

# Dysphagia Prevalence and Influencing Factors Among Community-Dwelling Older Adults: A Postprint

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## Abstract

Dysphagia is a common geriatric syndrome with an increasing incidence year by year, which can easily lead to complications such as aspiration pneumonia and asphyxiation. Currently, research on the status quo of dysphagia and its influencing factors in community-dwelling elderly populations is relatively scarce.

**Objective:** To investigate the current status of dysphagia among community-dwelling elderly in Shanghai, explore its influencing factors, and further analyze the incidence rate and influencing factors of dysphagia across different age strata.

**Methods:** This study employed a cross-sectional survey design. From July 2022 to May 2023, a total of 358 elderly individuals aged  $\geq 60$  years were recruited as study subjects using convenience sampling from outpatient clinics and home-based hospital beds at five community health service centers in Huangpu District, Baoshan District, and Fengxian District of Shanghai. Demographic data were recorded, and participants' Appendicular Skeletal Muscle Mass Index (ASMI), grip strength, and gait speed were measured. The Eating Assessment Tool questionnaire (EAT-10) was utilized to screen for dysphagia risk in the elderly.

**Results:** Among the 358 community-dwelling elderly individuals, 80 cases (22.35%) had dysphagia ( $EAT-10 \geq 3$ ). Multivariate logistic regression analysis revealed that age ( $\geq 80$  years) ( $OR=18.484$ , 95%CI=3.571~95.679), depressive status ( $OR=4.135$ , 95%CI=1.280~13.364), and history of choking ( $OR=13.650$ , 95%CI=4.345~42.877) were risk factors for dysphagia in community-dwelling elderly ( $P<0.05$ ), while high Barthel Index ( $OR=0.891$ , 95%CI=0.832~0.953) and high ASMI ( $OR=0.330$ , 95%CI=0.199~0.547) were protective factors ( $P<0.05$ ). When participants were stratified by age into 60-69 years, 70-79

years, and \$ \$80 years, the incidence rates of dysphagia were 5.0% (6/119), 11.1% (16/144), and 61.1% (58/95), respectively, with statistically significant differences among the three groups ( $P<0.05$ ). Among elderly aged 60-69 years, BMI, ASMI, and depressive status showed statistically significant differences between the dysphagia and non-dysphagia groups ( $P<0.05$ ); among those aged 70-79 years, grip strength, calf circumference, depressive status, Barthel Index, and history of choking showed statistically significant differences between the two groups ( $P<0.05$ ); among those aged \$ \$80 years, ASMI, grip strength, gait speed, Barthel Index, MMSE score, and history of choking showed statistically significant differences between the two groups ( $P<0.05$ ). Within the dysphagia group, ASMI and grip strength in elderly aged 70-79 years and \$ \$80 years were lower than those in the 60-69 years group; gait speed in elderly aged \$ \$70 years was lower than that in the 60-69 years group; the incidence of choking history in elderly aged \$ \$80 years was higher than that in the 60-79 years group, while Barthel Index and MMSE scores were lower than those in both the 60-69 years and 70-79 years groups ( $P<0.05$ ).

**Conclusion:** The prevalence of dysphagia is high among community-dwelling elderly populations in Shanghai, and the incidence gradually increases with advancing age, accompanied by a significant increase in influencing factors. Therefore, screening for dysphagia should be intensified among elderly individuals with advanced age, depressive status, and history of choking. Improving muscle mass and self-care ability, along with implementing more targeted prevention strategies across different age strata, can effectively reduce disease burden and improve prognosis.

## Full Text

### Current Status and Influencing Factors of Dysphagia among the Elderly in Communities

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## Abstract

**Background:** Dysphagia, a prevalent geriatric syndrome, has been witnessing an upward trend in incidence rates, potentially leading to severe complications like aspiration pneumonia and asphyxia. Despite its significance, research on the prevalence and determinants of dysphagia among community-dwelling elderly remains scarce.

**Objective:** This study aims to ascertain the prevalence of dysphagia among Shanghai's elderly community by identifying influencing factors and analyzing occurrence rates and determinants across different age brackets.

**Methods:** Employing a cross-sectional survey approach, the study was conducted from July 2022 to May 2023. Using convenience sampling, the study involved 358 individuals aged 60 and above, selected from the outpatient and home care services of five community health service centers in Huangpu, Baoshan and Fengxian Districts of Shanghai. Demographic data were collected, and measurements of the Appendicular Skeletal Muscle Index (ASMI), grip strength, and walking speed were taken. The Eating Assessment Tool-10 (EAT-10) was utilized to assess the risk of dysphagia among the elderly.

**Results:** Out of the 358 community-dwelling elderly individuals surveyed, 80 (22.35%) exhibited symptoms of dysphagia ( $EAT-10 \geq 3$ ). Multivariate Logistic regression analysis identified advanced age ( $\geq 80$  years) ( $OR=18.484$ , 95%CI=3.571-95.679), depressive state ( $OR=4.135$ , 95%CI=1.280-13.364), and a history of choking ( $OR=13.650$ , 95%CI=4.345-42.877) as significant risk factors for dysphagia ( $P<0.05$ ). Conversely, a high Barthel Index ( $OR=0.891$ , 95%CI=0.832-0.953) and a robust ASMI ( $OR=0.330$ , 95%CI=0.199-0.547) emerged as protective factors ( $P<0.05$ ). When stratified by age, the prevalence rates of dysphagia were 5.0% (6/119), 11.1% (16/144), and 61.1% (58/95) for the age groups 60-69, 70-79, and  $\geq 80$  respectively, with statistically significant differences ( $P<0.05$ ). Significant disparities were noted between dysphagia and non-dysphagia groups in terms of BMI, ASMI, and depression status for ages 60-69 ( $P<0.05$ ), grip strength, calf circumference, depression, Barthel Index, and choking history for ages 70-79 ( $P<0.05$ ), and ASMI, grip strength, walking speed, Barthel Index, MMSE scores, and choking history for ages  $\geq 80$  ( $P<0.05$ ). Within the dysphagia cohort, ASMI and grip strength in the 70-79 and  $\geq 80$  age groups were lower compared to the 60-69 age group ( $P<0.05$ ). The walking speed of individuals aged  $\geq 70$  was reduced relative to those aged 60-69 ( $P<0.05$ ). Additionally, individuals aged  $\geq 80$  showed a higher choking incidence and scored lower on the Barthel Index and MMSE than those aged 60-79 ( $P<0.05$ ).

**Conclusion:** The prevalence of dysphagia among community-dwelling elderly in Shanghai is notably high and progressively increases with age, with a corresponding rise in influencing factors. It is imperative to intensify dysphagia screening, particularly among the elderly with depressive symptoms or a history of choking. Enhancing muscle mass and self-care capabilities, coupled with age-specific preventive measures, can substantially alleviate the disease burden and improve prognoses.

**Keywords:** Dysphagia; Elderly; Prevalence; Communities; Root cause analysis

## 1. Subjects and Methods

Dysphagia is a common geriatric syndrome characterized by impaired structure and/or function of the organs involved in swallowing, including the jaw, lips, tongue, soft palate, pharynx, and esophagus, which prevents the safe and effective transport of food from the mouth to the stomach [1]. Over time, it often leads to serious complications such as chronic cough, choking, aspiration pneumonia, and even asphyxia, while also reducing social interaction and triggering mental health issues like depression [2]. The global prevalence of dysphagia is approximately 43.8% [3], with community-dwelling populations showing rates of 11.4%-33.7% [4]. Among high-risk conditions such as stroke and Parkinson's disease, the prevalence can reach 80% [5], significantly diminishing quality of life and increasing personal and societal economic burden. Dysphagia has been formally classified in the WHO International Classification of Diseases (ICD-10) under code R13 [6].

Current research both domestically and internationally has primarily focused on high-risk diseases, including neurological disorders (stroke, Parkinson's disease, Alzheimer's disease), and diseases of the oropharynx, digestive system, and respiratory system, with most studies conducted among hospitalized patients in general hospitals or nursing institutions. Research on community-dwelling elderly populations beyond these high-risk conditions remains limited. Age-related degenerative changes, such as reduced skeletal muscle mass, strength, and/or function—known as sarcopenia—can also affect swallowing-related muscle groups, thereby causing dysphagia [7]. This study aims to investigate the current status and influencing factors of dysphagia among community-dwelling elderly in Shanghai, excluding those with high-risk conditions, and to further stratify the analysis by age group to provide a theoretical basis for raising awareness and enabling early, targeted interventions.

### 1.1 Study Subjects

From July 2022 to May 2023, we enrolled study subjects using convenience sampling among elderly individuals aged  $\geq 60$  years from outpatient and home care services at five community health service centers in Huangpu, Baoshan, and Fengxian districts of Shanghai. Inclusion criteria were: (1) age  $\geq 60$  years; (2) stable condition with ability to eat orally; (3) informed consent provided, with no communication barriers and ability to complete assessments. Exclusion criteria were: (1) known diseases that could cause dysphagia, such as neurological disorders or organic lesions of the oropharynx or esophagus; (2) acute or terminal illness; (3) severe motor impairment preventing measurement of indicators; (4) presence of artificial joints or pacemakers that would interfere with bioelectrical impedance measurement.

## 1.2 General Information

We collected general demographic data including name, sex, age, education level, and marital status; lifestyle factors including smoking and drinking history (defined as smoking  $>1$  cigarette daily for  $\geq 6$  months [8] and drinking alcohol at least once weekly for  $\geq 12$  months [9]); and medical history including choking episodes, aspiration pneumonia, chronic diseases, and medication types.

## 1.3 Anthropometric Measurements

Standard measurements of height, weight, and calf circumference were obtained. Grip strength was measured using an electronic dynamometer (Xiangshan EH101) with the subject seated and elbow extended; the maximum value from three measurements (with  $\geq 1$  minute intervals) of the dominant hand was recorded. Appendicular skeletal muscle mass was measured using a bioelectrical impedance analyzer (InBody270) with the subject in a standing position. The Appendicular Skeletal Muscle Index (ASMI) was calculated as appendicular skeletal muscle mass divided by height squared. Walking speed was assessed using the 6-meter walk test, with subjects instructed to walk at normal speed through a 6-meter course; the average time from three trials was recorded.

## 1.4 Dysphagia Assessment

The Eating Assessment Tool-10 (EAT-10) was used to screen for dysphagia risk. The EAT-10 comprises 10 items related to swallowing difficulties, each scored from 0 (no impairment) to 4 (severe impairment), with a total possible score of 40. In this study, a total score  $\geq 3$  was considered indicative of abnormal swallowing function [10-11]. Meta-analyses have demonstrated that the EAT-10 is non-invasive and efficient [12], and the Chinese Expert Consensus on Dysphagia Assessment and Treatment (2017 edition) recommends its use for early screening to identify signs of aspiration and abnormal swallowing [1].

## 1.5 Comprehensive Assessment

Activities of daily living were evaluated using the Barthel Index [13], which includes 10 items (feeding, grooming, bathing, dressing, bowel and bladder control, toilet use, bed-to-chair transfer, walking on level ground, and stair climbing) scored in four levels (0, 5, 10, 15 points) based on the need for assistance. The total score ranges from 0-100, with higher scores indicating greater independence. Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS-15), with scores  $\geq 7$  indicating depression; higher scores reflect more severe depressive symptoms. This scale has demonstrated good reliability and validity for screening depression in Chinese elderly, with a Cronbach's  $\alpha$  coefficient of 0.793 [14]. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE), with scores of 27-30 considered normal and  $<27$  indicating cognitive impairment [15]. Nutritional status was assessed using the

Mini-Nutritional Assessment (short form) (MNA-SF), with scores of 12-14 indicating normal nutritional status, 8-11 indicating risk of malnutrition, and  $\leq 7$  indicating malnutrition [16].

## 1.6 Statistical Methods

Data analysis was performed using SPSS 26.0 software. Normally distributed continuous data were expressed as mean  $\pm$  standard deviation and compared between two groups using independent samples t-tests, among multiple groups using one-way ANOVA, and between specific groups using LSD-t tests. Non-normally distributed continuous data were expressed as median (P25, P75) and compared using non-parametric tests. Categorical data were expressed as frequencies and percentages and compared using  $\chi^2$  tests. Binary logistic regression analysis was used to explore influencing factors of dysphagia. Statistical significance was set at  $P < 0.05$ .

# 2. Results

## 2.1 General Characteristics

A total of 358 community-dwelling elderly individuals were included, with ages ranging from 60-96 years and a median age of 74 (68, 80) years; 171 (47.8%) were male and 187 (52.2%) were female. Sixty-three (17.6%) received home care services, while 295 (82.4%) visited community health service center outpatient clinics. The mean BMI was  $(22.7 \pm 3.2) \text{ kg/m}^2$ . ASMI was  $(6.28 \pm 1.22) \text{ kg/m}^2$  in males and  $(4.53 \pm 1.06) \text{ kg/m}^2$  in females. Grip strength was  $(19.67 \pm 9.52) \text{ kg}$  in males and  $(9.33 \pm 4.59) \text{ kg}$  in females. Walking speed was  $(1.25 \pm 0.26) \text{ m/s}$ . Calf circumference was  $(37.5 \pm 4.5) \text{ cm}$  in males and  $(34.5 \pm 4.5) \text{ cm}$  in females. The Barthel Index was  $(50 \pm 10) \text{ points}$ . The MMSE score was  $(25.5 \pm 3.5) \text{ points}$ . The depression status was 112 (31.3%) with depression and 246 (68.7%) without depression. The choking history was 188 (52.2%) with history and 170 (47.8%) without history.

Among the 358 community-dwelling elderly individuals, 80 (22.35%) had dysphagia (EAT-10  $\geq 3$ ). Specifically, 252 (70.4%) scored 0, 26 (7.3%) scored 1-2, 61 (17.0%) scored 3, 15 (4.2%) scored 4-7, and 4 (1.1%) scored 8. Among the 80 patients with dysphagia, symptom 9 ("I cough when I eat") was most common, reported by 61 (76.3%), followed by symptom 4 ("I have difficulty eating solid foods") reported by 58 (72.5%), and symptom 10 ("I feel anxious when swallowing") reported by 43 (53.8%).

## 2.3 Univariate Analysis of Dysphagia by Subject Characteristics

Significant differences between the dysphagia and non-dysphagia groups were observed in age, BMI, ASMI, grip strength, walking speed, calf circumference, Barthel Index, depression status, nutritional status, MMSE score, and choking history ( $P < 0.05$ ) (Table 1).

## 2.4 Multivariate Logistic Regression Analysis of Influencing Factors

Using the presence of dysphagia (no=0, yes=1) as the dependent variable and the 11 variables showing significant differences in univariate analysis (age, BMI,

ASMI, grip strength, walking speed, calf circumference, Barthel Index, depression status, nutritional status, MMSE score, and choking history) as independent variables, binary logistic regression analysis was performed. Variable assignments are shown in Table 2, and results are presented in Table 3. The analysis revealed that age  $\geq 80$  years, depressive state, and choking history were risk factors for dysphagia ( $P<0.05$ ), while high ASMI and high Barthel Index were protective factors ( $P<0.05$ ).

## 2.5 Analysis of Prevalence and Influencing Factors by Age Group

Subjects were stratified into three age groups: 60-69, 70-79, and  $\geq 80$  years. The prevalence rates of dysphagia were 5.0% (6/119), 11.1% (16/144), and 61.1% (58/95), respectively, with statistically significant differences ( $\chi^2=113.029$ ,  $P<0.05$ ). For the 60-69 age group, significant differences between dysphagia and non-dysphagia groups were found in BMI, ASMI, and depression status ( $P<0.05$ ). For the 70-79 age group, significant differences were observed in grip strength, calf circumference, depression status, Barthel Index, and choking history ( $P<0.05$ ). For the  $\geq 80$  age group, significant differences were noted in ASMI, grip strength, walking speed, Barthel Index, MMSE score, and choking history ( $P<0.05$ ).

Within the dysphagia cohort, comparisons across age groups revealed significant differences in ASMI, grip strength, walking speed, Barthel Index, MMSE score, and choking history ( $P<0.05$ ). Specifically, ASMI and grip strength in the 70-79 and  $\geq 80$  age groups were lower than in the 60-69 group; walking speed was reduced in those aged  $\geq 70$  compared to those aged 60-69; and individuals aged  $\geq 80$  had higher choking incidence and lower Barthel Index and MMSE scores compared to those aged 60-79 ( $P<0.05$ ) (Table 7).

## 3. Discussion

### 3.1 Current Status of Dysphagia among Shanghai's Community Elderly

As population aging intensifies, dysphagia has gradually become a common health concern that cannot be ignored among older adults. This study found a dysphagia prevalence of 22.3% among community-dwelling elderly in Shanghai, consistent with reports from Japan (22.9%) [17] and Beijing (25.82%) [18]. However, due to differences in study populations, geographic regions, and screening tools, reported prevalence rates vary across studies. A meta-analysis showed higher prevalence among elderly populations when dysphagia was diagnosed using the EAT-10 scale [19]. As this study was conducted during the COVID-19 pandemic and subject to various uncontrollable factors, the actual prevalence of dysphagia among community-dwelling elderly may be even higher.

Dysphagia in older adults can lead to malnutrition, choking, aspiration pneumonia, systemic infection, and even asphyxia, resulting in increased hospitalization

rates, medical costs, and reduced quality of life. Therefore, early screening for dysphagia in community-dwelling elderly is essential. The natural aging process brings declines in organ function, including tooth loss, reduced swallowing-related musculature [3], decreased tongue pressure [21], reduced saliva secretion, diminished pharyngeal reflexes, and cervical spine changes [3,22-23], all contributing to dysphagia. Consequently, early screening for dysphagia risk should be implemented promptly in community-dwelling elderly, with particular focus on the oldest old as a priority for screening and intervention. First, attention should be paid to oral health, with timely provision of dentures for those with missing teeth. Second, instructing older adults to maintain a sitting position during meals, selecting appropriate food types (primarily soft foods), and chewing slowly and thoroughly can effectively reduce the occurrence and progression of dysphagia and related complications.

### 3.2.1 Age

This study demonstrated that advanced age ( $\geq 80$  years) is a risk factor for dysphagia ( $OR=18.484$ ,  $P=0.001$ ), consistent with findings reported by Holland et al. [20]. Beyond the increased incidence of high-risk diseases with age, natural aging itself causes declines in physical organ function. Older adults commonly experience tooth loss, reduced masticatory and swallowing muscles [3], weakened tongue pressure [21], decreased saliva production, diminished pharyngeal reflexes, and cervical spine changes [3,22-23], collectively contributing to dysphagia. Therefore, early dysphagia risk screening should be prioritized in community-dwelling elderly, particularly among the oldest old.

### 3.2.2 ASMI

ASMI is a commonly used indicator for assessing systemic muscle distribution and represents an important parameter for sarcopenia, a progressive, age-related loss of skeletal muscle mass and strength. This study found that ASMI is a protective factor against dysphagia ( $OR=0.330$ ,  $P<0.001$ ), consistent with reports by Maeda et al. [24-25]. The swallowing process is complex, requiring coordination of approximately 25 pairs of muscles in the oropharynx and esophagus, in addition to neural and central regulation [26]. Generalized declines in muscle mass and strength may lead to weakening of swallowing-related muscles, thereby impairing swallowing function. In 2012, Kuroda et al. [27] first proposed the concept of “sarcopenic dysphagia,” which has gradually gained attention worldwide. Studies show that aging, reduced physical activity, malnutrition, and certain diseases contribute to sarcopenia and dysphagia in older adults, and that sarcopenia increases the risk of dysphagia [28]. Evidence suggests that sarcopenia-related dysphagia is more severe and has poorer prognosis than other types [29]. Therefore, early screening for both sarcopenia and dysphagia is necessary in the oldest old. Research indicates that targeted interventions for older adults with dysphagia and decreased muscle mass—including oral motor training such as the Shaker exercise and tongue-pressure resistance training (TPRT),

combined with systemic resistance exercise and nutritional interventions to increase protein intake—may be effective strategies for preventing and treating sarcopenic dysphagia [30-31]. This epidemiological investigation provides current data on the status of dysphagia and muscle condition among Shanghai's community-dwelling elderly, laying the groundwork for future studies on nutritional and exercise interventions for this population.

### 3.2.3 Activities of Daily Living

This study found that the Barthel Index is a protective factor against dysphagia ( $OR=0.891$ ,  $P=0.001$ ), consistent with reports by Chen et al. [32] and González-Fernández et al. [33]. The likely explanation is that age-related physical decline and limited mobility, combined with eating difficulties in dysphagic patients, lead to reduced daily activities and even long-term bed rest, causing muscle atrophy. Reduced food intake and resulting malnutrition further exacerbate disuse muscle atrophy, ultimately affecting swallowing-related muscles [34] and causing dysphagia. This creates a vicious cycle of mutual causality. These findings suggest that healthcare providers should pay early attention to swallowing function in elderly individuals with reduced self-care ability, provide reasonable nutritional supplementation, 适当增加康复锻炼, and promptly implement swallowing muscle rehabilitation training.

### 3.2.4 Choking History

Choking history is a significant risk factor for dysphagia ( $OR=13.650$ ,  $P<0.001$ ). This may be due to age-related declines in pharyngeal sensitivity, delayed epiglottic closure, and reduced coordination, making choking more likely when consuming liquids quickly or eating in supine positions. Additionally, weakened cough reflex in older adults prevents timely airway clearance, leading to aspiration pneumonia. Among the 57 participants with choking history in this study, 24 (42.1%) had been hospitalized for aspiration pneumonia. EAT-10 results showed that choking is an important early clinical manifestation of dysphagia, facilitating identification of high-risk individuals. Therefore, healthcare providers should be able to recognize covert aspiration in insidious cases of dysphagia to enable early identification and intervention. Older adults with choking during meals should be referred to specialists for further evaluation and diagnosis of dysphagia. Patient and family education on appropriate utensil selection, maintaining concentration during meals, and creating a pleasant dining environment is equally important for reducing choking episodes and preventing aspiration pneumonia and asphyxia.

### 3.2.5 Depressive State

This study found that depressive state is a risk factor for dysphagia ( $OR=4.135$ ,  $P<0.05$ ). Older adults with depression often experience low mood, slowed thinking, reduced cognitive function, and psychomotor retardation, which may progress to decreased appetite and food intake, resulting in dysphagia. However,

some reports suggest that many dysphagic patients have depressive symptoms that may distort scale scores, potentially limiting predictive value for dysphagia onset. Therefore, the relationship between depression and dysphagia requires further prospective investigation [35]. Nevertheless, dysphagia may lead to social isolation, and the resulting emotional and psychological changes affect quality of life [20,36]. Therefore, screening and assessment for dysphagia should be strengthened among depressed older adults, while also attending to the mental health of dysphagic patients. Family members should provide respect, patience, and confidence, and community healthcare workers should communicate with and listen to these individuals, providing psychological intervention when necessary to improve both life confidence and eating confidence.

With increasing age, the risk of dysphagia rises and influencing factors multiply. Age-stratified analysis revealed that for ages 60-69, primary influencing factors were BMI, ASMI, and depression status; for ages 70-79, they were grip strength, calf circumference, depression status, Barthel Index, and choking history; and for ages  $\geq 80$ , they were ASMI, grip strength, walking speed, Barthel Index, MMSE score, and choking history. Within the dysphagia group, muscle mass and strength declined significantly after age 70 compared to ages 60-69, while choking risk increased and self-care ability and cognitive function decreased after age 80. Therefore, after understanding older adults' underlying diseases, chronic medication use, and lifestyle factors, targeted prevention by age group is recommended: focus on mental health changes in those aged 60-69, muscle mass and strength in those over 70, and choking prevention, self-care ability, and cognitive function in those over 80. Personalized prevention strategies facilitate efficient dysphagia management and reduce disease burden on individuals and society.

#### 4. Conclusion

The prevalence of dysphagia among community-dwelling elderly in Shanghai is high, with age ( $\geq 80$  years), depressive state, and choking history identified as risk factors, while high ASMI and Barthel Index serve as protective factors. The prevalence and number of influencing factors increase with age. Therefore, dysphagia screening should be intensified among the oldest old, with targeted prevention strategies implemented across different age groups.

**Limitations:** This cross-sectional study had a limited sample size and geographic scope, restricting generalizability. The use of standing InBody measurements excluded bedridden individuals with potentially higher dysphagia prevalence. Additionally, only the EAT-10 screening tool was used; when possible, the gold standard videofluoroscopic swallowing study (VFSS) is recommended for definitive diagnosis.

**Author Contributions:** XU Su was responsible for study conception and design, data collection and analysis, and manuscript writing. CAI Wenwei supervised quality control and overall responsibility. LI Chenyi contributed to

manuscript revision. WANG Guanghui and XU Youduan participated in data collection and analysis.

**Conflict of Interest:** The authors declare no conflicts of interest.

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