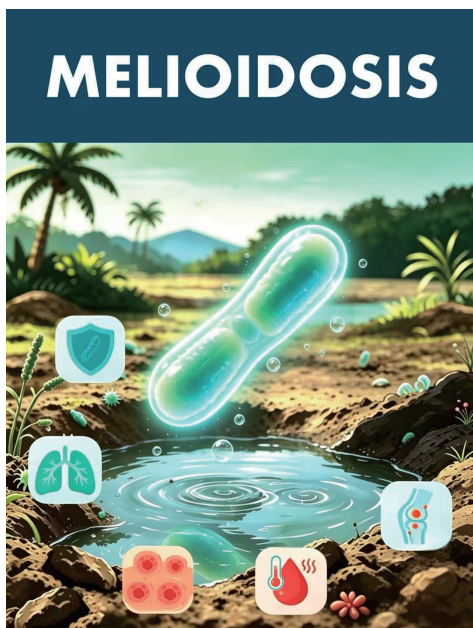


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Preplanned Studies

Emergence and Global Circulation of the HRSV BA Variant with a 7-AA Extension in the G Protein Under Persistent BA Predominance — Global, 1996–2025

Jinhua Song¹; Ke Lu¹; Huiwen Liu¹; Baicheng Xia¹; Pengbo Yu²; Liwei Sun³; Linqing Zhao⁴; Xiangpeng Chen⁵; Zhaoguo Wang⁶; Bing Zhu⁷; Yonghao Guo⁸; Huan Wei⁹; Xin Li¹⁰; Lei Cao¹; Huiling Wang¹; Yan Zhang^{1, #}

Summary

What is already known about this topic?

Human respiratory syncytial virus variant with a 7-amino-acid extension in the G protein of the BA genotype (BA-7AA) is associated with severe neonatal pneumonia outbreak, high intensive care unit occupancy and death. However, limited data are available on the epidemiology and transmission dynamics of the BA-7AA variants.

What is added by this report?

This study integrated publicly available sequences of the second hypervariable region of the G gene of the BA-7AA variant with those sequenced in this study to clarify the emergence and transmission dynamics of the BA-7AA variant.

What are the implications for public health practice?

By revealing the circulation of the BA-7AA variant, this study established a basis for forecasting and warning of the reemergence of BA-7AA variants associated with severe cases and outbreaks.

v2.3.6 and Bayesian stochastic search variable selection methods in BEAST v10.5.

Results: The study included 501 BA-7AA HVR2-G sequences (37 sequenced variants and 464 sequences downloaded from GenBank). BA-7AA variants were initially detected in 2013 and spread gradually to 33 countries by 2024, peaking in 2016, when 27.0% of the BA genotypes were BA-7AA variants. According to the phylogenetic tree, no distinct clusters circulating over time or by region were found during the past decade.

Conclusion: BA-7AA variants circulated worldwide from 2013 to 2024. This work will allow for extensive surveillance to identify BA-7AA variants and provide timely warning of a re-emergence.

ABSTRACT

Introduction: Human respiratory syncytial virus (HRSV) BA genotype variant with a 7-amino-acid extension in the G protein (BA-7AA) has been associated with severe neonatal pneumonia outbreaks, high intensive care unit occupancy, and death. It is vital to understand BA-7AA variant emergence and global circulation.

Methods: The second hypervariable region of the G gene (HVR2-G) sequence dataset was integrated with HVR2-G and whole-genome sequences downloaded from GenBank prior to September 17, 2025, together with the sequences obtained in this study from 2013 to 2024 in China. Phylogenetic analysis and transmission pathways analyses were performed using IQTREE

Human respiratory syncytial virus (HRSV) is a leading cause of lower respiratory tract infections in infants and young children worldwide (1). Eighty-two HRSV outbreaks were reported worldwide between 1962 and 2025. The highest outbreak rates were observed during the winter in neonatal intensive care units (ICUs) (30.49%), with children accounting for the highest percentage of cases (42.29%). The case fatality rate was the highest among older adults across all age groups. The HRSV-B subgroup is the most frequently reported (2).

In 2019, an outbreak of severe neonatal pneumonia in a postpartum care center in China caused by the HRSV-B BA9 genotype was reported after phylogenetic analysis of the second hypervariable region of the G gene (HVR2-G) (3). A 7-amino-acid (Q-R-L-Q-S-Y-A) extension mutation after the stop codon of the G protein was identified (BA-7AA variant). A comparison of the biological properties and virulence of infectious clones of the wild-type strain and a clone with a 7-amino-acid deletion revealed that

the mutated strain exhibited increased adaptability in mice and enhanced viral virulence (4). In addition, strains with a 7-amino-acid extension have also been reported to be associated with a high ICU occupancy rate and fatalities (5–6).

While BA genotypes have been well established as the dominant genotype since 2004–2005, limited data are available regarding the epidemiology and transmission dynamics of the BA-7AA variant (5–8). To clarify the molecular epidemiology of the BA-7AA variant, strains collected in China from 2013 to 2024 were sequenced, and phylogenetic analyses were performed together with sequences downloaded from GenBank (<https://www.ncbi.nlm.nih.gov/>).

Total RNA was extracted from nasopharyngeal or throat swabs of hospitalized patients with acute respiratory tract infection from eight regions (Jilin, Shaanxi, Gansu, Henan, Liaoning, Guangdong, Shandong, and Beijing) under the Chinese HRSV surveillance system, using the QIAamp RNA Mini Kit (QIAGEN, Valencia, CA, USA) according to the manufacturer's instructions. Reverse transcription–polymerase chain reaction (RT-PCR) and sequencing were performed as previously described (3).

A phylogenetic tree was constructed using IQTREE (version 2.3.6, <https://github.com/iqtree/iqtree2>) with the best-fit model TN+F+I+R3 chosen according to the Bayesian information criterion. Branch support values were estimated using an ultrafast bootstrap with 1000 replicates and an approximate likelihood ratio test with 1000 replicates. Tree visualization and editing were performed using TVBOT online (version 2.6.1, <https://www.chiplot.online/>, Shantou University, Shantou, China). To understand the transmission pathways of the BA-7AA variant, the Bayesian stochastic search variable selection (BSSVS) method in BEAST software (version 10.5, University of Auckland, Auckland, New Zealand) was used. The migration routes were summarized using Spread3 (version 0.9.7, <https://beast.community/spread3>) (9). A Bayes factor ≥ 3 and a posterior probability value > 0.5 were considered to significantly support the pairwise diffusion pathways. Pathways were visualized using Gephi software (version 0.10.1, <https://github.com/gephi>).

The HVR2-G and whole-genome sequences of HRSV were downloaded from GenBank on September 17, 2025, and the HVR2-G region was extracted from the whole genome to identify the BA-7AA variant. All the HVR2-G sequences were aligned with the reference HVR2-G sequence. Each sequence was

truncated to the stop codon of the G protein. Sequences with terminal deletions at either the 5' or 3' end exceeding 10% of the sequence length or with $>2.5\%$ ambiguous bases were excluded. The BA-7AA variant was used for phylogenetic analyses (Figure 1). To perform BSSVS analyses, one hundred thirty-three representative BA-7AA variant sequences reported in each country were collected. The BA-7AA variants sequenced in this study were submitted to the National Microbiology Data Center (NMDC) under accession numbers–NMDCN000ATPQ–NMDCN000ATQU (<https://nmdc.cn/resource/genomics/sequence>).

A total of 8,705 sequences were downloaded from GenBank, including 173 sequences without the 60-nt insertion that were excluded. Among the remaining 8,532 HVR2-G sequences, representing the dominant BA genotype between 1996 and 2025, there were 464 BA-7AA variants, which were combined with the 37 BA-7AA variants sequenced in our study to yield a

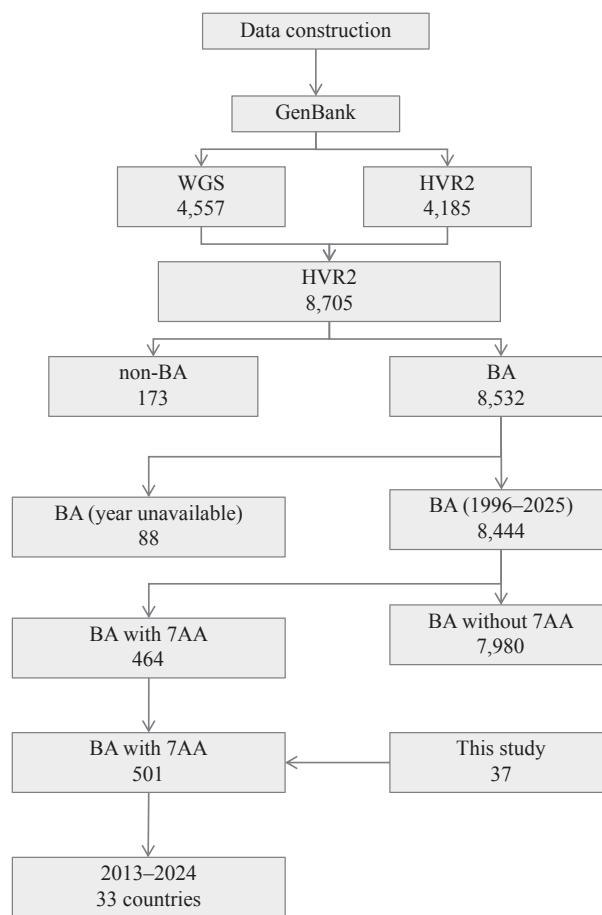


FIGURE 1. Dataset construction of HVR2-G of HRSV-B strains.

Abbreviation: HVR2=second hypervariable region; HRSV=human respiratory syncytial virus; WGS=whole genome sequence; BA=BA genotype.

total of 501 BA-7AA variants (Figure 1).

The BA-7AA variants were mostly detected between 2016 and 2018, with the highest numbers reported in Germany, Spain, Kenya, and China (Figure 2A). The BA-7AA variant was first detected in Shaanxi Province, China in 2013 (1.1% of the BA genotype). It accounted for 2.1% of BA cases reported in China, Germany, and Panama in 2014. By 2015, its prevalence had increased to 9.5% of BA cases in eight countries and peaked in 2016, accounting for 27.0% of the BA genotype, with reports from 12 countries. In 2017, it accounted for 19.6% of BA cases across 17 countries, and in 2018, it accounted for 11.3% of the BA genotypes across 15 countries. Finally, in 2019, it accounted for 6.4% of BA genotypes across 12 countries. Thereafter, the incidence decreased annually, although the BA-7AA variant continues to be detected in new countries. From 2022 to 2024, as the number of detected strains decreased, no new country reported the variant, and it was not detected in countries where it had previously been prevalent. By 2024, only one sequence was detected in Spain and China. As of September 2025, no BA-7AA variant had been identified in GenBank (Figure 2B and 2C).

A phylogenetic tree was constructed using the 501 BA-7AA variant sequences and 21 reference genotype strains. The results demonstrated that all BA-7AA sequences were grouped into a single cluster with the BA (BA9) genotype reference strains. Sequences from different periods and geographic regions were intermixed and no discernible temporal or geographic patterns were observed. Furthermore, after 11 years of circulation, no distinct branches with high bootstrap support values were identified in the phylogenetic tree (Figure 3, the sequence information used for phylogenetic analysis is available at <https://doi.org/10.57760/sciencedb.011nd>).

Based on the phylogenetic tree results, we attempted to predict the transmission pathways of BA-7AA variants using BSSVS analysis. Nine transmission pathways were revealed with a posterior probability greater than 0.5 using 133 representative variants (The sequences used for BSSVS analysis are available at <https://doi.org/10.57760/sciencedb.011nd>). Among these pathways, those from Germany to South Africa had the highest Bayes factor with a posterior probability of 0.997. The pathway from China to Australia received the second highest level of support, with a posterior probability of 0.992. The Bayes factors

and posterior probabilities for the remaining seven pathways were all less than 200 and 0.9, respectively (Figure 4).

DISCUSSION

As one of the major membrane surface glycoproteins, the G protein mediates the adhesion of viral particles to the host cell membrane, facilitating efficient viral binding, cell fusion, and viral release. The G protein contains a CX3C chemokine mimic motif, alters leukocyte migration patterns, and inhibits type I interferon production and antiviral immunity (10–11). Moreover, HVR2-G was chosen as the target for virus surveillance because of its highly variable characteristics, such as a 60-nt duplicated insertion in HRSV-B (BA genotype) and a 72-nt duplicated insertion in HRSV-A (ON1 genotype). In 2024, the HRSV genotyping consensus consortium defined the criteria for HRSV genetic typing and renamed these two genotypes, as A.D. and B.D. based on whole-genome sequences (12), which have evolved into six more lineages according to Nextstrain (<https://nextstrain.org/>).

Studies have shown that the duplicated region in the BA strain G protein augments viral attachment and fitness, and that the 72-nt insertion in the ON1 strain increases the efficiency of pseudotype lentiviral particle infection and enhances attachment function (13–14). Although the BA-7AA variant has a broad geographic distribution, it exhibits limited genetic variation during circulation. Nevertheless, the 7-AA insertion in the BA genotype improved viral adaptation in mice and enhanced viral virulence, which may contribute to its low prevalence and relatively low evolutionary divergence. Given the cost-effectiveness and practical utility of the HVR2-G region for virological surveillance, it is particularly valuable for studies investigating viral functions and characteristics in resource-limited regions.

Although the BA-7AA variant first appeared in the database of this study in 2013, it did not attract substantial attention until it was associated with the 2019 outbreak. This highlights deficiencies in the surveillance system, lack of timely coordination between clinical and public health efforts, and gaps in epidemiological information. Molecular epidemiological surveillance should be strengthened to enable prompt detection of variant strains. Furthermore, although the application of artificial

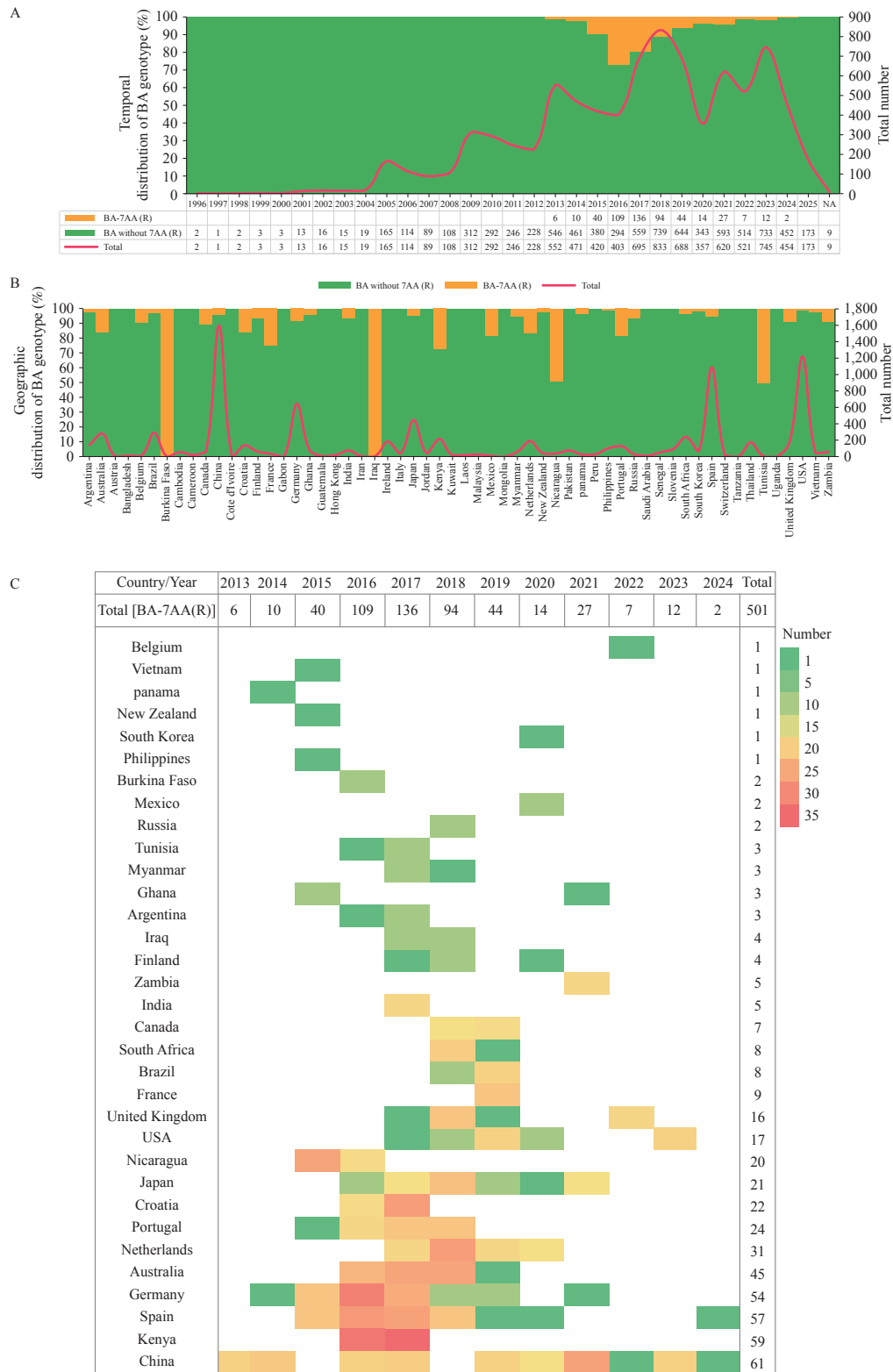


FIGURE 2. Temporal and geographic distributions of BA genotypes of HRSV subgroup B and the BA-7AA variants from 2013 to 2024. The total number of BA sequences is shown using a red line by (A) years or (B) regions; (C) Sequence numbers of BA-7AA by country and year.

Note: The percentages of BA-7AA variant and BA genotype without 7AA are colored with yellow and green bars, respectively, in panels (A) and (B).

Abbreviation: HRSV=human respiratory syncytial virus; NA=not available; USA=United States of America.

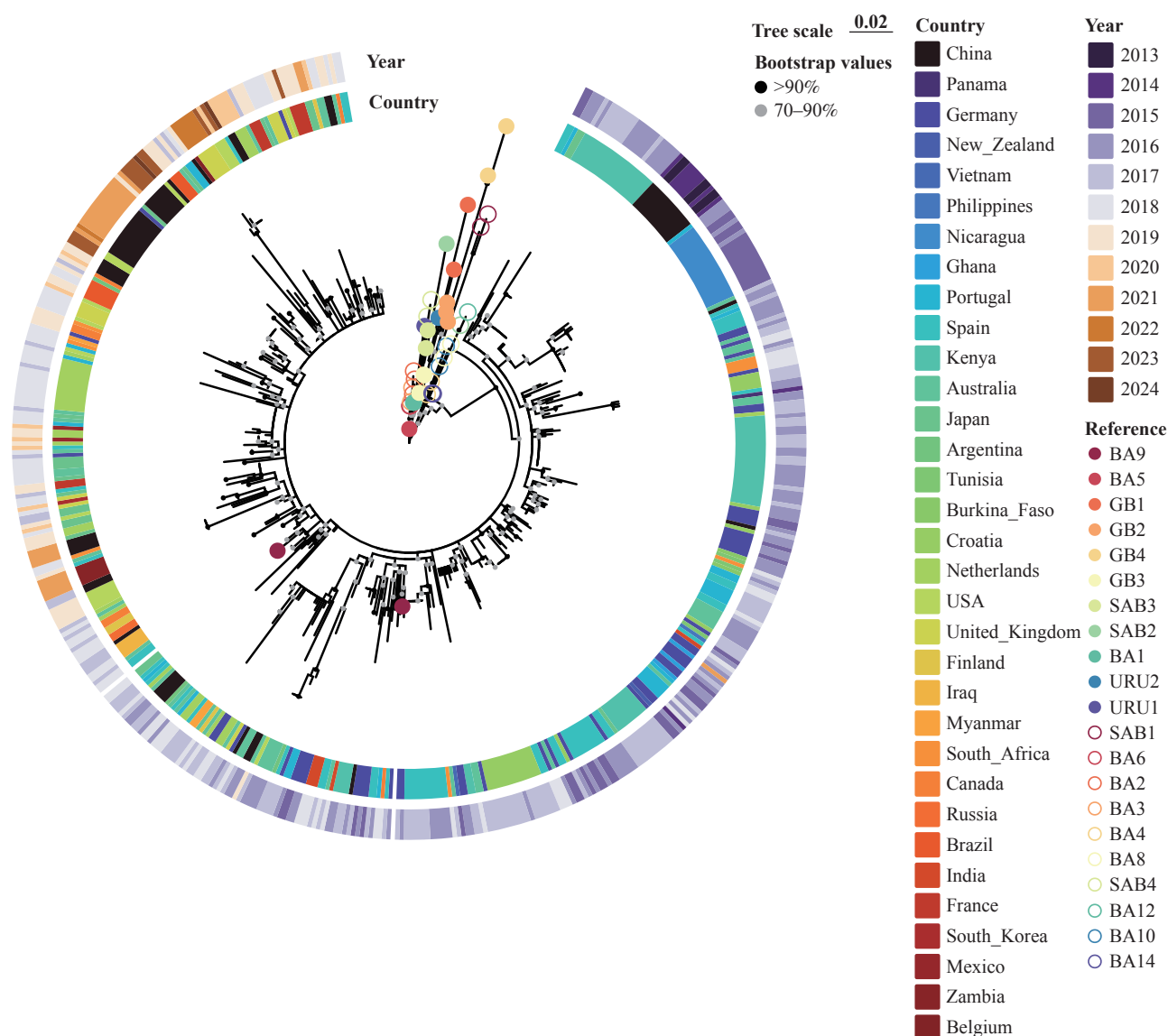


FIGURE 3. Phylogenetic tree of HVR2-G sequences of HRSV BA-7AA variants from 2013 to 2024.

Note: The inner ring shows the collection country of each sequence, and the outer ring shows the collection year of each sequence. Reference strains were colored with dots or rings.

Abbreviation: HVR2-G=second hypervariable region of the G gene; HRSV=human respiratory syncytial virus; USA=United States of America.

intelligence in the field of infectious diseases faces some challenges, it is possible to integrate AI-based predictions using a large accumulation of real-world data to enable an early warning system (15). Therefore, continuous monitoring of HRSV should be conducted to identify highly pathogenic strains, prevent healthcare system overload and outbreaks, and provide foundational support for the prediction, warning, prevention, and control of HRSV infection.

This study had several limitations. First, considerable variation in surveillance and sequencing efforts across countries may artificially inflate or

obscure certain patterns. Therefore, our results represent an exploratory descriptive analysis rather than a definitive account of the global spread of the virus. The absence of the BA-7AA variant by 2025 may be due to a delay in the current surveillance system. The lack of detailed epidemiological data and use of short fragments may introduce bias in the inference of transmission routes. Additionally, a comparative epidemiological analysis between the BA-7AA variants and BA strains without the 7-AA insertion was not feasible due to insufficient clinical metadata in our surveillance database and GenBank. However, the

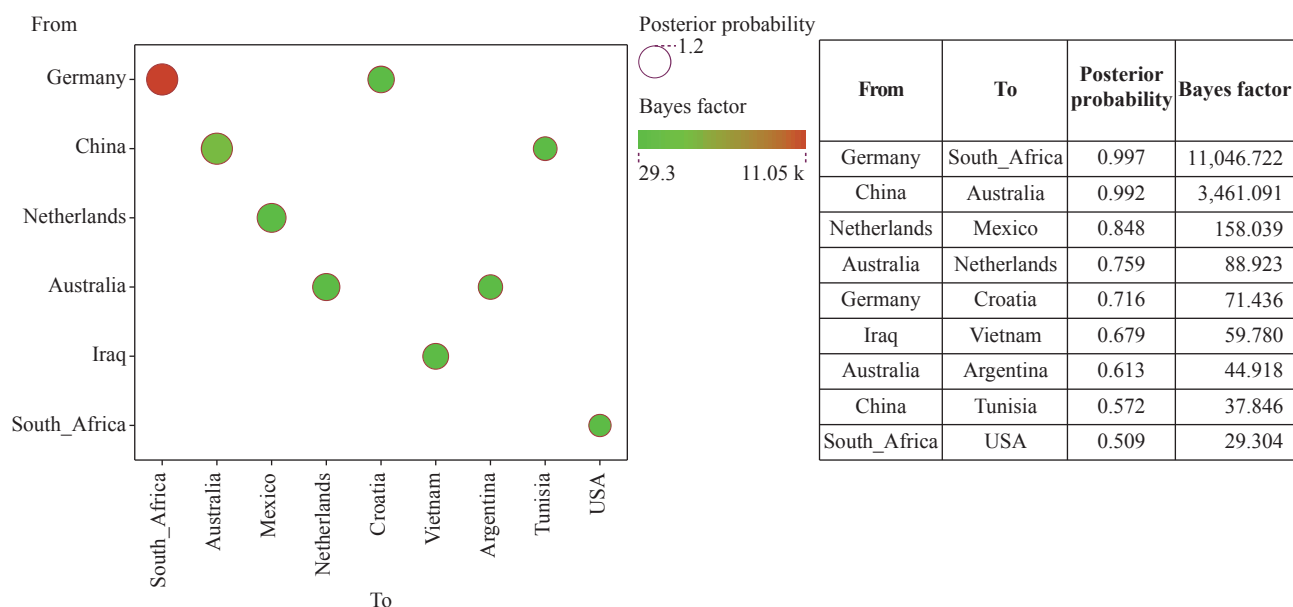


FIGURE 4. Spatial dispersal patterns of the HRSV-B BA-7AA variants, determined by Bayesian phylogeographic inference of HVR2-G sequences.

Note: The size of the circle represents the value of the posterior probability, and the Bayes factor is shown using a gradient from green to red.

Abbreviation: HRSV=human respiratory syncytial virus; HVR2-G=second hypervariable region of the G gene.

public health implications of BA-7AA require further investigation using prospective clinical data.

In conclusion, this study demonstrates the widespread circulation of the BA-7AA variant and enriches the HRSV surveillance database. Given its potentially increased pathogenicity, strengthened virological surveillance is warranted to predict the re-emergence of variants associated with severe cases and outbreaks.

Conflicts of interest: No conflicts of interest.

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Preplanned Studies

Bibliometric and Content Analysis of Artificial Intelligence in Smoking Cessation — Worldwide, 1982–2026

Aaron Wan Jia He¹; Ferrina Hoi Yan Cheung¹; Yuna Shao¹; Gen Li¹; Xiaoyun Xie²; Sophia Siu Chee Chan^{1, #}

Summary

What is already known about this topic?

Tobacco use remains a major public health challenge and the leading preventable cause of death worldwide. Artificial intelligence is increasingly applied in smoking cessation research, but its overall thematic landscape and development trends have not been systematically described.

What is added by this report?

This bibliometric and content analysis identified 1,728 publications on artificial intelligence (AI) in smoking cessation from inception to March 5, 2026. Research output increased markedly after 2017, with intervention as the dominant domain, while prediction and diagnosis emerged as closely related AI areas and monitoring remained substantially underexplored.

What are the implications for public health practice?

AI has strong potential to enhance tobacco control through digital interventions, predictive analytics, diagnostic support, and longitudinal monitoring. Expanding monitoring applications and strengthening trustworthy governance of AI may help improve smoking cessation strategies and support global tobacco control goals.

ABSTRACT

Introduction: Artificial intelligence (AI) is increasingly influencing smoking cessation research through digital intervention delivery, predictive modelling, diagnostic screening, and longitudinal monitoring. Although AI applications continue to expand, the overall trends of AI in tobacco control have not been systematically characterized. This study aimed to map the research landscape on smoking cessation and identify the major themes most relevant to current and emerging AI applications.

Methods: A bibliometric and content analysis of smoking cessation literature was conducted using nine electronic databases from inception to March 5, 2026.

Publications were analyzed by publication year, author frequency, thematic distribution, keyword co-occurrence, and time overlay visualization.

Results: The overall publication output has increased markedly since 2017. The publications were classified into four domains based on keywords: intervention (31.4%, 542/1,729), prediction (24.9%, 430/1,728), diagnosis (13.9%, 241/1,729), and monitoring (3.3%, 57/1,729). Time overlay analysis revealed new research hotspots, such as machine learning, real-time monitoring, and emerging nicotine products.

Conclusion: Smoking cessation studies primarily focus on digital interventions, whereas prediction and diagnosis are emerging sectors closely connected to AI. Monitoring is an underexplored area that suggests important future opportunities. Leveraging evolving AI applications could support tobacco control efforts in alignment with global strategies and national initiatives in China.

Tobacco use is a persistent major public health challenge and leading behavioral risk factor for death worldwide (1). Tobacco substantially increases mortality from health conditions including cancers, heart diseases, and chronic respiratory diseases (1). In China, tobacco use accounts for over 1 million deaths annually, and over 100,000 deaths are attributable to secondhand smoke exposure (2). However, smoking prevalence remains high, with the China CDC reporting a prevalence of 23.2% (male: 43.9%; female: 1.8%) among individuals aged ≥ 15 years in 2024 (3).

As smoking is the most preventable cause of death, a range of interventions and policies have been developed to reduce smoking prevalence and improve quality of life (1). Artificial intelligence (AI) has become increasingly important in smoking cessation research through digital intervention delivery, predictive modelling, diagnostic classification, and follow-up monitoring. Given its increased adoption in

tobacco control, a better understanding of its overall thematic evolution and publication trends is required. Bibliometric analysis offers a visualization-based approach to systematically map the research landscape using vast volumes of scientific data. Macrolevel evidence generated from factors such as authors, hotspots, and intellectual structure can inform research resource allocation and policy development. This study aimed to answer the following questions:

First, what is the overall publication trend for artificial intelligence in smoking-cessation research?

Second, what are the main research themes and their connections?

Third, what are the temporal patterns of the research topics, hotspots, and gaps?

Data extraction involved a comprehensive, single-day search over nine electronic databases (PubMed, APA PsycINFO, Cochrane Library, CINAHL, Scopus, Web of Science, Embase, MEDLINE, and ClinicalTrials.gov), covering inception to March 5, 2026, to capture the collective evolution of AI applications in smoking cessation research. The search strategy included keywords related to AI, tobacco control, and AI application approaches, as outlined

in Supplementary Table S1 (available at <https://weekly.chinacdc.cn/>). The AI keywords were based on the operational definition of AI as a computational method for data pattern extraction to enable automated decision-making (4). Classical and modern approaches were both included to capture the extended historical evolution of these algorithms. The records were limited to those published in English and were downloaded in RIS format.

Figure 1 shows the data screening and analysis. The initial search identified 4,052 entries. After deduplication, 1,728 records remained. Following coder training by the senior author (AWH), two screeners (HYFC, GL) conducted independent manual title and abstract screening. Records were coded into one of four research domains (intervention, diagnosis, monitoring, and prediction) or an unclassified category based on their principal research objectives and the domain definitions, subdomain categories, and relevant keywords in Table 1. The unclassified category comprised publications lacking meaningful relevance to AI and smoking cessation. Coding discrepancies were resolved through discussion with AWH. The records were analyzed using Python (version 3.12; The

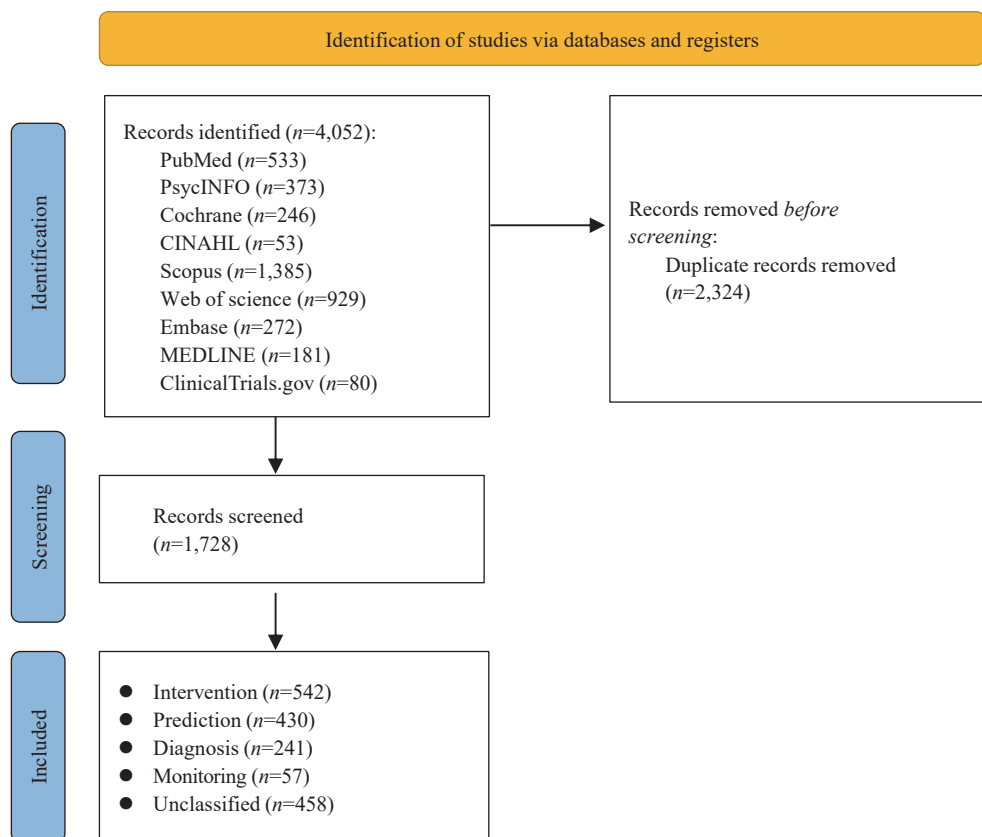


FIGURE 1. Workflow of the bibliometric analysis, including record identification, screening, and inclusion.

TABLE 1. Content analysis framework based on the four research themes for AI use in smoking cessation support.

Main domain	Definition	Subdomains	Normalized keyword groups
Intervention	Studies evaluating or delivering smoking cessation support	Behavioral intervention, digital intervention, pharmacotherapy, counseling, quitline, intervention evaluation	Intervention/treatment/therapy
			Intervention effect
			Trial/protocol
			Pharmacologic and non-pharmacologic intervention
			Behavioral/lifestyle/psychological intervention
			Health education/rehabilitation
			Counseling/brief advice
			Smoking cessation/cessation program/quitline
			Nicotine replacement therapy
			Cessation medications
Prediction	Studies using models or predictors to estimate cessation-related outcomes	Quit success prediction, relapse prediction, abstinence prediction, risk prediction, trajectory modeling	Digital intervention-related terms
			Motivational interviewing
			Prediction-related terms
			Forecasting/estimation/projection
			Predictive modeling
			Risk prediction/risk factor
			Trend prediction
			Probability/likelihood
			Prognostic/outcome-related terms
			Relapse prediction
Diagnosis	Studies identifying, screening, detecting, or classifying smoking-related status or conditions	Smoking status detection, nicotine dependence screening, diagnostic classification, biomarker/imaging-based detection	Cessation success prediction
			Diagnosis-related terms
			Detection/identification
			Screening
			Classification
			Diagnostic accuracy
			Biomarker/testing/imaging
			Smoking status assessment
			Nicotine/tobacco dependence assessment
			Withdrawal/craving assessment
Monitoring	Studies involving follow-up, surveillance, adherence, or longitudinal tracking	Remote monitoring, relapse monitoring, abstinence follow-up, adherence monitoring, surveillance	Quit readiness/motivation assessment
			Monitoring/tracking/surveillance
			Follow-up/reassessment/review
			Longitudinal/prospective observation
			Adherence/compliance
			Continuous/ambulatory monitoring
			Ecological momentary assessment

Note: There are four cluster themes for the content analysis. Publications were allocated to one of the four predefined primary application themes based on their dominant research direction. The framework contains the main domain (overall thematic category), definitions (conceptual meaning of each domain), subdomains (specific subthemes), and normalized keyword groups (merged synonyms, concepts, and variants).

Abbreviation: AI=artificial intelligence.

Python Software Foundation) for publication year, author appearance frequency, and thematic analysis.

VOSviewer (version 1.6.20; Leiden University, Netherlands) was used to create the author

collaboration network, keyword co-occurrence, and time overlap analysis of the records. The analysis used a minimum keyword occurrence threshold of 19, full counting, and standardization based on association strength.

Publications within the field began in 1982 and have continuously increased in volume. The complete Kneedle algorithm identified 2017 as a critical turning point, with a sensitivity parameter of $S=1$. The annual publication output (Figure 2A) increased gradually from two in 1982 to 49 in 2017. Following the inflection point, this number increased substantially, peaking at 282 in 2025. There were 578 publications in the 36 years up to 2017 and 1,088 in the 9 years after 2017.

Figure 2B presents the author collaboration network. The ten most-prolific authors contributed to 227 publications (13.1%). Prochaska from the University of Rhode Island contributed the most articles (39 publications), followed by Velicer from the same university (30 publications). Further author details are listed in Supplementary Table S2 (available at <https://weekly.chinacdc.cn/>).

Content analysis was conducted to characterize thematic emphasis within the research field. Using keyword-driven coding, the records were classified into four major AI application domains: intervention, prediction, diagnosis, and monitoring (Table 1; details in Supplementary Table S3, available at <https://weekly.chinacdc.cn/>). Intervention is the largest domain, comprising 542 records (31.4%), followed by prediction (430 records, 24.9%), diagnosis (241 records, 13.9%), and monitoring (57 records, 3.3%). The remaining 458 (26.5%) records were unclassified.

High-frequency keyword groups within each domain were used to characterize thematic emphasis and identify areas of importance, as outlined in Supplementary Table S3 (available at <https://weekly.chinacdc.cn/>). The intervention domain was dominated by treatment (425), smoking cessation (405), effect (285), trial (161), digital intervention (123), and counseling (74). The prediction domain was characterized by predictive modeling (338), prediction (318), forecasting (113), and prognostics (74). The diagnosis domain included detection (122), testing (110), and screening (78). Monitoring included surveillance (36), longitudinal (5), and adherence (5). The content analysis in Figure 2C maps the keywords across the four domains, revealing interdisciplinary relationships and close cross-theme research between certain domains (e.g., intervention and diagnosis,

monitoring and prediction).

The keyword co-occurrence analysis revealed research hotspots (Figure 2D). The red cluster keywords include "artificial intelligence," "tobacco control," "intervention," "health promotion," and "health behavior." The yellow cluster contains the AI subtheme of machine learning, where "diagnosis" and "monitoring" are the most closely related. The green cluster represents predictive modelling and its diverse implementations ("risk assessment," "risk factor"). The blue cluster keywords are related to general smoking-cessation research, such as "randomized controlled trial," "outcome," "self-efficacy," and "abstinence." The time overlay chart shows a clear evolutionary trend (Figure 2E). The keywords for the years before 2017 (purple and blue) represent core research themes ("smoking cessation," "artificial intelligence," "intervention," "treatment outcome," "nicotine") and earlier AI paradigms ("expert system," "data mining"). For 2017–2021 (green), AI applications emphasized "risk assessment," "screening," "classification," and "forecasting." From 2021 onwards, new research hotspots (yellow) include recent AI applications ("monitoring," "real-time," "machine learning"), recent AI platforms ("mobile phones," "chatbots"), and emerging alternative smoking products ("ASPs," "electronic cigarettes," "vaping"). High-resolution versions of Figures 2B–2E are provided in Supplementary Figures S1–S4 (available at <https://weekly.chinacdc.cn/>).

DISCUSSION

The use of AI is expanding rapidly everywhere. Our critical review and analysis of trends in the publications of the past 45 years reveal that interest in the use of AI within smoking cessation research is accelerating, especially in the last decade. The rising trend also suggests persistent expansion in the future. This expansion aligns with wider digital healthcare research patterns, which show accelerating development of AI in public health, personalized interventions, and clinical decision-support across various settings (5).

Within the four themes of AI in smoking-cessation research, current research primarily focuses on intervention-focused studies, underscoring sustained efforts on cessation strategies and potential targeted support for at-risk individuals. Applications for prediction and diagnosis are emerging to a lesser extent. The focus on prediction reflects attention to modelling and assessment. Diagnostic research

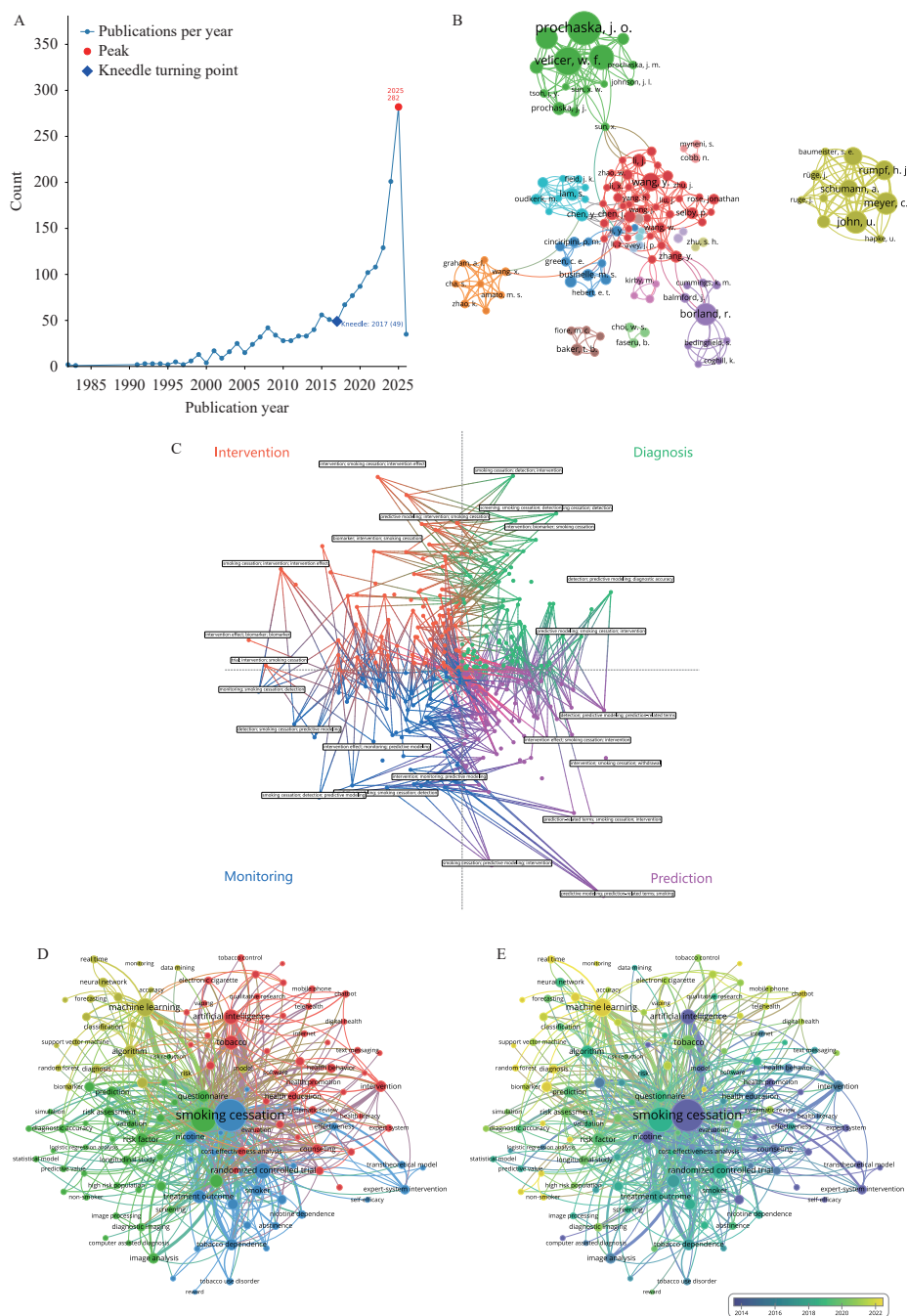


FIGURE 2. Bibliometric visualizations of AI application in smoking cessation research ($N=1,728$). (A) Annual number of publications from 1982 to 2026; (B) Author collaboration network of the top 146 authors; (C) Visualization of four research themes of intervention, prediction, diagnosis, and monitoring; (D) Keyword co-occurrence network; (E) Time overlay map.

Note: In the author collaboration network, each node represents an author in the field. Larger nodes indicate more records. The connections indicate coauthorship across publications, and thicker lines indicate more frequent collaboration. In the research theme visualization, each node represents a single publication placed in one of the four theme quadrants. The connections between nodes indicate the similarity between records, and thicker lines indicate stronger similarity through more shared keywords. Node proximity also reflects similarity. The labels indicate the most important keywords in each theme. In the keyword co-occurrence network, each node represents a keyword and larger node sizes reflect a higher frequency of occurrence within the literature. The connections between nodes represent co-occurrence relationships, and link strength depicts the volume of publications with shared occurrences. In the time-overlay map, node color indicates the average publication year of the corresponding literature for each keyword, with lighter colors representing newer research topics.

Abbreviation: AI=artificial intelligence.

indicates opportunities for early identification. By contrast, research on monitoring approaches using AI for tobacco control is relatively new and underexplored, indicating a gap in research and policy. AI can contribute to tobacco use monitoring with longitudinal tracking and real-time adaptive feedback systems, particularly within community and primary healthcare settings. AI-based sustained monitoring could improve time efficiency and minimize manual effort. A multifaceted approach is encouraged, and the four domains should be systematically integrated to achieve effective smoking cessation and sustained tobacco control.

Globally, AI will increasingly influence smoking cessation efforts, warranting standardized protocols specific to healthcare practices using the FUTURE-AI framework (6). These international consensus guidelines are based on six principles: fairness, universality, traceability, usability, robustness, and explainability. FUTURE-AI spans the lifecycle of healthcare AI, including its design, development, validation, deployment, and monitoring (6). The integration of human expertise and oversight into AI systems is also vital. Co-design among diverse stakeholders, including academics, clinicians, policymakers, patients, public-health practitioners, and the general public, should be actively promoted to effectively address the complex and evolving health needs of populations.

By 2030, the Chinese government aims to reduce its high smoking prevalence to below 20% in individuals aged ≥ 15 years within Healthy China Action (2019–2030) (2). Hong Kong has a current prevalence of 8.5% (538,100/6,353,200) and a target prevalence of 7.8% by 2025 (7). The action plan outlines the development of a comprehensive smoking-cessation service to promote brief advice interventions, national-level tobacco product surveillance, and routine outpatient smoking-history documentation, providing multiple integration points for the four themes of AI approaches in national tobacco-control efforts. Key applications include prediction models for personalized digital intervention delivery, patient tobacco-use screening, and longitudinal monitoring of smoking-related patterns.

This promising and expanding research and policy interest also carries potential risks. Notable challenges include bias and equity issues affecting fairness and the accuracy of predictions and interventions in algorithmic decision-making (8). AI involves data collection and utilization, which are beneficial for

model training and intervention personalization, but potentially subject to data leaks and misuse (8). Hence, since 2017, the Chinese government has taken early and steady actions to support and regulate AI use, laying the regulatory groundwork and establishing advisory committees (9–10). In 2020, voluntary ethical guidelines shifted to formal legal regulations, strengthening regulatory oversight of AI use (9). This oversight comprises three pillars: data protection, algorithmic governance, and content moderation (9). Data protection focuses on the ethical, safe, and responsible use of personal information. Algorithmic governance involves AI system registration and the use of reliable training datasets. Content moderation includes content labeling, transparency, and the strict control of harmful information. This adaptive, coordinated governance system in China may serve as a useful framework for the global implementation of AI in tobacco-control systems.

The findings in this report are subject to at least five limitations. First, the bibliometric analysis reflects publication activity from selected databases, excluding unpublished research and gray literature, limiting result comprehensiveness. Second, the restriction to English-language records may have caused the overrepresentation of research from countries where English is the primary language. Third, changes in the terminology definitions related to AI and tobacco products over time could affect the content analysis accuracy. Fourth, manual theme classification inherently involves subjective judgment, particularly for records spanning multiple domains. Finally, the bibliometric findings should not be interpreted as indicators of exact trends in practical implementation and policy progress.

Within its evolving landscape, AI holds substantial potential for advancing smoking cessation efforts across multiple research domains. Although smoking intervention, predictive analytics, and diagnostic support are the primary areas of AI application in current research, the use of AI in monitoring remains underutilized, indicating crucial opportunities to expand its expertise and deployment. With the global expansion of AI use in tobacco control, the adoption of FUTURE-AI frameworks is essential to ensure the systematic integration of AI into healthcare practices. In China, the comprehensive, multifaceted application of AI across the four research domains in alignment with national health strategies may provide valuable support for tobacco-control efforts.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLE S1. Search strategy for the bibliometric analysis of artificial intelligence in smoking cessation research.

Category	No.	Search term
Artificial intelligence	1	Artificial intelligence
	2	AI
	3	Artificial learning
	4	Computer reasoning
	5	Computational intelligence
	6	Computer intelligence
	7	Machine learning
	8	Supervised learning
	9	Unsupervised learning
	10	Reinforcement learning
	11	Hierarchical learning
	12	Transfer learning
	13	Decision tree*
	14	Random forest*
	15	Random decision forest
	16	SVM
	17	Bayesian
	18	Deep learning
	19	Neural networks
	20	Artificial neural networks
	21	Autoencoder
	22	Perceptrons
	23	Generative AI
	24	Large language model
	25	Generative pre-trained transformer
	26	ChatGPT
	27	Generative adversarial networks
	28	Natural language processing
	29	text mining
	30	Robotic*
	31	Expert System*
	32	Inference engines
	33	Fuzzy logic
	34	Fuzzy cognitive
	35	Computer vision
	36	Image analysis
	37	Image classification
	38	Image segmentation
	39	Machine vision
	40	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39

Continued

Category	No.	Search term
Smoking cessation	41	Smoking cessation
	42	Smoking intervention
	43	Smoking regulation
	44	Smoking abstinence
	45	Smoking reduction
	46	Smoking prevention
	49	Giving up smoking
	50	Stopping smoking
	51	Quit smoking
	52	Quitting smoking
	53	Reduce smoking
	54	Reducing smoking
	55	Tobacco cessation
	56	Tobacco use cessation
	57	Tobacco regulation
	58	Tobacco control
	59	Tobacco reduction
	60	Tobacco prevention
	61	Tobacco use disorder
	62	Tobacco dependen*
	63	Tobacco program
	64	Tobacco endgame
	65	Nicotine cessation
	66	Nicotine use disorder
	67	Nicotine addiction
	68	Nicotine dependence
	69	Nicotine gum
	70	Nicotine patch
	71	Nicotine replacement
	72	NRT
	73	41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66 OR 67 OR 68 OR 69 OR 70 OR 71 OR 72
Intervention	74	Prediction
	75	Predictive
	76	Predictive analytics
	77	Predictive learning model
	78	Machine predictive models
	79	Risk factor
	80	Risk assessment
	81	Risk-benefit assessment
	82	Risks and benefits
	83	Risk analysis
	84	Predictive value*

Continued

Category	No.	Search term
Intervention	85	Patient monitoring
	86	Health monitoring
	87	Remote monitoring
	88	Remote patient monitoring
	89	Telemonitoring
	90	Digital monitoring
	91	Continuous monitoring
	93	Adherence monitoring
	94	Behavioral monitoring
	95	Relapse monitoring
	96	Symptom monitoring
	97	Surveillance
	98	Intervention
	99	Treatment
	100	Therapy
	101	Cessation
	102	Regulation
Combined search terms	103	74 OR 75 OR 76 OR 77 OR 78 OR 79 OR 80 OR 81 OR 82 OR 83 OR 84 OR 85 OR 86 OR 87 OR 88 OR 89 OR 90 OR 91 OR 92 OR 93 OR 94 OR 95 OR 96 OR 97 OR 98 OR 99 OR 100 OR 101
	104	40 AND 73 AND 102

Abbreviations: AI=artificial intelligence; ChatGPT=chat generative pretrained transformer; NRT=nicotine replacement therapy; SVM=support vector machine.

* indicates a truncated wildcard, in which the listed keyword represents multiple word variations sharing the same root.

SUPPLEMENTARY TABLE S2. Top-10 authors contributing on artificial intelligence use in smoking cessation research from 1982 to 2026.

Rank	Author	Country	Number of publications
1	Prochaska JO	United States	39
2	Velicer WF	United States	30
3	Redding CA	United States	25
4	John U	Germany	22
5	Borland R	Australia	21
6	Meyer C	Germany	21
7	Rossi JS	United States	20
8	Rumpf HJ	Germany	17
9	Ulbricht S	Germany	16
10	Wang Y	China	16

SUPPLEMENTARY TABLE S3. The content analysis framework with the keyword library, based on four research themes for AI in smoking cessation support.

Main domain	Definition	Subdomains	Normalized keyword groups	Keywords library	Occurrence
Intervention	Studies evaluating or delivering smoking cessation support	Behavioral intervention, digital intervention, pharmacotherapy, counseling, quitline, intervention evaluation	Intervention/treatment/ therapy	Intervention; treatment; therapy; management; regimen	425
			Intervention effect	Effectiveness; efficacy; impact	285
			Trial/protocol	clinical trial*; randomized controlled trial; RCT; controlled trial; protocol	161
			Pharmacologic and non-pharmacologic intervention	Pharmacologic*; non-pharmacologic*	22
			Behavioral/lifestyle/ psychological intervention	Behavioral intervention*; lifestyle intervention*; psychological intervention*	17
			Health education/rehabilitation	Health education; rehabilitation	14
			Counseling/brief advice	Counseling; brief advice	74
			Smoking cessation/cessation program/quitline	Smoking cessation; cessation program*; quit smoking; quit attempt*; quitline	405
			Nicotine replacement therapy	Nicotine replacement therap*; NRT	70
			Cessation medications	Varenicline; bupropion	46
			Digital intervention-related terms	Digital intervention*; web-based; internet-based; online program*; mHealth; smartphone app*; mobile app*; telehealth; telemedicine; SMS; text message*; chatbot*; e-health; virtual coach*	123
			Motivational interviewing	Motivational interview*; motivational enhancement therap*; MET	37
Prediction	Studies using models or predictors to estimate cessation-related outcomes	Quit success prediction, relapse prediction, abstinence prediction, risk prediction, trajectory modeling	Prediction-related terms	Predict*; prediction; predictive; predictor*	318
			Forecasting/estimation/projection	Forecast*; estimate*; projection*; anticipated	113
			Predictive modeling	Model*; probabilistic model*; risk model	338
			Risk prediction/risk factor	Risk prediction; risk factor	44
			Trend prediction	Future trend*; trend analysis	3
			Probability/likelihood	Likelihood; probability	62
			Prognostic/outcome- related terms	Prognostic; outcome; expected outcome	74
			Relapse prediction	Relapse risk; relapse prediction; time to relapse	7
			Cessation success prediction	Quit success; cessation success; quit probability; cessation outcome*	31
Diagnosis	Studies identifying, screening, detecting, or classifying smoking-related status or conditions	Smoking status detection, nicotine dependence screening, diagnostic classification, biomarker/imaging-based detection	Diagnosis-related terms	Diagnos*; diagnostic; differential diagnosis; misdiagnos*	50
			Detection/identification	Detect*; detection; identify; identification; early detection	122
			Screening	Screen*; screening	78
			Classification	Classification; classify	47
			Diagnostic accuracy	False positive; false negative; sensitivity; specificity; accuracy	67
			Biomarker/testing/ imaging	Biomarker*; test*; imaging	110
			Smoking status assessment	Smoking status	29
			Nicotine/tobacco dependence assessment	Nicotine dependence; tobacco dependence; dependence level	20
			Withdrawal/craving assessment	Withdrawal symptom*; craving*; urge to smoke	15
			Quit readiness/motivation assessment	Readiness to quit; motivation to quit	2

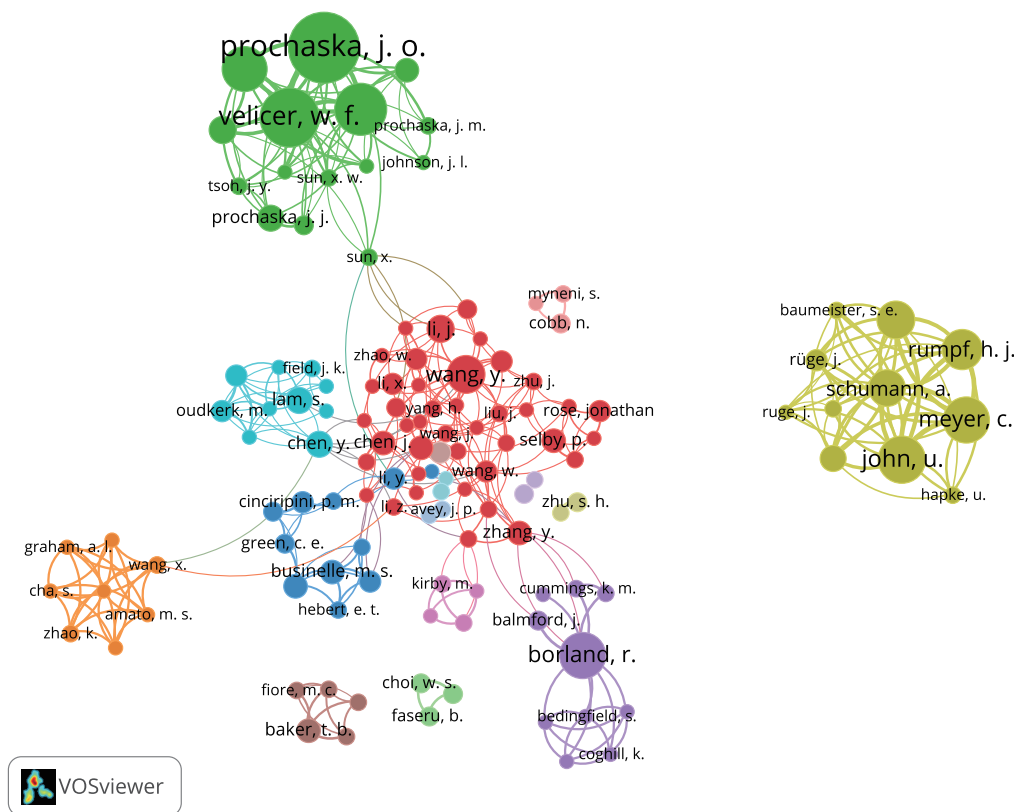
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Main domain	Definition	Subdomains	Normalized keyword groups	Keywords library	Occurrence
Monitoring	Studies involving follow-up, surveillance, adherence, or longitudinal tracking	Remote monitoring, relapse monitoring, abstinence follow-up, adherence monitoring, surveillance	Monitoring/tracking/surveillance	Monitor*; monitoring; surveillance; track*; observation	36
			Follow-up/reassessment/review	Follow-up; follow up; reassessment; periodic review; serial assessment	4
			Longitudinal/prospective observation	Longitudinal; prospective	5
			Adherence/compliance	Adherence; compliance	5
			Continuous/ambulatory monitoring	Continuous monitoring; ambulatory monitoring	1
			Ecological momentary assessment	Ecological momentary assessment; EMA	1

Note: There are four cluster themes for the content analysis. Publications were allocated to one of the four predefined primary application themes based on their dominant research direction. The framework contains the main domain (overall thematic category), definition (conceptual meaning of each domain), subdomains (specific subthemes), normalized keyword groups (merged synonyms, concepts, and variants), and keyword library (a full detailed list of extracted keywords used for analysis). The asterisk

Abbreviation: APP=application; CO=carbon monoxide; EMA=ecological momentary assessment; MET=motivational enhancement therapy; NRT=nicotine replacement therapy; RCT=randomized controlled trial; SMS=short message service.

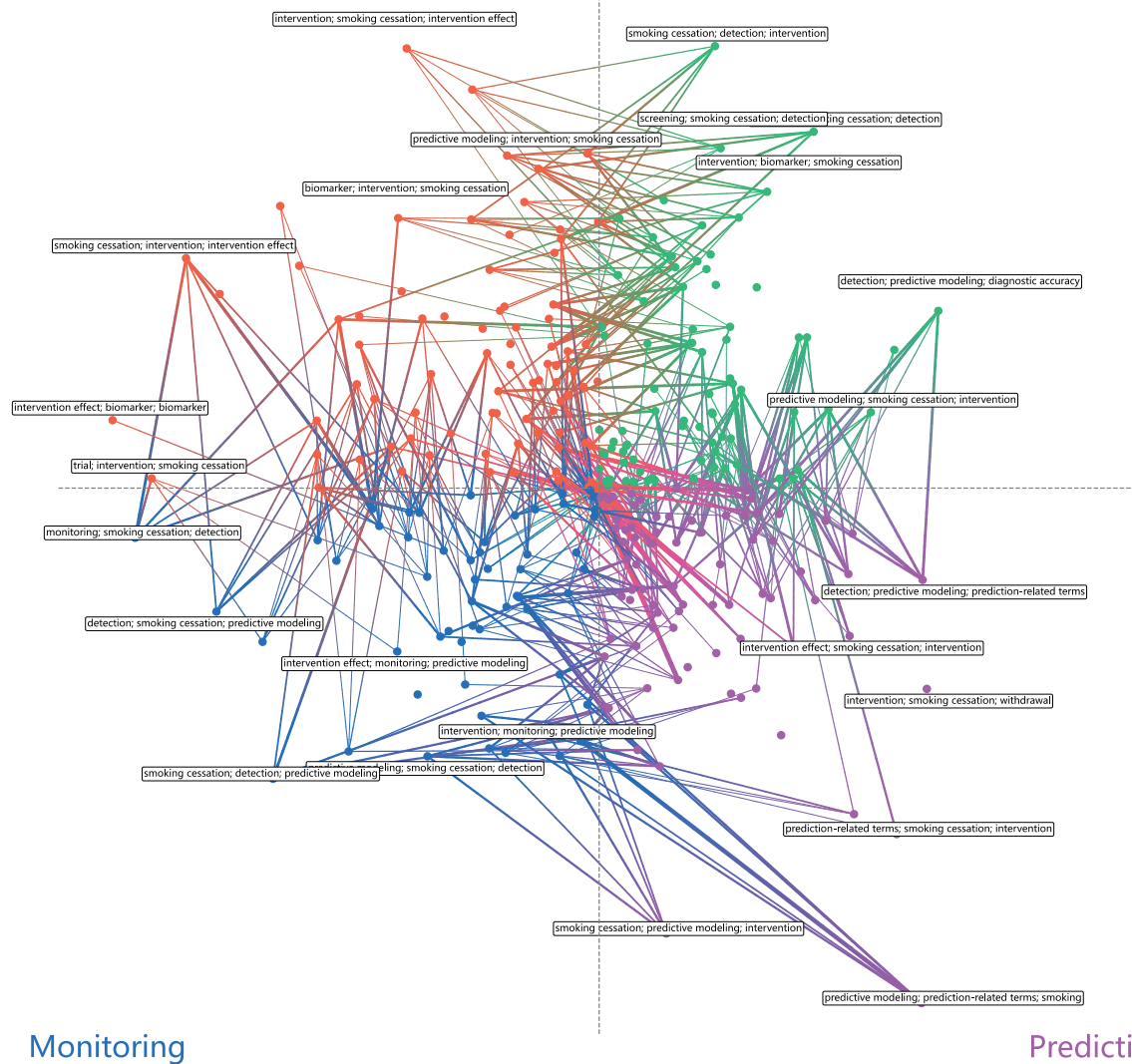
* Indicates a truncated wildcard, in which the listed keyword represents multiple word variations sharing the same root.



SUPPLEMENTARY FIGURE S1. Author collaboration network of the top 146 authors.

Intervention

Diagnosis



Monitoring

Prediction

SUPPLEMENTARY FIGURE S2. Visualization of the four research themes of intervention, prediction, diagnosis, and monitor.



SUPPLEMENTARY FIGURE S3. Keyword co-occurrence network.



SUPPLEMENTARY FIGURE S4. Time overlay visualization map.

Preplanned Studies

Fear of Hypoglycemia and Behavioral Patterns Among Patients with Diabetes — Beijing, China, September–December 2024

Yajing Tan^{1,&}; Lina Zhang^{2,&}; Meiting Luo^{1,3}; Jianying Dong^{2,4}; Fanghui Qi⁵; Qiqi Wang⁵; Wenhui Shi^{1,&}; Qi Pan^{2,4,&}

Summary

What is already known about this topic?

Hypoglycemia is a frequent complication among diabetic patients and can lead to serious clinical consequences. Increasing attention has been paid to the role of psychological factors, particularly fear of hypoglycemia, in blood glucose management.

What is added by this report?

Hypoglycemia management behavioral patterns among diabetic patients demonstrated notable aggregation and heterogeneity, with 35.94% classified into the low-management pattern (Class 1), 37.50% into the exercise-based pattern (Class 2), and 26.56% into the monitoring-based pattern (Class 3). Fear of hypoglycemia was positively associated with the monitoring-based pattern but negatively associated with the exercise-based pattern (both $P < 0.05$).

What are the implications for public health practice?

Personalized prevention and intervention strategies should be tailored to individual behavioral patterns. Community and healthcare institutions should strengthen health education and integrate psychological interventions alongside cognitive improvement. Interventions should aim to guide patients in channeling their fear of hypoglycemia into positive management motivation, thereby reducing hypoglycemia risk and enhancing overall management quality.

Methods: A community-based cross-sectional survey was conducted in Beijing, China, from September–December 2024, enrolling 704 patients with diabetes. Latent class analysis (LCA) was used to identify behavioral patterns associated with hypoglycemia management, and a structural equation model (SEM) was constructed to examine the associations of hypoglycemic events, fear, and cognition with these behavioral patterns.

Results: Three distinct categories of hypoglycemia-related behaviors were identified among patients with diabetes: Class 1 (35.94%, 253/704), Class 2 (37.50%, 264/704), and Class 3 (26.56%, 187/704). Fear of hypoglycemia had a positive effect on Class 3 ($\beta = 0.081$) but a negative effect on Class 2 ($\beta = -0.123$). Previous hypoglycemic events directly affected behavioral patterns (e.g., direct effect on Class 3, $\beta = 0.067$) and also exerted an indirect effect through fear of hypoglycemia (indirect effect, $\beta = 0.218 \times 0.081 = 0.018$). Higher levels of hypoglycemia-related cognition were positively associated with Class 3 ($\beta = 0.118$).

Conclusion: The heterogeneous patterns of hypoglycemia management behavior underscore the need for tailored interventions. Targeted hypoglycemia education combined with psychological support may help patients channel fear into positive management motivation, thereby improving self-management and reducing hypoglycemia risk.

ABSTRACT

Introduction: Hypoglycemia remains a critical challenge in diabetes management, with potentially severe consequences, including seizures, loss of consciousness, and death. Fear of hypoglycemia influences self-management behaviors among patients with diabetes. This study aimed to identify behavioral patterns of hypoglycemia management and examine how hypoglycemia-related fear and cognitive level affect these patterns.

Diabetes-related hypoglycemia, particularly hypoglycemia unawareness, can cause severe consequences, including loss of consciousness, seizures, and death (1), with approximately 21% of insulin-treated patients experiencing severe hypoglycemia annually (2). Current diabetes guidelines emphasize five key components of blood glucose management (the "five carriages") comprising health education, pharmacotherapy, glucose monitoring, dietary

management, and exercise (3). Psychological factors have garnered increasing attention, and the American Diabetes Association recommended incorporating psychological interventions into clinical practice guidelines in 2016 (4). However, research on fear of hypoglycemia has mainly focused on individual self-management behaviors, with limited evidence regarding broader behavioral patterns. Therefore, this study used latent class analysis (LCA) and structural equation modeling (SEM) to identify management patterns and examine the associations between fear of hypoglycemia and behavioral patterns, providing evidence for optimizing prevention and diabetes management.

The data were obtained from the "Survey of Hypoglycemia Cognition and Incidence in Community Diabetic Patients in Beijing Area." The required sample size was calculated using a formula for cross-sectional surveys, based on the reported misperception rate regarding hypoglycemia among people with diabetes ($p=34.36\%$) (5), $\alpha=0.05$, and a permissible error of $\delta = 0.1 \times p=0.034$. After accounting for a 10% nonresponse rate, the calculated sample size was 806 people. From September to December 2024, one community health center was randomly selected from each of five Beijing districts, and eligible patients were recruited according to predefined criteria.

Participants had confirmed diabetes, recent community follow-up records, complete medical information, and provided informed consent. Patients with an incomplete diabetes history, communication difficulties, or acute critical illness were excluded. A total of 806 community-dwelling diabetic patients were initially enrolled. After screening, 53 questionnaires with incomplete information and 49 participants who were uncertain whether they had experienced hypoglycemic events were excluded, yielding a final analytic sample of 704 subjects. The study was approved by the Ethics Committee of Beijing Hospital (Ethics No.: 2024BJYYEC-KY322-01), and all participants provided written informed consent.

A blood glucose level ≤ 70 mg/dL (3.9 mmol/L) accompanied by corresponding symptoms is typically regarded as hypoglycemia (1). In this study, hypoglycemic events were reported by participants after diabetes diagnosis, based on hypoglycemic symptoms or blood glucose < 3.9 mmol/L. Data were collected using a self-designed questionnaire that was reviewed by an expert panel and demonstrated good

internal consistency (Cronbach's $\alpha > 0.81$). The questionnaire assessed hypoglycemia history, education, medication risk, exercise, and dietary supplementation. Regular management was defined as blood glucose self-monitoring at least once per week or attending a diabetes-related medical visit at least once every three months. Fear of hypoglycemia was assessed using a self-reported item ranging from 0 to 10, with higher scores indicating greater fear. This approach was used to provide a brief assessment of overall fear while reducing respondent burden. Hypoglycemia-related cognitive level was evaluated using nine items covering diagnostic criteria, intervention strategies, appropriate food selection, fasting blood glucose targets, 2-hour postprandial blood glucose targets, glycosylated hemoglobin control goals, symptom recognition, awareness of precipitating factors, and awareness of serious complications. Each item was scored on a scale of 0 to 6, yielding a maximum total score of 54.

Statistical analyses were performed using R software (version 4.5.1; the R Foundation for Statistical Computing, Vienna, Austria). LCA was used to identify distinct behavioral patterns related to hypoglycemia management among diabetic patients. The optimal number of latent classes was determined based on entropy, Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and adjusted BIC (aBIC). Entropy values closer to 1 indicate superior classification accuracy, whereas lower AIC, BIC, and aBIC values reflect better model fit. Class 1 served as the reference group in subsequent analyses. An SEM was then constructed to examine the associations of hypoglycemic events, fear, and cognition with these behavioral patterns. Model fit was evaluated using the following indices: chi-square to degrees of freedom ratio (χ^2/df), Standardized Root Mean Square Residual (SRMR), Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and Tucker-Lewis Index (TLI). Acceptable model fit was defined as $\chi^2/\text{df} < 3.00$, SRMR < 0.08 , RMSEA < 0.08 , CFI > 0.90 , and TLI > 0.90 . Statistical significance was set at $P < 0.05$.

Among 704 diabetic patients, the mean age was 64.98 ± 10.71 years; 47.59% (335/704) were female (Table 1). Nearly half (48.15%, 339/704) reported experiencing hypoglycemic events. Hypoglycemia was more common among patients with lower education level, suburban residence, resident medical insurance, use of high-risk medications, inadequate monitoring, dietary supplementation, and higher fear and cognition scores.

TABLE 1. Basic characteristics of study subjects.

Variable	Total (N=704)	Hypoglycemic event		t/χ^2	P
		No (n=365)	Yes (n=339)		
Age (years)	64.98±10.71	64.74±10.32	65.24±11.13	0.62	0.53
Age group				0.09	0.77
<65 years old	293 (41.62)	150 (51.19)	143 (48.81)		
≥65 years old	411 (58.38)	215 (52.31)	196 (47.69)		
Gender				0.74	0.39
Male	369 (52.41)	197 (53.39)	172 (46.61)		
Female	335 (47.59)	168 (50.15)	167 (49.85)		
Education level				4.50	0.03
Junior high school and below	335 (50.43)	170 (47.89)	185 (52.11)		
High school or above	349 (49.57)	195 (55.87)	154 (44.13)		
Occupation				2.75	0.10
Unemployed	590 (83.81)	314 (53.22)	276 (46.78)		
Employed	114 (16.19)	51 (44.74)	63 (55.26)		
Living alone				0.04	0.85
No	637 (90.48)	331 (51.96)	306 (48.04)		
Yes	67 (9.52)	34 (50.75)	33 (49.25)		
Residential location				35.57	<0.01
Suburban	315 (44.74)	124 (39.37)	191 (60.63)		
Urban	389 (55.26)	241 (62.95)	148 (38.05)		
Medical insurance				31.94	<0.01
Residents' insurance	420 (59.66)	181 (43.10)	239 (56.90)		
Urban employee basic medical insurance	284 (40.34)	184 (64.79)	100 (35.21)		
Disposable annual income				5.08	0.17
Unclear	28 (3.98)	18 (64.29)	10 (35.71)		
0-49,999	261 (37.07)	126 (48.28)	135 (51.72)		
50,000-99,999	232 (32.95)	117 (50.43)	115 (49.57)		
≥100,000	183 (25.99)	104 (56.83)	79 (43.17)		
Health education				0.86	0.36
No	359 (50.99)	180 (50.14)	179 (49.86)		
Yes	345 (49.01)	185 (53.62)	160 (46.38)		
Hypoglycemic low-risk drug				30.20	<0.01
No	234 (33.24)	87 (37.18)	147 (62.82)		
Yes	470 (66.76)	278 (59.15)	192 (40.85)		
Regular management				4.65	0.03
No	274 (38.92)	156 (56.93)	118 (43.07)		
Yes	430 (61.08)	209 (48.60)	221 (51.40)		
Physical activity/Exercise				2.03	0.15
No	243 (34.52)	117 (48.15)	126 (51.85)		
Yes	461 (65.48)	248 (53.80)	213 (46.20)		
Snacking				5.39	0.02
No	310 (44.03)	176 (56.77)	134 (43.23)		
Yes	394 (55.97)	189 (47.97)	205 (52.03)		

Continued

Variable	Total (N=704)	Hypoglycemic event		t/χ^2	P
		No (n=365)	Yes (n=339)		
Smoking				1.12	0.57
Never smoked	425 (60.37)	225 (52.94)	200 (47.06)		
Previous smoker	116 (16.47)	55 (47.41)	61 (52.59)		
Smoking now	163 (23.15)	85 (52.15)	78 (47.85)		
Drinking alcohol				0.62	0.73
Never drank alcohol	450 (63.92)	232 (51.56)	218 (48.44)		
Once drank alcohol	74 (10.51)	36 (48.65)	38 (51.35)		
Drinking alcohol now	180 (25.57)	97 (53.89)	83 (46.11)		
Diabetes type				3.51	0.06
Type 1	51 (7.24)	20 (39.22)	31 (60.78)		
Type 2	653 (92.76)	345 (52.83)	308 (47.17)		
Fear of hypoglycemia (point)	4.00 (0.00, 7.00)	3.00 (0.00, 6.00)	5.00 (2.00, 8.00)	6.13	<0.01
Hypoglycemia-related knowledge (point)	24.00 (18.00, 30.00)	22.50 (15.00, 28.50)	25.50 (19.50, 30.00)	4.34	<0.01

LCA was conducted using hypoglycemia-related behavioral indicators aligned with the "five carriages" framework. The optimal number of latent classes was determined based on AIC, BIC, aBIC, and entropy values (Figure 1). Class 1 (35.94%, 253/704) showed low probabilities of engaging in all management behaviors. Class 2 (37.50%, 264/704) exhibited a higher probability of using low-risk medications and engaging in physical activity or exercise. Class 3 (26.56%, 187/704) was characterized by regular monitoring but relatively low probabilities of engaging in other behaviors.

SEM was used to examine relationships among behavioral classes, hypoglycemic events, fear, cognition, and demographics. All path coefficients reached significance ($P<0.05$), with good model fit (Figure 2): $\chi^2/\text{df}=0.756$ (18.889/25), SRMR=0.017, RMSEA=0.000, CFI=1.000, TLI=1.025. Fear of hypoglycemia was positively associated with Class 3 (the monitoring-based pattern, $\beta=0.081$) but negatively associated with Class 2 (the exercise-based pattern, $\beta=-0.123$). Hypoglycemic events influenced behavioral patterns both directly (Class 3, $\beta=0.067$) and indirectly through fear (Class 2, $\beta=0.218 \times -0.123 = -0.027$; Class 3, $\beta=0.218 \times 0.081 = 0.018$). Cognitive level was directly and positively associated with Class 3 ($\beta=0.118$).

DISCUSSION

The proportion of participants reporting hypoglycemic events was 48.15%, higher than the

32.18% reported among patients with type 2 diabetes in Xi'an (6). The inclusion of patients with type 1 diabetes, who had a higher proportion of reported hypoglycemic events than those with type 2 diabetes (60.78%/47.17%), as well as the use of self-reported events, may have contributed to the higher proportion observed in this study. Our findings align with Finn et al. (7) and Polonsky et al. (8), indicating that hypoglycemic events heighten patients' fear, and that fear exerts a double-edged effect. Specifically, concern about exercise-induced hypoglycemia reduces physical activity, whereas fear may promote glucose monitoring behaviors, albeit potentially leading to over-monitoring. These results imply that patients' awareness of hypoglycemia risk and their self-management practices require further optimization. Patients' hypoglycemia awareness level was positively associated with Class 3. Accurate diabetes-care knowledge may facilitate appropriate self-care behaviors (9), highlighting the importance of health education. However, even in the behavioral pattern with the highest proportion of patients receiving hypoglycemia-focused education, fewer than 60% received such education, indicating insufficient emphasis on non-pharmacological management.

Future diabetes management should integrate glucose monitoring, hypoglycemia risk assessment, symptom recognition, exercise guidance, hypoglycemia self-management skills, and psychological interventions, with enhanced health education for patients and caregivers (1). Polonsky et al. (8) proposed the "Four FEEL SAFE strategies" to address fear of

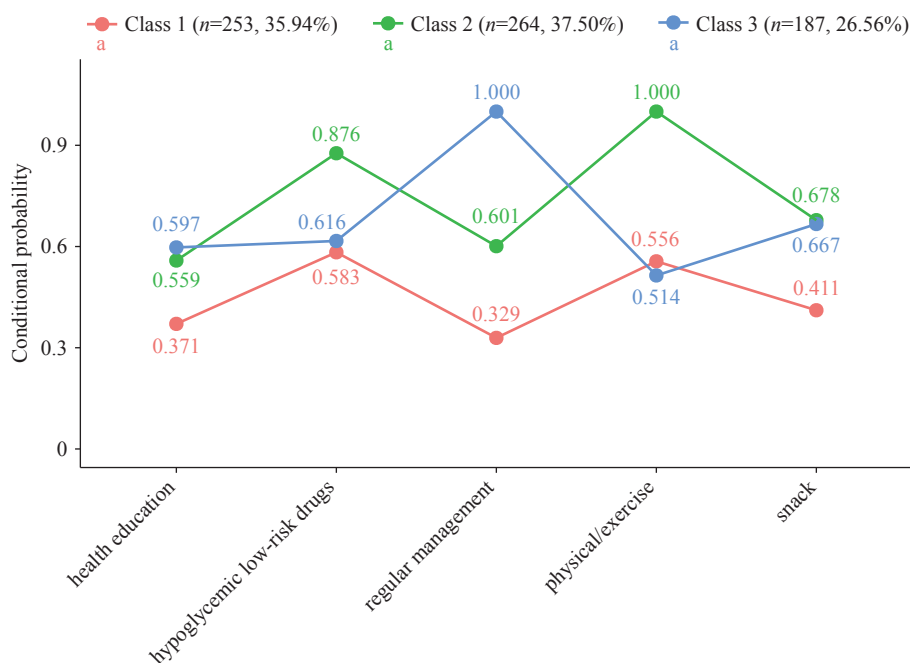


FIGURE 1. Latent class analysis (LCA) results.

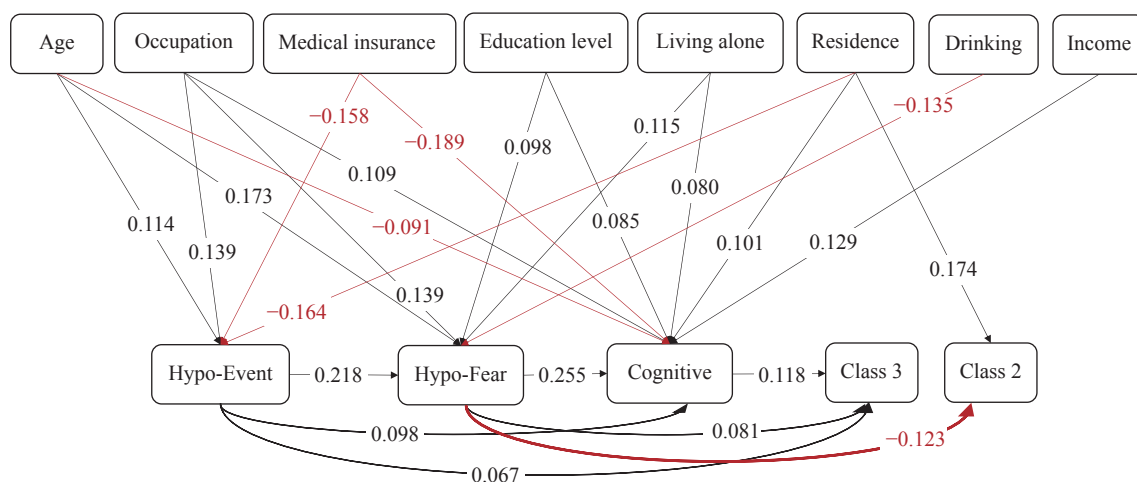


FIGURE 2. Structural equation model of factors influencing the hypoglycemia management model.

Abbreviation: Hypo-Event=hypoglycemic events; Hypo-Fear=fear of low blood sugar; Residence=residential location classified by community economic level.

hypoglycemia, including appropriate use of diabetes technologies, training to identify hypoglycemia symptoms, mastery of hypoglycemia management techniques, and incremental behavioral exposure. These strategies provide a pathway for hypoglycemia risk management and psychological intervention. Given that older patients are more prone to hypoglycemia unawareness (*1*), leveraging intelligent, individualized, and safe glucose monitoring tools, such as real-time continuous glucose monitoring (rt-CGM) systems, may help detect occult hypoglycemic events

through timely alerts, thus improving risk recognition and self-management and enhancing independent diabetes management (*10*). Healthcare professionals should strengthen awareness of hypoglycemia health education and enhance guidance on patient behavior management and health literacy to foster a rational understanding of hypoglycemia risk, balancing risk reduction with quality of life.

This study has several limitations. First, hypoglycemic events were assessed through participant self-report, which may have introduced recall bias,

particularly among middle-aged and older adults. Consequently, the occurrence of hypoglycemic events may have been overestimated or underestimated. Second, fear of hypoglycemia was assessed using a single item, which may not capture its multidimensional nature. Third, this study was conducted exclusively in Beijing communities, which limits sample representativeness and restricts the generalizability of the conclusions to other populations and settings. Finally, type 1 diabetes accounted for only 7.24% of participants, preventing subgroup comparisons between type 1 and type 2 diabetes.

This study identified distinct latent categories of hypoglycemia management behaviors among diabetic patients and demonstrated that hypoglycemic events, fear, and cognitive level exert direct or indirect effects on patients' behavioral patterns. These findings provide an evidence base for reducing hypoglycemia risk and optimizing personalized management strategies.

Ethical statement: The study was approved by the Ethics Committee of Beijing Hospital (Ethics No.: 2024BJYYEC-KY322-01), and all participants provided written informed consent.

Conflicts of interest: No conflicts of interest.

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Outbreak Reports

Investigation of a Fatal Imported Case of Melioidosis — Jingmen City, Hubei Province, China, May 2026

Kun Sun^{1,2,&}; Man Liu^{3,&}; Xinyang Zhou⁴; Dan Wu⁵; Ziheng Chen⁶; Qi Chen^{3,#}; Yang Wu³

Summary

What is already known about this topic?

Melioidosis, caused by the bacterium *Burkholderia pseudomallei* (*B. pseudomallei*), is endemic in tropical coastal regions.

What is added by this report?

This report describes a fatal imported case of sequence type 55 (ST55) melioidosis from Hainan Province. The patient developed sepsis and multiple organ failure and died within 2 days after admission; the diagnosis was confirmed only after death.

What are the implications for public health practice?

Clinicians in nonendemic areas should consider melioidosis in febrile travelers, obtain a thorough travel history, and use rapid polymerase chain reaction (PCR) diagnostics. Strengthening clinical awareness and laboratory capacity is essential for early detection and improved outcomes.

sequence type 55 (ST55). Based on the patient's epidemiological history, the case was classified as imported from Hainan Province.

Conclusion: This case underscores the need for clinicians in nonendemic regions to consider melioidosis in febrile travelers, obtain a thorough travel history, and use rapid molecular diagnostics, including polymerase chain reaction (PCR). Strengthening clinical awareness and laboratory capacity is essential to improve patient outcomes and public health preparedness.

On May 30, 2026, the Jingmen Center for Disease Control and Prevention (CDC) reported a positive blood culture for *Burkholderia pseudomallei* (*B. pseudomallei*) from a patient at Jingmen People's Hospital who died on May 25. The Hubei CDC immediately initiated an epidemiological investigation to identify the infection source and implement control measures to prevent further transmission.

ABSTRACT

Introduction: Melioidosis, caused by *Burkholderia pseudomallei* (*B. pseudomallei*), is endemic in tropical coastal regions. We report a fatal imported case of melioidosis in Hubei Province, China.

Methods: Clinical and epidemiological data were collected through a retrospective review of electronic medical records and semi-structured interviews with attending physicians and family members. Whole-genome sequencing (WGS) was performed for molecular source tracing.

Results: The patient had fever and palpitations for 2 weeks while in Hainan Province. On illness day 17 (hospital day 1), sepsis and acute kidney injury were evident at admission. Empiric imipenem/cilastatin, the first-line agent for severe *B. pseudomallei* infection, was initiated; however, the patient died of multiple organ failure 2 days later. *B. pseudomallei* was identified only after death, from blood culture. Multilocus sequence typing (MLST) identified the clinical isolate as

INVESTIGATION AND RESULTS

The 59-year-old man denied a history of diabetes or chronic kidney disease. However, ultrasonography on May 23 showed findings consistent with chronic kidney disease and bilateral renal calculi. On May 7, while in Hainan Province, he developed fever and fatigue with dizziness, palpitations, chest tightness, and nausea. His symptoms did not improve after treatment at a local clinic, and he returned to Jingmen on May 20.

At 15:56 on May 23, he presented to a county hospital with intermittent fever (38.3 °C), palpitations, chest tightness, and oliguria. On admission, his creatinine (CREA) was 1,711.3 μmol/L, indicating acute kidney failure and a critical condition, and procalcitonin (PCT) was 23.2 ng/mL, indicating severe infection. Empiric imipenem/cilastatin was initiated.

Nucleic acid and serological tests ruled out common pathogens (Supplementary Table S1, available at <https://weekly.chinacdc.cn/>), and a blood culture was performed.

On May 24, his condition deteriorated to sepsis with multiorgan dysfunction, and his family requested transfer to the municipal hospital. Tests that afternoon showed a marked decrease in white blood cell count (WBC, $1.11 \times 10^9/L$), severe thrombocytopenia [platelet count (PLT), $72 \times 10^9/L$], and elevated inflammatory markers, including C-reactive protein (CRP, 202.45 mg/L) and interleukin-6 (IL-6, >4,000 pg/mL). Hepatic injury worsened, with alanine aminotransferase (ALT) at 120 U/L and aspartate aminotransferase (AST) at 388 U/L. Renal function remained poor, with CREA at 823.5 $\mu\text{mol/L}$ and estimated glomerular filtration rate (eGFR) at 5.52 mL/min per 1.73 m^2 . Myocardial injury was evident, with B-type natriuretic peptide (BNP) >5,000 pg/mL and creatine kinase-myocardial band (CK-MB) at 81 U/L. Urinalysis showed proteinuria (++) , hematuria (++) , and bacteriuria (286.9/ μL), suggesting concurrent urinary tract involvement. Imipenem/cilastatin was continued.

On the morning of May 25, overt disseminated intravascular coagulation (DIC) developed, with platelet count falling to $26 \times 10^9/L$ and D-dimer increasing to 13.11 $\mu\text{g/mL}$ (Supplementary Table S2, available at <https://weekly.chinacdc.cn/>). The family then opted to withdraw treatment. He was discharged at 10:00 and died at home at 12:00 that day.

On May 26, the county hospital's blood culture identified *B. pseudomallei* but was not reported to the

local CDC. On May 30, the municipal hospital's blood culture also identified *B. pseudomallei* and was reported to the municipal CDC (Figure 1). On May 31, the assembled sequence was uploaded to PubMLST (<https://pubmlst.org>; ID: 7855). Comparison of the seven housekeeping genes (*ace*, *gltB*, *gmhD*, *lepA*, *lipA*, *narK*, *ndh*) yielded sequence type 55 (ST55). Phylogenetic analysis of strain HB26JM070BP01 with 65 domestic and geographically proximate *B. pseudomallei* strains assessed evolutionary relationships. It clustered most closely with strain 35 from Dongfang City, Hainan Province, isolated in 2019, at a distance of 3,349 single-nucleotide polymorphisms (SNPs) (Figure 2; Supplementary Table S3, available at <https://weekly.chinacdc.cn/>).

From March through May 20, the patient weeded betel nut nurseries in Hainan Province. Whether he had skin wounds was unknown; however, exposure to warm, moist soil remained a possible route of infection. After returning to Jingmen, he had no symptoms suggestive of bacterial shedding, such as cough, sputum, or vomiting. He lived in a self-built rural house with an independent septic tank, acceptable sanitation, and no obvious pollutants. Bathroom wastewater drained directly into the septic tank. His brother delivered all meals, and no visitors or contacts were recorded before hospitalization. During hospitalization, medical procedures and laboratory testing could have generated aerosols. After he died at home, his brothers bathed the body, and the wastewater drained through the bathroom floor drain into the septic tank. They placed the body in a paper

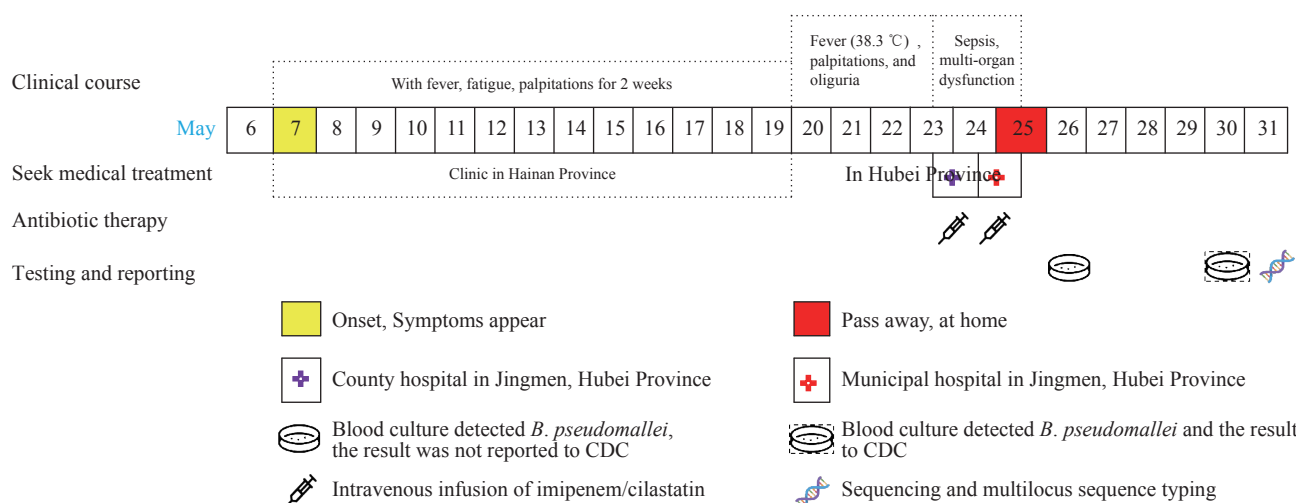


FIGURE 1. The timeline shows the clinical course, antimicrobial therapy, and pathogen identification for a fatal imported case of melioidosis in Hubei, China, 2026.

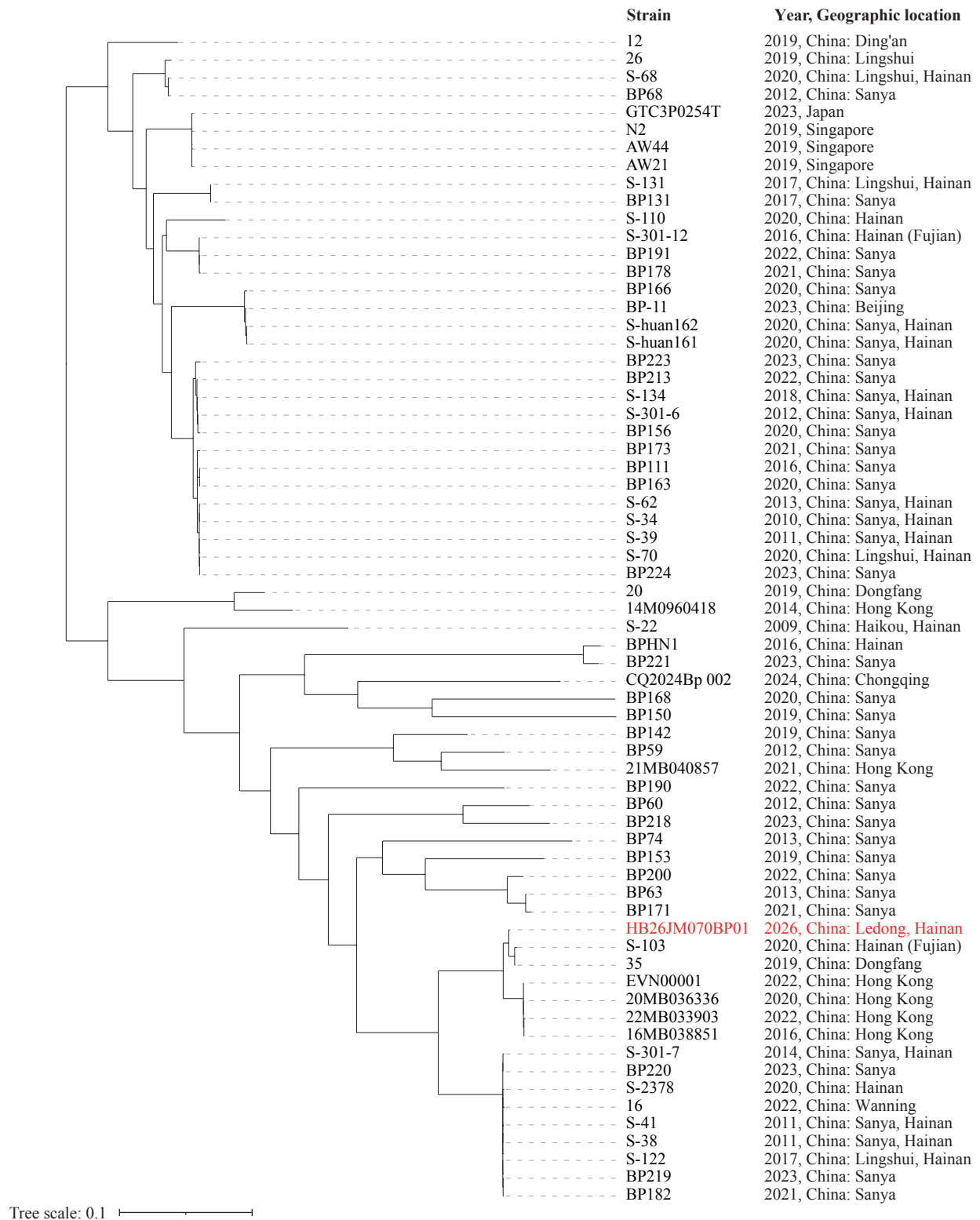


FIGURE 2. The phylogenetic tree comprises 66 *Burkholderia pseudomallei* strains.

coffin and transported it to a crematorium.

Environmental swabs ($n=54$) were collected from his residence ($n=13$; high-touch surfaces, toilet, and other sites), county and municipal hospitals ($n=39$; high-

touch surfaces and other sites), and the garbage station ($n=2$; a stretcher and a towel) (Table 1). Blood samples ($n=37$) were obtained from healthcare workers ($n=30$), individuals in direct contact with the deceased ($n=3$),

TABLE 1. The environmental sampling results from Jingmen, Hubei Province, China, 2026.

Sampling location	Total	The number of nucleic acid-positive	The number of nucleic acid-negative
Patient's residence	13	0	13
Garbage station	2	0	2
County hospital			
Department of infectious diseases	3	0	3
Laboratory department	10	0	10
Municipal hospital			
Ambulance	10	0	10
ICU	9	0	9
Laboratory department	7	0	7

Abbreviation: ICU=Intensive Care Unit

and family members ($n=4$). All samples tested negative for *B. pseudomallei* by polymerase chain reaction (PCR).

PUBLIC HEALTH RESPONSE

After the report, public health authorities initiated an epidemiological investigation, identified and monitored close contacts in healthcare, visitation, medical, and funeral settings, collected and tested environmental and clinical samples, and provided health education. Terminal disinfection targeted the septic tank, surfaces exposed to the patient, hospital wards, and transport vehicles.

No symptoms were observed among at-risk personnel during the 21-day monitoring period.

DISCUSSION

This is the first fatal imported melioidosis case reported in Jingmen, Hubei Province. The patient had resided in Hainan Province, where melioidosis is endemic. In 2024, Wuhan, Hubei Province, reported another imported case from Hainan Province, whose isolate was sequence type 46 (ST46), the predominant genotype circulating there (1). Together, these cases suggest that, although melioidosis is not endemic in Hubei, cross-regional importation poses a tangible risk warranting strengthened clinical awareness and public health surveillance.

The isolate belonged to ST55. Molecular epidemiological surveys have consistently identified ST55 as a predominant sequence type of *B. pseudomallei* in Hainan Province, accounting for 8.2% (10/122) – 13.2% (12/91) of clinical isolates, mainly in southwestern Hainan (2–4). He worked in Ledong

County, in southwestern Hainan, consistent with the reported distribution of ST55. His weed control work involved exposure to warm, moist soil, conditions that may facilitate *B. pseudomallei* infection.

The current case shared epidemiological exposures with the Wuhan case, including comparable age, farm work in Hainan Province, high-temperature and high-humidity environments, and daily contact with moist soil and surface water. However, the clinical courses and outcomes differed markedly. In that case, initial symptoms were periumbilical and joint pain, and blood culture confirmed the diagnosis on fever day 3, allowing timely imipenem administration and a favorable outcome (1). In contrast, he had intermittent fever for more than 2 weeks and had already developed sepsis and acute kidney failure by illness day 17, at presentation to the county hospital. Although imipenem, the first-line agent for severe *B. pseudomallei* infection (5), was initiated that day, the optimal therapeutic window had likely been missed, and he died of multiple organ failure. These findings underscore the importance of early pathogen screening and prompt intensified anti-infective therapy, particularly for patients with unexplained fever or sepsis returning from endemic regions.

The clinical manifestations of melioidosis are typically nonspecific and can resemble the common cold, pneumonia, sepsis, or tuberculosis (6–7). Here, he was treated at a local clinic in Hainan Province for nearly 2 weeks without improvement and subsequently presented to county and municipal hospitals in Hubei Province. At admission, he was critically ill, and blood cultures were obtained to identify the causative agent. However, *B. pseudomallei* was identified only after his death. This course highlights insufficient diagnostic awareness among primary care physicians, including

those in endemic areas. Blood culture, the diagnostic mainstay, is also time-consuming and has limited sensitivity, further complicating diagnosis (7–8).

Although autochthonous cases have been reported in inland provinces such as Anhui and Jiangxi, melioidosis remains extremely rare there (9). Healthcare workers in nonendemic regions may therefore have limited awareness of melioidosis and seldom include it in the differential diagnosis for febrile patients. Because melioidosis is not a legally notifiable infectious disease in China, medical institutions may also be less aware of the need to report it. This can delay the public health response and increase the risk of pathogen carriers shedding bacteria in nonendemic areas.

This case has several implications for public health practice in nonendemic regions. First, healthcare providers should maintain a high index of suspicion for melioidosis in febrile patients returning from endemic regions, including southern China and Southeast Asia, particularly those with reported skin wounds and exposure to contaminated soil or water. Second, clinical laboratories in nonendemic regions need diagnostic capacity, including rapid molecular methods such as PCR, to correctly identify *B. pseudomallei* and reduce turnaround time. Third, training in disease recognition and reporting should be strengthened at all levels of medical institutions, particularly county-level hospitals, community health service centers, and primary clinics that may encounter rare or emerging infectious diseases. Finally, CDCs in inland provinces should incorporate melioidosis into travel-related disease surveillance and develop rapid response plans for imported cases.

Conflicts of interest: No conflicts of interest.

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SUPPLEMENTARY MATERIALS

Laboratory Testing Methods

Nucleic Acid Test

Target genes: Real-time fluorescence PCR targeted the 115 bp fragment of the orf2 gene in type III secretion system gene cluster 1 (TTS1) of *B. pseudomallei*. Primers and probes: PCR used primer and probe sequences targeting TTS1-orf2 reported by Novak et al (1). Amplification with Rotor Gene was performed as follows: initial denaturation at 94 °C for 10 min, then 45 cycles of 94 °C for 15 s and 60 °C for 1 min. Cycle threshold (Ct): Samples with a Ct <40 were considered positive.

Genomic DNA Extraction and Sequencing

Total genomic DNA was extracted from inactivated *B. pseudomallei* strains using a bacterial genomic DNA extraction kit [Tiangen Biochemical Technology (Beijing) Co., Ltd., item number DP302]. DNA concentration and OD 260/280 ratio were measured with a NanoDrop Lite spectrophotometer, and DNA integrity and quality were assessed by 1.5% agarose gel electrophoresis. DNA that passed these checks was used directly for library construction, without PCR amplification. Paired-end sequencing was then performed on an Illumina MiSeq platform with a read length of 150 bp (PE150). Sequencing followed standard procedures, and raw data were output in FASTQ format for subsequent bioinformatics analysis.

Multilocus Sequence Typing (MLST)

The assembled sequence was aligned using the PubMLST *B. pseudomallei* MLST database (pubmlst.org/bpseudomallei) to determine the sequence type (ST). The isolated strain was identified as ST55.

Phylogenetic Analysis Method

Genomic Acquisition of Bacterial Strains

A search was conducted in the NCBI Genomes database using *B. pseudomallei* as the keyword, and genomes from China and from geographically proximate countries and regions were screened. Genomic contigs, integrity, and other indicators were also used for screening. Finally, 65 bacterial genomes were included, and the target genome

SUPPLEMENTARY TABLE S1. Hospital-based laboratory findings from nucleic acid and serum antibody testing for pathogens.

Sampling time	Test item	Report time	Method	Results
May 23, 16:13	Respiratory syncytial virus	May 24, 15:03	IgM antibody test	Negative (-)
	Adenovirus			
	Legionella pneumophila			
	Mycoplasma pneumoniae			
	Chlamydia pneumoniae			
	Dengue virus	May 24, 15:49	PCR	Negative (-)
	Chikungunya virus			
	Novel Bunyavirus			
	Influenza A virus			
	Influenza B virus			
May 24, 14:22	Hemorrhagic fever with renal syndrome virus	May 24, 17:03	IgM antibody test	Negative (-)
	Epstein-Barr virus DNA	May 26, 08:18	PCR	Negative (-)
	<i>Burkholderia pseudomallei</i>	May 26, 08:47	Blood culture	Positive (+)
May 24, 14:22	<i>Burkholderia pseudomallei</i>	May 30, 10:08	Blood culture	Positive (+)

Abbreviation: IgM=immunoglobulin M; PCR=polymerase chain reaction.

SUPPLEMENTARY TABLE S2. Dynamic changes in hospital-based laboratory test results for the case.

Test item	Reference range	County People's Hospital		Municipal People's Hospital	
		May 23, 16:13	May 24, 05:48	May 24, 14:00–17:00	May 25, 07:00–08:00
Inflammatory/infectious markers					
PCT (ng/mL)	≤0.5	23.20 ↑	35.31 ↑	57.92 ↑↑	54.80 ↑↑
IL-6 (pg/mL)	≤7.0	358.56 ↑	>5,000 ↑	>4,000 ↑	>4,000 ↑
CRP (mg/L)	≤8.0	110.10 ↑	–	202.45 ↑↑	–
Fer (ng/mL)	27–375	>1,500 ↑	–	–	1,685.30 ↑↑
Blood routine					
WBC (×10 ⁹ /L)	3.5–9.5	9.08	3.32 ↓	1.11 ↓↓	2.22 ↓
RBC (×10 ¹² /L)	4.3–5.8	1.8↓	2.6↓	2.5↓	2.17↓
NEUT (%)	45–75	97.6 ↑	98.2 ↑	94.4 ↑	93.2 ↑
LYM (%)	20–50	1.3 ↓	0.9 ↓	5.5 ↓	4.2 ↓
HGB (g/L)	130–175	54 ↓↓	76 ↓	71 ↓	66 ↓
PLT (×10 ⁹ /L)	125–350	149	110 ↓	72 ↓↓	26 ↓↓↓
DIC trend					
PT (s)	11.5–14.5	15.3 ↑	–	26.3 ↑↑	39.7 ↑↑↑
APTT (s)	29.0–42.0	41.3	–	85.4 ↑↑	80.8 ↑↑
INR	0.8–1.2	1.19	–	2.34 ↑↑	3.95 ↑↑
FIB (g/L)	2.0–4.0	3.84	–	3.12	1.24 ↓↓
DD (μg/mL)	<0.5	11.53 ↑	–	12.32 ↑	13.11 ↑
FDP (μg/mL)	≤5	–	–	50.74 ↑↑	51.65 ↑↑
Liver and kidney function and myocardial injury					
CREA (μmol/L)	57–97	1,711 ↑↑	860.3 ↑↑	823.5 ↑↑	–
BUN (mmol/L)	1.7–8.3	50.76 ↑↑	27.07 ↑↑	27.04 ↑↑	–
eGFR (mL/min per 1.73m ²)	≥90	2.17 ↓↓	5.08 ↓↓	5.52 ↓↓	–
ALT (U/L)	9–50	32	–	120 ↑↑	–
AST (U/L)	8–40	67 ↑	–	388 ↑↑↑	–
LDH (U/L)	135–225	457 ↑	715 ↑	777 ↑↑	–
CK (U/L)	24–190	473 ↑	460 ↑	836 ↑↑	–
CK-MB (U/L)	0–24	22	29 ↑	81 ↑↑	–
hs-cTnI (ng/L)	0–18.5	–	667.0 ↑↑	–	–
hs-cTnT (pg/mL)	≤20.0	–	–	–	299.7 ↑↑
N-terminal pro-BNP (pg/mL)	≤210.64	>35,000 ↑	>35,000 ↑	–	–
BNP (pg/mL)	≤100	–	–	>5,000 ↑↑	–
Electrolyte/acid-base					
K ⁺ (mmol/L)	3.5–5.3	3.73	3.09 ↓	3.18 ↓	–
Na ⁺ (mmol/L)	135–150	128.3 ↓	137.5	135.3 ↓	–
CO ₂ CP (mmol/L)	20–29	7.7 ↓↓	6.8 ↓↓	–	–
Ca ²⁺ (mmol/L)	2.1–2.9	1.63 ↓	2.60	2.08 ↓	–
Urinalysis					
Urine PRO	Negative (–)	–	–	(++)	–
Urine Occult BLD	Negative (–)	–	–	(++)	–
Urine RBC (pcs/μL)	≤10	–	–	15.40 ↑	–

Continued

Test item	Reference range	County People's Hospital		Municipal People's Hospital	
		May 23, 16:13	May 24, 05:48	May 24, 14:00–17:00	May 25, 07:00–08:00
Urine WBC (pcs/ μ L)	≤ 12	–	–	73.30 $\uparrow$	–
Urine Bacteria Count (pcs/ μ L)	≤ 130	–	–	286.90 $\uparrow$	–

Note: $\uparrow$ and $\downarrow$ indicate values above and below the reference range, respectively; two or three arrows indicate progressively greater deviation. – = not tested.

Abbreviation: PCT=procalcitonin; IL-6=interleukin-6; CRP=C-reactive protein; Fer=ferritin; WBC=white blood cell; RBC=red blood cell; NEUT=neutrophil percentage; LYM=lymphocyte percentage; HGB=hemoglobin; PLT=platelet; DIC=disseminated intravascular coagulation; PT=prothrombin time; APTT=activated partial thromboplastin time; INR=international normalized ratio; FIB=fibrinogen; DD=D-dimer; FDP=fibrin/fibrinogen degradation products; CREA=creatinine; BUN=blood urea nitrogen; eGFR=estimated glomerular filtration rate; ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDH=lactate dehydrogenase; CK=creatinine kinase; CK-MB=creatinine kinase-myocardial band; hs-cTnI=high-sensitivity cardiac troponin I; hs-cTnT=high-sensitivity cardiac troponin T; BNP=B-type natriuretic peptide; PRO=protein; BLD=blood.

SUPPLEMENTARY TABLE S3. Single-nucleotide polymorphism (SNP) distances between strain HB26JM070BP01 and 65 *Burkholderia pseudomallei* strains.

Strain	SNP distance	Strain	SNP distance
35	3,349	12	18,232
S-103	4,145	26	18,370
EVN00001	4,888	S-68	18,456
20MB036336	4,896	BP68	18,462
16MB038851	4,903	Reference	18,586
22MB033903	4,947	AW44	18,587
BP220	8,382	AW21	18,589
S-122	8,385	N2	18,594
S-301-7	8,389	BP156	18,607
S-38	8,390	BP-11	18,670
BP219	8,391	S-huan161	18,678
S-2378	8,392	S-huan162	18,679
S-41	8,397	S-39	18,681
BP182	8,399	S-34	18,682
16	8,554	S-62	18,683
BP63	12,694	S-70	18,694
BP200	13,063	BP166	18,702
BP171	13,270	S-110	18,723
BP153	13,992	BP224	18,752
BP74	15,085	14M0960418	18,897
BP60	15,608	BP223	18,897
S-22	15,785	BP163	18,937
BP218	16,004	BP111	18,945
BP190	16,111	BP173	18,966
BP142	16,352	BP213	18,984
21MB040857	16,552	S-134	19,004
BP59	16,850	S-301-6	19,006
S-301-12	17,290	BP150	19,043
BP191	17,606	CQ2024Bp_002	19,166
BP178	17,663	BP168	19,789
BP131	18,063	BPHN1	20,370
S-131	18,063	BP221	20,703
20	18,095		

(HB26JM070BP01) was added. The recommended GTC3P0254T strain (GCF030297255.1) in the NCBI Genomes database was used as the reference genome for SNP analysis.

SNP and Phylogenetic Analysis

SNP analysis of the genomes of the included strains was performed using Snippy (version 4.6.0; Melbourne, Australia). Short-sequence alignment was performed with BWA (version 0.7.18-r1243), mutation detection with FreeBayes (version 1.3.6; Boston, USA), and distance matrices of core and inter-strain SNPs were constructed with Snippy. After recombinant regions were removed using Gubbins (version 2.4.1; Hinxton, UK), phylogenetic analysis was conducted using IQ-TREE2 (version 2.4.0; Vienna, Austria) based on the GTR+ASC model, and 1,000 bootstrap tests were performed. The phylogenetic tree was visualized with iTOL (<https://itol.embl.de/>).

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