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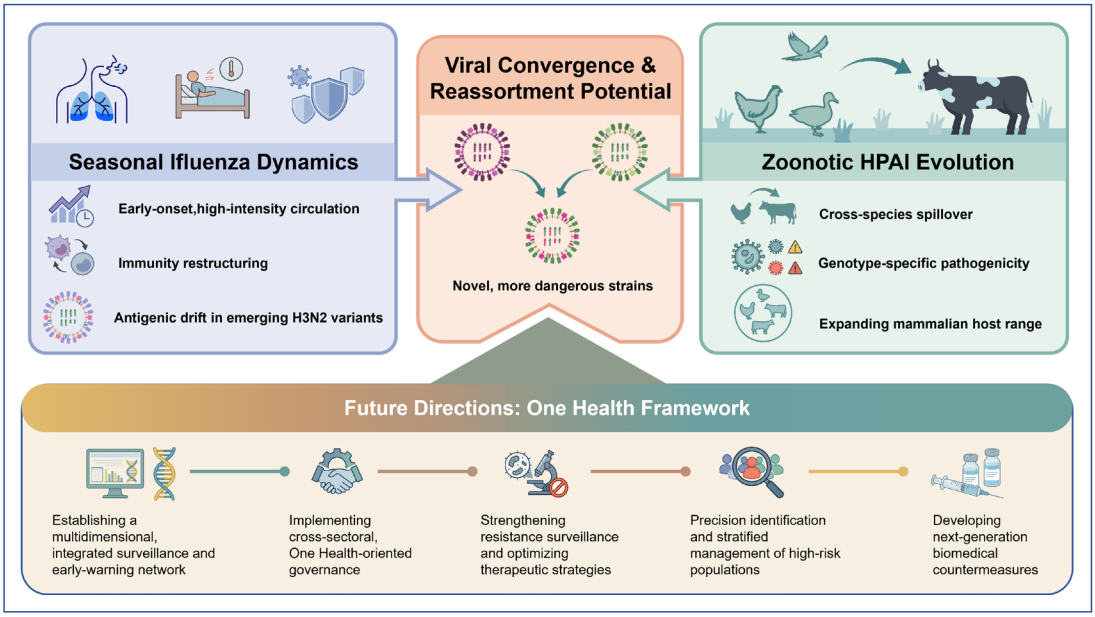

Conceptual framework of dual viral threats at the human–animal–environment interface and strategic future directions under the One Health paradigm (Page 411)

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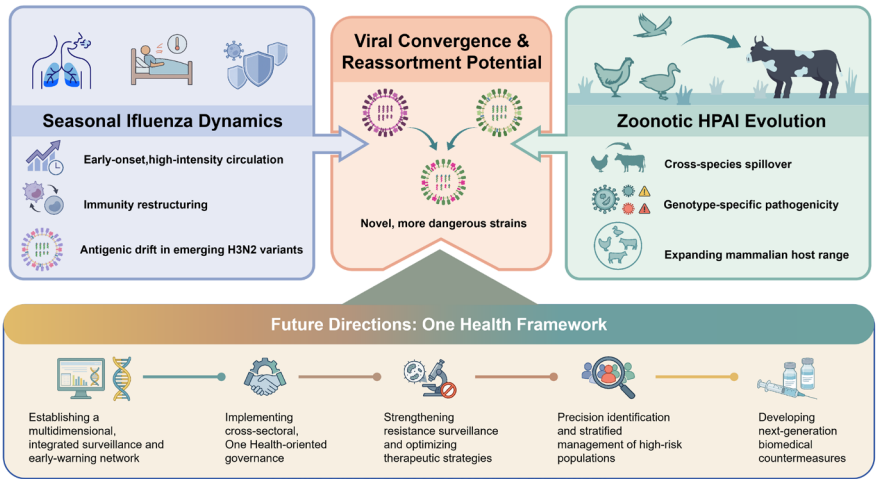

Conceptual framework of dual viral threats at the human–animal–environment interface and strategic future directions under the One Health paradigm. This schematic illustrates the compounding risks posed by the concurrent circulation of human and animal influenza viruses and outlines a comprehensive, integrated response strategy. (Top left) This box characterizes current seasonal influenza dynamics in human populations, highlighting challenges such as early-onset, high-intensity circulation, immunity restructuring, and antigenic drift in emerging variants (*e.g.*, H3N2). (Top right) This box depicts the ongoing evolution of zoonotic highly pathogenic avian influenza (HPAI), emphasizing the risks of cross-species spillover into novel hosts (including ruminants), genotype-specific pathogenicity, and an expanding mammalian host range. (Center) The box in the center illustrates viral convergence and reassortment potential, whereby the interface between human and animal reservoirs functions as a "mixing vessel", increasing the risk of novel, highly virulent strains emerging. (Bottom) The box at the bottom outlines five strategic pillars in the "Future Directions" panel within a One Health framework: (1) establishing a multidimensional, integrated surveillance and early-warning network; (2) implementing cross-sectoral, One Health oriented governance; (3) enhancing antiviral resistance surveillance and optimizing therapeutic strategies; (4) enabling precision identification and stratified management of high-risk populations; and (5) developing next-generation biomedical countermeasures to enhance global health security. (Page 411)

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EDITORIAL

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Converging threats: The intersection of seasonal influenza surges and zoonotic highly pathogenic avian influenza

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Abstract: The global landscape of influenza is becoming increasingly complex. In the Northern Hemisphere, seasonal influenza activity is exhibiting a pattern of "early onset, high intensity". At the same time, highly pathogenic avian influenza (HPAI) continues to circulate widely among wild birds and poultry, with a growing tendency to spillover into mammals, including dairy cattle, thereby substantially increasing the zoonotic risk. This convergence exposes the limitations of control systems that manage human and animal influenza separately. Given the ongoing cross-species adaptive evolution of influenza viruses at the human–animal–environment interface, global strategies need to pivot toward a fully integrated One Health paradigm as the organizing principle for preparedness and response. By synthesizing surveillance data and research capacity across human, animal, and environmental health sectors, the international community can build a more resilient defense network that both reduces the current disease burden and helps pre-empt the emergence of novel pandemic strains arising from viral reassortment.

Keywords: seasonal influenza, highly pathogenic avian influenza (HPAI), One Health, zoonoses, pandemic preparedness

1. Changing epidemiology of human seasonal influenza

Seasonal and zoonotic influenza are increasingly interacting within a shared respiratory viral ecosystem, creating new challenges for global health security. Against this backdrop, the epidemiology of human seasonal influenza itself is undergoing important changes.

Since 2020, the B/Yamagata lineage has almost disappeared from global surveillance networks (*1,2*). This presumed "functional extinction" is generally attributed to its slower antigenic evolution, accumulated population immunity from past epidemics, and the suppressive effects of non-pharmaceutical interventions (NPIs) during the COVID-19 pandemic (*3*). Currently, influenza A viruses, together with the B/Victoria lineage, are predominantly circulating, and many countries report influenza A as the predominant strain (*4,5*). Within this broader context, the 2025–2026 Northern Hemisphere season has followed an "early start, high intensity" trajectory: Early peaks have been observed in China and Japan, placing substantial strain on healthcare systems (*6,7*).

Early surveillance data suggest that a novel influenza A(H3N2) virus variant, designated "Subclade K", has emerged as a major driver of transmission this season (*8,9*). Antigenic drift appears to have diminished the match between circulating viruses and current vaccine strains, while several years of relatively low influenza circulation have led to an "immunity gap", thereby enhancing transmission and disproportionately affecting school-aged children, resulting in increased demands on healthcare system (*9,10*). Data from the WHO Global Influenza Surveillance and Response System (FluNet) indicate that many Northern Hemisphere countries are experiencing the concurrent circulation of influenza, SARS-CoV-2, and respiratory syncytial virus (RSV) (*11,12*). The co-circulation observed reflects a shift in population immunity and changes in viral ecological dynamics, thereby complicating clinical diagnosis and posing challenges for health system planning. Rapid urbanization and high population density contribute to increased transmission efficiency in urban environments (*13,14*). Concurrently, disparities in surveillance capacity and unequal access to vaccines in low- and middle-income countries may enable emerging variants to spread undetected, underscoring the necessity of a genuinely global approach to influenza risk management (*15,16*).

2. Cross-species transmission and global threat of highly pathogenic avian influenza (HPAI)

Highly pathogenic avian influenza (HPAI) H5N1 (clade 2.3.4.4b) continues to serve as the primary driver of a global panzootic, spreading through migratory bird flyways and demonstrating enhanced adaptability to mammalian hosts (*17,18*). The virus has repeatedly crossed species barriers, including causing infections in North American dairy cattle, thereby significantly elevating the risk of zoonotic transmission (*19-21*). Since 2024, a novel genotype (B3.13) has become established in U.S. dairy cattle, leading to outbreaks within dairy herds, while H5N1 viruses responsible for outbreaks in poultry, dairy cows, and other animal populations have been associated with approximately 70 reported human infections in the United States between 2024 and early 2025, predominantly among individuals with occupational exposure (*22,23*). Recent outbreaks in poultry in Ontario, Canada, further highlight the ongoing geographic expansion and severity of HPAI (*24*). Of particular concern is the diversification of H5 subtypes through cross-species transmission, exemplified by the first reported human case of H5N5 in the United States, which underscores both the genetic diversity among H5 viruses and their potential for spillover into humans (*25*).

Clinical and experimental evidence indicates genotype-specific differences in host adaptation and disease severity (*22,26*). Although D1.1 retains preferential binding to avian-type α-2,3-linked sialic acid receptors, its pronounced pathogenicity in humans warrants heightened vigilance (*26,27*). Mechanistically, avian influenza virus polymerases, such as the PB1 subunit, are adapted for efficient replication at the higher core body temperatures of birds (40–42°C) (*28*), a trait that may impair the protective efficacy of the human febrile response. This underscores the need for rapid diagnosis and early, aggressive clinical management in suspected zoonotic influenza cases.

A central virological concern is the potential for seasonal influenza viruses and HPAI viruses to undergo genetic reassortment in co-infected hosts such as swine, humans, or potentially dairy cattle, thereby generating novel reassortant strains that combine high intrinsic pathogenicity with efficient human-to-human transmissibility. Although no such reassortant has yet been detected in nature, experimental studies demonstrate both the feasibility and potentially severe consequences of such events, underscoring the need for high sensitivity and genomic resolution in global surveillance systems (*29-33*). In parallel, surveillance of H5N1 viruses — particularly clade 2.3.4.4b — has already identified mutations associated with reduced susceptibility or resistance to oseltamivir and baloxavir (*34,35*), highlighting the urgency of incorporating resistance monitoring in clinical decision-making and diversifying the antiviral toolbox beyond a small number of drug classes. Against this backdrop, the concurrent high-level circulation of human seasonal influenza and HPAI is not only overburdening surveillance and laboratory capacities but is also increasing opportunities for reassortment in intermediate hosts, raising concerns about the emergence of novel strains with pandemic potential (*36,37*). These converging dynamics at the human–animal–environment interface underscore the need for a One Health oriented approach to surveillance and control.

3. Building a resilient One Health surveillance and defense system

To effectively address the compounded risks posed by seasonal influenza and HPAI, a shift from a narrow focus on "seasonal influenza management" to a resilient, One Health oriented risk governance framework is increasingly recognized as necessary (*38,39*). Central to this transition is an integrated system for surveillance, early warning, and intervention that spans human, avian, and other mammalian hosts and encompasses influenza and other major respiratory viruses, enabling a shift from reactive seasonal responses to a proactive approach to "viral ecosystem management". Figure 1 presents a conceptual framework of the dual viral threats at the human–animal–environment interface and outlines strategic future directions for influenza control under a One Health paradigm (Figure 1).

3.1. Establishing a multidimensional, integrated surveillance and early-warning network

We recommend moving beyond single-pathogen surveillance toward a multidimensional, integrated system capable of detecting human respiratory pathogens (*e.g.*, influenza, SARS-CoV-2, RSV) and monitoring infections in livestock, wildlife, and key environmental reservoirs, such as wastewater. Strengthening whole-genome sequencing and bioinformatics capacity, coupled with modelling approaches and real-time digital data-sharing, would enable continuous tracking of the evolutionary trajectories, transmission chains, and resistance mutations of high-risk viruses such as H5N1 and facilitate earlier, risk-stratified interventions (*38,40,41*). Linking existing platforms (*e.g.,* national influenza centers, FluNet, and wastewater surveillance systems) within a unified analytic framework could substantially increase the sensitivity and timeliness of global early warning.

3.2. Implementing cross-sectoral, One Health oriented governance

Anchored in a One Health framework, global influenza control should include systematic upgrading of biosecurity standards in animal production and the phasing out of high-risk farming practices. At the national and regional level, joint risk assessment and emergency response mechanisms should be implemented across the agriculture,

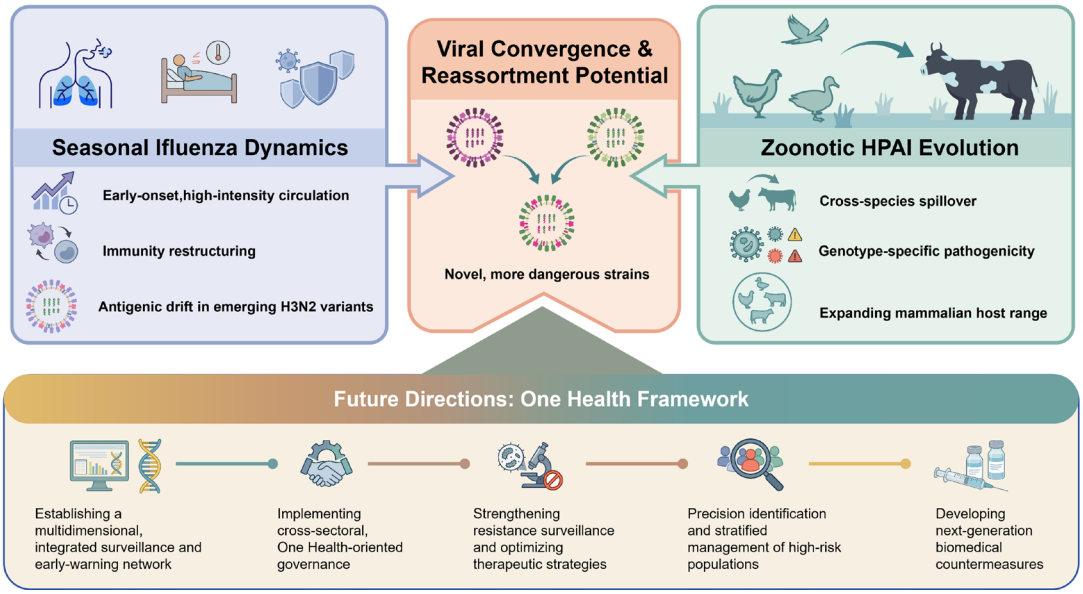

Figure 1. Conceptual framework of dual viral threats at the human–animal–environment interface and strategic future directions under the One Health paradigm. This schematic illustrates the compounding risks posed by the concurrent circulation of human and animal influenza viruses and outlines a comprehensive, integrated response strategy. (Top left) This box characterizes current seasonal influenza dynamics in human populations, highlighting challenges such as early-onset, high-intensity circulation, immunity restructuring, and antigenic drift in emerging variants (*e.g.*, H3N2). (Top right) This box depicts the ongoing evolution of zoonotic highly pathogenic avian influenza (HPAI), emphasizing the risks of cross-species spillover into novel hosts (including ruminants), genotype-specific pathogenicity, and an expanding mammalian host range. (Center) The box in the center illustrates viral convergence and reassortment potential, whereby the interface between human and animal reservoirs functions as a "mixing vessel", increasing the risk of novel, highly virulent strains emerging. (Bottom) The box at the bottom outlines five strategic pillars in the "Future Directions" panel within a One Health framework: (1) establishing a multidimensional, integrated surveillance and early-warning network; (2) implementing cross-sectoral, One Health oriented governance; (3) enhancing antiviral resistance surveillance and optimizing therapeutic strategies; (4) enabling precision identification and stratified management of high-risk populations; and (5) developing next-generation biomedical countermeasures to enhance global health security.

healthcare, and environmental sectors, along with routine occupational health surveillance and protection for high-risk workers (*39,42*). Legal and regulatory measures should be used to overcome data silos and to establish mandatory, transparent international platforms for information sharing and joint notification, in line with existing frameworks such as the International Health Regulations and One Health Joint Plan of Action. These measures are essential to close the "surveillance–decision–action" loop from animals and the environment to human populations.

3.3. Enhancing resistance surveillance and optimizing therapeutic strategies

Future influenza control should be underpinned by an integrated resistance surveillance system linking frontline clinical care with pathogen genomics. Sequencing-based assessment of susceptibility to oseltamivir, baloxavir, and other antivirals should be integrated into routine care pathways to facilitate the dynamic optimization of first-line and combination regimens, particularly in severe and high-risk patients. In parallel, therapeutic strategies that combine direct-acting antivirals with targeted immunomodulation (*43*), together with forward-looking pipelines focused on novel viral targets and critical host factors, are needed to build a multi-target therapeutic armamentarium to combat the continued emergence of resistant variants.

3.4. Precision identification and stratified management of high-risk populations

Next-generation influenza control will require the refined, evidence-based definition of high-risk groups. Recent data indicating that chronic hepatitis B virus carriers are more prone to severe liver injury when co-infected with influenza support their inclusion in priority tiers for surveillance and vaccination (*44*). Mechanistically complementary combination antiviral regimens should be prioritized for severe and high-risk patients (*45*), while aging-related biomarkers in older adults can be incorporated into risk-stratification tools to enable earlier identification of those at highest risk of severe outcomes (*46*). These approaches can guide targeted prevention, timely antiviral initiation, and intensified follow-up and better align clinical practice with population-level risk.

3.5. Developing next-generation biomedical countermeasures

There is a strategic need to invest in adaptable, platform-based technologies, with priority given to universal influenza vaccines targeting conserved epitopes and

rapidly updatable mRNA vaccine platforms capable of covering multiple subtypes, including HPAI viruses (*47,48*). In parallel, enhanced basic and translational research on cross-species transmission mechanisms, host immune response profiles, and host-targeted interventions will be essential to advancing mucosal immunization strategies, broadly neutralizing antibodies, and host-directed antivirals. Together, these efforts can build an expandable toolkit of biomedical countermeasures for future pandemic-scale influenza threats.

4. Conclusion

The world is confronting not isolated seasonal peaks or sporadic avian outbreaks, but an evolving viral ecosystem at the human–animal–environment interface. Siloed control models divided by host or sector are poorly suited to this reality. Strategic investment in One Health surveillance, adaptable vaccines and therapeutics, and cross-sectoral collaboration can strengthen early warning and response capacities, thereby improving global resilience to the next influenza pandemic.

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

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EDITORIAL

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Surgical treatments for early-stage hepatocellular carcinoma: Resection versus transplantation

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Abstract: Liver resection (LR) and liver transplantation (LT) are the two principal curative options for early-stage hepatocellular carcinoma (HCC), but the optimal choice for individual patients remains uncertain. Recent meta-analyses suggest that LT confers superior long-term survival compared with LR, particularly when tumor burden meets transplant criteria and donor availability is sufficient. Although LT requires lifelong immunosuppressive therapy, patient-reported quality of life appears comparable between LT and LR. Overall, current evidence indicates that LT may offer improved survival without compromising quality of life in appropriately selected patients.

***Keywords*:** hepatocellular carcinoma, liver transplantation, liver resection, quality of life

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third leading cause of cancer-related death worldwide (*1*). Liver resection (LR) and liver transplantation (LT) are the recommended first-line surgical treatments for HCC (*2*). A recent systematic review has demonstrated that LT offers better survival than LR (*3*). In this editorial, we focus on recent evidence comparing LT and LR for early-stage HCC and examine postoperative quality of life (QOL).

LT and living donor liver transplantation (LDLT)

Starzl *et al*. reported the first LT in 1963 (*4*). Since then, improvements in surgical techniques and perioperative patient care for LT have made LT a common, routine surgery. Mazzaferro *et al*. considered LT a standard treatment for HCC (*5*).

In Eastern countries, the scarcity of cadaveric donors prompts LDLT (*6*). Nonetheless, in both LDLT and deceased donor liver transplantation, the Milan criteria are mainly used as the indication for LT (*7*). The Milan criteria are the best-known criteria for LT (*5*). The criteria comprise a tumor ≤ 5 cm in diameter in patients with a single HCC and < 3 tumor nodules, each ≤ 3 cm in diameter in patients with multiple tumors.

The Milan criteria depend on morphological parameters and consider only 30% of the patients with HCC suitable for LT. Nevertheless, patients with tumors beyond the Milan criteria can have favorable outcomes after LT (*8*).

LR

LR is another curative surgical treatment for patients with HCC, resulting in long-term survival; however, LR is only applicable to a minority of patients. According to the Barcelona Clinic Liver Cancer staging and treatment guidelines, LR is recommended for patients with a single tumor without portal hypertension (*9*). However, these guidelines are not universally adopted, and Eastern guidelines, such as the Asian Pacific Association for the Study of the Liver guidelines (*10*), have radically different recommendations. There is growing evidence indicating that the prognosis after LR is comparable for 2–3 tumors (*11*). Therefore, the treatment most beneficial for patients with HCC up to three tumors remains unclear.

Comparing survival after LT and LR

Numerous studies have compared LT *vs*. LR in patients with early-stage HCC (*12*). Most studies reported superior long-term survival with LT compared with LR. As earlier meta-analyses have shown that LT results in better long-term survival, recent evaluations of treatment benefits now place increasing importance on patients' QOL, considering it just as crucial as the actual

therapy provided (*12*). As such, the focus is not only on achieving long-term survival but also on how patients live in relation to their disease and treatment (*13*).

One of the biggest differences between transplantation and resection is the low immune status caused by immunosuppressive agents in transplanted patients (*14*). Theoretically, a low immune status may increase the risk for infections, which may lower QOL scores. However, a previous study found no significant differences in QOL (*15*). In addition, daily treatment with immunosuppressants did not affect the recipients' physical QOL and psychological outcomes when compared with patients who underwent resection.

In conclusion, we highlight key considerations in the surgical management of early-stage HCC. The present evidence indicates that LT offers better survival outcomes in patients with acceptable tumor burden, provided that donor availability is sufficient. In addition, QOL after LT is comparable to that following LR, despite the requirement for lifelong immunosuppressive therapy.

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ORIGINAL ARTICLE
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Improved prognostic predictability of the latest Japanese TNM Classification in patients undergoing resection for distal cholangiocarcinoma

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Abstract: In March 2021, the Japanese TNM Classification for Cancer of the Biliary Tract (JCCB) was revised. This study aimed to validate the 7th edition of JCCB based on long-term outcomes after resection for distal cholangiocarcinoma (DCC). We retrospectively reviewed 107 patients with resected DCC without distant metastasis between 2007 and 2019. Survival curves according to TNM factors were compared between the 6th and 7th editions. The 5-year overall survival (OS) and recurrence-free survival rate (RFS) were 43.4% and 35.5%, respectively. Significant differences in OS were observed between T categories in the 7th edition (T1 *vs.* T2, $p = 0.049$; T2 *vs.* T3, $p = 0.027$), but not in the 6th. The N classification also showed better prognostic discrimination in both editions, with more refined stratification in the 7th. Stage grouping in the 6th edition failed to show significant OS differences, while the 7th edition demonstrated clear stratification (*e.g.*, Stage I *vs.* IIA, $p = 0.0274$; StageIIA *vs.* StageIIB, $p = 0.0043$; StageIIB *vs.* StageIIIA, $p = 0.0108$). These findings indicate that the revised T and N classifications in the 7th edition more accurately reflect postoperative prognosis for resected DCC. Overall, our results support the clinical validity and improved prognostic utility of the 7th edition compared with the 6th edition.

Keywords: overall survival, invasive tumor thickness, depth of invasion

1. Introduction

Bile duct cancer (BCC) accounts for 3% of all gastrointestinal cancers (*1*), and its incidence is gradually increasing worldwide, particularly in East Asia (*2,3*). Meanwhile, distal cholangiocarcinoma (DCC) accounts for 20% to 30% of all BCCs (*4*). The only curative treatment for DCC is surgery, with a 5-year survival rate of 22–47% (*5-7*).

The Japanese TNM Classification for Cancer of the Biliary Tract (JCCB) has been mainly used in Japan. In March 2021, it was revised from the 6th to the 7th edition, following the revision of the Union for the International Cancer Control (UICC) staging system from the 7th to the 8th edition (*8,9*). The 7th edition of JCCB exhibited close similarity to the 8th edition of the UICC and the 6th edition of JCCB to the 7th edition. Regarding the T factor, the classification in the 6th edition — based on the extent of tumor invasion — was revised in the 7th edition to reflect the depth of invasion (DOI) or invasive tumor thickness (ITT) in case the DOI could not be measured. As for the N factor, the previous classification in the 6th edition according to the presence or absence of lymph node metastasis (LNM) was changed into the latest classification in the 7th edition according to the number of lymph node metastasis (N0: 0 N1: 1–3 nodes N2: more than 4 nodes).

The present study aimed to validate the prognostic performance of the 7th edition of the JCCB by comparing survival outcomes according to the T, N, and stage categories defined in the 6th and 7th editions.

2. Patients and Methods

2.1. Study participants

A total of 109 patients who underwent surgical resection for DCC at Osaka Metropolitan University Hospital between January 1, 2007, and December 31, 2019, were initially identified. The inclusion criteria were: *i*) histologically confirmed DCC, *ii*) curative-intent surgical resection with available pathological assessment, and *iii*) complete clinical, pathological, and follow-up data. The exclusion criteria were: *i*) presence of distant metastasis

at the time of surgery, *ii*) recurrent or remnant bile duct cancer, *iii*) synchronous malignancies, and *iv*) insufficient clinical or pathological information.

Based on these criteria, two patients with distant metastasis were excluded, leaving 107 patients for the final analysis. All patients were followed for survival outcomes, with a median follow-up duration of 33.1 months (range, 3.4–132.2 months). Recurrence was defined as radiologic detection of new lesions consistent with tumor relapse on contrast-enhanced computed tomography or other imaging modalities.

2.2. Data collection

The demographic and clinical variables collected included age, sex, preoperative cholangitis, biliary drainage, serum albumin level, modified Glasgow prognostic score, serum carbohydrate antigen 19-9, operative procedure, presence or absence of portal vein and hepatic artery resections, surgical duration, intraoperative blood loss, DOI or ITT, histological grade, lymphatic invasion, venous invasion, perineural invasion, postoperative hospital length of stay, postoperative complications, and receipt of adjuvant chemotherapy.

The pathological T, N, and stage classifications were recorded according to both the 6th and 7th editions of JCCB (*10,11*). The 6th edition defines the T category based on the anatomic extent of tumor invasion into adjacent structures, whereas the 7th edition incorporates DOI or ITT as quantitative, measurement-based criteria. Similarly, the N category in the 6th edition is determined by the presence or absence of LNM, while the 7th edition classifies N status according to the number of metastatic lymph nodes (0, 1–3, or ≥ 4). These classification systems were systematically applied to each patient to enable direct comparison of staging between the two editions.

Tumor differentiation was classified according to the World Health Organization criteria as well-, moderately-, or poorly differentiated, as well as undifferentiated adenocarcinoma (*12*).

2.3. Statistical analysis

Survival rate was calculated using the Kaplan–Meier method, and the log-rank test was employed to compare the groups. Comparisons were made for T, N, and stage categories according to both the 6th and 7th editions of the JCCB. $P < 0.05$ was considered to indicate statistical significance. JMP® version 12 (SAS Institute, Cary, NC, United States) was used to conduct all statistical analyses.

2.4. Ethical approval

All patients provided informed consent for using their data in this study according to the institutional regulations of the study sites. This study was approved by the Ethics Committees of Osaka Metropolitan University (approval No.2020-241) and was performed in compliance with the Declaration of Helsinki.

3. Results

3.1. Patient characteristics

The baseline characteristics of the 107 patients are summarized in Table 1. The median age was 70 years (range, 30–86), and 74 patients (69.2%) were male. Preoperative cholangitis occurred in 27 patients (25.2%), and 103 patients (96.3%) underwent biliary drainage. Regarding surgical procedures, subtotal stomach-preserving pancreaticoduodenectomy was the most frequently performed (n = 75), followed by classical pancreaticoduodenectomy (n = 19) and bile duct resection (n = 8). A total of 36 patients (33.6%) received adjuvant chemotherapy after surgery, with S-1 being the most commonly administered regimen (n = 36), followed by gemcitabine (n = 9), tegafur–uracil (n = 6), and gemcitabine plus cisplatin (n = 6). Decisions regarding adjuvant chemotherapy were made at the discretion of the treating physicians.

3.2. Overall survival and relapse-free survival for resected distal cholangiocarcinoma

Patients who underwent DCC resection demonstrated a 5-year overall survival (OS) rate of 43.4% and a median survival time of 47.7 months (Figure 1A) as well as a 5-year relapse-free survival (RFS) rate of 35.5% and a median RFS of 29.2 months (Figure 1B).

3.3. Distribution of the 7th edition T factor in the 6th edition T factor

Table 2 presents the distribution of the 7th edition T factor in the 6th edition T factor. According to the 6th edition, 1/11/30/57/7/1 patients were classified into pTis/T1b/T2/T3a/T3b/T4, respectively. When the 7th edition was applied, distributions of pTis/T1/T2/T3/T4 changed to 1/40 (15 downgraded from T2, 16 downgraded from T3a in the previous edition)/37 (2 upgraded from T1b, 22 downgraded from T3a)/21 (2 patients upgraded from T2)/8 (7 patients upgraded from T3b).

3.4. Lymph node metastasis rate according to the T factor of the 6th and 7th editions

Table 3 presents LNM rate according to the T factor of the 6th and 7th editions. As can be seen from the table, LNM rates increased as the T factor increased in the 7th edition.

3.5. Survival curve according to T factor of the 6th and 7th editions

Table 1. Patient characteristics (*n* = 107)

Characteristics	Number
Age	
Median (range)	70 (30–86)
Sex	
Male	74
Female	33
Preoperative BMI[*]	
Median (range)	22.9 (15.2–35.6)
Preoperative cholangitis	
Absent	80
Present	27
Preoperative biliary drainage	
None	4
PTBD[†]	13
EBD[‡]	90
Preoperative serum Alb level median (range)	3.8 (2.7–4.8)
Preoperative mGPS[§]	
0	78
1	21
2	8
Preoperative CA19-9	
Normal	61
Elevated	46
Surgery	
PD[ǁ]	19
PpPD[¶]	4
SSPPD[**]	75
HPD[††]	1
BDR[‡‡]	8
Portal vein resection	
Present	8
Absent	99
Hepatic artery resection	
Present	3
Absent	104
Operation time (minutes), median (range)	500 (289–838)
Intraoperative blood loss volume (mL), median (range)	700 (210–4000)
DOI[§§] (ITT[ǁǁ]) (mm), median (range)	6 (0.5–28.0)
Histological grade	
pap	7
well	25
mod	63
por	11
Sig	1
T factor (6th edition)[¶¶]	
Tis	1
T1a	0
T1b	11
T2	30
T3a	57
T3b	7
T4	1
T factor (7th edition)[***]	
Tis	1
T1	40
T2	37
T3	21
T4	8
N factor (7th edition)[***]	
N0	65
N1	34
N2	8
Lymph node metastasis count median (range)	0 (0-10)
Stage (6th edition)[¶¶]	
0	1
IA	9
IB	24
IIA	31
IIB	41
III	1
Stage (7th edition)[***]	
0	1
I	30
IIA	30
IIB	30
IIIA	8
IIIB	8
Residual tumor	
R0	78
R1	18
R2	11
Lymphatic invasion (ly)	
0	42
1	38
2	18
3	4
X	5
Venous invasion (v)	
0	76
1	21
2	5
3	0
X	5
Perineural invasion (ne)	
0	19
1	32
2	30
3	22
X	4
Postoperative length of stay (day) median (range)	33 (12–225)
Postoperative complication (≥ CDIIIa)[†††]	
0	4
I	13
II	23
IIIa	58
IIIb	4
IVa	4
IVb	0
V	1
Adjuvant chemotherapy	
yes	36
no	71

[*]BMI: body mass index. [†]PTBD: percutaneous transhepatic biliary drainage.[‡]EBD: endoscopic biliary drainage. [§]mGPS: Modified Glasgow Prognostic Score. [ǁ]PD: pancreatoduodenectomy. [¶]PpPD: pylorus-preserving pancreaticoduodenectomy. [**]SSPPD: subtotal stomach-preserving pancreaticoduodenectomy. [††]HPD: hepatopancreatoduodenectomy. [‡‡]BDR: bile duct resection. [§§]DOI: depth of invasion. [ǁǁ]ITT: invasion of tumor thickness. [¶¶]by the 6th edition of the Japanese TNM Classification for Cancer of the Biliary Tract (JCCB). [***]by the 7th edition of the Japanese TNM Classification for Cancer of the Biliary Tract (JCCB). [†††]CD: Clavien–Dindo classification.

Figure 2A presents the survival curve according to the 6th edition T factor. The 5-year survival rates of pTis/T1b/T2/T3a/T3b/T4 were 100%/71.6%/56.2%/29.7%/13.1%/100%, respectively. A significant difference was observed in OS between pT3a and T3b ($p = 0.002$). In contrast, there was no significant difference in OS between the other groups (pTis *vs.* T1b, $p = 0.57$; pT1b *vs.* T2, $p = 0.39$; pT2 *vs.* T3a, $p = 0.68$; pT3b *vs.* T4, $p = 0.21$).

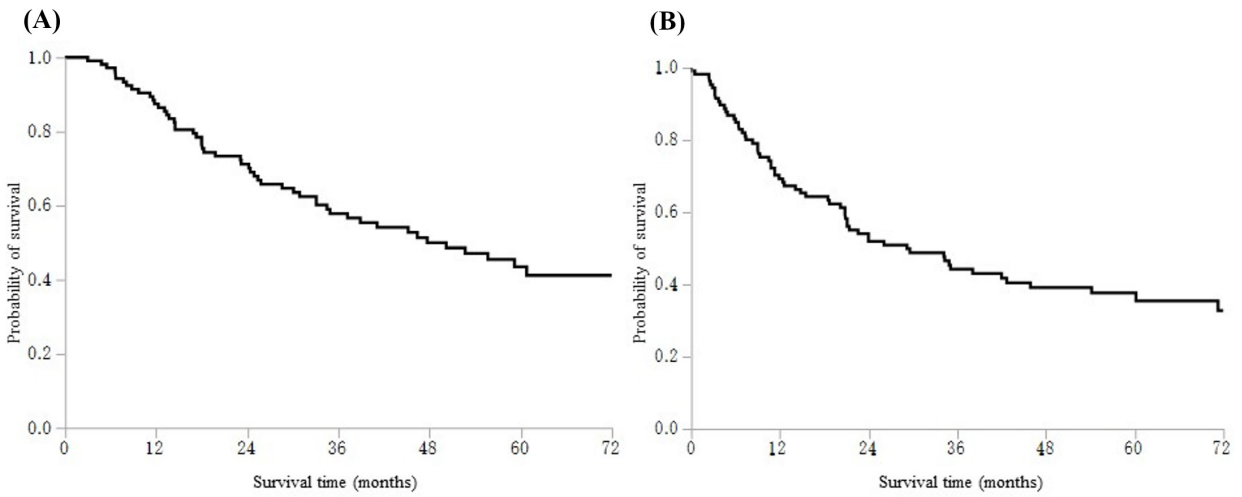

Figure 1. Survival curve of the resected distal cholangiocarcinoma (*n* = 107). (A) Overall survival 5-survival year rate: 43.4%, median survival time: 47.7 months; **(B)** Relapse-free survival: 35.5%, median relapse-free survival time: 29.2 months.

Table 2. Distribution of the T factor of the 7th edition from the 6th edition

T factor (6th)	*n*	T factor (7th)	*n*
Tis	1	Tis	1
T1a	0		
T1b	11	T1	9
		T2	2
T2	30	T1	15
		T2	13
		T3	2
T3a	57	T1	16
		T2	22
		T3	19
T3b	7	T4	7
T4	1	T4	1

Figure 2B presents the survival curve according to the 7th edition T factor. 5-year survival rates of pTis/T1/T2/T3/T4 were 100%/65.6%/40.1%/13.7%/0%. A significant difference in OS was observed between pT1 and T2 (p = 0.049) and between pT2 and T3 (p = 0.027). In contrast, no significant difference was observed between pTis and T1 (p = 0.39) and between T3 and T4 (p = 0.23).

3.6. Survival curve according to N factor of the 6th and 7th editions

Figure 3 presents the survival curve of the N factor of the 6th and 7th editions. 5-year survival rate was significantly higher in pN0 of the 6th edition than in pN1 of the 6th edition (pN0: 61.8% *vs.* pN1: 18.4%, $p < 0.0001$). In the 7th edition N factor, a significant difference in OS was observed between each group (pN0: 61.8%; pN1: 21.7%; pN2: 0% [pN0 *vs.* pN1: p = 0.0005, pN1 *vs.* pN2: p = 0.0052]).

3.7. Survival curve according to pStage of the 6th and 7th editions

Table 3. Lymph node metastasis rate according to the T factor of the 6th edition and the 7th edition

T factor (6th)	*n*	LNM	T factor (7th)	*n*	LNM
Tis	1	0% (0/1)	Tis	1	0% (0/1)
T1a	0		T1	40	25.0% (10/40)
T1b	11	27.3% (3/11)			
T2	30	20.0% (6/30)	T2	37	40.5% (15/37)
T3a	57	50.9% (29/57)	T3	21	61.9% (13/21)
T3b	7	71.4% (5/7)			
T4	1	0% (0/1)	T4	8	62.5% (5/8)

Figure 4 presents the survival curve according to pStage of the 6th and 7th editions. No significant difference in OS was observed between each pStage group of the 6th edition, whereas a significant difference was found between those of the 7th edition (pStage: 0%, Stage I: 83.0%, Stage IIA: 44.4%, Stage IIB: 19.3%, Stage IIIA: 0%, Stage IIIB: 0%; pStage I *vs.* Stage IIA: p = 0.027, Stage IIA *vs.* Stage IIB: p = 0.0043, Stage IIB *vs.* Stage IIIA: p = 0.01).

4. Discussion

Results of this study indicated that the 7th edition of the JCCB can more accurately predict survival outcomes for resected DCC than the 6th version. T classification of the 6th edition was based on which layer was invaded. Similar layer-based systems have been applied to other gastrointestinal cancers, such as those of the stomach, colon, and rectum, where the distinct and concentric nature of the wall layers provides strong prognostic value (*13,14*). Conversely, the extrahepatic bile duct is characterized by a relatively thin wall and non-uniform concentricity along its course (*15*). It consists of varying proportions of fibrous and loose connective tissues, making it difficult to distinguish

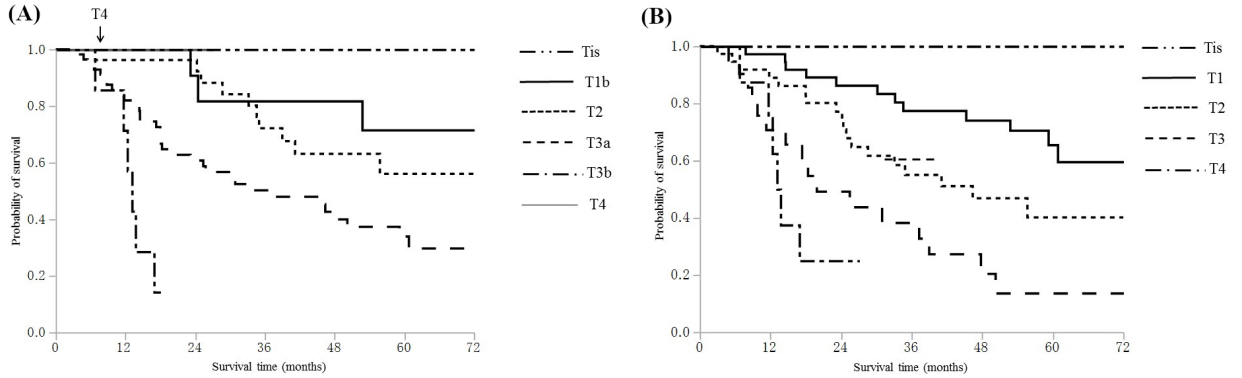

Figure 2. Survival curves according to the T factor. (A) 6th edition (pTis *vs.* T1b; $p = 0.57$, pT1b *vs.* T2; $p = 0.39$, pT2 *vs.* T3a; $p = 0.68$, pT3a *vs.* T3b; $p = 0.02$, pT3b *vs.* T4; $p = 0.21$); **(B)** 7th edition (pTis *vs.* T1; $p = 0.39$, pT1 *vs.* T2; $p = 0.049$, pT2 *vs.* T3; $p = 0.027$, pT3 *vs.* T4; $p = 0.23$).

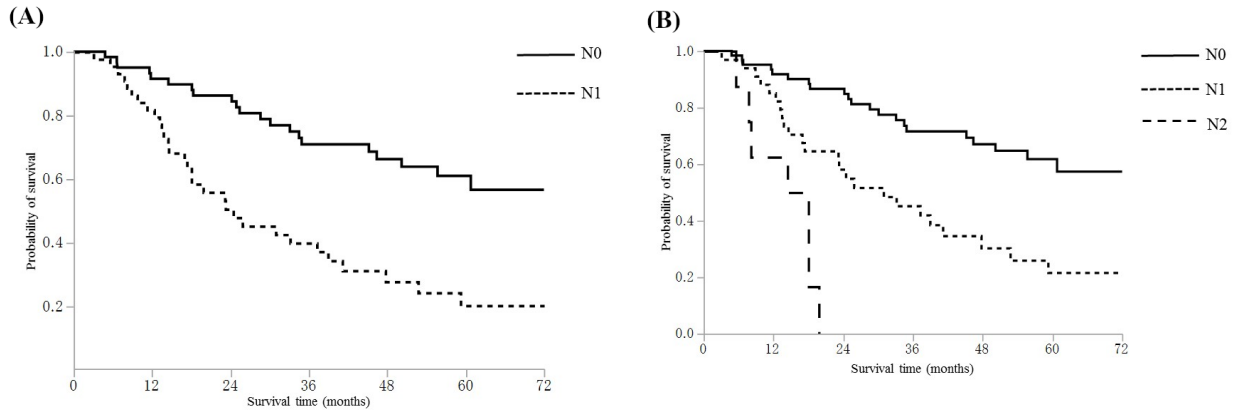

Figure 3. Survival curve according to the N factor. (A) 6th edition (pN0 *vs.* N1; $p < 0.0001$); **(B)** 7th edition (pN0 *vs.* N1; $p = 0.0005$, pN1 *vs.* N2; $p = 0.0052$).

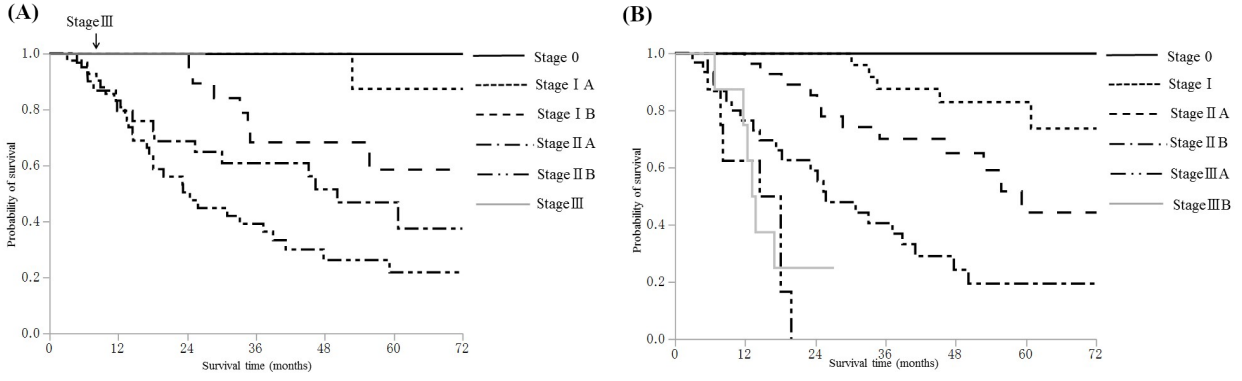

Figure 4. Survival curve according to stage. (A) 6th edition (pStage 0 *vs.* StageIA; $p = 0.09$, p StageIA *vs.* StageIB; $p = 0.09$ pStageIB *vs.* StageIIA; $p = 0.22$, pStageIIA *vs.* StageIIB; $p = 0.10$, pStageIIB *vs.* StageIII; $p = 0.37$); **(B)** 7th edition (pStage 0 *vs.* StageI; $p = 0.43$, pStageI *vs.* StageIIA; $p = 0.027$, pStageIIA *vs.* StageIIB; $p = 0.0043$, pStageIIB *vs.* StageIIIA; $p = 0.01$, pStageIIIA *vs.* IIIB; $p = 0.86$).

between invasion confined within the bile duct wall and invasion beyond it (*16*). Moreover, the presence of desmoplastic reactions, edematous stroma, congestion, necrosis, and inflammatory cell infiltration around invasive adenocarcinoma often obscures the histological architecture, making layer discrimination challenging even for experienced pathologists (*17*). The study found no significant difference in OS between each T factor, except between T3a and T3b, in the 6th edition. Previous studies also reported that the layer-based T classification failed to stratify postoperative survival in patients with DCC (*18,19*).

In contrast, the 7th (Japanese) edition classifies the T category based on either DOI or ITT, depending on measurability.

DOI has been widely used in other cancer types with shallow depth, such as cutaneous melanoma, where it serves as a strong prognostic indicator (*20*). Several studies have suggested that measuring depth of bile duct carcinoma invasion provides better prognostic discrimination than layer-based classifications (*15,21*). In this study, DOI was measured from the basal lamina of the adjacent normal bile duct epithelium to the deepest point of tumor invasion. However, in more advanced or circumferential tumors, the basal lamina is often indistinct or unidentifiable, making DOI measurement infeasible. In such cases, ITT was used as a substitute in the current T classification system. Aoyama *et al.* reported that the ITT classification exhibited a more favorable prognostic discrimination than the T classification of the 7th and 8th editions of the American Joint Committee on Cancer (AJCC) Staging (*22*). This study demonstrated that the updated T classification in the 7th edition provides a significant prognostic stratification among each T category, in contrast to the 6th edition, which failed to show such distinctions. Hence, it was deduced that T classification according to the use of ITT and DOI (when ITT could not be measured), rather than extent of tumor invasion, was more likely to reflect prognosis. However, a major limitation of the DOI and ITT classifications was that they did not permit reliable preoperative radiologic assessment by clinicians. Further validation in larger, multicenter studies is warranted to confirm prognostic utility and clinical applicability of this revised classification.

As for the N factor, the previous classification based solely on presence or absence of LNM had been revised in the 7th edition to a system based on number of LNM (0, 1–3, ≥ 4 or more nodes). In other gastrointestinal cancers — such as esophageal, gastric, and colorectal cancers — both the UICC classification and Japanese General Rules also adopt N classifications based on the number of LNMs, and these systems had been shown to accurately predict patient prognosis (*23-25*). Regarding DCC, Suzuki *et al.* reported that both number of positive lymph nodes and lymphatic invasion were significant prognostic factors following pancreaticoduodenectomy for DCC (*26*). In addition, several studies have demonstrated that the N categories defined in the 8th edition of the AJCC classification effectively predict patient outcomes (*19,21*). Others have found that absolute number of metastatic lymph nodes is a stronger predictor of survival compared to lymph node ratio (LNR) in DCC (*27*). Consistent with these findings, the present study also showed significant differences in OS between N0 and N1, and between N1 and N2, according to the latest classification. Recent reports have emphasized prognostic importance of both number of retrieved lymph nodes and lymph node ratio (*i.e.*, ratio of metastatic to total retrieved lymph nodes). Furthermore, some researchers have proposed that evaluation of at least 11 or 12 lymph nodes is necessary for accurate N staging in DCC (*19,28*). Schwart *et al.* reported that survival prediction in extrahepatic biliary duct cancer is strongly influenced by both total number of retrieved LNs and number of negative LNs (*29*). In contrast, Hong *et al.* found no significant association between survival and number of retrieved LNs (*30*). These discrepancies underscore need for further investigation into optimal number of examined lymph nodes and their prognostic value.

Our study demonstrates that the stage classification system in the 7th edition more accurately stratifies 5-year OS rates across stages than the 6th edition. This improvement appears to be attributable to the revised T and N classifications, which, as shown above, are significantly associated with patient prognosis.

Major limitations of the present study were the small sample size, its retrospective design, and the unstandardized adjuvant chemotherapy indications and regimens. Multicenter prospective studies with larger sample sizes are warranted to elucidate the validity of the latest edition of the JCCB.

In conclusion, as a result of the revisions of the T and N factor classifications, the 7th edition of the JCCB may more accurately predict survival outcomes for resected DCC than the 6th edition.

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The impact of healthy lifestyles on cognitive function in community-dwelling older adults: A cross-sectional study in Shanghai, China

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Abstract: Recent literature has demonstrated the link between lifestyle behavior factors and cognitive function, yet most evidence comes from Western populations. This study examined the associations between multiple healthy lifestyle factors and cognitive function among community-dwelling older adults in Shanghai, China. This cross-sectional study included 942 residents aged ≥ 60 years in Pudong District, Shanghai, China, who participated in China's national free physical examination program from July to September 2024. Cognitive function and cognitive impairment status were assessed by Mini-Mental State Examination (MMSE). Five healthy lifestyle factors were considered: never smoking, healthy body mass index, regular physical activity, light-to-moderate alcohol drinking and optimal night sleep duration. A composite healthy lifestyle score (0–5) was calculated. Results showed that regular physical activity and optimal night sleep duration were positively correlated with a MMSE score [β = 0.21 (95% confidence interval (CI): 0.09–0.34), p = 0.001; β = 0.15 (95% CI: 0.03–0.27), p = 0.016, respectively], and were significantly associated with lower odds of cognitive impairment [odds ratio (OR) = 0.69 (95% CI: 0.47–0.98); OR = 0.66 (95% CI: 0.45–0.95), respectively]. Compared with participants with ≤ 1 healthy lifestyle factor, the β (95% CI) of MMSE score for participants with 3, and 4–5 healthy lifestyle factors were 0.26 (0.08–0.44) and 0.25 (0.04–0.47), respectively; and the OR and 95% CI for participants with 3 healthy lifestyle factors were 0.59 (0.34–0.98). Adherence to multiple healthy lifestyle behaviors, particularly regular physical activity and adequate night sleep, was associated with better cognitive function among elders in Shanghai.

***Keywords*:** healthy lifestyle, cognitive function, community-dwelling elders, Shanghai, China

1. Introduction

With the rapid increase of the aging population in China, the prevalence of age-related diseases and conditions has markedly risen over the past decades (*1*). Among these, cognitive decline has emerged as a major public health concern, which impairs both life quality and work productivity, and substantially increases the risk of dementia (*2*). A nationwide survey conducted in China between 2015 and 2018 reported that approximately 15.5% of individuals aged 60 years and older experienced mild cognitive impairment, 6.0% were diagnosed with dementia, and 3.9% had Alzheimer's disease (*3*). These conditions not only severely affect individuals' quality of life but also pose a substantial burden on caregivers, families, and the financial and healthcare systems of society (*4*). However, cognitive decline does not necessarily lead to dementia and may be reversed or stabilized, thereby preventing progression to a pathological state (*5*). Therefore, identifying modifiable risk factors associated with cognitive impairment is essential for developing effective public health strategies and promoting healthy aging in China.

Extensive research has explored the risk factors of cognitive function, including aging, education, occupational status, chronic diseases, genetic and epigenetic factors as well as lifestyle behaviors (*6,7*). Among these, the management of a healthy lifestyle is becoming increasingly important (*2,8,9*). A growing body of evidence suggests that conventional modifiable healthy lifestyle factors, such as nonsmoking, moderate alcohol consumption, adequate sleep, normal body mass index (BMI), regular physical activity and adhering to a balanced diet rich in fruits, vegetables, fish and nuts, are all linked to better cognitive function and a reduced risk of dementia (*10,11*). However, lifestyle factors often cluster rather than act independently. Therefore, a combined healthy score, integrates multiple behaviors, has been proposed as a more comprehensive indicator of health outcomes.

Several large cohort studies in Western populations have consistently shown that adherence to multiple

healthy lifestyle factors is associated with slower cognitive decline (*12*). In China, a few studies have examined this association. Jia *et al.* found that subjects with favorable lifestyle factors experienced a slower memory decline than those in the unfavorable group in a cohort of 29,072 participants (*2*). Wang *et al.* observed that those in the highest quartile lifestyle score had a lower risk of cognitive impairment [odds ratio (OR) = 0.52 (95% confidence interval (95% CI): 0.41–0.65] among 5,716 participants with an average age of 82 years from the Chinese Longitudinal Healthy Longevity Survey (*13*). Nevertheless, evidence among community-dwelling older adults in China remains limited.

To address this gap, this study aimed to examine the associations between adherence to multiple healthy lifestyle factors and cognitive function among community-dwelling older adults in Shanghai, China.

2. Materials and Methods

2.1. Study population

This cross-sectional study used a convenience sampling approach, including 1,043 community-dwelling residents of Pudong District, Shanghai, China, who participated in China's national free physical examination program between July and September 2024. Individuals were included if they met the following criteria: *i*) adults aged 60 years or older; *ii*) had lived in the community for at least one year; and *iii*) were willing to participate and able to communicate effectively. The exclusion criteria were as follows: *i*) aged < 60 years (n = 2); *ii*) previously diagnosed Alzheimer's disease or other dementias (n = 3); *iii*) missing lifestyle data (including BMI, smoking status, alcohol drinking status, sleep duration time and exercise data) (n = 96). The final analytic sample comprised 942 participants, who completed the questionnaire, physical examination, and informed consent.

This study was reviewed and approved by the Research Ethics Committee of Shanghai Health Medical University (2024-SSF-24-04-005). All participants provided written informed consent, and the study was conducted in accordance with the Declaration of Helsinki. All methods were performed in accordance with relevant guidelines and regulations and followed the Strengthening. Reporting of Observational Studies of Epidemiology (STROBE) guidelines (*14*).

2.2. Assessment of cognitive function

In this study, cognitive function was assessed using the Mini-Mental State Examination (MMSE), which consisted of 30 items scored from 0 to 30, with higher scores indicating better cognitive performance (*15*). Cognitive impairment was defined as MMSE scores ≤ 17 for illiterate individuals, ≤ 20 for those with primary education, and ≤ 24 for those with junior school education or above (*16*).

2.3. Assessment of lifestyle factors and covariates

Information on demographic characteristics (*e.g.*, age, gender, education, marriage, family income and co-residence status), lifestyle behaviors (*e.g.*, smoking, alcohol drinking status, physical activity, and sleep duration) and comorbidities was collected through face-to-face interviews using a semi-structured questionnaire.

Education levels included illiterate, primary school, junior or high school, and college or above. Marital status was categorized into single (single, divorced or widowed) or married. Family income was categorized into < CNY 5,000, 5,000–10,000, 10,001–20,000, and > 20,000 monthly. Co-residence status consisted of living with family and living alone. Current smokers were defined as subjects who smoked > 1 cigarette/day for more than 6 months, and former smokers were defined as subjects who ever smoked but had stopped smoking for more than 6 months; otherwise, they were defined as never smokers (*17*). Individuals who drank alcohol > 1 time/week for > 6 months were considered as current alcohol drinkers, and former drinkers were those who had abstained from drinking for > 6 months; otherwise, they were defined as never alcohol drinkers. To estimate the daily alcohol consumption, we multiplied the average alcohol content of each type of alcoholic beverage by the daily volume consumed for that type, and then summed the results across all types. The average alcoholicity of liquor, beer, wine and rice wine were 42%, 4%, 12% and 10%, respectively (*18*). Participants engaging in moderate or vigorous physical activity for at least 30 minutes per session, three or more times per week, were considered regular physical activity (*19*). Participants were queried about their usual bedtime and wake-up time, and sleep duration was determined by calculating the interval between these two times (*20*).

In our study, comorbidities were grouped into six categories: *i*) circulatory diseases (coronary heart disease, stroke, hypertension); *ii*) chronic obstructive pulmonary disease (COPD); *iii*) malignant tumors; *iv*) diabetes; *v*) liver diseases; and *vi*) kidney diseases. We categorized the number of comorbidities into four groups: none, one, two, and three or more diseases (*21*). Professionally trained staff used calibrated instruments to measure weight and height. BMI was calculated as weight (kg) divided by the height (m^2).

2.4. Healthy lifestyle score

Based on previous evidence, we considered healthy behaviors to include a BMI ranging from 18.5 to < 24 kg/m^2, regular physical activity, never smoking, light to moderate alcohol consumption (< 15 g/day for women and < 30 g/day for men), as well as sleeping for 7.0–9.0

hours per night (*21,22*). For each lifestyle, the individuals received a score of 1 if he/she met the criterion for healthy lifestyle and 0 otherwise. The overall healthy lifestyle score was calculated as the sum of these individual components, ranging from 0 to 5.

2.5. Statistical analysis

For continuous data, the median and interquartile range, ranging from the first to the third quartile, were displayed. Categorical variables were presented as frequencies and percentages. Descriptive analyses were first conducted to compare characteristics between participants with and without cognitive impairment using nonparametric and chi-square tests as appropriate. To facilitate comparison of effect sizes and improve model interpretability, MMSE scores were standardized using Z-score transformation before regression analyses. Linear regression models were applied to investigate the relationships between healthy lifestyle factors and MMSE scores, and logistic regression models were used to examine the relationships between healthy lifestyle factors and cognitive impairment status. We initially adjusted for age and gender (model 1); further adjusted for marital status, education level, monthly family income, co-residence status, the number of comorbidities (model 2); and further adjusted for the other four lifestyles when evaluating each lifestyle factor in these regression models (model 3). Subgroup analyses were conducted stratified by age, gender, marital status, education level, family income monthly and co-living status to explore potential heterogeneity in the associations.

Two-sided p values < 0.05 were considered statistically significant. All analyses were performed using R software (version 4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics of study participants

The general characteristics of the study participants are shown in Table 1. A total of 942 community-dwelling older adults aged 64 to 88 years were included, comprising 389 men and 553 women. MMSE scores ranged from 5 to 30. Based on education-adjusted MMSE cutoffs, 148 participants (15.71%) were classified with cognitive impairment, whereas 794 (84.29%) had normal cognitive function. Compared with cognitive normal participants, those with cognitive impairment were older [aged: 71.00 (68.00–75.00) *vs*. 70.00 (67.00–73.00), p = 0.015], had lower monthly household income [> CNY 20,000: 5.41% *vs.* 10.58%, p < 0.001], slept longer at night [8.00 (7.00–9.00) *vs.* 8.00 (7.00–8.50), p = 0.007], and were less likely to be physically active [56.76% *vs.* 67.76%, p = 0.012]. They also had lower healthy lifestyle scores (p = 0.029).

3.2. Associations between healthy lifestyles and cognitive function

For regression analyses, MMSE scores were standardized to Z-scores to facilitate interpretation. Results of the linear regression analyses (Table 2 and Figure 1) showed that regular physical activity and optimal night sleep duration were positively associated with higher MMSE scores [β = 0.21 (95% CI: 0.09–0.34), p = 0.001; β = 0.15 (95% CI: 0.03–0.27), p = 0.016, respectively]. Compared with participants who had ≤ 1 healthy lifestyle factor, those with 3 and 4–5 healthy factors had significantly higher MMSE scores [β = 0.26 (95% CI: 0.08–0.44) and β = 0.25 (95% CI: 0.04–0.47), respectively; p for trend < 0.001].

Associations of individual healthy lifestyle factors and healthy lifestyle score with cognitive impairment status are shown in Table 3 and Figure 2. Regular physical activity or optimal night sleep duration was associated with lower odds of cognitive impairment [OR = 0.69 (95% CI: 0.47–0.98); OR = 0.66 (95% CI: 0.45–0.95), respectively]. Furthermore, a higher healthy lifestyle score (score = 3) was also associated with a reduced risk of cognitive impairment [OR = 0.59 (95% CI: 0.34–0.98)], compared to ≤ 1 healthy lifestyle factor.

3.3. Subgroup analyses

Subgroup analyses were conducted stratified by age, gender, marital status, education level, family income monthly and co-living status (Supplementary Tables S1-S6, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=114*). The positive associations of regular physical activity and optimal night sleep duration with MMSE score were mainly observed among participants aged ≥ 70 years [β = 0.21 (95% CI: 0.05–0.37) and β = 0.24 (95% CI: 0.09–0.39), respectively], whereas these associations were not significant among those aged < 70 years (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=114*). Among women, optimal night sleep duration was positively associated with higher MMSE scores [β = 0.18 (95% CI: 0.04–0.34), p = 0.014] (Supplementary Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=114*) and women with 3 healthy lifestyle factors had better MMSE score [β = 0.29 (95% CI: 0.04–0.55), p = 0.026] (Supplementary Table S2, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=114*).

When stratified by marital status, both regular physical activity and optimal night sleep duration were positively associated with MMSE scores among married participants (all p < 0.05, Supplementary Table S3, *https://www.globalhealthmedicine.com/site/*

Table 1. Characteristics of participants according to cognitive status

Variables	All participants	Cognitive impairment status		
		Yes	No	p^*
No	942	148	794	
Demographic factors				
Age (years old), median (IQR)	70.00 (67.00–74.00)	71.00 (68.00–75.00)	70.00 (67.00–73.00)	0.015
Males, *n* (%)	389 (41.30)	58 (39.19)	331 (41.69)	0.634
Marital status, *n* (%)				0.229
Single	156 (16.56)	30 (20.27)	126 (15.87)	
Married	786 (83.44)	118 (79.73)	668 (84.13)	
Education, *n* (%)				0.146
Primary school or below	381 (40.45)	69 (46.62)	312 (39.29)	
Junior or high school	533 (56.58)	77 (52.03)	456 (57.43)	
College or above	28 (2.97)	2 (1.35)	26 (3.27)	
Family income monthly (CNY), *n* (%)				< 0.001
< 5,000	194 (20.59)	53 (35.81)	141 (17.76)	
5,000–10,000	395 (41.93)	51 (34.46)	344 (43.32)	
10,001–20,000	261 (27.71)	36 (24.32)	225 (28.34)	
> 20,000	92 (9.77)	8 (5.41)	84 (10.58)	
Co-residence, *n* (%)				0.312
Living with family member	846 (89.81)	129 (87.16)	717 (90.30)	
Living alone	96 (10.19)	19 (12.84)	77 (9.70)	
Lifestyle factors				
Smoking status, *n* (%)				0.191
Never	661 (70.17)	112 (75.68)	549 (69.14)	
Current	143 (15.18)	21 (14.19)	122 (15.37)	
Former	138 (14.65)	15 (10.14)	123 (15.49)	
Alcohol drinking status, *n* (%)				0.794
Never	740 (78.56)	117 (79.05)	623 (78.46)	
Current	128 (13.59)	18 (12.16)	110 (13.85)	
Former	74 (7.86)	13 (8.78)	61 (7.68)	
Sleep duration (hours/night), median (IQR)	8.00 (7.00–9.00)	8.00 (7.00–9.00)	8.00 (7.00–8.50)	0.007
Regular physical activity, *n* (%)	622 (66.03)	84 (56.76)	538 (67.76)	0.012
Body mass index (BMI, kg/m^2), median (IQR)	24.50 (22.20–26.70)	25.20 (22.10–27.30)	24.50 (22.20–26.60)	0.172
Healthy lifestyle score, *n* (%)				0.029
0–1	170 (18.05)	32 (21.62)	138 (17.38)	
2	317 (33.65)	61 (41.22)	256 (32.24)	
3	329 (34.93)	38 (25.68)	291 (36.65)	
4–5	126 (13.37)	17 (11.48)	109 (13.73)	
Comorbidities				
No of comorbidities, *n* (%)				0.766
0	197 (20.91)	32 (21.62)	165 (20.78)	
1	273 (28.98)	46 (31.08)	227 (28.59)	
2	229 (24.31)	31 (20.95)	198 (24.94)	
3+	243 (25.80)	39 (26.35)	204 (25.69)	
Hypertension, *n* (%)	542 (57.54)	95 (64.19)	447 (56.30)	0.091
Stroke, *n* (%)	83 (8.81)	17 (11.49)	66 (8.31)	0.275
Diabetes, *n* (%)	209 (22.19)	35 (23.65)	174 (21.91)	0.720
CVD, *n* (%)	190 (20.17)	30 (20.27)	160 (20.15)	0.993
COPD, *n* (%)	26 (2.76)	3 (2.03)	23 (2.90)	0.749
Malignant tumors, *n* (%)	48 (5.10)	8 (5.41)	40 (5.04)	0.840
Liver diseases, *n* (%)	165 (17.52)	18 (12.16)	147 (18.51)	0.080
Kidney diseases, *n* (%)	48 (5.10)	6 (4.05)	42 (5.29)	0.672
MMSE score, median (IQR)	27.00 (24.00–29.00)	20.00 (16.00–23.00)	28.00 (26.00–29.00)	< 0.001

Note: Continuous variables were presented as the median (interquartile range, IQR), and categorical variables were presented as *n* (%). *Continuous variables were compared using the Kruskal-Wallis test, and categorical variables were compared by using Chi-square tests.

supplementaldata.html?ID=114). In analyses stratified by education, the positive associations of regular physical activity and night sleep duration with MMSE score remained significant in both the lower (primary school or below) and higher (junior high school or above) education groups (all p <0.05, Supplementary Table S4, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=114*).

When stratified by family income monthly, the beneficial associations of physical activity and optimal night sleep duration were observed only among participants with monthly income ≤ CNY 10,000 [β = 0.22 (95% CI: 0.06–0.38) and β = 0.17 (95% CI: 0.02–0.32), respectively], but not in the higher-income group [β = -0.13 (95% CI: -0.37–0.10) and β = 0.16 (95% CI: -0.05–0.37), respectively]. Similarly, the

Table 2. Association between healthy lifestyle factors and MMSE score

Lifestyles	*n*	Model 1		Model 2		Model 3	
		β (95% CI)	*p*	*β* (95% CI)	*p*	*β* (95% CI)	*p*
Normal BMI							
No	545	Ref		Ref		Ref	
Yes	397	0.12 (-0.01–0.25)	0.062	0.08 (-0.04–0.20)	0.176	0.09 (-0.03–0.21)	0.151
Never smoking							
No	281	Ref		Ref		Ref	
Yes	661	-0.10 (-0.30–0.10)	0.316	-0.07 (-0.25–0.12)	0.315	-0.07 (-0.26–0.11)	0.437
Light to Moderate alcohol intake							
No	863	Ref		Ref		Ref	
Yes	79	0.03 (-0.20–0.27)	0.806	0.03 (-0.20–0.25)	0.817	0.02 (-0.20–0.23)	0.855
Regular physical activity							
No	320	Ref		Ref		Ref	
Yes	622	0.30 (0.16–0.43)	< 0.001	0.22 (0.10–0.35)	0.037	0.21 (0.09–0.34)	0.001
Optimal night sleep duration							
No	420	Ref		Ref		Ref	
Yes	522	0.17 (0.05–0.30)	< 0.001	0.15 (0.03–0.27)	0.001	0.15 (0.03–0.27)	0.016
Healthy lifestyle score							
0-1	170	Ref		Ref		-	
2	317	-0.06 (-0.13–0.24)	0.537	-0.01 (-0.18–0.17)	0.975	-	-
3	329	0.35 (0.17–0.54)	< 0.001	0.26 (0.08–0.44)	0.004	-	-
4-5	126	0.34 (0.11–0.57)	0.003	0.25 (0.04–0.47)	0.021	-	-
P_{trend}			< 0.001		< 0.001		

Note: MMSE scores were standardized (Z-score). Multiple linear regression models were used to impute the *β* (95% CI), with adjustment for age, gender (model 1); further adjusted for marital status, education level, family income, co-residence status and the number of comorbidities (model 2); and further adjusted for the other four lifestyles when evaluating each lifestyle factor in the regression models (model 3).

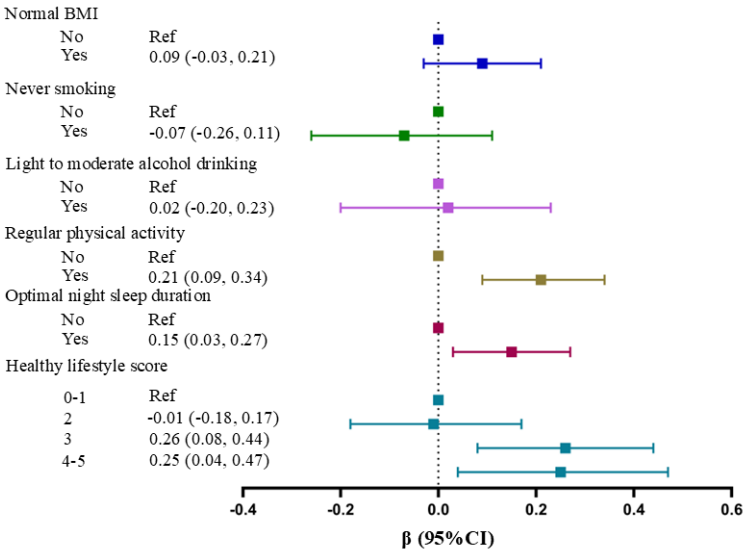

Figure 1. The associations between healthy lifestyle factors and MMSE score. Note: Multiple linear regression models were used to impute the *β* (95% CI), with adjustment for age, gender, marital status, education level, family income, co-residence status and the number of comorbidities and the other four lifestyle factors when evaluating each lifestyle factor in the regression models.

overall healthy lifestyle score was positively associated with MMSE score in the low-income group [*β* = 0.29 (95% CI: 0.07–0.51) for score = 3; *β* = 0.32 (95% CI: 0.04–0.59) for 4–5 healthy lifestyle factors], whereas no significant associations were found in those with higher income (Supplementary Table S5, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=114*).

Finally, according to co-residence status, optimal night sleep duration was associated with higher MMSE scores in participants living with family [*β* = 0.14 (95% CI: 0.02–0.27), *p* = 0.022], while other lifestyle factors showed similar trends across the two groups (Supplementary Table S6, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=114*).

Table 3. Association between lifestyle factors and cognitive impairment

Lifestyles	*n*	Model 1		Model 2		Model 3	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Normal BMI							
No	545	Ref		Ref		Ref	
Yes	397	0.93 (0.66–1.33)	0.691	0.94 (0.65–1.37)	0.772	0.96 (0.65–1.40)	0.818
Never smoking							
No	281	Ref		Ref		Ref	
Yes	661	1.54 (0.89–2.66)	0.132	1.54 (0.87–2.71)	0.137	1.60 (0.89–2.85)	0.110
Light to Moderate alcohol intake							
No	863	Ref		Ref		Ref	
Yes	79	0.92 (0.44–1.80)	0.824	0.92 (0.43–1.82)	0.814	0.98 (0.46–1.95)	0.954
Regular physical activity							
No	320	Ref		Ref		Ref	
Yes	622	0.66 (0.46–0.94)	0.023	0.68 (0.47–0.98)	0.042	0.69 (0.47–0.98)	0.049
Optimal night sleep duration (hours/night)							
No	420	Ref		Ref		Ref	
Yes	522	0.63 (0.44–0.89)	0.016	0.64 (0.44–0.93)	0.018	0.66 (0.45–0.95)	0.024
Healthy lifestyle score							
0-1	170	Ref		Ref		-	
2	317	1.01 (0.62–1.66)	0.963	1.12 (0.68–1.87)	0.644	-	-
3	329	0.55 (0.32–0.95)	0.029	0.59 (0.34–0.98)	0.049	-	-
4-5	126	0.67 (0.34–1.28)	0.230	0.72 (0.36–1.40)	0.345	-	-
P_{trend}			0.023		0.044		

Note: Multiple logistic regression models were used to impute the OR (95% CI), with adjustment for age, gender (model 1); further adjusted for marital status, education level, family income, co-residence status and the number of comorbidities (model 2); and further adjusted for the other four lifestyles when evaluating each lifestyle factor in the regression models (model 3).

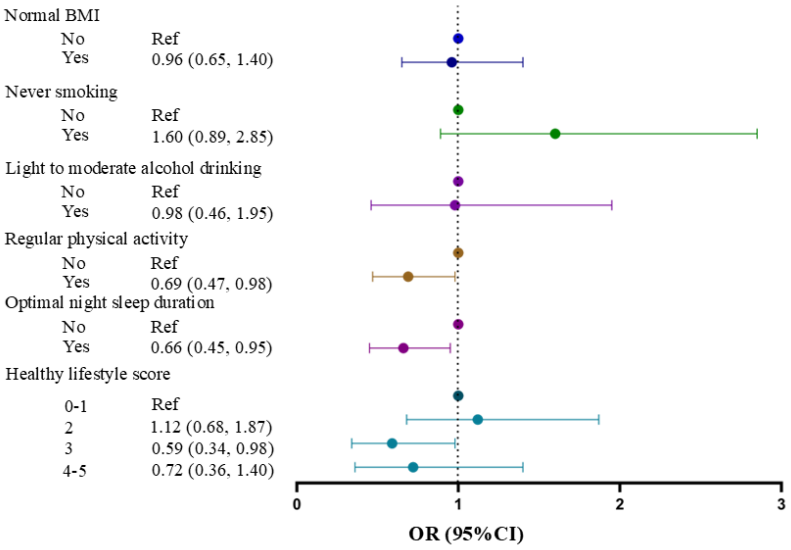

Figure 2. The associations between healthy lifestyle factors and cognitive impairment status. Note: Multiple logistic regression models were used to impute the OR (95% CI), with adjustment for age, gender, marital status, education level, family income, co-residence status and the number of comorbidities and the other four lifestyles when evaluating each lifestyle factor in the regression models.

4. Discussion

In this community-based cross-sectional study of older adults in Shanghai, we found that two healthy lifestyle factors (regular physical activity and optimal night sleep duration) were significantly associated with better cognitive function. Moreover, a higher overall healthy lifestyle score, defined from five healthy lifestyle components, was positively associated with MMSE scores in a dose–response manner. These findings provide population-based evidence from China supporting the importance of maintaining multiple healthy behaviors to promote cognitive health.

We found that regular physical activity was associated with higher MMSE scores and lower risk of cognitive impairment among Chinese elders [β = 0.21

(95% CI: 0.09–0.34), and OR = 0.69 (95% CI: 0.47–0.98)], consistent with previous evidence. The Lancet Commission on Dementia Prevention, Intervention, and Care identified physical inactivity as one of the major modifiable risk factors for dementia (*23*). A meta-analysis of thirty-seven cohort studies demonstrated that higher levels of physical activity were associated with a 35% reduced risk of cognitive decline [RR = 0.65 (95% CI: 0.55–0.76)] (*24*). Shanghai is a highly urbanized city with abundant community facilities and widespread health promotion programs for elders. Regular participation in group exercises such as tai chi and square dancing is common, contributing to higher physical activity and social engagement levels. In our sample, 66.03% of elders reported engaging in regular physical activity, whereas a nationally representative survey based on the China Family Panel Studies reported that only 39.1% of Chinese older adults participated in regular exercise (*25*). This higher prevalence of physical activity in Shanghai may partly explain the stronger association between physical activity and cognitive function observed in our study. Mechanistically, physical activity may enhance gray matter volume in the frontal and hippocampal regions and slow cortical thinning in memory-related areas such as the entorhinal cortex and medial parietal regions, thereby supporting better cognitive performance (*26,27*).

The present study showed that optimal night sleep duration of 7–9 hours was related to higher MMSE score [β = 0.15 (95% CI: 0.03–0.27)] and a lower risk of cognitive impairment [OR = 0.66 (95% CI: 0.45–0.95)]. These findings align with previous studies showing a U-shaped association between sleep duration and cognitive function. Ma *et al.* demonstrated that insufficient sleep (≤ 4 hours/night) or excessive (≥ 10 hours/night) were related to cognitive function decline among 20,065 participants from the English and Chinese cohort study (*28*). Similarly, Li *et al.* observed that sleep duration had an inverted U shape with cognitive scores, and both short (< 6 hours/day) and long sleep durations (> 8 hours/day) were associated with lower cognitive scores among 10,768 middle-aged and elder adults in the China Health and Retirement Longitudinal Study (*29*). Biologically, inadequate sleep may accelerate cortical thinning in frontotemporal regions, while excessive sleep has been associated with increased systemic inflammation, both of which can contribute to cognitive impairment (*30*).

However, in this study, no significant associations were observed for the other three lifestyle factors — nonsmoking, light to moderate alcohol drinking, and normal BMI, which differ from some previous reports (*31-34*). Participants recruited through community health examinations may represent a more health-conscious subgroup with fewer smokers and drinkers as well as healthier BMI. In addition, drinking in China is often embedded in social or festive contexts, making it difficult to isolate its biological effect on cognition from psychosocial influences. The relatively narrow BMI range in our sample and the inability of BMI to capture muscle mass or body composition may further obscure potential associations.

In our study, participants with 3 and 4–5 healthy lifestyle factors had significantly higher MMSE scores compared with those with one or none [β = 0.26 (95% CI: 0.08–0.44) and β = 0.25 (95% CI: 0.04–0.47), respectively]. However, only participants with 3 healthy lifestyle factors showed a significantly lower risk of cognitive impairment [OR = 0.59 (95% CI: 0.34–0.98)], while the association was not significant among those with 4–5 factors [OR = 0.72 (95% CI: 0.36–1.40)]. The lack of significance in the highest group may be due to the limited sample size. This finding is consistent with several large-scale studies. Wang *et al.* found that compared with subjects with one or none healthy behavior, those with 3 or 4 healthy lifestyle behaviors had 0.07 standard deviation higher cognitive Z-score in National Health and Nutrition Examination Survey 2011–2014 (*12*). Similarly, a study among African Americans and European American adults, showed that adherence to 4–5 healthy lifestyle factors was associated with a slower cognitive decline of 0.023–0.044 units/year (*35*). In a large European cohort study of 196,383 participants, Lourida *et al.* observed that participants with 4 healthy lifestyle factors exhibited a lower risk of Alzheimer's disease [HR = 0.64 (95% CI: 0.43–0.97)] compared to those without any healthy lifestyle factors (*36*). Together, these findings emphasize that adopting multiple healthy behaviors may be crucial for maintaining cognitive health and is positively associated with better cognitive function in older adults.

Subgroup analyses revealed that the associations between healthy lifestyle factors and cognitive function were more pronounced among elders, women and individuals with lower income. These findings suggest that sociodemographic context may modify the effects of healthy behaviors on cognition. Therefore, lifestyle-based cognitive health promotion in Shanghai should prioritize older adults with lower socioeconomic status.

The present study had several strengths. In this study, we conducted a comprehensive investigation into the relationships between healthy lifestyle factors and cognitive impairment. However, the study has several limitations to be addressed. First, this study used a convenience sample of elders who participated in a community-based physical examination program, which may have attracted individuals who were more health-conscious or in better health than the general elders. Therefore, selection bias cannot be completely ruled out, and the findings should be interpreted with caution when generalizing to other populations. Second, lifestyle behaviors, such as sleep duration or physical activity frequency, were self-reported and may be affected by recall bias or misreporting, although the interviews were

conducted by trained personnel following a standardized protocol. Third, though the definition of regular physical activity is consistent with previous Chinese community-based studies (*19*), this self-reported measure may not fully capture non-exercise physical activity. Fourth, although we included healthy lifestyle factors based on the previous evidence (*21,22*), some important factors, such as dietary and psychological issues were not considered in the present study. Moreover, although key chronic diseases such as hypertension, diabetes and stroke, *etc*. were included in the comorbidity categories, the variable remained relatively coarse and might not fully capture disease severity. Therefore, residual confounding cannot be entirely ruled out. In addition, the results of subgroup analyses may still be limited by smaller sample sizes. Therefore, the results should be interpreted with caution.

In conclusion, our findings suggest that adhering to a greater number of healthy lifestyle factors was associated with better cognitive function among older adults in Shanghai. Particularly, regular physical activity and adequate night sleep duration were positively correlated with cognitive performance. Although causal relationships cannot be established from this cross-sectional design, these associations highlight the potential importance of healthy lifestyle behaviors for maintaining cognitive health in aging populations.

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

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BRIEF REPORT
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Survey and analysis of sleep status among community-dwelling elderly diabetics: A cross-sectional study in Shanghai, China

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Abstract: Sleep is crucial to maintaining physiological stability and exhibits a bidirectional relationship with metabolic health. This study used random sampling to investigate sleep status and factors influencing it among 585 community-dwelling elderly diabetics (age ≥ 60 years) in Shanghai (April–August 2025). Data were collected through a self-designed general questionnaire, the Athens Insomnia Scale (AIS), and clinical biochemical tests. Univariate analysis and binary logistic regression were used to identify influencing factors. Results indicated a median AIS score of 4.0 (3.0, 6.0), with 26.84% of patients (157/585) experiencing sleep problems. Univariate analysis revealed significant correlations between sleep quality and sex, level of education, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), urine leukocytes, urine specific gravity, hypertension, the number of comorbidities, and diabetic peripheral neuropathy ($p < 0.05$ for all). Binary logistic regression analysis identified that being female (OR = 1.778, 95% CI: 1.115–2.836, $p = 0.016$), having a college degree or above (OR = 2.820, 95% CI: 1.305–6.092, $p = 0.008$), elevated glycated hemoglobin (OR = 1.460, 95% CI: 1.221–1.745, $p < 0.001$), elevated fasting blood glucose (OR = 1.490, 95% CI: 1.327–1.673, $p < 0.001$), and diabetic peripheral neuropathy (OR = 1.713, 95% CI: 1.046–2.804, $p = 0.032$) were independent risk factors for sleep disorders. Implementing individualized, multidimensional management for these high-risk populations is crucial to enhancing the overall effectiveness of diabetes prevention and control.

***Keywords*:** elderly, diabetes mellitus, sleep quality, insomnia, influencing factors

1. Introduction

As aging progresses, by 2023 China' s population age ≥ 60 years accounted for 20.83% (over 290 million) of the total population (*1*), and 30.2% of these elderly have diabetes (*2*), making China the global leader in the number of elderly diabetics (*3*). Health management is critical for chronic disease control. Sleep, a key factor in maintaining physiological stability, has a bidirectional regulatory association with metabolic health (*4*). The prevalence of sleep disorders in the elderly ranges from 9.67% to 81.1% (*5*), and diabetics often have more severe sleep issues — potentially tied to more nocturia, pain, thermal discomfort, and habitual snoring (*6*). In elderly diabetics, sleep disorders correlate with lower insulin sensitivity, poorer glucose metabolism, and higher risks of cardiovascular/neurodegenerative diseases, cognitive impairment, and all-cause mortality (*7*).

The 2022 consensus by the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) emphasized sleep health as central to diabetes lifestyle management (*8*). While existing studies have examined elderly diabetics' sleep, findings are inconsistent, with limited targeted data on communities in Shanghai. Additionally, few studies have addressed insomnia-related risk factors in this group, and domestic research largely summarizes specific clinical issues.

Thus, the current study seeks to ascertain sleep disorder prevalence and factors influencing it in this population, providing guidance for improved prevention and development of clinical care strategies.

2. Patients and Methods

2.1. Study population and sampling method

Using completely randomized sampling, elderly diabetics who underwent health examinations at the Sijing Town Community Healthcare Center in Songjiang District,

Shanghai, between April and August 2025 were selected as study subjects.

Inclusion criteria: *i*) Age ≥ 60 years; *ii*) Diagnosed with diabetes meeting the 1999 WHO diagnostic criteria for diabetes; *iii*) Permanent residence in this community for ≥ 6 months; *iv*) Being conscious, free of mental illness or cognitive impairment, and capable of communication; *v*) Voluntarily participating in the study and signing an informed consent form. Exclusion criteria: Use of sleep-related medications.

This study used sleep disorder prevalence as the outcome measure. Referencing prior research results of $P = 0.46$ (*9*), with a two-tailed $\alpha = 0.05$, $Z_{1-\alpha/2} = 1.96$, $d = 0.1p$, the sample size formula $N = Z^2_{1-\alpha/2} P(1-P) / d^2$ yielded a minimum sample size of 451 patients. Considering questionnaire response rates, the final plan included 480 patients. A total of 598 questionnaires were distributed, with 585 valid responses received, resulting in a response rate of 97.83% (Figure 1).

This study was approved by this hospital's Ethics Review Committee (2023K081) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. Survey content and research tools

2.2.1. General information questionnaire

The questionnaire was independently designed by the research team based on a literature review and clinical practice. The survey content encompasses three dimensions: *i*) Demographic and sociological characteristics: sex, age, and level of education; *ii*) Clinical diabetes data: duration of disease, family history, comorbidities, and diabetic complications; and *iii*) Health-related behaviors: smoking history, drinking history, and exercise habits.

2.2.2. Athens Insomnia Scale

The Athens Insomnia Scale (AIS), developed by the Ohio State University College of Medicine (*10*), was used to assess patients' sleep quality. This 8-item scale measures difficulty falling asleep, nighttime awakenings, early morning awakenings, insufficient total sleep time, poor sleep quality, daytime fatigue, daytime functional impairment, and daytime sleepiness. Each item is scored

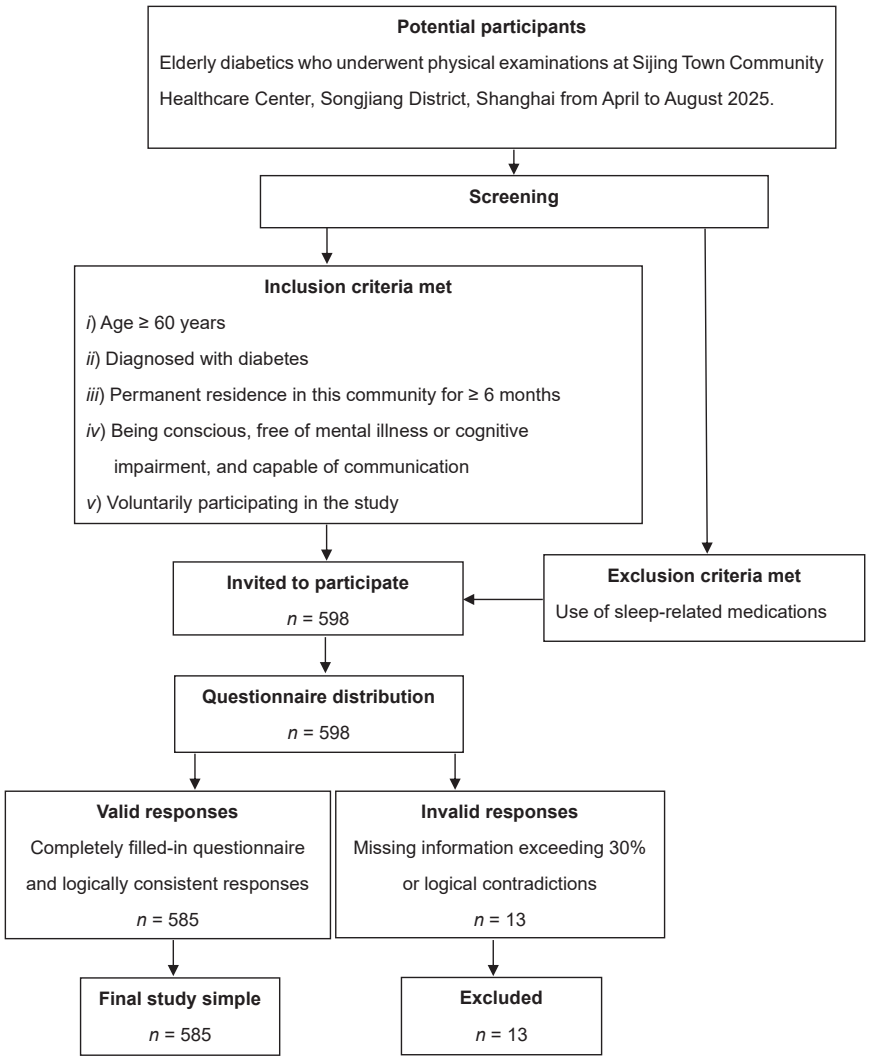

Figure 1. Participant flow diagram.

from 0 to 3 points (0 = no problem, 3 = severe problem), yielding a total score ranging from 0 to 24 points. Sleep quality status is categorized into four levels based on total score: no clinical insomnia (0–5 points), mild insomnia (6–9 points), moderate insomnia (10–15 points), and severe insomnia (≥ 16 points). The scale demonstrates good reliability and validity, with a Cronbach's α of 0.83.

2.2.3. Clinical and biochemical indicator testing

All indicator tests were conducted on the survey day by a professional medical team from the community health service center, including measuring height, weight, and blood pressure; calculating BMI; collecting blood after a 10-hour fast to measure glycated hemoglobin (HbA1c), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C); and collecting 24-hour urine specimens for measurement of urinary leukocytes, protein, glucose, ketones, pH, and specific gravity.

2.3. Method of data collection

Data were collected between April and June 2025 by a uniformly trained team (3 endocrinologists and 5 diabetes-specialized nurses) in three steps: *i*) On-site questionnaire survey: Patients were informed of study details face-to-face; after consent was obtained, and standardized guidance was provided to aid in completion; *ii*) Measurement of clinical indicators: Relevant indices were measured in designated rooms; *iii*) Quality control: On-site questionnaire checks ensured missing/inconsistent entries were verified and supplemented promptly.

2.4. Statistical methods

All data were entered into two databases and cross-checked by two operators to ensure accuracy. Data analysis was performed using the statistical software SPSS 31.0. Count data are expressed as patients (%). Comparisons were made using the chi-square χ^2 test or Fisher's exact probability test. For continuous data, normality and homogeneity of variance were first assessed. Data following a normal distribution were expressed as $\bar{\mathbf{x}} \pm \mathbf{s}$, and intergroup differences were compared using the independent samples *t*-test. Non-normally distributed data were expressed as M (P25, P75) and compared using the Mann-Whitney *U* test. Binary logistic regression analysis was performed to examine factors influencing sleep quality. $P < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Sleep status among community-dwelling elderly diabetics

Among 585 community-dwelling elderly diabetics, the median AIS score was 4.0 (3.0, 6.0). Using an AIS score > 6 as the cutoff, 157 elderly individuals (26.84%) had poor sleep quality. Of these, 118 (20.17%) had mild insomnia, 36 (6.15%) had moderate insomnia, and 3 (0.51%) had severe insomnia. The most prevalent problems with sleep quality according to the 8 items of the AIS were nocturnal awakenings (68.20%), followed by difficulty falling asleep (57.30%), early morning awakening (42.0%), daytime fatigue (40.10%), insufficient total sleep time (28.0%), poor sleep quality (26.8%), daytime functional impairment (25.5%), and daytime sleepiness (23.6%).

3.2. Univariate analysis of factors affecting sleep quality in elderly diabetics

Patients were divided into two groups: the good sleep quality group (AIS < 6 points) and the poor sleep quality group (AIS ≥ 6 points). Univariate analysis identified 9 factors significantly associated with sleep quality ($p < 0.05$), including sex, level of education, glycated hemoglobin, fasting blood glucose, history of hypertension, number of comorbidities, diabetic peripheral neuropathy, urinary leukocytes, and urine specific gravity (Table 1).

3.3. Multivariate analysis of factors affecting sleep quality in elderly diabetics

With "poor sleep quality (Yes = 1, No = 0)" serving as the dependent variable and the 9 statistically significant factors from univariate analysis serving as independent variables, multivariate logistic regression analysis was performed to control for confounding effects. Results indicated that sex, level of education, glycated hemoglobin, fasting blood glucose, and diabetic neuropathy were independent risk factors affecting sleep quality ($p < 0.05$) (Table 2). Results of multicollinearity testing indicated that among the 5 factors included, the tolerance values ranged from 0.952 to 0.990, and the variance inflation factors (VIFs) ranged from 1.010 to 1.051, indicating the absence of multicollinearity.

3.4. Sleep disorders in elderly diabetics: Prevalence, risk factors, and implications for community management

This study found that the prevalence of sleep disorders among community-dwelling elderly diabetics was 26.84%. This is comparable to the 30.0% reported in the 2019–2020 national survey of 12,369 urban/rural community residents age ≥ 60 years (*11*) but is significantly higher than the 19% in the general adult population (*12*), indicating that elderly diabetics remain a high-risk group for sleep disorders. The most prevalent problem was nighttime awakenings (57.3%), followed by difficulty falling asleep and early morning awakening,

Table 1. Univariate analysis of factors affecting sleep quality in elderly diabetics

Characteristics	Good sleep quality group (n = 428)	Poor sleep quality group (n = 157)	t/χ^2/Z	p
Sex (%)			11.257	< 0.001
Male	236 (55.14)	62 (39.49)		
Female	192 (44.86)	95 (60.51)		
Age (years), (%)			-0.324	0.746
60–69	189 (44.16)	66 (42.04)		
70–79	206 (48.13)	80 (50.96)		
≥ 80	33 (7.71)	11 (7.01)		
BMI (kg/m^2), (%)			-1.185	0.236
< 18.5	7 (1.64)	7 (4.46)		
18.5–23.9	167 (39.02)	64 (40.76)		
24.0–27.9	193 (45.09)	66 (42.04)		
≥ 28.0	61 (14.25)	20 (12.74)		
Level of education (%)			-2.677	0.007
Primary school or below	137 (32.01)	34 (21.66)		
Junior high school	143 (33.41)	55 (35.03)		
Senior high school	111 (25.93)	46 (29.30)		
College degree or above	37 (8.64)	22 (14.01)		
Disease duration (years), M (P_{25}, P_{75})	8 (4, 15)	10 (3,15)	-0.356	0.722
Smoking history (%)	88 (20.56)	22 (14.01)	3.226	0.072
Drinking history (%)	90 (21.03)	24 (15.29)	2.413	0.120
Depression (%)	1 (0.23)	2 (1.27)	2.436	0.119
Anxiety (%)	18 (4.21)	8 (5.10)	0.214	0.643
Hypertension (%)	260 (60.75)	111 (70.70)	4.905	0.027
Coronary heart disease (%)	62 (14.49)	31 (19.75)	2.376	0.123
Hyperlipidemia (%)	116 (27.10)	49 (31.21)	0.957	0.328
History of stroke (%)	43 (10.05)	20 (12.74)	0.866	0.352
COPD (%)	8 (1.87)	4 (2.55)	0.263	0.608
Number of comorbidities (patients, %)			-2.118	0.034
0–1	297 (69.39)	94 (59.87)		
2	93 (21.73)	45 (28.66)		
≥ 3	38 (8.88)	18 (11.46)		
Diabetic complications (%)				
Retinopathy	247 (57.71)	88 (56.05)	0.129	0.719
Neuropathy	83 (19.39)	44 (28.03)	5.037	0.025
Vascular disease	82 (19.16)	24 (15.29)	1.161	0.281
Diabetic foot	7 (1.64)	1 (0.62)	0.849	0.357
Exercise habits (days/week), (%)			-1.117	0.264
< 1	92 (21.50)	27 (17.20)		
1–3	27 (6.31)	25 (15.92)		
4–6	19 (4.44)	11 (7.01)		
7	290 (67.76)	94 (59.87)		
Glycated hemoglobin (%), M (P_{25}, P_{75})	6.60 (6.00, 7.30)	7.00 (6.35, 8.70)	-7.884	< 0.001
Fasting blood glucose (mmol/L), M (P_{25}, P_{75})	7.18 (6.25, 8.09)	8.61 (7.10,10.77)	-4.718	< 0.001
TG	1.43 (1.02,1.99)	1.40 (1.05, 2.05)	-0.155	0.877
TC	4.82 (4.09,5.70)	4.80 (4.20, 5.39)	-0.355	0.723
HDL-C	1.35 (1.13,1.56)	1.32 (1.13, 1.59)	-0.132	0.895
LDL-C	2.93 ± 1.04	2.90 ± 0.93	-1.203	0.229
Urine leukocytes (%)			-2.479	0.013
Negative (-)	324 (75.70)	104 (66.24)		
Weakly positive (±)	37 (8.64)	13 (8.28)		
Positive (+-++++)	67 (15.65)	40 (25.48)		
Urine protein (%)			-0.645	0.519
Negative (-)	345 (80.61)	131 (83.44)		
Weakly positive (±)	41 (9.60)	9 (5.73)		
Positive (+-++++)	42 (9.81)	17 (10.83)		
Urine glucose (%)			-0.323	0.747
Negative (-)	283 (66.12)	107 (68.15)		
Weakly positive (±)	11 (25.70)	1 (0.64)		
Positive (+-++++)	134 (31.31)	49 (31.21)		
Urine ketone bodies (%)			-0.638	0.523
Negative (-)	403 (94.16)	150 (95.54)		
Weakly positive (±)	7 (1.64)	1 (0.64)		
Positive (+-++++)	17 (3.97)	6 (3.82)		
Urine pH value, M (P_{25}, P_{75})	5.0 (5.0, 5.50)	5.0 (5.0, 5.50)	-1.203	0.229
Urine specific gravity, M (P_{25}, P_{75})	1.02 (1.01, 1.03)	1.02 (1.02, 1.03)	-2.603	0.009

Count data are expressed as patients (%). *Abbreviations:* BMI, body mass index; COPD, chronic obstructive pulmonary disease; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Table 2. Multivariate analysis of factors affecting sleep quality in elderly diabetics

Risk factors	β	SE	Wald $\chi 2$	p	OR	95% CI
Constant	-35.226	15.427	5.214	0.022	—	—
Sex (female)	0.576	0.238	5.846	0.016	1.778	1.115–2.836
Level of education (college degree or above)	1.037	0.393	6.956	0.008	2.820	1.305–6.092
Glycated hemoglobin	0.378	0.091	17.212	< 0.001	1.460	1.221–1.745
Fasting blood glucose	0.399	0.059	45.584	< 0.001	1.490	1.327–1.673
Diabetic neuropathy	0.538	0.252	4.578	0.032	1.713	1.046–2.804

Independent variable coding: Sex: Male = 1, Female = 2; Level of education: Primary school or below = 1, Junior high school = 2, Senior high school = 3, College degree or above = 4; Concurrent diabetic neuropathy: Yes = 1, No = 0.

which is consistent with the findings of Wang *et al.* (*13*). The current study found that sleep disorders are closely associated with multiple independent risk factors, which are specified below.

This study identified being female (OR = 1.778, $p = 0.016$) as an independent factor associated with a higher risk of a sleep disorder. The higher prevalence in elderly women aligns with the findings of Lu *et al.* (*14*) and is possibly linked to a postmenopausal decline in estrogen. An estrogen deficiency is associated with reduced nocturnal melatonin secretion, circadian rhythm disruption, and synergistic interactions with insulin resistance (*15-17*). Additionally, elderly women with diabetes may face greater emotional fluctuations, physical symptoms, and family burdens, which correlate with higher AIS scores (*18*). This finding overcomes the limitation of existing studies that focus only on physiological mechanisms, suggesting that medical personnel should enhance the management of elderly female patients from multiple perspectives – such as conducting regular quarterly screenings and organizing "female mutual aid groups."

A higher level of education (college or above) (OR = 2.820, $p = 0.008$) correlating with elevated risk echoes prior studies (*19*). While better-educated patients have greater awareness of diabetes-sleep comorbidity, this may lead to excessive worry about glycemic control and prognosis, which is associated with prolonged mental tension, increased nocturnal sympathetic activity, and shallower sleep (*20*). Post-retirement social role shifts (from active to static) may also trigger emotional dysregulation linked to sleep disorders. This conclusion contradicts the finding of some studies that "the higher the level of education, the better the sleep quality." Level of education may be associated with factors such as regional economic conditions and lifestyle, and it also fills the research gap regarding sleep risks among highly educated elderly diabetics in economically developed cities. In clinical practice, health education can be conducted through themed lectures to promote the self-management of diseases among elderly patients.

Elevated glycated hemoglobin (OR = 1.460, $p < 0.001$) and poor fasting blood glucose control (OR = 1.490, $p < 0.001$) were independently associated with sleep disorders. Chronic hyperglycemia is linked to advanced glycation end product (AGE) deposition in cerebral microvessels, which correlates with cerebral hypoperfusion and sleep regulatory center impairment (*21*); it also correlates with skin itching and nocturia, directly disrupting sleep continuity (*22*). Conversely, sleep disorders may act as a stressor correlating with neuroendocrine dysregulation (*e.g.*, delayed growth hormone secretion and heightened cortisol response), forming a bidirectional association with blood glucose control - consistent with the findings of Wu *et al.* (*23*) regarding sleep disturbances and the dawn phenomenon. This indicates that well-controlled blood glucose remains the crux of disease management for elderly diabetics, as it can delay the progression of pathological changes at the source.

Elderly diabetics with peripheral neuropathy had a 1.713-fold higher risk of sleep disorders ($p = 0.032$), which is consistent with studies reporting 41.9–96.79% poor sleep quality in neuropathic patients (*24-26*). This may correlate with neuropathic pain (affecting 25% of neuropathic patients), which is more pronounced at night and directly linked to sleep disruption (*27*); a bidirectional association between frequent awakenings and increased pain sensitivity may also exist (*28*). Additionally, restless leg syndrome-like symptoms and autonomic nervous system impairment (abnormal sweating and temperature regulation) may further disrupt sleep (*22,29*). This indicates that community medical personnel may need to conduct routine specialized screening for peripheral neuropathy among elderly diabetics, with a focus on those who have sleep disorders, and implement linked interventions for sleep and neuropathy to improve treatment outcomes.

Univariate analysis indicated that both positive urine leukocytes ($p < 0.05$) and abnormal urine specific gravity ($p < 0.05$) were associated with sleep quality; although neither indicator was included in the multivariate model, the aforementioned findings provide a new perspective for exploring the comorbidity mechanism between diabetes and sleep disorders, which can be further verified through prospective studies in the future.

3.5. Strengths and limitations of this study

The innovations of this study are: *i*) providing region-

specific data on sleep status among community-dwelling elderly diabetics in Shanghai, offering a direct reference for regional prevention; *ii*) analyzing sleep disorder mechanisms from a multidimensional perspective, establishing theoretical foundations for formulating integrated intervention strategies. Limitations include: *i*) as a cross-sectional study, it only identifies associations rather than definitive causal relationships; *ii*) sleep assessment relied on 1-month self-reported recall, which may introduce recall bias. Future large-scale prospective studies are warranted to validate these findings and clarify causal relationships.

4. Conclusion

This study found that the prevalence of sleep disorders among elderly diabetics in communities in Shanghai is not negligible. In the future, the rate of screening for and intervention with respect to relevant risk factors needs to be increased to improve the effectiveness of comprehensive management. Additionally, prospective studies could be conducted to further verify the relevant mechanisms.

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Responding to a super-aged society: A community-based model for early frailty detection using AI and smart meter data – Insights from Japan

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Abstract: Japan, at the forefront of a super-aged society where individuals age 65 and older constitute 29.3% of the total population, faces an urgent need for early detection of and intervention in reversible geriatric syndromes known as frailty to prevent older adults from becoming dependent on long-term care. One notable innovation is the frailty detection service "e-Frail Navi", which began operational in 2023 following pilot testing since 2020. This service analyzes household electricity consumption patterns using AI, sending alerts to municipal welfare departments when unusual behavioral patterns are detected, enabling early intervention through professional home visits. A groundbreaking community-based integrated care model leveraging digital technology, 29 municipalities have adopted it as of June 2025. However, several challenges remain regarding the use of such technology, including issues with the accuracy of frailty assessment, ethical and legal concerns, and the potential barriers to use posed by disparities in digital literacy and economic circumstances.

***Keywords*:** super-aged society, frailty, screening, AI system

1. Introduction

Population aging has become a serious global issue. According to reports from the World Health Organization (WHO), by 2030, one in six people worldwide will be age 60 years or older; by 2050, the global population age 60 years or older will double, reaching 2.1 billion; and the population age 80 years or older is estimated to triple between 2020 and 2050, reaching 426 million (*1*). Japan is also experiencing an unprecedented demographic shift. According to the annual report on an Aging Society published by the Cabinet Office in 2025 (*2*), the population age 65 and above has reached 36.24 million, accounting for 29.3% of the total population. This percentage is projected to rise to 30.8% by 2030. Amidst this rapid demographic shift toward an aged society, the health of older adults has become an increasingly pressing concern.

Frailty is a clinical syndrome in older adults and is characterized by progressive decline in physiological reserve and increased vulnerability to external stressors. It results in a heightened risk of postoperative complications, higher hospitalization rates, a longer duration of hospitalization each year, and increased mortality, marking it as a significant public health concern (*3,4*). According to a meta-analysis, the global prevalence of frailty among community-dwelling older adults ranges from 12% to 24%, based on data from 1,755,497 participants across 62 countries and regions (*5*). A Japanese epidemiological study (*6*) has reported that the prevalence of frailty among older adults age 65 and above is 8.7%, while approximately 40.8% are classified as prefrail. This indicates that nearly half of the older population in Japan faces health risks associated with frailty. However, frailty is influenced by a wide range of factors. In addition, frailty is a serious concern across all regions of Japan, as shown in Figure 1. According to one review, over 30 different factors have been identified as contributing to its development (*7*). That said, a reassuring fact is that frailty is a dynamic and reversible geriatric syndrome that lies between self-reliance and the need for care and is reversible. Reasonable preventive interventions can help older adults resume living independently (*8*).

How to identify frailty more accurately has become an urgent priority worldwide. There is no established gold standard for frailty screening globally. The most direct and effective tool for assessing frailty is the Frailty Screening Tool, but since there is no globally recognized gold standard, each country has adopted its own

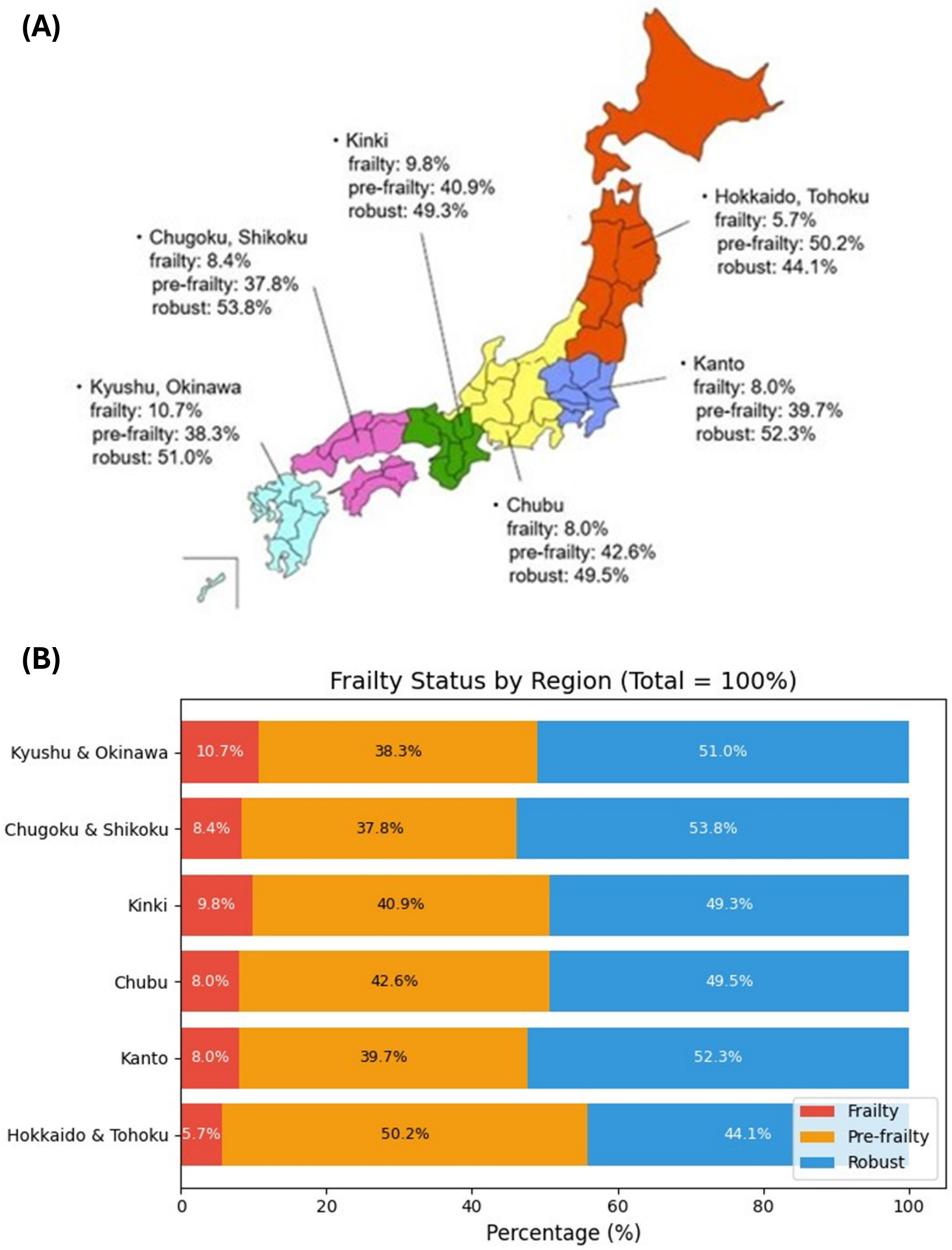

Figure 1. Frailty status by region in Japan. (A) The prevalence of frailty by region; **(B)** The breakdown for each region. *Data source*: *https://www.tmghig.jp/research/release/2020/0903.html*.

evaluation scale for domestic use (*9*).

In Japan, two primary methods are used to evaluate frailty: One is the Japanese version of the Cardiovascular Health Study frailty criteria (J-CHS) (*10*), which were developed based on Fried *et al*.'s phenotype model and the Cardiovascular Health Study (CHS) criteria, and which were revised in 2020. Another approach utilizes the Frailty Index (FI) based on the accumulation deficit model proposed by Rockwood *et al*. (*11*).

Conventional frailty assessments often relied on face-to-face, time-limited, subjective screening methods. This has led to concerns about difficulty in accurately evaluating individuals' daily living situations (*12*). Therefore, innovative, scalable, and non-intrusive methods of monitoring are needed to bridge the gap.

2. Technological innovations in Japan: Using electricity data and AI to prevent frailty

Japan has adopted significant measures to address the limitation of conventional frailty assessment methods through technological innovation. The integration of household electricity usage data with artificial intelligence (AI) algorithms has emerged as a promising approach for early detection and monitoring of frailty (*13*). As shown in Figure 2, one pioneering effort in this field is "e-Frail Navi", a frailty detection service developed by Chubu Electric Power and data science company JDSC since 2020 and officially launched in April 2023.

The frailty detection service "e-Frail Navi"

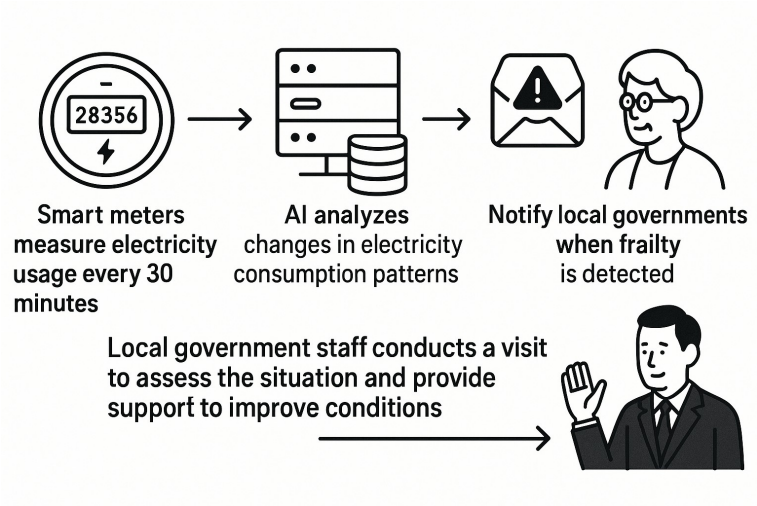

Figure 2. Structure of the frailty detection service "e-Frail Navi". *Data source*: *https://business-development.chuden.co.jp/service/e-frailtynavi.*

collects anonymized power consumption data from smart meters in individual households, particularly focusing on single-person elderly households. By analyzing fluctuations in electricity usage over time — such as changes in appliance use, cooking times, or heating patterns — the AI algorithm can infer daily routines and detect deviations that may indicate early signs of physical or cognitive decline. For instance, a noticeable delay in morning electricity use could suggest delayed waking and may signal fatigue or depression. Similarly, decreased evening activity may signal social withdrawal or mobility issues. Reduced usage of kitchen appliances may reflect decreased appetite or difficulty preparing meals — both of which are associated with frailty. Importantly, this approach requires no active participation from the older adult and is thus suitable even for those with cognitive impairment or reluctance to use wearable technology. When behavioral anomalies are detected, alerts are sent to municipal welfare departments to enable early intervention. Several municipalities have already incorporated this system into their community-based integrated care networks. This technology aligns with national policy goals of promoting "aging in place", preventing the progression of frailty, and reducing unnecessary hospitalizations and long-term care facility placements.

The practical implementation of AI-powered frailty monitoring systems has opened up new pathways for the integration of digital tools into eldercare. Moving forward, such systems could go beyond detecting frailty to identifying other age-related risks, such as dementia. At the individual level, further technological advances are expected to enable AI to establish personalized behavioral baselines and gradually improve the sensitivity and specificity of its predictions over time. From a societal perspective, such systems could transform community-based care models by providing a comprehensive understanding of individuals' health status and facilitating the formulation of personalized care plans.

Moreover, in the context of an aging population and declining birthrate, AI technologies can help reduce the burden on human caregivers and alleviate workforce shortages in the healthcare sector while maintaining the quality of care. For families living far from their elderly relatives, timely updates on their condition can provide reassurance and peace of mind.

3. Global uses and challenges

Many countries are integrating AI in healthcare. In the United States, Medicare-supported initiatives have the potential to incorporate AI-powered monitoring technologies into home healthcare services (*14*). The United Kingdom's NHS Long Term Plan advocates for digital health monitoring for older adults (*15*), and Germany's Digital Health Act encourages the utilization of digital health applications (*16*). However, few of these programs have specifically focused on early detection of frailty. Japan's AI-powered frailty monitoring model provides a scalable template and serves as a valuable reference for other countries seeking to enhance preventive care for aging populations. As of fiscal year 2023, 3 municipalities had adopted the system, with 10 additional adoptions expected in 2024 and a further 27 projected for 2025 (*17,18*). Additionally, since August 2025, a pilot program has been conducted to test an app designed to provide personalized guidance and feedback in coordination with the service (*19*).

However, several challenges exist for global adoption of this approach. First, there are concerns about the accuracy of this system as a tool for early detection of frailty. While empirical studies have reported accuracy rates exceeding 80%, with 8 out of 11 individuals diagnosed with frailty showing improved health status (*17*), accuracy varies among municipalities from year

to year, indicating room for further improvement. As this technology is adopted in more regions and the volume of data increases, its accuracy and practical utility can be verified and improved. Second, ethical and legal considerations are crucial. Issues such as data privacy, informed consent, and algorithmic transparency must be addressed. According to a survey by Mizuho Research & Technology, as of February 2025, there were 800 eligible participants in the surveyed regions, with approximately 160 actual users (*20*). Public trust in AI systems can be enhanced through robust governance frameworks, community education, and participatory design approaches that involve elderly individuals and their families in the development process. Third, disparities in digital literacy and economic status may limit the adoption of these technologies among vulnerable populations. In low- and middle-income countries, infrastructure limitations such as unreliable electricity supply and a low rate of smart meter usage can be significant barriers to implementation. Finally, establishing a global consensus on ethical standards and data governance is essential for the responsible use of AI in health-related contexts. The WHO and other international health organization can play a key role in providing policy guidelines to ensure safety, equity, and effectiveness.

4. Conclusion

Frailty monitoring using power consumption data and AI represents a promising frontier in geriatric care. Japan's experience provides valuable insights into the practical implementation, benefits, and challenges of this innovative approach. Amidst the global trend of aging, scalable and non-intrusive monitoring technologies will become essential components to support preventive care, enable early intervention, and promote healthy aging. By fostering cross-sectoral collaboration and international exchanges of knowledge, these tools can contribute to more resilient and responsive eldercare systems worldwide.

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Prevalence and risk factors of tuberculosis among slum dwellers and unhoused individuals in Ho Chi Minh City, Vietnam: Insights from a pilot study

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Abstract: Tuberculosis is reported as highly prevalent among slum dwellers and unhoused individuals worldwide. We conducted a study to estimate the prevalence of tuberculosis among slum dwellers and unhoused individuals in Ho Chi Minh City, Vietnam, and identified risk factors. An interview and chest X-ray screening of 367 slum dwellers and 32 unhoused individuals was conducted with sputum GeneXpert for X-ray-positive participants. The prevalence of bacteriologically confirmed tuberculosis was 1,504 per 100,000 population (1,362 among slum dwellers and 3,125 among unhoused individuals), and that of interview and chest X-ray positive status was 4,511 per 100,000 population (4,087 among slum dwellers and 9,375 among unhoused individuals). The above data represent 5.4- and 4.1-fold higher prevalence, respectively, compared to the general adult population of Vietnam based on point estimates. Interview and chest X-ray positive status was significantly associated with being 60 years or older (adjusted odds ratio = 5.039, $p = 0.005$) and having a monthly income below the median (adjusted odds ratio = 4.305, $p = 0.037$). The estimated high tuberculosis prevalences among the participants call for the need for systematic screening for tuberculosis disease among these populations.

***Keywords*:** tuberculosis, unstable housing, urban health, urban slum, slum dwellers, homelessness

1. Introduction

Ho Chi Minh City, Vietnam's largest city, had an estimated population of 9,543,600 in 2024 (*1*). Accelerated population growth has generated significant challenges for social welfare policy, most notably in the provision of adequate urban housing to address immediate housing demand (*2*). Around 2004, slums were estimated to comprise roughly 15% of the city's housing population. In 2024, over 2,350 unhoused (homeless) individuals were relocated to Social Protection Centers (*3*). This number is likely underestimated because it does not account for those who escaped relocation.

Tuberculosis has been reported as highly prevalent, particularly among slum dwellers and unhoused individuals worldwide. Systematic reviews have estimated tuberculosis prevalence among slum dwellers to be 3,150 per 100,000 population, with a pooled odds ratio for smear-positive tuberculosis incidence of 2.96 compared to national figures (*4,5*). Reviews focusing on unhoused individuals reported tuberculosis prevalence ranging from 2,600 to 7,700 per 100,000 (*6,7*). These figures far exceed the reported prevalence of 119–1,159 per 100,000 among the general population aged over 15 years in 22 high-burden countries in Asia and Africa during 2007–2016 (*8*).

We conducted a study with two objectives: *i*) to estimate the prevalence of tuberculosis disease among slum dwellers and unhoused individuals in Ho Chi Minh City who received services by Center for Supporting Community Development Initiative (SCDI), a Vietnam-based non-governmental organization (NGO); and *ii*) to identify risk factors associated with tuberculosis disease.

2. Study design

2.1. Participants

A cross-sectional survey was conducted among slum dwellers residing in 13 slum sites in Ho Chi Minh City,

served by the SCDI, and unhoused individuals in Ho Chi Minh City who received services through SCDI's outreach or drop-in programs and were aged 18 years or older. The survey took place from November 2023 to April 2024. The 13 slum sites were located across ten wards in four of the city's 16 urban districts. These sites included specific alleys, areas around hostels, and settlements of waste recyclers. Unhoused individuals were defined as those who had slept in locations other than a permanent home, including public spaces such as sidewalks, bus stations, under bridges, and parks, as well as workplaces, hammock cafés, and internet cafés within the past 30 days.

2.2. Sampling

Local collaborators initially approached slum dwellers residing in 13 slum sites. The pre-visits were guided by the local collaborators' knowledge of adult individuals in the target slums to identify all eligible participants. Individuals who expressed willingness to participate were listed. A total of 460 slum dwellers were listed, and all were subsequently visited by the survey teams. As a result, 367 individuals ultimately participated, yielding a response rate of 79.8%. For the unhoused population, all individuals who were contacted by SCDI, either through outreach or drop-in services, and agreed to participate were included. In total, 399 individuals with unstable housing conditions were selected for the study, comprising 367 slum dwellers and 32 unhoused individuals.

2.3. Tuberculosis screening

Face-to-face interviews were conducted using a structured survey instrument to collect information on participants' sociodemographic and economic backgrounds, a cough lasting more than two weeks, and any history of tuberculosis treatment. Chest X-rays were conducted for all 399 participants. For individuals whose X-ray results were compatible with pulmonary tuberculosis, sputum samples were tested by the National Tuberculosis Program using the GeneXpert system to confirm the presence of tuberculosis bacteriologically.

Our tuberculosis screening endpoints and their definitions were as follows: *i*) bacteriologically confirmed tuberculosis cases defined as participants who had abnormal chest X-ray image suspected of pulmonary tuberculosis and were positive for tuberculosis in sputum GeneXpert; and *ii*) interview and chest X-ray positive status defined as participants who had a cough lasting for at least two weeks and/or any history of tuberculosis treatment plus abnormal chest X-ray image compatible with pulmonary tuberculosis.

2.4. Statistical analysis

We estimated the prevalence of both bacteriologically confirmed tuberculosis cases and interview and chest X-ray positive status. We explored bivariate associations between explanatory variables and both bacteriologically confirmed tuberculosis cases and interview and chest X-ray positive status. Chi-square tests were used for categorical variables, while *t*-tests were applied to continuous variables. We then constructed a multiple logistic regression model, with interview and chest X-ray positive status as the dependent variable, and the variables that showed significant associations in the bivariate analysis as independent variables.

Statistical significance was set at $p < 0.05$. Multiple logistic regression was not performed for bacteriologically confirmed cases due to the small number of positive cases ($n = 6$). Data analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 27 (IBM Corp., Armonk, NY, USA).

2.5. Ethical considerations

The study protocol, explanation document with the informed consent form, consent withdrawal form, and questionnaire were reviewed and approved by both the Ethics Independent Review Board (IRB) of the National Center for Global Health and Medicine (NCGM), currently the Japan Institute for Health Security (JIHS), on 9 July 2023 (approval number: NCGM-S-004698-00), and the IRB of the Institute for Social Development Studies (ISDS), Vietnam, on 28 September 2023. Written informed consent, including participants' signatures, was obtained from all participants before their participation in the study.

3. Key research findings

3.1. Estimation of tuberculosis prevalence

Table 1 presents the estimated prevalence of bacteriologically confirmed tuberculosis cases and interview and chest X-ray positive status, with a breakdown between slum dwellers and unhoused individuals. The prevalence of bacteriologically confirmed tuberculosis cases among all participants was estimated at 1,504 per 100,000 population — 1,362 among slum dwellers and 3,125 among unhoused individuals, and that of interview and chest X-ray positive status at 4,511 per 100,000 — 4,087 among slum dwellers and 9,375 among unhoused individuals. In point prevalence, unhoused individuals showed higher estimates in both categories; however, the wide 95% confidence intervals (CIs) indicated no significant difference between slum dwellers and unhoused individuals.

In Vietnam, the second national tuberculosis

prevalence survey was conducted in 2017–2018, targeting a general adult population of 61,763 individuals aged 15 years or older. The prevalence of bacteriologically confirmed tuberculosis cases was 280 per 100,000 population (95% CI: 241–325), and the prevalence of interview and chest X-ray positive status was 1,100 per 100,000 population (95% CI not available) in the national survey (*9*).

3.2. Associated risk factors of interview and chest X-ray positive status

Table 2 lists the explanatory variables statistically significantly associated with interview and chest X-ray positive status in bivariate and multivariate analyses. In bivariate analysis, old age (≥ 60 years), a monthly income below the median, receipt of cash or in-kind support during the past year, lack of an ID card, a history of incarceration in prison, a reform school, or a compulsory education center, police detention, and having chronic medical conditions requiring ongoing treatment were significantly associated ($p < 0.05$). In multivariate analysis, only old age of 60 years or older (adjusted odds ratio 5.04, $p = 0.005$) and a monthly income lower than the median (adjusted odds ratio 4.31, $p = 0.037$) remained significantly associated after adjusting for confounding.

3.3. Lessons learned from screening implementation

To effectively screen the population with precarious housing and social vulnerability, trust-building through the organization providing day-to-day support, compensating for opportunity costs, protecting privacy, and preventing psychological trauma were critically important.

3.4. Limitations of this study

The present study has several limitations. First, because we used non-probability sampling without comprehensive sampling frames for both slum dwellers and unhoused individuals, we could not estimate the prevalence of tuberculosis in either group with precise statistical inference. Similarly, the associations between bacteriologically confirmed tuberculosis cases and interview and chest X-ray positive status and explanatory variables cannot be generalized for all slum dwellers and unhoused individuals in Ho Chi Minh City or other cities in Vietnam. Second, due to the limited sample size, the small number of bacteriologically confirmed tuberculosis cases precluded multivariable analysis for this gold-standard tuberculosis definition, and the wide 95% CI failed to demonstrate a statistically significant difference between our results

Table 1. Prevalence of bacteriologically confirmed tuberculosis cases and interview and chest X-ray positive status

Characteristics	Number of participants	Prevalence (per 100,000 population)	95% CI
Bacteriologically confirmed tuberculosis cases			
All participants	6/399	1,504	305–2,703
Slum dwellers	5/367	1,362	171–2,554
Unhoused people	1/32	3,125	-3,249–9,499
Interview and chest X-ray positive status			
All participants	18/399	4,511	2,466–6,557
Slum dwellers	15/367	4,087	2,052–6,122
Unhoused people	3/32	9,375	-1,302–20,052

Abbreviation: CI, confidence interval.

Table 2. Explanatory variables significantly associated with interview and chest X-ray positive status for tuberculosis

Explanatory variables	Bivariate analyses				Multivariate analyses			
	n	Chi^2	OR (95% CI)	*p*	*n*	Chi^2	OR (95% CI)	*p*
Old age (60 years or older)	52	16.41	6.13 (2.30–16.35)	0.000*	52	1.617	5.04 (1.62–15.67)	0.005*
Monthly income < median	153	11.05	6.52 (1.86–22.88)	0.003*	153	1.460	4.31 (1.09–16.94)	0.037*
Receipt of cash or in-kind support[a]	111	7.22	3.47 (1.33–9.02)	0.011*	-	-	-	-
Lack of ID card	47	8.43	4.15 (1.48–11.64)	0.007*	47	0.980	2.66 (0.81–8.73)	0.106
Ever been incarcerated[b]	25	8.07	4.86 (1.47–16.05)	0.010*	25	1.418	4.13 (0.91–18.67)	0.066
Ever been detained by police	30	5.61	3.80 (1.17–12.38)	0.027*	30	1.040	2.83 (0.66–12.07)	0.160
Have chronic condition requiring medication	79	4.33	2.73 (1.02–7.23)	0.045*	79	0.862	2.37 (0.80-6.99)	0.119

*$p < 0.05$. [a]Excluded from the multivariate regression model because it was not significant in the model constituted by all seven explanatory variables, and removal of it did not alter the regression coefficients (β) of the two significant variables by more than 15%, indicating that it is not an important confounder. [b]Ever been incarcerated in prison, reform school, or compulsory education centre. *Abbreviations*: ID, identification; *n*, number; OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio.

and those observed in the general population. Third, the study did not address several known risk factors, including smoking, alcohol use, illicit drug use, and malnutrition.

4. Challenges and strategies for tuberculosis screening among slum and unhoused communities

The estimated prevalence of bacteriologically confirmed tuberculosis cases and interview and chest X-ray positive status among our study participants were 5.4- and 4.1-fold higher than those among the general adult population of Vietnam, as estimated by the second national tuberculosis prevalence survey. Old age and poverty were identified as significant risk factors for interview and chest X-ray positive status.

These findings, combined with the aging of slum and unhoused populations in developing countries, including Vietnam, highlight the urgent need for systematic screening for tuberculosis disease among slum dwellers and unhoused individuals in Ho Chi Minh City as part of the End TB (Tuberculosis) Strategy of the World Health Organization (WHO), particularly given that Vietnam is one of the 39 high tuberculosis burden countries (*10*). Provider-initiated screening is particularly important for slum dwellers and unhoused individuals, who are often not reached through patient-initiated consultations because of their limited access to health services, even though they are not explicitly listed as risk groups in the WHO Handbook. Such screening is expected to improve individual outcomes and to reduce transmission and incidence at the population level (*11*).

Although older age and poverty were associated with increased tuberculosis risk, segmenting these populations by age and income is difficult; therefore, a population-based approach is recommended. Such efforts must also ensure the protection of these populations from stigmatization, discrimination, and harm (*11*). The lessons learned from implementing this study — including trust-building, compensating for opportunity costs, protecting privacy, and preventing psychological trauma — should be fully considered in the screening.

Given their precarious civil status, engagement of community actors — including civil society organizations such as SCDI — in collaboration with the National Tuberculosis Program, is crucial for identifying tuberculosis cases and ensuring their enrollment in community-based treatment in line with WHO recommendations, with appropriate follow-up and treatment adherence (*12,13*). An effective communication strategy is also essential to address the common perception among slum dwellers and unhoused individuals that public health services are slow and therefore inferior to private care.

In conclusion, when considered alongside the ongoing aging of slum and unhoused populations, our findings underscore urgent need for systematic tuberculosis screening among these groups in Ho Chi Minh City.

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Optimization of cefepime dosage regimens for *Pseudomonas aeruginosa* infections in Japanese patients based on a pharmacokinetic/pharmacodynamic analysis considering efficacy and safety: Is a 6 g daily dose and continuous infusion necessary?

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Abstract: In Japan, the approved maximum daily dose of cefepime (4 g) is lower than international standards (6 g), potentially compromising efficacy against *Pseudomonas aeruginosa* (*P. aeruginosa*) infections. Using Monte Carlo simulations with a population pharmacokinetic model for Japanese patients, we determined optimal dosing regimens across renal function levels. The target was 60% *f*T > MIC (percentage of time free drug concentration exceeds minimum inhibitory concentration), with ≥ 90% probability of target attainment for minimum inhibitory concentration (MIC) up to 8 mg/L. Lower doses sufficed for impaired renal function, while higher doses with prolonged infusion (2 g q8 (3 h)) were needed for creatinine clearance (CCr) 101–130 mL/min. For augmented renal clearance (CCr > 130 mL/min), continuous infusion (2 g loading dose followed by 4 g continuous infusion) achieved optimal attainment below neurotoxicity thresholds. Current approved dosing in Japan may be insufficient; adjustments including prolonged or continuous infusions are crucial for optimizing therapy.

***Keywords*:** cefepime, pharmacokinetics/pharmacodynamics, Monte Carlo simulations, sepsis

1. Introduction

The global increase in antimicrobial resistance necessitates judicious use of antibiotics, particularly in treating *Pseudomonas aeruginosa* (*P. aeruginosa*) infections. This bacterial pathogen ranks as the fifth most frequent cause of hospital-acquired infections in the USA and is a significant cause of ventilator-associated pneumonia and bloodstream infections worldwide (*1,2*). In Japan, a nationwide surveillance study from 2015 to 2017 reported that *P. aeruginosa* accounted for 8.0% of pathogens isolated from patients with healthcare-associated infections, with rates of antimicrobial resistance being a high concern (*3*). Cefepime, a fourth-generation cephalosporin with broad-spectrum activity and stability against many β-lactamases, is crucial for treating *P. aeruginosa* infections (*4*). However, a notable discrepancy exists regarding approved maximum daily cefepime dosing: Japan has approved 4 g/day, whereas many other countries have adopted 6 g/day. The efficacy of cefepime relates to its pharmacokinetic/pharmacodynamics (PK/PD) parameters, specifically the percentage of time that free drug concentration exceeds the minimum inhibitory concentration (%*f*T > MIC), with an optimal target of 60–70% *f*T > MIC (*5,6*). Achieving optimal PK/PD targets in septic patients is particularly challenging due to significant pathophysiological changes during critical illness. Sepsis induces complex alterations in drug disposition through mechanisms including increased cardiac output, enhanced renal blood flow, capillary leak syndrome, and changes in protein binding. For hydrophilic antibiotics, the volume of distribution can increase by up to 100% in septic patients compared to non-critically ill patients (*7*). Additionally, augmented renal clearance (ARC), defined as creatinine clearance ≥ 130 mL/min, can lead to suboptimal antimicrobial exposure (*8*). The 2024 Japanese Sepsis Guidelines recommend extended or continuous infusion of β-lactam antibiotics based on evidence suggesting improved target attainment and potentially better clinical outcomes in critically ill patients (*9*).

Furthermore, cefepime-induced neurotoxicity can

occur in patients with elevated trough concentrations (*10*). Despite the importance of optimizing cefepime dosages, PK/PD-based dosing strategies for *P. aeruginosa*-infected Japanese patients remain limited, particularly regarding renal function (*11,12*). This study aimed to determine optimal cefepime dosing regimens using Monte Carlo simulations (MCS) while evaluating whether proposed regimens maintain trough concentrations below neurotoxicity risk thresholds, addressing whether 6 g daily doses and continuous infusion are necessary for Japanese patients.

2. Pharmacokinetic parameters and Monte Carlo simulation

MCS were performed to generate concentration-time profiles for 1,000 virtual patients (body weight: 60 kg) stratified by renal function. A population pharmacokinetic (PPK) model developed by Yoshitsugu *et al.* was used in this study (*12*). The model is based on a two-compartment model with first-order elimination. The PPK analysis incorporated body weight and creatinine clearance (CCr) as covariates and was used to predict serum concentration-time profiles. Details of the model are presented in Supplementary Table S1 (*https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=115*). The model was validated for patients weighing 35–82 kg, with the upper limit for reliable predictions estimated to be approximately 90 kg (*12*). The unbound fraction of cefepime was set at 0.85, based on multiple literature sources reporting values between 0.79 and 0.90 (*13-15*).

Based on previous studies defining ARC as creatinine clearance ≥ 130 mL/min (*8*), simulations included scenarios up to 150 mL/min CCr to evaluate dosing requirements in patients with ARC. The choice of 60 kg body weight was based on a report by Yoshitsugu *et al.* (*12*), who demonstrated that for patients with 40–90 kg body weight and 10–50 mL/min CCr, the variations in serum concentration profiles and $T > MIC_{90}$ due to body weight differences were not significant. Therefore, for our simulations, we fixed the body weight at 60 kg to focus on effects of variations in renal function. Simulations were performed for the following dosing regimens: 1 g q24 (1 h), 1 g q12 (1 h), 2 g q12 (1 h), 2 g q8 (1 h), and 2 g q8 (3 h). Additionally, a continuous infusion regimen consisting of a 2 g loading dose (1 h) followed by 4 g continuous infusion was also simulated. Analysis was conducted using Phoenix™ version 8.3 software. The set PK/PD target of 60% *f*T > MIC was based on a study by Crandon *et al.*, who demonstrated the clinical relevance of cefepime against *P. aeruginosa* infections (*16*). For the MCS, a range of minimum inhibitory concentrations (MICs) (0.5–32 mg/L) was chosen to encompass typical cefepime MIC distribution for *P. aeruginosa*, including both susceptible and resistant strains. The probability of target attainment (PTA) was calculated for each dosing regimen across MICs, with a 90% or higher PTA considered as threshold for optimal dosing. For neurotoxicity assessment, we considered a trough concentration of 20 mg/L as the threshold for increased neurotoxicity risk for intermittent infusion regimens, whereas a steady-state concentration of 35 mg/L was used as the risk threshold for continuous infusion regimens (*10,17*). These thresholds were based on findings from Huwyler *et al.* (*10*), who observed that patients with trough levels exceeding 20 mg/L had a 5-fold higher risk of neurological events for intermittent dosing, whereas no toxicity was seen at any sample concentration below 35 mg/L for continuous infusions.

3. Optimal dosing regimens based on renal function

MCS results evaluating the PTA by different cefepime dosing regimens for different MICs against *P. aeruginosa* across various CCr ranges are shown in Figure 1. Table 1 provides a concise overview of optimal dosing strategies with an MIC of 8 mg/L for *P. aeruginosa* across different levels of renal function, as determined by our MCS results. For patients with severe renal impairment (CCr: 0–20 mL/min), a dosing regimen of 1 g q24 (1 h) achieved a 90% or higher PTA for MICs up to 8 mg/L. As renal function improved to 21–40 mL/min CCr, a dose of 1 g q12 (1 h) was sufficient to maintain a 90% or higher PTA for MICs up to 8 mg/L. For patients with 41–60 mL/min CCr, the optimal regimen was 2 g q12 (1 h), which provided adequate coverage (≥ 90% PTA) for MICs up to 8 mg/L. For patients with 61–100 mL/min CCr, an increase in dosing regimen to 2 g q8 (1 h) was needed to achieve a 90% or higher PTA for MICs up to 8 mg/L. However, this regimen failed to achieve the target PTA for MICs of 16 mg/L in patients with 80 mL/min or higher CCr. For patients with 101–130 mL/min CCr, extended infusion times were beneficial, with a regimen of 2 g q8 (3 h) maintaining a 90% or higher PTA for MICs up to 8 mg/L, outperforming the 1 h infusion at the same dose and frequency. Finally, for patients with ARC (CCr > 130 mL/min), continuous infusion was the optimal strategy, with a regimen of 2 g loading dose (1 h) followed by 4 g continuous infusion achieving a 90% or higher PTA for MICs up to 8 mg/L.

4. Safety profile: Neurotoxicity risk assessment

Our simulations of steady-state cefepime concentrations for the recommended dosing regimens (Supplementary Figure S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=115*) provided valuable insights into risk of neurotoxicity and potential benefits of continuous infusion. The majority of recommended regimens maintained trough concentrations below their respective thresholds, suggesting a lower risk of cefepime-induced neurotoxicity while still achieving

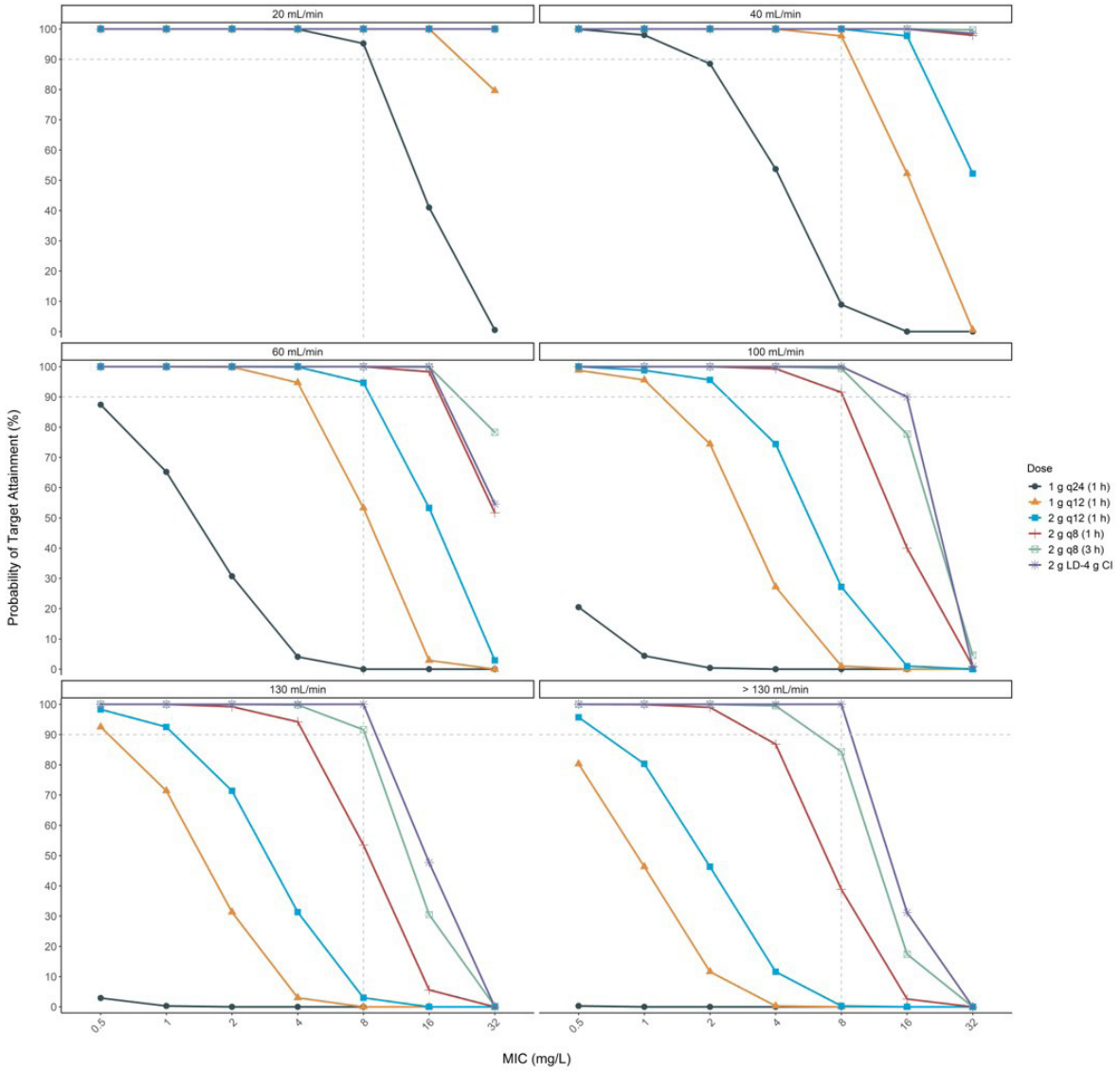

Figure 1. Probabilities of target attainment for 60% *f*T > MIC (percentage of time free drug concentration exceeds minimum inhibitory concentration) at various creatinine clearance (CCr) levels and minimum inhibitory concentrations (MICs). Simulation results were obtained for various dosing regimens, including intermittent infusions of different durations and continuous infusion. The results are stratified by CCr levels and MICs. *Abbreviations*: LD, loading dose; CI, continuous infusion.

Table 1. Recommended cefepime dosing regimens with a minimum inhibitory concentration of 8 mg/L for *Pseudomonas aeruginosa*

CCr (mL/min)	Dosing Regimen
0–20	1 g q24 (1 h)
21–40	1 g q12 (1 h)
41–60	2 g q12 (1 h)
61–100	2 g q8 (1 h)
101–130	2 g q8 (3 h)
> 130	2 g LD (1 h)–4 g CI

Abbreviations: CCr, creatinine clearance; LD, loading dose; CI, continuous infusion.

the desired PK/PD targets. However, for patients with CCr of 10 mL/min, 1 g q24 (1 h) resulted in trough concentrations above the safety threshold (geometric mean: 20.47 mg/L, 95% CI: 20.00–20.95). Therefore, for patients with CCr ≤ 10 mL/min, doses less than 1 g should be considered based on individual MIC values. Importantly, our simulation results for continuous infusion regimens demonstrated stable steady-state concentrations well below the neurotoxicity threshold of 35 mg/L, even in patients with ARC (CCr > 130 mL/min). For instance, the continuous infusion regimen maintained steady-state concentrations, with a geometric mean of 14.43 mg/L (95% CI: 14.26–14.60) for 140 mL/min CCr and 13.64 mg/L (95% CI: 13.48–13.81) for 150 mL/min CCr. This finding highlights the potential of continuous infusion in allowing for higher daily doses of cefepime without increasing risk of neurotoxicity, which is particularly relevant in patients with difficult-to-treat infections or ARC.

5. Clinical implications and comparison with international standards

The present study is one of the few to evaluate efficacy and safety of high-dose cefepime in Japanese patients. Our results suggest that cefepime doses higher than the current standard in Japan may be required for specific MICs against *P. aeruginosa* under different renal function levels. A Japanese study by Yamashita *et al.* found that in patients with CCr exceeding 100 mL/min, the current standard dosing regimen of 1 g q8 (3 g/day) was insufficient to achieve optimal therapeutic targets. They demonstrated that patients with normal renal function required 2 g q8 dosing to achieve adequate therapeutic concentrations, which aligns with international dosing recommendations. Their findings support our conclusion that higher doses (6 g/day) are necessary for Japanese patients with normal renal function, particularly when treating *P. aeruginosa* infections (*11*). The approved cefepime dosage in Japan (maximum 4 g/day) differs significantly from international standards, with several studies supporting efficacy and safety of the higher doses used globally. The Infectious Diseases Society of America guidelines recommend 2 g q8 (6 g/day) for severe infections (*18*), which has been supported by multiple clinical studies demonstrating improved clinical outcomes without increasing adverse events (*19,20*). The importance of continuous or extended infusion for β-lactam antibiotics, particularly in critically ill patients, has been increasingly recognized. The 2024 Japanese Sepsis Guidelines recommend extended or continuous infusion of β-lactam antibiotics based on evidence suggesting improved target attainment in critically ill patients (*9*). Recent practical guidelines from the Italian and French Societies of Infectious Diseases also support this approach.

Interestingly, PK differences do not appear to explain dosage discrepancies between Japan and other countries. A cefepime review report by the Japanese Pharmaceuticals and Medical Devices Agency showed similar maximum concentration (Cmax), steady-state area under the curve (AUC), and minimum concentration (Cmin) values between Japanese and non-Japanese patients across all levels of renal function. These findings suggest that racial differences in blood concentration profiles are unlikely to be the primary cause of the dosage discrepancies. Instead, other factors such as differences in prevalence of resistant bacteria or historical differences in clinical practice may have contributed to the lower approved dosage in Japan. Our study had several important limitations. First, our simulations were based on theoretical models and previously reported thresholds, which may not fully represent the complexity of individual patient responses. Clinical validation through prospective trials combining PK monitoring with neurological assessments is needed. Second, our data were based on serum concentrations and did not consider tissue concentrations at infection sites. Third, we targeted *P. aeruginosa* only and did not evaluate efficacy against other important pathogens. Finally, we did not consider PK/PD profiles in special patient populations, such as immunocompromised individuals or those with severe sepsis.

6. Recommendations for clinical practice

This study highlights the importance of reassessing cefepime dosing strategies in Japan. Our simulations indicated that the current standard dosing may not achieve optimal therapeutic targets in certain clinical scenarios, especially for less susceptible pathogens or patients with altered pharmacokinetics. Given complex pathophysiological changes in sepsis and the growing challenge of antimicrobial resistance in ICUs, continuous or extended infusions of β-lactams are increasingly important for optimizing therapeutic outcomes. Based on our simulations, we propose CCr-based cefepime dosing recommendations for an MIC of 8 mg/L against *P. aeruginosa* (Table 1). Although higher doses aligned with international practices may be beneficial, risk of neurotoxicity necessitates a cautious and individualized approach. Further clinical trials are needed to validate these findings and assess efficacy and safety of higher cefepime doses in Japanese patients, particularly focusing on continuous infusion strategies in septic patients with altered pharmacokinetics.

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

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LETTER

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Breast cancer screening challenges in women with breast augmentation: Evidence from a comprehensive health checkup program

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Abstract: Breast augmentation may compromise the accuracy of breast cancer screening and mammography in particular. The aim of this study was to assess its impact on screening practices and the need for diagnostic follow-up. Data from 1,596 women undergoing comprehensive health checkups in 2024 were retrospectively analyzed. Among 912 women screened for breast cancer, 853 underwent both a mammography and ultrasound, while 54 underwent ultrasound only. Additional evaluation was required in 41/853 (4.8%) of the combined screening group compared to 1/54 (1.9%) of the ultrasound-only group. Breast augmentation was identified in 13/912 (1.43%) using extended detection, and 13/912 (1.43%) in the dedicated field. These findings highlight the limitations of mammography in augmented breasts. Breast augmentation influences screening choices and may hinder cancer detection. Alternative modalities, such as diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) MRI or low-compression 3D mammography, should be considered to improve detection accuracy and patient outcomes.

***Keywords*:** comprehensive health checkup, breast augmentation, mammography, breast ultrasound

1. Introduction

Breast augmentation is commonly performed to achieve an aesthetically ideal breast shape, enhance self-confidence, and alleviate psychological distress (*1*). The three primary methods are silicone implant insertion, fat grafting, and hyaluronic acid injection. Silicone implants provide reliable volume enhancement, fat grafting offers a natural appearance using autologous fat (*2*), and hyaluronic acid injections are simple but temporary due to absorption (*3*). The method selected depends on individual preferences, including desired size and tolerance of foreign material.

This study evaluated the impact of breast augmentation on breast cancer screening practices and the frequency of additional diagnostic evaluations among individuals undergoing comprehensive health checkups (*4,5*).

2. Findings

Anonymized data from female examinees who underwent comprehensive health checkups at this facility between January and December 2024 were retrospectively analyzed. Documents related to information disclosure are posted on the hospital's website, and the study protocol was approved by the institutional ethics committee (No. NCGM-G-003291-00). All procedures were performed in accordance with the Declaration of Helsinki. Breast cancer screening included mammography and breast ultrasound in accordance with national recommendations. Mammography and breast ultrasound findings, overall assessments (A/B/C/D2/E**), and cancer diagnosis entries (presence of "Cancer" in the dedicated column) were extracted. Breast augmentation status was flagged using (a) the dedicated "Augmentation" field and (b) extended detection from mammography and ultrasound notes explicitly mentioning augmentation, implants, or fat injection.

For descriptive statistics, the mean ± SD and median [IQR] were calculated for age, and counts with percentages were calculated for categorical variables. For sparse outcomes and zero cells in 2 × 2 tables, Fisher's exact test and report odds ratios (ORs) with 95% confidence intervals (Haldane–Anscombe correction when appropriate) were used.

The overall assessments were categorized as follows: A: No abnormalities; B: Slight abnormality; C: Follow-up is required; D2: Further examination is required; and E: Under treatment. Internal consistency checks confirmed that there were no records of

Assessment A simultaneously flagged as cancer or D2, and there were no instances of both examinations being normal (mammography and ultrasound) that were flagged as D2 (Supplementary Table S1, *https://www.globalhealthmedicine.com/site/supplementaldata.html?ID=116*).

The mean age was 53.9 years (SD 12.1), with a median of 53 years (IQR [45–62]). A "normal" mammography was noted in 714/912 women (78.3%), and a "normal" ultrasound was noted in 496/912 (54.4%). Overall assessments were A in 458/912 women (50.2%), B in 407/912 (44.6%), C in 1/912 (0.11%), D2 in 42/912 (4.61%), and E in 2/912 (0.22%). Cancer diagnosis entries accounted for 5/912 women (0.55%) (Table 1). In terms of screening modalities, 853 women underwent both mammography and ultrasound, while 54 underwent ultrasound only. Additional evaluation (Assessment D2) was required in 41/853 (4.8%) of the combined group compared to 1/54 (1.9%) of the ultrasound-only group (Figure 1). The difference was not statistically significant (Fisher's exact test, $p = 0.507$). Augmentation was identified in 13/912 women (1.43%) according to both the dedicated field and extended detection from imaging notes. Of these 13 individuals, 10 were in the ultrasound-only group, while 3 underwent both modalities because no contraindications to mammography were documented.

Table 1. Baseline characteristics

Characteristic	Overall (*n* = 912)
Age (years)	53.9 ± 12.1; median 53 [45–62]
Augmentation (dedicated), *n* (%)	13 (1.43%)
Augmentation (extended), *n* (%)	13 (1.43%)
Mammography: No abnormalities, *n* (%)	714 (78.3%)
Mammography: Abnormal, *n* (%)	139 (15.2%)
Ultrasound: No abnormalities, *n* (%)	496 (54.4%)
Ultrasound: Abnormal, *n* (%)	411 (45.1%)
Assessment A, *n* (%)	458 (50.2%)
Assessment B, *n* (%)	407 (44.6%)
Assessment C, *n* (%)	1 (0.11%)
Assessment D2, *n* (%)	42 (4.61%)
Assessment E, *n* (%)	2 (0.22%)
Cancer diagnosis, *n* (%)	5 (0.55%)

A: No abnormalities; B: Slight abnormality; C: Follow-up is required; D2: Further examination is required; E: Under treatment.

3. Implications

These findings highlight the limitations of mammography in augmented breasts and raise concerns about whether ultrasound alone provides sufficient sensitivity for cancer detection. Silicone implants may hinder mammography due to capsular contracture or implant rupture, while fat grafting and hyaluronic acid injections can cause lumps, fat necrosis, or vascular occlusion, hampering interpretation (*6-9*). Alternative modalities such as diffusion-weighted whole-body imaging with background body signal suppression (DWIBS) MRI, which avoids breast compression, and low-compression 3D mammography may improve patient comfort and detection accuracy (*10,11*). Additionally, concerns about radiation exposure, particularly among foreign patients, underscore the need for non–X-ray-based screening options. Tailored screening strategies, including pain-free and radiation-free modalities, may be required to ensure effective follow-up and early diagnosis in this growing population.

This study is limited by its single-center retrospective design and small number of women with breast augmentation. Further research should clarify whether mammography can be safely recommended for patients

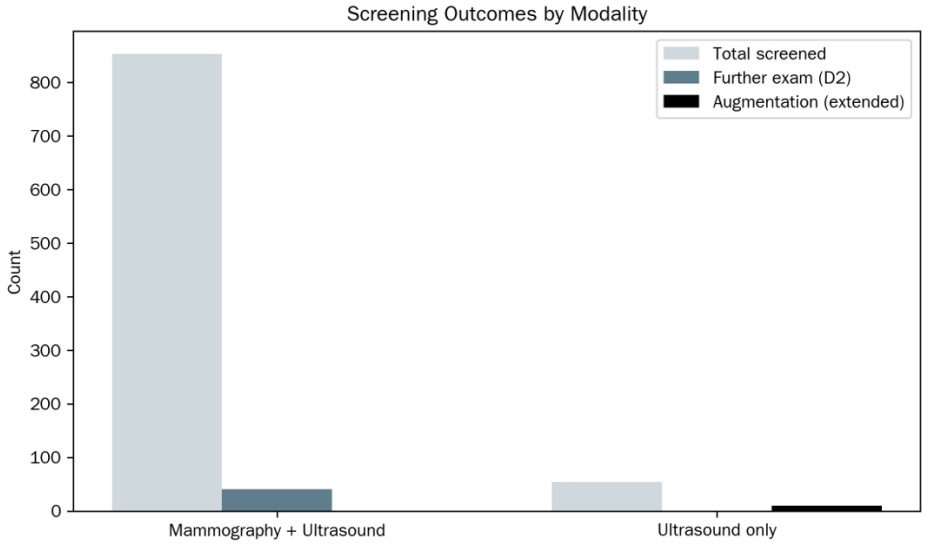

Figure 1. Screening outcomes by modality. Bars indicate the total count of women screened (light gray), those undergoing further examination D2 (dark gray), and those who underwent augmentation (black) for each modality. Counts: Combined 853 total / 41 D2 / 3 augmented; Ultrasound-only 54 total / 1 D2 / 10 augmented.

with fat grafting or hyaluronic acid injections, excluding those with silicone implants.

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CORRIGENDUM

In the article "Advantages of short-term antimicrobial treatment for pneumonia and aspiration pneumonia in older patients aged over 65: A nationwide inpatient database study" (*Global Health & Medicine, 2025; 7(1):28-38. DOI: 10.35772/ghm.2024.01087*), the authors identified errors in the Abstract (page 28) and Results (page 35) sections. The correct values and statements are provided below.

Abstract:

- Incorrect: The hazard ratio for the primary outcome was 1.04 (95% confidence interval: 0.99-1.10). The mean length of hospital stay was shortened to 9.74 days (range, 9.34-10.1) in the short-term treatment group.
- Correct: The hazard ratio for the primary outcome was 0.99 (95% confidence interval: 0.95-1.04). The mean length of hospital stay was shortened to 9.65 days (95% confidence interval: 9.25–10.1) in the short-term treatment group.

Results:

- Incorrect: In our subgroup analysis, the primary outcome was slightly more common in the long-term treatment group for patients who initially received anti-anaerobic antimicrobials. No significant difference was observed in the prevalence of AP between the groups.
- Correct: No significant differences were observed between the groups across all prespecified subgroups, including the prevalence of AP status.

The authors confirm that these corrections do not affect the conclusions of the article. They apologize for any inconvenience this may have caused.

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GHM
Global Health & Medicine

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

Types of Articles	Words in length (excluding references)	Figures and/or Tables	References
Original Articles	~5,000	~10	~50
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Mini reviews	~4,000	~5	~50
Policy Forum articles	~3,000	~5	~30
Communications	~2,000	~2	~20
Perspectives			
Comments			
Correspondence			
Editorials	~1,000	~1	~10
Letters	~1,000	~1	~10
News	~800	~1	~5

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

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

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

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

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

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

The main manuscripts should be assembled in the following order:

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

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