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Original Research

Establishment and application of national reference panels for SARS-CoV-2 antigen detection kit

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ABSTRACT

To develop a national reference panel for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen detection kit and establish a quality standard. The cultures of SARS-CoV-2 and other pathogens were collected to establish a national reference panel for SARS-CoV-2 antigen detection. The stability and homogeneity of the reference panel were evaluated. Based on World Health Organization (WHO) guidance and nucleic acid quantitative results, a quality standard reference panel was established. Currently, three generations of SARS-CoV-2 antigen national reference materials with batch numbers 370095–202001, 370095–202202, and 370095–202203 have been successfully established. These national reference panels comprised 8 positive samples, 20 negative samples, 1 repetitive sample, and 1 lower detection limit sample. The stability and homogeneity of the reference panel meet the requirements. The quality standards are as follows: the positive and negative coincidence rates are 8/8 and 20/20, respectively. The 10 test results of the medium and low-concentration repetitive reference materials should be positive, and the color rendering should be uniform (or the coefficient of variance should not be higher than 20.0%). The lower detection limit should be at least 5×10^5 U/mL (equivalent to copies/mL), and higher concentrations above the lower detection limit must be positive. A national reference panel for the SARS-CoV-2 antigen detection kit has been established. As the standard of SARS-CoV-2 antigen reagents, the reference panel has played a crucial role in the pre-marketing quality evaluation and post-marketing quality supervision in China.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus and has caused a pandemic of acute respiratory disease, named 'coronavirus disease 2019′ (COVID-19). As of May 31, 2023, 767,364,883 confirmed cases had been reported, 6,938,353 deaths [1]. In May 2023, the World Health Organization (WHO) determined that COVID-19 no longer constitutes a public health emergency of international concern (PHEIC). However, it remains a severe health issue in most parts of the world. The sensitivity and specificity of molecular detection are higher than other detection methods, which is the gold standard for diagnosing COVID-19 [2]. However, nucleic acid amplification detection has high requirements for laboratory biosafety facilities, protective equipment, laboratory personnel, product quality, and instruments, and the operation is tedious and time-consuming, which cannot meet the requirements for on-site and individual rapid detection [3]. The rapid SARS-COV-2 antigen detection kit has strong specificity, simple operation, good repeatability, convenience, low cost, fast (generate results in 10-30 min), and does not need special equipment and instruments, and hence very suitable for early clinical diagnosis and on-site screening [4]. Since the emergence of antigen detection, it has been widely applied in developing countries with relatively scarce medical resources, and some developed countries have also gradually promoted antigen detection [5].

Before entering the Chinese market, the rapid SARS-COV-2 antigen detection kit needs to require approval from the China National Medical Products Administration (NMPA). As of July 10, 2023, NMPA has approved 41 antigen rapid detection reagents. As of April 2023, 5 antigen detection kits had been included on the emergency use lists by WHO, 48 by the US Food and Drug Administration (FDA), and 203 by the Conformite Europeene (CE). However, it was not until the first half of 2023 that WHO established the *1st WHO International Standard for SARS-CoV-2 Antigen*, which makes it difficult to precisely evaluate

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HIGHLIGHTS

Scientific question

The performance of the antigen kit significantly impacts the clinical accuracy of coronavirus disease 2019 (COVID-2019) diagnosis. However, it was not until the first half of 2023 that the World Health Organization (WHO) established the *1st WHO International Standard for SARS-CoV-2 Antigen*, which makes it difficult to precisely evaluate the analytical performance of antigen kits during the early stage of the epidemic, especially the limit of detection (LoD).

Evidence before this study

Commercially available samples for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antigen diagnostic tests varied on their inactivation methods used and on the units used on viral titers. These variations impose great challenge when comparing among commercialized tests, which is pivotal for making scientifically informed decision on assay uses in accordance with public health policy. Therefore, it is very necessary to develop a national reference panel for the quality assessment of SARS-CoV-2 antigen detection kits.

New findings

A quantified national reference panel for SARS-CoV-2 antigen detection kit was developed and the quality standard was established. From 2020 to 2022, we have developed three generations of SARS-CoV-2 antigen national reference panels. The potency of the lower detection limit sample is defined in a universal unit (U/mL), which facilitates comparability of results for different SARS-CoV-2 antigen kits and evaluation of assay parameters. In our study the lower detection limit was 5×10^5 U/mL and higher concentrations above the lower detection limit were positive, which is higher than the study of Paul-Ehrlich-Institute, Germany (PEI) in which the viral load was around 10^6 copies/mL and higher.

Significance of the study

The reference panels offer a unified solution for SARS-CoV-2 assay development, quality control, and regulatory surveillance.

the analytical performance of antigen kits during the early stage of the epidemic, especially the limit of detection (LoD).

To promote the approval and quality improvement of SARS-COV-2 antigen diagnostic kits from 2020 to 2022, we have developed three generations of SARS-CoV-2 antigen national reference panels. The reference panels were used for the pre-marketing quality evaluation and post-marketing quality supervision in China according to the Provisions for In-vitro Diagnostic Reagent Registration and Filing.

2. Materials and methods

2.1. Material collection and preparation

As a directly affiliated institution of China's NMPA, the National Institutes for Food and Drug Control (NIFDC) plays an essential role in the approval process of COVID-19 diagnostic reagents, which includes providing technical guidance, developing national standards, and conducting testing and supervision and at the same time, establishing the 2019 novel coronavirus antigen and antibody test reagents and the relevant guidelines from the WHO and the FDA. For the positive samples, we selected eight different SARS-CoV-2 strains in the first batch, and subsequent batches, we included different variant strains. We selected the respiratory or other pathogenic strains that may have potential cross-reactivity with SARS-CoV-2 for the negative samples.

Positive specimens were cultured in Vero cells and obtained from the People's Liberation Army (PLA) Academy of Military Sciences, the First Affiliated Hospital of Zhejiang University Medical College, National Vaccine and Serum Institute, and the Sinovac Life Sciences Co., Ltd. Negative specimens were obtained from Guangzhou Standa Biotech Co., Ltd., National Institute for Viral Disease Control and Prevention, National Institute for Communicable Disease Control and Prevention and NIFDC. All of the positive and negative materials were inactivated. The negative samples were mainly inactivated by incubating with β-propiolactone (BPL) for 48 h at 4 ℃, and the harmful materials were inactivated by incubating with BPL for 48 h at 4 ℃ or by heating at 56 ℃ for 30 min. The inactivation verification methods included cell culture and pathological effect (CPE) observation, viral immunofluorescence staining, and viral nucleic acid detection.

The positive and negative materials were diluted or freeze-dried to prepare positive, negative, lower detection limit, and repetitive reference. Each panel has 30 vials, while each vial consists of 0.5 mL volume. The positive reference included 8 vials from different sources, concentrations, and characteristics, which can be used for evaluating the diagnostic sensitivity; the negative reference contained 20 vials, which may produce a cross-reaction, to examine the specificity of the diagnosis; the lower detection limit reference contained 1 vial, which can be used for evaluating detection threshold; the repetitive reference contains a vial, which can be used to assess the within-batch and between-batch repeatability of testing reagents.

2.2. Cooperative calibration and quality standard determination

After the national reference panel was subpackaged, we assigned a reporting universal unit of U/mL (the abbreviation of Unit/mL) to the detection limit reference material based on quantitative results on multiple digital PCR (dPCR) platforms [6], then used seven detection kits based on multiple methodological principles (including colloidal gold, immunofluorescence, enzyme-linked immunosorbent, and chemiluminescence) to calibrate the reference panel (see details in Table S1 in the supplementary data), and established the quality standard of the reference panel.

2.3. Homogeneity and stability of the national reference panel

Two SARS-CoV-2 antigen detection kits performed a homogeneity study including one kit based on chemiluminescence from Beijing Kewei Clinical Diagnostic Kit, Inc. and the other kit based on latex bead from ACON Biotech (Hangzhou) Co., Ltd.

We used ACON Biotech (Hangzhou) Co., Ltd. (Latex bead) and Hangzhou Biotest Biotech Co., Ltd. (Colloidal Gold) antigen detection kits to assess the stability of the panel.

2.4. Comparative sensitivity evaluation of antigen detection kits

The national reference panel was applied to the LoD evaluation of 26 approved SARS-CoV-2 antigen detection kits from 26 manufacturers. The product information and manufacturers are summarized in Table S2 in the supplementary data.

3. Results

3.1. Establishment of the national reference panel

There were 20 negative reference materials comprised of high-concentration cultures of common respiratory pathogens, numbered

Table 1
The technical specifications of the National Reference Panel.

Type	ID	Batch			Difference among the three batches
		370095–202001	370095–202202	370095–202203	
Negative reference materials	N1	*Staphylococcus aureus*	*Staphylococcus aureus*	*Staphylococcus aureus*	None
	N2	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	None
	N3	Measles virus	Measles virus	Measles virus	None
	N4	Mumps virus	Mumps virus	Mumps virus	None
	N5	Adenovirus type 3	Adenovirus type 3	Adenovirus type 3	None
	N6	Mycoplasma pneumoniae	Mycoplasma pneumoniae	Mycoplasma pneumoniae	None
	N7	Parainfluenza type 2	Parainfluenza type 2	Parainfluenza type 2	None
	N8	Human metapneumovirus	Human metapneumovirus	Human metapneumovirus	None
	N9	Coronavirus OC43	Coronavirus OC43	Coronavirus OC43	None
	N10	Coronavirus 229E	Coronavirus 229E	Coronavirus 229E	None
	N11	*Bacillus parapertussis*	*Bacillus pertussis*	*Bordetella pertussis*	Replace *Bacillus pertussis* with *Bacillus parapertussis* in batch 202202
	N12	Influenza B/Victoria	Influenza B/Victoria	Influenza B/Victoria	None
	N13	Influenza B/Yamagata	Influenza B/Yamagata	Influenza B/Yamagata	None
	N14	Influenza A/H1N1(2009)	Influenza A/H1N1(2009)	Influenza A/H1N1(2009)	None
	N15	Influenza A/H3N2	Influenza A/H3N2	Influenza A/H3N2	None
	N16	Influenza A/H7N9	Influenza A/H7N9	Influenza A/H7N9	None
	N17	Influenza A/H5N6	Influenza A/H5N6	Influenza A/H5N6	None
	N18	Epstein-Barr virus	Epstein-Barr virus	Epstein-Barr virus	None
	N19	Enterovirus CA16	Enterovirus CA16	Enterovirus CA16	None
	N20	Rhinovirus	Rhinovirus	Rhinovirus	None
Positive reference materials	P1	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	None
	P2	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	None
	P3	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	None
	P4	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Beta Variant)	Replace wild-type with Beta variant in batch 202203
	P5	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Gamma Variant)	Replace wild-type with Gamma variant in batch 202203
	P6	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Delta Variant)	Replace wild-type with Delta variant in batch 202203
	P7	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Omicron Variant)	Replace wild-type with Omicron variant in batch 202203
	P8	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	None
Lower detection limit reference material	S	SARS-CoV-2(Wild-typev	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	202001: no unitage, 202202 and 202203: with a unitage defined in U/mL
Repetitive reference material	R	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	SARS-CoV-2(Wild-type)	None

Abbreviation: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

N1-N20, respectively. The positive reference materials were prepared by dilution with BPL or heat-inactivated SARS-CoV-2 cultures with low concentrations and numbered P1-P8, respectively. The lower detection limit and repetitive reference materials are prepared using the same wild-type SARS-CoV-2 culture with different concentrations.

Three generations of SARS-CoV-2 antigen national reference materials, 370095–202001, 370095–202202, and 370095–202203, have been successfully established and supplied. The first two batches were liquid, while batch 202203 was freeze-dried. The other details of the technical specifications of the three batches are summarized in Table 1.

3.2. Cooperative calibration results and quality standard determination

Based on quantitative results on multiple dPCR platforms, we assigned a reporting universal unit of U/mL to the detection limit reference material from a BPL-inactivated SARS-CoV-2 whole-virus in the batches of 202202 and 202203. According to dPCR results, the unitage of the detection limit reference material was 2×10^8 U/mL (equivalent to 2×10^8 copies/mL); hence, the concentration of the dilution 1:400 was 5×10^5 U/mL.

Among the 7 kits involved in the cooperative calibration of batch 202001, 3 kits based on colloidal gold and immunofluorescence failed to detect the lower detection limit reference materials and high-concentration positive samples. The other four kits' negative and positive coincidence rates were 100%, and lower detection limit performance (the dilution rate) was 1:400, 1:1,600, 1:800, and 1:400, respectively.

Combined with the cooperative calibration results, the unitage of the detection limit reference material, performance of antigen kits based on different methodological principles, and the characteristics of SARS-CoV-2 viral load in infected patients, the quality standard for SARS-CoV-2 antigen detection kits were as follows:

1) Positive coincidence rate: P1-P8 should be positive; the coincidence rate was 8/8.
2) Negative coincidence rate: N1-N20 should be negative; the coincidence rate was 20/20.
3) Lower detection limit: 5×10^5 U/mL and higher concentration should be tested as positive.
4) Repeatability: 10 test results of the medium and low concentration repetitive reference materials should be positive, and the color rendering should be uniform (or the coefficient of variance should not be higher than 20.0 %).

3.3. Results of homogeneity and stability

A random sampling of 10 repetitive reference samples was used to evaluate the homogeneity and reproducibility. The evaluation results from the SARS-CoV-2 antigen detection kit based on chemilumines-

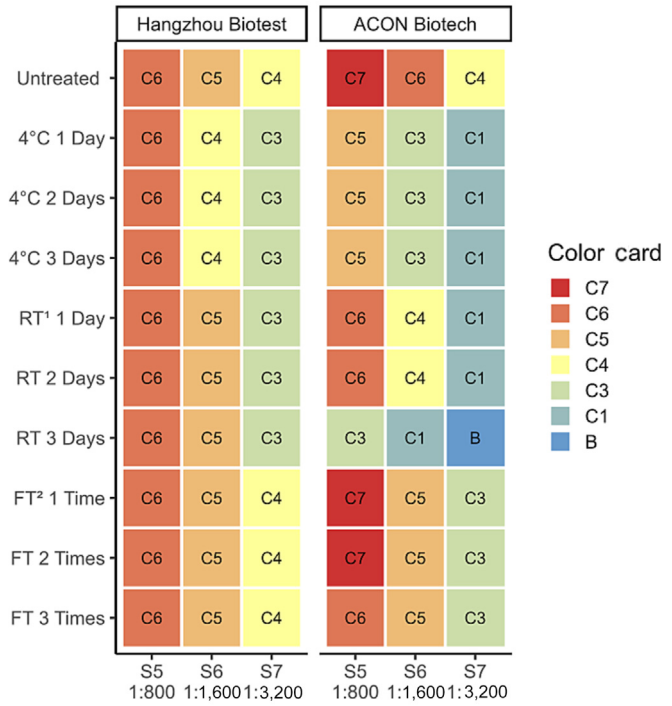

Fig. 1. Stability assessment of the lower detection limit sample *Notes:*[1]Room temperature; [2] Freezing and thawing.

cence showed that the coefficient of variation was 15.0%, which meets the quality evaluation requirements for qualitative products.

Stability results showed that except for 3 days of room temperature treatment, the other treatments, such as repeated freezing and thawing for 3 times, and 4℃ for 3 days, had no significant influence on the results (Fig. 1).

3.4. Comparative sensitivity evaluation of 26 approved antigen kits

Although the kits based on immunofluorescence were more sensitive than the others based on colloidal gold and latex bead, it was not widely used during the epidemic due to the need for special equipment. There was no significant difference between colloidal gold and latex bead. In addition, the LoD from the enterprise is inconsistent with our sensitivity evaluation results (Fig. 2).

4. Discussion

The performance of the antigen kit, especially LoD, significantly impacts the clinical accuracy of COVID-19 diagnosis [7]. LoD evaluation of SARS-CoV-2 antigen kits was affected by several factors in the early stage of the epidemic, including: (1) the LoD of different kits from different manufacturers were determined by using different samples, e.g., clinical nasal swabs, virus culture or recombinant antigen, which makes the LoDs incomparable; (2) most of the virus samples used for the LoD determination were inactivated by heating, which results in inaccurate performance assessment; (3) WHO has not established an international standard for SARS-CoV-2 Antigen detection kits. For these reasons, developing a national reference panel for the quality assessment of SARS-CoV-2 antigen detection kits is necessary.

During the past three years, three generations of SARS-CoV-2 antigen national reference materials prior to WHO international standards have been successfully established and supplied (Table 1). These national reference panels consist of 8 positive samples, 20 negative samples,1 repetitive sample, and 1 lower detection limit sample. The repetitive and lower detection limit samples were prepared with a BPL-inactivated SARS-CoV-2 culture (wild-type strain, EPI_ISL_424360) from the PLA Academy of Military Sciences. The positive reference materials of batch 202001 and 202202 were prepared with inactivated SARS-CoV-2 wild-type strains. However, batch 202203 was composed of wild-type, Beta, Gamma, Delta, and Omicron strains, which could help to evaluate the analytical reactivity. The reference was changed from liquid to freeze-dried, and the corresponding storage condition was changed from −70℃ or below to −20℃ or below to ensure the stability of the reference panel during storage, transportation, and usage.

A previous study showed a corresponding relationship between the gene copy number and the number of nucleocapsid proteins [8]. Therefore, we determined the concentration of the lower detection limit sample as 2×10^8 copies/mL by performing a collaborative study on multiple dPCR platforms in multiple laboratories [6]. Then, the copies/mL were directly converted to U/mL as the final quantitative Unit, and the value was assigned to 2×10^8 U/mL. In a

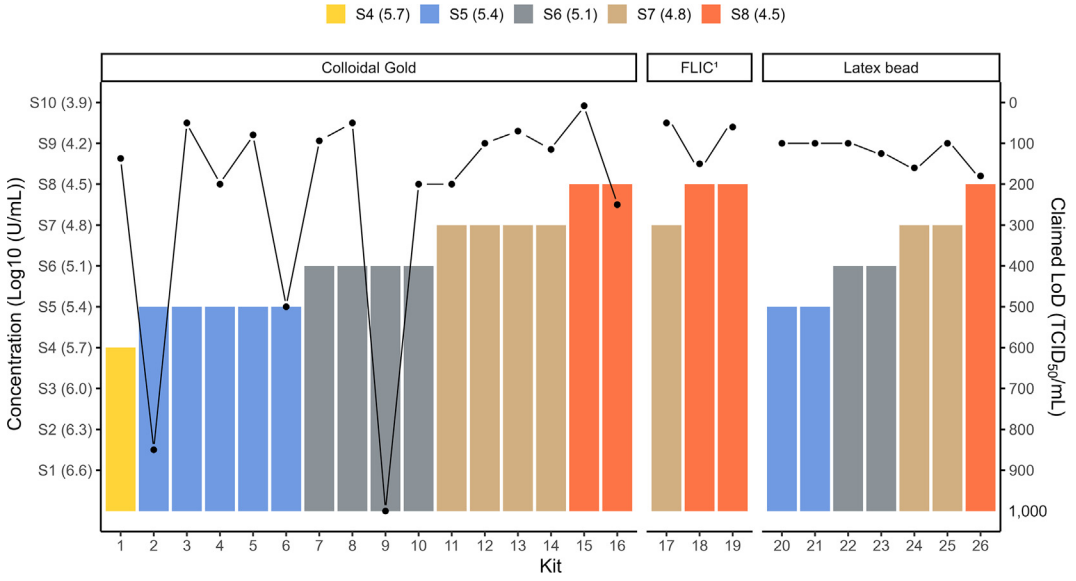

Fig. 2. The sensitivity evaluation of 26 antigen-approved kits. *Notes:*[1]Fluorescent immunochromatography. The bar chart indicates the material result of 26 approved antigen kits from the detection limit reference, and the line chart indicates the limit of detection (LoD) claimed by the enterprise.

comparative study from Paul-Ehrlich-Institute, Germany (PEI) [9], a minimum sensitivity of 75 % for panel specimens with a PCR quantification cycle (Cq) ≤ 25 was used to identify antigen kits eligible for reimbursement in Germany. According to the study, a PCR quantification cycle ≤ 25 equaled 10^6 virus RNA copies/mL. In our study, the lower detection limit was 5×10^5 U/mL, and higher concentrations above the lower detection limit were positive. This standard is higher than the study of PEI in which the viral load was around 10^6 copies/mL and higher [9]. These reference panels were used for the pre-marketing quality evaluation and post-marketing quality supervision in China.

When the reference panel (370095–202001) was calibrated, only 57% (4/7) of the kits could meet the standard of the lower detection limit. Notably, many of the kits failed to detect high concentrations of positive clinical samples, possibly due to a lack of high-quality antibody materials and insufficient reagent development. Nearly half of the products met the requirements of the national reference panel through continuous debugging and test verification in the early stage of the epidemic. In addition, our previous study showed that different inactivation methods and viral transport media significantly affect the sensitivity of the antigen kit [10]. Therefore, appropriate inactivation methods, such as BPL, should be selected. According to both the FDA and NMPA manuals, recombinant antigens are not recommended for LoD determination and evaluation; hence, the national reference panels used virus cultures as raw materials [11,12].

Compared with WHO international standard, the advantages of the national reference panels are as follows: (1) Composition: International standard consists of a single sample, while our reference panels were composed of multiple samples, including positive reference samples (as well as different SARS-CoV-2 variants), negative reference samples, lower detection limit reference sample and repetitive reference sample; (2) Purpose: International standard is used for traceability and calibration, while our reference panels were primarily used for pre-market testing, supervision sampling, and the other similar purposes; (3) Establishment process: In the establishment process, we conducted early evaluations of the impact of inactivation on the reference panels. We mainly employed the BPL inactivation method. BPL inactivation not only ensures biosafety but also avoids heat-inactivation's impact on assay detection; (4) Innovative quantification method: Digital PCR-based determination of the universal unit of U/mL provides higher reliability and traceability than the traditional units. Such a standard formulation allows faster and more comprehensive supplies, which is pivotal to improving accessibility and facilitating assay development, especially during outbreaks of emerging infectious diseases such as COVID-19.

A quantified national reference panel for the SARS-CoV-2 antigen detection kit was developed, and the quality standard was established. The potency of the lower detection limit sample is defined in a universal unit (U/mL), which facilitates comparability of results for different SARS-CoV-2 antigen kits and evaluation of assay parameters such as analytical sensitivities. The reference panels offer a unified solution for SARS-CoV-2 assay development, quality control, and regulatory surveillance.

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Tingting Ma: Data curation, Writing – original draft. **Donglai Liu:** Conceptualization, Data curation, Formal analysis. **Keliang Lyu:** Data curation. **Tingting Gao:** Data curation. **Dawei Shi:** Formal analysis. **Lanqing Zhao:** Data curation. **Shu Shen:** Formal analysis. **Yabin Tian:** Formal analysis. **Sihong Xu:** Conceptualization, Project administration, Resources, Supervision. **Haiwei Zhou:** Conceptualization, Project administration, Resources, Writing – review & editing.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bsheal.2023.10.002.

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