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Article

Effects of Nutritional Support Combined With Respiratory Training on Pulmonary Function in Patients With Obliterative Bronchiolitis: A Propensity Score Matching Study

Yunxia Chen[1], Yi Chen[2], Xinyu Yuan[1], Dan Qian[3], Xiangting Hu[3,*]

[1]Department of Respiratory and Critical Care Medicine, The Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital), 215000 Suzhou, Jiangsu, China
[2]School of Nursing, Fudan University, 200032 Shanghai, China
[3]Department of General Surgery, The Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital), 215000 Suzhou, Jiangsu, China
*Correspondence: 15862360975@163.com (Xiangting Hu)
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Abstract

Aims/Background: Obliterative bronchiolitis (OB) is a chronic, progressively obstructive lung disease characterized by fixed airflow limitation and a high burden of malnutrition. At present, whether a personalized regimen combining nutritional support with respiratory training could improve obliterative bronchiolitis patient outcomes remains unclear. Thus, this study aimed to explore the clinical efficacy of a comprehensive intervention combining nutritional support with respiratory training in OB patients, with a particular focus on assessing their pulmonary function. **Methods**: A retrospective analysis was conducted on 101 patients with OB who received treatment in The Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital) from January 2022 to March 2025. According to the type of intervention, the subjects were divided into the experimental group (56 cases, receiving comprehensive intervention) and the control group (45 cases, receiving nutritional support only). Propensity score matching was used to balance the baseline data at a 1:1 ratio, and 44 pairs of patients were successfully matched. Pre- and post-intervention data on pulmonary function indicators, nutritional indicators, oxidative stress and inflammatory indicators, as well as quality of life and symptom indicators of the included patients, were compared. Multiple linear regression analysis was performed to determine the independent factors affecting the changes in pulmonary function indicators before and after the intervention. **Results**: Regarding the nutritional status, the experimental group exhibited significant post-intervention improvement only in the Nutritional Risk Screening 2002 (NRS-2002) score when compared with the pre-intervention score ($p < 0.05$). After the intervention, the forced expiratory volume in the first second (FEV_1; $p = 0.002$) and forced vital capacity (FVC; $p < 0.001$) in the experimental group were significantly higher than those in the control group, while the malondialdehyde ($p < 0.001$), C-reactive protein ($p = 0.005$) and procalcitonin ($p < 0.001$) in the experimental group were significantly lower than those in the control group. The number of patients with modified British Medical Research Council (mMRC) dyspnea scale score <2 in the experimental group was significantly higher than that in the control group ($p = 0.006$), and the improvements in 6-minute walk distance (6MWD) and World Health Organization Quality of Life-Brief (WHOQOL-BREF) version scores were greater in the experimental group than in the control group. In addition, multiple linear regression analysis showed that compared with nutritional support alone, the comprehensive intervention was independently associated with greater improvements in FEV_1 ($p = 0.002$) and FVC ($p = 0.001$) but had no independent effect on improvements of FEV_1/FVC ($p = 0.556$). **Conclusion**: Comprehensive intervention combining nutritional support with respiratory training effectively improves the pulmonary function, oxidative stress, inflammatory status, quality of life, and respiratory symptoms in OB patients, with outcomes superior to those achieved with nutritional support alone.

Keywords: obliterative bronchiolitis; pulmonary function; nutritional support; respiratory training; propensity score matching

1. Introduction

Chronic small airway diseases are characterized by progressive airflow limitation and irreversible pulmonary function decline, posing a significant burden on global respiratory health. Among these diseases, chronic obstructive pulmonary disease (COPD) is the most common, with a global prevalence of approximately 10% in adults over 40 years old [1]. Previous studies have confirmed that a comprehensive intervention combining nutritional support and respiratory training can effectively improve pulmonary function and exercise capacity in COPD patients [2,3]. However, the efficacy of comprehensive intervention in obliterative bronchiolitis, another destructive but understudied small airway disease, remains largely unknown, although it shares similar clinical outcomes, such as refractory airflow limitation and poor prognosis, with COPD.

Obliterative bronchiolitis (OB) is a rare progressive inflammatory disease of small airways, characterized by subepithelial fibrosis, luminal stenosis, and bronchial obliteration. It mainly occurs as a secondary complication, with an estimated incidence of 1%–5% in patients after receiving lung transplants and up to 10% in hematopoietic stem

cell transplant recipients [4,5]. In addition, inhalation injury and connective tissue diseases (such as rheumatoid arthritis) are also common causes of OB [4,6]. Diagnosis typically relies on examining a constellation of clinical presentations, assessing fixed airflow obstruction on the pulmonary function tests, and analyzing high-resolution computed tomography (CT) findings. Unlike COPD driven by chronic smoking-related inflammation, OB is often associated with immune-mediated injury or chronic tissue repair dysfunction, which further exacerbates nutritional imbalance and respiratory muscle weakness in affected patients [7]. Current therapeutic strategies are largely limited to immunosuppressive agents and supportive care, with limited efficacy in reversing disease progression. This gap underscores the clinical relevance of our study.

Clinically, OB patients face unique challenges that highlight the necessity of non-pharmacological interventions. Firstly, malnutrition is very common in OB patients: Up to 45% of post-transplant OB patients present with hypoalbuminemia or weight loss, attributed to immunosuppressive drug-induced gastrointestinal side effects, chronic inflammation, and increased energy expenditure from labored breathing [8,9]. Malnutrition, in turn, impairs respiratory muscle strength and immune function, forming a vicious cycle that accelerates pulmonary function decline [10]. Secondly, OB-related bronchiolar obliteration leads to fixed airflow limitation, and pharmacologic treatments such as inhaled corticosteroids and long-acting bronchodilators can only alleviate symptoms in 30%–40% of patients and fail to reverse the underlying structural airway damage [11]. Respiratory training, capable of improving respiratory muscle endurance and alveolar ventilation, has shown promise in other obstructive lung diseases, but its efficacy in OB remains to be deciphered [12].

Notably, existing research on OB interventions is severely limited: Most studies focus on pharmacological strategies [13] or surgical options [14], while no studies have evaluated the combined effect of nutritional support and respiratory training. Moreover, observational studies on OB often suffer from selection bias (such as differences in age or comorbidities between intervention and control groups), which weakens the reliability of conclusions [15]. To address this gap and to explore non-pharmacological options in the clinical management of OB patients, this retrospective study investigated the clinical efficacy of a comprehensive intervention combining nutritional support with respiratory training in OB patients, with a particular focus on assessing their pulmonary function. The data analysis entailed the elimination of potential confounding factors using propensity score matching.

2. Methods

2.1 Study Population

This is a single-center, retrospective cohort study. A total of 101 consecutive patients with OB admitted to The Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital) between January 2022 and March 2025, who had complete follow-up records, were enrolled. The patients were divided into the experimental group (receiving comprehensive intervention integrating nutritional support and respiratory training; n = 56) and the control group (receiving nutritional support alone; n = 45) based on the intervention received. The diagnosis of OB was established based on consistent clinical features (such as progressive dyspnea, chronic cough), fixed airflow obstruction on pulmonary function tests (post-bronchodilator forced expiratory volume in the first second [FEV_1]/forced vital capacity [FVC] <0.7, FEV_1 $<80\%$ predicted), and definitive radiographic findings according to international guidelines [11,16]. This study was approved by the Ethics Committee of The Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital) (Approval No.2025-251266) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants and their legal guardians

Inclusion criteria of this study are as follows: (1) Patients aged $\geq$18 years old; (2) Patients diagnosed with OB; and (3) Baseline information and key outcome records before and after the interventions.

Exclusion criteria of this study are as follows: (1) Individuals with other serious chronic respiratory diseases (such as active asthma, COPD caused by emphysema, bronchiectasis); (2) Patients with severe heart, liver, or kidney dysfunction; (3) Patients with active malignant tumors; (4) Pregnant or lactating women; (5) Individuals who had recently undergone major surgery (within 3 months); (6) Individuals showing recent acute exacerbation or respiratory infections (within 4 weeks); (7) Individuals who had recently been subject to immunosuppressive therapy, systemic nutritional support, or pulmonary rehabilitation (within 3 months); (8) Individuals with contraindications to exercise (e.g., severe osteoporosis, arthritis, neuromuscular disorders); (9) Individuals with incomplete clinical data or who were lost to follow-up. The selection process of the study participants is illustrated in Fig. 1.

2.2 Intervention Measures

Before enrollment, all patients received inhaled corticosteroids (ICS) combined with long-acting bronchodilators (Symbicort Turbuhaler: H20140458, AstraZeneca AB, SE-151 85, Södertälje, Sweden) as the standard routine pharmacologic treatment prescribed in accordance with international guidelines. On the basis of the standard routine treatment administered, the patients were also given additional interventions based on the groups they were assigned to.

In the control group, the patients received standardized nutritional support only. This intervention involved a comprehensive nutritional assessment followed by an individualized dietary plan developed by clinical nutritionists.

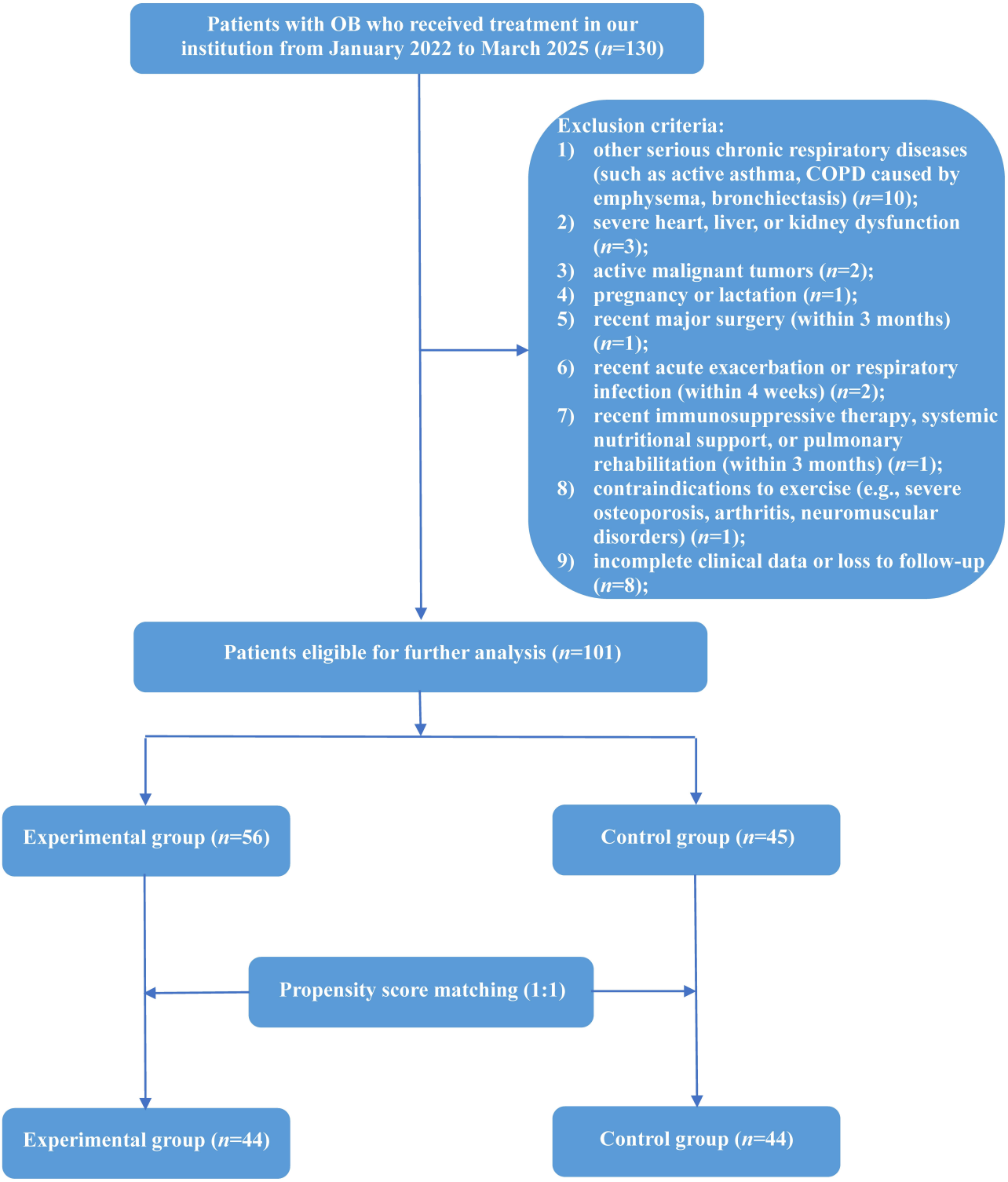

Fig. 1. Flowchart depicting patient selection process. Abbreviations: COPD, chronic obstructive pulmonary disease; OB, obliterative bronchiolitis.

The objective was to ensure an energy intake of approximately 25–35 kcal/kg/day and a protein intake of 1.2–1.5 g/kg/day, adjusted according to nutritional risk, comorbidities and tolerance, with emphasis on maintaining an oral diet supplemented by oral nutritional supplements (ONS). The ONS used was a standard, commercially available polymeric formula (Ensure®: H20181147, Abbott Laboratories, Chicago, IL, US), providing approximately 1.0–1.5 kcal/mL with balanced macronutrients. Short-term enteral nutrition transition was initiated if oral intake remained inadequate. Nutritional status was reassessed every 2–4 weeks by monitoring body weight, body mass index (BMI),

and albumin (ALB), as well as measuring the Nutritional Risk Screening 2002 (NRS-2002) scores, with adjustments to the dietary plan and energy/protein targets accordingly [17].

In the experimental group, the patients received the same individualized nutritional support as the control group (including the ONS protocol), plus a structured respiratory training program. The respiratory training was supervised by respiratory therapists and consisted of three components:

(1) Aerobic exercise training: The training consisted of 30–45 minutes of treadmill walking or stationary cycling at moderate intensity (initial target: 60%–80% of the maximum heart rate achieved in the baseline 6-minute walk test), 3–5 times per week. The exercise intensity was dynamically adjusted based on patient tolerance, assessed using the Borg Rating of Perceived Exertion (RPE) scale. The target RPE range was 3–5 (moderate to strong). If a patient consistently reported RPE <3, the intensity (speed, resistance, or duration) was increased. Conversely, if RPE consistently exceeded 5 or if oxygen saturation dropped below 88%, the intensity was reduced.

(2) Inspiratory muscle training (IMT): This training consisted of two sets of 15 breaths at an initial intensity of 30%–50% of maximal inspiratory pressure (MIP) using a threshold loading device (PowerBreathe®, 20162091286, Hälsa Enterprises Limited, Birmingham, UK), performed twice daily. The IMT load was increased by approximately 5%–10% of the initial MIP every 2 weeks if the patient could comfortably complete the sets, with the goal of progressively reaching 50%–60% of MIP.

(3) Breathing techniques: Participants received supervised instruction and practice in pursed-lip breathing and diaphragmatic breathing [18].

The intervention period for both groups was 12 weeks.

2.3 Data Collection

Complete clinical data of patients were collected from the electronic medical record system, including baseline information and outcome indicators before and after intervention. Outcome indicators were available in two classifications: primary outcome indicators (such as pulmonary function indicators) and secondary outcome indicators (such as nutritional indicators, oxidative stress and inflammatory indicators, quality of life and symptom indicators). Specific details are as follows:

(1) Baseline information: Data on baseline information such as age, gender, disease duration, history of smoking, history of malnutrition, and history of pulmonary infection were collected.

(2) Pulmonary function indicators: The Jaeger MasterScreen pulmonary function tester (CareFusion, Germany) was used to assess the pulmonary function according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) standard [19]. Parameters such as FEV_1, FVC, FEV_1/FVC, peak expiratory flow (PEF), and maximal voluntary ventilation (MVV) were recorded. Each indicator was measured at least 3 times, and the average value was computed.

(3) Nutritional indicators: Data on nutritional indicators, including BMI, ALB and NRS-2002 scores, were collected. Launched by the European Society for Parenteral and Enteral Nutrition (ESPEN) in 2002, the NRS-2002 is a widely used international tool for screening nutritional risk in hospitalized patients [20]. The NRS-2002 consists of three components, namely impaired nutritional status (0–3 points), disease severity (0–3 points), and age adjustment (0–1 point). The total score was computed by determining the sum of all components' scores. A total score of <3 indicates no nutritional risk, whereas a total score of ≥ 3 indicates a potential nutritional risk.

(4) Oxidative stress and inflammatory indicators: Data on superoxide dismutase (SOD) and malondialdehyde (MDA) levels were collected to assess the oxidative stress status of patients, while white blood cell (WBC), C-reactive protein (CRP) and procalcitonin (PCT) were used to reflect the inflammatory status of patients.

(5) Quality of life and symptom indicators: The quality of life and respiratory symptoms of patients were evaluated by using the 6-minute walk distance (6MWD) test, modified British Medical Research Council (mMRC) dyspnea scale, and World Health Organization Quality of Life-Brief (WHOQOL-BREF) version . The 6MWD refers to the maximum distance a patient can complete by walking at the fastest possible speed on flat ground for six minutes, reflecting the cardiopulmonary function and the overall functional status of patients [21]. The mMRC dyspnea scale is mainly utilized to assess the degree of dyspnea in patients with chronic respiratory diseases, especially COPD. The mMRC scale has five grades, ranging from 0 to 4, with grades ≥ 2 considered to be severe dyspnea [22]. Developed by the World Health Organization, the WHOQOL-BREF is a simplified version of the universal quality-of-life assessment tool, the WHOQOL-100 [23], which is commonly used to evaluate an individual's quality-of-life experience over the preceding two weeks [24]. It consists of 26 items, which can be divided into 4 core domains and 2 independent items (overall quality of life and overall health status). The core domains are the physical domain (7 items), the psychological domain (6 items), the social relationship domain (3 items) and the environmental domain (8 items). Each item is typically scored using a 5-point Likert scale. The raw scores are standardized and converted to 0 to 100 points, with a higher score indicating higher quality of life.

2.4 Propensity Score Matching

To mitigate potential selection bias and balance baseline characteristics between the experimental group and the control group, propensity score matching (PSM) was employed to generate matched datasets. The specific procedure was as follows:

(1) Estimation of propensity scores: A propensity score for each patient, defined as the conditional probability of receiving the comprehensive intervention (nutritional support + respiratory training) given the observed baseline covariates, was estimated using a non-parsimonious logistic regression model. The covariates included in the model were age, gender, BMI, disease duration, history of smoking, history of malnutrition and history of pulmonary infection. These variables were selected *a priori* based on their potential clinical relevance to both treatment assignment and key outcomes.

(2) Matching algorithm: Patients in the experimental group were matched 1:1 to those in the control group without replacement by using the nearest-neighbor matching algorithm. To ensure high-quality matching and minimize the risk of poor matches, we adopted a caliper width of 0.2 times the standard deviation of the logarithm of the propensity score.

(3) Assessment of matching quality: To assess the quality of matching, we calculated the standardized mean differences (SMDs) of all covariates before and after matching. After matching, the SMDs for all covariates were substantially reduced, with the SMD for most covariates decreased to below 10%. While an SMD <0.1 is ideal, an SMD <0.2 is often considered acceptable in practice for indicating a reasonable balance. The significant reduction in SMDs for all variables relative to their pre-matching values, coupled with the lack of statistically significant differences (all $p > 0.05$) in the post-matching comparisons (Table 1), indicates that PSM effectively improved balance.

(4) Outcome analysis: All subsequent comparative analyses of primary and secondary outcomes, as well as multiple linear regression analyses, were conducted exclusively on this propensity score-matched cohort.

2.5 Statistical Analysis

Since this is a retrospective study that consecutively enrolled eligible patients during the study period, a prospective sample size calculation was not performed. The final sample size was determined by the available patient population that met the inclusion and exclusion criteria between January 2022 and March 2025. Furthermore, we conducted a post-hoc power analysis for the primary outcomes of FEV_1 and FVC using G*Power software 3.1.9.7 (HeinrichHeineUniversität Düsseldorf, North RhineWestphalia, Germany). Based on the observed effect sizes (Cohen's d) from our matched cohort for the intergroup comparison of post-intervention values (d = 0.67 for FEV_1, and d = 0.81 for FVC), a sample size of 44 per group provides a statistical power (1-β) of 98.5% for FVC and 89.5% for FEV_1, at a two-sided α level of 0.05. This indicates that the study was adequately powered to detect clinically significant differences observed in these key pulmonary function parameters.

According to the data distribution, categorical variables are expressed as frequencies and percentages. Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed data are expressed as means and standard deviation (SD), while those that did not conform to the normal distribution are expressed as medians and interquartile range (IQR). Intergroup comparisons were performed using Student's *t*-test or Mann-Whitney *U* test for continuous variables, whereas categorical variables were compared using the Pearson's chi-square test or the continuity-corrected chi-square test. Intragroup comparisons of continuous variables were conducted using paired *t*-test or Wilcoxon signed-rank test. Intragroup comparisons of binary categorical variables were conducted using McNemar test. Multiple linear regression analysis was performed to determine the independent influencing factors of the changes in several key pulmonary function indicators, such as FEV_1, FVC and FEV_1/FVC, before and after intervention. Assumptions of linearity, independence of residuals, and homoscedasticity were examined. Multicollinearity was assessed using tolerance and the variance inflation factor (VIF), with a tolerance >0.2 and a VIF <5 indicating no significant multicollinearity. All statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Two-sided *p*-values $<$ 0.05 were considered statistically significant.

3. Results

3.1 Clinical Characteristics of the Study Population

A total of 101 patients with OB who underwent intervention were included and were allocated into the experimental group (n = 56) and the control group (n = 45) according to the intervention type. As shown in Table 1, there were significant differences in smoking history (p = 0.036) and the medical history of pulmonary infection (p = 0.042) between the two groups of patients, but no statistical differences in age, gender, BMI, disease duration, or history of malnutrition were detected (all $p > 0.05$). To balance the baseline characteristics of the two groups of patients to reduce the impact of confounding factors, a PSM analysis was performed at a 1:1 ratio to obtain a new matched cohort (44 pairs). After matching, all variables exhibited no statistical differences between the two groups of patients (all $p >$ 0.05), suggesting that the clinical characteristics of the two groups were well-balanced (Table 1).

3.2 The Impact of Intervention on Various Indicators in the Matched Cohort

In the matched cohort, no statistically significant differences were found in any pulmonary function indicators between the two groups of patients before the intervention (all $p > 0.05$). After the intervention, the FEV_1 (p = 0.002) and FVC ($p < 0.001$) in the experimental group were significantly higher than those in the control group, while FEV_1/FVC, PEF, and MVV remained not statistically sig-

Table 1. Clinical characteristic of OB patients before and after PSM.

Characteristic	Before PSM					After PSM				
	Experimental group (n = 56)	Control group (n = 45)	$t/z/\chi^2$	p-value	SMD	Experimental group (n = 44)	Control group (n = 44)	$t/z/\chi^2$	p-value	SMD
Age (years), median (IQR)	52.00 (49.25–55.00)	53.00 (50.00–54.00)	0.264	0.792	0.121	52.00 (49.25–55.00)	53.00 (50.25–54.00)	0.674	0.500	0.033
Gender, n (%)			0.484	0.487	0.138			0.752	0.386	0.186
Male	25 (44.64%)	17 (37.78%)				20 (45.45%)	16 (36.36%)			
Female	31 (55.36%)	28 (62.22%)				24 (54.55%)	28 (63.64%)			
BMI (kg/m^2), mean ± SD	25.16 ± 3.18	24.18 ± 3.30	1.524	0.131	0.305	24.92 ± 3.15	24.22 ± 3.33	1.023	0.309	0.218
Disease duration (months), mean ± SD	17.98 ± 3.88	17.73 ± 4.69	0.292	0.771	0.058	18.00 ± 4.04	17.77 ± 4.73	0.242	0.809	0.052
History of smoking, n (%)			4.389	0.036	0.426			2.285	0.131	0.326
No	40 (71.43%)	23 (51.11%)				29 (65.91%)	22 (50.00%)			
Yes	16 (28.57%)	22 (48.89%)				15 (34.09%)	22 (50.00%)			
History of pulmonary infection, n (%)			4.137	0.042	0.418			1.186	0.276	0.234
No	26 (46.43%)	30 (66.67%)				24 (54.55%)	29 (65.91%)			
Yes	30 (53.57%)	15 (33.33%)				20 (45.45%)	15 (34.09%)			
History of malnutrition, n (%)			0.228	0.633	0.095			0.080	0.777	0.061
No	48 (85.71%)	37 (82.22%)				37 (84.09%)	36 (81.82%)			
Yes	8 (14.29%)	8 (17.78%)				7 (15.91%)	8 (18.18%)			

Abbreviations: BMI, body mass index; IQR, interquartile range; OB, obliterative bronchiolitis; PSM, propensity score matching; SD, standard deviation; SMD, standardized mean difference.

Table 2. Comparison of pulmonary function indicators before and after intervention between the experimental group and the control group.

Variables	Experimental group (n = 44)	Control group (n = 44)	t/z	p-value
Before intervention				
FEV_1 (L)	1.04 ± 0.21	1.04 ± 0.25	0.119	0.906
FVC (L)	1.76 ± 0.24	1.87 ± 0.33	1.869	0.065
FEV_1/FVC	58.76 (45.80–75.57)	53.12 (43.62–72.06)	0.901	0.367
PEF (L/min)	154.16 ± 20.19	157.02 ± 16.29	0.731	0.467
MVV (L/min)	39.43 ± 8.59	38.57 ± 9.83	0.438	0.663
After intervention				
FEV_1 (L)	1.55 ± 0.24*	1.37 ± 0.29*	3.125	0.002
FVC (L)	2.34 ± 0.35*	2.12 ± 0.16*	3.811	<0.001
FEV_1/FVC	67.86 (56.29–77.30)*	65.29 (55.74–77.60)*	0.626	0.531
PEF (L/min)	191.57 ± 23.91*	185.47 ± 24.34*	1.186	0.239
MVV (L/min)	54.33 ± 11.38*	49.79 ± 10.32*	1.961	0.053

*$p < 0.05$ compared with the same variable before intervention in the same group.

Abbreviations: FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; MVV, maximal voluntary ventilation; PEF, peak expiratory flow.

nificant (all $p > 0.05$). Furthermore, in both the experimental and control groups, all pulmonary function indicators were significantly elevated following the interventions (all $p < 0.05$). This suggests that both intervention methods can significantly improve the pulmonary function of OB patients, and comprehensive intervention outperforms nutritional support alone in improving the FEV_1 and FVC. The analysis results for the pulmonary function indicators are shown in Table 2.

Both before and after the intervention, there were no statistically significant differences between the two patient groups in nutritional indicators such as BMI, ALB and NRS-2002 scores (all $p > 0.05$). In addition, among all the post-intervention nutritional indicators in the experimental group, only the NRS-2002 scores showed significant improvement when compared with those before the intervention ($p < 0.05$), while in the control group, there were no statistically significant differences in any of the three nutritional indicators before and after the intervention (all $p > 0.05$). The analysis results for the nutritional indicators are shown in Table 3.

Regarding the oxidative stress and inflammatory indicators, the between-group comparisons revealed statistically significant differences in SOD ($p = 0.017$) before the intervention, as well as MDA ($p < 0.001$), CRP ($p = 0.005$) and PCT ($p < 0.001$) after the intervention. In addition, all the indicators of both groups of patients after the intervention were significantly improved when compared with those before the intervention (all $p < 0.05$). The results suggested that both intervention methods can significantly improve the oxidative stress and inflammatory status of OB patients, with the comprehensive intervention outperforming nutritional support alone in improving the levels of MDA, CRP and PCT. Detailed analysis results for the oxidative stress and inflammatory indicators are depicted in Table 4.

As for the quality of life and symptom indicators, there were significant differences between the two groups of patients in terms of 6MWD ($p < 0.001$) and WHOQOL-BREF ($p < 0.001$) before the intervention, as well as mMRC ($p = 0.006$) after the intervention. Moreover, both groups of patients showed improvements in the quality of life and symptom indicators after the intervention relative to their preintervention measurements, apart from the quality of life in the control group (all $p < 0.05$). These results indicate that both intervention methods can improve the quality of life and symptoms of OB patients, and the combined intervention is more effective than single nutrition in treating dyspnea symptoms. Detailed analysis results for the quality of life and symptom indicators are presented in Table 5.

3.3 Factors Analysis for Improved Pulmonary Function in the Matched Cohort

Multiple linear regression analyses were conducted on the changes in FEV_1, FVC, and FEV_1/FVC (ΔFEV_1, ΔFVC, and ΔFEV_1/FVC; Δ was defined as Post-intervention - Pre-intervention) before and after the intervention in the matched cohort to identify the independent factors influencing the improvement of these pulmonary function indicators. As shown in Tables 6,7,8, disease duration ($p = 0.003$), history of malnutrition ($p = 0.030$), intervention methods ($p = 0.002$), and baseline FEV_1 ($p < 0.001$) were independent influencing factors of ΔFEV_1; intervention methods ($p = 0.001$) and baseline FVC ($p < 0.001$) were independent influencing factors of ΔFVC; and disease duration ($p = 0.012$) and baseline FEV_1/FVC ($p < 0.001$) were independent influencing

Table 3. Comparison of nutritional indicators before and after intervention between the experimental group and the control group.

Variables	Experimental group (n = 44)	Control group (n = 44)	$t/z/\chi^2$	p-value
Before intervention				
BMI (kg/m^2)	24.92 ± 3.15	24.22 ± 3.33	1.023	0.309
ALB (g/L)	39.80 (35.93–43.85)	39.55 (36.58–42.83)	0.138	0.890
NRS-2002 scores			0.448	0.503
<3	27 (61.36%)	30 (68.18%)		
≥3	17 (38.64%)	14 (31.82%)		
After intervention				
BMI (kg/m^2)	24.93 ± 3.07	24.24 ± 3.25	1.015	0.313
ALB (g/L)	40.10 (36.93–42.85)	39.65 (37.58–41.83)	0.250	0.802
NRS-2002 scores			1.544	0.214
<3	40 (90.91%)	36 (81.82%)		
≥3	4 (9.09%)*	8 (18.18%)		

*$p < 0.05$ compared with the same variable before intervention in the same group.
Abbreviations: ALB, albumin; BMI, body mass index; NRS, nutritional risk screening.

Table 4. Comparison of oxidative stress and inflammatory indicators before and after intervention between the experimental group and the control group.

Variables	Experimental group (n = 44)	Control group (n = 44)	t/z	p-value
Before intervention				
SOD (U/mL)	1274.74 ± 299.24	1130.55 ± 255.20	2.432	0.017
MDA (μmol/L)	10.15 (8.97–10.60)	10.05 (9.05–10.41)	0.492	0.622
WBC (10^9/L)	6.65 (5.70–8.59)	6.81 (5.40–10.09)	0.284	0.777
CRP (mg/L)	26.71 (16.26–37.72)	26.70 (14.70–33.33)	0.275	0.783
PCT (ng/mL)	3.23 (1.92–3.76)	3.42 (2.15–4.10)	0.764	0.445
After intervention				
SOD (U/mL)	1568.25 ± 349.10*	1441.96 ± 386.59*	1.608	0.111
MDA (μmol/L)	6.20 (5.52–7.60)*	8.15 (6.80–9.94)*	4.482	<0.001
WBC (10^9/L)	6.55 (5.60–8.49)*	6.71 (5.30–9.45)*	0.284	0.777
CRP (mg/L)	12.96 (10.58–17.16)*	19.26 (11.75–26.71)*	2.779	0.005
PCT (ng/mL)	1.11 (0.57–1.50)*	1.60 (1.33–1.91)*	4.686	<0.001

*$p < 0.05$ compared with the same variable before intervention in the same group.
Abbreviations: CRP, C-reactive protein; MDA, malondialdehyde; PCT, procalcitonin; SOD, superoxide dismutase; WBC, white blood cell.

factors of $\Delta FEV_1/FVC$. It can be seen that compared with nutritional support alone, the comprehensive intervention was independently associated with greater improvements in FEV_1 (B = 0.179, 95% confidence interval (CI) = [0.071, 0.288], β = 0.265) and FVC (B = 0.215, 95% CI = [0.090, 0.341], β = 0.246), but had no independent effect on improvements of FEV_1/FVC.

4. Discussion

In this propensity score-matched retrospective study, we found that comprehensive intervention program integrating individualized nutritional support with structured respiratory training demonstrated significant clinical benefits in patients with OB compared with nutritional support alone. Specifically, the experimental group showed statistically significant improvements in FEV_1 and FVC compared with the control group, with multiple linear regression analysis confirming that comprehensive intervention was an independent factor contributing to the improvements in these two pulmonary function indicators. Furthermore, the experimental group also exhibited lower post-intervention MDA, CRP, and PCT levels, indicating a greater ability of comprehensive intervention to mitigate systemic inflammation and oxidative damage compared with nutritional support alone. Notably, while the comprehensive intervention resulted in a significant reduction in nutritional risk (NRS-2002), nutritional parameters such as BMI and ALB did not demonstrate significant within-group improvements in either patient's group, suggesting that the observed clinical benefits may be mediated by mechanisms beyond mere weight gain. In addition, the significant improvements in

Table 5. Comparison of the quality of life and symptom indicators before and after intervention between the experimental group and the control group.

Variables	Experimental group (n = 44)	Control group (n = 44)	$t/z/\chi^2$	p-value
Before intervention				
6MWD (m)	429.00 (405.75–454.75)	471.50 (443.00–497.25)	4.165	<0.001
WHOQOL-BREF	66.61 ± 6.30	78.75 ± 5.23	9.832	<0.001
mMRC			0.000	1.000
0–1	3 (6.82%)	3 (6.82%)		
≥2	41 (93.18%)	41 (93.18%)		
After intervention				
6MWD (m)	485.00 (460.75–509.75)*	481.50 (453.00–507.25)*	0.776	0.438
WHOQOL-BREF	80.95 ± 5.75*	79.75 ± 5.23	1.028	0.307
mMRC			7.639	0.006
0–1	41 (93.18%)	31 (70.45%)		
≥2	3 (6.82%)*	13 (29.55%)*		

*$p < 0.05$ compared with the same variable before intervention in the same group.

Abbreviations: mMRC, modified British Medical Research Council; 6MWD, 6-minute walk distance; WHOQOL-BREF, World Health Organization Quality of Life-Brief.

Table 6. Multiple linear regression analysis of ΔFEV_1.

Variables	B value (SE)	95% CI	β value	t	p-value	Tolerance	VIF
Age (years)	0.013 (0.007)	[−0.001, 0.026]	0.155	1.823	0.072	0.820	1.220
Gender (Male vs. Female)	–0.079 (0.061)	[–0.201, 0.043]	−0.115	−1.285	0.203	0.736	1.359
Disease duration (months)	–0.020 (0.006)	[−0.032, −0.007]	−0.252	−3.115	0.003	0.930	1.107
History of smoking (Yes vs. No)	0.107 (0.077)	[−0.047, −0.260]	0.156	1.379	0.172	0.462	2.165
History of pulmonary infection (Yes vs. No)	0.044 (0.060)	[−0.076, 0.164]	0.063	0.727	0.470	0.775	1.291
History of malnutrition (Yes vs. No)	0.213 (0.097)	[0.021, 0.406]	0.238	2.210	0.030	0.510	1.963
BMI (kg/m^2)	0.012 (0.011)	[−0.010, 0.033]	0.112	1.094	0.277	0.562	1.778
ALB (g/L)	0.001 (0.007)	[−0.012, 0.015]	0.021	0.226	0.822	0.650	1.537
Intervention methods (Comprehensive intervention vs. Nutritional support)	0.179 (0.055)	[0.071, 0.288]	0.265	3.285	0.002	0.904	1.106
Baseline FEV_1	−0.683 (0.167)	[−1.016, −0.350]	−0.467	−4.082	<0.001	0.451	2.219

Model summary information: $R^2 = 0.546$, Adjusted $R^2 = 0.487$, $F = 9.273$, $p < 0.001$.

Abbreviations: ALB, albumin; BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in the first second; SE, standard error; VIF, variance inflation factor.

Table 7. Multiple linear regression analysis of ΔFVC.

Variables	B value (SE)	95% CI	β value	t	p-value	Tolerance	VIF
Age (years)	0.004 (0.008)	[−0.012, 0.021]	0.041	0.532	0.596	0.806	1.240
Gender (Male vs. Female)	−0.022 (0.070)	[−0.161, 0.117]	−0.024	−0.312	0.756	0.774	1.291
Disease duration (months)	0.003 (0.007)	[−0.012, 0.018]	0.032	0.436	0.664	0.879	1.138
History of smoking (Yes vs. No)	0.002 (0.079)	[−0.156, 0.160]	0.002	0.024	0.981	0.592	1.688
History of pulmonary infection (Yes vs. No)	0.014 (0.070)	[−0.127, 0.154]	0.015	0.194	0.847	0.767	1.304
History of malnutrition (Yes vs. No)	<0.001 (0.114)	[−0.228, 0.227]	<0.001	−0.003	0.998	0.494	2.024
BMI (kg/m^2)	−0.006 (0.013)	[−0.031, 0.019]	−0.042	−0.452	0.652	0.556	1.799
ALB (g/L)	−0.001 (0.007)	[−0.016, 0.013]	−0.015	−0.180	0.858	0.702	1.424
Intervention methods (Comprehensive intervention vs. Nutritional support)	0.215 (0.063)	[0.090, 0.341]	0.246	3.424	0.001	0.921	1.086
Baseline FVC	−1.038 (0.139)	[−1.315, −0.762]	−0.692	−7.480	<0.001	0.556	1.800

Model summary information: $R^2 = 0.634$, Adjusted $R^2 = 0.586$, $F = 13.316$, $p < 0.001$.

Abbreviations: ALB, albumin; BMI, body mass index; CI, confidence interval; FVC, forced vital capacity; SE, standard error; VIF, variance inflation factor.

Table 8. Multiple linear regression analysis of $\Delta FEV_1/FVC$.

Variables	B value (SE)	95% CI	β value	t	p-value	Tolerance	VIF
Age (years)	0.292 (0.408)	[−0.521, 1.104]	0.053	0.715	0.477	0.825	1.212
Gender (Male vs. Female)	−3.928 (3.796)	[−11.486, 3.631]	−0.084	−1.035	0.304	0.674	1.484
Disease duration (months)	−0.961 (0.373)	[−1.705, −0.218]	−0.182	−2.574	0.012	0.889	1.125
History of smoking (Yes vs. No)	3.214 (5.447)	[−7.632, 14.061]	0.069	0.590	0.557	0.325	3.080
History of pulmonary infection (Yes vs. No)	0.731 (3.538)	[−6.315, 7.776]	0.016	0.206	0.837	0.783	1.277
History of malnutrition (Yes vs. No)	8.346 (5.648)	[−2.901, 19.592]	0.137	1.478	0.144	0.520	1.921
BMI (kg/m^2)	0.600 (0.633)	[−0.661, 1.862]	0.084	0.947	0.346	0.564	1.775
ALB (g/L)	−0.053 (0.375)	[−0.799, 0.693]	−0.011	−0.143	0.887	0.699	1.431
Intervention methods (Comprehensive intervention vs. Nutritional support)	1.895 (3.203)	[−4.483, 8.272]	0.041	0.592	0.556	0.915	1.092
Baseline FEV_1/FVC	−0.915 (0.149)	[−1.212, −0.618]	−0.726	−6.132	<0.001	0.318	3.140

Model summary information: $R^2 = 0.656$, Adjusted $R^2 = 0.611$, $F = 14.690$, $p < 0.001$.

Abbreviations: ALB, albumin; BMI, body mass index; CI, confidence interval; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; SE, standard error; VIF, variance inflation factor.

indicators like 6WMD, mMRC and WHOQOL-BREF in the experimental group further demonstrate the important role of comprehensive intervention in improving exercise tolerance, dyspnea symptoms, and quality of life. To the best of our knowledge, this is the first study to investigate the clinical efficacy of a comprehensive intervention combining nutritional support with respiratory training in patients with OB, providing important insights into intervention strategies and research directions in the clinical management of OB patients.

Our findings are consistent with—and extend—the results of previous studies on nutritional support and pulmonary rehabilitation in chronic lung diseases. A systematic review of nutritional interventions in COPD patients showed that nutritional support can improve anthropometric measures and muscle strength, though its effects on pulmonary function are limited when used alone [25], consistent with our observation that patients receiving nutritional support alone did not show significant improvements in nutritional indicators and pulmonary function. In contrast, our research demonstrates that combining nutritional support with respiratory training yields superior outcomes, especially in terms of pulmonary function parameters such as FEV_1 and FVC. Notably, previous studies on pulmonary rehabilitation in COPD patients have reported inconsistent effects on systemic inflammation, with some studies showing no significant changes in inflammatory markers after high-intensity pulmonary rehabilitation [26]. However, our study found significant reductions in CRP and PCT in the experimental group, which might be attributed to the synergistic effect of nutritional support and respiratory training in addressing the specific pathological features of OB. In this study, baseline PCT levels of the patients were generally above the normal range (>0.05 ng/mL), while the WBC count did not show a significant increase. This phenomenon may be related to the characteristics of OB as a chronic inflammatory disease. In chronic inflammatory states, especially in the presence of structural lung damage, PCT levels may show a mild to moderate increase. This does not necessarily represent active bacterial infection but rather reflects persistent, low-grade immune activation and epithelial damage. In addition, our positive results in reducing oxidative stress (MDA) are robust and novel in the context of OB. Recent studies have found that organized exercise training can enhance the antioxidant defense mechanism in patients with chronic respiratory diseases, thereby reducing oxidative damage [27]. In the context of OB management, current treatment options remain limited, and there is a lack of direct evidence demonstrating the beneficial impacts of nutritional support combined with respiratory training. Previous research efforts have mainly centered on pharmacological or surgical strategies (such as azithromycin for bronchiolitis obliterans syndrome or retransplantation) [28], while non-pharmacological reports have evaluated pulmonary rehabilitation programs without prespecified nutritional components [18]. Our study fills this gap by providing evidence that comprehensive intervention can improve the key clinical outcomes of OB patients—a direction that has not been adequately addressed in previous literature. Furthermore, previous studies on transplantation-related bronchiolitis obliterans syndrome have shown significant improvements in 6MWD, physical fitness, subjective dyspnea, and some dimensions of quality of life following the implementation of pulmonary rehabilitation [29], consistent with the results of 6MWD, mMRC, and WHOQOL-BREF in the present study. It is worth noting that although there was no significant difference in pulmonary function indicators between the two groups before the intervention, the 6MWD and WHOQOL-BREF scores of the experimental group were significantly lower than those of the control group. This difference may reflect individual variations in patients' subjective symptom perception, comorbidities, muscle function or psychological state, and these factors were not captured during the PSM procedure.

The superior efficacy of comprehensive intervention observed in this research can be explained by several complementary mechanisms. Nutritional support may provide the necessary foundation for respiratory muscle function and immune regulation. Adequate protein intake is essential for maintaining the quality and strength of respiratory muscles, while micronutrients such as zinc, vitamin D, and selenium can enhance immune function and reduce the risk of respiratory infections [30]. This is also supported by the improvement of NRS-2002 in our experimental group, indicating a reduction in nutritional risk for the patients. It is noteworthy that within the patient group receiving comprehensive intervention, significant improvement was only observed in the NRS-2002 score, but not in objective measures such as BMI and ALB. This can be explained by the composite nature of the NRS-2002, which incorporates not only nutritional status but also disease severity. The significant improvements in respiratory function, exercise capacity (6MWD), and dyspnea (mMRC) achieved through respiratory training would directly lower the 'disease severity' component of the NRS-2002, thereby reducing the total score. In contrast, BMI and ALB—being less sensitive to short-term functional changes—tend to respond more slowly. Furthermore, in patients without severe baseline malnutrition, the primary role of nutritional support may shift from driving significant anabolic gains to preventing catabolism and supporting the increased metabolic demands of exercise, an effect that may not be fully captured by static measures like BMI and ALB over 12 weeks. On the other hand, respiratory training can enhance the endurance and efficiency of respiratory muscles. Diaphragmatic breathing and inspiratory muscle training can enhance ventilation capacity and oxygen utilization [31], which may explain the significant improvements in FEV_1 and FVC observed in our study. Meanwhile, the improvement of respiratory muscle strength and endurance can better overcome the increased airway resistance in OB patients, thereby reducing dynamic hyperinflation and subjective dyspnea (as shown in the improvement of mMRC score results) [3]. In addition, respiratory training can regulate the inflammatory response by increasing lymphatic drainage and improving systemic circulation, which helps to suppress inflammation [32]. The synergistic effect of nutritional support and respiratory training is particularly noteworthy. Nutritional support provides the essential substrates for muscle repair and function, while respiratory training enhances nutrient utilization and promotes physiological adaptation, thereby improving pulmonary function. This might explain why comprehensive intervention yields superior outcomes compared with nutritional support alone. Furthermore, the observed pattern of pulmonary function response is consistent with the pathophysiology of OB. Significant improvements in FVC and FEV_1 occurred without a corresponding change in the FEV_1/FVC ratio, reflecting the characteristic fixed airflow limitation of OB. This suggests that while comprehensive intervention can enhance respiratory muscle function and lung volumes, it cannot reverse the underlying structural narrowing of the small airways. Similarly, the PEF and MVV remained largely unaltered following the intervention, indicating their dependence on both respiratory muscle strength and the fixed airway obstruction characteristic of OB.

This study provides important clinical insights into the management of OB patients. Based on the research results, we recommend incorporating nutritional support combined with respiratory training into the standardized treatment plan for OB patients. Specifically, for patients with high nutritional risk reflected by NRS-2002 score $\geq$3, individualized nutritional support should be prioritized, followed by respiratory training to achieve optimal efficacy. This "stepwise intervention" strategy is in line with the NHS-recommended nutrition and exercise management framework for chronic respiratory diseases, which is further optimized for OB patients. From the perspective of functional improvement, comprehensive intervention has substantial practical utility in improving dyspnea, cardiopulmonary function, and the overall functional status, indicating that this strategy can effectively improve patients' ability to perform daily activities, as well as their life autonomy. Considering the progressive development characteristics of OB, early initiation of comprehensive intervention may delay the progression of the disease and reduce the risk of acute exacerbation. For clinicians, FEV_1 and FVC can be utilized as the primary indicators for evaluating the intervention efficacy, while the dynamic changes of biomarkers such as CRP, PCT and MDA should be continuously monitored for the purposes of treatment optimization.

This study has several limitations that should be considered when interpreting the results. First, the retrospective design and single-center data of this study may introduce selection bias. To address this, we employed PSM to balance key baseline characteristics. While PSM significantly improved the comparability of the groups, as evidenced by the substantial reduction in SMDs for all covariates and the absence of statistically significant differences in the matched cohort, a degree of residual imbalance persisted for some variables (such as BMI, history of smoking, and history of pulmonary infection). Although an SMD below 0.2 is generally considered acceptable and the observed residual imbalances are unlikely to fully account for the magnitude of the intervention effects we observed, they nonetheless represent a potential source of confounding that should be acknowledged. Second, this study has a limited sample size. Although post-hoc analysis indicated that the matched cohort (44 pairs) provided adequate power (89.5% and 98.5%) to detect the significant differences observed in FEV_1 and FVC, the sample size may still be insufficient to detect smaller effect sizes for other outcomes. This is a plausible explanation for the lack of statistically significant differences in certain parameters, such as the FEV_1/FVC ra-

tio and MVV. These non-significant findings should therefore be interpreted with caution. Third, due to the retrospective design, we were unable to obtain and account for the precise dosage and duration of glucocorticoid use prior to the intervention, which could represent a potential unmeasured confounder. However, we employed PSM on key clinical variables to minimize baseline differences, and all patients received guideline-based standard care, which can, to some extent, mitigate major disparities in background treatment. Furthermore, without monitoring the intervention compliance among the patients, the study was unable to analyze the impact of compliance differences on outcomes, which is crucial in nutrition and exercise intervention research. Finally, due to the lack of long-term follow-up data, we were also unable to assess the sustained effect of comprehensive intervention, especially for OB as a chronic progressive disease, whose advantages in long-term prognosis still need to be verified. Therefore, future research should include multicenter prospective randomized controlled trials to assess the efficacy of this comprehensive intervention framework across diverse clinical settings and populations, incorporating wearable devices to monitor exercise adherence. Additionally, extended follow-up periods are needed to clarify the impact of comprehensive intervention on the long-term prognosis of OB patients.

5. Conclusion

Compared with nutritional support alone, comprehensive intervention combining nutritional support with respiratory training provides greater improvements in pulmonary function, oxidative stress, inflammatory status, quality of life, and respiratory symptoms in patients with OB. Our findings provide new evidence for non-pharmacological interventions in the clinical management of OB patients, but larger-scale prospective randomized controlled trials are warranted for validation.

Key Points

• Both comprehensive intervention and nutritional support alone can significantly improve the pulmonary function, oxidative stress, inflammatory status, quality of life, and respiratory symptoms of obliterative bronchiolitis (OB) patients.

• Compared with nutritional support alone, comprehensive intervention has greater advantages in improving FEV_1, FVC, MDA, CRP, PCT, 6MWD, mMRC and WHOQOL-BREF in OB patients.

• Among the nutritional indicators analyzed, significant improvement was only observed in the NRS-2002 scores of OB patients receiving comprehensive intervention.

• Compared with nutritional support alone, comprehensive intervention was an independent factor associated with greater improvements in FEV_1 and FVC.

Availability of Data and Materials

All data included in this study are available from the corresponding author upon reasonable request.

Author Contributions

YXC and XYY designed this research program. XTH, YC, and DQ collected and analyzed the data. YXC drafted the initial manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Ethics Committee of The Fourth Affiliated Hospital of Soochow University (Suzhou Dushu Lake Hospital) (Approval No.2025-251266). Written informed consent was obtained from all participants and their legal guardians. All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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