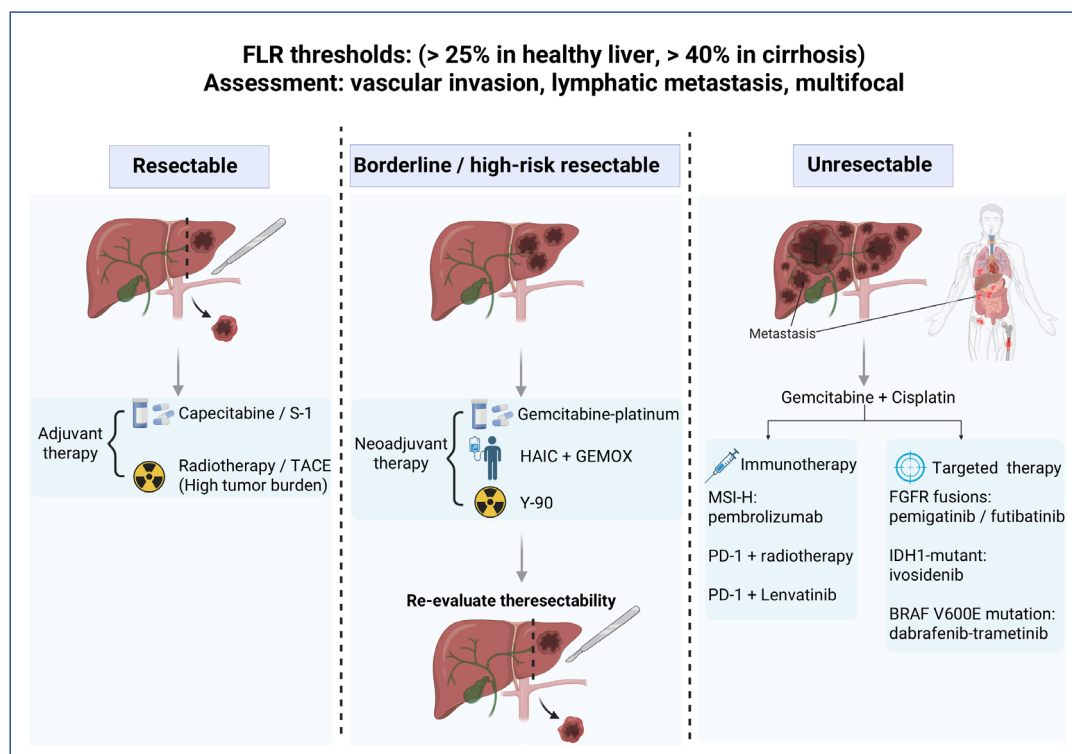




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Print ISSN: 2434-9186
Online ISSN: 2434-9194
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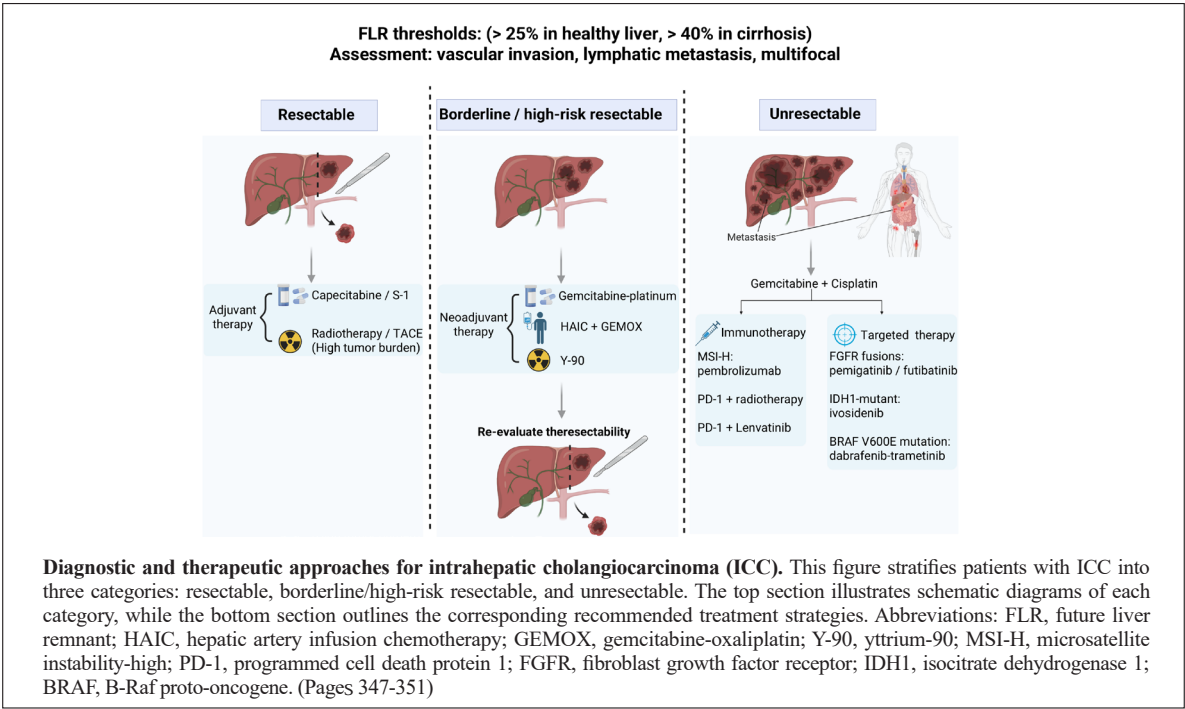
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COVER FIGURE



Perioperative and precision strategies in resectable intrahepatic cholangiocarcinoma

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Abstract: Intrahepatic cholangiocarcinoma (ICC) has a poor prognosis, with low rates of surgical eligibility and high recurrence. Effective perioperative strategies are essential. For adjuvant treatment, capecitabine (based on the BILCAP trial) and S-1 (from the ASCOT trial) have become standard regimens. Neoadjuvant therapy using gemcitabine-platinum combinations and locoregional strategies such as hepatic artery infusion chemotherapy (HAIC) and yttrium-90 radioembolization (Y-90 TARE) have improved resectability and survival outcomes. Molecular profiling has revealed actionable alterations in nearly 70% of ICCs. FGFR2 fusions, IDH1 mutations, and BRAF V600E mutations can be targeted with inhibitors such as pemigatinib, ivosidenib, and dabrafenib-trametinib, respectively, showing promising response rates in clinical trials. Immunotherapy has demonstrated efficacy in the microsatellite instability-high (MSI-H) subtype. Combination strategies involving PD-1 inhibitors with radiotherapy or anti-angiogenic agents are further expanding the potential for treatment. Future efforts should focus on standardizing resectability criteria, expanding access to molecular profiling, and accelerating Phase III trials.

Keywords: intrahepatic cholangiocarcinoma (ICC), adjuvant therapy, neoadjuvant therapy

1. Introduction

The management of intrahepatic cholangiocarcinoma (ICC) represents one of the most formidable challenges in hepatobiliary oncology (1). As the second most common primary liver malignancy, ICC accounts for approximately 20% of hepatic cancers, yet carries a disproportionately poor prognosis (2). Surgical resection remains the cornerstone of curative intent, but only 20–30% of patients present with technically resectable disease. Even among those undergoing complete resection, 5-year survival rates linger at 25–40%, with recurrence rates soaring to 50–70% due to micrometastatic spread (3). This sobering reality underscores the critical importance of effective perioperative therapies. To improve patient outcomes, surgeries should be performed at centers with extensive surgical experience (4). Additionally, recent advances in adjuvant and neoadjuvant approaches are reshaping the therapeutic landscape, though significant controversies persist regarding patient selection, regimen optimization,

and biomarker integration.

The determination of surgical candidacy extends beyond traditional TNM staging. While the 8th edition of the American Joint Committee on Cancer (AJCC) staging manual classifies solitary tumors without vascular invasion (T1a/b) as ideal candidates, clinical practice reveals nuanced complexities (5,6). Multifocal tumors present particular controversy — some studies suggest comparable outcomes to unimodal disease when completely resected, while others find no survival advantage over systemic therapy alone (7). The evaluation of nodal status further complicates decisions; up to 30% of patients deemed clinically node-negative (cN0) harbor occult metastases upon pathological examination, prompting guidelines to mandate routine lymphadenectomy (8,9). The 2023 EASL-ILCA criteria introduced quantitative parameters including future liver remnant (FLR) thresholds (> 25% in healthy liver, > 40% in cirrhosis) and emphasize tumor biology assessment. For borderline resectable cases or those with high-risk features (*e.g.*, large tumors abutting vessels

and advanced age), neoadjuvant therapy now serves as a bridge to potential resection (10,11).

2. Adjuvant therapy

Postoperative systemic therapy has evolved from empirical administration to evidence-based standardization. The landmark capecitabine compared with observation in resected biliary tract cancer (BILCAP) trial established capecitabine as a new backbone, demonstrating a 17-month median overall survival (OS) advantage over observation (53 vs. 36 months; hazard ratio [HR]: 0.75) (12). This was corroborated by the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) in which S-1 resulted in a 9.5% absolute improvement in 3-year OS (77.1% vs. 67.6%) (13). However, gemcitabine-based regimens show inconsistent results — while some retrospective analyses suggest a benefit, the PRODIGE 12 trial (gemcitabine plus oxaliplatin vs. observation after R0 or R1 resection in patients with biliary tract cancer) revealed no survival advantage of gemcitabine plus oxaliplatin (14). For patients with high-risk pathological features (R1 resection, lymph node involvement), multimodal approaches are gaining traction. Adjuvant radiotherapy significantly improves outcomes in margin-positive disease (< 1 mm), with the 3-year OS doubling from 20% to 55%, and it provides meaningful survival extension in node-positive patients (median OS of 19.1 vs. 9.5 months) (15). Transarterial chemoembolization (TACE) demonstrates selective utility in advanced-stage tumors (≥ 5 cm or TNM III/IV), improving the 5-year OS from 6.2% to 21.3%, though it paradoxically increases recurrence risk in early-stage disease (16,17).

3. Neoadjuvant therapy

The paradigm of preoperative treatment has transformed from an experimental approach to an essential strategy for high-risk resectable and borderline resectable ICC. Beyond facilitating tumor downstaging, neoadjuvant therapy eradicates micrometastases and enables better patient selection for aggressive surgery. Contemporary data suggest potential superiority over adjuvant approaches, with a propensity-matched analysis revealing a 7.5-month median OS advantage (40.3 vs. 32.8 months) for neoadjuvant chemotherapy (18). Gemcitabine-platinum combinations serve as the current backbone, achieving resection in 73% of initially unresectable patients in small-scale phase II studies (19). Locoregional strategies amplify this potential — hepatic artery infusion chemotherapy (HAIC) combined with systemic gemcitabine-oxaliplatin extends the median OS to 30.8 months compared to 18.4 months with systemic therapy alone in advanced cases (20). Emerging techniques like yttrium-90 radioembolization (Y-90 TARE) demonstrate significant tumor volume reduction

in 42.7% of patients, with ongoing trials evaluating combinatorial approaches (21).

4. Molecularly targeted therapies

The genomic landscape of ICC reveals actionable alterations in nearly 70% of tumors, ushering in an era of biomarker-directed therapy (22,23). Fibroblast growth factor receptor 2 (FGFR2) fusions (10–15% prevalence) are effectively targeted by selective inhibitors — pemigatinib achieves a 35.5% objective response rate (ORR) in refractory disease, while futibatinib results in a 34% ORR and 9.1-month median progression-free survival (PFS) (24). For IDH1-mutant ICC (10–20% prevalence), ivosidenib more than doubles the PFS compared to a placebo (2.7 vs. 1.4 months) with a manageable toxicity profile (25). BRAF V600E mutations (5–7%) respond to dabrafenib-trametinib combinations (41% ORR), though efficacy varies across non-V600E alterations (26). Despite the promising activity of molecularly targeted therapies, challenges remain regarding their optimal integration with locoregional therapies, management of acquired resistance, and the accessibility of comprehensive genomic profiling.

5. Immunotherapy

ICC is a highly desmoplastic cancer with abundant tumor stroma. Studies have revealed that pembrolizumab achieves response rates exceeding 40% in the microsatellite instability-high (MSI-H) subtype (27). Thus, immunotherapy for ICC represents a highly promising therapeutic strategy. Recent combination strategies show greater promise — PD-1 inhibitors coupled with radiotherapy yield an impressive 61.1% ORR and 22-month median OS in unresectable disease (28). Anti-angiogenic combinations (*e.g.*, PD-1 inhibitors with lenvatinib) demonstrate a disease control rate of 80.6%, albeit with significant toxicity (50.5% grade 3–4 adverse events) (29).

6. Future directions

The current standard of care for resectable ICC emphasizes a multimodal treatment approach (Figure 1). Three critical barriers are impeding progress: heterogeneous resectability criteria, limited access to molecular profiling, and the scarcity of phase III data. Artificial intelligence-assisted surgical planning may standardize FLR assessment, while liquid biopsy platforms offer cost-effective alternatives for dynamic biomarker monitoring (92.3% sensitivity for micrometastasis detection) (30). Global efforts like the ICC-RFC Project aim to accelerate trial enrollment, with innovative studies exploring TGF- β inhibition to overcome fibrotic barriers, neoantigen

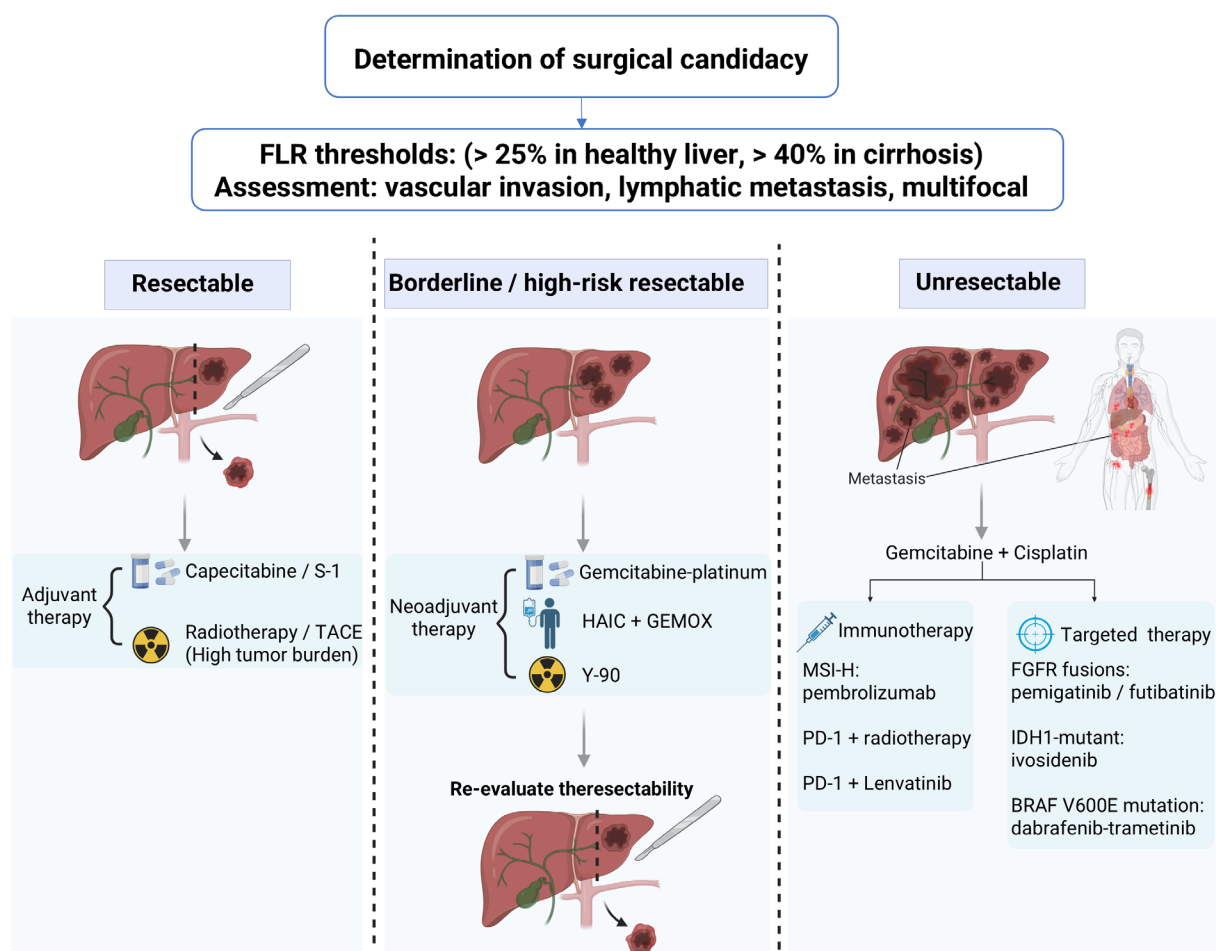


Figure 1. Diagnostic and therapeutic approaches for intrahepatic cholangiocarcinoma (ICC). This figure stratifies patients with ICC into three categories: resectable, borderline/high-risk resectable, and unresectable. The top section illustrates schematic diagrams of each category, while the bottom section outlines the corresponding recommended treatment strategies. *Abbreviations:* FLR, future liver remnant; HAIC, hepatic artery infusion chemotherapy; GEMOX, gemcitabine-oxaliplatin; Y-90, yttrium-90; MSI-H, microsatellite instability-high; PD-1, programmed cell death protein 1; FGFR, fibroblast growth factor receptor; IDH1, isocitrate dehydrogenase 1; BRAF, B-Raf proto-oncogene.

vaccines, and FGFR2-directed cellular therapies. The ongoing ACTICCA-1 trial, which evaluates adjuvant chemotherapy with gemcitabine and cisplatin vs. standard of care after curative-intent resection of biliary tract cancer, and the PRODIGE 57 trial, which investigates durvalumab plus tremelimumab with or without paclitaxel in advanced biliary tract cancer after platinum-based chemotherapy, will provide much-needed level I evidence for chemotherapy and targeted neoadjuvant approaches.

7. Conclusion

The therapeutic approach for resectable ICC has transformed from isolated surgical intervention to integrated multimodal strategies. Fluoropyrimidine-based adjuvant therapy is now the standard care for patients undergoing resection. while neoadjuvant

approaches expand curative opportunities for borderline resectable disease. Molecular stratification enables targeted therapy integration, though barriers to accessibility persist. As ongoing trials address existing evidence gaps, the future promises increasingly personalized pathways combining optimized local control with systemic precision — moving closer to the ultimate goal of a robust cure for this complex malignancy.

Funding: This work was supported by the National Natural Science Foundation of China (grants 82373365, 82173317), 2023/2023 IHPBA Kenneth Warren Fellowship, Tianjin Key Medical Discipline Construction Project (TJYXZDXK-009A).

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

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Received September 3, 2025; Reised September 25, 2025;
Accepted October 1, 2025.

Released online in J-STAGE as advance publication October 3,

2025.

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Reconceptualizing ageing societies: Six years of global dialogue from Japan

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Abstract: This article synthesizes six years (2019–2024) of the "Super Active Ageing Society" (SAAS) international conference series, which reconceptualizes ageing not as a burden to society but as a source of societal vitality. The SAAS conferences uniquely integrate three traditionally isolated domains — health, economic resilience, and welfare — into a cohesive framework that positions older adults as active contributors to society. In addition to themes such as preventive health, asset longevity, and extended workforce participation, the conferences promote intergenerational collaboration and financial sustainability. To achieve what older adults aspire to — remaining healthy, economically secured, and socially connected — demands a cross-sectoral response. Evolving from interdisciplinary presentations to strategic dialogues, the conferences were attended by a diverse range of participants, including but not limited to policymakers, researchers, practitioners, students, industry leaders, and civil society representatives. Collaboration with the Well Aging Society Summit Asia-Japan (WASS) fostered dialogue on Japan's ageing-related industries, in synergy with the SAAS. In these bilingual (Japanese and English) conferences, over 40% of on-line participants tuned in to the English channel, underscoring the international interest in the ageing discourse. Over the course of six conferences, the concept of a super active ageing society — integrating health, financial well-being, and social participation — is refined, offering new perspectives for both domestic and international policies and business strategies. The outcomes of this conference series clearly underscore the need for innovation and social transformation in ageing societies, and provide valuable insight for ongoing and future policy and institutional design.

Keywords: population aging, healthy longevity, financial gerontology, super-aged society, active aging

1. Introduction

Global life expectancy has continued a long-term upward trajectory despite a temporary decline during the COVID-19 pandemic (1). Among all nations, Japan currently has the highest level of population aging, and how to respond to the growing elderly demographics has been the foremost challenge for Japanese healthcare and public health over the past half century. This situation has been addressed in previous articles published in *Global Health & Medicine* (2-4).

The population ageing phenomenon is not unique to Japan. Many countries, particularly those in Asia, are already experiencing, or are poised to experience similar demographic shifts. For example, according to the UN World Population Prospects (UNWPP) 2024 (5,6), projections for Southeast Asia, a region presently characterized by a youthful population, indicate that total population will peak around 2055 and then enter a phase of decline driven by population ageing and low fertility rates. Furthermore, the UNWPP 2024 indicates that

within 30 years (2025–2054), 48 countries and regions including Iran, Turkey and Vietnam are projected to reach peak population size. Consequently, the experience of Japan during the early transition into a super-aged society along with the challenges and responses encountered offers valuable lessons for other nations worldwide.

In recognition of this global relevance, an interdisciplinary conference series was proposed in 2018 by two visionary leaders: the late Tsuyoshi Sunohara, then Managing Executive Officer of Nikkei Inc., and Keizo Takemi, then Member of the House of Councilors, the National Diet of Japan. Both believed that the evolving challenges of population ageing demand interdisciplinary collaboration and collective wisdom of the global community for their resolution. Mr. Takemi delivered the opening address in all six conferences.

At the time of the inception of the conference series, the "2025 Problem" had already emerged as an urgent national issue. Such concerns have been repeatedly voiced by the national leaders, most recently by Prime

Minister Shigeru Ishiba in his Policy Speech (7) at the opening session of the 217th Session of the National Diet on January 24, 2025. The Prime Minister emphasized the need to redesign the socio-economic systems that were initially constructed during the era of population growth. By 2025, the post-war baby boom generation will reach age 75 and enter the late-elderly cohort, triggering a rapid increase in demand for medical and long-term care services. Since healthcare and nursing care costs per capita rise markedly after age 75, questions about the sustainability of existing systems have been a core concern since more than a decade ago. To address this, the Japanese government pursued the Social Security and Tax Joint Reform Package in 2013 with the aim to secure funding and overhauling benefit structures. In parallel, the Community-based Integrated Care System (8), designed to balance accessibility and affordability of services at the local level, took shape around 2018.

While the wave of ageing continues to progress, a new concern, the "2040 Problem", has surfaced. This refers to structural difficulties anticipated when the so-called "second baby boom" generation enters old age. Many in that cohort endured prolonged periods of unstable employment due to the economic downturn, potentially resulting in a large population of elderly individuals with low pension entitlements. Moreover, the rise in single-person households and rapid urbanization are expected to expose limitations in traditional, community-based, mutual-support frameworks.

Addressing these multifaceted challenges will require policy architectures that transcend conventional boundaries of healthcare and welfare, embracing asset formation and management, employment support, and promotion of social participation. Furthermore, sharing the Japanese experience on the international stage and incorporating insights from other countries will enrich policy development or even lead to more robust international collaboration. In light of these potential opportunities, Nikkei Inc. launched a series of six international conferences beginning in 2019. This paper synthesizes and shares the discussions and outcomes of those meetings, offering insights to inform future policy and societal initiatives.

2. Super active ageing society

The conference series was named "Super Active Ageing Society (SAAS) Conference". The term "super active ageing society" — the focal concept of the conferences — captures both the evolving image of older adults in contemporary Japan and the redefinition of their social roles. Over the past fifty years, public perceptions of the elderly in Japan have changed markedly. For decades, older adults were principally viewed as a socially vulnerable group of individuals who are passive beneficiaries of welfare services. Yet, as both overall life expectancy and healthy life expectancy extend, concepts

such as "purpose in life" and "social participation" have emerged, valuing the older people's active stance of engagement with society.

In the twenty-first century, with the rapid rise in proportion of older adults, their role transitions from passive recipients of medical and long-term care to proactive "agents of health promotion and prevention" through maintaining and enhancing their own health. Then on-going debates on "Social Security Reform for All Generations" (9,10) reconceptualize older adults not only as beneficiaries but also as contributors to societal vitality.

While the concurrent extension of average life expectancy and healthy life expectancy represents a welcome development, it has also brought to light growing concerns regarding the financial sustainability to support prolonged later life. Increasingly, individuals express the desire to live their extended post-retirement years without economic anxiety, thereby highlighting the need to extend what is now referred to as "asset longevity". To achieve this, several key strategies have been proposed: the promotion of preventive medicine to further extend healthy life expectancy, technological innovations that help maintain physical functions in later life, application of artificial intelligence and big data to dramatically improve efficiency of medical and long-term care services, reconfiguration of employment systems to encourage older adults' continued participation in the workforce, and advancement of asset management practices tailored to ageing populations.

However, realization of these strategies requires more than technological or policy adjustments. It calls for a fundamental redefinition of ageing itself, reconstruction of intergenerational support systems, and interdisciplinary research that bridges medicine, engineering, economics, and legislation. Such research must be conducted through collaborative frameworks between academia and industry, with the aim to generate new industries and innovations suited to the realities of super-aged societies.

Just as the field of gerontology has long studied biological and social processes of ageing, the emergence of "financial gerontology" reflects growing recognition that asset longevity must evolve in tandem with extended life and health spans. This new discipline seeks to minimize the gap between financial and biological longevity through both theoretical investigation and practical application. Research activities in this domain aim to build a society in which older adults can enjoy both physical well-being and financial security. A pioneering initiative in this field is the "Study Group on Finance, Economics, and Healthcare in an Ageing Society" chaired by Professor Atsushi Seike. Established in 2016, the group's work culminated in publication of "Financial Gerontology" (11) in 2017, marking a significant milestone in the development of this emerging academic discipline.

Reflecting these shifts, the Nikkei Conference was named "Super Active Ageing Society" to embody a model in which older adults both sustain their communities and, when necessary, receive appropriate support, thereby forging a truly reciprocal societal relationship. The term "vibrant society" first appeared in Japan's 2001 White Paper on the Ageing Society (12), which describes "a rich and vibrant society" as ideal for an ageing nation. This term shapes the core values of the SAAS conferences.

3. Conference planning, governance, and overview

The design and structure of the program were developed under direction of the Steering Committee, and core members who prepared the inaugural conference held in 2019 are listed in Supplementary Table S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=113>). Titles and affiliations are presented as of that time. The composition of the committee reflects participation of experts from a broad spectrum of fields, including medicine, public health, social security, economics, labor, social inclusion, welfare, and academia, demonstrating the cross-border and interdisciplinary nature of the initiative. Among the committee members, designated officials from Ministry of Health, Labour and Welfare (MHLW), Ministry of Economy, Trade and Industry (METI), and Japan Medical Association represented the corresponding organizations. A formal system was in place to ensure that successor was promptly appointed whenever a predecessor was reassigned.

In 2021, METI nominated Professor Fumiaki Ikeno of Stanford University to join the Steering Committee as liaison person with the Well Ageing Society Summit Asia-Japan (WASS). To enhance gender and geographic balance, three overseas members were added in 2024: Professor Aya Goto (Harvard University), Professor John Eu-Li Wong (National University of Singapore; succeeding Professor Tan Chorh Chuan of Singapore's Ministry of Health), and Professor A. B. Dey (founding Professor of Geriatric Medicine at AIIMS, India). Despite these additions, the committee's core structure remained stable across six annual conferences, and the members have contributed to the conferences as planners, keynote speakers, and panelists. Notably, several international committee members including Professors Tan, Fried, Pigott, and Wong played pivotal roles in conceptualizing conference framework and facilitating invitation of distinguished global speakers.

Industry experts and moderators in later sessions also joined the Committee on an *ad hoc* basis to refine session themes and lead the session discussion. Professor Seike served as Chair of the Steering Committee, and the present author as Secretary-general. Nikkei Inc. served as organizer, providing secretariat services, coordinating speaker arrangements, and mobilizing resources from

sponsors.

The SAAS conference was convened annually in Tokyo from 2019 to 2024. Supplementary Table S2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=113>) summarizes the dates, themes, and program structures of the conferences, and Supplementary Table S3 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=113>) lists major presentations. The six programs can be viewed *via* web links (13-18). The third (2021), fourth (2022), and fifth (2023) meetings were integrated with the WASS of METI, forming joint events aimed at solving super-aged society challenges and promoting healthcare industry innovation in Japan and across Asia. All sessions were bilingual (Japanese and English). Only the first conference in 2019 was held fully in-person, while all subsequent conferences adopted a hybrid format (in-person plus online). The outcomes of the conferences were published on the Nihon Keizai Shimbun, the Financial Times, and Nikkei Asia. To ensure broad domestic and international dissemination, the recorded sessions of each conference, in both Japanese and English, are freely accessible online *via* Nikkei Channel (19) for approximately one year following the event, after which they are replaced by the subsequent year's recordings. Highlights of the conferences from 2021 can be accessed online *via* Nikkei Asia (20-23).

4. Evolution of conference format and themes

Between 2019 and 2024, the program design of the annual SAAS conference series evolved in stages, drawing on accumulated insights and participant feedback. From the inaugural meeting in 2019 through the third meeting in 2021, the program featured a broad array of speakers to highlight the need for interdisciplinary collaboration across the health, economic, and social participation domains (Supplementary Table S3, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=113>). The fifth (2023) and sixth meeting (2024), on the other hand, adopted a moderator-led format, strategically reducing the number of individual presentations and entrusting session chairs to summarize panel discussions and guide strategic dialogues. This shift signifies a purposeful progression beyond establishing conceptual foundations, advancing toward more substantial and focused practice-based and action-oriented debates. The full list of moderators in the 2023 and 2024 conferences is shown in Supplementary Table S4 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=113>).

As noted above, the WASS Conference was convened jointly with the SAAS Conference from 2021 to 2023. The 2021 WASS addressed personal health records; environmental, social, and governance investment; digital transformation in healthcare and long-term care; and response to global population ageing. The 2022 WASS

focused on industry policies such as inbound medical tourism, corporate health management, and digitalization of healthcare and long-term care in the web era. The 2023 WASS examined challenges and initiatives within the healthcare sector in Asia, and discussed regional collaboration and the export of institutional frameworks. The programs in 2021, 2022 and 2023 are included in the respective SAAS links (15-17).

5. Knowledge and social impact through six international conferences

Over six years, this international conference series has generated multifaceted outcomes such as promoting interdisciplinary cooperation, reframing domestic challenges as global issues, fostering intergenerational collaboration, engaging the private sector, and strengthening advocacy at home and abroad. The significance of each element is outlined below.

5.1. Expanding the horizons of interdisciplinary collaboration

The concept of a super active ageing society asserts that older individuals can fully contribute to societal vitality only when health, financial well-being, and social participation are seamlessly integrated. Realizing this vision requires collaboration among experts from medicine, economics, labor, welfare, and other fields, which underscores the importance of cross-sectoral collaboration. Accordingly, each year the conference structured its program around three core axes — health, finance and labor, and social participation. Each axis was expanded as needed by open sessions, synthesis sessions, and innovation sessions. In 2021 (the third conference) and 2022 (the fourth conference), lunchtime seminars with international focus were held in cooperation with the WHO Western Pacific Regional Office and the United States National Academy of Medicine. These two entities have developed a very comprehensive strategies; regional action plan on healthy ageing in the Western Pacific (24) and Global Roadmap for Healthy Longevity (25), respectively.

5.2. From domestic issues to global challenges

Traditionally, issues related to ageing have been viewed as a community-based health and welfare concern. However, as demographic shifts accelerate, ageing challenges have evolved into structural issues impacting the entire society. There is also growing recognition that global sharing of experiences and international deployment of human resources, services, and industries can yield mutual benefits. From this viewpoint, the third (2021) to the fifth SAAS Conference (2023) were partnered with the WASS of METI. This partnership fosters integration of international industrial

collaboration with policy dialogue, which serves as a valuable model for elevating domestic efforts to the level of global industrial policy.

5.3. Fostering intergenerational collaboration

Ageing is not an issue of one particular demographic cohort, but concerns societal sustainability across past, present, and future generations. This perspective was highlighted by active participation of young people in later conferences. In 2023, Mr. Shoichiro Hashimoto, a second-year high school student, raised the issue of ageism, which stems from the prejudice of younger generations toward older individuals and the sense of inferiority felt by many older adults. He emphasized that eliminating such attitudes would encourage greater social participation among senior citizens. In 2024, Associate Professor Takayuki Shiose of Kyoto University addressed the concept of co-creative learning between older and younger generations, introducing a gerontology study group composed of junior high school students. He noted that these generations have grown up in an ageing society and therefore naturally accept communities with a high proportion of senior citizens. They are also ready to contribute new ideas aiming to enhance well-being for all. These exchanges in panel discussions fostered meaningful intergenerational dialogue and cooperation.

5.4. Contributions from the private sector

Demographic shifts present both challenges and opportunities for the private sector, given the potential resources of older adults as workers, consumers, and social assets. Corporate presenters proposed new businesses such as secure management of seniors' financial assets, health investments aimed at improving quality of life, and work-style reforms to support continued employment among older adults. They also discussed the need for social systems and legal frameworks that encourage private sector initiatives in response to the rise in single-person elderly households, taking into account transformations in family and community structures.

5.5. Strengthening domestic and international advocacy

As shown in Figure 1, participants to the SAAS conferences grew steadily. The conferences were conducted with simultaneous Japanese–English interpretation, and the proportion of participants tuning in to the English channel increased each year, exceeding 40% in the most recent two conferences — an important indicator of enhanced international outreach. The attendee profile also diversified: industry representatives accounted for 73% of registrants in 2019, whereas the 2024 cohort included a balanced mix of healthcare and

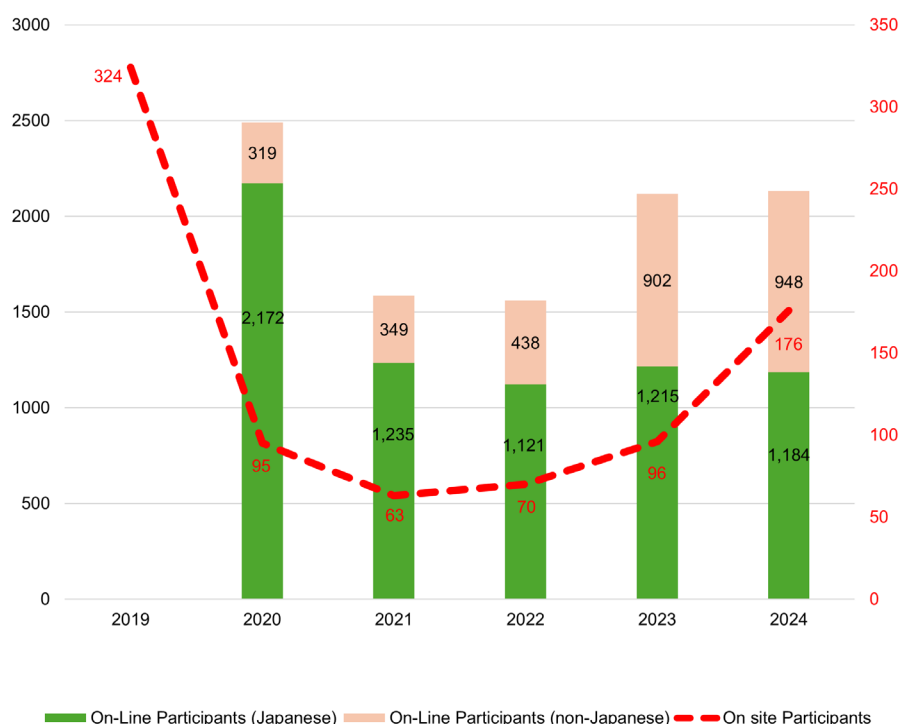


Figure 1. Changes in numbers of participants in the Super Active Aging Society Conference from 2019 to 2024. Green bar, on-line participants (Japanese channel); pink bar, on-line participants (English channel); red dashed line, on-site participants.

welfare professionals, public officials, and academics, confirming success of the conferences in attracting a wide range of stakeholders.

6. Conclusion

The SAAS Conferences approached the challenges of ageing societies not merely in the fields of welfare and healthcare, but as complex, structural issues spanning economics, industry, education, culture, and legal systems. Over the course of six conferences, the concept of a super active ageing society — integrating health, financial well-being, and social participation — was refined, offering new perspectives for both domestic and international policies and business strategies.

The reframing of domestic issues as global challenges fostered sharing of experiences across countries and encouraged international deployment of human resources and services, laying the groundwork for mutual benefits in both policy and industry. Through intergenerational cooperation and collaboration with the private sector, comprehensive discussions on societal sustainability were advanced, with active youth participation and creative proposals from interested businesses. Moreover, bilingual access and diverse participation strengthened advocacy both within and beyond national borders, contributing to greater international understanding and collaboration. The outcomes of this conference series clearly underscore the need for innovation and social transformation in ageing societies, and provide valuable insight for ongoing and future policy and institutional

design.

On July 29, 2025, a follow-up session was held with Professor Linda Fried, who visited Japan and delivered a keynote lecture entitled "*Healthy Ageing in a Changing Public Health Landscape: Creating the Opportunity for a Third Demographic Dividend*". Members of the Steering Committee who attended reaffirmed that connections and insights cultivated through the six conferences remain strong and continue to inspire new ideas, projects, and friendship. The relationships formed — across disciplines, generations, and borders — constitute a quiet yet enduring legacy. Each of the participants carries forward this shared sense of purpose and possibility, and all collectively commit to advancing the next phase of collaboration.

Acknowledgements

The author wishes to express profound gratitude to Professor Atsushi Seike, Chair of the Steering Committee, whose leadership and strategic vision were instrumental in shaping the direction and success of this initiative; and to all keynote speakers and panelists who offered insights that enriched both dialogue and outcomes of the event. The author is also deeply thankful to Nikkei, Inc. for generous support, and to the dedicated staff for their outstanding organization.

Funding: None.

Conflict of Interest: The author received an honorarium

from Nikkei Inc.; however, Nikkei Inc. had no role in the design, analysis, or writing of this manuscript.

Author's Note: The views expressed in this article are solely those of the author and do not reflect the official stance or collective opinion of the Steering Committee.

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Received September 19, 2025; Revised October 6, 2025; Accepted October 9, 2025.

Released online in J-STAGE as advance publication October 16, 2025.

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Research progress on intrinsic capacity in older adults: Concepts, epidemiology, assessments, influencing factors, adverse outcomes, and interventions

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Abstract: Intrinsic capacity (IC), introduced by the World Health Organization, is a core concept in the framework of healthy ageing. This study reviews the relevant concepts, epidemiology, assessments, influencing factors, adverse outcomes, and interventions concerning IC. IC refers to the composite of physical and mental capacities that an individual can draw on to live independently and thrive. Although IC is closely related to frailty and physiological reserve (PR), there are conceptual differences: IC represents the inherent functional reserve, frailty reflects the cumulative state of functional deficits, and physiological reserve emphasizes the ability to resist functional physical decline. IC assessments include comprehensive screening instruments of Integrated Care for Older People (ICOPE) and combinations of domain-specific scales; however, these approaches face challenges such as the inability to provide quantifiable results and the lack of standardized criteria, highlighting the urgent need to develop a standardized IC assessment system. Biomarkers may serve as supportive assessment tools, but their application is limited by cost and insufficient evidence, underscoring the need for future development of predictive models that integrate them. The main factors influencing IC include sociodemographic characteristics, physical health, psychosocial factors, and lifestyle. IC is strongly associated with health outcomes, serving as an effective predictor of several adverse outcomes. Interventions targeting IC primarily include ICOPE-guided multidomain interventions, along with other interventions such as multicomponent exercise, cognitive stimulation therapy, and dietary intervention; however, high-quality controlled trials remain limited, and the optimal timing and mechanisms of intervention require further investigation. This review offers important insights for clinical practice and research aimed at promoting healthy ageing among older populations.

Keywords: older adults, intrinsic capacity (IC), review, healthy ageing

1. Introduction

The trend of the global population distribution shifting towards older age groups is steadily increasing, with population ageing reaching serious proportions worldwide. From 2020 to 2030, the global population of individuals aged 60 and older is expected to increase from 1 billion to 1.4 billion, accounting for approximately one-sixth of the total global population. By 2050, this demographic is expected to double in size, reaching 2.1 billion (1). With the growth of the elderly population and the extension of life expectancy, the issue of longevity without health has become increasingly prominent (2), making the promotion of health among older adults crucial in the process of population ageing.

Healthy ageing has been introduced as an important global strategy to proactively address population ageing, aiming to improve the health, functional ability, and quality of life of older adults (3). It is a multidimensional concept encompassing physiological, psychological, and social aspects, and is defined as "the process of developing and maintaining the functional ability that enables wellbeing in older age", where functional ability refers to the capabilities that enable individuals to be and do what they have reason to value (4). To help older adults maintain stable functional performance, the World Health Organization (WHO) first introduced the concept of "intrinsic capacity (IC)" in the World Report on Ageing and Health in 2015, aiming to help older adults maintain stable functional performance by

shifting the focus of elder care from a "disease-centered" to a 'function-centered' approach, improving physical function and quality of life, and thereby promoting healthy ageing (3). With advancing age, the functions of organs and tissues gradually decline, leading to reduced physical function and an increased risk of adverse health outcomes. IC can comprehensively reflect the overall status of older adults and serve as a predictor of adverse health outcomes (5).

Therefore, by understanding the relevant concepts of IC, utilizing IC assessments for dynamic functional monitoring, identifying critical risk transition points in older adults, and implementing early risk factor detection alongside personalized interventions, it is possible to delay functional decline, reduce adverse outcomes, enhance well-being and quality of life, and ultimately promote healthy ageing. Therefore, this study reviews the relevant concepts, epidemiology, assessments, influencing factors, adverse outcomes, and interventions concerning IC, aiming to provide a valuable reference for future studies on IC among older adults.

2. Relevant concepts of IC

2.1. IC

IC, which refers to the composite of all the physical and mental capacities that an individual can draw on to live independently and thrive, represents the inherent functional reserve and reflects the foundation of older adults' capabilities and health status (4). While there is no universally uniform definition of IC at present, Wu *et al.* (6) identified four key attributes in their conceptual analysis: being oriented towards achieving the goal of healthy ageing, the inherent physiological reserve of an individual, the richness and interaction of the dimensions, and a dynamic and reversible developmental trajectory. WHO conceptualizes IC as comprising five dimensions: vitality, locomotion, cognition, psychology, and sensation, all of which are interrelated and influence each other (7).

IC is closely linked to functional ability, with IC serving as the foundation for functional ability, while functional ability is the manifestation of IC in a given environment. Both decrease with age, but functional decline is more pronounced in individuals with lower IC levels. IC spans the entire life course and addresses health deficits in older adults from the perspective of functional reserve, which plays a crucial role in maintaining quality of life and promoting healthy ageing (8).

2.2. Frailty

Frailty is a clinical condition characterized by the individual's increased vulnerability to endogenous and exogenous stressors. Frailty and IC are closely related

but conceptually distinct constructs (9), as illustrated in Table 1, both are derived from concepts rooted in the comprehensive assessment and management of older adults, with the shared goal of promoting a person-centered model of care. IC can be regarded as a refined conceptualization of frailty; its assessment helps predict frailty in older adults, and its enhancement contributes to delaying the onset of frailty (10). However, each has unique characteristics. Frailty represents the cumulative state of functional deficits, primarily applied in the cross-sectional assessment of elderly inpatients (11). In contrast, IC reflects an individual's physiological reserve, becomes increasingly impaired with advancing age, and is primarily used for longitudinal assessment of health status in older adults (12). Therefore, integrating both concepts can facilitate a more comprehensive understanding of ageing trajectories and support more targeted approaches to prevention and care.

2.3. Physical resilience

Physical resilience (PR) is defined as the ability to resist functional physical decline (13). Although PR is closely related to IC, with both representing the body's reserve capacity, their conceptual focus differs (14), as shown in Table 1, IC reflects an individual's overall health, encompassing physical, mental, and cognitive domains, whereas physical resilience refers to an adaptive, event-triggered ability to cope with and recover from physiological challenges. These concepts are complementary: strong physical resilience supports improved IC, while better IC can enhance physical resilience in older adults (15). IC and PR frameworks hold significant promise for transforming the geriatric medicine and ageing research. While IC represents only one of several determinants of PR, it constitutes a critical intervenable target for strengthening resilience in the older population (16).

3. Epidemiology of IC

Previous studies indicated that IC impairments are common among older adults. The prevalence of IC decline among older adults varies across regions and population characteristics (17). A systematic review and meta-analysis of 16 studies from four countries (18) found that the pooled detection rate of IC decline in older adults was 76.1%, with higher detection rates observed in developed countries, among women, and in hospital settings. Specifically, the pooled detection rate was 73.7% in China, with higher rates in mainland China and Hong Kong compared to Taiwan. An observational cohort study in China (19) examined the trajectory of IC in community-dwelling older adults, revealing a prevalence of IC impairment of 67.9%, which increased to 81.6% after two years. Among older adults with no IC impairment at baseline, 50.8% developed impairment

in at least one domain over two years. A study in Hong Kong (20) using the WHO ICOPE Brief Screening Instrument (Step 1) and Detailed Comprehensive Assessment (Step 2) found that 72.7% of participants exhibited IC impairment in Step 1, while 66.4% had impairments in at least one IC domain after Step 2. A study in Mexico (21) revealed that 87.8% of participants experienced impairment in at least one IC domain, with mobility being the most commonly affected at 47.6%. Furthermore, a survey conducted by Prince *et al.* across eight countries (22) revealed that only 30% of individuals maintained full capacity in all domains at baseline. These findings collectively suggest that the overall level of IC among older adults is poor, reflecting a concerning state of health.

4. Assessments of IC

Assessments for IC are currently limited worldwide, with two main methods commonly used:

i) The comprehensive screening instrument of Integrated Care for Older People (ICOPE) (23), which is based on the theoretical framework of the International Classification of Functioning Disability, and Health (ICF), consisting of nine domains. Individuals showing impairment in any domain are classified as having impaired IC. This is a brief yet highly focused preliminary assessment tool that enables rapid screening of the five core domains of IC in older adults and is currently widely used in large-scale cross-sectional studies. While this tool is easy to administer and efficiently identifies deficient areas, its inability to provide quantifiable results constrains its applicability in further research.

ii) WHO recommends assessment tools for each dimension of IC, which are combined to generate a composite IC score used to evaluate IC. Two main approaches are employed at present: aggregating scores through simple summation (24), arithmetic means (25), or Z-scores (26); and constructing a composite index based on domain-specific scores (27). The most commonly used tools include the gait speed test and chair stand test for locomotion; handgrip strength measurement and the Mini Nutritional Assessment (MNA) for vitality; Mini-Mental State Examination (MMSE) to evaluate cognition; Geriatric Depression Scale (GDS) and the Center for Epidemiological Studies Depression Scale (CES-D) for psychology; and self-reported vision and health questionnaires to assess sensation (28). While mature scales are available for the individual evaluation of the five domains of IC, there is notable inconsistency in the instruments used across studies. Due to the variation in assessment scales and procedures across different studies, it is difficult to merge data across dimensions, which complicates the scoring and judgment of IC. Future research should focus on developing a standardized IC assessment system, establishing IC

unified scoring indices and standardized quantification procedures, and formulating an IC assessment scale for older adults to provide practical tools for primary health evaluation.

Previous studies have shown that certain biomarkers are strongly associated with IC, which can serve as supportive tools for assessment. Ma *et al.* (29) found that Tumor Necrosis Factor Receptor 1 (TNFR1) levels are independently associated with declined IC, suggesting that chronic inflammation may underlie IC decline. Similarly, Lu *et al.* (30) discovered that plasma biomarkers of inflammation and mitochondrial damage can differentiate older adults with multiple impairments in IC from those with stable capacity. Lee *et al.* (31) observed that chronic inflammation, hyperglycemia, and low Dehydroepiandrosterone sulfate (DHEA-S) were associated with reduced IC, with low DHEA-S and vitamin D deficiency potentially serving as biomarkers for rapid decline in IC. The aforementioned studies demonstrated that low IC may be closely linked to inflammation and nutritional status, with specific biomarkers serving as early predictors of IC decline. Biomarkers can help reduce measurement errors when constructing IC scores and provide valuable references for assessments. By timely detecting and intervening in these biomarkers, the decline of IC can be slowed to some extent. As biomarker-based assessments of IC require substantial time and financial costs, relevant studies are limited and lack clear evidence. Therefore, future research should focus on developing predictive models incorporating biomarkers to assess IC decline, enabling early identification of high-risk individuals for timely interventions to preserve functional capacity and enhance the quality of life for older adults. In summary, Table 2 provides a comparative overview of tools for assessing IC, including their description, advantages, disadvantages, and expected future directions.

5. Factors influencing IC

Previous studies (32,33) have summarized that the main factors influencing IC include sociodemographic characteristics, physical health, psychosocial factors, and lifestyle. Sociodemographic characteristics primarily include age, gender, marital status, educational level, and socioeconomic status. IC declines with age and is more likely to be impaired in women, unmarried older adults, and individuals with lower education or economic status. Poor physical health, such as memory decline, urinary incontinence, constipation, slowness, chronic obstructive pulmonary disease, and osteoarthritis were related to IC decline (17). A study involving older adults from six countries (34) revealed that grip strength is strongly associated with other indicators of IC, confirming it as a single most important measure of IC. Establishing optimal handgrip strength thresholds may facilitate the early identification of individuals at risk of impaired IC,

Table 1. Conceptual comparison of intrinsic capacity, frailty, and physical resilience

Aspect	IC	Frailty	PR
Definition	The composite of all physical and mental capacities an individual can draw upon to live independently and thrive.	A clinical condition characterized by the individual's increased vulnerability to endogenous and exogenous stressors.	The capacity to resist functional physical decline.
Focus	Overall capacity across five domains: vitality, locomotion, cognition, psychology, and sensation.	Functional impairment and vulnerability.	Coping and recovery ability under physiological challenges.
Core Characteristics	Multidimensional, dynamic, and reversible.	Cumulative, deficit-oriented.	Adaptive and event-triggered.
Application	Longitudinal monitoring of older adults' health status and early detection of declines in function.	Cross-sectional assessment in clinical or hospital settings.	Utilized in rehabilitation to assess individual adaptability and guide intervention design.
Interrelationship	Conceptual foundation for functional ability.	Conceptually related to IC, with a shared emphasis on promoting a person-centered model of care; may be predicted by a decline in IC.	Complementary to IC: strong PR supports improved IC, while better IC can enhance PR.

IC, intrinsic capacity; PR, physical resilience.

Table 2. Comparative overview of tools for assessing intrinsic capacity

Assessment Method	Description	Advantages	Disadvantages	Expected Future Directions
ICOPE Screening Tool	A brief and standardized instrument developed by WHO based on the ICF framework, it screens five core domains of IC using nine items.	● Rapid and easy to administer; ● Widely implemented in large-scale population; ● Efficient in identifying deficient areas.	● Lacks quantifiable results; ● Limited for Longitudinal Monitoring; ● Lacks domain-specific granularity.	● Develop quantifiable scoring versions; ● Refine domain-specific assessments.
Combination of Domain-Specific Scales	IC domain-specific tools are used to generate a composite IC score <i>via</i> summation, arithmetic means, Z-scores, or a domain-based composite index.	● Enables quantitative tracking; ● Flexibility in tool selection per domain; ● Suitable for longitudinal cohort studies.	● Inconsistency in tools across studies; ● Lack of standardized scoring procedures; ● Difficulty in data integration; ● Complicated judgment of IC levels.	● Develop standardized IC assessment systems; ● Unify tools across studies; ● Create unified scoring indices and quantification procedures.
Biomarker-Based Assessment	Incorporates biological markers linked to IC decline.	● Enables early detection of IC decline <i>via</i> biomarkers; ● Helps reduce measurement errors in IC assessment; ● Improves understanding of IC-related biological mechanisms.	● High time and financial cost; ● Limited feasibility in routine clinical settings; ● Lack of robust, standardized evidence and validation.	● Develop predictive models incorporating biomarkers; ● Identify cost-effective biomarkers; ● Validate biomarkers for clinical screening.

ICOPE, Integrated Care for Older People; WHO, World Health Organization; ICF, International Classification of Functioning, Disability and Health.

Table 3. Overview of influencing factors on intrinsic capacity

Authors	Year	Country	Factors influencing intrinsic capacity	Ref.
Wei <i>et al.</i>	2024	France, Costa Rica, Mexico, Japan, Singapore, China, Belgium, Hong Kong, Latin America, India	Age, sex, marital status, occupation status, education, income/wealth, chronic diseases, hypertension, diabetes, disability, smoking status, alcohol consumption, physical activity, biomarkers/inflammatory markers, ethnicity, residence, housing index, social engagement, multimorbidity, medication adherence, polypharmacy, hospitalization, sleep health, cardiovascular mortality, respiratory mortality, fragility fracture, life-space mobility, nursing home stay, incontinence, and sarcopenia.	(33)
Leung <i>et al.</i>	2022	Hong Kong	Age, sex, education level, marital status, grip strength, physical activity, smoking, drinking, self-care capacity, loneliness, and social engagement.	(20)
Chen <i>et al.</i>	2021	China	Age, residence, education, marital status, income, exercise, meat intake, insomnia, memory decline, urinary incontinence, constipation, slowness, chronic obstructive pulmonary disease, and osteoarthritis.	(17)
Gutiérrez-Robledo <i>et al.</i>	2021	Mexico	Age, sex, years in school, self-rated health, chronic diseases, number of visits to a physician in the last year, and ≥ 2 affected activities of daily living.	(21)
Arokiasamy <i>et al.</i>	2021	China, Ghana, India, Mexico, Russia, South Africa	Age, education, wealth quintiles, work status, residence, marital status, body mass index, chronic conditions, and self-rated health status.	(34)
Huang <i>et al.</i>	2021	Japan	Age, sex, educational level, body mass index, medical history, and social frailty.	(36)
Huang <i>et al.</i>	2021	Japan	Age, sex, education level, body mass index, smoking status, alcohol consumption, physical activity, energy intake, and dietary pattern.	(37)
Lu <i>et al.</i>	2021	Hong Kong	Age, sex, education, marital status, number of chronic diseases, percentage of green space, land use diversity, number of leisure facilities, number of public transport facilities, number of community centres, number of commercial facilities, and number of healthcare facilities.	(39)

Table 4. Overview of adverse outcomes of intrinsic capacity

Authors	Year	Country	Adverse outcomes of intrinsic capacity	Ref.
Yang <i>et al.</i>	2024	China, Japan, Korea, Singapore, Malaysia, Thailand, India, United States, Netherlands, Italy, Spain, United Kingdom, Australia	• Physiological function: frailty, pneumonia onset, memory impairment, polypharmacy, incontinence, poor/fair self-rated health; • Clinical outcomes: IADL disability, ADL disability, mortality, falls, autonomy decline, incident dependence; • Resource utilization: hospitalization, nursing home stays, polypharmacy healthcare costs, emergency department visits; • Other domains: poor quality of life.	(41)
Zhao <i>et al.</i>	2024	China, United Kingdom, France, Japan, India, Australia, Belgium, Finland, Singapore	Disability, falls, hospitalisation, mortality, frailty, incontinence, polypharmacy, poor/fair self-rated health, nursing home stay, pneumonia, ADL disability, and IADL disability.	(5)
Zhou <i>et al.</i>	2023	China, India, Mexico, Latin America, United Kingdom, Belgium, France, Spain, Netherlands, Norway, United States, New Zealand	Physical function, frailty, falls, mortality, quality of life, and other adverse outcomes (hospitalization, pneumonia incidence, nursing home stays, emergency department visits, and prognosis in acute coronary syndrome).	(42)
Yu <i>et al.</i>	2021	China	Incident disability, recurrent falls, hospitalization, emergency department visits, and poor quality of life.	(43)
Charles <i>et al.</i>	2020	Belgium	Mortality, falls, repeated falls, and autonomy decline.	(44)
Page's <i>et al.</i>	2022	France	Higher healthcare costs.	(46)

IADL, instrumental activities of daily living; ADL, activities of daily living.

thereby supporting its use as a convenient tool for IC evaluation (35). In terms of psychosocial factors, Huang *et al.* (36) found a longitudinal association between social frailty and IC and its subdomains, with socially frail men being more prone than women to declines in psychological and cognitive functions. Similarly, Leung *et al.* (20) reported that older adults with reduced social engagement exhibited significantly IC.

The differences in lifestyle can impact the IC of older adults, as Chen *et al.* (17) found that poor lifestyle habits, such as smoking, alcohol consumption, lack of exercise, low meat intake, and insomnia, were negatively correlated with IC. It is worth mentioning that dietary patterns significantly impact the IC of older adults. In particular, dietary patterns rich in fruits, vegetables, and animal-based protein were linked to positive changes in IC, while dietary patterns high in sugar and fat were negatively associated with IC changes (37). Moreover, the association between dietary patterns and IC was found to be stronger in men than in women, suggesting that strategies to improve diet should consider gender differences (38). Lu *et al.* (39) reported that a favorable neighborhood physical environment, including green spaces, land use diversity, and accessible facilities, is positively associated with higher IC. This may be attributed to the fact that a favorable neighborhood physical environment encourages positive lifestyle habits, such as regular physical activity, independent mobility, and social engagement; meanwhile, exposure to natural environments helps alleviate stress and improve sleep quality, all of which contribute to enhancing the IC of older adults. Since lifestyle is the most easily modifiable among all influencing factors, efforts to improve IC should focus on correcting these unhealthy lifestyle-related behaviors. Table 3 presents an overview of influencing factors on IC.

Exploring the factors influencing IC can help guide interventions to maintain or improve it, thereby promoting health and enhancing the quality of life for older adults. At present, studies on the etiology and pathophysiological mechanisms of IC impairment are limited; most studies use cross-sectional designs to explore influencing factors, which cannot establish causal relationships. Therefore, future research should adopt prospective designs and focus on the underlying mechanisms and pathophysiological basis of IC decline to deepen exploration in this field.

6. Adverse outcomes of IC

The level of IC in older adults is strongly associated with health outcomes: higher IC in older adults reduces the risk of adverse outcomes, while its decline increases the risk of poor outcomes (40). A scoping review (41) that included 25 studies identified 17 adverse outcomes associated with IC, which were categorized into four domains: *i*) physiological function domain

Table 5. Overview of interventions for intrinsic capacity

Authors	Year	Country	Interventions for intrinsic capacity	Ref.
Liu <i>et al.</i>	2024	France, India, China, Vietnam, Japan, Korea, Thailand, Italy, Spain, Belgium, Germany, Netherlands, Portugal, Turkey, United Kingdom, Brazil, Chile, Colombia, Mexico	ICOPE-guided multidomain interventions: integrated care intervention, tailored interventions, physical activity interventions, cognitive training, psychological interventions, multidomain interventions, person-centred care, community-based integrated care, nutritional interventions, medication review, health education, function-oriented care, comprehensive geriatric assessment, goal-oriented care, remote monitoring, nurse-led care, and follow-up care.	(50)
Lee <i>et al.</i>	2024	Taiwan	ICOPE-guided multidomain intervention: physical activities, cognitive training, nutrition advice based on national dietary guidance for older adults, lectures on healthy aging, lifestyle modification, the management of chronic conditions, comprehensive geriatric assessment and allied health care services, and personalized care plans.	(51)
Yan Wang <i>et al.</i>	2024	China	ICOPE-guided multidomain intervention: in-home visits, tele-care sessions, health education, care coaching, living environment adaptation, rehabilitative therapies, nursing services, coordination of social care resources, personalised goal setting and care planning, comprehensive, person-centred assessment, screening for declines in intrinsic capacity, care plan execution and monitoring, referrals, engaging communities, supporting caregivers, use of decision support algorithms, online support system, training of integrated care managers, and quality assurance team reviews.	(52)
Blancafort <i>et al.</i>	2021	Spain	ICOPE-guided AMICOPE intervention: adapted physical activity, dietary advice, cognitive behavioral therapy, problem-solving, behavioral activation, life review, strengthening social support/staying socially connected, self-management, and behavior change strategies.	(54)
Huang <i>et al.</i>	2021	Japan	Aerobic training, resistance training, combined training, group training program, self-paced home training, and lectures about health promotion.	(25)
Sánchez-Sánchez <i>et al.</i>	2022	Spain	Twelve-week home-based individualised Vivifrail multicomponent physical exercise program (resistance, balance, flexibility, endurance, and gait retraining exercises).	(58)
Merchant <i>et al.</i>	2024	Singapore	Exercise 6 months, and cognitive stimulation therapy 3 months with Exercise 6 months.	(59)
Lim <i>et al.</i>	2022	Taiwan	Healthy eating intervention (nutrition education, group activities, use of customized dishware, encouragement of correct servings of six food groups based on the Taiwanese daily food guide for the elderly).	(61)

ICOPE , Integrated Care for Older People; AMICOPE, Aptitude Multi domain group based intervention to improve and/or maintain Intrinsic Capacity in Older People.

included frailty, pneumonia onset, memory impairment, polypharmacy, incontinence, and poor or fair self-rated health; *ii*) clinical outcomes domain comprised instrumental activities of daily living (IADL) disability, activities of daily living (ADL) disability, mortality, falls, autonomy decline, and incident dependence; *iii*) resource utilization domain covered hospitalization, nursing home stays, healthcare costs related to polypharmacy, and emergency department visits; *iv*) other domain primarily referred to poor quality of life. Another scoping review (42) that included fifteen longitudinal studies evaluated a range of adverse health outcomes, including physical function, frailty, falls, mortality, quality of life, and other adverse health outcomes.

IC, as an independent and emerging construct, is a highly effective predictor of several health outcomes, facilitating the early identification of high-risk populations (5). Previous studies have confirmed the predictive value of the multidimensional structure of IC for adverse outcomes. Yu *et al.* (43) reported that cognitive decline, limited mobility, visual impairment, and depressive symptoms predicted incident disability; visual impairment predicted recurrent falls; cognitive decline and limited mobility predicted emergency department visits; limited mobility predicted poor quality of life. Charles *et al.* (44) found that each one-point increase in balance performance and nutritional scores reduced mortality risk by 12% (Hazard ratio [HR] = 0.88; 95% confidence interval [CI]: 0.78–0.99) and 4% (HR = 0.96; 95% CI: 0.93–0.99), respectively. A one-point improvement in balance performance (HR = 0.87, 95% CI: 0.79–0.96) and nutritional status (HR = 0.96, 95% CI: 0.93–0.98) was associated with a reduced risk of falls. Lower nutritional scores were linked to higher autonomy decline risk (OR = 0.86; 95% CI: 0.77–0.96). Giudici *et al.* (45) reported that individuals with low vitality were 2.0 to 6.1 times more likely to accumulate frailty components over time. In addition, impairments in IC are linked to increased healthcare costs, with visual impairment significantly associated with increased immediate healthcare expenses (Cost Ratio [CR] = 1.48; 95% CI: 1.16–1.89), and persistent impairments in locomotor (CR = 1.27; 95% CI: 1.01–1.60) and psychological capacity (CR = 1.28; 95% CI: 1.03–1.59) related to higher annual healthcare expenditures (46). The adverse outcomes of IC are outlined in detail in Table 4. Therefore, regular assessment and monitoring of IC in older adults, combined with targeted interventions, can effectively enhance IC and reduce the risk of adverse health outcomes, and simultaneously lower healthcare costs.

7. Interventions for IC

Interventions targeting IC are primarily ICOPE-guided multidomain interventions, which are comprehensive intervention plans designed and implemented following

the systematic screening and individualized assessment of the five key domains of IC in older adults: cognitive, psychological, nutritional, physical, and sensory functions (47). This approach emphasizes multidomain integration, individualized care planning, community and family involvement, and dynamic evaluation with continuous adjustment, aiming to delay functional decline, preserve or enhance IC, improve quality of life, and promote healthy ageing (48). In addition to the aforementioned interventions, other interventions include multicomponent exercise, cognitive stimulation therapy, and dietary intervention. These interventions are summarized in Table 5.

ICOPE-guided multidomain interventions have been demonstrated to be an effective approach for enhancing IC in older adults. A systematic review incorporating 25 randomized controlled trials (49) suggested that multidomain interventions can help maintain IC in older adults and are also effective for those experiencing a decline in self-care abilities. Liu *et al.* (50) reported that ICOPE is a potentially effective approach for improving IC in older adults, with significant potential for enhancing cognition function and alleviating depressive symptoms in particular. Lee *et al.* (51) indicated that incorporating multidisciplinary interventions into primary health care significantly enhanced IC in older adults. A randomized controlled trial conducted in Beijing (52) demonstrated the feasibility of localizing and implementing the WHO's ICOPE approach in regions with fragmented resources such as China.

The first global pilot programs began in 2020 across four countries — China, France, Andorra, and India — progressing through three phases: preparation, setup, and implementation. In 2022, the WHO summarized the pilot program's outcomes for implementing ICOPE in the integrated care of older adults (53). A study conducted in Spain (54) described the development of a group-based, multi-domain intervention for community-dwelling older adults, which resulted in the creation of the Aptitude Multi domain group based intervention to improve and/or maintain Intrinsic Capacity in Older People (AMICOPE) intervention based on the ICOPE framework. The intervention included vivifrail exercise training, nutritional and dietary guidance, psychological group therapy, and cognitive stimulation. This study represents the initial phase of the UK Medical Research Council framework for designing and assessing complex interventions.

Physical activity is associated with higher IC in older adults, exerts significant positive effects on the domains of locomotion, cognition, psychology and vitality (55,56), and is widely recognized as a key intervention for promoting and maintaining IC (57). A single-blind randomized controlled trial (25) comparing the effects of aerobic training (AT), resistance training (RT), and combined training (AT+RT) on IC in older adults. Participants in the intervention group received

a 26-week group training program and self-paced home training, while the control group attended health promotion lectures. Findings indicated that a 26-week program of AT and RT with self-paced home training can enhance IC in community-dwelling older adults experiencing subjective memory concerns, although the benefits diminished over time. Multicomponent exercise is considered a potential intervention for maintaining/improving IC in older adults. Building on this, a study from Spain (58) found that the 12-week Vivifrail multicomponent exercise program effectively improves IC, particularly in the locomotion, cognition, and vitality domains among community-dwelling older adults with pre-frailty or frailty and mild cognitive impairment or mild dementia, compared with usual care.

In terms of cognitive stimulation therapy, previous studies have shown significant benefits for IC among older adults. A study conducted in Singapore (59) examined the effects of exercise (Ex) and cognitive stimulation therapy (CST) on the IC of community-dwelling pre-frail older adults. Participants were divided into a control group, an Ex group, and an Ex+CST group, with the combined group receiving CST during the first three months of the six-month intervention. Results showed that both Ex and Ex+CST significantly improved the composite IC score, particularly in the locomotion, vitality, and psychological domains. Notably, the Ex+CST group demonstrated greater improvements in the cognition domain. These benefits were sustained up to 12 months after the intervention. The study concluded that incorporating cognitive stimulation therapy into exercise-based interventions may be a more effective strategy for enhancing IC, especially in supporting cognitive function.

Dietary pattern has been shown to have a strong association with IC (37,60). A prospective single-group interventional quasi-experimental study in Taiwan (61) implemented a four-month texture-modified plant-based dietary intervention among 59 functional independent older adults residing in retirement homes to explore the intervention effects of improved dietary quality on IC. The findings revealed that participants with high adherence to the intervention experienced significant improvements in vitality (cardiorespiratory endurance, $p = 0.009$) and locomotion (gait speed, $p = 0.034$), despite declines in locomotion (chair-stand test, $p < 0.001$) and cognitive functions (Mini-Mental State Examination, $p = 0.022$). Enhanced IC further contributed to improvements in activities of daily living ($p = 0.034$). This study suggests that healthy eating can enhance vitality and locomotion domains of IC thus improving the functional ability of older adults.

An umbrella review encompassing 6,407 articles (62) identified mobility-focused interventions as the most studied among the seven domains of IC, highlighting the effectiveness of mobility/muscle strength training in improving locomotor function

in frail older adults or those with functional decline. Nevertheless, there is a lack of robust evidence for interventions addressing other domains of IC, especially sensory function and continence. Future research should prioritize high-quality trials in these underrepresented areas to support the development of evidence-based guidelines aimed at enhancing overall IC and promoting healthy ageing.

Taken together, multidisciplinary interventions based on the ICOPE framework are an effective approach to addressing IC decline. They hold promise as a strategy for improving IC in older adults and should be advocated as a feasible approach to promoting healthy ageing. However, there are few controlled intervention studies on IC, as well as insufficient exploration of the optimal timing for intervention and the underlying reasons for significant changes in IC. This underscores the necessity for clinical longitudinal studies to examine the effects of interventions on IC in the future, and the continuous development and improvement of strategies to address the decline of IC in older adults.

8. Conclusion

This study reviews the relevant concepts, epidemiology, assessments, influencing factors, adverse outcomes, and interventions concerning IC, aiming to offer a reference for further research on IC in older adults. By understanding the relevant concepts of IC, utilizing IC assessments for dynamic functional monitoring, identifying critical risk transition points in older adults, and implementing early risk factor detection alongside personalized interventions, it is possible to delay functional decline, reduce adverse outcomes, enhance well-being and quality of life, and ultimately promote healthy ageing.

Funding: This study was supported by National Nature Science Foundation of China [grant number 72474092, 72274087], Development Program of Gansu Province [grant number 23YFFA0006], Fundamental Research Funds for the Central Universities [grant number lzujbky-2024-it61, lzujbky-2024-ou12], and Nature Science Foundation of Gansu Province [grant number 22JR5RA218, 24JRRA596].

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

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Received March 12, 2025; Revised July 30, 2025; Accepted

September 8, 2025.

Released online in J-STAGE as advance publication September 18, 2025.

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Evaluation of the geographic distribution of patients with hepatocellular carcinoma and treatments in Japan using data from the Japanese national database

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Abstract: The National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), provided by the Ministry of Health, Labour and Welfare (MHLW), is an exhaustive repository that can be used to understand the nationwide epidemiology of hepatocellular carcinoma (HCC) in Japan. This study was conducted to clarify the geographic distribution of patients with HCC and treatments performed in each region of Japan using data from the NDB. A retrospective analysis was performed to determine the number of patients diagnosed, with HCC (International Classification of Diseases, 10th edition, code C22.0), who received treatment between 2016 and 2020. Number of incidences of HCC per 100,000 individuals in each Japanese region are 76 (Hokkaido), 63 (Tohoku), 55 (Kanto), 58 (Tokai), 74 (Hokuriku), 77 (Kinki), 93 (Chugoku), 101 (Shikoku), 93 (Kyushu), and 37 (Okinawa). Transarterial embolization/transarterial chemoembolization and curative treatments, including laparoscopic liver resection (LLR), open liver resection, and radiofrequency ablation, were the most frequently performed treatments in all regions, followed by systemic therapy. The proportion of patients receiving LLR was lowest in the Shikoku region (6.7%), which also had the lowest frequency of institutions certified by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) relative to the number of patients with HCC. Although the incidence of HCC varies across regions in Japan, the most frequently performed treatments remain consistent nationwide. This suggests that HCC treatment practices are largely standardized, regardless of geographic location. Certification by the JSHBPS appears to play a role in patient access to LLR.

Keywords: hepatocellular carcinoma, geographic distribution, Japanese national database

1. Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third leading cause of cancer-related mortality (1). In Japan, there are multiple nationwide registries, including the one maintained by the Japan Liver Cancer Association, which was previously referred to as the Liver Cancer Study Group of Japan (LCSGJ) (2,3). However, the nationwide follow-up survey conducted by the LCSGJ depended exclusively on data from approximately 500 specialized member institutions in Japan, and the presence of regional variations in treatment choices was

not investigated in the study.

In addition, previous reports have demonstrated regional differences in the number of patients with hepatitis C virus (HCV) infection (4). Given that chronic HCV infection is a risk factor for HCC (5,6), the number of patients with HCC might vary across different regions of Japan. Therefore, investigating geographic distribution and treatment approaches in each region of Japan is crucial for investigating the real-world burden of HCC in Japan.

In 2011, the Ministry of Health, Labour and Welfare (MHLW) of Japan started providing access to the National Database of Health Insurance Claims

and Specific Health Checkups of Japan (NDB) for research use (7). The NDB is a comprehensive resource of health policy and research information and can be used for analyzing geographic distribution and clinical management of HCC across Japan.

In this study, we examined the NDB to provide an up-to-date view of the landscape of HCC incidence and treatment in Japan.

2. Materials and Methods

2.1. Data source

This study used data from the NDB, an extensive database that compiles electronic insurance claims data for all healthcare services and products covered by Japan's national health insurance system (8). Researchers may apply to the MHLW to obtain access to the smallest set of NDB data required for their research. The data supplied by the MHLW are anonymized. The NDB contains comprehensive information on patient demographics, health status, diagnoses, medical and dental procedures, prescription records, insurance claims, and health examination data from all hospitals and clinics across Japan.

For this study, we requested and acquired data associated with the International Classification of Diseases, 10th Revision (ICD-10) codes relevant to liver cancer, covering the period from April 2015 to September 2021. Our research team was granted access to 323 million medical records, 130 million Diagnosis Procedure Combination records, and 384,000 prescription records. The study protocol was approved by Ethics Committee of the National Center for Global Health and Medicine (approval number 004253-03).

2.2. Patient selection

The diagnostic data in the NDB are organized using ICD-10 codes. We classified patients with the code C22.0 (liver cell carcinoma) as having HCC. Individuals for whom this diagnosis code was the first assigned, with a lookback period of at least 12 months, were considered newly diagnosed cases of HCC. While no specific exclusion criteria were applied in this study, we did exclude patients who lacked treatment-related data from the analysis. The analysis was performed to determine the number of patients diagnosed with HCC and received treatments between 2016 and 2020, during which we had access to complete annual data.

2.3. Treatments

Interventions for HCC 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). A combined analysis was performed for transarterial embolization (TAE, procedure code K615) and transarterial chemoembolization (TACE, procedure code G003-3). Microwave and radiofrequency ablation (RFA) were grouped under RFA (K697-2, K697-3). TAE and TACE were examined together. Patients who were initially prescribed sorafenib (medication code 620006778), regorafenib (622225801), lenvatinib (622416001, 622416101), ramucirumab (622417901, 622418001), atezolizumab (622594601, 629900601), bevacizumab (620004872, 620004873), or cabozantinib (622796901, 622797001) were considered to have received systemic therapy (ST). Japan was divided into 10 regions based on its prefectures (Supplementary Figure S1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=112>).

2.4. Statistical analysis

Descriptive statistics were used to summarize incidence rates of HCC per 100,000 individuals and proportions of different therapeutic interventions, including TAE/TACE, LLR, OLR, RFA, and ST, across the 10 defined Japanese regions.

To examine regional differences, the chi-square test was applied to compare incidence of HCC and proportions of treatments among the regions. When a statistically significant chi-square result was obtained, pairwise comparisons with the Bonferroni correction were conducted between regions.

All statistical analyses were conducted using R statistical software (version 4.4.1; R Foundation for Statistical Computing, Vienna, Austria). A two-tailed *p* value of < 0.05 was considered statistically significant unless otherwise specified.

3. Results

TACE/TAE was performed most frequently (38.6%) in the total cohort, followed by OLR (24.1%), RFA (18.1%), LLR (12.6%), and ST (6.6%) (Figure 1).

Figure 2 shows that the number of incidences of HCC per 100,000 individuals in each Japanese region are 76 (Hokkaido), 63 (Tohoku), 55 (Kanto), 58 (Tokai), 74 (Hokuriku), 77 (Kinki), 93 (Chugoku), 101 (Shikoku), 93 (Kyushu), and 37 (Okinawa). The differences in the incidences between regions are statistically significant (*p* < 0.0001).

Types of treatments in each region are presented in Table 1 and Figure 3. Relative frequency at which a specific treatment was selected was significantly different between regions. This was further investigated using pairwise comparisons versus the region with the lowest proportion for each treatment (Table 2), which revealed that the proportion of patients receiving LLR was lowest in Shikoku (6.7%). The number of institutions certified

by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) is shown in Table 3. The ratio of patients per number of certified institutions was the highest in Shikoku. Furthermore, frequency of patients receiving TACE/TAE was higher in the Hokuriku and Tohoku regions. However, TAE/TACE and curative treatments, including LLR, OLR, and RFA, were the most frequently performed treatments in all regions.

4. Discussion

Our analysis of the NDB revealed that HCC treatment in Japan has been equalized to some extent. Specifically, although the incidence of HCC varied across each Japanese region, TAE/TACE and curative treatments (including LLR, OLR, and RFA) were the most frequently used regimens in all regions, which suggests

standardization of HCC treatments.

Although previous reports from the LCSGJ have documented the number of treated patients with HCC, the most recent data cover only the period from 2014 to 2015 and do not report geographic distribution (3). Therefore, analyzing more recent trends in HCC treatment, in the context of geographical distribution, is crucial. Moreover, past nationwide surveys have focused only on specialized centers for HCC treatment. As such, a more in-depth analysis of the NDB is essential for understanding current epidemiology of HCC and daily practice in each Japanese region.

Although treatment protocols appeared standardized across regions, a significant disparity was observed in number of patients relative to population size. This discrepancy may be attributed to the geographical distribution of the hepatitis virus across regions (9). However, the NDB does not provide comprehensive patient characteristics, such as chronic hepatitis virus infection. Therefore, this issue needs further investigation.

LLR requires specific skills and equipment and is increasingly performed for treatment of liver tumors, owing to its benefit of reducing pain and intraoperative blood loss, particularly for minor liver resections (10). The frequency at which LLR is performed is reflective of the relative access to minimally invasive surgery in each region. For instance, LLR was less frequently performed in Shikoku, which is consistent with the high ratio of patients per number of certified institutions in this region. We suggest that a certification system for education and training of highly skilled surgeons in Japan (11) would result in JSHBPS accreditation of more skilled hepatobiliary-pancreatic surgeons, which should ultimately help increase access to LLR in regions such as Shikoku. The board certification system by JSHBPS is established to nurture surgeons capable of performing safe and reliable advanced surgery in the hepato-pancreatic-biliary field. The certification

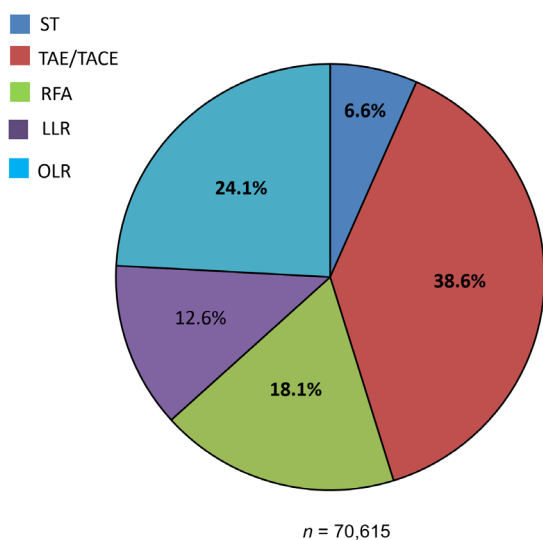


Figure 1. Nationwide proportions of HCC treatments.
Abbreviations: TAE/TACE, transarterial embolization/transarterial chemoembolization; OLR, open liver resection; RFA, radiofrequency ablation; LLR, laparoscopic liver resection; ST, systemic therapy.

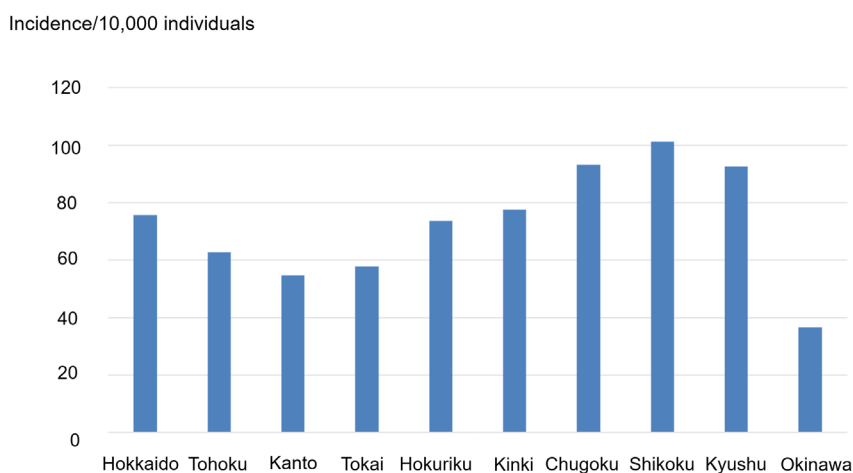


Figure 2. Distribution of HCC incidence per 10,000 individuals across regions from east to west Japan.

Table 1. Interregional differences in the frequency of HCC treatments in Japan

Treatment	Hokkaido (n = 3,850)	Tohoku (n = 6,541)	Kanto (n = 25,319)	Tokai (n = 8,487)	Hokuriku (n = 2,103)	Kinki (n = 15,687)	Chugoku (n = 6,582)	Shikoku (n = 3,618)	Kyushu (n = 11,621)	Okinawa (n = 539)	p value*
ST	319 (8.3)	386 (5.9)	1,387 (5.5)	585 (6.9)	130 (6.2)	749 (4.8)	367 (5.6)	157 (4.3)	542 (4.7)	36 (6.7)	< 0.001
OLR	969 (25.2)	1,157 (17.7)	5,429 (21.4)	1,727 (20.3)	354 (16.8)	2,864 (18.3)	1,531 (23.3)	641 (17.7)	2,237 (19.2)	143 (26.5)	< 0.001
LLR	368 (9.6)	478 (7.3)	2,331 (9.2)	752 (8.9)	219 (10.4)	2,187 (13.9)	829 (12.6)	244 (6.7)	1,392 (12.0)	64 (11.9)	< 0.001
RFA	597 (15.5)	766 (11.7)	4,750 (18.8)	1,176 (13.9)	305 (14.5)	2,532 (16.1)	688 (10.5)	491 (13.6)	1,402 (12.1)	64 (11.9)	< 0.001
TACE/TAE	1,023 (26.6)	2,471 (37.8)	8,039 (31.8)	2,782 (32.8)	795 (37.8)	4,805 (30.6)	1,938 (29.4)	977 (27.0)	4,249 (36.6)	191 (35.4)	< 0.001

*The chi-square test was used to compare regions. Data are expressed as numbers and (%) unless otherwise specified. The region with the lowest percentage is shown in bold. Abbreviations: ST, systemic therapy; OLR, open liver resection; LLR, laparoscopic liver resection; RFA, radiofrequency ablation; TACE/TAE, transarterial chemoembolization/transarterial embolization.

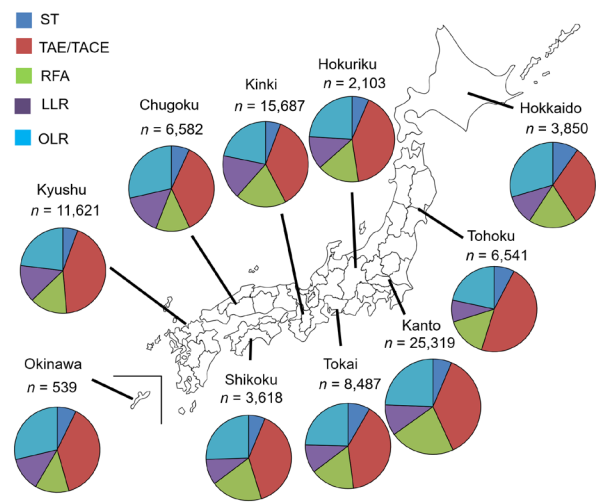


Figure 3. Treatments performed for hepatocellular carcinoma in each Japanese region. Abbreviations: TAE/TACE, transarterial embolization/transarterial chemoembolization; OLR, open liver resection; RFA, radiofrequency ablation; LLR, laparoscopic liver resection; ST, systemic therapy.

system is specific because, apart from annual volumes of advanced HPB surgeries, surgical records and videos are reviewed to guarantee quality of procedures. Studies have shown that LLR is performed more often at board-certified institutions than at non-certified institutions (12). In addition, limited geographical access may be a contributing factor to the low ratio. One previous study reported differences in the number of large medical centers and physician-to-bed ratio within each region of Japan, which might have also contributed to the discrepancy in frequency of LLR (13,14).

Sorafenib was the first approved ST for HCC (15). In Japan, most medications are typically covered by public health insurance shortly after their approval. Following approval of sorafenib, several other STs, such as lenvatinib, regorafenib, cabozantinib, and ramucirumab, became primary treatments for advanced HCC in Japan (16,17). However, ST accounted for the lowest proportion of patients (6.6%) in the national cohort (Figure 1), probably because more curative treatment options are currently preferentially used throughout Japan. The 180-day post-diagnosis duration might have been insufficient to accurately analyze the number of patients receiving ST.

Notably, the methodology employed in this study has certain limitations. First, data are analyzed retrospectively, and overlap with data of patients diagnosed with intrahepatic cholangiocarcinoma or mixed types is expected because differentiating these conditions without data from pathological examination is challenging. Second, information regarding specific patient characteristics, tumor stage, and prognosis is lacking. Third, sequential treatments are not correctly evaluated. Although we limited analysis to treatments administered within 180 days of diagnosis, sequential

Table 2. Region-based pairwise comparison of HCC treatment frequencies

Treatment	The lowest frequency	Proportion difference*1 (adjusted <i>p</i> value**2)								
ST	Shikoku 4.3%	Hokkaido +3.95% (<0.001)	Tokai +2.55% (<0.001)	Okinawa +2.34% (0.144)	Hokuriku +1.84% (0.019)	Tohoku +1.56% (0.007)	Chugoku +1.24% (0.061)	Kanto +1.14% (0.039)	Kinki +0.44% (1.000)	Kyushu +0.32% (1.000)
	Hokuriku 16.8%	Okinawa +9.70% (<0.001)	Hokkaido +8.34% (<0.001)	Chugoku +6.43% (<0.001)	Kanto +4.61% (<0.001)	Tokai +3.52% (0.003)	Kyushu +2.41% (0.083)	Kinki +1.42% (1.000)	Shikoku +0.88% (1.000)	Tohoku +0.86% (1.000)
LLR	Shikoku 6.7%	Kinki +7.20% (<0.001)	Chugoku +5.85% (<0.001)	Kyushu +5.23% (<0.001)	Okinawa +5.13% (<0.001)	Hokuriku +3.67% (<0.001)	Hokkaido +2.81% (<0.001)	Kanto +2.46% (<0.001)	Tokai +2.12% (0.001)	Tohoku +0.56% (1.000)
	Chugoku 10.5%	Kanto +8.31% (<0.001)	Kinki +5.69% (<0.001)	Hokkaido +5.05% (<0.001)	Hokuriku +4.05% (<0.001)	Tokai +3.40% (<0.001)	Shikoku +3.12% (<0.001)	Kyushu +1.61% (0.010)	Okinawa +1.42% (1.000)	Tohoku +1.26% (0.195)
TACE/TAE	Hokkaido 26.6%	Hokuriku +11.23% (<0.001)	Tohoku +11.21% (<0.001)	Kyushu +9.99% (<0.001)	Okinawa +8.86% (<0.001)	Tokai +6.21% (<0.001)	Kanto +5.18% (<0.001)	Kinki +4.06% (0.010)	Chugoku +2.87% (0.015)	Shikoku +0.43% (1.000)

*1The difference in treatment frequency between each region compared with the lowest frequency region was calculated. *2Adjusted *p* values for each pairwise comparison are shown. The Bonferroni method was used to adjust for multiplicity. Abbreviations: ST, systemic therapy; OLR, open liver resection; LLR, laparoscopic liver resection; RFA, radiofrequency ablation; TACE/TAE, transarterial chemoembolization/transarterial embolization.

Table 3. Number of institutions certified by the Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS) in each Japanese region

Treatment	Hokkaido (<i>n</i> = 3,850)	Tohoku (<i>n</i> = 6,541)	Kanto (<i>n</i> = 25,319)	Tokai (<i>n</i> = 8,487)	Hokuriku (<i>n</i> = 2,103)	Kinki (<i>n</i> = 15,687)	Chugoku (<i>n</i> = 6,582)	Shikoku (<i>n</i> = 3,618)	Kyushu (<i>n</i> = 11,621)	Okinawa (<i>n</i> = 539)
Number of certified institutions	11	28	108	27	10	52	25	10	34	2
Number of patients	350	234	234	314	210	302	263	362	342	270

Data are expressed as numbers. The region with the highest number is shown in bold.

treatments such as neoadjuvant chemotherapy are categorized as chemotherapy instead of surgical treatment. This duration might have underestimated the number of patients receiving ST. Furthermore, analysis across individual medical facilities is not feasible, and data on certain rarely used medications are excluded to maintain confidentiality and anonymity of the NDB dataset.

In conclusion, although incidence of HCC differs in each Japanese region, most frequently performed treatments selected in each region remains consistent. This finding suggests that HCC treatments are mostly standardized across regions.

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

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

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Received July 29, 2025; Revised September 25, 2025; Accepted October 6, 2025.

Released online in J-STAGE as advance publication October 12, 2025.

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Molecular epidemiology of drug-resistant tuberculosis in Jiangxi Province, China, 2022–2023

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Abstract: Drug-resistant tuberculosis (DR-TB) poses a critical public health challenge in Jiangxi Province, China, where regional resistance patterns remain understudied. This retrospective study analyzed 9,041 suspected TB patients (2022–2023), identifying 3,104 *Mycobacterium tuberculosis* (*M. tuberculosis*) cases via PCR-reverse blot hybridization assay (PCR-REBA). Among *M. tuberculosis*-positive cases, 19.3% exhibited drug resistance, including mono- (9.2%), double- (4.6%), triple- (3.8%), and quadruple-drug resistance (1.7%). Males had higher odds of rifampicin (OR = 1.407, 95% CI: 1.086–1.824, $p = 0.01$) and isoniazid (OR = 1.959, 95% CI: 1.538–2.495, $p < 0.001$) resistance. Dominant mutations included *rpoB* Ser531Leu (32.1%) for rifampicin and *katG* Ser315Thr (53.6%) for isoniazid resistance. Extrapulmonary TB showed higher susceptibility than pulmonary TB (e.g., rifampicin: 93.47% vs. 87.25%, $p = 0.002$). These findings highlight the urgent need for rapid molecular diagnostics and targeted interventions in Jiangxi to address distinct DR-TB patterns and demographic disparities.

Keywords: tuberculosis, drug resistance, molecular epidemiology, *rpoB*, *katG*

1. Introduction

Tuberculosis (TB), an ancient and formidable disease, remains one of the world's most lethal public health challenges (1). The causative agent, *Mycobacterium tuberculosis* (*M. tuberculosis*), was first isolated and identified by the pioneering Dr. Robert Koch in 1882 (2). Historically, TB has been the leading cause of death from a single infectious disease, only surpassed by SARS-CoV-2 during the 2020–2021 pandemic, and consistently been the foremost cause of mortality attributed to a single infectious agent (3). According to the World Health Organization's annual Global Tuberculosis Report, an estimated 10.6 million people worldwide contracted TB in 2022, leading to the devastating loss of 1.6 million lives, including 5.8 million men, 3.5 million women, and 1.3 million children (4). Despite its widespread prevalence, tuberculosis — a disease primarily affecting the lungs — continues to be a significant contributor to global morbidity and mortality. Nevertheless, its curability and the existence of preventive measures offer a glimmer of hope (5). Approximately 90–95% of individuals with latent tuberculosis infection (LTBI) remain asymptomatic, and it is estimated that 5–10% of

these latent infections will progress to active tuberculosis (ATB) over their lifetimes (6). Drug-sensitive tuberculosis is typically treated with a six-month multi-drug regimen of first- and second-line antibiotics to prevent relapse and drug resistance; however, the treatment duration for drug-susceptible TB can extend up to nine months, challenging medication adherence and raising the risk of treatment failure and resistance (7).

The escalating issue of antimicrobial resistance, particularly in the form of multidrug-resistant tuberculosis (MDR-TB), is anticipated to significantly impact global healthcare delivery and contribute to a rise in attributable deaths, necessitating an urgent, multifaceted strategy to foster the development of new antimicrobials, enhance diagnostic capabilities, and ensure the judicious and regulated use of existing treatments (8). MDR-TB, characterized by resistance to at least rifampicin and isoniazid, poses a growing public health threat, particularly in Eastern Europe, Russia, Asia, and sub-Saharan Africa, where it is difficult to diagnose, leads to higher mortality and morbidity, and often results in severe post-TB lung damage, despite recent advancements in diagnostics and therapeutics (9). Drug susceptibility testing is crucial for

accurately diagnosing MDR-TB, traditionally achieved through phenotypic methods that involve isolating *M. tuberculosis* from patient sputum and testing its growth in the presence of anti-TB drugs, but these methods are time-consuming, costly, and complex, often rendering them inaccessible in resource-limited settings (10). The spoligotyping technique has been successfully applied for detecting resistance-related mutations, and molecular diagnostic tools such as the PCR-based reverse blot hybridization assay (PCR-REBA) have been developed to address these challenges (11). PCR-REBA offers rapid detection of antimicrobial resistance genes in clinical specimens, which is particularly advantageous for timely and accurate diagnosis of drug-resistant tuberculosis (DR-TB).

This study aims to conduct a molecular epidemiology analysis of DR-TB circulation from clinical specimens obtained from patients in Jiangxi Province, China from April 2022 to December 2023. Employing PCR reverse dot hybridization technology, it systematically identified mutant genes associated with resistance to rifampicin, isoniazid, streptomycin, and ethambutol, focusing on specific mutations in key genes. This approach specifically targeted key gene mutations, including *rpoB*, *katG*, *fabG1*, *rpsL*, and *embB*, which are known to be associated with resistance to first-line TB drugs. By elucidating the molecular epidemiology of DR-TB in Jiangxi Province, the findings aim to inform the development of more effective strategies for prevention, diagnosis, and treatment of this critical public health issue.

2. Materials and Methods

2.1. Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was granted by the Ethics Committee of Jiangxi Province Chest Hospital (Jiangxi Third People's Hospital) with a waiver of informed consent due to the retrospective nature of the research and the use of anonymized data collected as part of routine clinical care.

2.2. Study design, site, and population

This research focused on TB and suspected TB patients admitted to the designated TB hospital in Jiangxi Province (the Third People's Hospital of Jiangxi Province, China) from April 2022 to December 2023. The patient data was collected and evaluated from archived results for the specimens detected using PCR-REBA. During the study period, patients were included if they were clinically suspected of TB and had PCR-REBA results. Only initial test results were analyzed for patients with multiple tests. Pulmonary TB was defined as *M. tuberculosis* detected in lung specimens; extrapulmonary TB involved other sites.

Prior treatment history was unavailable for retrospective analysis.

2.3. Specimen collection

All specimens were obtained from patients clinically suspected of having TB, encompassing various bodily secretions or fluids such as sputum cultures, nasopharyngeal swabs, bronchoalveolar lavage, lymph node aspirates, cerebrospinal fluid, and pleural fluid, as well as tissue samples including fine-needle aspirations, pleural biopsies, and lung biopsies.

2.4. Specimen processing

Purulent specimens, such as sputum, purulent fiberoptic bronchoscopy samples, and purulent pleural fluid, were treated with an equal volume of 4% NaOH and incubated for 10 minutes. After centrifugation at 12,000g for 5 minutes, the supernatant was removed. Solid specimens, including tissue and biopsy samples, were homogenized with an equal volume of sterile water. Fluid specimens, such as urine, cerebrospinal fluid (CSF), and clear pleural fluid, were centrifuged at 12,000g for 5 minutes, followed by the removal of the supernatant. After a subsequent centrifugation at 12,000g for 3 minutes, the supernatant was discarded.

2.5. DNA isolation

The bacterial pellet was resuspended in DNA lysis solution (Yaneng BioSciences, Shenzhen, China), followed by incubation at 100 °C for 10 minutes. Subsequently, the mixture was centrifuged at 12,000 r/min for 3 minutes. The resulting supernatant, containing genomic DNA, was either utilized immediately or stored at -80°C for subsequent analysis.

2.6. Real-time polymerase chain reaction (PCR)

Five microliters of each DNA sample were carefully added to the PCR tubes provided by Yaneng BioSciences, Shenzhen, China. These tubes were pre-filled with a reaction mixture comprising primers, TaqMan polymerase, and dNTPs. The experimental protocol and the real-time PCR program on the ABI instrument were set up as detailed below: The procedure began with an initial incubation at 50°C for 2 minutes, followed by a single cycle. The temperature was gradually increased from 50°C to 95°C at a rate of 1.4°C per second. This was maintained at 95°C for 10 minutes, completing the initial cycle. Subsequently, a denaturation step was carried out at 95°C for 45 seconds, transitioning to 62°C at a rate of 1.4°C per second, and then an annealing/extension step at 60°C for 30 seconds, which was repeated for 30 cycles. Following this, the temperature was ramped up from 62°C to 95°C at 1.4°C

per second, denaturing at 95°C for 30 seconds. It then transitioned from 95°C to 54°C at a rate of 1.4°C per second, annealed at 54°C for 30 seconds, and extended at 68°C for 45 seconds, repeated for another 30 cycles. The program concluded with a final extension at 68°C for 5 minutes. The reaction mixture was then prepared to detect the amplification of the target bacterial DNA using the 7500 Real-Time PCR System from Thermo Fisher Scientific in Waltham, MA, USA. The analysis of real-time PCR results was facilitated by Real-Time PCR Software, version 1.2.3. The amplification plots were reviewed for baseline and threshold value adjustments to ensure accuracy.

2.7. PCR-reverse blot hybridization assay (PCR-REBA Myco-ID)

The amplified PCR products were analyzed for the identification of DR-TB using the PCR-REBA Myco-ID kit (Yaneng BioSciences, Shenzhen, China), in accordance with the manufacturer's protocol.

2.7.1. Hybridization

The nylon membrane strip, labeled with probes, was placed into a 15ml conical centrifuge tube. It was then gently mixed with 5ml of a hybridization buffer, which consisted of 1x SSC (Saline Sodium Citrate) and 0.1% SDS (Sodium Dodecyl Sulfate). Additionally, 25µl of PCR product was incorporated into the mixture. The tube was securely capped and submerged in a boiling water bath set at 100°C for a duration of 10 minutes, ensuring that the hybridization liquid remained below the water level. After this pre-treatment, the tube was transferred to a hybridization box and maintained at a temperature of 59°C for 1.5 hours to facilitate the hybridization process.

2.7.2. Washing strips

A 40 mL volume of wash buffer, comprising 0.5x SSC and 0.1% SDS, was transferred into a 50 mL conical centrifuge tube equipped with a screw-top cap and preheated to 57°C within a water bath. Subsequently, the membrane strips were carefully removed from the 15 mL tube and immersed into the preheated wash buffer at 57°C, where they were subjected to gentle shaking for a duration of 15 minutes.

2.7.3. Colorimetric analysis

The strips were immersed in a 1:2,000 dilution of hybridization buffer for 30 minutes at ambient temperature. Subsequently, they were rinsed twice, each for 5 minutes, with the hybridization buffer at room temperature, followed by a brief cleaning in 0.1 mol/L sodium citrate for 2 minutes. The strips were then treated with a freshly prepared substrate solution consisting of

0.01% w/v tetramethylbenzidine dihydrochloride (TMB) (Yaneng BioSciences, Shenzhen, China) and 0.006% v/v hydrogen peroxide in 0.1M sodium citrate, while kept in the dark for 10 minutes. The color development process was halted by gently rinsing the membranes with distilled water, after which the band pattern of the colorimetric hybridization was visually assessed.

2.8. Statistical analysis

The statistical analysis was conducted using SPSS 27.0. Variables (age, sex, TB type) were selected based on known DR-TB risk factors identified in prior literature. Univariate logistic regression was performed to assess associations between demographic factors (age groups, sex) and resistance to individual drugs (rifampicin, isoniazid, streptomycin, and ethambutol), with the ≥ 65 age group and females as reference categories. Multivariable logistic regression adjusted for potential confounders, including age and sex, to isolate independent effects. Prevalence estimates were reported with 95% confidence intervals (CIs). To address multiple comparisons, Bonferroni correction was applied, and a significance threshold of $p < 0.05$ was maintained. Categorical data were presented as frequencies and percentages, and chi-square tests compared susceptibility patterns between pulmonary and extrapulmonary TB. Adjusted p -values and CIs for odds ratios (ORs) were included to ensure robust inference. All analyses were conducted using anonymized data to ensure patient confidentiality.

3. Results

3.1. Prevalence and patterns of DR-TB

Among the 9,041 nonrepeating patients included in the study, *M. tuberculosis* infection was identified in 3,140 cases (34.7%) via PCR-REBA, of which 599 (19.1%) exhibited DR-TB (Figure 1). The resistance patterns among the 3,140 *M. tuberculosis*-positive cases were as follows: 287 (9.2%) were resistant to a single first-line anti-tuberculosis drug (mono-resistant TB), 142 (4.6%) to two drugs (double-drug resistant TB), 118 (3.8%) to three drugs (triple-drug resistant TB), and 52 (1.7%) to all four first-line drugs (quadruple-drug resistant TB) (Table 1). The remaining 2,505 cases (80.6%) were susceptible to all tested drugs.

3.2. Age and gender disparities in DR-TB

Univariate logistic regression analysis revealed that, compared to the ≥ 65 years group, rifampicin resistant TB showed a significant difference in the 45–54 years group (OR = 1.497, 95% CI: 1.079–2.077, $p = 0.016$) (Table 2), but no significant differences were observed in other age groups. Similarly, compared to females,

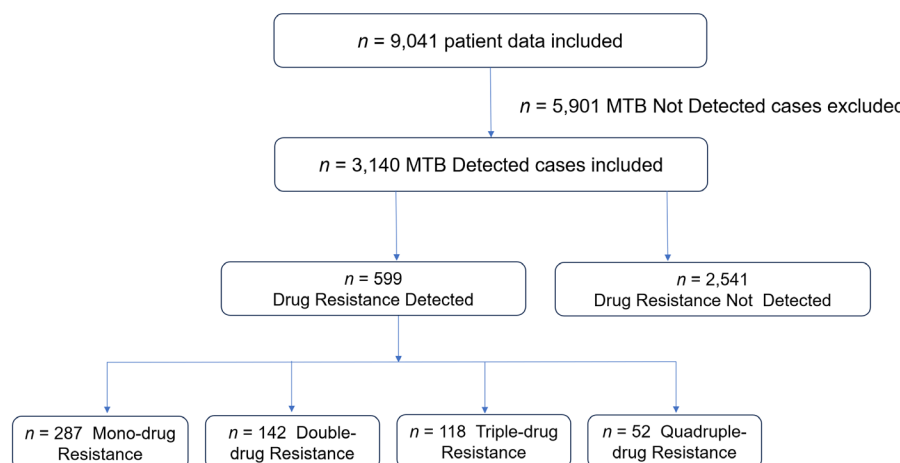


Figure 1. Schematic overview of the study's analysis on the circulation of DR-TB. DR-TB: drug-resistant tuberculosis.

Table 1. Resistance patterns of *M. tuberculosis* strains to first-line drugs

Types of DR-TB	Cases (n)	Frequency (%)
Mono-drug resistant TB	287	9.2
Double-drug resistant TB	142	4.6
Triple-drug resistant TB	118	3.8
Quadruple-drug resistant TB	52	1.7
Total DR-TB	599	19.3
Total <i>M. tuberculosis</i> -positive cases	3,104	100

DR-TB: drug-resistant tuberculosis; TB: tuberculosis.

rifampicin resistant TB was significantly more prevalent in males (OR = 1.407, 95% CI: 1.086–1.824, $p = 0.01$). In contrast, isoniazid resistant TB did not show significant differences across age groups when compared to the ≥ 65 years group. However, isoniazid resistant TB was significantly more common in males compared to females (OR = 1.959, 95% CI: 1.538–2.495, $p < 0.001$). Additionally, streptomycin resistant TB did not exhibit significant differences across age groups or between sexes. Regarding ethambutol resistant TB, a significant difference was observed in the 35–44 years group compared to the ≥ 65 years group (OR = 2.050, 95% CI: 1.050–4.002, $p = 0.035$), but no such differences were found in other age groups. Similarly, ethambutol resistant TB was significantly more prevalent in males compared to females (OR = 1.748, 95% CI: 1.065–2.869, $p = 0.027$).

3.3. Comparative analysis of antibiotic susceptibility in pulmonary and extrapulmonary TB

In this study, it compared the distribution of susceptibility and resistance patterns to four anti-TB drugs (rifampicin, isoniazid, streptomycin, and ethambutol) in pulmonary and extrapulmonary TB cases. For rifampicin, most pulmonary cases (87.25%) were susceptible, whereas a higher proportion of extrapulmonary cases (93.47%) showed susceptibility (Table 3). Conversely, resistance

was more frequent in pulmonary cases (12.75%) compared to extrapulmonary cases (6.53%). The χ^2 test confirmed a statistically significant difference ($\chi^2 = 9.557$, $p = 0.002$). Similarly, for isoniazid, pulmonary cases exhibited a susceptibility rate of 86.59%, while extrapulmonary cases had a slightly higher rate of 92.03%. Resistance was more common in pulmonary cases (13.41%) than in extrapulmonary cases (7.97%), with the difference being statistically significant ($\chi^2 = 6.602$, $p = 0.01$). For streptomycin, susceptibility rates were 90.99% in pulmonary cases and 94.53% in extrapulmonary cases, while resistance was more prevalent in pulmonary cases (9.01%) compared to extrapulmonary cases (5.47%). The χ^2 test showed a borderline significant difference ($\chi^2 = 3.926$, $p = 0.048$). Lastly, ethambutol demonstrated high susceptibility rates in both groups, with 96.17% in pulmonary cases and 98.87% in extrapulmonary cases. Resistance was minimal, with only 3.83% and 1.13% observed in pulmonary and extrapulmonary cases, respectively. The difference was statistically significant ($\chi^2 = 5.119$, $p = 0.024$).

3.4. Genetic mutations associated with rifampicin and isoniazid resistance

Analysis of 599 drug-resistant *M. tuberculosis* isolates revealed that mutations in the *rpoB* gene serve as the principal genetic basis for rifampicin resistance. Within the rifampicin resistance-determining region (RRDR), the most frequently observed mutation was *Ser531Leu*, accounting for 32.1% (192/599) of cases (Table 4). Additional mutations included *His526Asp* (11.0%, 66/599), *Asp516Val* (4.8%, 29/599), *Asp516Gly* (3.8%, 23/599), and *His526Tyr* (4.7%, 28/599). A rare variant, *Ser531Trp*, was detected in only 0.8% (5/599) of isolates. Resistance to isoniazid was primarily linked to mutations in the *katG* and *fabG1* genes. The *katG Ser315Thr* mutation, which confers high-level isoniazid resistance,

Table 2. Logistic regression analysis of socio-demographic factors associated with DR-TB

Types of DR-TB	Socio-demographic characteristics	Univariable Analysis*		Multivariable Analysis**	
		Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
Rifampicin Resistant	Age				
	0–14	1.077 (0.318–3.655)	0.905	1.249 (0.366–4.266)	0.723
	15–24	0.833 (0.555–1.252)	0.380	0.890 (0.590–1.341)	0.576
	25–34	1.050 (0.719–1.534)	0.799	1.114 (0.761–1.632)	0.578
	35–44	1.331 (0.908–1.952)	0.142	1.410 (0.959–2.073)	0.080
	45–54	1.471 (1.061–2.039)	0.021	1.497 (1.079–2.077)	0.016
	55–64	1.275 (0.935–1.740)	0.125	1.266 (0.927–1.727)	0.138
	≥ 65	1.000		1.000	
	Sex				
	Male	1.418 (1.100–1.828)	0.007	1.407 (1.086–1.824)	0.010
Isoniazid Resistant	Female	1.000		1.000	
	Age				
	0–14	1.376 (0.465–4.076)	0.564	1.626 (0.571–4.63)	0.362
	15–24	0.732 (0.482–1.112)	0.144	0.842 (0.559–1.269)	0.412
	25–34	1.005 (0.687–1.470)	0.981	1.108 (0.764–1.605)	0.589
	35–44	1.322 (0.902–1.937)	0.153	1.270 (0.878–1.837)	0.205
	45–54	1.433 (1.036–1.982)	0.030	1.038 (0.760–1.417)	0.814
	55–64	1.278 (0.942–1.735)	0.115	1.038 (0.773–1.394)	0.803
	≥ 65	1.000		1.000	
	Sex				
Streptomycin Resistant	Male	1.310 (1.021–1.68)	0.033	1.959 (1.538–2.495)	< 0.001
	Female	1.000		1.000	
	Age				
	0–14	0		0	
	15–24	0.680 (0.420–1.102)	0.118	0.702 (0.431–1.141)	0.153
	25–34	0.680 (0.420–1.102)	0.118	0.699 (0.430–1.136)	0.149
	35–44	1.111 (0.713–1.731)	0.643	1.139 (0.729–1.781)	0.567
	45–54	1.280 (0.883–1.856)	0.193	1.289 (0.888–1.869)	0.181
	55–64	1.007 (0.702–1.445)	0.969	1.003 (0.699–1.438)	0.989
	≥ 65	1.000		1.000	
Ethambuto Resistant	Sex				
	Male	1.245 (0.928–1.670)	0.144	1.168 (0.865–1.577)	0.310
	Female	1.000		1.000	
	Age				
	0–14	1.440 (0.187–11.108)	0.726	1.807 (0.232–14.098)	0.573
	15–24	1.337 (0.669–2.671)	0.410	1.481 (0.737–2.973)	0.270
	25–34	1.407 (0.715–2.767)	0.323	1.549 (0.784–3.061)	0.208
	35–44	1.885 (0.970–3.665)	0.062	2.050 (1.050–4.002)	0.035
	45–54	1.665 (0.911–3.043)	0.098	1.708 (0.934–3.125)	0.082
	55–64	1.003 (0.531–1.894)	0.993	0.989 (0.524–1.869)	0.974
	≥ 65	1.000		1.000	
	Sex				
	Male	1.587 (0.976–2.579)	0.062	1.748 (1.065–2.869)	0.027
	Female	1.000		1.000	

*Univariate analysis: Crude odds ratios for demographic factors associated with DR-TB. **Multivariable analysis: Adjusted for age, sex, and tuberculosis type. DR-TB: drug-resistant tuberculosis.

Table 3. Antibiotic susceptibility patterns in pulmonary and extra-pulmonary TB cases

Drugs	Groups	Pulmonary Cases (%)	Extra pulmonary Cases (%)	Total	χ^2	p-value
Rifampicin	Susceptible	2,477 (87.25)	272 (93.47)	2,749	9.557	0.002
	Resistant	362 (12.75)	19 (6.53)	381		
Isoniazid	Susceptible	2,356 (86.59)	254 (92.03)	2,610	6.602	0.010
	Resistant	365 (13.41)	22 (7.97)	387		
Streptomycin	Susceptible	2,484 (90.99)	259 (94.53)	2,743	3.926	0.048
	Resistant	246 (9.01)	15 (5.47)	261		
Ethambuto	Susceptible	2,533 (96.17)	263 (98.87)	2,796	5.119	0.024
	Resistant	101 (3.83)	3 (1.13)	104		

TB: tuberculosis.

Table 4. Frequency of SNPs in *rpoB*, *katG*, and *fabG1* genes among rifampicin- and isoniazid-resistant TB

Gene	SNP*	Cases (n)	Frequency (%)
<i>rpoB</i>	<i>Asp516Val</i>	29.0	4.8
<i>rpoB</i>	<i>Asp516Gly</i>	23.0	3.8
<i>rpoB</i>	<i>His526Tyr</i>	28.0	4.7
<i>rpoB</i>	<i>His526Asp</i>	66.0	11
<i>rpoB</i>	<i>Ser531Leu</i>	192.0	32.1
<i>rpoB</i>	<i>Ser531Trp</i>	5.0	0.8
<i>katG</i>	<i>Ser315Thr</i>	321	53.6
<i>fabG1</i>	<i>c.-15C>T</i>	67	11.2
Total		599	100

*SNP: single nucleotide polymorphism.

was the most prevalent (53.6%, 321/599). Meanwhile, the *fabG1 c.-15C>T* variant — associated with low-level resistance due to *inhA* promoter upregulation — was identified in 11.2% (67/599) of isolates.

4. Discussion

The molecular epidemiology of DR-TB in Jiangxi Province, China, presents distinct characteristics that both align with and diverge from patterns observed in other regions of China and globally. The present study, conducted from April 2022 to December 2023, revealed a DR-TB prevalence of 19.3% among *M. tuberculosis* positive cases, aligning with Hubei Province's reported rate (19.3%) but markedly higher than the 10.5% observed among students in Henan Province (12,13). However, Jiangxi's resistance profile demonstrates unique traits. Notably, mono-resistant TB accounted for 9.2% of cases in this study, mirroring a rising trend observed in neighboring Hubei — where mono-resistance increased from 8.5% (2020) to 12.9% during a similar period (12). These parallels between the two adjacent provinces suggest potential regional epidemiological linkages. Additionally, while the study data showed the *rpoB Ser531Leu* mutation as the most prevalent rifampicin resistance determinant (32.1%), studies from Zhejiang Province reported codon 526 mutations as dominant (> 75% of cases), with *Ser531Leu* being rare (< 5%) (14). These regional variations underscore the importance of localized surveillance and tailored intervention strategies.

The demographic patterns of DR-TB in Jiangxi provide further insights into the province's unique epidemiological landscape. The present findings confirmed the global trend of higher TB incidence among males (15,16), with male patients showing significantly greater susceptibility to both rifampicin (OR = 1.407, $p = 0.01$) and isoniazid resistance (OR = 1.959, $p < 0.001$). This gender disparity may be exacerbated in Jiangxi by factors such as higher smoking rates and occupational exposures among male populations. Age-specific analysis revealed that individuals aged 45–54 years had significantly higher rifampicin resistance (OR = 1.497, $p = 0.016$) compared to those ≥ 65 years, a pattern that

aligns with studies from Shandong Province (17); but contrasts with data from Western populations where elderly patients typically show higher resistance rates (18). This suggests that middle-aged adults in Jiangxi may represent a particularly vulnerable group, possibly due to chronic infection or treatment interruption during peak working years.

The mutation profile of DR-TB strains in Jiangxi offers critical insights for both diagnosis and treatment. The high frequency of the *katG Ser315Thr* mutation (53.6%), associated with high-level isoniazid resistance, has important clinical implications. This mutation renders standard isoniazid therapy ineffective (19), necessitating alternative regimens for affected patients. Particularly concerning is that this mutation reduces the efficacy of bedaquiline and linezolid-containing short-course MDR-TB regimens (20), which are increasingly used in China. The *fabG1 c.-15C>T* mutation, though less common (11.2%), presents a distinct challenge. This mutation confers low-level isoniazid resistance through *inhA* promoter upregulation (21) and responds to higher isoniazid doses, suggesting that routine detection of this mutation could guide more effective, personalized treatment strategies in Jiangxi. For instance, clinicians could consider escalating isoniazid doses or combining it with other agents like ethionamide, which targets the same pathway, to overcome resistance in cases harboring this mutation. The clinical significance of these findings is heightened by this observation that 8.7% of DR-TB cases showed quadruple-drug resistance, indicating the emergence of particularly challenging strains that may require novel therapeutic approaches.

Comparative analysis with national and global data reveals both consistencies and unique aspects of Jiangxi's DR-TB situation. While the *rpoB Ser531Leu* mutation's dominance in Jiangxi (32.1%) aligns with findings from Guizhou (22) and Changchun (23), its prevalence is markedly higher than in Zhejiang (14) and lower than in Northern Morocco (34.46%) (24) or Uganda (40%) (25). These differences likely reflect variations in treatment practices, strain genotypes, and population immunity. The rare occurrence of *Ser531Trp* (0.8%) in Jiangxi compared to Brazil (26) further suggests distinct evolutionary pressures or transmission patterns. Such regional variations emphasize the need for Jiangxi-specific resistance databases to inform clinical decision-making and public health planning.

The differential drug susceptibility between pulmonary and extrapulmonary TB cases in Jiangxi has important clinical implications. This study found significantly higher susceptibility rates in extrapulmonary cases across all first-line drugs, most notably for rifampicin (93.47% vs. 87.25%, $p = 0.002$) and isoniazid (92.03% vs. 86.59%, $p = 0.01$). This pattern, consistent with global reports (27), may reflect lower bacterial burdens in extrapulmonary sites or better drug penetration (28). These findings suggest that

standard first-line regimens may be more effective for extrapulmonary TB in Jiangxi, while pulmonary cases may require more aggressive monitoring and tailored regimens. The minimal resistance to ethambutol in both groups (3.83% pulmonary, 1.13% extrapulmonary) supports its continued use as a cornerstone of TB treatment in Jiangxi (29), though the emergence of even low-level resistance warrants vigilance.

The public health implications of these findings are substantial. The high prevalence of specific mutations like *rpoB Ser531Leu* and *katG Ser315Thr* suggests that molecular diagnostics should be prioritized in Jiangxi's TB control program. Techniques like PCR-REBA (11), used in this study, offer rapid detection of these mutations, and could significantly improve treatment outcomes. The data also highlight the need for targeted interventions for high-risk groups, particularly middle-aged males, who showed elevated resistance rates. The presence of *fabG1* mutations, though less common, underscores the value of comprehensive genetic testing to detect all resistance mechanisms, as these mutations may respond differently to treatment adjustments.

Looking forward, the study identifies several critical research needs for Jiangxi Province. Whole-genome sequencing could elucidate transmission networks and evolutionary pathways of resistant strains, as demonstrated in studies from Santa Catarina, Brazil (26). Investigation of social determinants, particularly factors driving the high resistance rates among middle-aged adults, could inform targeted interventions. The development of localized treatment algorithms incorporating Jiangxi's specific mutation patterns would optimize therapeutic outcomes. Additionally, continuous surveillance is essential to monitor emerging resistance patterns, especially given the province's economic development and increasing population mobility.

In conclusion, the present study provides a comprehensive molecular epidemiological profile of DR-TB in Jiangxi Province, revealing both shared and unique characteristics compared to other regions. The high prevalence of specific resistance mutations, demographic disparities in resistance patterns, and differential susceptibility between pulmonary and extrapulmonary cases all have immediate implications for TB control policies in Jiangxi. These findings underscore the necessity of implementing rapid molecular diagnostics, developing mutation-specific treatment guidelines, and tailoring interventions to high-risk populations. As DR-TB continues to evolve in Jiangxi, ongoing surveillance and research will be crucial to maintain progress toward TB elimination goals. The distinct patterns observed in the study highlight the importance of region-specific approaches in the global fight against DR-TB.

Acknowledgements

We thank all participants for their contributions and

extend our gratitude to the medical staff at Jiangxi Province Chest Hospital for their invaluable assistance.

Funding: This work was supported by a grant from Jiangxi Provincial Health Technology Project (Grant No. SKJP1220240338).

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

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- Received June 8, 2025; Revised August 14, 2025; Accepted September 1, 2025.
- Released online in J-STAGE as advance publication September 6, 2025.
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Coronary artery stenosis in Japanese hemophiliacs living with HIV-1 progressed dramatically over two years

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Abstract: Patients with hemophilia living with HIV-1 are at increased risk for coronary artery disease (CAD) due to overlapping factors, including chronic vascular inflammation, antiretroviral therapy-associated dyslipidemia, and reduced physical activity from hemophilic arthropathy. However, longitudinal data on cardiovascular outcomes in this population have been scarce. In this two-year longitudinal follow-up study, 58 patients were evaluated. The cohort was stratified into three groups based on baseline CCTA findings and treatment history: 47 with normal-to-mild stenosis, 3 with prior PCI or CABG, and 8 with moderate-to-severe stenosis. Among the moderate stenosis group, 7 underwent repeat CCTA, and 4 showed progression of coronary lesions. Of these, 3 developed severe stenosis requiring percutaneous coronary intervention (PCI), despite improvement in LDL-C through pharmacologic and lifestyle interventions. Overall, LDL-C significantly decreased ($p < 0.05$); however, pulse wave velocity (PWV), an indicator of arterial stiffness, worsened in about half of patients. In the revascularization group, PWV deterioration was significant ($p = 0.017$). Our earlier cross-sectional analysis of this population demonstrated that a considerable proportion had moderate-to-severe stenosis requiring intervention, underscoring the need for longitudinal assessment. These findings suggest that even under guideline-based cardiovascular management, there remains a considerable risk for CAD progression in HIV-infected hemophilia patients with moderate or greater stenosis. Therefore, repeat CCTA at two-year follow-up could be considered to facilitate early detection and guide timely intervention. Continuous monitoring, including imaging, and early intervention targeting modifiable risk factors may be important to reduce long-term cardiac risk in this vulnerable population.

Keywords: hemophilia, HIV-1, coronary artery disease, coronary computed tomography angiography, vascular inflammation, pulse wave velocity

1. Introduction

Hemophilia and HIV-1 infection are two distinct chronic conditions affecting Japanese hemophiliacs living with HIV-1 (JHLH). Traditionally, hemophilia has been considered protective against coronary artery disease (CAD) due to the inherent hypocoagulable state (1). However, recent advances in treatment have significantly extended life expectancy in these individuals, and recent epidemiological studies suggest that the incidence of CAD in hemophiliacs is now comparable to that of the general male population (2,3). Hemophiliacs often develop joint deformities from recurrent hemarthroses, limiting activity and masking CAD until advanced stages.

In addition to the risk imposed by hemophilia,

HIV infection further elevates the risk of CAD. This is attributed to chronic vascular inflammation and dyslipidemia, both of which are exacerbated by antiretroviral therapy (4). Thus, JHLH may represent a population at high risk of silent or rapidly progressive atherosclerosis.

In our previous Hem-IHD study conducted from December 2018 to December 2019, coronary computed tomography angiography (CCTA) identified moderate or severe coronary stenosis in 24.6% (14 of 57) of JHLH (5). Among the 12 patients who underwent coronary angiography (CAG), 7 required therapeutic intervention, including percutaneous coronary intervention (PCI) in 5 patients and coronary artery bypass grafting (CABG) in 1 patient. These findings raised concerns about CAD progression in this high-risk population, especially

among patients managed only with medication. Over two years have passed since initial screening, necessitating follow-up.

Despite the absence of significant stenosis in certain patients, the overall cardiovascular risk remains elevated, and ongoing risk assessment and management are crucial. While pharmacological interventions were initiated in the prior study, their long-term efficacy has not yet been systematically evaluated. Therefore, this study aims to assess the progression of CAD and the effectiveness of medical management in JHLH through longitudinal follow-up, with the goal of informing appropriate screening and intervention strategies in this vulnerable population.

2. Patients and Methods

2.1. Patients

Patients were classified into three groups: the first group included those with normal to mild stenosis; the second group included patients who had undergone PCI or CABG; and the third group comprised patients with moderate-to-severe stenosis on CCTA.

In the first group, which showed normal to mild stenosis, cardiovascular risk was assessed, and efforts were made to control modifiable risk factors. When necessary, medical therapy and lifestyle guidance were provided, and their effects evaluated. Patients with prior PCI or CABG were managed with risk factor control, and effectiveness assessed.

The third group consists of patients who were previously identified with moderate-to-severe coronary artery stenosis on CCTA and had been managed with

medical therapy alone. These patients underwent follow-up CCTA and cardiovascular risk assessment. If progression was identified, appropriate treatment was given. As HIV infection promotes vascular inflammation, inflammatory biomarkers were assessed in all participants.

This exploratory study, without a predefined endpoint, aimed to observe CAD progression in JHLH under routine care over two years.

2.2. Statistical analysis

Two-year changes in LDL-C, PWV, and HbA1c were assessed using paired *t*-tests in the overall cohort (*n* = 58). For CACS, available in a small subset of patients (*n* = 7), the Wilcoxon signed-rank test was used due to the small sample size and non-normal distribution. For Table 1, baseline characteristics were compared. Continuous variables were analyzed using the Mann–Whitney *U* test. Categorical variables were compared using the chi-square test. If expected cell frequencies were < 5 in > 20% of cells, Fisher's exact test was used. Analyses were conducted using SPSS version 26 (SPSS Inc., Chicago, IL, USA). A two-sided *p* value of < 0.05 was considered statistically significant.

2.3. Ethical considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. The study protocol was reviewed and approved by the Ethics Committee of Japan Institute for Health Security (JIHS), and was registered under the

Table 1. Baseline characteristics of patients with normal-to-mild vs. moderate-to-severe stenosis or prior PCI/CABG

Demographics and variables	Normal-to-mild stenosis (<i>n</i> = 47)	Moderate-to-severe stenosis (<i>n</i> = 11)	<i>p</i> -value
Age, median year (range)	47 (42–69)	62 (53–66)	0.07
BMI kg/m ² , median (IQR)	22.9 (20.2–24.2)	24.7 (22.4–26.4)	0.19
CAD risk factors			
Smoking history, <i>n</i> (%)	22 (46.8)	5 (45.5)	1.00
Hypertension, <i>n</i> (%)	24 (51.0)	5 (45.5)	1.00
Diabetes mellitus, <i>n</i> (%)	5 (10.6)	3 (27.3)	0.17
Dyslipidaemia, <i>n</i> (%)	20 (42.6)	7 (63.6)	0.32
Family history of CAS, <i>n</i> (%)	9 (19.1)	5 (45.5)	0.11
LVEF %, median (IQR)	64.6 (61.6–67.4)	65.4 (63.7–66.2)	0.64
PWV cm/sec, median (IQR)	1,425 (1,311–1,548)	1,653 (1,329–1,921)	0.13
HIV-related indicators			
Nadir CD4/μL, median (IQR)	130 (92–162)	112 (90–188)	0.64
Current CD4/μL, median (IQR)	461 (367–582)	399 (297–542)	0.18
Duration of undetectable VL, median year (IQR)	14.5 (11.5–17.8)	15.3 (7.2–17.5)	0.64
Duration of treatment for HIV, median year (IQR)	28 (25–30)	22 (20–28)	0.63
Duration of PI use, median year (IQR)	10 (3–17)	13.5 (1.6–18)	0.47
Duration of d-drug use, median year (IQR)	5.8 (0.2–9.1)	37 (0–90.5)	0.65
Hepatitis B, <i>n</i> (%)	3 (6.4)	1 (9.1)	1.00
Hepatitis C, <i>n</i> (%)	45 (95.7)	11 (100)	1.00

Abbreviations: BMI, body mass index; CAS, coronary artery stenosis; *n*, number; IQR, interquartile range; LVEF, left ventricular ejection fraction; PWV, pulse wave velocity; VL, viral load; PI, protease inhibitor; -drug, didanosine, zalcitabine, and stavudine.

approval number [NCGM-G-004171-00].

3. Results and Discussion

3.1. Overall evaluation over two years

A total of 58 patients participated in this study. The study population consisted of 47 patients with normal-to-mild stenosis on CCTA, 3 patients who had undergone therapeutic intervention in a previous study, and 8 patients with moderate-to-severe stenosis on CCTA, of whom 7 consented to repeat CCTA (Figure 1).

Characteristics were compared between normal-to-mild ($n = 47$) and moderate-to-severe or PCI/CABG patients ($n = 11$) (Table 1). Because of the small sample sizes in the moderate-to-severe stenosis group ($n = 8$) and the revascularization group ($n = 3$), these two groups were combined for statistical analysis. Continuous variables were expressed as median (IQR), except inflammatory markers as mean $\pm$ SD. Categorical variables were presented as counts and percentages. No statistically significant differences were observed between the two groups for any of the variables. A trend toward higher age was seen in the moderate-to-severe or PCI/CABG group ($p = 0.07$). Cardiovascular risk in JHLH was managed over a two-year follow-up period. Patients who required medical intervention received appropriate medical treatment, while those with

parameters within normal limits were managed with lifestyle interventions including exercise and dietary therapy.

No significant changes were observed in PWV or HbA1c ($p = 0.35$ and 0.23). For HbA1c, no consistent differences were noted across subgroups, and PWV findings varied by subgroup. A significant reduction in low-density lipoprotein cholesterol (LDL-C) was observed ($p < 0.05$) (Figure 2).

3.2. Forty-seven patients with normal to mild stenosis determined by CCTA

Among the five patients with diabetes mellitus, three demonstrated an improvement in HbA1c levels during the observation period.

LDL-C levels improved in more than half of the 47 patients (26 out of 47) following the initiation or up-titration of statins and other lipid-lowering agents (9 patients), in combination with dietary and exercise counseling. LDL-C significantly decreased from 119.8 ± 28.8 to 107.9 ± 21.5 mg/dL ($p = 0.007$).

In patients with hypertension, initiation or intensification of antihypertensive medications (8 patients), combined with lifestyle interventions, led to an improvement in blood pressure and a trend toward PWV reduction, from $1,499 \pm 215$ cm/s to $1,478 \pm 268$ cm/s.

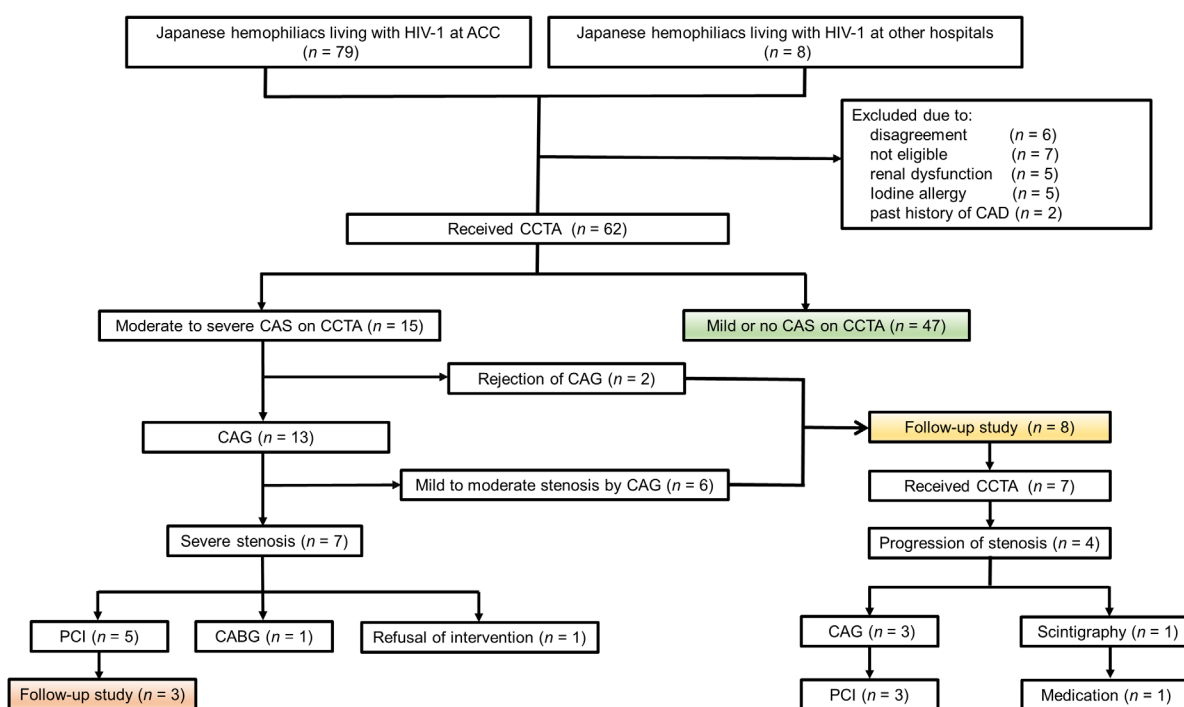


Figure 1. Study flow and patient selection. A total of 62 patients received screening tests. Of the 62 patients, 15 had moderate-to-severe stenosis at CCTA and 47 had no significant stenosis. Of the 15 patients with moderate-to-severe stenosis, 7 were determined to require treatment by CAG. Of the five patients who underwent PCI, three who gave consent participated in this study. Two patients who refused previous CAG and six patients who were not indicated for treatment also participated in this study. A total of 58 patients participated in the current 2-year follow-up. Abbreviations: CCTA, coronary computed tomography angiography; CAG, coronary angiography; PCI, percutaneous coronary intervention.

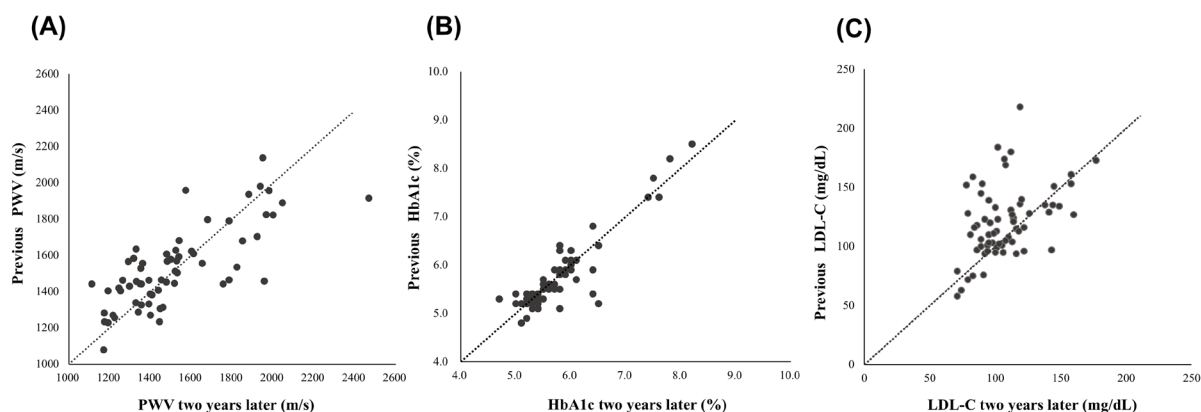


Figure 2. Scatter plot of PWV, HbA1c and LDL-C in 58 patients. (A) Scatter plot of PWV and (B) scatter plot of HbA1c, both showing no significant differences between the previous and current measurements; (C) Scatter plot of LDL-C, demonstrating a significant difference between the previous and current measurements. Scatter plots of PWV, HbA1c and LDL-C were created with previous values on the Y-axis and current values on the X-axis. Data points plotted to the left of the line of identity ($Y = X$) indicate improvement (decrease compared with baseline), while those to the right indicate worsening (increase compared with baseline). *Abbreviation:* PWV, pulse wave velocity.

3.3. Three patients who had undergone revascularization

In two patients who had undergone PCI in a previous study, follow-up coronary angiography at six months confirmed successful revascularization. The duration of dual antiplatelet therapy (DAPT) following drug-eluting stent (DES) implantation was approximately one month, with no reported bleeding complications associated with antiplatelet use. In patients who underwent CABG, graft patency was confirmed by CCTA at six months.

LDL-C levels improved in two patients following the initiation of statin therapy. In this small group of patients with a history of PCI or CABG, PWV significantly worsened during the observation period ($p = 0.017$).

3.4. Eight patients with suspected moderate or severe coronary artery stenosis on CCTA

Of the eight patients included in the study, two had a history of diabetes mellitus and were already receiving pharmacological treatment at baseline. Over the two-year observation period, one of these patients was instructed to initiate lifestyle modifications, including regular exercise and dietary changes, while continuing the same antidiabetic medication. As a result, the patient's HbA1c improved from 8.2% to 7.8%. The other patient had an increased dose of a sodium-glucose co-transporter 2 (SGLT2) inhibitor; however, no change in HbA1c was observed, remaining at 7.4%.

Following the initiation or up-titration of statins and ezetimibe, in combination with lifestyle counseling, all patients showed a significant improvement in LDL-C levels ($p = 0.020$).

Following dietary and exercise therapy instruction, PWV improved in 4 of the 8 patients. In contrast, 3 patients showed worsening, including one who initiated treatment with amlodipine during the study period.

In the remaining patient, PWV remained unchanged. Overall, the findings demonstrated heterogeneity, with no consistent group-level trend in PWV despite risk factor management. CCTA was performed in seven of the eight patients who provided informed consent. Despite improvements in LDL-C levels, progression of coronary stenotic lesions was suspected in four patients over the two-year period. Four patients showed progression of coronary artery stenosis, with stenosis rates increasing from 48.9% to 74.7% (Case 1), 45.9% to 75.7% (Case 2), 59.4% to 87.3%, and 32.5% to 90.1% (Case 3), respectively (Figure 3, A–C). In one patient, quantification of the degree of stenosis was difficult due to severe coronary artery calcification (Figure 3D).

Three patients (Cases 1, 2, and 3) subsequently underwent CAG, all of whom were deemed appropriate candidates for revascularization and received PCI. The other one patient underwent myocardial scintigraphy, which revealed no evidence of myocardial ischemia (Case 4).

High-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and intercellular adhesion molecule-1 (ICAM-1) were measured in all participants. However, in this study, we present only the cross-sectional data from the eight patients included in the follow-up CCTA cohort. Most values were within the respective reference ranges, and no consistent abnormalities or trends were identified; therefore, these results are reported descriptively. In the subset of patients with available CACS data ($n = 7$), a significant increase was observed over two years (median change: +32; $p = 0.043$, Wilcoxon signed-rank test). Given the small sample size, this result should be interpreted with caution.

3.5. Longitudinal progression of coronary artery stenosis in JHLH: Impact of risk factor management and the need for regular CCTA follow-up

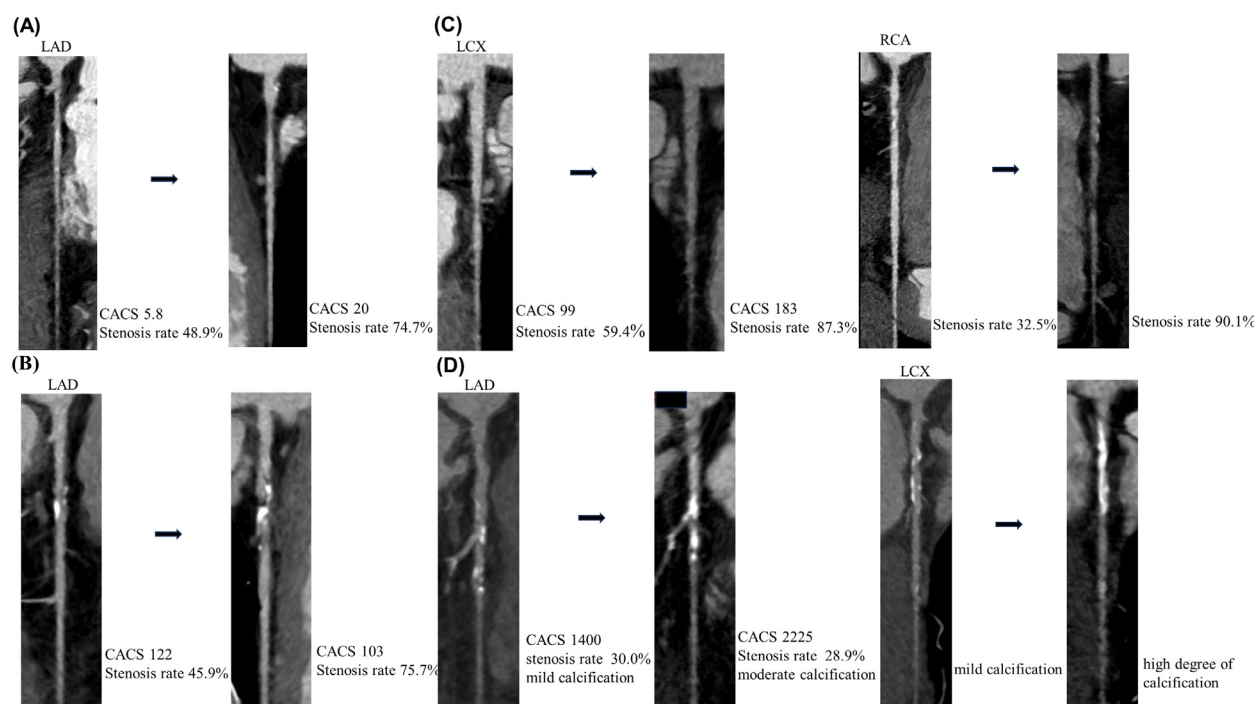


Figure 3. Comparison of CCTA findings in four patients with progression of stenosis. Panels A–D correspond to Cases 1–4. Images from each case are shown side by side, comparing baseline and two-year follow-up scans. Case 1 (**Panel A**): The stenosis rate of the left anterior descending artery (LAD) increased from 48.9% to 74.7%, with the coronary artery calcium score (CACS) rising from 5.8 to 20. Case 2 (**Panel B**): The LAD stenosis rate increased from 45.9% to 75.7%, while the CACS decreased from 122 to 103. Case 3 (**Panel C**): The left circumflex artery (LCX) stenosis rate increased from 59.4% to 87.3%, and the right coronary artery (RCA) stenosis rate from 32.5% to 90.1%, with the CACS rising from 99 to 193. Case 4 (**Panel D**): Coronary calcification reduced the accuracy of stenosis measurement, resulting in slightly lower values than two years earlier (LAD: 30.0% to 28.9%). No stenosis was detected in the LCX, but calcification was clearly aggravated.

We believe this study is the first to conduct a longitudinal follow-up of cardiovascular disease in JHLH, with a specific focus on coronary artery stenosis progression under guideline-based management. To support this claim, we performed a literature search in PubMed through August 2025 and found limited reports with serial CCTA or equivalent imaging in HIV-infected individuals, and none focused specifically on hemophilia. In particular, patients with moderate or severe coronary artery stenosis showed disease progression despite appropriate risk management, which differs from trends, reported in the general population (6-9).

According to Tarr *et al.*, in a CCTA follow-up conducted over a mean period of two years, no significant progression in coronary artery stenosis was observed between HIV-positive and HIV-negative individuals when viral load was well controlled (10). In contrast, significant progression has been reported in individuals with inadequate HIV viral suppression (11).

Other studies have shown that, in the absence of cardiovascular risk management, HIV-positive individuals had approximately twice the odds of progression of calcified plaque compared to HIV-negative individuals (odds ratio [OR] = 1.99, $p = 0.01$), and a trend toward increased progression of non-calcified plaque was also observed (OR = 1.64, $p = 0.07$) (12).

In HIV-positive patients, statin intervention has been

associated with plaque regression on follow-up CCTA, underscoring the importance of early initiation of statin therapy (13,14). Both studies evaluated plaque volume; however, the degree of stenosis was not described.

Early treatment of dyslipidemia is expected to improve LDL-C and PWV (15), whereas delayed intervention may result in PWV worsening despite LDL-C reduction. This suggests the importance of early risk factor control in this population.

In contrast to LDL-C, findings for arterial stiffness as measured by PWV were inconsistent. While overall changes were not significant, subgroup analyses showed divergent trends: improvement in some patients with normal-to-mild stenosis, significant worsening in the revascularization group, and heterogeneous responses in the moderate-to-severe stenosis group. These inconsistent results highlight the complexity of vascular remodeling in this population. However, due to the limited sample size, multivariate analyses could not be performed to identify contributing factors, and these findings should therefore be interpreted with caution.

In addition, blood pressure control (16,17), diabetes management (18), comprehensive cardiovascular risk management (19), and improvement in lifestyle habits (20) remain essential for preventing CAD.

The prior Hem-IHD study provided an opportunity to address coronary risk factors not only in patients with

significant stenosis but also in those without stenosis (5). In the present study, 4 of the 7 patients who underwent repeat CCTA showed progression of coronary artery lesions, and 3 developed severe stenosis requiring PCI despite improved risk factor management. Although a statistically significant increase in CACS was observed in this subset, the very small sample size limits the generalizability and statistical reliability of this finding; therefore, it should be interpreted as exploratory in nature.

These findings suggest that in JHLH, once moderate or greater stenosis is present, rapid progression is highly probable even under appropriate management. Therefore, repeat CCTA at approximately two years after Hem-IHD is recommended to enable early detection and timely intervention.

Potential contributing factors include persistent vascular inflammation due to HIV infection, co-infections such as HCV, and the administration of blood coagulation products (21).

Previous studies comparing HIV patients without hemophilia to JHLH have shown a significantly higher prevalence of CAD and elevated inflammatory markers in the latter (22), suggesting that hemophilia itself may contribute to vascular inflammation. In addition, FVIII administration has been reported to induce IL-6- and CXCL8-mediated inflammatory responses in patients with inhibitor formation (23), and regular intravenous administration of blood products may also play a role. Moreover, persistent HIV reservoirs have been linked to coronary artery plaque, indicating that HIV DNA quantification may serve as a marker for predicting cardiovascular events and guiding interventions (24).

All three patients who underwent revascularization experienced worsening PWV despite risk control, suggesting a potential for further lesion progression. Therefore, these findings highlight the potential importance of regular CCTA follow-up in JHLH patients with moderate-to-severe stenosis for the early detection of disease progression and timely intervention.

3.6. The limitations of this study

This study has several limitations. First, the sample sizes of the PCI/CABG group ($n = 3$) and the moderate-to-severe stenosis group ($n = 8$) were small, limiting the statistical power and reliability of subgroup analyses. Therefore, these results should be interpreted as descriptive. In addition, the overall number of eligible patients was inherently limited. The total number of Japanese patients with HIV infection due to contaminated blood products was 1,433, and approximately half have already passed away, leaving only 689 survivors nationwide. Despite this restriction, our cohort of 58 patients treated at the National Center for Global Health and Medicine represents one of the relatively larger series currently available, and

conducting a similar study at other institutions may involve certain difficulties.

Second, the study was exploratory in nature and did not include a predefined primary endpoint. Third, no adjustments were made for multiple comparisons, increasing the risk of type I error. Fourth, sample size calculations and power analyses were not performed, which may affect the interpretability of non-significant findings. Larger prospective studies with adequate sample sizes and clearly defined endpoints, such as major adverse cardiovascular events (MACE), are needed to validate these observations and clarify cardiovascular risks in this vulnerable population.

In conclusion, our study suggests that even under guideline-based cardiovascular management, there remains a considerable risk of CAD progression in HIV-infected hemophilia patients with moderate or greater stenosis. Therefore, repeat CCTA at two-year follow-up could be considered to facilitate early detection and guide timely intervention. Continuous monitoring, including imaging, and early intervention targeting modifiable risk factors may be important to reduce long-term cardiac risk in this vulnerable population.

Acknowledgements

The authors thank all staff members of AIDS Clinical Center and Department of Cardiology, National Center for Global Health and Medicine, Japan Institute for Health Security.

Funding: This study was supported in part by funds from NCGM (#21A1024).

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

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Received September 2, 2025; Revised October 1, 2025; Accepted October 6, 2025.

Released online in J-STAGE as advance publication October 10, 2025.

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Measles containing vaccine hesitancy and readiness in the post-COVID-19 era: A 7C model commentary

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic exposed the fragility of global immunization programs and intensified measles vaccine hesitancy, with global measles-containing-vaccine first-dose (MCV1) coverage falling from 86% in 2019 to 81% in 2021, with the number of unvaccinated children rising to 18 million. Using the 7C model of vaccine readiness, we highlight how Confidence, Complacency, Constraints, Collective responsibility, risk Calculation, Compliance, and Conspiracy beliefs shape parental decision-making in the post-pandemic era. Declining trust, low perceived disease risk, misinformation, and service barriers threaten progress towards measles eradication. We argue that recovery requires more than restoring coverage: resilient immunization strategies must address both structural barriers and psychological drivers of hesitancy. Clinician-led communication, accessible and free vaccination services, targeted social media engagement, and transparent informational dashboards are all essential tools for achieving effective disease management. Ultimately, vaccine readiness is not only about access – it is about trust, values, and resilience. Without decisive action, measles control will remain vulnerable to future global crises.

Keywords: COVID-19, measles-containing vaccine, vaccine uptake, vaccine hesitancy, vaccination readiness

1. Introduction

The onset of the coronavirus disease 2019 (COVID-19) pandemic posed a significant challenge to global healthcare systems and disrupted routine immunization programs. Measles cases doubled in 2022 compared to 2021, while the number of unvaccinated children rose from 13 million to 18 million globally (1). After the onset of the pandemic, the proportion of children receiving their measles-containing-vaccine first-dose (MCV1) decreased from 86% in 2019 to 81% in 2021 (2). As of 2024, the global MCV1 coverage remains around 84%, indicating that passive recovery will not prevent outbreaks – well below the 95% required to achieve herd immunity (2,3). Although these declines may appear as temporary setbacks, they point to a deeper issue – worsening vaccine hesitancy.

Vaccine hesitancy is a delay or refusal of vaccines despite the availability of services (4). It significantly impacts public health and was recognized by the World Health Organization (WHO) as "one of the top ten threats to global health", due to its potential to hinder the

progress toward herd immunity against measles. The 7C model of vaccine readiness provides a framework for understanding the psychological factors influencing vaccine hesitancy (5). The components include Confidence, Complacency, Constraints, Collective responsibility, risk Calculation, Compliance, and Conspiracy. Each component is considered a spectrum that includes vaccine acceptance on one end and vaccine refusal on the other (5). We use the 7C model as a lens to interpret the pandemic's impact on measles vaccine readiness.

2. Key observations through the 7C model

i) Confidence eroded as the politicization of the pandemic blurred perceptions of MCV safety. In the 7C model, confidence is defined as beliefs that relate to attitudes towards vaccination, trust in their safety and effectiveness, as well as in the systems that deliver them (Figure 1). Perceived adverse effects remain the leading reason for delay or refusal, with evidence suggesting that parents who reject MCV overestimate side-effect risk (6).

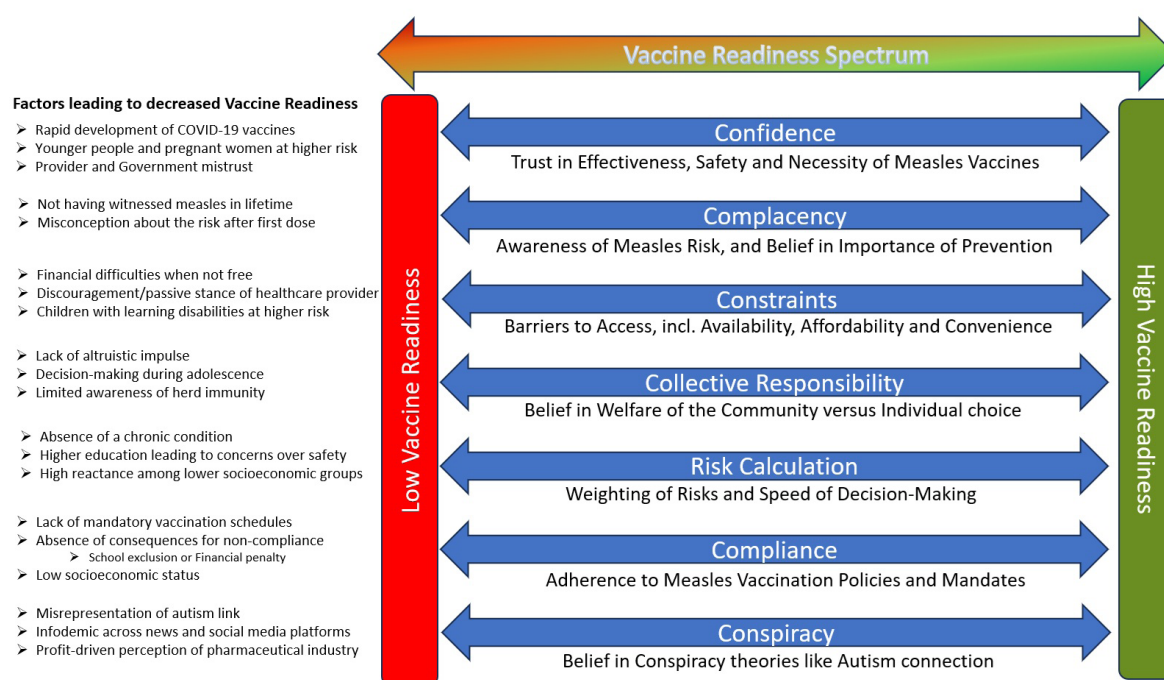


Figure 1. Measles-containing vaccine (MCV) hesitancy and readiness, and related factors.

ii) Complacency rises when perceived disease risk is low. Complacency refers to the level of recognized risk, perceived personal vulnerability, and severity of the disease. At the high end of the spectrum, people have minimal concern about the severity of vaccine-preventable diseases, leading to a perception that vaccination is optional or unnecessary. Complacency towards measles vaccination has emerged, particularly in regions where measles was previously well-controlled. Vaccine-hesitant parents believed the risks of vaccination were worse than measles itself, as they had never witnessed it (7). A significant number of parents in the United Kingdom under-recognized the potential severity and fatality of measles (8). In China, 20.5% of 2,178 caregivers identified complacency as a driver of vaccine hesitancy (9).

iii) Constraints in physical and information access reduce readiness to vaccinate. Constraints encompass systemic and individual barriers, including physical availability, geographical accessibility, affordability, or willingness to pay, and language literacy in a multiethnic context. In the United Kingdom (UK), the pandemic was associated with a significant drop in timely measles, mumps, and rubella (MMR) vaccine receipt, which increased the geographical clustering of measles susceptibility, especially in areas with historically low MMR coverage (10). Information about vaccination service availability is a distinct constraint for MCV: one in ten parents was unaware of ongoing vaccination appointments in the UK at the start of the pandemic (8). In Israel, ineffective official communication increased mistrust; service information must be paired with a clear communication strategy to counter this concern. Affordability issues create barriers to higher

immunization coverage when MCV is paid for out-of-pocket. In China, approximately 20% of parents reported the cost of out-of-pocket vaccines as a primary reason for hesitancy (9). In Sudan, approximately 12% of parents either partially vaccinated or did not vaccinate their children against measles due to vaccine availability or uncooperative vaccine providers (11).

iv) Collective responsibility represents ethical considerations and the protections of others. It is an individual's understanding of the broader societal benefits of vaccinations, particularly for the most vulnerable populations. The altruistic impulse to protect others significantly improves the willingness to get vaccinated (12). A unique neurobehavioral underpinning in young adults suggests that a decision-making tendency originating in adolescence may positively influence collective responsibility and, consequently, reduce vaccine hesitancy (13). The concept of herd immunity can motivate uptake but may dampen the effect of collective responsibility where local coverage is far from the threshold (3).

v) Risk Calculation involves individuals' engagement in extensive research about vaccines, weighing risks versus benefits, potentially leading to delayed acceptance, selective vaccination, or refusal. European countries reported lower proportions agreeing that the MMR vaccine was safe in 2022 compared to 2018 (14). A significant portion of German parents endorsed a measles vaccine mandate for children; however, lower socioeconomic status and higher levels of reactance negatively impacted vaccination intentions (15). Higher institutional trust was associated with lower reactance and more positive attitudes towards the mandate. This

suggests that trust mediates risk calculation and is therefore relevant to this component of vaccine readiness. Healthcare workers have a central role in guiding parental decisions regarding MCV risk calculation, with 96% of parents considering paediatricians their primary source of vaccination information (16).

vi) *Compliance refers to attitude toward vaccination policies and adherence to public health guidelines on vaccination* (17). It extends to support for monitoring communities and sanctioning unvaccinated individuals. In Italy, the threat of school exclusion and financial penalties for non-compliance with vaccination mandates had a positive impact on vaccination rates (18). In Germany, the 2020 measles vaccination mandate increased overall coverage but had unintended consequences; parents with lower socioeconomic status were less likely to comply (15).

vii) *Conspiracies beliefs persist. Conspiracy relates to the level of belief in conspiracy theories or trust in vaccination-related misinformation, also referred to as the infodemic.* The misrepresentation linking MCV to autism gave risk to many conspiracy theories and fostered scepticism among the general population (19). Despite conclusive evidence disproving the autism claim, fear persists and spreads via social media (6). This is confirmed by an inverse correlation between MMR vaccination coverage and internet search activity, tweets, and Facebook posts (20).

3. Policy and research implications

We argue that the COVID-19 pandemic, while primarily a health crisis, has also highlighted the fragility of vaccine confidence and public compliance. The rapid development and deployment of the COVID-19 vaccine affected public trust in vaccine safety and efficacy, and this showed the importance of transparent communication and vaccine literacy programs. Vaccine readiness is a spectrum of attitudes influenced by social, psychological, and environmental factors, as seen across the 7C model's antecedents (5). Using the model allowed us to investigate the issue from a unique perspective which can be applied in future reviews and studies. Confidence in vaccines is not merely a matter of individual assurance but a fundamental aspect of public health infrastructure, vulnerable to the effects of global and regional crises. Countries like the United Kingdom and Brazil, where measles vaccination coverage drastically fell, are examples of how swiftly gains in disease control can be reversed when public confidence decreases. To rebuild trust, transparent, clinician-led campaigns are needed to address safety concerns and counter misinformation. To raise awareness, local communities need to be educated about the severity of measles and the importance of receiving both MCV doses, especially in regions where the disease is no longer prominent. To remove barriers, vaccines need to be free, easily accessible, and accompanied by reminder systems. Through fostering social values, governments

need to promote the concept of protecting vulnerable groups by achieving herd immunity. Finally, we must strengthen policies by mandating school-entry vaccination requirements and funding catch-up campaigns whenever coverage has dropped.

Future research should focus on developing resilient immunization strategies that can withstand global crises. This involves not only addressing the immediate disruptions caused by such crises but also improving the public health systems to better prepare for future threats. The goal must extend beyond recovery: resilience of public health systems must be integral to health security. Only through a multidisciplinary approach can we restore and sustain high vaccination coverage rates, thereby protecting global health against both present and future challenges. Vaccine readiness is not just about managing diseases; it is about managing trust, expectations, and the foundational aspects of public health.

4. Conclusion and call to action

To address declining MCV uptake and rebuild public trust, we propose the following five key actions:

i) *Rebuild confidence with trusted voices.* Paediatricians and primary care providers should lead transparent communication with patients and their families. MCV has a strong safety record spanning over 60 years, and we, as physicians and public health professionals, should emphasize its importance not only for individual health but also for the population health.

ii) *Eliminate constraints.* Vaccines must remain free at the point of care. Active time-saving measures within the health system are also necessary to reduce logistical barriers, including appointment reminders, mobile vaccination units, and outreach in underserved areas.

iii) *Misconceptions must be countered.* Public health campaigns should present simple comparisons of disease risk versus vaccine risks. Parents trust personalized counselling, fact boxes, and clear framing, rather than abstract statistics.

iv) *We must overcome conspiracy narratives.* Health authorities should prioritize emotionally resonant pro-vaccine content on social media, rather than relying solely on debunking conspiracies.

v) *Use social media strategically and publish transparent data.* Sharing dashboards with MCV1 coverage at a district level increases individual and group accountability. Given that parents encounter TikTok before PubMed, health authorities should utilize social media and artificial-intelligence (AI) tools to counter recurrent myths in real time.

Funding: This work was supported by JSPS KAKENHI Grant Number 23K27850.

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

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Received May 21, 2025; Revised August 23, 2025; Accepted August 27, 2025.

Released online in J-STAGE as advance publication September 2, 2025.

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Parenting difficulties and support needs among parents having new children during the COVID-19 pandemic: A quantitative text analysis

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Abstract: Parents having new children during the coronavirus disease 2019 (COVID-19) pandemic were exposed to heightened parenting difficulties. However, pandemic-specific parenting difficulties and unmet support needs among these parents, especially fathers and parents with multiple children, remain underexplored. We conducted a study to clarify parenting difficulties and support needs of such parents by using quantitative text analysis of free-form descriptions collected from 809 Japanese parents in 2022 (first-child group: 163 fathers and 222 mothers; second-child group: 192 fathers and 232 mothers). Quantitative text analysis using KH Coder included co-occurrence network and correspondence analyses to identify parenting difficulties and support needs, stratified by sex, household income, and the presence of parenting consultants. Regarding parenting difficulties, fathers more often emphasized children's behavioral challenges, whereas mothers reported emotional struggles. Pandemic-related restrictions directly amplified parenting difficulties, including limited childcare resources, reduced social interaction, and infection-related concerns. Support needs across groups centered on financial assistance and childcare but varied by income, sex, and consultant availability. Fathers without consultants emphasized information and advice, while mothers without consultants stressed temporary childcare needs or illness-related support. Parenting difficulties and support needs reflected cultural gender norms. Policy implications include sustaining financial aid, developing gender-tailored interventions, and establishing crisis-resilient support systems.

Keywords: parents, early childhood, parenting difficulties, support needs, COVID-19

1. Introduction

Parents having new children during the coronavirus disease 2019 (COVID-19) pandemic were particularly exposed to parenting difficulties due to stress and feelings of isolation, with more than 60% reporting such experiences (1,2). However, there is limited understanding not only of the challenges faced by fathers or parents with multiple children but also of the specific nature of parenting difficulties related to the pandemic.

Additionally, evidence indicates that parents with new children during the COVID-19 pandemic had to navigate parenting with limited support, highlighting their need for support in managing both the pandemic and parenting (3). However, a gap remains between the actual support needs of parents and what has been addressed in research. Clarifying the specific parenting difficulties and support needs of these parents could be meaningful not only under normal circumstances but also in informing development of timely and effective intervention strategies in the event of future global crises. Therefore, we conducted a study to clarify the unique

parenting difficulties and support needs of both fathers and mothers having new children during the COVID-19 pandemic by analyzing free-form descriptions collected in our previous study.

2. Data analysis

This study analyzed free-form descriptions of general parenting difficulties, parenting difficulties related to the COVID-19 pandemic, and/or support needs from our previous study conducted in October 2022 (2). Participants were categorized into the first and second-child groups based on the birth order of children born during the COVID-19 pandemic. Additionally, we established subgroups of fathers and mothers within each group.

We performed quantitative text analysis on free-form responses using KH Coder (ver. 3; Koichi Higuchi, Kyoto, Japan) (4). All responses were reviewed to ensure that each sentence contained only one idea, and data were preprocessed by correcting misspellings, unifying synonyms, and standardizing variations. Morphological

analysis was conducted separately for the father and mother groups, segmenting responses into word units and merging incorrectly split. Common context-independent words, such as "child", were excluded. We performed co-occurrence network analysis to generate maps and calculated the number of respondents for each category. Categories were extracted by examining and interpreting the original data for groups of co-occurring words. In addition, we performed correspondence analysis to examine differences in outcomes based on external variables (household income and the presence or absence of parenting consultants). All analyses and interpretations were performed through collaborative discussion.

This study was approved by the Institutional Review Board of the National Center for Global Health and Medicine (approval no: NCGM-S-004562-00). Informed consent was electronically obtained from all participants.

3. Parenting difficulties

A total of 809 parents provided free-form responses, including 163 fathers and 222 mothers in the first-child group and 192 fathers and 232 mothers in the second-child group. Parents in the first-child group were slightly

younger. Approximately 90% had partners, and most fathers were employed, compared with 60% of mothers. In the first-child group, the most common child age was 1 year; in the second-child group, the most common child ages were 2 years and 0 years for the father and mother subgroups, respectively. The boy-to-girl ratio was 1:1 across all groups.

Regarding general parenting difficulties, 11–14 categories were identified in each group. The proportions of these categories were broadly similar across groups, with no clear sex differences. The most frequently reported difficulty was concern about how to discipline or treat children, which was expressed by approximately 10–20% of participants across groups. Other prominent difficulties included managing behavioral issues of children (Table 1). Correspondence analysis revealed differences by household income. Among low-income fathers in both groups, specific behavioral difficulties such as not sleeping were emphasized. Middle- and high-income paternal responses were similar; however, fathers in the first-child group often reported uncertainty or hesitation regarding their own parenting approaches, whereas fathers in the second-child group reported behavioral challenges such as tantrums. Among mothers,

Table 1. Proportion of respondents in each category

Category	First-child group		Second-child group	
	Fathers (n = 118) n (%)	Mothers (n = 178) n (%)	Fathers (n = 159) n (%)	Mothers (n = 193) n (%)
General parenting difficulties				
Concerns about disciplining my child	22 (19)	17 (10)	26 (16)	29 (15)
Difficulties when things do not go as expected	15 (13)	-	-	23 (12)
Communication difficulties with my child	12 (10)	20 (11)	-	13 (7)
Uncertainty about correct parenting approaches	-	26 (15)	-	17 (9)
Child does not follow instructions	10 (8)	11 (6)	32 (20)	28 (15)
Category	First-child group		Second-child group	
	Fathers (n = 78) n (%)	Mothers (n = 151) n (%)	Fathers (n = 107) n (%)	Mothers (n = 160) n (%)
Parenting difficulties related to the pandemic				
Lack of social interaction	17 (22)	51 (34)	13 (12)	57 (36)
Restricted outings and leisure	17 (22)	37 (25)	39 (36)	50 (31)
Coping with COVID-19 restrictions	15 (19)	26 (17)	21 (20)	29 (18)
Self-restraint due to fear of infection	-	34 (23)	-	24 (15)
Category	First-child group		Second-child group	
	Fathers (n = 110) n (%)	Mothers (n = 147) n (%)	Fathers (n = 119) n (%)	Mothers (n = 145) n (%)
Support needs				
Need for financial assistance	39 (35)	38 (26)	40 (34)	47 (32)
Need for childcare services	37 (34)	66 (45)	45 (38)	63 (43)
Need for accessible consultation	9 (8)	12 (8)	13 (11)	14 (10)
Need for support with unexpected events	9 (8)	14 (10)	6 (5)	9 (6)
Desire for improved parenting environment	-	13 (9)	-	12 (8)

parenting difficulties clearly varied by income. Low-income mothers in the first-child group struggled with children's behaviors that did not match expectations, whereas those in the second-child group faced challenges in managing sibling differences. In the middle-income group, mothers across both groups focused more on children's behavioral difficulties, including the terrible twos (physical aggression commonly seen in toddlers (5)). High-income mothers in the first-child group emphasized judging the appropriateness of their parenting, whereas mothers in the second-child group often experienced self-blame regarding their attitudes toward their children. Furthermore, parenting difficulties also differed depending on access to parenting consultants. Parents without a consultant tended to emphasize practical difficulties such as the lack of available support. In contrast, those with a consultant more often expressed general concerns about parenting.

4. Parenting difficulties related to the pandemic

Parenting difficulties related to the pandemic yielded 7–10 categories across groups. Common challenges included restrictions on outside activities and coping with infection, reported across all groups. Only mothers emphasized self-restraint due to concerns about infection. In the correspondence analysis, both groups of middle-income fathers reported difficulties related to restrictions on social activities including reduced interaction with others. High-income fathers in the first-child group more often emphasized the limitations of childcare resources, whereas fathers in the second-child group highlighted concerns about fewer opportunities for children to develop sociality and the increased burden of infection-control practices. Clear differences by income were also observed among first-child mothers. Low-income mothers described feelings of isolation due to staying at home, while high-income mothers expressed difficulties stemming from restrictions on leisure and opportunities for free outings. In contrast, mothers in the second-child group, regardless of income, more often reported difficulties related to restrictions on children's outdoor activities. When stratified by access to parenting consultants, parents without consultants tended to emphasize emotional difficulties such as insufficient support or lack of opportunities for relaxation. In contrast, parents with consultants, regardless of the number of children, more frequently highlighted challenges related to restrictions on social activities.

5. Support needs

Support needs were divided into 5–9 categories across groups. Common categories included the need for financial assistance and childcare support. Fathers more frequently expressed needs related to parenting consultation, whereas mothers more often hoped for

improvements in the parenting environment (Table 1).

Figure 1 presents differences in paternal support needs based on external variables. Support needs also varied by income level. Low-income fathers in the first-child group emphasized the need for support in unexpected events including infection or illness. Fathers in the middle- and high-income groups more consistently expressed needs for financial assistance and childcare services. Within the middle-income group, fathers in the first-child group emphasized the importance of support for couples, such as time together, while fathers in the second-child group more frequently referred to support specifically directed toward parents such as opportunities to take a break. Among mothers, differences in support needs by household income were observed only in the second-child group. Low-income mothers in this group tended to emphasize the need for assistance when they or their children became ill, as well as support from local centers. In contrast, high-income mothers more frequently expressed a desire for continuous parenting support and called for the abolition of income restrictions on such support. Responses in the first-child group, however, primarily centered on economic support and childcare services (Supplemental Figure S1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=111>). Support needs also differed according to consultants. Fathers without consultants expressed stronger needs for information and accessible places to seek advice, whereas fathers with consultants more frequently mentioned economic support. Among mothers, those without consultants tended to emphasize the need for temporary and safe childcare, whereas mothers with consultants highlighted more general forms of parenting support.

6. Cultural and gender context of parenting roles

This study yielded three key findings. First, although fathers and mothers shared many similar parenting difficulties, their emphases diverged. Fathers more often described concerns about children's behaviors, whereas mothers reported uncertainty and worries about their parenting practices. Second, pandemic-related restrictions directly amplified parenting difficulties, highlighting the unique impact of COVID-19 on family life. Third, while support needs were broadly consistent across groups, centered on financial assistance and childcare services, they also varied by sex, income level, and the access to parenting consultants. These findings suggest that support tailored to specific parental characteristics is essential for both ordinary times and crisis situations.

Gender differences in parenting difficulties and support needs were consistent with the findings of previous studies (6,7), but we also observed that the cultural context of parental roles in Japan was strongly reflected in the results. In Japan, social norms continue to assign disproportionate weight to the paternal role

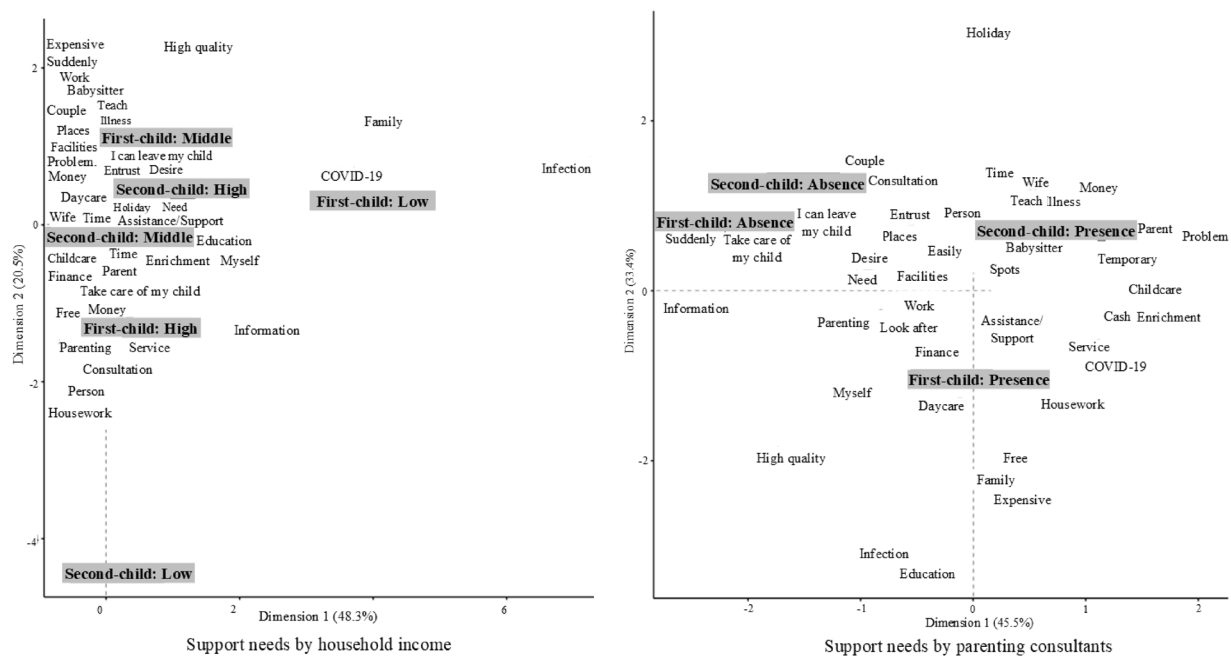


Figure 1. Correspondence analysis of support needs by household income and parenting consultants in fathers. Annual household income was classified as follows: Low: < 3,000,000 yen; Middle: 3,000,000–10,000,000 yen; High: > 10,000,000 yen. Parenting consultants were classified as follows: Presence: with consultants; Absence: without consultants.

as financial providers, which limits opportunities for active parenting and often positions fathers as secondary caregivers (8). Fathers with limited social resources faced particular challenges, as they lacked access to information and support that could help mitigate parenting difficulties. The COVID-19 pandemic exacerbated this imbalance, as fathers experienced increased parenting burdens while external resources, such as childcare facilities, were restricted (9). This underscores the importance of reforming societal perceptions of fatherhood and providing practical support. Such measures may include father-friendly parenting workshops addressing common difficulties such as crying or tantrums, peer-support networks for sharing strategies, and workplace policies that enable men to participate more actively in daily parenting.

Maternal parenting difficulties in our study were characterized by emotional concerns, including uncertainty about whether they were "good mothers", and feelings of isolation from staying at home to prevent COVID-19. These patterns reflect prevailing expectations that position mothers as primary caregivers. Mothers often experience psychological strain in the process of adapting to their maternal role (10). Traditional norms in Japan, epitomized by the "Good Wife, Wise Mother" ideal, continue to place disproportionate responsibility for caregiving on women (11). Such context may amplify mothers' tendencies toward self-criticism and feelings of inadequacy, thereby increasing their emotional burden during ordinary times and crises. Therefore, targeted interventions are needed, such as accessible counselling services, community-based support to enhance maternal

self-efficacy, and illness-related backup care that provides reassurance when formal services are disrupted.

The pandemic context also highlighted the need to strengthen support for parents. Restrictions on childcare access and reduced interpersonal exchange during the COVID-19 pandemic acted as stress multipliers for both fathers and mothers. These findings indicate that measures must ensure the sustainability of social activities for both parents and children during emergencies, when parenting support is most needed.

7. Policy implications and limitations

The findings of our study suggest policy implications such as sustaining financial aid, developing gender-tailored programs, and establishing crisis-resilient support systems that remain accessible even during pandemics. However, this study has some limitations. Some extracted words with low frequencies may have been overlooked, as quantitative text analysis relies on word frequency and co-occurrence patterns. Additionally, variability in the length of free-form responses may have limited the contextual accuracy of the analysis. Furthermore, the findings are culturally specific to Japanese parents, whose parenting practices and gender role expectations are shaped by unique social norms. Therefore, the generalizability of the results to other cultural contexts is limited. Future cross-cultural replication studies are required to examine whether similar patterns of parenting difficulties and support needs emerge in different sociocultural settings.

In conclusion, among parents having new children

during the COVID-19 pandemic, fathers more often described children's behavioral challenges, while mothers expressed emotional struggles, amplified by cultural norms and pandemic restrictions. These findings highlight important policy directions, including gender-tailored programs, sustainable financial aid, and crisis-resilient childcare, to promote healthy parenting.

Acknowledgements

We would like to thank the participants of this study. In addition, we are deeply grateful to Takahide Omori for his insightful discussions and valuable suggestions, which greatly contributed to the development of this article.

Funding: This research was supported by the Policy-based Medical Service Foundation in Japan.

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

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Received May 31, 2025; Revised August 29, 2025; Accepted September 4, 2025.

Released online in J-STAGE as advance publication September 10, 2025.

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Association between participation in HIV stigma reduction program and HIV prevention awareness among men who have sex with men in Mongolia

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Abstract: In 2024, we conducted a study to evaluate the effectiveness of a Mongolian non-governmental organization (NGO) stigma reduction program, "We are Living Under the Same Sky" (LUSS), by assessing the association between the program and two human immunodeficiency virus prevention outcomes, recognition of the Undetectable = Untransmittable (U=U) and the need for pre-exposure prophylaxis (PrEP), in 223 men who have sex with men (MSM). Results showed that the LUSS program was associated with the recognition of U=U and PrEP need by Mongolian MSM. The recognition of U=U was associated with coming-out experience and marital status. LUSS was associated with the PrEP need, which, in turn, was associated with MSM who engaged in active sexual behaviors. The LUSS program has increased the recognition of U=U and PrEP need among MSM, and it can be incorporated into new prevention interventions targeting MSM. LUSS has the potential to effectively raise awareness among MSM and other populations such as youth, educators, and healthcare providers.

Keywords: HIV prevention, Undetectable = Untransmittable (U=U), pre-exposure prophylaxis (PrEP)

1. Introduction

Mongolia reports approximately 20 new cases of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) annually, contributing to a relatively low national prevalence rate and number of new infections (1). However, men who have sex with men (MSM) account for approximately 60% of all cases, and the prevalence is particularly high among MSM sexual networks in Ulaanbaatar (2,3).

Despite amendments to the Constitution over time to explicitly prohibit discrimination against sexual minorities, prejudice and discrimination toward sexual minorities in Mongolian society remain prevalent (4-6). The pervasive social stigma and discrimination experienced by MSM from their surroundings, family members, law enforcement officers, and healthcare professionals considerably hinder their ability to engage in effective HIV and sexually transmitted infection (STI) prevention practices, access essential health services, and obtain the medical care they need (4,5).

In Ulaanbaatar, the Youth for Health Center NGO (hereafter referred to as the Mongolian NGO) has been conducting sexual health awareness activities, particularly HIV and STI prevention, health education, and human rights advocacy for gay, bisexual men and transgender women since the 2000s (7,8). They have collaborated with health professionals involved in HIV care to provide services such as confidential testing, treatment, and counseling (7,8). They launched the Mongolian version of the awareness program "We are Living Under the Same Sky" (LUSS) in 2011, following their participation in the "Living Together Project", developed by Japanese community-based organizations (9). Both programs have been implemented sharing the same message, which aimed to reduce stigma associated with HIV/AIDS and promote HIV testing in the gay community (9,10).

An evaluation study by Takaku *et al.* (9) showed that participation in the LUSS program was associated with awareness of HIV infection, discussions about HIV testing, and HIV testing behavior among MSM.

The LUSS program was suggested for continuous implementation in conjunction with new prevention interventions (9). In response to these results, the Mongolian NGO started new prevention programs, such as disseminating Undetectable = Untransmittable (U=U) messages and promoting pre-exposure prophylaxis (PrEP). We conducted a study to identify the relationship between the LUSS program and the recognition of U=U and need for PrEP among MSM in Mongolia. These findings are expected to contribute to the development of sustainable activities by Mongolian NGOs aimed at achieving the global goal of ending AIDS (11).

2. Study design

2.1. Survey methods

An internet survey was conducted by setting up an independent survey site on the web using an anonymous, self-administered questionnaire in the Mongolian language from May to August 2024. Using a network of outreach staff members of the Mongolian NGO, recruitment for the questionnaire survey was conducted through social networking sites such as Facebook and gay dating sites. The purpose of the survey and requests for cooperation were posted on the top page of the survey site. Those who read the request and answered "male" or "other" could proceed to the questionnaire page, whereas those who answered "female" could not proceed to the questionnaire page. The survey was administered once per person; therefore, those who responded for the first time were considered to be eligible.

For the survey site, respondents' data communication was encrypted using a Secure Sockets Layer. Access to the collected data was provided to those with administrator ID.

2.2. Participants

Mongolian men aged ≥ 18 years who responded to this survey for the first time and had experienced sexual intercourse with men were included in the analysis. In total, 274 men responded to all questions in the web-based survey; however, those aged < 18 years, who had never had sexual intercourse with a man, or had responded to the questionnaire more than twice were excluded from the study. The final analysis included 223 men.

2.3. Variables

Questions on basic demographics, coming-out experience, LUSS participation, and five HIV prevention outcomes, including condom use during anal sex with men in the past 6 months, the number of male sex partners in the past 6 months, HIV testing

behavior in the past year, recognition of U=U, and need for PrEP, were used for the survey (11-13). Recognition of U=U message and need for PrEP were selected as the Mongolian NGO activity outcomes in this study. The basic demographics included age, place of residence, sexual orientation, education, employment, and marital status.

Regarding the experience of participating in the LUSS program, those who had either participated in a reading event or watched a LUSS film were considered to have participated in the program, whereas those who had neither were considered to have not participated.

2.4. Statistical analyses

Two outcomes for the Mongolian NGO activities were used to examine their effectiveness, and each of which was used as the objective variable for the chi-square test and multiple logistic regression analysis. The LUSS participation experience, coming-out experience, five combination prevention outcomes, and basic demographics were used as independent variables. The significance level was set at 10%, and independent variables that were found to be significantly different according to the chi-square test were included in the multiple logistic regression analysis. Three respondents who reported an HIV-positive status were excluded from the need for PrEP analysis. SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis.

2.5. Ethical considerations

The methodology and questions for this survey were developed in consultation with the staff of the Mongolian NGO. The questionnaire was anonymous and did not include information that could lead to identification of research participants. An explanatory statement clearly stating the purpose of the study, strict adherence to privacy, handling of research data, and voluntary participation and responses was placed on the top page of the website. Only those who read and agreed to these conditions were allowed to answer the questions. Finally, each individual was considered to have participated in the study after submitting all responses. This study was approved by the Research Ethics Committee of the Nagoya City University Graduate School of Nursing (approval number: 23049) and conformed to the provisions of the Declaration of Helsinki (revised in 2013).

3. Key findings of this survey

3.1. Basic demographics of the research participants

Among the 223 respondents in the analysis, 201 (90.1%) reported living in Ulaanbaatar (Table 1). The most

common age group was 18–29 years ($n = 141$, 63.2%). The sexual orientations were gay (64.6%), bisexual (29.6%), and other, including transgender women (5.8%). In total, 159 (71.3%) had a vocational school degree or higher, and 192 (86.1%) were employed. Most respondents were single (94.2%). Sixty-three (28.3%) participated in LUSS, and 160 (71.7%) did not.

3.2. Multiple logistic regression for outcomes of the

Table 1. Basic demographics of the research participants ($n = 223$)

Variables	n (%)
Residence	
Ulaanbaatar	201 (90.1)
Other than Ulaanbaatar	22 (9.9)
Age group	
< 29 years	141 (63.2)
30–39 years	67 (30.0)
> 40 years	15 (6.7)
Employment	
Employed	192 (86.1)
Unemployed	31 (13.9)
Marital status	
No	210 (94.2)
Yes	13 (5.8)
Final education	
Junior high school	37 (16.6)
Senior high school	27 (12.1)
Diploma/trade/vocational certificate	19 (8.5)
Undergraduate degree	120 (53.8)
Postgraduate degree	20 (9.0)
Sexual orientation or gender identity	
Gay	144 (64.6)
Bisexual	66 (29.6)
Other	13 (5.8)
Have you been to a "We are Living Under the Same Sky" event?	
Yes	63 (28.3)
No	160 (71.7)

Mongolian NGO activities and LUSS participation

The tendency to recognize U=U was stronger among those who had participated in LUSS than among those who had not, with an adjusted odds ratio (AOR) of 3.32 (95% confidence interval [CI]: 1.69–6.54) (Table 2). Those who had a coming-out experience were more likely to recognize U=U than those who did not (AOR = 2.90, 95% CI: 1.16–7.25). In terms of marital status, those who were married were more likely to recognize U=U (AOR = 6.87, 95% CI: 1.99–23.78) than those who were single.

Regarding PrEP, those who participated in LUSS had a greater awareness of the need for PrEP than those who did not participate in LUSS (AOR = 2.00, 95% CI: 1.04–3.85). Those who had sex with 10 or more men in the past 6 months had a greater awareness of the need for PrEP than those who had sex with fewer than 10 men (AOR = 3.03, 95% CI: 1.10–8.33).

4. LUSS program and its impact on U=U recognition and PrEP awareness

This study's findings demonstrated that the LUSS program was associated with recognition of the U=U message and PrEP need among MSM in Mongolia. Multivariate analysis indicated that recognition of the U=U message was associated with having participated in the LUSS program, having a coming-out experience, and being married. A positive correlation was observed between U=U recognition and LUSS participation.

In Mongolia, 39% of PLHIV do not know their HIV-positive status, and the antiretroviral (ARV) treatment access rate is 83%, with 93% remaining below the viral load detection limit (14). Despite progress made, access rate for ARV treatment remains

Table 2. Multiple logistic regression for outcomes of the Mongolian NGO activities

Variables	I know U=U very much		I want to use PrEP before sex	
	OR (95% CI)	AOR (95% CI)	OR (95% CI)	AOR (95% CI)
Marital status				
No	1	1	–	–
Yes	3.83 (1.23–11.94)**	6.87 (1.99–23.78)***	–	–
Have you disclosed your sexual orientation to anyone?				
No	1	1	1	1
Yes	2.82 (1.19–6.67)**	2.90 (1.16–7.25)**	1.77 (0.95–3.29)*	1.61 (0.85–3.03)
Have you been to a "We are Living Under the Same Sky" event?				
No	1	1	1	1
Yes	3.05 (1.61–5.77)***	3.32 (1.69–6.54)****	2.11 (1.11–3.99)**	2.00 (1.04–3.85)**
How many men did you have sex in the past 6 months?				
< 10	–	–	1	1
> 10	–	–	3.13 (1.11–8.33)**	3.03 (1.10–8.33)**

* $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$, **** $p < 0.001$. Employment status, final education, HIV testing experience in the past year, and consistent condom use during anal sex showed no association. Abbreviations: NGO, non-governmental organization; HIV, human immunodeficiency; U=U, Undetectable=Untransmittable; PrEP, pre-exposure prophylaxis; OR, odds ratio; AOR, adjusted odds ratio; CI, confidence interval.

stagnant compared with that of developed countries (14). The inconsistent supply of ARV drugs makes it challenging for healthcare providers to communicate U=U messages publicly. Under these circumstances, the Mongolian NGO emphasized U=U as essential information for MSM in the LUSS program. The U=U message is likely to have spread among the MSM community because of its affinity with the objectives of the LUSS program. Recognition of U=U was also associated with coming-out experiences and marital status of respondents. This association may be related to prejudice against HIV and sexual minorities in the country (15).

In the present study, 60% of respondents showed a willingness to use PrEP. The need for PrEP was associated with participation in the LUSS program. Prior to obtaining approval from the Mongolian Ministry of Health, the Mongolian NGO promoted PrEP as a tool for HIV prevention and disseminated information about PrEP in LUSS while considering the stigma surrounding HIV. The findings also indicated an association between PrEP need and MSM who had engaged in active sexual behaviors. The results suggest that the PrEP need is high among MSM, especially in those who are sexually active, and that PrEP may be an effective prevention choice in combination with prevention behavior.

5. Context and role of the LUSS program in Mongolian society

The LUSS program was developed by members of the MSM community, who faced stigma in society. They continue to empower their community by promoting HIV knowledge and encouraging adoption of preventive behaviors.

The results showed that LUSS can also be incorporated into new prevention interventions targeting MSM. LUSS, predicated on the notion of reducing stigma toward sexual minorities and HIV, has the potential to effectively raise awareness among MSM, as well as other populations such as youth, educators, and healthcare providers. Expansion of the target population of LUSS has potential to reduce stigma in Mongolian society and improve access to HIV testing and healthcare for MSM.

6. Study limitations and future directions

This study had some limitations. First, this was a cross-sectional survey that captured the phenomenon in the target population at one point in time. Second, this study used a self-administered questionnaire. Sexual behavior and HIV testing are privacy issues, and it has been pointed out that participants tend to provide more socially desirable responses (16). Therefore, actual infection risk behaviors may be higher than that reported

in this study. Third, there is a lack of representativeness of participants. Participants were recruited from a network of Mongolian NGO outreach workers through personal referrals and social networking services. Therefore, it is possible that the participants were more likely to be close to network members of Mongolian NGO. Future evaluations should use research designs that overcome these limitations.

The LUSS program has demonstrated an impact on increasing recognition of the U=U message and PrEP need among MSM. The study's findings indicate that LUSS has potential application in new prevention interventions and may be feasible to implement in a wider target population. However, because of the limited number of study subjects in this study, a larger-scale and more representative study should be conducted in the future to assess HIV prevention intervention activities of Mongolian NGO.

Acknowledgements

We thank the co-researchers of this study, staff members of the Youth for Health Center NGO, stakeholders of Mongolia's HIV responses, and participants who cooperated in responding to the web survey. We express our deepest gratitude to Dr. Shinichi Oka (Center for AIDS Clinical Center, National Center for Global Health and Medicine), principal investigator of the Japan–Mongolia joint research project funded by the International Medical Research and Development Fund, who provided the basis for this study.

Funding: This study was conducted as part of the Grant-in-Aid for Scientific Research (C) "Association of Stigma with HIV Testing and Prevention Behaviors Among HIV-infected At-risk Populations from East Asia in Japan" (23K09920). The funders had no role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript.

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

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- Received August 3, 2025; Revised October 7, 2025; Accepted October 15, 2025.
- Released online in J-STAGE as advance publication October 18, 2025.
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Awareness of zoonoses in Lao PDR: A call for targeted health education

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Abstract: Zoonoses pose serious public health challenges. In Lao People's Democratic Republic, where > 70% of population engages in agriculture and livestock farming, public awareness of zoonoses remains unclear. We conducted a nationwide population-based survey with 347 individuals aged 12–40 years across 40 villages in 20 districts. Logistic regression analysis was used to identify factors associated with zoonoses awareness. Awareness was approximately 42.9% and was significantly higher among females and livestock owners. Lower awareness was observed among individuals with primary or secondary education compared with those with higher education, whereas no significant difference was found for those with no formal education. These findings highlight the need for targeted health education programs for populations with limited access to formal education and health information. A One Health approach, integrating human, animal, and environmental health sectors, should be prioritized to improve zoonoses awareness and reduce transmission risks, especially in rural and marginalized communities.

Keywords: Laos, zoonotic diseases, livestock ownership, multilevel analysis, ethnic minority, One Health

1. Introduction

Zoonoses are infectious diseases that can be transmitted between animals and humans, posing substantial public health challenges, particularly in low-income and middle-income countries (1). In Southeast Asia, close human-animal interactions, traditional agricultural practices, and limited public health infrastructure increase the risk of zoonoses transmission (2).

Despite their public health importance, awareness and knowledge of zoonoses among populations in Lao People's Democratic Republic (Lao PDR) remain poorly documented. Lao PDR is a predominantly agricultural country, with approximately 70% engaged in farming and livestock production (3). This emphasizes the need to strengthen public awareness to prevent spillover events, particularly in rural communities that reside near forested areas or experience high livestock exposure.

A One Health approach integrating human, animal, and environmental health sectors is essential for managing zoonoses in resource-limited settings. Notably, understanding the level of zoonoses awareness is crucial for designing effective health education campaigns, improving surveillance systems, and

reducing transmission risks.

2. Nationwide population-based survey in Lao PDR

We conducted a nationwide, population-based survey across 40 villages in 20 districts of Lao PDR in September 2023 to evaluate the awareness and understanding of zoonoses among the general population through a brief face-to-face interview using a single yes/no question: "Are you aware of diseases from animals?" Participants were originally recruited as part of a seroepidemiological study targeting individuals aged 4–40 years, but those < 12 years were excluded owing to cognitive limitations. After this exclusion, a total of 347 participants aged 12–40 years were analyzed. Prior to this survey, we conducted a pre-survey to assess the feasibility of including younger participants, particularly those aged 12–16 years, and confirmed that they were able to understand and appropriately respond to the questionnaire. Participants were selected using multistage cluster sampling with probability proportional to size to ensure geographic representation and population-weighted sampling. Sociodemographic data were collected and analyzed

using logistic regression to identify associated factors. Variables with a p -value < 0.05 in bivariate analysis were included in the multivariable logistic regression model. Written informed consent was obtained from all participants, and the study was approved by the institutional review boards in Japan and Laos. Overall, weighted analysis estimated zoonoses awareness at 42.9% (37.9–48.1). In multivariable analysis, females (adjusted odds ratio [AOR] = 2.38, 95% confidence interval [CI]: 1.47–3.86) and livestock owners (AOR = 2.27, 95% CI: 1.23–4.20) were significantly more likely to be aware than others. Awareness was significantly lower among those with primary (AOR = 0.37, 95% CI: 0.20–0.68) and secondary education (AOR = 0.40, 95% CI: 0.23–0.70) than among those with higher education (Table 1).

3. Factors affecting awareness

To the best of our knowledge, this is the first report on zoonoses awareness in Lao PDR, as identified through a PubMed literature search. Public awareness of zoonoses varies significantly across different regions. These disparities in zoonoses awareness highlight the global need for enhanced public education on zoonoses risks and transmission pathways. This study provides valuable insights into the awareness of zoonoses among residents in Lao PDR. Our findings highlight significant disparities in knowledge based on sex, educational attainment, and livestock ownership. These disparities may stem from sociodemographic factors and structural barriers, such as limited access to health education, language differences, or rural infrastructure constraints.

i) Sex: In this study, females were significantly more likely to be aware of zoonoses than males. This may reflect their roles in caregiving, household management, and food preparation in Lao PDR, which may expose them to more health information. While studies on sex and zoonoses awareness have shown mixed results across different settings (4,5), our nationally representative sample suggests that sex-based differences in awareness exist in Lao PDR. Future studies should explore the underlying reasons for this disparity.

ii) Education: Individuals with primary or secondary school education were significantly less likely to recognize zoonoses than those with higher education, whereas no significant difference was observed for participants with no education. This highlights the critical role of formal education in enhancing health literacy. Limited awareness in these groups may contribute to delayed awareness of zoonoses symptoms, underutilization of healthcare resources, and increased transmission risks within communities. Community-based educational programs are instrumental in improving public awareness of zoonoses. Therefore, culturally and age-appropriate educational interventions

should be implemented. To achieve sustainable and comprehensive improvements in zoonoses awareness and prevention, it is essential to adopt a One Health approach (6). Considering that zoonoses account for 60% of new diseases (7), effective education of the appropriate populations will protect the population from emerging infectious disease crises.

iii) Livestock ownership: Past studies indicate that occupational context shapes zoonoses awareness. In Nepal and Ethiopia, 72.1% and 75.5% of livestock farmers were aware of zoonoses (8,9). In Laos, awareness among livestock owners was 46.4% — higher than among non-owners yet lower than in Nepal and Ethiopia, likely reflecting differences in production systems, education, and access to health information. Livestock owners' more frequent and direct animal contact may also increase exposure to guidance from veterinarians, extension workers, or agricultural programs, which could contribute to higher awareness, although our study could not fully clarify the mechanism.

This study has some limitations. First, the small sample size, particularly among some ethnic and educational groups, may have reduced statistical power and limited generalizability. Second, only participants aged 12–40 years were included, excluding older adults who may have different awareness levels. Third, the outcome was measured using a single binary question, which may not fully capture depth of understanding. Finally, certain populations, including urban residents, persons with disabilities, and older adults, were not represented in the sample, which may limit the applicability of findings to the broader population.

In conclusion, $< 50\%$ of surveyed individuals were aware of zoonoses in Lao PDR. Awareness was significantly higher among females and livestock owners, and significantly lower among those with primary and secondary education than among those with higher education. These findings highlight the need for targeted health education programs to reduce disparities. A One Health approach — integrating human, animal, and environmental sectors — should be prioritized to improve awareness and prevent zoonotic risks, particularly in underserved rural communities.

Acknowledgements

We thank everyone who cooperated with our survey in Lao PDR.

Funding: This study was supported by the NCGM Intramural Research Fund (22A01, 22A2006, and 25A03) and NCGM COVID-19 Gift Fund (National Center for Global Health and Medicine COVID-19 Gift Fund). These funding bodies had no role in the study design; collection, analysis, and interpretation of data; and manuscript writing.

Table 1. Factors associated with the awareness of zoonoses

Items	Absolute number	Estimated proportion of zoonoses awareness			Bivariate analysis			Multivariable analysis		
		Weighted %	95% CI		Crude odds ratio	95% CI	p-value	Adjusted odds ratio	95% CI	p-value
Age group, years, range										
12–15	68	38.2	26.6–49.8		Reference					
16–24	116	39.0	30.0–47.9		1.03	0.56–1.91	0.922			
25–40	163	47.8	40.1–55.5		1.48	0.83–2.65	0.181			
Sex										
Male	130	31.6	23.5–39.6		Reference					
Female	217	49.7	43.0–56.4		2.15	1.36–3.39	0.001	Reference	1.47–3.86	<0.001
Marriage status										
Married	193	43.0	35.9–50.0		Reference					
Not married	154	42.9	35.0–50.7		0.99	0.65–1.53	0.98			
Ethnicity										
Lao	207	46.8	40.0–53.6		Reference					
Khmu	51	41.3	27.7–54.9		0.80	0.43–1.49	0.483			
Ka tang	20	34.7	13.8–55.6		0.60	0.23–1.58	0.304			
Brao	17	29.1	7.4–50.7		0.47	0.16–1.38	0.167			
Phou noi	9	66.7	35.7–97.6		2.27	0.55–9.41	0.256			
Ta-oi	10	30.2	1.6–58.9		0.49	0.12–1.97	0.316			
Pray	7	14.6	-11.9–41.2		0.20	0.02–1.67	0.135			
Other	26	34.8	16.4–53.3		0.61	0.26–1.43	0.253			
House type										
Traditional	146	36.9	29.1–44.8		Reference					
Modern	201	47.3	40.3–54.2		0.65	0.42–1.01	0.057			
Air conditioning*										
Yes	265	53.6	42.7–64.5		53.6	42.7–64.5	0.027	1.51	0.88–2.60	0.135
No	82	39.6	33.7–45.5		Reference					
Education										
No education**	24	33.1	14.2–52.0		33.1	0.13–0.84	0.021	0.39	0.13–1.13	0.082
Primary school	91	36.0	24.2–43.8		34.0	24.2–43.8	<0.001	0.37	0.20–0.68	0.002
Secondary school	127	37.0	28.5–45.4		37.0	28.5–45.4	0.001	0.40	0.23–0.70	0.001
High school or higher	105				Reference			Reference		
Occupation										
Farmer	161	39.7	32.1–47.3		Reference					
Housewife	14	35.8	10.5–61.6		0.85	0.27–2.66	0.776			
Labor	28	35.6	17.8–53.4		0.84	0.36–1.94	0.680			
Officer	12	58.1	30.0–86.2		2.11	0.64–6.96	0.220			
Private/Company worker	28	49.8	31.2–68.5		1.51	0.67–3.39	0.319			
Unemployed***	103	47.5	37.8–57.2		1.37	0.83–2.27	0.216			
Other	1	0	Omitted		-	-	-			
Income										
< 2 million Lao Kip	179	37.4	29.5–45.2		Reference					
> 2 million Lao Kip	168	47.2	37.0–57.5		1.67	1.08–2.56	0.020	1.59	0.99–2.54	0.053
Livestock owners										
Yes	276	46.4	40.5–52.3		2.08	1.18–3.66	0.011	2.27	1.23–4.20	0.009
No	71	29.4	18.7–40.0		Reference			Reference		

*Presence of an air conditioner in the household. **Defined as never having attended formal schooling. ***Students are categorized as unemployed.

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

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Received June 19, 2025; Revised August 23, 2025; Accepted August 29, 2025.

Released online in J-STAGE as advance publication September 2, 2025.

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Print ISSN: 2434-9186
Online ISSN: 2434-9194
Issues/Year: 6
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(As of August 2025)

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