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Respiratory health outcomes and treatment of patients with mild-to-moderate COPD not eligible for previous major randomized controlled trials

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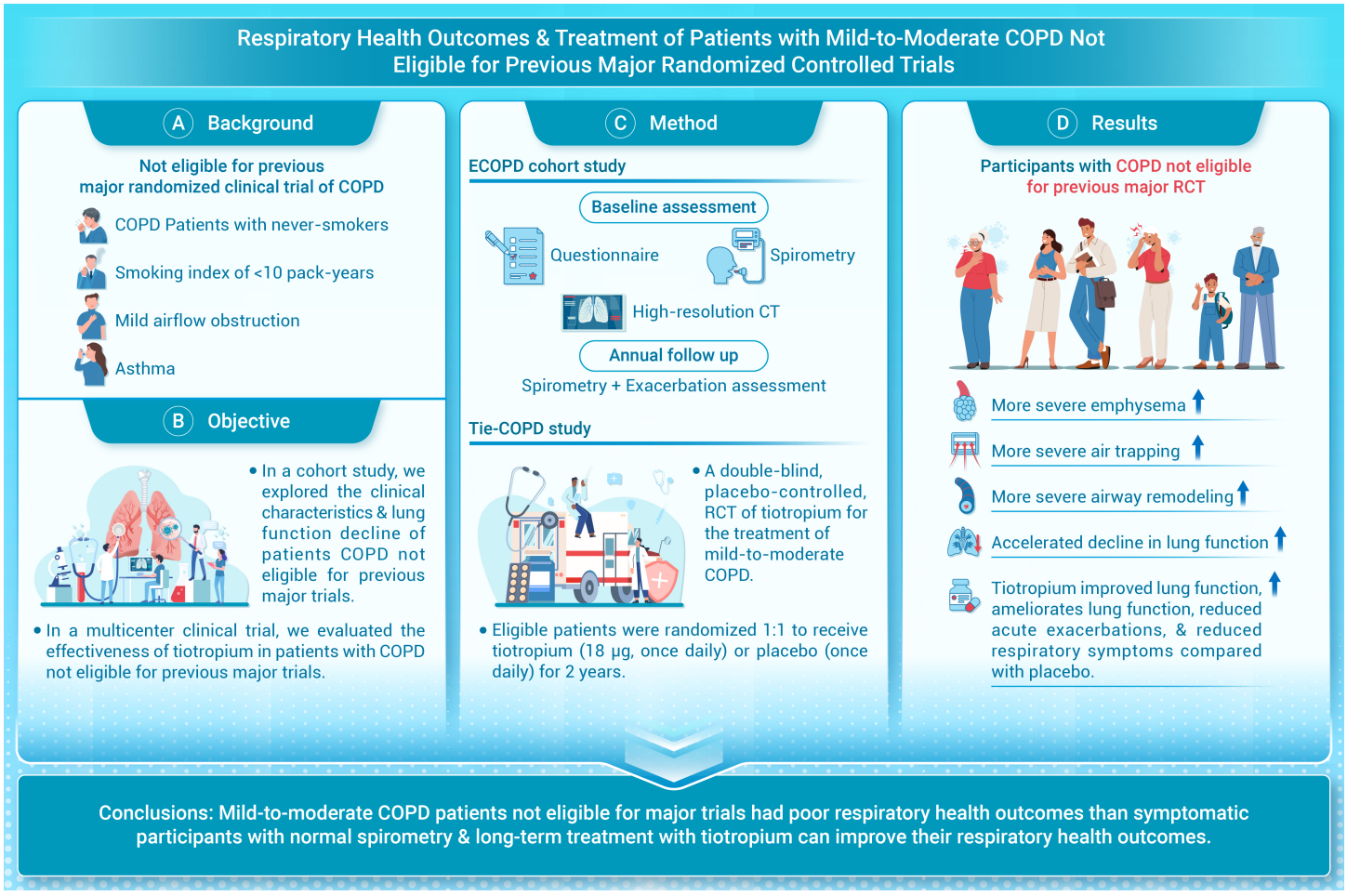
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Mild-to-moderate COPD not eligible for major trials have faster annual lung function decline than normal spirometry.
- Tiotropium improved respiratory outcomes in patients with mild-to-moderate COPD not eligible for major trials.
- Patients with mild-to-moderate COPD not eligible for previous major trials needs treatment and treatment is effective.

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Respiratory health outcomes and treatment of patients with mild-to-moderate COPD not eligible for previous major randomized controlled trials

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Many real-world patients with chronic obstructive pulmonary disease (COPD) are not eligible for previous major randomized clinical trials of COPD. Therefore, we aimed to explore the respiratory health outcomes and effectiveness of treatment among patients with mild-to-moderate COPD not eligible for previous major trials. In a cohort study, we explored the clinical characteristics and lung function decline of patients with mild-to-moderate COPD not eligible for previous major trials. In a post hoc analysis of multicenter clinical trial, we evaluated the effectiveness of tiotropium in patients with mild-to-moderate COPD not eligible for previous major trials. Patients not eligible for previous major trials were never-smokers; had a smoking index of <10 pack-years; or had a post-bronchodilator FEV_1 of ≥ 80% predicted, or asthma. Overall, 475 patients with mild-to-moderate COPD not eligible for major trials and 398 symptomatic participants with normal spirometry were included. Patients not eligible for major trials have more severe small airway dysfunction, emphysema, and faster annual lung function decline than symptomatic participants with normal spirometry. From the multicenter clinical trial, 428 patients with mild-to-moderate COPD not eligible for major trials were included. Tiotropium significantly increased pre-bronchodilator FEV_1 than placebo at 24 months (difference=128 [95% CI: 78–177] mL, P<0.001), reduced acute exacerbations (RR=0.55 [95% CI: 0.40–0.77], P<0.001), and ameliorated the annual decline in post-bronchodilator FEV_1 in patients not eligible for previous major trials. Mild-to-moderate COPD patients not eligible for major trials had poor respiratory health outcomes than symptomatic participants with normal spirometry and long-term treatment with tiotropium can improve their respiratory health outcomes.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) demonstrates pronounced heterogeneity among affected individuals. It affects hundreds of millions of people worldwide and poses a huge economic burden.[1,2] Over the past two decades, there has been great progress in the development of effective medications for the treatment of COPD, which have been verified through rigorous large-scale clinical trials.[3-6] Although these effective therapies have significantly improved the respiratory health outcomes of patients with COPD, these randomized controlled trials (RCTs) have adopted strict selection criteria in order to obtain positive results. For example, patients with more severe COPD or COPD with a single pathogenic factor would be more likely to be selected for clinical trials. Therefore, only a limited proportion of patients with COPD in the real-world setting meet the inclusion criteria.[7-9] Strict selection criteria greatly limit the extrapolation and generalizability of RCT results.[10] Therefore, there is an urgent need to develop patient-centered treatment models that take into account the diversity of patients to ensure that clinical trial study populations are representative of real-world patients.[11-13]

A previous study compiled the inclusion and exclusion criteria used in clinical trials on COPD, observing that patients with mild airflow limitation, a smoking index of <10 pack-years, or a previous diagnosis of asthma are often not eligible for previous major RCTs on COPD.[14] These patients account for 56% of the entire COPD population. Importantly, these patients are at a higher risk of acute exacerbation and all-cause mortality than symptomatic individuals with normal spirometry. The previous studies have evaluated the long-term prognosis of patients with COPD not eligible for previous major RCTs. However, the detailed clinical characteristics, structural lung changes, and lung function decline of this population were not evaluated. Moreover, there is no evidence on the pharmacological treatment of this patient population.

We hypothesized that patients with COPD not eligible for previous major RCTs would have more severe structural lung changes and a faster rate of lung function decline than symptomatic individuals with normal spirometry, and that tiotropium, as an inhaled medication, would be effective for the treatment of these patients. To fill this evidence gap, we performed a secondary analysis of a prospective cohort study to explore the clinical characteristics and the rate of lung function decline of patients with mild-to-moderate COPD not eligible for previous major RCTs. Furthermore, we conducted a secondary analysis of a RCT for mild-to-moderate COPD to evaluate whether tiotropium was effective for the treatment of these patients.

MATERIALS AND METHODS

ECOPD study design and participants

The ECOPD study was a prospective, observational, community-based cohort study to investigate the characteristics and prognosis of clinically relevant COPD subtypes. The study design and protocol have been published previously.[15] In brief, we selected participants from a large community screening program for COPD in people aged 40-80 years. We invited all patients with COPD (postbronchodilator forced expiratory volume in 1 second [FEV_1] / forced vital capacity [FVC] < 0.70) to participate in the ECOPD study. To ensure comparability with previous studies and with the Tie-COPD study,[14,16] the present study included the baseline and 2-year follow-up data of symptomatic individuals with normal spirometry and of patients with mild-to-moderate COPD from the ECOPD study. In the ECOPD study, baseline was between July 2019 and August 2021, and the last 2-year follow-up data were collected in September 2023. The ECOPD study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2018-53), and all participants provided written informed consent. The detailed inclusion and exclusion criteria are provided in the published protocol.[15]

Normal spirometry was defined as a post-bronchodilator FEV_1/FVC ratio of

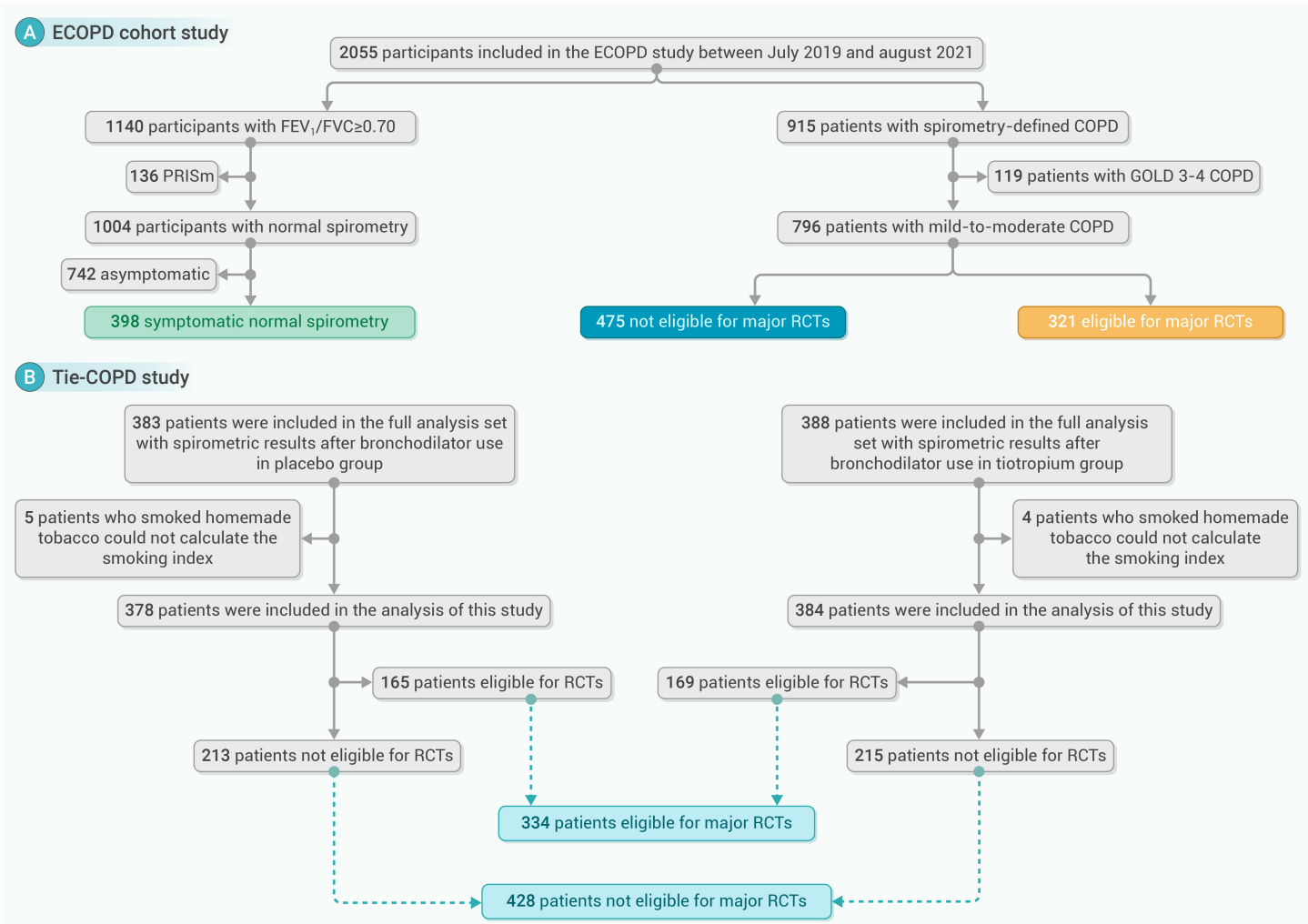

Figure 1. Study flowchart (A) Study flowchart of the ECOPD study. (B) Study flowchart of the Tie-COPD study.

≥ 0.70 and an FEV_1 ≥ 80% of the predicted value. Symptoms were defined as the presence of any one of chronic cough, chronic sputum, wheezing, or dyspnea. Mild-to-moderate COPD was defined as a post-bronchodilator FEV_1/FVC of < 0.70 and an FEV_1 ≥ 50% predicted according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) report.[17] We searched PubMed for studies up to 1 July 2025 using the keywords "COPD" and "clinical trials". Finally, 49 large-scale clinical trials for patients with stable COPD were included in the analysis. Most of them had requirements for smoking status, smoking index, lung function level and comorbid asthma (Table S1). Patients with mild-to-moderate COPD eligible for previous major RCTs had moderate airflow limitation (80% predicted > post-bronchodilator FEV_1 ≥ 50% predicted), a smoking index of ≥10 pack-years, and were without comorbid asthma. Patients with mild-to-moderate COPD not eligible for previous major RCTs were never-smokers, had a smoking index of <10 pack-years, had mild airflow limitation (post-bronchodilator FEV_1 ≥ 80% predicted), or had asthma.[14]

ECOPD study procedures

The participants completed a COPD epidemiological questionnaire and underwent pre-bronchodilator spirometry, post-bronchodilator spirometry, impulse oscillometry (IOS), and inspiratory and expiratory chest computed tomography (CT) at baseline. After their inclusion, pre-bronchodilator spirometry and post-bronchodilator spirometry were performed once per year. The outcomes of interest in the ECOPD study were the annual rate of lung function decline, structural lung lesions, and airway function indicators.

The COPD epidemiological questionnaire evaluated demographic information, smoking status, smoking index, biomass exposure, occupational history of dusts/gases/fumes, family history of respiratory diseases, chronic respiratory symptoms, and comorbidities.[18] The modified Medical Research Council (mMRC) dyspnea score and COPD assessment test (CAT) score were used to quantify respiratory symptom severity.[19]

Trained operators performed the spirometry assessments according to the operating and quality control standards recommended by the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[20] Based on the published study protocol, the predicted values were calculated using the European Community for Steel and Coal 1993 formula and multiplied by the Chinese conversion factor.[21,22] Recently, a race-neutral formula for estimating lung function has been developed.[23] We compared the results of the two estimates but found it with slight difference (Figure S1). Therefore, we continued to use the lung function prediction formula specified in the published protocol. The operation and quality control of IOS were also as recommended by the ERS.[24] The resistance at 5 Hz (R5) was considered as the total resistance, and at 20 Hz (R20) was considered as the central airway resistance. The difference between R5 and R20 (R5–R20) was considered as the peripheral airway resistance. Small airway dysfunction was defined when R5–R20 > 0.07 kPa/L/s.[25,26]

Inspiratory CT was performed at approximately total lung volume, while expiratory CT was performed at approximately residual volume.[15] Emphysema severity was determined by the percentage inspiratory lung volume with an inspiratory CT value lower than −950 Hounsfield units (HU). The severity of air trapping was determined by the percentage expiratory lung volume with an expiratory CT value below −856 HU. The severity of airway remodeling was determined by the square root of the wall area of a 10 mm lumen perimeter on inspiratory CT (inspiratory Pi 10).[27] Furthermore, we used

Table 1. Baseline demographic and clinical features of the participants in the ECOPD study.

Characteristic	Symptomatic Normal Spirometry (N=398)	Mild-to-moderate COPD		P Value
		Not eligible for Major RCTs (N=475)	Eligible for Major RCTs (N=321)	
Age — year	59.6±7.8	64.0±7.2 *	65.3±7.0 *†	<0.001
Male sex — no. (%)	237 (59.5)	395 (83.2) *	321 (100.0) *†	<0.001
Body mass index — kg/m^2	23.4±3.2	22.7±3.1 *	22.0±3.3 *†	<0.001
Smoking status — no. (%)				<0.001
Never smoked	199 (50.0)	122 (25.7) *	0 (0.0) *†	
Former smoked	48 (12.1)	104 (21.9) *	116 (36.1) *†	
Current smoked	151 (37.9)	249 (52.4) *	205 (63.9) *†	
Smoking index — pack-years‡	40.3±29.7	40.1±31.1	44.4±29.3	0.137
Biomass exposure — no. (%)	133 (33.3)	180 (37.9)	125 (38.9)	0.243
Occupational history of dusts/gases/fumes — no. (%)	65 (16.3)	107 (22.5)	99 (30.8) *†	<0.001
Family history of respiratory diseases — no. (%)	43 (10.8)	76 (16.0)	56 (17.6)	0.024
Previous medication for respiratory diseases — no. (%)	72 (18.1)	194 (40.8) *	158 (49.2) *	<0.001
Spirometric values at baseline				
Before bronchodilator use				
FEV_1 — liters	2.37±0.57	2.15±0.57 *	1.67±0.35 *†	<0.001
FEV_1 — % of predicted value	96.1±12.9	83.0±15.3 *	62.3±9.7 *†	<0.001
FVC — liters	3.12±0.75	3.48±0.83 *	3.06±0.56 †	<0.001
FEV_1/FVC — %	76.4±6.5	61.5±7.1 *	55.0±8.6 *†	<0.001
After bronchodilator use				
FEV_1 — liters	2.46±0.57	2.27±0.55 *	1.80±0.35 *†	<0.001
FEV_1 — % of predicted value	99.8±12.3	87.9±14.0 *	67.2±8.3 *†	<0.001
FVC — liters	3.12±0.73	3.59±0.81 *	3.20±0.53 †	<0.001
FEV_1/FVC — %	79.2±5.8	63.2±5.9 *	56.6±7.9 *†	<0.001
GOLD stage — no. (%)				<0.001
Mild (stage 1)	—	392 (82.5)	0 (0.0) †	
Moderate (stage 2)	—	83 (17.5)	321 (100.0) †	
Chronic respiratory symptoms — no. (%)				
Chronic cough	169 (42.5)	157 (33.1) *	136 (42.4) †	0.005
Chronic phlegm	247 (62.1)	188 (39.6) *	174 (54.2) †	<0.001
Dyspnea	209 (52.5)	137 (28.8) *	151 (47.0) †	<0.001
Wheeze	53 (13.3)	75 (15.8)	52 (16.2)	0.480
mMRC dyspnea scale score	0.60±0.06	0.33±0.58 *	0.57±0.68 †	<0.001
mMRC dyspnea scale score ≥2 — no. (%)	28 (7.0)	20 (4.2)	30 (9.3) †	0.014
CAT score	5.1±4.5	3.9±4.2 *	5.4±5.4 †	<0.001
CAT score ≥10 — no. (%)	57 (14.3)	41 (8.6) *	62 (19.3) †	<0.001
CCQ score	0.55±0.54	0.48±0.55	0.68±0.64*†	<0.001
Physician-diagnosed asthma — no. (%)	5 (1.3)	19 (4.0) *	0 (0.0) †	<0.001
Acute exacerbations during the preceding year — no. (%)	48 (12.1)	56 (11.8)	46 (14.3)	0.532

Data are mean ± standard deviation or n (%).

COPD, chronic obstructive pulmonary disease; RCT, randomized clinical trial; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD Assessment Test; mMRC, the modified Medical Research Council; CCQ, Clinical COPD Questionnaire.

* Significantly different from symptomatic normal spirometry (P<0.05).

† Significantly different from mild-to-moderate COPD not eligible for RCT (P<0.05).

‡ The smoking index was known for 199 patients who were current or former smokers in the symptomatic normal spirometry group, for 353 in the not eligible for major RCTs group, and for 321 in the eligible for major RCTs group.

the inspiratory and expiratory images to measure parametric response mapping emphysema (PRM^{Emph}) and functional small airway disease (PRM^{fSAD}) using AVIEW software.[28,29] PRM^{Emph} was defined as the percentage lung volume with CT values below −950 HU on inspiratory CT and below −856 HU on expiratory CT. PRM^{fSAD} was defined as the percentage lung volume with CT values above −950 HU on inspiratory CT and below −856 HU

Table 2. Baseline impulse oscillometry and computed tomography of the participants in the ECOPD study.

Variable	Symptomatic Normal Spirometry	Mild-to-moderate COPD		Not eligible for Major RCTs Compared to Symptomatic Normal Spirometry			
		Not eligible for Major RCTs	Eligible for Major RCTs	Unadjusted		Adjusted*	
				Effect Estimate (95% CI)	P Value	Effect Estimate (95% CI)	P value
Impulse oscillometry	N=360	N=439	N=290				
R5 — kPa/L/s	0.33±0.09	0.34±0.12	0.38±0.12	0.01 (-0.003 to 0.03)	0.114	0.04 (0.03-0.06)	<0.001
R20 — kPa/L/s	0.28±0.07	0.27±0.07	0.28±0.06	-0.005 (-0.015 to 0.004)	0.277	0.02 (0.01-0.03)	<0.001
R5-R20 — kPa/L/s	0.047±0.040	0.064±0.067	0.104±0.078	0.017 (0.009-0.026)	<0.001	0.023 (0.014-0.032)	<0.001
R5-R20 >0.07 kPa/L/s — no. (%) †	69 (19.2)	140 (31.9)	161 (43.5)	2.00 (1.42-2.75)	<0.001	2.85 (1.91-4.23)	<0.001
X5 — kPa/L/s	-0.10±0.04	-0.12±0.07	-0.15±0.08	-0.01 (-0.02-0.01)	0.003	-0.02 (-0.03 to -0.01)	<0.001
AX — kPa/L	0.39±0.32	0.64±0.79	1.12±1.01	0.25 (0.15-0.36)	<0.001	0.32 (0.21-0.43)	<0.001
Fres — Hz	13.1±3.8	15.1±5.6	19.1±5.9	1.9 (1.2-2.7)	<0.001	2.1 (1.4-2.8)	<0.001
Computed tomography	N=398	N=475	N=321				
Inspiratory LAA_{-950} — %	0.8±1.5	2.7±3.7	5.0±6.4	1.9 (1.3-2.4)	<0.001	1.1 (0.6-1.7)	<0.001
Inspiratory LAA_{-950} >5% — no. (%) †	7 (1.8)	67 (14.1)	102 (31.8)	9.17 (4.16-20.23)	<0.001	5.60 (2.47-12.71)	<0.001
Expiratory LAA_{-856} — %	7.6±10.8	21.5±17.5	30.1±18.7	13.9 (11.8-16.0)	<0.001	9.3 (7.8-12.0)	<0.001
Expiratory LAA_{-856} >20% — no. (%) †	34 (8.5)	191 (40.2)	215 (67.0)	7.20 (4.84-10.70)	<0.001	5.18 (3.37-7.95)	<0.001
PRM emphysema — %	0.4±1.3	2.1±3.5	4.6±6.2	1.7 (1.1-2.4)	<0.001	1.0 (0.5-1.6)	<0.001
PRM functional small airway disease — %	5.3±8.6	16.0±14.5	23.4±15.9	10.6 (8.5-12.8)	<0.001	7.6 (5.8-9.3)	<0.001
Inspiratory Pi 10 — mm	3.55±0.70	3.90±0.84	4.19±0.99	0.3 (0.2-0.5)	<0.001	0.5 (0.3-0.6)	<0.001

Data are mean ± standard deviation or n (%).

COPD, chronic obstructive pulmonary disease; RCT, randomized clinical trial; CI, confidence interval; R5, resistances at 5 Hz; R20, resistances at 20 Hz; R5-R20=resistances at 5 and 20 Hz; X5, reactance at 5 Hz; Ax, reactance area; Fres, resonant frequency in Hz; LAA_{-950}, the percentage of the low-attenuation area below −950 Hounsfield units on full-inspiration computed tomography; LAA_{-856}, the percentage of the low-attenuation area below −856 Hounsfield units on full-expiration computed tomography, PRM, parametric response mapping; Pi 10, square root of wall area of a 10-mm lumen perimeter.

Estimates as β coefficient unless otherwise noted.

* All were adjusted for age, sex, body mass index, and smoking status.

† Odds ratio.

on expiratory CT.

ECOPD study statistical analysis

The ECOPD study was exploratory, so no adjustment for multiple pairwise comparisons or sample size calculation was performed.[30] Multivariable logistic and linear regression analyses were used to identify differences in the categorical and continuous variables, respectively, between the groups. A random coefficient model with a random slope and intercept was used to identify differences in the annual rate of lung function decline between the groups.[31] Confounding factors included in the multivariable model included age, sex, BMI, and smoking status. When analyzing the annual rate of lung function decline, the corresponding baseline lung function indicators were additionally included in the multivariable model. Only individuals with available data were included in the analysis; no missing data imputation was performed.

Tie-COPD study design and participants

From October 2011 to September 2015, we conducted a double-blind, placebo-controlled, parallel-group RCT of tiotropium for the treatment of mild-to-moderate COPD at 24 hospitals (NCT01455129). Epidemiological surveys of COPD found that about 30%-40% of COPD patients in China do not smoke, and about 40% have mild airflow limitation.[18] Therefore, in order to make the results of the clinical trial more representative, the Tie-COPD study included mild-to-moderate COPD patients without restrictions on smoking status, smoking index, and mild airflow limitation. The Tie-COPD study protocol and findings have been published previously.[16,32] Eligible patients were randomized 1:1 to receive tiotropium (18μg, once daily) or placebo (once daily) for 2 years. Since the Tie-COPD study excluded patients with comorbid asthma during enrollment, patients with mild-to-moderate COPD not eligible for previous major RCTs in the Tie-COPD study were: never smokers, smoke index of <10 pack-years, or mild airflow limitation.

Tie-COPD study procedures

The patients were followed up once in the first month after enrollment and every 3 months thereafter. Acute exacerbation, CAT score, and Clinical COPD Questionnaire (CCQ) score were evaluated at baseline and at 1, 3, 6, 9, 12, 15, 18, 21, and 24 months after enrollment.[33]

Acute exacerbation was defined as at least two listed symptoms (cough, sputum, sputum purulence, wheezing, or dyspnea) that were new or had worsened and persisted for more than 48 hours, after excluding diseases such as cardiac insufficiency, pulmonary embolism, pneumothorax, pleural effusion, and cardiac arrhythmia.[16,34] Moderate exacerbation was defined as an event leading to outpatient or emergency department visit and treatment modification (including antibiotics, oral corticosteroids, or both). Severe exacerbation was defined as an event leading to hospitalization. Pre-bronchodilator spirometry and post-bronchodilator spirometry was followed up at baseline and at 1, 6, 12, 18, and 24 months after enrollment. If acute exacerbation occurred during the follow-up window, symptom, and lung function assessments were performed 2 weeks after the acute exacerbation had ended.

The primary outcome of the Tie-COPD study was the between-group difference in the change from baseline to 24 months in the pre-bronchodilator FEV_1. The secondary outcomes included the between-group differences in the change from baseline to 24 months in post-bronchodilator FEV_1, pre-bronchodilator FVC, and post-bronchodilator FVC; the incidence of acute exacerbations; the time to the first exacerbation; the annual rate of lung function decline from 1 to 24 months; the CAT score; and the CCQ score.

In the Tie-COPD study, the quality control standards used for spirometry and the formula used to calculate the lung function prediction value were

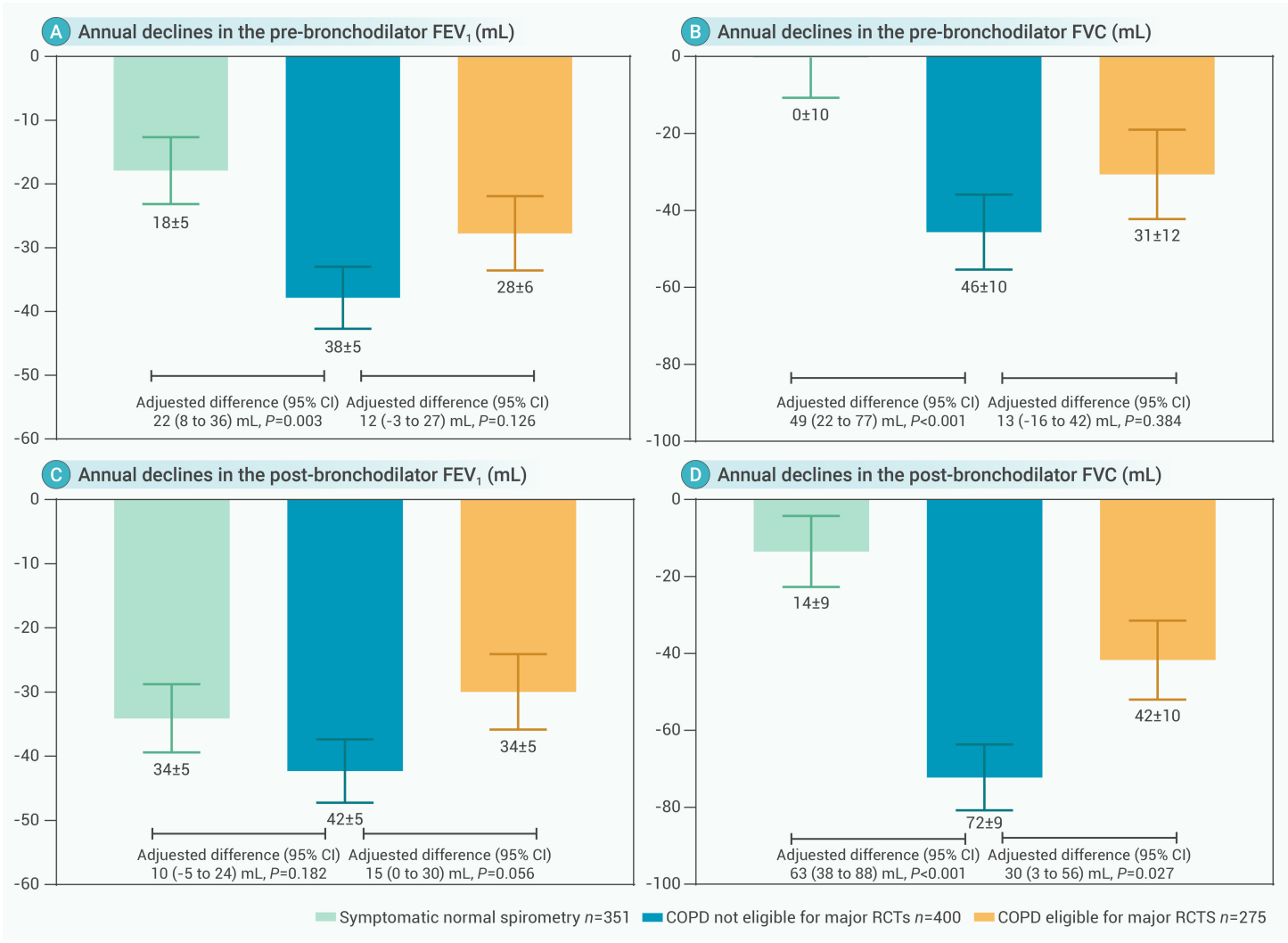

Figure 2. Annual decline in lung function among patients in the ECOPD study Annual decline in (A) pre-bronchodilator FEV_1, (B) pre-bronchodilator FVC, (C) post-bronchodilator FEV_1, and (D) post-bronchodilator FVC. The random coefficient regression model was adopted to analyze the annual lung function decline. All models were adjusted for age, sex, body mass index, baseline smoking status, and baseline corresponding lung function values.

consistent with those used in the ECOPD study.[20-22] Considering the multidimensional assessment of disease progression, we conducted an additional analysis of the first clinically important deterioration (CID). The first CID was defined as a decrease in FEV_1 of ≥100 mL, an increase in the CAT score of ≥2 units, or moderate-to-severe exacerbation.[35]

Tie-COPD study statistical analysis

The present study was a secondary analysis of the Tie-COPD study, so sample size calculation and correction for multiple comparisons were not performed. Repeated-measures analyses with mixed-effects models were used to identify differences in lung function and symptom scores at different time points. Random coefficient models were used to identify differences in the annual rate of lung function decline between the groups. Poisson regression with adjustment for overdispersion distribution and treatment duration was used to identify differences in acute exacerbation risk between the groups. Cox proportional-hazards regression was used to identify between-group differences in the time to the first exacerbation and in the time to the first CID. The data of patients who underwent randomization, received at least one dose of tiotropium or placebo, and had post-baseline efficacy measures were included in the full analysis set (FAS). All analyses were based on the FAS; no data imputation was performed.

RESULTS

Clinical characteristics of patients with mild-to-moderate COPD not eligible for previous major RCTs

Among the 1,004 participants with normal spirometry at baseline in the ECOPD study, 398 had any chronic respiratory symptom and were classified into the symptomatic normal spirometry group. Among the 915 patients with spirometry-defined COPD, 119 with GOLD stage 3–4 were excluded, and 796 with mild-to-moderate COPD were included. Among the patients with mild-to-moderate COPD, 475 (59.7%) did not meet the criteria for the previous major RCTs, while 321 (40.3%) did (Figure 1A). The baseline characteristics (age, sex, BMI, and pre-bronchodilator FEV_1 % of the predicted value) of mild-to-moderate COPD patients not eligible previous major RCTs were intermediate between the other two groups: symptomatic normal spirometry group and mild-to-moderate COPD eligible major RCTs group. (Table 1).

With regard to peripheral, central, and total airway resistance, patients with mild-to-moderate COPD not eligible for previous major RCTs had significantly higher values than symptomatic participants with normal spirometry in both the univariable and multivariable analyses. Patients with mild-to-moderate COPD not eligible for previous major RCTs had more severe emphysema (PRM^{Emph}: 2.1 ± 3.5 % vs. 0.4 ± 1.3 %, adjusted difference = 1.0 [95% CI: 0.5–1.6] %). They also had more severe air trapping (PRM^{fSAD}: 16.0 ± 14.5 % vs. 5.3 ± 8.6 %, adjusted difference = 7.6 [95% CI: 5.8–9.3] %) and airway remodeling (inspiratory Pi 10: 3.90 ± 0.84 mm vs. 3.55 ± 0.70 mm, adjusted difference = 0.5 [95% CI: 0.3–0.6] mm) than participants with symptomatic normal spirometry, but these measures were less severe than in patients with mild-to-moderate COPD eligible for previous major RCTs after adjusting for confounding factors (Table 2).

Table 3. Baseline characteristics of the patients not eligible for major RCTs in the Tie-COPD study.

Characteristic	Tiotropium Group (N=215)	Placebo Group (N=213)	P Value
Age — year	63.5±8.7	63.1±8.9	0.618
Male sex — no. (%)	155 (72.1)	161 (75.6)	0.411
Body-mass index — kg/m^2	22.7±3.4	22.7±3.3	0.946
Smoking status— no. (%)			0.446
Never smoked	82 (38.1)	77 (36.2)	
Current smoking	81 (37.7)	73 (34.3)	
Former smoking	52 (24.2)	63 (29.6)	
Smoking index — pack-years	31.7±63.9	37.1±90.2	0.475
Previous respiratory disease other than COPD — no. (%)	4 (1.9)	6 (2.8)	0.543
Spirometric values at baseline			
Before bronchodilator use			
FEV_1 — liters	1.96±0.58	2.00±0.61	0.458
FEV_1 — % of predicted value	81.5±14.9	82.8±7.7	0.391
FVC — liters	3.17±0.86	3.26±0.87	0.289
FEV_1/FVC — %	61.8±6.2	31.3±6.6	0.382
After bronchodilator use			
FEV_1 — liters	2.09±0.58	2.13±0.60	0.577
FEV_1 — % of predicted value	87.5±13.7	88.0±16.2	0.704
FVC — liters	3.29±0.86	3.37±0.88	0.303
FEV_1/FVC — %	63.7±5.7	62.8±5.9	0.147
GOLD stage — no. (%)			0.522
Mild (stage 1)	172 (80.0)	165 (77.5)	
Moderate (stage 2)	43 (20.0)	48 (22.5)	
mMRC dyspnea scale score	0.6±0.7	0.7±0.7	0.385
mMRC dyspnea scale score≥2 — no. (%)	20 (9.3)	22 (10.3)	0.721
CAT score	6.5±6.0	6.0±5.7	0.373
CAT score≥10 — no. (%)	52 (24.2)	45 (21.1)	0.450
CCQ score	0.9±0.7	0.8±0.7	0.242

Data are presented as mean ± standard deviation or n (%).

RCT, randomized clinical trial; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD Assessment Test; mMRC, the modified Medical Research Council; CCQ, Clinical COPD Questionnaire.

Lung function decline of patients with mild-to-moderate COPD not eligible for previous major RCTs

In the 2-year follow-up of the ECOPD study, patients with mild-to-moderate COPD not eligible for previous major RCTs had faster annual rates of decline in pre-bronchodilator FEV_1 (38 ± 5 mL/year vs. 18 ± 5 mL/year, adjusted difference = 22 [95% CI: 8–36] mL/year, P = 0.003), pre-bronchodilator FVC (46 ± 10 mL/year vs. 0 ± 10 mL/year, adjusted difference = 49 [95% CI: 22–77] mL/year, P < 0.001), and post-bronchodilator FVC (72 ± 9 mL/year vs. 14 ± 9 mL/year, adjusted difference = 63 [95% CI: 38–88] mL/year, P < 0.001) than symptomatic participants with normal spirometry (Figure 2). The difference in the annual rate of decline in post-bronchodilator FEV_1 did not reach statistical significance, but a trend was observed (42 ± 5 mL/year vs. 34 ± 5 mL/year, adjusted difference = 10 [95% CI: −5 to 24] mL/year, P = 0.182).

Effects of tiotropium on the treatment of patients with mild-to-moderate COPD not eligible for previous major RCTs

Overall, 383 patients in the placebo group and 388 patients in the tiotropium group were included in the FAS, and five and four patients, respectively, with no smoking index data were further excluded from each group. Of the remaining 378 patients in the placebo group, 213 (56.3%) did not meet the criteria for previous major RCTs, while 165 (43.7%) did. Of the 384 patients in the tiotropium group, 215 (56.0%) did not meet the criteria for major RCTs, while 169 (44.0%) did (Figure 1B). Patients with mild-to-moderate COPD not eligible for previous major RCTs were younger; less frequently male; had better lung function; and had lower CAT, mMRC, and CCQ scores than patients with mild-to-moderate COPD eligible for previous major RCTs (Table S2). There were no significant differences in the baseline clinical characteristics between the tiotropium and placebo groups among those with mild-to-moderate COPD not eligible for previous major RCTs (Table 3) or in patients with mild-to-moderate COPD eligible for previous major RCTs (Table S3).

Tiotropium significantly increased pre-bronchodilator FEV_1 at 24 months

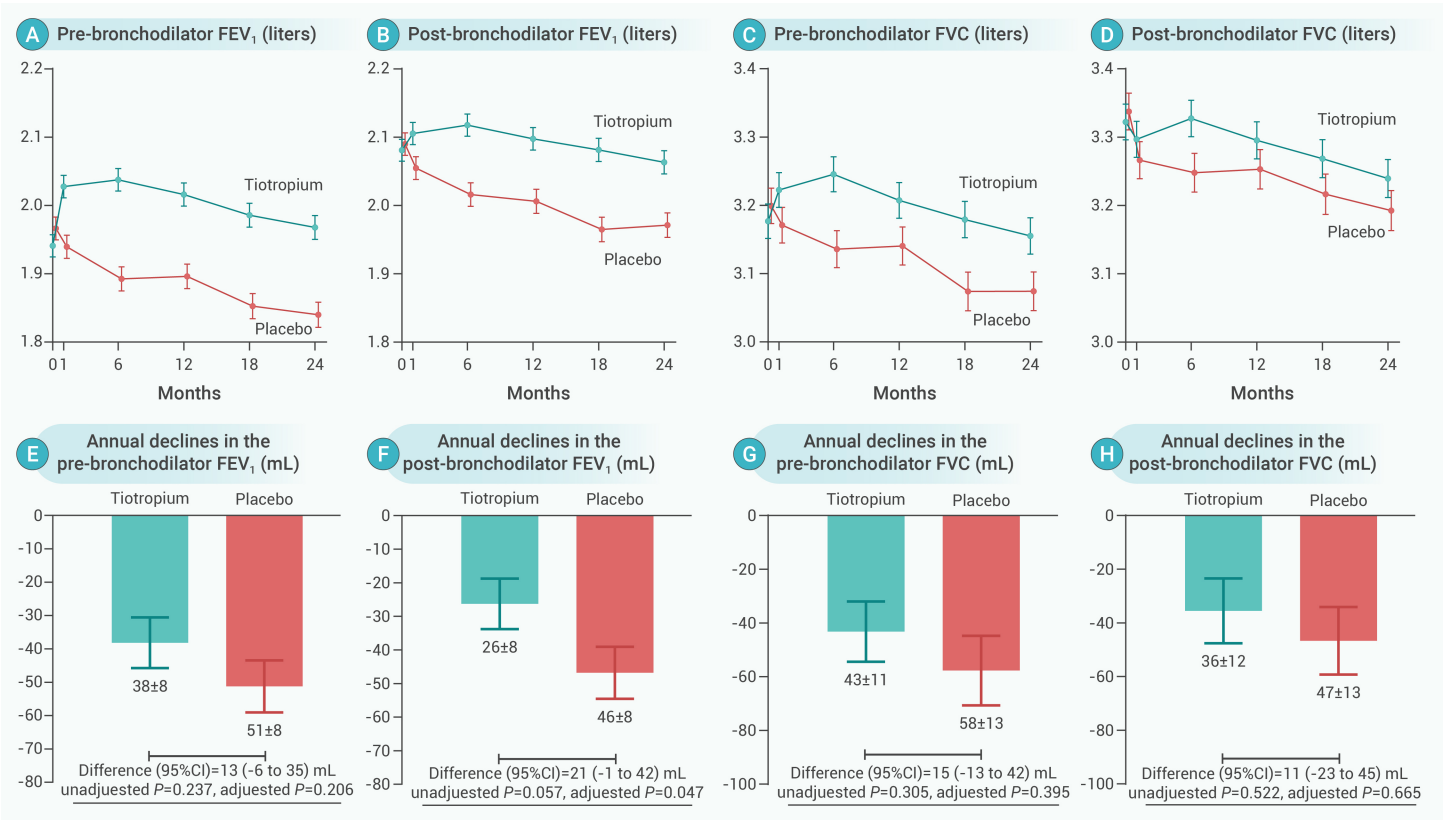

Figure 3. Mean lung function and annual lung function decline among patients with mild-to-moderate COPD not eligible for major randomized clinical trial in the Tie-COPD study Mean (A) pre-bronchodilator FEV_1, (B) post-bronchodilator FEV_1, (C) pre-bronchodilator FVC, and (D) post-bronchodilator FVC. Annual decline in pre-bronchodilator FEV_1 (E), post-bronchodilator FEV_1 (F), pre-bronchodilator FVC (G), and post-bronchodilator FVC (H) from 1 month to 24 months. The random coefficient regression model was adopted to analyze the annual lung function decline. The model included age, sex, body mass index, baseline smoking status, hospitalization, GOLD stage, and individual spirometric values at baseline according to the Tie-COPD study protocol.

compared with placebo in patients with mild-to-moderate COPD not eligible for previous major RCTs (difference = 128 [95% CI: 78–177] mL, P < 0.001) (Figure 3). At each visit, tiotropium significantly increased pre-bronchodilator FEV_1, post-bronchodilator FEV_1, and pre-bronchodilator FVC in patients with mild-to-moderate COPD not eligible for previous major RCTs (Table S4). Notably, from 1 to 24 months, tiotropium significantly slowed the annual rate of decline in post-bronchodilator FEV_1 (46 ± 8 mL/year vs. 26 ± 8 mL/year, difference = 21 [95% CI: −1 to 42] mL/year, unadjusted P = 0.057, adjusted P = 0.047) among patients with mild-to-moderate COPD not eligible for previous major RCTs. The annual rates of decline in pre-bronchodilator FEV_1, pre-bronchodilator FVC, and post-bronchodilator FVC were lower in the tiotropium group than in the placebo group, but the differences were not statistically significant (Figure 3). The frequency of acute COPD exacerbation was lower with tiotropium than with placebo (0.23 per patient-year vs. 0.42 per patient-year; relative risk = 0.55 [95% CI: 0.40–0.77], P < 0.001). Furthermore, tiotropium significantly delayed progression to the first acute exacerbation (hazard ratio = 0.62; 95% CI: 0.43-0.88, P = 0.008) and the first CID (hazard ratio = 0.62; 95% CI: 0.50-0.77, P < 0.001) (Figure 4). The CAT (5.4 ± 0.3 vs. 7.3 ± 0.3, difference = −1.9 [95% CI: −2.9 to −1.0], P < 0.001) and CCQ scores (0.75 ± 0.04 vs. 0.96 ± 0.05, difference = −0.22 [95% CI: −0.10 to −0.34], P < 0.001) were significantly lower in the tiotropium group than in the placebo group at 24 months (Table 4).

Effects of tiotropium on the treatment of patients with mild-to-moderate COPD eligible for previous major RCTs

Similarly, tiotropium increased pre-bronchodilator FEV_1, reduced exacerbations, and improved respiratory symptoms compared with placebo in patients with mild-to-moderate COPD not eligible for previous major RCTs (Tables S5–S7 & Figures S2–S4).

DISCUSSION

In both the ECOPD study and the Tie-COPD study, approximately 60% of patients with mild-to-moderate COPD did not meet the criteria of previous major RCTs. With regard to the ECOPD study, patients with mild-to-moderate COPD not eligible for previous major RCTs had more severe structural lung lesions and airway resistance, as well as a faster rate of lung function decline than symptomatic participants with normal spirometry. Secondary analysis of the Tie-COPD study indicated that tiotropium significantly improved lung function, reduced acute exacerbations, and reduced respiratory symptoms compared with placebo in patients with mild-to-moderate COPD not eligible for previous major RCTs.

The present study expands our understanding of the clinical characteristics and prognosis of patients with COPD not eligible for previous major RCTs, and it explores the effectiveness of long-term pharmacological treatment with tiotropium for the first time in this population. The inclusion of the patients with severe COPD or frequent acute exacerbations may facilitate statistically significant results in clinical trials, however, those patients account for a small fraction in clinical practice.[7-9] This has led to a lack of evidence-based medical evidence for the use of inhaled medications in a considerable number of patients with COPD. The present study found that patients with COPD not eligible for previous major RCTs had clinically significant disease and a faster rate of lung function decline, which means that they had a faster rate of disease progression. A previous study found that the patients with COPD not eligible for previous major RCTs had increased risks of exacerbation and all-cause mortality than those with normal spirometry.[14] Combining the previous study's findings with the results of the present study, we suggest that patients with COPD not eligible for previous major RCTs need necessary follow-up management, risk factor intervention, and even pharmacological intervention. The results of the secondary analysis of the Tie-COPD study provide an evidence base for the treatment of this group of patients with medication, effectively guiding clinical practice. When designing RCTs, more consideration should be given to achieving a patient-centered design, with the inclusion of a more diverse range of patients that is representative of the real-world population. This would enable the results of clini-

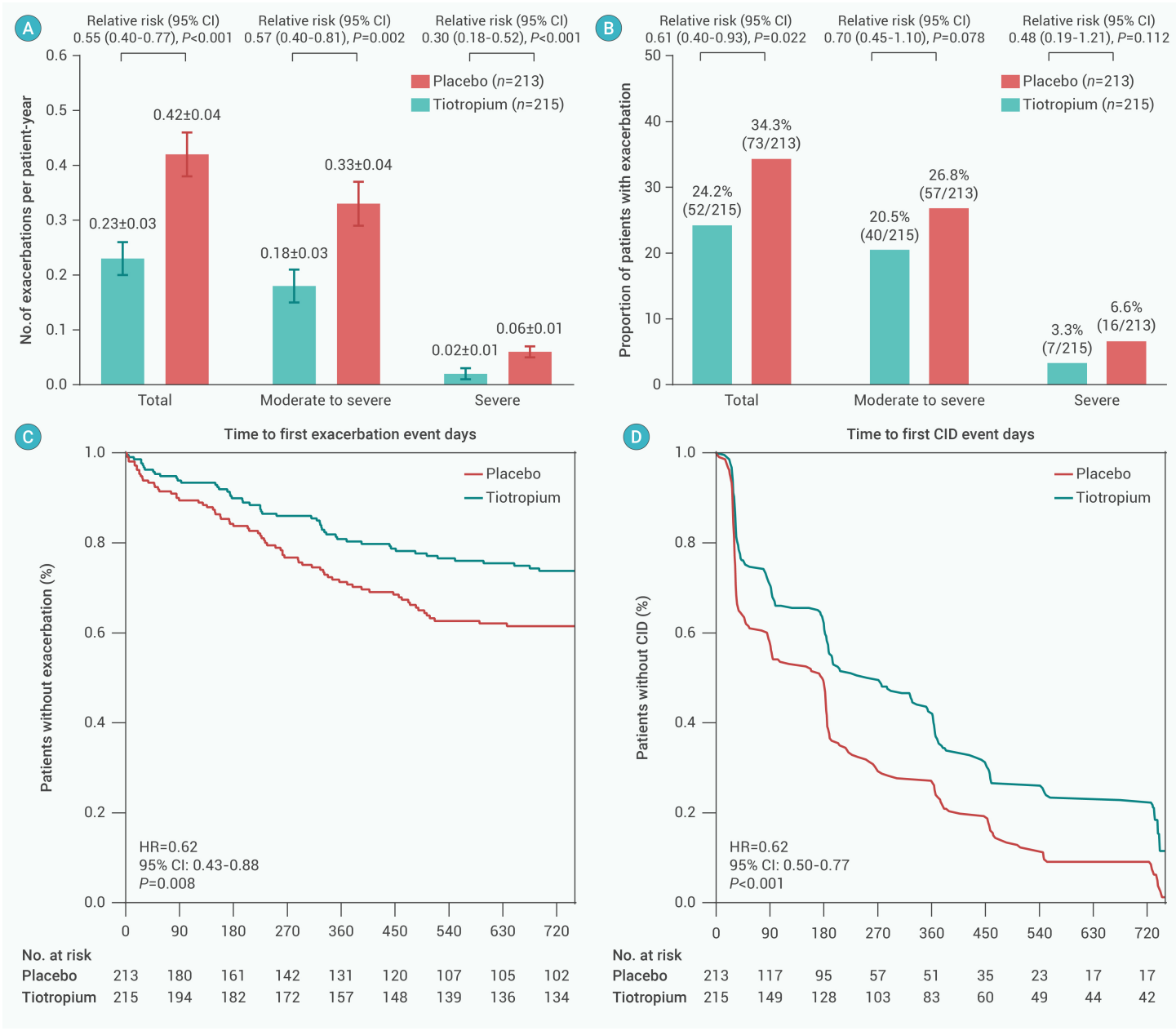

Figure 4. Acute exacerbations and CID among patients with mild-to-moderate COPD not eligible for major randomized clinical trial in the Tie-COPD study (A) Number of exacerbations per patient-year. (B) Proportion of patients with exacerbations. (C) Time to the first exacerbation. (D) Time to the first CID.

cal trials to be better applied to general patients with COPD.

Patients with COPD of GOLD stage 1 (mild airflow limitation) have been the most neglected group because of their limited symptoms and mild lung function impairment. As patients with mild airflow limitation have $FEV_1 \geq 80\%$ predicted and are similar to those with normal spirometry, it is only the increase in FVC that causes the FEV_1/FVC to fall below the diagnostic cutoff. However, compared to those with normal spirometry, patients with mild COPD have significant emphysema, air trapping, airway remodeling, gas exchange abnormalities, exercise ventilatory inefficiency, accelerated lung function decline, and a higher risk of respiratory disease-related mortality and all-cause mortality.[36-40] Around 70%–80% of patients with COPD who did not meet the criteria for the previous major RCTs had mild airflow limitation, which is one of the key reasons why these patients had a worse prognosis.

Over the past decade, the importance of non-smoking-related risk factors for COPD has been increasingly recognized. Approximately 30%–40% of patients with COPD have never smoked or have had low exposure to smoking. The risk factors for COPD among these individuals include exposure biomass, occupational dust, air pollution, poor lung growth and development, and lung infections.[41] Never-smokers with COPD have fewer respiratory symptoms and less severe emphysema, but they also have more pronounced airway lesions according to a previous study.[42] Furthermore, never-smokers with COPD have a higher risk of pneumonia and COPD hospitalization, but not a higher risk of all-cause mortality, than those with normal lung function.[43] Moreover, patients with COPD with low smoking exposure have higher risks of acute exacerbation and all-cause mortality than those with normal spirometry.[44] The above two factors are important reasons why patients with COPD who did not meet the criteria for major RCTs had a worse prognosis.

To reduce the disease burden of COPD, the goal of COPD intervention strategies needs to shift from reducing respiratory symptoms and acute exacerbations to delaying disease progression.[1,45] Patients with mild-to-moderate COPD have relatively mild lung function impairment and structural lung lesions. It is possible to delay COPD progression, similar to the remission or reversal of diabetes mellitus and hypertension.[46-48] Our previous clinical trial results showed that tiotropium slowed the rate of lung function decline in patients with mild-to-moderate COPD by 30%–40%.[16] In the

Table 4. Difference of CAT score and CCQ score of the patients not eligible for major RCTs in the Tie-COPD Study between the two groups at different time points.

Follow-up	Tiotropium (N=215)	Placebo (N=213)	Difference (Placebo−Tiotropium)	Adjusted P value*
CAT score				
Baseline	6.9±0.3	7.4±0.3	0.5 (-0.4 to 1.3)	0.292
Month1	5.6±0.3	6.8±0.3	1.2 (0.3 to 2.1)	0.008
Month 3	5.4±0.3	6.2±0.3	0.8 (0.0 to 1.7)	0.058
Month 6	5.5±0.3	6.7±0.3	1.1 (0.3 to 2.0)	0.011
Month 9	5.2±0.3	6.8±0.3	1.6 (0.7 to 2.5)	<0.001
Month 12	5.8±0.3	6.5±0.3	0.7 (-0.2 to 1.6)	0.130
Month 15	5.0±0.3	7.0±0.3	2.0 (1.1 to 2.9)	<0.001
Month 18	5.4±0.3	7.3±0.3	1.9 (1.0 to 2.8)	<0.001
Month 21	5.5±0.3	7.5±0.3	2.0 (1.0 to 2.9)	<0.001
Month 24	5.4±0.3	7.3±0.3	1.9 (1.0 to 2.9)	<0.001
CCQ score				
Baseline	0.93±0.04	0.94±0.04	0.01 (-0.10 to 0.13)	0.796
Month1	0.79±0.04	0.92±0.04	0.13 (0.02 to 0.24)	0.024
Month 3	0.74±0.04	0.87±0.04	0.13 (0.01 to 0.24)	0.028
Month 6	0.75±0.04	0.92±0.04	0.16 (0.05 to 0.28)	0.006
Month 9	0.72±0.04	0.96±0.04	0.24 (0.19 to 0.35)	<0.001
Month 12	0.79±0.04	0.92±0.04	0.12 (0.00 to 0.24)	0.042
Month 15	0.75±0.04	0.99±0.04	0.24 (0.12 to 0.36)	<0.001
Month 18	0.70±0.04	0.97±0.04	0.27 (0.15 to 0.39)	<0.001
Month 21	0.77±0.04	1.01±0.05	0.24 (0.12 to 0.36)	0.001
Month 24	0.74±0.04	0.96±0.05	0.22 (0.10 to 0.34)	<0.001

Plus−minus values are means ± SE.

RCT, randomized clinical trial; COPD, chronic obstructive pulmonary disease; CAT, COPD Assessment Test; CCQ, Clinical COPD Questionnaire.

* Mixed-effects model for repeated measures analysis is adopted. We adopted the measured values at each visit as the dependent variable and the fixed effects include treatment allocation, individual baseline value, baseline smoking status, follow-up, interactions between the treatment allocations and participating centers. Subjects served as the random effect. The follow-up was treated as the categorical variable.

present study, tiotropium slowed the annual decline in post-bronchodilator FEV_1 and delayed the incidence of CID in patients with COPD not eligible for previous major RCTs. Future targeted clinical trials should be conducted for COPD patients with mild airflow limitation or with less exposure to smoking to explore the possibility of reversing or halting the progression of COPD.

This study has several limitations that should be considered. First, the analysis of tiotropium for the treatment of patients with mild-to-moderate COPD not eligible for previous major RCTs was a secondary analysis. It is possible that the subgroup population did not meet the randomness principle and may be prone to false-positive results.[49] Therefore, confirmatory prospective clinical trials are needed to verify our observations. Second, although the proportion of patients with physician-diagnosed asthma was close to the latest data from the Chinese Asthma Epidemiological Survey,[50] some patients with asthma may not have been diagnosed by doctors and therefore classified into the group that met the major RCTs criteria. Finally, because the Tie-COPD study only enrolled patients with mild-to-moderate COPD, the present study was unable to analyze the effectiveness of medication among patients with severe-to-very-severe COPD who were non-smokers, had a smoking index of <10 pack-years, or had asthma.

CONCLUSION

Patients with mild-to-moderate COPD not eligible for major RCTs had worse respiratory health outcomes than symptomatic participants with normal spirometry. Long-term treatment with tiotropium improved respiratory health outcomes compared with placebo among patients with mild-to-moderate COPD who were not eligible for the previous major RCTs.

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AUTHOR CONTRIBUTIONS

F.W., Y.Z., and P.R. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. F.W., Z.D., Y.Z., and P.R. designed the study. All authors participated in data organization and data collection. F.W. participated in data analysis. All authors contributed to interpretation of the findings. F.W. and Z.D. drafted the manuscript. All authors contributed to article modification and the last version of the manuscript. All authors read and approved the final manuscript before submission.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

All participants provided informed consent. Ethical approval for the ECOPD study was obtained from the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (approval number: 2018-53). Ethical approval for the Tie-COPD study was obtained from the Ethics Committee of each center.

DATA AND CODE AVAILABILITY

Data generated or analyzed during the study are available from the corresponding author by request.

SUPPLEMENTAL INFORMATION

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