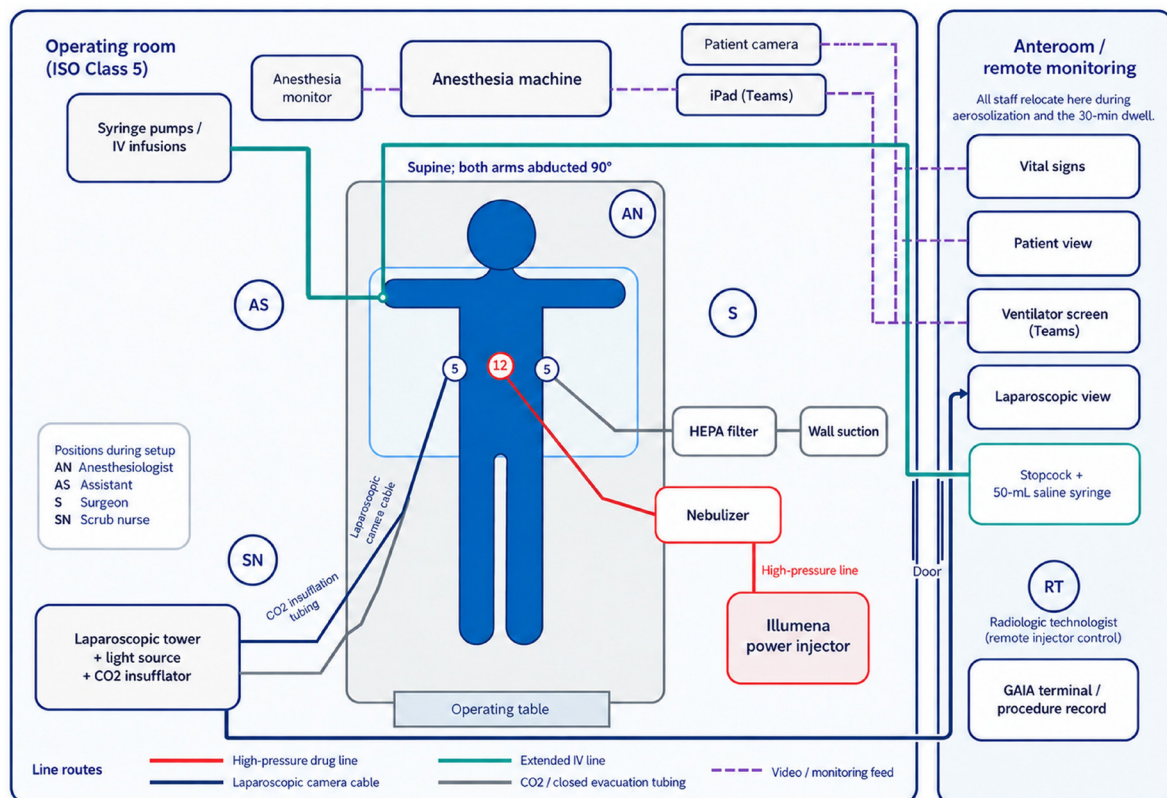




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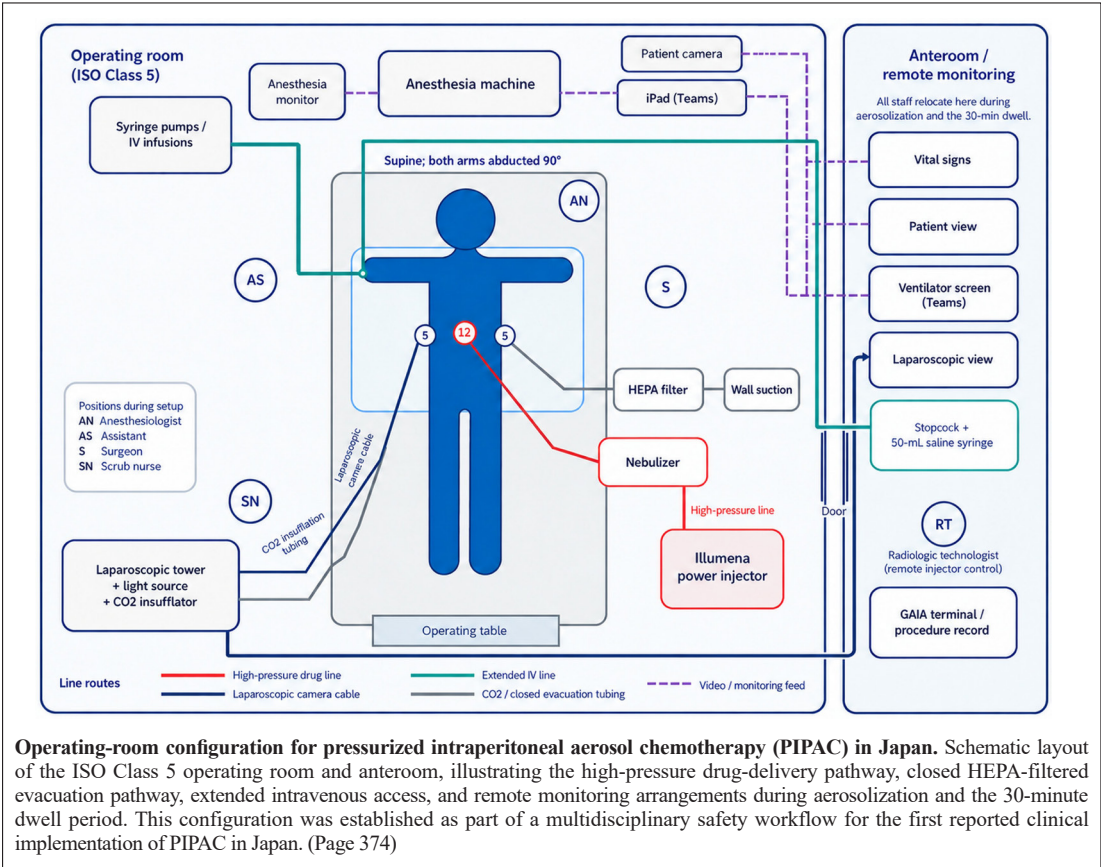
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COVER FIGURE



Clinical research on emerging medical technologies in Japan: Implementation, evaluation, and evidence generation

Takashi Karako*

National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan.

Abstract: Two articles in this issue report on early Japanese clinical implementation of histotripsy for liver tumors and pressurized intraperitoneal aerosol chemotherapy for peritoneal metastases. Together, these reports illustrate how procedure-dependent technologies enter a new healthcare system and how their early clinical use can be evaluated. The clinical value of such interventions depends on more than device access or operator skill. It requires patient selection, appraisal of evidence from abroad, regulatory and ethical review, simulations, multidisciplinary workflow, safety governance, and outcome assessment that separates technical completion from patient benefit. Japan has the clinical expertise and institutional structures to carefully introduce selected technologies, but first-in-country use should serve as a starting point for local evidence generation rather than an endpoint. A practical pathway is proposed in which initial clinical introduction is embedded within protocolized evaluation and followed by assessment of reproducibility and comparison with established treatment options.

Keywords: first-in-country use, multidisciplinary workflow, patient selection, regulatory science, complex interventions

1. A shared problem in early clinical introduction

In this issue of *Global Health & Medicine*, Ishizawa and colleagues report on the first clinical implementation of histotripsy for liver tumors in Japan, and Takeuchi and colleagues report on the first implementation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) for peritoneal metastases in Japan (1,2). The two technologies differ in target disease, physical principle, equipment, and therapeutic intent. Their shared importance lies elsewhere. Together, the two reports illustrate that safe and evaluable clinical introduction depends not only on the technology itself but also on local systems for training, governance, workflow, and evaluation.

Histotripsy has advanced through pivotal and early post-approval use that substantiates its feasibility and that sheds light on patient selection, while safety and local control continue to require careful follow-up (3,4). PIPAC has similarly been supported by rationale papers, technical guidance, and early-phase clinical data in patients with peritoneal metastases (5-7). Such evidence is necessary for introduction, but it is not sufficient for domestic dissemination. Local implementation requires answering a separate research question: can the

technology be used safely, reproducibly, and ethically within the Japanese clinical environment?

2. Protocolized first use, not demonstration alone

In both reports, treatment of the first patient was preceded by a structured process that included protocol development, training or observation, institutional review, and team preparation. In the PIPAC report, the implementation process was particularly explicit: international training, animal experiments, operating-room simulations, pharmacy and injector workflows, remote anesthesia management, closed evacuation, and a staged safety checklist were established before clinical use (2). The histotripsy report also emphasizes an approved clinical research protocol, operator training, simulations with operating-room staff, and early safety surveillance (1).

This distinction is important. A first-in-country procedure has limited scientific value if it is presented only as a technical achievement. Clear reporting of preparations, eligibility criteria, safety measures, outcome definitions, and limitations strengthens the value of these early clinical experiences and helps other institutions assess whether and how the pathway can be

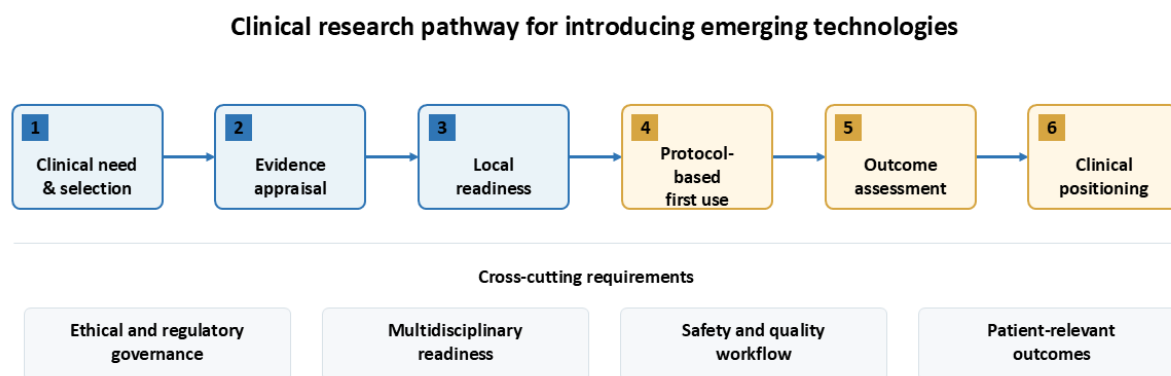


Figure 1. Clinical research pathway for emerging medical technologies in Japan. The pathway begins with a defined clinical need and patient selection, followed by appraisal of domestic evidence and evidence from overseas and assessment of local readiness. Early clinical use should follow a predefined protocol under appropriate ethical and regulatory oversight, with outcome assessment that separates technical completion from patient-relevant benefit. Broader clinical positioning should depend on reproducibility, safety, patient selection, comparative value, and feasibility in routine practice. Cross-cutting requirements include ethical and regulatory governance, multidisciplinary readiness, safety and quality workflow, and patient-relevant outcomes.

replicated.

3. Evaluation after technical success

Procedure-dependent technologies can be viewed as complex clinical interventions because their performance depends not only on the device or procedure itself but also on operator expertise, team coordination, and the clinical setting in which they are delivered. Reporting guidance such as the Template for Intervention Description and Replication (TIDieR) and broader methodological work on complex interventions are therefore relevant (8,9). For this reason, early reports should distinguish technical completion, short-term safety, biological effects, and patient-relevant benefit.

For histotripsy, early endpoints may include target visualization, treatment-zone coverage, perioperative adverse events, and short-term imaging. Later evaluation should address local tumor control, recurrence, liver function, quality of life, retreatment, and comparison with established options such as resection, thermal ablation, and radiotherapy. For PIPAC, early feasibility includes access, aerosolization, containment, occupational safety workflow, symptom burden, and recovery. Subsequent assessment should examine repeated administration, response within the peritoneal cavity, systemic treatment sequencing, quality of life, and selection relative to cytoreductive surgery, hyperthermic intraperitoneal chemotherapy, and systemic therapy.

4. A practical pathway for Japan

Japan is a suitable setting for evaluable introduction of select emerging technologies because it combines advanced clinical expertise with formal structures for clinical research oversight. The Clinical Research Act and related review systems provide a framework for enhancing

the reliability and transparency of clinical research conducted under applicable regulatory oversight in Japan (10). This framework can be used not only to control risk but also to generate evidence that is relevant to Japanese practice. Japan's universal health insurance system also gives local evidence generation particular importance. Once sufficient evidence has been established and appropriate reimbursement is obtained, a new technology may become accessible within a nationally regulated framework of care.

A practical pathway is summarized in Figure 1. It begins with a defined clinical need and patient selection, followed by appraisal of domestic evidence and evidence from abroad. Local readiness should then be assessed, including training, staffing, facilities, emergency plans, pharmacy or engineering requirements, data capture, and conflict-of-interest management. Protocol-based first use should be followed by outcome assessment that separates technical success from clinical benefit. Further evidence on reproducibility, safety, patient selection, and comparative clinical value is needed to inform decisions about broader dissemination. These considerations apply across all stages of implementation and evaluation.

5. Conclusion

The two reports in this issue should not be viewed simply as the arrival of two new technologies in Japan. They illustrate a broader requirement for contemporary clinical research: innovations must be introduced through pathways that are prepared, transparent, reproducible, and evaluable. First-in-country use is meaningful when it creates the conditions for generating evidence from local practice. The next task is therefore not rapid diffusion alone but disciplined evaluation that can determine when, for whom, and in relation to which established treatments these technologies should become part of routine care.

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**Address correspondence to:*

Takashi Karako, National Center for Global Health and Medicine, Japan Institute for Health Security, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: politang-ky@umin.ac.jp

Why do patients bypass primary care? Trust, resource concentration, and risk in China's tiered healthcare system: A comparative policy perspective

Jingyi Ma^{1,2}, Lingbo Wei³, Fei Ma^{1,2,4,*}

¹ Department of Outpatient and Emergency, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China;

² Institute of Hospital Development Strategy, China Hospital Development Institute, Shanghai Jiao Tong University, Shanghai, China;

³ Department of Finance, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China;

⁴ Hospital Ethics Committee, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Abstract: China's tiered healthcare system seeks to direct patients to clinically appropriate levels of care, and yet many patients continue to seek care directly at higher-level hospitals. This Policy Forum proposes a conceptual explanation linking resource and capability concentration, perceived institutional trust differentials, risk-avoidant choice of providers, and the amplification of reputation through family and social networks. Illustrative comparisons with the United Kingdom, the United States, Japan, and South Korea reveal related but non-equivalent forms of alternative healthcare access under different arrangements. The framework does not treat bypassing a tier as inherently irrational or claim that the proposed pathways have been causally established. Instead, it suggests that credible primary care, reliable referral benefits, continuity of care, risk-sensitive rules on access, aligned financial incentives, and trustworthy quality information must be developed together. The proposed framework is intended to guide empirical testing and policy evaluation rather than to rank healthcare systems or estimate the prevalence with which care is bypassed.

Keywords: healthcare utilization, choice of providers, institutional confidence, referral pathways, access policy, decision-making in the face of uncertainty

1. Introduction

China's tiered healthcare system is intended to direct routine, preventive, and chronic care toward primary-care facilities while reserving higher-level hospitals for patients who require specialized services (1). Its effectiveness therefore depends not only on the formal design of referral pathways but also on whether patients regard primary care as a credible, convenient, and clinically safe first point of contact. Reviews of China's primary healthcare system have identified persistent issues with workforce capability, incentives, integration, and measurement of quality (2).

When patients bypass primary care, tertiary-care hospitals may face avoidable congestion while community-based services remain underused. A national longitudinal study also reported a decline in the stated preference for primary healthcare between 2012 and 2018, although preference is not equivalent to observed utilization (3). Such choices should not automatically be characterized as irrational or noncompliant. In the face

of diagnostic uncertainty, a patient may select the facility perceived to offer the lowest risk of misdiagnosis, delay, or failed referral, even when that decision is less efficient from a system perspective. Recent qualitative work likewise suggests that habitual preferences and reflective risk assessment can interact in the bypassing of primary care (4).

This Policy Forum develops a mechanism-based explanation for the bypassing of primary care in China and it uses selected international examples to clarify how institutional access arrangements shape related care-seeking behaviors. Its principal contribution is a proposed pathway in which structural disparities influence perceived capability and trust, risk-avoidant reasoning translates those perceptions into choice of providers, and mechanisms of social reputation amplify the process.

2. Comparative context and analytical approach

A patient bypassing care should be distinguished

from other deviations from anticipated care pathways, including nonurgent emergency department use, specialist self-referral, urgent-care substitution, and preferring a hospital over a community provider. Choice of providers is shaped by patient, provider, and contextual factors, and the meaning of a particular choice depends on associated gatekeeping, insurance, payment, and referral arrangements (5).

This article uses a narrative and illustrative comparison based on selected policy documents and representative studies. The United Kingdom, the United States, Japan, and South Korea were chosen because they illustrate contrasting combinations of gatekeeping, direct-access options, financial guidance, and choice of providers. The comparison is neither a systematic review nor a ranking of national performance; differences in terminology, populations, and data sources preclude direct estimates of comparative prevalence.

Within the United Kingdom's National Health Service, access to specialists in hospitals generally requires referral from a general practitioner, subject to specified exceptions (6). In the United States, nonurgent emergency department use has been associated with convenience, barriers to access, and negative perceptions of alternatives, although definitions vary substantially across studies (7). Japan generally preserves direct access while applying additional charges at specified hospitals for some patients without a referral (8). South Korean evidence reveals the existence of a hospital preference among patients whose conditions may be manageable in primary care amidst a relatively broad choice of providers (9).

Table 1 summarizes the institutional access arrangements and the principal forms of bypassing care across the five settings. As shown in Table 1, these behaviors are related but not directly equivalent. The United Kingdom illustrates formal specialist-referral requirements, the United States illustrates nonurgent emergency-department use shaped partly by convenience and barriers to access, Japan illustrates direct hospital access moderated by additional charges, and South Korea illustrates a preference for hospitals amidst a relatively broad choice of providers. China's challenge therefore should be interpreted within its own tiered-care reforms rather than inferred from a single cross-national mechanism.

3. Mechanisms for the bypassing of primary care in China

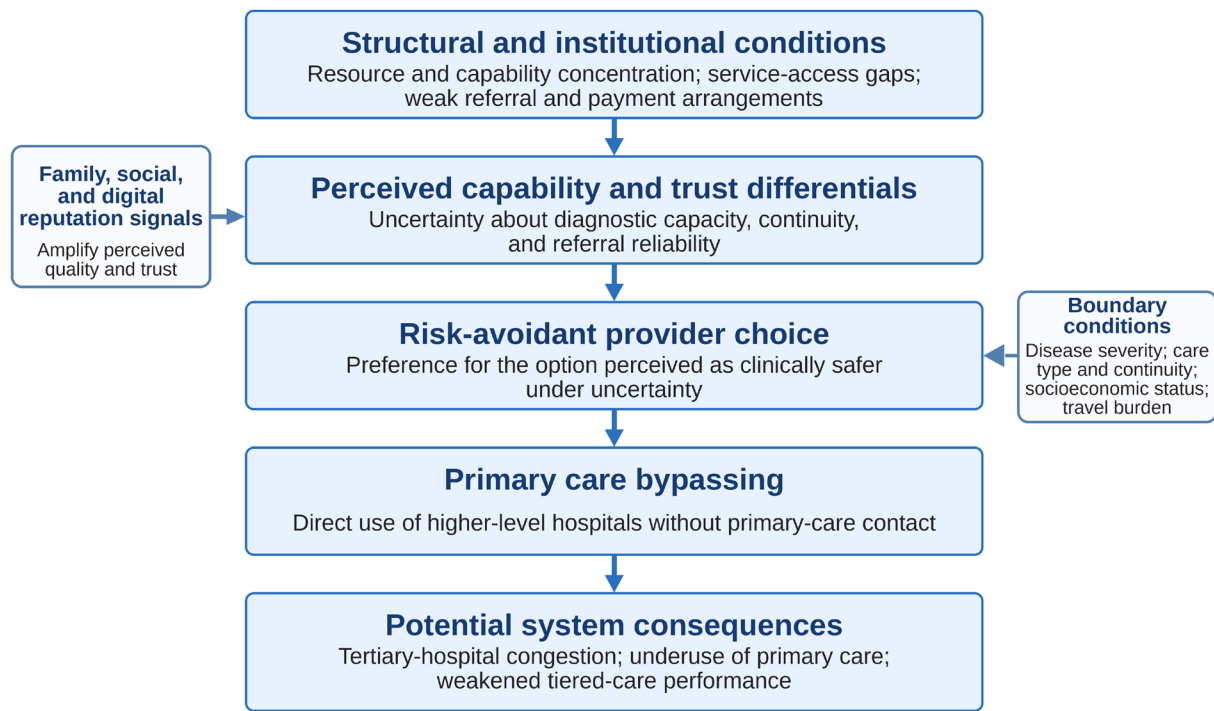
The proposed relationships are summarized in Figure 1. Resource concentration, service-access gaps, and limited referral or payment arrangements may contribute to perceived capability and trust differentials. In the face of uncertainty, these perceptions may encourage a risk-avoidant choice of providers, while family and social reputation signals may amplify perceived differences

Table 1. Conceptual comparison of healthcare-seeking behaviors related to bypassing care and access arrangements

Comparative dimension	China	United Kingdom	United States	Japan	South Korea
Formal primary care gatekeeping	Partial and regionally variable	General-practitioner referral is generally required for specialist care in a hospital	Arrangements vary by insurance plan, provider network, and service type	Relatively weak	Relatively weak
Direct access to hospitals	Generally permitted	Specified exceptions to the usual specialist-referral pathway exist	Emergency department access is possible; coverage and cost-sharing vary	Generally permitted; additional charges may apply at specified hospitals without a referral	Broad patient choice of provider
Main behavior related to bypassing care	Direct use of tertiary-care hospitals	Use of permitted alternative routes rather than direct specialist self-referral	Nonurgent emergency-department use associated with convenience, access barriers, and perceptions of alternatives	Direct use of specified large hospitals without a referral, subject in some cases to additional charges	Hospital rather than clinic use for conditions potentially manageable in primary care
Principal mechanisms considered	Perceived capability and trust gaps, resource concentration, few referrals, and risk avoidance	Gatekeeping, accessibility, and waiting time	Insurance design, affordability, continuity, convenience, and access	Choice of providers combined with referral incentives and additional charges	Choice of providers, reputation, and resource concentration
Interpretive relevance to China	Provision of a reference	Alternative entryways are accessed in the face of strong gatekeeping; not directly equivalent to bypassing care at the hospital level	Shows access- and payment-related substitution; definitions of nonurgent use vary	Limited financial guidance provided while substantial choice is retained	Hospital preference evident with broad choice but in a different institutional setting

Notes on evidence sources: The comparison is illustrative rather than exhaustive. The behaviors shown are functionally related but not directly equivalent, and the table should not be interpreted as a ranking of healthcare-system performance. Country descriptions are substantiated by the sources cited in the corresponding cells and main text.

Proposed pathways to primary care bypassing



Arrows indicate hypothesized, context-dependent relationships.

Figure 1. Proposed conceptual framework for the bypassing of primary care in China. Resource concentration, service-access gaps, and limited referral and payment arrangements may contribute to perceived capability and trust differentials. These differentials may shape a risk-avoidant choice of providers while family, social, and digital reputation networks may amplify the process. Proposed consequences include tertiary-care hospital congestion, underuse of primary care, and diminished performance by the tiered healthcare system. Arrows indicate hypothesized rather than empirically established causal relationships.

(4,5). Together, these mechanisms may increase the bypassing of primary care and contribute to tertiary-care hospital congestion, underuse of primary care, and diminished tiered-care performance.

3.1. Structural and institutional conditions

Highly qualified clinicians, advanced diagnostic technologies, and specialist services remain concentrated in tertiary-care hospitals and major urban centers. A systematic review has identified perceived quality, provider capability, accessibility, and resource distribution as important correlates of the level of care chosen (10). Spatial analysis in Sichuan further demonstrated substantial geographic variation in access to primary healthcare (11). Qualitative evidence indicates that patients may associate higher-level facilities with greater diagnostic reliability and clinical safety (12).

These disparities can make hospital rank a practical signal of expected quality. Observational evidence among middle-aged and older adults reveals the bypassing of primary care facilities, although the

determinants vary by population and setting (13). A recent study comparing tertiary-care hospitals to community clinics likewise found that provider attributes, patient experience, and family-doctor-related factors were associated with choice (14). Evaluations of tiered-care reform also suggest that primary care capacity, institutional coordination, and functional referral arrangements must develop together (15). Structural inequality therefore creates the conditions for the bypassing of primary care but does not, by itself, establish why a particular patient chooses a tertiary-care hospital.

3.2. Trust, uncertainty, and risk-avoidant decision-making

Institutional trust is best treated as an intervening mechanism rather than an independent or fixed patient attribute. When patients are uncertain about diagnostic capacity, medicine availability, continuity, or the reliability of onward referral, they may place greater confidence in tertiary-care hospitals. Research in China has linked doctor-patient trust with choice of providers

(16), and a township-health-center study found that patient experience and trust were positively associated with willingness to seek care (17). Evidence from Shanghai and Shenzhen also suggests that perceived primary-care quality can change following reforms, although effects may differ by setting (18). Reviews of primary healthcare reform confirm that perceived service quality and organizational capacity remain central implementation concerns (19).

Limited knowledge and distrust may further narrow the range of options patients regard as safe (20). Hospital attributes such as level, physician reputation, equipment, and access can influence first-visit preferences, although stated preferences in discrete-choice experiments should not be treated as equivalent to observed utilization (21). A cross-sectional study based on rational choice theory found that survival, economic, and social considerations were all associated with the choice of primary-care facilities (22). In the face of uncertainty, willingness to use primary care first may also vary with perceived severity and expected consequences of delay (23). The proposed mechanism is therefore probabilistic: perceived capability gaps may shape trust, and trust may influence risk evaluation, but these relationships require longitudinal or experimental testing.

3.3. Social amplification and boundary conditions

Care-seeking decisions may be embedded in family discussion, recommendations from acquaintances, and socially conveyed impressions of hospitals and physicians (4,5). Online physician effort and reputation have also been associated with patient choice on a large Chinese platform, although platform-based physician selection is not equivalent to bypassing primary care (24). These channels can amplify reputation signals, but the available evidence does not justify treating them as decisive or culturally uniform determinants. Their influence is likely to depend on disease severity, prior experience, continuity with a clinician, health literacy, socioeconomic resources, rural or urban residence, and travel burden.

Institutional incentives also shape the cost of acting on these perceptions. When reimbursement differences are modest, referral benefits are uncertain, and direct hospital access remains feasible, the opportunity cost of bypassing care may be low. Insurance pooling and benefit design can alter healthcare-seeking behavior and expenditure, but their effects may differ across regions and population groups (25). These conditions interact with trust and perceived risk rather than operating as isolated mechanisms.

Table 2 synthesizes how the proposed mechanisms may operate in China, their hypothesized pathways, potential system consequences, and corresponding policy responses. The mechanisms should be interpreted as interacting and context-dependent rather than as

Table 2. Proposed mechanisms of the bypassing of primary care in China and policy responses

Mechanism	Manifestation in China	Hypothesized pathway	Potential consequences	Policy response
Resource and capability gaps	Specialist staff, technology, and prestige are concentrated in tertiary-care hospitals and large cities	Visible disparities may increase perceived quality differences	Concentrated patient flows and regional inequity	Strengthen primary care capacity and integrated networks; monitor capability and access
Referral, access, and payment conditions	Referral benefits and reimbursement differences may be insufficient or unreliable	Low opportunity cost of direct hospital use may diminish primary-care-first pathways	Poor coordination and avoidable tertiary use	Provide reserved referral access, record exchange, feedback, and equitable financial incentives
Perceived uncertainty and trust differentials	Patients may be uncertain about diagnostic capacity, medicine availability, and referral reliability	Uncertainty may shift trust toward higher-level institutions	Underuse of primary care and delayed relationship building	Publish validated capability information and strengthen continuity of care
Risk-avoidant decision-making	Patients may prioritize the provider perceived as safest when severity is uncertain	Perceived consequences of error or delay may outweigh cost or convenience	Use of higher-cost services for lower-risk conditions	Use risk-stratified pathways with explicit high-risk exceptions and safety monitoring
Family, social, and digital reputation amplification	Advice, online communities, rankings, and physician reputation shape perceived quality	Informal signals may amplify capability and trust differentials	Further concentration of demand at prestigious hospitals	Provide understandable risk-adjusted quality information and govern commercial rankings

Source: Proposed by the authors as a conceptual synthesis of the literature cited in the main text. The pathways are hypothesized and have not been causally established.

independent or empirically established causal effects.

4. Policy implications

Bypassing care can arise from interacting structural, informational, and behavioral mechanisms, so a single administrative restriction is unlikely to be sufficient. Policy design should make the preferred pathway clinically reliable and operationally valuable while ensuring timely access for patients with potentially serious conditions.

4.1. Make primary care capabilities and continuity evident

Primary-care facilities should publish standardized information on the scope of care, availability of medicines, diagnostic capacity, clinician qualifications, hours of operation, and the rate of referral. Capability reporting should use comparable definitions and external quality assurance rather than promotional claims. Family-doctor evaluation should place greater weight on continuity, chronic-disease follow-up, post-referral contact, and patient-reported trust than on enrollment alone. Higher continuity in general practice has been associated with fewer admissions for ambulatory-care-sensitive conditions, although the evidence is observational (26). Contracted family doctor services in China may also facilitate more equitable use of basic public health services, but service quality and continuity—and not enrollment alone—should remain the policy focus (27).

4.2. Align referral, access, and financial incentives with clinical risk

Referral should provide tangible benefits, such as appointments with specialists, priority diagnostics, interoperable records, mutual recognition of appropriate test results, and timely feedback to the referring clinician. A recent national policy emphasizes closer ties between first-contact and referral services and improved continuity of care (28). Implementation should be assessed using clearly defined denominators for referral completion, waiting time, feedback return, and post-referral follow-up.

A risk-stratified approach is preferable to an inflexible universal gatekeeping requirement. Primary-care-first pathways may be suitable for defined low-risk conditions, whereas suspected cancer, medical emergencies, rapidly progressive symptoms, and other high-risk situations require direct or expedited specialist access. Higher reimbursement and lower out-of-pocket costs for primary care may encourage appropriate use, but safeguards are needed for low-income populations, people with disabilities, rural residents, and patients whose clinical risk is uncertain.

4.3. Provide quality information and evaluate implementation

Unvalidated rankings and physician-reputation signals should not substitute for credible quality information. Authorities and healthcare organizations should provide understandable, risk-adjusted indicators while explaining their limitations. A systematic review of public performance reporting found variable effects operating through patient selection and changing providers, underscoring the importance of careful design and evaluation (29). Evaluation should examine whether patients use formal information, whether potentially manageable tertiary-care hospital visits decline without increasing diagnostic delay, and whether effects differ by income, age, residence, and disease risk. Interrupted time-series, controlled before-and-after, or pragmatic implementation designs would provide stronger evidence than simple post-policy utilization counts.

5. Limitations and conclusions

This Policy Forum is conceptual and has several limitations. The literature was selected narratively rather than through a systematic search; the country examples are illustrative and use non-equivalent definitions; and national-level descriptions obscure regional and population heterogeneity. The proposed sequence among structural conditions, trust, perceived risk, and choice of providers has not been causally established. A Chinese scale-development study offers one starting point for measuring willingness to use primary care, but broader validation is still needed (30). Future studies should prespecify definitions of bypassing care, measure the proposed constructs with validated instruments, distinguish stated preferences from observed utilization, and test mediation and effect modification using longitudinal, quasi-experimental, or mixed-methods designs.

In conclusion, the bypassing of primary care in China may reflect a combination of resource and capability disparities, uncertainty about primary care and referral reliability, risk-avoidant decision-making, and reputation amplification. The comparative examples showed that related patterns may emerge under different access arrangements, but they do not substantiate a universal causal explanation. Reform should therefore focus on making primary care reliable, referrals valuable, financial incentives equitable, and quality information trustworthy. The framework offered here is a set of testable propositions for policy evaluation rather than a definitive account of patient behavior.

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**Address correspondence to:*

Fei Ma, Department of Outpatient and Emergency, Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, No. 1665 Kongjiang Road, Shanghai 200092, China.

E-mail: mafei@xinhuaamed.com.cn

Assessing an educational strategy to improve community health provider-led provision of cervical cancer screening services in western Kenya: A secondary analysis of the Elimisha-HPV cluster-randomized controlled trial

Purity Chepkoech^{1,5}, Stephanie B. Jordan^{2,5,*}, Breandan Makhulo³, Jenniffer Ambaka⁴, Francesca Odhiambo⁴, Evans Obuto Otieno⁴, Joe Egger¹, Megan Huchko^{1,3,5,5}

¹ Duke Global Health Institute, Duke University, Durham, NC, USA;

² Department of Emergency Medicine, Stanford University School of Medicine, Palo Alto, CA, USA;

³ Center for Global Reproductive Health, Duke Global Health Institute, Duke University, Durham, NC, USA;

⁴ Kenya Medical Research Institute, Nairobi, Kenya;

⁵ Department of Obstetrics and Gynecology, Duke University School of Medicine, Durham, NC, USA.

Abstract: Cervical cancer disproportionately impacts women in low- and middle-income countries (LMICs), where over 90% of global cervical cancer deaths occur. Lay health workers, such as community health promoters (CHPs), with appropriate training and support, can play a pivotal role in cervical cancer prevention. Our team developed a multi-level intervention, Elimisha-HPV, to support CHP-delivered human papillomavirus (HPV) testing in Kenya. The present analysis evaluates impact of Elimisha-HPV on the following CHP outcomes: *i*) knowledge of screening delivery and privacy, confidentiality, and professionalism; *ii*) stigma associated with cervical cancer, human immunodeficiency virus (HIV), and HPV; and *iii*) confidence to counsel in screening delivery. We used descriptive statistics and linear mixed effects regression models to evaluate intervention effects (intervention group, $n = 64$; control group, $n = 60$). For knowledge and privacy, no statistically significant effects were observed (knowledge: $\beta = -0.08$ [95% CI, -0.22 to 0.07]; privacy: $\beta = 0.04$ [95% CI, -0.05 to 0.13]). No statistically significant intervention effects were observed for stigma associated with cervical cancer, HIV, or HPV (cervical cancer: $\beta = 0.02$ [95% CI, -0.13 to 0.16]; HIV: $\beta = 0.01$ [95% CI, -0.11 to 0.13]; HPV: $\beta = 0.02$ [95% CI, -0.11 to 0.14]). For the confidence to counsel Likert scale-style questions, evaluated using descriptive and regression approaches, proportional increases were observed across both arms, but the main effect was not statistically significant ($\beta = 0.01$ [95% CI, -0.09 to 0.11]). Our findings align with previous work demonstrating that stigma surrounding cervical cancer in LMICs is difficult to effectively influence, and provide a foundation for shaping future stigma-reduction campaigns. ClinicalTrials.gov identifier: NCT05736588.

Keywords: reproductive health, global health, health services, implementation science

1. Introduction

Cervical cancer continues to pose a significant health threat to women in low- and middle-income countries (LMICs), with over 90% of global cervical cancer deaths occurring in LMICs, particularly in sub-Saharan Africa (1). Eastern Africa bears the highest burden globally, with elevated rates of both incidence and mortality (incidence rates of 40.1/100,000 compared to 6.2/100,000 in North America, and mortality rates of 28.6/100,000 compared to 2.1/100,000 in North America) (2). In Kenya, cervical cancer is the leading cause of cancer-related deaths among women, bearing an age-standardized incidence

rate of 33.8/100,000 (3). Low rates of screening and uptake of preventative treatment among eligible women persist as significant challenges in cervical cancer prevention efforts, driven by interplay of structural, individual, and sociocultural factors (4,5).

In addition to financial and logistical challenges to achieving population-wide coverage of screening, stigma related to human papillomavirus (HPV) and cervical cancer can pose obstacles to cervical cancer prevention efforts, similar to the effects of stigma associated with human immunodeficiency virus (HIV) (6,7). In many LMICs, stigma surrounding cervical cancer is fueled by multiple factors, including visible manifestations of

advanced cervical cancer (*e.g.*, wasting and bleeding) as well as real or perceived lack of treatment options. Furthermore, cervical cancer's association with HIV/AIDS and the fact that HPV is a sexually transmitted infection (STI) can add a layer of moral judgment that perpetuates cervical cancer stigma (7,8). These drivers of stigma may impact women's decisions to seek HPV/cervical cancer prevention services and affect trust in, and acceptability of, these services.

Healthcare providers' attitudes and behaviors in delivering cervical cancer services are shaped by these societal attitudes, which may impact their counseling and management of women (9). Anticipated or experienced discrimination, loss of confidentiality, and disrespect in healthcare settings can lead to hesitancy and a lack of trust among affected women, further complicating efforts to improve cervical cancer outcomes (8,10). As countries work to achieve the World Health Organization (WHO) goal to eliminate cervical cancer in the next century, it will be essential to implement strategies that effectively address stigma (11,12).

One increasingly common approach to screening delivery is through the use of lay providers from the community, who take on roles as community educators, advocates, and role models (13-15). In Kenya, this cadre is called Community Health Promoters (CHPs). CHPs' strong community ties, mobility, and cultural understanding enable them to reach rural populations that may otherwise be difficult to access (16). With appropriate training and support, CHPs are uniquely positioned to spearhead initiatives aimed at raising awareness, dispelling myths and misconceptions, and fostering acceptance of cervical cancer prevention services within their communities (12,17). However, despite their potentially pivotal role in cervical cancer prevention, they receive limited training in identifying and addressing stigma surrounding HPV and cervical cancer prevention. The majority of training CHPs receive on cervical cancer prevention is focused on HPV and cervical cancer risk factors, and signs and symptoms of invasive cancer, much of which can be stigmatizing (10,18). Educational interventions and counseling strategies for CHPs must be designed in a way that will not inadvertently increase stigma while equipping CHPs with knowledge and skills to convey accurate and actionable steps. Furthermore, previous research has demonstrated low baseline levels of health domain-specific knowledge and inadequate training and support resources for CHPs (19). Additionally, few CHPs are trained in client-centered approaches to patient care, which have also been found to improve patient satisfaction and outcomes (20).

Our team developed "Elimisha-HPV", a multi-level, stigma-responsive service delivery model for CHP-led, home-based HPV-screening in western Kenya. This work builds on primary analysis assessing the effect of the Elimisha-HPV intervention on cervical cancer screening

and follow-up. In complement to this analysis of primary effects of Elimisha-HPV, we sought to evaluate the intervention's specific components: *i*) CHPs' confidence in their ability to counsel women and provide HPV and cervical cancer prevention services; *ii*) CHPs' knowledge of cervical cancer prevention and privacy, confidentiality, and professionalism; and *iii*) CHPs' levels of stigma associated with cervical cancer, HIV, and HPV.

2. Materials and Methods

2.1. Study design, setting, and participants

Our study team partnered with the Kisumu County Health Management Team (CHMT) to conduct a cluster-randomized controlled trial (cRCT) of Elimisha-HPV in twelve community health units (CHUs) in two Kisumu sub-counties. Kisumu County is located in western Kenya, an area with high HIV prevalence and low coverage of cervical cancer screening services. In Kisumu, health facilities are linked with home-based services provided by CHPs through CHUs. Each CHU has approximately ten CHPs attached, as well as a facility-based supervisor.

After agreement with health facility management and CHU supervisors, all CHPs assigned to the selected CHUs were approached by our study team and invited to participate in the study activities. A CHP was included if they demonstrated an understanding of the study's objectives and commitment to participate in all training sessions.

2.2. Intervention and training procedures

Training across the twelve study health centers was carried out in six waves, each with CHPs and supervisors from two CHUs within the same study arm. Post-training, CHPs had hands-on mentorship with study staff before they were deployed to their respective communities to administer HPV/cervical cancer education, outreach, and HPV-based self-sampling services to women in their homes, utilizing either Elimisha-HPV or control strategies.

Training curriculum for both arms included two modules covering: *i*) HPV and cervical cancer pathogenesis, risk factors, HPV vaccination, screening, and treatment guidelines, and *ii*) counseling of women diagnosed with HPV/cervical cancer (see Supplement 1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=127>). The Elimisha-HPV curriculum also contained a module on communication, stigma, privacy, and confidentiality, with specific training on motivational interviewing. This module included definitions of stigma and examples of stigmatizing behavior and attitudes. Content on privacy, confidentiality, and motivational interviewing was provided through examples and role playing. The

additional Elimisha-HPV module was approximately half-a-day in length. Further details on differences between the standard training module and the Elimisha-HPV module are specified in Supplement 1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=127>).

Although the third module was unique to the Elimisha-HPV curriculum, all three modules were reviewed to ensure patient-centered communication and stigma-reducing language. Content of the curriculum was designed to address gaps in CHP training identified from our experience working in the region, incorporating best practices from the literature (21,22). Input from the Community Health Department of Kisumu County was sought to ensure linguistic, contextual, and cultural appropriateness. We adapted the WHO and the Kenya National guidelines for HPV-based cervical cancer screening (23,24).

Training was conducted in English by two experienced multilingual trainers fluent in Dholuo, Kiswahili, and English, because many CHPs asked questions in Dholuo or Kiswahili. We utilized a variety of instruction methods, including slide presentations, role plays, pictorials, scenario-based case studies, group discussions, and a video. Training sessions were held at locations chosen by the CHU supervisors, with approximately twenty CHPs from two CHUs attending each. For the intervention arm, training spanned two full days, while for the control group, it was conducted in one and a half days. The same trainers facilitated both intervention and control group sessions. Training was followed by mentorship in the field until the CHP was felt to be proficient. The post-test assessment was conducted after the second day of group training.

2.3. Survey administration and outcome measures

A self-administered pre/post-training survey in participants' preferred language, either English or Luo, was used to evaluate outcomes of interest. The first part of the survey aimed to evaluate CHPs' confidence in providing cervical cancer prevention services (3 Likert-scale items; minimum number of completed items required to be included in score calculation = 2), knowledge of HPV and cervical cancer prevention (5 closed-ended items; minimum number of completed items required to be included in score calculation = 3), and understanding of privacy, confidentiality, and professionalism in delivering HPV/cervical cancer services (9 vignette-based items; minimum number of completed items to be included in score calculation = 6) (25). The minimum number of completed items required for inclusion was set at approximately two-thirds of the total number of items.

Knowledge scores were measured numerically as the sum of all knowledge-related questions (theoretical sum score range: 5–24). Privacy, confidentiality, and

professionalism scores were measured numerically as the sum of all privacy-related questions (theoretical sum score range: 5–21). Missing values, "prefer not to answer" and "don't know" responses were excluded.

Confidence scores were measured using Likert-scale measurement (either "Strongly Agree", "Agree", "Disagree", "Strongly Disagree", "Don't know", "Prefer not to answer" or "Poor", "Fair", "Good", "Very Good", "Excellent", "Don't know"). In a supplementary analysis, a numerical composite confidence score was calculated, by converting Likert scale responses to a numeric scale ("Strongly Agree" = 4, "Agree" = 3, "Disagree" = 2, "Strongly Disagree" = 1; "Excellent" = 5, "Very Good" = 4, "Good" = 3, "Fair" = 2, "Poor" = 1), summing item scores for each participant-time observation, and then calculating mean composite score; no standardization or rescaling was applied. The dataset comprised 248 participant-time observations from 124 CHPs assessed at two time points (preintervention and postintervention). Five participant-time observations containing at least one "Don't know" or "Prefer not to answer" response were excluded, leaving 243 participant-time observations for supplementary analysis. Higher knowledge and privacy, confidentiality, and professionalism scores indicate better outcomes. In order to compare scores across domains, outcomes were analyzed using the mean item score.

The second section of the survey was a validated and pre-tested stigma assessment tool adapted from our prior work, consisting of 66 four-point Likert scale items with options to select "Strongly Agree", "Agree", "Disagree", or "Strongly Disagree" to the provided statements, measured numerically on a theoretical scale of 0–3 (0 = "Strongly Disagree", 1 = "Disagree", 2 = "Agree", 3 = "Strongly Agree"). This tool assessed CHPs' level of stigma associated with HPV (28 items; theoretical sum score range = 0–84; minimum number of completed items to be included in score calculation = 24), cervical cancer (14 items; theoretical sum score range = 0–42; minimum number of completed items to be included in score calculation = 10), and HIV (24 items; theoretical sum score range = 0–72; minimum number of completed items to be included in score calculation = 20).

In order to compare scores across domains, domains were analyzed using mean rather than sum scores. For all stigma domains, higher scores indicate higher levels of stigma (worse outcomes). For all stigma domains, no "missing" responses were observed. Additionally, participants' sociodemographic data, including age, gender, marital status, education level, number of years working as a CHP, and HPV/cervical cancer screening history were collected. Our outcomes were pre-specified secondary outcomes of the Elimisha-HPV trial.

2.4. Statistical analysis

Baseline CHP demographics were summarized using

means and standard deviations for continuous variables and counts and percentages for categorical variables. For stigma, knowledge, and privacy scores, a linear mixed effects constrained longitudinal regression model was used to determine the intervention effect (26). This model was implemented using the approach described in Equation 1 (see Supplement 2 for R code used to implement model, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=127>).

This model adjusts for individual (CHP) and cluster (CHU) variations, accounting for clustering of observations by CHU (12 total CHUs) and CHP using random intercepts for both CHU and CHP. CHPs were not treated as nested within CHUs (*i.e.*, separate random intercepts were employed for CHU and CHP).

The main intervention effect is indicated by the *Main Effect* coefficient, which reflects the effect of receiving the Elimisha-HPV training on post-test scores; this corresponds to the time-by-arm interaction term. Time was coded as numeric (1 = pre-intervention period; 2 = post-intervention period); study arm was coded as character ("Control" or "Intervention"); the time-by-arm interaction was coded as the product of time and study arm terms (1*Control, 1*Intervention, 2*Control, or 2*Intervention). Fixed effects were also included for time, whether the CHU was in a rural or urban area (reference category = rural), and the subcounty (Kisumu or Nyando) of the CHU (reference category = Kisumu).

For the Likert scale style confidence to counsel in cervical cancer screening delivery questions, descriptive statistics were used to summarize changes in distribution of confidence levels from the pre- to post-intervention periods. For supplementary analysis of the composite confidence score, the same linear mixed effect regression model used for the score-based analyses was employed (Supplement 3, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=127>).

Confidence intervals, *p*-values, and degrees of freedom were obtained using the "gtsummary" package in R (27). 95% confidence intervals were calculated using the standard formula of (estimate +/- 1.96 * standard error); two-tailed tests were used for *p*-value calculations, and degrees of freedom were calculated using the standard formula of number of observations minus number of constraints. Confidence intervals and *p*-values were calculated using default function employed by "gtsummary" (*i.e.*, "car: Anova").

Although cluster sample size was relatively small (*n* = 12 CHUs), given the sufficiently large total sample size (*n* = 124 CHPs, each observed twice, in the pre- and post-intervention period), no small-sample correction or degrees-of-freedom adjustment was applied. Confirmation using the Kenward-Roger small sample adjustment verified that parameter estimates, *p*-values, and confidence intervals were similar in adjusted and unadjusted models.

The constrained longitudinal model was implemented

using the lme4 package (Linear Mixed-Effects Model) and the linear mixed effects regression model function ("lme4::lmer") (28). All analysis were performed in R version 4.2 (29).

$$\text{Score} \sim \text{Time} + \text{Arm} * \text{Time} + \text{Rural} + \text{Sub-County} + (1 | \text{CHU}) + (1 | \text{CHP}) \quad (\text{Eq. 1})$$

2.5. Ethical approval

Ethical approval was obtained from the Institutional Review Board (IRB) at Duke University (protocol number: Duke Pro00111929) and the Scientific Ethics Review Unit (SERU) of the Kenya Medical Research Institute (KEMRI) (protocol number: KEMRI SERU 4692). This secondary analysis was conducted within the Elimisha-HPV cluster-randomized trial, which was registered on ClinicalTrials.gov at ID: NCT05736588.

3. Results

3.1. Study sample sociodemographic characteristics

Between September 25 and November 15, 2023, we conducted training and assessment of 124 CHPs attached to twelve CHUs situated across two sub-counties in Kisumu, western Kenya (64 in the intervention arm and 60 in the control arm) (Figure 1). The majority were female, married, and had worked as CHPs for at least three years (Table 1). Mean ages were similar across study arms (intervention: mean (SD) = 48.0 (8.2); control: mean (SD) = 49.4 (11.5)). Over half of the female CHPs reported a personal history of previous cervical cancer screening (51% in intervention; 62% in control), and among those who had screened, the majority had been screened with the Visual Inspection with Acetic Acid (VIA) method in the intervention and control arms (52% and 73%, respectively).

3.2. CHPs' stigma, knowledge, and privacy scores at baseline

Table 2 illustrates baseline average stigma scores across stigma, knowledge, and privacy domains. Baseline average stigma scores were generally low, reflecting low levels of stigma across all three health domains. Scores did not differ significantly between intervention and control arms for cervical cancer and HPV-related stigma; however, the intervention arm had a statistically significant higher score at baseline for HIV-related stigma (*p* = 0.023). Notably, cervical cancer stigma levels were generally higher than HPV and HIV-related stigma levels in intervention and control arms. For knowledge and privacy scores, no statistically significant differences were observed between intervention arms at baseline.

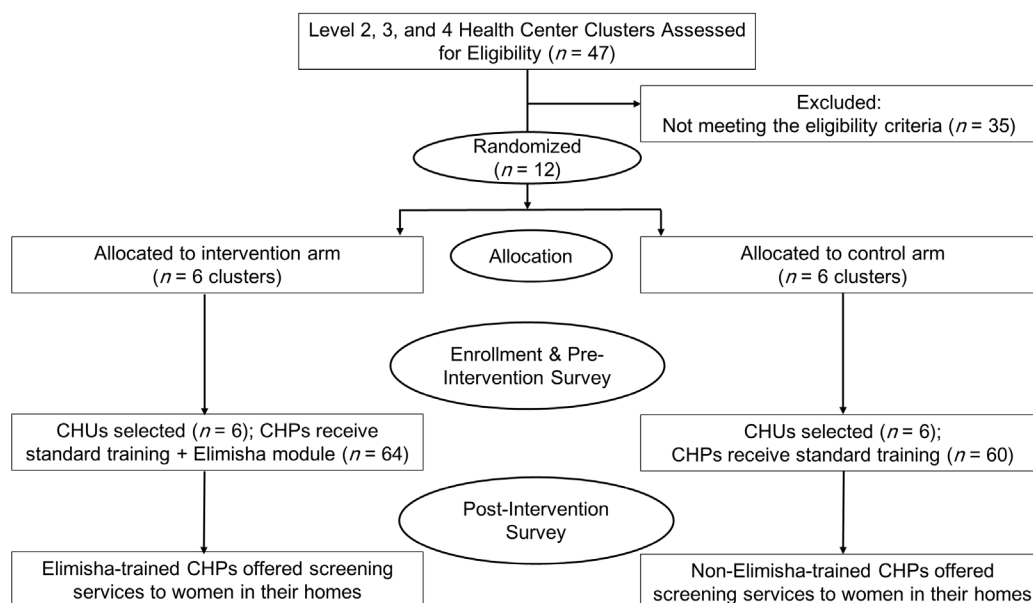


Figure 1. Flowchart of Elimisha-HPV study activities: study site selection, CHU randomization procedure, and participation in Elimisha-HPV activities (pre-intervention survey, CHP training, post-intervention survey, and screening delivery). Abbreviations: CHP, community health promoter; CHU, community health unit.

Table 1. Demographic characteristics of community health promoters participating in Elimisha-HPV

Characteristic	Control (n = 60) ¹	Intervention (n = 64) ¹
Age	49.4 (11.5)	48.0 (8.2)
Gender		
Female	50 (83%)	53 (83%)
Male	10 (17%)	11 (17%)
Marital Status		
Single	8 (13%)	5 (7.8%)
Married	43 (72%)	50 (78%)
Divorced/Separated	2 (3.3%)	1 (1.6%)
Widowed	7 (12%)	8 (13%)
Years as CHP ²		
< 1 year	4 (6.9%)	3 (4.7%)
1–3 years	0 (0%)	3 (4.7%)
≥ 3 years	54 (93%)	58 (91%)
Highest Education Level		
Up to Primary	15 (25%)	18 (28%)
Up to Secondary	42 (70%)	41 (64%)
Secondary+	3 (5.0%)	5 (7.8%)
Language		
English	45 (75%)	48 (75%)
Luo	15 (25%)	16 (25%)
Screening History (Women Only) ³		
Yes	31 (62%)	27 (51%)
No	15 (30%)	24 (45%)
Don't know	2 (4.0%)	0 (0%)
Prefer not to answer	2 (4.0%)	2 (3.8%)
Screening Method (Women Only) ⁴		
VIA	22 (73%)	14 (52%)
HPV Self-Sampling	2 (6.7%)	8 (30%)
Pap Smear	5 (17%)	1 (3.7%)
Other	1 (3.3%)	0 (0%)
Don't know	0 (0%)	4 (15%)

¹Mean (SD) for numerical variables; n (%) for categorical variables. ²Among (n = 58) non-missing CHPs for the control arm. ³Among (n = 50) female CHPs in the control arm, and (n = 53) female CHPs in the intervention arm. ⁴Among (n = 30) non-missing female respondents in the control arm, and (n = 27) non-missing female respondents in the intervention arm. Abbreviations: CHP, community health promoter; VIA, visual inspection with acetic acid; HPV, human papillomavirus.

Table 2. CHPs' average stigma, knowledge, and privacy scores at baseline

Characteristic	Control (n = 60) ¹	Intervention (n = 64) ¹	p-value ²
Stigma Scores ³			
Cervical Cancer	0.84 (0.64)	0.95 (0.54)	0.2
HIV	0.47 (0.44)	0.68 (0.54)	0.023
HPV	0.67 (0.48)	0.79 (0.41)	0.2
Knowledge and Privacy Scores ⁴			
Knowledge	2.67 (0.63)	2.46 (0.67)	0.12
Privacy	1.69 (0.38)	1.68 (0.35)	> 0.9

¹Mean (SD). ²Two-tailed tests. ³All stigma scores measured on a 0–3 point scale. Higher stigma scores indicate higher levels of stigma (worse outcomes). ⁴Knowledge and privacy questions are measured on scales ranging from 1–4 or 1–7, depending on the question. Higher knowledge and privacy scores indicate better outcomes. *Abbreviations:* CHP, community health promoter; HIV, human immunodeficiency virus; HPV, human papillomavirus.

3.3. Impact of Elimisha-HPV on stigma, knowledge, and privacy scores: linear mixed effects regression model results

The main effects of the Elimisha-HPV intervention on stigma and knowledge and privacy scores are summarized in the regression results illustrated in Table 3. The main effect of the intervention is indicated by the *Main Effect* coefficient, reflecting the effect of being in the intervention arm in the post-training period. Across all stigma domain outcomes (cervical cancer, HIV, and HPV), no statistically significant intervention effect was detected (cervical cancer: $\beta = 0.02$ [95% CI, –0.13 to 0.16], $p = 0.8$; HIV: $\beta = 0.01$ [95% CI, –0.11 to 0.13], $p = 0.9$; HPV: $\beta = 0.02$ [95% CI, –0.11 to 0.14], $p = 0.8$). For knowledge and privacy, confidentiality, and professionalism outcomes, no statistically significant effects were observed. For knowledge scores, intervention was associated with a non-statistically significant, negative effect ($\beta = -0.08$ [95% CI, –0.22 to 0.07]; $p = 0.3$). For privacy scores, intervention was associated with a non-statistically significant, positive effect ($\beta = 0.04$ [95% CI, –0.05 to 0.13]; $p = 0.4$).

3.4. Change in CHPs' confidence to counsel in cervical cancer screening delivery: pre- vs. post-intervention

Results of the Likert scale questions assessing CHP confidence to counsel women in cervical cancer screening delivery are summarized in Table 4. In the post-test period, confidence scores generally increased, with greater magnitudes of score increases observed in the control arm across all questions. For question 1 ("Confidence to counsel women about cervical cancer screening and treatment") increases in percentages of CHPs reporting "Strongly Agree" were substantial: in the control arm, 63% of respondents reported "Strongly Agree" in the post-intervention period, compared to

Table 3. Linear mixed effects regression models measuring the effect of Elimisha-HPV training on CHP stigma levels and knowledge and privacy scores

Variable	Cervical Cancer ¹	p-value ²	HPV ¹	p-value ²	HIV ¹	p-value ²	Knowledge ¹	p-value ²	Privacy ¹	p-value ²
Time	–0.21 (–0.35, –0.07)	0.003	–0.19 (–0.30, –0.07)	0.002	–0.08 (–0.20, 0.04)	0.2	0.51 (0.35, 0.66)	< 0.001	–0.02 (–0.10, 0.06)	0.7
Rural	—	0.3	—	0.5	—	0.4	—	0.3	—	0.2
Urban	—	—	—	—	—	—	—	—	—	—
County	0.17 (–0.12, 0.46)	0.2	0.09 (–0.18, 0.35)	0.3	0.12 (–0.14, 0.37)	0.068	0.16 (–0.12, 0.44)	0.5	–0.11 (–0.30, 0.08)	0.13
Kisumu	—	—	—	—	—	—	—	—	—	—
Nyando	0.23 (–0.09, 0.54)	—	0.14 (–0.14, 0.43)	—	0.26 (–0.02, 0.53)	—	0.12 (–0.19, 0.43)	—	–0.16 (–0.36, 0.05)	—
Main Effect ³	0.02 (–0.13, 0.16)	0.8	0.02 (–0.11, 0.14)	0.8	0.01 (–0.11, 0.13)	0.9	–0.08 (–0.22, 0.07)	0.3	0.04 (–0.05, 0.13)	0.4

¹ β (95% CI); ²Two-tailed tests; ³*Main Effect* coefficient represents the interaction of the *Time* and *Arm* coefficients, reflecting the effect of being in the intervention arm in the post-intervention period. Reference categories: for the "Rural" variable, "Rural" represents the reference category; for the "County" variable, "Kisumu" represents the reference category. *Abbreviations:* CHP, community health promoter; HPV, human papillomavirus; HIV, human immunodeficiency virus.

Table 4. CHPs' confidence to counsel in cervical cancer screening delivery: pre- vs. post-intervention by study arm

Questions	Control <i>n</i> = 60 ¹		Intervention <i>n</i> = 64 ¹	
	pre-test	post-test	pre-test	post-test
1. Confidence to counsel women about cervical cancer screening and treatment				
Strongly Agree	27 (45%)	38 (63%)	35 (55%)	41 (64%)
Agree	25 (42%)	18 (30%)	26 (41%)	18 (28%)
Disagree	5 (8.3%)	2 (3.3%)	1 (1.6%)	2 (3.1%)
Strongly Disagree	3 (5.0%)	2 (3.3%)	1 (1.6%)	3 (4.7%)
Don't Know	0 (0%)	0 (0%)	1 (1.6%)	0 (0%)
2. Knows where to refer women for screening				
Strongly Agree	30 (50%)	41 (68%)	44 (69%)	45 (70%)
Agree	27 (45%)	15 (25%)	19 (30%)	16 (25%)
Disagree	1 (1.7%)	2 (3.3%)	1 (1.6%)	2 (3.1%)
Strongly Disagree	2 (3.3%)	2 (3.3%)	0 (0%)	0 (0%)
Don't Know	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Prefer not to answer	0 (0%)	0 (0%)	0 (0%)	1 (1.6%)
3. Rate your current knowledge and understanding of cervical cancer				
Poor	2 (3.3%)	0 (0%)	0 (0%)	1 (1.6%)
Fair	19 (32%)	2 (3.3%)	17 (27%)	2 (3.1%)
Good	24 (40%)	19 (32%)	32 (50%)	23 (36%)
Very Good	8 (13%)	26 (43%)	9 (14%)	25 (39%)
Excellent	6 (10%)	13 (22%)	5 (7.8%)	12 (19%)
Don't Know	1 (1.7%)	0 (0%)	1 (1.6%)	1 (1.6%)

¹*n* (%).

45% in the pre-intervention period; in the intervention arm, 64% of respondents reported "Strongly Agree" in the post-intervention period, compared to 55% in the pre-intervention period. For question 2 ("Knows where to refer women for screening"), larger increases in confidence were observed in the control than intervention arm: 68% of control respondents reported "Strongly Agree" in the post-intervention period, compared to 50% in the pre-intervention period; in the intervention arm, 70% of respondents reported "Strongly Agree" in the post-intervention period, compared to 69% in the pre-intervention period. The largest increases in scores were observed for question 3 ("Rate your current knowledge and understanding of cervical cancer"). From the pre- to post-intervention period, the control arm demonstrated increases in selection of the "Very Good" response option of 13% to 43%, and the intervention arm demonstrated increases from 14% to 39%. Supplement 3 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=127>) contains regression analyses of confidence scores, employing a numerical coding of the Likert scale confidence questions. These results indicate a positive, non-statistically significant main effect of the intervention on confidence scores ($\beta = 0.01$ [95% CI, -0.09 to 0.11]; $p = 0.8$).

4. Discussion

In order to understand the components that impacted outcome of a multi-level cervical cancer prevention program, we examined impact of a novel educational

curriculum utilizing stigma-sensitive, patient-centered approaches for training CHPs to provide HPV-based cervical cancer screening in Kenya. Relative to other interventions, our CHP training incorporated a unique, four-tiered educational approach addressing: *i*) HPV, HIV, and cervical cancer stigma, *ii*) confidence to counsel of cervical cancer screening service delivery, *iii*) knowledge of privacy, confidentiality, and professionalism, and *iv*) motivational interview skills. Previous CHP-focused cervical cancer-related educational interventions typically address one of these dimensions (*e.g.*, stigma, knowledge of risk factors, or knowledge of service delivery) (30,31). Our training sought to augment knowledge alone with an understanding of drivers of screening decision-making and skills to help women determine whether to screen, in addition to enhancing understanding of and reducing cervical cancer-related stigma among CHPs in LMICs.

Our findings suggest that the educational intervention did not have a statistically significant effect on CHPs' stigma associated with cervical cancer, HIV, and HPV, knowledge of cervical cancer and awareness of privacy and confidentiality, or confidence to counsel in screening delivery. The effect estimates for HIV, HPV, and cervical cancer are all positive (HIV: $\beta = 0.01$ [95% CI, -0.11 to 0.13]; HPV: $\beta = 0.02$ [95% CI, -0.11 to 0.14]; cervical cancer: $\beta = 0.02$ [95% CI, -0.13 to 0.16]), though small in magnitude relative to the possible score ranges for these effects (theoretical range of 0–3). These point estimates correspond to 0.33%–0.67% of the total possible score range. Estimated intervention effects for the knowledge and privacy scores were also small in

magnitude (knowledge: $\beta = -0.08$ [95% CI, -0.22 to 0.07]; privacy: $\beta = 0.04$ [95% CI, -0.05 to 0.13]). For the Likert scale confidence questions, while proportional comparisons indicated increases in confidence to counsel from the pre- to post-test period, supplemental regression analyses indicated that the intervention effect on CHP confidence was not statistically significant ($\beta = 0.01$ [95% CI, -0.09 to 0.11]; $p = 0.80$). No established threshold for meaningful change to contextualize these effect sizes is available; as such, practical significance of these observed differences cannot be determined conclusively. Null results are possibly attributable to spillover effects between intervention arms. Specifically, given that the same instructors were used for both arms, there is a possibility of contamination between arms. Since trainers were familiar with the concepts of stigma and the use of non-stigmatizing language, some of their experience with Elimisha-HPV may have translated into the control training. The short duration between training and post-training surveys (two days) may have also limited our ability to evaluate changes in knowledge and behavior over the long-term.

Our findings are consistent with some studies conducted among community health workers in LMICs aiming to improve knowledge of HPV and cervical cancer and reduce stigma (30). For example, in a study of the effectiveness of an educational intervention aimed at reducing stigma and improving knowledge of HPV and cervical cancer among Nigerian men and women, Nkwonta *et al.* (2021) found that no significant changes were observed between study arms in the majority of stigma domains (30). However, still other interventions in LMICs have effectively influenced community health worker knowledge of cervical cancer; Ochomo *et al.* (2023) developed a dialogue-based training for community health workers in Nyando, Kenya, and found that overall knowledge scores, and knowledge of various aspects (risk factors, signs and symptoms, and screening) significantly improved post-training (31).

Our non-statistically significant findings may indicate spillover effects that minimize differences between study arms. Minimal between-arm differences could also be due to a lack of sufficient isolation of control and intervention participants, or a need for more pronounced differences between control and intervention arm educational materials, pedagogical strategies, and training instructors. Finally, it is also possible that a pedagogical approach that differs more starkly from the cultural norm would more effectively incite attitude and belief change. Though efforts were taken to ensure linguistic and cultural appropriateness of the intervention, it may be possible that inclusion of some culturally atypical educational methods would more significantly impact stigma and knowledge, due to their comparative novelty. Dedicating more attention to striking balance between cultural sensitivity and educational methods that effectively incite attitude and belief change may

represent a promising direction for future cervical cancer stigma-reduction focused interventions among CHPs in LMICs. In addition, previous stigma-reduction focused research has found that employing longer training periods, scheduling repeated trainings, and incorporating more contact-based and multicomponent interventions may enhance training effectiveness (32,33).

Although we had the opportunity to test a real-world educational intervention, our study had several limitations in its design and implementation. First, the training period lasted only two days, limiting CHPs' ability to fully internalize the concepts and actively engage with both the content and trainers. The short duration between training and post-training surveys also limited our ability to evaluate sustained retention of knowledge and behavior change over the long term, especially given that the two-day training was followed by mentored field work to further cement concepts and practices introduced in the training. Furthermore, given emphasis on relationship-building in the intervention arm, some of the impacts on CHP practice may not be fully captured by the written survey results. More robust assessment methods that capture subtle behavioral aspects of discrimination and stereotyping not captured by the Likert scale structure of our survey questions could improve representativeness of our findings. Finally, we employed the same trainers for both the intervention and control groups. As they were quite familiar with the concepts of stigma and the use of non-stigmatizing language, it is likely that some of their experience with Elimisha-HPV carried over into the control training, which would have minimized differences between arms.

5. Conclusion

Despite these limitations, our study provides insights on the gaps in CHP knowledge of key concepts and practices in cervical cancer service delivery and related stigma attitudes. As a key component of Elimisha-HPV, the CHP training may benefit from further refinement and evaluation. In future design and assessment of CHP programs, it will be vital to consider the inputs and perspectives of the community, CHPs themselves, and other healthcare professionals working with CHPs. Insight from this evaluation provides the foundation for shaping design of future content, assessment techniques, and support mechanisms to ensure quality of cervical cancer prevention services provided by CHPs. Such measures will be critical in improving cervical cancer screening uptake in western Kenya and similar areas, a key intervention to address high cervical cancer incidence rates in the region.

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- [§]*These authors contributed equally to this work.*
- ^{*}*Address correspondence to:*
 Stephanie B. Jordan, Department of Emergency Medicine,
 Stanford University School of Medicine, 900 Welch Road, Suite
 350, Palo Alto, CA 94304, USA.
 E-mail: sj349@stanford.edu

Association between maternal dysglycaemia and adverse perinatal outcomes: A retrospective cohort study using a Japanese mother–infant-linked claims database

Kouko Yamamoto^{1,2}, Noriko Ihana-Sugiyama^{2,3,4}, Takehiro Sugiyama^{1,2,4,5,6,*}, Kensuke Tomio⁷, Misao Nakanishi⁷, Takahiro Kido⁸, Yuta Taniguchi^{4,5}, Masao Iwagami^{4,5}, Taeko Watanabe^{4,5}, Mitsuru Ohsugi^{2,3}, Hajime Oishi⁷, Kohjiro Ueki^{3,9}, Nanako Tamiya^{4,5}

¹ Department of Health Services Research, Graduate School of Comprehensive Human Sciences, University of Tsukuba, Ibaraki, Japan;

² Diabetes and Metabolism Information Center, National Institute of Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

³ Department of Diabetes, Endocrinology and Metabolism, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

⁴ Health Services Research and Development Center, University of Tsukuba, Ibaraki, Japan;

⁵ Department of Health Services Research, Institute of Medicine, University of Tsukuba, Ibaraki, Japan;

⁶ Institute for Global Health Policy Research, Bureau of Global Health Cooperation, Japan Institute for Health Security, Tokyo, Japan;

⁷ Department of Obstetrics and Gynecology, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

⁸ Department of Child Health, Institute of Medicine, University of Tsukuba, Ibaraki, Japan;

⁹ Diabetes Research Center, National Institute of Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan.

Abstract: Claims-based perinatal studies in Japan are limited because normal pregnancies are not covered by health insurance. This study aimed to examine the association between maternal dysglycaemia and perinatal outcomes using a mother–infant-linked claims database. We conducted a retrospective cohort study using the JMDC Claims Database from April 2012 to March 2023. Singleton mother–infant pairs were presumed by family ID and categorised into six mutually exclusive claims-based categories: anti-diabetic prescriptions both before and during pregnancy with (Category 1) or without (Category 2) a pre-pregnancy type 1 diabetes code, prescriptions in prenatal period only (Category 3), prescriptions before pregnancy only (Category 4), a gestational diabetes (GDM) management-fee claim without anti-diabetic prescriptions (Category 5) and no identified claims-based indicator of dysglycaemia (Category 6). Outcomes included caesarean section, macrosomia, preterm birth, neonatal asphyxia, neonatal intensive care unit (NICU) admission and congenital malformations of the circulatory system. Among 115,113 presumed mother–infant pairs, 21.5% of mothers underwent caesarean section, with higher proportions in Categories 1 and 2 (40.6% and 48.3%). Highest point estimates were observed in Category 1 for most outcomes. Category 2 was associated with increased risks of caesarean section (adjusted risk ratio 2.04, 95% confidence interval 1.77–2.35), preterm birth (3.69, 2.57–5.28) and NICU admission (3.88, 3.02–4.99). Category 5 was positively associated with macrosomia (2.43, 1.64–3.62). Claims-based indicators of maternal dysglycaemia were associated with adverse perinatal outcomes. These findings suggest potential utility of mother–infant-linked claims data for Japanese perinatal monitoring, subject to further validation.

Keywords: gestational diabetes mellitus, diabetes in pregnancy, caesarean section, macrosomia, administrative health data

1. Introduction

Dysglycaemia during pregnancy, including pre-existing diabetes and gestational diabetes (GDM), is a well-established risk factor for adverse perinatal outcomes, including preterm birth, caesarean section and neonatal complications such as macrosomia (1,2). Globally, the prevalence of GDM has risen in parallel with increasing

maternal age and obesity and introduction of the International Association of Diabetes and Pregnancy Study Groups criteria has further increased the number of women diagnosed (3-5). Large studies in Asian countries have reported that even mild glucose intolerance is associated with adverse birth outcomes and nationwide claims-based studies in Korea have demonstrated recent increases in both GDM prevalence and caesarean section

rates (6,7). Collectively, these findings underscore importance of contemporary management of maternal dysglycaemia in the perinatal period in the context of changing epidemiology.

In Japan, as in many other countries, frequency of GDM has increased alongside advanced maternal age and lifestyle changes (8). Following the 2010 revision of diagnostic criteria, prevalence rose from approximately 2–3% to 7–13% and GDM is no longer a rare complication (9,10). Cohort studies from clinical institutions and government-led initiatives in Japan have provided important evidence on association between maternal dysglycaemia and perinatal outcomes (11,12); however, these studies are limited by potential selection bias and restricted generalisability (13). In contrast, health insurance claims databases provide large-scale, population-based data with high coverage, enabling epidemiological analyses at the population level. Studies from neighbouring countries such as Taiwan and Korea have demonstrated utility of such health insurance data to evaluate associations between GDM and perinatal outcomes, providing real-world evidence (6,7).

In Japan, normal pregnancy and delivery are not covered by public health insurance and are therefore not fully captured in claims data, making claims-based studies of maternal dysglycaemia and perinatal outcomes challenging (14). Nevertheless, a large mother–infant-linked claims database enables investigation of maternal and infant outcomes simultaneously using routinely collected healthcare data. Claims data can capture medically attended pregnancy complications, delivery-related interventions, and neonatal outcomes, and mother–infant linkage enables analysis of linked mother–infant pairs. Such approaches may complement existing cohort studies by providing large-scale real-world evidence to inform clinical practice and health policy in Japan.

Therefore, we applied a claims-based approach to perinatal epidemiology using a large Japanese mother–infant-linked claims database to examine association between maternal dysglycaemia and perinatal outcomes in both mothers and infants.

2. Materials and Methods

2.1. Study design and data source

This retrospective cohort study used the JMDC Claims Database (JMDC Inc., Tokyo, Japan) from April 2012 to March 2023. The JMDC Claims Database is a commercial database comprising health insurance data for approximately 17 million individuals. It primarily includes data from employment-based health insurance societies covering employees of large companies and their dependents. The database therefore mainly represents a working-age population and their families, with beneficiaries aged 0–74 years.

The JMDC Claims Database contains beneficiary information and health insurance claims. Claims data are categorised into diagnoses, procedures and prescriptions. Diagnoses are coded using the International Classification of Diseases, 10th Revision (ICD-10); drugs are coded using World Health Organization Anatomical Therapeutic Chemical classification; and procedures are coded using reimbursement points codes established by the Ministry of Health, Labour and Welfare. Detailed codes used to define study variables are listed in Supplementary Table S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>).

In the JMDC Claims Database, beneficiaries covered under the same insurance contract share a family ID, which serves as a proxy for household information and enables identification of family relationships among insured individuals and their dependents. In this study, we used this family ID to identify presumed mother–infant pairs. A shared family ID indicates coverage under the same insurance contract and does not by itself confirm a mother–infant relationship; the linkage is therefore described as a presumed mother–infant linkage throughout.

This study was approved by the Ethics Committee of University of Tsukuba (approval number 1882-2). The study used de-identified data from the JMDC Claims Database and the investigators had no access to personal identifiers or contact information. Therefore, informed consent and opt-out procedures were not applicable. The study conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

2.2. Study population

We identified presumed mother–infant pairs using the family identification number in the JMDC Claims Database. For each mother, we selected the first delivery during the study period and excluded pairs involving multiple births (Figure 1).

2.2.1. Inclusion criteria

Infants were defined as individuals whose insurance relationship was recorded as "child" and whose month of birth matched their month of insurance enrolment. Mothers were defined as female beneficiaries whose insurance relationship was recorded as "insured" or "dependent".

2.2.2. Exclusion criteria

Women whose insurance enrolment had ended before April 2012 were excluded. Infants born before April 2012 were excluded. When more than one adult woman shared the same family identification number, all such women were excluded because the mother could not be uniquely identified. Pairs in which mother and infant

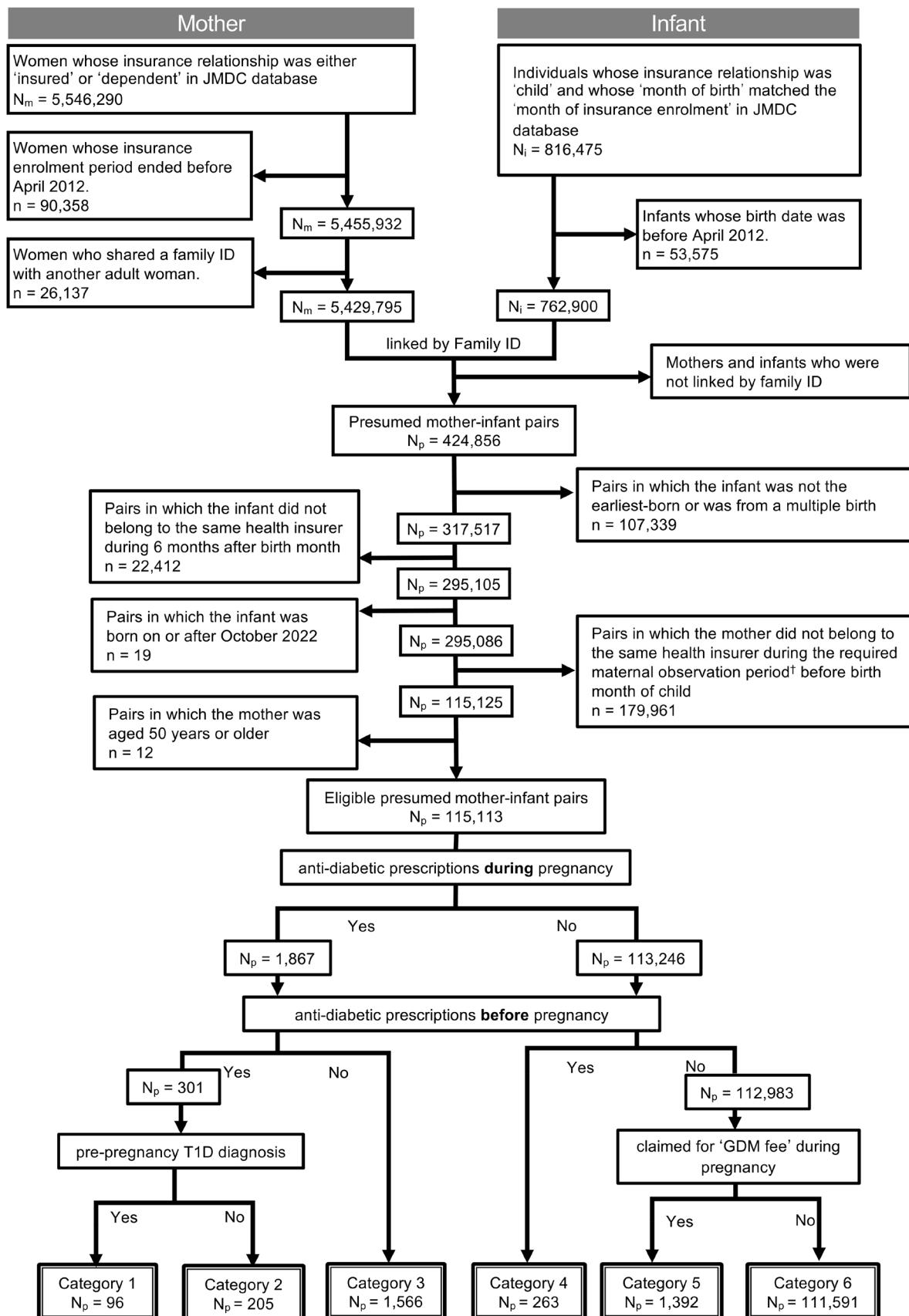


Figure 1. Flowchart of study population selection. The figure shows selection of eligible presumed mother–infant pairs from the JMDC Claims Database. Mothers and infants were linked using family IDs. Key exclusion criteria included discontinuous maternal insurance enrolment, infant disenrolment within 6 months after birth, non-earliest-born or multiple births, maternal age ≥ 50 years, and infant birth on or after October 2022. †: Observation period was defined as the operational pregnancy period (months -9 through 0 , with the infant's birth month defined as month 0) plus the preceding 6 months. For pregnancies ending in preterm birth, operational pregnancy period comprised months -8 through 0 . *Abbreviations:* GDM, gestational diabetes; N_i, number of infants; N_m, number of mothers; N_p, number of mother–infant pairs; T1D, type 1 diabetes.

could not be matched by family ID were excluded.

When a mother had more than one delivery recorded in the database, only the first was included. Multiple births were excluded, such that one singleton infant was analysed per mother. Infants who disenrolled from insurance within 6 months after birth were also excluded. To ensure that all included infants had the opportunity for complete 6-month follow-up, infants born on or after October 2022 (6 months prior to the end of the database period in March 2023) were excluded.

Mothers were excluded if they had any gap in insurance enrolment from 6 months before start of the operational pregnancy period through the infant's birth month (months -15 through 0, or -14 through 0 for preterm birth). Pairs in which the woman was aged 50 years or older were excluded because a mother–infant relationship is implausible at the upper extreme.

2.3. Pregnancy period

The infant's birth month was defined as month 0. The operational pregnancy period comprised the 10 calendar months from month -9 through the infant's birth. However, if the mother or infant met the claims-based definition of preterm birth shown in Supplementary Table S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>) (maternal ICD-10 O60.1/O60.3 or infant ICD-10 P07.2/P07.3), the operational pregnancy period comprised the 9 calendar months from month -8 through infant's birth. For classification of medication use, prescriptions recorded in months -7 through 0 were classified as occurring "during pregnancy", whereas those recorded in months -15 through -8 were classified as occurring "before pregnancy". For pregnancies ending in preterm birth, corresponding windows were months -6 through 0 and -14 through -7, respectively. This cutoff was selected to reflect timing of pregnancy recognition in clinical practice.

2.4. Measurements

All variables were extracted from the JMDC Claims Database using diagnostic, procedure and prescription claims, as well as beneficiary registry data. Data sources and claims codes used to define all variables are presented in Supplementary Table S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>), and assessment windows for key study variables are illustrated in the study design diagram (Supplementary Figure S1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>).

2.4.1. Exposure

The exposure was maternal dysglycaemia. Mothers were classified according to prescriptions for anti-diabetic

medications before and during pregnancy, diagnoses of type 1 diabetes (T1D) before pregnancy and claims for the home management fee for gestational diabetes (GDM fee) during pregnancy. The GDM fee is a reimbursement code unique to Japan that applies to pregnant women with high-risk GDM, overt diabetes in pregnancy or pre-existing diabetes; further details are provided in Supplementary Method S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>).

Mothers were classified into six mutually exclusive categories (Supplementary Figure S2 and Supplementary Table S6, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>). First, they were divided according to whether they had prescriptions for anti-diabetic medications before and/or during pregnancy. Mothers with prescriptions in both periods were further stratified by presence of a pre-pregnancy T1D diagnosis: those with such a diagnosis were classified as Category 1 (Anti-diabetic prescriptions before and during pregnancy, with a pre-pregnancy T1D diagnosis; Both-periods prescription, T1D-coded) and those without as Category 2 (Anti-diabetic prescriptions before and during pregnancy, without a pre-pregnancy T1D diagnosis; Both-periods prescription, no T1D code). Mothers with prescriptions only during pregnancy were classified as Category 3 (Anti-diabetic prescriptions in prenatal period only; Prenatal-only prescription), and those with prescriptions only before pregnancy as Category 4 (Anti-diabetic prescriptions before pregnancy only; Pre-pregnancy-only prescription). Among mothers with no prescriptions in either period, those with claims for the GDM fee during pregnancy were classified as Category 5 (GDM fee claim without anti-diabetic prescriptions; GDM fee only, no prescription) and those without such claims as Category 6 (No identified claims-based indicator of dysglycaemia; No identified indicator of dysglycaemia). These categories are claims-based proxies rather than confirmed clinical phenotypes and do not represent a gradient of clinical severity.

2.4.2. Outcomes

We assessed six perinatal outcomes: one maternal outcome (caesarean section) and five neonatal outcomes (macrosomia, preterm birth, neonatal asphyxia, admission to the neonatal intensive care unit [NICU] and congenital malformations of the circulatory system) (1,15).

A single qualifying claim within the outcome-specific assessment window was sufficient to meet a diagnosis-based criterion. When diagnoses were used in the definition, records flagged as suspected diagnoses were excluded.

2.4.3. Covariates

Insurance status (insured vs. dependent) and infant sex were extracted as baseline characteristics. Maternal age

group was selected a priori as a confounder. Hypertensive disorders of pregnancy (HDP) were identified as a factor that could potentially act as either a confounder or a mediator.

Because some women prescribed anti-diabetic medications before pregnancy may have received metformin for polycystic ovary syndrome (PCOS) rather than diabetes, a diagnosis of PCOS was also extracted for descriptive purposes.

2.5. Statistical analyses

Maternal characteristics, including insurance status, age group (< 30, 30–34 and ≥ 35 years) and the prevalence of hypertensive disorders of pregnancy, were summarised by maternal dysglycaemia category. Infant sex was also described.

Proportions of caesarean section, macrosomia, preterm birth, neonatal asphyxia, NICU admission and congenital malformations of the circulatory system were reported by maternal dysglycaemia category. Differences across categories were assessed using chi-square tests.

We examined associations between maternal dysglycaemia categories and perinatal outcomes using multivariable modified Poisson regression models with robust variance estimators. The primary estimate was the maternal-age-group-adjusted risk ratio; the primary model was therefore adjusted for maternal age group only. Given that HDP was considered to have characteristics more consistent with a mediator than with a confounder, the model additionally adjusted for HDP was treated as a secondary model. Estimates are reported as adjusted risk ratios (aRRs) with 95% confidence intervals (CIs) based on robust variance (vce(robust) in Stata); no additional clustering specification was used because each mother contributed only one mother–infant pair. Category 6 was used as reference category in all models, and no direct contrasts between Categories 1–5 were performed. There were no missing values for variables used in these analyses in the final analytic cohort.

In additional analyses, we described distribution of anti-diabetic medications prescribed before and during pregnancy. We also reported proportion of mothers who were prescribed metformin before pregnancy and had a diagnosis of PCOS. Furthermore, we evaluated association between maternal dysglycaemia and caesarean section within maternal age groups. As a sensitivity analysis, we reconstructed exposure categories using a common 10-calendar-month operational pregnancy period (months –9 through 0) for all pregnancies, irrespective of preterm-birth status, with prescriptions in months –7 through 0 classified as occurring "during pregnancy" and those in months –15 through –8 classified as occurring "before pregnancy" (Supplementary Table S5, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>).

For this sensitivity analysis, maternal continuous-enrolment criterion was also re-evaluated using months –15 through 0 for all pregnancies; no additional pairs were excluded.

All analyses were conducted using Stata version 17.0 (StataCorp, College Station, TX, USA). A two-sided *p* value of less than 0.05 was considered statistically significant.

3. Results

3.1. Maternal and infant characteristics

A total of 115,113 presumed mother–infant pairs were included in the analysis. Mothers were categorised into six groups according to dysglycaemia (Categories 1–5) or no identified claims-based indicator of dysglycaemia (Category 6) (Figure 1).

Overall, 38.0% of mothers were aged 35 years or over, with the highest proportion in Category 2 (62.4%). Hypertensive disorders of pregnancy were present in 4.7% of mothers overall and were most prevalent in Category 2 (30.2%). Female infants accounted for 48.6% of the cohort (Table 1).

3.2. Perinatal outcomes by maternal dysglycaemia category

Overall, 21.5% of mothers underwent caesarean section; the proportion was higher in Categories 1 and 2 (40.6% and 48.3%, respectively). Macrosomia occurred in 0.8% of infants overall and was most common in Category 1 (6.3%). Preterm birth occurred in 3.3% overall, with higher proportions in Categories 1 and 2 (14.6% and 12.7%, respectively). Neonatal asphyxia occurred in 3.2% of infants and NICU admission in 5.7%, with both outcomes more frequent in Categories 1–4. Congenital malformations of the circulatory system were recorded in 2.3% of infants overall. Differences across categories were statistically significant for all outcomes (*p* < 0.001) (Table 2).

3.3. Associations between maternal dysglycaemia and perinatal outcomes

In the primary model adjusted for maternal age group, Category 1 was associated with increased risks of several outcomes, including caesarean section (aRR 1.89, 95% CI 1.49–2.40), macrosomia (aRR 8.69, 95% CI 4.00–18.91), preterm birth (aRR 4.54, 95% CI 2.78–7.40), neonatal asphyxia (aRR 3.65, 95% CI 2.09–6.38), and NICU admission (aRR 6.26, 95% CI 4.73–8.28). Category 2 was also associated with increased risks of caesarean section (aRR 2.04, 95% CI 1.77–2.35), preterm birth (aRR 3.69, 95% CI 2.57–5.28), neonatal asphyxia (aRR 3.66, 95% CI 2.53–5.30), and NICU admission (aRR 3.88, 95% CI 3.02–4.99).

Table 1. Maternal and infant characteristics by maternal dysglycaemia category

Variables	Total	Anti-diabetic drug prescription						p value
		Before & during pregnancy		During pregnancy		Before pregnancy		
		T1D coded	No T1D code	Prenatal-only	Pre-pregnancy-only	GDM fee only	No prescription	
		Category 1	Category 2	Category 3	Category 4	Category 5	Category 6	
Total, n	115,113	96	205	1,566	263	1,392	111,591	
Insurance status, n (%)								
Insured	12,249 (10.6)	8 (8.3)	20 (9.8)	187 (11.9)	8 (3.0)	186 (13.4)	11,840 (10.6)	< 0.001
Dependent	102,864 (89.4)	88 (91.7)	185 (90.2)	1,379 (88.1)	255 (97.0)	1,206 (86.6)	99,751 (89.4)	
Age category, n (%)								
< 30 years	27,141 (23.6)	19 (19.8)	26 (12.7)	163 (10.4)	65 (24.7)	196 (14.1)	26,672 (23.9)	< 0.001
30–34 years	44,237 (38.4)	38 (39.6)	51 (24.9)	476 (30.4)	103 (39.2)	461 (33.1)	43,108 (38.6)	
≥ 35 years	43,735 (38.0)	39 (40.6)	128 (62.4)	927 (59.2)	95 (36.1)	735 (52.8)	41,811 (37.5)	
Hypertensive disorders of pregnancy, n (%)								
Yes	5,407 (4.7)	19 (19.8)	62 (30.2)	157 (10.0)	25 (9.5)	113 (8.1)	5,031 (4.5)	< 0.001
No	109,706 (95.3)	77 (80.2)	143 (69.8)	1,409 (90.0)	238 (90.5)	1,279 (91.9)	106,560 (95.5)	
Infant sex, n (%)								
Female	55,918 (48.6)	54 (56.3)	90 (43.9)	743 (47.4)	118 (44.9)	700 (50.3)	54,213 (48.6)	0.160
Male	59,195 (51.4)	42 (43.8)	115 (56.1)	823 (52.6)	145 (55.1)	692 (49.7)	57,378 (51.4)	

Note: Maternal and infant characteristics are summarised by maternal dysglycaemia category. Differences across categories were assessed using chi-square tests. Exposure categories were claims-based proxies and were defined as follows: Category 1, anti-diabetic prescriptions before and during pregnancy with a pre-pregnancy T1D diagnosis; Category 2, anti-diabetic prescriptions before and during pregnancy without a pre-pregnancy T1D diagnosis; Category 3, anti-diabetic prescriptions in prenatal period only; Category 4, anti-diabetic prescriptions before pregnancy only; Category 5, GDM fee claim without anti-diabetic prescriptions; and Category 6, no identified claims-based indicator of dysglycaemia. Abbreviations: GDM, gestational diabetes; T1D, type 1 diabetes.

Table 2. Perinatal outcomes by maternal dysglycaemia category

Variables	Total	Anti-diabetic drug prescription						p value
		Before & during pregnancy		During pregnancy		Before pregnancy		
		T1D coded	No T1D code	Prenatal-only	Pre-pregnancy-only	GDM fee only	No prescription	
		Category 1	Category 2	Category 3	Category 4	Category 5	Category 6	
Total, <i>n</i>	115,113	96	205	1,566	263	1,392	111,591	
Maternal outcome								
Caesarean section, <i>n</i> (%)	24,702 (21.5)	39 (40.6)	99 (48.3)	592 (37.8)	82 (31.2)	399 (28.7)	23,491 (21.1)	< 0.001
Neonatal outcomes								
Macrosomia, <i>n</i> (%)	875 (0.8)	6 (6.3)	5 (2.4)	41 (2.6)	3 (1.1)	25 (1.8)	795 (0.7)	< 0.001
Preterm birth, <i>n</i> (%)	3,788 (3.3)	14 (14.6)	26 (12.7)	145 (9.3)	8 (3.0)	52 (3.7)	3,543 (3.2)	< 0.001
Neonatal asphyxia, <i>n</i> (%)	3,700 (3.2)	11 (11.5)	25 (12.2)	123 (7.9)	24 (9.1)	58 (4.2)	3,459 (3.1)	< 0.001
Admission to NICU, <i>n</i> (%)	6,568 (5.7)	33 (34.4)	47 (22.9)	278 (17.8)	27 (10.3)	142 (10.2)	6,041 (5.4)	< 0.001
Congenital circulatory malformations, <i>n</i> (%)	2,662 (2.3)	7 (7.3)	10 (4.9)	54 (3.4)	11 (4.2)	35 (2.5)	2,545 (2.3)	< 0.001

Note: Proportions of perinatal outcomes are summarised by maternal dysglycaemia category. Exposure categories were claims-based proxies and were defined as follows: Category 1, anti-diabetic prescriptions before and during pregnancy with a pre-pregnancy T1D diagnosis; Category 2, anti-diabetic prescriptions before and during pregnancy without a pre-pregnancy T1D diagnosis; Category 3, anti-diabetic prescriptions in prenatal period only; Category 4, anti-diabetic prescriptions before pregnancy only; Category 5, GDM fee claim without anti-diabetic prescriptions; and Category 6, no identified claims-based indicator of dysglycaemia. Differences across categories were assessed using chi-square tests. Macrosomia: maternal ICD-10 O66.2 or infant ICD-10 P08.0/P08.1. Congenital circulatory malformations: ICD-10 Q20–Q28. Abbreviations: GDM, gestational diabetes; NICU, neonatal intensive care unit; T1D, type 1 diabetes.

Category 3 was also associated with increased risks of several outcomes, including preterm birth (aRR 2.71, 95% CI 2.31–3.18) and NICU admission (aRR 3.03, 95% CI 2.71–3.38). Category 4 was not associated with preterm birth (aRR 0.96, 95% CI 0.49–1.90), whereas increased risks were observed for caesarean section (aRR 1.49, 95% CI 1.25–1.79), neonatal asphyxia (aRR 2.96, 95% CI 2.02–4.33) and NICU admission (aRR 1.91, 95% CI 1.33–2.73). Category 5 was associated with an increased risk of caesarean section (aRR 1.26, 95% CI 1.16–1.37), macrosomia (aRR 2.43, 95% CI 1.64–3.62) and NICU admission (aRR 1.78, 95% CI 1.52–2.08). For congenital malformations of the circulatory system, the point estimate was highest for Category 1 (aRR 3.17), with more modest elevations in Categories 2–4; however, several confidence intervals were wide, with lower bounds close to unity. Estimates from the secondary model additionally adjusted for HDP were attenuated for several outcomes, but the directions of the principal associations were unchanged (Table 3).

3.4. Additional analyses

The distribution of anti-diabetic medications prescribed before and during pregnancy is shown in Supplementary Table S2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>). Before pregnancy, insulin and metformin were the most frequently prescribed medications, particularly in Categories 2 and 4. During pregnancy, insulin was the most commonly prescribed medication in Categories 1–3, whereas oral agents were infrequently prescribed.

Supplementary Table S3 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>) summarises analyses of metformin use before pregnancy. A total of 336 mothers were prescribed metformin before pregnancy, most commonly in Category 4 ($n = 221$) and Category 2 ($n = 108$). Among these mothers, 85 had a diagnosis of PCOS. The prevalence of PCOS among mothers prescribed metformin before pregnancy was 10.2% in Category 2 and 33.5% in Category 4.

Age-stratified analyses of caesarean section are shown in Supplementary Table S4 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>). Maternal dysglycaemia was associated with an increased risk of caesarean section in most categories. Point estimates varied numerically across age groups. No formal test of interaction was performed.

In the sensitivity analysis using a common 10-month operational pregnancy window for all pregnancies, exposure distribution changed only slightly: number of women in Category 2 increased from 205 to 206 and number in Category 6 decreased from 111,591 to 111,590, whereas numbers of women in Categories 1, 3, 4 and 5 were unchanged. The corresponding risk ratios were materially unchanged (Supplementary

Table S5, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>).

4. Discussion

4.1. Main findings of this study

Using a Japanese mother–infant-linked claims database, we found that several claims-based categories of maternal dysglycaemia were associated with adverse perinatal outcomes. Relative to Category 6, Category 1 showed highest point estimates for four of the six outcomes in the primary model, whereas Category 2 showed highest point estimate for caesarean section. For neonatal asphyxia, elevated point estimates were observed in both Categories 1 and 2. Associations with adverse perinatal outcomes were also observed across Categories 2–5, although specific outcomes and magnitudes of association differed by category. Categories 1–5 were not directly compared with one another. In the secondary model additionally adjusted for HDP, estimates were attenuated for several outcomes, but directions of the principal associations were unchanged. The highest point estimate for macrosomia was observed in Category 1, although Category 5 was also associated with more than a two-fold increased risk compared with Category 6. For congenital malformations of the circulatory system, point estimate was highest in Category 1, with more modest elevations in Categories 2–4, although confidence intervals were wide.

4.2. Comparison with previous studies

Overall caesarean rate in our cohort (21.5%) was similar to that reported in Japan's 2020 Survey of Medical Institutions (21.6%) (16). Condition-specific rates by dysglycaemia were also broadly consistent with those reported in a national birth cohort study by Yokomichi *et al.* (T1D, 37.9%; type 2 diabetes, 46.5%; GDM, 26.2–30.7%) (17). Caesarean rate in Category 5 was also similar to that reported in a single-centre retrospective study by Shindo *et al.* (28.6%) (18). Overall prevalence of macrosomia (0.8%) was comparable to previous estimates in the general population (19). However, rate of macrosomia among infants in Category 1 was higher than that reported by Yokomichi *et al.* (17), which may reflect differences in case numbers and exposure definitions.

Overall preterm birth rate (3.3%) was lower than national estimates (4.8–5.6%) (20), possibly because multiple births were excluded from our study population. Among mothers in Category 5, prevalence of preterm birth (3.7%) was substantially lower than that reported in a previous Japanese GDM registry study (21). This difference may reflect our narrower definition of Category 5, which was restricted to women with a GDM fee claim who did not receive anti-diabetic medication.

Table 3. Risk ratios for perinatal outcomes by maternal dysglycaemia category, primary and secondary models

Variables	Unadjusted	Primary model (adjusted for maternal age group)	Secondary model (adjusted for maternal age group and HDP)
Caesarean section (<i>n</i> = 24,702)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Category 6	ref.	ref.	ref.
Category 1	1.93 (1.51–2.46)	1.89 (1.49–2.40)	1.59 (1.27–2.00)
Category 2	2.29 (1.99–2.64)	2.04 (1.77–2.35)	1.54 (1.34–1.78)
Category 3	1.80 (1.68–1.92)	1.61 (1.51–1.72)	1.52 (1.43–1.62)
Category 4	1.48 (1.24–1.77)	1.49 (1.25–1.79)	1.40 (1.17–1.68)
Category 5	1.36 (1.25–1.48)	1.26 (1.16–1.37)	1.21 (1.11–1.31)
Macrosomia (<i>n</i> = 875)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Category 6	ref.	ref.	ref.
Category 1	8.77 (4.03–19.10)	8.69 (4.00–18.91)	8.67 (3.99–18.85)
Category 2	3.42 (1.44–8.16)	3.24 (1.36–7.76)	3.23 (1.35–7.73)
Category 3	3.67 (2.70–5.01)	3.50 (2.56–4.78)	3.49 (2.56–4.77)
Category 4	1.60 (0.52–4.94)	1.61 (0.52–4.96)	1.60 (0.52–4.95)
Category 5	2.52 (1.70–3.74)	2.43 (1.64–3.62)	2.43 (1.63–3.62)
Preterm birth (<i>n</i> = 3,788)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Category 6	ref.	ref.	ref.
Category 1	4.59 (2.83–7.46)	4.54 (2.78–7.40)	3.18 (1.94–5.23)
Category 2	3.99 (2.79–5.73)	3.69 (2.57–5.28)	2.16 (1.52–3.07)
Category 3	2.92 (2.49–3.42)	2.71 (2.31–3.18)	2.40 (2.04–2.82)
Category 4	0.96 (0.48–1.90)	0.96 (0.49–1.90)	0.84 (0.43–1.65)
Category 5	1.18 (0.90–1.54)	1.12 (0.85–1.46)	1.03 (0.79–1.34)
Neonatal asphyxia (<i>n</i> = 3,700)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Category 6	ref.	ref.	ref.
Category 1	3.70 (2.12–6.45)	3.65 (2.09–6.38)	2.92 (1.69–5.04)
Category 2	3.93 (2.72–5.69)	3.66 (2.53–5.30)	2.57 (1.76–3.76)
Category 3	2.53 (2.13–3.01)	2.37 (1.99–2.82)	2.20 (1.85–2.62)
Category 4	2.94 (2.01–4.32)	2.96 (2.02–4.33)	2.72 (1.86–4.00)
Category 5	1.34 (1.04–1.73)	1.28 (0.99–1.65)	1.22 (0.95–1.57)
Admission to NICU (<i>n</i> = 6,568)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Category 6	ref.	ref.	ref.
Category 1	6.35 (4.81–8.38)	6.26 (4.73–8.28)	4.96 (3.71–6.63)
Category 2	4.24 (3.29–5.45)	3.88 (3.02–4.99)	2.69 (2.10–3.46)
Category 3	3.28 (2.94–3.66)	3.03 (2.71–3.38)	2.80 (2.51–3.13)
Category 4	1.90 (1.33–2.71)	1.91 (1.33–2.73)	1.75 (1.22–2.51)
Category 5	1.88 (1.61–2.21)	1.78 (1.52–2.08)	1.69 (1.44–1.97)
Congenital circulatory malformations (<i>n</i> = 2,662)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Category 6	ref.	ref.	ref.
Category 1	3.20 (1.57–6.53)	3.17 (1.55–6.47)	2.77 (1.36–5.63)
Category 2	2.14 (1.17–3.92)	2.02 (1.10–3.70)	1.63 (0.89–2.98)
Category 3	1.51 (1.16–1.97)	1.43 (1.10–1.87)	1.37 (1.05–1.79)
Category 4	1.83 (1.03–3.27)	1.84 (1.03–3.29)	1.76 (0.98–3.14)
Category 5	1.10 (0.79–1.53)	1.06 (0.76–1.47)	1.03 (0.74–1.43)

Note: Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated using multivariable modified Poisson regression models. Primary model was adjusted for maternal age group; secondary model was adjusted for maternal age group and hypertensive disorders of pregnancy. Because HDP may lie on the causal pathway between maternal dysglycaemia and some perinatal outcomes, the model without HDP adjustment was designated primary model. *n* denotes number of events for each outcome; all models included all 115,113 presumed mother–infant pairs; there were no missing data. Exposure categories were claims-based proxies and were defined as follows: Category 1, anti-diabetic prescriptions before and during pregnancy with a pre-pregnancy T1D diagnosis; Category 2, anti-diabetic prescriptions before and during pregnancy without a pre-pregnancy T1D diagnosis; Category 3, anti-diabetic prescriptions in prenatal period only; Category 4, anti-diabetic prescriptions before pregnancy only; Category 5, GDM fee claim without anti-diabetic prescriptions; and Category 6, no identified claims-based indicator of dysglycaemia. *Abbreviations:* CI, confidence interval; GDM, gestational diabetes; HDP, hypertensive disorders of pregnancy; NICU, neonatal intensive care unit; ref, reference; RR, risk ratio; T1D, type 1 diabetes.

NICU admission among infants born to mothers in Category 5 (10.2%) was broadly comparable to that reported for the GDM group in a previous single-centre retrospective study (8.2%) (18), although differences in study populations and disease definitions should

be considered when interpreting this comparison. The proportion of congenital malformations of the circulatory system was higher in our study than in previous reports across all dysglycaemia categories. A plausible explanation is that these malformations were

identified from claims recorded during the first 6 months after birth, whereas previous studies primarily assessed diagnoses at delivery and in the neonatal unit (17).

4.3. Clinical implications

Pregnancies with anti-diabetic prescriptions both before and during pregnancy (Categories 1 and 2) were associated with increased risks of multiple adverse perinatal outcomes. Among women in Category 2, higher prevalence of advanced maternal age and hypertensive disorders of pregnancy, together with possibility of a higher body mass index (BMI), suggests that these risks may be influenced by multiple coexisting factors. Although this study did not evaluate effectiveness of specific interventions, previous studies have shown that management of dysglycaemia can improve perinatal outcomes (22,23). Our findings are consistent with the classification of pregnancies complicated by diabetes as high risk and with the existing emphasis on preconception glycaemic assessment and optimisation, comprehensive complication screening and individualised delivery planning. Further interventional research is needed to evaluate these strategies in contemporary clinical practice.

Among women in Category 3, risks of several outcomes, including preterm birth, NICU admission and neonatal asphyxia, were higher than in Category 6. These findings are consistent with current clinical priorities, including timely screening, treatment when clinically indicated and glycaemic management during pregnancy (24). The contribution of specific management strategies, including continuous glucose monitoring and insulin pump therapy, warrants further investigation.

Even among women in Category 5, risks of caesarean section, macrosomia and NICU admission were elevated compared with Category 6. These findings suggest that pregnancies identified by a GDM fee claim without anti-diabetic prescriptions may remain at increased risk of adverse outcomes. Further studies are needed to determine whether non-pharmacological management approaches, including nutritional counselling and self-monitoring of blood glucose, modify these risks.

4.4. Feasibility of claims-based perinatal assessment

By combining family IDs (mother–infant linkage) with prescription records, diagnoses and a Japan-specific reimbursement code (GDM fee), we can characterise perinatal risk profiles according to claims-based categories of maternal dysglycaemia. A key strength of this approach is availability of information on prescriptions and diagnoses before pregnancy, which is not subject to recall bias and can be used to classify maternal clinical characteristics.

This study also demonstrates feasibility of assessing perinatal outcomes using administrative claims data

in Japan. In particular, caesarean section rates, which are known to vary across regions and facilities, could be evaluated using population-based claims data (25). Furthermore, use of broader outcome definitions, including neonatal asphyxia, preterm birth, and NICU admission, enabled meaningful comparisons despite limited numbers of individual neonatal conditions. These findings suggest the potential utility of claims-based mother–infant linkage as a complementary approach for monitoring perinatal indicators, subject to further validation.

Although mother–infant linkage is currently unavailable in many large healthcare databases, implementing such linkage in national administrative data sources could extend this approach to rarer outcomes. Examples include the National Database of Health Insurance Claims (NDB), a nationwide Ministry of Health, Labour and Welfare database containing health insurance claims and specific health check-up data (26), and Diagnosis Procedure Combination data, which include discharge abstracts and administrative claims from acute-care inpatient hospitals (27). If linkage is feasible, national perinatal monitoring and regional or facility-level benchmarking, as well as real-world evaluation of perinatal care, could become potential future applications of such data, subject to further validation.

4.5. Limitations

This study has several limitations. First, miscarriages and stillbirths were not captured and were therefore excluded from the analysis, potentially leading to underestimation of the full burden of adverse outcomes associated with maternal dysglycaemia. In addition, important potential confounders, including BMI, smoking, socioeconomic status, and use of assisted reproductive technology, were unavailable. Although maternal age was included as an adjustment variable, residual confounding may remain because age was analysed in categories. Hypertensive disorders of pregnancy may act not only as a confounder but also as a mediator between maternal dysglycaemia and perinatal outcomes; therefore, adjustment for HDP in the secondary model may constitute overadjustment. Future studies using complementary data sources with more detailed clinical and social information are needed to address these limitations.

Second, the study population consisted of employees of large companies and their dependents. Our eligibility criteria also required continuous insurance enrolment for mothers throughout the operationally defined pregnancy period and preceding observation period, and for infants throughout the 6-month post-birth assessment window, which further selects families with stable employment-based coverage. Self-employed individuals, people covered by National Health Insurance, and families with frequent changes in health insurer are therefore likely to

be underrepresented, and large size of the database should not be taken to indicate national representativeness of all births in Japan. In addition, infants who disenrolled from insurance within 6 months after birth were excluded. If disenrolment is related to maternal dysglycaemia or to infant health status, this restriction could introduce selection bias.

Third, exposure definitions were based on insurance claims and may not fully correspond to clinical diagnoses or events. Laboratory data, including glucose values and HbA1c, were unavailable, and exposure categories were therefore defined using diagnoses, prescriptions and reimbursement codes as claims-based proxies for maternal dysglycaemia. Ascertainment of pre-pregnancy T1D diagnoses depended on length of available pre-pregnancy observation, although at least 6 months of observation was required; this may have resulted in misclassification between Categories 1 and 2. Categories 1–5 should not be interpreted as representing an ordered gradient of clinical severity. Category 3 may include clinically heterogeneous conditions that cannot be distinguished using this classification. The pre-pregnancy-only prescription group (Category 4) was also heterogeneous. Metformin accounted for most prescriptions in this group (221 of 263 mothers), and 74 of these mothers had a diagnosis of PCOS (Supplementary Table S3, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=131>), suggesting that some women were treated for PCOS during infertility treatment rather than for diabetes; this would be expected to attenuate observed associations towards Category 6. Conversely, Category 5 was defined by claims for the GDM home management fee, which is restricted to high-risk GDM, overt diabetes in pregnancy or pre-existing diabetes. Categories 3 and 5 together accounted for only 2.6% of the cohort, far below the reported prevalence of GDM in Japan (7–13%), so Category 6 almost certainly contained a substantial number of women with diet-controlled or unbilled GDM and represents absence of an identified claims-based indicator rather than confirmed normoglycaemia. If women with uncaptured dysglycaemia had higher outcome risks than truly normoglycaemic women, their inclusion in Category 6 would tend to attenuate elevated aRRs towards the null. However, because the extent and pattern of misclassification across the categories are unknown, the overall direction and magnitude of bias cannot be determined. In addition, the operational pregnancy period — and therefore both prescription-classification window and required maternal observation period — differed according to preterm-birth status in the primary analysis. In the sensitivity analysis, applying a common 10-month window and re-evaluating the maternal continuous-enrolment criterion resulted in no additional exclusions, only minimal changes in exposure classification, and no material changes in estimates. Nevertheless, this structural dependence remains a limitation of the primary analysis.

Fourth, outcome definitions were also based on insurance claims and may not fully correspond to clinically confirmed events or conditions. In particular, because measured birthweight was unavailable, maternal ICD-10 code O66.2 and infant codes P08.0 and P08.1 were used as claims-based proxies for excessive birthweight or heavy-for-gestational-age status and should not be interpreted as macrosomia confirmed using measured birthweight. Similarly, Q20–Q28 identified congenital malformations of the circulatory system recorded in claims and did not permit more detailed clinical confirmation. Differential ascertainment also cannot be excluded: women with recognised dysglycaemia and their infants may undergo more intensive fetal and neonatal surveillance, including ultrasonography, postnatal monitoring and echocardiography, which could increase likelihood that conditions are detected and recorded in claims and may have contributed to the observed associations.

Fifth, the mother–infant linkage was presumed rather than verified. A shared family identification number indicates coverage under the same insurance contract and does not by itself confirm a mother–infant relationship. The internal plausibility checks applied in this study — requiring an insurance relationship recorded as "child" with a month of birth matching the month of insurance enrolment, excluding family identification numbers shared by more than one adult woman, and excluding pairs in which the woman was aged 50 years or older — reduce ambiguity but do not independently establish relationship. Because normal pregnancy and delivery are not routinely covered by public health insurance in Japan, maternal delivery-related claims are not consistently captured and could not be used as a uniform concordance check across the cohort. Linkage errors may therefore remain in the retained cohort, and accuracy of the presumed mother–infant linkage has not been established.

Finally, despite the large cohort of more than 115,000 presumed mother–infant pairs, some paediatric outcomes remained uncommon and statistical precision was limited. Larger linked administrative databases may enable more robust evaluation of rare outcomes.

5. Conclusions

Using a Japanese mother–infant-linked claims database, we found that claims-based categories indicating maternal dysglycaemia were associated with adverse perinatal outcomes in real-world clinical practice. Highest point estimates relative to Category 6 were observed in Category 1 for most outcomes, while associations with adverse perinatal outcomes were also observed across Categories 2–5 with specific outcomes differing by category. These findings indicate that several claims-based categories were associated with adverse perinatal outcomes relative to Category 6, without

establishing differences between Categories 1–5 or effects of specific clinical management strategies.

This study also suggests potential utility of mother–infant-linked claims data to evaluate perinatal outcomes in Japan, where normal pregnancy and delivery are not routinely captured in health insurance claims. Subject to further validation, extension of this approach to larger administrative databases could facilitate national perinatal monitoring and benchmarking and support future epidemiological research on pregnancy complications and infant outcomes.

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- *Address correspondence to:*
 Takehiro Sugiyama, Department of Health Services Research, Institute of Medicine, University of Tsukuba, 1-1-1 Tenno-dai, Tsukuba, Ibaraki 305-8577, Japan.
 E-mail: tsugiyama@md.tsukuba.ac.jp

Association of NCCRP1 expression with T category and *in vitro* growth-related characteristics of head and neck squamous cell carcinoma FaDu cells

Hanako Koda^{1,2,3}, Teruki Hagiwara², Kazuhiko Yamada^{1,3}, Shusuke Yagi^{1,2,3}, Toru Igari⁴, Yuki I. Kawamura^{2,3,*}

¹ Department of Surgery, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

² Clinical Research Advancement Section, National Institute of Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

³ Course of Advanced and Specialized Medicine, Juntendo University Graduate School of Medicine, Tokyo, Japan;

⁴ Pathology Division of Clinical Laboratory, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan.

Abstract: Nonspecific cytotoxic cell receptor protein 1 (NCCRP1), which is expressed in normal squamous epithelium, has been reported as a prognostic marker for esophageal squamous cell carcinoma and triple-negative breast cancer. Here, we evaluated expression of NCCRP1 in head and neck squamous cell carcinoma (HNSCC) and adjacent normal mucosa, its association with clinicopathological features, and *in vitro* growth-related characteristics following forced NCCRP1 expression. In the present study, we evaluated expression levels of NCCRP1 in formalin-fixed, paraffin-embedded samples of specimens collected by biopsy and resection from 43 patients with HNSCC and examined association of NCCRP1 expression with clinicopathological characteristics. Human HNSCC FaDu cells with forced NCCRP1 expression were assessed using the MTT assay and the colony formation assay. We found that NCCRP1 was expressed in noncancerous spinosum and superficial epithelial layers of the oral cavity, nasopharynx, mesopharynx, hypopharynx, and larynx. NCCRP1 expression in HNSCC tissues showed considerable variation, contrasting to relatively uniform expression in noncancerous surrounding mucosa. Based on NCCRP1 staining proportion in tumor, 31 of the 43 patients (72.1%) were classified as NCCRP1-low and the remaining 12 (27.9%) patients as NCCRP1-high. NCCRP1 expression in HNSCC tissue showed an exploratory association with T category ($p = 0.0215$). HNSCC FaDu cells with forced NCCRP1 expression exhibited enhanced *in vitro* growth-related characteristics measured by the MTT and colony formation assays. NCCRP1 expression was associated with T category in this selected HNSCC cohort, and forced NCCRP1 overexpression in FaDu cells was associated with increased *in vitro* growth-related measurements. Nevertheless, these exploratory findings require validation in independent clinical cohorts and experimental models.

Keywords: nonspecific cytotoxic cell receptor protein 1, head and neck squamous cell carcinoma, T category, growth-related characteristics

1. Introduction

Head and neck cancer is the sixth most common cancer worldwide, with approximately 600,000 newly diagnosed and more than 400,000 deaths per year (1). Head and neck squamous cell carcinoma (HNSCC), the most common histologic type, can arise from anywhere within the head and neck region, including oral cavity, nasopharynx, mesopharynx, hypopharynx, and larynx (2). Treatment strategy for HNSCC depends on tumor location, and surgery and/or radiotherapy are the main therapeutic approaches in patients with early-stage HNSCC. The 5-year overall survival rate for patients with early-stage HNSCC has increased to 70–90% with advances in surgery and due to the relatively high

sensitivity of HNSCC to radiotherapy. However, early-stage HNSCC accounts for 30–40% of all cases and the clinical outcomes and prognosis of patients with advanced HNSCC remain poor, with 5-year overall survival rate remaining between 20% and 40% (3). Furthermore, HNSCC tends to overlap with cancers at other sites, such as esophageal cancer, and requires periodic evaluation even after treatment for HNSCC.

Nonspecific cytotoxic cell receptor protein 1 (NCCRP1) was originally identified in catfish as an antigen receptor expressed in nonspecific cytotoxic cells, which are considered evolutionary precursors of natural killer cells in mammals (4). Subsequent studies in zebrafish have revealed receptor-related signaling properties of NCCRP1 including signal transducer

and activator of transcription (STAT) signaling (5). Unlike the fish homologs, mammalian NCCRP1 lacks a transmembrane domain and has predominantly been reported to localize in the cytoplasm, indicating species-related functional differences (6). In humans, *NCCRP1* mRNA is distributed in tissues containing squamous epithelium, such as esophagus, oral cavity, skin, and tongue, but not in immune tissues. Recent studies have reported reduced expression of NCCRP1 in esophageal squamous cell carcinoma (ESCC) (7), pancreatic cancer (8), and triple-negative breast cancer (9); however, its impact on prognosis in these cancers may depend on context. Indeed, reduced NCCRP1 expression was associated with poor prognosis in ESCC whereas patients with NCCRP1-positive pancreatic cancer and triple-negative breast cancer had poor prognosis. Therefore, predicting the role of NCCRP1 in HNSCC is difficult based on current evidence.

In the present study, we aimed to retrospectively evaluate association of NCCRP1 expression with clinicopathologic features of 43 patients with HNSCC. Furthermore, we investigated influence on *in vitro* growth-related characteristics following forced NCCRP1 expression in HNSCC FaDu cells.

2. Materials and Methods

2.1. Patients

This retrospective study included 43 patients with histologically confirmed HNSCC who were diagnosed in the National Center for Global Health and Medicine (NCGM) between 2010 and 2022 and who met predefined eligibility criteria. In particular, the inclusion criteria were as follows: with histologically confirmed HNSCC, with formalin-fixed paraffin-embedded tumor tissue suitable for immunohistochemical evaluation, and with complete clinicopathological information. Patients whose tissue specimen was inadequate for immunohistochemical evaluation or who lacked essential clinical information were excluded. All patients who met these predefined inclusion criteria, including adequate tissue specimens and availability of required clinicopathological data during the study period, were included in the present analysis. No additional case selection was conducted according to NCCRP1 expression or study outcome. During the diagnostic biopsy procedure in some patients with small, early-stage HNSCC, the tumor was completely removed en bloc. Resected specimens provided sufficient pathological information to confirm the pathologic diagnosis of HNSCC. Of the 43 patients, 25 (58.1%) were evaluated using biopsy specimens and 18 (41.9%) using surgically or endoscopically resected specimens. Formalin-fixed, paraffin-embedded sections of these specimens were used for immunohistochemical analysis. Data on clinicopathologic parameters were retrieved from hospital

records. T categories were determined according to the TNM Classification of Malignant Tumors, 8th edition, published by the Union for International Cancer Control. The specimen used for NCCRP1 immunohistochemical assessment did not necessarily correspond to the source used for T-category determination. In patients who subsequently underwent surgical resection, pathological T category was determined from the definitive resection specimen. In patients who did not undergo surgical resection, including those treated with radiotherapy and/or chemotherapy, T category was determined clinically based on imaging and other clinical findings.

For this retrospective study, an opt-out procedure was approved by the Research Ethics Committee of the NCGM (approval no: 2417).

2.2. Immunohistochemical analysis

Paraffin-embedded sections containing formalin-fixed HNSCC specimens were deparaffinized and rehydrated. Antigen retrieval was performed using 10 mM sodium citrate buffer (pH 6.0) in an autoclave at 120°C for 10 min. An anti-NCCRP1 antibody (HPA048141; Sigma-Aldrich, St. Louis, MO) was used to determine NCCRP1 immunoreactivity. Diaminobenzidine staining was performed using the ImmPACT™ DAB Peroxidase Substrate kit (Vector Laboratories, Burlingame, CA), and hematoxylin was used for counterstaining. Pancreatic tissue sections were used as controls for NCCRP1 staining because acinar cells have been reported to specifically express NCCRP1 (10). All slides were reviewed by two or more observers who were blinded to the clinical and pathologic data. Tumor areas were identified with reference to hematoxylin and eosin-stained sections according to squamous cell carcinoma's characteristic histopathological features, including nuclear enlargement, nuclear pleomorphism, hyperchromasia, nuclear-to-cytoplasmic ratio increase, cellular polarity loss, keratinization, intercellular bridges, and atypical squamous cells' invasive nests or cords. We evaluated NCCRP1 staining within intratumoral areas, avoiding peripheral tumor regions near normal tissue. Clearly non-neoplastic areas, including necrotic areas, inflammatory regions, normal mucosa, and tumor margins near normal tissue, were excluded from assessment. Twenty fields were assessed in resection specimens and five in biopsy specimens. Because stromal components were often closely intermingled with tumor cells, the exact proportion of tumor tissues within the evaluated area could not be quantified. Therefore, we classified positive rates of NCCRP1 staining for each field into the following five categories: 15% or less, 15–30%, 30–50%, 50–70%, and 70% or more, and the median value across evaluated fields was used as the representative value for each case. The area occupied by tumor cells, including stromal components, was used as the denominator for positive rates of NCCRP1

staining. Based on NCCRP1 positivity, patients were further classified as NCCRP1-low ($\leq 30\%$) or NCCRP1-high groups ($> 30\%$). The five-category staining scores were assigned independently by observers before any consensus discussion. Agreement on the five-category scores was observed in 41 of 43 cases (95.3%). These percentages represent observed agreement; chance-corrected agreement was not formally assessed. When cases were classified as NCCRP1-high or NCCRP1-low using the 30% cutoff, the classification was concordant between observers in all 43 cases. Therefore, no disagreement occurred in final classification.

2.3. Cell lines and culture

FaDu, a human HNSCC cell line obtained from the American Type Culture Collection, was cultured in Minimum Essential Medium supplemented with 10% fetal calf serum and 1 mM sodium pyruvate. Cells were treated with MC-210 (KAC Co Ltd., Hyogo, Japan) before use. A separate mycoplasma test was not performed. Cell growth was assessed using the MTT assay following the manufacturer's protocol (Nacalai Tesque, Kyoto, Japan). For the MTT assay, different wells were used at different time points. In the colony formation assay, FaDu transfectants (400 cells/well) were seeded into 24-well plates. Following a 2-week incubation, colonies were stained with crystal violet. Staining image was obtained using a fluorescence microscope BZ-X710 (KEYENCE). Semi-quantification from images was performed using a BZ-X Analyzer (KEYENCE). All *in vitro* experiments were performed independently three times, with three technical wells per condition in each experiment. For each of the three independent experiments, the three technical wells were first summarized into a single experiment-level value, and the independent biological experiment was used as the unit of analysis. FaDu cells, which were authenticated by the supplier using short tandem repeat testing, were passaged in our laboratory for fewer than 6 months after resuscitation.

2.4. Transfection of *NCCRP1*

To construct the expression vector containing *NCCRP1*, a DNA fragment encoding the full-length *NCCRP1* open reading frame (OriGene Technologies, Rockville, MD) was used as a template. Briefly, *NCCRP1* gene was amplified by polymerase chain reaction using Primestar (Takara Bio, Shiga, Japan) and ligated into the pIRES2-EGFP vector (Clontech, Palo Alto, CA) using the In-Fusion HD cloning kit (Clontech). The resulting pIRES2-EGFP-NCCRP1 vector and empty pIRES2-EGFP vector (for mock-transfection) were transfected into FaDu cells using Lipofectamine LTX reagent (Life Technologies, Carlsbad, CA). Stable transfectants were isolated using a MoFlo™ XDP cell sorter (Beckman Coulter, Brea, CA).

2.5. RT-qPCR

Total RNA was isolated from cultured cells using the RNA easy Mini Kit (QIAGEN, Hilden, Germany). After treating RNA with DNase I, double-stranded complementary DNA (cDNA) was synthesized using the High-Capacity cDNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA, USA). Quantitative PCR was performed using ABI TaqMan. Threshold cycle numbers (Ct) were determined using Sequence Detector software and relative expression was calculated using the $2^{(-\Delta\Delta Ct)}$ formula (11) as described by the manufacturer, with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as calibrator gene according to the manufacturer's instructions. The TaqMan Gene expression assay IDs for the genes used in this study were *NCCRP1*, Hs01583969_m1 and *GAPDH*, Hs00266705_g1 (Applied Biosystems).

2.6. Western blotting

Protein extraction was prepared from cultured cells using M-PER Mammalian Protein Extraction Reagent (Thermo Fisher Scientific). After centrifugation at $12,000 \times g$ for 10 min at 4°C , supernatant was collected. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis for cell lysates (10 $\mu\text{g}/\text{lane}$) was performed using 5–20% gradient gels under reducing conditions. After electroblotting, the membrane was stained with anti-NCCRP1 (1:500, Sigma-Aldrich #HPA052812) or anti-tubulin (1:20,000, MBL #PM054) antibodies, followed by horseradish peroxidase-conjugated goat antirabbit antibodies (1:5,000, Santa Cruz #sc-2030) and Amersham ECL Prime Western Blotting Detection Reagent (Cytiva). Staining image was obtained using ImageQuant LAS4000 (Cytiva).

2.7. Statistical analysis

Continuous variables with approximately symmetric distributions were expressed as means $\pm$ standard deviation. Welch's *t* test was used for age comparison and mean difference with a 95% confidence interval (CI) was reported. For categorical variables, we used a two-sided Fisher's exact test for 2×2 tables and analyzed tables with more than two categories using a Fisher–Freeman–Halton test. In clinicopathological comparisons, exact unadjusted *p* values were reported. Missing values were not imputed, and analyses were conducted using all available data for each variable. For RT-qPCR, statistical testing was performed using ΔCt values obtained from three independent biological experiments using a paired-sample approach. Two-way ANOVA was used to analyze overall group, time, and group-by-time pattern for MTT data, and Sidák's multiple-comparisons test was used to compare mock and NCCRP1 transfectants on each day. For the colony formation assay, experiment-level values

were compared by paired *t*-test. All statistical analyses were performed using GraphPad Prism 8 statistical program (GraphPad Software, Inc., La Jolla, CA).

3. Results

3.1. NCCRP1 expression in HNSCC and normal adjacent mucosa

First, we performed immunohistochemical analysis to investigate protein expression and localization of NCCRP1 in HNSCC and normal adjacent mucosa specimens. Of 43 cases, NCCRP1 expression in noncancerous mucosa was evaluable in 40 samples. Among these 40 cases, NCCRP1 expression was detected in 97.5% (39/40), including oral cavity, nasopharynx, mesopharynx, hypopharynx, and larynx. NCCRP1 expression was observed in spinous and superficial epithelial layers of stratified squamous epithelium, where epithelial cells showed NCCRP1 staining in cytoplasm and nuclei (Figure 1A). In contrast, NCCRP1 expression in HNSCC tissues showed considerable variation. Therefore, we categorized the HNSCC cases based on proportion of NCCRP1-positive area in tumor tissues into the following five categories: 15% or less, 15–30%, 30–50%, 50–70%, and 70% or more (Figure 1D). Based on the bimodal distribution of NCCRP1 positivity,

we classified patients into NCCRP1-low ($\leq 30\%$) and NCCRP1-high ($> 30\%$) groups. Of the 43 tumor specimens, 31 (72.1%) HNSCC cases were classified as NCCRP1-low (Figure 1B) and the remaining 12 (27.9%) HNSCC cases as NCCRP1-high (Figure 1C).

3.2. Association of NCCRP1 expression with clinicopathologic features of HNSCC

We next investigated association of NCCRP1 expression with the clinicopathologic characteristics of HNSCC. Of the 31 NCCRP1-low cases, 26 (84%) showed 0–15% positivity, and 5 (16%) showed 15–30% positivity. Of the 12 NCCRP1-high cases, 9 (75%) showed 30–50% positivity, 2 (17%) showed 50–70% positivity, and 1 (8%) showed $\geq 70\%$ positivity (Figure 1D). In the NCCRP1-low group, 17 of 31 patients (54.8%) had biopsy specimens and 14 (45.2%) had resection specimens, whereas in the NCCRP1-high group, 8 of 12 patients (66.7%) had biopsy specimens and 4 (33.3%) had resection specimens. Distribution of specimen type across T categories is presented in Supplementary Table S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=132>).

In the overall cohort, mean patient age was 65.2 ± 9.23 years, and the majority of patients were male (95.3%). Mean age was 61.4 ± 12.67 years in the

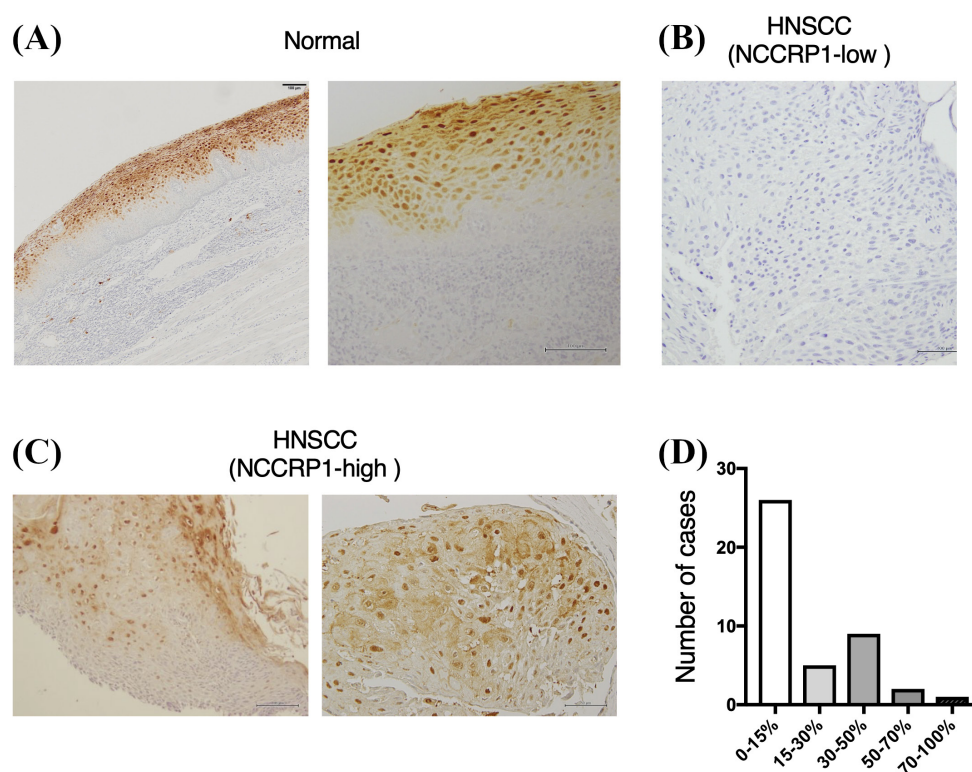


Figure 1. Nonspecific cytotoxic cell receptor protein 1 (NCCRP1) expression in head and neck squamous cell carcinoma (HNSCC) and adjacent noncancerous mucosa. (A) Representative images of formalin-fixed, paraffin-embedded samples of noncancerous head and neck mucosa stained with anti-NCCRP1 antibody. **(B)** Representative image of NCCRP1-low HNSCC. **(C)** Representative images of NCCRP1-high HNSCC. **(D)** Bimodal distribution of NCCRP1 positivity in HNSCC tissue.

NCCRP1-high group and 66.6 ± 7.25 years in the NCCRP1-low group; mean difference between groups was -5.23 years (95% CI, -13.56 to 3.11 , $p = 0.200$). A two-sided Fisher–Freeman–Halton exact test revealed a statistically significant difference of T category between the NCCRP1-high and NCCRP1-low groups ($p = 0.0215$, Table 1). Given sparse distribution of patients across T categories, we additionally summarized the T categories as T3–T4 in comparison with Tis–T2 as a secondary descriptive analysis to provide an interpretable effect estimate without fitting an overparameterized regression model. We found that T3–T4 tumors were observed in 5 of 12 patients (41.7%) in the NCCRP1-high group and 2 of 29 patients (6.9%) in the NCCRP1-low group, reflecting a conditional odds ratio of 8.97 (exact 95% CI, 1.18–113.19). The very wide CI further emphasizes substantial statistical uncertainty arising from the small and sparse dataset. No significant differences were identified for sex, tumor location, history of alcohol consumption, smoking, and pN stage between the NCCRP1-high and NCCRP1-low groups.

3.3. Association of forced NCCRP1 expression and *in*

vitro growth-related characteristics in HNSCC cells

To elucidate significance of NCCRP1 expression in HNSCC, we examined effect of NCCRP1 expression on *in vitro* growth-related characteristics by comparing FaDu cells expressing NCCRP1 to those that were mock-transfected. Basal *NCCRP1* mRNA expression in FaDu cells was extremely low, but the mock-transfected FaDu cells yielded measurable Ct values. As shown in Figure 2A, the NCCRP1-transfected FaDu cells exhibited $> 1,000$ fold higher *NCCRP1* mRNA levels than the mock-transfected FaDu cells. Western blotting further confirmed NCCRP1 overexpression at the protein level (Figure 2B). Supplementary Figure S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=132>) presents original Western blot image for Figure 2B. For MTT data, two-way ANOVA showed significant effects of group ($p = 0.002$), time ($p < 0.001$), and the group-by-time interaction ($p < 0.001$). In Sidák's multiple comparisons test, no significant differences between NCCRP1- and mock-transfected FaDu cells on days 1–3, whereas MTT signals of NCCRP1-transfected

Table 1. Comparison of clinicopathologic features of patients with NCCRP1-high and NCCRP1-low HNSCC

Characteristic	Total (%)	Number of patients (%)		<i>p</i> value
		NCCRP1-high	NCCRP1-low	
Number of patients	43	12	31	
Sex				0.0731
Male	41 (95.3)	10 (83.3)	31 (100)	
Female	2 (4.7)	2 (16.7)	0 (0.0)	
Mean age $\pm$ standard deviation (years)	65.2 ± 9.23	61.4 ± 12.67	66.6 ± 7.25	0.200
Alcohol ¹ ($n = 39$)				0.573
No	4 (10.3)	2 (16.7)	2 (7.4)	
Yes	35 (89.7)	10 (83.3)	25 (92.6)	
Smoking ² ($n = 39$)				0.4026
No	7 (17.9)	1 (8.3)	6 (22.2)	
Yes	32 (82.1)	11 (91.7)	21 (77.8)	
Tumor location				0.289
Oral cavity	5 (11.6)	2 (16.7)	3 (9.7)	
Oropharynx	3 (7.0)	2 (16.7)	1 (3.2)	
Hypopharynx	17 (39.5)	3 (25.0)	14 (45.2)	
Larynx	18 (41.9)	5 (41.7)	13 (41.9)	
T category ³ ($n = 41$)				0.0215*
Tis	6 (14.6)	1 (8.3)	5 (17.2)	
T1	19 (46.3)	5 (41.7)	14 (48.3)	
T2	9 (22.0)	1 (8.3)	8 (27.6)	
T3	3 (7.3)	1 (8.3)	2 (6.9)	
T4	4 (9.8)	4 (33.3)	0 (0.0)	
pN status ($n = 40$)				0.0865
N0	35 (87.5)	9 (81.8)	26 (89.7)	
N1	3 (7.5)	0 (0.0)	3 (10.3)	
N2	2 (5.0)	2 (18.2)	0 (0.0)	
Complicated by ESCC				0.723
No	15 (34.9)	5 (41.7)	10 (32.3)	
Yes	28 (65.1)	7 (58.3)	21 (67.7)	

Note: * $p < 0.05$. ¹Alcohol consumption was categorized based on the presence of habitual alcohol consumption. ²Smoking was categorized as "No" for patients who have never smoked and "Yes" for those who ever smoked. ³T category was based on pathological assessment of definitive resection specimens when available and on clinical assessment, including imaging and other clinical findings, in patients who did not undergo surgical resection. Abbreviations: HNSCC, head and neck squamous cell carcinoma; NCCRP1, nonspecific cytotoxic cell receptor protein 1.

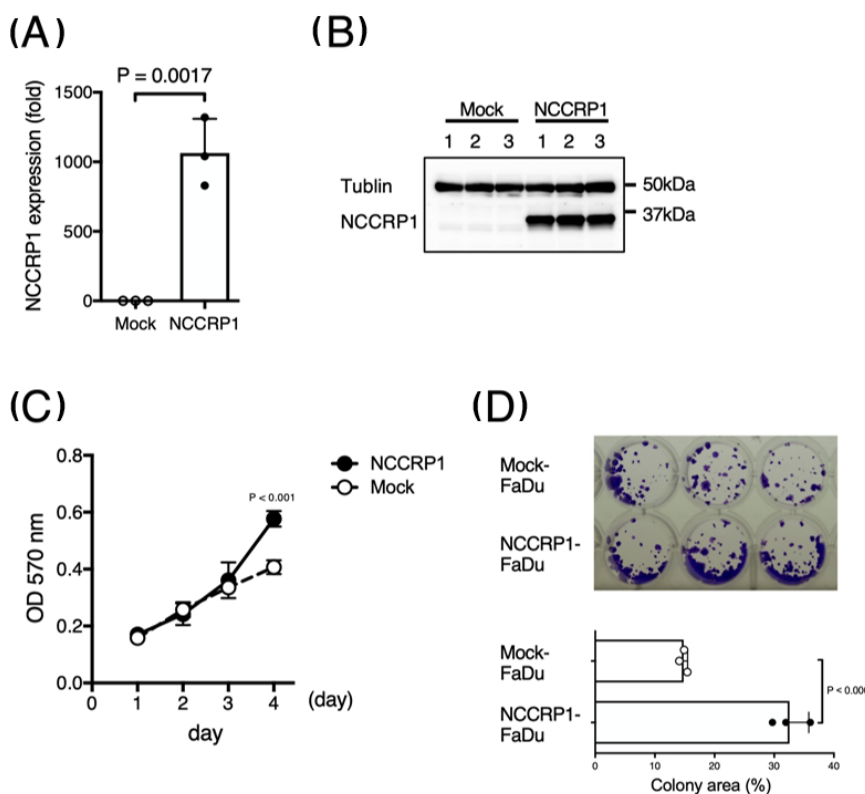


Figure 2. Effect of forced NCCRP1 expression on MTT signal and colony formation in FaDu cells. Transfection experiments were conducted three times independently and same results were obtained each time. There were three technical wells within each experiment. (A) NCCRP1 mRNA levels in mock-transfected and NCCRP1-transfected FaDu cells. Each point represents mean of three technical wells from one independent biological experiment; data are shown as mean $\pm$ standard deviation (SD) across three independent experiments. **(B)** Western blots of mock-transfected and NCCRP1-transfected FaDu cells for detection of NCCRP1 and tubulin. Lanes 1–3 illustrates independent biological repeats. **(C)** Growth curves of NCCRP1-transfected and mock-transfected FaDu cells determined by MTT assay. Cultures were started at a cell density of 2×10^3 /well. Different wells were used at different time points. Data are presented as mean $\pm$ SD from three independent biological experiments after averaging three technical wells within each experiment. **(D)** NCCRP1-transfected and mock-transfected FaDu cells were cultured for two weeks. Representative images of colonies visualized using crystal violet staining (upper panel). Areas with colonies were determined in three separate wells within each experiment. Each point represents mean of three technical wells from one independent biological experiment; data are shown as mean $\pm$ SD across three independent experiments (lower panel).

cells were significantly higher than that of mock-transfected cells on day 4 ($p < 0.001$; Figure 2C). Furthermore, NCCRP1-transfected FaDu cells formed colonies more efficiently than mock-transfected FaDu cells in the colony formation assay ($p < 0.0001$; Figure 2D). Although these results do not directly establish a proliferative function of NCCRP1 but demonstrated the association of NCCRP1 expression and *in vitro* growth-related characteristics in HNSCC.

4. Discussion

In the present study, we used immunohistochemical analysis to demonstrate that NCCRP1 is expressed in normal mucosa across all areas of the pharynx and larynx, while its expression in HNSCC tissues showed considerable variation and NCCRP1-high ($> 30\%$) was associated with T category. *In vitro* overexpression of NCCRP1 in FaDu cells was associated with enhanced growth-related characteristics measured by MTT assay and colony formation. A previous study has

demonstrated that suppression of NCCRP1 with siRNA leads to a significant decrease in growth of HeLa cells (6). These findings support our observations, although these assays do not distinguish proliferation from altered metabolism, survival, or oncogenic clonogenicity. Contrasting to previous reports demonstrating predominant localization of mammalian NCCRP1 in the cytoplasm (6), we observed nuclear staining of NCCRP1 in some normal and tumor specimens (Figure 1, A and C). Such nuclear localization of NCCRP1 should be interpreted cautiously and further validated using complementary approaches.

In this study, NCCRP1 expression showed an exploratory association with T category. This association should be interpreted cautiously because the present cohort was a small sample size and was highly selected; 95.3% of patients were male, hypopharyngeal and laryngeal tumors predominated, and 28 of 43 patients with HNSCC (65.1%; Table 1) had concomitant ESCC. The proportion of patients with both HNSCC and ESCC concomitantly in this study is substantially higher than

that generally reported. In a systematic review and meta-analysis of 15 studies, approximately 15% of 3,386 patients with HNSCC had esophageal second primary neoplasms (12). The difference in percentages of patients with concurrent HNSCC and ESCC is likely explained by the fact that our institution's referral pathway differs from that of other institutions. Numerous patients with HNSCC treated at our institution are initially identified during screening or diagnostic work-up for ESCC and are subsequently referred for head and neck lesion management. This referral pathway may also explain the predominance of male patients and hypopharyngeal/laryngeal tumors in our cohort. Furthermore, sampling bias related to specimen type should be considered. Although no significant difference was observed in proportion of biopsy/resection specimens, nonsignificant comparison does not demonstrate equivalence between these specimen types. Therefore, our findings are exploratory and future validation in larger, independent cohorts with a more representative distribution of HNSCC subsites, sex, and other patient characteristics are warranted.

Several additional limitations should be acknowledged. First, sample size was small, limiting the power of our results and preventing prognostic analysis and overparameterized multivariable analysis. Residual confounding is possible. Second, association of NCCRP1 expression with histological differentiation or HPV/p16 status were not examined because this information was not systematically available. Third, the 30% cutoff value used to define NCCRP1-low and NCCRP1-high expression was derived from the present cohort and has not been externally validated. Multiple clinicopathological comparisons were performed without adjustment for multiplicity; therefore, the possibility of false-positive findings cannot be excluded. In addition, the robustness of the observed association with T category to the cohort-derived 30% cutoff value remains uncertain because sensitivity analyses using alternative cutoffs were not performed. Therefore, the observed association should not be interpreted as being independent of potential confounding factors and requires further validation in an independent cohort.

5. Conclusion

NCCRP1 expression varied among HNSCC tissues and showed an exploratory association with T category in this selected cohort. In FaDu cells, forced NCCRP1 expression was associated with increased MTT signals and colony formation, suggesting a potential relationship between NCCRP1 expression and *in vitro* growth-related characteristics. These findings should be interpreted cautiously given the small, selected clinical cohort, the cohort-derived expression cutoff, and use of a single cell model. Validation in larger, independent clinical cohorts and additional experimental models,

together with mechanistic studies, is needed to clarify the biological and clinical significance of NCCRP1 in HNSCC.

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**Address correspondence to:*

Yuki I. Kawamura, Clinical Research Advancement Section, National Institute of Global Health and Medicine, Japan Institute for Health Security, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.

E-mail: kawamura.y@jihs.go.jp

Association of steatotic liver disease with long-term oncological outcomes after hepatic resection for hepatocellular carcinoma

Nobuhiro Hasui^{1,2}, Saori Funakoshi^{1,3}, Aya Yamazaki¹, Takuya Yanase¹, Shohei Kudo¹, Hirokazu Momose¹, Ryota Matsuki¹, Masaharu Kogure¹, Akimasa Hayashi³, Yutaka Suzuki⁴, Junji Shibahara³, Yoshihiro Sakamoto^{1,*}

¹ Department of Gastroenterological Surgery, Kyorin University School of Medicine, Mitaka, Tokyo, Japan;

² Division of Hepato-Biliary and Pancreatic Surgery, Tohoku Medical and Pharmaceutical University, Sendai, Miyagi, Japan;

³ Department of Pathology, Kyorin University School of Medicine, Mitaka, Tokyo, Japan;

⁴ Department of Surgery, Kyorin University Suginami Hospital, Tokyo, Japan.

Abstract: Hepatic steatosis manifests in obesity and systemic metabolic disorders. The nomenclature has recently shifted from nonalcoholic fatty liver disease/nonalcoholic steatohepatitis to steatotic liver disease (SLD), which includes metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction-associated steatotic liver disease with increased alcohol intake, and alcohol-related liver disease. This study retrospectively evaluated the association between SLD and long-term oncological outcomes in 85 patients undergoing hepatic resection for hepatocellular carcinoma (HCC) between 2018 and 2022. SLD was histologically defined as steatosis involving $\geq 5\%$ of non-tumorous hepatocytes. Of these patients, 47 did not have SLD (non-SLD group) and 38 had SLD. We compared recurrence-free survival (RFS) and overall survival (OS) between these groups. Patients with SLD exhibited a higher body mass index and more advanced fibrosis than those without SLD, whereas lifestyle-related diseases were comparably prevalent. Median RFS was not reached in the non-SLD group and was 21 months in the SLD group (log-rank $p = 0.054$). In exploratory multivariable analysis, SLD was associated with a higher cause-specific hazard of recurrence after adjustment for age, Barcelona Clinic Liver Cancer stage, viral hepatitis status, and diabetes mellitus (adjusted hazard ratio, 1.939; 95% confidence interval, 1.003–3.748). No significant association between SLD and OS was noted (hazard ratio, 0.962; 95% confidence interval, 0.399–2.315). These findings suggest a possible association between SLD and HCC recurrence after hepatic resection, whereas its association with OS remains uncertain.

Keywords: metabolic dysfunction, MASLD, SLD, overall survival, recurrence-free survival

1. Introduction

The global prevalence of steatotic liver disease (SLD) is estimated to be 25–40% and it continues to rise, driven by the increasing incidence of obesity and diabetes mellitus (DM) (1). A subset of patients with SLD develops steatohepatitis with progressive fibrosis, eventually leading to cirrhosis and hepatocellular carcinoma (HCC) (1).

Traditionally, the term nonalcoholic fatty liver disease (NAFLD) was widely used to describe fatty liver, encompassing a clinical spectrum from simple steatosis to nonalcoholic steatohepatitis (NASH) (2). In 2023, an international consensus proposed a new nomenclature collectively terming these conditions SLD, which includes metabolic dysfunction-associated steatotic liver disease (MASLD), alcohol-related liver

disease (ALD), and MASLD with increased alcohol intake (MetALD) (3). This updated classification enables a more comprehensive assessment of the respective contributions of metabolic dysfunction and alcohol consumption to hepatic steatosis.

In tandem with this classification shift, the epidemiology of HCC has evolved. Although the development of antiviral therapies has effectively controlled chronic viral hepatitis—leading to a decline in virus-related HCC—the proportion of cases associated with metabolic dysfunction and alcohol consumption continues to increase (4–6). Therefore, establishing new clinical evidence that reflects the evolving etiology of HCC is important.

Previous studies investigating the prognosis of patients with NASH-related HCC (NASH-HCC) have yielded conflicting results. Some studies demonstrate

better outcomes for patients with NASH-HCC than for those without, whereas others report the opposite (7-9). These discrepancies may be attributable to ambiguous definitions of the non-NASH cohort and varying proportions of viral- and alcohol-related liver diseases among the populations studied. Most of those non-NASH cases were associated with viral hepatitis, so the observed differences may have been confounded by the underlying liver disease rather than metabolic factors themselves. Moreover, these studies relied on the Brunt classification (10), a histological assessment that fundamentally differs from the recently proposed MASLD definition based on metabolic dysfunction. Consequently, previous findings regarding NASH-HCC cannot be directly extrapolated to SLD-related HCC.

Therefore, the current study aimed to evaluate the association between histologically defined SLD in the non-tumorous liver and recurrence-free survival (RFS) and overall survival (OS) in patients undergoing hepatic resection for HCC.

2. Patients and Methods

2.1. Study design and patients

This study was approved by the Medicine Research Ethics Committee and the Institutional Review Board of Kyorin University (project number R06-180, approval number 2510). All clinical investigations were conducted in accordance with the Declaration of Helsinki (as revised in 2013). The requirement for written informed consent was waived by the institutional ethics committee because of the retrospective nature of the study, and an opt-out approach was used to provide patients with the opportunity to decline participation.

Between April 2018 and December 2022, 86 patients with HCC underwent initial hepatic resection at this hospital. Following established diagnostic criteria, we histologically defined SLD as steatosis involving $\geq 5\%$ of non-tumorous hepatocytes (3). We excluded repeat hepatectomies for recurrent HCC. Of the total patients, 47 did not have SLD and 38 exhibited SLD in the background liver; one patient was excluded due to insufficient non-tumorous liver tissue for reliable histological assessment. Based on diagnostic criteria incorporating cardiometabolic risk factors and alcohol consumption history, the 38 patients with SLD were subclassified into MASLD ($n = 17$) and MetALD/ALD ($n = 21$) cohorts (3). No patients presented with specific-etiology or cryptogenic SLD (Figure 1).

2.2. Definition and classification of SLD

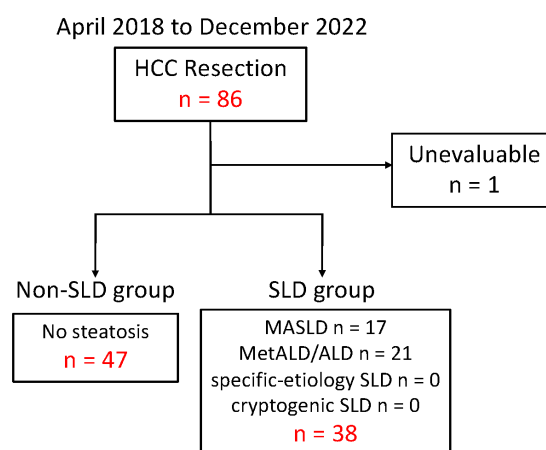
MASLD was diagnosed according to international consensus criteria. Patients with $\geq 5\%$ hepatic steatosis were classified as having MASLD if they exhibited at least one of the following cardiometabolic risk factors:

overweight/obesity (body mass index [BMI] ≥ 23 kg/m² for Asians), impaired glucose metabolism (hemoglobin A1c [HbA1c] $\geq 5.7\%$, type 2 DM, or antidiabetic treatment), elevated blood pressure ($\geq 130/85$ mmHg or antihypertensive treatment), hypertriglyceridemia (≥ 150 mg/dL or lipid-lowering treatment), or reduced high-density lipoprotein (HDL) cholesterol (< 40 mg/dL in men or < 50 mg/dL in women). We incorporated medication use into the corresponding cardiometabolic criteria. We excluded waist circumference and the homeostasis model assessment of insulin resistance (HOMA-IR) from the assessment because these data were unavailable for most patients. Consequently, MASLD was diagnosed based solely on the available cardiometabolic criteria (3).

Alcohol consumption was calculated using patient-reported drinking habits and quantities documented in medical records. To meet the MASLD criteria, alcohol consumption could not exceed 140 g/week for women and 210 g/week for men (3). Because alcohol consumption was retrospectively assessed from medical records, precise differentiation between MetALD and ALD was not possible in all patients. Therefore, these categories were combined as MetALD/ALD. This distinction was not central to the current study, which primarily focused on the association between histologically defined SLD and oncological outcomes.

According to guidelines, hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are not diagnostic components of MASLD; rather, they are considered separate or coexisting liver disease etiologies (3).

2.3. Histopathological assessment



Patients were observed until September 2025

Figure 1. Patient classification according to the presence of SLD. Abbreviations: ALD, alcohol-related liver disease; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, MASLD with increased alcohol intake; SLD, steatotic liver disease.

We identified histopathological findings from the original pathology reports. A gastrointestinal pathologist (A.H.), blinded to clinical outcomes, independently reassessed hepatic steatosis in the non-tumorous liver in all of the patients. The pathologist estimated the percentage of steatotic hepatocytes and classified patients according to the General Rules for the Clinical and Pathological Study of Primary Liver Cancer: st0, < 5%; st1, 5%–33%; st2, 34%–66%; and st3, $\geq$ 67% (11).

We retrospectively obtained all other pathological variables—including inflammatory activity, fibrosis stage, vascular invasion, and resection margin status (R0)—from the original reports, which had been routinely reviewed and approved by at least two board-certified pathologists, including a liver pathology specialist. Inflammatory activity in the non-tumorous liver was semiquantitatively graded as absent, mild, or moderate-to-severe, based on histological scoring systems proposed by the Nonalcoholic Steatohepatitis Clinical Research Network (12) and the METAVIR system (13). For statistical analysis, we dichotomized inflammatory activity as absent or present (mild or moderate-to-severe). All non-R0 resections were classified as R1 (microscopic margin positivity); no patients had macroscopic residual disease (R2).

2.4. Clinical and surgical variables

Baseline clinical characteristics included age, sex, BMI, a history of DM, hypertension, dyslipidemia, alcohol consumption, HbA1c, triglycerides (TG), and HDL cholesterol.

Baseline hepatic function parameters included a history of HBV or HCV infection, serum alpha-fetoprotein (AFP) levels, and protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels. Liver function was evaluated using the fibrosis-4 index, albumin-bilirubin (ALBI) score, indocyanine green retention rate at 15 minutes (ICG-R15), and Child–Pugh classification.

Assessed surgical and pathological characteristics included major hepatectomy (defined as the resection of three or more Couinaud segments) (14), tumor number, tumor size, microvascular invasion, fibrosis stage ($\geq$ F3), and Barcelona Clinic Liver Cancer (BCLC) stage $\geq$ B.

2.5. Follow-up and outcome definitions

The primary outcomes were RFS and OS. We also recorded postoperative recurrence and subsequent therapies. All patients were observed until September 2025.

After hepatic resection, patients were regularly followed with clinical assessments, laboratory tests, tumor markers (AFP and PIVKA-II), and contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) on an outpatient basis.

Depending on the patient's clinical condition, imaging was generally performed every 3–4 months during the early postoperative period and every 3–6 months thereafter. Recurrence was diagnosed based on characteristic HCC findings on contrast-enhanced CT, MRI, or other imaging modalities.

RFS was defined as the time from hepatic resection to the first documented recurrence. Patients who died without recurrence were censored at the date of death. Patients who remained recurrence-free were censored at the data cutoff date (September 30, 2025), whereas those lost to follow-up before the data cutoff were censored at the date of their last adequate assessment of recurrence. OS was defined as the time from hepatic resection to death from any cause or the last known date alive. Surviving patients were censored at the last known date alive.

2.6. Statistical analysis

Statistical analyses were performed using the software IBM SPSS Statistics (version 25.0; IBM Corp., Armonk, NY, USA). Continuous variables are expressed as medians with interquartile ranges and were compared using the Mann–Whitney *U* test. Categorical variables were compared using the chi-squared test or Fisher's exact test, as appropriate. Missing data were not imputed, and statistical analyses were performed using available cases for each variable. We estimated the median duration of follow-up using the reverse Kaplan–Meier method. Survival curves for RFS and OS were estimated using the Kaplan–Meier method and compared using the log-rank test. Survival estimates at each time point are reported with 95% confidence intervals (CIs), with the numbers at risk presented below the curves. A two-tailed *p* value < 0.05 was considered statistically significant. An exploratory subgroup analysis excluding patients with viral hepatitis was performed using the same endpoint definitions and censoring rules as in the primary analysis.

The association of SLD with recurrence was evaluated using cause-specific Cox proportional hazards regression, with recurrence as the event and deaths without recurrence treated as censored observations. A multivariable cause-specific Cox proportional hazards model incorporating SLD, age, BCLC stage, viral hepatitis status, and DM was constructed. SLD, DM, viral hepatitis status, and BCLC stage were coded as binary variables (SLD: non-SLD = 0, SLD = 1; DM: absent = 0, present = 1; viral hepatitis: absent = 0, HBV/HCV = 1; BCLC stage: 0/A = 0, B/C = 1), whereas age was modeled as a continuous variable per 1-year increase. Covariates were selected based on clinical relevance rather than univariable statistical significance. Hepatic functional reserve, histological fibrosis, and resection margin status were considered as potential covariates but were not included in the final model because of the limited number of recurrence events

and the risk of overfitting. The proportional hazards assumption for SLD was assessed using an interaction term between SLD and the natural logarithm of time. The linearity assumption for age was assessed by adding a quadratic term for mean-centered age to the Cox model.

3. Results and Discussion

Baseline clinical characteristics are summarized in Table 1. The median ages were 73 and 75 years in the non-SLD and SLD groups, respectively. The proportion of male patients was similar in the groups (81% vs. 84%). BMI was significantly higher in the SLD group than in the non-SLD group (24.7 vs. 22.2 kg/m², $p = 0.01$). The prevalence of lifestyle-related diseases did not differ significantly between the groups. Approximately 30% of patients in both groups were positive for HBV or HCV, and all had received antiviral therapy. The median FIB-4 index, ICG-R15, Child–Pugh classification, ALBI score,

AFP, and PIVKA-II levels did not differ significantly between the groups.

Surgical and pathological characteristics are summarized in Table 2. Tumor size tended to be larger in the non-SLD group than in the SLD group, but this difference was not significant (56 mm vs. 40 mm, $p = 0.10$). Advanced fibrosis ($\geq$ F3) was observed significantly more frequently in the SLD group than in the non-SLD group (58% vs. 30%, $p = 0.01$). An exploratory analysis revealed a weak positive correlation between the FIB-4 index and histological fibrosis ($r = 0.279$, $p = 0.010$) (Supplementary Methods/Results, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=130>). The degree of hepatic steatosis was assessed in the 85 evaluable patients, and 47 were classified as st0 (< 5% steatosis) and 38 as st1 (5%–33% steatosis). No patients were classified as st2 (34%–66%) or st3 ($\geq$ 67%).

The median duration of follow-up, estimated using

Table 1. Baseline clinical characteristics of patients with HCC who underwent liver resection

Variable	Non-SLD ($n = 47$)	SLD ($n = 38$)	p value
Age, years (median [range])	73 (30–88)	75 (52–86)	0.86
Sex, males (%)	38 (81%)	32 (84%)	0.69
Body mass index, kg/m ² (median [IQR])	22.2 (19.8–24.9)	24.7 (21.9–26.7)	0.01
Diabetes mellitus (%)	21 (45%)	22 (58%)	0.23
Hemoglobin A1c, % (median [IQR])	5.9 (5.8–6.9)	6.5 (5.9–7.1)	0.07
Hypertension (%)	27 (57%)	22 (58%)	0.96
Dyslipidemia (%)	22 (47%)	23 (61%)	0.21
Triglycerides, mg/dL (median [IQR])	99 (71–132)	106 (79–143)	0.41
HDL-cholesterol, mg/dL (median [IQR])	46 (39–58)	46 (36–55)	0.49
Alcohol consumption history (%)	29 (62%)	21 (55%)	0.55
HBV infection (%)	8 (17%)	9 (24%)	0.44
HCV infection (%)	6 (13%)	2 (5%)	0.24
Antiviral therapy among HBV/HCV patients, n (%)	14 (100%)	11 (100%)	–
FIB-4 index (median [IQR])	2.64 (1.93–3.11)	3.38 (2.12–4.01)	0.12
ICG-R15 (%) (median [IQR])	11.6 (7.4–13.1)	13.5 (8.4–16.1)	0.23
ALBI score (median [IQR])	–2.53 (–2.80––2.29)	–2.73 (–2.90––2.50)	0.18
Child–Pugh $\geq$ B (%)	3 (6%)	1 (3%)	0.42
AFP level, ng/mL (median [IQR])	4.5 (2.6–31.0)	9.3 (4.9–35.5)	0.07
PIVKA-II level, ng/mL (median [IQR])	189 (27–1803)	321 (70–751)	0.43

Note: Data are presented as n (%) or the median (IQR). Available sample sizes for variables with missing data were as follows: Triglycerides, $n = 46/37$; HDL cholesterol, $n = 39/34$ (non-SLD/SLD, respectively). *Abbreviations:* AFP, alpha-fetoprotein; FIB-4, fibrosis-4 index; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDL, high-density lipoprotein; ICG-R15, indocyanine green retention rate at 15 minutes; IQR, interquartile range; PIVKA-II, protein induced by vitamin K absence or antagonist-II, SLD, steatotic liver disease.

Table 2. Surgical and pathological characteristics of patients with HCC who underwent liver resection

Variable	Non-SLD ($n = 47$)	SLD ($n = 38$)	p value
Major hepatectomy (%)	11 (23%)	8 (21%)	0.80
Tumor number $\geq$ 2	6 (13%)	8 (21%)	0.31
R0 resection (%)	41 (87%)	36 (95%)	0.23
Tumor size, mm (median [range])	56 (10–170)	40 (10–150)	0.10
Microvascular invasion (%)	27 (57%)	18 (47%)	0.36
Micro portal vein invasion	23 (49%)	15 (39%)	0.38
Micro hepatic arterial invasion	2 (4%)	1 (3%)	0.69
Micro hepatic vein invasion	9 (19%)	3 (8%)	0.14
Inflammation (%)	19 (40%)	19 (50%)	0.38
Fibrosis stage $\geq$ F3 (%)	14 (30%)	22 (58%)	0.01
BCLC stage $\geq$ B (%)	12 (26%)	6 (16%)	0.27

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma; SLD, steatotic liver disease.

the reverse Kaplan–Meier method, was 57 months in the non-SLD group and 64 months in the SLD group.

We observed a total of 44 RFS events (recurrences) and 20 OS events (deaths), including six deaths before recurrence. The non-SLD group experienced 19 RFS events and 10 deaths, including four deaths before recurrence. The SLD group experienced 25 RFS events and 10 deaths, including two deaths before recurrence.

Median RFS was not reached in the non-SLD group and was 21 months (95% CI: 11.3–30.7 months) in the SLD group (log-rank $p = 0.054$). In univariable cause-specific Cox proportional hazards analysis, the HR for recurrence associated with SLD was 1.776 (95% CI: 0.977–3.236; $p = 0.060$). In multivariable cause-specific Cox analysis adjusted for age, BCLC stage, viral hepatitis status, and DM, the HR for recurrence associated with SLD was 1.939 (95% CI: 1.003–3.748; $p = 0.049$) (Table 3). The multivariable model included 85 patients and 44 recurrence events, with no missing data for the included covariates. There was no evidence of violation of the proportional hazards assumption for SLD ($p = 0.910$). In addition, the quadratic term for mean-centered age was not significant ($p = 0.423$), providing no evidence of a nonlinear association between age and the hazard of recurrence. Median OS was not reached in either group, with no significant differences between the

groups (log-rank $p = 0.930$). In univariable analysis, SLD was not significantly associated with OS (HR = 0.962; 95% CI: 0.399–2.315; $p = 0.930$) (Figure 2). The 3-year RFS estimates were 55.0% (95% CI: 38.2–69.0%) in the non-SLD group and 31.4% (95% CI: 16.3–47.7%) in the SLD group, while the corresponding 3-year OS estimates were 86.2% (95% CI: 72.0–93.5%) and 88.5% (95% CI: 72.2–95.4%), respectively.

In the exploratory subgroup analysis excluding patients with viral hepatitis, median RFS was 22 months (95% CI: 0.4–43.6 months) in the non-SLD group and 27 months (95% CI: 14.7–39.3 months) in the SLD group, with no significant differences between the cohorts (log-rank $p = 0.399$). In univariable analysis, SLD was not significantly associated with RFS (HR = 1.328; 95% CI: 0.681–2.588; $p = 0.404$). Median OS was 79 months (95% CI: 52.6–105.4 months) in the non-SLD group and 68 months (95% CI: 54.1–82.0 months) in the SLD group, with no significant differences between the cohorts (log-rank $p = 0.936$). Similarly, SLD was not significantly associated with OS in univariable analysis (HR = 0.959; 95% CI: 0.346–2.661; $p = 0.936$) (Supplementary Figure S1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=130>).

Recurrence and subsequent therapies are summarized in Table 4. Following recurrence, locoregional therapy

Table 3. Cox proportional hazards analyses for recurrence-free survival

Variable	Univariable HR (95% CI)	p value	Multivariable HR (95% CI)	p value
SLD (vs. non-SLD)	1.776 (0.977–3.236)	0.060	1.939 (1.003–3.748)	0.049
Age, years	0.971 (0.938–1.006)	0.105	0.971 (0.940–1.003)	0.072
BCLC stage ($\geq B$ vs. 0/A)	2.585 (1.326–5.037)	0.005	2.631 (1.318–5.253)	0.006
DM (yes vs. no)	0.685 (0.378–1.241)	0.212	0.599 (0.315–1.137)	0.117
Viral hepatitis status (yes vs. no)	0.461 (0.221–0.962)	0.039	0.518 (0.242–1.110)	0.091

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; RFS, recurrence-free survival; SLD, steatotic liver disease.

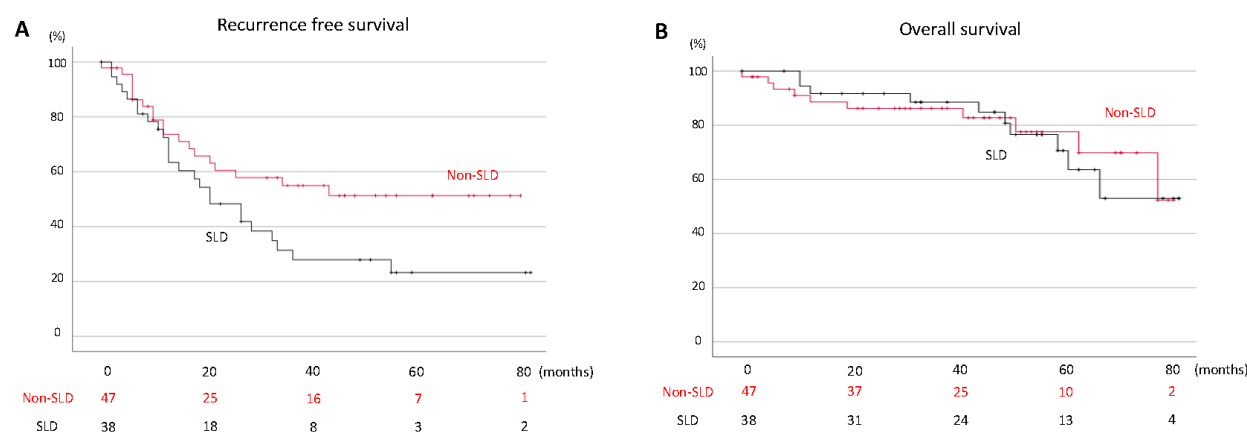


Figure 2. Kaplan–Meier curves for RFS and OS in patients with and without SLD. (A) RFS curves for patients with and without SLD (log-rank $p = 0.054$); (B) OS curves for the same patient groups (log-rank $p = 0.930$). Censored data are indicated by tick marks on the Kaplan–Meier plots. Abbreviations: OS, overall survival; RFS, recurrence-free survival; SLD, steatotic liver disease.

Table 4. Patterns of first recurrence among patients with recurrent HCC

Variable	Non-SLD (<i>n</i> = 47)	SLD (<i>n</i> = 38)	<i>p</i> value
Recurrence	19	25	
Site of first recurrence	<i>n</i> = 19	<i>n</i> = 25	
Intrahepatic recurrence	15 (79%)	22 (88%)	0.42
Extrahepatic recurrence	4 (21%)	3 (12%)	
Subsequent therapy	<i>n</i> = 19	<i>n</i> = 25	
Surgery/RFA/TACE	10 (53%)	21 (84%)	0.024
Chemotherapy/BSC	9 (47%)	4 (16%)	

Abbreviations: BSC, best supportive care; HCC, hepatocellular carcinoma; RFA, radiofrequency ablation; SLD, steatotic liver disease; TACE, transcatheter arterial chemoembolization.

(surgery/radiofrequency ablation/transcatheter arterial chemoembolization) was administered more frequently in the SLD group (84% vs. 53%), whereas chemotherapy or best supportive care was more common in the non-SLD group (16% vs. 47%, $p = 0.024$).

The findings of this exploratory study suggested a possible association between SLD and recurrence after hepatic resection for HCC, but it was not significantly associated with OS. These findings should be interpreted cautiously given the limited sample size and number of events.

The prognostic impact of SLD in patients with HCC remains controversial (15,16). Most previous studies have focused on NAFLD/NASH, where the conventional diagnostic framework required excluding other liver disease etiologies, including viral hepatitis and significant alcohol consumption. This restriction likely limited the evaluation of SLD in patients with multiple coexisting etiologies. In contrast, the recently introduced SLD/MASLD classification provides a positive diagnostic framework based on hepatic steatosis and cardiometabolic risk factors, allowing for the coexistence of other liver disease etiologies. In our cohort, approximately 30% of patients had HBV or HCV infections; however, all had received antiviral therapy.

Large cohort studies indicate that SLD increases the risk of HCC development (17,18). Chronic inflammation and lipotoxicity in SLD may induce persistent hepatocellular injury and impaired liver regeneration through mechanisms including endoplasmic reticulum stress and mitochondrial dysfunction, thereby contributing to the progression of hepatic fibrosis (19). Such a persistent carcinogenic background may contribute to recurrence after hepatic resection. Indeed, advanced fibrosis occurred significantly more frequently in the SLD group in our cohort. No significant association between SLD and OS was noted. One possible explanation is that our cohort was restricted to patients with sufficient hepatic functional reserve to undergo resection, with no significant differences in Child–Pugh classification, ALBI score, or ICG-R15 between the groups. Differences in post-recurrence treatment patterns, including the more frequent administration of locoregional therapies in the SLD group, may also have contributed; however, these explanations remain

hypothetical. The adjusted association between SLD and recurrence was imprecisely estimated, and there was no significant association with it in the exploratory virus-excluded subgroup. Therefore, these findings warrant cautious interpretation.

Previous studies have suggested that the prognostic impact of metabolic liver disease in HCC is complex. Coexisting obesity and DM correlate with poorer RFS and OS after hepatic resection for HCC (20). Conversely, SLD is not an independent predictor of HCC recurrence after radiofrequency ablation (21), nor is MAFLD independently associated with oncological outcomes after hepatic resection (22). These findings suggest the oncological impact of SLD depends not only on hepatic steatosis itself but also on accompanying metabolic abnormalities and the underlying liver condition.

These findings highlight the potential relevance of SLD in postoperative surveillance, although their clinical implications require further validation. No significant association between SLD and OS was noted, but our findings suggest that the presence of SLD alone may not necessarily preclude hepatic resection in appropriately selected patients with preserved hepatic functional reserve. Moreover, SLD is associated with an increased risk of cardiovascular disease and metabolic dysfunction (23). Therefore, long-term postoperative management should include not only surveillance for HCC recurrence but also management of metabolic risk factors, including obesity and DM, and cardiovascular risk.

This study has several limitations. First, the retrospective, single-center design, relatively small sample size, and limited number of RFS and OS events may have introduced selection bias and reduced statistical power. The limited number of recurrence events also restricted the number of covariates that could be included in the multivariable model to avoid overfitting. Therefore, residual confounding due to hepatic functional reserve, histological fibrosis, resection margin status, or other unmeasured factors cannot be excluded. Moreover, the retrospective assessment of alcohol consumption and metabolic factors may have limited the accuracy of etiological SLD subclassification, and particularly the distinction between MetALD and ALD. Second, restricting the study population to patients with sufficient hepatic functional reserve to undergo resection limits

the generalizability of our findings to those with more advanced liver dysfunction. Third, all patients with SLD presented with mild steatosis (st1); none exhibited moderate or severe steatosis. Additionally, analyzing hepatic inflammatory activity solely as a binary variable (absent or present) precluded a detailed assessment of severity. Consequently, we were unable to evaluate associations between steatosis or inflammation severity and postoperative outcomes. Fourth, conventional measures of hepatic functional reserve—including ICG-R15, Child–Pugh classification, and ALBI score—may not fully capture the heterogeneous parenchymal injury or impaired regenerative capacity associated with SLD.

In conclusion, this exploratory study suggests a possible association between SLD and HCC recurrence after hepatic resection, whereas its association with OS remains uncertain. Further studies with larger cohorts need to be conducted to validate these findings and clarify the prognostic significance of SLD in patients with HCC.

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

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**Address correspondence to:*

Yoshihiro Sakamoto, Department of Gastroenterological Surgery, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka-shi, Tokyo 181-8611, Japan.

E-mail: yosakamo@ks.kyorin-u.ac.jp

First reported clinical implementation of pressurized intraperitoneal aerosol chemotherapy in Japan: Program development and 30-day outcomes in two patients

Hiroshi Takeuchi^{1,*}, Yoshimasa Gohda¹, Joji Kitayama², Takako Kato³, Yui Hieda⁴, Hironao Shimano⁵, Hiroshi Kudo⁶, Norihiro Kokudo⁷

¹ Peritoneal Malignancy Center, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

² Department of Surgical Oncology, National Institute of Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

³ Department of Anesthesiology, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

⁴ Central Operating Theater, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

⁵ Radiological Physics and Technology Department, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

⁶ Pharmaceutical Department, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

⁷ Japan Institute for Health Security, Tokyo, Japan.

Abstract: Described here is the multidisciplinary implementation of pressurized intraperitoneal aerosol chemotherapy (PIPAC) at a Japanese institution and 30-day outcomes of its first two procedures, rather than an interim efficacy analysis of an ongoing five-patient pilot study. Preparation consisted of international training and clinical observation, two porcine experiments, two full-scale operating-room simulations, a four-stage checklist, remote anesthesia management, pharmacy and injector workflows, and high-efficiency particulate air-filtered closed evacuation. Simulations indicated that ventilator-specific parameters were unavailable on the remote vital-sign display, prompting a dedicated ventilator-screen video feed. On August 12, 2026, two men with unresectable peritoneal metastases from appendiceal mucinous adenocarcinoma underwent oxaliplatin-based PIPAC. Three-port access was achieved despite anticipated adhesions; peritoneal cancer index scores were 34 and 28. Oxaliplatin was prepared at 2 mg/mL with a measured circuit dead-space allowance; injector settings were 0.8 mL/s and a pressure limit of 290 pounds per square inch (psi). Both procedures, including aerosolization, a dwell time of 30 min, and closed evacuation, were completed without observed leakage, emergency re-entry, device malfunction, organ injury, or conversion. Patient 1 had exacerbated grade 2 abdominal pain, grade 2 anorexia, and grade 1 vomiting and was discharged on postoperative day 6. Patient 2 had no in-hospital adverse events and was discharged on postoperative day 2. Telephone assessment at 30 days identified no unplanned visit, readmission, re-intervention, or new clinically important adverse event; both patients were considered clinically suitable for next-cycle reassessment. This experience illustrates a structured pathway for clinical PIPAC implementation. Trial registration: jRCTs031260298.

Keywords: PIPAC, multidisciplinary workflow, peritoneal dissemination, occupational safety workflow, remote anesthesia management

1. Introduction

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a laparoscopic drug-delivery technique in which chemotherapy is nebulized into a pressurized pneumoperitoneum. It has been used in patients with unresectable peritoneal metastases and enables repeated assessment of the peritoneal cancer index (PCI), ascites, and biopsy specimens while using lower drug doses than conventional intraperitoneal perfusion (1-3).

Oxaliplatin-based PIPAC has shown technical feasibility and acceptable short-term tolerability in colorectal and appendiceal peritoneal metastases (2,3).

Introducing PIPAC into a new healthcare system requires coordinated preparation beyond acquisition of a nebulizer. Essential elements include regulatory approval; trained multidisciplinary personnel; a closed abdominal and evacuation circuit; ventilation and remote monitoring; cytotoxic-drug preparation and delivery; emergency re-entry planning; and a standardized

checklist (4,5). Early implementation reports from other countries have shown that documenting training, operating-room configuration, and workflow provide practical information distinct from subsequent efficacy analyses (6-8).

We initiated program development in January 2025 and performed our institution's first two clinical PIPAC procedures on August 12, 2026. This Brief Report describes the completed multidisciplinary implementation process and 30-day outcomes of those procedures. It does not present an interim analysis of the ongoing five-patient pilot study's primary endpoint of three-cycle completion or of antitumor efficacy.

2. Materials and Methods

2.1. Study design and ethics

This descriptive implementation report was prepared within a prospective, single-center pilot study of PIPAC for colorectal or appendiceal peritoneal metastases at the National Center for Global Health and Medicine, Japan Institute for Health Security. The Certified Review Board (CRB) of the Japan Institute for Health Security granted initial approval on December 10, 2025 (JIHS-C-005137-00; CRB3250001). Protocol version 1.3 was subsequently approved as an amendment on July 20, 2026, following committee review on July 13, 2026 (JIHS-C-005137-01). Institutional authorization was obtained before clinical use. The study was registered in the Japan Registry of Clinical Trials (jRCT; jRCTs031260298; first posted August 10, 2026) and conducted in accordance with the Declaration of Helsinki. Both patients provided written informed consent for participation and publication of anonymized clinical information and images. Final clinical follow-up was September 11, 2026 (postoperative day 30), and the data cutoff was September 15, 2026.

Reporting was organized using the Template for Intervention Description and Replication (TIDieR) checklist and relevant CAse REport (CARE) guideline items (9,10); the reporting map is provided in Supplementary Appendix S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>).

We reviewed English- and Japanese-language literature available through September 12, 2026, including PubMed-indexed publications, Ichushi-Web, J-STAGE, and publicly indexed CiNii Research records, using PIPAC and its English and Japanese equivalents. No report of clinical PIPAC performed in Japan before August 12, 2026 was identified. Search details are provided in Supplementary Appendix S2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>).

2.2. Patient selection

We enrolled patients aged 20 to <80 years with histologically confirmed colorectal or appendiceal cancer, laparoscopically confirmed peritoneal metastases, no extraperitoneal metastases, an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1, expected survival of at least 6 months, and adequate organ function (neutrophils $\geq 1,000/\mu\text{L}$, hemoglobin ≥ 8.0 g/dL, platelets $\geq 50,000/\mu\text{L}$, total bilirubin ≤ 1.5 times the upper reference limit, aspartate and alanine aminotransferases ≤ 100 U/L, and Cockcroft-Gault creatinine clearance ≥ 50 mL/min). Patients with PCI < 10 were excluded from PIPAC enrollment because they were considered potential candidates for cytoreductive surgery; no upper PCI limit was set. Other key exclusions were bowel obstruction requiring nasogastric decompression or parenteral nutrition, severe sensory dysfunction, active infection, and prior PIPAC or hyperthermic intraperitoneal chemotherapy. Previous fluoropyrimidine-based systemic therapy with refractoriness or intolerance was required; full criteria followed the approved protocol.

2.3. Program development and safety workflow

Program preparation included formal multidisciplinary training at the third International Society for the Study of Pleura and Peritoneum (ISSPP) PIPAC Workshop in Montpellier, observation of clinical PIPAC at the Institut du Cancer Montpellier, two porcine experiments, and two full-scale simulations in the intended operating room (Figure 1A). The team included surgeons, an anesthesiologist, operating-room nurses, a radiologic technologist, and a pharmacist. During simulations, the team found that the remote vital-sign display did not provide ventilator-specific parameters, including tidal volume and airway pressure. Before clinical use, a dedicated video feed of the ventilator screen was therefore added using an iPad and Microsoft Teams. Simulations were also used to finalize room layout, device and drug pathways, remote medication delivery, emergency re-entry, and closed evacuation. A four-stage checklist defined decision points before the procedure, before aerosolization, before re-entry after a dwell time of 30 min, and upon completion (Figure 1B; Supplementary Table S1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>). Each item was read aloud, confirmed by the team, and checked by an operating-room nurse.

2.4. Operating-room and anesthesia safety

Procedures were performed in an International Organization for Standardization (ISO) Class 5 operating room with laminar airflow. During aerosolization and the dwell time, staff remained in the anteroom and remotely monitored vital signs, the patient, the ventilator display, the laparoscopic view, and the injector (Figure

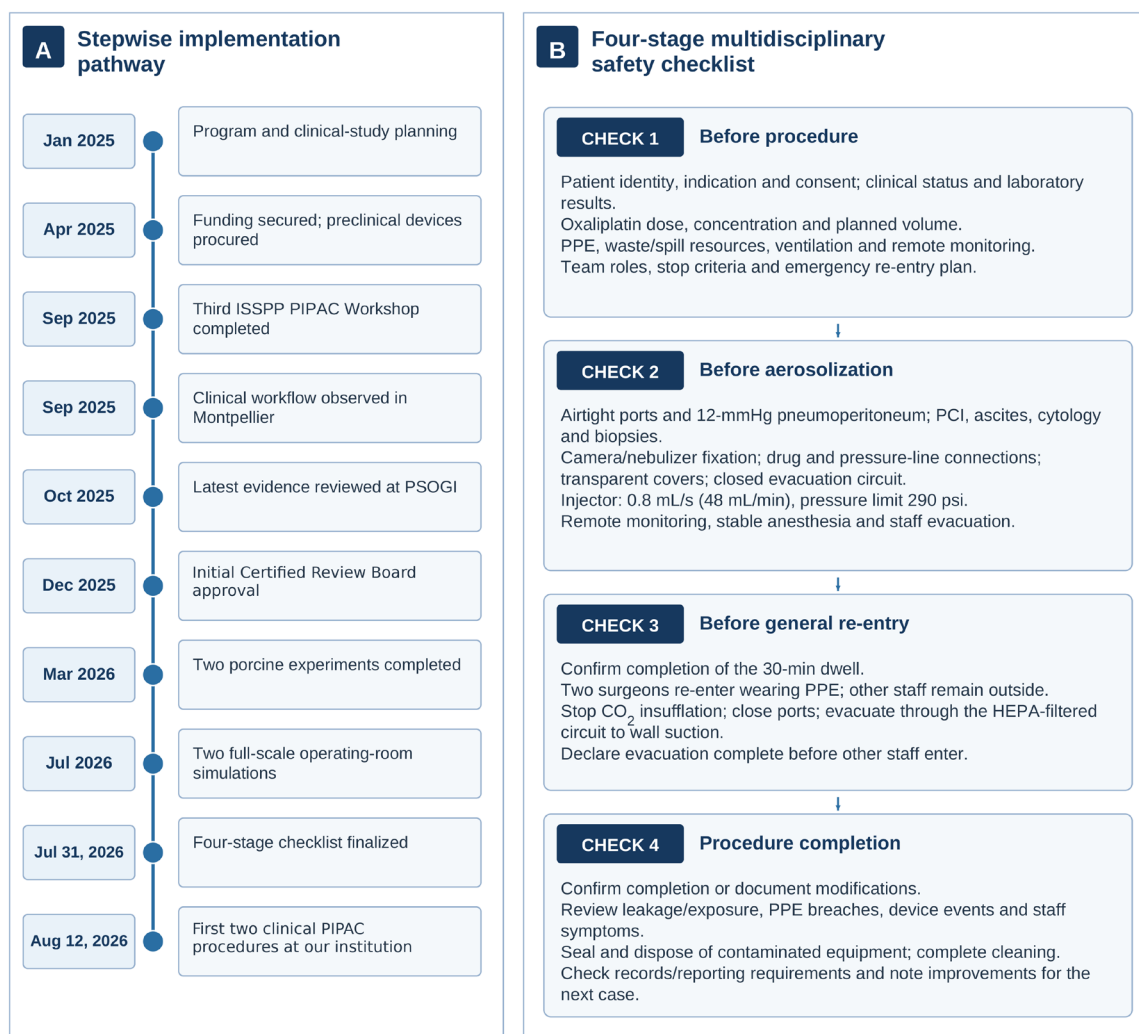


Figure 1. Stepwise development of the institutional PIPAC program in Japan. (A) The 19-month pathway from planning to the first two procedures. The December 2025 entry denotes initial CRB approval on December 10, 2025 (JIHS-C-005137-00). Protocol version 1.3 subsequently received amendment approval on July 20, 2026 (JIHS-C-005137-01), following a review on July 13. **(B)** The four-stage multidisciplinary safety checklist. Each checkpoint was read aloud, confirmed verbally by the team, and checked by an operating-room nurse. This is a summary of the institution-specific workflow; injector settings are the actual settings used. *Abbreviations:* CO₂, carbon dioxide; CRB, Certified Review Board; HEPA, high-efficiency particulate air; ISSPP, International Society for the Study of Pleura and Peritoneum; PCI, peritoneal cancer index; PIPAC, pressurized intraperitoneal aerosol chemotherapy; PPE, personal protective equipment; psi, pounds per square inch; PSOGI, Peritoneal Surface Oncology Group International.

2A and Figure 3). Seven extension tubes connected in series permitted intravenous medication from outside the room; a three-way stopcock and 50-mL saline syringe were placed at the external end. Emergency re-entry criteria included ventilation failure, unexplained shock, intravenous-line failure, inadequate anesthesia or patient movement, life-threatening arrhythmia, and cardiac arrest (11).

2.5. PIPAC procedure and drug preparation

Because preoperative computed tomography suggested periumbilical and upper-abdominal adhesions, a 12-mm balloon port was inserted infraumbilically using an open technique, followed by two 5-mm ports. Pneumoperitoneum was maintained at 12 mmHg. PCI,

adhesions, and ascites were documented; ascites was collected and four pre-exposure biopsies were mapped to PCI regions. The laparoscope was placed through a 5-mm port and the nebulizer through the 12-mm port. The ports, instruments, operative field, and pressure-resistant tubing were covered with transparent sterile drapes or waterproof sleeves (Figure 2).

The CapnoPharm nebulizer (CapnoPharm GmbH, Tübingen, Germany) was connected by pressure-resistant tubing to an Illumena high-pressure injector (Gadelius Medical K.K., Tokyo, Japan). Oxaliplatin was prepared in 5% dextrose at 2 mg/mL using the 92-mg/m² regimen reported for colorectal PIPAC and included in the approved protocol (2,5). Before clinical use, the internal volume of the intended circuit was measured by filling it with 5% dextrose and was 4 mL. An allowance of 8 mg

A Operating-room layout for PIPAC

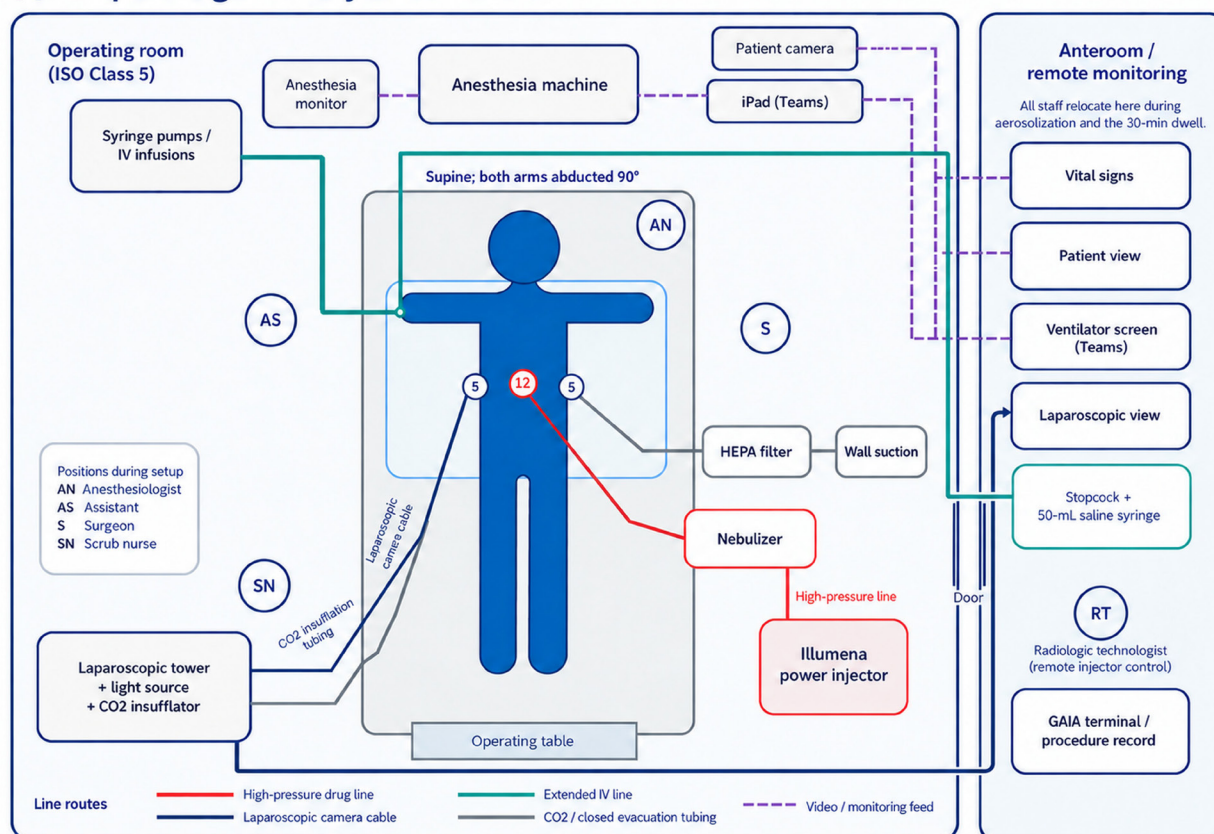
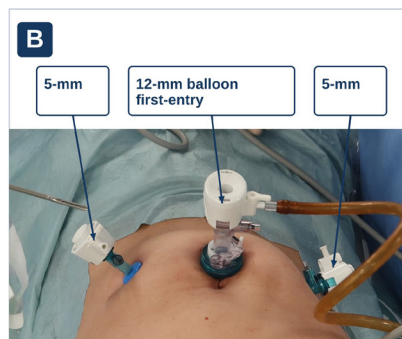


Figure 2. Operating-room and operative-field configuration. (A) Simplified operating-room layout and closed-system connections; the patient was positioned in the supine with both arms abducted to 90°. The physical drug pathway was the Illumena injector, pressure-resistant tubing, a nebulizer, and a 12-mm balloon port; the evacuation pathway consisted of a 5-mm port, closed tubing, a HEPA filter, and wall suction. (B) The three actual ports, from left to right in the photograph: 5 mm, 12-mm balloon first-entry port below the umbilicus, and 5 mm. Arrowheads identify the white port housings. (C) Mechanical securing of the laparoscope and nebulizer. (D) Transparent sterile draping of the ports, laparoscope, nebulizer, operative field, and pressure-resistant tubing. Abbreviations: AN, anesthesiologist; AS, assistant; CO₂, carbon dioxide; HEPA, high-efficiency particulate air; ISO, International Organization for Standardization; IV, intravenous; PIPAC, pressurized intraperitoneal aerosol chemotherapy; RT, radiologic technologist; S, surgeon; SN, scrub nurse. GAIA and Teams are system/product names.

(4 mL) was added to the body-surface-area-calculated amount before rounding and was included in the total quantity prepared for injection. The calculated doses were 183.08 and 172.96 mg, and the final preparations were 190 mg/95 mL and 180 mg/90 mL for Patients 1 and 2, respectively. The clinical pressure line was not separately primed before aerosolization; the allowance accounted for drug solution remaining in the circuit

at completion, rather than a separate priming dose. Prepared quantities were not independently measured intraperitoneal doses. The injector was set to 0.8 mL/s with a pressure limit of 290 pounds per square inch (psi; approximately 20 bar). This pressure ceiling is consistent with published PIPAC technical descriptions (12), and 0.8 mL/s has been evaluated experimentally with the CapnoPen nebulizer using saline (13).

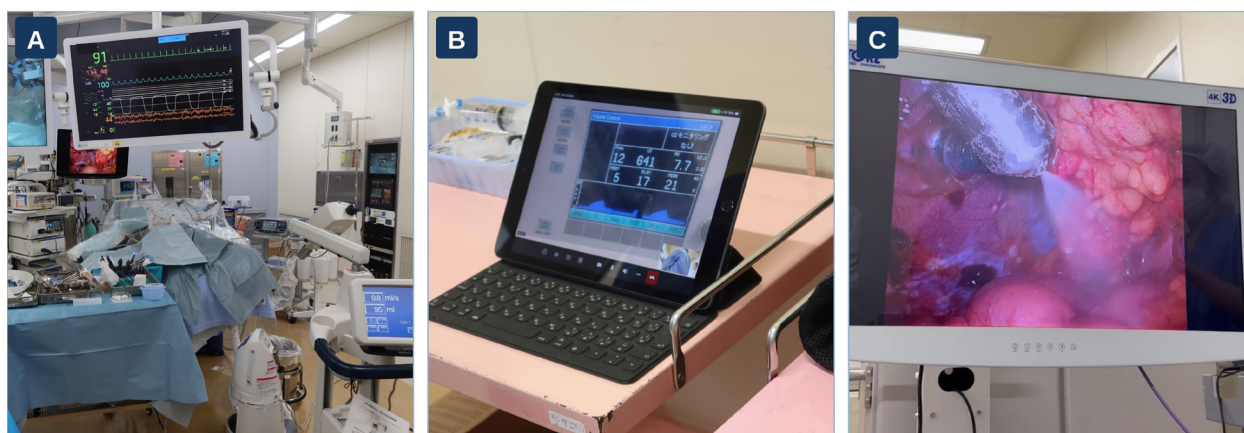


Figure 3. Remote monitoring during aerosolization and the dwell time. (A) Simultaneous display of the patient, vital signs, laparoscopic view, and high-pressure injector settings. **(B)** External display of the ventilator screen using Microsoft Teams. **(C)** Laparoscopic monitoring of aerosolization from outside the operating room. Patient-identifying text on the vital-sign monitor was obscured. *Abbreviation:* PIPAC, pressurized intraperitoneal aerosol chemotherapy.

After aerosolization, the pneumoperitoneum remained closed for a dwell time of 30 min. Two surgeons wearing personal protective equipment (PPE) then re-entered, stopped carbon dioxide insufflation, and evacuated the aerosol through a closed circuit with a high-efficiency particulate air (HEPA) filter connected to wall suction. Other staff re-entered only after evacuation was declared complete (Figure 2 and Figure 3).

2.6. Outcomes

We recorded technical completion, access, PCI, ascites, mapped biopsy sites, histology, cytology, procedural time logs, intraoperative events, CHECK 4 findings, laboratory results, in-hospital adverse events, and 30-day outcomes. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0 (14). The abdominal-pain grade was assigned retrospectively by the treating clinician using the clinical severity assessment and functional information, rather than the numerical rating scale (NRS) alone. Periods of aerosolization were transcribed from nursing and anesthesia event records. Day-30 status was assessed by telephone on September 11, 2026. Clinical suitability to proceed to next-cycle reassessment was judged based on the reported recovery and absence of new clinical problems; actual repeat administration remained conditional on confirmation of protocol-defined treatment criteria before the next procedure. Implementation of the occupational safety workflow was assessed using incident and leakage checks and staff symptom review; air, surface, and biological platinum concentrations were not measured. No hypothesis testing was conducted.

3. Results and Discussion

Two men ages 48 and 52 years with appendiceal

mucinous adenocarcinoma, extensive peritoneal metastases, and an ECOG performance status of 0 underwent consecutive PIPAC procedures (Table 1). Both had received oxaliplatin-based systemic therapy and were not candidates for complete cytoreduction. Infraumbilical access was achieved despite extensive omental and transverse-colon adhesions in Patient 1 and two small-bowel adhesions in Patient 2; no enterotomy or conversion occurred. PCI scores were 34 and 28, and pelvic ascites volumes were 30 and 40 mL, respectively. Representative laparoscopic findings are provided in Supplementary Figure S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>).

Operating-room times were 205 and 171 min, and operative times were 133 and 108 min for Patients 1 and 2, respectively. The charted periods of aerosolization were 11:28–11:30 for Patient 1 and 15:18–15:20 for Patient 2. These clock-time intervals were transcribed from nursing and anesthesia event records and were not independently validated as continuous injector-on durations. Both procedures included the planned dwell time of 30 min and high-efficiency particulate air-filtered closed evacuation. No drug leakage, suspected aerosol exposure, personal protective equipment breach, device malfunction, unplanned emergency re-entry, organ injury, transfusion, or conversion was reported. No immediate staff symptoms were reported at CHECK 4.

Baseline biopsies showed treated peritoneal dissemination of appendiceal adenocarcinoma in Patient 1 and mucinous adenocarcinoma dissemination or high-grade mucinous carcinoma peritonei after systemic chemotherapy in Patient 2. Ascites cytology was Class V (malignant) in both patients. These specimens reflected prior systemic treatment and were not interpreted as a response to the first PIPAC procedure.

Patient 1 had pre-existing cancer pain treated with extended-release hydromorphone (6 mg/day); the

Table 1. Patient characteristics, procedural details, pathology, and 30-day outcomes

Characteristic	Patient 1	Patient 2
Age/sex	48 years/male	52 years/male
Primary disease	Appendiceal mucinous adenocarcinoma	Appendiceal mucinous adenocarcinoma
Prior systemic therapy	FOLFOXIRI plus bevacizumab; then FOLFIRI plus bevacizumab	FOLFOX plus bevacizumab; then 5-FU/LV plus bevacizumab
ECOG performance status	0	0
PCI/pelvic ascites	34/30 mL	28/40 mL
Main adhesions	Omentum and transverse colon adhesions, from the umbilicus to the upper abdomen	Two small-bowel adhesions around the umbilicus and upper abdomen
Mapped biopsy regions	#8 × 2, #7, #6	#0 × 2, #7, #6
Prepared oxaliplatin quantity/volume†	190 mg/95 mL (calculated dose 183.08 mg)	180 mg/90 mL (calculated dose 172.96 mg)
Injector settings	0.8 mL/s (48 mL/min); pressure limit 290 psi	0.8 mL/s (48 mL/min); pressure limit 290 psi
OR/operative/anesthesia time	205/133/197 min	171/108/161 min
Charted aerosolization period*	11:28–11:30	15:18–15:20
In-hospital adverse events	Grade 2 abdominal pain exacerbation; grade 2 anorexia; grade 1 vomiting	None
Discharge	POD 6	POD 2
Peritoneal biopsy	Appendiceal adenocarcinoma dissemination after systemic chemotherapy	Mucinous adenocarcinoma dissemination/high-grade mucinous carcinoma peritonei after systemic chemotherapy
Ascites cytology	Class V (malignant)	Class V (malignant)
30-day outcome	No unplanned visit, readmission, re-intervention, or new clinically important adverse event reported by telephone; clinically suitable for next-cycle reassessment	No unplanned visit, readmission, re-intervention, or new clinically important adverse event reported by telephone; clinically suitable for next-cycle reassessment

*Clock-time intervals transcribed from nursing/anesthesia event records; they were not validated as continuous injector-on durations. †Circuit volume was measured beforehand with 5% dextrose (4 mL). An 8-mg (4-mL) allowance was added to the calculated amount before rounding and included in the total preparation for injection. The line was not separately primed before aerosolization; the allowance accounted for solution remaining in the circuit at completion. Prepared quantities are not independently measured intraperitoneal doses. Biopsies were collected before aerosolization during the first PIPAC procedure. Treatment-related histological changes refer to prior systemic chemotherapy. *Abbreviations:* CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; OR, operating room; PCI, peritoneal cancer index; PIPAC, pressurized intraperitoneal aerosol chemotherapy; POD, postoperative day; psi, pounds per square inch; 5-FU/LV, fluorouracil/leucovorin.

preoperative screening record documented an NRS score of 2/10. This screening result was not a separately documented measurement immediately before anesthesia. Pain increased to NRS 8/10 approximately 3 h after PIPAC, decreased to 6/10 on postoperative day (POD) 1, and returned to the preprocedural baseline by POD 4. On retrospective treating-clinician assessment, the exacerbation of pain was moderate and daily activities remained possible; it was classified as CTCAE v5.0 grade 2 abdominal pain on the basis of the moderate-pain criterion, and not the peak NRS score alone. Additional analgesia included intravenous acetaminophen 1,000 mg as needed, up to three times daily, and intravenous

flurbiprofen axetil 50 mg once daily. Grade 2 anorexia and grade 1 vomiting also occurred. Oral intake improved, and the patient was discharged on POD 6. Patient 2 had no in-hospital adverse events and was discharged on POD 2. Postoperative tests showed transient leukocytosis and increased C-reactive protein without clinically important hepatic or renal deterioration (Supplementary Table S2, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=133>), consistent with previously reported inflammatory changes after PIPAC (15). Upon telephone follow-up on September 11, 2026, neither patient reported an unplanned visit, emergency assessment,

readmission, reoperation, interventional radiology procedure, or new clinically important adverse event. Both were considered clinically suitable to proceed to next-cycle reassessment, subject to the protocol-required checks before repeat administration.

The principal contribution of this report is the implementation process. Over 19 months, international training and clinical observation were translated through preclinical experiments and full-scale simulations into a locally executable multidisciplinary workflow. Simulations allowed the team to rehearse room setup, remote anesthesia, extended intravenous access, drug preparation and injector operation, sterile containment, emergency re-entry, and high-efficiency particulate air-filtered evacuation before treating patients. The four-stage checklist established shared decision gates and explicit responsibilities across surgery, anesthesiology, nursing, radiology, and pharmacy. Comparable implementation reports also emphasize regulatory and logistical preparations before clinical treatment (6,8).

Remote anesthesia management was feasible in these two procedures without invasive monitoring or postoperative intensive care. Published experience emphasizes advanced preparation because direct access to the patient is restricted during aerosolization (11). Our setup combined external displays, remote intravenous access, defined emergency criteria, and readiness for protected re-entry. The occupational safety workflow was informed by exposure studies conducted under containment, ventilation, and remote-operation conditions (12,16-18) and combined engineering controls, personal protective equipment, incident and leakage checks, and staff symptom review. No exposure incident was noted; however, no air, surface, or biological platinum measurements were performed, so this report demonstrates implementation of the workflow rather than quantitative occupational safety.

Both patients had prior oxaliplatin exposure, so sensory symptoms and function should be compared to the baseline before repeat cycles (19); the protocol provides for treatment cessation or further dose reduction for grade ≥ 3 cumulative neurotoxicity. We used three ports for independent, stable positioning of the laparoscope, nebulizer, and evacuation circuit. In a published series, additional ports were required in 12% of procedures (20). Mapping each biopsy to a PCI region established a baseline for subsequent procedures.

This report is limited to the first treatment of two patients, a short follow-up, and clinical rather than quantitative occupational surveillance. It documents program development, workflow implementation, and technical completion but does not establish repeated-treatment feasibility, antitumor efficacy, or generalizability to other primary cancers.

In conclusion, international training, preclinical testing, full-scale simulation, remote anesthesia management, coordinated drug and device workflows,

closed evacuation, and a four-stage multidisciplinary checklist substantiated clinical implementation of PIPAC in Japan. Both procedures were completed as planned, and both patients were considered clinically suitable for next-cycle reassessment at telephone follow-up on day 30.

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Conflict of Interest: CapnoPharm's support has been disclosed. CapnoPharm had no role in the study design, patient selection, data collection, analysis, interpretation, manuscript preparation, or decision to submit or publish. The authors declare no additional conflicts of interest.

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- *Address correspondence to:*
 Hiroshi Takeuchi, Peritoneal Malignancy Center, National Center for Global Health and Medicine, Japan Institute for Health Security, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
 E-mail: takeuchi.h@jihs.go.jp

First clinical implementation of histotripsy for liver tumors in Japan

Takeaki Ishizawa^{1,*}, Masahiko Kinoshita¹, Sadaaki Nishimura¹, Hiroji Shinkawa¹, Ryoji Sada², Chiharu Tateishi³, Daisuke Tanaka³, Hisashi Motomura⁴, Takashi Mori⁵, Akira Yamamoto⁶, Sawako Uchida-Kobayashi⁷

¹ Department of Hepatobiliary-Pancreatic Surgery, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan;

² Medical Device Unit, Department of Clinical Engineering, Osaka Metropolitan University, Osaka, Japan;

³ Health and Medical Innovation, Department of Clinical Medical Science, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan;

⁴ Department of Plastic and Reconstructive Surgery, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan;

⁵ Department of Anesthesiology, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan;

⁶ Department of Diagnostic and Interventional Radiology, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan;

⁷ Department of Hepatology, Graduate School of Medicine, Osaka Metropolitan University, Osaka, Japan.

Abstract: Histotripsy is a nonthermal therapy that mechanically disrupts and liquefies tumor tissue by generating focused microbubbles using extracorporeal ultrasound. Following U.S. Food and Drug Administration approval for the treatment of liver tumors in 2023, its clinical use has rapidly expanded. Here, we report the first clinical implementation of histotripsy in Japan, focusing on its safety and feasibility. The first treatment was performed for a 1.8-cm postoperative recurrent hepatocellular carcinoma in segment 8, followed by a second treatment for a 2.5-cm recurrent colorectal liver metastasis in segment 2 after multiple resections of intra- and extra-hepatic metastases. Histotripsy treatment times were 22 and 40 min, respectively. Target tumor coverage was confirmed by intraoperative ultrasonography, and reduced tumor enhancement was confirmed by contrast-enhanced computed tomography performed the day after treatment. The patients were discharged on postoperative days 1 and 2, respectively. No major complications occurred during follow-up to postoperative days 14 and 19, respectively, although both patients experienced mild treatment-related pain and one developed fever. These initial experiences suggest feasibility of implementing histotripsy for liver tumors in Japan.

Keywords: histotripsy, hepatocellular carcinoma, liver metastasis

1. Introduction

Histotripsy is a nonthermal therapy that mechanically disrupts and liquefies tumor tissue by generating focused microbubbles using extracorporeal ultrasound (1). Because it does not require a surgical incision or needle puncture associated with conventional local ablative therapies, histotripsy has been described as an "incisionless" or "non-invasive" local treatment (2). It is expected to provide a new treatment option, particularly for patients with limited tolerance for conventional surgery. In the United States, histotripsy was approved by the Food and Drug Administration for treatment of liver tumors in 2023. It has also recently received the European CE mark, and its clinical application is expanding, although clinical experience remains limited in many countries. In Japan, regulatory approval of the treatment system has not yet been obtained, and no clinical use of histotripsy has been reported to date.

In July 2026, we performed the first histotripsy treatments for hepatocellular carcinoma (HCC) and colorectal liver metastasis (CRLM) in Japan under a specified clinical research protocol. Herein, we report treatment procedures and short-term outcomes through the first outpatient follow-up according to the study protocol.

2. Study protocol

The protocol for this first-in-Japan study (jRCTs052250263) was developed based on the #HOPE4LIVER multicenter study (3), which supported FDA approval of the technology, and previous reviews of histotripsy (4). Major inclusion criteria were as follows: *i*) typical HCC on contrast-enhanced CT or magnetic resonance imaging (MRI) or metastatic liver cancer, with a maximum tumor diameter of ≤ 3 cm; *ii*) no macroscopic vascular invasion or tumor thrombus; *iii*) entire target lesion

clearly visualized by abdominal ultrasonography without obscuration; and *iv*) a Child–Pugh score of ≤ 7 . Patients with significant portal hypertension, active concomitant malignancies, or severe cardiopulmonary disease were excluded.

Patients were admitted on morning of treatment and underwent histotripsy in the operating room in the afternoon. After treatment, they returned to a general ward. Blood tests and contrast-enhanced computed tomography (CT) were performed the following day, and patients were discharged on the same day if no clinically significant abnormalities were identified. Study follow-up was completed at an outpatient visit within 3 weeks after treatment if blood tests and abdominal ultrasonography showed no abnormalities. Adverse events were defined and graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Histotripsy procedures were planned according to previously reported protocols (3,4). The operator (T.I.) observed histotripsy procedures at an overseas institution, completed manufacturer-provided training, and obtained certification. Before the first treatment, a simulation was also performed with operating-room nurses, clinical engineers, and anesthesiologists to familiarize the team with patient positioning, device setup, and preparation of degassed water.

The study protocol was approved by the Certified Review Board of Osaka Metropolitan University Hospital (CRB5200004/jRCTs052250263). Written informed consent was obtained from both patients for participation in this clinical trial and for publication of study findings.

3. Case presentation

3.1. Case 1

The first histotripsy treatment was performed for a 1.8-cm recurrent HCC in the dorsal region of segment 8 following robot-assisted posterior sectionectomy. Patient was offered repeat hepatectomy and ablation as conventional curative treatment options and chose histotripsy as a treatment that might impose less physical burden. On day of admission, the patient underwent histotripsy in the operating room under general anesthesia with one-lung ventilation and was placed in the left semidecubitus position. A membrane-covered frame was placed over the treatment area and filled with degassed water. Treatment head of the Histotripsy System (HistoSonics, Plymouth, MN, USA) was immersed in the water, and target lesion was identified. A spherical treatment volume with a 5-mm margin was planned while maintaining adequate clearance from the treatment head. Acoustic voltage was adjusted at the center and vertices of the treatment volume along the X-, Y-, and Z-axes based on visualization of the bubble

cloud and the audible cavitation sound. Treatment was then initiated with a single press of the start button. After dorsal-to-ventral histotripsy, conventional ultrasonography confirmed that the target tumor was encompassed by the treatment area, with increased echogenicity, and showed no immediate complications. General anesthesia was subsequently discontinued (Figure 1, A–F). Total anesthesia time was 250 min, and the histotripsy treatment time was 22 min.

3.2. Case 2

The second histotripsy treatment was performed for a 2.5-cm recurrent CRLM in segment 2 in a patient who had previously undergone multiple surgical treatments for the primary tumor and metastatic lesions, including laparoscopic sigmoidectomy, three open hepatectomies culminating in a right hepatectomy, lymphadenectomy of the hepatoduodenal ligament, right adrenalectomy, and resection of local peritoneal dissemination. No recurrent colorectal cancer other than the liver metastasis was identified by imaging. However, having undergone repeated treatments, the patient felt unable to undergo another surgery or chemotherapy and therefore chose histotripsy. Treatment protocol was similar to that used in the first case, except that the patient was placed in the supine/reverse Trendelenburg position and bilateral high-frequency jet ventilation was used (Figure 1, G–L). Total anesthesia time was 181 min, and the histotripsy treatment time was 40 min.

After treatment, both patients experienced mild pain at the treatment site, which gradually resolved. Blood tests and contrast-enhanced CT performed on the following day showed no evidence of bleeding, bile leakage, or abscess formation. The first patient was discharged on postoperative day 1. The second patient developed fever and was discharged on postoperative day 2.

At follow-up visits on postoperative days 14 and 19, respectively, inflammatory markers and transaminase levels had returned toward baseline, whereas biliary enzyme levels remained elevated in Case 2 (Table 1). No complications, including ascites, portal or hepatic vein thrombosis, bile leakage, or biliary dilatation or stenosis, were detected by abdominal ultrasonography.

4. Discussion

In this initial clinical study, both patients underwent histotripsy with only mild abdominal pain and transient fever, and were discharged after one or two nights of hospitalization. No severe complications were identified at the first outpatient follow-up. These findings suggest that histotripsy can be implemented in Japanese clinical practice according to a protocol based on previous clinical studies.

Regarding safety of histotripsy, a multicenter analysis of 230 patients reported only three Clavien–Dindo grade

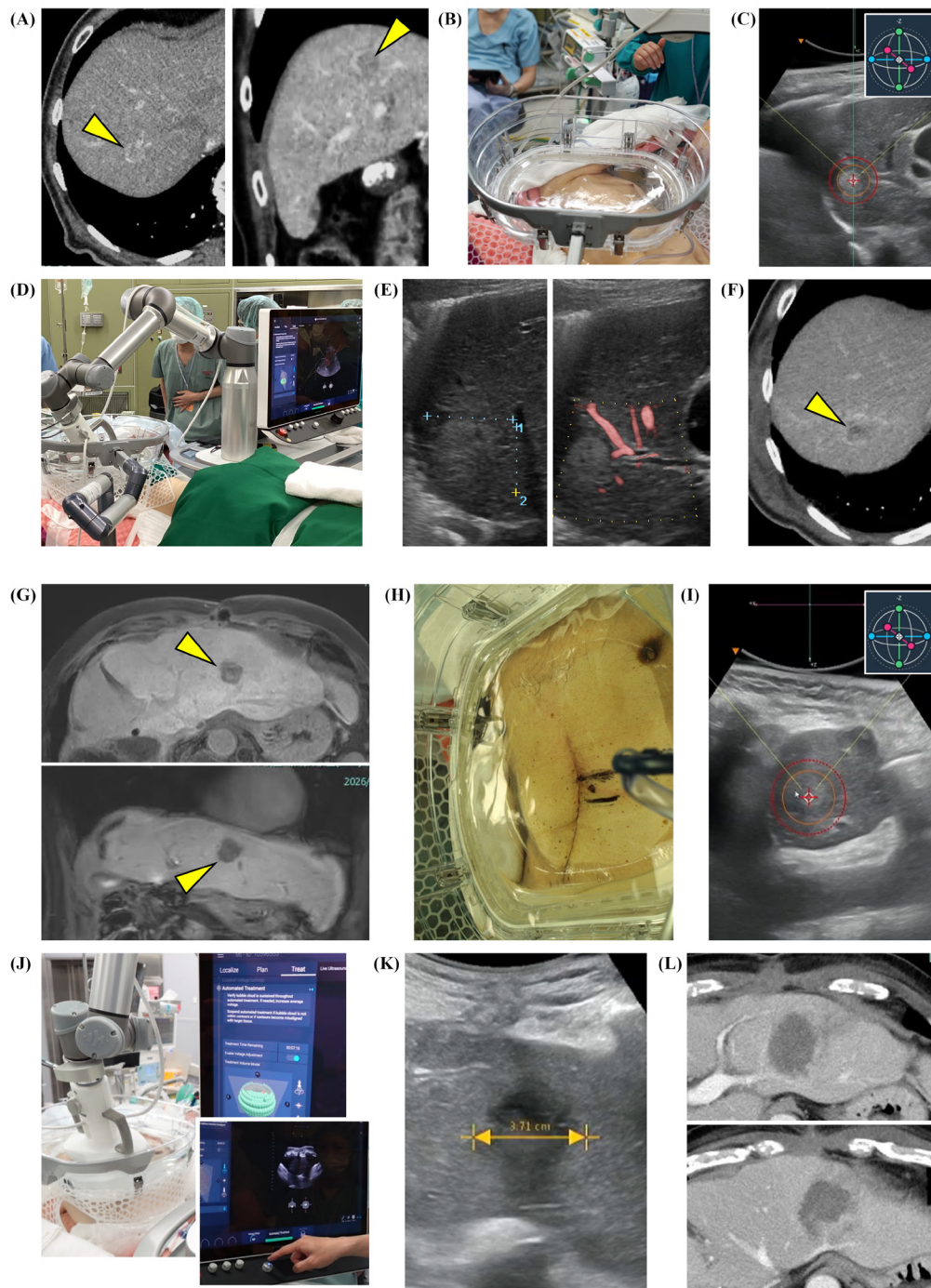


Figure 1. Histotripsy for hepatocellular carcinoma (Patient 1) and colorectal liver metastasis (Patient 2). **Patient 1:** Preoperative contrast-enhanced CT demonstrated a hyperenhancing tumor (arrowhead) in the dorsal region of segment 8 on the arterial-phase axial image (left) and a hypoenhancing lesion on the portal venous-phase coronal image (right) (A). Patient was positioned in the left semidecubitus position, and a membrane-covered frame was filled with degassed water (B). Intercostal ultrasonography using the Histotripsy System was performed to encompass the entire tumor within treatment volume (orange circle) while avoiding the lung, with a planned 5-mm treatment margin (red circle) (C). Histotripsy treatment was then initiated. Treatment volume was 15.3 cm³ and the mean acoustic voltage was 95% (D). Posttreatment ultrasonography demonstrated conversion of planned treatment area into a hyperechoic region (left) while preserving blood flow in the adjacent Glissonean pedicle (right) (E). Arterial-phase contrast-enhanced CT obtained the following day showed reduced tumor perfusion and hypoenhancement of the treated lesion (F). See Supplementary Video 1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=128>). **Patient 2:** Preoperative gadoxetic acid-enhanced MRI in the hepatobiliary phase demonstrated a hypointense tumor (arrowhead) in segment 2 of the hypertrophied left liver (G). Patient was positioned supine, and the membrane-covered frame was filled with degassed water; the previous hepatectomy scar was visible (H). Treatment volume was planned to avoid the heart (I). After adjustment of the acoustic voltage, histotripsy was initiated by pressing the start button. Treatment volume was 28.6 cm³ and the mean acoustic voltage was 60% (J). Posttreatment ultrasonography demonstrated a 3.7-cm hypoechoic area (K). Contrast-enhanced CT obtained the following day demonstrated a spherical hypoenhancing treatment zone encompassing the tumor. Except for a peripheral wedge-shaped area, arterial inflow to segment 2 (upper) and venous drainage from the segment 2 region into the left hepatic vein (lower) were preserved (L). See Supplementary Video 2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=129>).

Table 1. Patient demographics and perioperative blood test results

No.	Age (years) /sex	Diagnosis (maximum diameter) and previous surgical treatments	Blood tests	Before histotripsy	POD1	Outpatient Clinic*
1	78/M	HCC (1.8 cm) 1. Robot-assisted right posterior sectionectomy	WBC ($\times 10^3/\mu\text{L}$)	52	108	60
			CRP (mg/dL)	0.03	1.95	0.09
			Alb (g/dL)	4.3	3.5	4.2
			Cre (mg/dL)	1.09	0.85	1.07
			K (mmol/L)	4.1	4.2	4.4
			T-Bil (mg/dL)	0.8	1.1	0.8
			AST (U/L)	25	74	23
			ALT (U/L)	24	32	21
			ALP (U/L)	70	59	88
			γGTP (U/L)	107	81	131
			PT (INR)	1.02	1.09	1.05
2	76/M	CRLM (2.5 cm) 1. Sigmoidectomy 2. Open hepatectomies 3. Open hepatectomy with lymphadenectomy 4. Rt. adrenalectomy for peritoneal dissemination and lymphadenectomy 5. Open hepatectomy and resection of disseminated nodule	WBC ($\times 10^3/\mu\text{L}$)	52	72	57
			CRP (mg/dL)	0.49	3.04	1.19
			Alb (g/dL)	3.8	3.1	3.7
			Cre (mg/dL)	1.35	1.26	1.45
			K (mmol/L)	5.4	4.5	5.1
			T-Bil (mg/dL)	0.5	0.8	0.8
			AST (U/L)	31	568	57
			ALT (U/L)	12	275	45
			ALP (U/L)	156	166	416
			γGTP (U/L)	81	80	655
			PT (INR)	1.04	1.15	1.20

*At follow-up visits on postoperative days 14 for Case 1. and 19 for Case 2. *Abbreviations:* HCC, hepatocellular carcinoma; CRLM, colorectal liver metastasis; POD, postoperative day.

$\geq$ III complications (5). In the #HOPE4LIVER study, which included 47 patients (19 with HCC and 28 with metastatic tumors), pain ($> 22\%$) and pyrexia (12%) were the most common adverse device-related effects (ADEs), indicating that histotripsy is not completely symptom-free (3).

In the second case, the tumor was no longer separately identifiable within the treatment zone on contrast-enhanced CT performed the day after treatment, while marked elevation of transaminases was observed. A recent study by Chan *et al.* (6) similarly reported a median ALT level of approximately 130 U/L on postoperative day 1, with some patients showing levels exceeding 2,000 U/L. The authors suggested that increase in inflammatory cytokines accompanying transaminase elevation may be associated with tumor control; however, whether histotripsy induces an antitumor immune response remains unclear and requires further investigation. Conversely, portal vein thrombosis has been reported as a severe ADE in the #HOPE4LIVER study (3). Therefore, marked postoperative elevation of transaminases and biliary enzymes should be carefully evaluated for possible impaired blood flow or biliary congestion in the remnant liver parenchyma.

In the #HOPE4LIVER study, the 1-year local tumor control rate was 90% in the post-hoc analysis, whereas efficacy rate in the primary assessment was 63.4% (3). This discrepancy suggests that immediate post-treatment imaging may not reliably indicate local tumor control, as the treated area can show variable morphology and enhancement patterns after histotripsy.

Therefore, long-term clinical surveillance with imaging and tumor marker assessments is required to evaluate local tumor control in these two cases. Further randomized controlled studies with longer follow-up are required to determine role of histotripsy in relation to established curative-intent treatments, including surgical resection and thermal ablation, particularly for small HCCs. For liver metastases, it has been hypothesized that histotripsy may induce systemic antitumor immune responses through release of tumor antigens without thermal damage (7). Although reductions in non-targeted tumors have been reported (8,9), whether this potential "abscopal-like effect" can be reproduced remains to be demonstrated.

In conclusion, our first two clinical experiences suggest feasibility of implementing histotripsy for liver tumors in Japan. Further accumulation of cases and long-term follow-up are warranted to clarify its safety, local tumor control, and potential systemic antitumor effects.

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*Address correspondence to:

Takeaki Ishizawa, Department of Hepatobiliary-Pancreatic Surgery, Graduate School of Medicine, Osaka Metropolitan University, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan.

E-mail: tish-osk@omu.ac.jp

Infectious disease communication for international students: A survey of association-accredited Japanese language schools in Japan

Mio Kato^{1,*}, Kyoko Sudo², Azusa Iwamoto³, Miwa Kanda³, Masami Fujita³

¹ National Institute of Infectious Diseases, Japan Institute for Health Security, Tokyo, Japan;

² The National College of Nursing, Japan Institute for Health Security, Tokyo, Japan;

³ Bureau of Global Health Cooperation, Japan Institute for Health Security, Tokyo, Japan.

Abstract: Japanese language schools are in daily contact with many newly arrived international students, yet little is known about how they obtain and communicate infectious disease information. In February–March 2025, we mailed a newly developed questionnaire to all 103 Japanese language schools accredited by the Association for the Promotion of Japanese Language Education; 38 (36.9%) responded. Of the responding schools, 32/38 (84%) had an infirmary, and 7/38 (18%) had a staff member designated for health matters. In total, 29/38 (76%) collected infectious disease information, mainly from government sources *via* websites (22/29, 76%). Of all schools, 32/38 (84%) provided information to students; among these, 22/32 (69%) used plain Japanese and 18/32 (56%) used students' native languages, most often through explanations during classes (25/32, 78%). Among schools providing information, reported challenges included language barriers (14/32, 44%), cultural differences as perceived by staff (11/32, 34%), and confirming students' understanding (10/32, 31%). These exploratory institutional observations suggest that ready-to-use materials in plain Japanese and students' languages, and closer links with local public health centers, could be considered; their usefulness for students warrants further evaluation.

Keywords: international students, risk communication, health literacy, plain Japanese

1. Why language schools matter for infectious disease communication

During public health crises, foreign language speakers with language barriers are particularly vulnerable to health disparities resulting from information gaps (1). In Japan, the coronavirus disease 2019 (COVID-19) pandemic exposed multiple barriers to healthcare access for foreign residents, including language barriers, lack of awareness of available services, and fear of discrimination (2,3). Multilingual resources developed during the pandemic (4) often faced challenges in reaching their intended audiences (5), and community-based support and volunteer translation helped to fill gaps (6).

Japan has 2,727 Japanese language education institutions and facilities serving 263,170 learners (7). Japanese language schools are in daily contact with many international students, often during their first months in Japan. From the perspective of acculturation theory, which describes how individuals adapt psychologically and socioculturally in a new cultural environment (8), language education institutions can be understood as settings that support not only language acquisition but also broader sociocultural adaptation of newcomers,

including their ability to access and act on health-related information. Previous studies in these schools have addressed tuberculosis screening and outbreaks (9,10), health screening for vaccine-preventable diseases (11), and access to HIV testing (12). Although previous studies have examined selected health issues in Japanese language schools, evidence on how these institutions collect and communicate infectious disease information remains limited. Therefore, we surveyed association-accredited schools to describe, from the institutional perspective, how they obtain and communicate this information and which challenges staff perceive.

2. Survey approach: A postal questionnaire to association-accredited schools

From February 25 to March 17, 2025, we mailed a questionnaire to all 103 Japanese language schools accredited by the Association for the Promotion of Japanese Language Education through its evaluation and accreditation of educational activities, as listed on the Association's website in February 2025. Questionnaires were addressed to each school by name at the address given in the Association's list. When an address was

unclear, it was identified by an internet search. These schools represent a restricted subset of Japanese-language education institutions in Japan (7).

Because no existing instrument addressed this topic, the research team developed a new self-administered questionnaire in Japanese based on study aims, without adapting an existing instrument or using a specific conceptual framework; the draft was reviewed by the co-authors (expert review), and no formal pilot testing was conducted. The 10 items covered institutional characteristics and health resources, collection of infectious disease information, provision of information to students (languages, means, and content priorities), student consultations, and perceived challenges and needs. Plain Japanese (*Yasashii Nihongo*) was presented as a distinct category from standard Japanese in the questionnaire, consistent with its established use in the Japanese language education and multicultural co-existence fields (13,14). As questionnaires were addressed to schools, position of the staff member who completed each one (e.g., teacher, principal, or administrative manager) is unknown. Skip instructions directed only those schools that collected information to the items on sources, methods, frequency, and reasons, and only those schools that provided information to students to the items on languages, means, content priorities, and challenges. The full questionnaire is provided as Supplementary Questionnaire 1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=134>).

Results are reported descriptively as n/N (%), where N is the item-specific denominator: all 38 responding schools or the subset directed to the item by a skip instruction. Missing responses were not imputed and are reported as a separate category. Complete distributions are provided in Supplementary Tables S1 and S2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=134>). Analyses were performed using JASP version 0.19.3 (University of Amsterdam, The Netherlands).

For the challenges item, respondents could select one or more of six pre-specified categories and describe the specific situation for each in a free-text field. Free-text responses, all written in Japanese, were analyzed in Japanese. One researcher developed subcodes within each category inductively on the basis of content similarity, and coding was then reviewed by the co-authors; no independent double coding was performed, and revisions arising from the review were agreed by discussion. For reporting, the authors translated illustrative statements into English; the coding framework and these statements, which are condensed English paraphrases rather than verbatim quotations, are presented in Supplementary Table S3 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=134>).

The chairperson of the Ethics Committee for Life Science and Medical Research Involving Human Subjects of the National Institute of Infectious Diseases

determined by e-mail that formal ethical review was not required because the survey concerned institutional practices rather than individuals; no reference number was issued. The survey was conducted for research and publication, with school staff responding on behalf of their institutions; it was not an audit of individual schools or staff. Participation was voluntary, and return of the completed questionnaire was regarded as consent to participate. Schools were asked to provide their name; therefore, responses were identifiable at the institutional level to the research team, but no respondent names or other personal information were requested. School names were removed before analysis, and no institution is identifiable in this report. The study was conducted in accordance with principles of the Declaration of Helsinki (as revised in 2013), consistent with the committee's determination.

3. Principal observations

3.1. Few designated health staff and variable links with medical institutions

Responses were received from 38 of 103 schools (36.9%) in 15 prefectures, including 12 in Tokyo. Median enrolment was 242 students (interquartile range [IQR], 179–340; $n = 37$), and Nepal, China, and Myanmar were the most commonly reported main countries of origin (Supplementary Table S1, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=134>). Of responding schools, 32/38 (84%) had an infirmary (*hokenshitsu*) and 7/38 (18%) had a staff member designated for health matters (no, 30/38; missing, 1/38); four of these seven reported a nursing qualification (Table 1). Twenty-two schools (22/38, 58%) had an arrangement with a medical institution for in-person consultation, 15/38 (39%) reported no such arrangement, and 1/38 (3%) did not respond; only 1/38 (3%) reported an online consultation arrangement. Unlike schools defined under Article 1 of the School Education Act, Japanese language schools are not necessarily subject to full requirements of the School Health and Safety Act (15). This regulatory context may be relevant to health staffing; however, our data cannot show whether it explains patterns observed. In other school settings, school health staff have been described as coordinating outbreak responses (16).

3.2. Official sources accessed online, usually at irregular intervals

Of responding schools, 29/38 (76%) collected infectious disease information. Among these, the most common sources were local governments and public health centers (18/29, 62%), national government agencies such as the Ministry of Health, Labour and Welfare (17/29, 59%), and mass media (14/29, 48%); websites were the main method of access (22/29, 76%) (Table 1). Collection was

Table 1. Key institutional and communication findings among the responding schools

Item	n/N (%)
Institutional health resources	
School infirmary	32/38 (84)
Staff member designated for health matters ^a	
Yes	7/38 (18)
No	30/38 (79)
Missing	1/38 (3)
Arrangement with a medical institution for in-person consultation	
Yes	22/38 (58)
No	15/38 (39)
Missing	1/38 (3)
Collection of infectious disease information	
Collected infectious disease information	29/38 (76)
Main sources ^b (N = 29)	
Local governments and public health centers	18/29 (62)
National government agencies (e.g., Ministry of Health, Labour and Welfare)	17/29 (59)
Mass media	14/29 (48)
Association for the Promotion of Japanese Language Education	10/29 (34)
Accessed via websites ^b (N = 29)	22/29 (76)
Frequency of collection (N = 29)	
Irregular	24/29 (83)
Monthly	2/29 (7)
Daily	1/29 (3)
Missing	2/29 (7)
Provision of information to students	
Provided infectious disease information to students	32/38 (84)
Language ^b (N = 32)	
Plain Japanese	22/32 (69)
Students' native languages	18/32 (56)
Standard Japanese	16/32 (50)
Means ^b (N = 32)	
Explanation during classes	25/32 (78)
On-campus notices	24/32 (75)
Messaging applications (e.g., LINE, WeChat)	12/32 (38)
Student consultations on infectious diseases	
Frequency (N = 38)	
At least once a month	2/38 (5)
About once every few months	17/38 (45)
Rarely	16/38 (42)
Never	2/38 (5)
Missing	1/38 (3)
Topics ^b (N = 38)	
How to use medical institutions	28/38 (74)
How to respond when symptoms develop	26/38 (68)
Prevention methods	1/38 (3)

Values are n/N (%), where N is the number of schools to which the item applied: all responding schools (N = 38), schools that collected information (N = 29), or schools that provided information to students (N = 32). Missing responses are shown separately and were not imputed. Complete distributions for all items are given in Supplementary Tables S1 and S2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=134>).

^aA staff member designated to be responsible for infirmary and health matters; 4 of the 7 reported a nursing qualification (nurse, n = 3; public health nurse, n = 1), and the other 3 did not report a qualification. ^bMultiple responses allowed; percentages do not total 100%. Only the most frequent categories are shown.

irregular in 24/29 (83%) schools, monthly in 2/29 (7%), and daily in 1/29 (3%) (missing, 2/29). Reasons for collection are shown in Supplementary Table S2 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=134>). Whether timing and scope of this information met schools' needs was not assessed.

3.3. Plain Japanese and classroom explanations as main channels

Thirty-two schools (32/38, 84%) provided infectious disease information to students. Among these, 22/32

(69%) used plain Japanese, 18/32 (56%) used students' native languages, and 16/32 (50%) used standard Japanese; 28/32 (88%) used plain Japanese, native languages, or both. Information was delivered mainly through explanations during classes (25/32, 78%), on-campus notices (24/32, 75%), and messaging applications such as LINE or WeChat (12/32, 38%). Prevention methods (27/32, 84%) and how to use medical institutions (22/32, 69%) were most often rated as high priority (4 or 5 on a 5-point scale), and epidemiological statistics least often (4/32, 13%); the item on symptoms and how to respond was left blank

by 20/32 schools (Supplementary Table S2, <https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=134>).

Student consultations about infectious diseases occurred at least monthly in 2/38 (5%) schools, approximately once every few months in 17/38 (45%), rarely in 16/38 (42%), and never in 2/38 (5%) (missing, 1/38). Most common topics were how to use medical institutions (28/38, 74%) and how to respond when symptoms develop (26/38, 68%). These data cannot indicate whether infrequent consultations reflect low need, unmet need, or help-seeking elsewhere.

3.4. Language, perceived cultural differences, and confirming understanding as main reported challenges

Among the 32 schools that provided information, 27 (84%) reported at least one challenge (Figure 1). Language barriers were reported by 14/32 (44%); respondents described difficulty translating medical terminology, limitations of translation applications, and being unable to cover every student's native language. Cultural differences were reported by 11/32 (34%) respondents who perceived differences among students in awareness of prevention, hygiene practices such as handwashing, mask-wearing, and willingness to seek medical care. These statements reflect staff perceptions rather than measured characteristics of any student population. Confirming students' understanding was reported by 10/32 (31%); respondents noted that students might answer "yes" without understanding and that materials were mostly text with few images.

4. Implications for practice: shared materials and local public health links

Several proportionate steps could be considered. First, as responding schools mainly used plain Japanese and

classroom explanations, public health authorities could consider preparing short, illustrated materials in plain Japanese and major student languages that staff can use directly in class. Plain Japanese has been proposed as a practical strategy for conveying health information to people with limited Japanese proficiency (13,14); however, plain Japanese alone may be insufficient for accurately conveying specialized medical terminology, and a shared plain-Japanese glossary of key medical terms may be useful. Second, links between local public health centers and language schools could be considered, for example, by including schools in routine distribution of outbreak notices; public health centers have previously provided tuberculosis screening and health education at language schools (9). Third, remote medical interpreting (17) and simple checks of understanding, such as asking students to explain key points in their own words, may help address staff concerns about comprehension. Whether any of these measures improves students' understanding, care-seeking, or health outcomes was not assessed and warrants further evaluation, ideally incorporating students' own perspectives (18,19).

5. Limitations

This survey has important limitations. Sampling frame was restricted to association-accredited schools, and only 38 of 103 invited schools responded. No information was available on non-responding schools; therefore, direction and magnitude of non-response bias cannot be determined, and the findings should not be generalized beyond responding schools. Each school's responses were provided by a single staff member whose position was not recorded, and self-reported data may reflect intended rather than actual practices. The questionnaire was newly developed and has not been formally validated; some items had substantial missing data, and free-text responses were coded by a single researcher

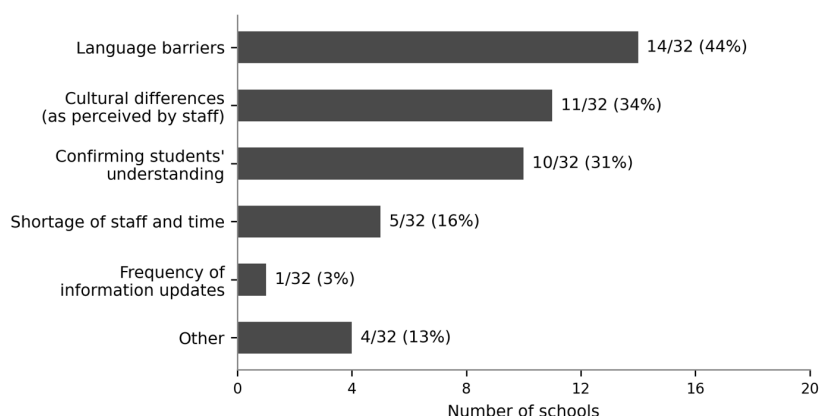


Figure 1. Challenges in providing infectious disease information to international students reported by responding schools that provided such information (N = 32). Note: Schools could select more than one of six pre-specified categories; percentages therefore do not total 100%. Five schools selected no category. "Cultural differences" reflects staff perceptions rather than measured characteristics of students. Subcodes and illustrative statements are presented in Supplementary Table S3 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=134>).

with review by the co-authors. The survey assessed institutional practices only; it did not assess the accuracy of the information provided, students' comprehension, behavioral change, healthcare use, or health outcomes. The findings are therefore descriptive and exploratory.

6. Conclusion

Among the responding association-accredited Japanese language schools, most collected infectious disease information from official online sources and conveyed it to students in plain Japanese or their native languages, mainly through classroom explanations, whereas few had staff designated for health matters. Staff reported challenges related to language, perceived cultural differences, and confirming students' understanding. Ready-to-use materials in plain Japanese and students' languages and closer links with local public health centers should be considered, and their usefulness warrants an evaluation that includes students' perspectives.

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**Address correspondence to:*

Mio Kato, Center for Emergency Preparedness and Response, National Institute of Infectious Diseases, Japan Institute for Health Security, 1-23-1 Toyama, Shinjuku, Tokyo 162-8640, Japan.

E-mail: kato.mio@jihs.go.jp

ACCESS Japan Registry: Toward a nationwide evidence platform for foreign visitors requiring emergency hospitalization in Japan—Rationale, design, and governance of a multicenter registry

Soichiro Saeki^{1,2,3,*}, Chihaya Hinohara¹, Eri Yamada³, Kaori Minamitani^{3,4}, Ryo Kawasaki³

¹ International Health Care Center, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

² Emergency Medicine and Critical Care, National Center for Global Health and Medicine, Japan Institute for Health Security, Tokyo, Japan;

³ Division of Public Health, Department of Social Medicine, Graduate School of Medicine, the University of Osaka, Osaka, Japan;

⁴ International Medical Relations Center, Rinku General Medical Center, Osaka, Japan.

Abstract: Japan has experienced a rapid increase in inbound tourism, with a record 42,683,600 foreign visitors in 2025, a 15.8% increase from the previous year and well above the pre-pandemic peak of 31.88 million in 2019, but such short-term visitors are excluded from Japan's public health insurance system, exposing patients and institutions to substantial financial and clinical risks. Despite growing clinical and policy demand, no comprehensive national database of emergency hospitalizations among inbound foreign visitors exists. Against this background, we established the ACCESS Japan Registry (Assessment of Cross-Cultural Medical Access and Emergency & Support Systems for Foreign Patients in Japan), the first multicenter registry in Japan that is designed for nationwide expansion and that targets inbound foreign visitors who require emergency hospitalization in Japan. Foreign nationals on short-term visas who require emergency hospitalization are registered in the registry, and patient demographics, clinical data (diagnosis per the International Classification of Diseases, 10th Revision (ICD-10), length of stay, outcomes), administrative and financial data (hospitalization costs, unpaid bills), and language support information are collected *via* Research Electronic Data Capture (REDCap). The ACCESS Japan Registry will provide the first systematic, multicenter evidence base on emergency hospitalizations of inbound foreign visitors in Japan, informing healthcare policy, international emergency medicine, and global travel medicine research. Here we describe why such a platform is needed, how it was developed, how it is governed, and what it can and cannot deliver.

Keywords: inbound foreign visitors, emergency hospitalization, registry, travel medicine, Japan

1. Why the ACCESS Japan Registry is needed

Global expansion of international travel has fundamentally transformed the landscape of emergency medicine and public health worldwide. Japan has emerged as one of the world's most dynamic tourist destinations, with inbound visitor numbers increasing more than fourfold over the decade prior to the COVID-19 pandemic, reaching 31.88 million in 2019 (1). Inbound travel has since recovered and surpassed that level: 42,683,600 foreign visitors entered Japan in 2025, a 15.8% increase over 2024 and the highest figure ever recorded (2). Scale of the population at risk is therefore substantially larger today than pre-pandemic figures on which most existing evidence is based. Geographic dispersal of tourists, facilitated by low-cost carriers and regional revitalization policies, has extended the reach of inbound tourism to rural and semi-urban areas, meaning that acute-care

hospitals across the country—not only major urban centers—are increasingly confronting the challenge of managing foreign patients in emergency settings (3).

Short-term visitors to Japan are, by definition, excluded from the national public health insurance system, as coverage under the system is contingent upon residency status (4). Consequently, full cost of emergency medical care falls on the patient, generating multiple layers of clinical and institutional risk. From the patient's perspective, financial barriers may delay presentation to healthcare facilities and compromise adherence to recommended treatment. From the institutional perspective, unpaid medical bills represent a growing operational concern (5), particularly when patients are repatriated before discharge or before financial settlement can be arranged (6). Language and cultural barriers further complicate care delivery, contributing to diagnostic delays, miscommunication regarding consent

and treatment, and reduced patient satisfaction (3).

Despite scale and urgency of these challenges, the epidemiological profile of inbound foreign visitors who require emergency hospitalization in Japan remains almost entirely undocumented. Existing national statistics and published studies have predominantly focused on resident foreign nationals or on outpatient emergency department visits rather than on hospitalized short-term visitors (3). A systematic review of studies conducted in Japanese emergency departments identified significant heterogeneity across institutions and highlighted the absence of nationally representative data on this population (3). This information gap is not unique to Japan; to our knowledge, no multicenter registry focusing specifically on emergency hospitalizations among inbound foreign visitors has been established in any country.

To address this critical gap, we established the ACCESS Japan Registry (Assessment of Cross-Cultural Medical Access and Emergency & Support Systems for Foreign Patients in Japan), a multicenter observational registry, designed for nationwide expansion, targeting short-term foreign visitors who require emergency hospitalization in Japan. In this Perspective we describe rationale, design, data collection protocol, and governance of the registry, and outline the anticipated research outputs and policy implications, together with the registry's current stage of development and its principal limitations.

2. Development and current status

The registry was conceived in fiscal 2025, prompted by single-center experience at the National Center for Global Health and Medicine, where clinical and financial consequences of emergency hospitalization among uninsured short-term visitors were evident in daily practice but were not captured by any existing data source (7). The multicenter infrastructure—the common data dictionary, the REDCap instrument, and the participation framework—was developed during 2025 and 2026, and hospitalizations occurring on or after 1 April 2022 are eligible for retrospective registration so that the post-pandemic recovery of inbound travel is covered. Central ethical approval for the multicenter registry was granted by the Institutional Review Board of the Japan Institute for Health Security (JIHS) on 1 July 2026, and the first participating hospital obtained local institutional authorization on 10 July 2026. As of 10 August 2026, one hospital had completed local authorization and was contributing data, three further hospitals had confirmed participation and were completing local authorization or system setup, and an additional fourteen hospitals were at earlier stages of the participation process. Because data entry began only recently, the number of registered cases remains very small; we therefore do not report case counts at this stage and state transparently that the registry is in an early expansion phase, with operational data to be reported once a meaningful volume of cleaned

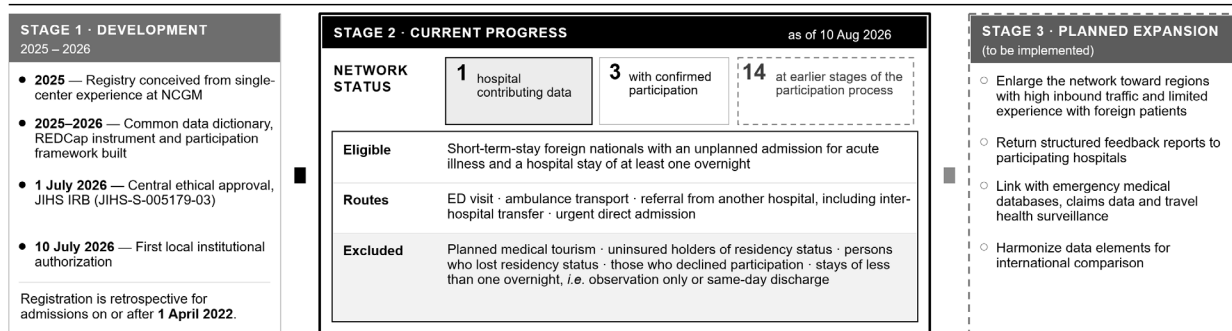
records has accumulated.

The primary objective of the ACCESS Japan Registry is to construct a comprehensive multicenter case database of inbound foreign visitors who require emergency hospitalization in Japan, with the explicit intention of expanding toward nationwide coverage. This infrastructure will serve as foundational evidence base for subsequent analytical studies addressing the following domains: *i*) epidemiological profile of emergency hospitalizations among inbound foreign visitors, including disease patterns, routes of access to care, severity at presentation, and clinical outcomes; *ii*) healthcare economic challenges, including magnitude of unpaid medical bills at discharge, proportion that remains uncollected after institutional billing and recovery process, and factors predicting non-payment; *iii*) role of language and cultural barriers in care delivery, including utilization and mode of delivery of medical interpretation services; *iv*) prognostic determinants and factors influencing length of stay and clinical outcome; and *v*) evidence-based policy recommendations for improving emergency healthcare systems for foreign visitors and for advancing international travel medicine practice. Overview of the ACCESS Japan Registry is presented in Figure 1.

The ACCESS Japan Registry is a multicenter, non-interventional observational registry study. Data are collected retrospectively from medical and administrative records generated during routine clinical care; no additional examinations, interventions, or patient contact are conducted for research purposes. Participating facilities are acute-care hospitals in Japan that have agreed to contribute data through the registry platform. Recruitment of participating institutions is ongoing, with outreach directed at hospitals with established emergency and acute-care departments, particularly those with prior experience in managing foreign patients.

The registry platform is built on REDCap (Research Electronic Data Capture), a validated, web-based data management system developed at Vanderbilt University (8) and operated on an electronic data capture system hosted at the University of Osaka (9). Access to servers and systems is restricted by user accounts and passwords, and a full audit trail is recorded. Data are entered electronically by designated personnel at each participating facility *via* a secure internet connection. The registry is jointly administered by JIHS and the University of Osaka. Each entry is assigned a unique study identification code with no systematic relationship to the patient's medical record number, ensuring that personally identifiable information is not transmitted to or stored within the central database; because each participating hospital retains the local linkage key, the central dataset is more accurately described as coded (pseudonymized) rather than anonymized. A detailed schematic overview of the registry, covering patient flow and eligibility, the four data collection domains, coding and storage, governance and access tiers, and anticipated research and policy

A. DEVELOPMENT PATHWAY AND CURRENT STATUS



B. DATA COLLECTED, DATA FLOW AND GOVERNANCE

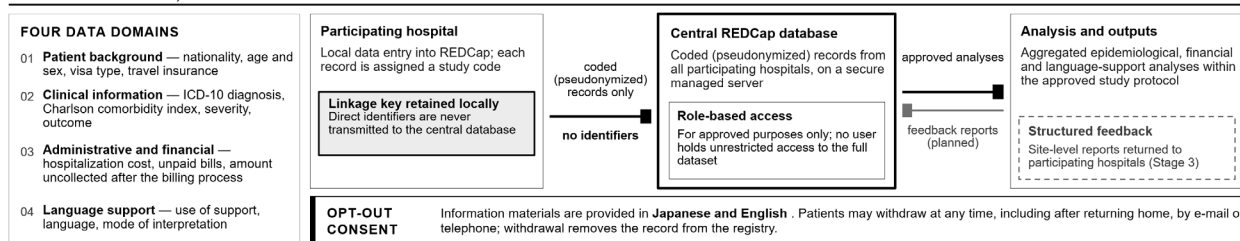


Figure 1. Development, current operation, and planned expansion of the ACCESS Japan Registry. Abbreviations: ACCESS Japan, Assessment of Cross-Cultural Medical Access and Emergency & Support Systems for Foreign Patients in Japan; JIHS, Japan Institute for Health Security; REDCap, Research Electronic Data Capture; ICD-10, International Classification of Diseases, 10th Revision; PII, personally identifiable information.

impact, is provided as Supplementary Figure S1 (<https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=126>).

3. Registry framework and governance

3.1. Eligibility criteria and operational definitions

Eligible participants are foreign nationals whose residency status in Japan is classified as "short-term stay" (*i.e.*, individuals without residency status under the Immigration Control and Refugee Recognition Act) who require emergency hospitalization during their stay in Japan. For registry purposes, emergency hospitalization is defined as an unplanned inpatient admission arising from an acute condition, irrespective of the route of access: presentation to the emergency department, arrival by ambulance, urgent referral from another facility, and urgent direct admission to a ward are all eligible. A formal inpatient admission of at least one overnight stay is required; emergency department observation, short-stay observation, and same-day admission and discharge without an overnight inpatient stay are not eligible. Patients arriving by inter-hospital transfer are eligible and are captured as referred cases in the route-of-access variable, with hospitalization registered by the hospital that provides the inpatient care; because no central identifier links records across institutions, the referral variable is used to flag episodes that may belong to a single patient pathway across facilities.

The following cases are excluded from the registry: *i*) cases of planned medical tourism in which the

hospitalization was part of a pre-arranged treatment plan for a condition identified prior to entry into Japan, and treatment was completed as planned; *ii*) individuals who, despite holding a Japanese residency visa (*e.g.*, diplomatic personnel), are not enrolled in the public health insurance system; *iii*) individuals who have lost their legal residency status due to overstay or expiry of a visa other than a short-term stay visa; and *iv*) individuals who explicitly decline participation in the registry. These exclusion criteria were developed to define a clinically and administratively homogeneous target population of uninsured short-term visitors, thereby ensuring interpretability and policy relevance of the resulting dataset.

3.2. Data collection and data quality

All data collected through the ACCESS Japan Registry are derived exclusively from existing medical and administrative records generated during routine clinical care. The registry captures four domains.

Domain 1: Patient Background—age, sex, nationality, country of residence, primary language, purpose of travel, number of days elapsed between arrival in Japan and symptom onset or hospital presentation, intended duration of stay, and travel insurance status.

Domain 2: Clinical Information—chief complaint, major pre-existing conditions (classified by diagnostic category), Charlson comorbidity index (CCI) (10), mode of arrival at the hospital, severity at triage (based on standardized triage criteria), admitting clinical department, primary diagnosis (coded per ICD-10), total length of hospital stay, length of intensive care unit

stay where applicable, surgical or invasive procedures performed, and clinical outcome at discharge.

Domain 3: Administrative and Financial Information—total hospitalization costs, presence and amount of unpaid bills at the time of discharge, and amount that remains uncollected at close of each institution's standard billing and recovery process, recorded as an observed institutional outcome rather than as a subjective estimate of recoverability.

Domain 4: Language Support Information—use of professional medical interpretation services, language of interpretation, and mode of interpretation (in-person, telephone, or video). Each data element was selected based on its relevance to the study objectives and its availability within the routine clinical record. Total estimated data entry time per case is approximately 15 to 20 minutes.

Cases are identified at each participating hospital by screening admission records and emergency department logs for patients without Japanese public health insurance, and all eligible cases within the study period are registered consecutively to minimize selection at the case level. Triage severity is recorded using each institution's standardized triage scale, and the scale used is captured as a variable so that heterogeneity can be handled in analysis. Diagnoses are coded with ICD-10 by trained local personnel using a shared coding list, and outcomes at discharge are taken from discharge summary. Automated range and logic checks are implemented in REDCap at data entry, and the coordinating office performs central checks for missing values, outliers, and internally inconsistent records, with queries returned to the contributing site for resolution.

3.3. Ethical framework, data protection, and governance

The study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Biological Research Involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science and Technology; the Ministry of Health, Labour and Welfare; and the Ministry of Economy, Trade and Industry of Japan. Central ethical approval has been obtained from the Institutional Review Board of JIHS (approval number: JIHS-S-005179-03), and each participating hospital additionally obtains authorization from its institutional director before starting data entry, in accordance with the Japanese multi-institutional review framework. Secondary analyses using registry data are conducted under separately developed research protocols, each of which requires independent ethics committee approval prior to initiation. Central ethical review for all participating institutions, including the University of Osaka, was provided by the JIHS Institutional Review Board under a single-review procedure; no separate ethics committee review was conducted at collaborating institutions. The University of Osaka participates as a co-research institution responsible for the registry data-

management infrastructure and obtained institutional authorization from its director (authorization number: K25496) before commencing its registry-related data-management activities. Each participating hospital likewise obtains institutional authorization before beginning data entry.

Given challenges of obtaining individual informed consent from short-term foreign visitors—including early repatriation, language barriers, and the large number of eligible cases—consent is obtained through an opt-out procedure (11,12). Information about the registry is publicly disclosed on the JIHS website (13), through institutional notice boards at participating hospitals, and in written materials provided to eligible patients, where feasible. Patients or their representatives who wish to decline participation may do so by contacting the designated study coordinator at their treating hospital. Because many eligible patients cannot read Japanese and may leave Japan shortly after discharge, opt-out materials are provided in both Japanese and English at every participating hospital, and the opt-out contact route remains available after repatriation by e-mail as well as by telephone.

Data access and utilization rights are stratified according to institutional role (Table 1). Access is role-based and limited to authorized personnel for approved registry purposes, and no user category has unrestricted access to the complete dataset. Investigators at JIHS and the University of Osaka, as the central coordinating institutions, may access the complete registry dataset for registry management, data quality assurance, and approved analyses; use of such data for publication or conference presentation is subject to deliberation by the full research team. Participating institutions may access their own institutional data in full. They may access aggregate registry data upon request to the coordinating office. Access to registry-wide line-level data, whether or not intended for publication or presentation, requires a formal application and deliberation by the full research team.

4. Potential contribution, limitations, and future directions

The ACCESS Japan Registry is expected to generate the first systematic, multicenter evidence on clinical and socioeconomic profiles of inbound foreign visitors who require emergency hospitalization in Japan. Preliminary analyses are anticipated to characterize distribution of presenting diagnoses, with particular interest in conditions that are disproportionately prevalent in travelers—including infectious diseases, cardiovascular emergencies, trauma, and psychiatric crises—as well as conditions that may be complicated by delayed presentation attributable to financial deterrents or language barriers. The registry will also enable an analysis of financial burden borne by healthcare institutions, including frequency and magnitude

Table 1. Data Utilization Policy

Data Type	JHHS / the University of Osaka	Participating Institutions
Own institutional data	Full access for approved registry purposes	Full access for approved registry purposes
Aggregate registry data (no raw data)	Full access for approved registry purposes	Upon request to coordinating office
Full registry line-level data (not for publication)	Registry management, quality assurance, and approved analyses only	Application + team deliberation
Full registry line-level data (for publication / presentation)	Team deliberation	Application + team deliberation

of unpaid bills and factors associated with successful or unsuccessful debt recovery, an area of immediate operational relevance to hospital administrators and health policy makers alike.

Beyond its domestic significance, the ACCESS Japan Registry is positioned to make a substantive contribution to the international field of travel medicine. Emergency hospitalization represents the most severe end of the travel-related illness spectrum, yet it remains least systematically studied. Existing travel medicine research has predominantly focused on outpatient presentations, infectious diseases among returning travelers, and pre-travel consultation practices. The ACCESS Japan Registry addresses a distinct and underrepresented dimension of this field by capturing in-country emergency hospitalizations in real time, thereby providing data that cannot be obtained from traveler surveillance systems or post-travel health registries.

Several limitations should be acknowledged at this early stage. Participation is voluntary and current participants are weighted toward hospitals with prior experience in caring for foreign patients, so the present dataset is not nationally representative and is subject to selection bias at institutional level. Because no population denominator exists for foreign visitors at risk within each hospital catchment area, the registry cannot estimate national incidence rates of emergency hospitalization; it can describe case mix, care processes, and outcomes of registered episodes. Interpretation of the interpreting variables is likewise constrained: the registry records whether and how interpretation was used, but it does not measure interpretation quality or effectiveness of interpretation on clinical outcomes. Patient pathways that span more than one hospital may be represented by more than one record, and cases managed without an overnight inpatient admission are outside the registry scope. Finally, retrospective abstraction from routine records limits granularity and completeness of some variables, particularly financial outcomes recorded after discharge.

The registry infrastructure also has potential for future expansion. Four directions are prioritized. First, the participating network will be enlarged beyond the current early adopters toward hospitals in regions with high inbound traffic but limited experience with foreign

patients, which is the practical route to genuine national coverage. Second, structured feedback reports will be returned to participating hospitals, so that participation delivers immediate operational value and sustains data quality. Third, network linkage with emergency medical databases, insurance claims data, and international travel health surveillance systems could substantially enhance the registry's analytical power and facilitate cross-national comparisons. Fourth, harmonized data elements will be developed to enable international comparison with other high-volume destination countries. Moreover, the methodological framework established by this registry—including the opt-out consent model, REDCap-based data capture, and ethical governance structure for multi-institutional data sharing—may serve as a replicable model for similar registry initiatives in other high-volume tourist destination countries.

The ACCESS Japan Registry represents the first systematic attempt to document and analyze emergency hospitalizations among inbound foreign visitors in Japan through a multicenter platform designed for nationwide expansion. By capturing comprehensive clinical, administrative, and socioeconomic data from acute-care hospitals in Japan, the registry will generate evidence that is urgently needed to improve the quality and equity of emergency care for foreign visitors, to address the financial sustainability of healthcare institutions, and to inform evidence-based policy in both domestic healthcare governance and international travel medicine. We invite eligible acute-care institutions across Japan to participate in this registry and contribute to creation of a globally valuable epidemiological resource.

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

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*Address correspondence to:

Soichiro Saeki, International Health Care Center, National Center for Global Health and Medicine, Japan Institute for Health Security, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: saeki.so@jihs.go.jp

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Types of Articles	Words in length (excluding references)	Figures and/or Tables	References
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Communications	~2,000	~2	~20
Perspectives			
Comments			
Correspondence			
Editorials	~1,000	~1	~10
Letters	~1,000	~1	~10
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