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RESEARCH ARTICLE

Frequency and factors related to drooling in Chinese patients with multiple system atrophy: a cross-sectional study

Yalan Chen[1] · Hongyan Huang[1] · Pingping Ning[1] · Quanzhen Zhao[1] · Hui Wang[1] · Qiuyan Shen[1] · Yanming Xu[1]

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Abstract

Purpose Drooling is a common symptom of neurodegenerative diseases. We aimed to explore the frequency of drooling and its relationship to clinical features in a relatively large cohort of Chinese patients with multiple system atrophy (MSA).

Methods We conducted a cross-sectional survey of 143 patients with MSA. Patients with drooling were identified as those with a score ≥ 1 on item 6 of the Unified Parkinson's Disease Rating Scale. Additional scales were used to rate daily functionality, neurologic and cognitive capabilities, levels of anxiety and depression, and sleep quality. These results were compared between patients with and without drooling.

Results The frequency of drooling in this cohort was 59.4% (85/143). Drooling was associated with significantly poorer scores on the Unified MSA Rating Scale (subscore I, subscore II, subscore IV, total score), Pittsburgh Sleep Quality Index, Hamilton Depression Scale, Hamilton Anxiety Scale, and Mini-Mental State Examination. After adjusting for confounders, regression analysis identified two independent risk factors for drooling: parkinsonism-associated MSA (OR 2.54, 95% CI 1.15–5.65) and hypomimia (OR 3.18, 95% CI 1.32–7.68).

Conclusions Drooling is relatively common among Chinese MSA patients, and parkinsonism-associated MSA and hypomimia appear to be independent risk factors for drooling. The severity of this symptom correlates with the presence of severe motor symptoms, anxiety, depression, and sleep disorders.

Keywords Multiple system atrophy · Drooling · Frequency · Non-motor symptoms

Introduction

Multiple system atrophy (MSA) is a rare and rapidly progressive neurodegenerative disorder that presents with autonomic failure accompanied by either parkinsonism (MSA-P) or cerebellar ataxia (MSA-C), or a combination of both [1]. The etiology of MSA is not completely clear, but phenotypic pathologic changes have been linked to mutations in α-synuclein protein with subsequent formation of oligodendroglial cytoplasmic inclusion bodies [2, 3]. Genetic background and environmental factors are likely to underpin disease susceptibility [4].

Past work has focused on the impairment of motor function in MSA, but recently the focus has shifted to the role of non-motor symptoms including urinary disorders, sleep disruption, stridor, depression, anxiety, and gastrointestinal dysfunction such as drooling, dysphagia, and constipation [5, 6]. Drooling is defined as excessive pooling of saliva in the oral cavity due to overproduction of saliva or impaired salivary clearance. Impaired clearance can result from difficulties swallowing or an inability to maintain saliva within the oral cavity [7, 8]. Drooling has several negative physical effects, such as poor oral hygiene, increased intra-oral occult bacteria, difficulty eating and speaking, increased risk of aspiration pneumonia, and reduced quality of life [9].

Drooling is a relatively common symptom of many neurodegenerative disorders, such as motor neuron disease and Parkinson's disease [10, 11], but its prevalence in MSA is unclear. To address these questions, we conducted a cross-sectional investigation of the frequency of drooling and clinical features associated with it in a Chinese cohort of patients with MSA.

✉ Yanming Xu
neuroxym999@163.com

[1] Department of Neurology, West China Hospital, Sichuan University, 37 Guo Xue Xiang, Chengdu 610041, Sichuan, People's Republic of China

Methods

Study population

A consecutive series of patients with MSA were recruited from West China Hospital of Sichuan University from February 2016 to April 2018. All patients met the diagnostic criteria for probable MSA [12]. Patients were excluded if they had a family history of MSA, were unable to communicate, or refused to participate in the study. This study was approved by the Ethics Committee of West China Hospital of Sichuan University, and informed consent was obtained from all patients prior to enrollment.

Measurements and rating scales

Sociodemographic characteristics and clinical features were collected for baseline measurements, including: sex, age, age at disease onset, disease duration, smoking habits, drinking habits, farming history, dysarthria, dysphagia, stridor, hyposmia, excessive sweating, inability to focus, obstructive sleep apnea, concurrent diseases, and current medications (levodopa or dopamine agonists).

Subjects were classified as having MSA-P if they exhibited parkinsonism signs without cerebellar features or as having MSA-C if they displayed predominantly cerebellar signs with minimal or no parkinsonism, and if the cerebellar signs preceded any parkinsonism by at least 1 year [13].

All patients were examined by a certified neurologist using standardized interview questions. The Unified MSA Rating Scale (UMSARS) was used to assess overall disease severity based on the following subcategories: UMSARS I (history review, range 0–4), UMSARS II (motor examination scale, range 0–4), and UMSARS IV (global disability scale, range 1–5) [14]. A higher total UMSARS score (UMSARS I + II) as well as higher score on each subcategory indicated a worse disease state. Item 1 on UMSARS II (facial expression) was used for hypomimia scoring and item 12 (posture) for degree of stooping.

Psychologic features were examined using the Mini-Mental State Examination (MMSE), for which a lower score reflects impaired cognition, the Hamilton Depression Rating Scale (HAMD), and the Hamilton Anxiety Rating Scale (HAMA) [15]. High scores in the HAMD and HAMA suggest greater levels of depression and anxiety, respectively. Sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI), on which a higher score reflects lower sleep quality. Levodopa responsiveness was defined as a significant and sustained improvement in the patient's motor function after drug administration.

Evaluation of drooling

Presence of drooling was evaluated using item 6 (Salivation) of the Unified Parkinson's Disease Rating Scale (UPDRS, range 0–4), on which a higher score indicates greater drool burden. Patients were asked to self-report their salivary secretion using the following scale: 0, normal; 1, slight but definite excess of saliva in the mouth, may occur at night; 2, moderately excessive saliva, may have minimal drooling; 3, marked excess of saliva with some drooling; 4, marked drooling requiring constant use of a tissue or handkerchief. Patients with a score of ≥ 1 were considered to have drooling.

Statistical analysis

Continuous variables are presented as mean ± SD and categorical variables as frequency and proportion. Student's *t* tests were used to compare continuous variables (with Mann-Whitney *U* test when appropriate), and categorical variables were compared using either the chi-squared or Fisher's exact test, as appropriate. Spearman's correlation test was used to assess the relationship between drooling score and clinical variables, including MMSE, HAMA, HAMD, PSQI, and UMSARS scores (I, II, IV, total). Variables that were considered clinically relevant or that showed a univariate relationship with outcome were entered into a multivariate logistic regression model to identify predictors of drooling. Several parameters, including MSA-P subtype, UMSARS I, UMSARS II, hypomimia, and MMSE, were used as covariables. A factor was considered to be significantly related to drooling when $p < 0.05$ or if the 95% confidence interval (95% CI) of the odds ratio (OR) did not include 1.00. Statistical analysis was conducted using SPSS 19 (IBM, Chicago, IL, USA). Differences were considered significant when $p < 0.05$.

Results

A total of 148 patients were assessed for inclusion in our study, none of whom had familial MSA. In the end, 143 patients with MSA were included, of which more than half self-reported drooling ($n = 85$; Table 1). Men accounted for 63.6% of the study population. The distribution of patients across all possible scores on UPDRS item 6 was as follows: 0, 58 patients (40.5%); 1, 48 (33.6%); 2, 26 (18.2%); 3, 9 (6.3%); 4, 2 (1.4%). MSA-P was more frequent in our population than MSA-C (69.2% vs. 30.8%). The MSA-P subtype was more frequent among drooling patients (78.8%) than among non-drooling patients

Table 1 Baseline characteristics of Chinese patients with multiple system atrophy patients with or without drooling

Characteristic	All patients ($N=143$)	Drooling patients ($N=85$)	Non-drooling patients ($N=58$)	p
Male sex	91 (63.6%)	51 (60.0%)	40 (69.0%)	0.274[a]
MSA-P	**99 (69.2%)**	**67 (78.8%)**	**32 (55.2%)**	**0.003[a]**
Age (years)	64.25 ± 10.36	65.32 ± 9.27	62.69 ± 11.68	0.155[b]
Age at disease onset (years)	61.86 ± 10.21	62.87 ± 9.12	60.38 ± 11.55	0.172[b]
Disease duration (years)	2 (1–3)	2 (1–3)	2 (1–3)	0.663[c]
Smoking history	45 (31.5%)	28 (32.9%)	17 (29.3%)	0.646[a]
Drinking history	36 (25.2%)	24 (28.2%)	12 (20.7%)	0.307[a]
Farming history	25 (17.5%)	13 (15.3%)	12 (20.7%)	0.404[a]
Medication				
Levodopa	91 (63.6%)	57 (67.1%)	34 (58.6%)	0.303[a]
Dopamine agonists	17 (11.9%)	10 (11.8%)	7 (12.1%)	0.956[a]
Levodopa responsiveness	36 (39.1%)	24 (42.1%)	12 (34.3%)	0.456[a]
Comorbidity				
Hypertension	33 (23.1%)	20 (23.5%)	13 (22.4%)	0.876[a]
Diabetes mellitus	17 (11.9%)	11 (12.9%)	6 (10.3%)	0.638[a]

All values shown are n (%) or median (interquartile range). Boldfaced values differ significantly between the drooling and non-drooling groups

MSA-P multiple system atrophy-parkinsonism

[a]Chi-squared test

[b]Student's t test

[c]Mann-Whitney U test

(55.2%). Drooling or non-drooling patients did not differ significantly in demographic or clinical variables including age, age at disease onset, disease duration, lifestyle (smoking, drinking, and farming), or concurrent diseases (hypertension or diabetes mellitus). The two groups did not differ significantly in rates of levodopa or dopamine agonist use.

Patients with drooling showed greater levels of physical disability based on the UMSARS score (Table 2), which included significantly higher rates of orthostatic symptoms (50.6% vs. 32.8%), hypomimia (91.8% vs. 77.6%), and stooped posture (90.6% vs. 75.9%). They also showed higher levels of anxiety and depression. Conversely, patients who did not drool showed a significantly greater ability to function in their daily lives, greater neurologic capabilities, and better sleep quality.

Increased scores for facial expression and posture examinations, indicating hypomimia and stooping, showed a positive linear relationship with drooling frequency (Fig. 1). Risk of drooling was significantly higher in the presence of hypomimia (OR 3.18, 95% CI 1.32–7.68) or MSA-P subtype (OR 2.54, 95% CI 1.15–5.65) (Table 3).

Drooling severity showed an association with UMSARS I, UMSARS II, and total UMSARS scores as well as with levels of anxiety and depression (Fig. 2). These associations were supported by Spearman's correlation analysis (Table 4), which also showed a significant inverse correlation between drooling severity and cognitive ability as measured on the MMSE.

Discussion

To the best of our knowledge, this is the first study to investigate the frequency of drooling and clinical features associated with drooling in patients with MSA. Our study shows that MSA, particularly MSA-P, is associated with drooling. We also show that the presence and severity of drooling correlate with various motor and non-motor symptoms.

Using a comprehensive definition of drooling as accumulation of saliva in the mouth during the day or night, we found that 59.4% of our Chinese MSA patient population was positive for drooling. This is similar to the 56% prevalence reported for Parkinson's disease patients [8]. However, our frequency is markedly higher than in two previous reports in China and South Korea, which reported 29.7% [16] and 10.17% [17]. Such variability could be attributed to differences in diagnostic criteria, demographic or clinical characteristics of the study sample, and assessment questionnaires.

We systematically evaluated a series of clinical factors that could possibly contribute to drooling in MSA. In our patient population, MSA-P subtype and hypomimia symptoms were independently associated with drooling

Table 2 Occurrence and severity of motor and non-motor symptoms among Chinese MSA patients with or without drooling

Characteristic	All patients ($N=143$)	Drooling patients ($N=85$)	Non-drooling patients ($N=58$)	p
Stridor	20 (14.0%)	12 (14.1%)	8 (13.8%)	0.956[a]
Dream enactment behavior	69 (48.3%)	43 (50.6%)	26 (44.8%)	0.498[a]
Hyposmia	47 (32.9%)	28 (32.9%)	19 (32.8%)	0.982[a]
Excessive sweating	45 (31.5%)	32 (37.6%)	13 (22.4%)	0.054[a]
Divided attention	46 (32.2%)	32 (37.6%)	14 (24.1%)	0.089[a]
Orthostatic symptoms	**62 (43.4%)**	**43 (50.6%)**	**19 (32.8%)**	**0.035[a]**
UMSARS IV	**2 (1–2)**	**2 (1–2)**	**1 (1–2)**	**0.014[b]**
Dysarthria	99 (69.2%)	64 (75.3%)	35 (60.3%)	0.057[a]
Dysphagia	35 (24.5%)	24 (28.2%)	11 (19.0%)	0.206[a]
Hypomimia	**123 (86.0%)**	**78 (91.8%)**	**45 (77.6%)**	**0.016[a]**
Stooped posture	**121 (84.6%)**	**77 (90.6%)**	**44 (75.9%)**	**0.017[a]**
HAMA	**12 (6–18)**	**15 (7–22.5)**	**8 (4–12.5)**	**0.000[b]**
HAMD	**10 (5–16)**	**12 (7.5–18)**	**7 (3–12.25)**	**0.000[b]**
MMSE	**25 (21–28)**	**24 (19.5–27)**	**27 (23–29)**	**0.001[b]**
PSQI	**6 (3–12)**	**8 (4–12)**	**5.5 (3–10)**	**0.018[b]**
UMSARS I	**14.13 ± 6.46**	**16.15 ± 6.08**	**11.16 ± 5.85**	**0.000[c]**
UMSARS II	**17.33 ± 7.15**	**19.69 ± 6.86**	**13.86 ± 6.13**	**0.000[c]**
Total UMSARS	**31.45 ± 12.84**	**35.85 ± 12.14**	**25.02 ± 11.09**	**0.000[c]**

Values shown are *n* (%) or median (interquartile range). Boldfaced values differ significantly between the drooling and non-drooling groups

UMSARS Unified MSA Rating Scale, *UMSARS I* section I (history review), *UMSARS II* section II (motor examination scale), *UMSARS IV* section IV (global disability scale), *total UMSARS* section I + II, *HAMD* Hamilton Depression Rating Scale, *HAMA* Hamilton Anxiety Rating Scale, *MMSE* Mini-Mental State Examination, *PSQI* Pittsburgh Sleep Quality Index

[a]Chi-squared test

[b]Mann-Whitney *U* test

[c]Student's *t* test

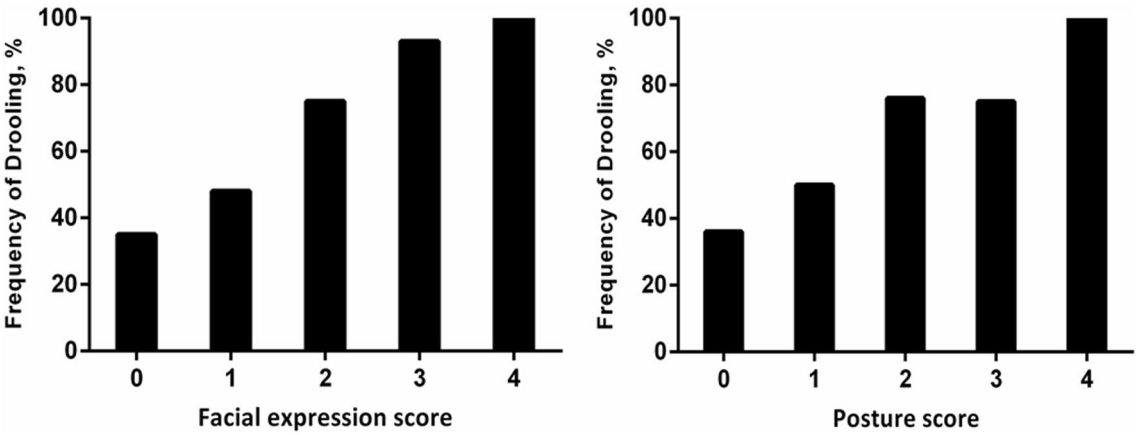

Fig. 1 Drooling frequency among patients with different UMSARS scores for facial expression (item 1) and posture (item 12). Higher scores indicate worse condition. A significant linear trend was observed for facial expression ($p=0.000$) and posture ($p=0.004$), based on the chi-squared test

occurrence. Moreover, the frequency of drooling increased proportionally with the severity of hypomimia (Fig. 1). Severe hypomimia, defined as a score of 3–4 on UMSARS II item 1, is characterized by involuntary mouth opening that allows accumulated saliva to drip from the mouth. Further studies should explore whether and how hypomimia contributes to risk of drooling in MSA.

Table 3 Multivariate logistic regression analysis between clinical variables and drooling in patients with multiple system atrophy

Clinical variable	OR	95% CI	*p*
MSA-P	**2.54**	**1.15–5.65**	**0.006**
UMSARS I	1.09	0.98–1.20	0.11
UMSARS II	1.07	0.97–1.17	0.175
Hypomimia	**3.18**	**1.32–7.68**	**0.002**
MMSE	0.96	0.88–1.04	0.31

Significant results are shown in boldface

UMSARS Unified MSA Rating Scale, *UMSARS I* section I (history review), *UMSARS II* section II (motor examination scale), *MMSE* Mini-Mental State Examination, *MSA-P* multiple system atrophy-parkinsonism

Our observations in MSA patients suggest a significant correlation of drooling with motor function and psychologic symptoms. Our drooling patients had more severe motor impairment and overall neurologic dysfunction (Fig. 2). They showed higher levels of anxiety, depression, and sleep disorders, consistent with previous findings in Parkinson's disease [18]. We also detected an inverse correlation between drooling severity and MMSE score, consistent with the reported correlation between drooling and dementia in Parkinson's disease [19]. Our study suggests that drooling in MSA may indicate more serious cognitive impairment, which should be verified and extended in future work.

Considering the similar pathophysiology of MSA and Parkinson's disease, we investigated factors related to drooling in Parkinson's disease [18, 20]. In contrast to the situation with Parkinson's, we did not find that age, male gender, age at disease onset, disease duration, dysarthria, hyposmia, or dysphagia was associated with drooling in our MSA patients. Many studies have suggested that oropharyngeal dysphagia is a major contributor to the pathophysiology of drooling in Parkinson's disease [7]. However, none of our patients scored worse than 3 on UMSARS I item 2 (swallowing), suggesting no prominent dysphagia. Rather, our data are consistent with the possibility that a more stooped posture (associated with a lower-dipping head) aggravates drooling in MSA, which should be explored further.

This study has several limitations. First, our sample came from only one center, and our hospital is one of the largest referral centers in China, such that our patients typically show a relatively short disease course. This raises the risk of selection bias and potentially limits the generalizability of our results. Our results should be confirmed in larger, preferably population-based samples. Second, our study

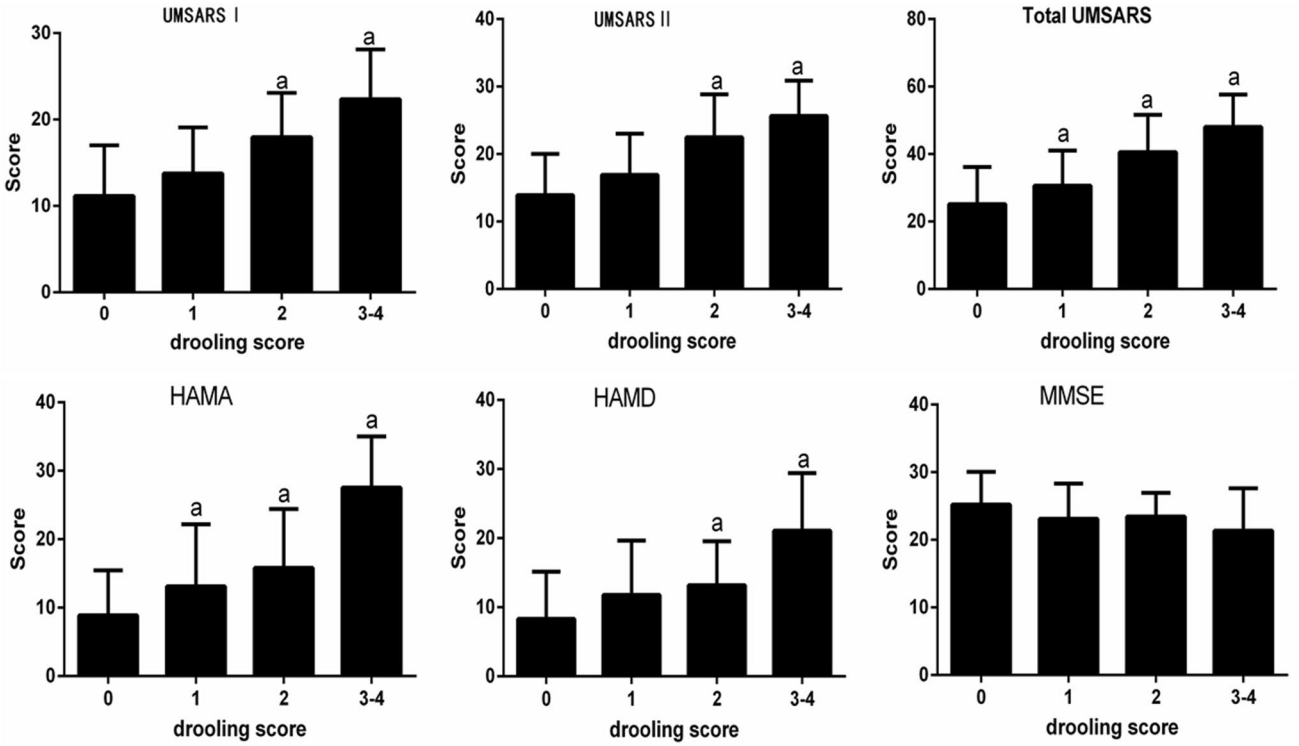

Fig. 2 Relationships between drooling severity and clinical variables. *UMSARS* Unified MSA Rating Scale, *UMSARS I* section I (history review), *UMSARS II* section II (motor examination scale), *total UMSARS* sections I + II, *HAMD* Hamilton Depression Rating Scale, *HAMA* Hamilton Anxiety Rating Scale, *MMSE* Mini-Mental State Examination. [a]$p < 0.05$ vs. patients without drooling (Dunnett post hoc test after analysis of variance testing). Frequencies of drooling scores: score 0, 58 patients; 1, 48 patients; 2, 26 patients; 3, 9 patients; 4, 2 patients

Table 4 Spearman's correlation coefficients relating drooling score with scores on clinical assessment tests

Assessment test	*R*	*p*
MMSE	**−0.276**	**0.001**
HAMA	**0.452**	**0.000**
HAMD	**0.403**	**0.000**
PSQI	**0.217**	**0.009**
UMSARS IV	**0.278**	**0.001**
UMSARS I	**0.502**	**0.000**
UMSARS II	**0.528**	**0.000**
Total UMSARS	**0.537**	**0.000**

Significant results are shown in boldface

UMSARS Unified MSA Rating Scale, *UMSARS I* section I (history review), *UMSARS II* section II (motor examination scale), *UMSARS IV* section IV (global disability scale), *total UMSARS* section I + II, *HAMD* Hamilton Depression Rating Scale, *HAMA* Hamilton Anxiety Rating Scale, *MMSE* Mini-Mental State Examination, *PSQI* Pittsburgh Sleep Quality Index

population did not include cases of familial MSA. Although MSA is typically sporadic, familial cases have been reported [21]. Whether our findings are relevant to that form of MSA should be investigated.

Third, our evaluation of drooling was subjective. Currently, there is no single, standardized evaluation for drooling that can account for many confounding factors, such as eating or talking. Consequently, we used UPDRS item 6 to define drooling, and this item correlates most strongly with recently developed drooling-specific questionnaires [22]. Fourth, levodopa or dopamine receptor agonists are used more often to treat MSA-P than MSA-C, and levodopa can affect salivary production [23, 24]. Our results should ideally be verified in studies involving drug-naïve patients.

Further work should take care to examine temporal factors of drooling, including the time of day when it occurs, whether it began before or after onset of motor symptoms, length of time between the sensation of saliva accumulation and loss of saliva from the mouth, and how frequency of saliva loss changes over time. Future work should also examine the potential effects of drooling on mental health and quality of life, since our study found increased anxiety and depression in drooling patients.

Conclusions

We determined frequency of drooling in a single-site population of Chinese patients with MSA, and we identified MSA-P subtype and hypomimia as independent risk factors. Moreover, we found evidence that drooling in MSA correlates with severe motor dysfunction, anxiety, depression, and sleep disorders. Further studies are needed to confirm these findings.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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