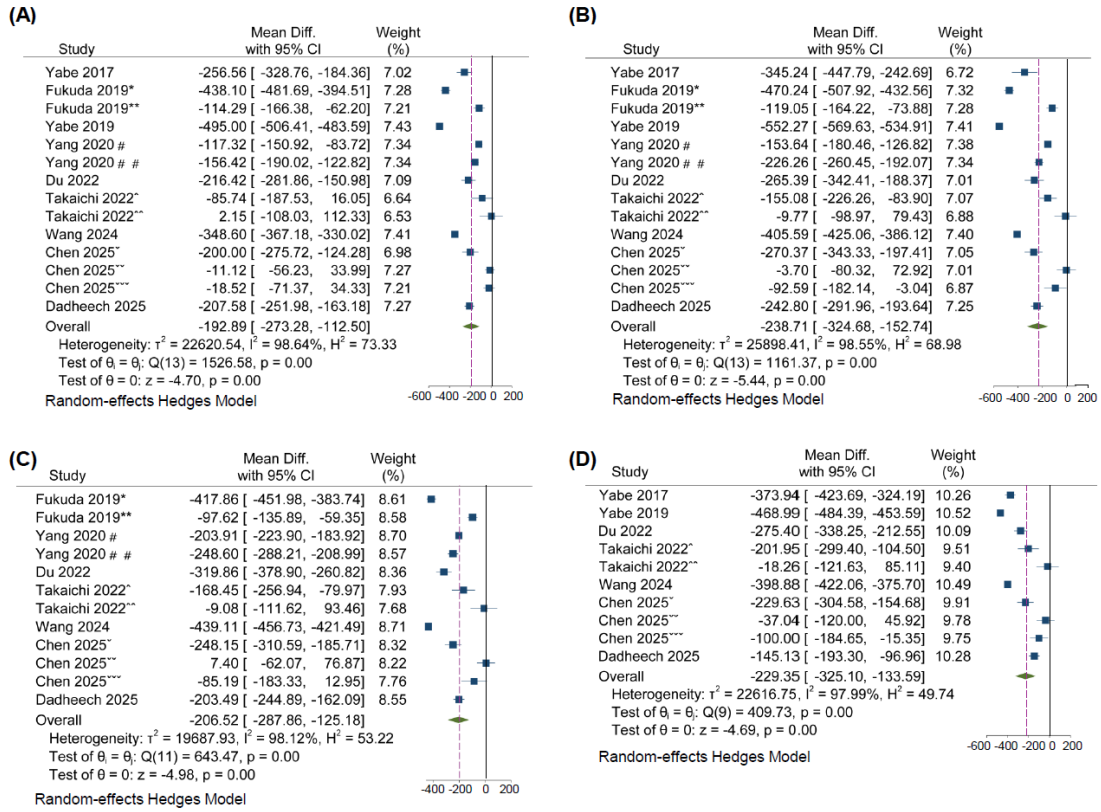

Figure 5. Effectiveness of hiPSC-derived-β cell/islet transplantation at improving GTT outcomes. (A) Forest plot of improvement on the GTT 30 min after glucose injection; **(B)** Forest plot of improvement on the GTT 60 min after glucose injection; **(C)** Forest plot of improvement on the GTT 90 min after glucose injection; **(D)** Forest plot of improvement on the GTT 120 min after glucose injection. *Abbreviations*: GTT, glucose tolerance test. List of symbols in the figures (The different symbols represent the attributes of the intervention): *fiber i.p., **fiber s.c., #IPCs-scrambled-shRNA, ##IPC-shRNA-LSD1-927, ^vascularized hiPS β-cell spheroid tissue, ^^non-vascularized hiPS β-cell spheroid tissue, ˇMVF-vascularized islets, ˇˇHUVEC-vascularized islets, ˇˇˇun-vascularized islets.

Table 3. Subgroup analysis to explore the sources of heterogeneity in blood glucose and glucose tolerance outcomes

Assessed outcomes	β-cell source	Heterogeneity (I^2, p)
BG level (1 W)	β cells	$I^2 = 95.8\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 94.7\%$, $p < 0.001$
BG level (2 W)	β cells	$I^2 = 97.7\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 94.9\%$, $p < 0.001$
BG level (3 W)	β cells	$I^2 = 98.1\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 92.5\%$, $p < 0.001$
BG level (4 W)	β cells	$I^2 = 97.8\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 91.6\%$, $p < 0.001$
BG level (2 M)	β cells	$I^2 = 0.0\%$, $p = 0.744 > 0.05$ (No significant heterogeneity)
	organoid-derived β-like cells	N/A
GTT outcome (30 min)	β cells	$I^2 = 99.3\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 96.2\%$, $p < 0.001$
GTT outcome (60 min)	β cells	$I^2 = 99.3\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 97.5\%$, $p < 0.001$
GTT outcome (90 min)	β cells	$I^2 = 97.7\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 99.5\%$, $p < 0.001$
GTT outcome (120 min)	β cells	$I^2 = 95.5\%$, $p < 0.001$
	organoid-derived β-like cells	$I^2 = 97.1\%$, $p < 0.001$

In the IPGTT subgroup using NOD-SCID mice, heterogeneity across all time points (30, 60, 90, and 120 min) was mitigated to varying degrees (I^2 = 80.5%, 87.6%, 88.6%, and 78.5%, respectively). And in the IPGTT subgroup combined with low-dose cell infusion, heterogeneity effectively decreased at the 90-min mark (I^2 = 68.0%, p = 0.044). These findings indicate that discrepancies in the form of GTT administered are a significant driver of the high level of heterogeneity observed in this meta-analysis.

3.4.3. Sensitivity analysis of BG levels

In week 1, the pooled WMD remained remarkably stable, with 95% CIs fluctuating narrowly between -1.98 and -1.49, suggesting that no single study had excessive influence. In week 2, however, slight variations were observed; the lower and upper bounds of the CIs ranged from -2.30 to -1.10 and -1.80 to 0.80, respectively. Notably, the exclusion of the study by Wu *et al*. (*3*) or that by Chen *et al.* (*12*) caused the upper bound to approach or slightly transcend the line of no effect (WMD = 0), indicating that these specific trials were pivotal to the significance of the week 2 findings.

The results for weeks 3 and 4 exhibited a high level of integrity, with CIs ranging from -4.20 to -2.95 and -3.98 to -2.25, respectively. In both instances, the pooled estimates were not significantly attenuated by the removal of any individual study, and the CIs did not cross the null line. At the 2-month follow-up, exclusion of the study by Yoshihara *et al*. (*6*) shifted the CI to [-10.19, -7.47] compared to a range of [-7.47, -6.01] for other exclusions. This identifies the study by Yoshihara (*6*) as a high-contribution study; however, the overall direction and significance of the effects remain unchanged.

3.4.4. Sensitivity analysis of GTT outcomes

At 30 min, excluding individual studies yielded pooled effect sizes ranging from -3.11 to -0.10 (overall WMD: -2.48). Similarly, at 60 and 90 min, the recalculated effect sizes fluctuated between -2.98 and -0.54 (-2.30 overall) and -3.00 and -0.40 (-1.80 overall), respectively. At 120 min, marked stability was evident; the pooled results remained constant at -2.76 (95% CI: -3.05 to -2.47), despite the overall pooled estimate of -1.00.

4. Implications for practice and research

The current study performed a meta-analysis of 12 eligible studies to verify the effectiveness of hiPSC-based transplantation in the treatment of diabetes. Results revealed that the transplantation of hiPSC-generated-β cells (*6-10,18,23*) or stem cell-generated islets (*3,11-13,24*) led to a significant reduction in BG levels and improved GTT performance in animal models of diabetes. Importantly, the effectiveness of both cell and organoid transplantation increased over the transplantation period. This suggests the reliability of hiPSC-generated β-cells and islets within the follow-up period. To the extent known, this is the first meta-analysis to elucidate the effectiveness of hiPSC-based transplantation in treating animals with diabetes. The current findings may provide a working foundation for further use of this technology in clinical settings.

4.1. Study quality

This study used the SYRCLE Risk of Bias Tool to evaluate study quality (Figure 2 and Supplementary Materials, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=119*) and Egger's test to assess potential publication bias (Figure 3). A small number of studies were included, many of which did not report allocation concealment. However, all of the indices are objective, so this issue may not have influenced the final results (*25*). Egger's test was used to conduct a comprehensive evaluation of publication bias. Although the funnel plots exhibited a degree of visual asymmetry, Egger's linear regression test yielded no significant evidence of bias ($p > 0.05$) in both BG levels and GTT outcomes. This discrepancy suggests that the observed asymmetry likely stems from inherent inter-study heterogeneity rather than systematic suppression of negative findings. Consequently, the pooled estimates for BG levels and GTT outcomes in this meta-analysis are considered statistically stable and representative of the available evidence.

4.2. Reduction in BG levels

The most important issue in diabetes therapy is to control BG to a certain level and to avoid a large daily amplitude of glycemic excursions, regardless of the use of exogenous insulin, hypoglycemic medication, or any other therapy. In this regard, a reduction in BG levels is regarded as the most intuitive and one of the most important indices for evaluating the effectiveness of a certain treatment in patients and animal models. Accordingly, studies assessing the effectiveness of certain treatments have commonly adopted this index. In the field of regenerative medicine involving the transplantation of β-like cells or hiPSC-derived islets, a sustained reduction in BG levels often means successful generation of insulin-producing β-like cells/islets, or what are known as functional β-like cells/islets. Based on β-like cells/islets, an islet organoid should have a vascular structure to maintain a stable blood supply, enabling it to mimic a natural islet and to secrete insulin. The concept of islet organoids is still in its infancy. However, the basic index to evaluate the success of islet organoid generation remains a reduction in BG levels.

The follow-up period in most of the included studies was four weeks, and only four studies (*6,10-12*) conducted a relatively longer two-month follow-up. The meta-analysis suggested that transplantation of hiPSC-derived β-cells or islets reduced BG levels, and the hypoglycemic efficiency tended to increase from W1 to 2 months after treatment (Figure 4). However, the highly heterogeneous nature of the included studies resulted in different findings for each time point. The current results revealed that after transplantation in W1, BG levels began to decrease, except in one study (*3*) that transplanted hiPSC-derived islets (Figure 4A). Only one study (*10*) involving hiPSC-derived β-cells noted an increase in W2

(Figure 4B). Two studies (*7,10*) that transplanted hiPSC-derived β-cells and one study (*24*) that transplanted hiPSC-derived islets noted an increase in W3 (Figure 4C). One study (*7*) that transplanted hiPSC-derived β-cells and another (*24*) that transplanted hiPSC-derived islets noted an increase in W4 (Figure 4B). In the studies that ended two months after transplantation, no increase was noted, including two studies (*6,10*) that transplanted hiPSC-derived β-cells and two recent studies (*11,12*) that transplanted islet organoids. These findings confirmed that the hypoglycemic efficiency tended to increase over time. Studies noting an increase were found to have been conducted in earlier years, for example, that by Kondo *et al*. (*7*) and Yabe *et al*. (*10*) with hiPSC-derived β-cells and that by Takaichi *et al*. (*24*) with hiPSC-derived islets. One plausible interpretation of this is that it reflects the limitations of the technology at that time. Moreover, these findings imply that four weeks is too short a time to evaluate the amelioration resulting from transplantation since the BG levels were still unstable at that time point. However, the optimal time for evaluation needs to be studied further.

4.3. Amelioration of GTT outcomes

The GTT is commonly used to examine insulin sensitivity and islet function in patients with diabetes. In animal studies in regenerative medicine, the GTT is used to test the quality and quantity of insulin produced by β-like cells/islets. Results indicated that BG levels decreased significantly from 30 min to 120 min after glucose administration (Figure 5), confirming the quality and quantity of insulin secreted by the transplanted cells/islets.

4.4. Subgroup analysis and sensitivity analysis

4.4.1. Subgroup analysis

The multi-dimensional subgroup analyses performed in this study revealed that the source of β cells was not a primary contributor to the heterogeneity observed. Conversely, subgroups stratified by cell infusion dose, mouse strain, and the form of GTT administered exhibited a marked decrease in I^2 values. Although the heterogeneity in these subgroups did not consistently fall below the 50% threshold, its tendency to decline significantly identified these three factors as core drivers of statistical inconsistencies across studies. To enhance the robustness and reproducibility of future findings, an imperative step is to implement standardized experimental protocols, particularly by unifying cell dosages, selecting consistent animal models, and harmonizing the method of GTT administration. Moreover, expanding the sample size within a rigorous, standardized framework is essential to minimizing heterogeneity and ensuring the consistency of therapeutic evaluations in β-cell transplantation research.

4.4.2. Sensitivity analysis

Week 2 data from several studies might have influenced the results, but the overarching results from the sensitivity analysis of BG levels across all temporal intervals remained consistent. The consistency of the WMD and the fact that the 95% CIs remained entirely within the significant range confirm that the glycemic outcomes of this meta-analysis were statistically robust and highly reliable.

In the sensitivity analysis of GTT outcomes, data from all temporal intervals confirmed that the removal of any constituent study did not result in a substantial shift in the pooled WMD. The re-estimated effect sizes were consistent with the primary results, and all 95% CIs remained entirely on one side of the line of no effect (WMD = 0). Collectively, these results suggest that GTT outcomes in this meta-analysis are not influenced by any single study, thereby ensuring the overall reliability of the findings.

4.5. Strengths and weaknesses of the evidence

The current study assessed BG levels and improvement on the GTT, which are commonly and easily measured in animal studies, as indices. Studies on β-like cells and islet organoids were included, which helped to provide a general impression of the effectiveness of stem cell-based therapies to treat diabetes in animal models. The SYRCLE Risk of Bias Tool and Egger's test were used to confirm the quality of the included studies. Subgroup analyses and sensitivity analysis were performed to explore the causes of high heterogeneity. These analyses help to improve the interpretability and reliability of the results. Analysis of the data revealed the high level of effectiveness of the transplanted cells and islets. Moreover, results revealed improvement after transplantation, which implied the stability of the generated β-like cells/islets over time. These findings are promising for the future adoption of regenerative medicine approaches to cure patients with diabetes. The BG data imply that four weeks might be too short a time to evaluate the efficiency of implanted cells/islets, which future studies may wish to account for.

However, the current study had several limitations. First, the limited number of eligible studies with a high level of heterogeneity might have led to biased conclusions. Second, inter-reviewer agreement based on Cohen's kappa was not tested during data extraction, and this may have diminished the reliability of this study. Third, other important diabetes-related indices, such as C-peptide levels (*13*), HbA1c levels, and BETA-2 scores (*26*), are indispensable to a comprehensive understanding of the effects of transplantation on diabetes, but they were not tested here. A small number of studies have

used those indices, but their methodologies were varied and heterogeneous. Most of the identified studies did not use those indices, precluding their inclusion in this study. A lack of these key indicators may weaken the strength of the conclusions. Accordingly, the authors propose adopting a standardized methodology for these important diabetes-related indices so that they can be compared among different studies. Fourth, the long-term effectiveness of the treatment could not be evaluated. Fifth, vascularization could not be evaluated. Vascularization is an important topic in β-cell replacement therapy, and whether islet organoids are vascularized or non-vascularized may play a crucial role in their long-term survival. However, only a few of the included studies (*12,24*) compared the effects of vascularized and non-vascularized islets. Sixth, due to the high heterogeneity of this study, other than subgroup and sensitivity analysis, more rigorous analysis, such as meta-regression might be helpful to get robust evidence. Seventh, we used Egger's test to evaluate the potential publication bias, however, due to the insufficient nature of the available literature (12 literatures) to date, this might cause biased results. Future studies should address the issues mentioned here for a more in-depth and comprehensive analysis.

In summary, transplantation of hiPSC-derived β-like cells/islets to treat diabetes is indeed a promising approach for both patients and clinicians, but it is still far from clinical use because many technological challenges must be addressed. The first consideration is safety. An example is the possibility of tumorigenicity or overgrowth of the transplanted cells/organoids. Any adverse events, such as transplantation-induced systemic immune responses and reactions at the transplantation site, should be evaluated. The second consideration is effectiveness. Is this transplantation actually effective? How long are its therapeutic effects sustained? And is it effective over the long term? The third consideration is mechanisms. What is the nature of graft behavior after implantation? Which behaviors are beneficial and which are harmful? What is the state of off-target differentiation? The fourth consideration is technology. How can graft survival be enhanced? What role does vascularization play? Only once these problems are fully addressed can hiPSC-derived β-like cells/islets be used clinically. These preclinical aspects cannot be directly studied in humans, so animal studies are a powerful tool with which to explore these aspects. However, available animal studies on this topic are thus far limited. Despite the limited number of included studies, the current study confirmed the hypoglycemic effects of transplantation. The effectiveness of both cell- and organoid-based transplantation increased over the four-week transplantation period. These findings may help with future animal studies and clinical transplantation. Thus, well-designed and insightful animal studies are anticipated.

5. Conclusions

This meta-analysis was performed to evaluate the hypoglycemic effects of hiPSC-based transplantation in animal models of diabetes. Current evidence suggests that β-like cell/islet transplantation contributes to reduced BG levels, with effectiveness tending to increase over the transplantation period. Improvements in glucose tolerance were also observed, indicating the enhanced insulin-related functional activity of the transplanted β-like cells/islets. Overall, this meta-analysis synthesizes existing preclinical evidence and it highlights the need for future well-designed studies to assess this approach's translational potential prior to clinical study.

Funding: This study was supported by grants from the National Key R&D Program of China (2025YFC3408900), the Shenzhen Medical Research Fund (SMRF.D2301015), the Shenzhen Science and Technology Program (JCYJ20220818103407016), the National Natural Science Foundation of China (82172107), the Guangdong Basic and Applied Basic Research Foundation (2024A1515011222), the Special Funds for Strategic Emerging Industry of Shenzhen (Grant No. F-2022-Z99-502266), the Shenzhen Longgang District Special Fund for Scientific and Technological Innovation (LGKCYLWS2022007), and the Shenzhen Fund for Construction of High-level Hospitals (no.23274G1001).

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

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Received January 20, 2026; Revised March 24, 2026; Accepted April 6, 2026.

Released online in J-STAGE as advance publication April 17, 2026.

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Global Health & Medicine. 2026; 8(4):265-273.
MINI-REVIEW
DOI: 10.35772/ghm.2026.01042

Multidisciplinary interventions for the prevention of aspiration pneumonia in super-aged societies: A scoping review

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Abstract: Aspiration pneumonia is associated with significant morbidity and is a leading cause of mortality among older adults, with a disproportionately high burden in super-aged societies such as Japan. Despite international guidelines recommending a multidisciplinary team (MDT) approach, evidence supporting collaborative interventions remains fragmented. We conducted a scoping review, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews guidelines, to map multidisciplinary interventions for aspiration pneumonia prevention. MEDLINE, the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature were searched through December 2024 for studies involving three or more healthcare disciplines. Among the 309 identified studies, 10 met the inclusion criteria. All included studies targeted primary prevention in high-risk populations; none addressed recurrence prevention, despite 30-day recurrence rates reaching approximately 30%. MDTs consistently included physicians, nurses, and speech-language pathologists, whereas pharmacists (2/10) and dental professionals (2/10) were relatively underrepresented, despite robust evidence supporting interventions within these professional domains. Seven studies reported a significant reduction in the incidence of aspiration pneumonia; however, the only randomized controlled trial showed no effect on pneumonia. The current evidence base, predominantly comprising observational and quality improvement studies, should be interpreted as preliminary and heterogeneous in terms of study design and outcome measurement. Evidence gaps remain in secondary and tertiary prevention and optimal team composition. Future trials in patients with prior aspiration pneumonia should investigate whether incorporation of professionals from disciplines with established intervention effectiveness, such as pharmacists and dental professionals, into MDTs translates into improved aspiration pneumonia outcomes.

***Keywords*:** aspiration pneumonia, multidisciplinary team, aged, dysphagia, scoping review

1. Introduction

Population aging is accelerating worldwide, with the number of adults aged 65 years projected to double to 1.6 billion by 2050 (*1*). Japan, the world's leading super-aged society (defined as ≥ 21% of the population aged ≥ 65 years), with 29.3% of the population at age 65 years or older (*2*), exemplifies the healthcare challenges arising from this demographic shift. Among the most pressing is aspiration pneumonia, which poses a disproportionate burden in Japan, accounting for > 60% of community-acquired pneumonia hospitalizations (*3,4*), compared with only 5%–15% in Western countries (*3,5*). This disparity highlights a unique, yet increasingly global, challenge of managing this complex and multifactorial condition in aging populations.

Aspiration pneumonia in older adults cannot be adequately managed using respiratory expertise alone. Komiya *et al*. (*6*) demonstrated that approximately 73% of older patients with pneumonia were treated by non-pulmonologists, with no significant differences in mortality compared with pulmonologist-managed cases. This finding suggests that aspiration pneumonia management extends beyond traditional respiratory medicine and requires the coordinated efforts of multiple healthcare professionals addressing its multifactorial nature.

International guidelines support this multidisciplinary approach. The British Thoracic Society Clinical Statement emphasizes that the prevention, identification, and treatment of aspiration pneumonia require a multidisciplinary team (MDT) approach involving physicians, nurses, speech-language pathologists (SLPs), nutritionists, pharmacists, and physical/occupational

therapists (*3*). Similarly, the World Health Organization's Integrated Care for Older People framework identifies domains such as malnutrition, mobility limitations, and cognitive decline that require coordinated MDT interventions (*7*). Recent efforts to systematize clinical approaches, including the "Diagnose, Treat, and SUPPORT" framework by Yoshimatsu *et al*. (*8*), cited in the Japanese Respiratory Society guidelines (*9*), have emphasized multidisciplinary collaboration as a core competency. However, although their framework identified multidisciplinary collaboration as essential, the cited evidence focused primarily on individual interventions rather than on coordinated collaborative care models.

Despite the recognized importance of multidisciplinary collaboration, the evidence base remains fragmented, with a limited understanding of how various interventions function synergistically in team-based approaches. Our previous scoping review (*10*) found limited evidence for the effectiveness of swallowing rehabilitation in patients with aspiration pneumonia, highlighting the need for comprehensive collaborative strategies.

To address these knowledge gaps, we conducted a scoping review to systematically map the existing evidence on MDT collaborative interventions for aspiration pneumonia. Our primary aims were to *i*) identify and categorize different models of multidisciplinary care for aspiration pneumonia management, *ii*) examine the effectiveness of collaborative interventions on clinical outcomes, and *iii*) identify the gaps and areas that require further investigation. This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines.

2. Literature search strategy and process

2.1. Study design and framework

This review was designed and conducted in accordance with the PRISMA-ScR guidelines (*11*) and the methodological framework proposed by Arksey and O'Malley (*12*) to ensure methodological rigor and transparency.

2.2. Search strategy

A comprehensive search was performed on August 27, 2025, targeting studies published until December 31, 2024. Three databases were searched: MEDLINE (via PubMed), the Cochrane Library, and the Cumulative Index to Nursing and Allied Health Literature (CINAHL). The search strategy combined terms related to aspiration pneumonia and multidisciplinary care: ("aspiration pneumonia") AND ("multidisciplinary" OR "interdisciplinary" OR "interprofessional" OR "collaborative" OR "medical team"). The search was limited to human studies published in English. The complete search strategy with all terms is provided in Supplementary Appendix S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=124*).

2.3. Eligibility criteria

Studies were selected using the Population, Concept, and Context framework. The population included patients diagnosed with aspiration pneumonia and high-risk groups, such as older adults with dysphagia, post-stroke patients, and individuals with neurodegenerative diseases. Eligible studies described collaborative MDT interventions involving professionals from three or more healthcare disciplines working together in a coordinated manner. This threshold was adopted to differentiate multidisciplinary intervention research from routine clinical practice. Definition of MDTs as teams comprising professionals from two or more disciplines would include physician–nurse collaborations, which represent the standard composition of inpatient care across virtually all hospitalized patients, rendering the analytical distinction between multidisciplinary interventions and conventional clinical practice less meaningful. For Context, no restrictions were applied to healthcare settings. The exclusion criteria were pediatric populations, single- or two-discipline interventions, case reports, letters, editorials, conference abstracts, review articles, guidelines, commentaries, non-English full-text articles, preprints, protocol papers without results, and qualitative studies.

2.4. Study selection and data extraction

Title and abstract screening was initially conducted by one researcher according to the predefined eligibility criteria, and the screening decisions were subsequently verified by a second researcher through independent review of the screening list. Discrepancies between the two researchers were resolved through discussion until a consensus was reached. Articles that met the inclusion criteria underwent full-text review, and ambiguous cases were similarly resolved by consensus between the two researchers. Data were extracted using a standardized form, summarizing the study characteristics, participating professionals and their disciplines, nature of interventions, outcome definitions, and main findings. The study selection process adhered to the PRISMA-ScR framework (Figure 1).

3. Evidence overview

3.1. Search results and study selection

The initial database search yielded 309 articles from MEDLINE (n = 156), Cochrane Library (n = 14), and

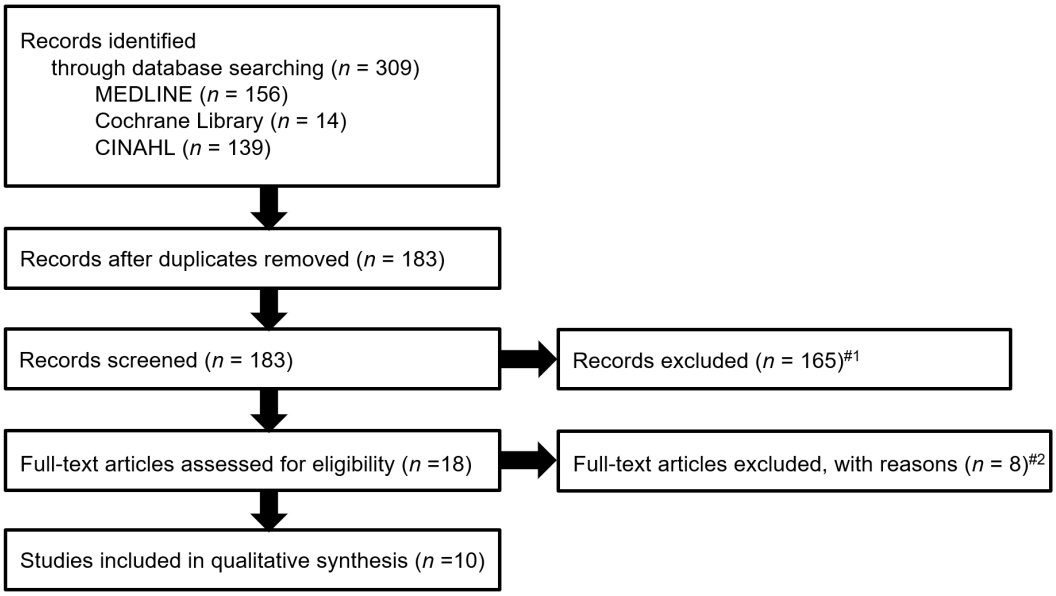

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) flow diagram for study selection. #1indicates the records excluded during title and abstract screening (*n* = 165), and #2indicates the full-text articles excluded after the eligibility assessment (*n* = 8).

CINAHL (*n* = 139). After removing the duplicates, 183 unique records were retained for screening. After screening the titles and abstracts, 18 full-text articles were assessed for eligibility. Eight articles were excluded during the full-text review: two did not evaluate aspiration pneumonia prevention, four did not address multidisciplinary collaboration, one was a descriptive study without control groups, and one had data inconsistencies between the abstract and results. Finally, 10 studies met the inclusion criteria (Figure 1).

3.2. Study characteristics

The 10 included studies (*13-22*) spanned nearly three decades (1995–2024) and used various designs: before-after studies (*n* = 3), quality improvement projects (*n* = 3), retrospective cohort studies (*n* = 3), and one randomized controlled trial (RCT) cluster. All the studies focused on high-risk populations rather than on patients with established aspiration pneumonia. The target population included post-stroke patients with dysphagia (*n* = 3), acute stroke patients (*n* = 2), older adults with swallowing disorders (*n* = 2), mixed-risk populations (*n* = 2), and older orthopedic patients (*n* = 1). The key characteristics and findings are summarized in Table 1.

3.3. Multidisciplinary team composition and interventions

The teams comprised professionals from three to seven healthcare disciplines. The most frequently represented professionals were nurses (*n* = 10), physicians (*n* = 9) and SLPs (*n* = 9). Dietitians and physical/occupational therapists were each represented in five studies, whereas pharmacists and dental professionals were included in only two studies. Interventions were categorized as comprehensive care pathways (*n* = 4), multidisciplinary rounds/teams (*n* = 3), quality improvement initiatives (*n* = 3), and standardized screening protocols (*n* = 2). The key components included dysphagia screening and assessment (*n* = 7), nutritional management (*n* = 2), medication management (*n* = 2), staff education and training (*n* = 2), communication protocols (*n* = 2), and oral care optimization (*n* = 1). As interventions were often multicomponent, the categories were not mutually exclusive.

3.4. Clinical outcomes

All the studies reported the incidence of aspiration pneumonia. Seven studies showed statistically significant reductions, one reported the elimination of new cases without statistical analysis, and two showed no significant differences. Notably, the only RCT cluster by Middleton *et al*. (*15*) demonstrated that a standardized multidisciplinary protocol reduced death and disability but did not significantly reduce the incidence of pneumonia.

4. Synthesis and implications

4.1. Effectiveness and limitations of current evidence

Most studies (7/10) reported statistically significant reductions in the incidence of aspiration pneumonia, suggesting the potential effectiveness of collaborative MDT approaches. However, this evidence remains preliminary and heterogeneous, and several important

Table 1. Summary of included studies: Multidisciplinary approaches to aspiration pneumonia prevention

No.	Authors (Year)	Title	Journal, volume (number): pages	Study design	Key findings	Multidisciplinary team composition
1	Webb DJ *et al.* (1995)	Effects of a Specialized Team on Stroke Care: The First Two Years of the Yale Stroke Program	Stroke, 26(8):1353-1357	Before–after study	Introduction of a specialized stroke team reduced length of hospital stay and urinary tract infections but did not change aspiration pneumonia incidence	Physicians, nurses, PTs/OTs
2	Rather MR *et al.* (2010)	Impact of a Stroke Admission Protocol—A Quality Improvement Project	J Clin Outcomes Manag, 17(2):75-85	Quality improvement (QI) project	Implementation of a standardized admission protocol improved adherence and reduced complications, including aspiration pneumonia	Physicians, nurses, SLPs, PTs/OTs
3	Middleton S *et al.* (2011)	Implementation of Evidence-Based Treatment Protocols to Manage Fever, Hyperglycemia, and Swallowing Dysfunction in Acute Stroke (QASC): A Cluster Randomized Controlled Trial	Lancet, 378(9791):1699-1706	Cluster randomized controlled trial	Stroke unit protocols for fever, glucose, and swallowing management reduced death and disability but did not significantly reduce pneumonia	Physicians, nurses, SLPs
4	Gandolfi M *et al.* (2014)	Improving Post-Stroke Dysphagia Outcomes Through a Standardized and Multidisciplinary Protocol: An Exploratory Cohort Study	Dysphagia, 29(6):704-712	Retrospective cohort study	A standardized multidisciplinary dysphagia protocol for reducing aspiration pneumonia, in-hospital mortality, and tube feeding at discharge	Physicians, nurses, SLPs, dietitians, PTs/OTs
5	Aoki S *et al.* (2016)	The Multidisciplinary Swallowing Team Approach Decreases Pneumonia Onset in Acute Stroke Patients	PLoS One, 11(5):e0154608	Before–after study	Establishment of a multidisciplinary swallowing team reduced aspiration pneumonia incidence from 15.9% to 6.9% in patients with acute stroke	Physicians, nurses, SLPs, dietitians, PTs/OTs, pharmacists, dental professionals
6	Sakakura K *et al.* (2017)	Impact of a Multidisciplinary Round Visit for the Management of Dysphagia Utilizing a Wi-Fi–Based Wireless Flexible Endoscopic Evaluation of Swallowing	Ann Otol RhinolLaryngol, 126(1):47-53	Retrospective cohort study	Use of Wi-Fi-based FEES during multidisciplinary rounds reduced aspiration pneumonia incidence (51.6%→13.9%) and improved FOIS scores	Physicians, nurses, SLPs, dietitians, dental professionals
7	O'Malley MB *et al.* (2018)	Project SITUP: An Interdisciplinary Quality Improvement Initiative to Reduce Aspiration Pneumonia	J Nurs Care Qual, 33(2):116-122	QI project	An interprofessional algorithm for aspiration risk screening reduced aspiration pneumonia incidence from 12 to 7 cases per 1000 patients	Physicians, nurses, SLPs
8	Teeling SP *et al.* (2019)	Reducing Risk of Nutritional Deficits by Optimizing Access to Mealtime Assistance: A Lean Six Sigma Quality Improvement Project	Int J Qual Health Care, 31(Suppl 1):6-13	QI project	A Lean Six Sigma-based feeding assistance program eliminated new cases of aspiration pneumonia and improved nutrition while reducing food waste	Nurses, SLPs, dietitians
9	Taveira I *et al.* (2021)	Recognizing Dysphagia: Implementation of an In-Hospital Screening Protocol	Irish J Med Sci, 190(2):605-608	Before–after study	Hospital-wide dysphagia screening protocol reduced aspiration pneumonia incidence (from 11.7% to 2.4%) and mortality	Physicians, nurses, SLPs
10	Higashikawa T *et al.* (2024)	Orthogeriatric Co-Management at a Regional Core Hospital as a New Multidisciplinary Approach in Japanese Hip Fracture Operation	J Orthop Sci, 29(4):273-277	Retrospective cohort study	Orthogeriatric co-management, including swallowing assessment and pharmacist input, reduced aspiration pneumonia (7.1%→2.4%) and shortened hospital stay	Physicians, nurses, SLPs, dietitians, PTs/OTs, pharmacists

Abbreviations: SLPs, speech-language pathologists; PTs, physical therapists; OTs, occupational therapists; FEES, fiberoptic endoscopic evaluation of swallowing; FOIS, Functional Oral Intake Scale.

limitations must be considered. The predominance of before-and-after studies and quality improvement projects, with only one RCT, limit the strength of the conclusions. The sole RCT cluster by Middleton *et al*. (*15*) showed no significant effect on pneumonia incidence, suggesting that the effects demonstrated in observational studies may not be reproducible with more rigorous designs.

Beyond the overall effectiveness of MDT approaches, each of the four functional intervention components central to aspiration pneumonia prevention—dysphagia screening, oral care, medication review, and nutritional management—have an established evidence base at the component level. Regarding dysphagia screening and management, screening serves as the foundational process for identifying patients at risk of aspiration, and our previous scoping review (*10*) demonstrated that subsequent compensatory approaches such as postural adjustments and food texture modification have shown effectiveness, consistent with the European Society for Swallowing Disorders and European Union Geriatric Medicine Society white paper (*23*). For nutritional management, the same scoping review (*10*) supports the effectiveness of dietary texture modification as part of compensatory strategies for reducing the aspiration risk. With respect to oral care, systematic reviews have provided robust evidence of pneumonia prevention in hospitalized older adults and nursing home residents (*24,25*). Regarding medication review, a systematic review (*26*) and individual studies have demonstrated the effectiveness of pharmacological interventions in the reduction of aspiration pneumonia (*27-29*). Thus, each of the four functional domains is supported as a component of comprehensive aspiration pneumonia prevention by existing evidence, providing the conceptual basis for the multidisciplinary framework illustrated in Figure 2.

A structured assessment of heterogeneity across the included studies revealed substantial variability among the four dimensions. First, the populations ranged from patients with acute stroke to long-term care residents and patients across multiple diagnostic groups, with widely differing baseline aspiration risk profiles. Second, the settings included acute care hospitals, rehabilitation units, long-term care facilities, and mixed settings, each with distinct staffing patterns, care continuity, and resource availability. Third, the components (combinations of dysphagia screening, oral care, medication review, and nutritional management), intensity (from single-discipline protocols to comprehensive team-based bundles), and duration of interventions varied considerably. Fourth, the outcomes of pneumonia incidence, mortality, length of stay, and process measures, were often defined heterogeneously across studies. This substantial heterogeneity inherently limits the comparability of findings across studies and the strength of conclusions that can be drawn from this body of evidence.

4.2. Gap in secondary and tertiary prevention

All identified studies targeted primary prevention in

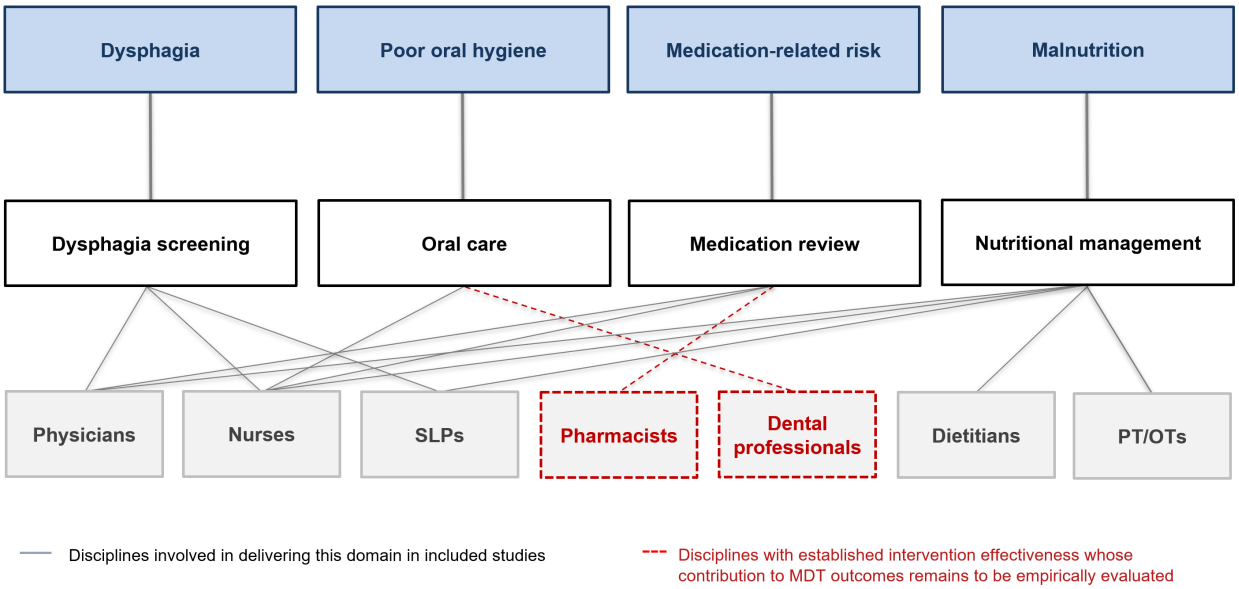

Figure 2. Conceptual framework: MDT interventions for aspiration pneumonia prevention. The framework integrates three layers: aspiration pneumonia risk factors (upper layer: dysphagia, poor oral hygiene, medication-related risk, and malnutrition), four functional intervention domains identified in this review (middle layer: dysphagia screening, oral care, medication review, and nutritional management), and professionals from seven healthcare disciplines (lower layer: physicians, nurses, speech-language pathologists, pharmacists, dental professionals, dietitians, and physical/occupational therapists). Solid lines indicate professionals involved in delivering each intervention domain across the included studies. Dashed red lines and dashed red boxes indicate pharmacists and dental professionals, whose intervention effectiveness has been established but whose contribution to MDT outcomes in aspiration pneumonia prevention remains to be empirically evaluated. *Abbreviations*: MDT, multidisciplinary team; SLPs, speech-language pathologists; PT/OTs, physical/occupational therapists.

high-risk populations, and no study examined MDT interventions in patients who had already developed aspiration pneumonia; therefore, the aspects of recurrence prevention and long-term sequela management remain essentially unaddressed. This constitutes a critical evidence gap, particularly because of the high recurrence rates. Ocrospoma and Restrepo (*30*) reported 30-day recurrence rates of approximately 30%, with mortality rates as high as 30% at 30 days and 70% at 2 years after admission. Noguchi *et al*. (*31*) further demonstrated that recurrence within 30 days increased from 13.0% for patients with 0–1 risk factor to 54.2% for those with 4 risk factors, highlighting the substantial burden and poor prognosis associated with this condition. Given the disproportionate burden of aspiration pneumonia in Japan (*4*) and the demographic trajectory of other aging societies, establishment of evidence for both recurrence prevention and sustained post-acute care is an urgent priority. The absence of MDT-based research addressing these aspects represents a critical knowledge gap that warrants prioritization in future research.

Although no included study examined MDT interventions for recurrence prevention, evidence does exist for individual intervention components that have demonstrated effectiveness in aspiration pneumonia prevention in high-risk populations, including pharmacological interventions (*27,32-34*) and oral hygiene interventions (*24,25*). The effectiveness of these intervention components, when systematically incorporated into MDT models, in preventing recurrence in patients with previous aspiration pneumonia needs to be empirically evaluated. Notably, medication review and oral care were among the less frequently incorporated interventions in the MDT models identified in this review, with medication review implemented in 2 of the 10 included studies and oral care in only 1 included study. Future studies should be specifically designed for the setting of recurrence prevention, examining whether the systematic incorporation of pharmacist-led medication review and dental professional-led oral care into MDT strategies translates into reduced recurrence in patients with previous aspiration pneumonia.

4.3. Underrepresentation of pharmacists and dental professionals

Analysis of the MDT composition revealed a core triad of physicians, nurses, and SLPs, with relatively limited participation of pharmacists (2/10 studies) and dental professionals (2/10 studies). This pattern raises questions, given that interventions within these professional domains, such as pharmacological optimization and oral hygiene care, have demonstrated effectiveness in preventing aspiration pneumonia in other study contexts. Santos *et al*. (*26*) examined 13 intervention studies for aspiration pneumonia prevention and demonstrated positive results in three pharmacological intervention studies (*32-34*) and one oral hygiene study (*35*). Regarding pharmacological interventions, Arai *et al*. (*27*) showed that angiotensin-converting enzyme inhibitors significantly reduced the risk of aspiration pneumonia. Additionally, our analysis using the Japanese Adverse Drug Event Report database (*28*) revealed that anticholinergic drugs with dopamine-blocking properties are the primary risk factors for aspiration pneumonia, which requires the expertise of pharmacists. Notably, the 2022 revision of Japanese healthcare reimbursement removed pharmacists from becoming mandatory members of the multidisciplinary dysphagia team (*29*). Nevertheless, our clinical study demonstrated that 22.0% of patients requiring MDT dysphagia intervention required pharmaceutical intervention (*29*). The effect of the 2022 reimbursement change on the quality of multidisciplinary dysphagia care remains an empirical question that warrants further investigation. To our knowledge, no study has directly evaluated whether the incorporation of pharmacists or dental professionals into MDTs improves aspiration pneumonia outcomes; this absence of direct evidence itself constitutes an important research gap.

Systematic reviews have provided robust evidence regarding oral care. Sjögren *et al*. (*24*) found absolute risk reductions of 6.6–11.7% for oral hygiene interventions in hospitalized older adults and nursing home residents, and Kaneoka *et al*. (*25*) demonstrated a significant reduction in pneumonia risk (risk ratio, 0.61; 95% confidence interval: 0.40–0.91; $p = 0.02$) in non-ventilated patients. Prospective studies should determine whether the underrepresentation of these disciplines in current MDT models reflects a missed opportunity for optimization, or whether their integration would translate into measurable outcome improvements.

4.4. Role distribution and evidence-based effectiveness of different disciplines

Our previous scoping review (*10*) revealed that evidence for exercise-based swallowing rehabilitation in aspiration pneumonia prevention remains limited, although compensatory approaches such as dietary texture modification and postural adjustments have shown effectiveness. This is consistent with the white paper of the European Society for Swallowing Disorders and European Union Geriatric Medicine Society (*23*), which emphasizes the importance of compensatory strategies in older adult populations. This suggests that effective aspiration prevention may benefit from a distributed approach in which each discipline contributes specific expertise to complementary intervention strategies rather than relying primarily on any single professional group. In healthcare settings where SLPs, who play a central role in swallowing rehabilitation, may not be permanently available, foundational aspiration prevention interventions can still be effectively delivered through

collaboration among dietitians, physical/occupational therapists, and nursing staff, although specialized dysphagia assessment remains within the scope of SLP practice.

4.5. Factors affecting the effectiveness of multidisciplinary collaboration

Whether involving more disciplines is more effective in the management of aspiration pneumonia has not yet been verified. Previous studies have emphasized that the effectiveness of MDTs depends largely on communication, coordination, and collaborative interactions rather than the number of participating disciplines (*36,37*). What appears crucial is not simply the size of the team but the quality of collaboration within it. Future studies should focus on a detailed analysis of the specific intervention content delivered by each discipline, interactions between interventions, and mechanisms by which they affect outcomes, to identify the most effective MDT collaboration models.

4.6. Implications for super-aged societies worldwide

Although the disproportionate burden of aspiration pneumonia in Japan provides a particularly compelling case for optimizing MDT approaches, the challenges identified in this review are relevant globally. As the population ages worldwide, healthcare systems increasingly face the need to develop efficient, evidence-based, and collaborative care models for aspiration pneumonia prevention. The gaps identified in study design quality, team composition, and prevention strategies beyond the primary level represent priorities for the international research community. Developing cost-effective intervention models adaptable to diverse healthcare settings, including resource-limited environments, is essential for addressing this growing global health challenge.

4.7. Limitations

This study has several limitations. First, the inclusion criterion of professionals from three or more disciplines may have excluded effective two-discipline collaborations. However, this threshold was necessary to ensure that included studies addressed the multifactorial nature of aspiration pneumonia and to differentiate multidisciplinary intervention research from studies describing routine collaborative care. Second, our search was limited to MEDLINE, the Cochrane Library, and CINAHL, potentially missing relevant studies from other databases. Furthermore, our search strategy required explicit terms reflecting multidisciplinary or interprofessional care, and this may have excluded studies describing collaborative interventions under alternative terminology. This limitation reflects an inherent trade-off between specificity and sensitivity in search strategies for scoping review. Third, the heterogeneous definitions and implementation methods of "multidisciplinary interventions" across studies limited the detailed analysis of specific intervention content. In addition, the definition of aspiration pneumonia varied across the included studies. As we have previously demonstrated (*38*), the lack of unified diagnostic criteria for aspiration pneumonia poses inherent challenges for outcome comparison across studies. Finally, the screening process involved one reviewer with verification by a second reviewer. Although this approach is consistent with the methodological flexibility permitted in scoping review guidelines, including the Joanna Briggs Institute methodology, and discrepancies were resolved by consensus, the possibility of selection bias cannot be entirely excluded.

5. Conclusions

This scoping review identified 10 studies examining MDT interventions for aspiration pneumonia prevention, revealing critical gaps: predominance of observational study designs, exclusive focus on primary prevention despite high recurrence rates, and limited participation of pharmacists and dental professionals in MDTs despite the established effectiveness of interventions within these professional domains. The current evidence base remains preliminary, with substantial heterogeneity in study designs, populations, and outcome definitions, precluding definitive conclusions regarding the comparative effectiveness of specific MDT compositions or intervention components. Future studies should prioritize rigorous RCTs targeting patients with established disease, determine whether the inclusion of underrepresented disciplines with proven intervention effectiveness translates into improved clinical outcomes, and develop comprehensive care models that address the complex and multifactorial nature of aspiration pneumonia across diverse healthcare systems facing population aging.

Funding: None.

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

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Received April 22, 2026; Revised May 20, 2026; Accepted June 9, 2026.

Released online in J-STAGE as advance publication June 23, 2026.

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Global Health & Medicine. 2026; 8(4):274-284.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2026.01050

Factors associated with digital health literacy among community-dwelling older adults in Japan: An in-person cross-sectional study

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Abstract: Digital health literacy (DHL) is increasingly important as health information, appointment systems, patient portals, and other services move online. However, evidence in older adults remains limited and is often based on online surveys that may underrepresent digitally disadvantaged groups. This in-person cross-sectional study examined factors associated with DHL among 91 community-dwelling older adults in Japan. Participants completed paper-based questionnaires and performance-based assessments, including a modified 15-item score from the Japanese Digital Health Literacy Instrument (DHLI-J), the Japanese version of the Montreal Cognitive Assessment (MoCA-J), and the Nine-Hole Peg Test (NHPT). Group comparisons, bivariate correlations, and hierarchical multiple regression analyses were performed, with structural equation modeling (SEM) as a supplementary analysis. Higher modified DHLI-J scores were associated with younger age, longer personal computer use, better cognitive function, better manual dexterity, greater digital confidence and interest, and better well-being. In the final regression model (adjusted R^2 = 0.37), older age was independently associated with lower modified DHLI-J scores, whereas better cognitive function and greater confidence in using digital devices were independently associated with higher scores. The exploratory supplementary SEM showed acceptable fit ($\chi^2(11) = 13.96$, $p = 0.24$; $\chi^2/df = 1.27$; comparative fit index (CFI) = 0.97; root mean square error of approximation (RMSEA) = 0.06) and indicated positive cross-sectional associations between digital attitudes and DHL and between DHL and well-being; these associations should not be interpreted as causal. These findings may inform user- and system-level strategies intended to reduce digital exclusion and support more equitable digital health access, although access to digital health services and equity outcomes were not measured.

***Keywords*:** digital divide, digital confidence, community-based assessment, health care access, well-being

1. Introduction

Digital transformation in health care has accelerated worldwide, with health information, appointment systems, telehealth, and patient portals increasingly delivered through digital technologies (*1*). However, benefits of these services are not distributed evenly. Older adults may face barriers related to access, usability, confidence, and opportunities for meaningful engagement, resulting in persistent digital exclusion, even when devices are available (*1,2*). In Japan, one of the most rapidly aging countries, this issue is particularly important as the public and private sectors continue to expand digital health-related services and expect citizens to navigate them independently.

Digital health literacy (DHL) refers to the skills required to seek, understand, appraise, and apply digital health information and services (*2*). The Digital Health Literacy Instrument (DHLI) conceptualizes DHL as a multidimensional construct that includes operational and navigation skills, information searching, reliability evaluation, and relevance determination (*2*). A Japanese version of the DHLI (DHLI-J) was recently developed, enabling empirical examination of DHL in older Japanese populations (*3*). Existing reviews indicate that DHL in later life is associated with age, educational and socioeconomic resources, confidence-related constructs, health status, and broader social resources (*4-7*). At the same time, these reviews noted considerable heterogeneity in study populations and measurement approaches, making it difficult to determine which correlates remain robust when assessing digital skills in older adults who are not selected on the basis of digital participation.

A methodological challenge in this literature is that many studies rely on online surveys (*4-7*).

Because online participation requires a degree of digital access and competence, such designs may systematically underrepresent older adults with lower skills, confidence, or greater functional difficulty (*8,9*). Consequently, the average DHL and its correlates may be estimated from samples that are already selectively digitally engaged. This limitation is especially important when the variables of interest include cognition and hand function, because these factors may influence not only digital task performance but also willingness or ability to participate in online-only research. In-person assessment may reduce selection based on the ability or willingness to complete an online survey and may therefore include device-owning older adults with lower digital confidence or greater functional limitation. However, an in-person design does not capture digital exclusion arising from a lack of device ownership, which may represent a barrier before DHL can be assessed.

The functional demands of contemporary digital health environments are increasingly complex (*2,8*). Searching for health information, navigating websites or patient portals, interpreting unfamiliar terminology, and recovering from input errors can place substantial demands on attention, working memory, comprehension, and executive control (*2,8*). Likewise, common digital operations, such as tapping, scrolling, typing, and handling authentication procedures, depend on fine motor control and manual dexterity (*10,11*). Although cognitive aging and age-related upper-limb changes are well recognized, few DHL studies have directly integrated performance-based cognitive and manual assessments into explanatory models, especially within Japanese community settings (*4-7,10,11*). Clarifying these task-related demands is important because they represent plausible real-world barriers, even for older adults who nominally have access to devices.

DHL may also have broader relevance to healthy aging, community participation, and equitable access to care. Technology use has been linked to quality of life and psychosocial well-being among older adults (*12*). Digital inclusion may support independence, access to health information, communication, and health-related decision-making, whereas limited DHL may deepen existing inequities when essential services are shifted online. Scoping reviews suggest that DHL is positively associated with mental health and well-being (*5-7*), although evidence focused specifically on community-dwelling older adults remains limited. From a public health perspective, clarifying how cognitive function, manual dexterity, digital attitudes, and well-being are interconnected may help municipalities, community health providers, and health systems design digital services that are not only available but also genuinely usable for older adults.

This study aimed to identify factors associated with DHL among community-dwelling older adults in Japan using an in-person assessment. Specifically, we compared participant characteristics across descriptive categories of the modified DHLI-J score, examined bivariate associations between the modified DHLI-J score and demographic, digital-use, cognitive, physical, and psychosocial variables, and identified its independent correlates using hierarchical multiple regression. In addition, we used supplementary structural equation modeling (SEM) to examine a prespecified pattern of cross-sectional associations among age, cognitive/physical functioning, digital attitudes, DHL, and well-being. By combining in-person community-based assessments with functional and psychosocial measures, this study sought to generate methodologically sound evidence that may inform strategies for more equitable digital health access in an aging society.

2. Materials and Methods

2.1. Study design and participants

This cross-sectional study recruited community-dwelling older adults from a municipality in Japan through community centers and local outreach linked to community-based preventive activities. The eligibility criteria were age ≥ 65 years and ownership of a personal computer or mobile device, such as a smartphone or tablet. Individuals were excluded if cognitive impairment, including dementia, made it difficult to complete the questionnaire or if informed consent could not be obtained. Individuals were also excluded if they were unable to rise from a chair, maintain standing, or walk, because these abilities were required to complete the physical function assessments. Written informed consent was obtained from all participants.

In total, 96 individuals attended the assessment sessions. Five were not included in the final analytical sample: one did not provide informed consent, one did not meet the prespecified device-ownership eligibility criterion because they owned neither a personal computer nor a mobile device, two were aged < 65 years, and one had incomplete questionnaire data. The final sample included 91 participants.

The study was approved by the Research Ethics Committee of the Faculty of Human Sciences, University of Tsukuba (Tokyo Area Committee) (approval number: TO23-112) and conducted in accordance with the Declaration of Helsinki.

2.2. Procedures

Participants completed paper-based questionnaires and underwent in-person assessments administered by trained rehabilitation professionals. Data were collected across two community assessment sessions. The in-

person design was chosen to reduce reliance on online survey completion among device-owning participants and to measure cognitive and physical functions directly.

2.3. Measures

DHL was assessed using the DHLI-J (*3*). The full DHLI-J consists of 21 items covering seven domains: operational skills, information searching, evaluating reliability, determining relevance, navigation skills, adding self-generated content, and protecting privacy. Items 16–18 assess the ability to add self-generated content, whereas items 19–21 assess privacy protection when posting messages on web forums, community websites, or social media. Because of substantial noncompletion of these six posting-related items, the content-creation and privacy-protection domains were excluded from the score. The modified score was the mean of items 1–15 after reverse scoring. Possible scores ranged from 1 to 4, with higher scores indicating greater DHL. Internal consistency of the retained 15 items was assessed using Cronbach's alpha. This modified 15-item score covers five of the seven original DHLI-J domains and should not be regarded as psychometrically equivalent to the validated 21-item DHLI-J.

Cognitive function was assessed using the Japanese version of the Montreal Cognitive Assessment (MoCA-J) (*13*). Manual dexterity was measured with the Nine-Hole Peg Test (NHPT), with shorter completion times indicating better dexterity. The NHPT has demonstrated acceptable reliability in adult patients (*14*). The test was administered once for each hand, and the mean completion times for the dominant and nondominant hands were used for analysis.

Physical function was characterized by grip strength, usual gait speed, and skeletal muscle index (SMI). Grip strength was measured twice per hand, and the maximum value for each hand was recorded; the mean of the left and right maxima was used for analysis. Usual gait speed was assessed using a 6-m walk test performed twice at a comfortable pace, and the mean speed was calculated. Body composition was assessed using the InBody 570 (InBody Co., Ltd., Seoul, Korea), from which SMI was derived.

Additional variables included age, sex, body mass index (BMI), number of cohabiting family members, educational attainment, self-rated economic status, current digital device use, years of digital device use, daily duration of digital device use, confidence in using digital devices, and interest in digital technologies. Confidence in using digital devices was assessed using a single item with five response options: not confident at all, not confident, neutral, confident, and very confident. Responses were coded from 1 to 5, with higher scores indicating greater confidence. Interest in digital technologies was assessed using a separate single item with five response options: not interested at all, not very interested, neutral, interested, and very interested. Responses were coded from 1 to 5, with higher scores indicating greater interest. Well-being was measured with the World Health Organization Five Well-Being Index (WHO-5) (*15,16*). Frailty risk was screened with the Kihon Checklist (KCL). Life satisfaction was recorded as a supplementary psychosocial variable.

2.4. Sample size planning

The sample-size calculation was based on the planned bivariate association analysis. Using G*Power version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany), a minimum sample of approximately 82 participants was estimated to detect a medium correlation ($r = 0.30$) with an alpha of 0.05 and power of 0.80. The final analyzable sample included 91 participants. This calculation was not specifically designed to establish adequate statistical power for the full 11-predictor regression model or the supplementary SEM.

2.5. Statistical analysis

For descriptive comparison only, participants were divided at the midpoint of the modified 1–4 DHLI-J score into groups with scores ≥ 2.5 and < 2.5. This threshold has not been validated as a clinical or public health cutoff. All primary correlation and regression analyses treated the modified DHLI-J score as a continuous variable. Between-group comparisons used independent-samples *t* tests for approximately normally distributed continuous variables, Mann–Whitney *U* tests for non-normally distributed variables, Fisher's exact tests for 2×2 categorical variables, and Fisher–Freeman–Halton exact tests for $r \times c$ contingency tables. No inferential tests were conducted for variables with no between-group variation.

Bivariate associations between the modified 15-item DHLI-J score and study variables were examined using Pearson or Spearman correlation coefficients, as appropriate. No adjustment for multiple comparisons was applied; therefore, the between-group comparisons and bivariate correlation analyses should be interpreted as exploratory. Hierarchical multiple linear regression analyses were performed using the modified 15-item DHLI-J mean score as the dependent variable. Demographic variables were entered into Model 1; cognitive and physical function variables were added to Model 2; and digital attitudes were added to Model 3. Variables were selected to reflect plausible explanatory domains rather than to maximize statistical parsimony alone. Multicollinearity was assessed with tolerance and variance inflation factor values. Independence of residuals was evaluated using the Durbin–Watson statistic. Linearity and homoscedasticity were assessed with a plot

of standardized residuals against standardized predicted values, and normality of residuals was examined using a normal probability–probability (P–P) plot. Influential observations were evaluated using standardized residuals and Cook's distance. A sensitivity analysis was performed by repeating the final regression model after excluding the observation with the largest Cook's distance.

As a supplementary exploratory analysis, SEM was used to examine a prespecified pattern of cross-sectional associations among age, a latent cognitive/physical function construct, a latent digital attitudes construct, the modified DHLI-J score, and well-being. Model fit was evaluated with the chi-square statistic, comparative fit index (CFI), and root mean square error of approximation (RMSEA). Because the sample size was planned for bivariate association analysis and the data were cross-sectional, the SEM was interpreted as exploratory; the directions of the specified paths did not establish temporal ordering or causal relationships.

All analyses were performed using IBM SPSS Statistics version 30.0 and IBM SPSS Amos version 30.0 (IBM Japan Ltd., Tokyo, Japan). Statistical significance was set at $p < 0.05$.

3. Results

3.1. Participant characteristics and group comparisons

The participant flow is summarized in Figure 1. All 91 participants (100%) completed items 1–15, whereas 43 (47.3%) completed all six posting-related items (items 16–21). Cronbach's alpha for the modified 15-item DHLI-J was 0.94. Table 1 presents participant characteristics by descriptive DHLI-J score group. The participants (n = 91) had a mean age of 74.7 ± 4.6 years; 71 (78%) were women and 20 (22%) were men. Participants scoring ≥ 2.5 were younger than those scoring < 2.5 (73.6 ± 3.9 *vs.* 76.0 ± 5.3 years, $p = 0.014$), reported better self-rated economic status ($p = 0.032$), and were more likely to use a personal computer (77% *vs.* 49%, $p = 0.008$). They also had a longer duration of personal computer use (22.6 ± 11.1 *vs.* 15.2 ± 9.2 years, $p = 0.015$).

In addition, participants with modified DHLI-J scores ≥ 2.5 reported greater confidence in using digital devices ($p = 0.008$) and greater interest in digital technologies ($p = 0.003$). They also had better well-being (WHO-5, 17.2 ± 4.7 *vs.* 14.7 ± 4.6; $p = 0.014$), faster NHPT completion time (median, 21.1 *vs.* 22.6 s; $p = 0.028$), and higher MoCA-J scores (median, 26 *vs.* 24; $p = 0.001$). No between-group differences were observed in sex, BMI, number of cohabiting family members, educational attainment, years of smartphone use, daily duration of digital device use, life satisfaction score, KCL score, grip strength, SMI, or gait speed (all $p > 0.05$). These descriptive comparisons suggest that scores ≥ 2.5 were associated with more favorable digital attitudes and better cognitive and manual performance rather than with general physical function alone; however, the grouping should not be interpreted as distinguishing clinically high from low DHL.

3.2. Bivariate associations with the modified DHLI-J score

The correlational analyses are shown in Table 2. Higher modified DHLI-J scores were negatively associated with age ($r = -0.35$, $p < 0.001$) and NHPT completion time ($\rho = -0.25$, $p = 0.019$), indicating lower DHL with older age and slower manual performance. They were also positively associated with years of smartphone use (ρ =

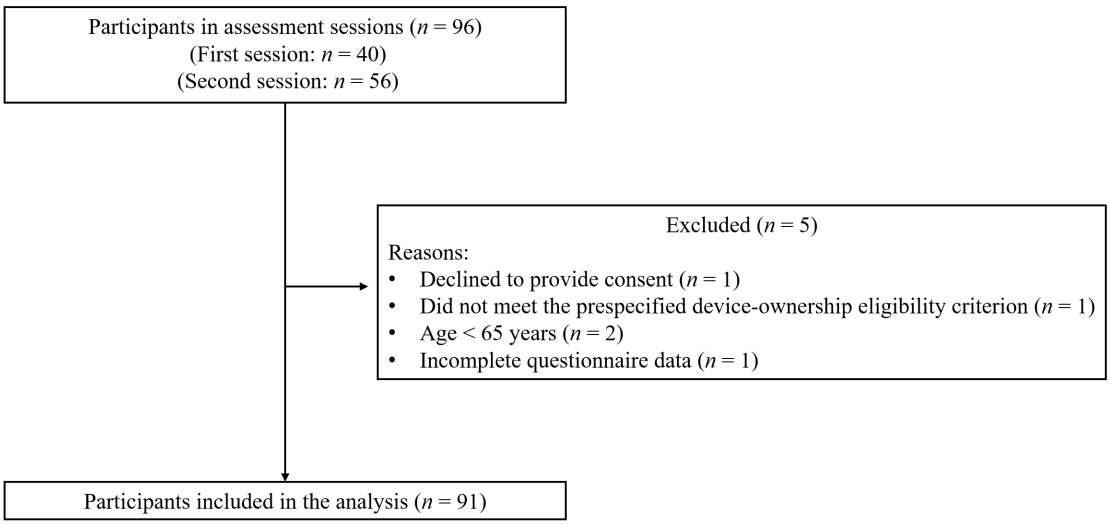

Figure 1. Participant flow diagram. *Note*: A total of 96 individuals attended the assessment sessions (Session 1: $n = 40$; Session 2: $n = 56$). Five individuals were not included in the final analytical sample because they did not provide informed consent (n = 1), did not meet the prespecified device-ownership eligibility criterion ($n = 1$), were aged < 65 years ($n = 2$), or had incomplete questionnaire data ($n = 1$). The final analytical sample included 91 participants.

Table 1. Participant characteristics according to modified 15-item DHLI-J groups

Variable	Total (n = 91)	Modified DHLI-J score ≥ 2.5 (n = 52)	Modified DHLI-J score < 2.5 (n = 39)	p
Age, years, mean ± SD[a]	74.7 ± 4.6	73.6 ± 3.9	76.0 ± 5.3	0.014*
Sex, n (%)[b]				0.804
Male	20 (22)	12 (23)	8 (21)	
Female	71 (78)	40 (77)	31 (79)	
BMI, kg/m², mean ± SD[a]	22.5 ± 2.8	22.7 ± 2.6	22.4 ± 3.0	0.643
Long-term care insurance certification, n (%)[b]				
Not certified	91 (100)	52 (100)	39 (100)	—
Number of cohabiting family members, n (%)[c]				0.292
0	15 (17)	5 (10)	10 (28)	
1	40 (44)	26 (50)	14 (36)	
2	25 (27)	15 (29)	10 (26)	
3	8 (9)	4 (8)	4 (10)	
4	0 (0)	0 (0)	0 (0)	
5	3 (3)	2 (4)	1 (3)	
Educational attainment, n (%)[c]				0.193
Junior high school	1 (1)	0 (0)	1 (3)	
High school	54 (59)	33 (63)	21 (54)	
Vocational school	10 (11)	3 (6)	7 (18)	
Junior college	16 (18)	11 (21)	5 (13)	
University	9 (10)	4 (8)	5 (13)	
Graduate school	1 (1)	1 (2)	0 (0)	
Economic status, n (%)[c]				0.032*
Very poor	0 (0)	0 (0)	0 (0)	
Poor	24 (27)	9 (17)	15 (38)	
Comfortable	64 (70)	40 (77)	24 (62)	
Very comfortable	3 (3)	3 (6)	0 (0)	
Digital devices currently used, n (%)[b]				
Smartphone (yes)	91 (100)	52 (100)	39 (100)	—
Personal computer (yes)	59 (65)	40 (77)	19 (49)	0.008**
Tablet (yes)	18 (20)	9 (17)	9 (23)	0.597
Feature phone (yes)	15 (16)	8 (15)	7 (18)	0.781
Duration of digital device use, years				
Smartphone, median [IQR][d]	8 [5–10]	10 [6–10]	6 [5–10]	0.326
Personal computer, mean ± SD[a]	20.2 ± 11.0	22.6 ± 11.1	15.2 ± 9.2	0.015*
Tablet, median [IQR][d]	5 [3–7]	7 [5–10]	4 [3–7]	0.387
Feature phone, median [IQR][d]	15 [10–20]	12.5 [10–25]	20 [8–20]	0.955
Daily duration of digital device use, n (%)[c]				0.877
Less than 30 min	18 (20)	9 (17)	9 (23)	
30–59 min	34 (37)	19 (37)	15 (38)	
60–119 min	28 (31)	17 (33)	11 (28)	
120–179 min	7 (8)	5 (10)	2 (5)	
≥ 180 min	4 (4)	2 (4)	2 (5)	
Confidence in using digital devices, n (%)[c]				0.008**
Not confident at all	7 (8)	3 (6)	4 (10)	
Not confident	39 (43)	16 (31)	23 (59)	
Neutral	40 (44)	28 (54)	12 (31)	
Confident	5 (5)	5 (10)	0 (0)	
Very confident	0 (0)	0 (0)	0 (0)	
Interest in digital technologies, n (%)[c]				0.003***
Not interested at all	1 (1)	0 (0)	1 (3)	
Not very interested	21 (23)	7 (13)	14 (36)	
Neutral	27 (30)	13 (25)	14 (36)	
Interested	38 (42)	28 (54)	10 (26)	
Very interested	4 (4)	4 (8)	0 (0)	
WHO-5 score, mean ± SD[a]	16.1 ± 4.8	17.2 ± 4.7	14.7 ± 4.6	0.014*
Life satisfaction score, median [IQR][d]	7 [5–8]	8 [5–9]	7 [5–8]	0.066
Modified 15-item DHLI-J mean score, mean ± SD[a]	2.49 ± 0.54	2.88 ± 0.29	1.98 ± 0.32	< 0.001***
Kihon Checklist score, median [IQR][d]	3 [1–5]	2.5 [1–4.5]	3 [2–5]	0.387
Grip strength, kg, median [IQR][d]	23.5 [21.0–28.5]	24.0 [21.0–29.5]	23.5 [20.5–28.5]	0.558

Note: Values are reported as mean ± SD, median [IQR], or n (%). Participants were categorized descriptively using modified DHLI-J scores ≥ 2.5 and < 2.5; this midpoint is not a validated clinical or public health cutoff. [a]Independent-samples t-test; [b]Fisher's exact test (2 × 2); [c]Fisher–Freeman–Halton exact test (2 × k); [d]Mann–Whitney U test. No statistical test was performed for variables with no between-group variation (—), including long-term care insurance certification and smartphone use. *p < 0.05, **p < 0.01, ***p < 0.001. *Abbreviations*: DHLI-J, Japanese version of the Digital Health Literacy Instrument; BMI, body mass index; WHO-5, World Health Organization Five Well-Being Index; KCL, Kihon Checklist; SMI, skeletal muscle index; MoCA-J, Japanese version of the Montreal Cognitive Assessment; SD, standard deviation; IQR, interquartile range.

Table 1. Participant characteristics according to modified 15-item DHLI-J groups (continued)

Variable	Total (n = 91)	Modified DHLI-J score ≥ 2.5 (n = 52)	Modified DHLI-J score < 2.5 (n = 39)	p
Skeletal muscle index (SMI), median [IQR][d]	6.20 [5.80–7.00]	6.30 [5.85–7.00]	6.10 [5.75–6.90]	0.659
Usual gait speed, m/s, mean ± SD[a]	1.37 ± 0.18	1.39 ± 0.20	1.34 ± 0.16	0.234
Nine-Hole Peg Test, s, median [IQR][d]	21.4 [19.8–23.8]	21.1 [19.7–22.7]	22.6 [20.2–27.7]	0.028*
MoCA-J score, median [IQR][d]	25 [22–27]	26 [24–27.5]	24 [20–26]	0.001**

Note: Values are reported as mean ± SD, median [IQR], or n (%). Participants were categorized descriptively using modified DHLI-J scores ≥ 2.5 and < 2.5; this midpoint is not a validated clinical or public health cutoff. [a]Independent-samples t-test; [b]Fisher's exact test (2 × 2); [c]Fisher–Freeman–Halton exact test (2 × k); [d]Mann–Whitney U test. No statistical test was performed for variables with no between-group variation (—), including long-term care insurance certification and smartphone use. *p < 0.05, **p < 0.01, ***p < 0.001. *Abbreviations*: DHLI-J, Japanese version of the Digital Health Literacy Instrument; BMI, body mass index; WHO-5, World Health Organization Five Well-Being Index; KCL, Kihon Checklist; SMI, skeletal muscle index; MoCA-J, Japanese version of the Montreal Cognitive Assessment; SD, standard deviation; IQR, interquartile range.

Table 2. Correlations between the modified 15-item DHLI-J score and participant characteristics and functional measures

Variable	Correlation coefficient	p
Age (years)[†]	r = –0.35	< 0.001***
BMI (kg/m²)[†]	r = 0.06	0.558
Years of smartphone use[‡]	ρ = 0.21	0.046*
Years of tablet use[‡]	ρ = 0.38	0.124
Years of personal computer use[†]	r = 0.33	0.012*
Years of feature phone use[‡]	ρ = 0.13	0.639
WHO-5[†]	r = 0.35	< 0.001***
Kihon Checklist (KCL)[‡]	ρ = –0.21	0.050
Life satisfaction[‡]	ρ = 0.27	0.010*
Grip strength (kg)[‡]	ρ = 0.09	0.414
Nine-Hole Peg Test (s)[‡]	ρ = –0.25	0.019*
Skeletal muscle index (SMI)[‡]	ρ = –0.01	0.899
MoCA-J[‡]	ρ = 0.37	< 0.001***
Usual gait speed (m/s)[†]	r = 0.11	0.290
Confidence in using digital devices[‡]	ρ = 0.62	< 0.001***
Interest in digital technologies[‡]	ρ = 0.56	< 0.001***

Note: [†]Pearson's correlation coefficient; [‡]Spearman's rank-order correlation coefficient. *Correlations for years of device use were calculated among users of each device.* *p < 0.05, ***p < 0.001. *Abbreviations*: DHLI-J, Japanese version of the Digital Health Literacy Instrument; BMI, body mass index; WHO-5, World Health Organization Five Well-Being Index; KCL, Kihon Checklist; SMI, skeletal muscle index; MoCA-J, Japanese version of the Montreal Cognitive Assessment.

0.21, p = 0.046), years of personal computer use (r = 0.33, p = 0.012), confidence in using digital devices (ρ = 0.62, p < 0.001), interest in digital technologies (ρ = 0.56, p < 0.001), MoCA-J score (ρ = 0.37, p < 0.001), WHO-5 score (r = 0.35, p < 0.001), and life satisfaction (ρ = 0.27, p = 0.010). KCL score showed a borderline negative association with the modified DHLI-J score (ρ = −0.21, p = 0.050). These patterns suggest that DHL was most strongly associated with digital attitudes, although it was also meaningfully associated with cognition, manual dexterity, and subjective well-being.

3.3. Hierarchical multiple regression

The results of the hierarchical multiple regression analysis are presented in Table 3. In Model 1, older age and poorer self-rated economic status were associated with lower modified DHLI-J scores. After cognitive and physical variables were added to Model 2, the MoCA-J score emerged as a significant positive correlate, whereas association with economic status was attenuated. In the final model (Model 3), which also included digital attitudes, older age remained independently associated with a lower modified DHLI-J score (B = −0.03, p < 0.01), whereas a higher MoCA-J score (B = 0.04, p < 0.05) and greater confidence in using digital devices (B = 0.17, p < 0.05) were independently associated with a higher modified DHLI-J score. The final model explained 44.8% of the variance in the modified DHLI-J score (adjusted R^2 = 0.37). Interest in digital technologies was not statistically significant after accounting for confidence and the other covariates (B = 0.12, p > 0.05).

Regression diagnostics indicated no substantial violations of the model assumptions. In the final model, tolerance values ranged from 0.204 to 0.928 and variance inflation factors ranged from 1.078 to 4.905, indicating no severe multicollinearity. The Durbin–Watson statistic was 2.172. Standardized residuals ranged from −1.775 to 2.106. The plot of standardized residuals against standardized predicted values showed no clear evidence of nonlinearity or heteroscedasticity, and the normal P–P plot indicated no substantial departure from normality. The maximum Cook's distance was 0.119. A sensitivity analysis excluding the observation with the largest Cook's distance did not materially alter the main findings; therefore, all 91 participants were retained in the primary analysis.

3.4. Supplementary exploratory structural equation model

As a supplementary exploratory analysis, SEM was used to examine prespecified cross-sectional associations among age, cognitive/physical functioning, digital attitudes, DHL, and well-being (Figure 2). The model showed acceptable fit: $\chi^2(11)$ = 13.96, p = 0.24; χ^2/df = 1.27; CFI = 0.97; RMSEA = 0.06. Age was negatively

associated with the latent cognitive/physical function construct (β = −0.49, p = 0.002). Within the specified model, digital attitudes were positively associated with DHL (β = 0.45, p = 0.001), and DHL was positively associated with well-being (β = 0.34, p < 0.001). The direct paths from the cognitive/physical function construct to DHL (β = 0.56, p = 0.074) and from age to DHL (β = −0.04, p = 0.820) were not statistically significant. Given the cross-sectional design and modest sample size, these coefficients describe associations within the specified model and do not establish temporal ordering or causal relationships.

4. Discussion

4.1. Main findings

This in-person cross-sectional study examined factors associated with DHL among community-dwelling older adults in Japan and yielded three main findings.

Table 3. Hierarchical multiple regression models for the modified 15-item DHLI-J mean score

Factor	Model 1 B (SE)	Model 1 β	Model 2 B (SE)	Model 2 β	Model 3 B (SE)	Model 3 β
Age, years	–0.04 (0.01)***	–0.38***	–0.04 (0.01)**	–0.30**	–0.03 (0.01)**	–0.25**
Sex (female = 1)	0.11 (0.13)	0.09	0.42 (0.25)	0.32	0.20 (0.24)	0.15
Educational attainment	–0.02 (0.05)	–0.03	–0.03 (0.05)	–0.06	–0.01 (0.04)	–0.04
Economic status	0.35 (0.10)***	0.33***	0.26 (0.10)*	0.24*	0.19 (0.10)	0.17
MoCA-J score			0.04 (0.02)*	0.27*	0.04 (0.02)*	0.23*
Nine-Hole Peg Test (s)			–0.02 (0.01)	–0.19	–0.02 (0.01)	–0.15
Skeletal muscle index (SMI)			–0.05 (0.10)	–0.09	0.03 (0.09)	0.06
Usual gait speed, m/s			–0.02 (0.28)	–0.01	0.08 (0.26)	0.03
Grip strength, kg			–0.01 (0.01)	–0.10	–0.01 (0.01)	–0.17
Confidence in using digital devices					0.17 (0.08)*	0.23*
Interest in digital technologies					0.12 (0.06)	0.20

Note: The dependent variable was the modified 15-item DHLI-J mean score. *B*, unstandardized coefficient; SE, standard error; β, standardized coefficient. Model 1 included age, sex, educational attainment, and economic status as covariates. Model 2 additionally included the MoCA-J score, Nine-Hole Peg Test completion time, skeletal muscle index, gait speed, and grip strength. Model 3 also included confidence in using digital devices and interest in digital technologies. Sex was coded as 1 = female and 0 = male. R^2: Model 1 = 0.23, Model 2 = 0.34, Model 3 = 0.45. Adjusted R^2: Model 1 = 0.20, Model 2 = 0.26, Model 3 = 0.37. $F(df_1, df_2)$: Model 1 = 6.58*** (4, 86), Model 2 = 4.55*** (9, 81), Model 3 = 5.82*** (11, 79). *p < 0.05, **p < 0.01, ***p < 0.001. *Abbreviations*: DHLI-J, Japanese version of the Digital Health Literacy Instrument; MoCA-J, Japanese version of the Montreal Cognitive Assessment.

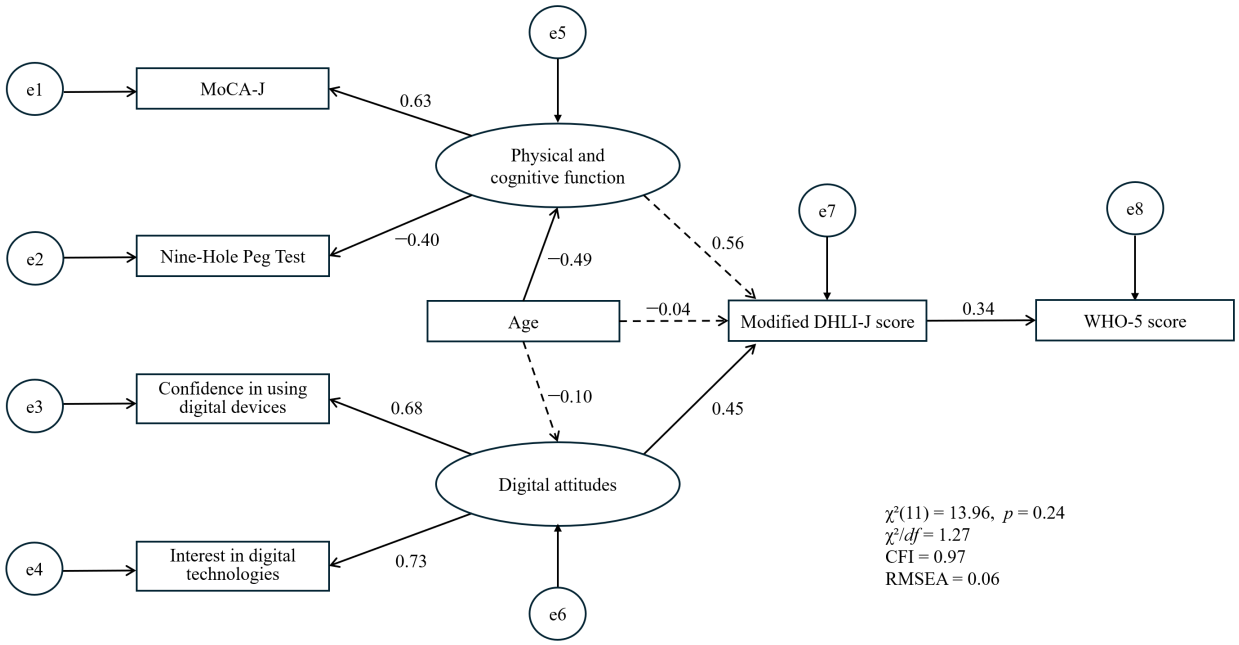

Figure 2. Exploratory structural equation model of cross-sectional associations among digital attitudes, cognitive/physical function, the modified DHLI-J score, and well-being. *Note*: n = 91. The values shown are the standardized regression coefficients. Solid lines indicate significant paths (P < .05), and dashed lines indicate nonsignificant paths. Arrows indicate prespecified cross-sectional relations and do not imply temporal or causal direction. Model fit indices were $\chi^2(11)$ = 13.96, p = 0.24; χ^2/df = 1.27; CFI = 0.97; RMSEA = 0.06. *Abbreviations*: DHLI-J, Japanese version of the Digital Health Literacy Instrument; WHO-5, World Health Organization Five Well-Being Index; MoCA-J, Japanese version of the Montreal Cognitive Assessment; CFI, comparative fit index; RMSEA, root mean square error of approximation; *df*, degrees of freedom.

First, DHL was associated with age, cognitive function, manual dexterity, digital attitudes, and well-being at descriptive and bivariate levels. Second, after adjusting for demographic and functional variables, older age, lower cognitive function, and lower confidence in using digital devices were independently associated with lower modified DHLI-J scores. Third, the exploratory supplementary SEM was broadly consistent with the regression findings and indicated positive cross-sectional associations between digital attitudes and DHL and between DHL and well-being. Taken together, these findings suggest that DHL in later life is associated not only with age and digital experience but also with cognitive demands and confidence-related factors; however, the cross-sectional design does not establish causal relationships among these variables.

A key feature of this study was its in-person design. Online recruitment may disproportionately include older adults with sufficient digital confidence, skills, and functional capacity to complete an online survey. By using paper-based questionnaires and direct performance-based assessments, the present study may have included device-owning older adults with lower digital confidence or greater cognitive and physical difficulty than those who typically participate in online-only research. However, ownership of a personal computer or mobile device was a prespecified eligibility criterion. Therefore, the in-person design reduced reliance on online survey participation but did not capture older adults without access to their own digital devices. This distinction is important because lack of device ownership may constitute a barrier before DHL can even be assessed.

4.2. Comparison with previous studies

Our results are broadly consistent with previous reviews indicating that age, socioeconomic resources, and self-efficacy-related constructs are associated with digital or eHealth literacy among older adults (*4-7*). The present study extends the literature in two ways. First, it provides in-person evidence from a Japanese community sample using the DHLI-J, together with performance-based measures. Second, the findings suggest that the apparent importance of specific correlates may depend on how participants are recruited and assessed. In this study, confidence was strongly associated with DHL in both the correlational analysis and the final regression model, whereas the contribution of self-rated economic status weakened after cognitive and attitudinal variables were included in the analysis. This pattern is consistent with the possibility that socioeconomic advantage may operate partly through greater opportunities to accumulate successful digital experiences and, in turn, increase confidence in using digital tools.

The association between cognitive function and the modified DHLI-J score is plausible, given the task demands of contemporary digital health environments. This interpretation is also consistent with broader evidence linking technology use and digital engagement to cognitive aging (*17*). Searching for health information, navigating patient portals, comparing sources, interpreting instructions, and recovering from errors require attention, working memory, comprehension, and executive function. The MoCA-J score remained significant in the final regression model, suggesting that these demands are relevant beyond chronological age or device ownership alone. In practical terms, some older adults who appear to have adequate access to digital devices may still struggle with multi-step or unfamiliar health-related digital tasks because these tasks rely on higher-order cognitive processes.

Manual dexterity may represent one of several task-related constraints. This interpretation is consistent with previous findings that manual dexterity is associated with executive functioning in community-dwelling older adults and with broader cognitive processes related to manual performance (*18,19*). Common digital actions, such as tapping, typing, scrolling, and authentication, rely on precise finger movements. In this study, NHPT performance differed between the descriptive score groups and correlated significantly with the modified DHLI-J score, although it did not remain independently significant in the final regression model. This pattern is nonetheless informative, suggesting that hand function may contribute to DHL, in part, through variance shared with age, cognition, and digital experience. For service design, this suggests that apparently minor manipulation demands, especially on touch screens or small interfaces, may accumulate into substantial access barriers for some older adults.

4.3. Public health and community implications

The positive association between the modified DHLI-J score and WHO-5 well-being is also noteworthy and consistent with prior discussions of the role of technology use in quality of life and psychosocial well-being in older adults, as well as reviews linking DHL to mental health and well-being indicators (*5,12*). Because the study was cross-sectional, the direction of this association cannot be determined. Higher DHL may facilitate engagement with health information and digitally delivered services; conversely, better well-being may increase the motivation or capacity to engage with digital technologies, and both variables may be influenced by unmeasured social or health-related factors. The positive coefficient between DHL and well-being in the exploratory SEM should therefore be interpreted as a cross-sectional association within the specified model rather than evidence that DHL improves well-being. From a global health and health systems perspective, DHL may nevertheless be relevant when considering older adults' engagement with increasingly digital services, although actual service access, use, and equity outcomes were not measured in

this study.

Confidence in using digital devices may be a target for intervention, consistent with prior work linking eHealth literacy to self-efficacy in community-dwelling older adults (*20*). Recent evidence also suggests that DHL interventions in older adults can improve literacy-related outcomes and associated self-efficacy constructs, although the intervention content and measurement approaches remain heterogeneous (*21*). However, because confidence was assessed using a single item and the present study was cross-sectional, intervention studies are needed to determine whether increasing confidence improves DHL.

The findings may inform two complementary types of intervention. User-level interventions could focus on confidence-building through guided practice, repeated successful experiences, reassurance that mistakes can be corrected, and opportunities to ask for help without embarrassment. System-level interventions could reduce task burden through plain language, simpler navigation, larger touch targets, less burdensome authentication, accessible design, timely human support, and continued availability of non-digital alternatives. Community salons, preventive care programs, municipal outreach activities, and rehabilitation-led education sessions may be suitable settings for identifying older adults who need additional support with digital health tasks before such difficulties limit their access to care. These findings may therefore inform community-based digital inclusion strategies in super-aged societies.

4.4. Interpretation of the supplementary SEM

SEM served as a supplementary exploratory analysis rather than the primary analytic framework. The model showed acceptable fit ($\chi^2(11) = 13.96$, $p = 0.24$; $\chi^2/df = 1.27$; CFI = 0.97; RMSEA = 0.06), and the pattern of associations added context to the regression findings. Within the specified cross-sectional model, age was associated with the latent cognitive/physical function construct, whereas digital attitudes were associated with DHL. The nonsignificant association between the cognitive/physical latent factor and DHL may reflect limited power or overlap with age and digital attitudes and should not be interpreted as evidence that functional constraints are unimportant. Because the model was based on cross-sectional data from a modest sample, the directions of the arrows reflect the hypothesized model specification and do not establish temporal ordering, mediation, or causality. The SEM should therefore be regarded as complementary and hypothesis-generating rather than confirmatory.

4.5. Strengths and limitations

This study has several strengths. The most important is its in-person design, which reduced dependence on online survey participation among device-owning older adults and allowed us to include performance-based measures of cognition and manual dexterity. The study also incorporated demographic, digital, physical, and psychosocial variables, allowing a broader characterization of the factors associated with DHL than would have been possible with questionnaires alone. In addition, the convergence of findings across group comparisons, correlations, regression analyses, and supplementary SEM increased confidence in the overall interpretation.

This study has some limitations. First, participants were recruited from community-based prevention activities and may therefore have been relatively health-conscious, socially active, and functionally independent, which may limit the generalizability of the findings to the broader older population. In addition, ownership of a personal computer or mobile device was a prespecified eligibility criterion, and one attendee who owned neither device was excluded. The findings therefore primarily apply to community-engaged older adults who own digital devices and may underestimate barriers among frail, homebound, socially isolated, or cognitively impaired older adults. Moreover, the study could not assess digital exclusion among older adults who do not own digital devices, because such exclusion may occur before DHL can be meaningfully evaluated. Exclusion of individuals who were unable to rise from a chair, maintain standing, or walk further limits the generalizability of the findings to older adults with substantial mobility limitations. Second, because the study was cross-sectional, the direction of the observed associations could not be determined. Better well-being may facilitate digital engagement, and higher DHL may in turn be associated with better well-being. The study also did not directly measure access to or use of digital health services or equity outcomes; therefore, the findings should be interpreted as informing strategies for equitable access rather than demonstrating equity. Third, the present study used a modified 15-item DHLI-J because only 43 of 91 participants completed all six items concerning content creation and privacy protection in online posting contexts. Although the retained items showed high internal consistency (Cronbach's $\alpha = 0.94$), the modified score covered only five of the seven original domains and should not be considered psychometrically equivalent to the validated 21-item DHLI-J. Accordingly, the findings do not reflect skills related to online content creation or privacy protection during posting. Fourth, potentially important contextual variables such as occupational history, prior technology-related work experience, social support, and availability of assistance from family members or peers were not measured. In addition, confidence in using digital devices and interest in digital technologies were assessed with single-item measures rather than validated multidimensional scales. Fifth, dichotomization

at a mean score of 2.5 served only for descriptive comparison and should not be interpreted as a validated clinical or public health cutoff. Finally, the sample size was modest for SEM, and the cross-sectional design precluded causal interpretation; therefore, the supplementary model should be regarded as exploratory despite its acceptable fit indices.

5. Conclusions

In this in-person cross-sectional study of community-dwelling older adults in Japan, the modified DHLI-J score was independently associated with age, cognitive function, and confidence in using digital devices. Manual dexterity was also associated with DHL at the bivariate level, indicating that digital health tasks involve meaningful motor and cognitive demands. The exploratory supplementary SEM indicated positive cross-sectional associations between digital attitudes and DHL and between DHL and well-being, but these associations should not be interpreted as causal. These findings may inform user-level strategies that build confidence and system-level strategies that reduce the cognitive and manual demands of digital health environments. However, the findings primarily apply to community-engaged older adults who own digital devices and do not provide direct evidence regarding equitable access to digital health services. Further research should directly examine access to and use of digital health services, particularly among older adults who do not own digital devices.

Acknowledgements

The authors gratefully acknowledge the older adults who participated in this study. The authors also thank the staff of the municipal Older Adults Support Division for their assistance with recruitment and coordination, as well as the rehabilitation professionals and research staff who supported the performance-based assessments and data collection.

Funding:This work was supported by JSPS KAKENHI (Grant-in-Aid for Scientific Research (C)) Grant Number JP23K10536.

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

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Received May 7, 2026; Revised July 14, 2026; Accepted August 6, 2026.

Released online in J-STAGE as advance publication August 11, 2026.

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Global Health & Medicine. 2026; 8(4):285-296.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2026.01055

Factors associated with control of arterial hypertension in Francisco Morazán, Honduras

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Abstract: Hypertension constitutes a major public health problem in Honduras. In 2019, 34% of Hondurans had hypertension, but only one-third achieved blood pressure control. In limited-resource settings, health system limitations complicate chronic disease oversight. This study aimed to identify individual and facility-level factors associated with blood pressure control among patients with hypertension attending primary care centers in Francisco Morazán, Honduras. A cross-sectional study was conducted with 486 patients with hypertension from eight primary health care centers. Medical records from the six months preceding the November-December 2024 collection period were evaluated to examine hypertension control factors (< 140/90 mmHg). Multivariable logistic regression and multilevel modeling were employed to identify associated factors. Seeking other medical care outside the primary clinic was associated with higher odds of blood pressure control (adjusted odds ratio (aOR) = 5.09; $p < 0.001$). Referral to higher levels of care (aOR = 0.11; $p < 0.001$) and morbid obesity (aOR = 0.14; $p = 0.005$) were associated with lower odds of achieving hypertension control. Being female and exhibiting higher perceived disease severity showed positive trends; however, these decreased after multilevel adjustment. None of the facility-level variables reached statistical significance. Several patient-level factors were associated with blood pressure control, whereas no statistically significant facility-level associations were detected in this sample. Because only eight health centers were included, the facility-level analysis should be considered exploratory. Reinforcing obesity management protocols and strengthening referral systems may contribute to improving hypertension management.

***Keywords*:** hypertension, primary health care, multilevel analysis, Honduras, obesity

1. Introduction

Noncommunicable diseases (NCDs) disproportionately affect vulnerable populations, accounting for 43 million deaths worldwide in 2021. Unfortunately, 73% of these deaths occurred mainly in low- and middle-income countries (LMICs), where resources for managing chronic diseases are often limited. Cardiovascular diseases, cancer, chronic respiratory conditions, and diabetes mellitus are the primary causes of mortality associated with NCDs (*1*).

In Central America, Honduras faces a severe NCD-related crisis. Most deaths in this country are due to NCDs; by 2021, 47.7% of all deaths could be attributed to NCDs (*2*). The age-standardized NCD mortality rate in Honduras is 560 per 100,000 people, surpassing the rates of 440 in El Salvador, 310 in Nicaragua, and 440 in Guatemala (*3*). Ischemic heart disease, stroke, and kidney disease are among the top ten causes of death in Honduras and represent major NCD-related conditions closely linked to poorly controlled hypertension (*2*).

Arterial hypertension is a major risk factor for cardiovascular and renal disease (*4,5*). Prompt diagnosis and treatment are important to reduce NCD mortality. Despite health system efforts, hypertension control remains deficient in Honduras. In 2019, prevalence of hypertension among adults aged 30–79 years reached 34%, but only 33% of those diagnosed achieved adequate blood pressure (BP) control (*6*). This finding suggests persistent barriers to effective management.

In limited-resource settings such as Honduras, health systems experience financial and human resource shortages, rendering control of chronic conditions especially challenging. The Honduran public health sector, which covers approximately 60% of the population, is characterized by a fragmented structure with different management capacities (*7*). The primary health system is organized into units of varying

complexity, such as integrated health centers (*Spanish: centro integral de salud; CISs*) and primary health care units (*Spanish: unidad de atención primaria en salud; UAPSs*) (*8*). Although these facilities typically include a physician, these units often suffer from poor communication both among themselves and with higher levels of care, limiting chronic disease management.

The Honduran health system is transitioning from a centralized to a decentralized model. In this framework, authority over decentralized facilities may be vested in local governments or nongovernmental organizations (NGOs), while centralized units remain under the direct control of the Ministry of Health (*9*). However, this transition has been slow. Consequently, only a minority of health care centers currently operate under a decentralized model.

Because hypertension control is multifactorial, few studies in Honduras have focused on exploring possible factors from both patient and health facility perspectives (*10,11*). Many studies may neglect behavioral factors that are associated with disease management in real-world settings (*12,13*).

This study aimed to identify factors associated with insufficient hypertension control in primary care centers (CISs and UAPSs) in Francisco Morazán, Honduras. By addressing these knowledge gaps, this research provides evidence to support design of more efficient, context-specific interventions and improved resource allocation, ultimately contributing to reducing the high burden of NCDs in the country.

2. Materials and Methods

2.1. Study design, setting and sampling procedures

A cross-sectional study was conducted in the department of Francisco Morazán, Honduras. Data collection occurred between November and December 2024, and medical records from the preceding six-month period were evaluated. A two-stage cluster sampling method was employed. The study was conducted in collaboration with the Central American Technological University (UNITEC), Honduras, the Francisco Morazán Departmental Health Region, and participating primary healthcare centers, which provided administrative support, and access to the study sites.

At the first stage, eight primary health centers were randomly selected from 21 eligible facilities (CISs and UAPSs) located in the study area. Eligibility criteria for these facilities included having at least one general practitioner on staff and sufficient physical accessibility for data collection. The specific characteristics of the eight selected facilities; including their administration type (centralized *vs.* decentralized) and geographic zone, are summarized in Table 1.

At the second stage, individual participants were selected *via* simple random sampling from daily clinical attendance lists using a computer-generated random sequence. Sampling flow is shown in Figure 1, which reveals selection of health centers and subsequent inclusion of hypertensive patients.

Sample size was determined using Cochran's model and was based on an expected prevalence of controlled hypertension of 33% (*6*), a 95% confidence level, and a 5% margin of error, which yielded an initial sample size of 340 participants. To account for the cluster sampling design, a design effect (Deff) of 1.30 was applied. Furthermore, the total was increased by 10% to account for potential nonresponses or incomplete records, resulting in a final target sample of 490 participants. To ensure representativeness across centers with varying patient volumes, the sample was distributed *via* proportional allocation on the basis of monthly hypertensive patient volume of each facility.

Patients were eligible for inclusion if they were 18 years old or older, had a confirmed diagnosis of arterial hypertension at least six months prior to the study, and resided within the area of the participating health center. Exclusion criteria included clinical factors, such as pregnancy, cognitive impairments, or lack of clinical evaluation at the facility within the past six months, and logistical factors, specifically medical records lacking essential contact information needed for patient follow-up.

2.2. Study variables and measurement

The primary outcome was BP control status, classified as controlled or uncontrolled. In accordance with the National Hypertension Management Protocol of the

Table 1. Facility-level structural capacity, clinical workload, and patient hypertension control status

Geographic Zone	Level of Care (UAPS/CIS)	Type of Administration	Medical Staff	Workload (Patients/ Doctor/Day)	Hypertensive Participants (*n*)	Proportion Controlled (%)
Center A	UAPS	Centralized	4	10–19	42	64.29
Center B	CIS	Centralized	17	30–39	188	26.06
Center C	UAPS	Centralized	3	10–19	57	56.14
Center D	UAPS	Centralized	3	10–19	32	50.00
South E	UAPS	Decentralized	3	20–29	69	53.62
South F	CIS	Decentralized	14	20–29	46	54.35
South G	CIS	Decentralized	10	20–29	26	42.31
South H	CIS	Decentralized	11	40–49	26	61.54

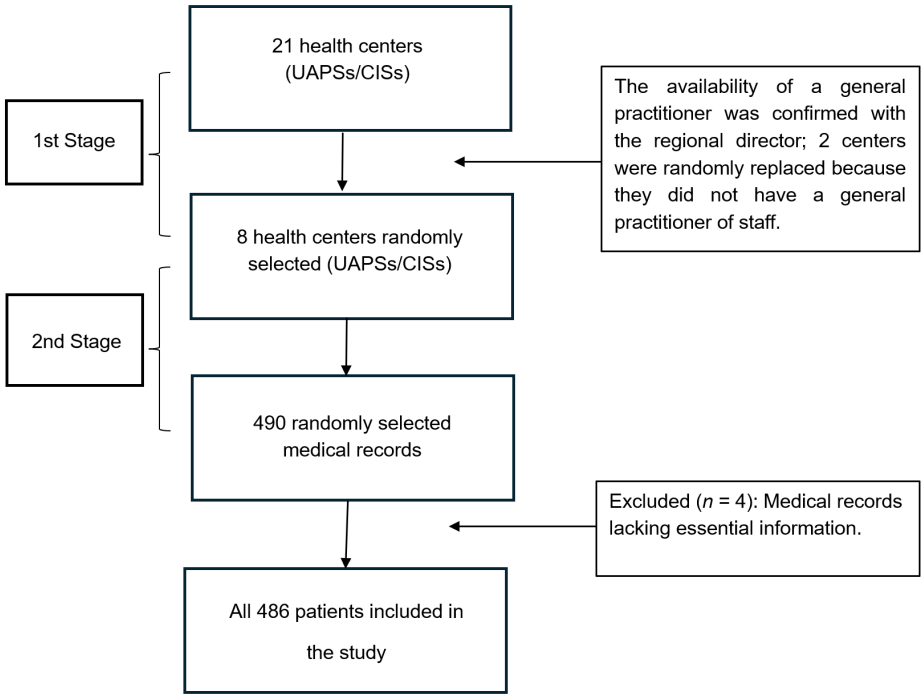

Figure 1. Flowchart of the study selection and participant enrollment process. This flowchart illustrates a multisampling method. Twenty-one potential health centers were initially selected, and 8 were randomly selected. Following administrative verification with the regional director, two centers were randomly replaced because of the absence of a general practitioner. A total of 490 medical records were screened for eligibility. Four records were excluded because of incomplete essential clinical data. The final analysis included a total of 486 medical records and their corresponding participants.

Secretariat of Health of Honduras (*14*), a therapeutic target of < 140/90 mmHg was established. BP control was assessed using BP measurements recorded during the most recent three months of follow-up. Medical records from the most recent six months were reviewed for each participant. BP control was determined using the mean of all BP measurements available during the most recent three-month evaluation period within this six-month review window. When more than one BP measurement was available, the average of all recorded measurements was calculated. If only one BP measurement was available during the three-month period, that measurement was used for classification. Therefore, at least one BP measurement during the most recent three-month period was required, whereas BP measurements were not required for each month within that period. Although the national protocol recommends stricter targets for patients at greater cardiovascular risk, a fixed target was applied in this study. This adjustment was selected because of limited availability of lipid profile data in primary care settings, which prevented formal cardiovascular risk stratification for all participants. Additionally, pulse pressure was analyzed as a clinical indicator of arterial stiffness. Pulse pressure was calculated as the difference between the systolic and diastolic BP values. To ensure a stable measurement of chronic BP burden, an average pulse pressure was derived from all clinical records available for each participant over the six-month study period.

Collected data included variables at both the health facility and patient levels. At the facility level, structural factors were assessed through structured interviews with the physicians in charge. Prevention and promotion activities were measured *via* a study-specific composite score (range: 4–36) developed on the basis of institutional assessment tools for NCDs. This score evaluated community and clinical prevention strategies. Owing to the lack of established thresholds, scores were categorized as low (< 18), moderate (18–27), or high (> 27) by dividing the score range into equal segments to facilitate group comparison.

Availability of medication was determined by the physical presence of six essential drug classes for hypertension on the survey day, following the World Health Organization (WHO) Package of Essential Noncommunicable (PEN) Disease Interventions (*15*). Similarly, technology and infrastructure were evaluated according to WHO-PEN guidelines, with a focus on essential diagnostic instruments for laboratory, preclinical, and clinical areas.

At the patient level, socioeconomic status (SES) was assessed through a modified SES Short-Form Questionnaire (SES-SQ) (*16*). Individual autonomy was assessed using Partners for Applied Social Sciences (PASS) health-seeking behavior model (*17*), which focuses on decision-making power under social and economic constraints. Pluralistic treatment-seeking was assessed separately and included use of home remedies,

traditional treatments, and biomedical care. Lifestyle factors and self-care practices, including physical activity, salt intake, tobacco use, and alcohol consumption, were evaluated on the basis of the National Hypertension Protocol of Honduras (*14*). Medication adherence was assessed *via* a self-report scale adapted from the Morisky and Hill-Bone instruments (*18*). Furthermore, service quality was measured with a modified Primary Care Satisfaction Scale (PCSS) (*19*). Finally, dimensions of illness interpretation, pluralistic treatments, and health system navigation (referrals and attendance at other facilities) were included to account for external factors associated with BP control.

Data were collected through three structured instruments (A, B, and C) involving medical record extraction and face-to-face or telephone interviews. All the instruments were designed in English, translated into Spanish by the principal investigator, and pilot-tested at a rural health center. Field data collection was led by the principal investigator, a Honduran physician, with support of three trained Honduran nurses recruited as research assistants. The principal investigator and trained research assistants conducted participant interviews and obtained informed consent prior to data collection. Written informed consent was obtained during face-to-face interviews, fingerprint consent was used for participants unable to read or write after the consent form had been read aloud, and verbal informed consent was obtained only for telephone interviews when in-person interviews were not feasible because of participants' remote residence. Medical records were reviewed using standardized data collection procedures. Data collection was conducted in Spanish by the principal investigator and trained research assistants.

Participation was voluntary and involved minimal risk. Participants were informed that they could withdraw from the research without repercussions. To ensure anonymity, data were coded, redacted, and stored in a password-protected cloud drive or under lock and key at UNITEC.

2.3. Statistical analysis

The final analytical sample comprised 486 participants after excluding individuals with incomplete data for variables of interest. Statistical analysis was conducted using Stata/SE version 18.0. A descriptive analysis was implemented to summarize clinical, demographic, and behavioral characteristics of the participants, with categorical variables expressed as absolute frequencies and percentages. The analytical phase followed a three-stage approach including bivariable, multivariable, and multilevel logistic regression analyses. A significance level of $p < 0.05$ was established, with p-values reported to three decimal places.

At the first stage, bivariable logistic regression was employed to estimate crude associations between patient-level independent variables and BP control, and crude odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Facility-level variables were excluded from this bivariable stage to avoid unreliable estimates due to the small number of clusters ($n = 8$). At the second stage, to identify independent factors associated with BP control, a multivariable logistic regression model was developed. Variables showing significant associations in bivariable analyses were considered for inclusion in the multivariable and multilevel models. Variables retained a priori based on established clinical relevance and previous evidence included age, socioeconomic status, smoking status, physical activity, salt intake, and treatment adherence. Multicollinearity was assessed using the generalized variance inflation factor (GVIF), and only variables with GVIF values < 2.0 were retained in final models. Missing data were handled using a complete-case approach, and participants with incomplete information for variables included in regression models were excluded.

Sparse categories were assessed during model development. Individual comorbidities with small numbers were summarized descriptively and were not included separately in regression models; instead, a binary variable indicating presence of any comorbidity was used. Body mass index (BMI) categories were retained according to clinically established thresholds to preserve clinically meaningful differences across BMI levels. Referral variables were analyzed separately according to their source (medical records or patient reports). Because the ≥ 5 consultations category included only five participants, a sensitivity analysis combining this group with the 3–4 consultations category was performed; however, the original three-category classification was retained because the alternative categorization did not alter overall interpretation of the findings and preserved clinically meaningful consultation frequency groups.

Finally, multilevel logistic regression analysis was conducted using a random-intercept model, with the eight health centers included as the clustering unit to account for the hierarchical structure of the data. Apparent discriminatory performance of the final model was assessed using the area under the receiver operating characteristic curve (AUC-ROC).

2.4. Ethical approvals

The study protocol received formal ethical approval from the Institutional Review Board of the School of Tropical Medicine and Global Health, Nagasaki University (Approval No. NU_TMGH_2024_305_1; approved on September 6, 2024), and Research Ethics Committee of UNITEC, Honduras (IRB00012967, Act No. 011-2024; approved on September 30, 2024).

In addition, administrative permission to conduct the study at the selected primary healthcare centers was granted on November 19, 2024, by the Francisco Morazán

Departmental Health Region of Ministry of Health of Honduras (Official Letter No. 809-2024-JRSFM). Ethical approvals covered participant recruitment, informed consent, medical record review, protection of participant privacy and confidentiality, and subsequent data analysis by the research team, while the administrative authorization permitted study implementation within participating health facilities.

3. Results

3.1. Characteristics of the study population and bivariable analysis of hypertension control

A total of 486 clinically diagnosed patients with hypertension under active pharmacological treatment were included in the final analytical sample. Of these, 213 (43.8%) had controlled blood pressure and 273 (56.2%) had uncontrolled blood pressure. As indicated in Table 1, significant variability in BP control was observed across centers. Center A and South H achieved the highest control rates (> 60%), whereas Center B, the facility with highest patient volume, achieved the lowest control rate (26.06%). Facilities with lower patient-to-doctor ratios (10–19 patients/day) generally had higher BP control rates than those with heavier workloads (30–49 patients/day). Patients managed under decentralized administration and those receiving UAPS-level care demonstrated higher proportions of BP control (53.29% and 56.00%, respectively).

The study population was predominantly female (78.2%), aged 60 years or older (52.9%), and exhibited a low socioeconomic status (70.4%). Bivariable analysis (Table 2) showed that sex was a significant factor, with women being 1.6 times more likely to achieve BP control than men. With respect to illness perception, patients who viewed hypertension as a severe condition attained twice the odds of BP control than those who perceived it as mild (OR: 2.21; 95% CI: 1.39–3.51).

Several clinical variables were strongly associated with insufficient BP control. BMI was strongly associated with uncontrolled hypertension. Notably, patients with morbid obesity (BMI ≥ 40) exhibited 88% lower odds of control (OR: 0.12; 95% CI: 0.03–0.37) than those with normal weight. Similarly, a pulse pressure ≥ 60 mmHg and the presence of any comorbidity (OR: 0.67) were significantly associated with lower odds of BP control.

Health care utilization patterns revealed mixed associations. Frequent consultations (3–4 in six months) were associated with lower BP control (OR: 0.38), whereas patients who sought other medical care beyond their routine follow-ups were four times more likely to achieve BP control (OR: 4.0; 95% CI: 2.63–6.08). Neither medication adherence, salt intake, nor the use of pluralistic treatments was significantly associated with BP control in this population. While 6.8% of patients reported being referred to higher levels of care, no counter referrals were recorded from hospitals back to the primary health centers. These variables included sex, body mass index (BMI), any comorbidity, severity of illness, number of medical consultations, other medical care, and referral according to patient report.

3.2. Multivariable analysis of hypertension control

Multivariable logistic regression results are presented in Table 3. After adjusting for potential confounders, several clinical and patient-related factors remained significantly associated with BP control. Compared to male patients, female patients were significantly more likely to achieve hypertension control (adjusted odds ratio (aOR) = 1.77; 95% CI: 1.01–3.15; $p = 0.047$). In terms of BMI, a clear inverse relationship was observed between obesity and BP control; patients with Class I obesity (aOR = 0.42; $p = 0.006$), Class II obesity (aOR = 0.35; $p = 0.020$), and Class III obesity (aOR = 0.14; $p = 0.004$) attained significantly lower odds of hypertension control than those with normal BMI.

The use of other medical care services showed the strongest positive association with BP control (aOR = 5.15; 95% CI: 3.10–8.78; $p < 0.001$). Conversely, patients with a history of referral to higher levels of care exhibited significantly lower odds of achieving BP control (aOR = 0.11; 95% CI: 0.04–0.31; $p < 0.001$). Other factors, including age group, smoking status, physical activity, and socioeconomic status, were not significantly associated with hypertension control in the multivariable model.

3.3. Multilevel analysis of hypertension control

The multilevel model produced findings consistent with the multivariable analysis for the primary factors associated with hypertension control, although certain patient-level associations were attenuated after the clustering effect of health centers was accounted for (Table 4). The estimated variance of the health center level random intercept was 0, indicating no evidence between center variation. Factors such as receiving other medical care and patient referrals remained highly significant. Specifically, patients receiving additional medical care had five times higher odds of BP control (aOR = 5.09; 95% CI: 2.98–8.70; $p < 0.001$), while patients with a history of referral to higher levels of care were significantly less likely to achieve BP control (aOR = 0.11; 95% CI: 0.04–0.33; $p < 0.001$). The association between BMI and BP control remained generally consistent across both models, with higher obesity categories being associated with lower odds of BP control, particularly in the morbid obesity group (aOR = 0.14; 95% CI: 0.03–0.54; $p = 0.005$).

In contrast, several variables that were statistically significant in the multivariable model (not accounting for the cluster effect) revealed attenuated associations

Table 2. Characteristics and factors associated with blood pressure control in hypertensive patients

Variable	*n*	(%)	Controlled, *n* (%)	OR (95% CI)	*p*-value
Age					
18–39	39	8.0	18 (46.2)	Reference	–
40–59	190	39.1	92 (48.4)	1.09 (0.55–2.19)	0.796
≥ 60	257	52.9	103 (40.1)	0.78 (0.40–1.54)	0.473
Female	380	78.2	176 (46.3)	1.61 (1.03–2.51)	0.037
Socioeconomic Status (SES-SQ Modified)					
Low	342	70.4	153 (44.7)	Reference	–
Middle	126	25.9	51 (40.5)	0.84 (0.55–1.27)	0.410
High	18	3.7	9 (50.0)	1.23 (0.48–3.19)	0.662
Quality of Service					
Poor	9	1.9	3 (33.3)	0.63 (0.16–2.57)	0.520
Moderate	112	23.0	49 (43.8)	0.99 (0.64–1.51)	0.940
High	365	75.1	161 (44.1)	Reference	–
Decision Power					
Moderate	249	51.2	103 (41.4)	Reference	–
Low	101	20.8	52 (51.5)	1.50 (0.94–2.39)	0.085
High	136	28.0	58 (42.6)	1.05 (0.69–1.60)	0.807
Illness Interpretation					
Severity of Illness					
Mild	111	22.8	36 (32.4)	Reference	–
Moderate	107	22.0	39 (36.4)	1.19 (0.68–2.09)	0.533
Severe	268	55.1	138 (51.5)	2.21 (1.39–3.51)	0.001
Susceptible to Complications	401	82.5	184 (45.9)	1.64 (1.00–2.67)	0.048
Knowledge of Illness Causes					
Does not know	257	52.9	121 (47.1)	Reference	–
Lifestyle	142	29.2	54 (38.0)	0.68 (0.45–1.05)	0.082
Genetics	30	6.2	14 (46.7)	0.98 (0.46–2.09)	0.966
Others (anxiety, stress, *etc*.)	57	11.7	24 (42.1)	0.82 (0.46–1.46)	0.496
Number of Medical Consultations (Last 6 Months)					
1–2 consultations	259	53.3	141 (54.4)	Reference	–
3–4 consultations	222	45.7	69 (31.1)	0.38 (0.26–0.55)	< 0.001
≥ 5 consultations	5	1.0	3 (60.0)	1.26 (0.21–7.06)	0.805
Average BMI					
< 18.5	8	1.6	4 (50.0)	0.84 (0.19–3.68)	0.820
18.5–24.9	138	28.4	75 (54.3)	Reference	–
25.0–29.9	157	32.3	73 (46.5)	0.73 (0.46–1.15)	0.170
30.0–34.9	121	24.9	45 (37.2)	0.50 (0.30–0.81)	0.005
35.0–39.9	38	7.8	13 (34.2)	0.44 (0.20–0.91)	0.027
≥ 40	24	4.9	3 (12.5)	0.12 (0.03–0.37)	< 0.001
Average Pulse Pressure					
< 60 mmHg	393	80.9	202 (51.4)	Reference	–
≥ 60 mmHg	93	19.1	11 (11.8)	0.13 (0.07–0.25)	< 0.001
Comorbidity					
Type 2 diabetes	137	28.2	58 (42.3)	0.92 (0.61–1.37)	0.680
Renal disease*	3	0.6	0 (0.0)	-	–
Previous stroke	8	1.6	3 (37.5)	0.77 (0.18–3.24)	0.717
Heart failure*	1	0.2	1 (100)	–	–
Ischemic heart disease	5	1.0	2 (40.0)	0.85 (0.14–5.15)	0.863
Others (prediabetes, obesity, *etc.*)	46	9.5	11 (23.9)	0.37 (0.18–0.75)	0.006
Any comorbidity	178	36.6	67 (37.6)	0.67 (0.43–0.98)	0.037
Previous Referrals (According to Medical Record)	10	2.1	1 (10.0)	0.14 (0.01–0.75)	0.062
Previous Referrals (According to Patient)	33	6.8	6 (18.2)	0.26 (0.11–0.65)	0.004
Other Medical Care	139	28.6	94 (67.6)	4.00 (2.63–6.08)	< 0.001

*Statistical comparison is limited because of the small number of patients; no *p*-value or confidence interval is reported. No significant associations were obtained for smoking, alcohol consumption, salt intake, physical activity, or medication adherence (all $p > 0.05$).

in multilevel analysis. Female sex, which demonstrated a significant association in the non-adjusted model ($p = 0.047$), shifted to marginally significant after accounting for the effect of health center clustering (aOR = 1.69; 95% CI: 0.95–3.01; $p = 0.072$). Similarly, the association for 3–4 consultations ($p = 0.294$) was no longer statistically significant after accounting for clustering at the health-center level. A sensitivity analysis combining the 3–4 and ≥ 5 consultation categories yielded similar findings. Although the association became statistically significant in the multivariable model, it remained non-significant in the multilevel model and therefore did not alter overall interpretation of the study findings. The original three-category classification was retained because it represents clinically meaningful consultation frequencies. No facility-level variables reached statistical

Table 3. Multivariable analysis of patient factors associated with hypertension control

Patient-related factors	Crude OR	Adjusted OR	95% CI	*p*-value
Age				
18–39 years old	Reference	Reference	–	–
40–59 years old	1.09	0.95	0.42–2.21	0.910
≥ 60 years old	0.78	0.49	0.20–1.16	0.104
Gender				
Male	Reference	Reference	–	–
Female	1.61	1.77	1.01–3.15	0.047
Average BMI				
< 18.5	0.84	0.56	0.10–3.19	0.506
18.5–24.9	Reference	Reference	–	–
25.0–29.9	0.73	0.72	0.42–1.23	0.233
30.0–34.9	0.50	0.42	0.23–0.77	0.006
35.0–39.9	0.44	0.35	0.14–0.83	0.020
≥ 40	0.12	0.14	0.03–0.47	0.004
Smokers				
Never	Reference	Reference	–	–
Used to smoke	1.07	2.19	0.92–5.19	0.073
Passive smokers	1.32	1.33	0.74–2.41	0.341
Active smokers	2.71	3.10	0.50–26.6	0.244
Frequency of Physical Activity				
No	Reference	Reference	–	–
Yes	1.36	1.30	0.82–2.08	0.269
Adherence to Treatment				
Low adherence	Reference	Reference	–	–
Moderate adherence	0.80	0.78	0.42–1.45	0.426
High adherence	0.80	0.89	0.46–1.73	0.724
Salt Intake				
< 1 teaspoon of salt	Reference	Reference	–	–
≥ 1 teaspoon of salt	1.10	1.03	0.66–1.61	0.882
Does not know	1.30	1.33	0.54–3.24	0.535
Any Comorbidity				
No comorbidity	Reference	Reference	–	–
Any comorbidity	0.67	0.93	0.60–1.47	0.769
Socioeconomic Status				
Low	Reference	Reference	–	–
Middle	0.84	0.93	0.56–1.57	0.800
High	1.23	0.93	0.26–3.30	0.908
Severity of Illness				
Mild	Reference	Reference	–	–
Moderate	1.19	1.00	0.53–1.90	0.999
Severe	2.21	1.68	0.98–2.92	0.062
Number of Medical Consultations				
1–2 consultations	Reference	Reference	–	–
3–4 consultations	0.38	0.57	0.37–0.90	0.015
≥ 5 consultations	1.26	1.07	0.13–10.54	0.948
Other Medical Care				
No	Reference	Reference	–	–
Yes	4.00	5.15	3.10–8.78	< 0.001
Referrals (According to the patient)				
No	Reference	Reference	–	–
Yes	0.26	0.11	0.04–0.31	< 0.001

Crude and adjusted odds ratios were calculated using the same complete-case analytical sample (n = 486; 213 participants with controlled blood pressure and 273 with uncontrolled blood pressure).

significance; these findings should be interpreted as exploratory given the limited number of health centers included in the analysis. The multilevel model demonstrated acceptable discriminatory performance, with an AUC-ROC value of 0.79 (95% CI: 0.75–0.83).

4. Discussion

The multilevel analysis identified several patient-level factors associated with hypertension control among primary care patients in Francisco Morazán, Honduras, including attending other medical care, referral to higher levels of care, and obesity. No statistically significant facility-level associations were detected in this sample. However, given the limited number of health centers included, these findings should be interpreted as exploratory.

A critical finding was that patients seeking care at

Table 4. Multilevel logistic regression: Patient-level and health center-level variables

Level	Variable	Adjusted OR	95% CI	*p*-value
Individual level (1st level)	Age			
	18–39 years old	Reference	–	–
	40–59 years old	0.99	0.42–2.33	0.979
	≥ 60 years old	0.52	0.21–1.26	0.150
Individual level (1st level)	Gender			
	Male	Reference	–	–
	Female	1.69	0.95–3.01	0.072
Individual level (1st level)	Average BMI			
	< 18.5	0.58	0.10–3.29	0.538
	18.5–24.9	Reference	–	–
	25.0–29.9	0.71	0.41–1.23	0.220
	30.0–34.9	0.43	0.23–0.79	0.007
	35.0–39.9	0.37	0.15–0.91	0.031
	≥ 40	0.14	0.03–0.54	0.005
Individual level (1st level)	Smokers			
	Never	Reference	–	–
	Used to smoke	2.30	0.95–5.54	0.064
	Passive smokers	1.33	0.72–2.48	0.364
	Active smokers	2.60	0.40–17.0	0.280
Individual level (1st level)	Frequency of Physical Activity			
	No	Reference	–	–
	Yes	1.30	0.81–2.09	0.280
Individual level (1st level)	Adherence to Treatment			
	Low adherence	Reference	–	–
	Moderate adherence	0.82	0.44–1.55	0.543
	High adherence	0.93	0.47–1.85	0.845
Individual level (1st level)	Salt Intake			
	< 1 teaspoon of salt	Reference	–	–
	≥ 1 teaspoon of salt	0.99	0.63–1.55	0.953
	Does not know	1.38	0.55–3.46	0.492
Individual level (1st level)	Any Comorbidity			
	No comorbidity	Reference	–	–
	Any comorbidity	1.04	0.65–1.67	0.876
Individual level (1st level)	Socioeconomic Status			
	Low	Reference	–	–
	Middle	0.96	0.56–1.65	0.881
	High	1.29	0.35–4.76	0.701
Individual level (1st level)	Severity of Illness			
	Mild	Reference	–	–
	Moderate	0.90	0.46–1.74	0.750
	Severe	1.31	0.73–2.35	0.375
Individual level (1st level)	Number of Medical Consultations			
	1–2 consultations	Reference	–	–
	3–4 consultations	0.75	0.44–1.28	0.294
	≥ 5 consultations	1.67	0.19–15.0	0.645
Individual level (1st level)	Other Medical Care			
	No	Reference	–	–
	Yes	5.09	2.98–8.70	< 0.001
Individual level (1st level)	Referrals (According to the patient)			
	No	Reference	–	–
	Yes	0.11	0.04–0.33	< 0.001
Health Center (2nd Level)	Type			
	UAPS	Reference	–	–
	CIS	0.85	0.23–3.21	0.814
Health Center (2nd Level)	Administration			
	Decentralized	Reference	–	–
	Centralized	0.90	0.23–3.48	0.877
Health Center (2nd Level)	Prevention and Promotion Activities			
	Low	N/A	N/A	N/A
	Moderate	Reference	–	–
	High	0.99	0.36–2.73	0.981
Health Center (2nd Level)	Technology Available Laboratory			
	Low	N/A	N/A	N/A
	Moderate	Reference	–	–
	High	0.58	0.17–2.00	0.392

Adjusted odds ratios were calculated using the same complete-case analytical sample (n = 486; 213 participants with controlled blood pressure and 273 with uncontrolled blood pressure).

Table 4. Multilevel logistic regression: Patient-level and health center-level variables (continued)

Level	Variable	Adjusted OR	95% CI	*p*-value
Health Center (2nd Level)	Technology Available Clinic			
	Low	Reference	–	–
	Moderate	0.54	0.11–2.55	0.437
	High	0.54	0.18–1.64	0.280

Adjusted odds ratios were calculated using the same complete-case analytical sample (n = 486; 213 participants with controlled blood pressure and 273 with uncontrolled blood pressure).

additional facilities, public or private, were more than five times more likely to achieve BP control (aOR = 5.09; $p < 0.001$). While all citizens theoretically have access to primary health care, this pattern suggests that relying on a single facility may present challenges for long-term management in resource-constrained settings. This association likely reflects proactive health care-seeking behavior to compensate for resource gaps at local clinics. However, this association should be interpreted cautiously, as patients who sought care at multiple facilities may also have had greater health awareness, better socioeconomic resources, or improved access to health services. Therefore, this association should not be interpreted as evidence that seeking care at multiple facilities directly improves BP control.

Socioeconomically disadvantaged patients in remote areas face barriers, such as transportation costs and travel times, that preclude them from seeking care from multiple providers. Consequently, vulnerable populations may remain dependent on a single facility. While access to primary care exists, it may not be sufficient to achieve BP control, a finding that is consistent with studies linking health care access disparities to BP outcomes (*20*).

Our findings deviate from the doctor-shopping phenomenon typical of high-income settings. While literature from the U.S., Taiwan, and France presents associations between multiple consultations and fragmented care and reduced continuity (*21*), the Honduran context is different. In a resource constrained health system, seeking other medical care likely represents an effort by patients to ensure treatment continuity and medication access, rather than a lack of coordination. These findings suggest that resource constraints and limited system coordination may encourage patients to seek care across multiple providers.

In Honduras, patients are referred to higher-complexity facilities precisely because they present with resistant hypertension or comorbidities (*14*). Therefore, referral status should not be interpreted as an independent factor associated with poor BP control but rather as a marker of greater clinical complexity at the time of referral. Association between referrals and uncontrolled BP reflects the fact that these patients were already at high-risk at enrollment. However, absence of documented counter referrals suggests a gap in the integrated care loop. Information on whether referrals were completed was not available in the medical records; therefore, the effectiveness of the referral process itself could not be evaluated. These findings highlight importance of strengthening referral and counter-referral coordination to reduce fragmented care and support consistent, stage-appropriate follow-up for high-risk patients within the health system.

We observed a clear association between insufficient BP control and high BMI, which conforms to evidence linking obesity to increased cardiovascular risk (*22*). This phenomenon is particularly concerning given the high prevalence of obesity in Honduras, which affects 30.3% of women and 18.3% of men (*23*). Consequently, these findings suggest the importance of weight management through expanded health screenings and early intervention strategies to prevent further clinical complications. Within primary healthcare, these strategies should be further strengthened through routine weight monitoring, dietary counseling, promotion of regular physical activity, and integrated cardiovascular risk management, particularly for patients with obesity and related comorbidities.

The trend toward better control among women observed in multilevel analysis ($p = 0.072$) agrees with the findings of studies in Jordan and Brazil. One possible explanation for this pattern is better treatment adherence, proactive health decision-making, and more robust social support networks, as suggested in previous studies (*24,25*). However, after accounting for clustering at the health-center level, this association was attenuated and no longer reached statistical significance. Physiological mechanisms, such as a more favorable anti-inflammatory immune response (*26*) and the cardioprotective effects of estrogen (*27*), may contribute to better BP control in women. One possible explanation, supported by previous literature, is that traditional gender roles in Honduras may limit healthcare attendance among some men. For example, work responsibilities among primary breadwinners may reduce opportunities to attend routine clinic visits without economic consequences.

Previous studies have suggested that sociocultural constructions, such as machismo, may be associated with health-seeking behaviors related to BP control. In many Latin American contexts, seeking care or admitting vulnerability can be stigmatized as a sign of weakness, thus discouraging men from addressing chronic conditions (*28*). While women seemingly exhibit better clinic attendance, they still face gender-based barriers

such as economic dependence and restricted mobility. Although decision-making power was not significantly associated with BP control in this study, it remains a critical factor of health-seeking behavior in the region.

Patients attending 3–4 consultations during the previous six months had lower odds of BP control in the multivariable model; however, this association was no longer statistically significant in the multilevel model. This result deviates from findings of previous research, in which a positive correlation between the number of outpatient visits and successful BP control is typically revealed (*29*). It is possible that our results did not follow this trend in the final model because the sample size in specific groups, such as the group with ≥ 5 consultations, were very small.

Perceived disease severity indicated a notable trend toward significance in multivariable analysis, which may suggest that patients who view their condition as serious may be more likely to adhere to treatment and engage in proactive self-management. While our findings agree with those of studies in Iran and Vietnam linking risk perception to compliance (*30-32*), this association varies by social context. Furthermore, extreme perceived severity can be counterproductive, as heightened emotional stress and worry are linked to treatment nonadherence (*33,34*).

Unexpectedly, former smokers tended to achieve better hypertension control ($p = 0.064$). While smoking cessation stops further cardiovascular damage, its physiological benefits are often long-term (*35,36*). However, similar paradoxes in other studies suggest that compared with nonsmokers, successful quitters may develop an elevated sense of health consciousness and superior treatment adherence (*37,38*). Further research is needed to clarify behavioral mechanisms underlying this association.

No facility-level variables reached statistical significance in the multilevel model. However, these findings should be interpreted cautiously because only eight health centers were included, limiting the statistical power to detect facility-level associations. A possible explanation for the absence of significant facility-level associations is that all facilities followed comparable clinical procedures and national hypertension guidelines. The descriptive findings support this interpretation of relative homogeneity. Notably, most facilities demonstrated high performance in terms of prevention activities and reported moderate to high levels of diagnostic technology.

The strengths of this study include use of multilevel modeling to account for nested data and the reliance on medical records to reflect routine clinical practice. However, its cross-sectional design precludes causal inference. Limitations include potential documentation errors or missing behavioral data in physical records, and the small number of health centers, which limited the precision and statistical power to estimate facility-level associations. Some categories included a limited number of observations, which may have reduced the precision of the corresponding estimates; therefore, these results should be interpreted with caution. Specifically, estimates for the underweight BMI category, participants with ≥ 5 medical consultations, current smokers, and patients referred to higher levels of care may be less precise because of the small number of observations in these groups. Additionally, data on smoking duration and dietary patterns were unavailable. BP measurements were retrospectively obtained from routine clinical records. Although BP measurements were routinely performed by physicians and nurses following the National Hypertension Management Protocol of Honduras, adherence to standardized measurement procedures and consistency of BP devices across facilities could not be independently verified, which may have introduced measurement variability. Additionally, detailed information on antihypertensive treatment regimens, including number and classes of medications and treatment intensification, was not collected. These factors may also be associated with BP control and should be considered in future studies.

5. Conclusions

In this Honduran population, several patient-level factors were associated with hypertension control, whereas no statistically significant facility-level associations were detected in this sample. Because only eight health centers were included, the facility-level analysis should be considered exploratory. Referred patients and those with morbid obesity may represent particularly vulnerable subgroups, which highlights the need to reinforce implementation of existing metabolic management protocols at the primary level. Seeking other medical care was strongly associated with better BP control. This association may reflect proactive health-seeking behavior, greater health awareness, better access to additional health services, or ability to compensate for resource limitations within the primary care system. These findings suggest the importance of strengthening the capacity, continuity, and coordination of hypertension care within primary healthcare services to promote health equity and reduce patients' reliance on seeking care across multiple facilities. Improving the counter-referral system may further strengthen communication between different levels of care and support long-term clinical follow-up.

Acknowledgements

The authors would like to express their sincere gratitude to Hiromu Ito, Department of International Health and Medical Anthropology, Nagasaki University, for his support and assistance in editing the manuscript. The authors also thank Dr. Juan Pablo Bulnes and

Lia Loredo Paz from UNITEC, as well as Alexandra Sánchez, for their support in data collection. Special gratitude is extended to Dr. Asunción Lagos, Head of the Decentralized Health Network of Francisco Morazán, and Dr. Margarita Moreno, Coordinator of the Jicarito Health Network, Francisco Morazán, for their administrative cooperation and for granting access to the primary health care facilities involved in this study.

Funding: This study was partially funded by the School of Tropical Medicine and Global Health, Nagasaki University.

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

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Received May 15, 2026; Revised August 11, 2026; Accepted August 17, 2026.

Released online in J-STAGE as advance publication August 21, 2026.

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Global Health & Medicine. 2026; 8(4):297-310.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2026.01076

Reforming World Health Organization governance in a changing global health architecture: An integrated governance analysis informed by field observation, interview data, and policy mapping

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Abstract: Between January 2025 and early 2026, the World Health Organization (WHO) faced three interrelated structural pressures: a budget shortfall exceeding US$1.05 billion triggered by the announced United States withdrawal; a weakening of strategic governance functions at the Executive Board (EB) and the Programme, Budget and Administration Committee (PBAC); and the parallel emergence, outside WHO, of multiple Global Health Architecture reform agendas, including the Lusaka Agenda, the Accra Reset, the UN80 Initiative, and the America First Global Health Strategy. This study presents an integrated governance analysis using four complementary data sources: participant observation of WHO governing-body sessions (EB158, February 2026; the 79th World Health Assembly, WHA79, May 2026); semi-structured interviews with 10 professional staff serving at WHO headquarters and in regional and country offices; policy mapping of relevant reform-agenda documents, classified into four domains; and a companion quantitative analysis of governing-body document release timing. Triangulation revealed late release of budget documents, an unprecedented proposal to draw over US$ 400 million from the Programme Support Cost, contested governance reform, field-level constraints in prioritization, human-resource management and financial accountability. The findings suggest a bidirectional problem in which constraints on Secretariat function and difficulties in substantive Member State deliberation reinforce each other, while reforms remain headquarters-centric and may contribute to implementation gaps at regional and country levels. As a policy implication, the forthcoming Director-General selection and the UN80-linked reform cycle offer an opportunity for governance reform. These developments may offer opportunities for WHO Member States, including Japan and the Global South, to strengthen WHO's coordinating role.

***Keywords*:** sustainable financing, global health diplomacy, UN80 initiative, multilateralism, Global South

1. Introduction

1.1. Background: The governance crisis surfaced at the 79th World Health Assembly

On 20 January 2025, the new United States Administration announced its withdrawal from World Health Organization (WHO) and suspension of both assessed and voluntary contributions. As WHO's largest contributor (approximately 16% of its 2022–2023 budget), loss of United States funding, together with aid reduction by other Member States, left WHO a projected 2026–2027 budget gap of over US$1.7 billion, later narrowed to around US$1.05 billion (*1-4*). At the 42nd Programme, Budget and Administration Committee (PBAC) and the 78th World Health Assembly (WHA) in May 2025, the proposed 2026/27 programme budget of US$ 4.2 billion was tabled. Late release of the budget document, mid-session presentation of revised figures and financial assumptions absent from the original budget paper, and a proposal to draw over US$ 400 million from the Programme Support Cost (PSC) together constrained Member State scrutiny, and the budget was endorsed de facto without thorough review (*5,6*).

This sequence of events highlighted structural vulnerability of an Organization heavily dependent on a small number of major donors (*7,8*). In discussing WHO financing, this article distinguishes among assessed contributions (obligatory, un-earmarked, and predictable), voluntary contributions (the majority of which are

earmarked by contributors for specific programmes), the WHO Investment Round launched in 2024 to mobilise more flexible voluntary funding, and the broader question of sustainable financing addressed through Member State-led reform processes described below. These categories carry distinct governance implications and are treated separately in the analysis. We interpret it, however, not merely as a "financial problem" but as surface manifestation of a deeper structural governance crisis. Even before the United States announcement, some Global Health Architecture (GHA) reform agendas had begun to emerge, and others followed shortly thereafter, in parallel from outside WHO—the Lusaka Agenda (2023) (*9*), the Accra Reset (2025) (*10*), the UN80 Initiative (2025) (*11*), and the America First Global Health Strategy (2025) (*12*)—reflecting broader discontent with the WHO and its governance by Member States (*13,14*).

WHO itself has been advancing several internal reforms, including the Working Group on Sustainable Financing (WGSF) (WHA75(8)) (*15*), the Agile Member States Task Group on Strengthening WHO's Budgetary, Programmatic and Financing Governance (AMSTG) (EB152/33; WHA76(18)) (*16,17*), and the Member State-led governance reform submitted at the 158th session of the Executive Board (EB) (EB158/36) (*18*). These reforms, however, are insufficiently integrated, and decision-making in the WHA, EB, and PBAC increasingly fails to discharge strategic and normative functions originally expected of them.

1.2. Gaps in existing research

This governance crisis is unfolding bidirectionally. On the Secretariat side, limited financial and human resources make strategic judgement, priority setting, and budget management increasingly difficult (*19*). On the Member-State side, late release of decision-making documents compresses time available for domestic inter-ministerial coordination, regional-group consultation, and expert pre-consultation, constraining deliberative function that Member States are expected to exercise as sovereign right. In addition, rise of Global South has been accompanied by a growing number of countries that treat health as a strategic national interest and engage actively through their permanent missions in Geneva. Within these increasingly multipolar negotiation dynamics, major donor states, by contrast, contribute large sums but exert little substantive influence over WHO's work, fuelling donor disengagement.

Within the reform discourse (WGSF, AMSTG, EB158/36), "timing of document submission" and "ensuring prior consultation" have repeatedly emerged as concerns (*15-18*), yet empirical studies that longitudinally quantify the phenomenon and connect it to field-level experience remain limited. Similarly, few systematically examine how reform agendas formulated at headquarters are received and operationalised at WHO regional offices (ROs) and country offices (COs), and what implementation gaps arise. Studies that map full landscape of GHA reform agendas under a unified analytical framework and locate WHO's position within it are also scarce (*20,21*).

1.3. Research objectives

Building on this problem framing, the central analytical question of this study is how constraints on Secretariat capacity and constraints on substantive Member State deliberation interact with each other, and how this interaction conditions WHO's ability to respond to reform agendas reshaping the GHA. The three research questions (RQs) below operationalise this central question:

RQ1: How do the principal structural challenges of WHO governance; namely its fiscal base, human-resource and programme management, and the framework for engagement with non-state actors, manifest in deliberations of the central governing bodies (PBAC, EB, WHA) and in operations of WHO's ROs and COs?

RQ2: How constrained are time and information available to Member States for substantive deliberation, and how does this constraint shape governance outcomes? (The release timing of Secretariat documents, used as a measurable proxy for this constraint, is analysed quantitatively in a companion paper by our group (*22*); the present article draws on those findings and interprets them alongside the field, interview, and policy-mapping evidence.)

RQ3: How is interaction between Secretariat capacity and Member State deliberation, identified in RQ1 and RQ2, situated within the external reform agendas reshaping the GHA, and what do these agendas imply for WHO's coordinating role and for engagement of major contributing Member States?

In addressing these questions, the article seeks to make two contributions: first, an empirically grounded account of how constraints on the Secretariat and constraints on substantive Member State deliberation interact with each other; and second, a systematic mapping of the current GHA reform landscape that locates WHO's position within it. All subsequent sections are organised around this single analytical framework.

2. Materials and Methods

The study was designed as an integrated governance analysis drawing on multiple complementary sources of evidence: *i*) a quantitative analysis of WHO governing-body document release timing reported separately by Komada *et al.* (*22*); *ii*) field observation of WHO governing body meetings (EB, WHA, PBAC); *iii*) semi-structured interviews with professional staff at WHO

headquarters, regional and country offices; and *iv*) a policy mapping of principal GHA reform agendas. By combining these methods and triangulating findings across them, we aimed to capture structural challenges of WHO governance that no single approach can adequately illuminate. The four sources were integrated through a convergent mixed-methods design: each source was first analysed separately, and findings were then brought together at the interpretation stage through the triangulation procedure described in Section 2.5. Each source was assigned a primary analytical role in advance: document release timing analysis addressing RQ2; field observation addressing RQ1 and RQ2 at the level of the central governing bodies; qualitative interviews addressing RQ1 at the RO and CO levels; and policy mapping addressing RQ3. Table 1 summarises data sources, their settings and samples, and their contribution to the integrated analysis.

2.1. Document release timing data (reported separately)

A quantitative analysis of release timing of Secretariat documents in WHO's central governing bodies (EB, PBAC, WHA) is reported in a companion paper by our group (*22*). That analysis measured the interval—between document release and session start—of governing-body documents from 2016 through 2026 and quantifies a longitudinal trend of progressively later release for the WHA, with EB timelines partly recovering after the COVID-19 pandemic period. The present paper draws on its core findings and interprets them together with the field observation, qualitative interview, and policy mapping data described below. The two papers are designed as companion outputs of a single research project: Komada *et al.* (*22*) present the quantitative analysis of document release timing, while the present article provides integrative interpretation that combines that analysis with field observation, qualitative interviews, and policy mapping.

2.2. Field observation at WHO governing body meetings

Two of the authors (HS, HN) attended the PBAC 43 (28–30 January 2026), the 158th session of the WHO EB (EB158, Geneva, 2–7 February 2026), PBAC 44 (13–15 May 2026) and the WHO WHA (WHA79, Geneva, 18–23 May 2026) as members of the Japanese government delegation. Field notes were taken during sessions on finance and budget, governance reform, GHA reform and the UN80 Initiative, and relations with non-State actors, covering Member State interventions, chair rulings, amendments to draft decisions, and the dynamics of informal caucuses. Field notes were recorded contemporaneously in written form during the sessions and consolidated by the observing authors immediately after each session. Notes were organised by agenda item, and analysis proceeded by structured comparison of the notes against corresponding official documents and records of each session; the governance implications summarised in Table 2 were derived from this comparison and reviewed within the research team. Observation was confined to public deliberations and public documents, in line with the obligation of confidentiality. No non-public information, including content of closed sessions, informal consultations not open to observers, or internal government communications, was used in this study. Because the observing authors attended these sessions as members of the Japanese government delegation, their access reflects an insider position; a statement on positionality is provided in Section 2.6, and associated limitations are discussed in Section 4.5.

2.3. Interviews

The interview component was intended to provide contextual and explanatory insight regarding operational realities across organizational levels. As one component of overall governance analysis, interviews were used

Table 1. Overview of the four data sources and their contribution to the integrated analysis

Data source	Setting / sample	Analytical role in the integrated design	Research question
Document release timing (companion paper, Komada *et al.* (*22*))	WHO governing body documents (EB, PBAC, WHA), 2016 to 2026	Quantifies the structural compression of Member State deliberation time; provides the quantitative foundation on which the integrated interpretation builds	RQ2
Field observation	PBAC43, EB158, PBAC44, and WHA79 (January to May 2026); public sessions and public documents only	Documents how governance constraints manifest in the deliberations of the central governing bodies	RQ1, RQ2
Semi-structured interviews	10 professional staff (P3 to P5, all in programme functions) serving at WHO HQ (n = 2), in one RO (n = 2), and in COs (n = 6) in two WHO regions, October 2025 to March 2026	Identifies how headquarters-level reforms are experienced and operationalised at regional and country levels	RQ1
Policy mapping	Official documents of the principal GHA reform initiatives, 2023 to 2026	Locates WHO's position within the external reform landscape and identifies the horizontal coordination gap	RQ3

Table 2. Principal observations from selected governance issues discussed at EB158 and subsequently followed through PBAC 44 and WHA 79

Agenda item	Observation	Governance implication (analytical interpretation)
2026/27 programme budget (EB158/3, EB158/4)	Late release of the budget document; introduction of new assumptions during the session; proposal to draw over US$ 400 million from the Programme Support Cost (PSC); no strategic risk assessment presented to the session; adoption without substantive amendment.	Compressed timelines and mid-session changes constrained substantive Member State scrutiny; pattern consistent with endorsement of Secretariat proposals under time pressure (developed in Section 4.1).
Member State-led governance reform (EB158/36, EB158/37)	Proposals to limit the number of agenda items, streamline resolution/decision management, and improve meeting efficiency; North–South divergence over "inclusiveness" and "transparency".	Reform direction confirmed but binding force limited; no institutional design to mediate the trade-off between inclusiveness and agility.
GHA reform and UN80 (EB158/44)	Expectations expressed for WHO's "convening power" alongside methodological tension between comprehensive (Global South) and time-bound (high-income) processes.	Discussion on the connection between UN-wide reform and WHO's core functions is nascent; limited space for active Member-State debate.
Engagement with non-State actors (FENSA operations)	Renewal of relations with specific NGOs became politicised; Framework of Engagement with Non-State Actors (FENSA) procedure formally observed, decision adopted with reference to "Member States' sovereign rights".	Limits of rule-based governance when politicised; limited anticipatory risk identification and preventive engagement.
2026/27 budget execution and financing (PBAC44; Document A79/15)	Financing, Implementation and Performance Framework released two days before the linked PBAC session; execution/outlook papers tabled late; venue split across two sites during concurrent Hantavirus and Ebola emergencies.	Recurrence of the EB158 budget-timing pattern; minimal time for Member-State scrutiny of financial performance under operational strain.
Human resources: annual report (Document A79/21)	Staff of 8,569 as of 31 December 2025 (down 9.4% year on year); projected to decline to 7,283 by 30 June 2026, approximately 23% below the 9,401 staff recorded as of 1 January 2025 (A79/21; A79/21 Add.1); recruitment to resume under a restructured process prioritising matching of separated and serving staff, with new appointments on temporary contracts (Secretariat presentation, field observation).	Workforce contraction shaped by contractual and fiscal structures rather than strategic or programmatic criteria; risk to institutional capacity and continuity.
GHA reform and UN80 (joint task force)	Agreement on the composition and timeline of a joint Member State task force on GHA reform; the UN80 stakeholder-coordination proposal at PBAC44 was again tabled late.	Member-State-led step toward the horizontal coordination function the paper identifies as unassigned, but late documentation again constrained deliberation.
Conduct of proceedings and membership	Opening-day disputes over agenda adoption required repeated votes (Ukraine, Gaza, Gulf items); right-of-reply exchanges required chair intervention; the Taiwan question recurred; a resolution accepted Argentina's withdrawal and welcomed a possible return.	Intensifying politicisation crowds out substantive technical deliberation and extends the FENSA pattern (Row 4) into the plenary; membership volatility underscores the fragility of the universal participation and financing base.

Note: The "Observation" column reports what was directly observed in public sessions and official documents. The "Governance implication" column presents the research team's analytical interpretation, derived through structured comparison of field notes with corresponding official documents and records of each session (Section 2.2); these interpretations are developed further in the Discussion (Sections 4.1 to 4.3).

to inform interpretation of findings derived from field observation and policy analysis. Rather than seeking a comprehensive representation of WHO staff perspectives, interviews were intended to generate insight into governance-related challenges and implementation realities across organizational levels.

Between October 2025 and March 2026, we conducted semi-structured interviews with 10 professional staff serving at WHO headquarters (HQ, n = 2), in one regional office (RO, n = 2), and in country offices (COs, n = 6) located in two WHO regions. Specific regions are deliberately not named: each WHO region has a single Regional Office, and naming the region of the participating RO would identify the office concerned, and for CO participants the combination of a named region with grade and functional area could narrow identification within small country teams. For the same reason, attributes are reported only as aggregate counts and are not cross-tabulated. This safeguard formed part of the anonymisation approach explained

to participants. Participants were selected by purposive sampling to ensure diversity across grade (P5, P4, P3) and duty station (HQ, RO, CO); all 10 participants were serving in programme functions. Participants were recruited through professional networks of the research team, followed by snowball referral, with attention to avoiding concentration in any single office or functional area. Interviews were conducted in English or Japanese, according to preference of the participant. Memos were prepared in the language of the interview, and themes were developed and reported in English; no formal cross-language validation procedures were applied, consistent with the contextual role of the interview component described above. Each interview lasted 60–90 minutes, conducted in person or online, with memo-form records used to safeguard anonymity. Interviews were not audio-recorded and no verbatim transcripts were produced; instead, detailed written memos were taken during and immediately after each interview, and identifying details (name, office, country, and specific programme references) were removed at the point of recording. Accordingly, illustrative statements presented in Table 3 are composite reconstructions, each synthesising accounts from multiple participants on the basis of these memos, generalised and anonymised to protect participants; they are not verbatim quotations and are therefore presented without quotation marks.

The interview guide was developed by the research team on the basis of the research questions and the issues identified through field observation and document analysis. The same core domains were used in all interviews, with follow-up questions adapted to each participant's role and duty station; the guide was not formally piloted.

Topics included: (a) priority setting under Fourteenth General Programme of Work (GPW14) and three-tier (HQ–RO–CO) alignment; (b) human-resource management (WHO Representative appointments, mid-level appointments, junior development); (c) staff reductions under fiscal stress and equity; (d) financial accountability and external review; (e) relations with private foundations and other non-State actors; and (f) strategic engagement of major donors including Japan.

Analysis was informed by the general principles of thematic analysis (*23*) but the interview component was not designed or analysed as a stand-alone qualitative study. Memos were openly coded by one author (HS), and candidate themes were inductively extracted. The candidate themes and their interpretation were then presented by HS to the co-authors (KK, HN) and discussed at meetings of the research group of the funding project; themes were refined in light of the comments received before being finalised. Theme validity was anchored through team discussion and cross-referencing with the field observation data. Consistent with the role of the interview component described above, themes are presented as structured contextual findings, and no claim of thematic saturation is made (Section 4.5). The sample was considered adequate for this contextual purpose because participants were selected for direct professional experience of governance challenges under study and because the interview findings inform the analysis only in triangulation with other data sources. This rationale is broadly consistent

Table 3. Three core themes from interviews and illustrative composite statements (paraphrased and anonymised)

Theme	Structural problem	Illustrative composite statement (paraphrased and anonymised)
1. Limited operationalisation of GPW14 prioritisation and three-tier alignment	Institutional mechanisms for sustained HQ–RO–CO alignment are not fully established; under fiscal stress, the lack of agreed prioritisation across the three tiers leaves country and regional offices without a basis for deciding what to scale down.	When everything is treated as a priority, there is no shared basis for saying what should be protected and what should be set aside as resources shrink. We end up responding case by case rather than strategically.
2. Limited strategic linkage in human-resource management	Selection systems for senior leadership posts (including WHO Representatives) and mid-level appointments do not systematically assess capacities most needed in country settings—such as relationships with health authorities and resource mobilisation; post-appointment evaluation mechanisms remain to be institutionalised; under fiscal stress, the categories of staff most affected by reductions are determined more by contract type than by strategic value.	What the country actually needs from a senior post is the ability to engage the Ministry of Health and to mobilise resources. Current selection process does not really test for that, and there is no review afterwards. Technical specialisations in some offices are concentrated in areas of the leadership's background; expertise that the field actually asks for is at times not present.
3. Limited transparency in financial accountability	Information on resource allocation across countries and programmes is not always fully visible at the professional-staff level; institutionalised independent external review of regional and country office finances is not yet in place; expansion of private-foundation funding can create tension between funder priorities and WHO's normative agenda.	Even as a professional officer, I do not always have a clear picture of how regional and country budgets are allocated, or who reviews those decisions independently. When we accept earmarked funding, the topic does not always sit at the centre of our country strategy, and we then need to find space for our core work around it.

with the principle of information power, so that sample adequacy was to be judged by relevance of participants' experience to the study objectives rather than by numerical representativeness alone. The resulting themes are presented in Section 3.3.

2.4. Policy mapping of GHA reform agendas

We systematically collected official documents (strategies, declarations, final reports, decisions) of the principal GHA-related reform initiatives and compared them along three dimensions: *i*) actor; *ii*) objective; and *iii*) reform focus. Initiatives were included if they met three criteria: *i*) they claim system-level relevance to the GHA, rather than relevance to a single disease programme or institution; *ii*) they are articulated in official, publicly available documents issued by an identifiable institutional actor between 2023 and 2026; and *iii*) they were actively referenced in WHO governing body deliberations during the observation period. Initiatives that are primarily national health strategies, disease-specific replenishment campaigns, or academic proposals without an institutional sponsor were excluded. Documents were identified through monitoring of the issuing organisations' official publications and of documents referenced in WHO governing body proceedings during the observation period, and the document set was finalised and verified in early June 2026. Principal documents included the Lusaka Agenda, Accra Reset, America First Global Health Strategy, UN80 Initiative, Gavi Leap, Wellcome Trust strategic documents, WGSF final recommendations, AMSTG report, EB158/36 governance reform, and EB158/44 GHA reform. They were classified into four domains—financing efficiency; sovereignty, technology transfer and domestic production; institutional and governance reform; and ideas, knowledge and normative formation—and we analysed within-domain dynamics, cross-domain relationships, and WHO's position in each. The classification was developed iteratively within the research team: documents were grouped according to their principal reform focus, and groupings were consolidated into the four domains through team discussion. Positioning of each initiative along the two axes of Figure 1 reflects the research team's qualitative judgement of its principal orientation, consolidated through team discussion; placement is heuristic rather than derived from quantitative scoring. Full list of documents analysed, with issuing organisation, publication date, reason for inclusion, assigned domain, and basis for classification, is provided in Supplementary Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=125*). We note that the initiatives differ substantially in origin, purpose, scope, and political orientation; the four-domain classification is intended as an analytical device for locating WHO's position in the reform landscape, not as a claim that initiatives within a domain are equivalent.

2.5. Triangulation

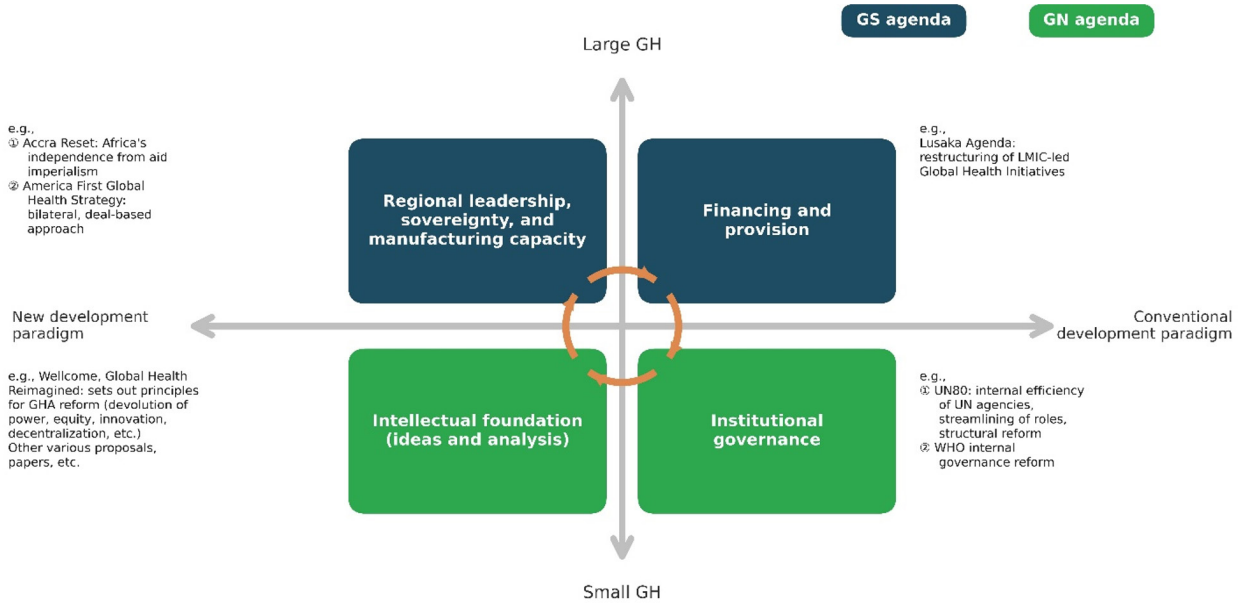

Figure 1. Mapping of contemporary reform proposals across the Global Health Architecture (GHA) debate. Proposals are positioned along two axes (vertical, scope of global health ambition; horizontal, new versus conventional development paradigms) and grouped into four domains. Dark blue denotes Global South (GS) agendas and green denotes Global North (GN) agendas; curved arrows represent WHO's horizontal coordinating role across the four domains. *Abbreviations*: GN, Global North; GS, Global South. *Source: Health, Labour and Welfare Research. Study on Strengthening Governance of the World Health Organization; Principal Investigator: Hiroki Nakatani, summary to be published in the MHLW Research Grant Database (in Japanese), Project ID: 25BA2001.*

Findings from the four data sources were triangulated to overcome limitations of any single method and to capture the structural problems of WHO governance in their multilayered form. Specifically, the quantitative finding of "structural compression of deliberation time" was connected to *i*) field observation of decision-making at WHO governing bodies, *ii*) qualitative interview accounts of perceptions and experience outside HQ, and *iii*) policy mapping of GHA reform agendas. The integration enables a structural interpretation of vertical relationships among the micro (operational), meso (RO/CO organisational), and macro (GHA structural) layers.

2.6. Ethical considerations and positionality

Interviewees received prior explanation of the study's purpose, data use, and anonymization policy, and provided verbal informed consent. Statements were generalized and anonymized so that no individual could be identified; remarks that might be construed as criticism of specific individuals within WHO were recast as institutional or structural issues. Although the authors attended these WHO governing body meetings as members of the Japanese government delegation, reporting in this study was restricted to public deliberations and publicly available documents, in line with the obligation of confidentiality. As part of governance analysis, the expert interviews were conducted with WHO staff in their professional capacity, collecting professional views on organizational, financial, and governance matters, and no information concerning any individual's health or other personal circumstances was collected. On this basis, the investigators judged that the study falls outside the scope of Japan's Ethical Guidelines for Medical and Biological Research Involving Human Subjects, which apply to research using information relating to individuals' health; no formal institutional determination was sought, and this position is one of non-applicability rather than exemption or approval. In addition to the safeguards above, consent was noted in the interview memo, identifying details were removed at point of recording, anonymised memos are retained by the corresponding author with access limited to the research team, and there was no supervisory or evaluative relationship between the researchers and participants, who were free to decline or withdraw at any time. In addition, because the study relied in part on interpretation of governance processes observed by members of the research team, consideration of author positionality is important for assessing potential sources of bias.

With regard to positionality, the authors combine professional histories in the Japanese government, WHO, academia, and civil society, and two authors (HS, HN) observed the governing bodies as members of the Japanese government delegation. This position provided proximity to deliberative dynamics and access to practical context of negotiations, but it also means that analysis is conducted from the standpoint of a major contributing Member State and may carry interpretive bias. To mitigate this, observation was restricted to public proceedings, factual claims were anchored in citable public documents, interpretations were deliberated within the research team, and associated limitations are stated explicitly in Section 4.5.

3. Results

Each subsection below reports findings from a single data source, identified in the subsection heading: Section 3.1 summarises quantitative findings reported in the companion paper (*22*); Section 3.2 reports field observation findings; Section 3.3 reports interview findings; and Section 3.4 reports policy mapping findings. Interpretation across sources is reserved for the Discussion (Section 4).

3.1. Structural compression of Member State deliberation time (summary of quantitative findings)

Komada *et al.* (*22*) show that over the past decade release of Secretariat documents has moved markedly closer to the session date for the WHA, while the EB has followed a different trajectory. For the WHA, the average interval between document release and opening of the session fell from roughly one month in 2016 to 2019 to 10.9 days for WHA79 (2026), the shortest interval observed. For the EB, after a sharp contraction during the COVID-19 pandemic period, the interval recovered to approximately 45 days before EB158 (2026). This divergence indicates that timely circulation remains operationally feasible but is not consistently applied across governing bodies, and that persistent compression is concentrated in the WHA (see Komada *et al.* (*22*) for details). A recent illustration is the Financing, Implementation and Performance Framework for the 2026 to 2027 Programme Budget (Document A79/15), released only two days before the PBAC session linked to WHA79, mirroring the late budget-document pattern observed at EB158 (Table 2). This compression structurally reduces time available to Member States for domestic scrutiny, inter-ministerial coordination, regional-group consultation, and expert pre-consultation.

The present article does not seek to re-verify these quantitative findings; instead, it uses them as a foundation for integrated interpretation of field manifestations and higher-order structural drivers described in the following sections.

3.2. Field observation of governance dysfunction at EB158 and WHA79

Consistent with the Komada *et al.* (*22*) findings, constraints on Member State deliberation were observed in multiple settings at EB158 and WHA 79. Table 2

summarises the principal observations. The interpretive connection between these observations and structural compression of deliberation time referenced in Section 3.1 is developed in Section 4.1.

Field observation at WHA79 (May 2026) corroborated and extended these patterns. The Assembly convened across two sites (the Palais des Nations and WHO headquarters) while managing concurrent hantavirus and Ebola emergencies, and several Secretariat papers, including the 2026/27 budget execution outlook and the proposal for stakeholder coordination on the UN80 Initiative considered at the linked PBAC44 session, were again released only shortly before deliberation, leaving limited room for substantive scrutiny. The human-resources annual report (Document A79/21) recorded a staff complement of 8,569 as of 31 December 2025 (down 9.4% year on year), and its addendum on the prioritization and realignment process (Document A79/21 Add.1) projected a complement of 7,283 by 30 June 2026, a reduction of approximately 23% relative to the 9,401 staff recorded as of 1 January 2025. In presenting the reports, the Secretariat signalled a phased resumption of recruitment under a restructured process that prioritises matching of separated and serving staff before external candidates, and places new appointments on temporary contracts (field observation, WHA79). These figures give quantitative form to field accounts in Theme 2 (Section 3.3), in which staff reductions follow contractual and procedural structures more than strategic or programmatic criteria. At the same time, the Assembly reached agreement on several governance-relevant items, including a one-year extension of negotiations on the Pathogen Access and Benefit-Sharing (PABS) system under the Pandemic Agreement, composition and timeline of a joint task force on GHA reform, and a resolution welcoming possible return of Argentina. Deliberation was also more politicised than at EB158: disputes over agenda adoption on the opening day required repeated votes, exchanges of the right of reply between delegations required the chair to intervene, and the politicisation observed in decisions under the Framework of Engagement with Non-State Actors (FENSA) (Table 2) extended into the plenary. Interpretation of these patterns is taken up in Section 4.1.

3.3. Reform impact outside headquarters (qualitative interview findings)

Interviews with professional staff at WHO ROs and COs surfaced three common structural challenges in how HQ-level reforms are experienced at RO and CO levels. Illustrative composite statements, each synthesising accounts from multiple participants as described in Section 2.3, are provided in Table 3.

Theme 1: Limited operationalization of GPW14 prioritisation and three-tier alignment

A recurring observation across duty-station levels was that prioritisation under the 14th General Programme of Work (GPW14, 2025–2028) has yet to translate fully into practice. Respondents described how priorities intended to be pursued jointly by WHO HQ, ROs, and COs can blur into a situation in which "everything is a priority", as mechanism for division of labour and coordination across the three tiers remain undeveloped. Under fiscal stress, this makes it harder to decide what to protect and what to scale down, and responses tend to be taken case by case rather than within a shared strategic framework.

Theme 2: Limited strategic linkage in human-resource management

Multiple respondents noted that linkage between organisational strategy and HR practice has not yet been systematically established in appointment of WHO Representatives and other senior and mid-level posts. The examination- and roster-based qualification system used for WHO Representative selection does not by itself capture some of the capacities most needed in the field, such as relationships with national health authorities and resource mobilization, and institutionalised post-appointment evaluation and feedback mechanisms are not yet in place for WHO Representatives and for other senior leadership positions. Appointments at the P4/P5 level are shaped by judgement of unit Directors, so that staffing reflects technical priorities and professional expertise of individual units alongside the organisation's broader programme priorities, which can at times create a mismatch between available human resources and work required. Under fiscal stress, staff reductions tend to follow legal and contractual structures of employment more than strategic or programmatic criteria; consequently junior, non-regular, and locally recruited staff are more often affected, while long-tenured staff are largely retained. Several respondents suggested that this pattern, shaped more by procedural feasibility rather than substantive judgement, may over time weaken the medium- to long-term human-resource base of the Organization.

Theme 3: Limited transparency in financial accountability

Respondents noted that strengthening flow of resource-allocation and expenditure information in both directions across WHO headquarters, ROs, and COs would support not only financial accountability but also the three-tier alignment discussed above. Developing independent external review further, and articulating accountability lines for specific decisions more clearly, were likewise seen as ways to reinforce both strategic budget execution and organisational trust. Respondents also reflected on the broader tension that can accompany expansion of fundraising from private foundations: priorities of individual funders do not always align fully with WHO's normative agenda, and the need to mobilise resources can at times draw programmatic attention toward areas that are not always central to the Organization's strategic priorities. Accounts varied in

emphasis across duty stations rather than in direction. Consistent with the contextual role of the interview component (Section 2.3), these themes are presented as structured contextual findings rather than as generalisable results.

3.4. Mapping of GHA reform agendas (policy mapping findings)

Mapping the principal GHA reform agendas revealed four domains within the current GHA reform landscape (Figure 1 and Table 4). The agendas mapped comprised the Lusaka Agenda, Accra Reset, America First Global Health Strategy, UN80 Initiative, Gavi Leap, Wellcome Trust strategic documents, WGSF, AMSTG reports, EB158/36, and EB158/44.

Domain 1: Financing efficiency. Centred on the Lusaka Agenda and the Gavi Leap, focusing on aligning limited resources with national health strategies and improving efficiency.

Domain 2: Sovereignty, technology transfer and domestic production. The Accra Reset and the America First Global Health Strategy, while differing politically, both emphasise national sovereignty, domestic industrial base, and visibility of outcomes.

Domain 3: Institutional and governance reform. The UN80 Initiative, WGSF, AMSTG, EB158/36, and EB158/44 belong here, aiming at financial stabilisation, decision-making efficiency, and organisational restructuring.

Domain 4: Ideas, knowledge and normative formation. The Wellcome Trust is emblematic: emphasising scientific evidence and long-term perspective while bearing no governance responsibility.

These four domains are organised around distinct constraints and objectives; they are partly complementary and partly in tension. As noted in Section 2.4, initiatives grouped within each domain differ in origin, purpose, and political orientation; the classification reflects their principal reform focus rather than any equivalence among them. A critical observation is twofold: none of the external reform agendas engages with the redesign of WHO governance itself, and the WHO-internal reform streams included in the mapping (WGSF, AMSTG, EB158/36, EB158/44) are directed principally at financial stabilisation and internal efficiency rather than at defining a horizontally coordinating role across the four domains. None of the mapped agendas, external or internal, explicitly assigns WHO itself a horizontally coordinating role across all four domains (*20,24*).

4. Discussion

4.1. Integrated interpretation: bidirectional difficulty of substantive deliberation

Existing discussion of WHO governance has tended to treat three problems as separate, each addressed by

Table 4. Four-domain classification of GHA reform agendas

Domain	Principal initiatives	Reform focus	WHO's position
1. Financing efficiency	Lusaka Agenda/Gavi Leap	Coordination across Global Health Initiatives, alignment with national health strategies, avoidance of duplication, results orientation	Identified as one coordinating actor; the cross-GHI financing rationalisation pursued here has not been operationally linked to WHO's internal financial stabilisation under WGSF
2. Sovereignty and production	Accra Reset / America First Global Health Strategy	National sovereignty, domestic production capacity, technology transfer, bilateral cooperation, visibility of outcomes	Faces a fundamental challenge to the model of universal norm expansion; no coordination interface yet developed between these agendas and WHO's internal governance reforms
3. Institutional/ governance reform	UN80 / WGSF / AMSTG/ EB158/36 /EB158/44	WGSF: financial stabilisation through raising assessed contributions; AMSTG: transparency, accountability, and decision-making efficiency under Member State-led governance; EB158/WHA79: meeting and decision management while framing WHO as convening and coordinating actor; UN80: UN-wide budget reduction, organisational restructuring, mandate review	WHO's internal reforms (WGSF, AMSTG, EB158/WHA79) strengthen institutional base for a coordinating role, but substantive alignment with UN-wide reform (UN80) remains to be worked through
4. Ideas / norms	Wellcome Trust	Scientific evidence, long-term perspective, knowledge as public good	WHO remains the principal institution responsible for translating evidence and ideas into globally recognised norms and coordinated action, yet no dedicated mechanism currently links the growing ecosystem of knowledge-generating actors with system-wide governance processes.

its own reform agenda: late release of governing-body documents, weakening of Secretariat capacity, and difficulty of substantive Member-State deliberation. Integrated reading made possible by our four data sources points to a different framing. Document release timing (Section 3.1), governance dynamics observed at EB158 (Section 3.2), field-level structural challenges identified through interviews (Section 3.3), and WHO's position within current GHA reform agendas (Section 3.4) are not parallel phenomena that can be addressed in isolation. They are mutually constitutive elements of a single bidirectional dynamic, in which Secretariat constraints and Member-State deliberative constraints sustain one another. Late release of documents, for example, is not problematic in isolation; combined with weak strategic governance, it reinforces a pattern of de facto endorsement of Secretariat proposals, as observed at EB158 and WHA79 (Section 3.2). Constraints on Member State deliberation likewise arise less from any single procedural failure than from the interaction of compressed deliberation time (Section 3.1), fiscal stress (Sections 3.2 and 3.3), and intensifying politicisation (Section 3.2). Read separately, each data source would support only a partial diagnosis: that the Secretariat is under-resourced, that Member States are under-prepared, or that the reform agenda is fragmented. Read together, they indicate that none of these elements can be addressed effectively without addressing the others.

This mutual reinforcement is sustained by feedback operating in two directions. From below, field-level constraints identified in Section 3.3, namely limited three-tier alignment, weak strategic linkage in human resources, and limited transparency in financial accountability, mean that governance decisions taken at headquarters do not reliably translate into improved performance in ROs and COs. Member States therefore deliberate without confidence that better decisions will produce visibly better outcomes, which reduces incentive to invest in substantive engagement. From above, the HQ-centric framing of current GHA reform agendas concentrates attention on document timing and meeting efficiency, leaving field-level conditions that determine whether reforms actually work largely outside the reform scope.

Taken together, these two dynamics suggest that the current reform cycle addresses the manifestations most visible at headquarters while leaving field-level conditions that sustain mutual reinforcement largely outside its scope. Without engaging that field-level component, the bidirectional difficulty is unlikely to be interrupted even where HQ-level governance improves. Recent reform discussions in the EB, PBAC, and WHA illustrate this pattern: they have advanced Member State-led arrangements at the headquarters level while leaving the RO and CO structural challenges identified in Section 3.3 largely unaddressed, thereby contributing to the implementation gap discussed in Section 4.3.

It should be emphasised that Member States are not merely constrained actors in this dynamic. Field observations in Section 3.2 indicate that Member States themselves shape the agenda, multiply agenda items and reporting requests, delay consensus through politicised disputes, and invoke sovereign prerogatives in ways that crowd out substantive technical deliberation, as seen in repeated votes over agenda adoption, exchanges of the right of reply, and politicisation of FENSA-related decisions. The bidirectional dynamic described here is therefore jointly produced: Secretariat constraints compress space for deliberation, and Member State behaviour in turn consumes and fragments deliberative space that remains.

4.2. Connection with GHA reform

The four domains identified in Section 3.4 do not simply describe parallel agendas. Together, they generate a structural demand for horizontal coordination that none of them assigns. Each places coordination responsibility elsewhere: the Lusaka Agenda on the Global Health Initiatives themselves; the Accra Reset and the America First Global Health Strategy on national governments and bilateral cooperation; and UN80 on the UN system as a whole. The Wellcome Trust, for its part, positions itself as a knowledge provider, with a remit centered on evidence and long-term perspective rather than system-wide governance coordination. While such actors contribute substantially to agenda-setting and knowledge generation, no corresponding mechanism exists to translate these ideas systematically into globally accepted norms and coordinated action across the broader GHA landscape. The need for an actor that can hold these pressures together, reconciling financing efficiency with sovereignty and institutional restructuring with normative continuity, therefore arises from coexistence of these agendas rather than from any single one of them.

In our reading, this gap is the central strategic question for WHO governance. We interpret that WHO may be well placed to coordinate across all four domains; this is an interpretation grounded in WHO's institutional characteristics rather than a conclusion directly demonstrated by the study data, and it rests principally on the mandate in Article 2(a) of the WHO Constitution, which lists among the Organization's functions to act as "the directing and coordinating authority on international health work". The Accra Reset and the Wellcome Trust sharpen this point. The former reframes international health as a matter of sovereignty and industrial capacity rather than universal norm extension; the latter positions itself around evidence and long-term perspective rather than system-wide coordination. Neither sovereignty-focused agendas nor knowledge-focused actors can themselves take on the coordinating role, which leaves it unclaimed unless WHO claims it explicitly.

WHO's internal reforms each address a distinct

precondition for this role. The WGSF aimed to stabilise the financial base by raising assessed contributions; the AMSTG sought to improve transparency, accountability, and decision-making efficiency under Member State-led governance; and EB158/WHA79 accelerated meeting and decision management while explicitly framing WHO as convening and coordinating actor in the GHA. In practice, however, their connections to the external GHA agendas have remained largely discursive. WGSF's financial stabilisation has not been operationally linked to the cross-GHI financing rationalisation pursued by the Lusaka Agenda; governance improvements under AMSTG have not produced a coordination interface with sovereignty-focused agendas such as the Accra Reset and the America First Global Health Strategy; and the EB158/WHA79 reference to UN80 has not been worked through into substantive alignment with UN-wide reform. Internal reforms have therefore strengthened the financial and organisational base needed to play the coordinating role, without yet engaging the strategic question of how that role should be structured in relation to external agendas.

4.3. HQ-centrism of reform and implementation gap

The integrated reading of our data sources points to an implementation gap that is more than an oversight; it is reproduced by the way reform processes themselves are structured. Reform discourse in the EB, PBAC, and WHA concentrates on actors and instruments that are procedurally visible within those venues, namely delegations, document timelines, and decision and agenda management, while WHO RO and CO conditions enter discussion only indirectly, mediated through Secretariat reports. Reform success is correspondingly measured by HQ-level process completion (resolutions adopted, governance instruments revised) rather than by changes in field-level performance. This procedural framing offers a structural explanation for why field-level constraints identified in Section 3.3 persist even as HQ-level reforms advance.

Implications are twofold. First, evaluation of reform should explicitly include WHO RO and CO indicators of whether HQ-level decisions translate into operational change. Without such indicators, reform discourse continues to address manifestations most visible at HQ while leaving conditions that determine reform efficacy outside its scope. Second, organisational decisions on downsizing, function transfer, and resource allocation should be assessed not only through the logic of financial rationalisation but through their consequences for WHO's core normative and coordinating functions (*25*), especially at the field level. Under fiscal constraint, an organisationally shared strategic vision of what to protect and what to entrust needs to operate across HQ, ROs, and COs, supported by feedback mechanisms that allow field-level realities to inform HQ-level reform choices.

4.4. Policy implications

Implications set out in this section are normative policy recommendations derived interpretively from the findings; they are presented separately from empirical results in Section 3 and should be read as the authors' policy judgement rather than as findings themselves. The findings yield policy implications across four layers. In terms of feasibility, recommendations differ in the level at which action is required: some are feasible at the level of the Secretariat and the Director-General; others require collective Member State decision-making through the PBAC, EB, and WHA processes, including the governance reform stream under EB158/36 and the joint task force on GHA reform; and others again require coordination beyond WHO, with other global health institutions and with the UN80 process.

(a) Member States

What is required of Member States goes beyond procedural fixes to document timing and meeting management; it is the willingness to take collective responsibility for the strategic direction of WHO governance itself. As this study has shown, none of the external reform agendas explicitly assigns WHO a horizontally coordinating role across the four GHA domains. The strategic question of whether WHO should assume this role, and under what governance structure, must be answered by Member States as a collective body.

Concretely, this requires: *i*) formation of strategic agreement on the maintenance and strengthening of WHO's core normative and coordinating functions; *ii*) substantive engagement with the definition of WHO's role as a horizontal coordinator across the four GHA domains; *iii*) institutionalisation of feedback mechanisms that bring WHO RO and CO realities into reform discussions; and *iv*) development of national capacity to articulate the strategic purposes of each state's WHO contribution and to express them substantively in deliberations.

These responsibilities are shared by all Member States, irrespective of region or income level. The growing presence of the Global South and the multipolarisation of negotiation dynamics should not be read as a return to a bipolar contest among Member States; rather, relationships among Member States need to be reconstructed as a collective responsibility for the strategic direction of WHO.

(b) WHO Secretariat and Director-General

What is required of the Secretariat goes beyond procedural improvements to document timelines and risk assessment; it is the responsibility to articulate substantive strategic choices that Member States can engage with. Under constraints identified in this study, the Secretariat needs to make its own strategic judgements explicit: which core functions it intends to protect, which functions it proposes to delegate or share, and how it intends to position WHO within the four

GHA domains. Such substantive choices give Member States real content to scrutinise and decide upon, rather than leaving deliberation as a reactive process oriented toward documents whose strategic implications are not articulated. The Secretariat also needs to build RO and CO realities into its strategic proposals at the outset, rather than treating field-level operationalisation as a post-decision implementation question.

The Director-General (DG) carries additional responsibility of articulating WHO's strategic positioning as the horizontal coordinating actor that no external GHA agenda has explicitly assigned. This requires the DG to set out, proactively, how WHO's mandate under Article 2(a) of the Constitution is to be operationalised across the four GHA domains, and to lead mediation not only between Member States but also between headquarters and regional and country offices whose realities must inform that strategic positioning.

(c) Next Director-General selection

Selection of the next DG is, in light of these findings, a particularly important moment for embodying leadership required for WHO governance redesign at the GHA maturation stage (*26*). Required qualities include: *i*) ability to operate normative and managerial functions complementarily; *ii*) mediation capacity in political disputes; *iii*) constructive collaboration with the Global South; and *iv*) strategic linkage with UN80 and GHA reform.

(d) Role of Japan

Japan is discussed as an illustrative case of a major contributing Member State; the research team's institutional base makes the case that the authors can specify in greatest detail (Section 4.5). Findings suggest three areas in which a major contributor can support WHO governance: *i*) clarifying the strategic objectives of its engagement with WHO; *ii*) aligning financial and human-resource contributions with those objectives; and *iii*) fostering constructive partnerships with countries of the Global South in support of WHO's coordinating and normative functions. For Japan, these translate into priorities such as universal health coverage, healthy ageing, and infectious disease control, building on its record of measured, evidence-based engagement in the EB. The same logic applies to other major contributing Member States, whose combined behaviour will substantially determine whether the deliberative space identified in this study can be restored.

4.5. Limitations

This study has the following limitations. First, the interview component was based on a small purposive sample (n = 10, drawn from the headquarters, one RO, and COs in two WHO regions, all serving in programme functions). It was intended to provide contextual insight rather than a comprehensive representation of staff views. Formal thematic saturation was not assessed. Second, although field observation covers both EB158 (February 2026) and WHA79 (May 2026), these two sessions are close in time, and longitudinal observation across multiple governance cycles will be needed to capture change over time. Third, quantitative analysis of document release timing is reported in a companion paper (*22*); the present article uses its findings as reference. Fourth, as the study was conducted by a Japanese research team, policy implications for Japan's WHO engagement receive particular attention. Fifth, the authors' positionality shapes the analysis: two authors observed the governing bodies as members of the Japanese government delegation, and analysis was conducted from the standpoint of a major contributing Member State; this insider position afforded access and contextual understanding but may introduce interpretive bias, which we sought to mitigate through measures described in Section 2.6. Sixth, the purposive and network-based recruitment of interview participants may have produced selection bias, and views of participating staff cannot be assumed to represent the entire workforce of the RO and COs concerned. In addition, distribution of participants across regions and offices was not reported in order to protect anonymity, which constrains readers' ability to assess composition of the sample. Seventh, policy mapping involves interpretive judgement in classifying heterogeneous initiatives, and alternative groupings are possible. These limitations notwithstanding, the study provides empirically grounded insights into emerging governance dynamics within WHO. Comparative and international collaborative studies are warranted to complement these limitations.

5. Conclusions

WHO faces one of the most significant structural governance challenges since its founding. The integrated approach of this study supports interpretation that this challenge takes the form of a bidirectional structure: constraints on Secretariat function and difficulty of substantive Member-State deliberation reinforcing each other and that HQ-level reform proceeds with an implementation gap at regional and country levels.

As a policy conclusion, we propose that the maturing GHA stage requires redefinition of WHO as the horizontally coordinating actor across the four domains (financing efficiency; sovereignty and production; institutional governance; and ideas and norms), and a governance design that operates normative and managerial functions in a complementary manner. The next Director-General selection and the unfolding UN80-linked reform cycle constitute a critical opportunity to advance that redesign. The practical implication of this study is that reform effort directed at either side of the bidirectional dynamic alone, whether at Secretariat document management or at Member State meeting efficiency, is unlikely to restore substantive deliberation;

redesign needs to address both sides together, and to build regional and country office realities into the reform process from the outset.

Acknowledgements

We thank the professional staff at WHO regional and country offices who kindly took part in the semi-structured interviews. The views expressed are those of the authors and do not necessarily represent the views of their institutions.

Funding: This study was funded by the Health, Labour and Welfare (MHLW) Sciences Research Grant (research project: Study on Strengthening Governance of the World Health Organization; Principal Investigator: Hiroki Nakatani, summary to be published in the MHLW Research Grant Database (in Japanese), Project ID: 25BA2001) (*27*).

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

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Received June 16, 2026; Revised August 21, 2026; Accepted August 24, 2026.

Released online in J-STAGE as advance publication August 27, 2026.

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Global Health & Medicine. 2026; 8(4):311-315.
ORIGINAL ARTICLE
DOI: 10.35772/ghm.2026.01027

Laparoscopic liver resection for patients with intrahepatic cholangiocarcinoma using data from the Japanese National Database: A nationwide observational study

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Abstract: Since 2011, the Ministry of Health, Labour and Welfare (MHLW) has made the data from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) available for research purposes. Recent trends in treatments and prognosis for intrahepatic cholangiocarcinoma (ICC) were analyzed using data from this comprehensive database. This repeated cross-sectional study employed NDB open data to determine the number of patients with ICC and those treated for ICC from fiscal years (FY) 2016 to 2020. The International Classification of Diseases version 10 (ICD-10) code of C22.1 (ICC) was used to define ICC patients. The number of patients diagnosed with ICC and treated in Japan did not change during the study period (FY2016: 1,119; FY2017: 1,136; FY2018: 1,213; FY2019: 1,185; FY2020: 1,194). The number of patients who underwent open liver resection (OLR) did not change either (FY2016: 748; FY2017: 771; FY2018: 807; FY2019: 760; FY2020: 753). On the other hand, patients who underwent laparoscopic liver resection (LLR) increased during the study period (FY2016: 84; FY2017: 118; FY2018: 143; FY2019: 171; FY2020: 195). This was primarily due to the increase in the number of patients who received laparoscopic liver resection larger than subsegmentectomy (FY2016, 57; FY2017, 81; FY2018, 98; FY2019, 101; FY2020, 133). The median postoperative survival was 5.25 years in the OLR group and was not reached in the LLR group. The national database analysis revealed that while the number of patients diagnosed with and treated for ICC has remained stable, the adoption of minimally invasive surgery has increased, possibly because of advancements in treatment techniques, resulting in good survival outcomes.

***Keywords*:** intrahepatic cholangiocarcinoma, laparoscopic liver resection, Japanese national database

1. Introduction

The incidence of intrahepatic cholangiocarcinoma (ICC) is increasing globally, and treatment advances are remarkable for patients with ICC (*1*). Because most ICC patients are diagnosed at advanced stages, the prognosis remains unfavorable (*2*). The Liver Cancer Study Group of Japan is one of several nationwide registries in Japan (*3*). Nevertheless, the data submitted to this registry is exclusively sourced from approximately 500 Japanese specialized institutes. The National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB) open data is another promising data source for analyzing the number of ICC patients and treatments. Since 2011, the Ministry of Health, Labour, and Welfare (MHLW) has provided comprehensive electronic claims data for insured treatments in this database (*4*). This database offers a precise understanding of ICC treatments performed in Japan.

Laparoscopic surgery, particularly in colorectal surgery, has gained widespread acceptance based on the positive outcomes demonstrated in randomized controlled trials (*5*). In the context of liver surgery, numerous studies have reported favorable results following laparoscopic liver resection (LLR) for patients with hepatocellular carcinoma (*6-8*). However, little is known about the impact of LLR in ICC patients.

Therefore, this study aimed to examine this NDB open data to identify population-based national trends in the number of patients with ICC, their treatments, and their prognosis.

2. Materials and Methods

2.1. Data source

The NDB open data, a comprehensive database that aggregates electronic insurance claims data for all medical services and products covered by Japan's national health insurance system, was utilized in this study (*9*). Researchers may submit an application to the MHLW to obtain access to the NDB open data, which is subject to their research requirements. The data supplied by MHLW is anonymized. The NDB open data contains comprehensive information on patient demographics, health status, diagnoses, medical and dental procedures, and prescription data, as well as insurance claims and health exam records from all hospitals and clinics in Japan.

For this study, we requested and obtained data on International Classification of Diseases, 10th Revision (ICD-10) codes for liver cancer, spanning the period from April 2015 to September 2021. The MHLW provided our research team with access to 323 million medical records, 130 million Diagnostic Procedure Combination records, and 384,000 prescription records.

2.2. Statement of ethics

The study protocol was reviewed and approved by the Ethics Committee of the National Center for Global Health and Medicine (approval number: NCGM-S-004253-03). The data supporting the findings of this study are available upon request from the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB Open Data) (*https://www.mhlw.go.jp/ndb/opendatasite/*).

The NDB Open Data consists of anonymised data that is publicly available on the website and accessible to third parties, without any personal patient information. Therefore, informed consents were not required for this study.

2.3. Patients selection

At the NDB open data, diagnostic data are categorized employing ICD-10 codes. Patients diagnosed under ICD-10 code C22.1 (ICC) were defined as having ICC. Patients lacking treatment-related data were excluded from the analysis.

2.4. Treatments and outcomes

Interventions for ICC were defined as treatments administered within 180 days of diagnosis. Liver resection cases were classified as either open liver resection (OLR, procedure code K695) or laparoscopic liver resection (LLR, procedure code K695-2). The extent of liver resection was further categorized into subsegmentectomy or more extensive resection, and partial resection, as documented in the insurance claims. Transarterial embolization (TAE, procedure code K615) and transarterial chemoembolization (TACE, procedure code G003-3) were considered together. Patients treated with sorafenib (medication code 620006778), lenvatinib (622416001 and 622416101), regorafenib (622225801), cabozantinib (622796901 and 622797001), ramucirumab (622417901 and 622418001), bevacizumab (620004872 and 620004873), and atezolizumab (622594601 and 629900601) were categorized as receiving molecular targeted therapies. The information concerning cancer stage, liver function, or margin status was not available due to the nature of the database.

Time to death, defined as the duration from treatment initiation to death, was evaluated for patients who underwent surgery between 2016 and 2020. Time to death was determined from information relating to death that was captured from the "outcome at the time of discharge" field and/or "destination after discharge" field in the Diagnosis and Procedure Combination discharge summary data. The discharge date was used as the date of death for statistical calculations. The patient's insurance information was followed up until September 2021. Patients for whom the date of death could not be confirmed were censored at their latest recorded visit date during the study period (*10*).

2.5. Statistical analysis

The number and percentage of treated patients were analyzed. Patient counts were ascertained for each fiscal year (FY), commencing in April, between FY2016 and FY2020. Statistical analyses were performed using the R software (version 4.4.2).

3. Results

Table 1 and Figure 1 illustrate the trends of treatment for ICC. During the study period, the number of patients diagnosed with ICC and treated remained comparable (FY2016: 1,119; FY2017: 1,136; FY2018: 1,213; FY2019: 1,185; FY2020: 1,194). Consequently, the number of patients who received OLR remained steady (FY2016: 748; FY2017: 771; FY2018: 807; FY2019: 760; FY2020: 753). Conversely, patients who underwent LLR increased significantly (FY2016, 84; FY2017, 118; FY2018, 143; FY2019, 171; and FY2020, 195). Additionally, we investigated the extent of liver resection for patients who underwent LLR. The number of patients who underwent laparoscopic partial resection increased marginally (FY2016: 27; FY2017:

Table 1. Trends in treatments for intrahepatic cholangiocarcinoma

Treatment	2016 *n* = 1,119 (%)	2017 *n* = 1,136 (%)	2018 *n* = 1,213 (%)	2019 *n* = 1,185 (%)	2020 *n* = 1,194 (%)
Open liver resection	748 (66.8)	771 (67.9)	807 (66.5)	760 (64.1)	753 (63.1)
Laparoscopic liver resection	84 (7.5)	118 (10.4)	143 (11.8)	171 (14.4)	195 (16.3)
Transarterial chemoembolization/ transarterial embolization	168 (15.0)	134 (11.8)	146 (12.0)	120 (10.1)	116 (9.7)
Molecular targeted drugs	37 (3.3)	34 (3.0)	27 (2.2)	59 (5.0)	68 (5.7)

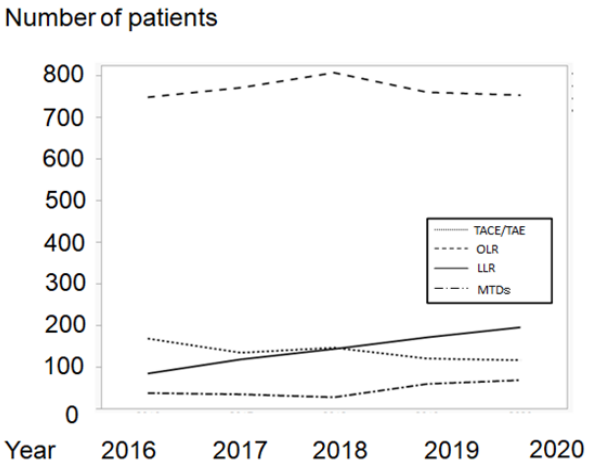

Figure 1. Trends in treatments for intrahepatic cholangiocarcinoma in the national administrative database. *Abbreviations*: TACE/TAE, transarterial chemoembolization/ transarterial embolization; OLR, open liver resection; LLR, laparoscopic liver resection; MTDs, molecularly targeted drugs.

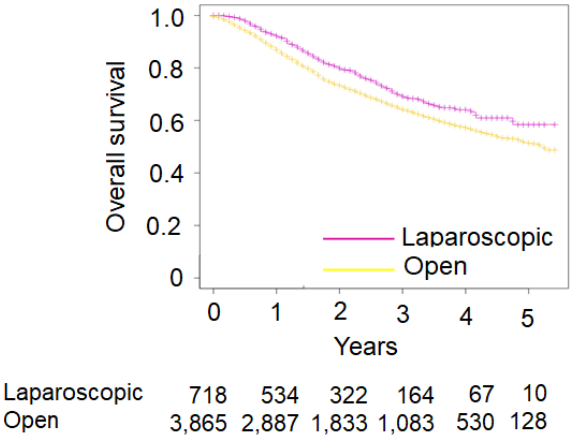

Figure 2. Kaplan-Meier estimates of survival by liver resection type using national administrative data. Numbers below the X-axis indicate the number of patients at risk.

37; FY2018: 45; FY2019: 70; FY2020: 62). However, there was a substantial increase in the number of patients who underwent laparoscopic procedures that included at least a subsegmentectomy (FY2016: 57; FY2017: 81; FY2018: 98; FY2019: 101; and FY2020: 133). The median postoperative survival was 5.25 years in the OLR group and was not reached in the LLR group. The five-year survival rate was 58.4% in the LLR group and 51.2% in the OLR group (Figure 2).

4. Discussion

The study findings revealed that the number of patients diagnosed with and treated for ICC remained consistent over time. In contrast, the number of those undergoing LLR increased, with good long-term survival outcomes, likely due to advancements in surgical techniques.

Although previous reports from the Liver Cancer Study Group of Japan have documented the number of treated ICC patients, the most recent data pertain only to 2014 to 2015 (*3*). Consequently, it is imperative to examine the most recent developments in the treatment of ICC. Additionally, previous nationwide surveys have focused exclusively on specialized centers for ICC treatment. Hence, reviewing this extensive and valuable database (NDB open data) is imperative for understanding the current epidemiology of and treatments for ICC.

Technical advancements in LLR have led to its increasing use in treatment of hepatic tumors. This is due to the advantage of reduced intraoperative blood loss, particularly in patients requiring minor liver resections (*6*). This is consistent with our research, which indicates a substantial increase in the number of patients who are undergoing LLR. Additionally, laparoscopic subsegmentectomy has become increasingly common in recent years (*11*), contributing substantially to the increase in LLR procedures.

In this study, median postoperative survival was not reached in patients undergoing LLR with a five-year survival rate of 58.4%. This finding may be explained by preferential use of LLR for a higher number of patients with early-stage ICC. Indeed, the frequency of subsegmentectomy or larger was more infrequent in patients who underwent LLR (65.8% *vs*. 90.0%). Although stage data were not available in this database, the unreached median survival was considered sufficient to justify this treatment strategy for patients with ICC whenever possible. The reported median survival after hepatectomy for ICC using the Surveillance,

Epidemiology, and End Results (SEER) database was 34 months (*12*). Therefore, survival analysis using NDB, the Japanese national database, revealed that patients receiving LLR had good survival, supporting the recommendation of LLR for patients with ICC whenever suitable. Although a previous study demonstrated an increased risk of lymph node metastasis with LLR in patients with ICC (*13*), there is growing evidence supporting the feasibility of LLR in these patients (*14,15*). There is also a recent report exploring the oncological benefit of LLR in patients with ICC, attributed to the lower biological impact of surgery and shorter interval between surgery and initiation of adjuvant treatments (*16*). Although this database did not include data on lymph node dissection and adjuvant therapies, and laparoscopic lymph node dissection is technically challenging, the survival benefit of LLR might be partly due to differences in nodal staging or adjuvant treatment.

One limitation of our study is that the data were analyzed retrospectively. Furthermore, there was a lack of precise prognostic data and comprehensive patient characteristics. Therefore, prolonged survival in patients receiving LLR might be due to the frequent proportion of early-stage ICC patients. Additionally, the death rate captured in this study only included patients who were admitted before death; therefore, some patients who died before admission were not analyzed which might have led to overestimation of survival and should be considered as proxy measures. However, it is notable that the study revealed a substantial increase in use of minimally invasive surgery, or LLR, in recent years, with good survival outcomes.

In conclusion, while the number of patients diagnosed with and treated for ICC has remained stable, adoption of minimally invasive surgery has increased, possibly because of advancements in treatment techniques, resulting in good survival outcomes.

Funding: This work was supported by a grant from the National Center for Global Health and Medicine, Tokyo, Japan.

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

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Received March 10, 2026; Revised April 24, 2026; Accepted May 7, 2026.

Released online in J-STAGE as advance publication May 13, 2026.

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Global Health & Medicine. 2026; 8(4):316-321.
BRIEF REPORT
DOI: 10.35772/ghm.2026.01057

Practical application of indocyanine green fluorescence imaging in left hepatopancreatoduodenectomy for cholangiocarcinoma with right-sided ligamentum teres

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Abstract: We report the surgical techniques and outcomes of hepatopancreatoduodenectomy (HPD) using indocyanine green fluorescence imaging (ICG-FI) for Bismuth type IIIb perihilar cholangiocarcinoma in a patient with right-sided ligamentum teres. ICG-FI was used in three ways: *i*) positive staining to delineate the liver transection line, *ii*) confirmation of vascular perfusion, and *iii*) visualization of the bile duct. Because the bile duct of the ventral region of the right paramedian sector (RPM) drained into the left hepatic duct, an extended left hepatectomy including resection of the ventral region of the RPM was planned. Although the anatomical anomaly made it difficult to identify the liver transection line between the ventral and dorsal regions of the RPM using landmarks such as the hepatic veins and the falciform ligament, positive staining of the dorsal region of the RPM enabled accurate delineation of the transection line. As there was suspected tumor invasion into the right side of the main portal vein, wedge resection and reconstruction with short-axis suturing were performed. Subsequently, fluorescence was observed to pass through both the right hepatic artery and the reconstructed portal vein uninterruptedly, indicating continuous blood flow. ICG-FI also facilitated identification of the right hepatic duct. It was divided at the root, and the resection margin was confirmed to be negative by intraoperative frozen-section examination. HPD was successfully completed, achieving R0 resection with an operative time of 789 minutes and blood loss of 650 mL. The patient developed a pancreatic fistula, which resolved with drain management and antibiotic therapy, and was discharged on postoperative day 36. Integrated use of ICG-FI provided useful adjunctive guidance in this technically challenging case.

***Keywords*:** indocyanine green, fluorescence-guided surgery, right-sided ligamentum teres

1. Introduction

Right-sided ligamentum teres (RSLT) is a rare congenital anatomical anomaly that arises when the umbilical vein connects to the right paramedian branch of the portal vein instead of left portal vein (*1*). Reported incidence of RSLT ranges from 0.2% to 1.2% (*2,3*). RSLT is frequently associated with anatomical variations of the portal vein, hepatic veins, and biliary system (*4,5*). Consequently, hepatic resection in patients with RSLT requires meticulous preoperative evaluation and intraoperative decision-making (*5*), and it is particularly challenging in cases of cholangiocarcinoma with complex biliary and vascular anomalies (*4*). When extensive resection such as left hepatopancreatoduodenectomy (HPD) is required, accurate intraoperative identification of the hepatic transection line and critical structures becomes essential for patient safety. Despite advances in preoperative imaging, intraoperative confirmation of functional anatomy remains limited, particularly in patients with rare anatomical variations such as RSLT.

Since introduction of indocyanine green (ICG) fluorescence imaging (ICG-FI) into surgical practice, there has been a substantial expansion of its clinical applications. In the field of hepatobiliary and pancreatic surgery, ICG-FI has been widely used to intraoperatively identify liver tumors (*6*), visualize hepatic segments (*7*), and delineate the biliary tract (*8*), thereby contributing to improved surgical safety and oncological radicality. Moreover, ICG-FI has recently been applied not only to liver parenchyma but also to evaluation of vascular perfusion in the hepatic artery, portal vein, and hepatic veins (*9*). The ICG-FI technique has attracted increasing attention as a real-time intraoperative modality for assessing organ perfusion and patency of reconstructed vessels.

Although individual applications of ICG-FI for hepatic demarcation, vascular perfusion assessment, and biliary visualization have been previously reported (*7-9*), to our knowledge, their integrated use during left HPD in a patient with RSLT has not previously been described. Herein, we present an integrated use of ICG-FI to safely perform left HPD in a patient with cholangiocarcinoma and RSLT.

2. Materials and Methods

2.1. Preoperative evaluation

A 77-year-old man with a medical history of hypertension, dyslipidemia, diabetes mellitus, and gastroesophageal reflux disease presented with brown urine and was diagnosed with Bismuth type IIIb perihilar cholangiocarcinoma. Liver function was well preserved (Table 1). Contrast-enhanced computed tomography (CT) revealed bile duct wall thickening, predominantly involving the root of the left hepatic duct (LHD) and extending to the confluence of the cystic duct (Figure 1). Imaging also revealed RSLT originating from the right portal branch, with the gallbladder located on its left side. The bile duct of the ventral region of the right paramedian sector (RPM) drained into the LHD, while the portal vein of this region drained into the right-sided umbilical portion. Therefore, an extended left hepatectomy including the ventral region of the RPM was planned. The future liver remnant volume after extended left hepatectomy was 568 mL, corresponding to 52% of the total liver volume. Figure 2 shows the preoperative simulation based on CT imaging and planned transection lines. Transection of the distal bile duct was initially planned at the superior border of the pancreas. If intraoperative frozen-section examination revealed malignancy at the distal bile duct margin, additional pancreatoduodenectomy with distal bile duct resection was planned. This strategy was explained to the patient preoperatively, and informed consent was obtained.

2.2. Intraoperative ICG-guided evaluation

RSLT was observed intraoperatively (Figure 3a). ICG-FI was applied for the following three purposes: *i*) positive staining to delineate the liver transection line by injecting ICG into the portal vein branch (*10,11*); *ii*) confirmation of vascular perfusion (*9*); and *iii*) identification of a hepatic duct (*8*). Method *ii*) was achieved through intravenous injection of ICG. Method *iii*) was subsequently performed using the same intravenous ICG injection, without additional administration. ICG-FI was performed using the IMAGE1 S™ Rubina® Lens system with IMAGE1 S™ 4U Rubina® camera head and Rubina® Lens, NIR/ICG Exoscope 90° (KARL STORZ, Tuttlingen, Germany). Fluorescence images were observed using the Overlay and Monochromatic display modes. Brightness and gain were automatically controlled by the imaging system, and no manual adjustments were performed or recorded.

2.3. Ethics statement

This study was approved by the Institutional Review

Table 1. Laboratory findings with normal reference ranges

Laboratory test	Result	Normal range	Unit
WBC	5,700	3,300–8,600	cells/μL
Hb	12.4	13.7–16.8	g/dL
Plt	24.2	15.8–34.8	$\times 10^4$/μL
Alb	4.2	4.1–5.1	g/dL
T-Bil	0.9	0.4–1.5	mg/dL
D-Bil	0.5	0.0–0.4	mg/dL
AST	23	13–30	IU/L
ALT	66	10–42	IU/L
ALP	245	38–113	IU/L
GGT	849	13–64	IU/L
LDH	115	124–222	IU/L
Cr	0.84	0.65–1.07	mg/dL
PT	82	70–130	%
CRP	0.36	0.00–0.14	mg/dL
CEA	3.6	≤ 5.0	ng/mL
CA19-9	6.0	≤ 37	U/mL
ICG-R15	7.1	0.0–10.0	%

Abbreviations: WBC, white blood cell; Hb, hemoglobin; Plt, platelets; Alb, albumin; T-Bil, total bilirubin; D-Bil, direct bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; LDH, lactate dehydrogenase; Cr, creatinine; PT, prothrombin time; CRP, C-reactive protein; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; ICG-R15, indocyanine green retention rate at 15 min.

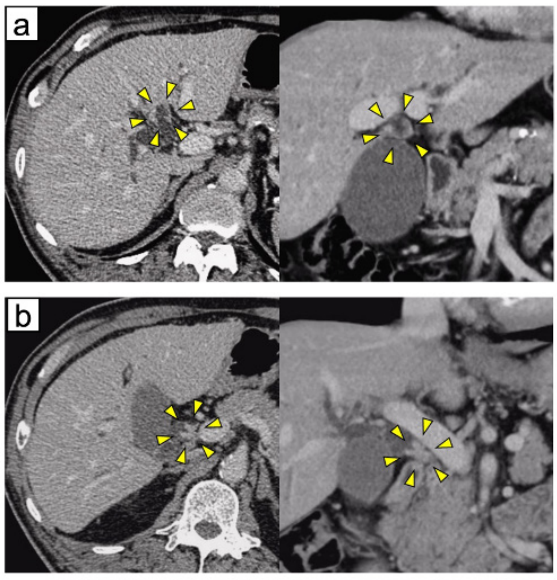

Figure 1. Preoperative contrast-enhanced computed tomography. Axial (left) and coronal (right) images reveal bile duct wall thickening, predominantly involving the root of the left hepatic duct **(a)** and extending to confluence of the cystic duct **(b)**. The lesion is indicated by yellow arrowheads. There was no tumor invasion of the right hepatic artery.

Board of Osaka Metropolitan University Hospital (approval #2020-227) and was conducted in accordance with the Declaration of Helsinki, as revised in 2013. Written informed consent was obtained from the patient prior to surgery for use of the clinical data and for publication of case details and accompanying images.

3. Results and Discussion

3.1. Surgical technique

Although the RSLT originated between the ventral and dorsal regions of the RPM, the falciform ligament was attached toward the left hepatic lobe. Consequently, the falciform ligament was not applicable as a reliable landmark for determining the liver transection line (Figure 3b). Furthermore, there were no clear anatomical landmarks, such as hepatic veins, present between the ventral and dorsal regions of the RPM. It was considered technically difficult to perform extrahepatic isolation and division of the portal vein branch supplying ventral region of the RPM; therefore, positive staining was employed. As it would have been technically challenging to puncture the portal vein branch supplying the ventral region of the RPM, the portal vein branch supplying the dorsal region of the RPM was punctured under ultrasonographic guidance, and a mixture of 0.25 mg of ICG and 5 mL of indigo carmine was injected. Immediately after injection, the dorsal region of the RPM was selectively stained, clearly delineating the boundary between ventral and dorsal regions, which corresponded to the planned liver transection line (Figure 3b). Because there was suspected tumor invasion into the right side of the main portal vein, wedge resection and reconstruction with short-axis suturing were performed. In addition to intraoperative Doppler ultrasonography for blood flow assessment, ICG (2.5 mg) was intravenously injected to evaluate blood flow in the preserved right hepatic artery and reconstructed portal vein. Fluorescence was observed to pass through both vessels uninterruptedly (Figure 4a). Hepatic parenchymal transection was performed along the line visualized by positive staining, enabling identification of the umbilical portion. After division of the RSLT continuous with the umbilical portion, the Glissonian pedicle of the ventral region of the RPM extending from the umbilical portion toward

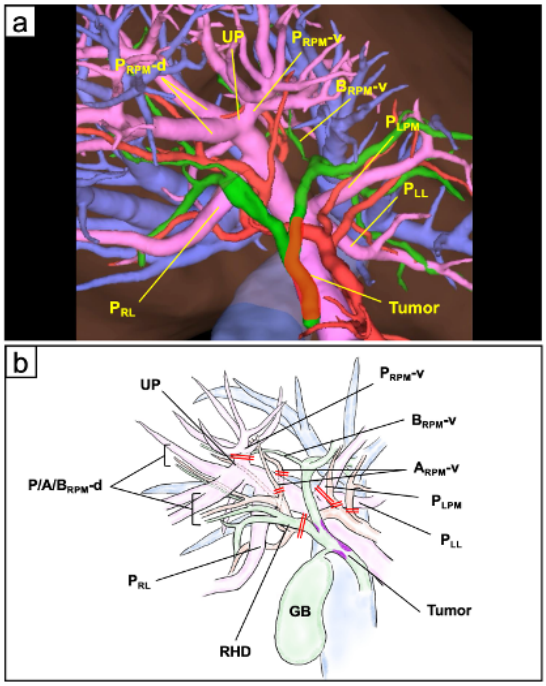

Figure 2. Preoperative evaluation. (a) The portal vein, bile duct, hepatic vein, and hepatic artery are shown in purple, green, blue, and red, respectively, on three-dimensional reconstructed contrast-enhanced computed tomography imaging. Extent of tumor is indicated by the red region of the bile duct. **(b)** Preoperative schematic showing planned resection line (double red line). *Abbreviations*: UP, umbilical portion; P/A/B_{RPM}-d, dorsal branch of the right paramedian portal vein/hepatic artery/bile duct; P_{RPM}-v, ventral branch of the right paramedian portal vein; B_{RPM}-v, ventral branch of the right paramedian bile duct; A_{RPM}-v, ventral branch of the right paramedian hepatic artery; P_{LPM}, left paramedian portal vein; P_{LL}, left lateral portal vein; P_{RL}, right lateral portal vein; RHD, right hepatic duct; GB, gallbladder.

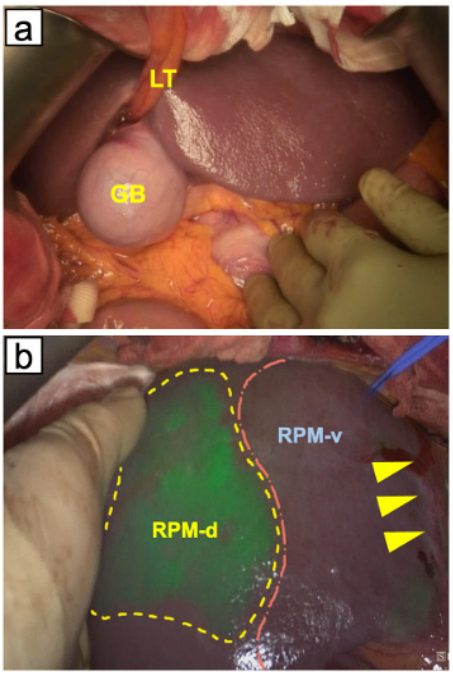

Figure 3. Intraoperative findings. (a) The ligamentum teres is located on the right side of the gallbladder. **(b)** Positive staining of dorsal region of right paramedian sector (RPM). Indocyanine green fluorescence is observed in the dorsal region of the RPM (dotted yellow line) using a positive staining technique. Liver transection line (orange point-and-line representation) is delineated along boundary between ventral and dorsal regions of the RPM, which differs from adjacent portion of the ligamentum teres (yellow arrowheads). *Abbreviations*: LT, ligamentum teres; GB, gallbladder; RPM-d, dorsal region of the right paramedian sector; RPM-v, ventral region of the right paramedian sector.

the resected liver side was identified and divided, thereby completing the planned hepatic parenchymal transection. Using ICG-FI, the right hepatic duct within the hilar plate was visualized and divided at its root (Figure 4b). Intraoperative frozen-section examination confirmed no malignancy at the right hepatic duct margin. After portal vein reconstruction and before hepatic parenchymal transection, intraoperative frozen-section examination of the distal bile duct margin on the duodenal side revealed adenocarcinoma rather than atypical cells. Given the possibility of vertical tumor invasion, including pancreatic invasion, we determined that R0 resection could be achieved by adding pancreatoduodenectomy, as anticipated in the preoperative surgical plan. Left hepatectomy was therefore continued, followed by pylorus-preserving pancreatoduodenectomy after removal of the liver specimen. Operative time was 789 minutes, and estimated blood loss was 650 mL. The total intraoperative dose of ICG was 2.75 mg, consisting of 0.25 mg for positive staining and 2.5 mg administered intravenously.

3.2. Postoperative outcomes

The patient developed a postoperative pancreatic fistula that was classified as Grade B according to International Study Group of Pancreatic Surgery classification (*12*) and Grade IIIa according to Clavien–Dindo classification. The pancreatic fistula resolved with antibiotic therapy and appropriate drain management, including drain replacement and repositioning. There were no other postoperative complications such as liver failure. The patient was discharged on postoperative day 36. Contrast-enhanced CT performed on postoperative day 41 demonstrated patency of both the right hepatic artery and portal vein, with no evidence of hepatic ischemia. Although adenocarcinoma was detected at the distal bile duct margin on the duodenal side, additional resection resulted in histopathologically negative proximal and final distal bile duct margins, confirming an R0 resection. Final pathological diagnosis was pT2aN0M0, stage II disease according to the 8th edition of the UICC TNM Classification of Malignant Tumours. At 18 months postoperatively, there is no evidence of recurrence.

3.3. Clinical implications of ICG-FI during surgery

This report demonstrates that integrated use of ICG-FI provided useful adjunctive guidance in this particular technically challenging case involving complex biliary and vascular anomalies associated with RSLT. The present case was classified as the bifurcation type in the portal system and the symmetrical type in the bile system based on previous reports (*4,5*). The patient had multiple

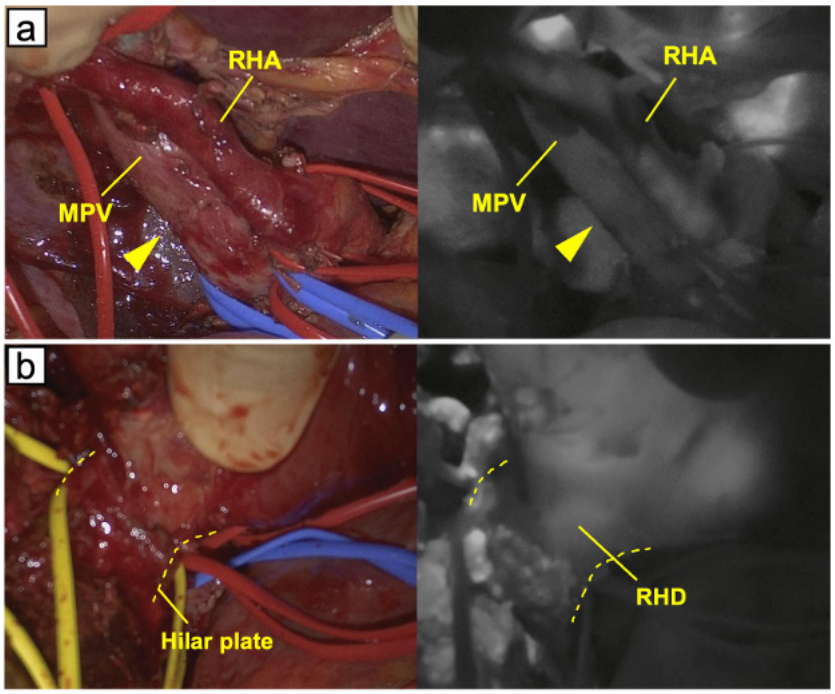

Figure 4. Indocyanine green fluorescence imaging performed to confirm vascular perfusion and visualize the bile duct. (a) Indocyanine green fluorescence imaging (ICG-FI) in Monochromatic display mode demonstrated uninterrupted fluorescence passage through right hepatic artery and reconstructed portal vein (yellow arrowhead) after wedge resection of main portal vein. Blood flow was assessed in combination with intraoperative Doppler ultrasonography. Following intravenous ICG injection, fluorescence was observed in right hepatic artery at 30 seconds and in reconstructed portal vein at 40 seconds, with uninterrupted passage through both vessels. **(b)** ICG-FI in Monochromatic display mode shows right hepatic duct within the hilar plate (dotted yellow line), visualized 95 minutes after intravenous injection of 2.5 mg of ICG. *Abbreviations*: RHA, right hepatic artery; MPV, main portal vein; RHD, right hepatic duct.

anatomical variations, namely RSLT and anomalous biliary drainage in which only the bile duct from the ventral region of the RPM drained into the LHD. Based on these anatomical findings and extent of tumor spread, liver transection along the boundary between the ventral and dorsal regions of the RPM was required. Despite the ligamentum teres originating between the ventral and dorsal regions of the RPM, the falciform ligament was deviated and attached toward the left hepatic lobe. As a result, there was no reliable anatomical landmark to delineate the boundary between these regions during extended left hepatectomy. Therefore, positive staining with ICG was used to accurately identify and define the liver transection line. ICG-FI enabled clear visualization of the intended transection line, allowing precise and safe hepatic parenchymal transection without excessive or insufficient resection (*7*).

ICG-FI was also useful for intraoperative visualization of blood flow in the reconstructed portal vein and preserved hepatic artery, demonstrating uninterrupted fluorescence passage through these vessels in real time. In this case, vascular flow was assessed using ICG-FI in conjunction with intraoperative Doppler ultrasonography. This complementary assessment may be helpful for intraoperative evaluation of reconstructed vessels and in determining need for revision of vascular reconstruction (*9*). In addition, even in cases with anatomical vascular and biliary variations, such as those requiring identification of the course of the right hepatic duct, ICG-FI may serve as a valuable real-time navigation tool to facilitate intraoperative understanding of complex anatomy (*9,13,14*).

We acknowledge that each application of ICG-FI used in this case—hepatic demarcation, vascular perfusion assessment, and biliary visualization—has been previously reported (*15-18*). However, the novelty of this report lies not in the technique itself, but in its strategic integration and application in a rare and complex anatomical setting. When performing HPD, even minor errors in hepatic transection or vascular reconstruction can lead to fatal outcomes, as reflected by high morbidity and mortality rates of HPD despite recent advances in perioperative management (*19-22*). Moreover, in challenging HPD cases such as those involving RSLT, conventional anatomical landmarks may be unreliable. In addition to preoperative imaging evaluation, ability to confirm hepatic perfusion and biliary anatomy in real time may reduce reliance on subjective anatomical interpretation and enhance procedural safety.

3.4. Limitation of this study

This report has several limitations. First, interpretation of fluorescence findings was qualitative and therefore subject to operator-dependent judgment. Second, near-infrared fluorescence has limited tissue penetration, which may restrict visualization of deeper anatomical structures. Third, this report is based on a single case performed at an experienced hepatobiliary-pancreatic center, which may limit generalizability of our findings to other patients or institutions. Nevertheless, integrated ICG-FI may serve as a useful adjunct in cases with rare and complex anatomical variations.

4. Conclusion

Integrated use of ICG-FI provided useful adjunctive guidance in this technically challenging case of left HPD for perihilar cholangiocarcinoma with RSLT. Specifically, ICG-FI assisted in delineating the hepatic transection line and anatomically identifying the right hepatic duct. Uninterrupted fluorescence passage was observed through the preserved right hepatic artery and reconstructed portal vein, while vascular flow was assessed in conjunction with intraoperative Doppler ultrasonography. These findings illustrate feasibility of combining complementary ICG-FI applications in this individual case; further cases are required to evaluate reproducibility and broader clinical utility of this approach.

Funding: None.

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

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Received May 19, 2026; Revised August 17, 2026; Accepted August 21, 2026.

Released online in J-STAGE as advance publication August 26, 2026.

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Print ISSN: 2434-9186
Online ISSN: 2434-9194
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Shalev AY. Post-traumatic stress disorder: Diagnosis, history and life course. In: Post-traumatic Stress Disorder, Diagnosis, Management and Treatment (Nutt DJ, Davidson JR, Zohar J, eds.). Martin Dunitz, London, UK, 2000; pp. 1-15.

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

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(*As of August 2026*)

Global Health & Medicine
Japan Institute for Health Security,
1-21-1 Toyama Shinjuku-ku, Tokyo 162-8655, Japan
URL: *www.globalhealthmedicine.com*
E-mail: *office@globalhealthmedicine.com*

Print ISSN: 2434-9186 Online ISSN: 2434-9194

GHM

Global Health & Medicine

Volume 1, Number 1
October, 2019

www.globalhealthmedicine.com