Safety and efficacy of different doses of erythromycin for non-cystic fibrosis bronchiectasis in the stable phase: A randomized controlled trial

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ABSTRACT

Objective: To evaluate the efficacy and side effects of different doses of erythromycin in patients with stable non-cystic fibrosis bronchiectasis (NCFB).

Method: Altogether, 148 patients diagnosed with stable NCFB were enrolled in this study and randomly assigned to one of the following four treatment groups: Group A received erythromycin 250 mg/day; Group B received erythromycin 375 mg/day; Group C received erythromycin 500 mg/day; and Group D received a placebo. Each group consisted of 35 patients. The dataset comprised lung function data and computed tomography(CT), St. George's Respiratory Questionnaire (SGRQ), modified Medical Research Council, bronchiectasis severity index(BSI), and E-FACED scores, which were collected before and at 6 months after treatment. These were subjected to a univariate analysis.

Result: Groups C and D exhibited significant differences in forced expiratory volume in 1 second, forced vital capacity (FVC), quality of life, and CT Bhalla, BSI, and E-FACED scores ($P < 0.05$). Additionally, Groups B and D demonstrated significant differences in FVC and SGRQ, BSI, and E-FACED scores ($P < 0.05$). Contrarily, Group A exhibited non-significant differences.

Conclusion: The oral erythromycin regimen at a dose of 500 mg/day can improve the lung function and quality of life of stable NCFB patients.

KEYWORDS

bronchiectasis, erythromycin, curative effect, adverse reaction

1. INTRODUCTION

Bronchiectasis, a common chronic respiratory disease worldwide, can lead to recurrent cough and infection-related complications, ultimately resulting in an accelerated loss of lung function and diminished quality of life(Eklöf et al., 2022; Kartsiouni et al., 2022). The primary clinical symptoms of bronchiectasis include cough, dyspnea, hemoptysis, and recurrent respiratory tract infections. However, these clinical symptoms lack sufficient specificity and often necessitate the identification of permanent airway dilation on radiographic images to aid in diagnosis, which may lead to diagnostic and treatment delays(Eklöf et al., 2022; Macfarlane et al., 2021). Furthermore, bronchiectasis can be categorized into cystic fibrotic bronchiectasis and non-cystic fibrotic bronchiectasis (NCFB). Recently, NCFB has garnered considerable attention due to its increasing morbidity, disability risk, associated mortality, and the growing burden on the healthcare system(Li et al., 2019).

Macrolide antibiotics not only exhibit antibacterial properties but also possess immunomodulatory effects, which can reduce airway inflammation and frequency of acute exacerbations in patients with bronchiectasis. In addition, these antibiotics considerably decrease the sputum volume, interleukin-8 (IL-8) level, total cell count, and neutrophil ratio in the bronchoalveolar lavage fluid (BALF)(Li et al., 2019). To date, several high-quality randomized controlled trials and meta-analyses have supported the efficacy of azithromycin, erythromycin, and roxithromycin in preventing the deterioration of NCFB. Notably, macrolides are the only therapeutic agents proven to mitigate the progression of bronchiectasis in randomized, double-blind, placebo-controlled trials(Altenburg et al., 2013; Li et al., 2019; Serisier et al.,

2013; Wong et al., 2012; Zhuo et al., 2014). Erythromycin, a widely used macrolide, also plays an important role in the management of bronchiectasis. However, both literature reviews and clinical practice indicate that the optimal dosage of erythromycin for patients with NCFB remains a topic of debate(Li et al., 2019; Mao et al., 2022; Shibuya et al., 2001). Consequently, the present study aimed to investigate the appropriate dosage of erythromycin for stable NCFB patients to provide new insights for the treatment of this condition.

2. MATERIAL AND METHODS

2.1 Study design and patients

This randomized controlled study collected basic information from all patients diagnosed with stable NCFB who were admitted to the respiratory department of Fengdu General Hospital between February 2022 and February 2024. The inclusion criteria for selecting the study participants were as follows: patients who met the diagnostic criteria established in the Chinese expert consensus on the diagnosis and treatment of bronchiectasis in adults(Group & Pulmonary Infection Assembly, 2021); had experienced at least two distinct pulmonary exacerbations within the past 12 months that required systemic antibiotic treatment and involved daily sputum production; and had been clinically stable for at least 4 weeks prior to study enrollment. The exclusion criteria were patients younger than 18 years or older than 85 years, those with cystic fibrosis, those exhibiting liver or kidney dysfunction, those who were allergic to erythromycin, those who experienced fewer than two exacerbations in the past year, those on steroids requiring long-term treatment, those with diabetes, or pregnant or breastfeeding women. The present study was approved by the ethics committees of Fengdu General Hospital (2021SC0425-9) and was conducted in accordance with guidelines stipulated in the Declaration of Helsinki. Written informed consent was obtained from all participants.

Patients were randomly assigned to one of the following four groups (Random Grouping Method in Excel): Group A received oral erythromycin at 250 mg/day; Group B received oral erythromycin at 375 mg/day; Group C received oral erythromycin at 500 mg/day; and Group D received a placebo. Participants and those assessing outcomes were blinded after assignment to interventions. The patients were followed up after 6 months of continuous medication. The execution of this project, along with its quality control, is entrusted to external personnel. The final deadline for the study was August 31, 2023. The comprehensive procedure is illustrated in Figure 1.

2.2 Data collection

In accordance with the pre-established inclusion and exclusion criteria, a total of 160 patients (A = 40, B = 40, C = 40, D = 40) were enrolled in this study. At the end of the study, two patients from Group A, four from Group B, one from Group C, and five from Group D were lost to follow-up. Prior to the administration of the

pharmaceutical agent, data on the lung function parameters, quality of life, and CT Bhalla, BSI, and E-FACED scores were collected for each patient. The occurrence of adverse drug reactions and results of bacterial cultures of the sputum or BALF specimens were monitored at 2-month intervals. The lung function parameters, quality of life, and CT Bhalla, BSI, and E-FACED scores were reassessed after a 6-month period. All data were verified independently by two researchers, with the CT Bhalla score representing the mean of the assessments conducted by an imaging physician and a respiratory physician. Patient follow-up information and ID numbers were used for the identification of the data collected.

2.3 CT Bhalla score

The SIEMENS Healthineers 128-row spiral computed tomography scanner (SOMATOM Definition AS) was used, as it can meet all the diagnostic and evaluation needs of the present study. The total CT Bhalla score comprised the bronchiectasis degree, bronchial wall thickness, small airway abnormality and mosaic attenuation scores. Please refer to Table 1 for further details.

2.4 Pulmonary function test

Forced expiratory volume in 1 second (FEV1), FEV1% predicted value (FEV1%Pre), and forced vital capacity (FVC) were measured with the Jaeger pulmonary function instrument (MASTERSCREENDIFFUSION+APS, CareFusion Germany 234 GmbH, Hoechberg, Germany).

2.5 Quality of life

Quality of life was assessed using the St. George's Respiratory Questionnaire (SGRQ) and modified Medical Research Council (mMRC) dyspnea scale. The SGRQ comprises the following three components: symptom score, which evaluates the patient's symptoms; activity score, which assesses the patient's daily activities; and impact score, which measures the disease's effect on the patient's social activities and psychological well-being. Each item within these components carries a specific weight, and the final score is calculated by taking the ratio of the sum of the weights of the positive items to the total weight, multiplied by 100. The scores for the three subcomponents can be calculated individually, or a total SGRQ score can be derived from the overall sum of the positive item weights in relation to the total weight. The mMRC score is defined as follows: 0 = no obvious dyspnea except with strenuous activity; 1 = shortness of breath when walking fast or climbing a gentle slope; 2 = walking more slowly as compared to peers or at one's own pace on flat ground; 3 = needing to stop to breathe after walking 100 meters or a few minutes on level ground; and 4 = unable to leave the house due to considerable breathing difficulties or experiencing shortness of breath when changing clothes.

2.6 BSI rating scale

The BSI scale incorporates several factors, including age, body mass index (BMI), predicted FEV1 value, number of hospitalizations in the past 2 years,

number of acute exacerbations in the past year, mMRC score, bacterial colonization status (such as patina or other types), and radiographic involvement. The BSI scores of 0–4, 5–8, and ≥9 indicate mild, moderate, and severe diseases, respectively.

2.7 E-FACED score

The E-FACED scoring system encompasses several factors, including lung function, age, radiation coverage, microbiological data, and symptoms. A forced expiratory volume in 1 second percentage of predicted (FEV1%Pre) of <50% is assigned a score of 0, whereas a FEV1%Pre of >50% is assigned a score of 1. Patients aged ≤70 years receive a score of 0, whereas those aged ≥70 years receive a score of 2. The radiation coverage of one leaf is scored as 1, whereas that of two leaves or more is scored as 2. The absence of *Pseudomonas aeruginosa* (PA) was scored as 0, and its presence was scored as 1. Similarly, the absence of dyspnea was scored as 0, whereas its presence was scored as 1. The total scores from these criteria were summed as follows: patients scoring 0–2 are classified as having mild bronchiectasis, with <5% chance of mortality over the next 5 years; those scoring 3–5 are classified as having moderate bronchiectasis; and patients scoring 6–7 are classified as having severe bronchiectasis, which is associated with a higher mortality rate.

2.8 Statistical analysis

Statistical analysis was conducted using Excel for data summarization and SPSS 28.0 for data analysis. The measurement data were assessed for normality and reported as mean ± standard deviation. The analysis of variance was employed to compare multiple groups. For the data collected before and after treatment, the analysis of covariance was performed using the data distribution prior to treatment as a covariate to adjust the post-treatment data. The LSD-t test was utilized for pairwise comparisons between the groups. Categorical data are expressed as counts or rates. The chi-square test or Fisher's Exact Probability test was applied for group comparisons. All statistical tests were two-tailed, with a significance level set at $\alpha = 0.05$.

3. RESULTS

Baseline data were collected for all cases, encompassing information on patients' sex, age, smoking index, BMI, and comorbidities, primarily chronic obstructive pulmonary disease (COPD) and cardiovascular disease. There were no significant differences were observed in the baseline data among the enrolled cases in the four groups ($P > 0.05$, Table 2).

3.1 Comparison of CT Bhalla score and pulmonary function test values before and after treatment

Following a 6-month treatment course, significant overall differences were observed in both FEV1 (L) and FVC (L) before and after treatment ($P < 0.05$). However, no significant differences were noted in FEV1%Pre. As illustrated in

Table 3, after the 6-month treatment, the total CT scores in Group C exhibited a downward trend, whereas those in Group D showed an upward trend, showing a significant difference ($P < 0.05$) (**Figure 2A**). The FEV1 in Group C displayed an upward trend, whereas that in Group D exhibited a downward trend, again showing a significant difference ($P < 0.05$) (**Figure 2B**). Furthermore, a significant difference was observed in the FVC between Groups B and C, and Group D. Additionally, a significant difference in FEV1 was observed between Groups B and C ($P < 0.05$). However, no significant difference was identified in FEV1%Pre among the groups ($P > 0.05$) (**Figure 2C–D**).

3.2 Results of the quality of life assessment before and after treatment

Following the 6-month treatment course, no significant differences were observed in the mMRC scores between Groups A and B, and Group D ($P > 0.05$). Contrarily, the SGRQ scores for Groups B and C exhibited a declining trend, with a significant difference noted between Groups B and C, and Group D (**Figure 3A–B**, Table 4).

3.3 Comparison of the BSI and E-FACED scores before and after treatment

The mean difference in the BSI and E-FACED scores was significant at the 6-month follow-up ($P < 0.05$). After the six-month treatment course, Groups B and C exhibited a significant reduction in the BSI and E-FACED scores, as compared with Group D ($P < 0.05$). Contrarily, no significant change in the BSI and E-FACED scores were observed in Group A (**Figure 3C–D**, Table 4).

3.4 Adverse drug reactions and new cases of drug resistance

At the end of the study, Group A had two new cases of *multidrug-resistant P. aeruginosa* (MDR-PA), Group B had one new case, Group C had two new cases, and Group D had one new case ($P > 0.05$). Furthermore, there was no significant difference in the overall incidence of adverse reactions among the four groups ($P > 0.05$, Table 5).

4. Discussion

NCFB is a chronic respiratory disease characterized by recurrent bacterial infections, chronic airway inflammation, accumulation of airway secretions, and irreversible abnormal dilation and distortion of the bronchial tubes and bronchioles resulting from airway destruction. The changes in the airway structure can also lead to mucus accumulation, chronic airway infections, and persistent neutrophilic inflammation, which may result in progressive lung injury and a poor prognosis(Choo et al., 2018; Imam & Duarte, 2020; Macfarlane et al., 2021). Between 2008 and 2017, the total mortality rate among patients with bronchiectasis was approximately 10.8%, whereas the incidence of respiratory failure was approximately 22%. More than half of the patients presented with multiple bacterial, viral, or even fungal infections at the time of diagnosis(Huang et al., 2023). Therefore, clinicians should emphasize the importance of preventing or treating co-

infections in patients with bronchiectasis.

Macrolides are categorized into 14-, 15-, and 16-membered ring macrolides based on the number of lactone rings(Paçacı Çetin et al., 2021). These 15-membered macrolides exhibit potentially beneficial effects at each stage of the "vicious cycle" of bronchiectasis. Macrolide drugs mitigate airway inflammation in patients with bronchiectasis by decreasing the secretion of pro-inflammatory cytokines in epithelial cells, inhibiting the recruitment of white blood cells to the airway, suppressing neutrophil activation, and reducing oxidative stress. This multifaceted action contributes to the inhibition of bacterial infection and results in decreased cough and sputum production(Keir et al., 2021; Pollock & Chalmers, 2021). Numerous studies have confirmed that macrolides, including erythromycin, can reduce the frequency of acute exacerbations and improve the lung function of patients with bronchiectasis(Mao et al., 2022; Wu et al., 2014), which aligns with our study findings. Patients taking erythromycin for extended periods of time were more likely to experience improvements in lung CT imaging, lung function, and overall quality of life, with a regimen of 500 mg/day identified as the most effective. Several mechanisms may contribute to these benefits. First, erythromycin exerts a notable inhibitory effect on airway epithelial cells, neutrophils, and IL-8, leading to a substantial reduction in granulocyte accumulation within the airways and lungs, thereby alleviating the inflammatory response(Li et al., 2019). Additionally, the adhesion of neutrophils to epithelial cells decreases, which may enhance the cytotoxic effects of macrophages, lymphocytes, and other immune cells, effectively safeguarding the airway epithelial cells and limiting tissue damage to manageable levels(Keir et al., 2021). Second, erythromycin also markedly diminishes the neutrophil activity and improves airway hyperreactivity(Ichikawa et al., 1992; Lin et al., 2000; Maekawa et al., 2020). Furthermore, erythromycin inhibits the synthesis of PA proteinase and exotoxin, considerably reducing the adhesion of PA to the airways and drastically lowering mucus secretion, thereby controlling mucosal mucus production to very low levels, optimizing ciliary movement, and effectively managing expectoration and frequency of exacerbations(Tsang et al., 2003; Yazdanian et al., 2023). Therefore, we propose that the use of macrolides should be continued for a period following the resolution of acute symptoms in patients with NCFB to decrease the bacterial load and enhance the long-term prognosis.

In patients with bronchiectasis, infections caused by PA and *Haemophilus influenzae* and neutrophil-mediated chronic airway infections are important contributors to disease progression and poor prognosis. PA was found to be numerically dominant, and patients infected with this pathogen exhibited a considerably worse prognosis, whereas those with a predominance of *H. influenzae* tended to present with milder symptoms(Faverio et al., 2016; Lommatzsch, 2020;

Rogers et al., 2015). Consequently, clinicians frequently opt for long-term antibiotic therapy in patients with bronchiectasis. However, some researchers argue that macrolide maintenance therapy may increase the risk of antimicrobial resistance(Park & Olivier, 2015; Sobala et al., 2022; Somayaji & Goss, 2019), with limited studies indicating that erythromycin can induce resistance in PA. The MDR-PA is associated with gene mutations, including gyrA, gyrB, parC, and parE(Mao et al., 2022). The present study found that the different doses of erythromycin did not demonstrate an effect on secondary MDR-PA in patients with NCFB, which is in line with the findings of other researchers(Wu et al., 2014). For patients with NCFB in the chronic maintenance phase, erythromycin remains a prudent choice for maintenance therapy, particularly in the absence of established guidelines for optimal antibiotic selection and current evidence-based medicine(Verma et al., 2021; Wang et al., 2021). However, it is important to note that our sample size is limited and our study is a single-center investigation, thereby broader research to further explore these issues is needed.

5. CONCLUSIONS

The present study assessed the efficacy and safety of various doses of erythromycin in patients with stable NCFB. Our study findings indicate that an oral regimen of erythromycin at a dosage of 500 mg/day markedly enhanced the lung function, reduced the symptoms of bronchiectasis, and improved the quality of life of stable NCFB patients, while exhibiting minimal adverse reactions and demonstrating good safety. Our research offers a potential therapeutic strategy for clinicians managing stable NCFB.

Experimental ethics

This study was approved by the Medical Ethics Committee of Fengdu General Hospital—approval: (2021SC0425-9). In accordance with national legislation and system requirements, patients' written informed consent was obtained to participate in this study. In this report, personally identifiable information of patient data is privacy-protected.

Competing interests

The authors declare that they have no competing interests.

Data availability

All data used in this study are available from the corresponding authors on reasonable request.

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Table 1 Bhalla scoring standard

Content of assessment	0	1	2	3
Degree of bronchiectasis*	not have	1-2	2-3	> 3
wall thickness#	no thickening	Close or identical	1-2	> 2
extent of dilatation	non-expanding	1-5 lung segments	6-9	> 9
extent of abscess	no abscess	1-5 lung segments	6-9	> 9
extent of mucus plugging	non-clogging	1-5 lung segments	6-9	> 9
dilatation grading	non-expanding	> Class 4	> 5	> 6
consolidation of lung	not have	lung subsegment	Lung segment and above	NA
extent of emphysema	not have	1-5 lung segments	> 5	NA
Number of pulmonary bullae	not have	Unilateral and < 4	Bilateral and <4	> 4

*: The ratio of the diameter of the bronchial lumen to that of the neighbouring vessel.
#: Ratio of bronchial wall thickness to surrounding neighbouring wall thickness.

Table 2 The baseline data

variable	Group A	Group B	Group C	Group D	Total	χ2/F	*P*
Male, n (%)	21(55.26%)	21(58.33%)	23(58.97%)	20(57.14%)	85(57.43%)	0.124	0.989
Age, years	58.13±11.36	55.11±16.19	55.05±14.46	55.66±12.41	56±13.65	0.425	0.735
BMI, kg/m^2	21.08(20.36,21.62)	21.06(20.36,21.76)	21.14(20.44,21.84)	21.40(20.79,22.01)	21.15(20.83,21.47)	0.269	0.848
Smoking, n (%)	15(39.47%)	16(44.44%)	17(43.59%)	17(48.57%)	65(43.92%)	0.618	0.892
Complication							
COPD, n (%)	9(26.68%)	8(22.22%)	8(20.51%)	7(20%)	32(21.62%)	0.186	0.980
Cardiovascular disease, n (%)	4(10.53%)	6(16.67%)	5(12.82%)	5(14.29%)	20(13.51%)	1.549	0.997
Others	5(13.16%)	4(11.11%)	3(7.69%)	4(11.43%)	16(10.81%)	0.628	0.890

COPD: Chronic Obstructive Pulmonary Disease, BMI: body mass index.

Table 3 Comparison of CT Bhalla score and Pulmonary function test

Group	treatment	CT score	FEV1(L)	FEV1% Pre	FVC(L)
A (n=38)	Before	9.58±2.74	1.62±0.09	75.12±2.98	2.41±0.34
	After	9.26±2.04	1.66±0.22	74.86±2.44	2.49±0.33
B (n=36)	Before	9.5±2.67	1.65±0.22	74.67±3.37	2.39±0.44
	After	8.94±2	1.7±0.26	74.32±1.43	2.55±0.33 [a]
C (n=39)	Before	9.41±2.12	1.64±0.27	75.27±3.16	2.35±0.37
	After	8.41±1.77 [a]	1.76±0.42[a]	74.82±1.66	2.58±0.42[a]
D (n=35)	Before	9.57±2.52	1.68±0.26	74.86±3.49	2.41±0.3
	After	9.8±2.87	1.57±0.24	74.73±2.13	2.39±0.21
ANOVA	*F*,*P*(Before)	0.037, 0.990	0.462, 0.709	0.252, 0.860	0.226, 0.878
	F,*P*(After)	2.605, 0.054	2.661, 0.050	0.588, 0.624	2.265, 0.084
Corrected ANOVA	*F*,*P*(After)	1.908, 0.153	1.008, 0.368	0.925,0.400	0.602, 0.549
ANCOVA	*F*,*P*(After)	3.573, 0.031	3.383, 0.038	0.845, 0.432	3.319, 0.040
A vs D	*LSD-t, P*	1.045, 0.298	-1.299, 0.196	-0.284, 0.777	-1.273, 0.205
B vs D	*LSD-t, P*	1.646, 0.102	-1.851, 0.066	0.884, 0.378	-2.010, 0.046
C vs D	*LSD-t, P*	2.720, 0.007	-2.758, 0.007	-0.198, 0.843	-2.434, 0.016

a: P < 0.05, compared with group D

Table 4 Comparison of SGRQ, BSI, E-FACED and mMRC scores before and after treatment

Group	treatment	SGRQ score	mMRC score	BSI score	E-FACED score
A (n=38)	Before	62.42±8.36	2.95±0.52	8.53±2.37	4.63±0.85
	After	63.47±6.37	2.95±0.23	9.55±1.69	5.05±0.57
B (n=36)	Before	63.53±10.36	2.86±0.59	8.69±1.69	4.72±0.91
	After	62.17±7.42 [a]	2.92±0.65	7.58±1.23[a]	3.64±0.54[a]
C (n=39)	Before	62.23±9.76	2.92±0.48	8.54±2.19	4.69±1.08
	After	59.1±5.84 [a]	2.69±0.52 [a]	6.95±1.45[a]	3.05±0.22[a]
D (n=35)	Before	62.14±10.61	2.89±0.47	8.63±2.25	4.69±0.96
	After	66.31±8.65	2.94±0.59	9.63±1.66	5.11±1.21
ANOVA	*F*,*P*(Before)	0.156, 0.926	0.204, 0.894	0.051, 0.985	0.058, 0.982
	F,*P*(After)	6.565, 0.000	2.129, 0.099	30.264, 0.000	78.007, 0.000
Corrected ANOVA	*F*,*P*(After)	4.511, 0.013	3.041, 0.052	32.550, 0.000	184.912, 0.000
ANCOVA	*F*,*P*(After)	8.922, 0.000	2.070, 0.131	33.534, 0.000	71.183, 0.000
A vs D	*LSD-t, P*	1.706, 0.090	-0.037, 0.970	0.213, 0.831	0.369, 0.713
B vs D	*LSD-t, P*	2.459, 0.015	0.212, 0.832	5.665, 0.000	8.676, 0.000
C vs D	*LSD-t, P*	4.358, 0.000	2.076, 0.040	7.571, 0.000	12.353, 0.000

a: P < 0.05, compared with group D

Table 5 Comparison of drug resistance and adverse reactions

group	n	MDR-PA	Stomach upset	Headache	Palpitation	Dysfunction of liver and kidney	Total n(%)
A	38	2(5.26)	1(2.63)	0(0.00)	1(2.63)	1(2.63)	3(7.89)
B	36	1(2.78)	2(5.56)	1(2.78)	0(0.00)	0(0.00)	3(8.33)
C	39	2(5.13)	1(2.56)	0(0.00)	1(2.56)	0(0.00)	2(5.13)
D	35	1(2.86)	0(0.00)	1(2.86)	1(2.86)	0(0.00)	2(5.72)
$\chi 2$		0.538	2.09	2.2	0.993	2.914	0.445
P		0.910	0.554	0.532	0.803	0.405	0.931

MDR-PA: *multidrug-resistant P. aeruginosa*

Figure 1. Flowchart of the study participants

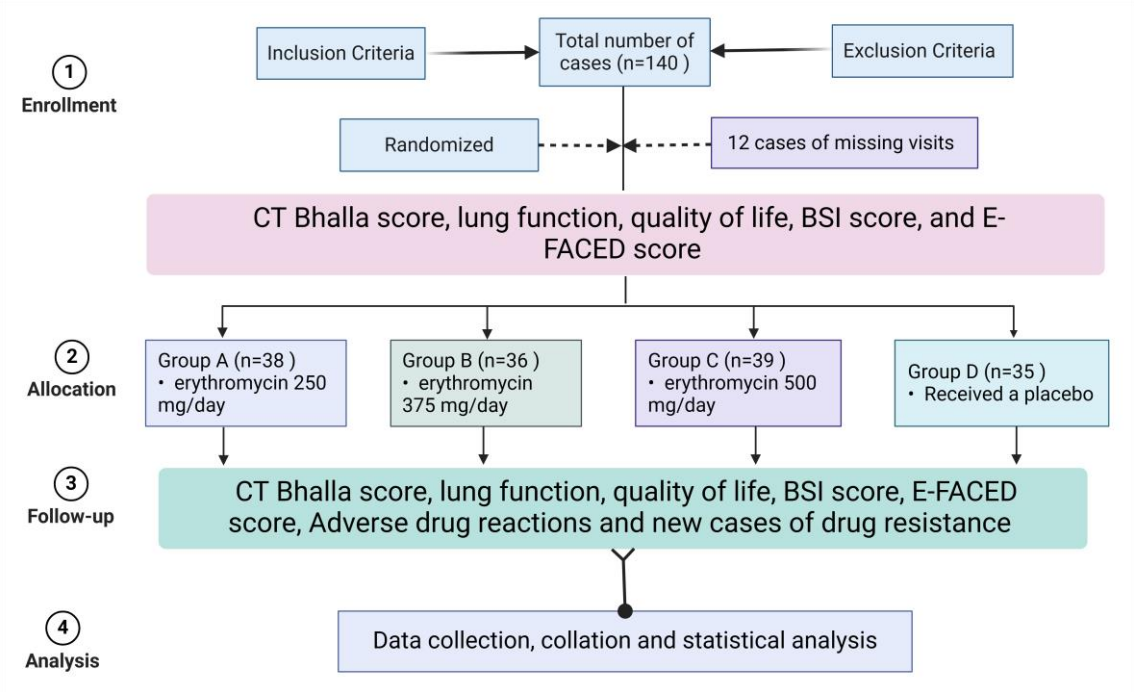
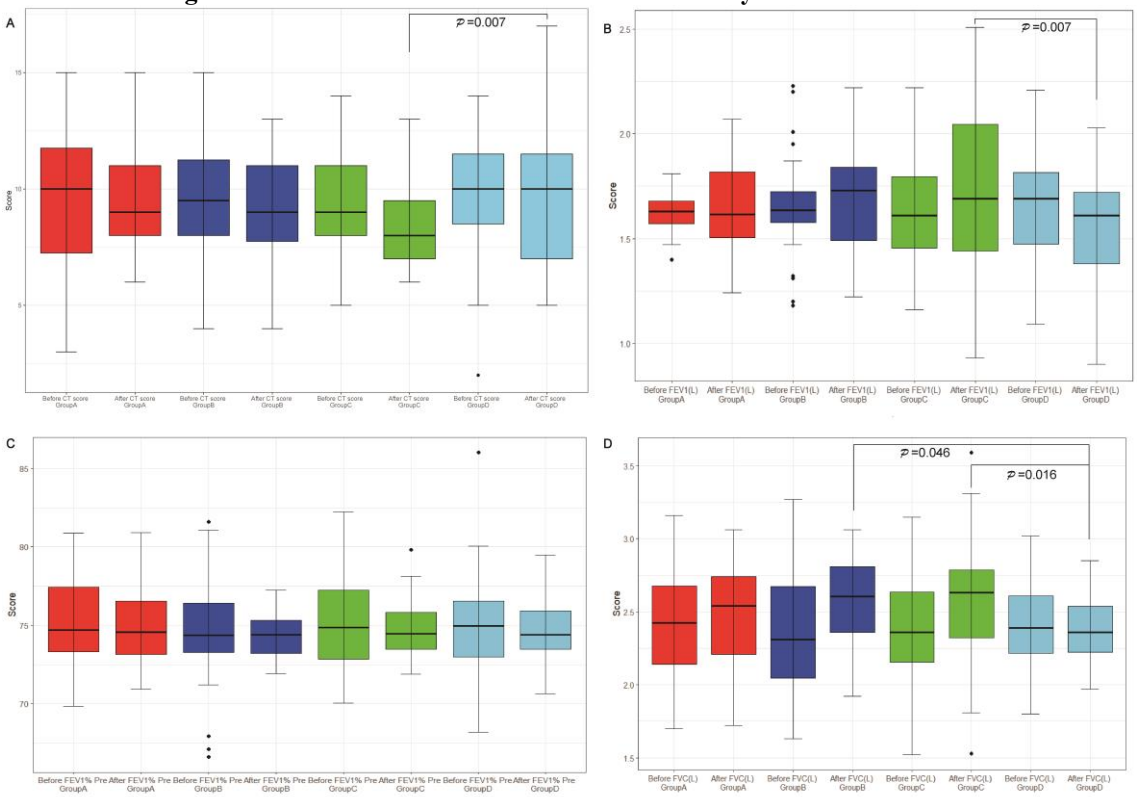
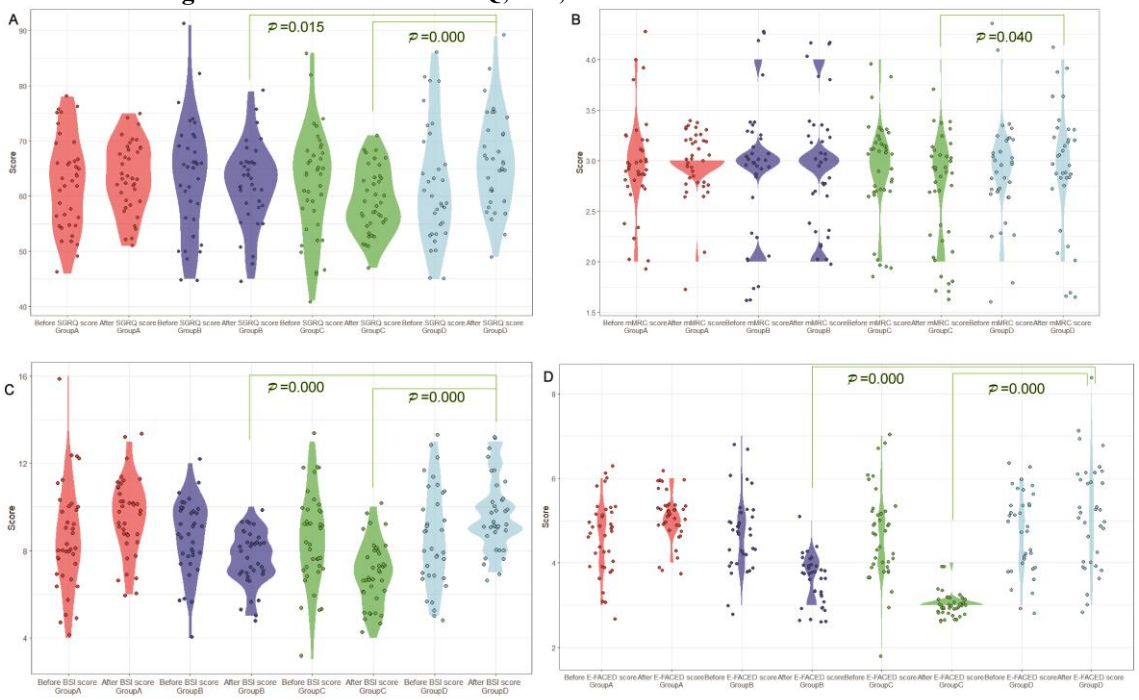


Figure 2. Results of CT Bhalla score and Pulmonary function test



Group A (n=38) received a dosage of 250 mg/day, Group B (n=36) received 375 mg/day, Group C (n=39) received 500 mg/day, and Group D (n=35) was administered a placebo. FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; FEV1%Pre, FEV1% predicted.

Figure 3. Results of the SGRQ, BSI, E-FACED and mMRC scores



Group A (n=38) received a dosage of 250 mg/day, Group B (n=36) received 375 mg/day, Group C (n=39) received 500 mg/day, and Group D (n=35) was administered a placebo. FEV1,forced expiratory volume in 1 s; FVC, forced vital capacity; FEV1%Pre, FEV1% predicted.