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META-ANALYSIS

The Incidence and Risk Factors of Frailty in Patients with Chronic Obstructive Pulmonary Disease: A Meta-Analysis

Xiuyun Chen, MM, Siping Sun, MM, Hong Chen, MM, Xiuyun Sun, MM, Aichun Yang, MM, Qing Wang, MM, Bin Shi, MM

ABSTRACT

Objective • COPD patients have a high incidence of frailty and numerous complications, which seriously affect their quality of life. This study systematically evaluated and analyzed the current state of frailty incidence and risk factors in COPD patients to reduce the prevalence of frailty and enhance their quality of life.

Method • The Cochrane Library, PubMed, Embase, Web of Science, CBM, CNKI, VIP, and Wanfang databases were searched for relevant studies from the inception of each database until November 2022. A thorough literature screening, quality evaluation, and data extraction was conducted. Meta-analysis was performed using RevMan5.3Meta. Twelve articles were selected as most relevant to this review; 10 were in Chinese, and 2 were in English.

Results • The results showed that the incidence of asthenia in COPD patients was 26% (OR 0.26, 95% CI 0.17~0.34).

Discussion • The main risk factors for frailty in COPD patients were age (OR 1.32, 95% CI 1.30~1.34), GOLD pulmonary function class (OR 3.18, 95% CI 2.14~4.71), mMRC score (OR 3.90, 95% CI 1.53~9.92), comorbidity (OR 2.17, 95% CI 1.48~3.18), polypharmacy (OR 6.74, 95% CI 3.23~14.08), malnutrition (OR 3.32, 95% CI 1.77~6.24), depression (OR 1.37, 95% CI 1.07~1.76) and ≥2 admissions within 1 year (OR 4.84, 95% CI 2.45~9.57).

Conclusion • The study presented comprehensive evidence through meta-analysis and proposed that the prevalence of frailty in COPD patients is 26%. Risk factors were identified, including age, pulmonary function class according to GOLD criteria, mMRC score, comorbidity polypharmacy malnutrition, depression, or 2 or more hospital admissions within a year. It is recommended that clinical medical staff identify these risk factors at an early stage. (*Altern Ther Health Med.* 2025;31(1):216-221).

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent respiratory condition in China, characterized by high incidence, disability, and mortality rates.[1-2] Research on the epidemic reveals that COPD-related deaths in China account for 30% of global fatalities. The prevalence of COPD among individuals age 40 and above ranges from 5 to 19%. Furthermore, over 27% of the population aged 60 and over suffer from COPD, leading to a significant burden on the nation's healthcare system.[3]

Frailty in the elderly refers to a decline in their physical resilience, making them more susceptible to harm. They have a reduced ability to maintain internal stability, and even minor external factors can have serious consequences, such as acute illness, disability, falls, confusion, and even death.[4] Studies indicate that frailty occurs in 9 to 78% of patients with COPD.[5] Frailty in COPD patients leads to various complications, including infections, disabilities, and hospital readmissions. These complications increase the risk of death and greatly affect patients' quality of life.[6] Therefore, it is crucial to identify frailty early. This study aims to conduct a meta-analysis to identify the main risk factors for frailty in COPD patients. This will provide healthcare professionals valuable information for early recognition and intervention measures.

DATA AND METHODS

Literature Search Strategy

A literature search was conducted in various databases, including the Cochrane Library, PubMed, Embase, Web of Science, CBM (Chinese Biomedical Databases), CNKI (Chinese National Knowledge Infrastructure), VIP, and

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Wanfang databases. The search period ranged from the establishment of each database to November 2022. The search method involved using free words and subject words. Chinese words were translated into English and the structure of the search was as follows: ("Pulmonary Disease, Chronic Obstructive" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Diseases" OR "COAD" OR "COPD" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Pulmonary Disease" OR "Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "Chronic Airflow Obstructions" OR "Chronic Airflow Obstruction") AND ("Frail Elderly" OR "Frail OR frail syndrome") AND ("relative risk" OR "cohort studies").

Literature Inclusion and Exclusion Criteria

The following criteria were used to select articles from the literature search results: (1) the study definitively identified the subject of an article as COPD patients; (2) each selected article included tools for assessing frailty and outcome indicators that yielded data capable of providing odds ratios (OR) value and 95% confidence interval (CI) data; (3) and the study was either a cross-sectional or cohort study.

Retrieved articles that did not match the subject or research content or were reviews, conference reports, etc., were explicitly excluded. Additionally, retrieved articles that could not be obtained in full text or had duplicated results in another study were also excluded.

Data Extraction

Two researchers conducted separate searches and evaluations based on the specific inclusion and exclusion criteria. They then cross-verified their findings. In instances where any uncertainties arose during the cross-verification process, a consensus was reached with the involvement of a third researcher. The relevant information was extracted in accordance with standardized data categories, which included the first author's name, year of publication, geographical region, type of research design, sample size, measurement tools utilized, prevalence of frailty, factors influencing frailty, and 95% CI.

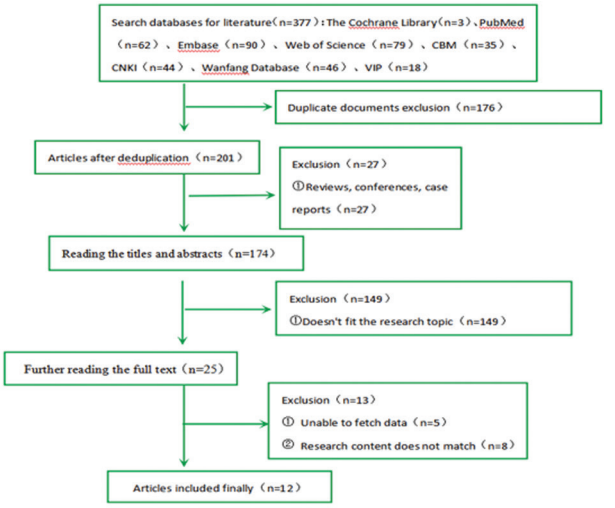
Methodological Quality Assessment

Twelve articles were included in the study; 10 were in Chinese, and 2 were in English. The literature quality was evaluated using the Newcastle-Ottawa Scale (NOS) (Chinese version).[7] This evaluation tool comprises 3 columns and a total of 8 items. Each item is assigned a score of 1 for meeting the standard, 2 for the highest comparability between groups, and 9 for the highest score. Two researchers independently performed the literature quality evaluation, and any disagreements were resolved through negotiations or seeking third-party arbitration.

Statistical Method

The statistical analysis was performed using Revman 5.3 software. The statistics used were the *OR* value (multiplier relationship of increase) and the 95% CI. To assess heterogeneity in the pooled data, the I^2 and Q tests were performed. The fixed effect model was applied if the research results were homogeneous (Conditions: $P \geq 0.10$ and $I^2 \leq 50\%$). Conversely, if there was heterogeneity, the random effect model was used (Conditions: $P < .10$ and $I^2 < 50\%$). The sensitivity analysis was performed using the one-by-one exclusion method, comparing 2 factors after excluding the literature: (1) changes in heterogeneity and (2) changes in the combined effect size OR value. A funnel plot was created to assess publication bias, and a significance level of $P < .05$ was considered statistically significant.

Figure 1. Screening Process and Results



RESULTS

Literature Screening Results

A total of 377 articles were retrieved, of which 176 were found to be duplicates, and 27 were reviews, conferences, and case reports. NoteExpress excluded these. After carefully reviewing the titles and abstracts, an additional 149 articles were excluded, leaving 25 for preliminary screening. Upon closer examination of the full text, 13 articles were deemed irrelevant and excluded, resulting in a final selection of 12 articles.[8-19] A visual representation of the literature screening process is shown in Figure 1.

Characteristics of Included Articles

Of the 12 articles included, 2 were in English, and 10 were in Chinese. The total number of samples reported across these 12 articles was 6860, with 1928 cases in study groups and 4932 cases in control groups. The incidence of asthenia ranged from 8.3% to 44.7%. Table 1 shows the characteristics of the included articles.

Methodological Quality Evaluation of Included Articles

NOS (Chinese version) was used to evaluate the quality of articles. Of the 12 articles in this study, 8 were grade A, and 4 were grade B.

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Table 1. Basic Characteristics of 12 Included Articles

Inclusion Study	Country	Year	Type	Sample No.		Incidence of Frailty	Age	Survey Tool	Risk Factors
				Study	Control				
Qingqing Hong[8]	China	2020	Case Control	53	79	40.15%	≥65	Fried	6
Xufen Qian[9]	China	2021	Case Control	43	217	16.54%	≥60	FRAIL	15,7,11,17,19
Kui Xia[10]	China	2019	Case Control	85	191	30.80%	80	FRAIL	1,5,7,8,11,12,14
Yulan Gao[11]	China	2020	Case Control	50	339	12.85%	60~86	EFS	1,5,6,9
Gang Tian[12]	China	2018	Case Control	169	209	44.70%	≥55	Fried	7,20
Pei Chen[13]	China	2018	Case Control	30	363	8.30%	43~80	FRAIL	1,5,16,31
Yan Liu[14]	China	2021	Case Control	21	147	12.50%	60~83	FRAIL	15,21,22, 29
Ji Wang[15]	China	2019	Case Control	53	194	21.46%	60~88	Fried	1,2,5,6,7,8,18,23,24,26,27,28,30
Wen Zhou[16]	China	2021	Case Control	236	358	39.73%	40~80	TFI	6,16,32,33
Yuchun Wang[17]	China	2022	Case Control	1009	2470	29.00%	65~89	FRAIL	1,3,5,7,13,14,24,25,34
Elsa Naval[18]	Spain	2021	Case Control	31	96	24.41%	57~77	Fried	1,6,14
Soo Kyung Park[19]	Korea	2021	Case Control	148	269	35.5%	55~75	TFI	2,3,5,7,14

Note: Survey Tool Scales: Simple Frailty Questionnaire (FRAIL), Tilburg Frailty Indicator (TFI), Fried Scale (Fried), Edmonton Frail Scale (EFS).

Influencing factors: 1. Age, 2. Education level, 3. Smoking history, 4. BMI, 5. GOLD pulmonary function class, 6. mMRC score, 7. Comorbidity, 8. Polypharmacy, 9. Combined inflammation 10. Course of disease, 11. Malnutrition, 12. Mild cognitive impairment, 13. Anxiety, 14. Depression, 15. Poor disease acceptance, 16. At least 2 hospitalizations in the past 1 year, 17. Prolonged length of hospital stay due to COPD exacerbations in the past 1 year, 18. Weekly activity, 19. Lack of training, 20. Shortness of breath when climbing stairs, 21. Hemoglobin, 22. 25-OH-D, 23. Total protein(TP), 24. Albumin (Alb), 25. Prealbumin, 26. Alanine aminotransferase (ALT), 27. Triglycerides (TG), 28. C-reactive protein (CRP), 29. IL-6, 30. Pulmonary hypertension (PAH), 31. Irregular inhalation of steroids, 32. Sleep disorder, 33. Visual impairment, 34. TCM constitution type.

Table 2. Methodological Quality Assessment

Inclusion Study	Selection of Research Subjects (4 Scores)				Comparability between groups (2 scores)	Exposure (3 Scores)			Total Scores
	Whether cases are properly defined and diagnosed	Representativeness of cases	Control selection	Definition of comparison	Comparability of cases and controls	Exposure investigation and assessment methods	Case and control investigation methods	Non-response rate	
QingqingHong[8]	1	1	1	1	1	1	1	0	7
Xufen Qian[9]	1	1	1	0	1	1	1	1	7
Kui Xia[10]	1	1	1	0	1	1	1	0	6
Yulan Gao[11]	1	1	1	0	1	1	0	0	5
Gang Tian[12]	1	1	1	0	1	1	1	0	6
Pei Chen[13]	1	1	1	1	1	1	1	1	8
Yan Liu[14]	1	1	1	1	2	1	1	0	8
Ji Wang[15]	1	1	1	1	1	1	1	0	7
Wen Zhou[16]	1	1	1	1	1	1	1	0	7
Yuchun Wang[17]	1	1	1	0	1	1	1	0	7
Elsa Naval[18]	1	1	1	1	0	1	1	0	6
Soo Kyung Park[19]	1	1	1	1	1	1	1	1	8

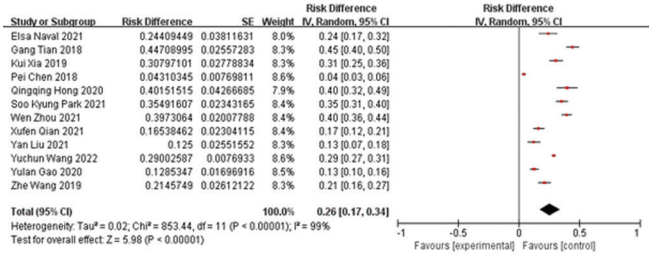
Table 3. Meta-analysis of Risk Factors for Frailty in Patients with COPD

Influencing Factors	Effect Model		Effect Model	Meta-Analysis Results				Number of articles (No.)
	P value	I^2 value (%)		*Z* value	*P* value	Combined OR values	95% *CI*	
Age	.39	4	FEM	34.39	<.001	1.32	1.30~1.34	7[9-11,13,15,17-18]
GOLD pulmonary function class	.005	68	REM	5.75	<.001	3.18	2.14~4.71	7[9-11,13,15,17,19]
mMRC score	<.001	94	REM	2.85	<.001	3.90	1.53~9.92	5[8,11,15-16,18]
Comorbidity	.001	79	REM	3.98	.001	2.17	1.48~3.18	6[9-10,12,15,17,19]
Polypharmacy	.15	52	REM	5.08	<.001	6.74	3.23~14.08	2[10,15]
Malnutrition	.30	80	REM	3.74	<.001	3.32	1.77~6.24	2[9-10]
Depression	<.001	82	REM	2.48	.010	1.37	1.07~1.76	4[10,17-19]
≥2 admissions within 1 year	.13	56	REM	4.54	<.001	4.84	2.45~9.57	2[13,16]

Meta-Analysis of the Incidence of Frailty in COPD Patients

All 12 articles[8-19] reported the incidence of frailty. The heterogeneity test (I^2=99%, P < .001) showed high heterogeneity among the included studies. The incidence of frailty in COPD patients was about 26% (95% CI 0.17-0.34), P < .001) under the random effect model (see Figure 2).

Figure 2. Meta-analysis of the Incidence of Frailty in Patients with Chronic Obstructive Pulmonary Disease



Meta-Analysis of Risk Factors for Frailty in COPD Patients

The 12 articles involved 34 influencing factors. Factors mentioned in more than 2 articles were considered for the analysis, resulting in 10 risk factors being examined. The findings revealed that age, GOLD (Global Initiative for Obstructive Lung Disease), pulmonary function classification, mMRC (Modified Medical Research Council Dyspnea Scale score, comorbidity, polypharmacy, malnutrition, depression, and hospital admission more than twice in 1 year were all significant factors influencing the occurrence of frailty in patients with COPD (P < .001, as shown in Table 3.

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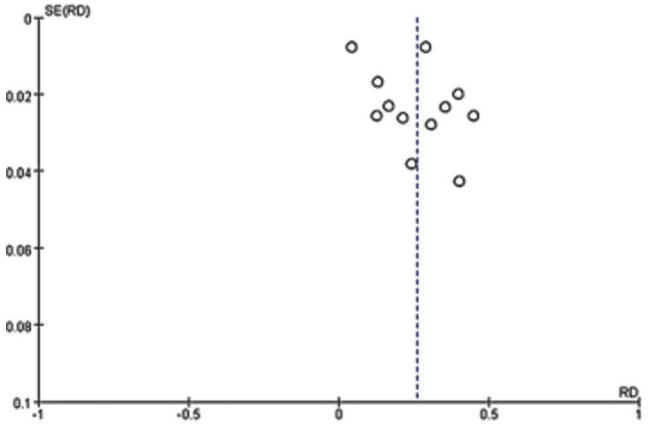
Figure 3. Funnel of Frailty Status and Risk Factors Meta-analysis in COPD Patients



Sensitivity Analysis & Publication Bias

When conducting a study that includes a wide range of articles with different characteristics, it is important to use sensitivity analysis to address heterogeneity. In this particular study, some of the articles exhibited heterogeneity. However, after systematically excluding 12 cross-sectional studies one by one, the overall effect remained relatively stable. The range of OR values varied between 0.24 and 0.27, with a 95% CI of 0.16-0.19 to 0.33-036. This suggests that the results of the meta-analysis were consistent. Additionally, the 12 articles reported the incidence of frailty. The funnel plot, depicted in Figure 3, demonstrates that the effect points of each study are distributed symmetrically around the combined effect size.

DISCUSSION

Methodological Quality Evaluation, Sensitivity Analysis, and Publication Bias of Included Articles

Of the 12 articles included in the study, except for 4 articles graded B[10-12,18], all others were graded as A. All of these articles were case-control studies, and they provided better verification of causality. To assess heterogeneity, sensitivity analysis was conducted by excluding individual articles one by one, and the results indicated that the combined effect size remained relatively stable. The funnel plot analysis revealed no significant publication bias. However, it should be noted that this study did not include gray literature, and the number of articles included was small, so there is still a possibility of publication bias.

Higher Incidence of Frailty in Patients with COPD

According to the meta-analysis findings, the incidence of frailty in COPD patients was 26%, which was higher than the frailty rate (22.6%) among the general hospital population of China.[20] Frailty may be associated with dyspnea, decreased physical activity, endocrine dysfunction, and inflammatory disorders. However, studies have shown that frailty is not an inevitable result of aging, and reasonable intervention can delay or even reverse the frailty process.[21] It is suggested that medical staff should assess the frailty of COPD patients early, control risk factors, and delay or modify the onset of frailty.

Risk Factors for Frailty in COPD Patients

Higher Risks of Frailty in Elderly COPD Patients. The results of this study show that age is a risk factor for the development of frailty in patients with COPD. As individuals grow older, the likelihood of experiencing frailty in COPD patients increases significantly, which aligns with the research conducted by Liu Changhu et al.[22] There are several potential reasons for this phenomenon: firstly, as individuals age, the respiratory system's defense capabilities in COPD patients gradually diminish, leading to frequent respiratory tract infections. Secondly, reduced physical activity and declining skeletal muscle function and mobility contribute to an increased risk of frailty. Therefore, it is recommended that healthcare professionals conduct personalized assessments of frailty risk and implement interventions for COPD, particularly for the elderly population.

GOLD Pulmonary Function Class and mMRC Score are Risk Factors for Frailty in COPD Patients. COPD patients who have a higher pulmonary function class and dyspnea score are at an increased risk of frailty. As the pulmonary function class continues to increase, the degree of dyspnea worsens. To alleviate the shortness of breath, patients are forced to reduce activity. This reduction in exercise volume can result in muscle atrophy and dyskinesia. Consequently, muscle atrophy and dyskinesia contribute to a further decrease in exercise volume, creating a vicious cycle that exacerbates the risk of frailty in COPD patients.[23] Studies have shown that exercise training is the basis of pulmonary rehabilitation in patients with COPD. Moderate exercise training can effectively slow down the progression of muscle atrophy and dyskinesia in patients with COPD and help delay or reverse frailty.[24] Therefore, it is evident that COPD patients should engage in appropriate exercise training under the guidance of doctors. This will improve patient and family awareness of exercise training, enhance compliance, improve lung function, and reduce the risk of frailty.

COPD Patients with Comorbidity, Polypharmacy and Malnutrition Predispose to Frailty. The findings of this study indicate that having multiple health conditions is a contributing factor to frailty in patients with COPD. The risk of frailty increases by 2.17 times, consistent with the research results of Hou Ping et al.[25] Studies have shown that the comorbidity rate of COPD patients ranges from 38% to 97.7%.[26-27] The coexistence of multiple diseases reduces the patient's resistance to the external environment and increases the patient's susceptibility and severity of frailty. Therefore, preventing and managing frailty should involve actively addressing existing conditions, paying attention to cardiovascular health parameters such as blood pressure and blood lipids, and monitoring renal function in patients with kidney diseases. This approach can help prevent complications and reduce the incidence of comorbidities. Furthermore, COPD patients who take multiple medications face a 6.74 times higher risk of developing frailty compared to those who do not take multiple medications. Gnjidic et al.[28] demonstrated that reducing medication usage can lead to worsening of COPD symptoms.

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Conversely, taking multiple medications can increase the risk of side effects, thereby increasing the likelihood of frailty and subsequent adverse events.

Furthermore, COPD patients who take multiple medications face a 6.74 times higher risk of developing frailty compared to those who do not take multiple medications. Pulmonary rehabilitation guidelines emphasize that multidisciplinary treatment is the primary approach to treating chronic respiratory diseases. Multidisciplinary teams make necessary adjustments to medication usage by carefully considering the associated risks. It is crucial to conduct a thorough assessment of the potential dangers of polypharmacy in patients with COPD.[28] Research studies have shown that rational drug therapy not only helps in reducing medical expenses but also decreases the likelihood of frailty in older patients.[29] But,Gnjidic et al.[30] demonstrated that reducing medication usage can lead to worsening of COPD symptoms. Conversely, taking multiple medications can increase the risk of side effects, thereby increasing the likelihood of frailty and subsequent adverse events.It is prompted that clinical medical staff should use the drugs reasonably for patients with COPD. They should comprehensively consider the benefits and risks of medication, weigh the advantages and disadvantages, and use it with caution. It is recommended to take non-drug methods such as multidisciplinary collaboration for treatment to reduce the risk of weakness.

The results of this study show that malnutrition is a risk factor for frailty in COPD patients, which aggravates the progression of frailty and is one of the important biological mechanisms of frailty.[31] *The 2022 Dietary Guidelines for Chinese Residents* additionally highlight the importance of maintaining optimal nutritional status, implementing scientifically balanced diets, and mitigating the impact of malnutrition on frailty as a means to reduce its risk in elderly patients.[32] Hence, timely attention to nutritional needs is crucial.

Depressed COPD Patients have Higher Risks of Frailty. The results of this study showed that the risk of frailty in depressed COPD patients increased by 1.37 times, which was consistent with the research results of Uchmanowicz et al.[33] COPD, being a chronic illness, is characterized by a long duration and slow healing process. As the disease progresses, the patient's quality of life declines, social activities are restricted, and the economic burden continues to increase. Consequently, patients often experience long-term depression. The presence of depression further hampers treatment compliance, creating a detrimental cycle that accelerates the onset of frailty.[34] It is recommended that healthcare professionals consistently monitor the mental and psychological state of COPD patients, promptly address negative emotions, and delay the onset of frailty.

≥2 Hospital Admissions within 1 Year are Risk Factors for Frailty in COPD Patients. Studies have shown that individuals with COPD experience acute exacerbations that require hospitalization approximately 3 to 5 times per year. Furthermore, there is a significant likelihood of readmission within 30 days for some COPD patients.[35] Wang Lu et al.[36] showed that the readmission rate of COPD frailty patients within 3 months was 84.9%, while non-frail COPD patients were only 9.4%. Another study by Zhao Mei et al.[37] suggested that frailty is a contributing factor to repeated admissions of COPD patients, indicating that frailty and repeated admissions may be reciprocal causation and mutual influence. It is recommended that medical staff should not only take measures to prevent frailty but also dynamically observe changes in patients' conditions and strengthen continuous care. This approach can help prevent repeated admissions and reduce the risks of frailty of COPD patients during exacerbations.

CONCLUSION

In summary, the incidence of frailty in COPD patients was 26%, higher than that of general hospitalized patients. Factors such as age, GOLD pulmonary function class, mMRC score, comorbidities, polypharmacy, malnutrition, depression, and hospital admission more than twice within a year were found to be risk factors for frailty in COPD patients. The clinical medical staff needs to assess the frailty tendency of COPD from various perspectives, identify those at high risk of frailty early on, and implement individualized intervention measures for modifiable factors. This approach can help reduce the incidence of frailty in COPD patients and enhance their long-term quality of life. However, it should be noted that this study had limited literature inclusion, excluded gray literature, and relied solely on cross-sectional studies, which may introduce some bias to the research findings. Therefore, future high-quality prospective cohort studies are necessary to validate these findings.

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CONFLICT OF INTEREST

The author indicated no conflict of interest.

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