Synergistic Impact of Symptom Clusters on Health-related Quality of Life in Patients With Chronic Obstructive Pulmonary Disease: a Secondary Data Analysis

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Abstract

Background: Clinical experiences and middle range Theory of Unpleasant Symptoms indicate that the existence of symptom clusters (SCs) may synergistically affect patients' health-related quality of life (HRQoL). However, no studies have examined this issue. The aim of this study was to identify symptom clusters and quantify the synergistic impact of symptom clusters on health-related quality of life among patients with chronic obstructive pulmonary disease (COPD).

Methods: Secondary data analysis of cross-sectional data collected via convenience sampling from patients with COPD in a Chinese university hospital. Assessments included modified MRC dyspnoea scale, Beck Depression Inventory, Beck Anxiety Inventory and Pittsburgh Sleep Quality Index. Health-related quality of life was assessed using the St George's Respiratory Questionnaire. Chi-squared tests were used to identify symptom clusters. Multiple linear regressions were used to examine associations between symptom clusters and health-related quality of life.

Results: 106 COPD subjects were recruited. Three symptom clusters were identified in COPD patients and comprised of dyspnoea and depression (OR=2.69, 95%CI:1.19-6.02); anxiety and sleep (OR=2.72, 95%CI:1.20-6.15); depression and anxiety (OR=6.13, 95%CI:2.57-14.60). Two symptom clusters were identified in patients with severe-stage COPD, which were anxiety and sleep (OR=6.21, 95%CI:1.70-22.74), depression and anxiety (OR=5.33, 95%CI:1.64-17.40). All three symptom clusters (anxiety and sleep; dyspnoea and depression; depression and anxiety) were independently associated with health-related quality of life (β=14.56, 95%CI: 5.80-23.31; β =13.95, 95%CI:5.72-22.18; β=13.30, 95%CI:6.88-19.73).

Conclusions: This is the first study to validate the synergistic impacts of symptom clusters on health-related quality of life in COPD patients compared with single symptoms. These findings, which offer a detailed understanding of symptom clusters present in COPD, provide a basis to guide efficient clinical assessment and management symptom-related distress.

Background

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity worldwide, and a chronic disabling lung condition characterised by airflow limitation [1]. It is estimated that COPD is anticipated to become the third leading cause of death in 2030[2]. People with COPD experience multiple distressing physical and psychological symptoms including breathlessness, fatigue, anorexia, pain, depression, anxiety, cough, daytime sleepiness and insomnia, dry mouth and sexual dysfunction [3]. Moreover, patients with COPD experience recurrent exacerbations, which is associated with a decline in exercise capacity, health-related quality of life (HRQoL) and self-efficacy [4].

Symptom management strategies of the people with COPD involve pharmacological and non-pharmacological methods [5]. Numerous studies have investigated the effectiveness of different management strategies for a single symptom. While some people with COPD may experience only a single symptom, a large proportion of people experience multiple concurrent symptoms [6]. A symptom

cluster refers to a group of two or more symptoms that occur together and are related to each other [7]. The science of symptom management has highlighted a conversion from a focus of targeting single symptoms to exploring symptom clusters that may improve symptom management by focusing on multiple symptoms at the same time [8]. A comprehensive understanding of the phenomenon of symptom clusters in people with COPD allows for more thorough symptom assessment and conduct strategies of targeted symptom management to improve patient-centred outcomes and experiences of care [9, 10].

Although increasing evidence has shown that symptom clusters occur in people living with COPD, many issues remain unsolved. Specifically, there is no consensus on the definition of symptom clusters, either methodologically or conceptually, both in the clinical practice and research [11]. Validation of the concept of symptom cluster is complicated and difficult because evaluating symptom interrelationships manifests a host of methodological challenges, specifically the study design, theoretical framework, measurement tools, symptom dimensions, statistical methods to identify the cluster, statistical “cut-off” points to define clusters, characteristics of study samples may all contribute to these inconsistencies of symptom clusters [12]. Among previous studies, different symptom assessment tools were used, and each involved a different array of symptoms [13–18].

There were two approaches of symptom selected in cluster identification which first proposed by Xiao [12], including ‘most-common symptom approach’ and ‘all-possible symptom approach’. The ‘most-common symptom approach’ is known as ‘a priori’ cluster identification that referred to researchers first selecting several commonly experienced symptoms, assuming that these most-common symptoms could be grouped as a cluster [19–22]. Furthermore, clinical evidence showed that dyspnoea, anxiety, depression and sleep disorder are the most well-known and common symptoms in COPD population [6, 13, 23, 24]. The ‘all-possible symptom approach’ targets all potential symptoms that people with COPD might experience to identify clusters, which yields the results of symptom cluster after statistical analysis [25–27]. However, a limitation of the ‘all-possible’ approach is that it lacks an explanation of the clinical meaning for symptom clusters identified by statistical methods [12]. Additionally, in the previous studies which focused on investigating symptom clusters in people living with COPD, most of them adopted the ‘all-possible symptom approach’ [13, 17, 18, 28], few studies used the ‘most-common symptom approach’.

Clinical experiences and middle range ‘Theory of Unpleasant Symptoms’ indicate that the existence of symptom clusters can significantly increase symptom burden and synergistically affect patients’ HRQoL compared with the single symptom [29, 30]. To our knowledge, no studies have specifically evaluated the synergistic impacts of symptom clusters on HRQoL in the COPD population.

Methods

Aim

The aim of this study was to: (i) identify symptom clusters in people living with COPD and (ii) examine the synergistic impact of symptom clusters on HRQoL in the COPD population compared with the single symptoms.

Design

This is a secondary data analysis of a cross-sectional survey via convenience sampling, originally designed to investigate factors associated with HRQoL in patients with COPD in China. The original data was collected between January to August 2018 after obtaining approval from the Second People's Hospital of Huai'an's Ethical Committee in China (approval number: HEYLL20181A).

Setting and sample

This cross-sectional study was conducted in the Department of Respiratory and Critical Care Medicine of the Second People's Hospital of Huai'an, China, which is tertiary health care and urban teaching hospital with 1,200 beds. In general, healthcare in China is administered through three different systems: hospitals, primary healthcare facilities and public health institutions [31]. In terms of the locus of service provision, China has inherited a largely hospital-based delivery system managed through the Ministry of Health and local governments [32]. This study is reported following STROBE guidelines for reporting of observational studies [33].

The eligible criteria for patients to be included in the data set were as follows: (i) a primary diagnosis of COPD as a confirmed by a pulmonologist according to the post-bronchodilator Spirometry, (ii) The forced expiratory volume in one second (FEV1)/ Forced vital capacity (FVC) ≤ 70% on pulmonary function test [34], (iii) an aged 18 years or older, and (iv) the abilities to read, write and understand Chinese and abilities to give written informed consent. Exclusion criteria included that the patient had speech or hearing difficulties that made their involvement impossible.

Measurements

The demographic and clinical characteristics of participants were assessed using a self-completed socio-demographic and clinical questionnaire, including gender, age, living place, marital status, living state, education level, hospitalization cost, monthly income, smoking and alcohol history, exercise situation, time since diagnosed, stage of COPD, number of exacerbations and days in hospital in last 12 months. Dyspnoea was measured using modified Medical Research Council (mMRC) dyspnoea scale which consists in five statements that describe the entire range of dyspnoea from none (Grade 0) to being completely incapacitated by the illness (Grade 4) [35]. Based on the severity of the symptom, if the total score is 0, is recoded to 'None'; the total score is 1 or 2, is recoded to 'Moderate'; the total score is 3 or 4, is recoded to 'Severe'. Depressive symptoms were measured using the 4-point, 21-item Beck Depression Inventory (BDI). The total possible score ranges from 0 to 63 with a clinical cut-off point of nine [36]. Based on the severity of the symptom, the total score is 1–16, is considered to 'mild'; a total score of 17–30, is considered to be 'Moderate' and a total score is > = 31 is considered to be 'severe'. Anxiety was measured using the 4-point, 21-item Beck Anxiety Inventory (BAI). The total possible score ranges from 0

to 63, with a clinical cut-off point of seven [37]. A higher score indicates more severe anxiety. Based on the severity of the symptom, the total score is 0–21, is recoded to 'Mild'; the total score is 22–35, is recoded to 'Moderate'; the total score is ≥ 36, is recoded to 'severe'. Sleep quality was measured through the 19-item Pittsburgh Sleep Quality Index (PSQI), which contains 7 domains: duration of sleep, sleep syndrome, sleep latency, daytime dysfunction caused by sleepiness, sleep efficiency, overall sleep quality, and use of sleep medications, with a clinical cut-off point of five [38]. Based on the severity of the symptom, the total score is 0–10, is recoded to 'Mild'; the total score is 11–15, is recoded to 'Moderate'; the total score is 16–21, is recoded to 'severe'. HRQoL was measured using the 50-items St George's Respiratory Questionnaire (SGRQ) with three subscales: symptom, activity and impact [39]. Scores range from 0 to 100, with higher scores indicating more limitations.

Data collection

A research nurse identified eligible patients by screening medical records. Eligible participants were fully informed about the purpose of the study, questionnaires and time commitments, potential benefits and risks, and were contacted no sooner than 48 hours later to ensure they have sufficient time to consider participation. Three researchers subsequently conducted a face-to-face interview.

Data analysis

All the data was anonymized for analyses. Descriptive statistics were used to summarize the patients' characteristics. Results are expressed as frequencies and percentages. According to cut-offs for each of the scales used to measure symptoms [35–38], we transformed the symptom-related variables into binary variables. To identify symptom clusters, Chi-squared tests, odds ratio (OR) and its 95% confidence interval (95% CI) were calculated. Multiple linear regression (MLR) was conducted to examine the independent association of symptom clusters and HRQoL and illustrate the synergistic impacts of symptom clusters on HRQoL. Controlled variables entered into MLR were selected via correlation analysis, analysis of variance and clinical experience. MLR results were reported in terms of beta values (β) and 95% CIs. STATA/IC 15.1 was used for all statistical analyses.

Results

Characteristics of the subjects

The demographic and clinical characteristics of participants were summarised in Table 1. A total of 106 participants completed this survey. Of these, 82(77.4%) were male and the largest age group was 71–80 years old (n = 48; 45.3%). 56 (52.8%) of patients lived in urban areas; 50 (47.2%) patients lived in rural locations. The majority of participants were married (n = 95; 89.6%); and lived with their spouse (n = 60; 56.6%). 59.4% (n = 63) had achieved elementary schooling; 52.8%(n = 56) had commercial health insurance (CHI) to pay for hospitalization costs; 46.2%(n = 49) and had a monthly income of approximately over $302 dollars. 50%(n = 53) were former smokers and 43.4% (n = 46) previously drank alcohol. Nearly half of the participants (n = 51, 48.1%) never regularly exercised. The majority of the

participants (n = 54, 50.9%) has been diagnosed with COPD between one and ten years. Regarding of the severity of COPD based on the ‘Gold criteria’, approximately 50% (n = 53) of participants were categorized as ‘Gold 3’ commensurate with severe COPD; 34.9% (n = 37) of participants were categorized as ‘Gold 2’ commensurate with moderate COPD, 13.2%(n = 14) of participants were categorized as ‘Gold 4’ commensurate with very severe COPD and 1.9% (n = 2) of participants were categorized as Gold 1 commensurate with mild COPD.

Table 1
Sociodemographic and clinical variables of the sample [N = 106]

Variables:	Frequency	%
Sex		
Male	82	77.4
Female	24	22.6
Age in Years		
< 60	4	3.8
60–70	27	25.5
71–80	48	45.3
> 80	27	25.5
Living Place		
City	56	52.8
Rural	50	47.2
Marital Status		
Married	95	89.6
Single	11	10.4
Living State		
Alone	10	9.4
Living with spouse	60	56.6
Living with children	29	26.4
Living with parents	7	6.6
Education level		
Elementary school or less	63	59.4
Middle school	27	25.5
High school	9	8.5
≥College	7	6.6
Hospitalization cost		

Variables:	Frequency	%
Publicly funded free medical care	47	44.3
Commercial insurance	56	52.8
Self-funded	3	2.8
Monthly income per Yuan		
< 500	30	28.3
500–1000<	12	11.3
1000–2000	15	14.2
> 2000	49	46.2
Smoking history		
Current smoker	26	24.5
Never smoker	27	25.5
Former smoker	53	50.0
Alcohol history		
Current drinking	18	17.0
Never drinking	42	39.6
Former drinking	46	43.4
Exercise situation		
Never	51	48.1
≤ 2 times per week	35	33.0
3–5 times per week	14	13.2
> 5 times per week	6	5.7
Time since diagnosed [Years]		
1–10	54	50.9
11–20	27	25.5
21–30	11	10.4
> 30	14	13.2

Variables:	Frequency	%
FEV1 in % predicted		
Gold I [Mild]	2	1.9
Gold II [Moderate]	37	34.9
Gold III [severe]	53	50.0
Gold IV [very severe]	14	13.2
Number of exacerbations in the last 12 months		
No	6	5.7
One	32	30.2
Two	38	35.9
≥Three	30	28.3
Days in hospital in last 12 months		
≤ 14	37	34.9
15–28	54	50.9
29–42	8	7.6
≥ 42	7	6.6

Overall, 35.9% (n = 38) of participants experienced two COPD exacerbations in the last 12 months, and 50.9% (n = 54) of participants had experienced 15–28 days in hospital in last 12 months before the questionnaire was administered.

Symptom clusters in COPD patients

Three symptom clusters were identified (Table 2). Symptom cluster 1 comprised dyspnoea and depression (OR = 2.69, 95%CI = 1.19 to 6.02). Symptom cluster 2 consisted of anxiety and sleep (OR = 2.72, 95%CI = 1.20 to 6.15). Symptom cluster 3 comprised depression and anxiety (OR = 6.13, 95%CI = 2.57 to 14.60).

Table 2
Symptom clusters in COPD patients [N = 106]

Dyspnoea	**Depression**		**Total**	**OR**	**CI**
	Yes	**No**			
Yes	24	25	49	2.69	1.19–6.02
No	15	42	57		
Total	39	67	106		
Anxiety	**Sleep**		**Total**	**OR**	**CI**
	Yes	No			
Yes	32	13	45	2.72	1.20–6.15
No	29	32	61		
Total	61	45	106		
Depression	**Anxiety**		**Total**	**OR**	**CI**
	Yes	No			
Yes	27	12	39	6.13	2.57–14.60
No	18	49	67		
Total	45	61	106		

Symptom clusters in patients with severe-stage COPD

Only two symptom clusters were identified in the ‘severe’ stage of COPD. Specifically, they included symptom cluster 1 comprising anxiety and sleep (OR = 6.21, 95%CI = 1.70 to 22.74) and symptom cluster 2 comprising depression and anxiety (OR = 5.33, 95%CI = 1.64 to 17.40) (Table 3).

Table 3
Symptom clusters in patients with severe-stage COPD[N = 53]

Anxiety	**Sleep**		**Total**	**OR**	**CI**
	Yes	**No**			
Yes	19	4	23	6.21	1.70-22.74
No	13	17	30		
Total	32	21	53		
Depression	**Anxiety**		**Total**	**OR**	**CI**
	Yes	No			
Yes	16	9	25	5.33	1.64–17.40
No	7	21	28		
Total	23	30	53		

Association between symptom clusters and HRQoL

Gender, marital status, living state, educational level, stage of disease and number of exacerbations in the last 12 months were selected as controlled variables. The linear regression model identified associations between symptom clusters and HRQoL (Table 4). According to the multiple linear regression adjusted for the controlled variables above, all three SCs (anxiety and sleep; dyspnoea and depression; depression and anxiety) were independently associated with HRQoL (β = 14.56, 95%CI: 5.80-23.31; β = 13.95, 95%CI:5.72–22.18; β = 13.30, 95%CI:6.88–19.73).

Table 4
The association between symptom clusters and health-related quality of life [N = 106]

Variable	Health-related quality of life [unadjusted]		Health-related quality of life [adjusted]	
	Coef.	95% CI	Coef.	95% CI
Anxiety and sleep cluster	20.76	[2.82,28.69]	14.56	[5.80,23.31]
Anxiety	13.89	[3.18,24.60]	11.19	[-0.15,22.53]
Sleep	8.73	[-0.29,17.74]	6.87	[-2.00,15.75]
Dyspnoea and depression cluster	22.58	[15.42, 29.73]	13.95	[5.72,22.18]
Dyspnoea	13.02	[5.64,20.39]	8.01	[0.18,15.85]
Depression	12.76	[2.56,20.39]	11.55	[1.56,21.54]
Depression and anxiety cluster	20.46	[14.07,26.85]	13.30	[6.88,19.73]
Depression	7.52	[-2.57,17.61]	8.12	[-1.54,17.79]
Anxiety	9.57	[0.88,18.26]	8.99	[-1.24,19.23]

Furthermore, with regards to associations between symptom clusters/singular symptoms and HRQoL, we noticed that the beta value of the Dyspnoea & Depression cluster was higher than that of the singular dyspnoea symptom and depression symptom (β = 13.95; β = 8.01; β = 11.55). Singular anxiety symptom(95%CI=-0.15-22.53) and sleep symptom(95%CI=-2.00-15.75) were not associated with HRQoL. The Anxiety & Sleep cluster was significantly associated with HRQoL (β = 14.56, 95%CI = 5.80-23.31). Singular depression symptom(95%CI=-1.54-17.79) and anxiety symptom(95%CI=-1.24-19.23) were not associated with HRQoL. The Depression & Anxiety cluster was significantly associated with HRQoL (β = 13.30, 95%CI = 6.88–19.73).

Discussion

Main Findings

This is the first study to examine the synergistic impacts of symptom clusters on HRQoL when compared to the presence of single symptoms in COPD patients. The beta coefficient is the degree of change in the outcome variable in multiple linear regression. The higher the absolute value of the beta coefficient, the stronger the association [40]. Specifically, based on the results presented in Table 4, the beta value of dyspnoea and depression cluster (β = 13.95, 95%CI = 5.72–22.18) was higher than that of singular dyspnoea symptom (β = 8.01, 95%CI = 0.18–15.85) and singular depression symptom (β = 11.55, 95%CI = 1.56–21.54), which means that the association between symptom cluster and HRQoL is stronger than

the association between singular symptom and HRQoL. As for the other two symptom clusters (anxiety and sleep; depression and anxiety), symptom clusters were significantly associated with HRQoL while singular symptoms were not. Therefore, our results validated the synergistic impacts of symptom clusters on HRQoL. In addition, these findings are also empirically supported and consistent with the 'Theory of Unpleasant Symptoms' that assumes that symptoms in a cluster are shown to exert synergistic effects on important patient outcomes, for example, functional states, HRQoL, medical expenses, mortality and self-care ability [41–43].

Symptom clusters in people with COPD

Although patients with COPD often experience multi-dimensional symptoms, in this study we adopted the 'most-common symptom approach' to identify symptom clusters, which aimed to provide an efficient, flexible, concise and more clinically defined model [44]. Therefore, our study measured four common symptoms in COPD patients and identified three symptom clusters in COPD patients: dyspnoea and depression; depression and anxiety; anxiety and sleep. The first symptom cluster was dyspnoea and depression, similar to our finding, Kunik et al. identified that depression often occurred together with breathing problem [45]. A strong association between psychological symptoms and dyspnoea was also found in prior research [46]. In addition, the aetiology and mechanisms of the increased prevalence of depression in patients with COPD are not well understood [47]. As expected, COPD causes the irreversible airflow limitation resulting in a decrease in the oxygen supply to the brain and loss of regional grey matter accompanied by impairment of white matter microstructural integrity, which was associated with disease severity and might underlie the psychological changes of COPD [48]. Screening for presence and levels of depression may be necessary for people with COPD. The second symptom cluster was anxiety and sleep, which was not observed in previous studies. These inconsistent findings between our study and prior research might be due to differences in symptom measurements and statistical methods among the studies [49]. However, some studies reported anxiety had been shown to have a negative effect on sleep quality in COPD population [24, 50]. This finding highlighted when anxiety or sleep disorder was identified, clinicians might anticipate and probe further into the other related symptom [7]. The third symptom cluster was depression and anxiety, which was consistent with the study by Lim and colleagues which identified the mood cluster consisted of depression and anxiety in the South Korea COPD patients [51]. In addition, many studies have reported that subjects with COPD have concurrent depression and anxiety [52–54]. It is noteworthy this study identified three symptom clusters in patients with COPD, two symptom clusters in patients with severe-stage COPD. From the 'Theory of Unpleasant Symptoms' [29], Lenz and colleagues stated that physiological factors influence the symptom clusters, this study empirically confirmed that an association between stage of the disease and symptom clusters.

Association between symptom clusters and health-related quality of life

Our study identified that all the symptom clusters were significantly correlated with HRQoL in COPD population. The result of a correlation between the depression-anxiety symptom cluster and HRQoL in this study is consistent with a previous study, which revealed that psychological symptom clusters are a

significant predictor of HRQoL [17]. Our results reinforce the significant effect of psychological symptom clusters on HRQoL in people living with COPD. The other two symptom clusters influencing HRQoL were the dyspnoea-depression and anxiety-sleep symptom clusters. Although no prior studies have assessed the correlation between these two symptom clusters and HRQoL in patients with COPD, our results are consistent with the results of previous studies on individual symptoms [55–58]. These findings should be considered when developing targeted and effective symptom management strategies to improve HRQoL in COPD patients; in particular, such symptom management programmes should pay more attention to psychological symptom clusters.

Clinical and research implications

Our study identified that patients with COPD experience numerous co-existing symptoms which frequently grouped as a cluster with synergistic impacts for quality of life. For health professionals, these findings provide a better understanding of symptom cluster phenomena. Although comparatively little is known about the scientific aetiology for the synergistic impacts of symptom clusters on quality of life, our findings support the importance of simultaneously managing symptom clusters; that is, collective symptom management. For example, cognitive behavioural techniques could collectively manage psychological symptoms involving depression and anxiety [59]; exercise therapy could simultaneously reduce depression [60] and dyspnoea [61]. Therefore, identification of symptom clusters in the clinical setting may help to develop effective symptom assessments and their management strategies designed to improve COPD-associated HRQoL. Our findings also provided preliminary evidence that patients with COPD existed variability of symptom clusters based on the stage of the disease. Future research should pay more attention to this specific clinical factor which is associated with symptom clusters within context.

Limitations of study and data

Firstly, the sample size in this study was relatively small, which may decrease the likelihood of detecting a significant difference when one truly exists. Secondly, this study did not record any data on the type of comorbidities. It may be difficult to clarify symptoms which are attributable to COPD. Thirdly, information concerning anxiety and depression was obtained through self-report and may be underestimated due to Chinese culture [62]. Cross-cultural psychologists have reported that Chinese cultures are more likely to use physical symptoms as an idiom of distress than Western countries [63]. Finally, the findings were limited in terms of their general applicability since data collection was limited to one university hospital, and accordingly, large-scale studies are needed to obtain more reliable information regarding COPD symptom clusters.

Conclusions

This study adds important evidence on the science of examining the presence of clinically significant symptom clusters present among people living with COPD. The present study provides an emerging empirical basis for focusing on symptom clusters and associated HRQoL outcomes in people with COPD.

This study also identified that symptom clusters varied by stage of disease in COPD patients. To our knowledge, this is the first study to demonstrate synergistic impacts of symptom clusters on HRQoL in COPD patients, as compared with single symptoms. Given the findings in this study, we consider that to incorporate an evaluation of symptom clusters may facilitate identification and treatment of symptoms having an additive and detrimental effect on HRQoL. It may provide a better understanding of this phenomenon which can contribute to efficient symptom management and alleviate symptom distress among persons with COPD.

Abbreviations

SCs: Symptom clusters; HRQoL: Health-related quality of life; COPD: Chronic obstructive pulmonary disease; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; mMRC: Modified Medical Research Council; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; PSQI: Pittsburgh Sleep Quality Index; SGRQ: St George's Respiratory Questionnaire; OR: Odds ratio; MLR: Multiple linear regression; 95% CI: 95% confidence interval; β: Beta values

Declarations

Ethics approval and consent to participate

The original cross-sectional study was approved by the Second People's Hospital of Huai'an's Ethical Committee in China (approval number: HEYLL20181A). All the patients provided written informed consent before participation.

Consent for publication

Not applicable

Availability of data and materials

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

F.F., W.G. and J.K. designed the work; F.F and XH. Z analyzed the data. W.G. and J.K provided academic supervision. All authors reviewed the findings, agreed with the interpretation, contributed to writing the paper, had full access to all data in the study, and read and approved the final version. The corresponding author (F.F.) had final responsibility for the decision to submit for publication.

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