# ADVANCED THERAPEUTIC DELIVERY FOR THE MANAGEMENT OF CHRONIC RESPIRATORY DISEASES

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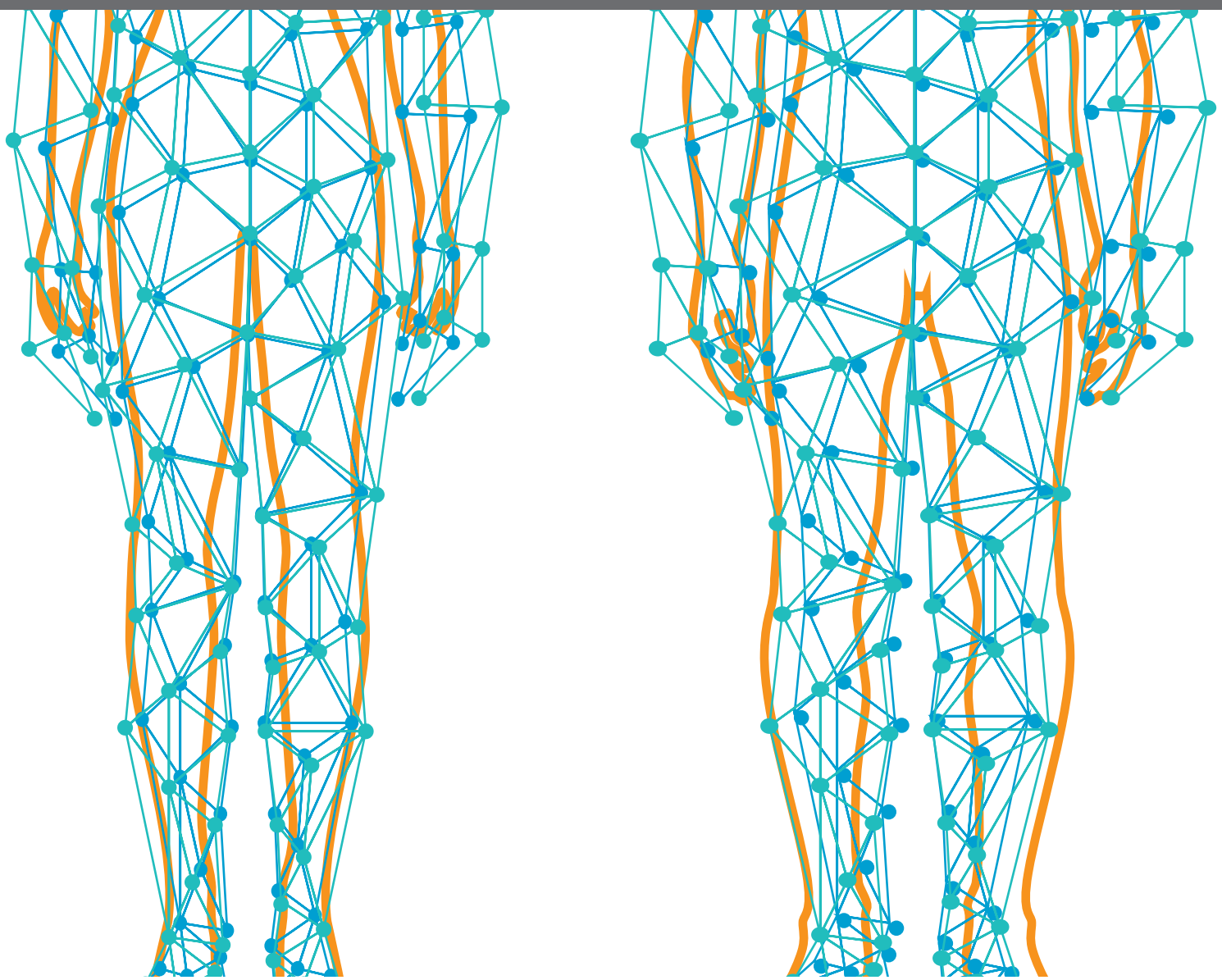

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# ADVANCED THERAPEUTIC DELIVERY FOR THE MANAGEMENT OF CHRONIC RESPIRATORY DISEASES

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# Editorial: Advanced therapeutic delivery for the management of chronic respiratory diseases

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Editorial on the Research Topic
Advanced therapeutic delivery for the management of chronic respiratory diseases

The management of chronic respiratory/lung diseases (CRDs), utilizing outdated conventional therapeutic models has urged the need for drug repurposing, and has renewed the interest in discovery of novel, advanced therapeutic approaches. Novel advanced drug delivery systems are lately emerging with a versatility to manage CRDs (1, 2). Contemporary scientists have become more inclined toward exploring the application of nanoparticle-based formulations (3, 4) or genetic materials such as siRNA, miRNA, and decoy oligonucleotide-targeted/loaded delivery system (5, 6) to effectively manage inflammatory lung diseases or to delay the exacerbation of CRDs. Interestingly, a considerable number of drug-loaded nanocarriers have proven to be effective in *in vitro* and *in vivo* studies (7–9). There has been a lack of robust therapeutic delivery methods for the management of CRDs. Conventional oral drug delivery approaches are associated with low systemic bioavailability, and deterioration in the gastrointestinal sites. Therefore, higher doses are required to attain therapeutic efficacy which might result in multiple unwanted/off-target effects (1). Advanced therapeutic delivery systems may be employed to overcome these risks by enhancing the potency of therapeutics with comparatively less dose and fewer off-target effects than conventional approaches. Therefore, more scientific studies are essential to further validate the implementation of different advanced drug delivery systems for CRDs.

In our special issue, we had invited submissions ranging from original research, brief reports, and review (narrative/systematic) articles that fall within the scope of our theme, "Advanced Therapeutic Delivery for the Management of Chronic Respiratory Diseases." A total of ten articles were published on this topic, including six original research articles, one brief research report, and three systematic review articles.

A meta-analysis by Huang, Pei et al., reported that the bacterial lysates could be beneficial for COPD patients. Twenty studies were pooled in this meta-analysis where, the data suggests that the lysates were efficacious to alleviate symptoms, with decreased exacerbation rate and mean number of exacerbations with acceptable side effects.

Another meta-analysis by Yu et al., suggested that proton pump inhibitor treatment could decrease the case fatality rate in COPD, occurrence of gastrointestinal hemorrhage, and number of acute exacerbations. As the study was limited to China, the authors suggested the need for large-scale randomized control trials to further validate their findings and avoid high risk of bias.

Kim et al., highlighted that the use of statin was not correlated with the incidence of COPD in adults. Nevertheless, it was linked with a decreased likelihood of exacerbations in COPD participants, with a greater risk reduction with lipophilic statin use.

Hong et al., studied the variations in intensive care unit outcomes corresponding to the chemotherapy type administered to patients with lung cancer (LC). It was observed that the targeted chemotherapy may contribute to increasing access to critical care for LC and improved critical care outcomes of LC patients.

Lai et al., reported on clinical and inflammatory features of the AtyPical Asthma in China (APAC) cough variant asthma cohort. Cough variant asthma was found to be distinctive from classic asthma with regards to clinical features, lung function, and airway inflammation. Quality of life in APAC cohort was poorly diminished despite better asthma control scores.

Huang, Fu et al., investigated the predictors of a minimal clinically important difference following omalizumab treatment in adult patients with severe allergic asthma (SAA). Interestingly, no predictor of lung function or asthma control was found. The findings suggest that their study might be helpful when choosing treatment for adult patients with SAA to benefit the most from omalizumab treatment.

A brief research report by Li et al., explored the potential of transpedal lymphangiography procedure using a high dose (>20 ml) ethiodized oil in the management of postoperative chylothorax. It was observed that high dose ethiodized oil was feasible, safe, and effective model for the management of high-flow (>1,000 ml/day) postoperative chylothorax.

Liu et al., studied the application of adjusted single-breath helium dilution (SBHD) for the measurement of total lung volume in the patients with obstructive lung disease (OLD). The SBHD approach was correlated with whole-body plethysmography to measure the total lung volume. However, SBHD method presents limitations in determining the total lung volume in patients with OLD. The authors established SBHF as a functional and reliable correction equation to precisely examine the total lung volume of patients with OLD.

A systematic review and meta-analysis by Lu et al., highlighted the effectiveness of telemonitoring (TM) to reduce the COPD exacerbation occurrence in patients with past exacerbation history. It was found that TM can decrease patient visits to the emergency room, exacerbation-related readmissions, acute exacerbation-related hospital stay, mortality, and the St. George's respiratory questionnaire score. This study suggested that execution of TM could be a promising strategy that could ease the long-term management of acute exacerbation COPD.

Ju et al., investigated the epidemiology and prognosis of invasive fungal disease (IFD) in Chinese lung transplant recipients (LTRs). The most prevalent pathogens were *Aspergillus* (57.3%), *Candida* (19.5%), and *Pneumocystis jiroveci* (13.4%). With the multivariate logistic regression analysis, it was revealed that anastomotic disease, cytomegalovirus (CMV) pneumonia, and pre-transplantation IFD were linked with increased odds of IFD, while double-lung transplantation was linked with decreased odds of IFD. The anastomotic disease was linked with increased odds of death and that *Pneumocystis jiroveci* pneumonia prophylaxis was linked with decreased odds of death. This study concluded that IFD is prevalent among LTRs in Southern China, with *Aspergillus* the most common pathogen suggesting optimization of prophylaxis based on likely pathogens.

In conclusion, this topical collection has provided some new experimental data and updated reviews about the advanced therapeutic delivery for the management of chronic respiratory diseases.

## Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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ORIGINAL RESEARCH
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# Measurement of the Total Lung Volume Using an Adjusted Single-Breath Helium Dilution Method in Patients With Obstructive Lung Disease

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**Background:** Whole-body plethysmography (WBP) is the gold standard for measuring lung volume, but its clinical application is limited as it requires expensive equipment and is not simple to use. Studies have shown that the single-breath helium dilution (SBHD) method, which is commonly used in clinical practice, significantly underestimates lung volume in patients with obstructive lung disease (OLD). By comparing the differences in lung volume measured using SBHD and WBP, we aimed to establish a correction equation for the SBHD method to determine the total lung volume in patients with OLD of different severities.

**Methods:** From 628 patients with OLD simultaneously subjected to SBHD and WBP, 407 patients enrolled between January 2018 and November 2019 were in the training group and 221 enrolled between December 2019 and December 2020 were in the prospective verification cohort. The multiple linear regression equation was used for data in the training group to establish a correction equation for SBHD to determine the total lung volume, and this was validated in the prospective validation cohort.

**Results:** There was a moderate positive correlation between total lung capacity (TLC) determined using the SBHD [TLC (SBHD)] and WBP methods [TLC (WBP)] ($r = 0.701$; $P < 0.05$), and the differences between TLC (SBHD) and TLC (WBP) ($\Delta$TLC) were related to the severity of obstruction. As the severity of obstruction increased, the TLC was underestimated by the SBHD method. We established the following correction equation: $TLC\ (adjusted\ SBHD)\ (L) = -0.669 + 0.756*TLC(SBHD)\ (L) - 0.047*\frac{FEV1}{FVC} + 0.039*height\ (cm) - 0.009*weight(kg)$ ($r2 = 0.753$ and adjusted $r2 = 0.751$). Next, we validated this equation in the validation cohort. With the correction equation, no statistical difference was observed between TLC (adjusted SBHD) and TLC (WBP) among the obstruction degree groups ($P > 0.05$).

**Conclusions:** The SBHD method is correlated with WBP to measure the total lung volume, but the SBHD method presents limitations in determining the total lung volume in patients with obstructive lung disease. Here, we established an effective and reliable correction equation in order to accurately assess the total lung volume of patients with OLD using the SBHD method.

**Keywords: obstructive lung disease, total lung capacity, the single-breath helium dilution, whole-body plethysmography, correction equation**

## INTRODUCTION

The American Thoracic Society/European Respiratory Society (ATS/ERS) has proposed the following definitions of various lung disease patterns (1): (i) obstructive lung disease is defined as the forced expiratory volume in 1 s (FEV1)/vital capacity (VC) ratio below the fifth percentile of the predicted value; (ii) restrictive lung disease is described as a reduction in the total lung capacity (TLC) below the fifth percentile of the predicted value and a normal FEV1/VC ratio; and (iii) mixed lung disease was characterized by FEV1/VC and TLC below the fifth percentile of the predicted value. Generally, when the VC is reduced and FEV1/(F) VC is normal, it is used to infer the presence of restrictive lung disease; however, in ∼40% of such cases, TLC is not reduced (2, 3). It is difficult to determine the exact nature and severity of a ventilation defect (obstructive, restrictive, or mixed) by measuring the FEV1 using only a spirometer without an accurate measurement of lung volume (1). Therefore, a precise lung volume measurement is essential to determine whether there are ventilation defects and provide good value for diagnosing and treating respiratory diseases (4, 5).

Various methods can be used to determine the TLC. The ATS/ERS guide proposes whole-body plethysmography (WBP), helium dilution, nitrogen wash-out, computed tomography (CT), and chest X-ray (CXR) to determine the TLC (4). WBP and gas dilution are the most commonly used methods to detect the lung volume in pulmonary function laboratories (6). The accuracy of the WBP method for measuring lung volume is not affected by a considerably uneven distribution of ventilation and is more accurate than other methods. However, to date, due to the high cost of the body box and complicated operation technology, its clinical application is limited. The single-breath helium dilution (SBHD) method is convenient, rapid, inexpensive, and widely used. However, this method assumes that the gas is evenly distributed in the lungs (4, 7–9), and the reliability of the test results is low in patients with a significantly uneven ventilation distribution. A regression equation of the SBHD method (10) was established to predict the multiple-breath TLC for patients with moderate to severe obstruction. Compared with SBHD, the test time of the multiple-breath helium dilution method is long, and the accuracy of measuring the TLC is high. But the two dilution methods underestimate TLC when compared with values determined by WBP which measures total thoracic volume regardless of the degree of ventilation of areas with severe air trapping. Owing to the aforementioned considerations, the purpose of our study was to compare the difference between the SBHD method and WBP in determining the total lung volume in patients with obstructive pulmonary disease and establish a correction equation to improve the accuracy of the SBHD method for measuring the lung volume in these patients.

**Abbreviations:** ATS/ERS, American Thoracic Society/European Respiratory Society; CT, computed tomography; CXR, chest X-ray; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LLN, lower limits of normal; OLD, obstructive lung disease; SBHD, single-breath helium dilution; TLC, total lung capacity; TLC (WBP), total lung capacity determined by whole-body plethysmography; TLC (SBHD), total lung capacity determined by the single-breath helium dilution method; ΔTLC, the difference between total lung capacity determined by whole-body plethysmography and total lung capacity determined by the single-breath helium dilution method; WBP, whole-body plethysmography.

## MATERIALS AND METHODS

### Participants

Six hundred twenty-eight participants with obstructive pulmonary disease who undertook the SBHD and WBP tests were continuously enrolled from January 2018 to December 2020. We included 407 patients enrolled from January 2018 to November 2019 as the modeling group, and 221 patients enrolled from December 2019 to December 2020 served as the verification cohort.

The inclusion criteria were as follows: (1) age 18–80 years and (2) comply with the ATS/ERS definition of obstructive lung disease (2).

The exclusion criteria were as follows: (1) contraindications for spirometry, pulmonary diffusion function test, and WBP (1, 4, 5, 7) and (2) a history of lung surgery and recent history of chest trauma.

This study was approved by the institutional review board of Second Affiliated Hospital of Zhejiang University School of Medicine.

### Study Protocol

We recorded each participant's sex, age (years), weight (kg), and height (cm). All participants had an adequate pharmacological washout (short-acting bronchodilators were withdrawn 8 h, long-acting bronchodilators were withdrawn 48 h, and theophylline was withdrawn 24 h) before the start of the protocol. Each participant underwent spirometry and SBHD tests first, and then the WBP test after resting for 10 min (11). All lung function tests were conducted using a JAEGER spirometer (MasterScreen Body; Germany). We obtained predicted values of FEV1 for normal lung function and the lower limit of normal (LLN) of FEV1

from a nationwide study of reference values for spirometry in the Chinese population (12).

WBP: The participant sits in a body box, wears a nose clip, and breathes calmly. A valve is closed at the end of tidal expiration, and shallow and rapid breathing is required at a frequency of 0.5–1.0 Hz (13). Small changes in the lung volume and oral pressure were measured. As there was no gas flow in the airway, the oral pressure approximated alveolar pressure and the lung volume were calculated according to the Boyle's law.

SBHD: After the participant breathes calmly and steadily, they fully exhale to the residual volume position, evenly and quickly inhale the mixed gas to ≥90% VC, hold their breaths for 8–10 s, and then, exhale evenly and moderately to the residual volume position in 2–4 s. The percentage concentration of alveolar helium before and after dilution can be used to calculate alveolar volume, and the TLC can be obtained by adding the alveolar volume to the estimated dead space volume (4, 7).

## Result Processing

According to the ATS/ERS guidelines (1), the severity of obstruction is grouped according to FEV1%pred as follows: mild, FEV1%pred ≥ 70%; moderate, FEV1%pred 60–69%; moderately severe, FEV1%pred 50–59%; severe, FEV1%pred 35–49%; and very severe, FEV1%pred < 35%.

## Statistical Analysis

Statistical analysis was performed using SPSS Statistics 23.0 software (IBM SPSS, Armonk, NY, USA). A paired *t*-test was used to compare means between groups. The one-way analysis of variance was used to compare means among multiple groups, Wilcoxon test was used for non-parametric indicators, and Pearson correlation was used for correlation analysis. Results with $P < 0.05$ were considered statistically significant. Multiple linear regression analysis was used to establish a regression equation model for predicting TLC (WBP), and the variables included in the model were significant at $P < 0.05$. Bland-Altman plots were used to assess the agreement of the different methods for measuring the total lung volume.

# RESULTS

## Overall Patient Characteristics and TLC Measurements

The baseline features and lung function results of the 628 subjects are shown in **Table 1**. The average age of the patients was 61.79 ± 11.1 years. The proportion of male patients was relatively high, ∼3.5 times that of female patients. The ratio of patients in the five obstruction groups was similar(23.41%, 24.04%, 17.52%, 19.43%, and 15.60%). TLC (SBHD) (4.83 ± 0.94 L) was significantly lower than TLC (WBP) (6.30 ± 1.27 L; $P$ =0.000). There were no significant differences in sex, age, weight, or TLC between the training and validation groups. We further compared the results of the two methods to determine whether TLC was normal. We found that underestimation of TLC by the SBHD method easily caused misjudgment of lung disease patterns. We defined the misjudgment as: when the SBHD method judged TLC < LLN, but WBP judged TLC ≥ LLN, the proportion of this false result in the population. With the increase in the severity of obstruction, the misjudgment rate showed an upward trend, rising from 16 to 64% (**Figure 1**).

**TABLE 1 |** Anthropometric characteristics and functional parameters in the 628 subjects.

| Variable | Whole ($n$ = 628) | Training ($n$ = 407) | Validation ($n$ = 221) |
|---|---|---|---|
| **Sex, %** | | | |
| Male | 77.87 | 74.69 | 83.71 |
| Female | 22.13 | 25.31 | 16.29 |
| Age, years | 63.00 (56.00-70.00) | 63.00 (54.00, 69.00) | 64.00 (57.00, 71.00) |
| Height, cm | 163. 50 (159.00, 168.50) | 163.00 (158.00, 168.50) | 164.50 (161.00, 169.00) |
| Weight, kg | 61. 00 (54.00, 69.00) | 60.00 (54.00, 68.00) | 62.00 (55.00, 70.00) |
| BMI, kg/m$^2$ | 22.94 (20.66, 25.01) | 22.90 (20.55, 24.84) | 22.99 (0.23) |
| **ATS/ERS classification** | | | |
| Mild | 23.41% | 20.39% | 28.96% |
| Moderate | 24.04% | 22.11% | 27.60% |
| Moderately severe | 17.52% | 18.43% | 15.84% |
| Severe | 19.43% | 21.13% | 16.29% |
| Very severe | 15.60% | 17.94% | 11.31% |
| FVC, L | 2. 72 (2.28, 3.30) | 2. 70 (2.22, 3.31) | 2. 76 (2.40, 3.28) |
| FVC%pred | 81. 00 (68.93, 92.20) | 80.56 ± 16.47 | 82.70 (71.05, 94.75) |
| FEV1, L | 1. 48 (1.04, 1.93) | 1.40 (1.00, 1.83) | 1.63 (1.17, 1.99) |
| FEV1%pred | 58.8 (41.95, 68.50) | 56.80 (39.20, 67.40) | 61.37 ± 19.88 |
| FEV1/FVC% | 54.82 (44.18, 63.63) | 53.53 (42.60, 62.15) | 58.42 (47.37, 65.27) |
| TLC (SBHD)%pred | 83.05 (75.30, 91.40) | 82. 90 (74.70, 91.20) | 83.43 ± 12.43 |
| TLC (WBP)%pred | 108.25 (97.18, 118.43) | 109. 40 (98.70, 120.60) | 105. 50(96.40, 115.20) |
| ΔTLC, L | 1. 30 (0.79, 2.00) | 1. 35 (0.80, 2.08) | 1. 24 (0.77, 1.75) |

*Data presented as median delta and 25-75% interquartile range or mean ± SD. BMI, body mass index; ATS/ERS, American Thoracic Society/European Respiratory Society; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 s; TLC, total lung capacity; SBHD, single-breath helium dilution; WBP, whole-body plethysmography; ΔTLC: the difference between total lung capacity determined by whole-body plethysmography and total lung capacity determined by the single-breath helium dilution method.*

## Severity of Obstruction and TLC

We calculated the absolute difference between TLC (SBHD) and TLC (WBP) in each patient and defined it as ΔTLC. Pearson correlation analysis was used to evaluate TLC (SBHD) and TLC (WBP), as well as the correlations of ΔTLC with FEV1%pred and ΔTLC with FEV1/FVC. The results showed that TLC (SBHD) and TLC (WBP) were moderately positively correlated (r = 0.701; $P$ =0.000) (**Figure 2A**), the correlation coefficient between ΔTLC and FEV1%pred was r = −0.618 ($P$ =0.000) (**Figure 2B**), and the correlation coefficient between ΔTLC and FEV1/FVC was r = −0.685 ($P$ =0.000) (**Figure 2C**). After establishing the correction

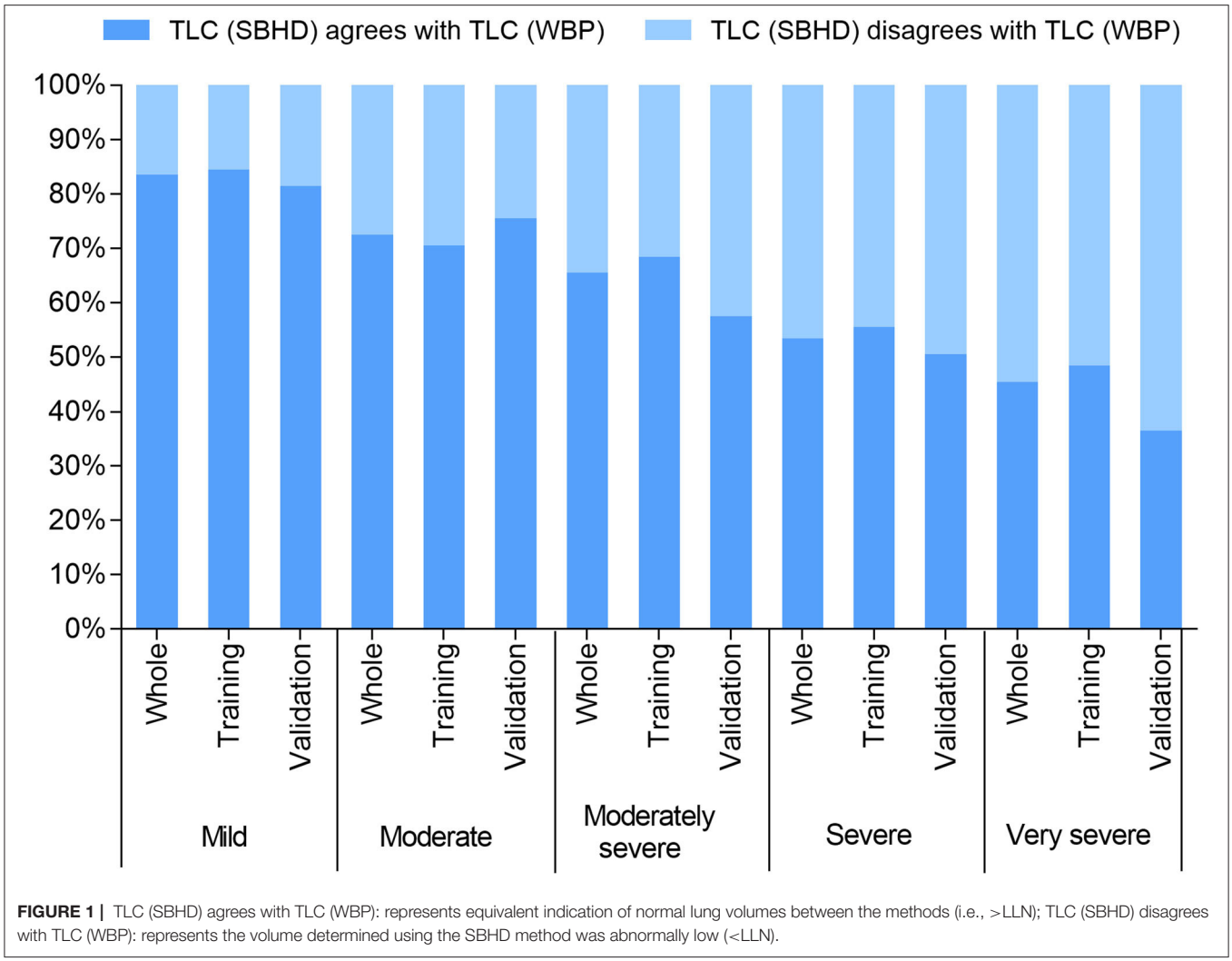


**FIGURE 1 |** TLC (SBHD) agrees with TLC (WBP): represents equivalent indication of normal lung volumes between the methods (i.e., >LLN); TLC (SBHD) disagrees with TLC (WBP): represents the volume determined using the SBHD method was abnormally low (<LLN).

equation, the TLC (adjusted SBHD) and TLC (WBP) correlations were further improved (r = 0.873; $P = 0.000$) (**Figure 2D**).

## Establishment of the TLC (SBHD) Correction Equation

We compared TLC (SBHD) with TLC (WBP) in the training cohort of 407 cases, and the results showed that TLC (SBHD) (4.78 ± 0.95 L) was significantly lower than TLC (WBP) (6.31 ± 1.31 L; $P = 0.000$; **Table 2**), and multiple linear regression analysis was used to establish a regression equation for predicting TLC (WBP), including sex, age, height, weight, FEV1/FVC, and TLC (SBHD). In the multivariate analysis, sex and age were not significant and were excluded from the model. The resulting regression equation model is as follows: TLC (adjusted SBHD) (L) = −0.669 + 0.756 ∗ TLC (SBHD) (L) − 0.047 ∗ FEV1/FVC + 0.039 ∗ height (cm) − 0.009 ∗ weight (kg) ($r^2 = 0.753$ and adjusted $r^2 = 0.751$). Furthermore, after grouping by different degrees of obstruction, there was no statistical difference between the TLC (adjusted SBHD) and TLC (WBP) (Mild, $P = 0.082$; Moderate, $P = 0.97$; Moderately severe, $P = 0.39$; Severe, $P = 0.53$; Very severe, $P = 0.99$; **Table 3**).

## Validation of the TLC (SBHD) Correction Equation

We validated the aforementioned correction model in a validation cohort of 221 patients. We first compared TLC (SBHD) and TLC (WBP) in different obstruction degree groups. TLC (SBHD) was lower than TLC (WBP) ($P = 0.000$; **Table 4**), and this was consistent with the trend in the training group. We then applied the correction equation. The overall TLC in the validation group was 6.28 ± 1.07 L after correction, which was not statistically different from TLC (WBP) (6.27 ± 1.20 L; $P = 0.88$) (**Table 2**). Moreover, in the different obstruction degree groups, there were no statistically significant differences in TLC (SBHD) vs. TLC (WBP) after adjustment using the regression model (Mild, $P = 0.58$; Moderate, $P = 0.82$; Moderately severe, $P = 0.10$; Severe, $P = 0.61$; Very severe, $P = 0.37$; **Table 4**).

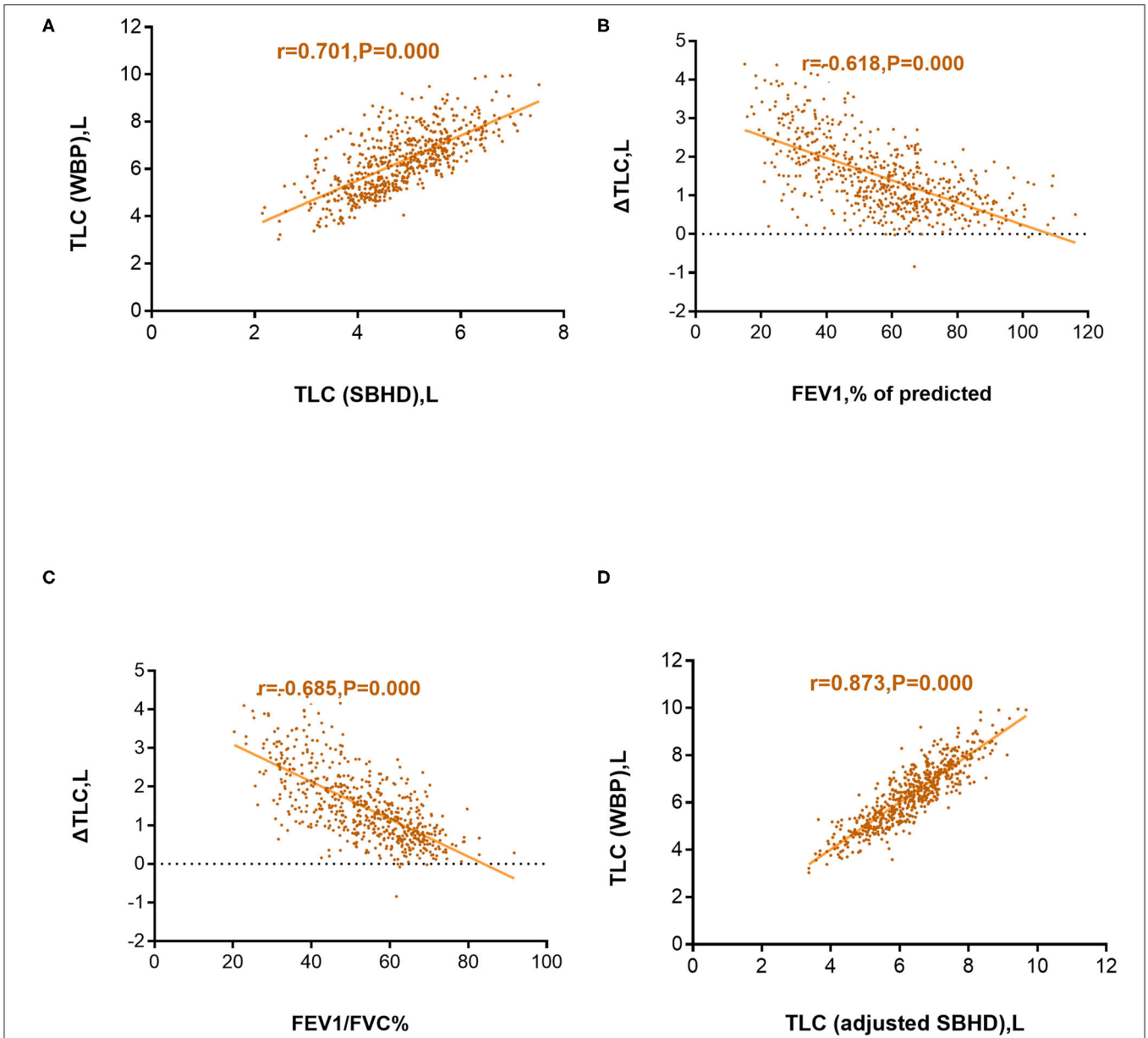


**FIGURE 2 |** Correlation between the total lung capacity determined by whole-body plethysmography [TLC (WBP)] and total lung capacity determined using the single-breath helium dilution method [TLC (SBHD)] **(A)**; Correlation between the difference in TLC (WBP) and TLC (SBHD) (ΔTLC) and predicted forced expiratory volume in 1 s (FEV1%pred) **(B)**; Correlation between ΔTLC and FEV1/forced vital capacity (FVC%) **(C)**; Correlation between TLC (WBP) and TLC (adjusted SBHD) **(D)**.

We used Bland–Altman plots to compare TLC (WBP) with TLC (adjusted SBHD) in all 628 patients. There was a very good agreement between TLC (WBP) and TLC (adjusted SBHD) in **Figure 3**.

## DISCUSSION

In the study, we established a correction model for the SBHD method using WBP as the gold standard; to the best of our knowledge, our study sample size is currently the largest. We found that the SBHD method and WBP are moderately positively correlated in patients with obstructive lung disease, and the difference between the two gradually increases as the degree of airflow obstruction increases. We established a correction equation for the SBHD method, which allows SBHD to accurately assess the total lung volume in patients with obstructive pulmonary disease with different degrees of obstruction.

For patients with obstructive pulmonary disease, the SBHD method significantly underestimated lung volumes, which is consistent with previous findings. In a retrospective cross-sectional study, Coertjens et al. (14) found that the TLC (WBP) was higher than the TLC (SBHD) ($p < 0.01$). In groups of patients

with mild to moderate OLD and severe OLD, the difference in TLC between the methods ranged from 1.58 to 2.00 L. Similarly, Milite et al. (15) measured TLC (SBHD), by the helium dilution rebreathing method [TLC (RBHD)] and TLC (WBP) in 55 outpatients with emphysema. In these patients with emphysema, TLC (SBHD) was underestimated compared with TLC (WBP) and TLC (RBHD), as FEV1%pred decreased ($P < 0.001$).

A possible explanation for the underestimation of the SBHD method is that the lung function of patients with OLD primarily manifests as airflow limitation. As the disease progresses, air trapping in the small peripheral airways, functional residual capacity or residual volume is significantly increased, airflow limitation causes compensatory responses in the body, the patient over-breathes, the chest cavity is overinflated, and the TLC is significantly increased (11, 16). The SBHD method calculates the total lung volume based on the percentage concentration of alveolar helium before and after dilution. Because patients with OLD have air trapping and uneven gas distribution, the inert gas cannot reach the area of air trapping. Thus, the TLC (SBHD) is lower than the actual value, because WBP can measure the trapped air not in communication with the airways in accordance with the Boyle's law. Therefore, WBP is usually preferred over the SBHD method in measuring the lung volume of patients with OLD.

An additional explanation of the discrepancy between WBP and SBHD methods is that plethysmography may overestimate TLC in airway obstruction due to a compliant extrathoracic airway (17). O'Donnel et al. (18) and Tantucci et al. (19) used an approach similar to ours and compared the TLC measured by WBP to that obtained by CT in patients. O'Donnell et al. (18) reported that WBP overestimates the lung volume, particularly among subjects with FEV1 < 30% of the predicted value. However, Tantucci et al. (19) arrived at an opposite conclusion. Their study showed that the results obtained by CT and WBP were similar, and the lung volume measured by WBP was not systematically overestimated. In our study, the data in **Tables 3**, **4** illustrate the rising TLC by WBP as the degree of airway obstruction gets worse. Although it is apparent that patients with OLD will have increased TLC, in our study, we instructed patients to take shallow and rapid breaths at a frequency of 0.5–1.0 Hz to reduce the oral pressure and alveolar pressure imbalance caused by wheezing frequency (13). Considering all studies and data currently available, WBP remains the most accurate method for determination of TLC.

The choice of methods for measuring the lung volume depends on cost, availability, convenience, and accuracy. Although the multiple-breath helium dilution method enables a more even distribution of the inhaled gas, the testing time is

**TABLE 2 |** Differences (mean ± standard deviation) in TLC in different groups of subjects.

| Variable | Whole ($n = 628$) | Training ($n = 407$) | Validation ($n = 221$) |
|---|---|---|---|
| TLC (SBHD), L | 4.83 ± 0.94 | 4.78 ± 0.95 | 4.91 ± 0.90 |
| TLC (WBP), L | 6.30 ± 1.27 | 6.31 ± 1.31 | 6.27 ± 1.20 |
| TLC (adjusted SBHD), L | 6.29 ± 1.11 | 6.30 ± 1.14 | 6.28 ± 1.07 |
| *P*-value | 0.00 | 0.00 | 0.00 |
| *P'*-value | 0.82 | 0.98 | 0.88 |

*P-value indicates TLC (SBHD) vs. TLC (WBP); P'-value indicates TLC (adjusted SBHD) vs. TLC (WBP). TLC, total lung capacity; SBHD, single-breath helium dilution; WBP, whole-body plethysmography.*

**TABLE 3 |** Differences (mean ± standard deviation) in TLC in the training group of subjects stratified by airflow limitation severity.

| Variable | Mild ($n = 83$) | Moderate ($n = 90$) | Moderately severe ($n = 75$) | Severe ($n = 86$) | Very severe ($n = 73$) |
|---|---|---|---|---|---|
| TLC (SBHD), L | 5.09 ± 0.85 | 4.78 ± 0.92 | 4.69 ± 1.08 | 4.73 ± 0.83 | 4.58 ± 1.03 |
| TLC (WBP), L | 5.99 ± 1.09 | 5.94 ± 1.12 | 5.93 ± 1.32 | 6.76 ± 1.25 | 7.01 ± 1.42 |
| TLC (adjusted SBHD), L | 5.91 ± 0.96 | 5.95 ± 1.03 | 5.98 ± 1.24 | 6.70 ± 0.91 | 7.01 ± 1.11 |
| *P*-value | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| *P'*-value | 0.082 | 0.97 | 0.39 | 0.53 | 0.99 |

*P-value indicates TLC (SBHD) vs. TLC (WBP); P'-value indicates TLC (adjusted SBHD) vs. TLC (WBP). TLC, total lung capacity; SBHD, single-breath helium dilution; WBP, whole-body plethysmography.*

**TABLE 4 |** Differences (mean ± standard deviation) in TLC in the validation group of subjects stratified by airflow limitation severity.

| Variable | Mild ($n = 64$) | Moderate ($n = 61$) | Moderately severe ($n = 35$) | Severe ($n = 36$) | Very severe ($n = 25$) |
|---|---|---|---|---|---|
| TLC (SBHD), L | 5.03 ± 1.05 | 4.96 ± 0.75 | 5.03 ± 0.83 | 4.68 ± 0.85 | 4.62 ± 0.97 |
| TLC (WBP), L | 5.85 ± 1.14 | 6.07 ± 1.13 | 6.34 ± 1.03 | 6.57 ± 1.20 | 7.29 ± 1.04 |
| TLC (adjusted SBHD), L | 5.82 ± 1.12 | 6.06 ± 0.88 | 6.49 ± 0.98 | 6.63 ± 0.93 | 7.17 ± 0.96 |
| *P*-value | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| *P'*-value | 0.58 | 0.82 | 0.10 | 0.61 | 0.37 |

*P-value indicates TLC (SBHD) vs. TLC (WBP); P' value indicates TLC (adjusted SBHD) vs. TLC (WBP). TLC, total lung capacity; SBHD, single-breath helium dilution; WBP, whole-body plethysmography.*

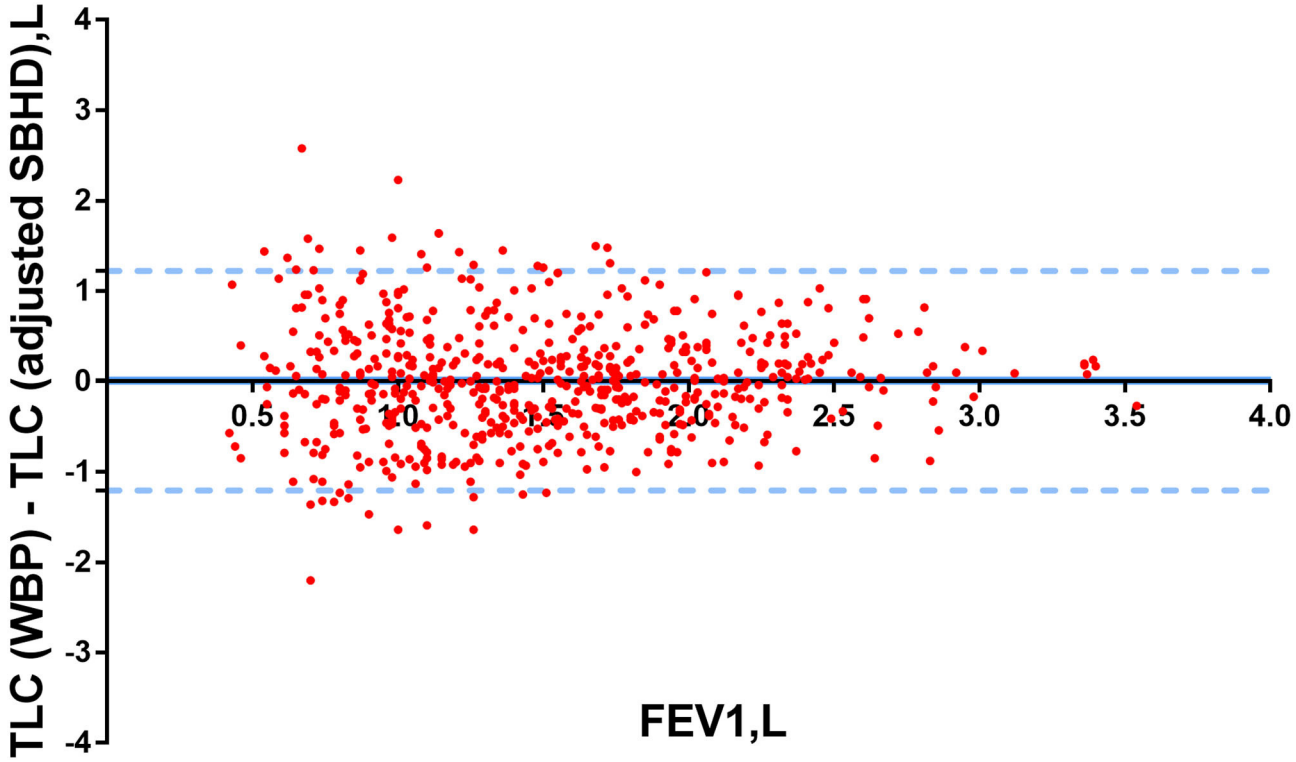


**FIGURE 3 |** Bland–Altman plots were used to determine the differences in TLC (WBP) and TLC (adjusted SBHD) in patients. Y-axis: the differences between TLC (WBP) and TLC (adjusted SBHD), X-axis: FEV1 (L).The limits of agreement were calculated as ±1.96 SDs of the differences.

longer. In patients with severe airflow obstruction, the difference between the two helium dilution methods is as high as 34%, and the two still underestimated the lung volume compared with the total lung volume measured by WBP (20). CT can accurately calculate the anatomical lung volume (21, 22), but its usefulness may be limited by several factors, such as clinical conditions, radiation dose, and economic constraints (23, 24). A recent study of five global centers (25) proposed a new measure of absolute vital capacity, the Minibox™ method. The MiniBox™ is based on a combination of first principles and inductive statistics, by analysis of gas pressures and air flows immediately preceding and following airway occlusions, derives TLC during tidal breathing. The results showed no significant differences between the TLC values obtained by WBP and those using the Minibox™ method, but this new measurement method has not yet been included in the ATS/ERS guidelines and further research is needed to verify its accuracy.

The correction equation of TLC (SBHD) adjusted for the degree of airflow obstruction constitutes an important contribution of our study. Hopkins Asthma and Allergy Center (10) established a regression equation to show that the alveolar volume measured using the SBHD method can predict the multiple-breath TLC in patients with moderate to severe obstruction. In our study, a more comprehensive regression model was used, and the degree of difference between the WBP and SBHD methods was compared across severities of obstruction based on FEV1%pred, not across the FEV1/FVC ratio, as was done by Punjabi. In fact, assessing the degree of obstruction should not be based on FEV1/FVC, but instead on FEV1%pred; therefore, the current study is more accurate in this regard. Similarly, Coertjens et al. (14) established a correction for the SBHD method to measure the lung volume in patients with OLD; however, this study had a small number of patients, few included variables, a low regression model fit, and no validation cohort.

In our study, we included physiological factors, such as sex, age, height, and weight, in establishing the correction equation to improve the fit of the regression model. It is known that age, sex, weight, height, and ethnicity are the main physiological determinants of lung volumes (26–28). Height is positively correlated with lung volume (29), whereas obese subjects tend to show a decrease in lung volume with weight gain (30). This is consistent with our results. In our correction equation, TLC (adjusted SBHD) is positively correlated with height and negatively correlated with body weight. Although age and sex also had an effect on the lung volume (31, 32), the loss of significance of these two indexes in the process of establishing the correction model might be related to the low weighted value of sex and age indexes.

Our study had certain limitations. First, we only included test patients from a single hospital, and we will conduct multi-region and multi-center verification in the future. Moreover, the

number of female patients was smaller than that of male patients, especially in the severe and highly severe groups. Domestic epidemiological surveys (33–35) have shown that the prevalence of chronic obstructive lung disease is significantly higher in men (11.9%) than in women (5.4%) and only 12.0% of people with COPD reported a previous pulmonary function test (33). This is mainly because the smoking rate in men (58.2%) is considerably higher than that in women (4.0%). In addition, women with COPD have a significantly lower inspection rate of pulmonary function test than men (35), and follow-up studies are needed to increase the number of female patients. Third, the population in our research involved all Chinese patients. We are not sure whether this correction equation is applicable to other ethnicities. The aforementioned questions will be addressed in future studies.

## CONCLUSIONS

In summary, in patients with lung disease affected by airway obstruction, the SBHD method underestimated lung volumes, and the difference between TLC (SBHD) and TLC (WBP) increased gradually with increasing degrees of airflow obstruction. After using the correction equation, the TLC (WBP) values can be more accurately predicted based on TLC (SBHD). The use of the correction equation makes the simple and low-cost SBHD method a reliable method for measuring the TLC of patients with OLD, providing important value in the diagnosis and treatment of respiratory diseases as well as in the course of observation and preoperative evaluation of patients.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the institutional review board of Second Affiliated Hospital of Zhejiang University School of Medicine. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

YX, GH, and YZ were involved in the conception and design. QL, LZ, PF, JL, BS, LH, YW, and GH were in charge of data acquisition, analysis, statistical analysis, and interpretation of data. QL, LZ, and YX were responsible for drafting and critical revision of the manuscript. All authors have read and approved the final manuscript.

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# Effectiveness of Telemonitoring for Reducing Exacerbation Occurrence in COPD Patients With Past Exacerbation History: A Systematic Review and Meta-Analysis

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**Background:** Although an increasing number of studies have reported that telemonitoring (TM) in patients with chronic obstructive pulmonary disease (COPD) can be useful and efficacious for hospitalizations and quality of life, its actual utility in detecting and managing acute exacerbation of COPD (AECOPD) is less established. This meta-analysis aimed to identify the best available evidence on the effectiveness of TM targeting the early and optimized management of AECOPD in patients with a history of past AECOPD compared with a control group without TM intervention.

**Methods:** We systematically searched PubMed, Embase, and the Cochrane Library for randomized controlled trials published from 1990 to May 2020. Primary endpoints included emergency room visits and exacerbation-related readmissions. *P*-values, risk ratios, odds ratios, and mean differences with 95% confidence intervals were calculated.

**Results:** Of 505 identified citations, 17 original articles with both TM intervention and a control group were selected for the final analysis ($N = 3,001$ participants). TM was found to reduce emergency room visits [mean difference (MD) −0.70, 95% confidence interval (CI) −1.36 to −0.03], exacerbation-related readmissions (risk ratio 0.74, 95% CI 0.60–0.92), exacerbation-related hospital days (MD −0.60, 95% CI −1.06 to −0.13), mortality (odds ratio 0.71, 95% CI 0.54–0.93), and the St. George's Respiratory Questionnaire (SGRQ) score (MD −3.72, 95% CI −7.18 to −0.26) but did not make a difference with respect to all-cause readmissions, the rate of exacerbation-related readmissions, all-cause hospital days, time to first hospital readmission, anxiety and depression, and exercise capacity. Furthermore, the subgroup analysis by observation period showed that longer TM (≥12 months) was more effective in reducing readmissions.

**Conclusions:** TM can reduce emergency room visits and exacerbation-related readmissions, as well as acute exacerbation (AE)-related hospital days, mortality, and the SGRQ score. The implementation of TM intervention is thus a potential protective therapeutic strategy that could facilitate the long-term management of AECOPD.

**Systematic Review Registration:** This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and was registered at International Prospective Register of Systematic Reviews (number: CRD42020181459).

**Keywords: telemonitoring, chronic obstructive pulmonary disease, acute exacerbation of chronic obstructive pulmonary disease, telehealth, telehomecare, telecare, telephone monitoring, telemedicine**

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) refers to a progressive, irreversible disease characterized by persistent airway limitation, and its symptoms often worsen over time (1, 2). Acute exacerbation of COPD (AECOPD) is defined as an acute worsening of respiratory symptoms affecting patients' health status, lung function, and COPD-related costs (2, 3). Acute exacerbations (AEs) account for ∼70% of COPD-related direct medical costs, with over 18 billion spent on direct costs annually worldwide (4). Given the magnitude of these numbers, using telehealth to achieve even a small percentage gain in savings is of interest (5). Despite the substantial impact that exacerbations may have, patients with COPD often have difficulty recognizing early deterioration based on symptoms and cannot respond adequately or in a timely manner, indicating an urgent need to develop effective management options to help patients recognize the early onset of AECOPD (6, 7).

Telemonitoring (TM) refers to the use of electronic information and communication technologies to support distance healthcare, allowing information exchange between supervising clinicians and long-distance patients regarding symptoms or physiological measurements and enabling access to healthcare services (5, 8, 9). TM has been using a wide range of technological devices, varying from an information and communication technologies platform including a web-based call center (10); a tablet cable computer with a web camera, a microphone, and measurement equipment (11); electronic diary on the website (12); a telephone line to a central data management unit to a monitoring platform *via* a touch-screen computer and a mobile modem (13), etc. TM has recently begun to be used for the management of patients with COPD (14, 15). It has attracted interest as a potential solution to the global challenge of providing care for aging populations and thus may also be an alternative to self-management (SF) to reduce the impact of AECOPD (6, 16, 17). The early detection of exacerbations may decrease healthcare costs by informing individualized interventions to prevent further exacerbation events, decelerate disease progression, and reduce mortality (18). Since 2006, there have been a lot of studies on TM for remote periodic management of COPD (10). Recent studies have reported that TM may be beneficial for COPD patients (14, 19–22), whereas others have shown that TM is unlikely to result in statistically significant improvements in the exacerbation rate (23, 24), so there were no consistent conclusions that have been reached on whether it can reduce exacerbations. As previous studies revealed, a patient with past exacerbation histories would have more risks for future exacerbations (25), and the reduction of exacerbations is one of the current COPD management goals gaining enthusiastic promotion by policy makers (26). It was supposed that the inclusion criteria of various studies with or without past exacerbation histories might produce different conclusions. Therefore, as for the goal of reducing the frequent exacerbations, we designed to conduct this meta-analysis focusing on patients with exacerbations in the past 12 months with the potential significance who might benefit from TM so as to provide an answer for the appropriate selection of TM for COPD patients.

## MATERIALS AND METHODS

### Search Strategy and Selection Criteria

Three English databases, PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL), were comprehensively searched. The language was limited to English only, with no date restrictions, allowing retrieval of papers from the inception of the databases to May 2020. Both keywords and Medical Subject Heading (MeSH) terms were used, including "Pulmonary Disease, Chronic Obstructive," "telemonitoring," "telecare," "telehomecare," "telehealth," "telephone monitoring," "telemedicine," "telepathology," "telecommunication," "Disease Progression," "exacerbation," and combinations of these search terms. The reference lists of all the included studies were examined for relevant articles from 1990 to May 2020. The search strategy used in this study is included in the **Supplementary Material**.

### Study Selection

The inclusion criteria were as follows: (a) randomized controlled trials (RCTs), including pilot studies; (b) patient diagnosed with COPD according to the Global Initiative for Chronic

**TABLE 1 |** TM studies and pooled clinical outcomes.

| Clinical outcomes | | Type of variable | No. of studies | No. of patients |
|---|---|---|---|---|
| **Primary endpoints** | | | | |
| ER visits | | Continuous | 6 (5, 11, 12, 27–29) | 1,099 |
| Re-admissions | AE-related readmissions | Dichotomous | 7 (10–13, 17, 30, 31) | 1,281 |
| | Rate of AE-related readmissions | Continuous | 9 (5, 6, 9–12, 14, 28, 31) | 1,573 |
| | All-cause readmissions | Dichotomous | 4 (10, 11, 16, 17) | 772 |
| **Secondary endpoints** | | | | |
| LOS | AE-related hospital days | Continuous | 6 (5, 11, 13, 14, 17, 28) | 1,073 |
| | All-cause hospital days | Continuous | 7 (9, 11, 13, 14, 16, 29, 31) | 2,201 |
| Mortality | | Dichotomous | 11 (5, 9–11, 13, 14, 28, 29, 31–33) | 2,307 |
| Time to first hospital readmission | | Continuous | 3 (14, 16, 31) | 887 |
| HRQoL | SGRQ, total | Continuous | 6 (14, 27–29, 31, 33) | 1,212 |
| | EQ-5D, change | Continuous | 2 (6, 28) | 195 |
| | EQ-VAS, change | Continuous | 2 (6, 28) | 195 |
| Anxiety and depression | HADS-A, change | Continuous | 2 (13, 28) | 444 |
| | HADS-D, change | Continuous | 2 (13, 28) | 444 |
| Physical capacity | 6MWT, distance, change | Continuous | 2 (30, 32) | 81 |

*Readmission is defined as hospitalization to the same or different hospital for any reason within the following year after discharge (9). LOS was defined as hospital days per admission (days), and the number of days of an admission was calculated as the number of midnights during the admission dates, with the exception of a patient discharged on the same day who was allocated a 1-day LOS (5). TM, telemonitoring; ER, emergency room; AE, acute exacerbation; LOS, length of stay; HRQoL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire; EQ-5D, EuroQol five-dimension scale; EQ-VAS, EuroQol visual analog scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; 6MWT, 6-min walking test.*

Obstructive Lung Disease (GOLD): had a post-bronchodilator forced expiratory volume in 1 s ($FEV_1$)/forced vital capacity $<0.70$; (c) a TM intervention (telemedicine, telehealthcare, telerehabilitation, teleconsultation, telecare, telehealth, mobile tool, apps, call center, etc.); (d) the TM device should periodically monitor significant parameters or symptoms and transmit these records to the researchers; (e) comparison with a control group (usual care, ordinary health care, blank control, face-to-face support, etc.); (f) reporting at least one of the following exacerbation-related main outcomes: emergency room (ER) visits, readmissions, or mortality; (g) patients had at least one exacerbation or hospitalization/ER visit due to COPD in the past 36 months; and (h) the observation period was at least 6 months.

The exclusion criteria were as follows: (a) duplicate study; (b) nonrandomized controlled trial; (c) not an original article (e.g., review papers, editorials, commentaries on articles, study protocols, abstracts of communications or meetings review articles, conference posters, and unpublished gray literature); (d) comparison between two different TM interventions; (e) included only regular telephone calls, video consultation, or teleconference interventions without clinical TM data; and (f) not published or translated in English.

## Data Extraction and Quality Assessment

The data extraction strategy is provided in the **Supplementary Materials**. The extracted data included first author, year of publication, region, study design, duration of study, sample size, age, sex, lung function, characteristics of recruited patients with COPD, characteristics of the intervention, control group, study outcomes, and results.

The risk of bias of the included studies was evaluated by two reviewers (Y.W. and Y.S.) according to the Cochrane Collaboration risk of bias tool for RCTs, as shown in the **Supplementary Material**.

## Outcome Measures

### Primary Endpoints

In this meta-analysis, the primary endpoints were moderate to severe exacerbations, defined as those resulting in a visit to the ER or hospital admission (9). Hence, ER visits or readmissions are used as proxies for the exacerbation rate. We classified the admission into AE-related and all-cause admissions since the management and follow-ups of admissions could be tracked with the outcomes and causes of admissions. However, for the ER visits, most studies {except only one (27)} did not present the definite cause classifications of ER visits. We supposed that ER visits had various outcomes, such as admission, discharge from ER, transfer to other medical centers, etc. Thus, it was difficult to track the outcomes and causes of admissions. So, we did not divide ER visits into AE-related and all-cause ER visits. The outcomes reported in this article were estimated at the longest follow-up. For the study purpose, we considered the following outcomes as the primary endpoints (**Table 1**):

1) ER visits;
2) Readmissions: exacerbation-related (AE-related) readmissions, all-cause readmissions, and the rate of AE-related readmissions.

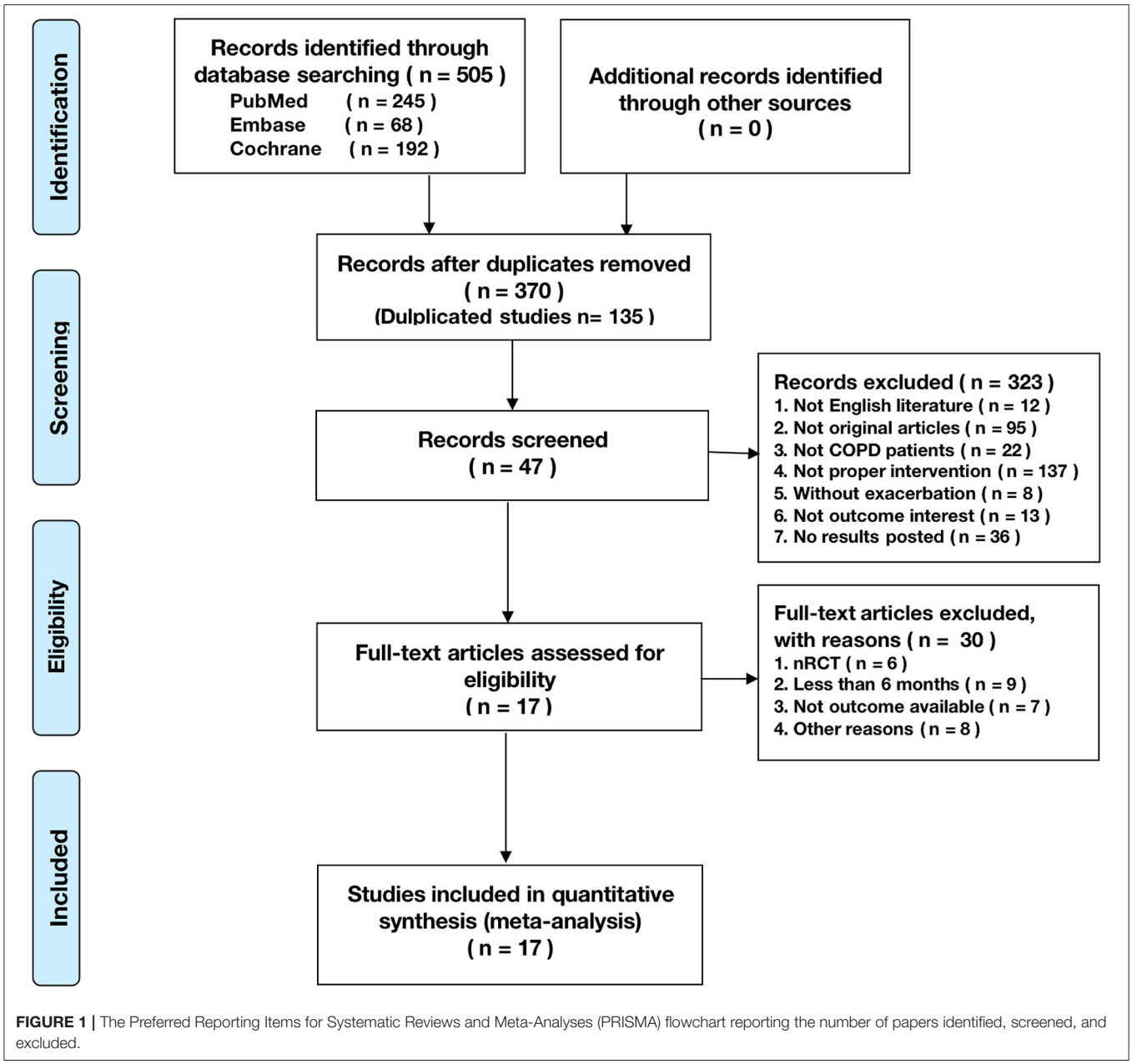


**FIGURE 1 |** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart reporting the number of papers identified, screened, and excluded.

### Secondary Endpoints

For the study purpose, we considered the following outcomes as the secondary endpoints:

1) Length of stay (LOS): AE-related hospital days and all-cause hospital days;
2) Mortality;
3) Time to first hospital readmission;
4) Health-related quality of life (HRQoL): St. George's Respiratory Questionnaire (SGRQ, total score) and change in the EuroQol five-dimension scale (EQ-5D) and EuroQol visual analog scale (EQ-VAS) scores between baseline and the end of the study;
5) Anxiety and depression: change in Hospital Anxiety and Depression Scale (HADS-A and HADS-D) scores between baseline and the end of the study;
6) Exercise capacity: change in the 6-min walking test (6MWT) distance between baseline and the end of the study.

## Data Synthesis and Analysis

A narrative description of each study was produced. The data from the RCTs were analyzed using intention-to-treat protocols. The variable analysis and data synthesis methods are shown in the **Supplementary Material**.

For the outcomes of interest, prespecified subgroup analyses were performed based on the duration of follow-up, as this factor may affect the impact of the intervention. Shorter-term (no more than 6 months) and longer-term (more than 6 months) effects of TM interventions may differ. In addition, we performed exploitative analyses by using different cutoff points for follow-up times (e.g., 6, 9, and 12 months).

In addition, a sensitivity analysis was carried out to examine the stability of the combined results for the primary outcomes only under different assumptions and thereby investigate the robustness of the effect sizes found in this review. We were unable to use statistical methods (e.g., funnel plots and Egger's regression test) to assess publication bias because the number of studies included in the analysis was small ($n < 10$). Hence, sensitivity analyses were performed to identify whether the review findings were dependent on study characteristics using random-effects vs. fixed-effects modeling or by analyzing specific populations (patient number ≥100 or TM with SF intervention). We conducted all meta-analyses with Review Manager, version 5.3.

# RESULTS

## Characteristics of the Included Studies

A total of 505 citations were identified by a comprehensive search of the literature; 17 articles involving 3,001 people were identified as relevant to this study, and these publications were ultimately selected for inclusion in the meta-analysis for critical appraisal (**Figure 1**; **Supplementary Table 1**) (5, 6, 9–14, 16, 17, 27–33). Thirty studies were excluded after evaluation for the reasons documented in **Figure 1**. The assessment of patients before enrollment in the study was identical for both groups in terms of (1) the SGRQ total score and (2) history of previous exacerbations requiring inpatient hospitalizations/ER visits. The participants in the intervention group and control group received the same clinical care and had access to the same healthcare services. The only difference between

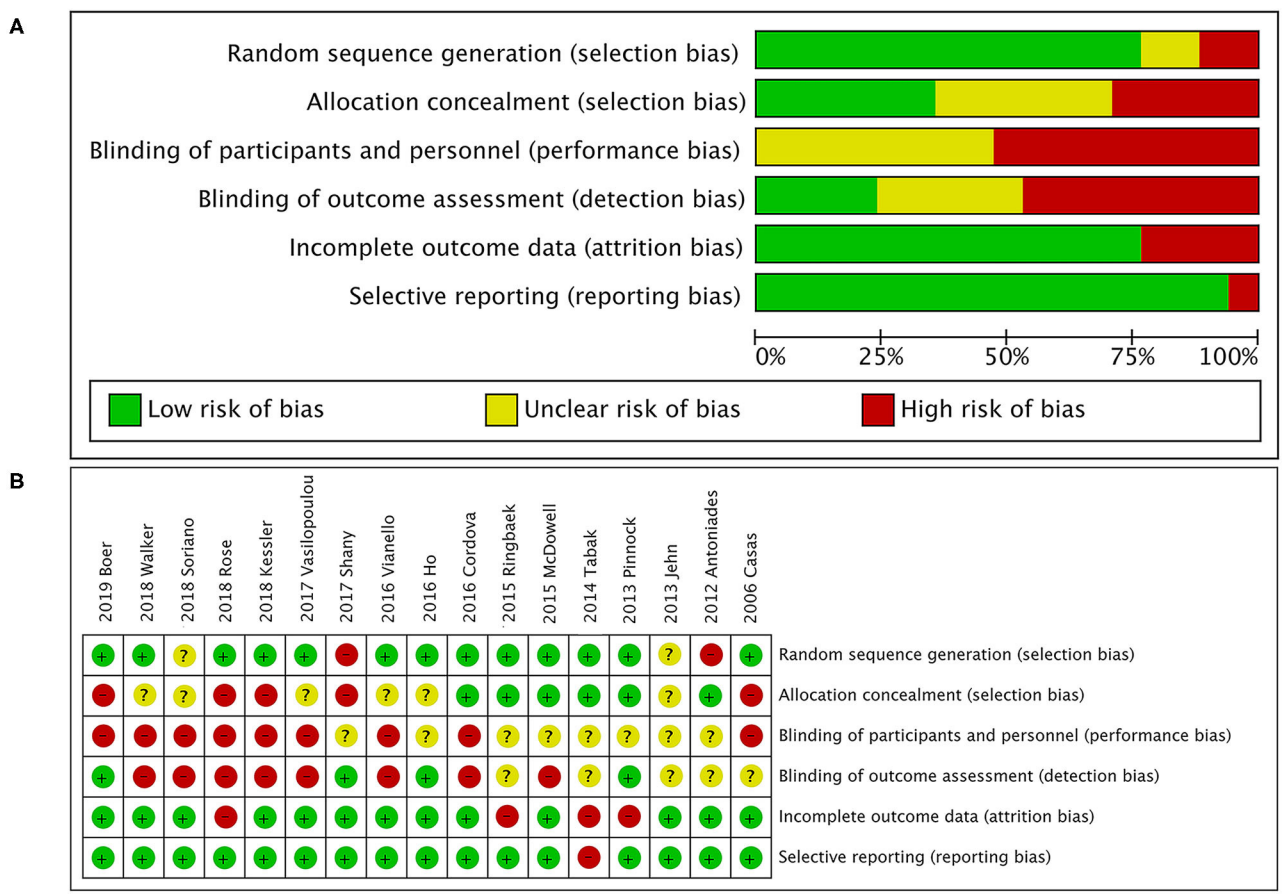


**FIGURE 2 |** Quality assessment. **(A)** Risk of bias graph; **(B)** risk of bias summary. The overall risk of bias in randomized controlled trials (RCTs) was rated as moderate to high for issues related to blinding. Owing to the type of intervention, patients and health care research team could not be blinded for group assignment, as it was responsible for the personalized and technical support of the TM tool. In addition, most studies had reasonable random sequence generation. However, only six studies specified whether data collectors and outcome assessors were masked to treatment allocation.

the two groups was that the former received TM services. Six studies showed beneficial effects of TM intervention on COPD-related clinical outcomes (5, 10, 12, 17, 30, 33), and 11 studies showed that it did not reduce exacerbations (6, 9, 11, 13, 14, 16, 27–29, 31, 32). **Figure 2** shows the assessment of risk of bias in the trials. Various remote TM of vital signs allows clinicians to monitor a COPD patient remotely with reference and availability of the physiological signs, respiratory symptoms, and activity levels in a diffuse manner due to the technology updating. In order to make the diffusiveness clearly presented, we added a table as the summary of the TM methods and comparison in supplement (**Supplementary Table 3**).

## ER Visits

Six RCTs provided data comparing ER visits between the TM and control groups (5, 11, 12, 27–29). The TM group had fewer ER visits [$P = 0.04$, mean difference (MD) = −0.70, 95% confidence interval (CI) (−1.36, −0.03)]. High heterogeneity was found ($P = 0.000$, $I^2 = 95\%$). When we reviewed the included studies again because of the substantial degree of heterogeneity, we found one study by Vasilopoulou et al. in which ER visits due to AECOPD but not associated with hospital admission might reflect a different degree of AECOPD severity than in other studies and had more frequent data transmitting interval for 5 days per week, 10 h per day, which made the patients have excellent adherence and very good compliance (27). When we performed sensitivity analysis by removing this study from the analysis, the heterogeneity dropped from $I^2 = 94\%$ to $I^2 = 9\%$. An analysis of the total population showed significantly fewer ER visits in the TM group [$P = 0.02$, MD = −0.14, 95% CI (−0.26, −0.02), $I^2 = 9\%$]; see **Figure 3**.

We omitted the studies with relatively small sample sizes ($n < 100$) or TM without SF to perform a sensitivity analysis and to examine the stability of the pooled results for ER visits. As shown in **Table 2**, no significant effect was observed from the exclusion of any single study, and the pooled results indicated good stability (MD = −0.76, $P = 0.04$). There were also no differences in the results between the fixed and random statistical effects (MD = −0.27; $P = 0.000$).

## Readmission

### AE-Related Readmissions

In a pooled analysis of all seven RCTs (10–13, 17, 30, 31), the usage of TM led to a greater reduction in exacerbation-related readmissions than the control treatment, with statistically significant between-study heterogeneity [$P = 0.006$, risk ratio (RR) = 0.74, 95% CI (0.60, 0.92), $I^2 = 73\%$]. Then, the results were stratified by the observation period, and the subgroup analysis compared the periods of 6 or 9 months with that of 12 months. The effect of sequentially recalculating the pooled estimates for the studies in which the sample size was over 100 or the intervention was TM plus SF did not significantly alter the effect on AE-related readmission (RR = 0.82, $P = 0.02$; RR = 0.87,

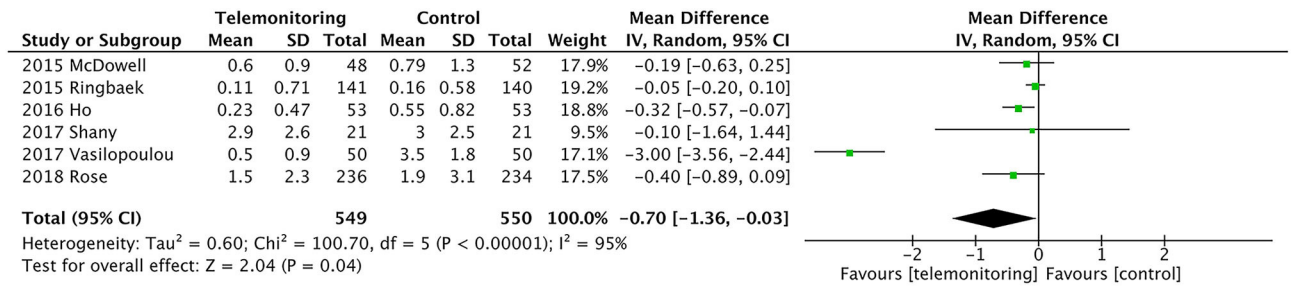


**FIGURE 3 |** A meta-analysis of ER visits. Df, degrees of freedom; M-H, Mantel–Haenszel.

**TABLE 2 |** Sensitivity analyses specific to sample size ≥100 or intervention of TM with SF.

| Methods | Main endpoints | No. of studies | No. of patients | MD/RR | 95% CI | *P* | $I^2$ |
|---|---|---|---|---|---|---|---|
| Sample size ≥100 | ER visits | 5 (11, 12, 27–29) | 1,057 | MD = −0.76 | [−1.47 to −0.05] | 0.04 | 96% |
| | AE-related readmissions | 5 (10–13, 31) | 1,195 | RR = 0.82 | [0.69, 0.97] | 0.02 | 66% |
| TM with SF intervention | ER visits | 3 (27–29) | 670 | MD = −0.98 | [−1.26 to −0.69] | 0.00 | 97% |
| | AE-related readmissions | 4 (10, 13, 17, 31) | 591 | RR = 0.87 | [0.79, 0.94] | 0.01 | 26% |

*The effect of the pooled estimates for the studies in which the sample size was over 100 or the intervention was TM plus SF did not significantly alter the effect on ER visits and AE-related readmissions. The power of studies with small sample size (<100) (5, 17, 30) did not meet the minimum requirements of the research (0.34, 0.37, and 0.66, respectively). So, after the exclusion of the above studies with small sample size, the conclusion was in accordance to the overall conclusion. Similarly, the alike pattern was found in TM-plus-SF populations. In other words, after the sensitivity analysis, it was proved that our final conclusion was consistent with the conclusion from the subgroup analysis of specific populations (patient number ≥100 or TM-plus-SF intervention group). MD, mean difference; RR, risk ratio; CI, confidence interval.*

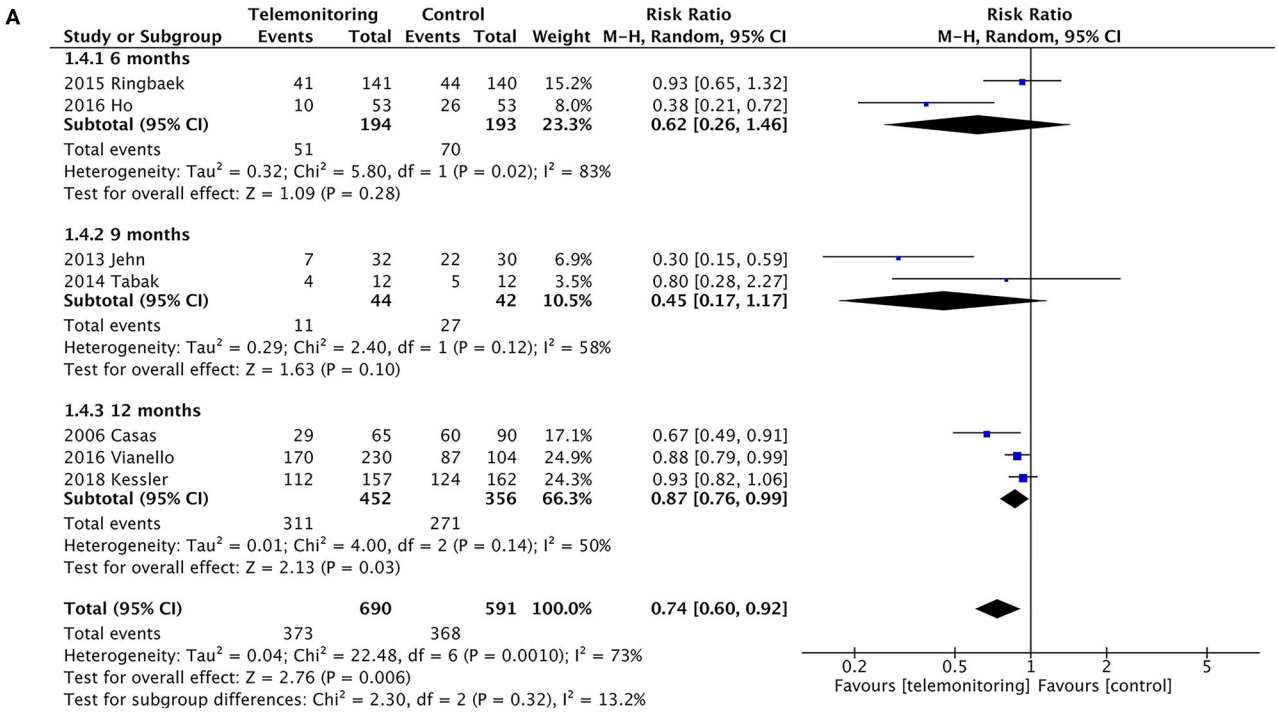


**FIGURE 4 |** A meta-analysis of readmissions. **(A)** Exacerbation-related readmissions (subgroup analysis with observation period). A sensitivity analysis using the fixed-effect model resulted in a similar effect size [RR = 0.81, 95% CI (0.74–0.88)] compared to random-effects modeling. One study (Soriano et al.) (9) could not be included in the meta-analysis for it only collected the number of participants who have at least one exacerbation (ER visit or hospitalization) in the past 12 months, resulting in the failure of exacting the required data. Subgroup analysis. In the subgroup in which follow-up duration was 6 or 9 months, it did not reduce readmissions [$P = 0.28$, RR = 0.62, 95% CI (0.26, 1.46) and $P = 0.10$, RR = 0.45, 95% CI (0.17, 1.17), respectively]. Statistically, heterogeneity was found in both subgroups ($I^2 =$ 83% and 58%). However, the subgroup of 12 months showed a greater reduction on readmissions [$P = 0.03$, RR = 0.87, 95% CI (0.76, 0.99), $I^2 = 50\%$]. Additionally, a sensitivity analysis was performed for the primary outcome to test an overall pooled effect. The results were no different between fixed and random statistical effects (RR = 0.81; $P = 0.000$). **(B)** The rate of exacerbation-related readmissions. **(C)** All-cause readmissions. Low heterogeneity was found ($P = 0.29$, $I^2 = 27\%$).

$P = 0.01$, respectively). Details are shown in **Figure 4**; **Table 2**.

### Rate of AE-Related Readmissions

Calculations were performed using a continuous variable for the rate of hospitalizations for each patient. The pooled results of the nine trials for the rate of exacerbation-related readmissions were homogeneous ($P = 0.34$), and the mean difference was −0.05 (95% CI was −0.14–0.05) in favor of TM (5, 6, 9–12, 14, 28, 31). A slight heterogeneity was found ($P = 0.18$, $I^2 = 30\%$). Only four of the nine trials, however, showed a benefit of TM (**Figure 4**) (5, 10, 12, 28).

### All-Cause Readmissions

The dichotomous variables included the number of readmissions for any cause. Four studies were included (10, 11, 16, 17), with no statistically significant difference [$P = 0.29$, RR = 0.92, 95% CI (0.78, 1.08)]; see **Figure 4**.

## Secondary Outcomes

Among the secondary outcomes observed, AE-related hospital days, mortality, and the SGRQ score, representing quality of life, were improved by TM [AE-related hospital days, MD = −0.60, 95% CI (−1.06, −0.13), $P = 0.01$; mortality, OR = 0.71, 95% CI (0.54, 0.93), $P = 0.01$; SGRQ score, MD = −3.72, 95% CI

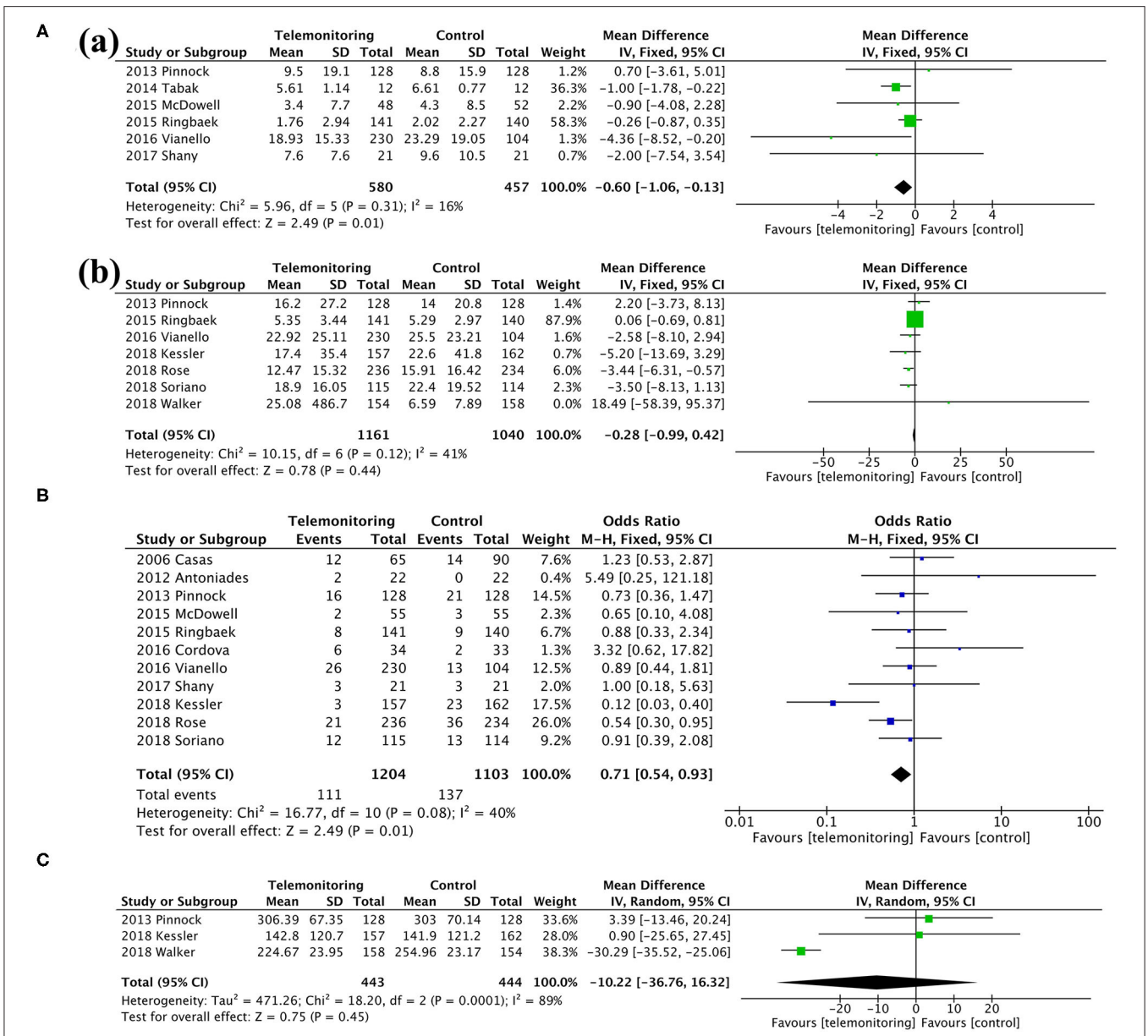


**FIGURE 5 |** A meta-analysis of secondary outcomes. **(A)** Length of stay: (a) exacerbation-related hospital days and (b) all-cause hospital days. **(B)** Mortality. **(C)** Time to first hospital readmission.

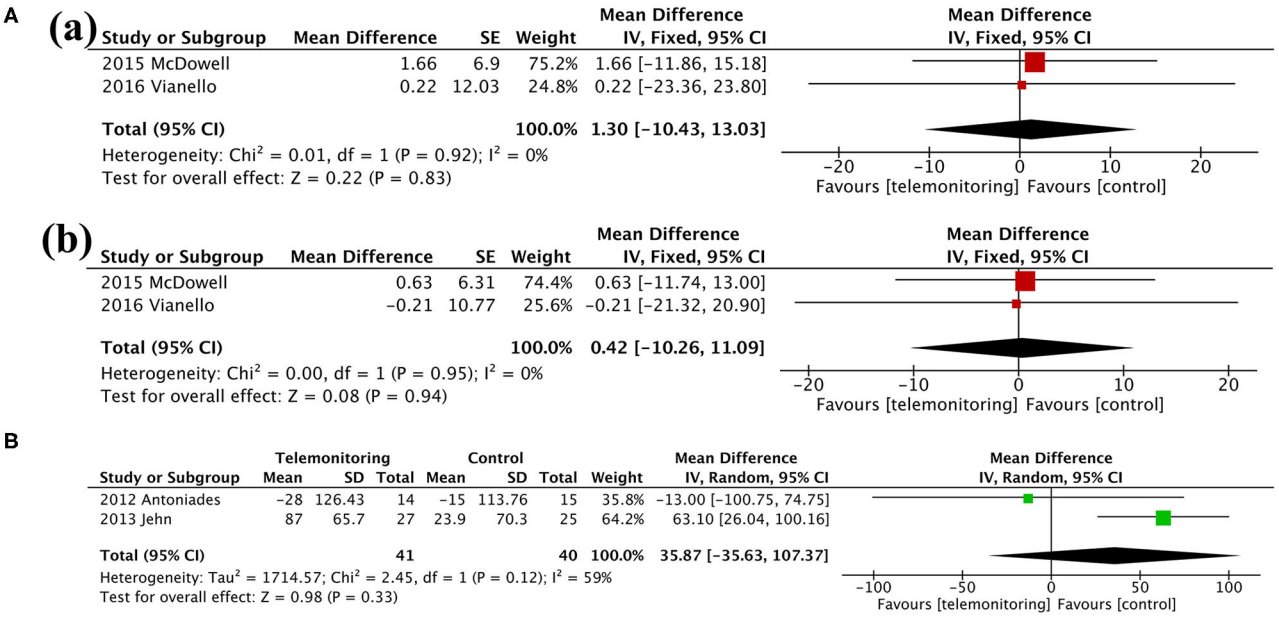


**FIGURE 6 |** Meta-analysis. **(A)** Anxiety and Depression: (a) HADS-A and (b) HADS-D. **(B)** Exercise capacity: 6MWT. HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; 6MWT, 6-min walking test.

**TABLE 3 |** The pooled results of HRQoL of TM on AECOPD.

| Clinical outcomes | No. of studies | No. of patients | Pooled results | | | |
|---|---|---|---|---|---|---|
| | | | *P* | MD | 95% CI | $I^2$ |
| SGRQ (total), baseline | 10 (5, 10, 14, 16, 27–31, 33) | 1,893 | 0.44 | −0.65 | [−2.27, 0.98] | 0% |
| SGRQ (total), outcome | 6 (14, 27–29, 31, 33) | 1,212 | 0.04 | −3.72 | [−7.18 to −0.26] | 54% |
| EQ-5D, change | 2 (6, 28) | 195 | 0.9 | −0.03 | [−0.45, 0.40] | 0% |
| EQ-VAS, change | 2 (6, 28) | 195 | 0.84 | 4.54 | [−39.37, 48.45] | 0% |

(−7.18, −0.26), $P = 0.04$], as shown in **Figures 5**, **6**; **Table 3**. The detailed results regarding the secondary outcomes are shown in the **Supplementary Materials**.

## DISCUSSION

Patients with COPD, most of whom are elderly, often have difficulty recognizing early symptom deterioration and do not respond in a timely or adequate manner in the course of symptom worsening (27). TM technology is constantly being improved and has developed from monitoring daily parameters transmitted to a call center *via* computers to simply tapping a touch screen or app on a mobile phone, complemented by measurements with a pulse oximeter, spirometer, and other instruments (6, 32). To date, studies on the effects of electronic healthcare in the management of chronic disease have focused on the use of applications of and wearable devices (6, 34). Remote monitoring of vital signs enables clinicians to track a patient's physical signs and respiratory symptoms from a distance using a wide range of technical equipment for the early detection of exacerbations (27). Telehealth technology has become more convenient and could promote patient–physician communication, facilitating patients' ability to promote increased levels of physical activity and health status and increasing their awareness of compliance with treatment (17). In this context, telehealthcare has been proposed as a novel management strategy that could minimize the likelihood of exacerbation and hospitalization. However, the results of the effect of TM on AECOPD are still uncertain, especially in the population with high risks of AECOPD. The findings of our meta-analysis provide evidence that TM reduces exacerbation-related rehospitalizations and ER visits in the long term for patients with a past AECOPD history. In our analysis, all studies were RCTs; however, some of them had relatively small sample sizes ($n < 50$) (5, 17, 32), and most of the studies were unblinded {except four articles that were researcher blinded (5, 6, 12, 14)} due to the necessity of the monitoring equipment. The principal findings of this systematic review

imply that TM reduced ER visits, AE-related readmissions, AE-related hospital days, mortality, and the SGRQ score but did not make a difference in the rate of AE-related readmissions, all-cause readmissions, all-cause hospital days, time to first hospital readmission, change in the EQ-5D score, change in the EQ-VAS score, anxiety and depression, or exercise capacity. As a consequence, the result was in favor of the usage of TM as a protective strategy in the management of AECOPD. Additionally, after a sensitivity analysis including studies with a larger sample size or a TM-plus-SF intervention, similar results were found.

The strongest predictor of the frequency of future exacerbation remains the number of exacerbations in the prior year (35, 36). Patients hospitalized for COPD exacerbation are at higher risk of readmission in the following year; hence, we aimed to reduce these adverse events in patient care (12). Thus, we only included studies that had a population of high-risk patients with a history of exacerbations, as the majority of them experienced ER visits or hospitalizations before enrollment in the trials. Exacerbations become more frequent as COPD progress (37). Regarding the AE-related readmission rate and the mean number of AE-related readmissions, we had controversial results, which can at least in part be explained by the fact that the meaningful index for the frequent AECOPD patients was the occurrence of AE but not the frequency of AE. In other words, the history of AECOPD but not the mean number of AECOPD indicates high risks of exacerbations. Similarly, the studies containing both outcomes had consistent results that TM used to care for patients with COPD exacerbation improves outcomes in terms of COPD-related readmissions, but not in average number of AE-related readmissions (11, 31).

In regard to the comparison between the beneficial effects on exacerbation-specific readmissions and all-cause readmissions, a better detection sensitivity of TM for AE-related admissions was found but not in all-cause readmissions. This can be explained by the fact that the home telemedicine group had the advantage of spirometry and physical symptom monitoring (markers of reliable predictors of AECOPD), which may have more rapid detection of respiratory symptoms or deterioration of lung function leading to timely medical treatment. Unsurprisingly, it is reasonable to assume that these physiological parameters cannot always reflect changes in patients' health status, which may reduce the ability to recognize a wide range of comorbidities (e.g., heart failure, diabetes, cancer, etc.), resulting in non-significant difference in all-cause readmissions. Consequently, our results were in accordance with most previous studies (20–22). Our exacerbation-related secondary outcomes, similarly, demonstrated the same pattern for AE-related hospital days and all-cause hospital days.

Findings from our meta-analysis showed an overall beneficial effect on the SGRQ score over 6 months. However, the total SGRQ score results were inconsistent in other articles (20, 22, 24, 38). This may be due to the different parameters monitored. Monitoring respiratory parameters (e.g., $SpO_2$ and HR) alone might be an optimal choice for ensuring beneficial effects on respiratory-related quality of life. In addition, the lack of improvement in the EQ-5D score, which describes and evaluates the health status of patients in broad disease areas, could be explained by the limited and specific monitoring range of respiratory system. In line with the lack of evidence of an improved EQ-5D score, TM did not seem to have a positive impact on patients' emotional distress, in particular on the severity of anxiety and/or depression (13, 28). Previous studies showed that anxiety and depression are related to the oxygen saturation, breathlessness, or activity endurance of patients but not to acute exacerbation frequency (39). Even though TM devices could provoke anxiety under the SF approach, we found no differences between the two groups regarding psychiatric disease. Therefore, early detection of AE through TM could not ameliorate psychological problems. Furthermore, the lack of change in the 6MWT distance suggested that the intervention could not improve exercise capacity either (30, 32).

In our meta-analysis, significant diffuseness of TM could be observed. TM technology has constantly developed and reformed, from monitoring of daily parameters transmitted to a call center *via* computers, simply tapping on the touch screen, to applications on the mobile phone complemented by measurements with a pulse oximeter and spirometer. In a word, TM technology developed with the update of technology of information, communication, computer, etc. As time went by, the relatively old-fashioned remote TM was updated and replaced by the newly developed technologies. Thus, in this meta-analysis, the interventions of TM presented as inevitable and wide-ranged diffuseness. For the effect of some specific type of TM, due to the rapid progress and update of technology, studies were quite limited for the conclusion for one specific TM device. However, for the overall effect of the TM intervention, the evidence was sufficient and the conclusion was robust. To optimize engagement, TM interventions would be attractive, rewarding, safe, tailored to patient needs, adapt seamlessly to variations in local connectivity, as well as provide flexibility in monitoring capability to meet individual clinical need. Nonetheless, it would still be challenging for the relatively high economic cost of telehealth for chronic disease due to the long-time usage, which restricts its implementation in the majority of healthcare settings. Thus, more researches are being needed on the clinical effects of the TM tools when used appropriately.

## Strengths and Limitations

An advantage of our study was that we aimed to determine the long-term clinical effectiveness of TM on exacerbations. The studies included in our review had a median follow-up of 12 months, and the minimum was 6 months. Our study analyzed subgroups by observation period. When the duration was 12 months, TM reduced rehospitalization to a greater extent than at 6 or 9 months, which did not significantly reduce readmission.

Additionally, some studies discussed patient compliance and satisfaction rates (16, 17, 32). Though the lack of data availability from some studies did now allow pooling of the data, all these studies drew consistent conclusions that patients were very positive about the benefits of TM.

The deployment of TM for AECOPD had a favorable effect on ER visits, readmissions, quality of life, and cost-effectiveness

based on a long-term perspective, especially an observation period of more than 12 months. Nonetheless, more detailed research is needed to fully understand its potential. Additionally, we studied TM in a special group of patients with COPD who had a previous episode of exacerbation requiring hospitalization, indicating the high risks of exacerbations, and confirmed the validity of TM. Thus, the application of TM for COPD may provide the potential ability for the early detection of AECOPD and the initiation of the early and timely management of disease.

Our review has several limitations. First, in RCTs performed in the COPD population included in our analysis, for controlled comparison, spirometry criteria in the GOLD guideline is employed as the inclusion criteria. Surely, due to many patients without spirometry are clinically diagnosed with COPD, we would miss many individuals treated for COPD, and studies in the real world might serve as an important complement to RCTs. Secondly, although most of the included studies were RCTs, a potential risk of bias was found in several domains and lack of some information, such as with respect to a lack of blinding and selection bias, which also reduced the possibility of drawing robust conclusions. In fact, it is not clear by what mechanisms telemonitoring works. More studies are required to answer the way patients are changed and managed (e.g., more attentive medical team, better knowledge of the patients and their abilities to follow instructions, better compliance, etc.). Besides, we conducted a sensitivity analysis to investigate differences in effect size and in strength of conclusions. If the sufficient power was not satisfied (generally set as 0.8), the results obtained were not credible and influence the final conclusion. Thus, we performed the sensitivity analysis. Based on the current sample size ($<$100), the power of the excluded studies (5, 17, 30) calculated were 0.34, 0.37, and 0.66, respectively, which did not meet the minimum requirements of the research. After the exclusion of the above studies with small sample size, the conclusion was in accordance to the overall conclusion. In other words, after the sensitivity analysis, it was proved that our conclusion was consistent with the conclusion from the subgroup analysis of specific populations (patient number $\geq$100) and sufficient power was satisfied. However, after the exclusion of the studies with small sample size, there might be publication bias. Third, even though TM cases and controls were given the same basic instructions that differed only regarding the TM intervention, the complexity of the basic instructions, especially the high quality of usual care, might make the results less accurate or underestimate the effectiveness of TM due to the good control of disease, which reduces the AECOPD. Fourth, with the rapid development and update of technologies, wide-ranged diffuseness was inevitable. Finally, issues such as patient adherence, satisfaction rate, and cost were not established due to the lack of published information. A cost-effectiveness analysis was based on the cost of the intervention during the study period. We could not synthesize this outcome in a meta-analysis because the expenditure of each patient differed across countries and devices. Moreover, the cost difference varied between patients, being greatest in those who were hospitalized in the previous year.

## CONCLUSIONS

Based on the available evidence presented in this meta-analysis, TM actually reduced ER visits and AE-related readmissions and reduced AE-related hospital days and mortality in patients with AECOPD, especially when the TM intervention was carried out for more than 12 months. The rapid progress and reformation of TM in practice might require more repeated control studies to conclude the effect and benefit of some special TM types. Thus, TM represents a new option for the management of the disease.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

GH determined the conception and design of the work, searched the literature, selected targeting studies, extracted and interpreted the data, conducted the meta-analysis, wrote the manuscript, and approved the final version of the manuscript. GH and J-wL carried out interpretation of data for the work. J-wL, YW, and YS assessed risk of bias and grade of the evidence. YW, YS, QZ, L-mY, Y-xW, and J-hG assisted in crafting the research questions and protocol. X-lL assisted with the statistical analysis. GH, Q-yW, and YY provided critical revisions that were important for intellectual content. All authors contributed toward selection of the studies and acquisition of data and contributed to the article and approved the submitted version.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.720019/full#supplementary-material

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## GLOSSARY

COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of COPD; AE, acute exacerbation; TM, telemonitoring; SF, self-management; RCT, randomized controlled trial; $FEV_1$, forced expiratory volume in 1 s; ER, emergency room; LOS, length of stay; HRQoL, health-related quality of life; SGRQ, St. George's Respiratory Questionnaire; EQ-5D, EuroQol five-dimension scale; EQ-VAS, EuroQol visual analog scale; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; 6MWT, 6-min walking test; SD, standard deviation; NR, not reported; BP, blood pressure; HR, heart rate; $SPO_2$, pulse oxygen saturation; TEMP, temperature; PEF, peak expiratory flow; RR, respiratory rate; MD, mean difference; CI, confidence intervals; OR, odds ratio; RR, risk ratio.

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# Epidemiology and Prognosis of Invasive Fungal Disease in Chinese Lung Transplant Recipients

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This study explored the epidemiology, risk factors, and prognosis of invasive fungal disease (IFD) in Chinese lung transplant recipients (LTRs). This retrospective cohort study included patients who received lung transplants at four hospitals in South China between January 2015 and June 2019. The participants were divided into IFD and non-IFD (NIFD) groups. The final analysis included 226 LTRs (83.2% males) aged 55.0 ± 14.2 years old. Eighty-two LTRs (36.3%) developed IFD (proven or probable diagnosis). The most common pathogens were *Aspergillus* (57.3%), *Candida* (19.5%), and *Pneumocystis jiroveci* (13.4%). Multivariate logistic regression revealed that anastomotic disease [odds ratio (OR): 11.86; 95% confidence interval (95%CI): 4.76–29.54; $P < 0.001$], cytomegalovirus (CMV) pneumonia (OR: 3.85; 95%CI: 1.88–7.91; $P = 0.018$), and pre-transplantation IFD (OR: 7.65; 95%CI: 2.55–22.96; $P < 0.001$) were associated with higher odds of IFD, while double-lung transplantation (OR: 0.40; 95%CI: 0.19–0.79; $P = 0.009$) was associated with lower odds of IFD. Logistic regression analysis showed that anastomotic disease was associated with higher odds of death (OR: 5.01; 95%CI: 1.24–20.20; $P = 0.02$) and that PJP prophylaxis was associated with lower odds of death (OR: 0.01; 95%CI: 0.001–0.11; $P < 0.001$). Invasive fungal disease is prevalent among LTRs in southern China, with *Aspergillus* the most common pathogen. Prophylaxis should be optimized based on likely pathogens.

**Keywords: invasive fungal infections, lung transplantation, aspergillosis, Candida, risk factors, prophylaxis**

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## INTRODUCTION

Lung transplantation is the only effective treatment for several end-stage lung diseases such as chronic obstructive pulmonary disease, pulmonary fibrosis, cystic fibrosis, and pulmonary vascular disease. According to the report released by the International Heart and Lung Transplant Association, more than 4,000 patients receive lung transplants each year worldwide, and more than 60,000 people have undergone lung transplantation to date (1). Improvements in surgical techniques and postoperative management strategies in recent years have led to an increase in the survival rate of lung transplant recipients (LTRs). According to a 2016 report, adult patients who underwent primary lung

transplantation between January 1990 and June 2014 had a median survival of 5.8 years and unadjusted survival rates of 89% at 3 months, 80% at 1 year, 65% at 3 years, 54% at 5 years, and 32% at 10 years (2).

Lung infection is the major cause of morbidity and mortality in LTRs. Invasive fungal disease (IFD) is one of the main infectious complications after solid organ transplantation (3). The incidence of IFD is particularly high among LTRs and ranges from 16.4 to 60% (4–6). Importantly, IFD after lung transplantation is associated with a reduced survival rate (4–6). Numerous factors have been suggested to increase the risk of IFD in an LTR, including *Aspergillus* colonization before or within 1 year after transplantation, single-lung transplant, chronic rejection, age, idiopathic pulmonary fibrosis, airway ischemia, diabetes mellitus, renal replacement therapy, cytomegalovirus (CMV) infection, and hypogammaglobulinemia (5–8). Nevertheless, further research is needed to explore the risk factors for IFD after lung transplantation fully.

Lung transplantation surgery was introduced into China relatively recently; hence objective research in the field of lung transplantation in China has been limited by a lack of eligible patients. However, lung transplantation has developed rapidly in China during the past few years: procedures have increased by 20–30% year-on-year, and the total number of operations reached 500 in 2019 (9). The continued growth and success of lung transplantation in China is partly due to a well-validated multidisciplinary approach to patient care that extends from the pre-transplantation period through the post-transplantation course. Additionally, the growth and development of lung transplantation in China have been helped by a legal system construct that guarantees organ procurement and utilization (10). Sharing and comparing China's experiences with the rest of the world may provide important lessons for the future of lung transplantation. However, there are no published reports describing the prevalence and prognosis of pulmonary IFD among LTRs in China.

Therefore, the present study aimed to investigate the epidemiology and prognosis of IFD in LTRs in China. Furthermore, we describe data that might help guide the prophylaxis and treatment of IFD in LTRs in China.

# METHODS

## Study Design and Participants

This multi-center retrospective cohort study enrolled lung or lung-heart transplant recipients from four hospitals in South China (The First Affiliated Hospital of Guangzhou Medical University, The Fifth Affiliated Hospital of Sun Yat-sen University, Gaozhou People's Hospital, and Shenzhen People's Hospital). All transplantations were conducted between 1 January 2015 and 30 June 2019. The inclusion criteria were as follows: (1) age $\geq$ 18 years old; and (2) single-lung transplantation, double-lung transplantation, or combined heart-lung transplantation. Patients with incomplete medical data or who missed follow-up appointments were excluded from the final analysis. This study was approved by the ethics committees of the four participating hospitals. The requirement for informed consent was waived due to the retrospective nature of this study.

## Collection of Clinical Data

The following data were extracted from the medical records: age, gender, body mass index (BMI), pre-transplantation clinical information (including *Aspergillus* airway colonization and history of IFD), original indications for lung transplantation, and the results of investigations for fungal disease such as thoracic imaging, bronchoscopy, fungal culture using samples of sputum or bronchoalveolar lavage fluid, serum level of (1, 3)-β-D-glucan, galactomannan test, and histopathology (11).

## Donors

All donors donated their organs after cardiocirculatory or brain death. The distribution and donation of every organ were processed within the judicial system for all study participants, as a voluntary citizen-based deceased organ donor program has been in place in China since January 2015. The civilian organ donation program has been the sole source of organs for transplantation in China (12). Since January 2015, the Law of the People's Republic of China has clarified that all organs should be derived from donors and that organ transplantation should abide by the regulations of organ donation. Written informed consent was obtained from the donors when alive or from their family members.

## Diagnosis of IFD and Identification of Pathogens

The diagnosis of pulmonary IFD was made in accordance with the revised definitions provided by the European Organization for Research and Treatment of Cancer/Mycoses Study Group (13), 2016 Guidelines of the American Society for Infectious Diseases (14), Clinical Practice Guideline For The Management Of Candidiasis (15), 2018 Clinical Practice Guide for Prosthetic Yeast Infections and Clinical Practice Guidelines for *Cryptococcal* Infections (16, 17), and Chinese Clinical Specifications for Invasive Fungal Diseases of Organ Transplant Recipients (2019 edition) (18). The detailed criteria are presented in **Supplementary Table 1**.

Airway IFD in the absence of lung lesions on pulmonary imaging was defined as isolation of fungus in culture with histopathological evidence of tissue invasion or necrosis, ulceration, or pseudomembranes on bronchoscopy. In accordance with a recent international guideline (18), bronchoscopy and biopsy were performed to identify the presence of any anastomotic lesions such as decay, necrosis, ulceration, stenosis, cracking, or fistula formation. The airway anastomosis was regularly examined by bronchoscopy from the second day after surgery. If healing of the anastomosis was satisfactory, the airway was examined every 2–3 days during the first week and then once weekly after that. The frequency of bronchoscopy was gradually reduced unless an anastomotic lesion or infection was detected, in which case more regular examinations were re-introduced.

According to the guidelines described above, the diagnosis of IFD was categorized as proven, probable, possible, or undefined.

In the present study, proven and probable cases were assigned to the IFD group. If a patient experienced two or more episodes of IFD after transplantation, only the first episode was considered to calculate incidence. If a patient had two or more types of fungal infection at the same time after transplantation, the primary and secondary fungal pathogens were defined according to their life-threatening severity.

For the most common aspergillosis in the study, the diagnostic criteria were as follows: clinically compatible illness plus one or more of the following: (1) isolation of *Aspergillus* species from a normally sterile site; (2) hyphae consistent with the presence of *Aspergillus* in a biopsy specimen or aspirate, plus a culture of *Aspergillus* from the same organ; (3) radiologic evidence of pulmonary lesions that were not attributable to other factors and a culture of bronchoalveolar-lavage fluid that was positive for aspergillus; (4) or tracheobronchial lesions confirmed by bronchoscopy, with a positive culture for *Aspergillus*.

## Antifungal Prophylaxis

Recipients diagnosed with a fungal infection before transplantation were administered regular antifungal therapy for 6 months, and lung transplantation was performed only after the lung lesions were stable. Recipients with fungal colonization before transplantation were given regular antifungal therapy for 2 months before lung transplantation.

Systemic antifungal and topical antifungal prophylaxis were used after lung transplantation for all recipients without IFD or fungal colonization before transplantation. Voriconazole (50–300 mg po q12 h for 3 months, with the dose adjusted to maintain a drug concentration of 0.75–3.0 μg/ml), was given for systemic prophylaxis. Aerosol inhalation of amphotericin B (5 mg bid for 4 months) was used as the topical medication.

Sulfamethoxazole was administrated orally for 6 months as prophylaxis against *Pneumocystis jiroveci* pneumonia (PJP). The main reasons for certain patients failing to receive preventive treatment were bone marrow suppression, renal function impairment, gastrointestinal intolerance, drug allergy, and discontinuation due to poorly-tolerated adverse effects.

## Immunotherapy

All four participating transplant centers utilized a standardized immunosuppressive scheme that included induction and triple immunosuppression maintenance therapy (19). The latter consisted of a calcineurin inhibitor (cyclosporin A or tacrolimus), mycophenolate sodium (or mycophenolate mofetil), and oral prednisolone. Tacrolimus was administered twice daily at a dose of 0.075 mg/kg ideal body weight to achieve serum levels of 13–17 ng/ml during the first month, 12–16 ng/ml during the second month, and 11–15 ng/ml during the third month. Methylprednisolone was administered at a dose of 500 mg at induction. Oral/injected steroids were titrated to 15 mg daily by 1 week and then maintained at 0.25 mg/kg body weight after that. Induction therapy was prescribed to part of the LTRs, based on the individual condition. The medications used for induction therapy included interleukin-2 receptor antibody (basiliximab) and rabbit anti-human thymocyte immunoglobulin (r-ATG). A small number of patients who had infectious diseases such as bronchiectasis or who were regarded to be at low risk of rejection did not receive induction therapy. Most patients were considered to be at medium risk of rejection and received basiliximab 20 mg IV on day 0 and day 4. A small number of patients regarded to be at high risk of rejection received r-ATG instead of basiliximab. In addition, r-ATG was prescribed for rejection prophylaxis or treatment.

## Follow-Up

Outpatient and inpatient follow-up was carried out until May 30, 2020. Survival was defined as the time from transplantation to death or the last day of follow-up.

## Statistical Analysis

The statistical analysis was performed using SPSS 21.0 (IBM Corp., Armonk, NY, USA), and data were plotted using Prism 5 (GraphPad Software, San Diego, CA, USA). Normally distributed continuous data are expressed as mean ± standard deviation (SD), and categorical data are described as frequency (percentage). For the analysis, the study participants were divided into IFD and non-IFD (NIFD) groups according to whether they had been diagnosed (proven or probable) with at least one episode of IFD during the follow-up period. Inter-group comparisons were made using Student's *t*-test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Univariate logistic regression analysis was performed to screen for factors associated with IFD, and significant variables ($P < 0.05$) were entered into a multivariate logistic regression model to identify independent risk factors. Odds ratios (ORs) and 95% confidence intervals (95%CIs) were calculated. The log-rank test was employed to compare Kaplan-Meier survival curves. The level of statistical significance was set at $P < 0.05$.

# RESULTS

## Demographic and Clinical Characteristics of the Study Participants

A total of 249 lung or heart-lung transplantation recipients were screened for inclusion in this study, and 23 of these cases were excluded due to missing data. Therefore, the final analysis included 226 LTRs (188 males, 83.2%) aged 55.0 ± 14.2 years old. There were 66 cases (29.2%) of left-lung transplantation, 67 cases (29.6%) of right-lung transplantation, 80 cases (35.4%) of double-lung transplantation, and 13 cases (5.8%) of heart-lung transplantation. The primary indications for lung transplantation included idiopathic interstitial lung disease (41.2%), chronic obstructive pulmonary disease (29.6%), and connective tissue disease-related interstitial lung disease (CTD-ILD; 7.5%). Seventy-three recipients (32.3%) received immune induction therapy, and all recipients received maintenance immunosuppressive therapy with standard triple therapy. Additionally, 55 patients (24.3%) received prophylaxis against PJP. The baseline demographic and clinical characteristics of the study participants are summarized in **Table 1**.

Among the 226 study participants, 82 recipients (36.3%) had at least one episode of pulmonary and/or airway IFD, with

**TABLE 1 |** Demographic and epidemiologic characteristics of the study participants in the IFD and NIFD groups.

| | All ($N = 226$) | IFD ($n = 82$) | NIFD ($n = 144$) | *P* |
|---|---|---|---|---|
| Age (years), mean ± standard deviation | 55.01 ± 14.23 | 55.80 ± 14.77 | 53.77 ± 14.37 | 0.84 |
| Sex (female/male) | 38/188 | 10/72 | 28/116 | 0.16 |
| Body mass index (kg/m$^2$), mean ± standard deviation | 19.97 ± 3.36 | 19.85 ± 3.21 | 20.18 ± 3.61 | 0.24 |
| Indications for transplantation, *n* (%) | | | | |
| Bronchiectasis | 11 (4.9%) | 5 (6.1%) | 6 (4.2%) | 0.54 |
| Chronic obstructive pulmonary disease | 67 (29.6%) | 27 (32.9%) | 40 (27.8%) | 0.55 |
| Idiopathic interstitial pneumonia | 93 (41.2%) | 27 (32.9%) | 65 (45.1%) | 0.29 |
| Connective disease-related interstitial lung disease | 17 (7.5%) | 11 (13.4%) | 7 (4.9%) | 0.04* |
| Pulmonary arterial hypertension | 12 (5.3%) | 1 (1.2%) | 11 (7.6%) | 0.048* |
| Occupational lung diseases | 15 (6.6%) | 7 (8.5%) | 8 (5.6%) | 0.42 |
| Other end-stage lung diseases | 11 (4.9%) | 4 (4.9%) | 7 (4.9%) | 0.99 |
| *Double-lung transplantation, *n* (%) | 80 (35.4%) | 23 (28.1%) | 57 (39.6%) | 0.09 |
| Lung-heart transplantation, *n* (%) | 13 (5.8%) | 1 (1.2%) | 12 (8.3%) | 0.035 |
| Early acute renal insufficiency, *n* (%) | 53 (23.5%) | 21 (25.6%) | 32 (22.2%) | 0.65 |
| Pre-transplantation IFD, *n* (%) | 36 (15.9%) | 25 (30.5%) | 11 (7.6%) | <0.001* |
| Cytomegalovirus infection, *n* (%) | 195 (86.3%) | 72 (87.8%) | 123 (85.4%) | 0.89 |
| Cytomegalovirus pneumonia, *n* (%) | 62 (27.4%) | 37 (45.1%) | 25 (17.4%) | 0.001* |
| Induction therapy, *n* (%) | 73 (32.3%) | 26 (31.7%) | 47 (32.6%) | 0.92 |
| Anastomotic disease, *n* (%) | 41 (18.1%) | 34 (41.5%) | 7 (4.9%) | <0.001* |

*IFD, invasive fungal disease.*
**Not including heart-lung transplantation.*

the diagnosis proven in 32 cases (14.16%) and probable in 50 cases (22.12%). There were no significant differences between the IFD and NIFD groups in age, sex, BMI, the proportion of patients receiving double-lung transplants, the incidence of early acute renal insufficiency, CMV infection, or use of induction therapy. However, CTD-ILD was a more common indication for transplantation in the IFD group than in the NIFD group (13.4 vs. 4.9%, $P = 0.04$), whereas pulmonary arterial hypertension was a less common indication for transplantation in the IFD group (1.2 vs. 7.6%, $P = 0.048$). Furthermore, the proportion of patients who underwent heart-lung transplantation was lower in the IFD group than in the NIFD group (1.2 vs. 8.3%, $P = 0.035$). In addition, pre-transplantation IFD (30.5 vs. 7.6%, $P < 0.001$), post-transplantation CMV pneumonia (45.1 vs. 17.4%, $P = 0.001$), and post-transplantation anastomotic disease (41.5 vs. 4.9%, $P < 0.001$) were more common in the IFD group than in the NIFD group.

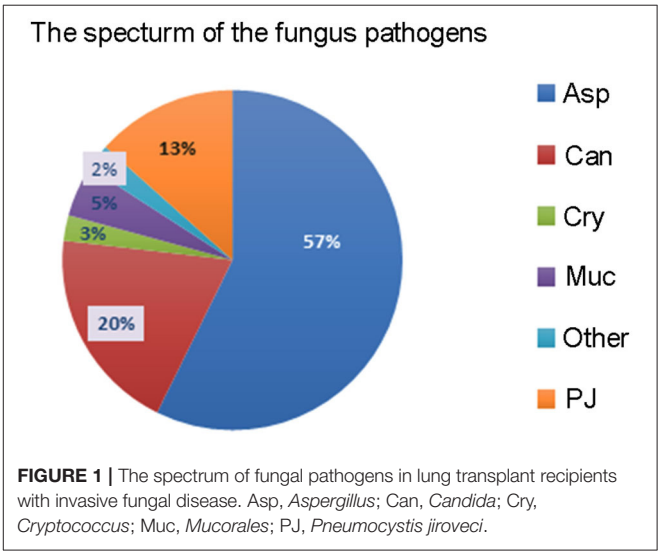


**FIGURE 1 |** The spectrum of fungal pathogens in lung transplant recipients with invasive fungal disease. Asp, *Aspergillus*; Can, *Candida*; Cry, *Cryptococcus*; Muc, *Mucorales*; PJ, *Pneumocystis jiroveci*.

## Fungal Pathogens

The most common fungal pathogens identified in the 82 LTRs with IFD were *Aspergillus* (47 cases, 57.3%), *Candida* (16 cases, 19.5%), and *P. jiroveci* (11 cases, 13.4%; **Figure 1**). The median time to diagnosis was 168 days (range, 0–720 days) for invasive pulmonary aspergillosis (IPA), 31.5 days (range, 0–165 days) for invasive candidiasis, and 333 days (range, 40–465 days) for PJP (**Figure 2**).

*Candida* was isolated from respiratory specimens in 70 recipients. However, only 16 cases had a proven diagnosis of invasive airway candidiasis with *Candida* observed in anastomotic tissue. The other recipients were considered to have colonization with the fungus. Among the 16 proven cases of invasive candidiasis, two patients had positive blood culture results, and the clinical manifestations and imaging data were consistent with systemic and pulmonary infection. All cases of PJP were in recipients who did not receive prophylaxis against *P. jiroveci*.

## Factors Associated With IFD

In the univariate analysis, anastomotic disease, CMV pneumonia, and pre-transplantation IFD were associated with higher odds

of IFD. In contrast, induction with basiliximab, double-lung transplantation, and PJP prophylaxis were associated with lower odds of IFD (**Table 2**). The multivariate analysis revealed that anastomotic disease (OR: 11.86; 95%CI: 4.76–29.54; $P < 0.001$), CMV pneumonia (OR: 3.85; 95%CI: 1.88–7.91; $P = 0.018$), and pre-transplantation IFD (OR: 7.65; 95%CI: 2.55–22.96; $P < 0.001$) were independently associated with higher odds of IFD, while double-lung transplantation (OR: 0.40; 95%CI: 0.19–0.79; $P = 0.009$) was independently associated with lower odds of IFD.

## Prognosis of IFD

The follow-up time ranged from 7 to 67 months. Kaplan-Meier survival curves showed that 1-year all-cause mortality was significantly higher in recipients with IFD than recipients without IFD (47.6 vs. 25.2%, $P < 0.001$; **Figure 3**). In addition, there were seven LTRs with intracranial IFD in the present study, and six of these patients died from systemic IFD within 4–37 days. Hence, the mortality rate of systemic IFD reached 85.7% among the LTRs in the present study. Logistic regression analyses of the 82 patients with IFD (**Table 3**) showed that anastomotic disease was independently associated with higher odds of death (OR: 5.01; 95%CI: 1.24–20.20; $P = 0.02$) and that prophylaxis against PJP was independently associated with lower odds of death (OR: 0.01; 95%CI: 0.001–0.11; $P < 0.001$).

# DISCUSSION

The objective of this retrospective study was to analyze the epidemiology, risk factors, and prognosis of IFD in LTRs at four hospitals in China. Optimization of the prophylaxis regimen

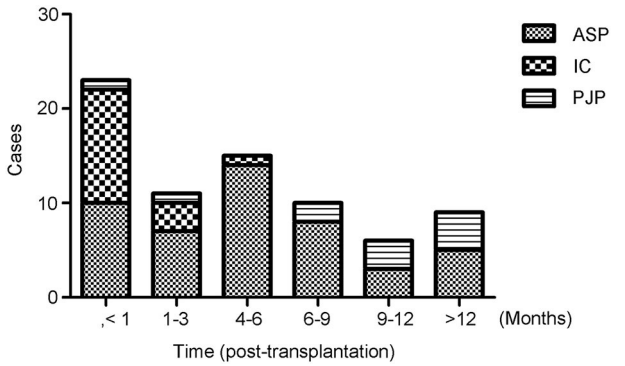


**FIGURE 2 |** Timing of the diagnosis of invasive fungal disease (IFD). The median time after transplantation at which the diagnosis of IFD was made was 168 days (range, 0–720 days) for invasive pulmonary aspergillosis, 31.5 days (range, 0–165 days) for invasive candidiasis, and 333 days (range, 40–465) days for *Pneumocystis jiroveci* pneumonia.

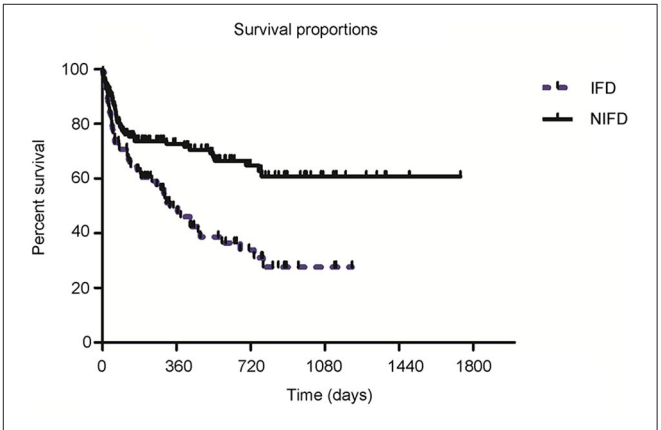


**FIGURE 3 |** Survival curves for lung transplant recipients in the invasive fungal disease (IFD) and non-IFD (NIFD) groups. One-year mortality was 47.6% in the IFD group and 25.2% in the NIFD group ($P < 0.001$).

**TABLE 2 |** Logistic regression analyses of factors associated with invasive fungal disease in lung transplant recipients.

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95%CI) | *P* | OR (95%CI) | *P* |
| Age | 1.41 (0.89–2.50) | 0.23 | | |
| Gender (male vs. female) | 1.74 (0.80–3.80) | 0.15 | | |
| Body mass index | 1.50 (0.82–2.72) | 0.18 | | |
| Anastomotic disease (yes vs. no) | 12.43 (5.16–29.98) | <0.001 | 11.86 (4.76–29.54) | <0.001 |
| Cytomegalovirus infection (yes vs. no) | 1.16 (0.52–2.62) | 0.72 | | |
| Cytomegalovirus pneumonia (yes vs. no) | 3.91 (2.12–7.22) | <0.001 | 3.85 (1.88–7.91) | 0.018 |
| Induction with r-ATG (yes vs. no) | 1.86 (1.07–3.22) | 0.70 | | |
| Early acute renal insufficiency (yes vs. no) | 1.47 (0.77–2.80) | 0.24 | | |
| Pre-transplantation IFD (yes vs. no) | 3.28 (1.64–6.54) | <0.001 | 7.65 (2.55–22.96) | <0.001 |
| Induction with basiliximab (yes vs. no) | 0.45 (0.21–0.97) | 0.04 | 0.43 (0.17–1.09) | 0.08 |
| *Lung transplantation type (double-lung vs. single-lung) | 0.49 (0.28–0.87) | 0.015 | 0.40 (0.19–0.79) | 0.009 |
| Prophylaxis against *Pneumocystis jiroveci* pneumonia | 0.52 (0.29–0.96) | 0.035 | 0.70 (0.34–1.46) | 0.34 |

*OR, odds ratio; 95%CI, 95% confidence interval; r-ATG, rabbit anti-human T lymphocyte immunoglobulin; AKI, acute kidney injury; CRRT, continuous renal replacement therapy.*
**Heart-lung transplantation included in double-lung transplantation.*

**TABLE 3 |** Logistic regression analyses of factors associated with mortality in patients with invasive fungal disease.

| Factor | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95%CI) | *P* | OR (95%CI) | *P* |
| Single-lung transplantation | 1.67 (0.62–4.47) | 0.32 | 0.90 (0.25–3.27) | 0.87 |
| Anastomotic complication | 4.20 (1.54–11.48) | 0.005 | 5.01 (1.24–20.20) | 0.02 |
| Previous invasive fungal infection | 0.59 (0.21–1.63) | 0.31 | 0.50 (0.13–1.94) | 0.32 |
| Cytomegalovirus pneumonia | 1.20 (1.49–2.92) | 0.69 | 0.61 (0.17–2.18) | 0.45 |
| Prophylaxis against *Pneumocystis jiroveci* pneumonia | 0.02 (0.002–0.13) | <0.001 | 0.01 (0.001–0.11) | <0.001 |

*OR, odds ratio; 95%CI, 95% confidence interval.*

according to the likely pathogens might help reduce the incidence of IFD in LTRs.

In the present study, the median time to occurrence of IPA was 6 months after transplantation. The timing of IPA occurrence in our cohort of LTRs is not unexpected given that all the study participants were administered triazole antifungal medications continuously for 3–4 months after transplantation, with some patients also receiving inhaled amphotericin B. A prior study by Doligalski et al. (20) reported that the median time to IPA was 10.5 months, but a later onset than that observed in our study. One possible explanation for this difference may be that the duration of routine early prophylaxis was longer for the LTRs in Doligalski's study than in ours since the 2004 American Society of Transplantation guidelines recommended continuing prophylaxis for 4–8 months after lung transplantation (21).

*Pneumocystis jiroveci* was the third most common causative pathogen of IFD, and 11 cases of PJP were identified in this study. The incidence of PJP (13.4%) in this study was comparable to that described previously (22). *Pneumocystis jiroveci* pneumonia prophylaxis was only given to 24.3% of the LTRs in our study, and not surprisingly, all cases of PJP occurred in the LTRs who did not receive prophylaxis. Our findings agree with those of Wang et al. (23), who found that PJP occurred early after transplantation in patients not receiving prophylaxis but much later in those given preventive therapy. Previous research has indicated that the incidence of PJP is significantly higher in thoracic organ transplant recipients than in other solid organ transplant recipients (24). Thus, some guidelines recommend a longer duration of prophylaxis or even lifelong prophylaxis for LTRs (25). In the present study, PJP-IFD did not occur in any of the LTRs who received 6 months of prophylactic therapy. Therefore, it is possible that 6 months of prophylaxis may be sufficient to prevent PJP and that lifelong therapy is not required. Further research is needed to establish whether 6 months of prophylaxis against PJP is adequate in LTRs.

Our multivariate logistic regression analysis indicated that a history of pre-transplantation IFD, CMV pneumonia, post-transplantation anastomotic disease, and single-lung transplantation were risk factors for IFD in LTRs. Our results are consistent with several previous studies (7, 8, 26, 27). Patients experiencing CMV disease are at an increased risk of subsequently developing IFD because of a combination of shared host-specific risk factors and pathogen-specific risk factors (28). The mechanism may involve impaired cellular function induced by CMV pneumonia in the immunosuppressed host. Patients with anastomotic complications may have a damaged mucosa that predisposes them to secondary fungal infection. Airway fungal infection causes a deterioration in the local blood supply that impairs local tissue repair, creating a vicious cycle between anastomotic disease and fungal infection (12, 25, 29). In addition, our study found that a history of pre-transplantation IFD increased the risk of post-transplantation IFD. There are various possible causes of IFD after transplantation. (1) If IFD is present before transplantation, antifungal treatments might not be able to completely remove the residual or colonized fungal pathogens in the airway or lung tissue. Therefore, if single-lung transplantation is carried out, any trace of fungal pathogens remaining in the other lung and airway can cause reinfection, resulting in IFD of the transplanted lung. Even after double lung transplantation, fungi remaining or colonizing the airway might become pathogenic again after transplantation. The use of broad-spectrum antibiotics during the perioperative period and high doses of immunosuppressants after transplantation will lower the immune function of the LTRs, increasing the risk of IFD. (2) If IFD was already present before transplantation but remained undiscovered until found during or after the operation, the risk of IFD is significantly increased due to the surgical trauma and the use of high-dose immunosuppressants, and IFD is also likely to spread to other organs. (3) Patients with IFD before transplantation and treated with azole drugs for at least 2–3 months are more prone to fungal breakthrough or triazole drug resistance than patients who did not receive azole drugs. Pathogenic fungi have developed many strategies to evade the host immune system (30). Immunological and genetic studies indicate a crucial role for human immune defects in fungal infections. Therefore, identifying appropriate prophylactic and immunotherapeutic targets is considered the most promising strategy for reducing morbidity and mortality in LTRs (31).

Connective tissue disease-related interstitial lung disease patients had more factors related to IFD. Before transplantation, these patients had been treated with glucocorticoid, mycophenolate, cyclophosphamide, or other immunosuppressive agents due to the treatment needs of the primary disease. Before transplantation, they belonged to the high-risk group of CMV infection and IFD or might have been infected with CMV or IFD. Thus, these patients are at a higher risk of IFD with enhanced immunosuppressant use

after transplantation. In contrast, in patients with pulmonary hypertension, the primary disease belonged to pulmonary vascular disease, which was neither infectious nor required immunosuppressive treatment before transplantation. So, these patients had no or relatively lower risk factors for IFD before transplantation.

In the present study, 1-year all-cause mortality was significantly higher in the IFD group (47.6%) than in the NIFD group (25.2%). Previous investigations have reported mortality rates ranging from 19 to 72% (4, 6, 23, 32–34). Since IFD often develops in patients with a more serious disease, it is difficult to establish whether IFD *per se* contributes to the poor outcome in LTRs. Our data and those described by others (35, 36) indicate that the mortality rate in transplant recipients with IFD remains unacceptably high and that preventing the occurrence of IFD remains a worthy goal. We suggest that long-term prophylactic antifungal therapy be recommended for the following four groups of patients: single-LTRs, patients with preexisting pulmonary mycopathy or fungal infection, patients with postoperative CMV pneumonia, and patients with postoperative airway anastomotic lesions. In addition, we would recommend long-term prophylaxis in patients with PJP as this would be expected to improve the prognosis.

There are some limitations to this study. First, this was a retrospective study, so that the analysis may be prone to selection bias or information bias. Second, lung transplantation was introduced in China relatively recently, which limited the number of recipients available for inclusion in the study. As a result, reliable subgroup analyses could not be carried out. Third, the limited sample size precluded us from evaluating which subgroups of pathogens were risk factors for IFD and mortality. Fourth, although the study participants were recruited from four hospitals, the treatment regimens used were similar and may not represent the regimens used in other hospitals in China.

Invasive fungal disease is prevalent among LTRs in China, with *Aspergillus* being the most prevalent pathogen. A history of pre-transplantation IFD, the occurrence of CMV pneumonia and the development of an anastomotic disease may increase the risk of IFD in LTRs. Additionally, IFD is associated with an increased rate of all-cause mortality at 1 year. Therefore, optimizing preventive strategies according to the clinical manifestations and pathogenic species may help reduce the incidence of IFD and improve outcomes in LTRs.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

## ETHICS STATEMENT

The requirement for informed consent was waived due to the retrospective nature of this study. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

JH and RC conceived and supervised the study. CJ designed the study, performed the experiments, analyzed the data, interpreted the data and drafted the manuscript. CJ, QL, XX, QC, and CL performed the experiments. RC coordinated the follow-up arrangement and collected the study samples. RC and QL analyzed and interpreted the data. JH and RC made manuscript revisions. All authors reviewed the results and approved the final version of the manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.718747/full#supplementary-material

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# Preliminary Exploration of Transpedal Lymphangiography With High-Dose Ethiodized Oil Application in the Treatment of Postoperative Chylothorax

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**Objective:** To preliminarily explore the safety and effectiveness of transpedal lymphangiography (TL) with high-dose ethiodized oil application (>20 ml) in the treatment of high-output postoperative chylothorax.

**Methods:** From 1 July 2020 to 1 July 2021, a total of 7 patients with high-flow postoperative chylothorax (>1,000 ml/d) were retrospectively reviewed in a single center. Clinical data, including surgery types, technical and treatment success of TL, and adverse events of TL, were collected and analyzed.

**Results:** Seven patients (5 cases of non-small cell lung cancer; 2 cases of esophageal carcinoma) with a median age of 62 years (range: 30–70 years) occurred postoperative chylothorax after tumor resection with mediastinal lymphadenectomy. All patients received conservative treatment including total parenteral nutrition and somatostatin administration for a median of 20 days (range: 15–31 days) that failed to cure the chylothorax, so TL was performed as a salvage. Before TL, the median daily chyle output was 1,500 ml/day (range: 1,100–2,000 ml/day). The technical success rate of TL was 100% (7/7), with the median volume of ethiodized oil of 27.6 ml (range: 21.2–30.0 ml) injected in TL. Ruptured thoracic duct was identified in 5 patients (5/7, 71%) in fluoroscopy and chest CT after TL. The treatment success rate of TL was 86% (6/7). In 6 patients, the thoracic drainage was removed after a median of 7 days (range: 4–13 days) from TL performance. No adverse event of TL was reported.

**Conclusion:** Transpedal lymphangiography with high-dose ethiodized oil application (>20 ml) is a feasible, safe, and effective modality for the treatment of high-flow (>1,000 ml/day) postoperative chylothorax.

**Keywords: lymphangiography, ethiodized oil, chylothorax, postoperative complications, thoracic neoplasms**

# INTRODUCTION

Postoperative chylothorax is a rare and refractory complication after thoracic surgery. It can lead to a large amount of nutrient loss, including protein, triglycerides, and other substances, resulting in electrolyte imbalance, malnutrition, and severe infection (1–3). Especially for patients with high-output chylothorax (>1,000 ml/d), if treatment is ineffective, life-threatening sequelae might occur with a mortality rate of up to 50% (1–3). Conservative treatment (e.g., total parenteral nutrition, somatostatin, etc.) is the first-line choice for postoperative chylothorax (3–6). However, there are some defects when treating patients with high chyle output, such as unsatisfactory efficiency and long treatment period with poor tolerability (3–6). Surgical repair, as a salvage treatment after the failure of conservative treatment, has a high occurrence rate of secondary surgery-related complications and the risk of death (up to 38 and 25%, respectively) (4–7).

The conventional transpedal lymphangiography (TL) is a classic diagnosis method for postoperative chylothorax with a therapeutical effect. The viscous ethiodized oil injected in TL can embolize the lymphatic leakage site (8). In literature, TL was reported with an overall treatment success rate of over 50% and a complication rate of <3% when treating postoperative chylothorax (5, 7, 9). Compared to surgical repair, TL is minimally invasive and can be tolerated by critically ill patients. Therefore, TL holds the potential as second-line management where conservative treatment fails. In conventional TL, it was empirically recommended that ethiodized oil should not exceed 20 ml (5, 8–11). Nevertheless, this recommended ethiodized oil dose may be insufficient for treating high-dose postoperative chylothorax because of the poor treatment efficiency rate of 35% (5, 10). Increasing the ethiodized oil dose in TL may benefit the leakage embolization and improve treatment efficiency. So far, it still lacks objective evidence on the safety or clinical efficacy of TL treatment with high-dose ethiodized oil (>20 ml) application in TL. This retrospective study preliminarily explored the safety and effectiveness of TL with high-dose ethiodized oil application (>20 ml) in the treatment of high-output postoperative chylothorax when conservative treatment failed.

# MATERIALS AND METHODS

## Definitions and Standards

The clinical and pathological staging of malignant tumors is based on the 8th edition of TNM Classification of Malignant Tumors (12, 13). Diagnostic criteria for postoperative chylothorax: 1. Exclusion of other postoperative complications of pleural effusion, such as malignant pleural effusion, inflammatory exudation, etc.; 2. Milk-like pleural drainage (**Figure 1A**), triglyceride level of drainage fluid higher than 110 mg/dL, or positive chylomicrons test (11, 14, 15). The technical success of TL is defined as the opacification of the thoracic lymphatic system under fluoroscopy (11, 16, 17). The treatment success of TL is defined as immediate cessation or gradual reduction of lymphatic leakage after TL leading to the removal of thoracic drainage within 2 weeks without the requirement of other treatments (6, 11, 18, 19). The lymphatic duct leakage is identified as definite ethiodized oil extravasation out from thoracic duct visualized in dynamic fluoroscopy, or the ectopic presence of the ethiodized oil in the pleural space observed in chest CT after TL (20).

## Patients

This study retrospectively collected a total of 7 patients with postoperative chylothorax after thoracic surgery admitted to this center from July 2020 to July 2021. The TL was indicated following: 1. fulfill the postoperative chylothorax diagnostic criteria; 2. after conservative treatment including total parenteral nutrition and somatostatin for more than 2 weeks, no progressive decrease of the thoracic chyle output; 3. after multidisciplinary team discussion (including physicians from departments of respiratory medicine, thoracic surgery, interventional radiology, and anesthesiology), it was decided to give priority to TL treatment; 4. obtain written informed consent of the patient. Contraindications for TL treatment follow: severe pulmonary dysfunction identified by pulmonary function test, pulmonary arteriovenous malformations/fistula, and right-to-left shunt heart disease (11).

## TL Procedure

After dermal sterilization, 1 ml of a 1:3 mixture of methylthioninium chloride (20 mg/2 ml, JUMPCAN pharmaceutical group Co., LTD, Jizhou, China) and 1% lidocaine was injected into each interdigital space on either left or right foot to dye the dorsal lymphatic vessels (**Figure 1B**). After 20 min, incise the dorsal skin of the foot under local anesthesia to separate the subcutaneous lymphatic vessel (**Figures 1C,D**). Afterwards, puncture the target lymphatic vessel by using a 26-G trocar needle (Jerui, WEGO, Weihai) (**Figure 1E**) and fix it with suture and sterile tapes (**Figure 1F**). Then, connect the trocar with an infusion pump (WZS-50F6, Zhejiang Smiths Medical, Hangzhou, China) to conduct the ethiodized oil injection (super-fluid ethiodized oil, Hengrui, Jiangsu, China). The pressure restriction and infusion velocity of the pump was set as a "High" model and 0.4 ml/min, respectively. From then, fluoroscopy (Artis Zee, Siemens Healthineers, Erlangen, Germany) was performed every 2–5 min to dynamically observe the opacification of the lymphatic vessels from the foot to the left jugular vein angle. Unlike the previous reports in which the operator ceased the injection after 6 to 12 ml of ethiodized oil application no matter whether the thoracic duct was opacified, the endpoint of injection in this study was the visualization of the left jugular vein angle (20–22). Then, the needle was removed and the dorsal wound of the foot was sutured. The chest CT (SOMATON emotion 16, Siemens, Germany) was immediately performed (filling phase) to identify the specific lymphatic leakage site with 3-dimensional reconstruction (scan parameters: 120 kv, adaptive current, and B30f iterative reconstruction) (20). If there is no lymphatic fistula, the same chest CT examination will be re-performed 24 h later (nodal phase) for further diagnosis (20).

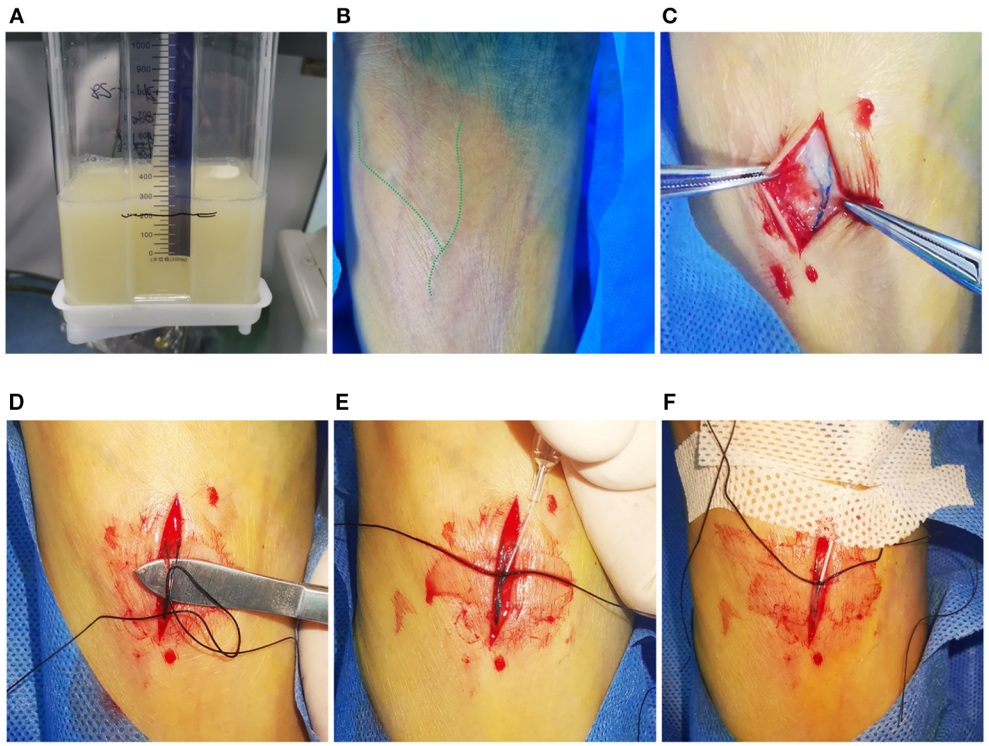


**FIGURE 1 |** Typical visual demonstration of chylothorax drainage and cannulation of pedal lymphatic vessel in TL procedure. **(A)** Typical visual demonstration of chylothorax drainage. **(B)** 20 min after dye injection between interdigital spaces, superficial lymphatic vessels could be observed with tinted blue color (alongside the green dash line) on dorsal foot. **(C)** After incision, subcutaneous lymphatic vessels can be clearly found with deep blue color. **(D)** Meticulous separation of the target lymphatic vessels. **(E)** Manual puncture of the lymphatic vessel by using a 26-G intravenous needle. **(F)** After fixation of the trocar by suture and sterile tape, the ethiodized oil can be injected afterwards.

## Study Goals

Record the time of the lymphatic opacification at the levels of the knee joint space, upper femoral head, L5/Th12/Th5 vertebrae, and left jugular veinous angle from start of ethiodized oil injection during TL. Identify the technical success of TL and thoracic duct rupture in fluoroscopy and following chest CT. Evaluate the treatment success and adverse event of TL from the institutional electronic records.

## Statistical Analysis

The data in this study were analyzed using Excel 2019 (Microsoft, USA). Quantitative and counting data are presented as median with range and count with percentages of the total, respectively. Since no group comparison is performed, only descriptive analysis is used.

# RESULTS

The median age of 7 patients (4 males and 3 females) was 62 years (range: 30–70 years). Two and 5 patients were diagnosed with esophageal carcinoma and non-small cell lung carcinoma, respectively. All patients underwent surgical tumor resection with mediastinal lymphadenectomy. After surgery, postoperative chylothorax occurred in 5 patients on the right side and 2 on the left side. TL treatment was performed at a median of 20 days (range: 15–31 days) after surgery. The median daily chyle output before TL was 1,500 ml/day (range: 1,100–2,000 ml/day). The details are shown in **Table 1**.

The technical success of TL was 100% (7/7). The median volume of ethiodized oil injected in TL was 27.6 ml (range: 21.2–30.0 ml) (**Table 2**). The median time of lymphatic opacification at the levels of knee joint space, upper femoral head, L5 vertebra, Th12 vertebra, Th5 vertebra, and the left jugular venous angle from the start of ethiodized oil injection were 4 min (range: 3–7 min) and 10 min (range: 9–12 min), 22 min (range: 15–34 min), 42 min (range: 33–51 min), 52 min (range: 47–62 min) and 69 min (53–75 min) (**Table 2**; **Figure 2**). Lymphatic duct leakage, including definite ethiodized oil extravasation out from thoracic duct in dynamic fluoroscopy and the ectopic presence of the ethiodized oil in the pleural space in chest CT after TL, was identified in 5 patients (5/7, 71%) (**Table 2**; **Figure 2**). No Adverse event of TL was recorded.

After TL, 6 patients experienced a progressive decrease of the daily chyle output. The median time for removing the thoracic drainage after TL was 7 days (range: 4–13 days). The treatment success rate of TL was 86% (6/7). One patient without significant reduction of daily chyle output after TL underwent further percutaneous afferent lymphatic vessel sclerotherapy (ALVS) on the 8th day after TL, who was cured later (11).

**TABLE 1 |** Basic characteristics.

| Patient ID | Sex | Age (years) | Diagnosis | Clinical staging | Surgery | Mediastinal lymphadenectomy | Location of the tumor | Postoperative pathological staging | Pathological diagnosis | Side of chylothorax | Daily chyle output before TL (ml/d) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Female | 62 | Non-small cell lung cancer | IA2 (1bN0M0) | Anatomical pulmonary resection | Yes | Upper lobe of right lung | IA2 (1bN0M0) | Invasive adenocarcinoma | Right | 1,500 |
| 2 | Male | 64 | Non-small cell lung cancer | IA2 (1bN0M0) | Anatomical pulmonary resection | Yes | Upper lobe of right lung | IA2 (1bN0M0) | Invasive adenocarcinoma | Right | 1,100 |
| 3 | Female | 30 | Non-small cell lung cancer | IA2 (1bN0M0) | Anatomical pulmonary resection | Yes | Lower lobe of right lung | IA2 (1bN0M0) | Invasive adenocarcinoma | Right | 2,000 |
| 4 | Male | 62 | Non-small cell lung cancer | IA2 (1bN0M0) | Anatomical pulmonary resection | Yes | Upper lobe of left lung | IA2 (1bN0M0) | Invasive adenocarcinoma | Right | 1,500 |
| 5 | Female | 70 | Non-small cell lung cancer | IA2 (1bN0M0) | Sublobar resection | Yes | Upper lobe of right lung | IA2 (1bN0M0) | Invasive adenocarcinoma | Left | 1,200 |
| 6 | Male | 64 | Esophageal carcinoma | II (T2N0M0) | Esophagectomy | Yes | Middle third of esophagus | IB (T2N0M0G1) | Well-differentiated squamous cell carcinoma | Left | 1,700 |
| 7 | Male | 56 | Esophageal carcinoma | II (T2N0M0) | Esophagectomy | Yes | Middle third of esophagus | IIA (T2N0M0G2) | Moderately differentiated squamous cell carcinoma | Right | 2,000 |
| Median (minimum-maximum) | | 62 (30–70) | | | | | | | | | 1,500 (1,100–2,000) |

*The clinical and pathological staging are based on the 8th edition of TNM Classification of Malignant Tumors (12, 13). TL, transpedal lymphangiography.*

**TABLE 2** | Details of TL treatment.

| Patient ID | Time of TL after surgery (days) | Foot of lymphatic cannulation | Technical success of TL | Time of lymphatic opacification level from ethiodized oil injection (min) | | | | | Volume of ethiodized oil injected in TL (ml) | Definite ethiodized oil extravasation identified in fluoroscopy | Ectopic presence of the ethiodized oil in the pleural space identified in filling-phase CT | Ectopic presence of the ethiodized oil in the pleural space identified in nodal-phase CT | Treatment success | Time of drainage removal after TL (days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Knee joint space | Superior margin of femoral head | L5 | Th12 | Th5 | Left jugular venous angle | | | | | | |
| 1 | 20 | Right foot | Yes | 5 | 10 | 15 | 40 | 60 | 75 | 30.0 | Yes | Yes | n.a. | Yes | 7 |
| 2 | 31 | Left foot | Yes | 7 | 10 | 30 | 50 | 55 | 69 | 27.6 | No | No | No | Yes | 13 |
| 3 | 16 | Right foot | Yes | 3 | 9 | 22 | 45 | 52 | 70 | 28.0 | Yes | Yes | n.a. | Yes | 8 |
| 4 | 15 | Right foot | Yes | 3 | 10 | 18 | 33 | 48 | 55 | 22.0 | No | No | No | Yes | 7 |
| 5 | 16 | Right foot | Yes | 3 | 12 | 22 | 42 | 47 | 53 | 21.2 | Yes | Yes | n.a. | Yes | 4 |
| 6 | 20 | Left foot | Yes | 4 | 10 | 24 | 39 | 50 | 63 | 25.2 | Yes | Yes | n.a. | Yes | 5 |
| 7 | 22 | Right foot | Yes | 5 | 11 | 34 | 51 | 62 | 72 | 28.8 | Yes | Yes | n.a. | No | n.a. |
| Median (minimum-maximum) | 20 (15–31) | | | 4 (3–7) | 10 (9–12) | 22 (15–34) | 42 (33–51) | 52 (47–62) | 69 (53–75) | 27.6 (21.2–30) | | | | | 7 (4–13) |

*Filling-phase CT indicated simultaneous chest CT after TL, while nodal-phase CT indicated chest CT 24 h after TL (20). TL, transpedal lymphangiography; n.a., no applicable.*

## DISCUSSION

In this retrospective study, 5 and 2 patients had chylothorax complications after lung cancer and esophageal cancer resection, respectively, with a daily chyle output of more than 1,000 ml/d. After 15–31 days of ineffective conservative treatment, all patients received TL treatment with high-dose ethiodized oil application (>20 ml). The technical success was achieved in all patients, with the median volume of ethiodized oil injected in TL of 27.6 ml. The treatment success rate of TL was 86% (6/7). No Adverse event of TL was reported.

So far, TL has been increasingly used to manage postoperative chylothorax with a technical success rate of 95–100% (5, 6, 8, 9, 23). Except for the embolization effect, ethiodized oil can induce sterile inflammation at the fistula, beneficial for subsequent histological repair (8). However, the traditional manual injection of ethiodized oil in TL was unstable with the velocity between 0.2 and 0.5 ml/min and tiring over hours' operation (8, 21). So, we improved the injection method by connecting an infusion pump commonly used, replacing the primordial handy injection. This simple technical improvement can stabilize the injection pressure and velocity. Moreover, it benefits the standardization of TL procedure for the research purpose. For instance, the mean time of lymphatic visualization at different targets can be statistically analyzed: 10 min for superior margin of femoral head (groin region), 42 min for Th12 (cistern chyli region), and 69 min for left jugular venous angle (whole thoracic duct).

In previous studies, the ethiodized oil usage in TL was mostly around 10 ml (5, 8–11, 18, 20–22). But after accomplishment of injection, the ethiodized oil probably only reached pelvic or abdominal lymphatic vessels, so interventionalists always needed to monitor for more than 4 h until the ethiodized oil flowed into the thoracic duct (8, 11, 20–22). With the increase of ethiodized oil dose to more than 20 ml, we can visualize the left jugular vein angle as the endpoint of ethiodized oil injection, resulting in a more reliable thoracic duct embolization. It explained why the treatment success rate of TL for the high-flow postoperative chylothorax reached 86% (6/7) in our cohort, which was higher than 35% in previous reports (5, 10). Similarly, a recent report also showed that high-dose ethiodized oil (>40 ml) application in intranodal lymphangiography (INL) was feasible and safe (24). It achieved a treatment success rate of 83% without any adverse event for the treatment of high-flow postoperative chylothorax, similar to our findings (24). However, we need to point out: in INL, part of the ethiodized oil was wasted because of the extravasation from the punctured lymph node, so we can't confirm how much of the ethiodized oil genuinely entered the lymphatic system (8, 24). But in TL, the needle was fixed with suture resulting in a more reliable ethiodized oil injection without any waste, resulting in less usage of ethiodized oil than INL (21).

Nevertheless, the interventionalists need to pay attention to the risk of ectopic embolism caused by ethiodized oil. Although most ethiodized oil in TL is filtered and gradually resolved in lymph nodes, a small portion of ethiodized oil in the lymphatic vessels can enter the subclavian vein into the pulmonary circulation, which was filtered by a regular

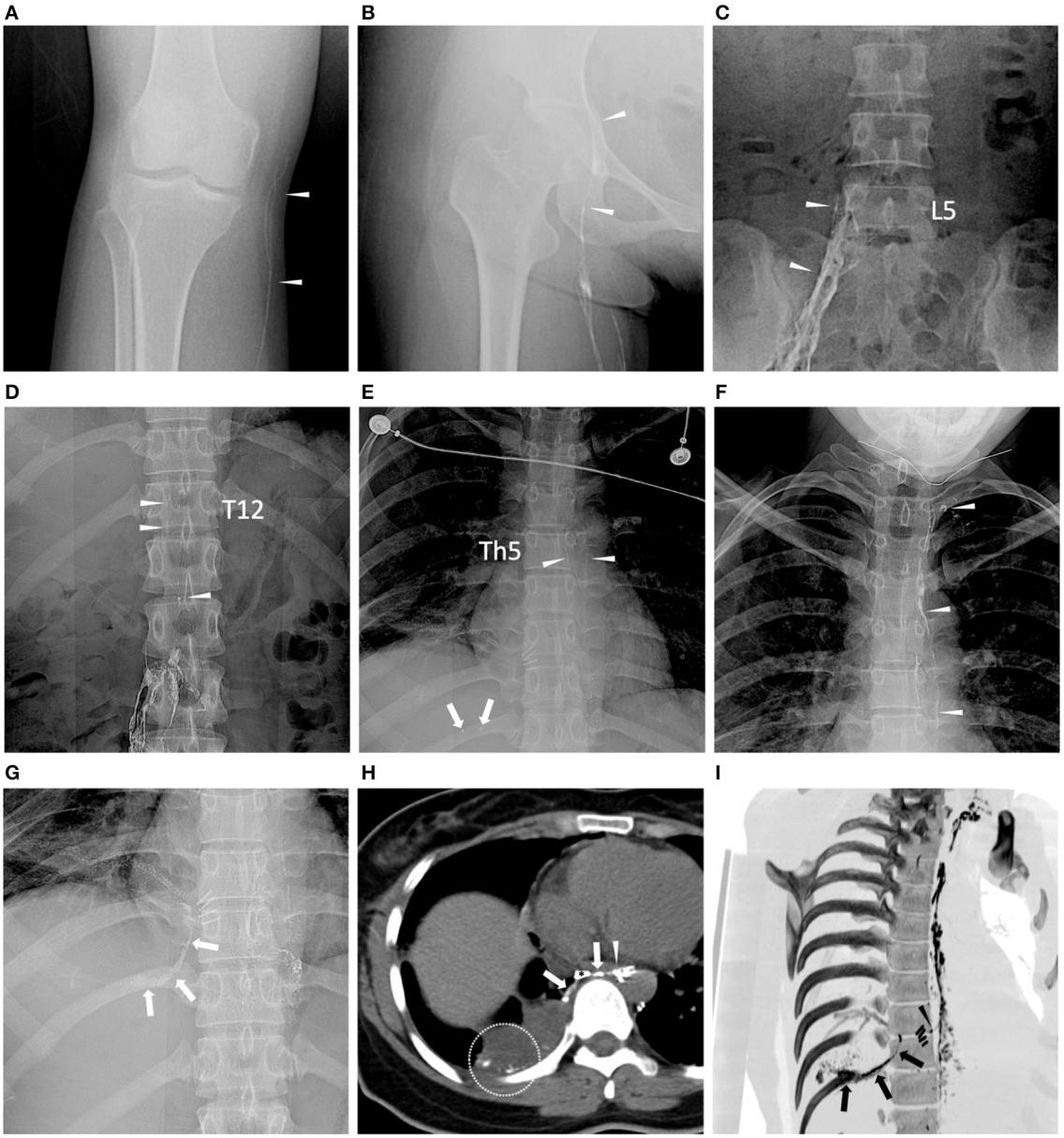


**FIGURE 2 |** Dynamic opacification of lymphatic vessels in fluoroscopy and chest CT. Images were obtained from the same patient with non-small cell lung carcinoma (*Patient ID: 3*). **(A–F)** 3, 9, 22, 45, 52, and 60 min after ethiodized oil injection, respectively, lymphatic vessels (white arrowheads) at the level of knee joint space, upper femoral head, L5, Th12 and Th5 vertebrae, and left jugular venous angle were consecutively opacified and dotted ethiodized oil extravasation [**(E)** white arrows) can be observed in the course. **(G)** After completing the ethiodized oil injection (28.0 ml), fluoroscopy demonstrated more definite ethiodized oil extravasation (white arrows). **(H)** Following CT (axial image with 5 mm thickness) after TL showed a rupture of the thoracic duct (white arrowhead) near the metal clips (*) and thread-like ethiodized oil extravasation (white arrows) can be observed, as well as the free ethiodized oil in the right pleural effusion (within the white circle). **(I)** Reconstructed oblique CT image with maximum Intensity projection (MIP) showed more intuitive opacification of the thoracic duct, leakage site (black arrowhead) near the metal clips, and the ethiodized oil extravasation in the right pleural cavity (black arrows). It indicated a possibility of iatrogenic damage to the thoracic duct in the surgery.

pulmonary capillary bed (25). But in patients with comorbidities, such as severe pulmonary dysfunction, pulmonary arteriovenous malformations, and right-to-left shunt heart disease, the ethiodized oil might enter systematic circulation leading to lethal cerebral embolism (11, 25, 26). So, strict clinical estimation before TL is essential.

Among the 7 patients, the lymphatic duct leakage presenting with definite ethiodized oil extravasation out from thoracic duct and the ectopic presence of the ethiodized oil in the pleural space was identified in 71% of patients (5/7), similar to 64–86% reported in the literature (10, 14, 21, 27). It implied an iatrogenic injury of the thoracic duct in the

prior surgeries. Chest CT after TL is routinely performed in our cohort because it has higher diagnostic sensitivity for leakage site identification than fluoroscopy. It can provide more explicitly anatomical details of the lymphatic system (20, 28, 29). If TL treatment fails, these CT data can also assist in planning further lymphatic interventional therapies, such as ALVS mentioned above and thoracic duct embolization (8, 9, 11, 20, 22).

This study has limitations. First, the sample size is minimal. Second, it lacks a comparison to conventional TL with ethiodized oil usage of <20 ml. In the cases with high-dose postoperative chylothorax (>1,000 ml/d), conventional TL showed a poor efficiency rate of about 35%, so it was rarely solo performed (5, 10). Instead, conventional TL with percutaneous lymphatic intervention (e.g., thoracic duct embolization or ALVS) was the optimal choice with a higher efficiency rate of 75–100% (9). However, by comparing the literature, the results of our study suggest that TL with high-dose ethiodized oil application probably has a better therapeutic effect.

In summary, the results in this preliminary study suggest TL with high-dose ethiodized oil is a feasible, safe, and effective method for treating high-flow postoperative chylothorax. It holds the potential as the second-line choice when conservative treatment fails. Besides, this study works out stable ethiodized oil injection using a commonly used infusion pump, advantaging TL performance.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

FP, LL, and XW contributed to the conception, design of the study, and wrote sections of the manuscript. WZ, DL, and LY collected, analyzed, and interpreted the data. All authors contributed to the article and approved the submitted version.

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# Predictors of a Minimal Clinically Important Difference Following Omalizumab Treatment in Adult Patients With Severe Allergic Asthma

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Several factors have been found to be predictors of a good response following omalizumab treatment in patients with severe allergic asthma (SAA). However, it remains unclear whether clinical characteristics can predict a minimal clinically important difference (MCID) following omalizumab treatment in this population. Therefore, the aim of this study was to investigate the features associated with an MCID following omalizumab treatment in adult patients with SAA. Of the 124 participants enrolled in this retrospective, cross-sectional study, 94, 103, 20 and 53 achieved the MCID following treatment with omalizumab and were considered to be responders of exacerbation reduction (no exacerbation during the 1-year follow-up period or ≧50% reduction in exacerbations from baseline), oral corticosteroid (OCS) sparing (no use of OCS to control asthma during the study period or a reduction of the monthly OCS maintenance dose to <50% of baseline), lung function (an increase of ≧230 ml in the forced expiratory volume in 1 s from baseline) and asthma control (an increase of ≧3 points in the asthma control test score from baseline), respectively. Normal weight [<25 vs. ≧30 kg/m$^2$, odds ratio (OR) = 3.86, $p$ = 0.024] was predictive of a responder of reduction in exacerbations following omalizumab treatment while subjects with a blood eosinophil level of

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<300 cells/μL (<300 vs. ≧300 cells/μL, OR = 5.81, $p = 0.001$) were more likely to exhibit an MCID in OCS sparing. No factor was found to be a predictor of lung function or asthma control. When choosing treatment for adult patients with SAA, our findings may help to select those who may benefit the most from omalizumab treatment.

**Keywords: anti-IgE, asthma, minimal clinically important difference (MCID), omalizumab, predictor**

## INTRODUCTION

Asthma is a heterogeneous respiratory disease that involves airflow limitation due to chronic airway inflammation. It has been reported to affect 1–18% of the general population and is categorized into five Global Initiative for Asthma (GINA) steps (Step 1–5) based on the strength of treatment needed to control symptoms and exacerbations. Severe asthma, defined as asthma which cannot be controlled despite the use of GINA Step 4 or 5 pharmacological therapies, good inhaler technique and adherence, and optimal management of contributory factors, is estimated to occur in 3.6% of asthmatic patients (1, 2).

Omalizumab is an anti-immunoglobulin E (IgE) monoclonal antibody that reduces circulatory free IgE, and it is approved for the treatment of moderate to severe IgE-mediated asthma. The GINA recommendations suggest the use of omalizumab as add-on therapy for severe asthma owing to its noticeable impact on medical resource utilization, quality of life and beneficial treatment outcomes, including improved exacerbation rate, reduced oral corticosteroid (OCS) maintenance dose, better asthma control and improvements in lung function in both adult and pediatric patients with severe allergic asthma (SAA) (1, 3–10).

The statistical significance is the most widely used evidence to guide treatment decision making in both clinical trials and daily practice while this does not necessarily imply the clinical relevance. To overcome this gap, it is crucial to determine the minimal clinically important difference (MCID), first described in 1989 by Jaeschke et al. and defined as the smallest improvement in a treatment outcome considered worthwhile by an individual patient, for healthcare providers. Several MCID cut-off values have been proposed and validated in the population of asthma, with most of the cut-offs are associated with patient-reported outcomes, lung function and exercise tolerance (11–14). Nevertheless, the MCID has rarely used as a tool for assessing the treatment response of biologics for patients with severe asthma.

The GINA guidelines state that a blood eosinophil count ≧260 cells/μL, a fractional exhaled nitric oxide (FeNO) level ≧20 parts per billion, the presence of allergen-driven symptoms, and childhood-onset asthma are statistically significant predictors for a good therapeutic response to omalizumab in reducing exacerbations for patients with SAA (1). However, little is known about whether clinical characteristics are associated with the MCIDs, particularly those regarding the goals of asthma management proposed by the GINA strategy (1), following treatment with omalizumab in this population.

We hypothesized that the baseline clinical features could predict a worthwhile response to omalizumab as an add-on therapy for patients with SAA. Therefore, we investigated the pre-omalizumab treatment clinical characteristics associated with an MCID in reducing exacerbations, OCS sparing, and improvements in lung function and asthma control, the most representative and clinically vital treatment goals recommended by the GINA strategy (1), following treatment with omalizumab in adult patients with SAA.

## MATERIALS AND METHODS

### Study Design, Setting, and Population

This retrospective cross-sectional study was approved by the Institutional Review Board and Ethics Committee of Taichung Veterans General Hospital (TCVGH) (Approval No. CE19015B) and implemented in accordance with the Declaration of Helsinki. The need for informed consent from participants was waived because of the retrospective nature of this study and data extraction based on an electronic medical chart review. The study was conducted at TCVGH, a tertiary referral center in central Taiwan, be-tween January 2010 and January 2019, and enrolled patients diagnosed of SAA who applied for reimbursements for omalizumab from the Taiwan National Health Insurance (NHI) according to the judgment of very experienced pulmonologists and immunologists in charge of asthma management. Patients whose applications were not ap-proved were excluded from this study (8).

### Data Collection

As detailed elsewhere (8), the investigators collected clinical data, including base-line demographics, clinical features and laboratory findings, medications related to asthma management, and co-morbidities for each participant. Moreover, the treatment outcomes of interest, including exacerbation history, usage of OCSs, spirometric data and asthma control test (ACT) scores were also recorded at baseline and the end of 1-year follow-up (8).

### Definition of MCID (Responder) According to Treatment Outcome of Interest

Responders with regards to a reduction in exacerbations were defined as those who had no exacerbations during the study period or who had a ≧50% reduction in the number of exacerbations in the 1-year follow-up period compared to the year prior to enrollment. An exacerbation was defined as a worsening of respiratory symptoms and lung function that required OCS treatment for ≧3 days at an outpatient service, emergency visit or hospitalization (15, 16). The patients who did not meet these criteria were defined as non-responders.

Responders with regards to OCS sparing were defined as those who did not use OCS to control asthma during the study period, or whose monthly OCS maintenance dose at the end of study was <50% compared to that at enrollment. Maintenance pharmacological therapy for SAA was defined as >7 days of OCS prescriptions in the outpatient department. The patients who did not meet these criteria were defined as non-responders.

The patients with an MCID according to lung function and ACT following omalizumab treatment were defined as those with an increase of ≧230 ml and ≧3 points in the forced expiratory volume in 1 s (FEV1) and ACT score, respectively, between the end and start of the 1-year follow-up period (13, 14). The patients who did not meet these criteria were defined as non-responders.

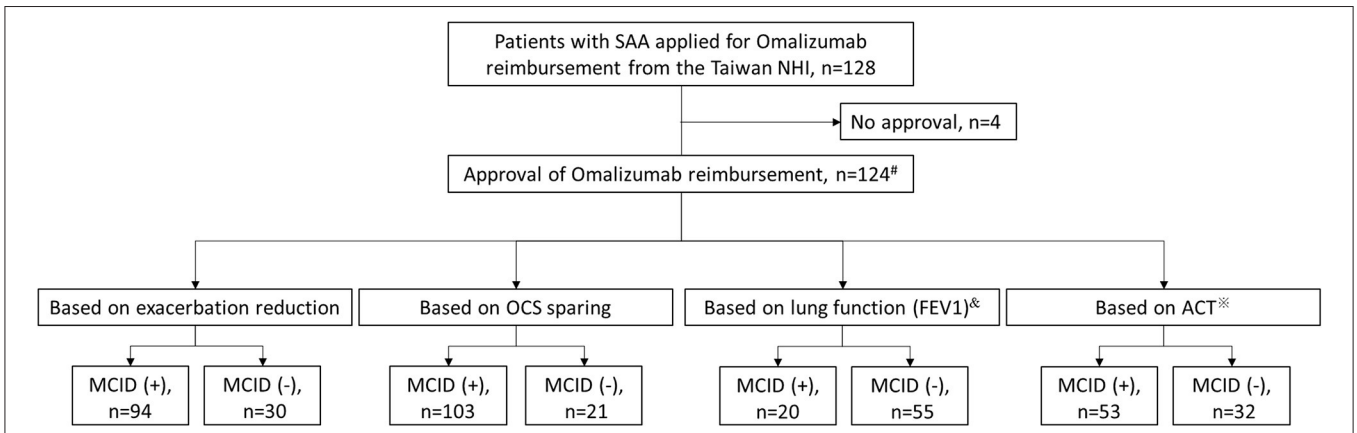


**FIGURE 1 |** Patient enrolment flow chart. #14 patients received omalizumab for only 4 months because of administrative issues from the Taiwan NHI, while the rest had at least 10 months of omalizumab treatment during the 1-year follow-up period. &Only 75 patients had binary results of lung function measurement for analysis. ※Only 85 patients had binary results of ACT for analysis. ACT, asthma control test; FEV1, forced expiratory volume in 1 s; MCID, minimal clinically important difference; NHI, National Health Insurance; OCS, oral corticosteroid; SAA, severe allergic asthma.

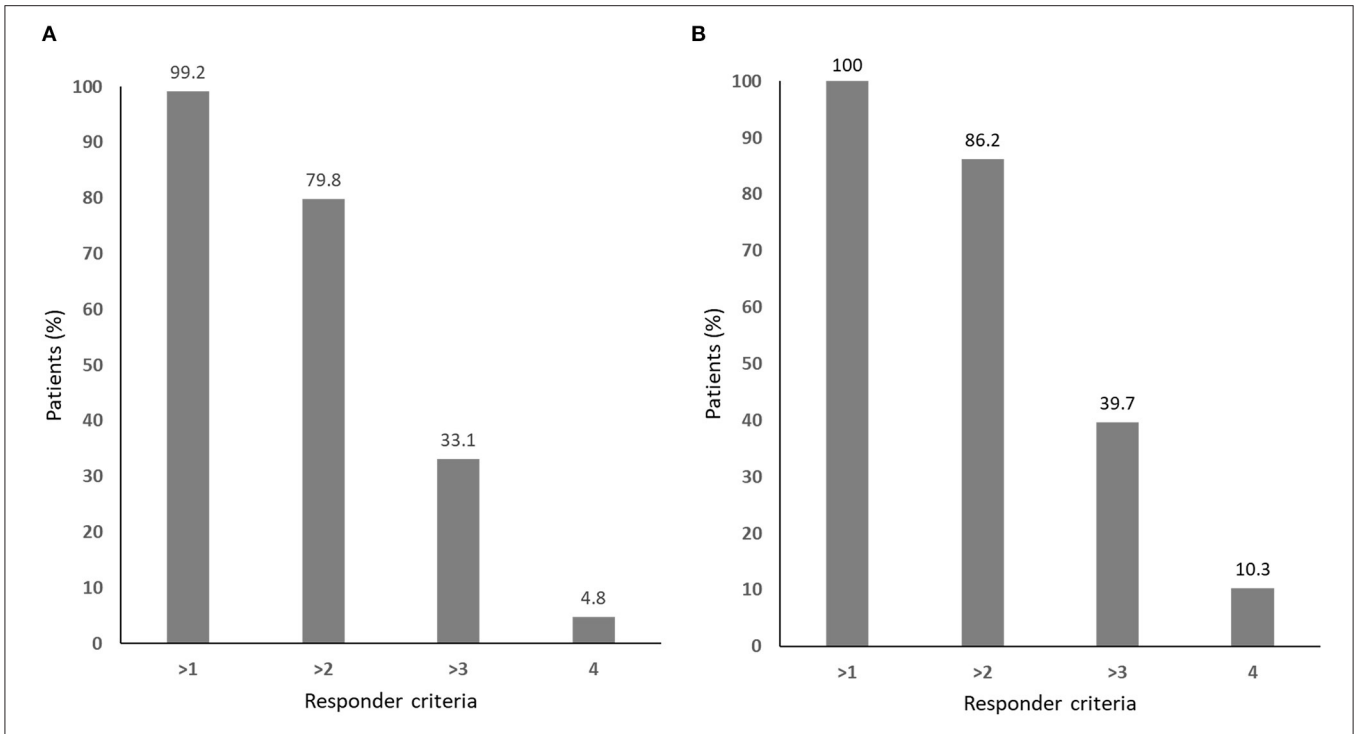


**FIGURE 2 |** The responder distribution for **(A)** all patients ($n$ = 124) and **(B)** those without missing values in any of the four responder criteria ($n$ = 58).

**TABLE 1 |** Baseline information of the enrolled participants and the responder analysis based on exacerbation reduction and oral corticosteroid sparing.

| | Exacerbation reduction | | | OCS sparing | | | |
|---|---|---|---|---|---|---|---|
| | **Responder (*n* = 94)** | **Non-responder (*n* = 30)** | ***p*-value** | **Responder (*n* = 103)** | **Non-responder (*n* = 21)** | ***p*-value** | **Total (*n* = 124)** |
| **Age (years)** | | | 0.303 | | | 0.886 | |
| Mean ± SD | 61.4 ± 15.9 | 58.9 ± 15.3 | | 60.7 ± 16.0 | 61.6 ± 14.7 | | 60.8 ± 15.7 |
| Median (Q1, Q3) | 64.0 (50.8, 74.0) | 57.0 (48.5, 68.3) | | 62.0 (50.0, 71.0) | 61.0 (50.5, 73.5) | | 62.0 (50.0, 71.0) |
| Male gender | 49 (52.1%) | 18 (60.0%) | 0.587 | 56 (54.4%) | 11 (52.4%) | 1.000 | 67 (54.0%) |
| **BMI (kg/m$^2$)#** | | | 0.032* | | | 0.792 | |
| Mean ± SD | 25.8 ± 4.3 | 27.6 ± 4.5 | | 26.2 ± 4.5 | 26.0 ± 4.2 | | 26.2 ± 4.4 |
| Median (Q1, Q3) | 25.0 (22.5, 28.3) | 26.4 (25.1, 30.1) | | 25.3 (23.3, 29.6) | 25.6 (22.6, 27.5) | | 25.3 (23.1, 29.4) |
| <25 | 47 (50.0%) | 6 (20.0%) | | 44 (42.7%) | 9 (42.9%) | | 53 (42.7%) |
| ≧25, <30 | 28 (29.8%) | 15 (50.0%) | | 35 (34.0%) | 8 (38.1%) | | 43 (34.7%) |
| ≧30 | 19 (20.2%) | 9 (30.0%) | | 24 (23.3%) | 4 (19.0%) | | 28 (22.6%) |
| **Smoking (pack-year)** | | | 0.046* | | | 0.837 | |
| Mean ± SD | 7.3 ± 14.6 | 15.7 ± 28.0 | | 9.9 ± 20.3 | 6.4 ± 10.1 | | 9.3 ± 19.0 |
| Median (Q1, Q3) | 0.0 (0.0, 10.0) | 0.0 (0.0, 22.5) | | 0.0 (0.0, 10.0) | 0.0 (0.0, 20.0) | | 0.0 (0.0, 13.8) |
| ≧10 | 24 (25.5%) | 11 (36.7%) | | 29 (28.2%) | 6 (28.6%) | | 35 (28.2%) |
| **Smoking history** | | | 0.139 | | | 0.500 | |
| Never smoker | 66 (70.2%) | 16 (53.3%) | | 68 (66.0%) | 14 (66.7%) | | 82 (66.1%) |
| Ex-smoker | 25 (26.6%) | 11 (36.7%) | | 29 (28.2%) | 7 (33.3%) | | 36 (29.0%) |
| Current smoker | 3 (3.2%) | 3 (10.0%) | | 6 (5.8%) | 0 (0.0%) | | 6 (4.8%) |
| **Time for asthma history (years)** | | | 0.407 | | | 0.934 | |
| Mean ± SD | 3.7 ± 3.6 | 4.0 ± 3.2 | | 3.8 ± 3.6 | 3.7 ± 3.1 | | 3.7 ± 3.5 |
| Median (Q1, Q3) | 2.6 (0.8, 5.4) | 3.5 (0.9, 6.6) | | 2.9 (0.8, 5.7) | 2.0 (0.9, 6.1) | | 2.8 (0.9, 5.8) |
| Total IgE (kU/L) | | | 0.764 | | | 0.813 | |
| Mean ± SD | 750.3 ± 723.8 | 722.3 ± 757.4 | | 725.2 ± 693.8 | 833.4 ± 896.4 | | 743.5 ± 729.0 |
| Median (Q1, Q3) | 530.0 (259.0, 985.5) | 464.5 (287.0, 856.8) | | 510.0 (269.0, 954.0) | 472.0 (317.0, 1050.0) | | 507.5 (274.8, 968.3) |
| WBC ($10^9$/L) | | | 0.171 | | | 0.757 | |
| Mean ± SD | 8.1 ± 2.5 | 9.5 ± 3.9 | | 8.5 ± 3.0 | 8.2 ± 2.7 | | 8.5 ± 2.9 |
| Median (Q1, Q3) | 7.7 (6.4, 9.0) | 7.9 (6.5, 12.6) | | 7.7 (6.5, 9.9) | 8.0 (6.3, 9.0) | | 7.9 (6.5, 9.8) |
| **Blood absolute eosinophil count (cells/μL)** | | | 0.117 | | | 0.003* | |
| Mean ± SD | 422.4 ± 893.2 | 338.3 ± 539.8 | | 362.5 ± 854.7 | 596.0 ± 606.1 | | 402.1 ± 820.5 |
| Median (Q1, Q3) | 236.0 (129.3, 418.7) | 135.8 (73.4, 443.3) | | 205.2 (109.3, 364.0) | 518.4 (206.8, 793.6) | | 223.2 (111.3, 422.2) |
| ≧300 | 36 (38.3%) | 10 (33.3%) | | 31 (30.1%) | 15 (71.4%) | | 46 (37.1%) |
| **Number of allergens tested** | | | 1.000 | | | 0.245 | |
| Mean ± SD | 1.9 ± 1.6 | 1.9 ± 1.4 | | 2.0 ± 1.5 | 1.6 ± 1.6 | | 1.9 ± 1.5 |
| Median (Q1, Q3) | 2.0 (1.0, 3.0) | 2.0 (1.0, 3.0) | | 2.0 (1.0, 3.0) | 1.0 (0.0, 3.0) | | 2.0 (1.0, 3.0) |
| **Initial Omalizumab dose (mg/month)** | | | 0.488 | | | 0.362 | |
| Mean ± SD | 447.7 ± 227.3 | 478.5 ± 232.4 | | 465.8 ± 239.1 | 406.3 ± 161.4 | | 455.4 ± 228.0 |
| Median (Q1, Q3) | 450.0 (300.0, 600.0) | 450.0 (300.0, 600.0) | | 450.0 (300.0, 600.0) | 450.0 (300.0, 525.0) | | 450.0 (300.0, 600.0) |
| **Inhaled medication** | | | 1.000 | | | 0.475 | |
| Medium-dose ICS/LABA ± Tiotropium | 40 (42.6%) | 13 (43.3%) | | 46 (44.7%) | 7 (33.3%) | | 53 (42.7%) |
| High-dose ICS/LABA ± Tiotropium | 54 (57.4%) | 17 (56.7%) | | 57 (55.3%) | 14 (66.7%) | | 71 (57.3%) |
| **Oral medication** | | | 0.296 | | | 0.235 | |
| None | 7 (9.4%) | 4 (13.3%) | | 10 (9.7%) | 1 (4.8%) | | 11 (8.9%) |
| Montelukast alone | 53 (56.4%) | 20 (66.7%) | | 59 (57.3%) | 14 (66.7%) | | 73 (58.9%) |
| Methylxanthines alone | 12 (12.8%) | 1 (3.3%) | | 9 (8.7%) | 4 (19.0%) | | 13 (10.5%) |
| Montelukast + Methylxanthines | 22 (23.4%) | 5 (16.7%) | | 25 (24.3%) | 2 (9.5%) | | 27 (21.8%) |
| **OCS maintenance dose (mg/month)** | | | 0.351 | | | 0.173 | |

*(Continued)*

**TABLE 1 |** Continued

| | Exacerbation reduction | | | OCS sparing | | | |
|---|---|---|---|---|---|---|---|
| | **Responder (*n* = 94)** | **Non-responder (*n* = 30)** | ***p*-value** | **Responder (*n* = 103)** | **Non-responder (*n* = 21)** | ***p*-value** | **Total (*n* = 124)** |
| Mean ± SD | 94.8 ± 191.8 | 98.0 ± 173.0 | | 94.0 ± 194.6 | 103.3 ± 146.2 | | 95.6 ± 186.8 |
| Median (Q1, Q3) | 0.0 (0.0, 140.0) | 0.0 (0.0, 140.0) | | 0.0 (0.0, 140.0) | 0.0 (0.0, 210.0) | | 0.0 (0.0, 140.0) |
| Early cessation of Xolair treatment | 12 (12.8%) | 2 (6.7%) | 0.515 | 12 (11.7%) | 2 (9.5%) | 1.000 | 14 (11.3%) |
| **Co-morbidity** | | | | | | | |
| Depression | 19 (20.2%) | 4 (13.3%) | 0.566 | 16 (15.5%) | 7 (33.3%) | 0.068 | 23 (18.5%) |
| Insomnia | 21 (22.3%) | 5 (16.7%) | 0.684 | 22 (21.4%) | 4 (19.0%) | 1.000 | 26 (21.0%) |
| Osteoporosis | 10 (10.6%) | 2 (6.7%) | 0.729 | 9 (8.7%) | 3 (14.3%) | 0.426 | 12 (9.7%) |
| Cerebrovascular disease | 9 (9.6%) | 5 (16.7%) | 0.324 | 11 (10.7%) | 3 (14.3%) | 0.705 | 14 (11.3%) |
| GERD | 26 (27.7%) | 11 (36.7%) | 0.478 | 30 (29.1%) | 7 (33.3%) | 0.903 | 37 (29.8%) |
| COPD | 26 (27.7%) | 10 (33.3%) | 0.715 | 30 (29.1%) | 6 (28.6%) | 1.000 | 36 (29.0%) |
| DM | 18 (19.1%) | 5 (16.7%) | 0.972 | 18 (17.5%) | 5 (23.8%) | 0.540 | 23 (18.5%) |
| Food or drug allergy | 7 (7.4%) | 3 (10.0%) | 0.703 | 9 (8.7%) | 1 (4.8%) | 1.000 | 10 (8.1%) |
| Atopic disease※ | 82 (87.2%) | 28 (93.3%) | 0.515 | 91 (88.3%) | 19 (90.5%) | 1.000 | 110 (88.7%) |
| AERD | 1 (1.1%) | 0 (0.0%) | 1.000 | 1 (1.0%) | 0 (0.0%) | 1.000 | 1 (0.8%) |
| OSAS | 5 (5.3%) | 0 (0.0%) | 0.335 | 4 (3.9%) | 1 (4.8%) | 1.000 | 5 (4.0%) |

*$p < 0.05$.

#*Categorized based on the World Health Organization recommendations.*

※*Atopic disease included allergic dermatitis, allergic rhinitis, allergic conjunctivitis and food allergies.*

*AERD, aspirin-exacerbated respiratory disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; GERD, gastro-esophageal reflux disease; ICS, inhaled corticosteroid; IgE, immunoglobulin E; LABA, long-acting beta-agonist; OCS, oral corticosteroid; OSAS, obstructive sleep apnea syndrome; Q, quartile; SD, standard deviation; WBC, white blood count.*

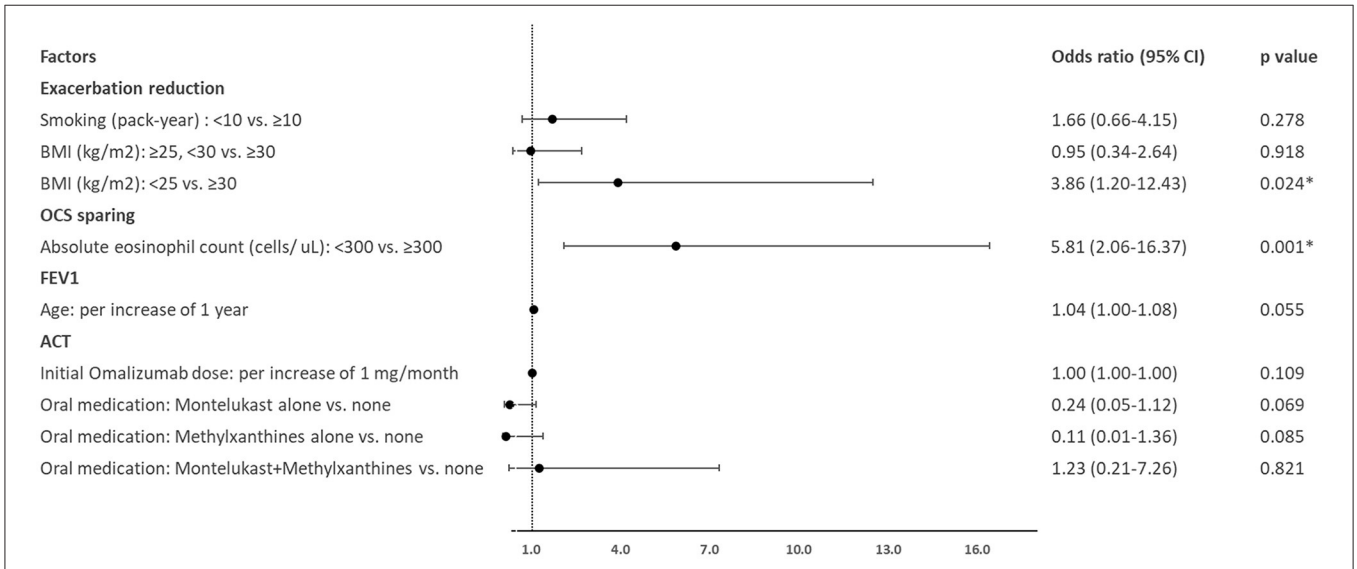


**FIGURE 3 |** The factors associated with a minimal clinically important difference according to the treatment outcome of interest. ACT, asthma control test; BMI, body mass index; CI, confidence interval; FEV1, forced expiratory volume in 1 s; OCS, oral corticosteroid. *$p < 0.05$.

## Statistical Analysis

Categorical variables were presented as frequency and percentage and compared using the chi-squared test between the responders and non-responders. Continuous variables were presented using mean and standard deviation, and median and inter-quartile range, and were compared using a paired sample *t*-test or Wilcoxon signed-rank-test according to the normality assumption between the study groups. Logistic regression models were used to analyze independent factors if they were significant in the univariate analysis for patients with binary results of

**TABLE 2 |** The factors associated with the responder of lung function improvement.

| | FEV1 | | | |
|---|---|---|---|---|
| | **Responder ($n = 20$)** | **Non-responder ($n = 55$)** | ***p*-value** | **Total ($n = 75$)** |
| **Age (years)** | | | 0.047* | |
| Mean ± SD | 56.3 ± 17.5 | 63.8 ± 13.2 | | 61.8 ± 14.7 |
| Median (Q1, Q3) | 54.5 (42.5, 71.5) | 65.0 (55.0, 70.0) | | 63.0 (51.0, 70.0) |
| Male gender | 12 (60.0%) | 27 (49.1%) | 0.565 | 39 (52.0%) |
| **BMI (kg/m$^2$)** | | | 0.848 | |
| Mean ± SD | 27.2 ± 5.3 | 26.6 ± 4.4 | | 26.8 ± 4.6 |
| Median (Q1, Q3) | 26.0 (24.0, 30.5) | 26.3 (23.4, 29.9) | | 26.3 (23.5, 30.2) |
| **Smoking (pack-year)** | | | 0.875 | |
| Mean ± SD | 9.9 ± 13.8 | 10.4 ± 18.4 | | 10.3 ± 17.2 |
| Median (Q1, Q3) | 0.0 (0.0, 20.0) | 0.0 (0.0, 20.0) | | 0.0 (0.0, 20.0) |
| **Smoking history** | | | 0.545 | |
| Never smoker | 12 (60.0%) | 34 (61.8%) | | 46 (61.3%) |
| Ex-smoker | 6 (30.0%) | 19 (34.5%) | | 25 (33.3%) |
| Current smoker | 2 (10.0%) | 2 (3.6%) | | 4 (5.3%) |
| **Time for asthma history (years)** | | | 0.679 | |
| Mean ± SD | 3.2 ± 2.8 | 4.2 ± 4.2 | | 3.9 ± 3.9 |
| Median (Q1, Q3) | 2.3 (0.8, 5.2) | 2.8 (0.7, 6.6) | | 2.8 (0.8, 6.5) |
| **Total IgE (kU/L)** | | | 0.774 | |
| Mean ± SD | 614.2 ± 443.3 | 670.0 ± 530.0 | | 655.1 ± 506.0 |
| Median (Q1, Q3) | 425.0 (311.0, 836.8) | 532.0 (219.0, 875.0) | | 510.0 (289.0, 860.0) |
| **WBC ($10^9$/L)** | | | 0.679 | |
| Mean ± SD | 9.0 ± 2.9 | 8.8 ± 3.4 | | 8.9 ± 3.2 |
| Median (Q1, Q3) | 8.2 (6.6, 11.9) | 7.9 (6.4, 10.6) | | 7.9 (6.5, 10.8) |
| **Blood absolute eosinophil count (cells/μL)** | | | 0.375 | |
| Mean ± SD | 496.6 ± 671.3 | 319.2 ± 427.6 | | 366.5 ± 505.3 |
| Median (Q1, Q3) | 265.7 (111.8, 576.1) | 207.9 (111.2, 352.8) | | 220.0 (111.7, 384.0) |
| **Number of allergens tested** | | | 0.686 | |
| Mean ± SD | 2.1 ± 1.7 | 1.9 ± 1.4 | | 1.9 ± 1.5 |
| Median (Q1, Q3) | 2.0 (1.0, 3.0) | 2.0 (1.0, 3.0) | | 2.0 (1.0, 3.0) |
| **Initial omalizumab dose (mg/month)** | | | 0.725 | |
| Mean ± SD | 443.4 ± 156.8 | 435.6 ± 226.2 | | 437.7 ± 208.9 |
| Median (Q1, Q3) | 450.0 (300.0, 600.0) | 412.5 (300.0, 600.0) | | 450.0 (300.0, 600.0) |
| **Inhaled medication** | | | 0.522 | |
| Medium-dose ICS/LABA ± Tiotropium | 4 (20.0%) | 17 (30.9%) | | 21 (28.0%) |
| High-dose ICS/LABA ± Tiotropium | 16 (80.0%) | 38 (69.1%) | | 54 (72.0%) |
| **Oral medication** | | | 0.833 | |
| None | 2 (10.0%) | 6 (10.9%) | | 8 (10.7%) |
| Montelukast alone | 14 (70.0%) | 33 (60.0%) | | 47 (62.7%) |
| Methylxanthines alone | 2 (10.0%) | 6 (10.9%) | | 8 (10.7%) |
| Montelukast + Methylxanthines | 2 (10.0%) | 10 (18.2%) | | 12 (16.0%) |
| Initial OCS maintenance dose (mg/month) | | | 0.519 | |
| Mean ± SD | 87.5 ± 191.2 | 64.0 ± 129.3 | | 70.3 ± 147.3 |
| Median (Q1, Q3) | 0.0 (0.0, 140.0) | 0.0 (0.0, 140.0) | | 0.0 (0.0, 140.0) |
| Early cessation of Xolair treatment | 2 (10.0%) | 5 (9.1%) | 1.000 | 7 (9.3%) |
| **Co-morbidity** | | | | |
| Depression | 1 (5.0%) | 8 (14.5%) | 0.430 | 9 (12.0%) |
| Insomnia | 2 (10.0%) | 12 (21.8%) | 0.328 | 14 (18.7%) |
| Osteoporosis | 2 (10.0%) | 5 (9.1%) | 1.000 | 7 (9.3%) |
| Cerebrovascular disease | 1 (5.0%) | 5 (9.1%) | 1.000 | 6 (8.0%) |

*(Continued)*

**TABLE 2** | Continued

| | FEV1 | | | |
|---|---|---|---|---|
| | **Responder ($n = 20$)** | **Non-responder ($n = 55$)** | ***p*-value** | **Total ($n = 75$)** |
| GERD | 7 (35.0%) | 17 (30.9%) | 0.955 | 24 (32.0%) |
| COPD | 4 (20.0%) | 19 (34.5%) | 0.355 | 23 (30.7%) |
| DM | 2 (10.0%) | 9 (16.4%) | 0.717 | 11 (14.7%) |
| Food or drug allergy | 3 (15.0%) | 2 (3.6%) | 0.114 | 5 (6.7%) |
| Atopic disease※ | 19 (95.0%) | 49 (89.1%) | 0.667 | 68 (90.7%) |
| AERD | 1 (5.0%) | 0 (0.0%) | 0.267 | 1 (1.3%) |
| OSAS | 0 (0.0%) | 3 (5.5%) | 0.560 | 3 (4.0%) |

*$p < 0.05$.
※*Atopic disease included allergic dermatitis, allergic rhinitis, allergic conjunctivitis and food allergies.*
*FEV1, forced expiratory volume in 1 s; also see **Table 1**.*

treatment outcomes of interest. A significant difference was defined as a two-sided $p$-value $< 0.05$. The data of all patients were de-identified before analysis.

## RESULTS

**Figure 1** shows the patient enrolment flow chart. Of the 128 patients with SAA who applied for reimbursements for omalizumab during the study period, 124 received approval and were included in the final analysis. Among the 124 enrollees, 110 patients received omalizumab treatment for at least 10 months during the 1-year follow-up period while 14 subjects received only 4 months of omalizumab because of the administrative issue from the Taiwan NHI (8). Only 75 and 85 patients had binary results of lung function measurements and ACT scores, respectively, at enrollment and the end of the 1-year follow-up period for further investigation. Of the 124 patients, 94 (75.8%), 103 (83.1%), 20 (26.7%), and 53 (62.4%) were identified as responders according to a reduction in exacerbations, OCS sparing, and improvements in lung function and asthma control, respectively.

Nearly all of the patients met one or more of the responder criteria, while only 4.8% of the patients with complete data and 10.3% of the those with missing values met all four responder criteria, respectively (**Figure 2**).

The mean age of the 124 patients was 60.8 ± 15.7 years (**Table 1**). More than a quarter of the patients had substantial smoking exposure, defined as ≧10 pack-years of cigarette smoking in their lifetime (35/124, 28.2%), while less than half were normal weight, de-fined as a body mass index <25 kg/m$^2$ (53/124, 42.7%). Furthermore, of the 124 patients, 46 (37.1%) had blood eosinophilia of ≧300 cells/μL (**Table 1**).

Compared to the non-responders regarding reduction in exacerbations, the responders had a significantly higher and lower proportion of normal weight and substantial smoking exposure, respectively (**Table 1**), while the former was independently associated with an MCID in a reduction in exacerbations (**Figure 3**).

Responders with OCS sparing had a lower blood eosinophil level expressed by absolute count (cells/μL) compared to the non-responders (**Table 1**). The logistic regression analysis showed that <300 cells/μL of circulating eosinophils was a significant predictor of an MCID in the sparing of OCS to control asthma (**Figure 3**).

The patients who exhibited an MCID in FEV1 improvement following omalizumab treatment were younger than those who did not (**Table 2**), although a younger age was not independently predictive of this treatment outcome (**Figure 3**).

The responders with an improvement in ACT following omalizumab treatment were associated with a higher initial dose of omalizumab and more use of either montelukast alone or methylxanthines alone to control asthma (**Table 3**). None of these characteristics could independently predict an MCID in an improvement in ACT score (**Figure 3**).

## DISCUSSION

In this study of 124 adult patients with SAA, 75.8, 83.1, 26.7, and 62.4% were considered to be responders following omalizumab treatment according to a reduction in exacerbations, OCS sparing, and improvements in lung function and asthma control, respectively. The responders with a reduction in exacerbations were characterized by normal weight and less smoking exposure; OCS sparing by a lower blood eosinophil level; lung function improvement by a younger age; and asthma control improvement by a higher initial dose of omalizumab and more use of either montelukast alone or methylxanthines alone to control asthma. In addition, normal weight was a significant predictor of an MCID in a reduction in exacerbations following omalizumab treatment; a circulatory eosinophil level of <300 cells/μL in OCS sparing; and none in improvements in lung function or asthma control.

Our results showed that normal weight and less smoking exposure were associated with an MCID in a reduction in the annual number of exacerbations, and the former was an independent predictor. In contrast to our study, Casale et al. enrolled a relatively young population (a mean age of 47.3 years) with allergic asthma who were candidates for omalizumab treatment, and found that those with an increased number of exacerbations in the year prior to the study as well as female

**TABLE 3 |** The responder analysis for the asthma control improvement.

| | ACT | | | |
|---|---|---|---|---|
| | **Responder ($n = 53$)** | **Non-responder ($n = 32$)** | ***p*-value** | **Total ($n = 85$)** |
| **Age (years)** | | | 0.993 | |
| Mean ± SD | 63.0 ± 14.6 | 62.6 ± 15.4 | | 62.9 ± 14.8 |
| Median (Q1, Q3) | 62.0 (52.5, 74.5) | 64.0 (51.3, 76.5) | | 63.0 (51.5, 75.5) |
| Male gender | 28 (52.8%) | 21 (65.6%) | 0.352 | 49 (57.6%) |
| **BMI (kg/m$^2$)** | | | 0.910 | |
| Mean ± SD | 26.9 ± 4.8 | 26.9 ± 4.1 | | 26.9 ± 4.5 |
| Median (Q1, Q3) | 26.5 (22.8, 30.3) | 26.0 (23.8, 29.9) | | 26.3 (23.4, 30.0) |
| **Smoking (pack-year)** | | | 0.209 | |
| Mean ± SD | 11.8 ± 24.5 | 11.7 ± 16.7 | | 11.8 ± 21.8 |
| Median (Q1, Q3) | 0.0 (0.0, 20.0) | 0.5 (0.0, 20.0) | | 0.0 (0.0, 20.0) |
| **Smoking history** | | | 0.220 | |
| Never smoker | 36 (67.9%) | 16 (50.0%) | | 52 (61.2%) |
| Ex-smoker | 15 (28.3%) | 13 (40.6%) | | 28 (32.9%) |
| Current smoker | 2 (3.8%) | 3 (9.4%) | | 5 (5.9%) |
| **Time for asthma history (years)** | | | 0.083 | |
| Mean ± SD | 3.4 ± 3.6 | 4.3 ± 3.1 | | 3.7 ± 3.4 |
| Median (Q1, Q3) | 1.9 (0.6, 5.0) | 4.1 (1.5, 6.6) | | 2.9 (0.8, 6.1) |
| **Total IgE (kU/L)** | | | 0.116 | |
| Mean ± SD | 878.8 ± 886.4 | 605.2 ± 638.7 | | 775.8 ± 809.2 |
| Median (Q1, Q3) | 538.0 (326.0, 1026.0) | 431.5 (205.5, 847.8) | | 505.0 (285.0, 903.0) |
| **WBC (10$^9$/L)** | | | 0.098 | |
| Mean ± SD | 8.2 ± 3.1 | 9.2 ± 3.1 | | 8.6 ± 3.1 |
| Median (Q1, Q3) | 7.5 (5.9, 9.9) | 8.3 (7.1, 11.3) | | 7.9 (6.4, 10.5) |
| **Blood absolute eosinophil count (cells/μL)** | | | 0.608 | |
| Mean ± SD | 304.0 ± 285.5 | 391.5 ± 538.8 | | 336.9 ± 399.2 |
| Median (Q1, Q3) | 226.1 (114.7, 378.8) | 248.0 (111.4, 412.7) | | 241.7 (111.6, 394.7) |
| **Number of allergens tested** | | | 0.934 | |
| Mean ± SD | 2.0 ± 1.6 | 2.1 ± 1.7 | | 2.1 ± 1.6 |
| Median (Q1, Q3) | 2.0 (1.0, 3.0) | 2.0 (1.0, 3.0) | | 2.0 (1.0, 3.0) |
| **Initial Omalizumab dose (mg/month)** | | | 0.041* | |
| Mean ± SD | 488.5 ± 193.3 | 408.6 ± 240.2 | | 459.2 ± 213.7 |
| Median (Q1, Q3) | 550.0 (300.0, 600.0) | 300.0 (300.0, 600.0) | | 450.0 (300.0, 600.0) |
| **Inhaled medication** | | | 0.331 | |
| Medium-dose ICS/LABA ± Tiotropium | 20 (37.7%) | 8 (25.0%) | | 28 (32.9%) |
| High-dose ICS/LABA ± Tiotropium | 33 (62.3%) | 24 (75.0%) | | 57 (67.1%) |
| **Oral medication** | | | 0.020* | |
| None | 4 (7.5%) | 5 (15.6%) | | 9 (10.6%) |
| Montelukast alone | 37 (69.8%) | 15 (46.9%) | | 52 (61.2%) |
| Methylxanthines alone | 6 (11.3%) | 1 (3.1%) | | 7 (8.2%) |
| Montelukast + Methylxanthines | 6 (11.3%) | 11 (34.4%) | | 17 (20.0%) |
| **Initial OCS maintenance dose (mg/month)** | | | 0.288 | |
| Mean ± SD | 50.2 ± 89.1 | 127.5 ± 233.2 | | 79.3 ± 162.5 |
| Median (Q1, Q3) | 0.0 (0.0, 122.5) | 0.0 (0.0, 140.0) | | 0.0 (0.0, 140.0) |
| Early cessation of Xolair treatment | 6 (11.3%) | 3 (9.4%) | 1.000 | 9 (10.6%) |
| **Co-morbidity** | | | | |
| Depression | 9 (17.0%) | 5 (15.6%) | 1.000 | 14 (16.5%) |
| Insomnia | 13 (24.5%) | 5 (15.6%) | 0.484 | 18 (21.2%) |
| Osteoporosis | 4 (7.5%) | 4 (12.5%) | 0.468 | 8 (9.4%) |
| Cerebrovascular disease | 6 (11.3%) | 3 (9.4%) | 1.000 | 9 (10.6%) |

*(Continued)*

**TABLE 3** | Continued

| | ACT | | | |
|---|---|---|---|---|
| | **Responder ($n = 53$)** | **Non-responder ($n = 32$)** | ***p*-value** | **Total ($n = 85$)** |
| GERD | 16 (30.2%) | 11 (34.4%) | 0.872 | 27 (31.8%) |
| COPD | 14 (26.4%) | 15 (46.9%) | 0.091 | 29 (34.1%) |
| DM | 12 (22.6%) | 3 (9.4%) | 0.207 | 15 (17.6%) |
| Food or drug allergy | 5 (9.4%) | 2 (6.3%) | 0.706 | 7 (8.2%) |
| Atopic disease※ | 50 (94.3%) | 26 (81.3%) | 0.075 | 76 (89.4%) |
| AERD | 0 (0.0%) | 0 (0.0%) | NA | 0 (0.0%) |
| OSAS | 4 (7.5%) | 0 (0.0%) | 0.292 | 4 (4.7%) |

*$p < 0.05$.
※*Atopic disease included allergic dermatitis, allergic rhinitis, allergic conjunctivitis and food allergies.*
*ACT, asthma control test; also see* ***Table 1***.

patients were more likely to be responders with a reduction in exacerbations defined using a similar criteria to our study (5, 17). The inconsistencies in the features between our study and Casale et al.'s may mainly be due to the disparity in age of the study populations (a mean age of 60.8 vs. 47.3 years) (5). In addition, previous studies have reported that obesity, co-morbidities and the presence of nasal polyps were risk factors for exacerbations, while more clinically severe asthma (as evaluated by emergency visits and hospitalizations for asthma in the previous year, FEV1 % predicted <65 vs. ≥65, inhaled beclomethasone dipropionate dose <600 vs. ≥600 μg per day, and long-acting beta-agonist use vs. non-use) and high Th2-driven inflammatory biomarkers (including FeNO, peripheral blood eosinophils, and serum periostin and total IgE) were associated with a greater reduction in exacerbations following treatment with omalizumab (4, 6, 18, 19).

We also found that a peripheral blood eosinophil level of <300 cells/μL could predict responders with OCS sparing. Hanania et al. reported that a high level of FeNO could predict less albuterol use (4). In contrast, Sposato et al. reported that obesity was independently associated with the excessive use of short-acting beta-agonists and increased dose of medications to control asthma, and that nasal polyps were associated with the use of a higher inhaler corticosteroid dose (18).

Further, our study showed that the responders with lung function improvement were younger compared to the non-responders, and that the patients with a higher initial omalizumab dose and more use of oral medications to control asthma were associated with an MCID in asthma control. In contrast, Casale et al. reported that patients with uncontrolled asthma and receiving asthma medications in addition to inhaled corticosteroids (ICS)/long-acting beta-agonists were more likely to be associated with an MCID in lung function, defined as a rise in FEV1 ≧120 ml from baseline, while those with higher baseline circulatory eosinophil levels were more likely to be responders with asthma control according to a definition similar to ours (5). Again, the discrepancy in the characteristics between these two studies may be explained by the difference in age of the study population (a mean age of 60.8 vs. 47.3 years) and in the definition of a response in lung function (an FEV1 improvement of ≧230 vs. ≧120 ml) (5, 17). Conversely, Sposato et al. reported that patients had a reduced response following omalizumab treatment in both lung function and asthma control if they were older or obese, and had co-morbidities, particularly chronic heart disease (18). Taken together, these findings suggest that the SAA patients who had an MCID in the treatment outcomes of interest following omalizumab treatment had a predictable clinical behavior, although the discrepancies in age and in the definition of a responder led to differences in the predictors.

Obese patients with asthma have an increased risk of severe disease, which may arise from many factors, such as changes in airway anatomy, adipokines, glucose-insulin metabolism, oxidative stress, inflammation, and genetic and epigenetic variants (20). Furthermore, similar to our finding that the SAA patients with normal weight were more likely to be responders with a reduction in exacerbations, previous reports have shown that obesity may reduce ICS response and negatively influence the beneficial effect of omalizumab in terms of asthma control in patients with asthma (1, 21). These findings show that obesity has a great impact on the severity and prognosis of asthma, and that obesity is a particular phenotype of asthma.

The predictive value of total IgE and blood eosinophil levels with regards to the therapeutic benefit of omalizumab in patients with allergic asthma has yet to be shown in previous studies, although we found that a blood eosinophil level of <300 cells/μL was predictive of an MCID in OCS sparing in the SAA patients (7, 19, 22). This disparity could be explained by the use of different treatment outcomes for analysis between the present study and other studies (OCS sparing vs. reduction in exacerbations).

Similar to the response rates of 75.8 and 62.4% for a reduction in exacerbations and improvement in asthma control, respectively, Casale et al. reported response rates of 77.8 and 64.7% (5). However, we found a lower response rate of 26.7% for an improvement in lung function defined as an increase in FEV1 ≧230 ml between enrollment and the end of the study compared to 35.9% defined as a ≧120 ml improvement in FEV1 between the end and start of the study reported by Casale et al. (5, 13, 23). As expected, the definition of a responder affected the

difference in response rate of treatment outcomes of interest in the asthmatic patients.

The main strength of the current study is that the diagnosis of SAA was made according to the GINA recommendations by clinicians who were actively involved in the management of asthma, while the initiation of omalizumab treatment in all patients was suggested by both the physician in charge and the Taiwan NHI committee for SAA (1), This ensured a valid study population of patients with SAA and reached a strong consensus on whether or not omalizumab should be an add-on therapy for SAA patients, although 14 of the 124 participants discontinued omalizumab treatment after 4 months because of administrative issues with the Taiwan NHI. This may compensate for the limitations of this study, which include the incomplete binary results of lung function tests and ACT data, older age of the participants, and the small number of cases. Due to these limitations, our results should be interpreted with caution, and they may not be generalizable to a younger population.

## CONCLUSIONS

It is extremely important to take clinical features into consideration when managing patients with asthma at different GINA steps, particularly at GINA step 5, because several inflammatory biomarkers used to predict a good therapeutic response to the biologic treatment, such as FeNO and periostin, are not always available in all hospitals or areas/countries. We identified several clinical characteristics associated with an MCID in terms of a reduction in exacerbations, OCS sparing, and improvements in lung function and asthma control in adult patients with SAA. This information could help when selecting patients who may benefit more from omalizumab treatment to manage asthma. Future well-designed studies including more subjects and more potential and easily-obtained inflammatory biomarkers are warranted to more accurately predict an MCID following omalizumab treatment.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board and Ethics Committee of Taichung Veterans General Hospital (Approval No. CE19015B). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

W-CH: conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft preparation, visualization, project administration, and agreement on the published version of the manuscript. P-KF, M-CC, C-SC, W-NH, K-LL, J-LW, W-TH, Y-DW, C-WH, and M-FW: methodology, formal analysis, investigation, data curation, writing—review and editing, visualization, and agreement on the published version of the manuscript. Y-HC and J-YH: conceptualization, methodology, validation, formal analysis, investigation, data curation, writing—review and editing, visualization, supervision, and agreement on the published version of the manuscript. All authors contributed to the article and approved the submitted version.

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# Clinical and Inflammatory Characteristics of the Chinese APAC Cough Variant Asthma Cohort

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**Background:** The AtyPical Asthma in China (APAC) cohort is a multi-center prospective, observational cohort set-up to investigate the clinical, pathophysiological features, prognosis, and mechanisms of cough variant asthma (CVA).

**Objectives:** To present the characteristics of newly physician-diagnosed adults with CVA ($n = 328$) compared to mild-moderate classic asthma (CA, $n = 206$).

**Methods and Main Results:** CVA subjects showed a higher proportion of female (67.1 vs. 55.3%, $P = 0.0084$), abnormal laryngopharyngeal sensations (71 vs. 51%, $p < 0.0001$) than CA, but presented with near normal spirometry and higher methacholine PD20-FEV1 values [4.2 (1, 8.6) vs. 0.8 (0.4, 4.7), $P < 0.0001$]. Lower fractional exhaled nitric oxide (FENO) levels [38.5 (19.8, 72.5) vs. 53. (28.5, 92.2), $P = 0.0019$], blood eosinophil counts [0.2 (0.1, 0.4) vs. 0.3 (0.2, 0.5), $P = 0.0014$], and sputum eosinophils

[2.3 (0.3, 8.0) vs. 12.2 (2, 34.5), $p < 0.0001$] were found in CVA. Despite lower total serum IgE levels in CVA, there was similar proportion of atopy in both groups. The prevalence of cough in CA was 86.4%, while CVA reported more severe cough on Visual Analog Scale, Cough Evaluation Test, and Leicester Cough Questionnaire, similar anxiety and depression scores but better asthma control scores as reflected by Asthma Control Test compared to CA. No correlation was found between cough assessment outcomes and sputum eosinophil count, blood eosinophil count, FENO, spirometry variables, or PD20-FEV1.

**Conclusion:** Cough variant asthma is distinctive from classic asthma in regard to clinical features, lung function, and airway inflammation. Quality of life is badly impaired as well in spite of better asthma control scores.

**Keywords: cough variant asthma (CVA), classic asthma (CA), airway inflammation, bronchial hyperresponsiveness, cough**

## INTRODUCTION

Bronchial asthma is characterized by wheeze, dyspnea, chest tightness, and cough, and by variable expiratory airflow limitation (1). While cough occurs usually in association with wheeze and dyspnea in patients with classic asthma (CA), it can also present as the sole manifestation of asthma as first described by Corrao and colleagues in cough variant asthma (CVA) (2). CVA has been recognized as specific form of asthma that is usually diagnosed by bronchial hyperresponsiveness (BHR) and/or diurnal variability in lung function (1, 3, 4). CVA has also been identified as one of the most common causes of chronic cough (ranging from 10 to 42%) (5, 6). According to the onset, triggers, severity, airway inflammation or response to treatment, asthma can be divided into different phenotypes, such as early-onset or late-onset, severe asthma, steroid-resistant asthma, or eosinophilic asthma. By contrast, CVA, one of the most common phenotypes of asthma remains ill-understood partly due to the lack of appreciation that an isolated cough may be caused by asthma (1).

Although some studies have shown that CVA shares similarities with CA in terms of BHR and airway eosinophilic inflammation (7, 8), others have reported milder BHR and airway inflammation in CVA (9). Such discrepancies maybe partly due to reports from single centers, their retrospective design, and the small sample size studied. Another consideration is the lack of information on the inflammation accompanying CVA. Cough associated with asthma can be troublesome and can be a prominent symptom, and the therapeutic efficacy of asthma therapies on cough can be variable in both CVA and CA, which can result in potentially significant physical, psychological, and social morbidity (10–12). The discovery of new treatment targets of asthmatic cough and identification of treatable traits suited to individualized treatment have been hindered by a poor understanding of the physiological, pathological, and molecular mechanisms of asthmatic cough.

To address these issues, we set up the AtyPical Asthma in China (APAC) cohort, a multi-center prospective, observational cohort, with the aim of (i) investigating the clinical features, airway inflammation and prognosis of CVA, (ii) identifying multidimensional phenotypes, treatable traits, and new treatment targets of CVA, and (iii) thereby improving the evaluation and treatment strategies of atypical asthma. In this study, with the aim of investigating the distinct characteristics of CVA, we present the cross-sectional assessment of patients with CVA and those suffering from mild-moderate CA from the APAC cohort consisted of analyses of baseline clinical features, lung function, blood, and airway inflammatory measurements.

## METHODS

### Study Design and Subjects

This was a multicenter, prospective, observational cohort study for newly physician-diagnosed adult CVA recruited from outpatient clinics of 17 centers located in nine provinces of China. From December 2017 to February 2020, consecutive newly physician-diagnosed adult CVA and CA subjects were recruited at a ratio of 2:1. Eligible subjects underwent a baseline visit with (1) detailed medical history and physical examination recorded in a standard case report frame; (2) completion of Asthma Control Test (ACT), Cough Evaluation Test (CET), Cough Visual Analog Scale (VAS), Leicester Cough Questionnaire (LCQ), Self-rating Anxiety Scale (SAS), and Self-Rating Depression Scale (SDS); (3) performance of spirometry and assessment of variable airflow limitation; and (4) induced sputum test, fractional exhaled nitric oxide (FENO), chest radiograph, and hematological profiles. The control-based asthma management according to the Global Initiative for Asthma (GINA) guidelines and the Chinese Guidelines for Diagnosis and Management of Cough (2015) (4) were used as

**Abbreviations:** APAC, AtyPical Asthma in China; CA, classic asthma; CVA, cough variant asthma; BHR, bronchial hyperresponsiveness; ACT, asthma control test; CET, cough evaluation test; VAS, visual analog scale; LCQ, leicester cough questionnaire; SAS, self-rating anxiety scale; SDS, self-rating depression scale; FENO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow; PD20-FEV1, the accumulated provocative dose resulting in a 20% decrease in FEV1; Blood-Eos, blood eosinophils; Sputum-Eos, sputum eosinophils; BMI, body mass index.

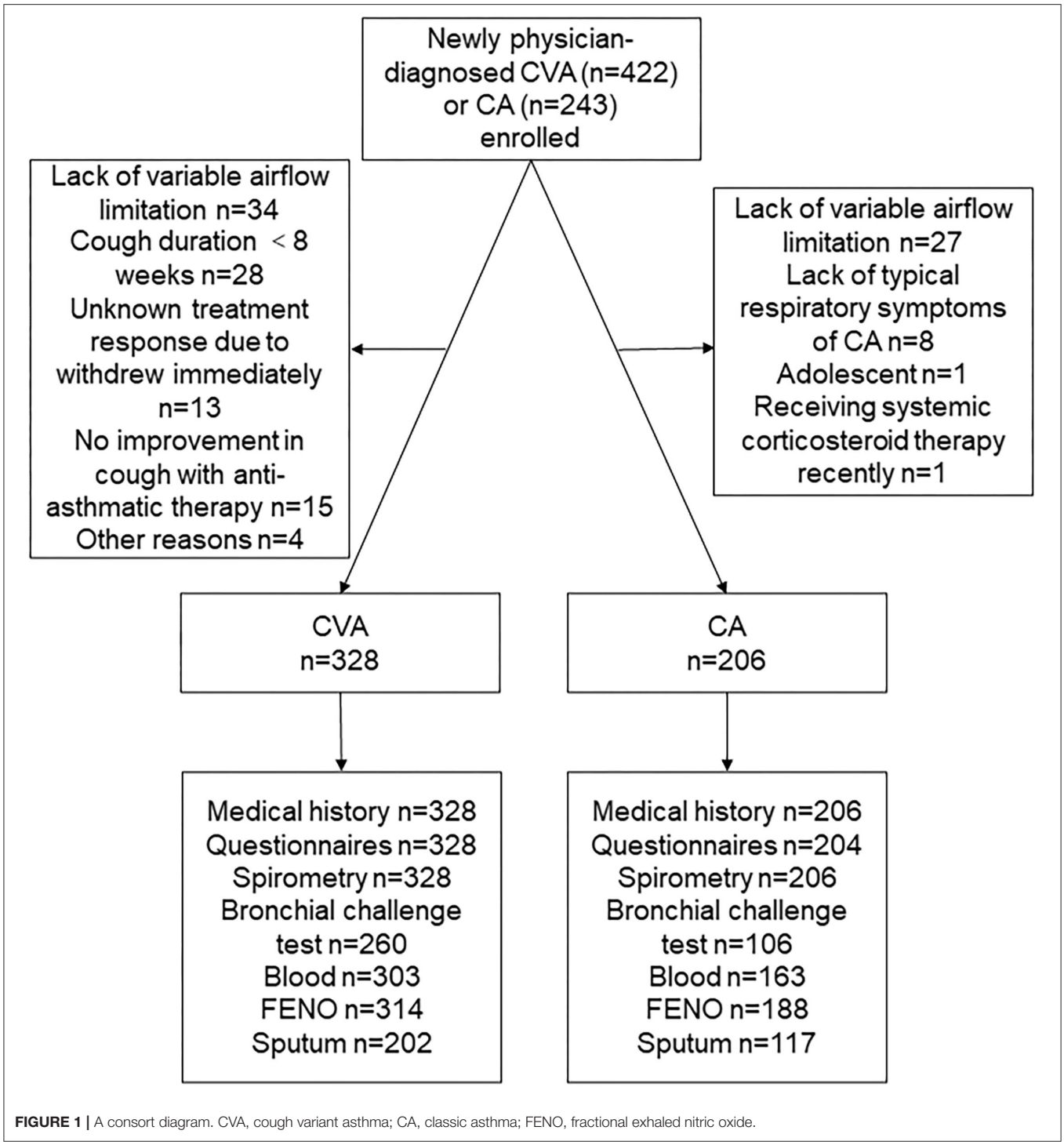


**FIGURE 1 |** A consort diagram. CVA, cough variant asthma; CA, classic asthma; FENO, fractional exhaled nitric oxide.

general principles of treatment, and asthma management was the responsibility of the physicians at the recruitment sites. The participants with CVA were reviewed monthly after enrollment for at least 6 months.

The diagnosis of asthma was made according to Global Initiative for Asthma (GINA) guidelines and Chinese Guidelines for Diagnosis and Management of Cough (2015) (1, 4). CVA was diagnosed on the basis of (1) chronic cough as the sole or predominant symptom lasting for more than 8 weeks, (2) evidence of variable airflow limitation [positive bronchial challenge test (fall in FEV1 from the baseline of $\geq$ 20% with 12.8 μmol of methacholine or with 7.8 μmol of histamine), or positive bronchodilator reversibility test (increase in FEV1 $\geq$ 12% and 200 ml from the baseline)], and (3) cough improved with

**TABLE 1 |** Demographic characteristics of subjects.

| | All subjects | CVA | CA | *P* value |
|---|---|---|---|---|
| Number of subjects | 534 | 328 | 206 | |
| Age (years) | 41.9 ± 12.7 | 41.0 ± 12.6 | 43.3 ± 12.9 | **0.0419** |
| Female | 334 (62.5%) | 220 (67.1%) | 114 (55.3%) | **0.0084** |
| BMI | 23.4 ± 3.6 | 23.4 ± 3.8 | 23.4 ± 3.1 | 0.8162 |
| Duration of disease (month) | 17.0 [5.0, 60.0] | 13.0 [4.0, 48.0] | 24.0 [5.0, 68.5] | 0.0858 |
| Current-smoker | 63 (11.8%) | 32 (9.8%) | 31 (15.0%) | 0.0877 |
| Smoking index (pack-years) | 10.0 [3.6, 20.0] | 10.0 [4.6, 20.0] | 7.5 [3.4, 20.0] | 0.4241 |
| **Educational status** | | | | |
| Primary school or illiteracy | 231 (47.0%) | 149 (49.2%) | 82 (43.4%) | 0.4266 |
| High school | 192 (39.0%) | 112 (37.0%) | 80 (42.3%) | |
| College | 69 (14.0%) | 42 (13.9%) | 27 (14.3%) | |
| Past history of allergies | 136 (25.5%) | 80 (24.4%) | 56 (27.2%) | 0.5357 |
| Food | 51 (9.6%) | 28 (8.5%) | 23 (11.2%) | 0.3927 |
| Drug | 67 (12.5%) | 46 (14.0%) | 21 (10.2%) | 0.2434 |
| Other | 36 (6.7%) | 18 (5.5%) | 18 (8.7%) | 0.2003 |
| Family history of allergic diseases | 164 (30.7%) | 101 (30.8%) | 63 (30.6%) | 1.0000 |
| Asthma | 85 (15.9%) | 46 (14.0%) | 39 (18.9%) | 0.1653 |
| Eczema | 27 (5.1%) | 12 (3.7%) | 15 (7.3%) | 0.0975 |
| Allergic rhinitis | 104 (19.5%) | 68 (20.7%) | 36 (17.5%) | 0.4164 |

*Data are presented as n (percentage), mean ± standard deviation, or median [interquartile range]. CVA, cough variant asthma; CA, classic asthma; BMI, body mass index.*

**TABLE 2 |** Clinical features and comorbidities of subjects.

| | All subjects | CVA | CA | *P* value |
|---|---|---|---|---|
| Cough | 506 (94.8%) | 328 (100.0%) | 178 (86.4%) | **<0.0001** |
| **Concomitant symptoms** | | | | |
| Runny nose | 140 (26.2%) | 89 (27.1%) | 51 (24.8%) | 0.6123 |
| Postnasal dripping | 44 (8.2%) | 26 (7.9%) | 18 (8.7%) | 0.8649 |
| Sneezing | 219 (41.0%) | 131 (39.9%) | 88 (42.7%) | 0.5856 |
| Nasal itching | 142 (26.6%) | 76 (23.2%) | 66 (32.0%) | **0.0310** |
| Hyposmia | 37 (6.9%) | 20 (6.1%) | 17 (8.3%) | 0.4357 |
| Nasal congestion | 154 (28.8%) | 89 (27.1%) | 65 (31.6%) | 0.3177 |
| Itchy throat | 249 (46.6%) | 172 (52.4%) | 77 (37.4%) | **0.0009** |
| Itching below the throat | 57 (10.7%) | 43 (13.1%) | 14 (6.8%) | **0.0311** |
| Pharyngeal foreign body sensation | 124 (23.2%) | 86 (26.2%) | 38 (18.4%) | **0.0494** |
| Frequent throat clearing | 106 (19.9%) | 71 (21.6%) | 35 (17.0%) | 0.2295 |
| Abnormal laryngopharyngeal sensations* | 338 (63.3%) | 233 (71.0%) | 105 (51.0%) | **<0.0001** |
| Acid regurgitation | 71 (13.3%) | 46 (14.0%) | 25 (12.1%) | 0.6208 |
| Heartburn | 17 (3.2%) | 9 (2.7%) | 8 (3.9%) | 0.6334 |
| Belching | 31 (5.8%) | 20 (6.1%) | 11 (5.3%) | 0.8615 |
| **Comorbidities** | | | | |
| Rhinitis | 241 (45.1%) | 142 (43.3%) | 99 (48.1%) | 0.3232 |
| Sinusitis | 44 (8.2%) | 24 (7.3%) | 20 (9.7%) | 0.4141 |
| Eczema | 29 (5.4%) | 18 (5.5%) | 11 (5.4%) | 1.0000 |
| GERD | 13 (2.4%) | 11 (3.4%) | 2 (1.0%) | 0.1469 |
| OSA | 6 (1.1%) | 4 (1.2%) | 2 (1.0%) | 1.0000 |
| Hypertension | 47 (8.9%) | 29 (8.8%) | 18 (8.9%) | 1.0000 |

*Data are presented as n (percentage). CVA, cough variant asthma; CA, classic asthma; Cough VAS, cough visual analog scale; GERD, gastro-esophageal reflux disease; OSA, obstructive sleep apnoea. *Abnormal pharyngeal sensations included itchy throat, itching below the throat, pharyngeal foreign body sensation, or frequent throat clearing.*

anti-asthmatic therapy during the follow-up (4). A diagnosis of CA was accepted based on variable respiratory symptoms, such as wheeze, shortness of breath, chest tightness and/or cough, and evidence of variable airflow limitation. Exclusion criteria included (1) experiencing respiratory tract infection within the previous 4 weeks; (2) receiving antiasthma medications within the previous 4 weeks, including oral or inhaled corticosteroid, leukotriene receptor antagonist, or antihistamine agents; (3) obvious abnormality of chest imaging; (4) suspected other causes of chronic cough; and (5) pregnancy, breast-feeding, usage of angiotensin converting enzyme inhibitors drug, history of drug or alcohol abuse, other pulmonary disease, or significant comorbidity likely to influence the conduct of the study.

The local ethics committees at each center approved the study. The research was registered on Chinese Clinical Trial Registry (ChiCTR1800014845). All the participants signed informed consent to participate.

## Assessment

The serum levels of total and specific IgE antibodies were measured by ImmunoCap (Phadia AB, Uppsala, Sweden). Specific IgE antibody levels to common allergens, including dust mite (Dermatophagoidespteronyssinus and Dermatophagoidesfarina), cockroach, mold mix (Penicillium, Cladosporium, Aspergillus, Candida, Alternaria and Helminthosporiumcarposaprum), mixed weed pollens (ragweed, mugwort, dandelion, oxeye daisy, and golden rod), and mixed dander (cat, dog, cattle, and horse) were measured. Atopy was defined as at least one positive specific IgE (>0.35 KU/L) to any of these allergens.

Spirometry and bronchial challenge test were performed according to the current ATS/ERS guidelines (13, 14). The provocative cumulative dose of methacholine causing a 20% fall in FEV1 (PD20-FEV1) was used as a measure for BHR.

FENO was measured in accordance with the standard procedure (15). Briefly, the subjects were informed to exhale to the residual air position, and then inhale deeply *via* a mouthpiece and then exhale with a constant flow (0.05 L/s) for 10 s using NIOX VERO (Aerocrine Company, Sweden).

Sputum was induced and processed as described previously (4). Briefly, sputum was induced with 3% saline. Sputum plugs were selected and mixed with four times its volume of 0.1% dithiothreitol. The cell smear was stained with hematoxylin-eosin. The differential cell count was obtained by counting 400 non-squamous cells.

ACT was used for assessment of asthma control (16). The cough VAS is a 100-mm scale on which the patients indicated the severity of cough. CET is a validated 5-item test to evaluate the full impact of chronic cough with regard to physical, social, and psychological aspects (17). Cough-related quality of life was assessed by LCQ that contained 19 items divided into three domains (physical, psychological, and social) (18). The SAS and SDS were used for general anxiety and depression assessment, respectively.

## Statistical Analysis

Data were expressed as frequency (percentage), mean ± standard deviation or median, and interquartile range [25%, 75%]. Missing data were not imputed. Statistical comparisons between groups were performed with independent sample *t*-test for normally distributed data, Mann–Whitney U test for skewed data, and Chi-square tests or Fisher's exact test for categorical variables. The correlation of two parameters was tested with Spearman's correlation test and was plotted through the "corrplot" R package. All analyses were conducted using R software Version 3.6.3 (http://CRAN.R-project.org, R Foundation, Vienna, Austria).

# RESULTS

## Demographic Characteristics

From December 2017 to February 2020, 422 newly physician-diagnosed CVA and 243 newly physician-diagnosed CA were recruited. Of the recruited participants, 131 participants were excluded for lacking of variable airflow limitation, cough lasting <8 weeks in physician-diagnosed CVA, withdrew, or other reasons (**Figure 1**). A total of 328 subjects with CVA and 206 subjects with CA were finally included for the following analysis.

Compared with patients with CA, the proportion of female (67.1 vs. 55.3%, $P = 0.0084$) was higher and in patients with CVA. There was no significant difference in body mass index, duration of disease, smoking history, educational status, past history of allergies, or family history of asthma between CVA and CA (**Table 1**).

## Clinical Features and Comorbidities

Cough was a very common symptom in CA with prevalence of up to 86.4%. Compared with CA, the proportion of patients who experienced itchy throat (52.4 vs. 37.4%, $P = 0.0009$), itching below the throat (13.1 vs. 6.8%, $P = 0.0311$) or pharyngeal foreign body sensation (26.2 vs. 18.4%, $P = 0.0494$) was higher in CVA. More patients with CVA (71 vs. 51%, $P < 0.0001$) experienced abnormal laryngopharyngeal sensations (itchy throat, itching below the throat, pharyngeal foreign body sensation, or frequent throat clearing). There was no significant difference between CA and CVA, in terms of runny nose, postnasal dripping, sneezing, nasal congestion, hyposmia, acid regurgitation, heartburn, or belching (**Table 2**).

Allergic rhinitis was common in both CVA (43.3%) and CA (48.1%). The prevalence of sinusitis, eczema, gastro-esophageal reflux disease or other comorbidities was <10%, with no significant difference reported in both groups (**Table 2**).

**TABLE 3 |** Questionnaire assessment.

| | All subjects | CVA | CA | *P* value |
|---|---|---|---|---|
| ACT | 17.4 ± 3.7 | 18.2 ± 3.4 | 16.2 ± 3.8 | **<0.0001** |
| ACT scores <20 | 367 (69.0%) | 200 (61.0%) | 167 (81.9%) | **<0.0001** |
| CET | 13.1 ± 4.5 | 13.5 ± 4.1 | 12.4 ± 5.0 | **0.0067** |
| Cough VAS (mm) | 50.7 ± 25.2 | 53.7 ± 21.7 | 45.7 ± 29.5 | **0.0004** |
| LCQ-total | 14.2 ± 3.6 | 13.9 ± 3.3 | 14.8 ± 4.1 | **0.0060** |
| LCQ-physical | 4.7 ± 1.1 | 4.6 ± 1.0 | 4.8 ± 1.3 | **0.0211** |
| LCQ-psychological | 4.6 ± 1.4 | 4.4 ± 1.3 | 4.9 ± 1.5 | **0.0006** |
| LCQ-social | 5.0 ± 1.4 | 4.9 ± 1.4 | 5.1 ± 1.5 | 0.0653 |
| SAS | 38.8 ± 9.8 | 38.4 ± 9.2 | 39.6 ± 10.6 | 0.1980 |
| SDS | 38.8 ± 11.6 | 38.3 ± 11.5 | 39.4 ± 11.8 | 0.3252 |

*Data are presented as mean ± standard deviation or n (percentage). CVA, cough variant asthma; CA, classic asthma; ACT, asthma control test; CET, cough evaluation test; LCQ, leicester cough questionnaire; SAS, self-rating anxiety scale; SDS, self-rating depression scale.*

## Subjective Questionnaire Assessment

The ACT score reflected poor asthma control in both groups, but the ACT score of CA was significantly lower than that of CVA (16.2 ± 3.8 vs. 18.2 ± 3.4, $P < 0.0001$). Cough of CVA was slightly more severe than that of CA (VAS: 53.7 ± 21.7 vs. 45.5 ± 29.5, $P = 0.0004$; CET: 13.5 ± 4.1 vs. 12.4 ± 5, $P = 0.0067$). The cough-specific quality of life reflected by LCQ was lower in CVA, while general anxiety and depression reflected by SAS and SDS scores, respectively, were similar between CVA and CA (**Table 3**).

## Lung Function and Inflammatory Biomarkers

FEV1 (% predicted), FVC (% predicted), and the FEV1/FVC ratio of the patients with CVA were nearly normal and were significantly higher than that in patients with CA (**Table 4**). The PD20-FEV1 values in CVA were higher than that in CA [4.2 (1, 8.6) vs. 0.8 (0.4, 4.7), $P < 0.0001$].

Compared to CA, there was significantly lower FENO [38.5 (19.8, 72.5) vs. 53 (28.5, 92.2), $P = 0.0019$, **Figure 2A**], blood eosinophil count [0.2 (0.1, 0.4) vs. 0.3 (0.2, 0.5), $P = 0.0014$, **Figure 2B**], and sputum eosinophil count [2.3 (0.3, 8.0) vs. 12.2 (2, 34.5), $P < 0.0001$, **Figure 2C**] in CVA. Similarly, the proportion of sputum eosinophilia (≥ 2.5%), elevated FENO (≥ 25 ppb), or elevated blood eosinophil count ($\geq 0.3 * 10^9$) in CVA was significantly lower than that of CA respectively (**Table 4**). The proportion of elevated FENO, sputum, or blood eosinophils was 73.1% in CVA, which was significantly lower than that in CA (82.3%). Although lower total serum IgE values [106.6 (35.3, 269.5) vs. 160.6 (67.8, 412.8), $P = 0.0013$] were present in CVA, there was a similar proportion of atopy in both groups.

## Medications

At entry, initial treatment was similar between CVA and CA. About 95.7% of CVA and 93.7% of CA were prescribed

**TABLE 4 |** Lung function and inflammatory features.

| | All subjects | CVA | CA | *P* value |
|---|---|---|---|---|
| **Spirometry** | | | | |
| FEV1 (% predicted) | 85.8 ± 17.4 | 91.1 ± 12.5 | 77.5 ± 20.6 | **<0.0001** |
| FVC (% predicted) | 97.4 ± 14.8 | 100.0 ± 12.8 | 93.2 ± 16.8 | **<0.0001** |
| FEV1/FVC (%) | 74.4 ± 11.4 | 77.6 ± 8.5 | 69.3 ± 13.4 | **<0.0001** |
| MMEF (% predicted) | 54.7 ± 22.5 | 60.0 ± 20.3 | 45.7 ± 23.2 | **<0.0001** |
| PD20-FEV1 (μmol) | 2.8 [0.6, 8.0] | 4.2 [1.0, 8.6] | 0.8 [0.4, 4.7] | **<0.0001** |
| FENO (ppb) | 44.0 [20.2, 80.8] | 38.5 [19.8, 72.5] | 53.0 [28.5, 92.2] | **0.0019** |
| Blood neutrophils (%) | 58.4 [52.1, 63.9] | 58.7 [52.0, 63.8] | 57.5 [52.2, 63.9] | 0.8169 |
| Blood-Eos (%) | 3.7 [1.9, 6.1] | 3.2 [1.6, 5.7] | 4.3 [2.4, 7.0] | **0.0039** |
| Blood-Eos ($10^9$) | 0.2 [0.1, 0.4] | 0.2 [0.1, 0.4] | 0.3 [0.2, 0.5] | **0.0014** |
| Total IgE (KU/L) | 128.9 [41.5, 305.6] | 106.6 [35.3, 269.5] | 160.6 [67.8, 412.8] | **0.0013** |
| Atopy (any specific IgE ≥ 3.5 (KU/L)) | 228 (46.0%) | 140 (44.4%) | 88 (48.6%) | 0.4211 |
| **Differential cells in induced sputum** | | | | |
| Eosinophil (%) | 3.4 [0.4, 18.2] | 2.3 [0.3, 8.0] | 12.2 [2.0, 34.5] | **<0.0001** |
| Neutrophil (%) | 66.5 [36.6, 89.2] | 73.1 [45.0, 91.1] | 53.0 [28.8, 83.0] | **0.0004** |
| Macrophage (%) | 16.2 [4.2, 36.5] | 16.3 [4.2, 37.1] | 15.8 [4.5, 35.2] | 0.9162 |
| Lymphocyte (%) | 0.7 [0.2, 1.4] | 0.8 [0.2, 1.5] | 0.6 [0.2, 1.2] | 0.1733 |
| Elevated Sputum-Eos (≥2.5%) | 179 (56.1%) | 97 (48.0%) | 82 (70.1%) | **0.0002** |
| Elevated Blood-Eos (≥0.3 *$10^9$) | 204 (43.8%) | 122 (40.3%) | 82 (50.3%) | **0.0470** |
| Elevated FeNO (≥25 ppb) | 356 (70.9%) | 207 (65.9%) | 149 (79.3%) | **0.0021** |
| Elevation of Sputum-Eos, FENO or Blood-Eos | 406 (76.6%) | 239 (73.1%) | 167 (82.3%) | **0.0203** |

*Data are presented as mean ± standard deviation, median [interquartile range] or n (percentage). CVA, cough variant asthma; CA, classic asthma; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MMEF, maximum mid-expiratory flow; FENO, fractional exhaled nitric oxide; Blood-Eos, blood eosinophil count; Sputum-Eos, sputum eosinophil count.*

with inhaled corticosteroids in combination with long-acting beta two agonists. Within the CVA and CA groups, 53.2 and 52.4%, respectively, received leukotriene receptor antagonists, and 14.6 and 8.5%, respectively, received antihistamines therapy.

## Correlation Analysis

There was no significant correlation between cough assessment outcomes (VAS or CET) and indexes of airway inflammation (sputum eosinophils, blood eosinophils, and FENO), spirometry variables or PD20-FEV1 (**Figure 3A**). ACT was weakly but significantly correlated with FEV1 (% predicted), the FEV1/FVC ratio, and sputum eosinophils, respectively. PD20-FEV1 showed weak correlation with sputum eosinophil count. However, those correlations were not found when CVA (**Figure 3B**) or CA (**Figure 3C**) was analyzed separately.

# DISCUSSION

In this large APAC asthma cohort, we compared patients with newly physician-diagnosed CVA with mild-moderate classic asthma in terms of baseline clinical features, lung function, and inflammatory characteristics. CVA showed female predominance, higher incidence of abnormal laryngeal symptoms, higher ACT scores and slightly more severe cough, while CVA had better lung function, milder BHR, and less severe eosinophilic inflammation as reflected by sputum eosinophil counts, blood eosinophil counts, and FENO, compared with CA. There were comparable proportions of atopy, comorbidities, and accompanying symptoms, as well as a similar degree of general anxiety and depression between CVA and CA.

Asthma and atopic conditions are usually more prevalent in women as from adolescence (19). Compared with CA, while there was a similar proportion of atopy, female predominance in patients with CVA was observed in the current study, as we previously reported (20, 21). The patients with chronic cough also showed female predominance, which might be related to the heightened cough sensitivity reported in females (22). In the current study, we found a similar incidence of rhinitis in CVA and CA. We have recently reported the prevalence of rhinitis in patients with CVA to be 47.1% (21), compared to 43.3% in the current study. There was no significant difference between these two conditions in terms of the incidence of sinusitis, allergic eczema, gastro-esophageal reflux disease, or other comorbidities, indicating that comorbidities may play a little role in the clinical and pathophysiologic differences between CVA and CA.

Sputum eosinophils, blood eosinophils, and FENO are used as biomarkers of airway eosinophilic or Type 2 inflammation (1, 23). We found a high proportion of CVA with sputum and blood eosinophilia, and elevated FENO, as has been previously reported (7–9, 24). But eosinophilic inflammation was milder in CVA compared to CA. However, other studies have reported that there was no significant difference in blood sputum eosinophilia between CA and CVA (7, 8, 24), which may have been due to the small sample size of these studies (12 to 41 subjects per group). Lower FENO in CVA compared to CA has also been reported in other studies (9, 25), together with the proportion of airway eosinophilic inflammation in CVA being significantly lower than that in CA. Nearly one-quarter of patients with newly diagnosed CVA in APAC had non-eosinophilic inflammation according to sputum eosinophil counts, FENO, or blood eosinophil counts. Apart from this large sample size from our multi-center study, another strength of our data is the "natural state" of illness since all our subjects were newly diagnosed CA and CVA who had not received standard anti-asthmatic treatment previously.

There are also conflicting reports regarding BHR with studies showing comparable levels (7, 8, 24), while others showed milder BHR in CVA (9). These differences may be attributed to the different populations and small sample size as well. We found that BHR was milder in CVA than in CA,

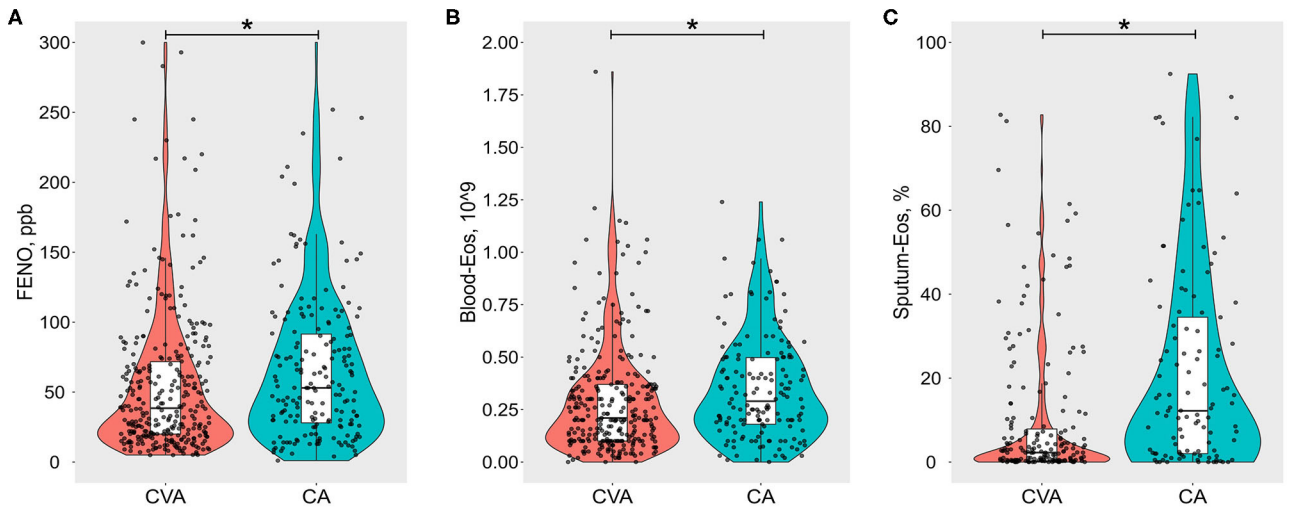


**FIGURE 2 |** Violin-boxplots of **(A)** fractional exhaled nitric oxide (FENO, ppb), **(B)** blood eosinophil count per $10^9$ (Blood-Eos), and **(C)** sputum eosinophil % (Sputum-Eos) between cough variant asthma (CVA) and classic asthma (CA). The boxes represent median and interquartile range values. Raw data are denoted by black dots, each representing one subject. *Refers to $p < 0.05$.

and we found that sputum eosinophils correlated with BHR. However, the relationship between eosinophils and BHR has been questioned since the anti-IL-5 antibody failed to suppress BHR in spite of a significant reduction in sputum eosinophils (26). There are other potential factors that can contribute to BHR, such as abnormalities of airway smooth muscle, presence of airway remodeling and non-eosinophilic inflammation, and abnormalities in the neural control of the airway caliber (27). However, none of these by themselves fully explain BHR.

Anxiety and depression are common and are comorbidities associated with uncontrolled asthma (28). Compared with CA, the patients with CVA showed comparable general anxiety and depression with slightly worse cough related to quality of life in our data. One study has reported that the patients with CVA were more depressed and anxious than patients with CA (29), suggesting that cough caused similar impact on quality of life in patients with CVA as with CA in spite of minimal or no report of wheeze or dyspnea in CVA. These co-morbid psychological conditions should be considered in the patients with CVA. CVA showed better asthma control status than CA, as assessed by ACT. However, cough is not a symptom that is measured in the ACT questionnaire (16). Increased cough frequency is an indicator of a more severe and difficult to control disease in asthma (30, 31). In addition, the ACT score was only mildly correlated with spirometry or airway inflammation for the whole asthma group, but there was no correlation when CVA or the CA group was analyzed separately, which may lead to an underestimation of the CVA control. Cough frequency reflected asthma control independent of airflow obstruction and inflammation (31). Therefore, the asthma control status of CVA or of cough-predominant asthma should be assessed thoroughly with the inclusion of cough, which is not currently the case.

In this study, the patients with CVA had nearly normal spirometry, which was significantly better compared to the patients with CA. The near-normal spirometric indices with milder bronchial responsiveness are likely factors that account for the absence of wheezing in CVA (32, 33). Cough in the patients with CA was also common. Although CVA presented with more severe cough than in CA, the difference was very modest and was less than the minimal clinically important difference, suggesting that cough was also a bothersome feature of CA, which is not captured on ACT scores. The general assumption underlying the mechanisms of asthmatic cough is that the cough reflex is stimulated by airway inflammatory mediators, mucus, and bronchoconstriction (34). Allergen-induced bronchoconstriction and airway eosinophilia result in increased cough reflex sensitivity associated with an increased cough (35). CVA also showed heightened cough response to bronchoconstriction, and coughing occurred with even mild bronchoconstriction (36). Muscarinic receptor stimulation, bronchoconstriction or bronchodilatation may have no direct effect on the sensitivity of the cough receptors (37). BHR, spirometry, and airway inflammation did not correlate with indices of cough severity, indicating that these parameters may not account for the clinical differences found between CVA and CA.

Neural dysfunction is a feature of asthma as demonstrated by the exaggerated capsaicin-evoked cough responses in asthmatics (38). Furthermore, features of laryngeal hypersensitivity, such as tickle in the throat, throat clearing, and irritation in the throat, are common in patients with chronic cough (39, 40), together with an abnormal sensation in the laryngeal area frequently associated with cough hypersensitivity (40, 41). Compared with CA, a higher proportion of the patients with CVA experience cough-related laryngopharyngeal symptoms, indicating cough hypersensitivity in CVA. In addition, abnormal pharyngeal sensations were distinct features of CVA, irrespective of sex and age (**Supplementary E-Table 1**). Although we did

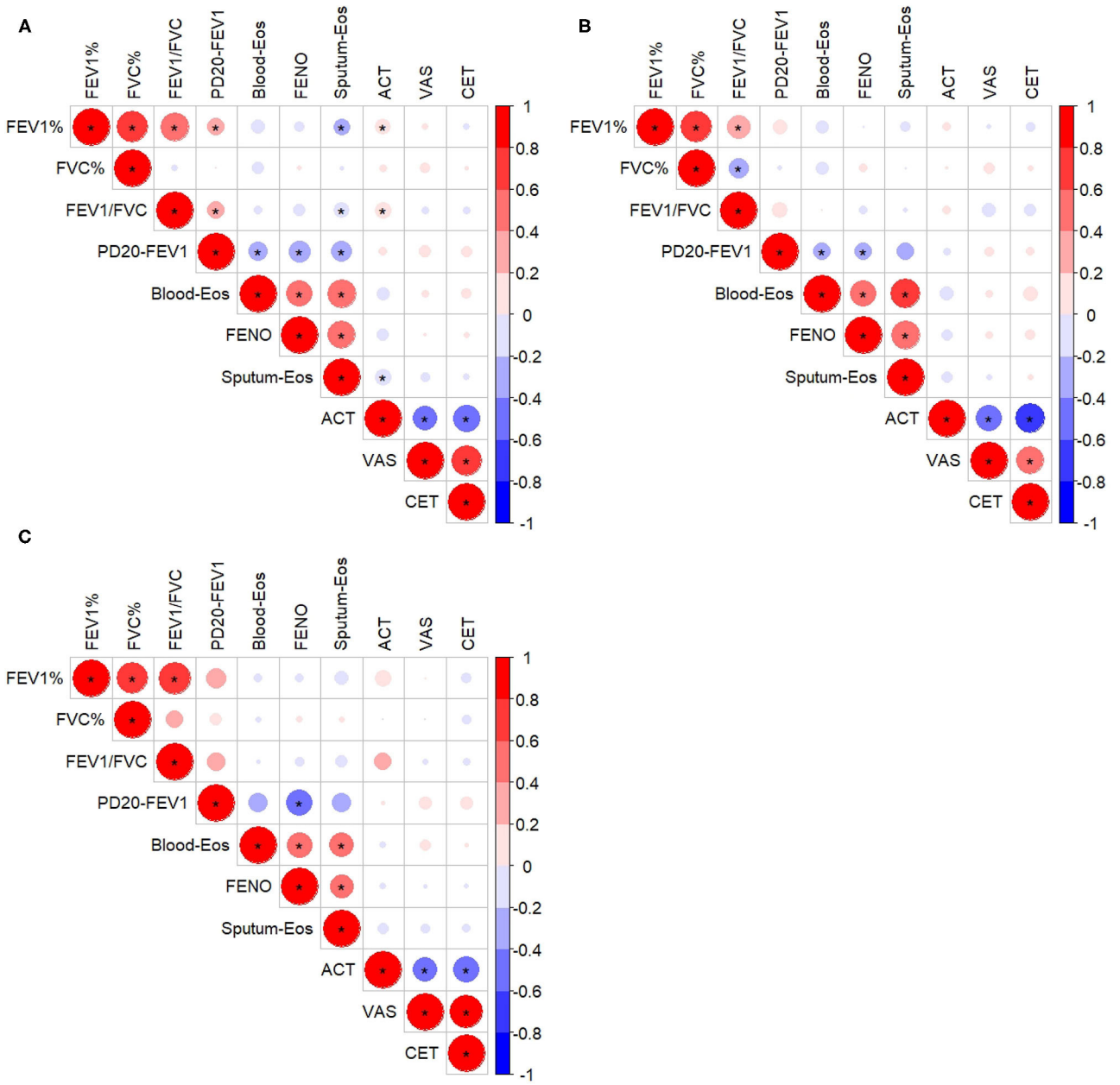


**FIGURE 3 |** Correlation among inflammatory indexes, lung function, and questionnaire assessments in all the subjects **(A)**, the subjects with cough variant asthma **(B)**, and the subjects with classic asthma **(C)**. *Refers to $p < 0.05$. FEV1%, forced expiratory volume in 1 s, % predicted; FVC, forced vital capacity, % predicted; Blood-Eos, blood eosinophil count; FENO, fractional exhaled nitric oxide; Sputum-Eos, sputum eosinophil count; ACT, asthma control test; VAS, cough visual analog scale; CET, cough evaluation test; PD20-FEV1, provocative cumulative dose of methacholine causing a 20% fall in FEV1. The size of the circle and the intensity of the color represent the correlation coefficient, with the larger size and deeper color indicating a higher correlation coefficient value; a red color indicates a positive correlation, while blue color indicates a negative correlation.

not measure cough challenge sensitivity, such as capsaicin inhalation challenge, cough hypersensitivity has been reported to be enhanced in the patients with CVA (11, 20), as well as in CA (38). Therefore, cough hypersensitivity may underlie the asthmatic cough. Cough related to cough hypersensitivity is likely resistant to the mainstay treatment consisting of inhaled corticosteroids and/or add on beta 2 agonists, which successfully relieve airway inflammation and airflow obstruction (42). We previously found that heterogeneity of cough hypersensitivity mediated by TRPV1 and TRPA1 was presented in the patients with chronic refractory cough (43). The heterogeneity underlying the development and persistence of chronic cough and cough hypersensitivity begins with the multiple peripheral and central neural pathways capable of eliciting cough and extends to the

phenotypic and endotypic presentations that can vary between individual asthmatics with cough (44). Central neuromodulators, such as gabapentin, amitriptyline, and pregabalin, as well as the antagonists of the P2X3 receptor, mainly expressed on the C fibers of the primary afferent sensory nerves, are promising antitussives (45). These neuromodulators and new medications that targeted cough hypersensitivity may improve refractory asthmatic cough. A better understanding of how heterogeneity of cough hypersensitivity is expressed across CA and CVA is needed, which would unveil the pathophysiological and molecular mechanisms of asthmatic cough and facilitate the development of more personalized clinical approaches to manage asthmatic cough.

There are some limitations to our study. First, medical history and symptom assessment were assessed by questionnaires, which may be prone to recall bias. Second, the cough features were only measured by subjective questionnaires with lack of objective measures, such as cough count monitoring or cough reflex sensitivity test. The use of such objective measures of cough would be helpful to understand the asthmatic cough more completely. Third, the success rate in obtaining adequate quality sputum for analysis was only in the 57–62% range, which may lead to bias in the assessment of airway inflammation.

In conclusion, we describe the clinical characteristics of newly physician-diagnosed cough variant asthma in one of the largest cohorts of CVA from a multi-center study in China using standard questionnaires with evaluation of cough, airflow obstruction, bronchial hyperresponsiveness, and biomarkers of inflammation. A higher proportion of females, abnormal pharyngeal symptoms, better lung function, milder bronchial hyperresponsiveness, less severe airway eosinophilic inflammation, together with the absence of wheeze, distinguishes CVA from CA. To enable better understanding of disease mechanisms, it would be important to characterize the cough and cough hypersensitivity that spans across both CA and CVA. In addition, cough is a symptom that should be assessed as part of asthma control.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (no. 201675). The patients/participants provided their written informed consent to participate in this study.

## AUTHOR CONTRIBUTIONS

KL, HS, NZ, and RoC: conception and design. WZ, FW, YZ, LL, WLi, FY, ZJ, YD, SL, JL, YY, YJ, CQ, LZ, MC, ZQ, HL, RuC, WL, JX, XY, GS, and DS: recruiting subjects and acquisition of data. MJ, KL, WZ, HS, and NZ: analysis and interpretation. KL, WZ, HS, NZ, and KC: critical review and editing. All authors participated in manuscript writing and editing and read and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.807385/full#supplementary-material

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# Differences in ICU Outcomes According to the Type of Anticancer Drug in Lung Cancer Patients

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**Purpose:** We investigated the intensive care unit (ICU) outcomes of patients who used targeted therapy compared to those who received cytotoxic chemotherapy.

**Materials and Methods:** This study was based on Korean administrative health insurance claims from 2015 to 2019. We extracted data on lung cancer patients (>18 years old) who were admitted to the ICU after receiving chemotherapy.

**Results:** 6,930 lung cancer patients who received chemotherapy within 30 days before ICU admission were identified; the patients received cytotoxic chemotherapy (85.4%, $n = 5,919$) and molecular targeted therapy (14.5%, $n = 1,011$). Grade 4 neutropenia was identified only in the cytotoxic chemotherapy group (0.6%). Respiratory failure requiring ventilator treatment was more common in the cytotoxic chemotherapy group than in the targeted therapy group (HR, 3.30; 95% CI, 2.99–3.63), and renal failure requiring renal replacement therapy was not significantly different between the two groups (HR, 1.57; 95% CI, 1.36–1.80). Patients who received targeted chemotherapy stayed longer in the ICU than the cytotoxic chemotherapy. The 28-day mortality was 23.4% (HR, 0.79; 95% CI, 0.67–0.90, $p < 0.05$) among patients who received targeted agents compared with 29.6% among patients who received cytotoxic chemotherapy.

**Conclusion:** Targeted chemotherapy for lung cancer may contribute to increasing access to critical care for lung cancer patients, which may play a role in improving critical care outcomes of lung cancer patients.

**Keywords: lung cancer, mortality, intensive care unit, chemotherapy, targeted agents**

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## INTRODUCTION

Treatment outcomes for critically ill patients have improved, not only for patients without cancer but also for patients with cancer (1). As a result of the evolution of intensive care unit (ICU) admission strategies, the increase in adherence to sepsis bundle after sepsis survival, and efforts to apply protective lung strategies for mechanical ventilators, ICU outcomes have continuously improved over the last two decades (2). Improvements in cancer treatment outcomes caused by the advent of immunotherapies and targeted therapies allows better outcomes of ICU treatment since many cancer patients are able to recover.

Recent survival improvements with targeted agents and immunotherapies in patients with non-small cell lung cancer (NSCLC) has led physicians to more complex situations where additional factors should be considered in determining critical care for patients with lung cancer (3). The decision whether to proceed to ICU treatment including with mechanical ventilation or hemodialysis has been a complicated and difficult matter for critically ill patients with lung cancer in clinical practice. This decision may have been made reluctantly in that ICU admissions for patients with lung cancer result in high mortality rates (4), high economic burden (5, 6), and poor quality of life after ICU discharge (7). On the other hand, the decision may be positively considered in that ICU survival rates have been improved by significant advances in infection control and critical care (8). Several studies found that patients who were prescribed targeted agents were more likely to continue treatment until near death (9). Additionally, a study showed that patients who received targeted agents tended to receive more aggressive treatments near death, admission to the ICU, and mechanical ventilation (10).

Recently, several studies have showed the overall outcomes of lung cancer patients admitting to ICU according to modality receiving treatment (10, 11), helping physicians to make more careful decisions about ICU treatments for patients with lung cancer. However, little is known about the benefits of ICU treatment in patients with lung cancer who are were treated with targeted therapies or immunotherapies. Therefore, we investigated the outcomes of ICU admission among patients with lung cancer from a national population-based database according to the chemotherapeutic treatment.

# MATERIALS AND METHODS

## Data Source

This is a retrospective observational cohort study that analyzed claims data from the Health Insurance Review and Assessment (HIRA) service in Korea between January 1, 2015 and December 31, 2019. Korea has a single payer national health system. The Korean National Health Insurance (NHI) covers approximately 97% of Koreans, while the 3% of remaining Koreans who cannot afford national insurance are covered by the Medical Aid Program since 1989, and HIRA has reviewed all claims data submitted by the NHI. The national health system manages and supervises the medical use information of all Koreans until death or loss of citizenship.

## Subjects

The study population consisted of lung cancer patients aged 18 years and older who were admitted to the ICU after receiving chemotherapy. We excluded patients who: (1) were >100 years of age, (2) have not received chemotherapy prior to admission to the ICU, and (3) presented with multiple primary lung cancer. We identified patients having cancer (code C34.x of the International Classification of Diseases 10$^{th}$ revision) between January 1, 2015 and December 31, 2019. Follow-up was until December 05, 2020. We identified ICU admissions with codes of ICU services (codes AJ001–AJ590900). Chemotherapy was defined by Korean drug and anatomical therapeutic chemical codes (L01). Chemotherapy-related ICU admission was defined as receiving chemotherapy within 30 days before admission to the ICU.

## Ethics

The research protocol was approved by HIRA. Ethical approval for this study was exempted by the Dongguk University Hospital Institutional Review Board (DUIH 2020-10-040) because the authors only accessed previously collected data.

## Comorbidities and Concomitant Medical Therapy

Comorbidities were defined if claims data existed from 6 months before the index lung cancer diagnosis. Comorbidity diagnoses were defined using ICD-10 codes. The patients' underlying medical conditions were assessed using the Charlson comorbidity index (12). Concomitant medical therapy was defined by the procedure code of the Korean NHI.

## Statistical Analysis

The primary end point was all-cause ICU mortality. The secondary end points were 28-day, 60-day, and 90-day mortality. ICU admissions related to chemotherapy were divided into two groups depending on the type of chemotherapy: cytotoxic agents and targeted agents. Baseline variables and patient characteristics for each group are presented as percentages or as means with standard deviations. Between-group comparisons were estimated using $\chi^2$ tests for categorical data and Student's *t*-tests for continuous data. We used the Kaplan–Meier curve and log-rank test to compare survival data. We performed multivariate analysis using Cox regression adjusted for sex, age, Charlson comorbidity index, lines of treatment for cancer, ventilator support and renal replacement therapy, length from diagnosis with lung cancer and admission into the ICU, receiving surgery or radiation therapy prior to ICU admission, and the year of diagnosis with lung cancer to assess the effect of several factors on survival time. *P*-values of $< 0.05$ were considered statistically significant. All analyses were carried out using R v.3.4.4 (using the packages "survival" and "ggplot2").

# RESULTS

From 2015 to 2019, 6,930 lung cancer patients received chemotherapy within 30 days before admission to the ICU. Most of the patients (85.4%, $n = 5{,}919$) received cytotoxic chemotherapy, and 14.5% ($n = 1{,}011$) received molecular targeted therapy (EGFR, 13.0% or ALK; tyrosine kinase inhibitor, 1.5%) (**Table 1**). Critically ill patients who received targeted therapy before ICU admission were older (66.7 vs. 65.1 years, $p < 0.01$), showed a female predominancy (56.9 vs. 19.6%, $p < 0.01$), and had fewer comorbidities (1.8 vs. 2.1, $p < 0.01$) than patients receiving cytotoxic chemotherapy. There were more patients with metastatic lung cancer in the targeted therapy group than in the cytotoxic group (75.5 vs. 66.0%, $p < 0.01$).

Patients with targeted therapy were treated less frequently with other treatments for cancer, such as surgery (6.6 vs. 22.4%, $p < 0.01$) or radiation therapy (28.8 vs. 43.4%, $p < 0.01$) than

**TABLE 1 |** Population characteristics according to chemotherapy.

| Variable | Total | Cytotoxic chemotherapy | Targeted chemotherapy | *P*-value |
|---|---|---|---|---|
| No. of patients | (*N* = 6,930) | 5,919 (85.4%) | 1,011 (14.6%) | |
| Age at diagnosis for lung cancer | 65.0 ± 9.9 | 64.8 ± 9.5 | 66.2 ± 11.8 | <0.01 |
| Age at ICU admission | 65.4 ± 9.8 | 65.1 ± 9.5 | 66.7 ± 11.8 | <0.01 |
| No. of females | 1,735 (25.0%) | 1,160 (19.6%) | 575 (56.9%) | <0.01 |
| No. of chemo-regimens before ICU | 1.5 ± 0.9 | 1.6 ± 1.0 | 1.1 ± 0.4 | <0.01 |
| Metastatic lung cancer | 4,671 (67.4%) | 3,908 (66.0%) | 763 (75.5%) | <0.01 |
| CCI at ICU admission | 10.0 ± 3.6 | 9.9 ± 3.7 | 10.5 ± 3.4 | <0.01 |
| CCI before diagnosis of lung cancer | 2.1 ± 2.3 | 2.1 ± 2.3 | 1.8 ± 2.4 | <0.01 |
| Mechanical ventilation | 2,961 (42.7%) | 2,568 (43.4%) | 393 (38.9%) | <0.01 |
| Renal replacement therapy | 476 (6.9%) | 413 (7.0%) | 63 (6.2%) | 0.42 |
| Neutropenia | 35 (0.5%) | 35 (0.6%) | 0 (0%) | 0.03 |
| ICU LOS (days) | 23.0 ± 51.0 | 22.3 ± 47.2 | 27.5 ± 69.3 | 0.02 |

*CCI, Charlson Comorbidity Index; ICU, intensive care unit; LOS, length of stay.*

**TABLE 2 |** ICU outcomes in critically ill patients with lung cancer.

| Variable | Total | Cytotoxic chemotherapy | Targeted chemotherapy | *P*-value |
|---|---|---|---|---|
| Overall ICU mortality | 4,676 | 4,020 (67.9%) | 656 (64.9%) | <0.01 |
| Overall ICU mortality at 28-day | 1,988 | 1,751 (29.6%) | 237 (23.4%) | <0.01 |
| Overall ICU mortality at 60-day | 2,490 | 2,186 936.9%) | 304 (30.1%) | <0.01 |
| Overall ICU mortality at 90-day | 2,560 | 2,246 (37.9%) | 314 (31.1%) | <0.01 |

*ICU, intensive care unit.*

those who received cytotoxic chemotherapy. Among patients who received targeted chemotherapy before admission to the ICU, 12.1% of patients had a history of cytotoxic chemotherapy. In comparison, 12.6% of patients who received cytotoxic chemotherapy just before ICU admission had a history of targeted therapy.

Critically ill patients who had received targeted therapy before admission to the ICU were treated less often with a mechanical ventilator (38.9 vs. 43.4%, $p < 0.01$). However, renal replacement therapy did not show a statistical difference in the two groups. In addition, patients who had received targeted therapy before ICU admission stayed significantly longer in the ICU than those who received cytotoxic chemotherapy (27.5 ± 69.3 vs. 22.3 ± 47.2, $p = 0.02$). Among survivors, the targeted therapy group also stayed longer in the ICU (26.0 ± 62.2) than those treated with cytotoxic therapy (21.2 ± 44.8, $p = 0.05$).

The overall ICU mortality rate at 28, 60, and 90 days was significantly lower in patients who received targeted agents before ICU than those who received cytotoxic chemotherapy (**Table 2**). The 28-day mortality rate was 23.4% (237/1,011 patients) for patients who received targeted agents before admission to the ICU (log-rank test, $p < 0.001$; HR 0.72; 95% CI, 0.63–0.83, **Figure 1A**). Cumulative mortality rates at 28 days in patients who received chemotherapy as a first-line regimen (log-rank test, $p < 0.001$; HR for targeted chemotherapy 0.81; 95% CI, 0.72–0.92, **Figure 1B**) and in patients who received chemotherapy as a second-line regimen (log-rank test, $p < 0.001$; HR 0.60; 95% CI, 0.42–0.86, **Figure 1C**) were also statistically significant in both groups.

In the multivariable analysis, receiving targeted agents just before admission to the ICU (HR, 0.79; 95% CI, 0.67–0.90) was significantly associated with ICU mortality at 28 days. Age at ICU admission (HR, 1.03; 95% CI, 1.02–1.03) and being male (HR, 1.45; 95% CI, 1.29–1.63) were also significantly associated with ICU mortality at 28 days (**Table 3**). Respiratory failure requiring a mechanical ventilator in the ICU (HR, 3.30; 95% CI, 2.99–3.63) and renal failure (HR, 1.57; 95% CI, 1.36–1.80) requiring renal replacement therapy were independently associated with aggravated mortality.

## DISCUSSION

In this study, we investigated the effect of targeted therapies on outcomes of ICU treatments compared to cytotoxic chemotherapy in patients with lung cancer. Lung cancer patients receving targeted therapies had a significantly lower ICU mortality rate (HR, 0.79; 95% CI, 0.67–0.90 at 28 days), despite that they were significantly older and had a greater need for mechanical ventilation or renal replacement therapy in the ICU. This result suggests that the advent of targeted therapies could contribute to the improvement of treatment outcomes for critically ill patients with lung cancer.

Despite recommendations for limited therapeutic efforts in the management of critically ill patients with metastatic cancer admitted to the ICU, cancer patients account for about 20% of all patients admitted (13). Critically ill patients with lung cancer receving cytotoxic chemotherapy or targeted therapy may require

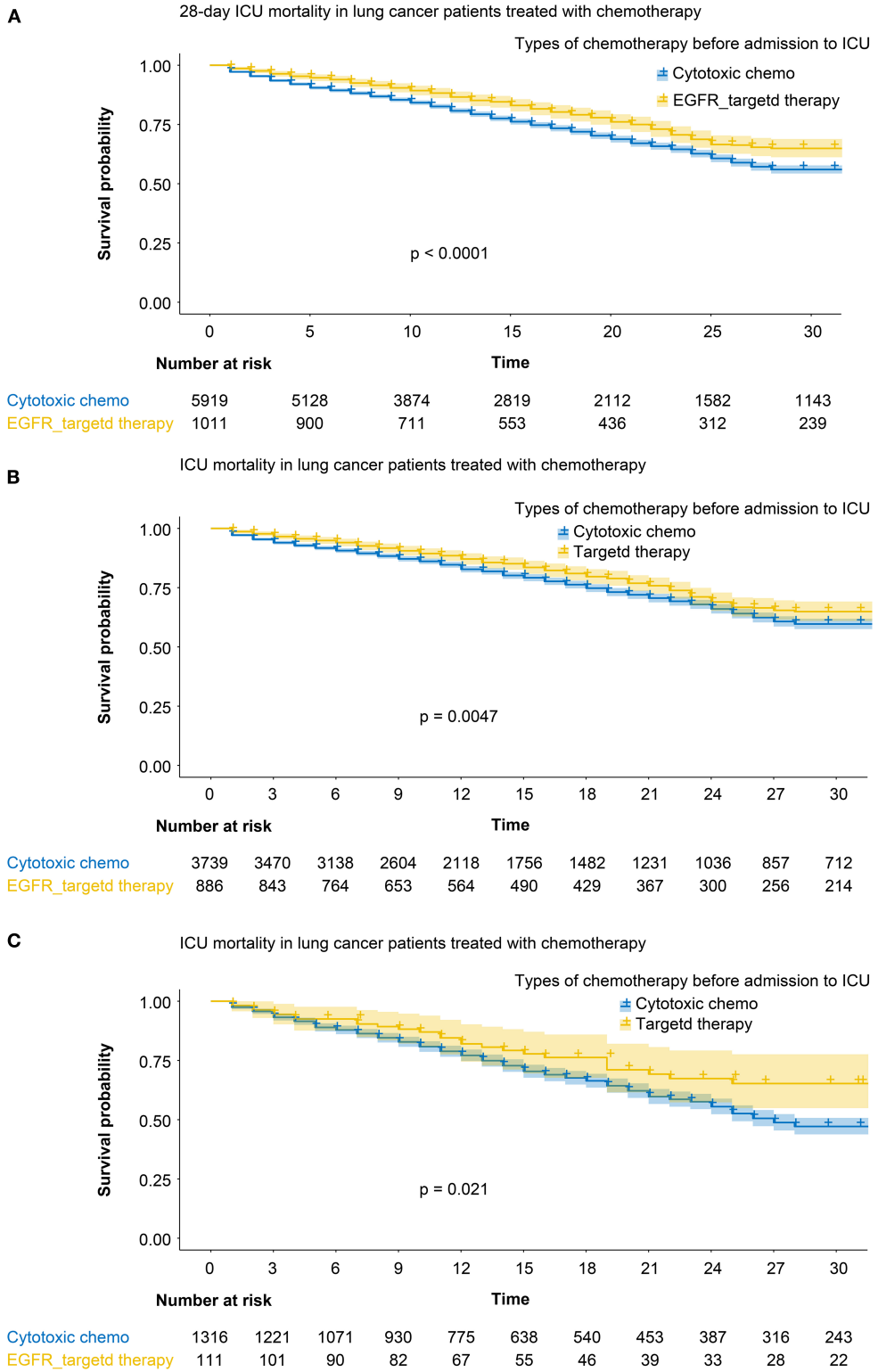


**FIGURE 1 | (A)** 28-day mortality rate among the patients who received targeted agents (yellow line) and those who received cytotoxic chemotherapy (blue line). **(B)** Cumulative mortality rates in patients who received chemotherapy as a first-line regimen. Yellow line: targeted agents, blue line: cytotoxic chemotherapy. **(C)** Cumulative mortality rates in patients who received chemotherapy as a second-line regimen. Yellow line: targeted agents, blue line: cytotoxic chemotherapy.

**TABLE 3 |** Cox proportional hazard analysis for ICU mortality.

| | Unadjusted HR | | | Adjusted HR | | |
|---|---|---|---|---|---|---|
| | **HR** | **95% CI** | ***p*-value** | **HR** | **95% CI** | ***p*-value** |
| Targeted therapy | 0.72 | 0.64–0.81 | <0.01 | 0.78 | 0.67–0.90 | <0.01 |
| Age at ICU admission | 1.00 | 1.00–1.00 | <0.01 | 1.03 | 1.02–1.03 | <0.01 |
| Male | 1.4 | 1.30–1.60 | <0.01 | 1.45 | 1.29–1.63 | <0.01 |
| No. of chemo-regimens before ICU | 1.1 | 1.1–1.2 | <0.01 | 0.86 | 0.83–0.92 | <0.01 |
| Years of diagnosis for lung cancer | 0.87 | 0.84–0.89 | <0.01 | 0.97 | 0.99–1.06 | 0.15 |
| Metastatic lung cancer | 0.82 | 0.75–0.89 | <0.01 | 2.19 | 1.86–2.57 | <0.01 |
| CCI | 0.95 | 0.94–0.96 | <0.01 | 0.87 | 0.85–0.89 | <0.01 |
| Mechanical ventilation | 2.00 | 1.80–2.10 | <0.01 | 3.30 | 2.99–3.63 | <0.01 |
| Renal replacement therapy | 1.60 | 1.40–1.80 | <0.01 | 1.57 | 1.36–1.80 | <0.01 |

*CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; LOS, length of stay.*

ICU level of care, because most of the patients can have an advanced stage and aggressive cares may be a part of only life-sustaining treatments regarding as high mortality rates and side effects after ICU discharge (8). Recently, cancer patients receiving targeted therapy tend to continue treatment almost until death (14). This might be because targeted agents are more tolerable and more effective in advanced lung cancer than cytotoxic agents. Previous studies on critically ill patients with advanced lung cancer did not reflect recent trends in the emergence of targeted therapies (15). The advent of targeted therapies for lung cancer provides the impetus to reconsider the triage strategy and use of the ICU for cancer patients.

A recent study reported a significant improvement in the ICU mortality rates of cancer patients (16). The 28-day mortality in critically ill patients with cancer was reported to be about 50–60% in studies (17) up to the 2000's, but it was reported to be about 30–40% in a more recent study (18). Ostermann et al. (19) reported that the mortality of cancer patients improved from 31.3% in 2003–2005 to 26.0% in 2012–2014, while the change in mortality of non-cancer patients was insignificant, from 20.9 to 23.9%. The improvement in lung cancer mortality rate seems more likely to be a synergistic effect of cancer-related therapies rather than the overall improvement of diagnosis and treatment in the ICU.

Chen et al. reported that anticancer therapy in the ICU improved short-term ICU mortality for treatment-naïve patients with locally advanced lung cancer (20). However, in their subgroup analysis, they did not show a signifiant difference in ICU mortality at 28 days among those treated with cytotoxic chemotherapy and targeted therapy, but the number of study subjects was small. Our study shows that an overall survival benefit from ICU treatments could be achieved in patients receiving targeted therapy compared with lung cancer patients receiving cytotoxic chemotherapy. Consistent with previous studies, the presence of organ failure including respiratory failure or renal failure in critically ill patients was an important factor associated with mortality in critically ill patients with lung cancer (21). These results suggest that lung cancer patients receiving targeted therapy could be considered more suitable for ICU treatment.

This study had several limitations. First, we analyzed administrative data. Therefore, it was not available about sociodemographic characteristics and questionnaire data and not seletable for genetic and behavioral disorders. In addition, information on cancer staging or subtypes, such as SCLC or NSCLC, was also not detailed. Based on whether the lung cancer had metastasized, we could assume whether the cancer was at a more advanced stage. However, this cannot replace direct staging of lung cancer. Second, in this study, most patients with SCLC would have been classified into the cytotoxic chemotherapy group. Third, we had no information on the reasons for critical care. Therefore, our results should be interpreted with caution.

Still, this study might be meaningful because it is the first study to show that patients who received targeted cancer therapy could have better outcomes in the ICU, unlike those treated with drugs such as cytotoxic chemotherapy. However, further validation is needed to confirm our results. The effect of cancer stage, which was not identified in this study, on improving ICU treatment outcomes of targeted therapy also needs to be confirmed in future studies.

## CONCLUSION

It remains difficult to predict which cancer patients will recover with critical care. For continuous improvement of ICU treatment, it is necessary to consider the patient's current condition, including the type of chemotherapy, the patient's treatment intention, the responsiveness to cancer treatment, the future treatment plan, the level of ICU treatment, the possibility of lung treatment, and other factors. Future studies would shed more light on the underlying interactions of these parameters and could help in developing novel diagnostic and therapeutic strategies for lung cancer management.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because our database was provided by HIRA. We only accessed deidentified previously collected administrative

data. Requests to access the datasets should be directed to https://opendata.hira.or.kr.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Dongguk University Hospital Institutional Review Board (DUIH 2020-10-040). The Ethics Committee waived the requirement of written informed consent for participation. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

## AUTHOR CONTRIBUTIONS

All authors listed contributed to the conception and design of the work, to the acquisition, analysis, interpretation of the data, to drafting the manuscript and approved it for publication.

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# Effectiveness of Proton-Pump Inhibitors in Chronic Obstructive Pulmonary Disease: A Meta-Analysis of Randomized Controlled Trials

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**Background:** Although several randomized controlled trials (RCTs) have been published in recent years, the role of proton-pump inhibitors (PPI) in patients with chronic obstructive pulmonary disease (COPD) remains controversial. This preliminary meta-analysis was conducted to evaluate the clinical efficacy of PPI in patients with COPD.

**Methods:** RCTs related to PPI in the treatment of patients with a definite diagnosis of COPD were enrolled in this meta-analysis. PubMed, Embase, Cochrane Library, CNKI, Wanfang and VIP databases were retrieved to identify eligible studies from database establishment to September 22, 2021. Two researchers independently screened the articles, extracted the data and evaluated the risk of bias in the included studies independently. The study complied with PRISMA 2020 guideline for this study. The meta-analysis was performed using RevMan 5.3. Heterogeneity among studies was tested using the $I^2$ test. The results were presented as risk ratios (RRs) with 95% confidence intervals (CIs).

**Results:** A total of 15 RCTs, including 1,684 patients, were enrolled. The meta-analysis revealed that PPI plus conventional treatment was superior to conventional treatment with respect to the case fatality rate (RR = 0.30; 95% CI, 0.18–0.52; $P < 0.001$), the incidence of gastrointestinal bleeding (RR = 0.23; 95% CI, 0.14–0.38; $P < 0.001$), the incidence of other adverse reactions (RR = 0.33; 95% CI, 0.28–0.39; $P < 0.001$) and the number of acute exacerbations [mean difference (MD) = −1.17; 95% CI, 1.75 to −0.60: $P < 0.001$] in patients with COPD. No significant differences were found in clinical efficacy (RR = 1.08; 95% CI, 0.95–1.22; $P = 0.25$), FEV1/FVC (MD = 3.94; 95% CI, −8.70 to 16.58; $P = 0.54$) and nosocomial infection rate (RR = 1.31; 95% CI, 0.57–3.00; $P = 0.52$) between the two groups.

**Discussion:** This comprehensive meta-analysis suggested that PPI treatment for COPD may reduce the case fatality rate, incidence of gastrointestinal bleeding and other adverse reactions and number of acute exacerbations. However, the present meta-analysis also has some limitations of the evidence, such as the high risk of bias of the included studies, and predominance of included studies from China, which may result in publication bias. Therefore, further large-scale RCTs are needed to confirm our findings.

**Systematic Trial Registration:** Identifier: CRD42022301304.

**Keywords: proton pump inhibitors, chronic obstructive pulmonary disease, clinical efficacy, gastroesophageal reflux disease, meta-analysis**

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## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory disease characterized by persistent airflow limitation and dyspnoea. It is the third leading cause of death worldwide and causes a huge economic burden to society because of its chronic disease course, repeated acute exacerbations and effects on performing activities of daily living (1). Previous studies have shown that the prevalence of gastroesophageal reflux disease (GERD) in patients with COPD was higher than that in the normal population. GERD may cause acute exacerbation of COPD and is considered an independent risk factor for COPD death (2–4). COPD and GERD are mutually causal, forming a vicious circle, which seriously affects the quality of life (5). Proton-pump inhibitors (PPI) are the first-line drugs for the treatment of GERD. PPI therapy for patients with COPD complicated with GERD may reduce the number of acute exacerbations of COPD, thus delaying disease progression of the disease and improving clinical outcomes.

Thus, far, the pathogenesis of COPD remains unclear. Many patients with COPD complicated with GERD have not received formal diagnosis and treatment, and numerous GERD cases are asymptomatic. In addition, the systemic efficacy and mortality risk of PPI in patients with COPD are controversial. Herein, we conducted a comprehensive meta-analysis of randomized controlled trials (RCTs) to explore the clinical efficacy and safety of PPI therapy in patients with COPD.

## METHODS

### Eligibility Criteria

RCTs were strictly screened following the PICOS principle (participants, interventions, comparisons, outcomes and study design). The inclusion criteria were as follows: (1) the participants were diagnosed with COPD according to the COPD Global Initiative (GOLD guidelines) (6); (2) RCTs compared conventional treatment plus PPI treatment with conventional treatment alone, and (3) RCTs were included regardless of the absence or presence of blind. The exclusion criteria were as follows: (1) basic experiments, animal experiments, repeated publications, and documents that cannot extract key information such as intervention measures and outcome indicators, and (2) the articles that have obvious experimental design errors or data errors.

### Information Sources and Search Strategy

The search conducted using a combination of subject terms and entry terms as follows: Pulmonary Disease, Chronic Obstructive, Chronic Obstructive Lung Disease, Chronic Obstructive Pulmonary Diseases, COAD, COPD, Chronic Obstructive Airway Disease, Chronic Obstructive Pulmonary Disease, Airflow Obstruction, Chronic, Airflow Obstructions, Chronic, Chronic Airflow Obstructions, Chronic Airflow Obstruction, Proton-pump Inhibitors, Inhibitors, Proton-pump, Proton-pump Inhibitor, Inhibitor, Proton-pump, Pump Inhibitor, Proton, Omeprazole, Esomeprazole, Esomeprazole, Rabeprazole, Pantoprazole, Ilaprazole, Lansoprazole, etc. Moreover, the references of the included articles were screened to determine appropriate related studies.

### Data Collection and Quality Assessment

Two researchers (Fei Yu and Qi-hui Huang) screened the articles and extracted data independently according to the PRISMA 2020 recommendations (7). Discussion or third-party negotiation was conducted in case of a dispute. If necessary, the authors of the enrolled studies were contacted by email or telephone to obtain information that was not presented in the article but was important to the present study. The following details were extracted from each study: basic information of the studies, baseline characteristics of the research object, test grouping, specific treatment measures, key elements of the bias risk assessment, outcome indicators and specific data.

In this study, the primary outcome indicators were the case fatality rate and clinical efficacy. The secondary outcome indicators include forced expiratory volume in 1/forced vital capacity (FEV1/FVC), gastrointestinal bleeding, other adverse reactions, nosocomial infections and number of acute exacerbations. Two investigators independently (Fei Yu and Qi-hui Huang) evaluated the risk of bias in the included studies and cross-checked the results. The second version of the Cochrane tool for assessing RoB in RCTs (RoB2) was used (8). This tool consists of the following five parts: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcomes and bias in the selection of the reported result. The risk levels are classified as low risk of bias, some concerns and high risk of bias. In addition, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) was used to rate the level of evidence of the outcomes obtained in this study (9). Assessment of the quality of evidence considers five aspects: limitations, inconsistencies, indirectness, inaccuracy and publication bias.

### Statistical Analyses

RevMan 5.3 was used for statistical analysis. Results of the meta-analysis of categorical variables were presented as Risk Ratios (RRs) with 95% confidence intervals (CIs), and the results of the analysis of continuous variables were presented as mean difference (MD) with 95% CIs. The results were expressed by $P$-value, and $P < 0.05$ indicated the difference between two intervention measures. Heterogeneity test was conducted on the results of the study. The $I^2$ test was used to analyze the heterogeneity among the results of the study within the group. If the heterogeneity test results were $P \geq 0.1$ and $I^2 < 50\%$, the fixed-effects model was selected. In contrast, if $P < 0.1$ or $I^2 \geq 50\%$, the random-effects model was used. Sensitivity analysis and subgroup analysis were conducted when the heterogeneity was significant.

## RESULTS

In the present meta-analysis, 122 relevant studies were retrieved: 9 from PubMed, 39 from EMBASE, 1 from the Cochrane Library, 21 from the VIP, 33 from the CNKI and 28 from the WanFang

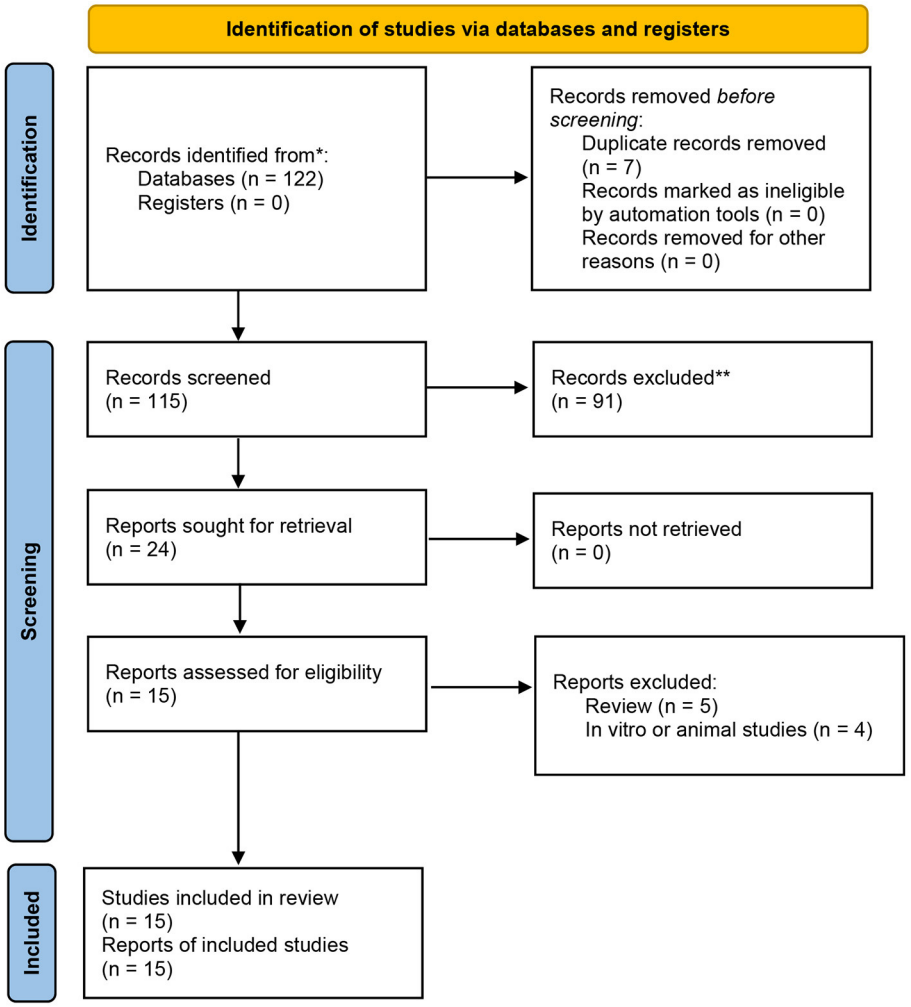


**FIGURE 1 |** The PRISMA 2020 flow chart.

database. After screening, 15 RCTs (10–24) were identified for this meta-analysis. Overall, these studies included 1,684 patients, 806 of whom received conventional treatment (control group) and 878 of whom received conventional treatment pklus PPI therapy (PPI group). The details of literature search and selection procedures are showed in **Figure 1**. The basic information of all patients is shown in **Table 1**.

## Quality Assessment

As previous mentioned, we used RoB2 to assess the risk of bias and the GRADE to rate the level of evidence of the outcomes in this meta-analysis (8, 9). Risk assessment results suggested that five studies were at low risk (14, 16, 18, 20, 23), three had some concerns (10, 13, 19) and seven studies had high risk (11, 12, 15, 17, 21, 22, 24). The risk of bias for each included study is shown in **Figure 2** and the GRADE evidence levels of all outcomes are shown in **Table 2**.

## Case Fatality Rate

A total of nine studies (12, 13, 15–19, 23, 24) compared the case fatality rates between the PPI group ($n = 523$) and the control group ($n = 450$). The results of the heterogeneity test showed $I^2 = 0\%$, so the fixed-effects model was used for combined analysis. Results of the meta-analysis revealed that the case fatality rate of the PPI group can be significantly reduced compared with that of the control group (RR = 0.3; 95% CI, 0.18–0.52; $P < 0.0001$) (**Figure 3**).

## Clinical Efficacy

Six studies (14, 15, 20, 22–24) reported the clinical efficacy of PPI therapy in the PPI group ($n = 390$) in comparison with the control group ($n = 307$). The heterogeneity test showed $I^2 = 59\%$. The sensitivity analysis suggested that the study conducted by Zu et al. (20) might be the source of heterogeneity. Therefore, a random-effects model analysis was used. The results of the meta-analysis presented the lack of significant difference between the two groups (RR = 1.08; 95% CI, 0.95–1.22; $P = 0.25$) (**Figure 4**).

**TABLE 1 |** The basic characteristics of involved trials.

| References | Study period | Patients | Sample size | Mean medical history | Intervention | | Outcome indicators |
|---|---|---|---|---|---|---|---|
| | | | T/C | T/C | T | C | |
| Sasaki et al. (10) | 2005.10–2007.03 | COPD | 50/50 | / | CT + Lansoprazole 15 mg QD | CT | g |
| Huang (11) | 2016.11–2018.02 | COPD + AE + RF | 40/40 | / | CT + Pantoprazole 40 mg Q12H | CT | ade |
| Wang (12) | 2013.04–2014.10 | COPD + AE + RF | 100/100 | 5.78 ± 2.84/ 5.58 ± 2.92 | CT + Pantoprazole 40 mg Q12H | CT | ade |
| Li (13) | 2015.10–2016.10 | COPD + AE + RF | 31/31 | 5.43 ± 2.34/ 5.76 ± 2.15 | CT + Pantoprazole 40 mg Q12H | CT | ade |
| Xiong (14) | 2016.10–2017.10 | COPD + AE + RF | 32/32 | 4.5 ± 3.3/ 4.0 ± 3.0 | CT + Pantoprazole 40 mg Q12H | CT | bde |
| Zhen (15) | 2014.03–2016.04 | COPD + AE + RF | 34/34 | 10.2 ± 1.3/ 9.8 ± 1.4 | CT + Pantoprazole 40 mg BID | CT | abe |
| Gu (16) | 2016.01–2017.09 | COPD + RF | 32/35 | 15.6 ± 2.4/ 15.9 ± 2.6 | CT + Pantoprazole 40 mg QD | CT | ade |
| Xu and Jiao (17) | 2013.01–2014.03 | COPD + AE + RF | 50/50 | / | CT + Pantoprazole 40 mg BID | CT | ade |
| Hu (18) | 2013.07–2014.08 | COPD | 63/63 | 4.89 ± 1.33 | CT + Omeprazole 20 mg QD | CT | defg |
| Hu and Hua (19) | 2010.01–2014.01 | COPD + AE + RF | 74/80 | / | CT + Pantoprazole 40 mg Q12H | CT | ade |
| Zu (20) | 2018.01–2019.01 | COPD + GRED | 42/41 | 9.6 ± 2.5/ 8.8 ± 1.9 | CT + Esomeprazole | CT | bc |
| Zan et al. (21) | 2012.01–2012.06 | COPD + AE + GRED | 48/50 | / | CT + Omeprazole 20 mg BID | CT | c |
| Xiao (22) | 2019.01–2019.09 | COPD + AE + RF | 120/120 | 9.12 ± 2.07/ 9.22 ± 2.64 | CT + Pantoprazole 40 mg Q12H | CT | be |
| Zhang et al. (23) | 2015.1–2017.05 | COPD + AE | 102/50 | / | CT + Pantoprazole | CT | abdef |
| Zhi et al. (24) | 2017.11–2018.11 | COPD + AE | 60/30 | 13.1 ± 1.1 | CT + Pantoprazole | CT | abde |

*COPD, chronic obstructive pulmonary disease; AE, acute exacerbations; RF, respiratory failure; CT, conventional treatment; a, case fatality rate; b, clinical efficacy; c, Forced expiratory volume in one second/Forced vital capacity (FEV1/FVC); d, gastrointestinal bleeding; e, other adverse reactions; f, nosocomial infections; g, the number of acute exacerbations; /, unspecified.*

## Incidence of Gastrointestinal Bleeding

A total of 10 studies (12–14, 16–19, 23, 24) reported gastrointestinal bleeding events, including 584 and 511 cases in the PPI group and control group, respectively. The heterogeneity test showed $I^2 = 0\%$; therefore, a fixed-effects model was employed. The results of the meta-analysis revealed that the incidence of gastrointestinal bleeding can be significantly reduced in patients with COPD who received PPI (RR = 0.23; 95% CI, 0.14–0.38; $P < 0.00001$) (**Figure 5**).

## Incidence of Other Adverse Reactions

Eleven studies (11–19, 22, 23) reported other adverse events except gastrointestinal bleeding, including 738 and 665 cases in the PPI group and control group, respectively. The heterogeneity test showed $I^2 = 0\%$; thus, a fixed-effects model was used. Compared with conventional treatment alone, PPI therapy in patients with COPD can reduce the incidence of other adverse reactions (RR = 0.33; 95% CI, 0.28–0.39; $P < 0.00001$) (**Figure 6**).

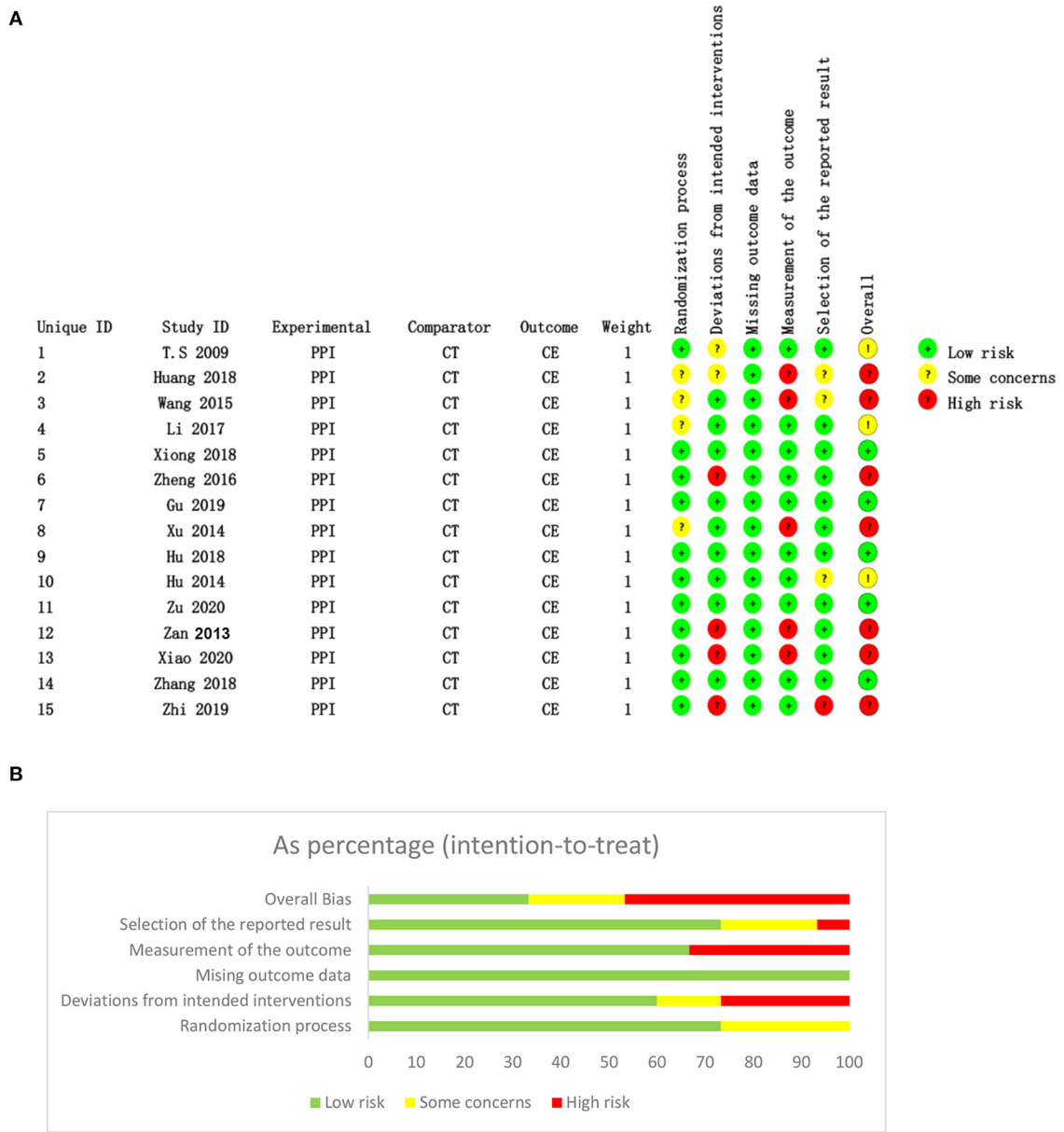


**FIGURE 2 |** Risks of bias assessed by RoB2 for each included study ($n = 15$). **(A)** Risk of bias graph; **(B)** risk of bias summary. CT, conventional treatment; CE, clinical efficacy.

## Number of Acute Exacerbations

Two studies (10, 18) reported the number of acute exacerbations, including 113 cases each in the PPI and control groups. The heterogeneity test showed $I^2 = 85\%$; therefore, a random-effects model was chosen. Compared with conventional treatment alone, PPI therapy in patients with COPD can reduce the number of acute exacerbations (MD = −1.17; 95% CI, −1.75 to −0.60; $P < 0.0001$) (**Figure 7A**).

## FEV1/FVC

Two studies (20, 21) reported on pulmonary ventilation function, including 90 and 91 cases in the PPI group and control group, respectively. The heterogeneity test showed $I^2 = 96\%$; therefore, a random-effects model was chosen. The results of the meta-analysis showed no significant difference between the two groups (MD = 3.94; 95% CI, −8.70 to −16.58; $P = 0.54$) (**Figure 7B**).

## Nosocomial Infection Rate

Two studies (18, 23) reported the occurrence of nosocomial infections, including 165 and 113 cases in the PPI group and control group, respectively. The heterogeneity test showed $I^2 = 0\%$; therefore, a fixed-effects model was used. The results of the meta-analysis revealed no significant difference between the two groups (RR = 1.31; 95% CI, 0.57–3.00; $P = 0.52$) (**Figure 7C**).

**TABLE 2 |** The evidence level of the outcomes obtained in this study was evaluated using GRADE.

| Quality assessment | | | | | | | No of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **No of studies** | **Design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **PPI** | **Conventional treatment** | **Relative (95% CI)** | **Absolute** | | |
| **Case fatality rate** | | | | | | | | | | | | |
| 9 | Randomized trials | Serious[a] | No serious inconsistency | No serious indirectness | No serious imprecision | Reporting bias[a] | 16/523 (3.1%) | 42/450 (9.3%) | RR 0.3 (0.18 to 0.52) | 65 fewer per 1,000 (from 45 fewer to 77 fewer) | ⊕⊕◯◯ LOW | |
| | | | | | | | | 8.6% | | 60 fewer per 1,000 (from 41 fewer to 71 fewer) | | |
| **Clinical efficacy** | | | | | | | | | | | | |
| 5 | Randomized trials | Serious[a] | No serious inconsistency | No serious indirectness | No serious imprecision | None | 290/348 (83.3%) | 213/266 (80.1%) | RR 1.1 (1.02 to 1.19) | 80 more per 1,000 (from 16 more to 152 more) | ⊕⊕⊕◯ MODERATE | |
| | | | | | | | | 70% | | 70 more per 1,000 (from 14 more to 133 more) | | |
| **Incidence of gastrointestinal bleeding** | | | | | | | | | | | | |
| 10 | Randomized trials | Serious[a] | No serious inconsistency | No serious indirectness | No serious imprecision | Reporting bias[a] | 16/584 (2.7%) | 67/511 (13.1%) | RR 0.23 (0.14 to 0.38) | 101 fewer per 1000 (from 81 fewer to 113 fewer) | ⊕⊕◯◯ LOW | |
| | | | | | | | | 15.1% | | 116 fewer per 1,000 (from 94 fewer to 130 fewer) | | |
| **Incidence of adverse reactions** | | | | | | | | | | | | |
| 11 | Randomized trials | Serious[a] | No serious inconsistency | No serious indirectness | No serious imprecision | Reporting bias[a] | 122/678 (18%) | 334/635 (52.6%) | RR 0.33 (0.28 to 0.39) | 352 fewer per 1000 (from 321 fewer to 379 fewer) | ⊕⊕◯◯ LOW | |
| | | | | | | | | 48% | | 322 fewer per 1,000 (from 293 fewer to 346 fewer) | | |
| **The number of acute exacerbations (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | Randomized trials | Serious[a] | Serious[a] | No serious indirectness | No serious imprecision | None | 113 | 113 | – | MD 1.17 lower (1.75 to 0.6 lower) | ⊕⊕◯◯ LOW | |
| **FEV1/FVC (Better indicated by lower values)** | | | | | | | | | | | | |
| 2 | Randomized trials | Serious[a] | No serious inconsistency | Serious[a] | No serious imprecision | None | 90 | 91 | – | MD 3.94 higher (8.7 lower to 16.58 higher) | ⊕⊕◯◯ LOW | |
| **Nosocomial infection rate** | | | | | | | | | | | | |
| 2 | Randomized trials | Serious[a] | Serious[a] | No serious indirectness | Serious[a] | None | 17/165 (10.3%) | 7/113 (6.2%) | RR 1.31 (0.57 to 3) | 19 more per 1,000 (from 27 fewer to 124 more) | ⊕◯◯◯ VERY LOW | |
| | | | | | | | | 6.8% | | 21 more per 1,000 (from 29 fewer to 136 more) | | |

[a] *means Risk of bias graph.*

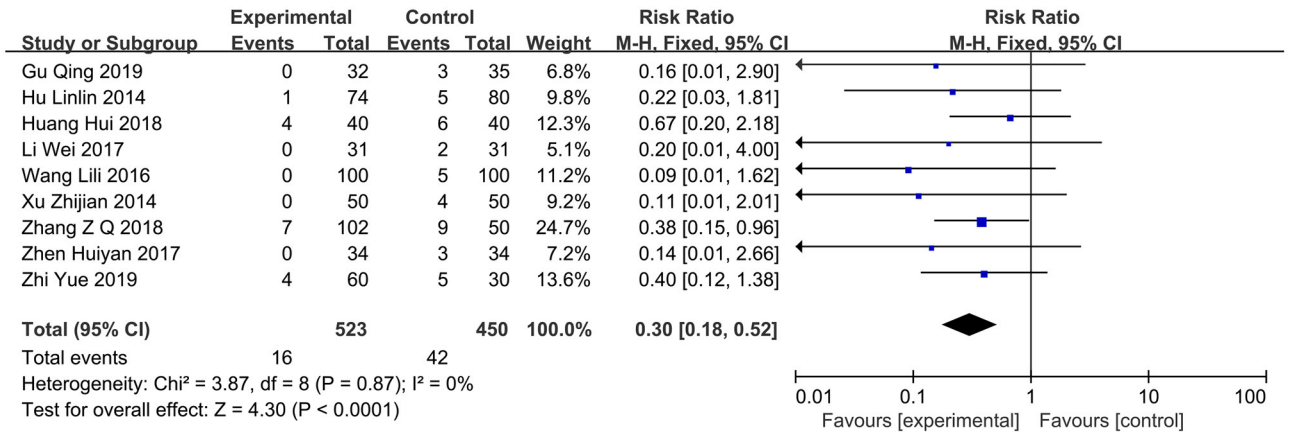


**FIGURE 3 |** Forest plot of the case fatality rate between the PPI treatment group and the conventional treatment group. PPI, proton-pump inhibitor.

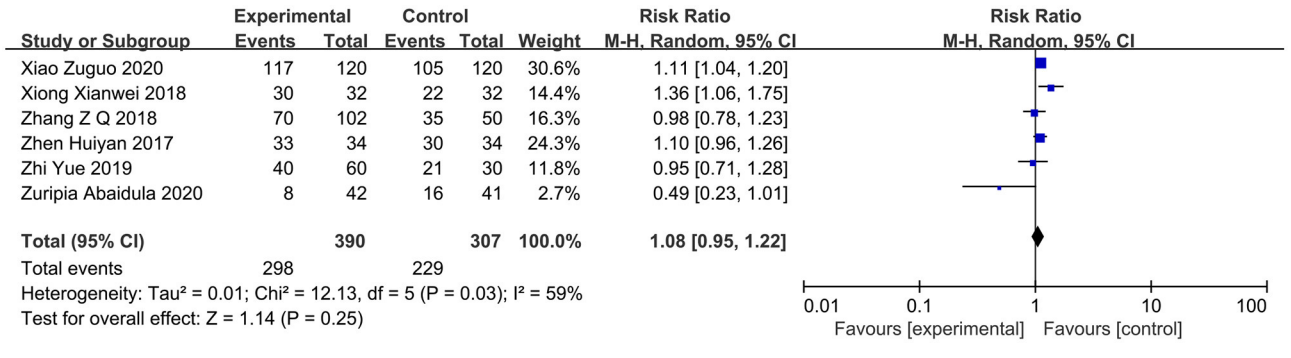


**FIGURE 4 |** Forest plot of the clinical efficacy between the PPI treatment group and the conventional treatment group. PPI, proton-pump inhibitor.

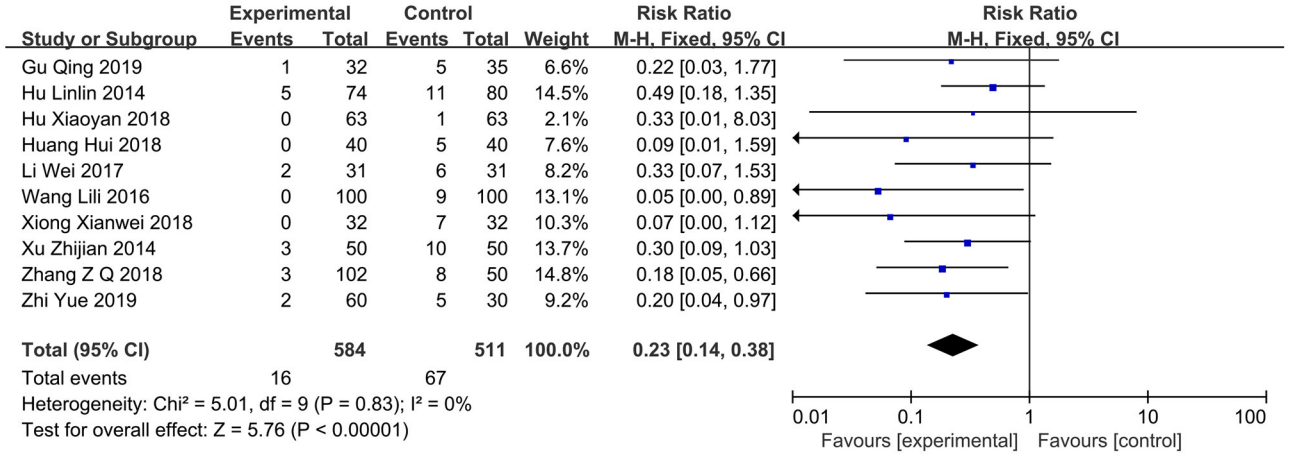


**FIGURE 5 |** Forest plot of the incidence of gastrointestinal bleeding between the PPI treatment group and the conventional treatment group. PPI, proton-pump inhibitor.

## Publication Bias

The present study included 15 studies, of which, 13 were from China. Therefore, there may be some publication bias in this study. We used funnel plots to verify publication bias (**Figure 8**). The graph that is not completely symmetrical indicated some

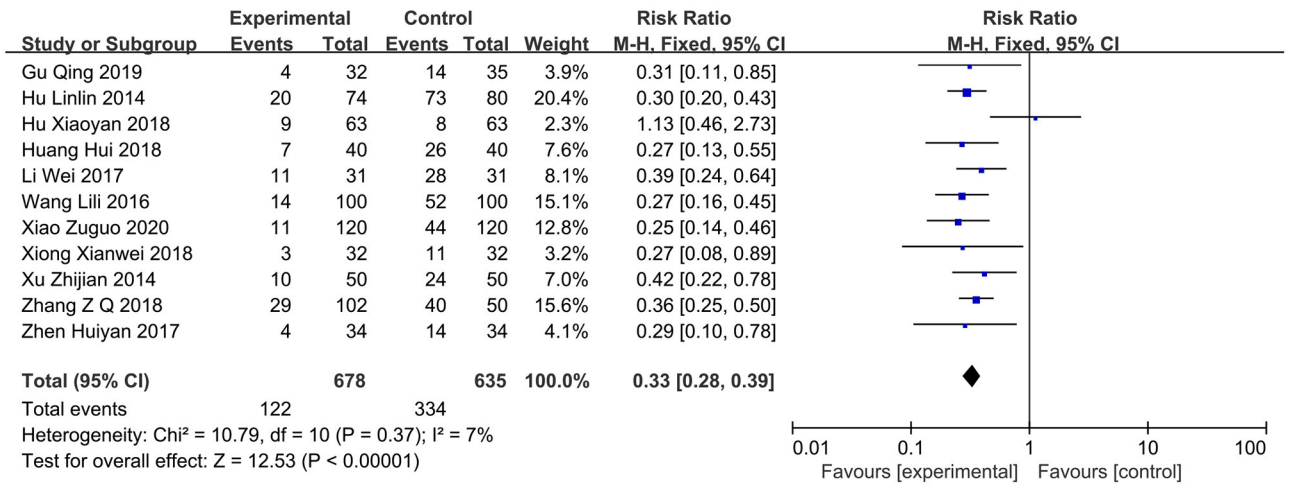


**FIGURE 6 |** Forest plot of the incidence of other adverse reactions between the PPI treatment group and the conventional treatment group. PPI, proton-pump inhibitor.

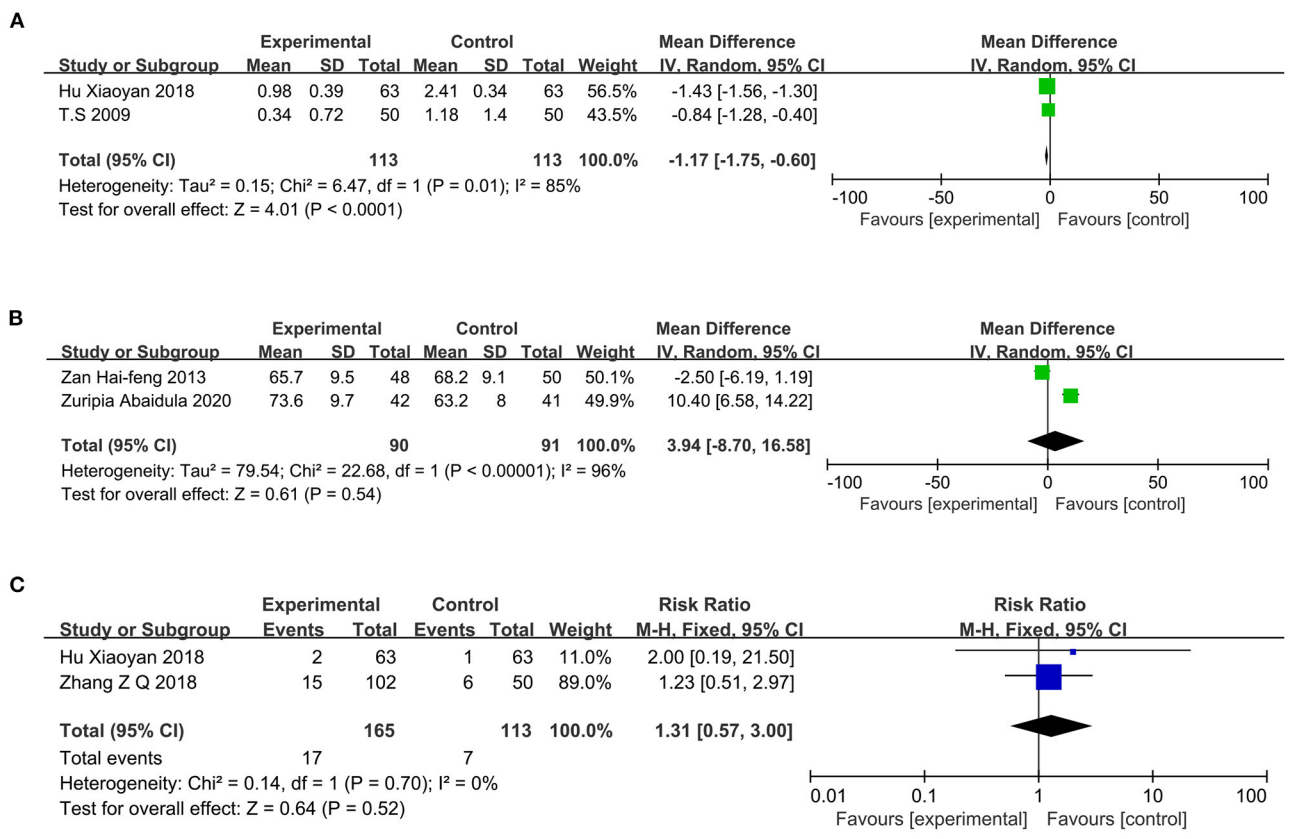


**FIGURE 7 | (A)** Forest plot of the number of acute exacerbations between the PPI treatment and conventional treatment groups; **(B)** Forest plot of FEV1/FVC between the PPI treatment and conventional treatment groups; **(C)** Forest plot of nosocomial infection rate between the PPI treatment and conventional treatment groups. FEV1/FVC, forced expiratory volume in 1 s/forced vital capacity; PPI, proton-pump inhibitor.

publication bias. This is also one of the limitations of the present study.

## DISCUSSION

Recently, several RCTs have focused on the role of PPI in patients with COPD. A study suggested that PPI therapy was safe and feasible in patients with COPD (25). A systematic review in the Cochrane database also tried to explore the effect of PPI therapy on patients with COPD. However, this study was only at the design stage, and no specific conclusions have been drawn (26). Therefore, we conducted this meta-analysis to clarify this issue. The results of this study suggested that PPI therapy in patients with COPD can reduce the case fatality rate, occurrence of gastrointestinal bleeding, other adverse reactions and number of acute exacerbations. The findings from this study may provide some guidance for the application of PPI in patients with COPD.

The results of the present study can be attributed to the following aspects: First, patients with COPD have long-term hypoxia, the gastrointestinal tract is the most sensitive organ for ischemia and hypoxia, and there are varying degrees of gastric mucosal damage. Especially, for older people who often have atherosclerosis and long-term use of non-steroidal drugs, the risk of gastrointestinal bleeding is high (27, 28). PPI is an H+/K+-ATPase inhibitor that has a strong inhibitory effect on gastric acid secretion and a protective effect on the gastric mucosa. It can effectively prevent and treat upper gastrointestinal bleeding, promote enteral nutrition support for patients immediately, enhance immunity and reduce abdominal distension and incidence of adverse reactions, such as diarrhea (25). Second, the clinical manifestations of COPD include repeated coughing, sputum expectoration and wheezing, which are closely related to a deteriorated condition (29). PPI can reduce the irritation of gastric acid and reflux of gastric contents on the esophagus and bronchi and relieve cough, sputum production and other uncomfortable clinical manifestations. Moreover, it can reduce the incidence of minor spiration caused by gastroesophageal reflux and avoid the occurrence of aspiration pneumonia (30). Third, previous studies have found that local or systemic inflammatory infection is an important factor for the pathogenesis of COPD, and more evidence supports the use of PPI to reduce inflammation (29–32). PPI can improve neurogenic inflammation, reduce plasma and sputum substance levels, block gastric acid secretion and selectively inhibited tumor necrosis factor-αand interleukin-1β secretion by Toll-like receptor-activated human monocytes *in vitro*, in the absence of toxic effects. Thus, the risk of infection in patients with COPD was reduced (1, 2). Fourth, mortality outcomes of patients with COPD are closely related to the frequency of acute exacerbations. PPI can reduce the risk of infection and the number of acute exacerbations in COPD patients, thereby reducing the risk of death. Fifth, 12 RCTs included in this study enrolled patients with acute exacerbations or even respiratory failure requiring hospitalization. Such patients have poor lung function on admission. Conventional treatments such as antibiotic therapy, nebulisation, resolving phlegm and administration of antispasmodic and anti-asthmatic drugs have contributed most to the improvement of respiratory function. Compared with conventional treatment, short-term PPI therapy during hospitalization cannot show a significant improvement in FEV1/FVC indicators. Sixth, in recent years, studies have found that the intestinal microbiota can regulate the systemic immune response, thereby affecting the function of extraintestinal organs. The gut-lung axis has received increasing attention on whether long-term PPI therapy causes bacterial overgrowth in the small intestine, bacterial peritonitis, intestinal flora shift, etc. There is currently no high-quality evidence (25, 33–35).

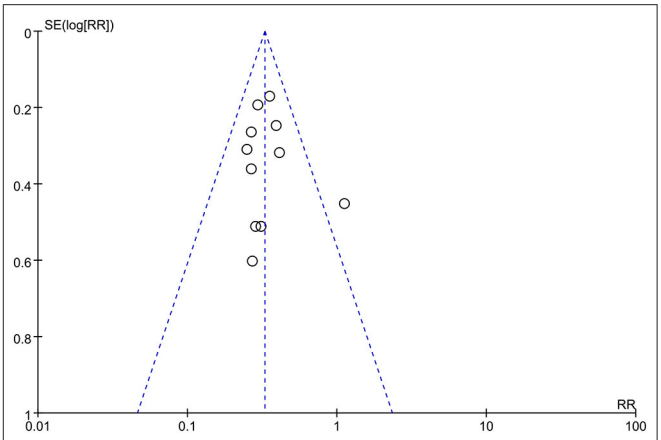


**FIGURE 8 |** Funnel plot of the effect of proton-pump inhibitor therapy on patients with chronic obstructive pulmonary disease.

The preset study analyzed the effect of PPI therapy on the occurrence of nosocomial infections in patients with COPD, and tried to explore the contribution of PPI to the overall inflammatory response. However, two articles were finally included. The results were not statistically significant, and the effect of PPI therapy on the occurrence of nosocomial infections in patients with COPD has not been proved yet.

However, this study has the following limitations: First, the included studies had fewer patients with stable COPD, the study sample size was limited, and the clinical data of the population needed to be integrated to further improve the evidence. Second, most of the included studies did not report specific randomization methods and allocation concealment, and there was a greater risk of bias. Third, most of the included studies focus on Asian populations with limited geographic distribution; thus, multi-ethnic population studies are needed to provide evidence. Fourth, this meta-analysis had some publication bias. Finally, the high heterogeneity of some results may affect the reliability of these results, thus, we used a random-effects model to combine the results to make the results more reliable.

In summary, the currently available limited evidence shows that PPI therapy of patients with COPD can reduce the case fatality rate, incidence of adverse reactions including gastrointestinal bleeding and number of acute exacerbations. At present, PPI therapy is not yet recommended in COPD guidelines. PPI is mainly used in patients with digestive system

diseases. Therefore, PPI therapy may be beneficial to patients with COPD with high-risk factors of the digestive system.

## CONCLUSION

PPI therapy has significant effects on patients with COPD in reducing the number of acute attacks, adverse reactions, and mortality. This conclusion requires further verification in larger-scale RCTs.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

## AUTHOR CONTRIBUTIONS

FY and QH: conceptualization, writing, review, and editing. FY, YY, and QH: methodology. LZ and QH: supervision. LZ: project administration. All authors contributed to the article and approved the submitted version.

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# The Influence of Prior Statin Use on the Prevalence and Exacerbation of Chronic Obstructive Pulmonary Disease in an Adult Population

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**Background:** Statins have anti-inflammatory and antioxidant properties, and previous studies have reported the positive effects of statins on chronic obstructive pulmonary disease (COPD) outcomes. However, the effects of statins on the development and acute exacerbations of COPD remain unclear. Therefore, this study aimed to assess the relation between statin use and COPD occurrence in all participants and the link between statin use and COPD acute exacerbations in participants with COPD.

**Methods:** This case-control study comprised 26,875 COPD participants and 107,500 control participants who were 1:4 matched from the Korean National Health Insurance Service-Health Screening Cohort. Conditional logistic regression was used to evaluate the probability of COPD occurrence associated with previous statin use. In addition, unconditional logistic regression was employed to assess the risk of exacerbations related to statin use among COPD participants. These relations were estimated in subgroup analysis according to statin type (lipophilic vs. hydrophilic).

**Results:** The association between previous statin use and the occurrence of COPD did not reach statistical significance in the overall population (adjusted odds ratio [aOR] = 0.96, 95% confidence interval [CI] = 0.93–1.00, $P = 0.059$). However, statin use decreased the probability of exacerbations in participants with COPD (aOR = 0.79, 95% CI = 0.74–0.85, $P < 0.001$). Lipophilic statins decreased the probability of exacerbations, whereas hydrophilic statins were not associated with a decreased likelihood of exacerbations (aOR = 0.78, 95% CI = 0.72–0.84, $P < 0.001$ for lipophilic statins; aOR = 0.89, 95% CI = 0.78–1.02, $P = 0.102$ for hydrophilic statins).

**Discussion:** Statin use was not associated with the occurrence of COPD in the adult population. However, statin use was associated with a reduced probability of exacerbations in participants with COPD, with a greater risk reduction with lipophilic statin use.

**Keywords: chronic obstructive pulmonary disease, hydroxymethylglutaryl-CoA reductase inhibitors, symptom flare up, prevalence, cohort studies**

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease, but it has a progressive nature characterized by airflow limitation and decreased lung function (1). Acute exacerbations (AEs) of COPD are important events in COPD management because AEs can lead to hospitalization, worsening quality of life, progression of the disease, and increased mortality (2, 3). In addition, exacerbations become more frequent and more severe as the disease progresses (4). Therefore, several interventions, including smoking cessation, patient-education programs, triple therapy [combination of an inhaled glucocorticoid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting beta-agonist (LABA)], and the addition of phosphodiesterase-4 (PDE4) inhibitors, are recommended to prevent AEs (5, 6). However, the effects of these interventions on exacerbation frequency are still limited, suggesting that further adjunctive therapies are required.

Statins are competitive inhibitors of 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-CoA) reductases, which catalyze the rate-limiting step in cholesterol biosynthesis (7). Statins were reported to have anti-inflammatory and antioxidant effects in addition to their lipid-lowering properties (8). Due to these pleiotropic effects, statins have been suggested to have favorable effects in patients with COPD (9). Previous systematic reviews have reported that statins reduce the risk of mortality, hospitalization, and levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) in COPD patients (10, 11). A recent randomized controlled trial (RCT) stated that one year of treatment with simvastatin at 40 mg per day decreased the risk of exacerbations (12). However, a well-known RCT, the Prospective Randomized Placebo-Controlled Trial of Simvastatin in the Prevention of COPD Exacerbations (STATCOPE), showed that simvastatin did not have any preventive effect on AEs in COPD (13). One possibility for the discrepancy between the two studies might be different characteristics between the participants. In the STATCOPE trial, participants with subclinical cardiovascular risk were excluded; however, the recent RCT by Schenk et al. enrolled those with diabetes and subclinical cardiovascular diseases. Therefore, real-world studies of COPD patients with various comorbidities need to be conducted to assess the effect of statins on AEs in COPD.

Systemic and respiratory inflammation is believed to be the major cause of lung damage in COPD (14, 15). Cigarette smoke and other exposures, such as biofuel or air pollutants, are well-established inducers of inflammation, oxidative stress, activation of inflammatory cells, and apoptosis and are suggested to be pathogenic mechanisms. These factors lead to airflow limitation and respiratory symptoms in susceptible individuals. Peak lung function in young adults and the rate of decrease in lung function are two essential factors that determine COPD susceptibility later in life (16). The VA Normative Aging Study demonstrated that statin use reduced lung function decline in the general population (17). In addition, Keddissi et al. showed that statins were associated with a slower decline in lung function in current and former smokers (18). As statins have a potent anti-inflammatory effect on airways and systems, the hypothesis that pharmacological intervention with statins can decrease the risk of COPD development needs to be confirmed. Therefore, we hypothesized that statins could prevent COPD occurrence in adults receiving statin treatment compared to those not taking statins.

This study aimed to evaluate the effect of statins on COPD by analyzing a nationwide healthcare database. The primary objective was to estimate the relation between the dates of statin prescription and occurrence of COPD in comparison with control participants. The secondary objective was to analyze the association between the dates of statin prescription and acute exacerbations in participants with COPD compared to COPD participants without acute exacerbations.

**Abbreviations:** AE, acute exacerbation; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; HMG-CoA, 3-hydroxy-3-methyl glutaryl coenzyme A; ICS, inhaled glucocorticoid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; PDE4, phosphodiesterase-4; SBP, systolic blood pressure; OR, odds ratio; RCT, randomized controlled trial.

## MATERIALS AND METHODS

### Data Sources

The Korean National Health Insurance Service-Health Screening Cohort (NHIS-NSC) data were used for this study; a comprehensive description of this cohort is provided elsewhere (19, 20). The ethics committee of Hallym University (2019-10-023) approved this study.

### Study Population and Design

Chronic obstructive pulmonary disease participants were selected from 514,866 participants with 615,488,428 medical claim codes ($n$ = 39,325). The control group was chosen from all participants without a history of COPD during 2002–2015 ($n$ = 475,541). To measure the previous 2 years of statin medication history, we excluded participants with COPD from 2002 to 2003 ($n$ = 11,834). Among the control participants, we excluded 1,444 participants who died before 2004. Control participants who were diagnosed with ICD-10 codes J42, J43 (except J430), or J44 and did not have a prescription for COPD drugs during 2002–2015 were excluded ($n$ = 94,371). COPD participants without records of total cholesterol ($n$ = 11), blood pressure ($n$ = 1), or fasting blood glucose ($n$ = 1) were excluded (**Figure 1**). COPD participants were 1:4 matched with control participants for age, sex, income, and region of residence. To diminish the possibility of selection bias, the control participants were selected with random number order. The index date of each participant with COPD was set as the first date of the treatment, and that of the control was set by their matched COPD participant. During the matching process, 603 COPD participants and 272,226 control participants were excluded. Finally, 26,875 COPD participants were 1:4 matched with 107,500 control participants for this study. Then, previous statin use was evaluated (primary object).

The selected participants with COPD were classified into those who experienced AEs of COPD ($n$ = 4,896) and those who experienced non-acute exacerbations (NAEs) of COPD

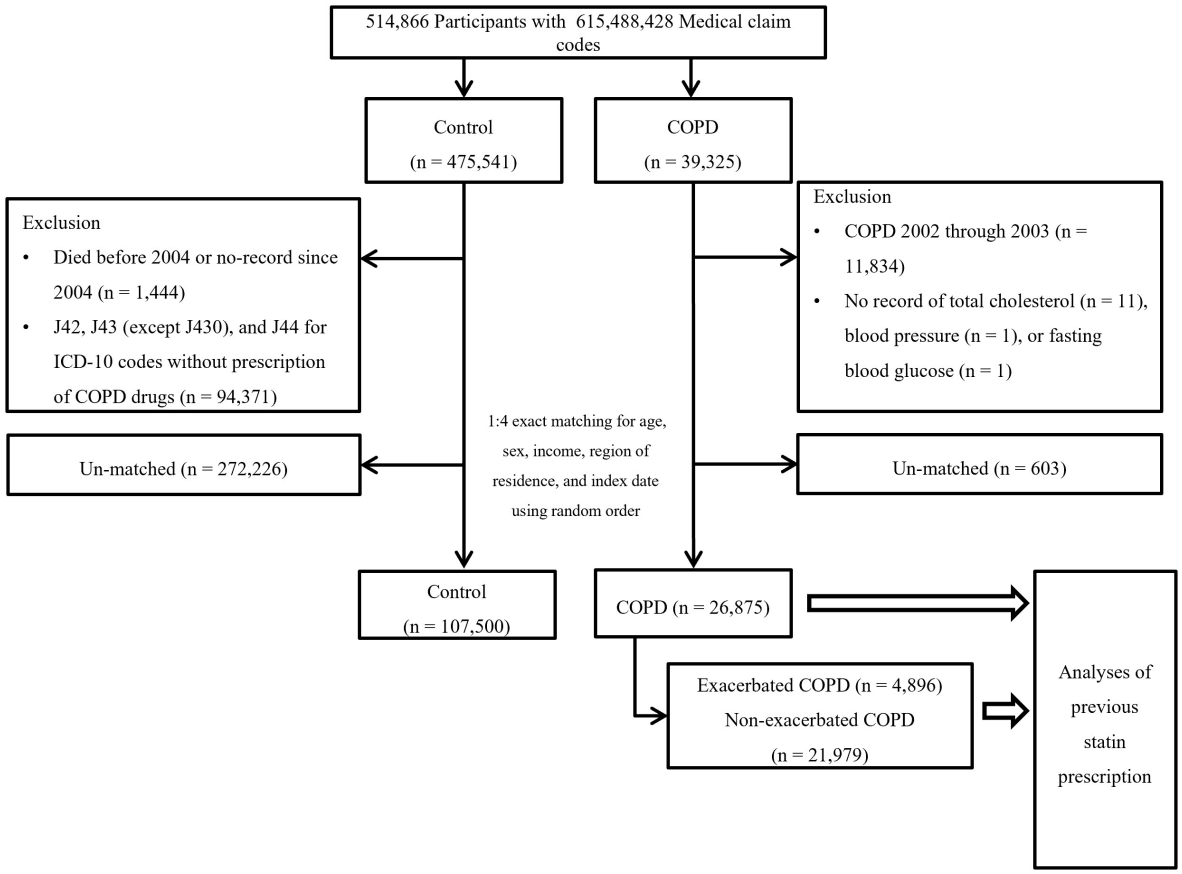


**FIGURE 1 |** Schematic illustration of the participant selection process used in the present study. Of a total of 514,866 participants, 26,875 participants with COPD were matched with 107,500 control participants for age, sex, income, and region of residence (primary objective). The participants with COPD were classified as having exacerbated COPD (*n* = 4,896) or non-exacerbated COPD (*n* = 21,979) (secondary objective). COPD, chronic obstructive pulmonary disease.

(*n* = 21,979), and their history of previous statin use (secondary objective) was analyzed. In this analysis, we defined a new index date to assess the effects of statins on COPD exacerbations. For exacerbations of COPD, the first exacerbation date was set as the index date. For non-exacerbated COPD, a new random index date between the onset of COPD and the last follow-up date was chosen for fair comparison of previous statin use.

The prescription dates of statins were counted as a continuous variable for 2 years (730 days) before the index dates in COPD participants and control participants. The statins in this study included atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin. Based on pharmacological class, pravastatin and rosuvastatin were classified as hydrophilic statins, and atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin were categorized as lipophilic statins (21).

## Outcome Variables

Chronic obstructive pulmonary disease was defined by ≥2 occurrences of unspecified chronic bronchitis (J42), emphysema (J43), and other COPD (J44), except MacLeod syndrome (J430), as well as ≥2 prescriptions for COPD-related medications, including LAMAs, LABAs, ICSs combined with LABAs, short-acting muscarinic antagonists, short-acting beta2 agonists, methylxanthine, PDE4 inhibitors, and systemic beta agonists (22).

If participants with COPD had a history of admission or were treated/diagnosed by emergency medical doctors, they were classified as having exacerbated COPD, and the other participants with COPD were classified as having non-exacerbated COPD (23, 24).

## Covariates

Ten age groups were divided into 5-year intervals: 40–44, 45–49, 50–54,. . ., and 85+ years old. Income was grouped into five classes [lowest (1) through highest (5)]. The region of residence was divided into urban and rural areas following a previous study (25). Other covariates, such as smoking, alcohol consumption, and body mass index (BMI, kg/m$^2$), were categorized in the same way as in a previous study (26). Blood pressure (systolic and diastolic), fasting blood glucose, and total cholesterol were measured. The Charlson Comorbidity Index (CCI) without respiratory disease was measured (0–29 score). Asthma was

defined as participants who were treated for asthma (J45) or status asthmaticus (J46) following our previous study (25).

Dyslipidemia was defined if participants were treated ≥2 times for disorders of lipoprotein metabolism and other lipidemias (E78) before the index date to improve the accuracy of the diagnosis (27).

## Statistical Analyses

The demographic characteristics were compared between the COPD participants and controls and between exacerbated COPD and non-exacerbated COPD participants using standardized differences.

To estimate the odds ratios (ORs) with 95% confidence intervals (CIs) of 1 year of statin prescriptions for COPD (primary objective), conditional logistic regression was used. In this analysis, crude and adjusted models (adjusted for obesity, smoking, alcohol consumption, total cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose, dyslipidemia history, asthma history, and CCI score) were computed. The analysis was stratified by age, sex, income, and region of residence.

To estimate the ORs with 95% CIs for AEs (secondary objective) in those with a 1-year history of statin use, unconditional logistic regression was utilized. In this examination, crude and adjusted models were calculated using the same method as that used for the primary object.

For subgroup analyses, we divided participants by age (division point of 60 years old), sex, income, and region of residence for COPD and COPD exacerbations. We performed further subgroup analyses according to other covariates and the type of statin.

SAS version 9.4 (SAS Institute Inc., Cary, NC, United States) was utilized for the statistical analyses. Two-tailed analyses were used, and statistical significance was indicated by $P$ values $< 0.05$.

# RESULTS

A total of 26,875 participants with COPD and 107,500 individually matched control participants were included in this study. The general characteristics of the participants are exhibited in **Table 1**. Among the 26,875 COPD patients, 12.5% ($n$ = 4,896) were categorized into the AE group, and the others ($n$ = 21,979) were categorized into the NAE group.

When we first examined the relation between previous statin prescription and COPD occurrence, there was no significant association in the overall population (OR = 0.96, 95% confidence interval [CI] = 0.93–1.00, $P$ = 0.059 in the adjusted model, **Table 2**). However, subgroup analyses showed that statin prescriptions were associated with decreased incidences of the COPD diagnosis in the overweight and asthma groups (OR = 0.90, 95% CI 0.84–0.98, $P$ = 0.010 for overweight and OR = 0.91, 95% CI 0.87–0.97, $P$ = 0.001 for asthma, **Supplementary Table 1** and **Supplementary Figure 1**).

Next, we examined the effect of statins on AEs among participants with COPD. Statin prescription was associated with a decreased OR for AEs in both model 1 and model 2 (OR = 0.74, 95% CI = 0.69–0.78, $P < 0.001$ for model 1, OR = 0.79, 95% CI = 0.74–0.85, $P < 0.001$ for model 2, **Table 3**). Regardless of age (≥60 years), sex, income, and region of residence, statin prescription showed a significantly decreased OR for AEs in this cohort ($P$ = 0.05 for all, **Table 3**). Subgroup analyses also showed decreased ORs in all subgroups except underweight ($P$ = 0.122 for underweight, $P < 0.05$ for others, **Supplementary Table 2** and **Supplementary Figure 2**).

We further analyzed the effect of statins on COPD diagnosis and AEs according to the pharmacological classification of statins (hydrophilic vs. lipophilic). Neither hydrophilic nor lipophilic statin prescription had any association with COPD diagnosis (OR = 0.98, 95% CI = 0.91–1.07, $P$ = 0.686 for hydrophilic statins and OR = 0.96, 95% CI = 0.92–1.00, $P$ = 0.065 for lipophilic statins in model 2, **Figures 2A,B** and **Supplementary Tables 3**, **4**). However, hydrophilic statin prescriptions were associated with a decreased incidence of AEs in model 1 (OR = 0.83, 95% CI = 0.73–0.94, $P$ = 0.005), but this association disappeared in the fully adjusted model 2 (OR = 0.89, 95% CI = 0.78–1.02, $P$ = 0.102, **Figure 3A** and **Supplementary Table 5**). Lipophilic statin prescriptions decreased the incidences of AEs in both model 1 and model 2 (OR = 0.72, 95% CI = 0.67–0.77, $P < 0.001$ for model 1 and OR = 0.78, 95% CI = 0.72–0.84, $P < 0.001$ for model 2, **Figure 3B** and **Supplementary Table 6**).

# DISCUSSION

This population-based case-control study showed that statin use decreased the probability of emergency room (ER) visits and hospitalizations due to COPD exacerbations among participants with COPD, which was consistent with the results of previous studies (10–12, 28–31). The novelty of our study includes the demonstration of different anti-inflammatory effects of statins according to their tissue selectivity; lipophilic statins showed a more profound effect on the prevention of exacerbations than hydrophilic statins. Furthermore, we examined the relationship between previous statin use and COPD occurrence in the general population using this cohort for the first time; however, previous statin use did not have any significant association with COPD occurrence.

COPD is considered a chronic systemic inflammatory syndrome, and comorbid conditions are highly prevalent in COPD patients. In particular, cardiovascular diseases are the most common comorbidities, where systemic inflammation plays a pivotal role in both conditions (14). Statins have been prescribed for the primary prevention of atherosclerotic cardiovascular diseases because they effectively lower low-density lipoprotein (LDL) cholesterol levels. In addition, the pleiotropic effects of statins, such as stabilizing the endothelium and reducing inflammatory mediators and oxidative stress, contribute to a decrease in cardiovascular morbidity (32, 33). Decreased lung function has been linked to oxidative stress and increased inflammation, and studies have proven that statins decrease proinflammatory cytokine levels in the sera of COPD patients (28, 29) and slow lung function decline (17, 18).

**TABLE 1 |** General characteristics of participants.

| Characteristics | Total participants | | | COPD exacerbation | | |
|---|---|---|---|---|---|---|
| | COPD | Control | Standardized difference | Exacerbated COPD | Non-exacerbated COPD | Standardized difference |
| Age (years), *n* (%) | | | 0.00 | | | 0.41 |
| 40–44 | 302 (1.1) | 1,208 (1.1) | | 9 (0.2) | 24 (0.1) | |
| 45–49 | 1,555 (5.8) | 6,220 (5.8) | | 65 (1.3) | 476 (2.2) | |
| 50–54 | 2,912 (10.8) | 11,648 (10.8) | | 207 (4.2) | 1,934 (8.8) | |
| 55–59 | 3,758 (14.0) | 15,032 (14.0) | | 353 (7.2) | 3,047 (13.9) | |
| 60–64 | 4,429 (16.5) | 17,716 (16.5) | | 574 (11.7) | 3,375 (15.4) | |
| 65–69 | 5,259 (19.6) | 21,036 (19.6) | | 793 (16.2) | 3,959 (18.0) | |
| 70–74 | 4,751 (17.7) | 19,004 (17.7) | | 1,105 (22.6) | 4,168 (19.0) | |
| 75–79 | 2,864 (10.7) | 11,456 (10.7) | | 1,039 (21.2) | 3,127 (14.2) | |
| 80–84 | 927 (3.5) | 3,708 (3.5) | | 583 (11.9) | 1,431 (6.5) | |
| 85 + | 118 (0.4) | 472 (0.4) | | 168 (3.4) | 438 (2.0) | |
| Sex, *n* (%) | | | 0.00 | | | |
| Male | 15,126 (56.3) | 60,504 (56.3) | | 3,440 (70.3) | 11,686 (53.2) | 0.36 |
| Female | 11,749 (43.7) | 46,996 (43.7) | | 1,456 (29.7) | 10,293 (46.8) | |
| Income, *n* (%) | | | 0.00 | | | 0.09 |
| 1 (lowest) | 5,097 (19.0) | 20,388 (19.0) | | 1,061 (21.7) | 4,121 (18.8) | |
| 2 | 3,907 (14.5) | 15,628 (14.5) | | 709 (14.5) | 2,998 (13.6) | |
| 3 | 4,423 (16.5) | 17,692 (16.5) | | 752 (15.4) | 3,440 (15.7) | |
| 4 | 5,615 (20.9) | 22,460 (20.9) | | 963 (19.7) | 4,515 (20.5) | |
| 5 (highest) | 7,833 (29.2) | 31,332 (29.2) | | 1,411 (28.8) | 6,905 (31.4) | |
| Region of residence, *n* (%) | | | 0.00 | | | 0.21 |
| Urban | 10,201 (38.0) | 40,804 (38.0) | | 1,423 (29.1) | 8,559 (38.9) | |
| Rural | 16,674 (62.0) | 66,696 (62.0) | | 3,473 (70.9) | 13,420 (61.1) | |
| Total cholesterol (mg/dL), mean (SD) | 199.2 (38.6) | 197.4 (39.2) | 0.05 | 192.9 (41.1) | 198.4 (38.7) | 0.14 |
| SBP (mmHg), mean (SD) | 129.6 (17.9) | 128.1 (17.5) | 0.08 | 129.7 (18.4) | 127.8 (17.3) | 0.10 |
| DBP (mmHg), mean (SD) | 79.5 (11.1) | 78.7 (10.8) | 0.08 | 79.2 (11.2) | 78.6 (10.7) | 0.05 |
| Fasting blood glucose (mg/dL), mean (SD) | 102.2 (33.6) | 99.8 (30.5) | 0.07 | 100.2 (31.3) | 99.8 (30.3) | 0.01 |
| Obesity[†], *n* (%) | | | 0.13 | | | 0.36 |
| Underweight | 1,237 (4.6) | 2,777 (2.6) | | 487 (10.0) | 750 (3.4) | |
| Normal | 9,853 (36.7) | 38,188 (35.5) | | 2,135 (43.6) | 7,718 (35.1) | |
| Overweight | 6,577 (24.5) | 29,456 (27.4) | | 1,013 (20.7) | 5,564 (25.3) | |
| Obese I | 8,327 (31.0) | 34,087 (31.7) | | 1,132 (23.1) | 7,195 (32.7) | |
| Obese II | 881 (3.3) | 2,992 (2.8) | | 129 (2.6) | 752 (3.4) | |
| Smoking status, *n* (%) | | | 0.16 | | | 0.28 |
| Non-smoker | 17,741 (66.0) | 77,066 (71.7) | | 2,711 (55.4) | 15,030 (68.4) | |
| Past smoker | 2,838 (10.6) | 12,290 (11.4) | | 572 (11.7) | 2,266 (10.3) | |
| Current smoker | 6,296 (23.4) | 18,144 (16.9) | | 1,613 (33.0) | 4,683 (21.3) | |
| Alcohol consumption, *n* (%) | | | 0.03 | | | 0.05 |
| <1 time a week | 19,169 (71.3) | 75,384 (70.1) | | 3,396 (69.4) | 15,773 (71.8) | |
| ≥1 time a week | 7,706 (28.7) | 32,116 (29.9) | | 1,500 (30.6) | 6,206 (28.2) | |
| Dyslipidemia, *n* (%) | 6,395 (23.8) | 24,119 (22.4) | 0.03 | 851 (17.4) | 5,544 (25.2) | 0.19 |
| Asthma, *n* (%) | 16,322 (60.7) | 16,308 (15.2) | 1.06 | 3,642 (74.4) | 12,680 (57.7) | 0.36 |
| CCI score, *n* (%) | | | 0.18 | | | 0.58 |
| 0 | 15,410 (57.3) | 71,046 (66.1) | | 1,740 (35.5) | 13,670 (62.2) | |
| 1 | 4,512 (16.8) | 14,996 (14.0) | | 973 (19.9) | 3,539 (16.1) | |
| ≥2 | 6,953 (25.9) | 21,458 (20.0) | | 2,183 (44.6) | 4,770 (21.7) | |
| Date of statin prescription (day), mean (SD) | 54.0 (161.4) | 52.8 (161.8) | 0.01 | 71.8 (188.5) | 108.4 (226.1) | 0.18 |
| Date of hydrophilic statin prescription | 9.1 (68.2) | 8.7 (66.6) | 0.01 | 14.8 (88.6) | 18.8 (98.9) | 0.04 |
| Date of lipophilic statin prescription | 44.9 (145.7) | 44.1 (146.7) | 0.01 | 57.0 (166.5) | 89.5 (205.6) | 0.17 |

*CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation.*
*[†]Obesity was categorized as a body mass index (kg/m$^2$) <18.5 (underweight), ≥18.5–<23 (normal), ≥23–<25 (overweight), ≥25–<30 (obese I), and ≥30 (obese II).*

**TABLE 2 |** Odds ratios (95% confidence intervals) of the dates of statin prescription (1 year) for the occurrence of COPD.

| Characteristics | Odds ratios for COPD | | | |
|---|---|---|---|---|
| | Crude† | *P*-value | Adjusted†‡ | *P*-value |
| Total participants (*n* = 134,375) | | | | |
| Statin prescription (1 year) | 1.02 (0.99–1.05) | 0.267 | 0.96 (0.93–1.00) | 0.059 |
| Age < 60 years old (*n* = 42,635) | | | | |
| Statin prescription (1 year) | 1.02 (1.18–0.01) | 0.012* | 0.88 (1.06–0.46) | 0.457 |
| Age ≥ 60 years old (*n* = 91,740) | | | | |
| Statin prescription (1 year) | 0.97 (1.04–0.93) | 0.935 | 0.93 (1.01–0.14) | 0.140 |
| Males (*n* = 75,630) | | | | |
| Statin prescription (1 year) | 1.02 (0.98–1.06) | 0.403 | 0.98 (0.93–1.04) | 0.468 |
| Females (*n* = 58,745) | | | | |
| Statin prescription (1 year) | 1.02 (0.97–1.06) | 0.463 | 0.94 (0.89–1.00) | 0.036* |
| Low income (n = 67,135) | | | | |
| Statin prescription (1 year) | 1.06 (1.01–1.11) | 0.015* | 0.98 (0.93–1.04) | 0.537 |
| High income (*n* = 67,240) | | | | |
| Statin prescription (1 year) | 0.99 (0.95–1.03) | 0.506 | 0.95 (0.90–1.00) | 0.054 |
| Urban (*n* = 51,005) | | | | |
| Statin prescription (1 year) | 1.06 (1.01–1.10) | 0.023* | 0.99 (0.94–1.05) | 0.815 |
| Rural (*n* = 83,370) | | | | |
| Statin prescription (1 year) | 0.99 (0.95–1.03) | 0.619 | 0.94 (0.89–0.99) | 0.021* |

*CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.*
**Conditional logistic regression, significance at P < 0.05.*
†*Models were stratified by age, sex, income, and region of residence.*
‡*Adjusted for total cholesterol, SBP, DBP, fasting blood glucose, obesity, smoking, alcohol consumption, history of dyslipidemia, history of asthma, and CCI scores.*

**TABLE 3 |** Odds ratios (95% confidence intervals) of the dates of statin prescription (1 year) for the exacerbation of COPD.

| Characteristics | Odds ratios for aggravated COPD | | | |
|---|---|---|---|---|
| | Model 1† | *P*-value | Model 2‡ | *P*-value |
| COPD participants (*n* = 26,875) | | | | |
| Statin prescription (1 year) | 0.74 (0.69–0.78) | <0.001* | 0.79 (0.74–0.85) | <0.001* |
| Age < 60 years old (*n* = 6,115) | | | | |
| Statin prescription (1 year) | 0.79 (0.64–0.96) | 0.020* | 0.76 (0.61–0.96) | 0.018* |
| Age ≥ 60 years old (*n* = 20,760) | | | | |
| Statin prescription (1 year) | 0.74 (0.69–0.78) | <0.001* | 0.80 (0.74–0.85) | <0.001* |
| Males (*n* = 15,126) | | | | |
| Statin prescription (1 year) | 0.75 (0.69–0.80) | <0.001* | 0.83 (0.76–0.90) | <0.001* |
| Females (*n* = 11,749) | | | | |
| Statin prescription (1 year) | 0.72 (0.65–0.80) | <0.001* | 0.72 (0.65–0.81) | <0.001* |
| Low income (*n* = 13,081) | | | | |
| Statin prescription (1 year) | 0.71 (0.65–0.78) | <0.001* | 0.78 (0.71–0.86) | <0.001* |
| High income (*n* = 13,794) | | | | |
| Statin prescription (1 year) | 0.64 (0.58–0.71) | <0.001* | 0.80 (0.73–0.87) | <0.001* |
| Urban (*n* = 9,982) | | | | |
| Statin prescription (1 year) | 0.72 (0.65–0.80) | <0.001* | 0.76 (0.68–0.85) | <0.001* |
| Rural (*n* = 16,893) | | | | |
| Statin prescription (1 year) | 0.75 (0.69–0.80) | <0.001* | 0.81 (0.75–0.88) | <0.001* |

*CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.*
**Unconditional logistic regression, significance at P < 0.05.*
†*Model 1 was adjusted for age, sex, income, and region of residence.*
‡*Model 2 was adjusted as model 1 plus total cholesterol, SBP, DBP, fasting blood glucose, obesity, smoking, alcohol consumption, history of dyslipidemia, history of asthma, and CCI scores.*

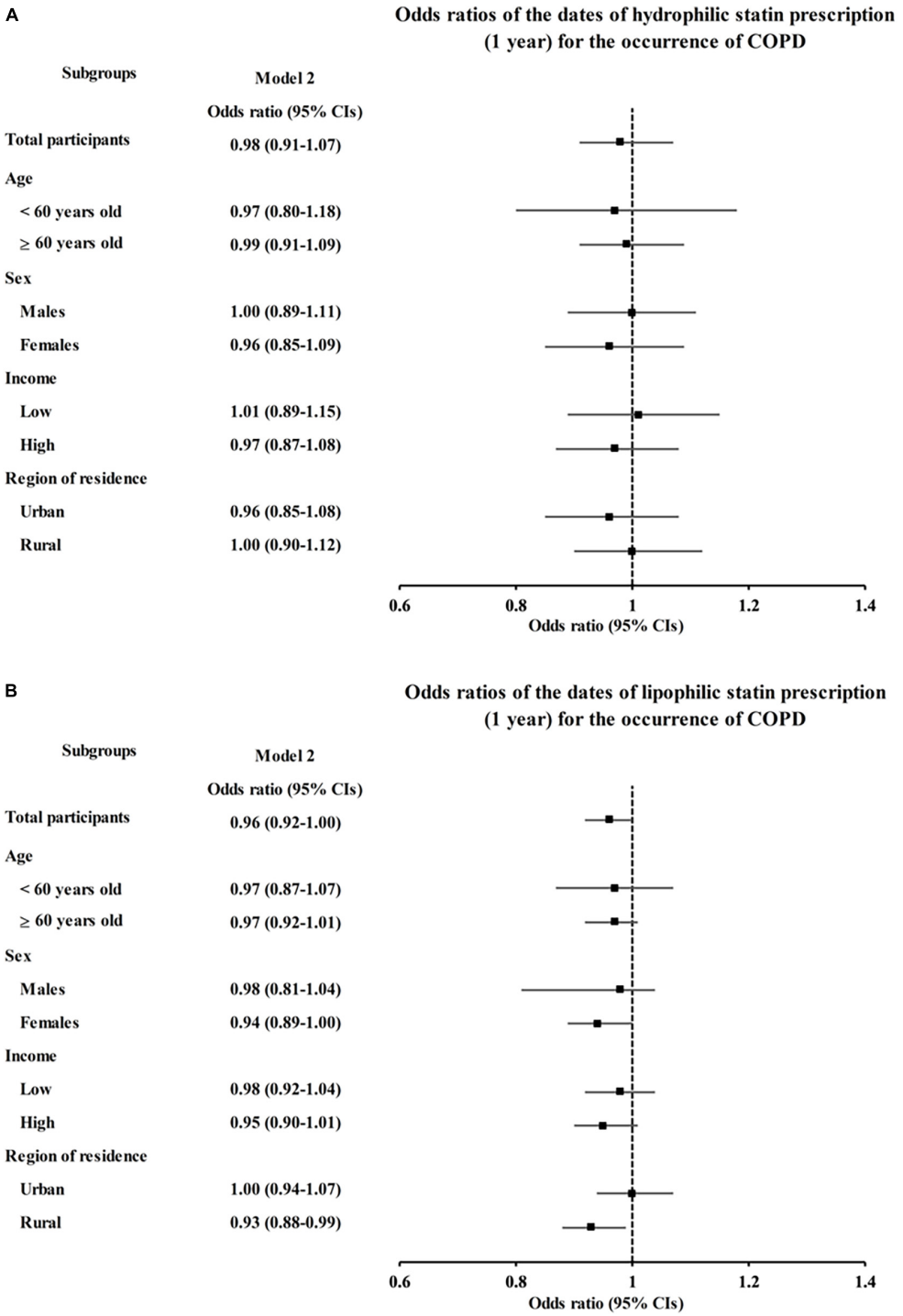


**FIGURE 2 |** Adjusted odds ratios (95% CIs) of statin prescriptions per 1 year for COPD by subgroup: **(A)** hydrophilic statins and **(B)** lipophilic statins. Model 2 was adjusted for age, sex, region of residence, total cholesterol, SBP, DBP, fasting blood glucose, obesity, smoking, alcohol consumption, history of dyslipidemia, history of asthma, and CCI scores. CI, confidence interval; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Therefore, this study explored whether statin use decreases COPD development in an adult population. However, in this study, previous statin use did not decrease the probability of COPD occurrence in the adult population; nonetheless, the overweight and dyslipidemia subgroups showed a small but significant decrease in COPD occurrence (aOR 0.90, 95% CI

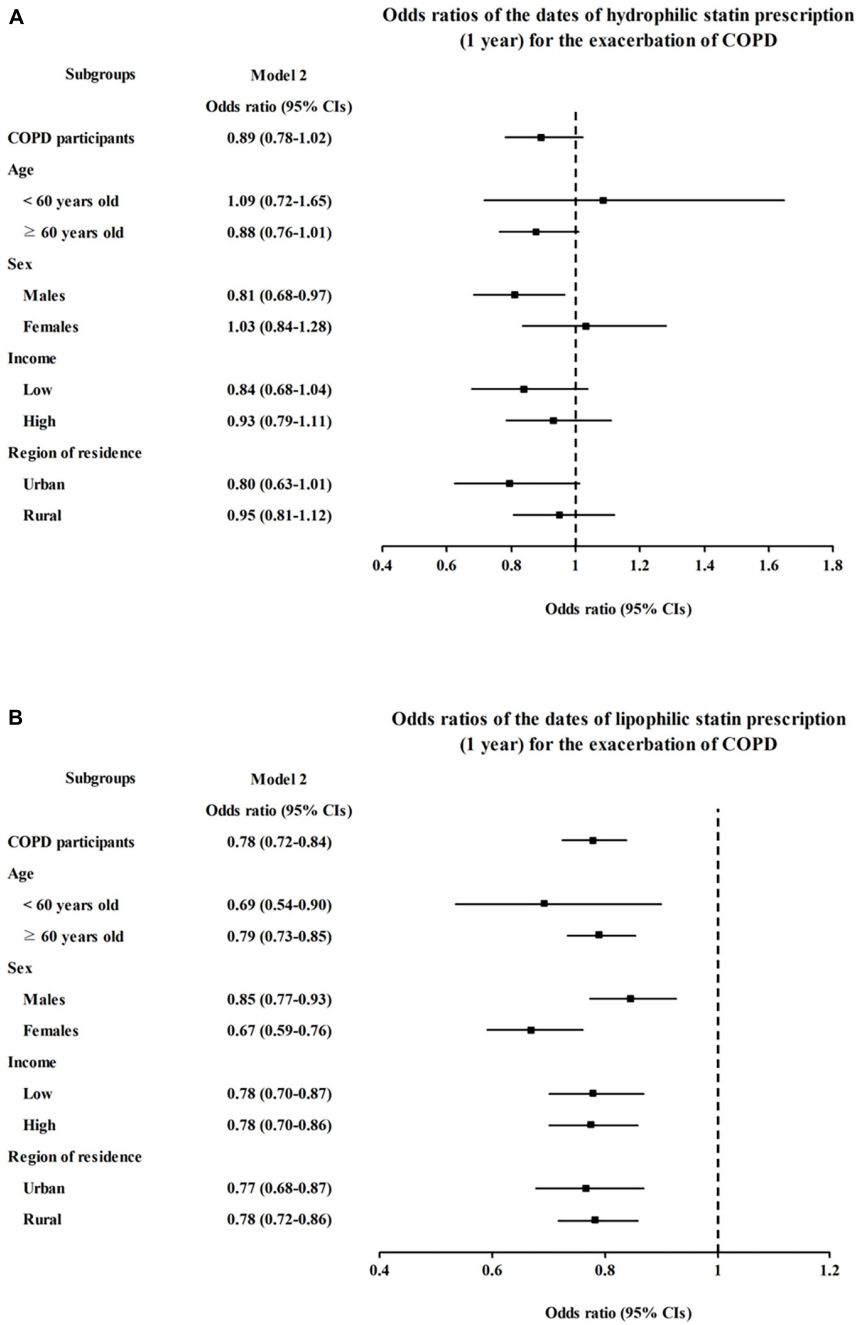


**FIGURE 3 |** Adjusted odds ratios (95% CIs) of statin prescriptions per 1 year for COPD exacerbation by subgroup: **(A)** hydrophilic statins and **(B)** lipophilic statins. Model 2 was adjusted for age, sex, region of residence, total cholesterol, SBP, DBP, fasting blood glucose, obesity, smoking, alcohol consumption, history of dyslipidemia, history of asthma, and CCI scores. CI, confidence interval; CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; SBP, systolic blood pressure.

0.94–0.98, $P = 0.010$ for overweight, aOR = 0.95, 95% CI 0.91–0.99, $P = 0.24$ for dyslipidemia, **Supplementary Table 1**). These results imply that the effects of statins on COPD occurrence might be confined to individuals with cardiovascular diseases or that statins play a limited role in the primary prevention of COPD in general.

Statin use significantly decreased the risk of AEs among COPD patients (OR = 0.79, 95% CI 0.74–0.85, $P < 0.001$), in accordance with previous studies. Population-based case-control studies demonstrated that statin use affects AEs in COPD patients requiring hospitalization (OR = 0.67∼0.70, and HR = 0.66) (29–31, 34). A recent RCT by Schenk et al. showed

that the rate of exacerbations was 1.45 events (patient-years) in the simvastatin group and 1.9 events (patient-years) in the placebo group (incidence rate ratio = 0.77, 95% CI 0.60–0.99) (12). However, the STATCOPE trial showed that simvastatin did not influence exacerbation rates or the time to a first exacerbation in COPD patients (1.36 ± 1.61 AEs for simvastatin and 1.39 ± 1.73 AEs for controls, respectively, $P = 0.54$) (13). The discrepancies among the STATCOPE trial, the RCT by Shenk et al. and other observational studies might originate from different characteristics between the study participants, as the STATCOPE trial excluded individuals with an increased risk of recurrent AEs and higher cardiovascular comorbidities, which might be different from the real-world situation. In our subgroup analyses, statins had a greater protective effect in individuals with high total cholesterol, high blood pressure, and high fasting glucose than in those without high cholesterol, high blood pressure, or high fasting glucose (OR = 0.77 vs. OR = 0.81 for high cholesterol, OR = 0.80 vs. OR = 0.78 for hypertension, OR = 0.84 vs. OR = 0.73 for hyperglycemia, **Supplementary Table 2**). Our results suggested that statins might be more beneficial for individuals with COPD and underlying cardiovascular disease.

Moreover, we analyzed the effect of statins on AEs according to the pharmacological class of the statin and found that lipophilic statins such as atorvastatin, simvastatin, fluvastatin, and pitavastatin have more potent preventive effects against AEs. Two RCTs chose simvastatin because it showed pleiotropic effects in *in vitro* studies and a maximal reduction in serum CRP levels at the usual dose (20–40 mg per day) without an increase in side effects (12, 13). Network meta-analysis showed supporting evidence that fluvastatin and atorvastatin (lipophilic) had a higher cumulative probability of reducing CRP in COPD patients than rosuvastatin (hydrophilic) (97.7% for fluvastatin, 68.9% for atorvastatin, and 49.3% for rosuvastatin) (28). Subgroup analyses showed that for reducing CRP, the standardized mean difference (SMD) was significantly higher for lipophilic statins than for hydrophilic statins (-0.72 for atorvastatin, -0.54 for simvastatin, and -1.66 for fluvastatin vs. -0.36 for pravastatin and -0.57 for rosuvastatin). These data suggested that the biological effects of the type of statin should be considered for further research on statins in COPD.

There are some limitations to our study. First, we defined AEs as hospitalizations or ER visits based on claim codes for patients with COPD. Therefore, our operational definition reflects only the severe degree of AEs according to the Global Initiative for Chronic Obstructive Lung Disease guidelines (1), while a mild degree of AEs was not included in this study. Second, detailed clinical variables such as cardiovascular comorbidity, pulmonary hypertension, inflammatory markers such as CRP, and lung function data were not available from the claim code dataset; therefore, these factors could not be considered in our analyses. Third, we used prescription dates of statins to calculate the duration of statin therapies; however, this may not reflect drug compliance.

However, this study has some strengths. Although we could not find any significant relationship between previous statin use and COPD occurrence, this is the first study to report the effect of statins on COPD development using a population cohort. In the present study, we reported different biological effects on AEs according to the type of statin. While statins are equivalent in potency for reducing cholesterol, they differ in their pleiotropic impact caused by lipophilicity among the types of statins. Lipophilic statins can pass through cells by passive diffusion and are distributed in diverse tissues. In contrast, hydrophilic statins are liver-specific and need carriers for uptake; therefore, they cannot exert other pleiomorphic effects on extrahepatic tissues (35). This study proved that lipophilic statins decreased the risk of AEs in COPD, which is supported by previous mechanistic studies.

In conclusion, our study showed that statin use was related to a decreased probability of COPD exacerbations requiring ER visits or hospitalization. The protective effect of lipophilic statins against AEs was more profound than that of hydrophilic statins. However, one year of statin treatment did not affect COPD occurrence in this cohort.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## ETHICS STATEMENT

This study was approved by the Institutional Review Board (IRB) of Hallym University (IRB No: 2019-10-023), and the need for written informed consent was waived as all participants data were obtained in an anonymous manner. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

HC and J-HK designed this study and drafted the manuscript. HC, MK, and JK contributed to data collection and data analysis. J-YP and YH contributed to the interpretation of the data and revised the manuscript. SJ and K-SJ contributed to the final version of the manuscript. All authors read and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.842948/full#supplementary-material

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SYSTEMATIC REVIEW
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# A Meta-Analysis on the Efficacy and Safety of Bacterial Lysates in Chronic Obstructive Pulmonary Disease

*Yongkang Huang[1†], Yongjian Pei[1†], Yajuan Qian[1†], Zhen Yao[1], Chen Chen[1], Juan Du[2], Minhua Shi[1] and Tong Zhou[1*]*

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**Background:** Chronic obstructive pulmonary disease (COPD) is a common and frequently encountered disease of respiratory apparatus and is vulnerable to infection. Increasing studies reveal that bacterial lysates play an encouraging role in preventing exacerbations in these patients. We here investigated the efficacy and safety of bacterial lysates in COPD.

**Methods:** We performed systematic research on PubMed, EMBASE, the Cochrane Library (CENTRAL), and Web of Science by using the keywords and their synonyms for studies published before January 11, 2022. Two researchers screened the studies of literature independently according to the inclusion and exclusion criteria and extracted data from the included studies. Another two researchers assessed the risk of bias of each included using the Cochrane risk-of-bias tool. Meta-analysis was conducted using R (version 4.1.1, The R Foundation for Statistical Computing) and Review Manager (version 5.4.0, The Cochrane Collaboration).

**Results:** A total of 12 studies were included in this meta-analysis, and the pooled results showed that bacterial lysates were effective to reduce exacerbation rate (overall: relative risk [RR] = 0.83, 95% confidence interval [CI] 0.72–0.96; alkaline bacterial lysate subgroup [OM-85]: RR = 0.87, 95% CI 0.77–0.98; mechanical bacterial lysate subgroup [Ismigen]: RR = 0.70, 95% CI 0.41–1.20) and mean number of exacerbations (overall: MD = −0.42, 95% CI −0.75 to −0.08; alkaline bacterial lysate subgroup [OM-85]: MD = −0.72, 95% CI −1.35 to −0.09; mechanical bacterial lysate subgroup [Ismigen]: MD = −0.02, 95% CI −0.21 to 0.17). Bacterial lysates were also found beneficial in alleviating symptoms. The side effects were acceptable and slight.

**Conclusion:** Bacterial lysates can benefit patients with COPD by reducing exacerbations and alleviating symptoms. OM-85 is the preferable product based on the existing evidence. Further studies are needed to validate these findings.

**Systematic Review Registration:** [www.crd.york.ac.uk/prospero/], identifier [CRD42022299420].

**Keywords: chronic obstructive pulmonary disease, bacteria lysates, OM-85, Ismigen, efficacy, safety**

**Abbreviations:** COPD, chronic obstructive pulmonary disease; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; SD, standard derivation; MD, mean difference; SMD, standard mean difference; CI, confidence interval; FEV1/predicted, forced expiratory volume in one second/predicted value; RR, relative risk.

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## BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a preventable, treatable chronic respiratory disease that results from the airway or alveolar abnormalities and is one of the main causes of death globally (1). Furthermore, the population with COPD will increase with aging and continued exposure to risk factors (2). The goal of COPD treatment is to relieve symptoms and reduce exacerbations, improve the quality of life, and decelerate progression. Bronchodilators are the main treatment in most COPD guidelines. However, acute exacerbations still occur despite an optimal bronchodilator regimen. Moreover, older adults who have low economic and education levels account for a large proportion of those with COPD (3). For these people, an inhaler with a bronchodilator might not be the most acceptable and economical choice. New treatments are still needed.

Bacterial lysates are antigen-containing products derived from several common bacteria that infect humans, including *Staphylococcus aureus*, *Staphylococcus pneumoniae*, *Staphylococcus pyogenes*, and *Haemophilus influenzae*. Based on the preparation method, they are classified as alkaline or mechanical bacterial lysates. Commercial products of both types are available; OM-85 and Luivac are alkaline bacterial lysates and Ismigen is a mechanical bacterial lysate. Studies have shown that bacterial lysates reduce infections and antibiotic use (4) and are cost-effective (5, 6). A systematic review and meta-analysis of COPD found that OM-85 reduced the exacerbation rate and need for antibiotics (7). However, the study evaluated a single alkaline bacterial lysate and it was published nearly 7 years ago. As several important clinical trials have been conducted since then (8–10), an updated, comprehensive meta-analysis is warranted.

## METHODS

This systematic review and meta-analysis evaluated the efficacy and safety of bacterial lysates in COPD based on the latest evidence. The study was registered at PROSPERO (registration number: CRD42022299420) and followed the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (11).

### Inclusion and Exclusion Criteria

#### Participants

The participants were adults (age > 16 years) suffering from COPD, characterized by persistent respiratory symptoms and airflow limitation defined by a post-bronchodilator $FEV_1/FVC$ ratio < 0.70.

#### Type of Intervention and Comparator

The intervention was a bacterial lysate, including OM-85, Ismigen, MV130, Luivac LW50020, Lantigen, and Ribomunyl. The comparator was a placebo or blank.

#### Type of Studies

A randomized controlled trial or cohort study.

#### Outcomes

The primary efficacy outcome was the effect of the bacterial lysate on the rate and frequency of acute exacerbations; secondary efficacy outcomes included respiratory tract infections, hospitalization rate, and symptom improvement (sputum, severity of dyspnea, frequency of cough, and fever). Safety was evaluated based on adverse effects associated with the therapy, including symptoms and the overall rate of adverse events.

The studies reviewed met the above criteria, and studies were excluded if they used the same or overlapping data by the same authors or lacked any one of the predefined outcomes.

### Literature Search Strategy

Data were retrieved from PubMed, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science by an experienced researcher using keywords and their synonyms for studies published before January 11, 2022. Search terms were modified to be commensurate with each database's index terms, such as Medical Subject Heading (MeSH) in PubMed and Emtree in EMBASE. Relevant citations listed the references in each included study were also screened for eligibility to minimize retrieval bias. **Supplementary Appendix 1** lists the search terms.

### Study Selection

Two trained researchers selected studies independently. Duplicates were identified and removed by comparing the author, title, and publication year. The remaining studies were scanned by the title and abstract, and irrelevant studies were omitted, while the full texts of the others were read. Studies listed in the references of included studies were also screened for eligibility.

### Quality Assessment

Two researchers independently assessed the quality of all selected studies. The Cochrane risk-of-bias tool was chosen and included the following items: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases (12). When there was a disagreement between the researchers, the study was re-evaluated by a third researcher and determined by the majority.

### Data Extraction

Two researchers extracted the following data from each included study independently: study authors, publication year, country, number of participants, source of cases, type of bacteria lysate, dosages, administration routes, control, outcomes, study period, follow-up, and registration number; participant demographics, smoking history, forced expiratory volume in 1 s/predicted value ($FEV_1$/predicted), and concomitant medications and diseases; and pre-established efficacy and safety outcomes. When results were reported at multiple time points, the one nearest 3 months after the last drug dose was chosen. If per-protocol and intention-to-treat analyses were both reported, the results from the intention-to-treat analysis were preferred. Any disagreements

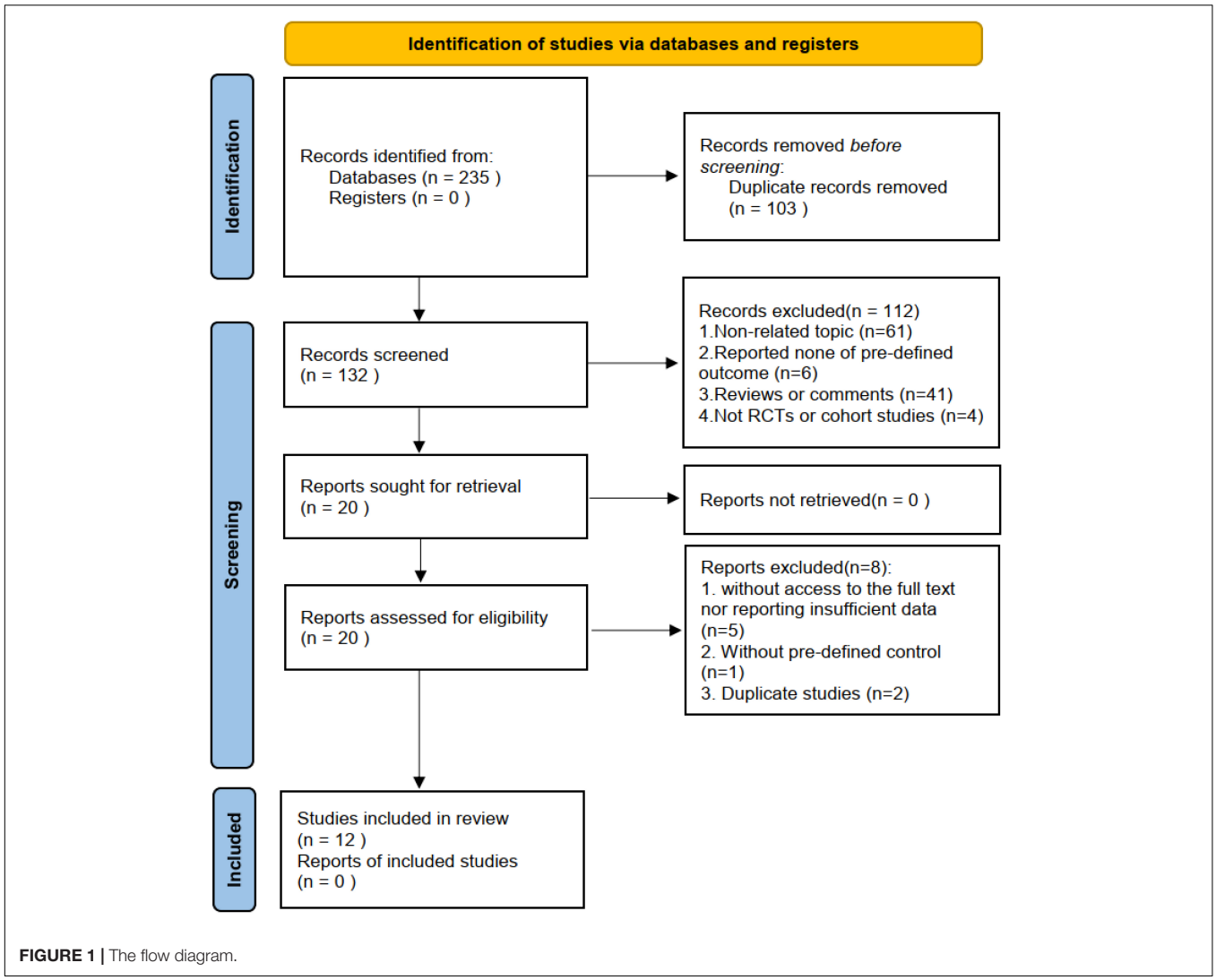


**FIGURE 1 |** The flow diagram.

between the two researchers were resolved by consensus or cross-checking with a third researcher. If the information of interest was not reported directly, we tried to deduce it from the existing information or obtain it by communicating with the principal investigator by email.

## Statistical Analysis

An independent statistician performed the statistical analysis using Review Manager version 5.4.0 (The Nordic Cochrane Centre, The Cochrane Collaboration) and R version 4.1.1 (The R Foundation for Statistical Computing). For continuous variables, we reported the mean and standard derivation (SD), the mean difference (MD) or standard mean difference (SMD), and 95% confidence interval (CI). When the units used were consistent, MD was preferable; otherwise, SMD was chosen. For dichotomous variables, we reported the frequency or proportion, relative risk (RR), and 95% CI.

The chi-square test and $I^2$ statistic were used for identifying and measuring heterogeneity. The *P*-value of chi-square test of less than 0.1 and $I^2$ of more than 50% indicate heterogeneity, and in this case, a Galbraith radial plot was generated, and meta-regression analysis was used to explore the underlying causes of heterogeneity. A random-effects model was applied for the synthesis, and subgroup analysis was performed, if possible. When there was no heterogeneity, a fixed-effects model was preferred. The results of the meta-analysis are shown with forest plots. We also conducted sensitivity analysis and funnel plot analysis if applicable.

# RESULTS

## Study Selection

The database search yielded 235 studies. Of these, 103 studies were removed as duplicates by comparing the title, publication year, and authors. The abstracts of the remainder were assessed to determine eligibility. This led to the removal of 61 studies that did not involve patients with COPD or did not focus

**TABLE 1 |** The characteristics of the included studies.

| Author | Number of participants (bacterial lysate/control) | Major inclusive criteria | Study design | Type of bacteria lysate | Administration way | Dosages and session |
|---|---|---|---|---|---|---|
| Avdeev et al. (8) | 30/30 | Patients with frequent exacerbations of COPD (group C and D according to the GOLD classification) | Parallel RCT, multicenter | Ismigen | Sub-lingual | A cycle consisted of sublingual consumption of one tablet per day for 10 consecutive days, followed by 20 days of standard treatment for three consecutive months |
| Zeng et al. (14) | 78/72 | Stable COPD patients | Parallel RCT, single center | OM-85 | Oral | A capsule (OM-85 7 mg) or placebo daily for 10 consecutive days per month, for 6 consecutive months |
| Tang et al. (9) | 192/192 | Age 40–75 years, male or female, physician-diagnosed chronic bronchitis, or COPD (for 6 months) suffering from an acute exacerbation according to the GOLD definition at enrollment and an FEV1 between 40 and 70% of the predicted value within the 6 months before enrollment. | Parallel RCT, multicenter | OM-85 | Oral | One capsule (OM-85 7 mg) or placebo daily for 10 consecutive days per month, for 3 consecutive months (12 weeks) |
| Braido et al. (10) | 146/142 | A documented diagnosis of moderate, severe or very severe COPD, according to the GOLD 2006 | Parellel RCT, multicenter | Ismigen | Sub-lingual | A cycle consisted of sublingual consumption of one tablet per day for 10 consecutive days, followed by 20 days of standard treatment for 3 consecutive months. After 3 months without any PMBL treatment, a second cycle of therapy (as described above) was undertaken. At the end of the second treatment period, a second three-month period without PMBL was observed |
| Ricci et al. (13) | 12/11 | Patients aged 40 years or older with documented moderate, severe or very severe COPD | Parellel RCT, single center | Ismigen | Sub-lingual | A cycle of 90-day treatment wherein the first 10 days of each 30 days 1 tablet of either PMBL or placebo was given. This was followed by a 90-day 'rest' period (no treatment). |
| Nishantha et al. (15) | 24/21 | Stable COPD patients with moderately severe or severe disease staging, presenting during May – September 2012 | Parallel RCT, single center | Ismigen | Sub-lingual | Daily on the first 10 days of three successive months |
| Olivieri (16) | 340 | Patients aged over 40 years old, with COPD stage II or III, with a history of at least 2 documented AE-COPD in the previous year, and an FEV1 between 30 and 80% | Parallel RCT, multicenter | OM-85 | Oral | A capsule daily during month 1, and 1 capsule daily for 10 days in months 3–5. |

*(Continued)*

**TABLE 1 |** (Continued)

| Author | Number of participants (bacterial lysate/control) | Major inclusive criteria | Study design | Type of bacteria lysate | Administration way | Dosages and session |
|---|---|---|---|---|---|---|
| Cazzola et al. (17) | 33/30 | Patients suffering from moderate-to-very severe COPD, who were under regular treatment with salmeterol/fluticasone (SFC) 50/500 mg BID | Parellel RCT, single center | Ismigen | Sub-lingual | one capsule daily the first 10 days of three consecutive months |
| Solèr et al. (18) | 142/131 | Outpatients aged 40 years old of both sexes with a history of chronic bronchitis or mild COPD at the time of an AE | Parallel RCT, multicenter | OM-85 | Oral | A capsule of OM-85 or placebo per day for 30 days, followed by three 10-day courses for months 3, 4, and 5 |
| Li et al. (19) | 49/41 | Patients with chronic bronchitis complicated with COPD | Parallel RCT, multicenter | OM-85 | Oral | A capsule daily for the first 10 days of each month for 3 consecutive months |
| Collet et al. (20) | 191/190 | Patients with a history of heavy smoking and an FEV1 value between 20 and 70% of predicted | Parallel RCT, multicenter | OM-85 | Oral | A capsule per day for 30 days followed by a repeat course of 10 consecutive days of therapy per month for 3 months |
| Xinogalos et al. (21) | 33/29 | – | Parellel RCT, multicenter | OM-85 | Oral | A capsule (7 mg)/day for 1 month; 1 capsule/10 days for months 3, 4, and 5 |

| Author | Control | Outcomes | Study period | Follow up | Treatment duration | Drop up | Registration number | Country |
|---|---|---|---|---|---|---|---|---|
| Avdeev et al. (8) | Blank | The severity of symptoms, frequency of recurrence of COPD exacerbations, readmissions, need for emergency care and changes in basic therapy of COPD | NR | 3 months | 3 months | NR | NR | Russia |
| Zeng et al. (14) | Blank | The number of acute exacerbations per person per year, quality of life, lung function, T cell subsets | 2015.07–2016.07 | 6 months | 6 months | NR | NR | China |
| Tang et al. (9) | Placebo | The proportion of patients with recurrent acute exacerbations during the 12-week treatment period. Secondary efficacy endpoints included the proportion of patients with recurrent acute exacerbations over the 22-week study period, the proportion of patients treated | 2005–2008 | 10 weeks | 12 weeks | 19 (4.9%) | China Food and Drug Administration TG0504BCV | China |
| Braido et al. (10) | Placebo | The primary outcome is the number of exacerbations, the secondary outcome is the time from the randomization to the first exacerbation, the average interval between the first and second exacerbation, the effects of Ismigen on symptoms | July 31, 2009, to June 16, 2012 | 3 months | 3 months, 2 cycle | NR | EudraCT 2007-000006-67 | Italy |
| Ricci et al. (13) | Placebo | Serological changes, exacerbation rate and symptom | Fall in 2019 to fall in 2010 | About 3 months | 3 months | 0 | NR | Italy |
| Nishantha et al. (15) | Placebo | Infective exacerbations and symptoms improvements | 2012 | 6 months | NR | NR | NR | Sri Lanka |
| Olivieri (16) | Placebo | The rate and duration of AECOPD, the rate of treatment-emergent adverse events | 2011 | NR | NR | NR | NR | NR |

*(Continued)*

**TABLE 1 |** (Continued)

| Author | Control | Outcomes | Study period | Follow up | Treatment duration | Drop up | Registration number | Country |
|---|---|---|---|---|---|---|---|---|
| Cazzola et al. (17) | Blank | Symptoms, diagnosis of exacerbation, concomitant medications and hospitalization | Begin from September 2007 | 3 months | 3 months | 0 | NR | Italy |
| Solèr et al. (18) | Placebo | The primary endpoint was the mean rate of AEs occurring within the study period | NR | 1 month | 5 months | 40 (14.65%) | NR | Switzerland and Germany |
| Li et al. (19) | Placebo | The frequency of acute exacerbation, symptom scores, and lung function were recorded | NR | 9 months | 3 month | 0 | NR | China |
| Collet et al. (20) | Placebo | The primary outcome was the occurrence of at least one such episode during the 6 months. Secondary outcomes included total number of acute exacerbations and hospitalization for a respiratory problem, as well as all hospitalization, change in baseline respiratory symptoms, and change in quality of life | Begin from November 07, 1994 | 2 months | 4 months | 15 (3.93%) | NR | Canada |
| Xinogalos et al. (21) | Placebo | Clinical manifestations, frequency, duration and severity of acute exacerbations, consumption of conventional medications and serum immunoglobulin levels | Autumn/winter of 1990–1991 | 2 months | 4 months | – | – | – |

*COPD, chronic obstructive pulmonary disease; GOLD, the global initiative for chronic obstructive lung disease; NR, not reported.*

**TABLE 2 |** The characteristics of the included participants.

| Author, year | Age (years) Mean [95% CI] or Mean ± SD | | Gender (male/total) | | Smoking history Mean ± SD | | FEV1/predicted (%) Mean ± SD | | Concomitant respiratory medications | | | Diabetes | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Bacterial lysates | Control | Bacterial lysates | Control | Bacterial lysates | Control | Bacterial lysates | Control | Long-terms effect bronchodilator | Flu vaccination | Pneumonia vaccination | Bacterial lysates | Control |
| Avdeev et al. (8) | 69.4 ± 9.4 | 69.9 ± 7.9 | 28/30 | 30/30 | 30/30 | 30/30 | 31.3 ± 8.7 | 33.2 ± 7.7 | Yes | NR | NR | NR | NR |
| Zeng et al. (14) | 70.1 ± 5.7 | 69.2 ± 6.1 | 67/78 | 63/72 | 63/78 | 61/72 | 49.15 ± 4.74 | 49.06 ± 2.73 | Yes | No | No | NR | NR |
| Tang et al. (9) | 63.0 ± 9.4 | 63.2 ± 8.9 | 141/192 | 133/192 | 123/192 | 120/192 | 54.0 ± 10.0 | 55.0 ± 9.7 | Yes | Allowed | NO | NR | NR |
| Braido et al. (10) | 69.3 ± 8.6 | 68.6 ± 9.4 | 107/146 | 91/142 | 123/146 | 120/142 | 52.18 ± 18.99 | 52.66 ± 16.26 | Yes | Allowed | NR | 19/146 | 10/142 |
| Ricci et al. (13) | 65–89 | | 16/28 | | – | – | – | – | Yes | Allowed | NR | – | – |
| Nishantha et al. (15) | 50–58 | | 24/24 | 21/21 | – | – | – | – | – | – | – | – | – |
| Cazzola et al. (17) | 66.6 ± 7.8 | 66.2 ± 8.0 | 25/33 | 26/30 | ≥20/33 | ≥16/30 | 47.7 ± 9.0 | 46.2 ± 8.9 | Yes | Allowed | NR | NR | NR |
| Solèr et al. (18) | 57.3 [55.7, 58.9] | 57.9 [56.2, 59.6] | 78/142 | 57/131 | 87/142 | 77/131 | 85[81.7, 88.3] | 82.6[79.9, 86.1] | Yes | Allowed | NR | NR | NR |
| Li et al. (19) | 67 ± 4 | 65 ± 5 | 27/49 | 22/41 | 49/49 | 41/41 | 50.9 ± 21 | 53.2 ± 19.7 | Yes (sustained-released theophylline) | NR | NR | NR | NR |
| Collet et al. (20) | 65.3 ± 7.7 | 66.9 ± 7.7 | 133/191 | 135/190 | 78/191′ | 59/190′ | 67.7 ± 15.3 | 68.4 ± 15.6 | NR | Allowed | NR | NR | NR |
| Xinogalos et al. (21) | 56.03 ± 12.67 | 59.75 ± 12.89 | – | – | – | – | – | – | – | – | – | – | – |

*FEV1/predicted, forced expiratory volume in one second/predicted value; NR, not reported.*

on the clinical application of bacterial lysates, 41 citations of reviews, 6 studies without pre-defined outcomes, and 4 studies that were not a randomized controlled trial or cohort study. The remaining 20 studies were subject to a whole-text review. Subsequently, eight studies were voted out, namely, two duplicate studies; five without access to the full text or reporting insufficient data; and one without a pre-defined control. During the process, we found that the study by Ricci et al. (13) was ancillary to the AIACE study (2), but retained it because it reported complementary data. Ultimately, this meta-analysis included 12 studies, namely, nine randomized controlled trials and three abstracts of randomized controlled trials with sufficient data (8–10, 13–21). **Figure 1** summarizes the study selection process.

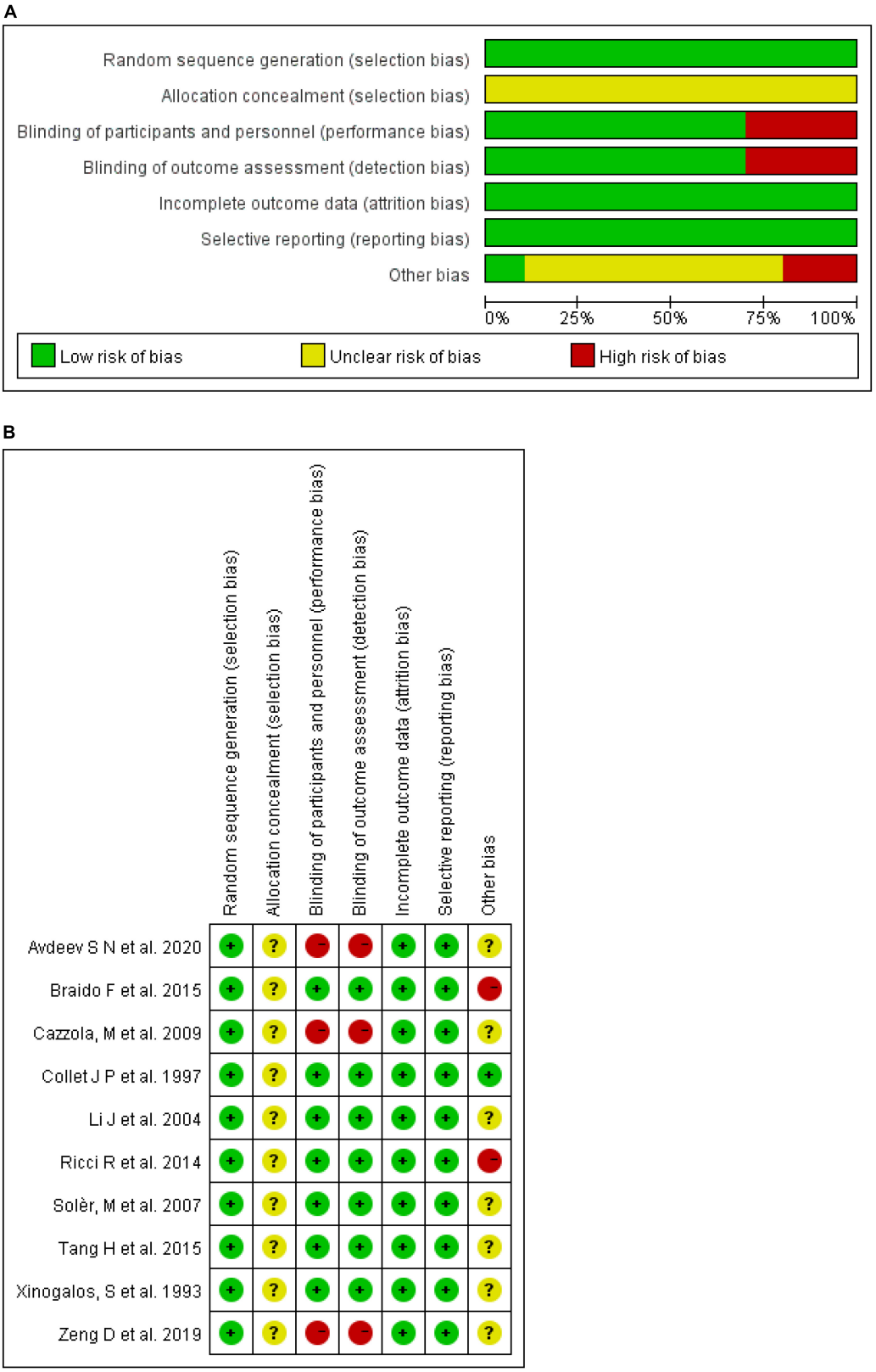


**FIGURE 2 |** Risk of bias. **(A)** Each risk of bias item presented as percentages across all included studies. **(B)** Each risk of bias item for each included study.

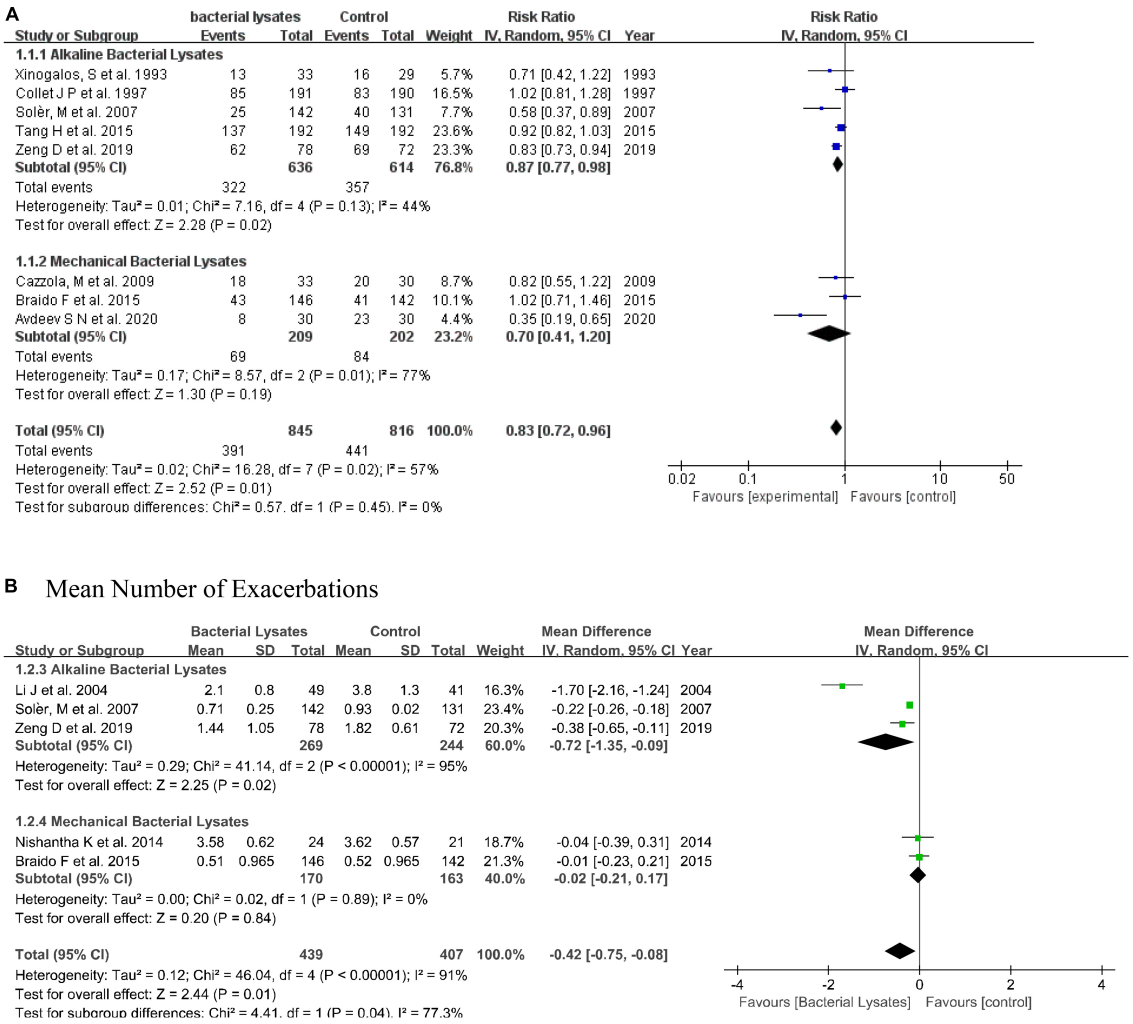


**FIGURE 3 |** Forest plot of the efficacy of bacterial lysates on exacerbations. **(A)** Forest plot of rate of exacerbation. **(B)** Forest plot of mean number of exacerbations.

## Characteristics of the Included Studies and Participants

Of the included studies, seven focused on OM-85 (alkaline bacterial lysate) and five on Ismigen (mechanical bacterial lysate), and studies were conducted in Italy ($n$ = 3), China ($n$ = 3), Russia ($n$ = 1), Canada ($n$ = 1), Switzerland and Germany ($n$ = 1), Sri Lanka ($n$ = 1), and not reported ($n$ = 2). Three studies were blank-control, while the others were placebo-control. All studies were parallel randomized controlled trials, with four single-center and eight multicenter studies. Two studies were registered. The majority of cases in the studies were men, in accordance with the real-world population. Most studies allowed flu vaccination. The $FEV_1$/predicted ranged from less than 30% to more than 80%. The characteristics of the included studies and participants are summarized in **Tables 1**, **2**, respectively.

## Quality of the Included Studies

Eligible studies with sufficient information were assessed using the Cochrane risk-of-bias tool. As shown in **Figure 2**, three studies with a blank control were at a high risk of both performance and detection bias. No study mentioned allocation concealment, which was deemed an unknown risk. Braido et al. (10) were funded by a pharmaceutical company and considered high risk. Tang et al. (9) were also sponsored by *OM Pharma* but all the authors assume responsibility for the integrity and completeness of the data and data analyses, and considered an unknown risk. The others did not include a *conflict of interest* section and were considered an unknown risk. There were low risks in random sequence generation, attrition bias, and reporting bias in all studies assessed. **Figure 2** summarizes the quality of the included studies.

## Efficacy and Safety of Bacterial Lysates

### Efficacy on Exacerbation

Nine studies reported the rate of exacerbation with detailed numbers. Excluding the study by Ricci et al. (13), data from eight studies were subtracted for the meta-analysis. The pooled result indicated that bacterial lysates could reduce the exacerbation rate

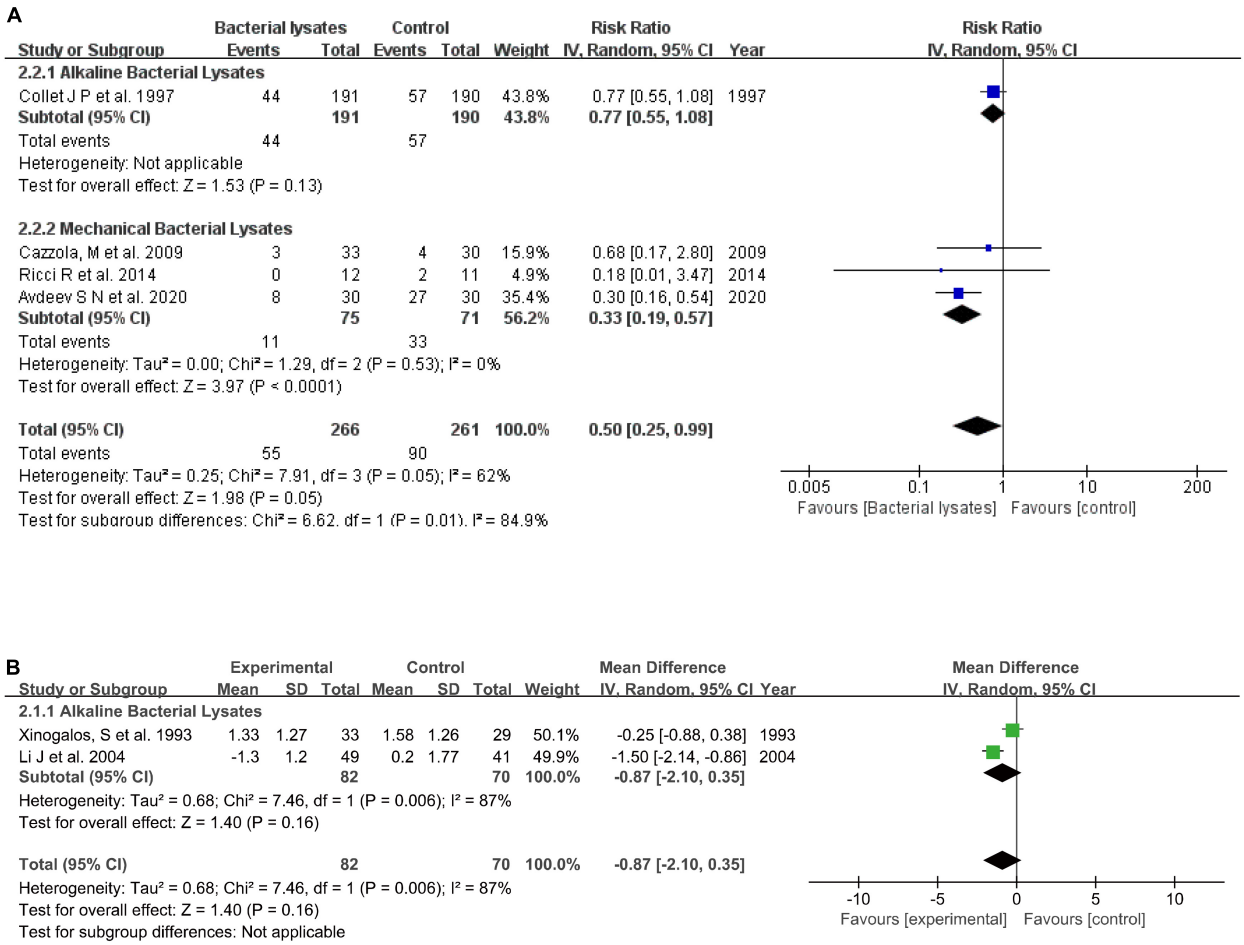


**FIGURE 4 |** Forest plots of the efficacy of bacterial lysates on respiratory infections and hospitalization. **(A)** Rate of hospitalization. **(B)** Mean number of respiratory infections.

by 17% (RR = 0.83, 95% CI 0.72–0.96, $P$ = 0.01; heterogeneity: $P$ = 0.02, $I^2$ = 57%). The alkaline bacterial lysate (OM-85) subgroup reduced the exacerbation rate by 13% (RR = 0.87, 95% CI 0.77–0.98, $P$ = 0.02; heterogeneity: $P$ = 0.13, $I^2$ = 44%), while the mechanical bacterial lysate (Ismigen) subgroup reduced the exacerbation rate by 30% (RR = 0.70, 95% CI 0.41–1.20, $P$ = 0.19; heterogeneity: $P$ = 0.01, $I^2$ = 77%); however, the difference was not significant.

We also evaluated the efficacy of bacterial lysates on exacerbation using the mean number of exacerbations. In line with the rate of exacerbation, the pooled result showed that bacterial lysates were associated with fewer exacerbations (MD = −0.42, 95% CI −0.75 to −0.08, $P$ = 0.01; heterogeneity: $P$ < 0.001, $I^2$ = 91%). Both the alkaline (MD = −0.72, 95% CI −1.35 to −0.09, $P$ = 0.02; heterogeneity: $P$ < 0.001, $I^2$ = 95%) and mechanical (MD = −0.02, 95% CI −0.21 to 0.17, $P$ = 0.20; heterogeneity: $P$ = 0.89, $I^2$ = 0) bacterial lysates decreased the mean number of exacerbations in the subgroup analysis. Another study also reported that mechanical bacterial lysates were effective at reducing exacerbations (22), but was excluded from this synthesis for lack of data. The forest plots are shown in **Figure 3**.

## Efficacy on Hospitalization and Respiratory Infections

Four studies reported the hospitalization rate. Overall, bacterial lysates reduced hospitalization (RR = 0.50, 95% CI 0.25–0.99, $P$ = 0.05; heterogeneity: $P$ = 0.05, $I^2$ = 62%). The subgroup analysis indicated that alkaline bacterial lysate treatment resulted in a 37% reduction in hospitalization (RR = 0.77, 95% CI 0.55–1.08, $P$ = 0.13), while mechanical bacterial lysates resulted in a greater reduction in hospitalization (RR = 0.33, 95% CI 0.19–0.57, $P$ < 0.001; heterogeneity: $P$ = 0.52, $I^2$ = 0). Moreover, Braido et al. (10) showed that mechanical bacterial lysates prolonged the interval between the first and second exacerbations (70.36 vs. 123.89 days, $P$ = 0.03). Regarding the effect on respiratory infections, data from two studies showed the alkaline bacterial lysates induced an insignificant reduction in the mean number of respiratory infections (MD = −0.87, 95% CI −2.10 to 0.35, $P$ = 0.16; heterogeneity: $P$ = 0.006, $I^2$ = 87%). **Figure 4** shows the forest plots.

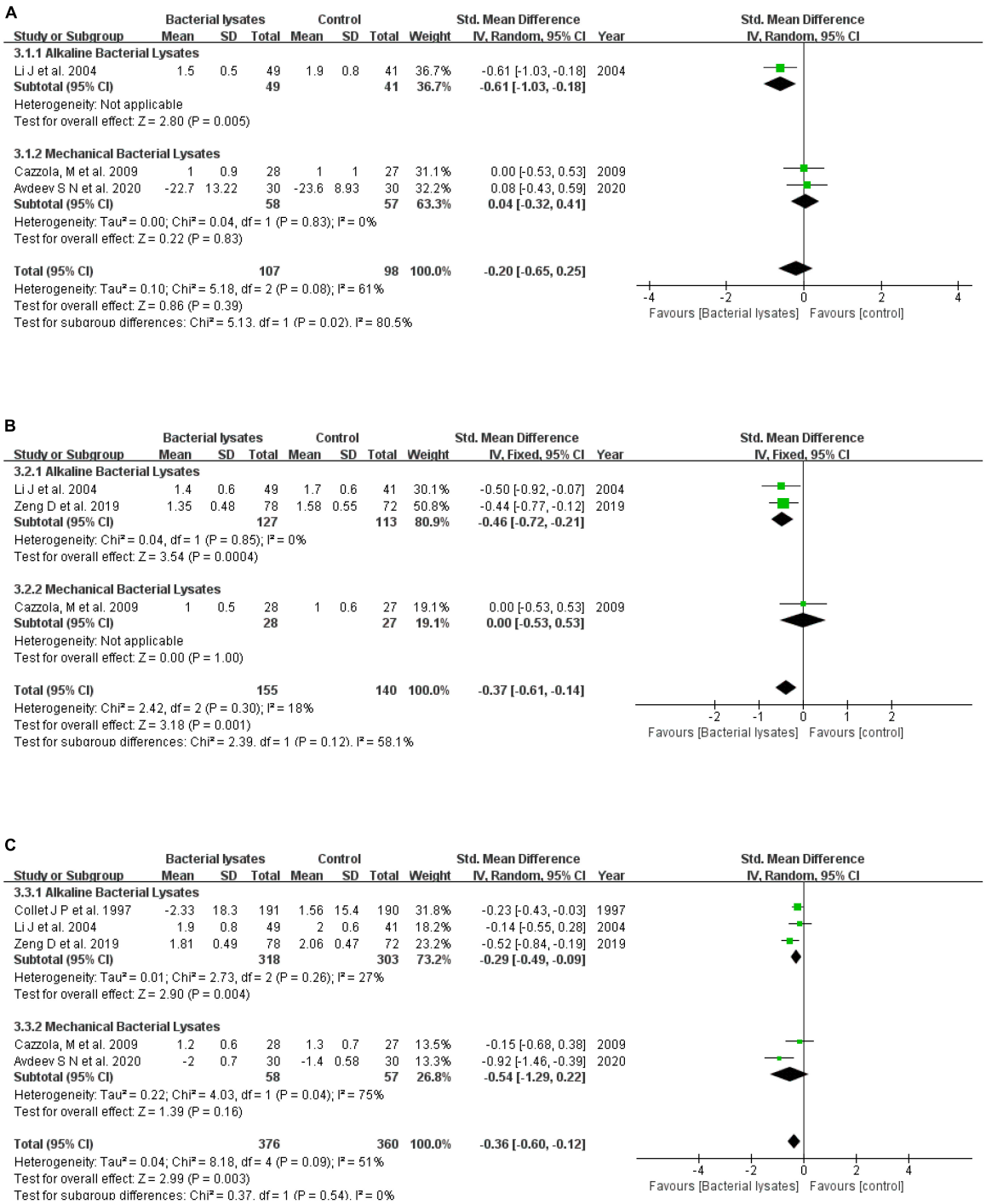


**FIGURE 5 |** Forest plots of the efficacy of bacterial lysates on symptoms. **(A)** Sputum, **(B)** cough, and **(C)** severity of dyspnea.

## Efficacy on Symptoms

Symptoms were evaluated mainly using the changes in sputum, cough, severity of dyspnea, and fever.

Four studies reported a change in sputum, with two studies each examining alkaline and mechanical bacterial lysates. Collet et al. (20) described a difference between the OM-85 group and control without detailed data, while Li et al. (19) showed that alkaline bacterial lysates helped improve sputum (score $1.5 \pm 0.5$ vs. $1.9 \pm 0.8$, $P < 0.01$). Overall, bacterial lysates reduced the sputum slightly but insignificantly (SMD = −0.20, 95% CI −0.65 to 0.25, $P = 0.39$; heterogeneity: $P = 0.08$, $I^2 = 61\%$), while mechanical bacterial lysates had no significant effect on sputum

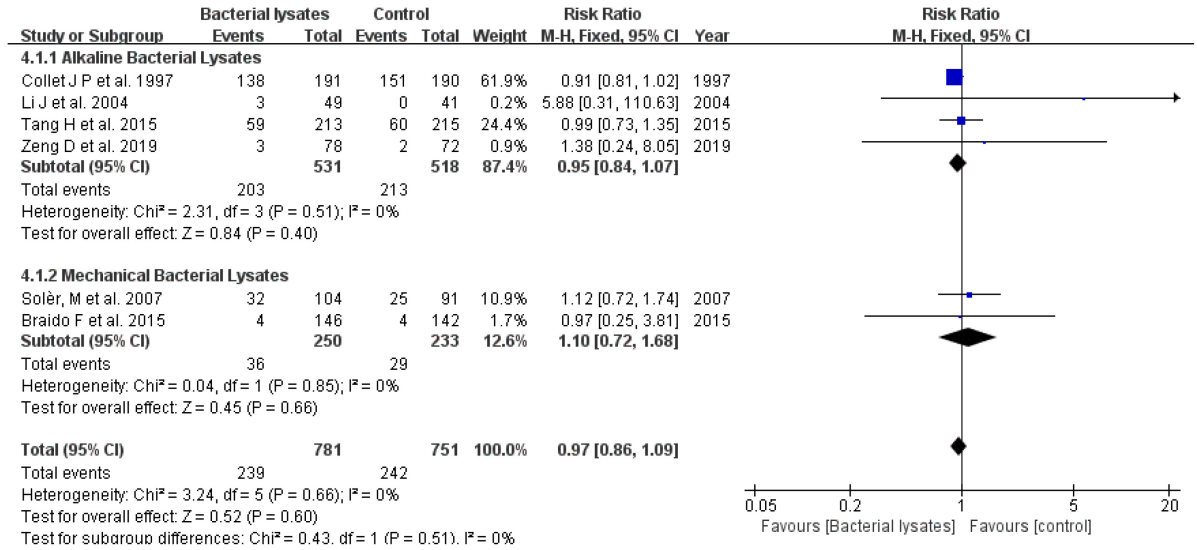


**FIGURE 6 |** Safety of bacterial lysates: the forest plot of the rate of adverse events.

**TABLE 3 |** The detailed adverse effect.

| Author, year | Treatment | The most symptoms reported | |
|---|---|---|---|
| | | Treatment group | Control group |
| Zeng et al. (14) | OM-85 | Nausea, Thirst | Thirst |
| Tang et al. (9) | OM-85 | Common cold, nausea, abdominal pain, headache | Common cold, headache, dizziness, nausea |
| Solèr et al. (18) | OM-85 | Respiratory system manifestations such as acute exacerbations, tonsillitis, symptoms of influenza, sinusitis | |
| Li et al. (19) | OM-85 | Dyspepsia, skin pruritus | Not mentioned |
| Collet et al. (20) | OM-85 | Abdominal with gastroenteritis, miscellaneous, pulmonary and respiratory issues | Miscellaneous, pulmonary and respiratory issues, abdominal with gastroenteritis |

(SMD = 0.04, 95% CI −0.32 to 0.41, $P$ = 0.83; heterogeneity: $P$ = 0.83, $I^2$ = 0).

Five studies reported a change in cough. Collet et al. (20) (OM-85) and Solèr et al. (18) (Ismigen) also reported a difference between the two groups. Cazzola et al. (17) reported the same outcome (cough score 1.0 ± 0.6 vs. 1.0 ± 0.5). The remaining two eligible studies found OM-85 and improved cough. Data from the three studies for the meta-analysis gave an SMD of −0.46 for alkaline bacterial lysates (95% CI −0.72 to −0.21, $P$ < 0.001; heterogeneity: $P$ = 0.85, $I^2$ = 0) and −0.37 for the overall effect of bacterial lysates (95% CI −0.61 to −0.14, $P$ = 0.001; heterogeneity: $P$ = 0.30, $I^2$ = 18%).

Six studies reported a change in the severity of dyspnea. Solèr et al. (18) stated that there was no substantial difference between Ismigen and the control on dyspnea. Pooled results of the remaining five eligible studies indicated that bacterial lysates alleviated dyspnea (SMD = −0.36, 95% CI −0.60 to −0.12, $P$ = 0.003; heterogeneity: $P$ = 0.09, $I^2$ = 51%). Both alkaline (SMD = −0.29, 95% CI −0.49 to −0.09, $P$ = 0.004; heterogeneity: $P$ = 0.26, $I^2$ = 27%) and mechanical (SMD = −0.54, 95% CI −1.29 to 0.22, $P$ = 0.16; heterogeneity: $P$ = 0.04, $I^2$ = 75%) bacterial lysates helped improve the severity of dyspnea, but a difference did not reach significance. **Figure 5** shows the forest plots.

One study examined the effect of OM-85 on fever (10), reporting that the mean number of days with fever was 0.06 for the treatment group and 0.11 for the placebo group ($P$ < 0.001).

### Safety of Bacterial Lysates

The difference in adverse effects between the bacterial lysates and control was similar and insignificant (RR = 0.97, 95% CI 0.86–1.09, $P$ = 0.60; heterogeneity: $P$ = 0.66, $I^2$ = 0; **Figure 6** shows the forest plot). The adverse effects reported in most studies were acceptable and slight. **Table 3** summarizes the symptoms.

## Heterogeneity Analysis

As the forest plots show, heterogeneity was present in the efficacy assessments. First, we conducted a subgroup analysis. The forest and radial plots (**Figure 7**) analyzing the effect on the exacerbation rate showed obvious heterogeneity for mechanical bacterial lysates; Avdeev et al. (8) included patients with a lower $FEV_1$/predicted and found a higher RR, and might be the source of heterogeneity. After removing this study, the heterogeneity decreased (overall: RR = 0.88, 95% CI 0.79–0.97, $P$ = 0.009; heterogeneity: $P$ = 0.24, $I^2$ = 25%; mechanical bacterial lysate subgroup: RR = 0.92, 95% CI 0.71–1.21, $P$ = 0.57; heterogeneity: $P$ = 0.42, $I^2$ = 0). Examining the mean number of exacerbations,

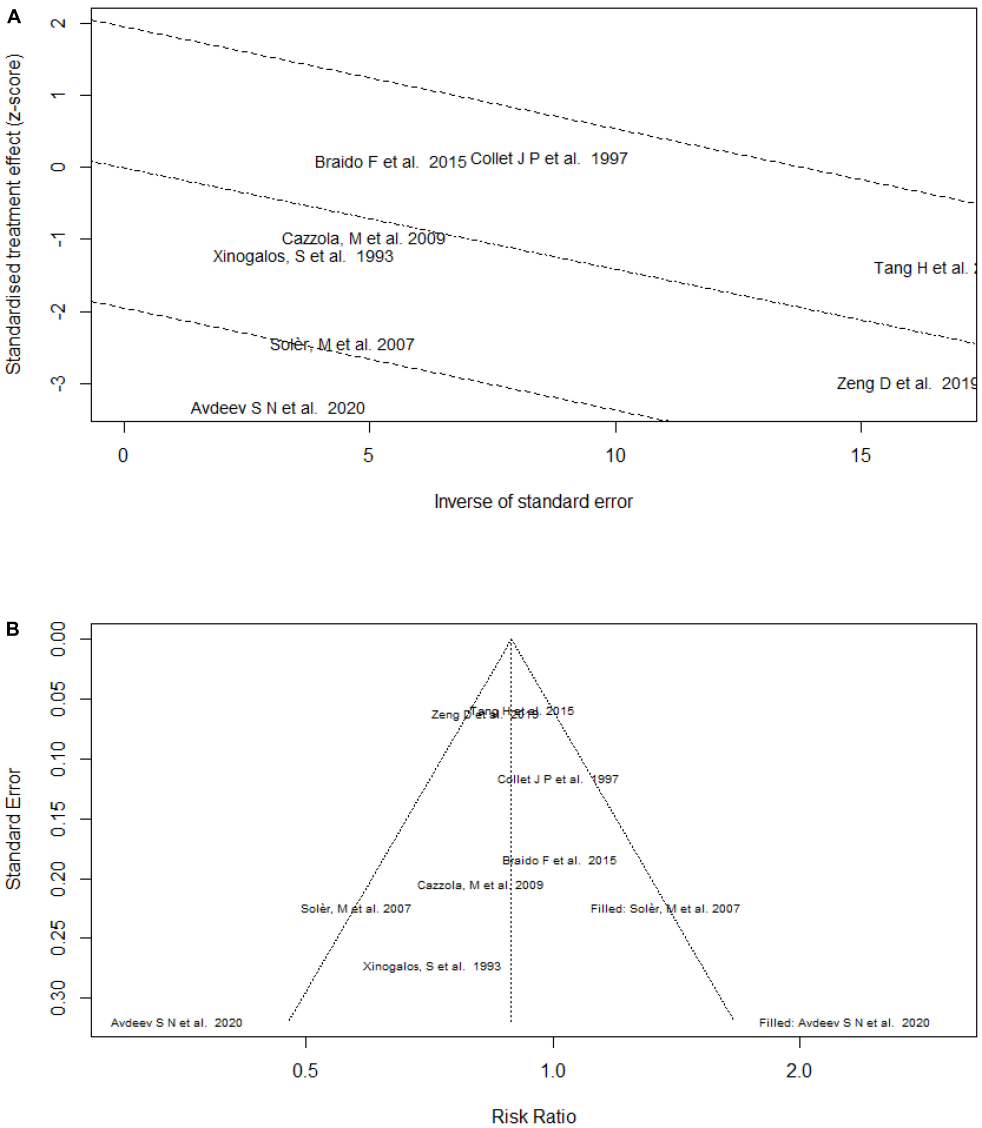


**FIGURE 7 |** Radial plot and funnel plot of the efficacy of bacterial lysates on the rate of exacerbation. **(A)** Radial plot of the efficacy of bacterial lysates on the rate of exacerbation. **(B)** Funnel plot of the efficacy of bacterial lysates on the rate of exacerbation.

we noticed that the effect size differed among studies, but all supported the use of bacterial lysates. The heterogeneity decreased in the subgroups when analyzing the secondary efficacy outcomes.

Considering the limited number of studies (23), we also conducted a meta-regression of the rate of exacerbation. This suggested that the type of bacterial lysate (*P*-value of meta-regression 0.698) and publication year (*P*-value of meta-regression 0.727) was unlikely to be the cause of heterogeneity.

## Sensitivity Analysis

We performed a sensitivity analysis to evaluate the robustness of the efficacy results. A meta-analysis with an alternative model was used to assess whether the statistical method affected the results. As shown in **Table 4**, the value of the estimated effect was rather close. Moreover, we performed an influence analysis that examined the impact of each study on the final pooled effect size by re-synthesizing the included studies, by omitting one at a time (**Figure 8**). This indicated that the result remained stable no matter which study was removed.

## Publication Bias

Considering the limited number of included studies that were not suitable for statistical testing, the publication bias was assessed using a funnel plot. As shown in **Figure 7**, publication bias appeared to present, so a trim analysis was performed to help quantify its influence. However, with the addition of studies, it remained similar (RR = 0.88 [trim analysis] vs. RR = 0.83 [accrual]).

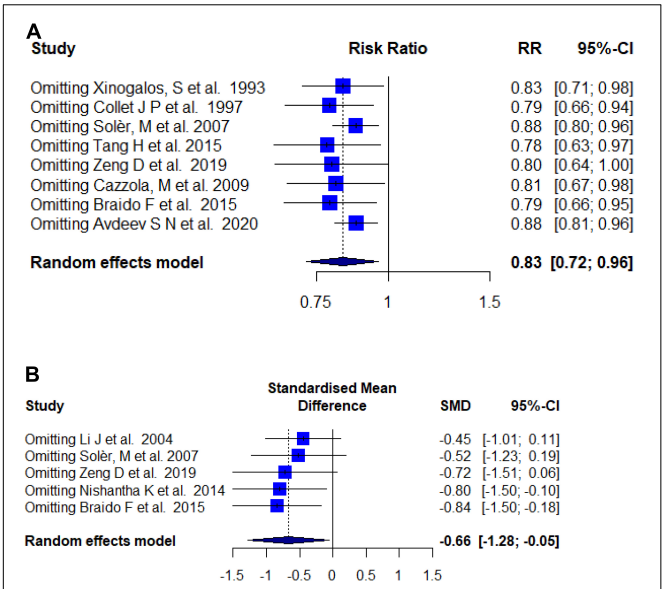


**FIGURE 8 |** Sensitivity analysis. **(A)** Influence analysis of the rate of exacerbation. **(B)** Influence analysis of the mean number of exacerbations.

**TABLE 4 |** Results of the meta-analysis by the alternative model.

| Outcome (effect factor) | Model used (estimated value [95% CI]) | |
|---|---|---|
| | Random | Fixed |
| Rate of exacerbation (RR) | 0.83 [0.72, 0.96] | 0.87 [0.81, 0.93] |
| Mean number of exacerbations (MD) | −0.42 [−0.75, −0.08] | −0.23 [−0.27, −0.19] |
| Mean number of respiratory infections (MD) | −0.87 [−2.10, 0.35] | −0.87 [−1.32, −0.42] |
| Rate of hospitalization (RR) | 0.50 [0.25, 0.99] | 0.61 [0.46, 0.81] |
| Sputum (SMD) | −0.20 [−0.65, 0.25] | −0.23 [−0.51, 0.04] |
| Cough (SMD) | −0.37 [−0.63, −0.11] | −0.37 [−0.61, −0.14] |
| Severity of dyspnoea (SMD) | −0.36 [−0.60, −0.12] | −0.32 [−0.47, −0.18] |
| Adverse effects (RR) | 0.93 [0.84, 1.03] | 0.97 [0.86, 1.09] |

## DISCUSSION

The use of bacterial lysates dates to the 1970s and they are most often used clinically to prevent or treat an infection. Evidence has accrued demonstrating their role in pediatric respiratory tract infections, and they are recommended in some guidelines (24). As they can be given orally, studies are examining their role in COPD.

Using published evidence, we evaluated the efficacy and safety of bacterial lysates in patients with COPD in this meta-analysis. This showed that bacterial lysates reduced exacerbations. This result was consistent with the former analysis by pan et al. (7) who included 4 randomized controlled trials focused on OM-85. The combined results of the RR in the OM-85 subgroup of our study and that of Pan et al. were 0.87 (95% CI 0.77–0.98) and 0.8 (95% CI 0.65–0.97), respectively. The results were also supported by several other studies that revealed that bacterial lysates were effective at reducing the exacerbations of chronic bronchitis (25, 26), which can lead to COPD. Several studies have linked the mechanism underlying the effects of lysates to the gut–lung axis. As oral immunomodulators, both mechanical and alkaline bacterial lysates interact with mucosa-associated lymphoid tissues in the gut, bronchi, and upper airways, which function as an integrated unit (27–29). On delivery to the body, the bacterial lysate antigens are captured and recognized by the pattern recognition receptors of immune cells in the mucosa, including dendritic cells. These then transmigrate to lymph nodes and bloodstream and trigger an immune cascade. As a result, secretory immunoglobulin A increases and there is an extensive non-specific immune response to pathogens and toxins (30–32). Moreover, bacterial lysates promote the production of antiviral cytokines, including INF-γ, facilitate neutrophil chemotaxis, and modulate the Th1/Th2 ratio, enhancing the immune status (31, 33–35). Consistent with this, fewer bacterial colonies were cultured in sputum from patients treated with bacterial lysates (19, 23), and less seroconversion was seen clinically (14).

Moreover, we assessed the efficacy of bacterial lysates on symptoms, which was not analyzed in the former meta-analysis. We found that bacterial lysates reduced the hospitalization rate, alleviated cough, and improved dyspnea slightly. There were also non-significant improvements in sputum production and the mean number of respiratory infections. Intriguingly, in the subgroup analysis, OM-85 was significantly more effective than Ismigen overall, although Ismigen might be more effective in reducing the hospitalization rate.

Of note, heterogeneity was seen in most results. This might have been due to the type of bacterial lysate, as seen in the subgroup analysis. In addition, the growing understanding of the disease and emerging drugs, which could be represented by the year, could also have influenced the outcomes. Thus, subsequent meta-regressions were performed. However, neither the type of bacterial lysate nor the year was a source of heterogeneity. Moreover, there was a publication bias in the rate of exacerbation, especially in the alkaline bacterial lysate subgroup. Nevertheless, the included studies all favored OM-85. In addition, it might be explained by differences in the population's lung function, which was correlated with exacerbation risk. Importantly, a sensitivity analysis showed that our results were stable and reliable.

In summary, our results showed that bacterial lysates can reduce exacerbations and alleviate symptoms in patients with COPD.

Nevertheless, our study had several limitations. First, some studies did not report sufficient data in the abstract and were too old to obtain the full text, so they were removed from the meta-analysis. Second, the measurements in the studies, such as symptom evaluation, were not standardized, which could affect the quantitative analysis. In addition, several studies described the predefined outcomes rather than presenting detailed data and could not be included in the meta-analysis. Heterogeneity was also a problem, as discussed above. The included studies also had methodological issues, such as explicit allocation concealment, an important factor for evaluating selection bias, which could lead to bias and reduce the strength of the evidence.

## CONCLUSION

Bacterial lysates can benefit patients with COPD by reducing exacerbations and alleviating symptoms. OM-85 is the preferable product based on the existing evidence. Further studies are needed to validate these findings.

## DATA AVAILABILITY STATEMENT

The original contributions presented in this study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

TZ provided study conception and funding support. YH designed search terms with the help of YP and YQ. YH completed the literature searching and mainly drafted the manuscript. YP and YQ finished study selection, quality assessment and revised the manuscript. YH and JD conducted quality assessment. MS did the data analysis and offered funding support. ZY and CC coped with the disagreement between the authors. All authors read and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.877124/full#supplementary-material

**Supplementary Appendix 1 |** PRISMA checklist.

**Supplementary Appendix 2 |** Lists the search terms.

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