**Original Research**

# Tiotropium in Patients With Airflow Limitation According to the Fixed Ratio But Not the Lower Limit of Normal: A Secondary Analysis of the Tiotropium in Early-COPD Study

Kunning Zhou, MD[1*] Fan Wu, MD, PhD[1*] Zhishan Deng, MD, PhD[1] Qi Wan, MD Suying Huang, MD[1,2] Nanshan Zhong, MD, PhD[1,2] Yumin Zhou, MD, PhD[1,2] Pixin Ran, MD, PhD[1,2] on behalf of the ECOPD study investigators.

[1]State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, National Center for Respiratory Medicine, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China

[2] Guangzhou National Laboratory, Bio-Island, Guangzhou, China

* *Authors contributed equally*

***Address correspondence to:***
Pixin Ran, MD, PhD and Yumin Zhou, MD, PhD
State Key Laboratory of Respiratory Disease
National Clinical Research Center for Respiratory Disease
National Center for Respiratory Medicine
Guangzhou Institute of Respiratory Health
The First Affiliated Hospital of Guangzhou Medical University
Guangzhou National Laboratory
Guangzhou, China
Email: pxran@gzhmu.edu.cn
Email: zhouyumin410@126.com

***Running Head*: Tiotropium in COPD With Fixed Ratio Not Lower of Normal**

***Keywords*:** COPD; tiotropium; fixed ratio; lower limit of normal; Tie-COPD

***Abbreviations*:**

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***This article has an online supplement.***

**Abstract**

**Background:** Patients with airflow limitation according to the fixed ratio but not the lower limit of normal (LLN) (FR+LLN−) have a poorer respiratory prognosis and higher mortality than the normal fixed ratio. However, whether tiotropium treatment improves respiratory health outcomes in patients with FR+LLN− remains unclear.

**Methods:** This was a secondary analysis of the 24-month Tie-COPD study, a multicentre, randomized, double-blind clinical trial comparing tiotropium with placebo for mild-to-moderate COPD. FR+LLN− was defined as a post-bronchodilator $FEV_1$/FVC ratio of <0.70 but ≥LLN. The primary endpoint was the between-group difference in the change from baseline to 24 months in pre-bronchodilator $FEV_1$. Key secondary endpoints included the between-group difference in the annual decline in pre-bronchodilator $FEV_1$ and exacerbations.

**Results:** In the Tie-COPD study, 92 patients (12%) had FR+LLN−. Tiotropium resulted in a significantly higher pre-bronchodilator $FEV_1$ at 24 months (difference, 191 mL; 95% confidence interval [CI] 99, 283), with a least-squares mean (LSM) change from baseline of 47 mL (95% CI −13, 108) versus −140 mL (95% CI −215, −64) with placebo. The annual decline in the pre-bronchodilator $FEV_1$ was 24 mL/year with tiotropium and 89 mL/year with placebo (difference 60 mL/year; 95% CI 2, 118) from 30 days through 24 months. Tiotropium reduced total exacerbations compared with placebo (relative risk=0.50; 95% CI 0.27, 0.94).

**Conclusions:** This study demonstrated tiotropium treatment improved lung function, ameliorated lung function decline, and reduced exacerbations compared with placebo


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in patients with FR+LLN-, providing evidence-based medicine evidence for the treatment in this population.




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## Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous pulmonary condition with diverse lung lesions, complex clinical trajectories, and various disease presentations, making it a critical global health challenge.[1] COPD ranks as the third leading cause of mortality worldwide, with its disease burden exacerbated by population aging and persistent environmental risk factors such as tobacco use and air pollution.[2,3] The clinical complexity of COPD is further compounded by diagnostic uncertainties, particularly regarding its two essential spirometry criteria: the fixed ratio (the post-bronchodilator forced expiratory volume in one second [$FEV_1$]/forced vital capacity [FVC] ratio of <0.70) and the lower limit of normal (LLN) criterion. Significant diagnostic discordance exists between these two criteria. Specifically, COPD exists in 3%–23% of patients in the general population with airflow limitation according to the fixed ratio (FR) criterion but not the LLN criterion (FR+LLN−) in clinical practices.[4-7] Previously dismissed FR+LLN− was previously dismissed and considered as "over-diagnosed COPD"; however, emerging evidence has challenged this viewpoint. The majority of studies have reported that patients with FR+LLN− have more serious chronic respiratory symptoms, more accelerated lung function decline, more frequent exacerbations, and more severe hospitalizations.[5-7] Crucially, studies have shown that patients with FR+LLN− exhibited greater ventilatory inefficiency and an increased mortality risk compared with those with a normal fixed ratio.[8,9] These findings underscore the clinical tendency for patients with FR+LLN− to have a poorer prognosis than those in whom both of the two criteria are normal. There is currently no


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evidence for the pharmacological treatment of patients with FR+LLN−, and there is no consensus on the therapeutic value in patients with FR+LLN−, which may restrict the disease management of this population in clinical practice.

Tiotropium is a potent drug used for the clinical management of COPD. As a long-acting anticholinergic bronchodilator, tiotropium selectively binds to muscarinic receptors on the smooth-muscle cells in the airways. Tiotropium treatment has been shown to inhibit goblet cell metaplasia induced by neutrophil elastase and mucin production in vitro in a rat model of COPD, indicating that tiotropium may help to treat mucus overproduction in COPD. In addition, maintenance tiotropium treatment has demonstrated significant advantages for improving lung function, delaying the rate of lung function decline, and reducing acute exacerbations, chronic pulmonary symptoms, and clinically important deterioration in mild-to-moderate COPD in various clinical studies.[4-7,11-13]

Our team previously conducted the Tie-COPD study, which did not use ≥LLN as an exclusion criterion. Owing to the lack of evidence on the effectiveness of tiotropium in patients with COPD with FR+LLN−, we conducted this secondary analysis of the Tie-COPD study using the baseline and follow-up data of patients with COPD with FR+LLN− treated with tiotropium to explore whether tiotropium improved respiratory health outcomes in this population.

## Methods

### *Study design*


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This was a secondary analysis of the Tie-COPD study (NCT01455129), which was a multicentre, randomized, double-blind clinical trial conducted to investigate the efficacy and safety of tiotropium in patients with mild-to-moderate COPD. The trial design and the results of the Tie-COPD study have been published previously. [12,14] The Tie-COPD study recruited a large cohort of patients from 24 centres in China who were diagnosed with COPD of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 1–2 (defined as a post-bronchodilator $FEV_1/FVC$ of <0.70 and an $FEV_1$ ≥50% predicted) plus chronic respiratory symptoms, a history of exposure to COPD-risk factors, or both. The patients with GOLD stage 1-2 COPD were randomly assigned in a 1:1 ratio to receive either tiotropium (18 μg once daily) or placebo for 2 years. Follow-up of these patients was scheduled at 1 month and every 3 months thereafter. Patients with COPD exacerbations during the 4 weeks prior to screening, and those with asthma, large-airway disease, and/or severe systemic disease, were excluded from the Tie-COPD study.

The trial protocol was approved by the local institutional review board or independent ethics committee of each sites.[12, 14] All patients provided written informed consent for participation. The study was conducted in accordance with the principles ,of the Declaration of Helsinki.

***Spirometry, symptom, and exacerbation assessment***

At each follow−up visit, data on smoking status, chronic respiratory symptoms, exacerbations, and medication administration were collected. Lung function data were collected at 1, 6, 12, 18, and 24 months during the follow-up period of this study.


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Spirometry assessment was performed by homogeneously trained technicians, following the normative operation methods and standard quality-control principles recommended by the American Thoracic Society and Europe Respiratory Society.[15,16] There was at least a 6-hour interval between the administration of short-acting bronchodilators and spirometry testing. The post-bronchodilator spirometry examination was required to have been performed when 20 minutes after inhaling 400 μg albuterol. According to the published protocol of the Tie-COPD study, the predicted $FEV_1$ was obtained using the reference values from the European Coal and Steel Community 1993, adjusting for conversion factors for the Chinese population (0.95 for males and 0.93 for females).[17,18] In the present secondary analysis, we recalculated the LLN of FEV1/FVC using the latest Chinese equations. The Global Lung Function Initiative (GLI) race-neutral formula was not used to recalculate the LLN of FEV1/FVC because the GLI race-neutral formula has not been validated in the Chinese population.[19-21] Patients with FR+LLN- were defined as having a post-bronchodilator $FEV_1$/FVC of <0.70 but ≥LLN. Patients with airflow limitation according to both the fixed ratio criterion and the lower limit of normal criterion (FR+LLN+) were defined as having a post-bronchodilator $FEV_1$/FVC of <0.70 and <LLN meanwhile. Respiratory symptoms were assessed using the modified British Medical Research Council dyspnoea scale, COPD Assessment Test (CAT) score and Clinical COPD Questionnaire (CCQ).[22] COPD exacerbation was defined as new onset or deterioration of at least two of the following five symptoms: cough, sputum production, purulent sputum, wheezing, and dyspnea persisting for at least 48 hours, excluding other causes, such as left and




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right heart insufficiency, pulmonary embolism, pneumothorax, pleural effusion, and arrhythmia.[12,23] The severity of acute COPD exacerbations was assessed and recorded by well-trained staff according to the following categories. Moderate exacerbations were defined as those resulting in outpatient or emergency department visits and the need for COPD medication. Severe exacerbations were defined as those resulting in hospitalization.

***Outcomes***

The primary outcome was the difference between the tiotropium and the placebo groups in the change from baseline to 24 months in the pre-bronchodilator $FEV_1$.

The secondary endpoints were the between-group difference in the change from baseline to 24 months in post-bronchodilator $FEV_1$, the between-group difference in the change in pre-bronchodilator and post-bronchodilator FVC from baseline to 24 months, the between-group difference in the annual decline in $FEV_1$ and FVC before and after bronchodilator use from 30 days to 24 months, the annual frequency of acute exacerbations, the CAT score, and the CCQ score.

***Statistical methods***

This study was a secondary analysis; therefore, no sample size calculation was performed. We included all eligible patients with FR+LLN− from the full analysis set of the Tie-COPD study in this secondary analysis. Normally distributed continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as n (%). We evaluated the differences between the clinical characteristics at baseline between the two groups using the two-sample t-test, chi-




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square test, or Fisher's exact test, as appropriate. We used repeated-measures analysis of variance to clarify the between-group difference in the change from baseline to 24 months in the pre-bronchodilator $FEV_1$ and other lung function indicators before and after the bronchodilator use. The random coefficient regression model was used to assess the between-group difference in the annual rate of lung function decline rate from 30 days to 24 months based on the pre-bronchodilator $FEV_1$ and other spirometry indicators. The measurement values collected at each screening visit were regarded as the dependent variables in the analyses, combined with group, visit (used as a continuous variable), and interactions between groups and visits as fixed effects, and patients as random effects. The Poisson regression model was used to compare the frequency and severity of acute COPD exacerbations, considering the exposure to the trial regimen doses and adjusting for overdispersion (i.e., the presence of greater variability in the data set than the expected heterogeneity in the exacerbation rates). We also used repeated-measures analysis of variance model analyses to clarify the between-group difference in the change from baseline to 24 months in the CAT scores and the CCQ scores. All analyses were conducted using SAS version 9.4.



## Results

Of the 841 randomized patients, 771 were included in the full analysis set in the Tie-COPD study. Of these, 92 patients (12%) had FR+LLN- (53 in the tiotropium group, 39 in the placebo group). There were no significant differences in the baseline clinical characteristics between the tiotropium group and the placebo group (**Table 1**), including


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age (69.4 ± 6.2 years vs. 69.9 ± 5.4 years, respectively), sex, post-bronchodilator percentage predicted $FEV_1$ (87.8% ± 13.4 % vs. 88.4% ± 17.8 %), and $FEV_1$/FVC (68.8% ± 1.0 % vs. 68.8% ± 1.0 %).

***Primary endpoint***

The least-squares mean (LSM) change from baseline to 24 months in the pre-bronchodilator $FEV_1$ was 47 mL (95% confidence interval [CI] −13, 108) in the tiotropium group and −140 mL (95% CI −215, −64) in the placebo group (**Figure 2**). Tiotropium led to a significantly higher pre-bronchodilator $FEV_1$ at 24 months compared with placebo (LSM difference 191 mL; 95% CI 99, 283). The improvement was generated from month 6 and was sustained through month 24.

***Secondary end points***

The results of the between-group difference in the change from baseline to 24 months in post-bronchodilator $FEV_1$, and pre-bronchodilator and post-bronchodilator FVC are shown in **Figure 2**. Tiotropium led to a significantly greater post-bronchodilator $FEV_1$ at 24 months (LSM difference 139 mL; 95% CI 38, 223) than placebo. The LSM change from baseline to 24 months in post-bronchodilator $FEV_1$ was 15 mL (95% confidence interval [CI] −44, 75) in the tiotropium group and −130 mL (95% CI −220, −71) in the placebo group. This improvement was generated from month 6 and was sustained through month 24. Tiotropium also resulted in a significantly higher pre-bronchodilator FVC at 24 months than placebo. The between-group LSM difference from baseline to 24 months was 175 mL (95% CI, 44 to 306). The LSM change from baseline to 24 months was 33 mL (95% CI −55, 122) in the tiotropium group and −126 mL (95% CI




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−237, −16) in the placebo group. Tiotropium led to a significantly higher post-bronchodilator FVC at 24 months than placebo. The between-group LSM difference in post-bronchodilator FVC was 100 mL (95% CI −33, 233). The LSM change from baseline to 24 months was −13 mL (95% CI −101, 75) in the tiotropium group and −109 mL (95% CI −219, 1) in the placebo group.

**Figure 2** shows that the tiotropium group exhibited lower lung function decline from baseline to 24 months than the placebo group, as shown by the pre-bronchodilator and post-bronchodilator $FEV_1$ and/or FVC values. The annual decline in pre-bronchodilator $FEV_1$ in the tiotropium group was lower than in the placebo group (24 mL/year versus 89 mL/year, respectively; difference 60 mL/year; 95% CI 2, 118) from 30 days through 24 months. Similar results were observed for the post-bronchodilator $FEV_1$. The between-group difference from 30 days through 24 months in the annual decline in post-bronchodilator $FEV_1$ was 67 mL/year (95% CI 13, 122), with an annual decline of 23 mL/year in the tiotropium group compared with 90 mL/year in the placebo group. Tiotropium reduced the annual decline in pre-bronchodilator FVC compared with placebo (34 mL/year vs. 102 mL/year, respectively; difference 52 mL/year; 95% CI −35, 139). Similarly, tiotropium reduced the annual decline in post-bronchodilator FVC compared with placebo (39 mL/year vs. 111 mL/year; difference 60 mL/year; 95% CI −25, 146) from 30 days through 24 months.

The annual frequency of acute COPD exacerbations was lower in the tiotropium group than in the placebo group (0.22 ± 0.05 per patient-year vs. 0.43 ± 0.09 per patient-year, respectively; relative risk [RR]=0.50; 95% CI, 0.27-0.94). Similar results were


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observed for moderate-to-severe COPD exacerbations (0.19 ± 0.05 per patient-year vs. 0.38 ± 0.09 per patient-year; RR=0.49; 95% CI, 0.28–0.94) and severe COPD exacerbations requiring hospitalization (0.03 ± 0.01 per patient-year vs. 0.10 ± 0.03 per patient-year; RR=0.31; 95% CI, 0.11–0.85) (**Figure 3**).

As for chronic respiratory symptoms, the tiotropium group demonstrated significantly reduced CAT scores from baseline to 24 months (LSM change −1.55; 95% CI −2.26, −0.83) compared with the placebo group (LSM change −0.09; 95% CI −0.82, 0.64). The between-group difference was −1.92 (95% CI −2.85, −1.00) (**Figure 4**). The LSM change in the CCQ score from baseline to 24 months in the tiotropium group was −0.22 (95% CI −0.34, −0.10) compared with 0.02 (95% CI −0.07, 0.11) in the placebo group. The between-group difference was −0.18 (95% CI −0.28, −0.09).

In patients with FR+LLN+, the LSM change from baseline to 24 months in pre-bronchodilator $FEV_1$ was 30 mL (95% confidence interval [CI] −1, 60) in the tiotropium group and −129 mL (95% CI −159, −99) in the placebo group (**Supplementary Figure 1**). Tiotropium led to a significantly greater pre-bronchodilator $FEV_1$ at 24 months (LSM difference 141 mL; 95% CI 98, 184) than placebo. Similar findings were observed in the post-bronchodilator $FEV_1$, pre-bronchodilator FVC, and post-bronchodilator FVC. From 30 days through 24 months, the annual decline in the post-bronchodilator $FEV_1$ was 28 mL per year in the tiotropium group and 44 mL per year in the placebo group, with a between-group difference of 17 mL/year (95% CI 1, 34). The groups did not differ significantly in the annual decline of the pre-bronchodilator $FEV_1$, pre-bronchodilator FVC, and post-




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bronchodilator FVC. Tiotropium also resulted in a lower frequency of total exacerbations (0.50 ± 0.60 per patient-year vs. 0.88 ± 0.09 per patient-year, respectively; RR=0.56; 95% CI, 0.46-0.67) compared to placebo (**Supplementary Figure 2**). In terms of chronic respiratory symptoms, the tiotropium group showed visibly reduced CAT scores from baseline to 24 months (LSM change −1.70; 95% CI −2.36, −1.05) compared with the placebo group (LSM change −0.24; 95% CI −0.90, 0.41). The between-group difference was −1.21 (95% CI −2.85, −1.00) (**Supplementary Figure 3**). The above results remain stable in CCQ scores.

## Discussion

The secondary analysis revealed that tiotropium improved lung function, and reduced lung function decline, exacerbations, and chronic respiratory symptoms compared with placebo in patients diagnosed with airflow limitation according to the commonly used fixed ratio of 0.70 but not the LLN.

To our knowledge, this is the first study to investigate the effectiveness of pharmacological treatment for patients with FR+LLN−. Patients with FR+LLN− are prone to a better health status than those with FR+LLN+ and exhibit better lung function, fewer respiratory symptoms, and better respiratory outcomes, and thus this group of patients is often considered to be over-diagnosed COPD. However, patients with FR+LLN− are associated with increased respiratory symptoms, poorer lung function, a higher risk of exacerbations, and a higher risk of mortality than patients in whom both criteria are normal.[5-9] The present study provided evidence-based medicine




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evidence supporting the pharmacological treatment of this special population.

Three novel findings of this study may contribute to guiding the treatment of patients with FR+LLN− in clinical practice. First, we demonstrated that tiotropium visibly improved $FEV_1$ at month 24 by approximately 139 mL to 191 mL than placebo in patients with FR+LLN−. The 24-month duration of the Tie-COPD study captured longitudinal lung function trajectories more reliably. Second, tiotropium effectively reduced the annual rate of lung function decline in patients with FR+LLN− compared to placebo during the 24 months. Tiotropium alleviated the annual decline in postbronchodilator $FEV_1$ (23 mL/year vs. 90 mL/year in the placebo group) over 24 months. The 23 mL/year annual decline in prebronchodilator $FEV_1$, an effect size comparable to that observed with tiotropium in patients with GOLD 2–3 COPD (34 mL/year in the UPLIFT study), suggests its biological plausibility despite diagnostic reclassification.[24] Third, tiotropium reduced exacerbations and alleviated chronic pulmonary symptoms in patients with FR+LLN− compared with placebo. Overall, the effectiveness of tiotropium for improving respiratory health outcomes among patients with FR+LLN− was multi-dimensional.

The proportion of patients with FR+LLN− in the Tie-COPD study was 12%, which is consistent with previous studies, and whether these special populations require treatment is an interesting question.[4-7] In this study, the rate of annual decline in prebronchodilator $FEV_1$ was 89 mL in the placebo group, which is much higher than the natural age-related decline of approximately 30 mL/year in healthy aging individuals.[25,26] The annual decline in prebronchodilator $FEV_1$ was 89 mL in the


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placebo group in this analysis, which is higher than the value of 53 mL in the placebo group of the entire Tie-COPD study. A similar trend was observed for postbronchodilator $FEV_1$.[12] These findings indicate that patients with FR+LLN− have faster lung function decline than the overall population with mild-to-moderate COPD. Moreover, the disease burden of patients with FR+LLN− is heavier than that of those with a normal fixed ratio.[4-7] The above information has challenged the conventional viewpoint that these milder cases may not require pharmacological intervention, indicating that patients with FR+LLN− may require integrated management, early intervention, and long-term follow-up to improve their respiratory outcomes.

Tiotropium is a long-acting anticholinergic bronchodilator that selectively binds to muscarinic receptors on smooth-muscle cells in the airway. Previous studies have shown that tiotropium ameliorates airway limitation, reduces air trapping and exertional dyspnea, and improves exercise tolerance and health-related quality of life among patients with COPD.[27] The results of the present study reveal that tiotropium effectively improved lung function, delayed lung function decline, and reduced the risk of acute exacerbation among patients with FR+LLN−, supporting the pharmacological intervention and management of these patients in clinical practice. Large population-based cohort studies and clinical trials are still needed to verify the efficacy of pharmacological treatment in patients with FR+LLN− and to explore appropriate therapeutic medication.

The impact of the two criteria of interest (fixed ratio and LLN) on the diagnosis of COPD has always been a key issue in respiratory medicine. The use of the fixed ratio


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for the diagnosis of COPD was first recommended in the GOLD 2001 guidelines, originating from large-sample prevalence results.[28] The fixed ratio has been used ever since, owing to its simplicity and suitability for use in clinical practice and its standardization.[1] However, one of the problems that arose with the use of the fixed ratio was the underdiagnosis of younger patients and the overdiagnosis of older patients.[29] The LLN criterion is based on the 5th percentile of the normal distribution of the healthy population and is adjusted for age, sex, height, and race, which had greater potential for accurately reflecting patients' lung function.[11,30] However, the latest strategy proposed the implementation of a more inclusive diagnosis of COPD, allowing for the detection of early disease before irreversible pathological changes have occurred, enabling early disease interception.[31] The incidence of COPD detected by the LLN criterion is lower than that detected by the fixed ratio criterion (6.1% vs. 7.6%) among patients aged 40–49 years, which may not conform to the latest prevention and treatment strategy for COPD.[32,33] Moreover, previous studies have evidenced that the fixed ratio criterion is no less effective for detecting COPD-relevant hospitalization and mortality than the LLN criterion or other fixed thresholds used to define airflow limitation.[34] Last, patients with FR+LLN− are visibly older, have fewer symptoms, have a higher risk of cardiovascular disorders and/or mortality than those with FR−LLN−, indicating that satisfying the LLN criterion may not suggest that the respiratory system is healthy, even though they have a lower risk of exacerbations than FR−LLN−.[4, 35-37] Our findings support the use of the fixed ratio criterion to identify patients who are at a high risk of clinically significant COPD. Therefore, this criterion may be suitable for use in routine




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clinical practice and COPD treatment, especially in low- and/or middle-income countries that have not conducted large-scale studies to calculate their own LLN formulas.

This study has some potential limitations. This was a post hoc analysis and no preplanned sample size calculation was performed. This may have led to false-positive results and insufficient power to classify the differences between the tiotropium and placebo groups. Moreover, a potential imbalance in the clinical characteristics between the two groups may have influenced the study results. Furthermore, the sample size was small, and thus we could not conduct clinically relevant subgroup analyses.

## Conclusion

The results of this secondary analysis of the Tie-COPD study demonstrated that tiotropium improved lung function, ameliorated lung function decline, reduced acute exacerbations, and reduced chronic pulmonary symptoms compared with placebo in patients with FR+LLN−, providing evidence for the pharmacological treatment of this population.




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**Authors' contributions**

(I) Conception and design: K Zhou, F Wu, P Ran, Y Zhou; (II) Administrative support: P Ran, N Zhong, Y Zhou; (III) Provision of study materials or patients: P Ran, Y Zhou; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: F Wu, K Zhou, Z Deng, Q Wan, N Zhong, P Ran, Y Zhou; (VI) Manuscript writing: K Zhou, F Wu, Z Deng, Q Wan, N Zhong, P Ran, Y Zhou; (VII) Final approval of manuscript: All authors.

**Data sharing statement**

Our data concerning the Tie-COPD study is shareable.



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Juan Du, Xiwei Hu; *The Second People's Hospital of Hunan Province*: Jianping Gui, Jia Tian; *Huizhou First Hospital*: Bin Hu, Zhe Shi; *The Affiliated Zhongshan Hospital of Fudan University*: Chunxue Bai, Xiaodan Zhu; Shenzhen Sixth People's Hospital: Ping Huang, Xiufang Du; *The First People's Hospital of Foshan*: Gang Chen, Minjing Li; *Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology*: Yongjian Xu, Jianping Zhao; *Xinqiao Hospital*: Changzheng Wang, Qianli Ma; *The First Affiliated Hospital of Jinan University*: Shengming Liu; *Shanghai Xuhui Central Hospital*: Ronghuan Yu; *The First Affiliated Hospital Sun Yat-sen University*: Canmao Xie; *The Second People's Hospital of Zhanjiang*: Xiongbin Li; *Shaoguan Iron and Steel Group Company Limited Hospital*: Tao Chen; *Beijing Chao-Yang Hospital*: Yingxiang Lin; *Lianping County People's Hospital*: Weishu Ye, Xiangwen Luo, Lingshan Zeng, Shuqing Yu. We thank Emily Woodhouse, PhD, from Liwen Bianji (Edanz) (www.liwenbianji.cn) for helping us polish the English text of a draft of this manuscript.




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**Table 1. Baseline characteristics of the patients with classified as normal using the lower limit of normal criterion but obstructed using fixed ratio criterion.**

| Variable | Placebo Group (N=39) | Tiotropium Group (N=53) | P Value |
|---|---|---|---|
| Age — year | 69.9±5.4 | 69.4±6.2 | 0.718 |
| Male sex — no. (%) | 38 (97.4) | 48 (90.6) | 0.237 |
| Body-mass index — $Kg/m^2$ | 22.4±3.5 | 22.3±3.1 | 0.951 |
| Smoking status — no. (%) | | | 0.311 |
| Never smoked | 6 (15.4) | 15 (28.3) | |
| Current smoking | 13 (33.3) | 17 (32.1) | |
| Former smoking | 20 (51.3) | 21 (39.6) | |
| Smoking index — pack-year | 48.1±94.7 | 39.7±60.3 | 0.604 |
| **Spirometric values at baseline** | | | |
| Pre-bronchodilator $FEV_1$ — liters | 2.05±0.50 | 1.95±0.46 | 0.324 |
| Pre-bronchodilator $FEV_1$ of predicted value — % | 83.4±17.1 | 82.2±13.8 | 0.712 |
| Pre-bronchodilator FVC — liters | 3.08±0.72 | 2.94±0.65 | 0.310 |
| Pre-bronchodilator $FEV_1$/FVC — % | 66.4±2.99 | 66.3±2.98 | 0.977 |
| Post-bronchodilator $FEV_1$ — liters | 2.16±0.50 | 2.07±0.46 | 0.341 |
| Post-bronchodilator $FEV_1$ of predicted value — % | 88.4±17.8 | 87.8±13.4 | 0.841 |
| Post-bronchodilator FVC — liters | 3.15±0.73 | 3.01±0.65 | 0.343 |
| Post-bronchodilator $FEV_1$/FVC — % | 68.8±0.99 | 68.8±1.03 | 0.799 |
| **GOLD stage** — no. (%) | | | 0.304 |
| 1 (mild) | 24 (61.5) | 38 (71.7) | |
| 2 (moderate) | 15 (38.5) | 15 (28.3) | |
| mMRC score | 0.6±0.5 | 0.7±0.7 | 0.604 |
| CAT score | 4.6±3.5 | 6.3±5.6 | 0.591 |

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

**Abbreviations: 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.


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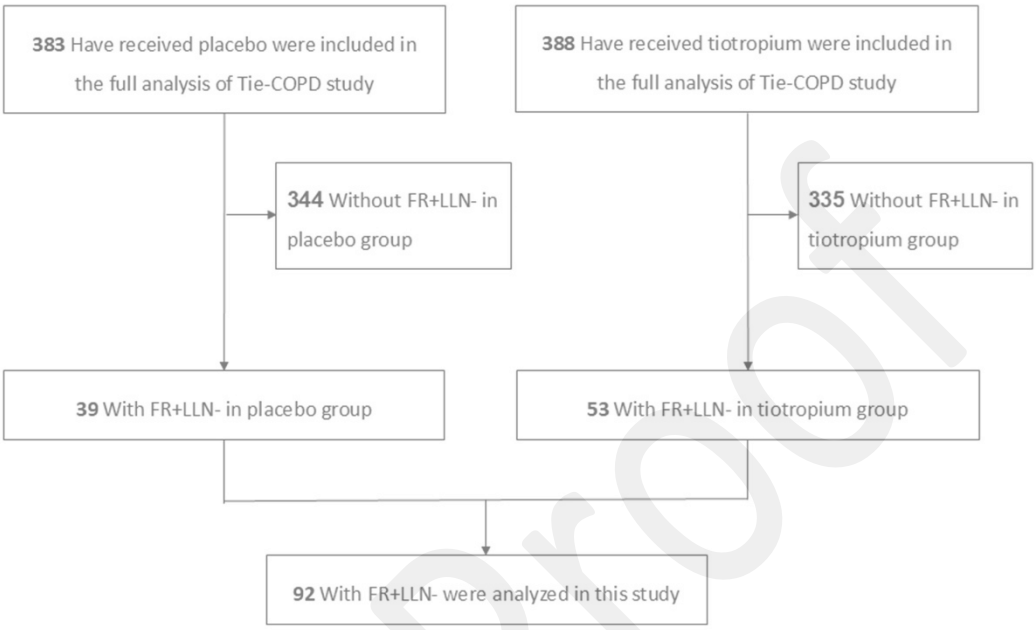
## Figure legends

**Figure 1. Study flow chart**




**Abbreviations: COPD** = chronic obstructive pulmonary disease; FR+LLN-, patients with classified as normal using lower limit of normal criterion but obstructed using fixed ratio criterion.




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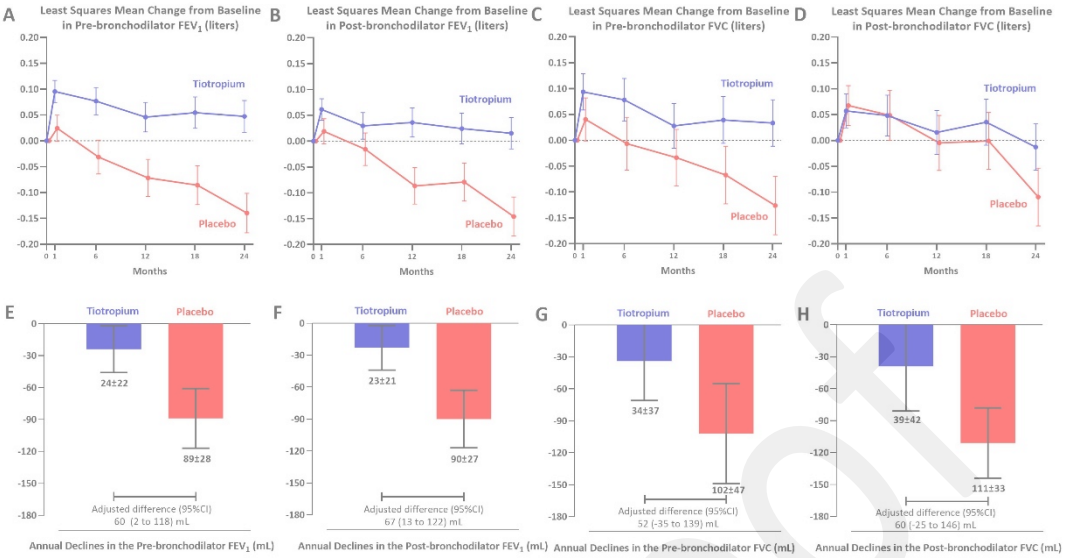
**Figure 2. Mean and annual declines in $FEV_1$ and FVC before and after the bronchodilator used in the patients in this study.**




Data are mean ± standard error

A, B, C, and D have shown the least squares mean change from baseline in the $FEV_1$ and FVC before and after the bronchodilator used in the patients with classified as normal using lower limit of normal criterion but obstructed using fixed ratio criterion between the placebo group and the tiotropium group. E, F, G, and H were adjusted for confounding factors including age, sex, body mass index, smoking status, baseline classification of Global Initiative for Chronic Obstructive Lung Disease, and baseline spirometric values, and have shown annual declines in the $FEV_1$ and FVC before and after the bronchodilator used in the patients with classified as normal using lower limit of normal criterion but obstructed using fixed ratio criterion between the placebo group and the tiotropium group.

**Abbreviations: $FEV_1$**, forced expiratory volume in one second; **FVC** = forced vital capacity.




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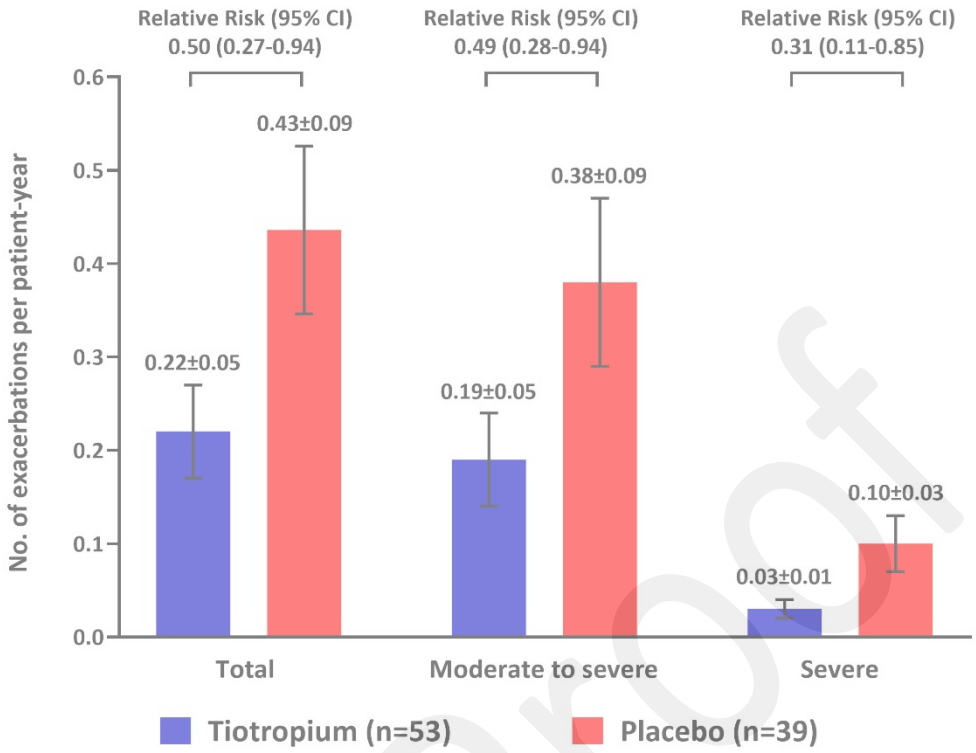
**Figure 3. Difference in acute exacerbations over time in this study.**




Data are mean ± standard error.




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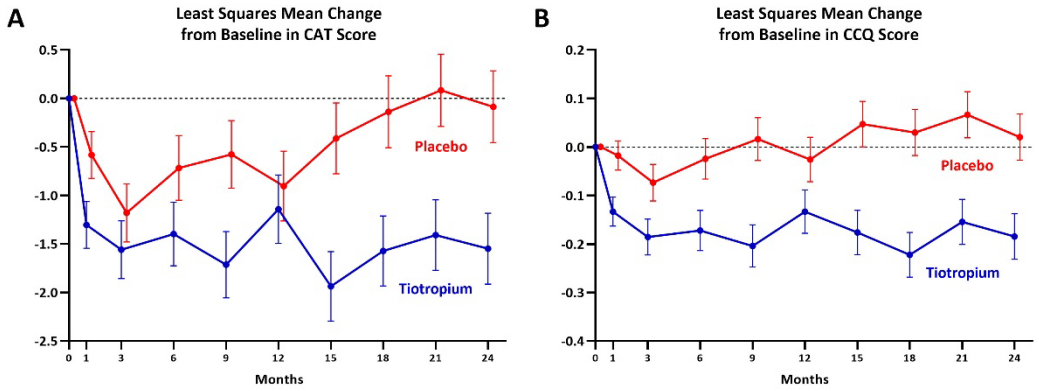
**Figure 4. The difference in CAT Scores and CCQ scores at different time points over time in this study.**




Data are mean ± standard error.

(**A**) CAT over time; **(B)** CCQ over time.

**Abbreviations: CAT**, COPD assessment test; **CCQ**, clinical COPD questionnaire.

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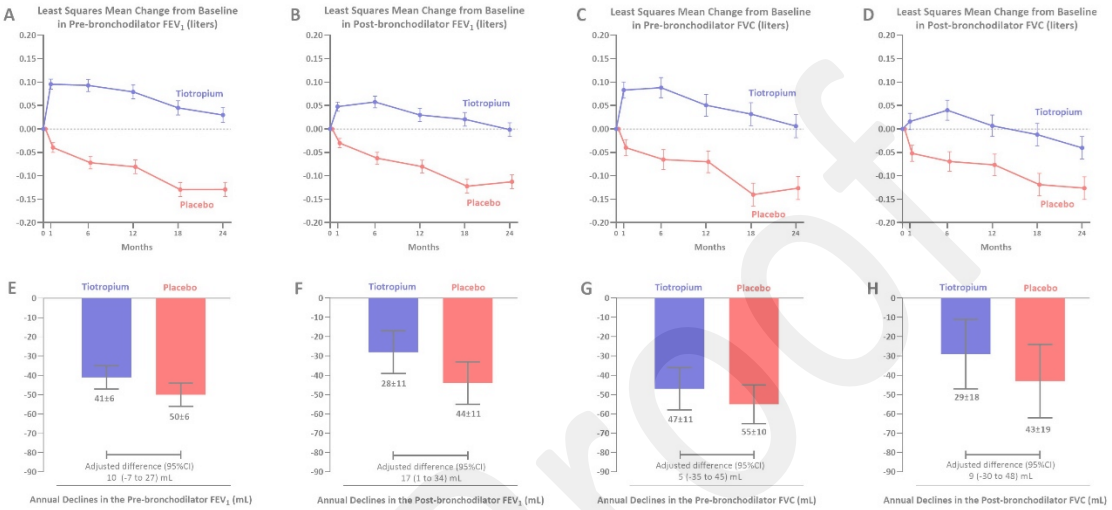
**Online Supplement**

**Supplementary Figure 1. Mean and annual declines in $FEV_1$ and FVC before and after the bronchodilator used in the patients in patients with airflow limitation according to both the fixed ratio criterion and the lower limit of normal criterion.**




Data are mean ± standard error

A, B, C, and D have shown the least squares mean change from baseline in the $FEV_1$ and FVC before and after the bronchodilator used in the patients with classified as normal using lower limit of normal criterion but obstructed using fixed ratio criterion between the placebo group and the tiotropium group. E, F, G, and H were adjusted for confounding factors including age, sex, body mass index, smoking status, baseline classification of Global Initiative for Chronic Obstructive Lung Disease, and baseline spirometric values, and have shown annual declines in the $FEV_1$ and FVC before and after the bronchodilator used in the patients with classified as normal using lower limit of normal criterion but obstructed using fixed ratio criterion between the placebo group and the tiotropium group.

**Abbreviations: $FEV_1$**, forced expiratory volume in one second; **FVC** = forced vital capacity.

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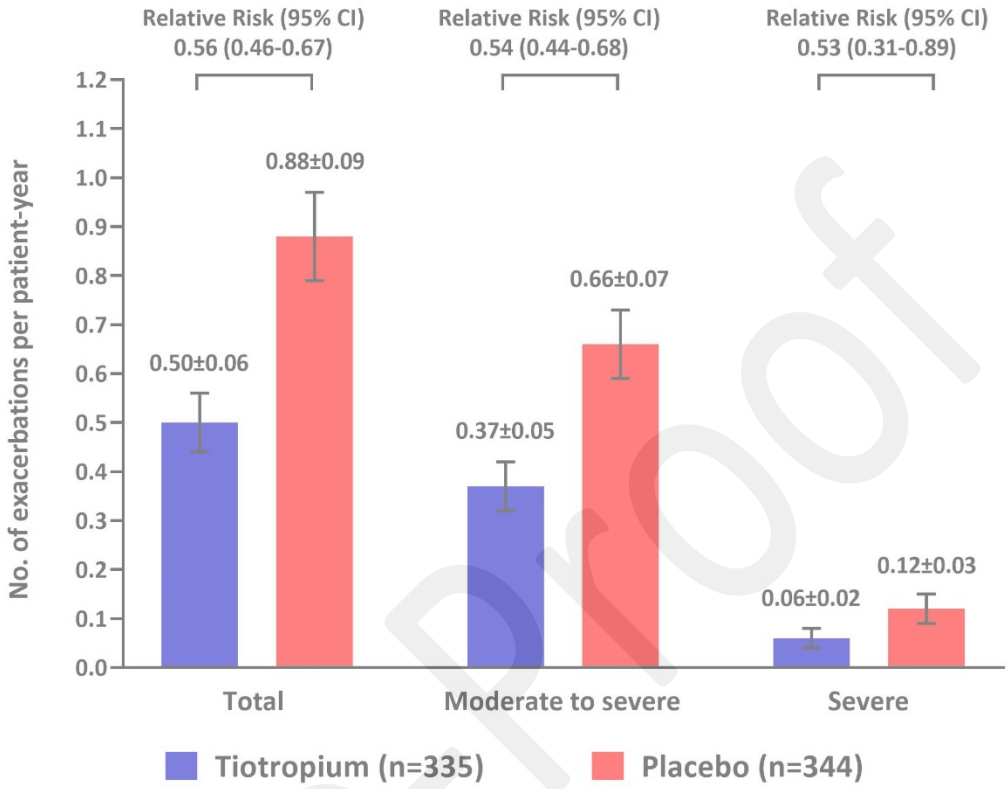
**Supplementary Figure 2. Difference in acute exacerbations over time in patients with airflow limitation according to both the fixed ratio criterion and the lower limit of normal criterion.**




Data are mean ± standard error.

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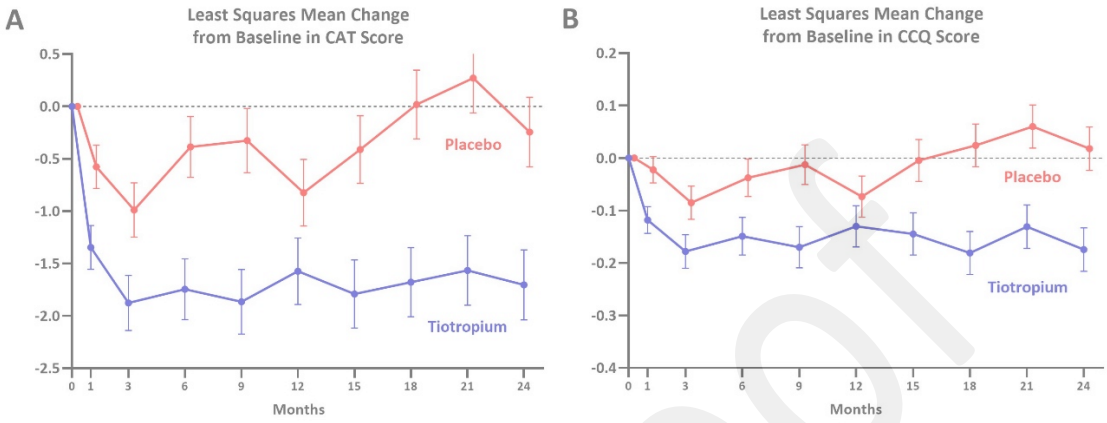
**Supplementary Figure 3. The difference in CAT Scores and CCQ scores at different time points over time in patients with airflow limitation according to both the fixed ratio criterion and the lower limit of normal criterion.**




Data are mean ± standard error.

(**A**) CAT over time; **(B)** CCQ over time.

**Abbreviations: CAT**, COPD assessment test; **CCQ**, clinical COPD questionnaire.

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