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REVIEW

Long-term macrolide treatment for the prevention of acute exacerbations in COPD: a systematic review and meta-analysis

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Background: Acute exacerbation of COPD (AECOPD) is associated with an increased hospitalization and mortality. Azithromycin and erythromycin are the recommended drugs to reduce the risk of exacerbations. However, the most suitable duration of therapy and drug-related adverse events are still a matter of debate. The aim of this meta-analysis was to assess the current evidence regarding the efficacy and safety of long-term macrolide treatment for COPD.

Materials and methods: We comprehensively searched PubMed, Embase, the Cochrane Library, and the Web of Science and performed a systematic review and cumulative meta-analysis of all randomized controlled trials (RCTs) and retrospective studies.

Results: Eleven RCTs and one retrospective study including a total of 2,151 cases were carried out. Long-term macrolide treatment significantly reduced the total number of cases with one or more exacerbations (OR=0.40; 95% CI=0.24–0.65; $P<0.01$) and the rate of exacerbations per patient per year (risk ratio [RR]=0.60; 95% CI=0.45–0.78; $P<0.01$). Subgroup analyses showed that the minimum duration for drug efficacy for both azithromycin and erythromycin therapy was 6 months. In addition, macrolide therapy could improve the St George Respiratory Questionnaire (SGRQ) total score ($P<0.01$) but did not achieve the level of clinical significance. The frequency of hospitalizations was not significantly different between the treatment and control groups ($P=0.50$). Moreover, chronic azithromycin treatment was more likely to increase adverse events ($P<0.01$).

Conclusion: Prophylactic azithromycin or erythromycin treatment has a significant effect in reducing the frequency of AECOPD in a time-dependent manner. However, long-term macrolide treatment could increase the occurrence of adverse events and macrolide resistance. Future large-scale, well-designed RCTs with extensive follow-up are required to identify patients in whom the benefits outweigh risks.

Keywords: AECOPD, macrolide, azithromycin, adverse events

Introduction

COPD is a preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation.[1] The incidence of COPD is gradually increasing. It is estimated that the number of COPD cases is more than 300 million worldwide, with a global prevalence of 11.7%.[2] Meanwhile, there are around 3 million deaths annually across the world.[2] Recently, in China, a large-scale epidemiological investigation shows that the overall prevalence of spirometry-defined COPD was 8.6%, accounting for 99.9 million adults with COPD.[3] The high morbidity and mortality of COPD is also associated with significant economic and social burden. Acute exacerbations of COPD (AECOPDs) refer to an acute worsening of respiratory symptoms that require

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additional therapy and are usually associated with increased airway inflammation and mucus production and marked gas trapping.[1] AECOPD is an important event in the management of COPD and a major determinant of health status and prognosis for patients with COPD. Exacerbations also account for the greatest proportion of the total COPD burden on the health care system.[1] Therefore, prevention of exacerbations is essential for the management of COPD.

Exacerbations are mainly triggered by respiratory viral and bacterial infections although air pollution, smoking, and ambient temperature may also contribute to these events. Currently, there are two main strategies to prevent AECOPDs; these include pharmacological interventions with long-acting bronchodilators, inhaled corticosteroids (ICS), phosphodiesterase-4 inhibitors, and mucoregulators and nonpharmacological interventions such as vaccines, smoking cessation, pulmonary rehabilitation, and lung volume reduction.[1] However, the effects of these measures are limited, and approximately, one-third of patients with COPD experience one or more exacerbations every year.[4] Moreover, chronic inflammation plays an important role in the pathogenesis of COPD, which leads to the widespread use of corticosteroids for treatment. However, high-dose corticosteroid inhalation provides little benefit in terms of improving the FEV_1 and may have long-term detrimental effects.[5] Thus, it is important to identify new and effective anti-inflammatory pharmacological therapies for COPD.

In previous studies, the continuous and prophylactic use of antibiotics has not been routinely recommended for COPD patients owing to insufficient evidence in reducing incidence of AECOPDs and concerns about the antibiotic-related side effects and drug resistance.[1] However, in 2017, the GOLD recommended for the first time that treatment with azithromycin or erythromycin for 1 year in patients prone to exacerbations can reduce the risk of exacerbations compared to usual care.[6] Macrolides are of unique interest because, in addition to their antibacterial and antiviral effects, they possess anti-inflammatory effect and immunomodulating activity.[7,8] These properties have been suggested to contribute to reducing disease progression of diffuse pan-bronchiolitis,[9] cystic fibrosis,[10] non-cystic fibrosis bronchiectasis,[11] and idiopathic pulmonary fibrosis.[12] Accordingly, macrolides should be considered as a potential therapy in COPD.

Several randomized controlled trials (RCTs) have been conducted to test this hypothesis with different conclusions. Furthermore, some meta-analyses have also been conducted to evaluate these findings, with the conclusion that prophylactic macrolide therapy is effective in decreasing the frequency of exacerbations in patients with COPD.[13–17] However, the most suitable drug, drug dose, duration of therapy, and target population remain unclear.[18] There is also no agreement on the long-term safety related to the emergence of macrolide resistance and adverse events.[19] Recently, several relevant trials have been newly published, and the revised GOLD 2017 document has also proposed prophylactic macrolide therapy. Therefore, we performed a systematic review and an updated meta-analysis to assess the efficacy and safety of long-term macrolide treatment for the prevention of AECOPDs.

Materials and methods

Literature search strategy

A literature search was performed on May 1, 2018, without restriction to regions, time, and publication types. The primary sources were the Cochrane Library and the electronic databases of PubMed, Embase, and the Web of Science. We used the following search term in the [Title/Abstract]: (COPD OR COAD OR Chronic Obstructive Pulmonary Disease OR Obstructive Pulmonary Disease OR Chronic Obstructive Airway Disease) AND (Azithromycin OR Erythromycin OR Macrolide OR Macrocyclic Lactone) AND (Exacerbation OR AE). We also used the "Related Articles" function to broaden the search and selected relevant articles from the reference lists of all retrieved studies, review articles, and conference abstracts.

Inclusion and exclusion criteria

To be included in the analysis, a study had to fulfill the following criteria: 1) it was a RCT or retrospective comparative study (cohort or case-control study); 2) it enrolled adults with a diagnosis of stable COPD but not AECOPD; 3) the prophylactic use of macrolides must have been administered orally at least one time a week for a period of at least 3 months; and 4) it had at least one of the quantitative outcomes mentioned in the following section of this article. The exclusion criteria included the following: 1) the study included patients with asthma, bronchiectasis, cystic fibrosis, or other genetic diseases; 2) it had a limited data on exacerbations; and 3) the article type was an editorial, letter to the editor, review article, case report, conference abstract, or an animal experimental study.

Data extraction and outcomes of interest

Data from the included studies were extracted independently by two of the authors (Yanan Cui and Lijuan Luo). Any disagreement was resolved by the adjudicating senior author (Yan Chen), and a final consensus was reached among all

the authors. We extracted the first author, year of publication, country, study design, sample size, population characteristics, antimicrobial agent, dose administered, duration of the treatment, and information on outcome measures. The primary outcomes were the total number of patients with one or more exacerbations and the rate of exacerbations per patient per year. The secondary outcomes were the number of patients requiring hospitalization, health-related quality of life based on the St George Respiratory Questionnaire (SGRQ) score, and the total number of patients who experienced adverse events.

Quality assessment and statistical analyses

The methodological quality of RCTs was assessed by the Cochrane risk of bias tool.[20] The modified Newcastle-Ottawa Scale that consists of patient selection, comparability of study groups, and assessment of outcome was used to assess the methodological quality of retrospective studies.[21] A score of 0–9 (allocated as stars) was allocated to the relevant study. RCTs including five or more items of low risk of bias and retrospective studies achieving six or more stars were considered to be of high quality.

Pooling analyses of the total number of patients with exacerbations, hospitalizations, and adverse effects were performed with Review Manager 5.3 (Cochrane Collaboration, Oxford, UK), and the OR was used to compare dichotomous variables. Meanwhile, the risk ratios (RRs) for exacerbations per patient per year and the mean differences in change of SGRQ score were pooled with Comprehensive Meta-Analysis V2.2. Further, 95% CIs were calculated for all clinical end points. Statistical heterogeneity was quantified using the I^2 statistic. The random-effects model was used if there was a heterogeneity between studies (I^2>40%); otherwise, the fixed-effects model was used.[20] Subgroup analyses were performed to compare different macrolides and macrolide therapy duration. Sensitivity analyses were performed by deleting studies with the highest or lowest weight and were conducted only for high-quality RCTs. Funnel plots were used in the analysis of potential publication bias.

Results

Literature search

A total of 626 potentially relevant articles were initially identified (80 from PubMed, 170 from Embase, 101 from the Cochrane Library, and 275 from the Web of Science). After screening the titles and abstracts, 346 articles were excluded. Of the remaining 51 articles with full texts, 12 studies including 2,151 cases fulfilled the predefined inclusion criteria and were included for the final analysis (Figure 1). Eleven studies were RCTs,[22–32] and one report was a retrospective observational study.[33] Examination of the reference lists of the included studies and the review articles did not yield any further relevant studies for evaluation.

Characteristics of eligible studies

The characteristics of included studies are shown in Table 1. These studies, published between 2001 and 2018, were mostly conducted in UK. The study population, with ages generally ranging from 65 to 73 years, included more men than women. Most of the patients had moderate-to-severe COPD diagnosed by current spirometric criteria, with mean FEV_1 of 33.9%–56.5% of the predicted value. A total of 1,078 patients were allocated to the macrolide treatment group (seven studies for azithromycin, three studies for erythromycin, one study for clarithromycin, and one study for roxithromycin), and 1,023 were allocated to the control group. The duration of macrolide therapy was more than 3 months but less than 1 year. Evaluation suggested that the quality of the enrolled RCTs was ideal (Figure 2), and the retrospective study also received seven stars (Table 2).

Primary outcomes

Eleven studies involving 1,910 cases reported the total number of patients with one or more exacerbations.[22–28,30–33] In a pooled analysis of the 11 studies, long-term macrolide treatment significantly reduced AECOPDs compared with the control group (OR=0.40; 95% CI=0.24–0.65; P=0.0003, I^2=62%; Figure 3). In the subgroup analyses of the specific macrolide (Figure 4A), AECOPDs were significantly decreased in both the azithromycin-treated group (OR=0.48; 95% CI=0.31–0.76; P=0.002, I^2=35%) and the erythromycin-treated group (OR=0.22; 95% CI=0.09–0.53; P=0.0008, I^2=53%). However, for clarithromycin therapy, only one trial reported the frequency of AECOPD and showed no statistical difference between the treated and control groups.[23] In addition, macrolide treatment for 3 or 6 months did not improve the exacerbation rate (P=0.25 and 0.15, respectively), whereas the OR showed a reduction of 72% (OR=0.28; 95% CI=0.12–0.68; P=0.005, I^2=81%) among the total number of patients with AECOPDs taking macrolides for 12 months, compared with the controls (Figure 4B).

Nine studies[22,23,25–28,30–32] including 1,631 patients reported the rate ratios for exacerbations per patient per year. Pooling the data of these studies showed a significant reduction in the rate of exacerbations (RR=0.60; 95% CI=0.45–0.78; P<0.01, I^2=63.73%) following the macrolide treatment (Figure 5).

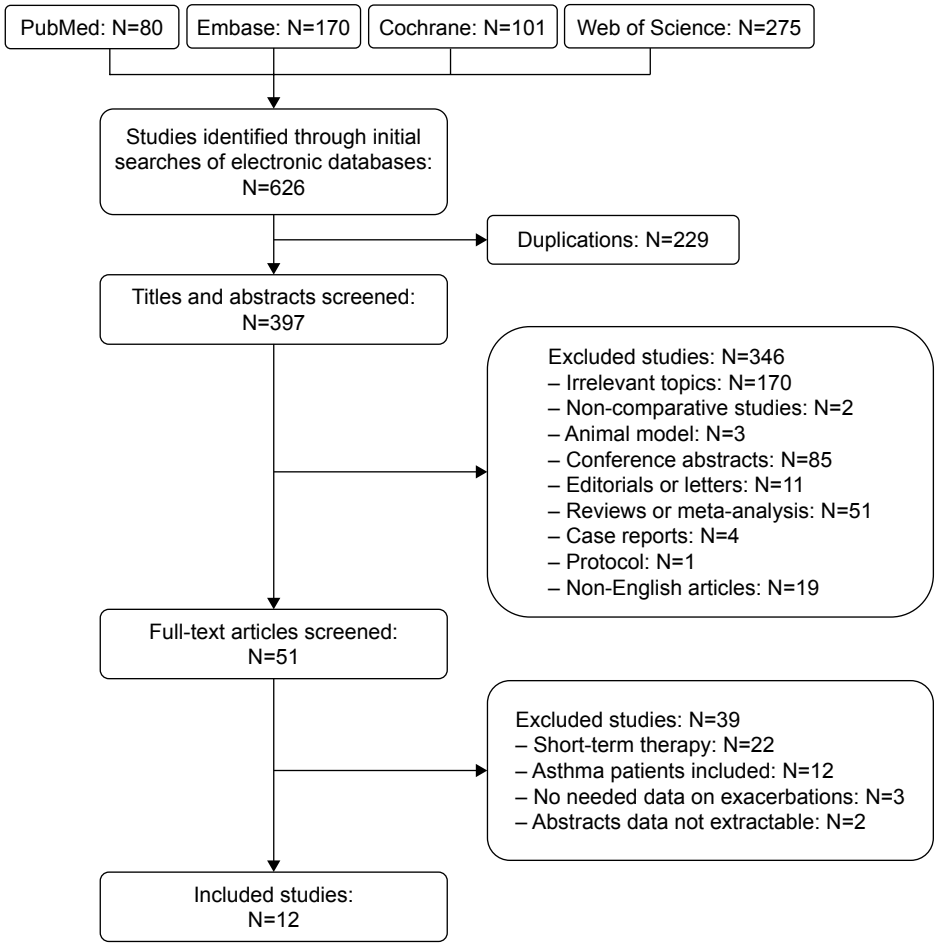


Figure 1 Flow diagram of studies identified, included, and excluded.

Secondary outcomes

Pooling the data of four trials[24,25,28,31] including 324 patients, which reported the number of patients requiring hospitalization, showed that there was no significant difference between the macrolide treatment and control groups (OR=0.60; 95% CI=0.14–2.65; P=0.50, I^2=69%; Figure 6).

As for health-related quality of life, five studies[19,21,23,27,29] involving 872 patients reported the mean differences in change in total SGRQ score. Macrolide treatment apparently improved the total SGRQ score (mean difference=–2.47; 95% CI=–3.72 to 1.22; P<0.01, I^2=13.72%; Figure 7). Although we found a statistically significant reduction of SGRQ score in the treatment group, the change was not clinically significant (≥4-point reduction).

All included studies[22–33] reported on the total number of patients who experienced nonfatal adverse events during follow-up after treatment with macrolides compared with the control group. Prophylactic macrolide therapy was more likely to increase adverse events (OR=1.63; 95% CI=1.30–2.04; P<0.01, I^2=35%; Figure 8). In subgroup analyses, there was a tendency for more adverse events in the azithromycin- and roxithromycin-treated groups (OR=1.51; 95% CI=1.17–1.95; P=0.002, I^2=45% and OR=3.21; 95% CI=1.56–6.60; P=0.002, respectively). However, three studies using erythromycin[27,28,31] and one study using clarithromycin[23] showed no significant difference between the two groups (P=0.60 and 0.18, respectively; Figure 9A). Moreover, the pooled data showed that patients treated with macrolides for 3 or 12 months suffered more drug-related adverse events than those in the control groups (both P<0.05). Moreover, there was no statistical difference between the 6-month treatment subgroup and the control (P=0.10; Figure 9B). Gastrointestinal reactions were the most frequent adverse events in the treatment groups, and hearing decrements were also frequent in such patients.

Sensitivity analyses and publication bias

After eliminating studies with the highest or lowest weight[22,25] and a retrospective study,[33] nine RCTs that included five or more items of low risk of bias using the Cochrane risk of bias tool were included in the sensitivity analyses.[23,24,26–32] Of note, in subgroup analyses of the 6-month therapy including only

Table 1 Characteristics of included studies

Study	Year	Country	Design	Sample size	Population characteristics (treatment/control)			Treatment arms	Duration of treatment (months)	Primary outcome	Secondary outcomes
					Mean age (years)	Men (%)	Mean FEV_1% predicted				
Albert et al[22]	2011	USA	RCT	1,117	65/66	59/59	39/40	Azithromycin 250 mg once daily; placebo	12	The time to the first acute exacerbation of COPD	Quality of life, nasopharyngeal colonization with selected respiratory pathogens, adherence, SGRQ, SF-36, hearing
Banerjee et al[23]	2005	UK	RCT	67	65.1/68.1	–	42.5/43.9	Clarithromycin 500 mg once daily; placebo	3	Health status	Sputum bacterial quantitative load, infective exacerbation rate, shuttle walk test, serum C-reactive protein levels
Berkhof et al[24]	2013	the Netherlands	RCT	84	67/68	74/76	49.8/47.4	Azithromycin 250 mg once 3 days/week; placebo	3	Mean LCQ total and domain scores	SGRQ, SF-36, FEV_1, blood values, microbiology
Blasi et al[25]	2010	Italy	RCT	22	72/73	91/82	–	Azithromycin 500 mg 3 days/week; standard care	6	The number of exacerbations and hospitalizations	Time to first exacerbation and hospitalization, steroid and antibiotic use, evaluation of the inflammatory cytokines values in the EBC, mortality, quality of life, safety
Brill et al[26]	2015	UK	RCT	99	67.9/68.7	64/75	44/53	Azithromycin 250 mg once 3 days/week; placebo	3	The change in total cultured bacterial load in sputum from baseline	Bacterial numbers by 16S qPCR, sputum inflammatory markers, bacterial resistance, lung function, health status, adherence to therapy, exacerbations, adverse events, comparison of airway load measurements using quantitative culture and 16S qPCR
He et al[27]	2010	China	RCT	36	68.8/69.3	83.3/88.9	44.3/42.1	Erythromycin 125 mg 3 times daily; placebo	6	Neutrophil number in sputum; exacerbations	Spirometry, quality of life, inflammatory markers in sputum, sputum bacteriology, adherence, safety
Naderi et al[33]	2018	Canada	R	195	67.8/70.8	59.8/47.8	34.8/39.9	Azithromycin 250 mg once at least 3 times per week; placebo	≥6	Exacerbations and health service use	Changes in exacerbations according to patient and disease characteristics and adverse effects
Seemungal et al[28]	2008	UK	RCT	109	66.5/67.8	62/64	49.3/50.6	Erythromycin 250 mg twice daily; placebo	12	Exacerbations and airway inflammation	Spirometry, sputum testing for bacteria, adverse events

(*Continued*)

Table 1 (*Continued*)

Study	Year	Country	Design	Sample size	Population characteristics (treatment/control)			Treatment arms	Duration of treatment (months)	Primary outcome	Secondary outcomes
					Mean age (years)	Men (%)	Mean FEV_1% predicted				
Shafuddin et al[29]	2015	New Zealand	RCT	191	67.6/66.7	85.6/71.3	33.9/35.8	Roxithromycin 300 mg once daily; placebo	3	COPD exacerbations over 48-week posttreatment period	COPD exacerbations over the 12-week treatment period, and the first and last 24-week posttreatment periods, FEV_1, FVC, CRQ scores, adverse events
Simpson et al[30]	2014	Australia	RCT	30	71.7/69.9	60.0/66.7	56.5/51.1	Azithromycin 250 mg once daily; placebo	3	Airway bacterial load, sputum neutrophil proportion, levels of CXCL8	Exacerbations, symptom score, SGRQ, CCQ, lung function and CT scores, side effect
Suzuki et al[31]	2001	Japan	RCT	109	69.1/71.7	85.5/81.5	–	Erythromycin 200–400 mg once daily; riboflavin 10 mg once daily	12	The frequency of the common cold	The frequency of the subsequent exacerbation
Uzun et al[32]	2014	the Netherlands	RCT	92	64.7/64.9	47/40	44.2/45.0	Azithromycin 500 mg once 3 days/week; placebo	12	Rate of exacerbations of COPD	Time to first exacerbation, hospital admission for acute exacerbations, change in the treatment of exacerbations, FEV_1, FVC, 6 minutes walking test, quality of life, macrolide-resistant microorganisms, adverse events

Abbreviations: CCQ, Clinical COPD questionnaire; CRQ, chronic respiratory disease questionnaire; CXCL8, a neutrophils chemokine; EBC, exhaled breath condensate; LCQ, Leicester Cough Questionnaire; R, retrospective cohort study; RCT, randomized controlled trail; SF-36, the Medical Outcomes Study 36-Item Short-Form Health Survey; SGRQ, St George's Respiratory Questionnaire; qPCR, quantitative PCR.

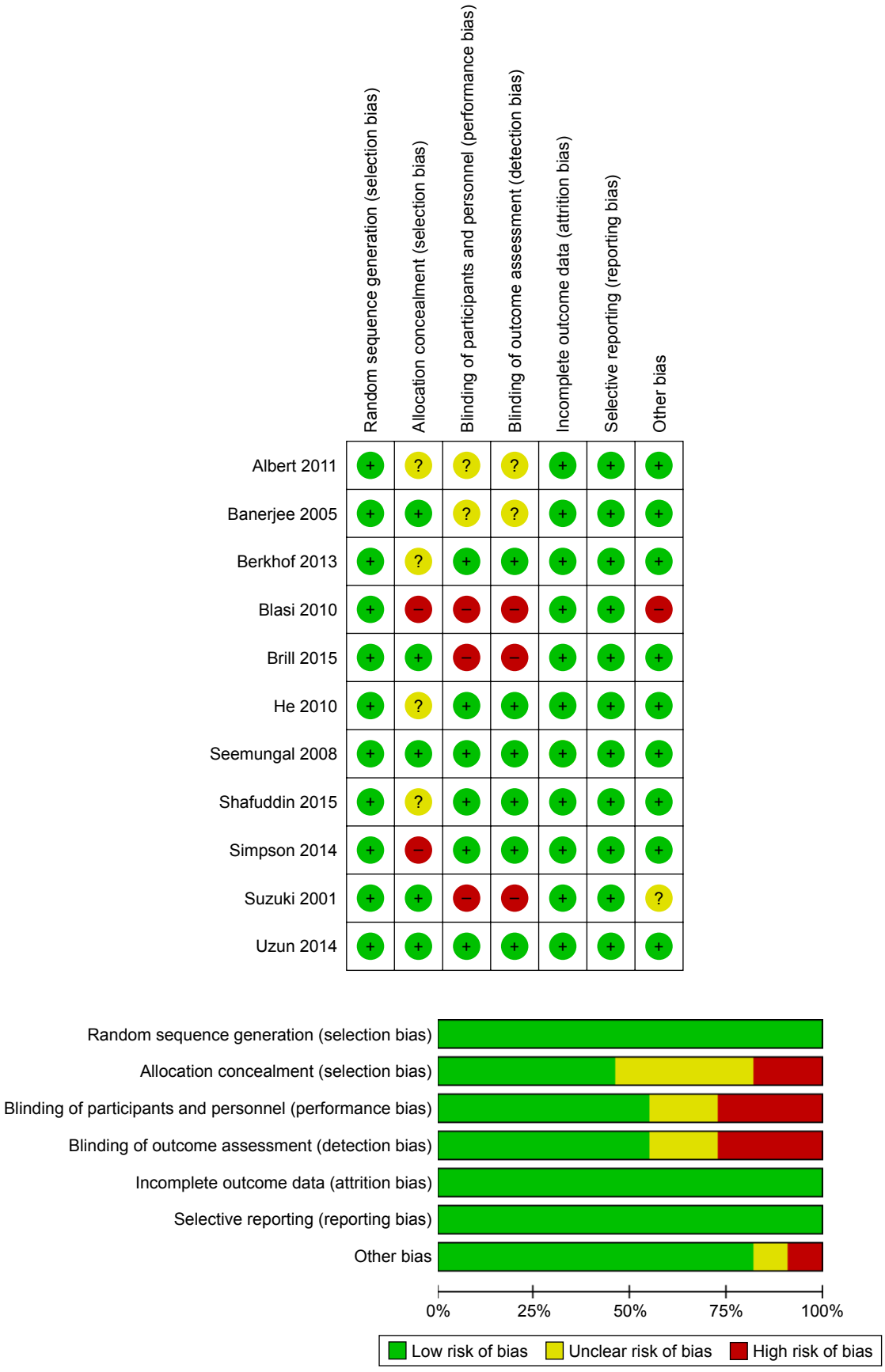


Figure 2 Graph of the bias risk of the enrolled RCTs.
Note: The other bias refers to intention-to-treat analysis.
Abbreviation: RCT, randomized controlled trail.

Table 2 Risk of bias in the retrospective study

Study	Selection			Comparability		Outcome		Quality score
	Representative exposed group	Representative reference group	Assignment for exposed group[a]	Comparable for 1, 2, 3, 4[b]	Comparable for 5, 6, 7, 8[b]	Assessment of outcome	Adequate follow-up	
Naderi et al[33]	Yes	Yes	Yes	2, 4	6, 7	Yes	Yes	★★★★★★★

Notes: Comparability variables: 1=age; 2=gender; 3=FEV_1 (%) of predicted; 4=corticosteroids inhalation medication; 5=body mass index; 6=smoking status; 7=any inhalation medication; 8=exacerbation previous year. [a]Details of criteria for adequate random assignment of patients to the exposed group were provided. [b]If all characteristics were comparable, two stars; if two or three characteristics were comparable, one star; otherwise, no star.

three related studies, we retained two studies[25,27] with similar weight and excluded the retrospective study.[33] There was no change in the significance of any of the outcomes except for the number of patients with exacerbations using macrolide treatment for 6 months and the adverse events of azithromycin treatment (Figures S1–S5 and Table S1). In contrast with our previous results, macrolide treatment for 6 months could also reduce the number of AECOPDs (P=0.02), and drug-related adverse events showed no significant differences between the azithromycin-treated group and control group (P=0.36; Table S1). The degree of between-study heterogeneity decreased slightly for exacerbations, hospitalizations, and the RRs for exacerbations per patient per year but not for SGRQ total score or drug-related adverse effects.

Figure 10 shows a funnel plot of the studies included in this meta-analysis that reported the total number of patients with one or more exacerbations. All studies showed an even distribution around the vertical axis, indicating no obvious publication bias.

Discussion

Finding a way to effectively control chronic inflammation in COPD may be a key in reducing the number of AECOPDs. Macrolides have drawn particular attention to their various functions including antimicrobial effects, anti-inflammatory effects, immune-modulating activity, and inhibitory effects on mucus secretion.[34] The GOLD 2017 report also first proposed the use of azithromycin (250 mg/day or 500 mg three times per week) or erythromycin (500 mg two times per day) for 1 year in patients prone to exacerbations.[6] Many studies have reported the use of macrolides for the prevention of AECOPDs. However, the most suitable drug, drug dose, duration of therapy, and long-term efficacy and safety remain unclear. We believe that our study has contributed valuable information in this area, which is highly needed.

This meta-analysis of 11 RCTs and one retrospective observational study including 2,151 patients comparing the efficacy and safety of long-term prophylactic macrolide treatment and controls showed that macrolide treatment significantly reduced the risk of exacerbations and improved the total SGRQ score in patients with COPD. However, we found no significant differences in AECOPD-related hospitalizations. Moreover, there was a tendency toward greater drug-related adverse effects. Although macrolide treatment for AECOPD prevention has been reported by previous meta-analyses, we sought to provide such analysis on overall large sample of patients.

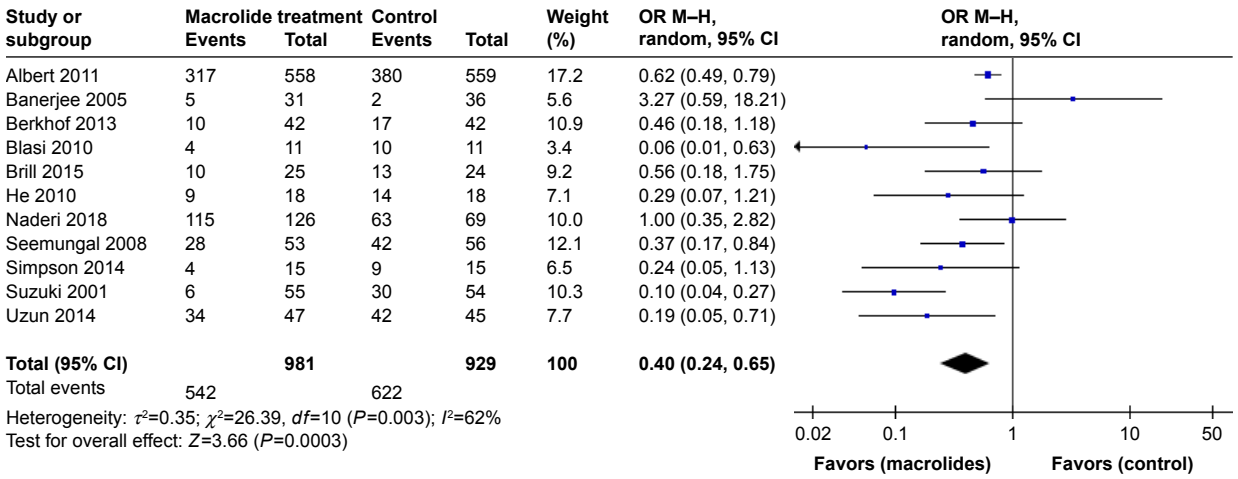
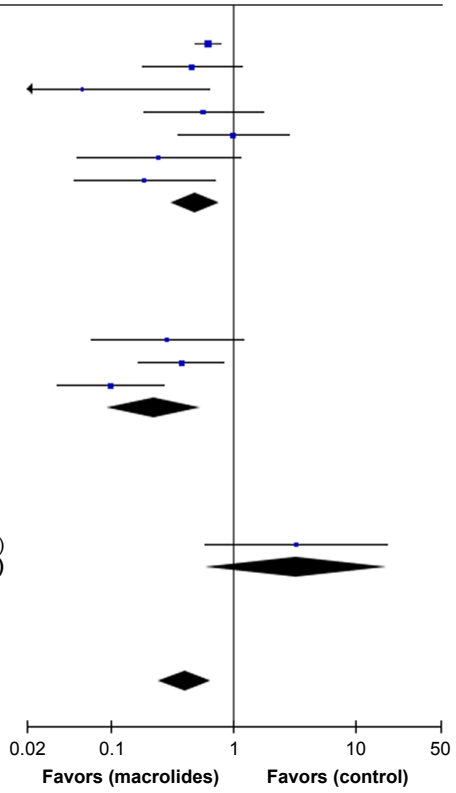


Figure 3 Forest plot and meta-analysis of the total number of patients with one or more exacerbations treated with macrolides compared with the control.
Abbreviation: M–H, Mantel–Haenszel method.

A

Study or subgroup	Macrolide treatment Events	Total	Control Events	Total	Weight (%)	OR M–H, random, 95% CI
Azithromycin						
Albert 2011	317	558	380	559	17.2	0.62 (0.49, 0.79)
Berkhof 2013	10	42	17	42	10.9	0.46 (0.18, 1.18)
Blasi 2010	4	11	10	11	3.4	0.06 (0.01, 0.63)
Brill 2015	10	25	13	24	9.2	0.56 (0.18, 1.75)
Naderi 2018	115	126	63	69	10.0	1.00 (0.35, 2.82)
Simpson 2014	4	15	9	15	6.5	0.24 (0.05, 1.13)
Uzun 2014	34	47	42	45	7.7	0.19 (0.05, 0.71)
Subtotal (95% CI)		**824**		**765**	**64.9**	**0.48 (0.31, 0.76)**
Total events	494		534			
Heterogeneity: τ^2=0.12; χ^2=9.17, *df*=6 (*P*=0.16); I^2=35%						
Test for overall effect: *Z*=3.16 (*P*=0.002)						
Erythromycin						
He 2010	9	18	14	18	7.1	0.29 (0.07, 1.21)
Seemungal 2008	28	53	42	56	12.1	0.37 (0.17, 0.84)
Suzuki 2001	6	55	30	54	10.3	0.10 (0.04, 0.27)
Subtotal (95% CI)		**126**		**128**	**29.4**	**0.22 (0.09, 0.53)**
Total events	43		86			
Heterogeneity: τ^2=0.32; χ^2=4.25, *df*=2 (*P*=0.12); I^2=53%						
Test for overall effect: *Z*=3.35 (*P*=0.0008)						
Clarithromycin						
Banerjee 2005	5	31	2	36	5.6	3.27 (0.59, 18.21)
Subtotal (95% CI)		**31**		**36**	**5.6**	**3.27 (0.59, 18.21)**
Total events	5		2			
Heterogeneity: not applicable						
Test for overall effect: *Z*=1.35 (*P*=0.18)						
Total (95% CI)		**981**		**929**	**100**	**0.40 (0.24, 0.65)**
Total events	542		622			
Heterogeneity: τ^2=0.35; χ^2=26.39, *df*=10 (*P*=0.003); I^2=62%						
Test for overall effect: *Z*=3.66 (*P*=0.0003)						
Test for subgroup differences: χ^2=7.73, *df*=2 (*P*=0.02); I^2=74.1%						



B

Study or subgroup	Macrolide treatment Events	Total	Control Events	Total	Weight (%)	Odds ratio M–H, random, 95% CI
Three-month treatment						
Banerjee 2005	5	31	2	36	5.6	3.27 (0.59, 18.21)
Berkhof 2013	10	42	17	42	10.9	0.46 (0.18, 1.18)
Brill 2015	10	25	13	24	9.2	0.56 (0.18, 1.75)
Simpson 2014	4	15	9	15	6.5	0.24 (0.05, 1.13)
Subtotal (95% CI)		**113**		**117**	**32.2**	**0.60 (0.26, 1.42)**
Total events	29		41			
Heterogeneity: τ^2=0.33; χ^2=5.37, *df*=3 (*P*=0.15); I^2=44%						
Test for overall effect: *Z*=1.16 (*P*=0.25)						
Six-month treatment						
Blasi 2010	4	11	10	11	3.4	0.06 (0.01, 0.63)
He 2010	9	18	14	18	7.1	0.29 (0.07, 1.21)
Naderi 2018	115	126	63	69	10.0	1.00 (0.35, 2.82)
Subtotal (95% CI)		**155**		**98**	**20.4**	**0.34 (0.08, 1.47)**
Total events	128		87			
Heterogeneity: τ^2=1.03; χ^2=5.44, *df*=2 (*P*=0.07); I^2=63%						
Test for overall effect: *Z*=1.44 (*P*=0.15)						
Twelve-month treatment						
Albert 2011	317	558	380	559	17.2	0.62 (0.49, 0.79)
Seemungal 2008	28	53	42	56	12.1	0.37 (0.17, 0.84)
Suzuki 2001	6	55	30	54	10.3	0.10 (0.04, 0.27)
Uzun 2014	34	47	42	45	7.7	0.19 (0.05, 0.71)
Subtotal (95% CI)		**713**		**714**	**47.3**	**0.28 (0.12, 0.68)**
Total events	385		494			
Heterogeneity: τ^2=0.59; χ^2=15.56, *df*=3 (*P*=0.001); I^2=81%						
Test for overall effect: *Z*=2.83 (*P*=0.005)						
Total (95% CI)		**981**		**929**	**100**	**0.40 (0.24, 0.65)**
Total events	542		622			
Heterogeneity: τ^2=0.35; χ^2=26.39, *df*=10 (*P*=0.003); I^2=62%						
Test for overall effect: *Z*=3.66 (*P*=0.0003)						
Test for subgroup differences: χ^2=1.52, *df*=2 (*P*=0.47); I^2=0%						

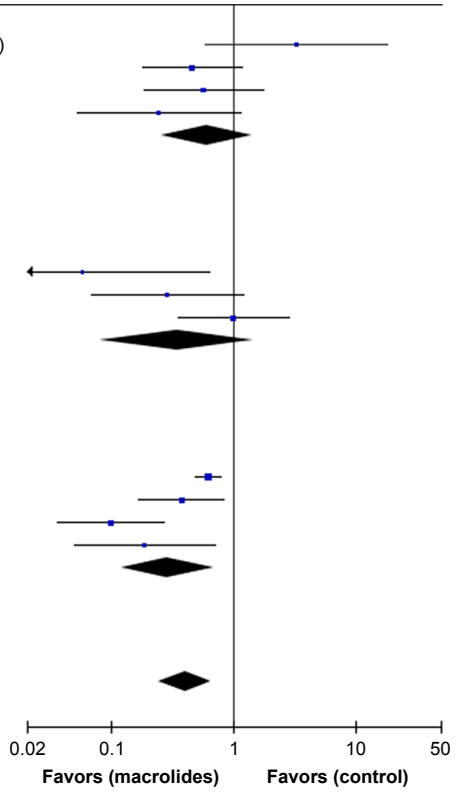


Figure 4 Forest plot and subgroup analyses of the total number of patients with one or more exacerbations treated with macrolides compared with the control: (**A**) different types of macrolides and (**B**) different durations of treatment.
Abbreviation: M–H, Mantel–Haenszel method.

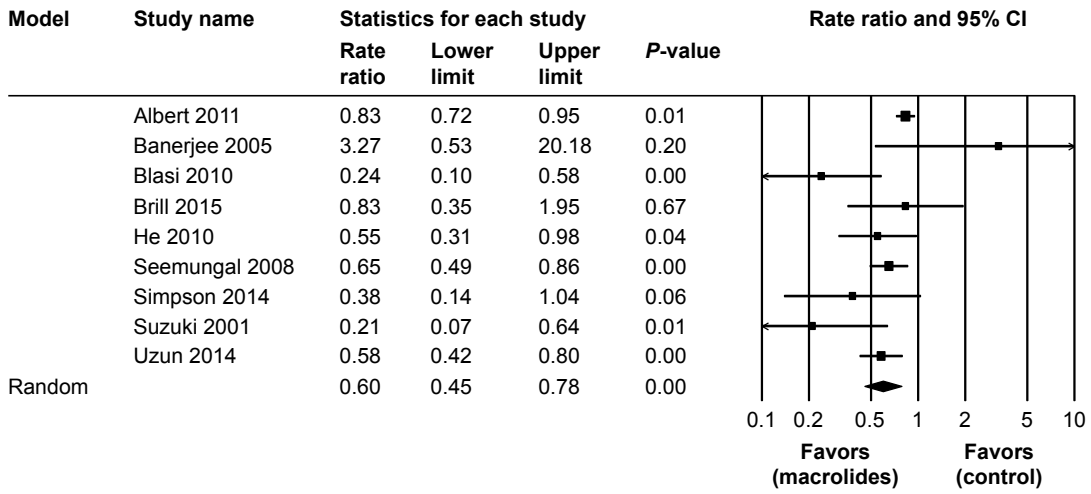


Figure 5 Forest plot and meta-analysis of risk ratios for exacerbations per patient per year treated with macrolides compared with the control.

The most common macrolides prescribed in the clinic are erythromycin, clarithromycin, and roxithromycin as 14-membered ring antibiotics and azithromycin as a 15-member compound. Recently, Huckle et al[35] concluded that the use of continuous low-dose azithromycin or erythromycin therapy was supported to improve exacerbation-related COPD outcomes, but the evidence is incomplete regarding clarithromycin and roxithromycin. In our subgroup analyses, both azithromycin and erythromycin therapy could reduce the occurrence of AECOPDs, in keeping with a previous meta-analysis.[14] Banerjee et al[23] observed no differences in clinical outcomes between the clarithromycin and placebo groups. However, this may be because of the low dose and short duration of clarithromycin treatment. There were no available data on the number of patients with exacerbations and the rate ratio of the exacerbation rate related to roxithromycin therapy.[29]

The suitable duration of macrolide treatment has not been determined. A significant improvement in the prognosis of diffuse panbronchiolitis has reportedly been attributed to the use of long-term therapy with macrolide for no less than 6 months, the effect of which is also because of anti-inflammatory and immunoregulatory effects.[36] Our study including more patients indicated that only long-term macrolide treatment for at least 12 months reduced exacerbations. Nevertheless, treatment for 6 months was also effective in the sensitivity analyses upon excluding the study by Naderi et al.[33] The authors recruited patients who were prescribed azithromycin for a minimum of 6 months,[33] and the various durations of therapy may influence the results of our analysis. This indicated a relatively long-term macrolide therapy for at least 6 months to be suitable for prevention of exacerbations in COPD patients. Moreover, Naderi et al[33] performed their study with a follow-up period of 32±22 (mean±SD) months in the azithromycin group and showed for the first time that the benefits of long-term azithromycin treatment persist beyond 1 year.

Regarding hospitalizations and the health-related quality of life, which are key variables in patients with COPD, there is no accordant conclusion among studies. In our meta-analysis, macrolide treatment did not reduce the rate of hospitalizations. It has been widely accepted that the

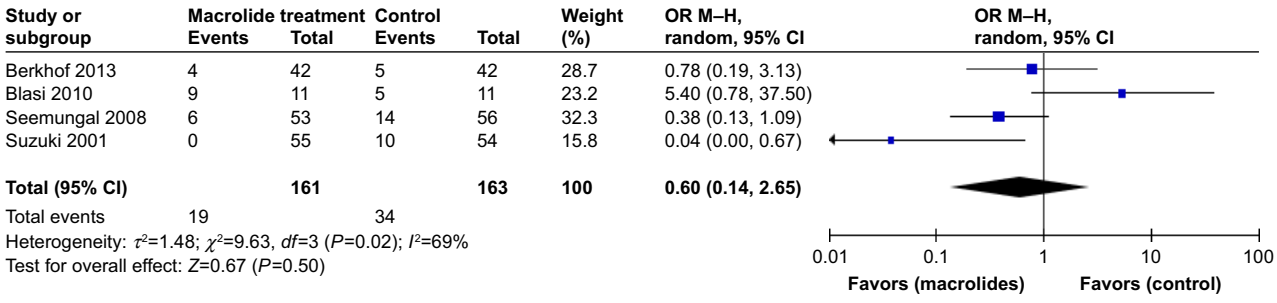


Figure 6 Forest plot and meta-analysis of the total number of patients requiring hospitalization treated with macrolides compared with the control.
Abbreviation: M–H, Mantel–Haenszel method.

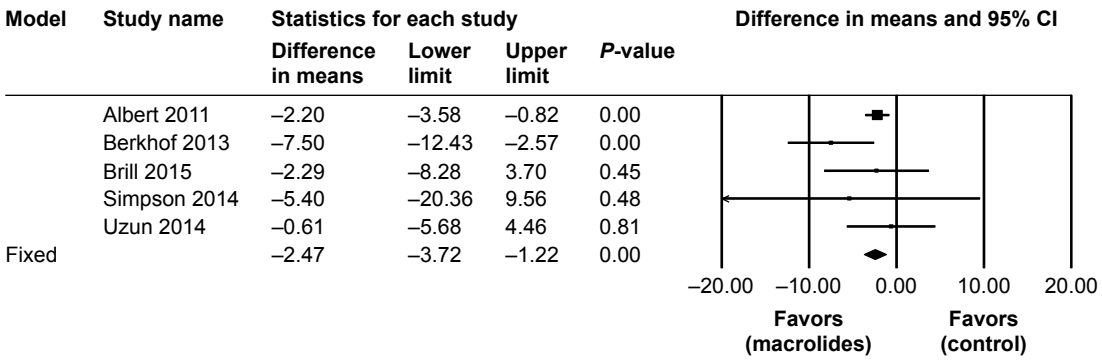


Figure 7 Forest plot and meta-analysis of the mean differences in change in total SGRQ score among patients treated with macrolides compared with the control.
Abbreviation: SGRQ, St George Respiratory Questionnaire.

minimum clinically important difference (MCID) in the SGRQ score was –4 units.[37] Although our study showed an improvement of SGRQ in the treatment group, this change did not exceed the MCID of at least 4 units. Researchers have proposed that the greatest differences between frequent and infrequent exacerbators in the SGRQ are in the symptoms scale.[38] Furthermore, Uzun et al[32] reported that although azithromycin did not improve SGRQ, it had a clinically and statistically significant average treatment effect in the symptom component score of SGRQ. The improvement of SGRQ in our analysis might be attributable to the reduction in exacerbations.

There were still some other relevant aspects of treatment with macrolides, which we did not analyze due to the limited reported data. The positioning of macrolides in addition to usual care should be considered. As recommended by most guidelines, long-acting bronchodilators or ICS are commonly used to treat stable COPD. Some studies reported that macrolide treatment could reduce the exacerbation frequency and overcome any effect of ICS.[28,32] Another crucial issue is to identify patients who benefit most from macrolide therapy. A post hoc analysis showed that greater efficacy was seen in older patients and milder GOLD stages, while treatment was less beneficial in active smokers.[39] In *New England Journal of Medicine*, Wenzel et al[40] suggested that long-term azithromycin prophylaxis should be considered in patients with a history of COPD with ≥2 acute exacerbations in the previous year. In addition, the appropriate treatment regimen remains unknown, although studies involving patients with cystic fibrosis and bronchiectasis recommended an intermittent regimen of three times per week, and it was reported that daily dosing might lead to more side effects of azithromycin.[41] Further studies are still required to address these inconsistencies among results.

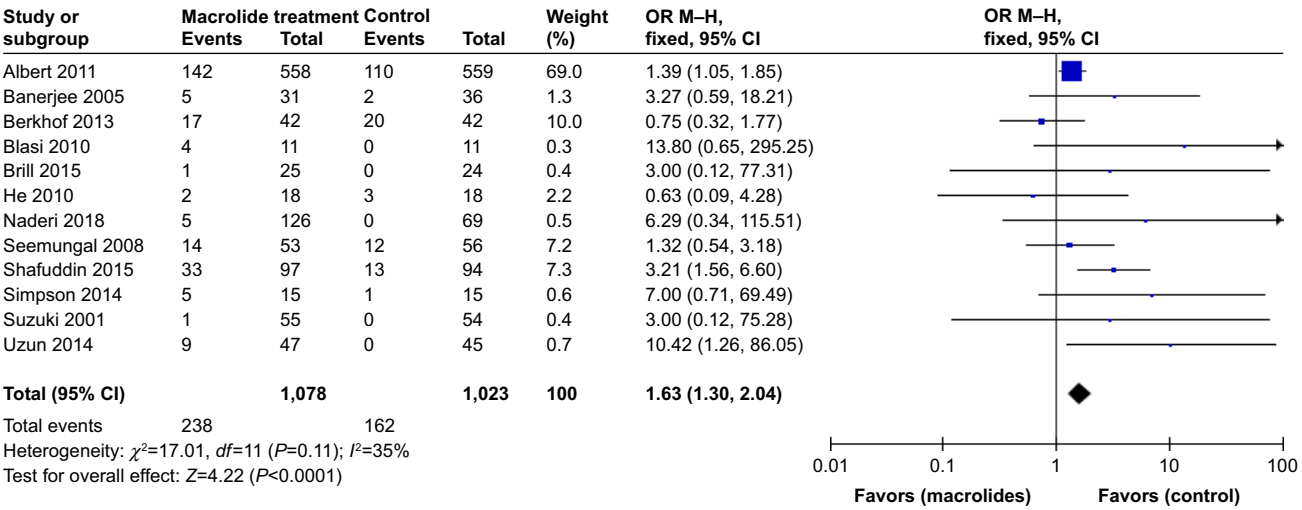


Figure 8 Forest plot and meta-analysis of the total number of patients who experienced adverse events during follow-up after treatment with macrolides compared with the control.
Abbreviation: M–H, Mantel–Haenszel method.

It has been recognized that long-term macrolide treatment is related to various adverse effects. In our study, azithromycin therapy was more likely to be associated with side effects, but the sensitivity analyses showed no significant difference. The heterogeneity of the excluded study by Albert et al[22] with a disproportionate number of patients and hearing impairment as its main outcome measures may explain the absence of a significant difference in the sensitivity analyses. As for nonfatal drug-related adverse events caused by erythromycin, clarithromycin, and roxithromycin treatment, the power of the subgroup analyses might be restricted because of the limited study number and population size. In addition, macrolide treatment for 3 or 12 months increased the risk of adverse effects, but not treatment for 6 months. These may be attributed to early individual intolerance with 3 months of treatment and the effect of cumulative drug and antibiotic resistance with 12 months of treatment. The sensitivity analyses further confirmed the accuracy and validity of the results.

The common adverse effects include gastrointestinal reactions, impairment of liver function, and hearing impairment.[22,32] Cardiovascular toxic effects including QT interval prolongation are potentially important adverse events that should be considered. An observational retrospective study revealed an increased risk of cardiovascular death within 5 days of azithromycin therapy compared with amoxicillin or ciprofloxacin therapy.[42] Another large retrospective cohort study found a small but significant increase in the odds of myocardial infarction observed in patients receiving azithromycin therapy.[43] As a result, it is recommended to monitor QT interval, aminotransferase levels, and hearing impairment.[40] Furthermore, antimicrobial resistance is a great concern in community populations.[44] Albert et al[22] reported that patients receiving azithromycin are less likely to become colonized

A

Study or subgroup	Macrolide treatment Events	Total	Control Events	Total	Weight (%)	OR M–H, fixed, 95% CI
Azithromycin						
Albert 2011	142	558	110	559	69.0	1.39 (1.05, 1.85)
Berkhof 2013	17	42	20	42	10.0	0.75 (0.32, 1.77)
Blasi 2010	4	11	0	11	0.3	13.80 (0.65, 295.25)
Brill 2015	1	25	0	24	0.4	3.00 (0.12, 77.31)
Naderi 2018	5	126	0	69	0.5	6.29 (0.34, 115.51)
Simpson 2014	5	15	1	15	0.6	7.00 (0.71, 69.49)
Uzun 2014	9	47	1	45	0.7	10.42 (1.26, 86.05)
Subtotal (95% CI)		**824**		**765**	**81.5**	**1.51 (1.17, 1.95)**
Total events	183		132			
Heterogeneity: χ^2=10.88, *df*=6 (*P*=0.09); I^2=45%						
Test for overall effect: *Z*=3.15 (*P*=0.002)						
Erythromycin						
He 2010	2	18	3	18	2.2	0.63 (0.09, 4.28)
Seemungal 2008	14	53	12	56	7.2	1.32 (0.54, 3.18)
Suzuki 2001	1	55	0	54	0.4	3.00 (0.12, 75.28)
Subtotal (95% CI)		**126**		**128**	**9.9**	**1.23 (0.57, 2.65)**
Total events	17		15			
Heterogeneity: χ^2=0.79, *df*=2 (*P*=0.67); I^2=0%						
Test for overall effect: *Z*=0.53 (*P*=0.60)						
Clarithromycin						
Banerjee 2005	5	31	2	36	1.3	3.27 (0.59, 18.21)
Subtotal (95% CI)		**31**		**36**	**1.3**	**3.27 (0.59, 18.21)**
Total events	5		2			
Heterogeneity: not applicable						
Test for overall effect: *Z*=1.35 (*P*=0.18)						
Roxithromycin						
Shafuddin 2015	33	97	13	94	7.3	3.21 (1.56, 6.60)
Subtotal (95% CI)		**97**		**94**	**7.3**	**3.21 (1.56, 6.60)**
Total events	33		13			
Heterogeneity: not applicable						
Test for overall effect: *Z*=3.17 (*P*=0.002)						
Total (95% CI)		**1,078**		**1,023**	**100**	**1.63 (1.30, 2.04)**
Total events	238		162			
Heterogeneity: χ^2=17.01, *df*=11 (*P*=0.11); I^2=35%						
Test for overall effect: *Z*=4.22 (*P*<0.0001)						
Test for subgroup differences: χ^2=4.90, *df*=3 (*P*=0.18); I^2=38.8%						

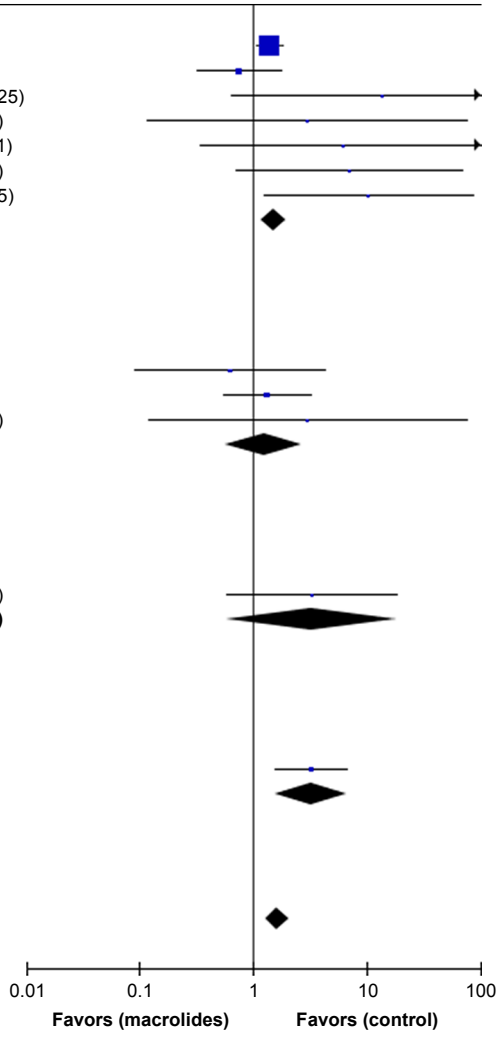


Figure 9 (*Continued*)

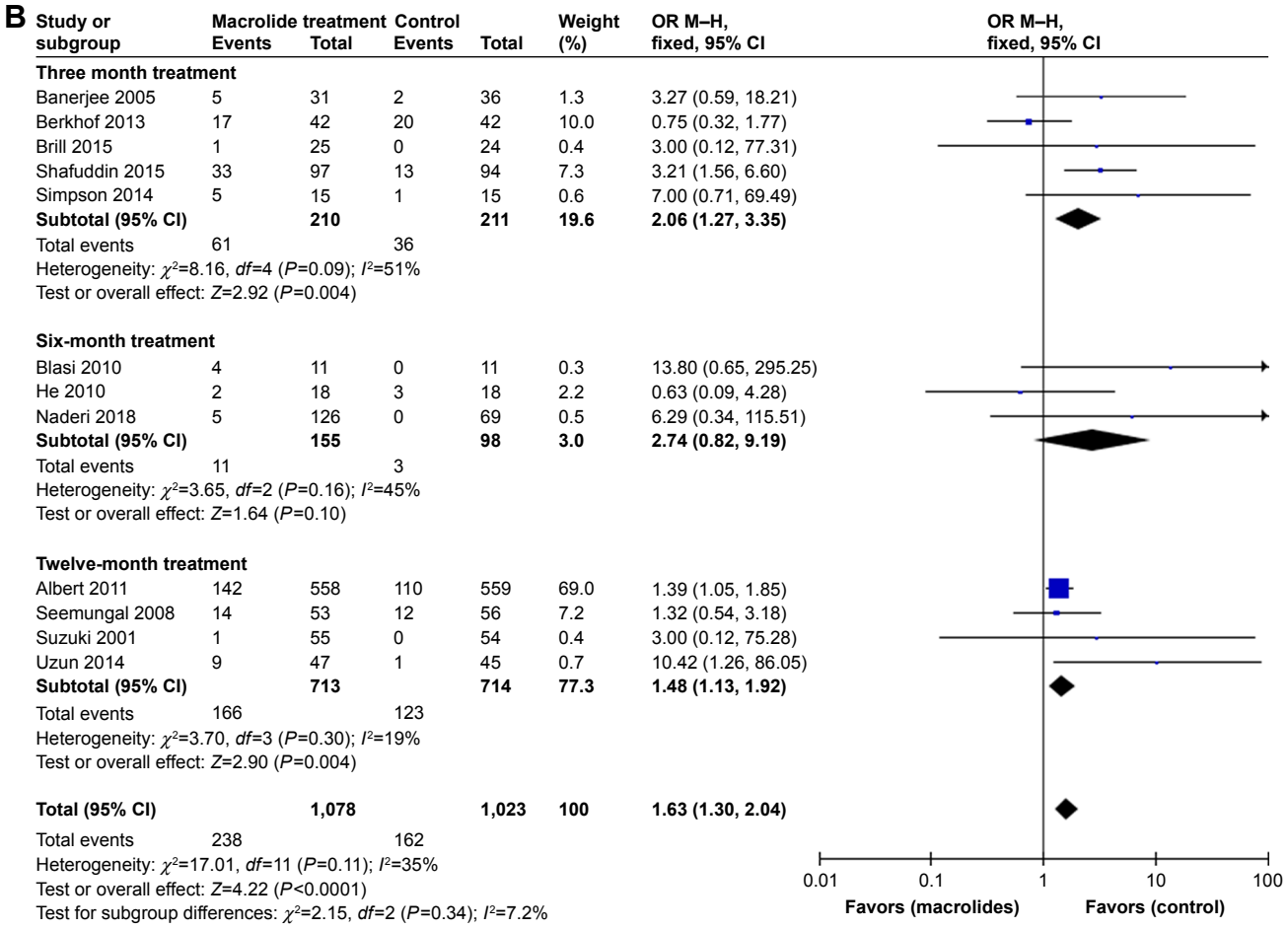


Figure 9 Forest plot and subgroup analyses of the total number of patients who experienced adverse events during follow-up after treatment with macrolides compared with the control: (**A**) different types of macrolides and (**B**) different durations of treatment.
Abbreviation: M–H, Mantel–Haenszel method.

with respiratory pathogens but are twice as likely to become colonized with macrolide-resistant organisms than control individuals. To overcome the potential effect of antimicrobial resistance of traditional long-term macrolide therapy, some novel macrolides, with anti-inflammatory and immunomodulating effects but without antibiotic effects, have the potential to become the drugs of choice.[45,46]

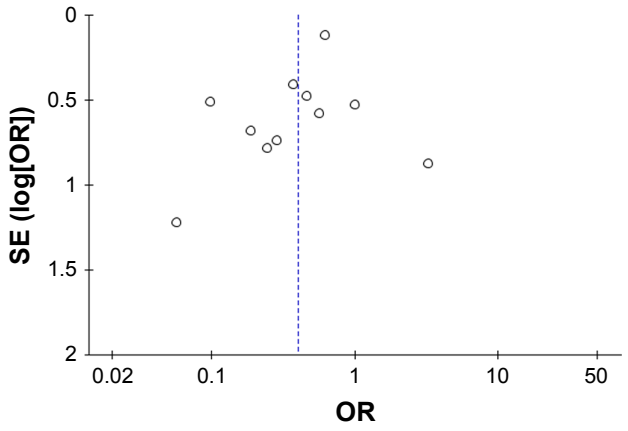


Figure 10 Funnel plots illustrating meta-analysis of the total number of patients with one or more exacerbations after treatment with macrolides compared with the control.
Abbreviation: SE, standard error.

The present meta-analysis has some limitations. First, some of the included studies were published several years ago, and there was only one retrospective observational study included. However, this meta-analysis was conducted at an appropriate time, because the GOLD 2017 report recommended the long-term macrolide treatment for the prevention of AECOPDs for the first time and the treatment duration and drug-related adverse events remain controversial. It is important to urgently accumulate more relevant evidence. Besides, the retrospective study included in our meta-analysis was valuable, because it was the only one that was newly published in 2018 with a follow-up period of more than 1 year. Hence, we provide the most up-to-date information in this area. Second, there were limited data providing the rates and dichotomous and continuous variables needed in our meta-analysis. We then used both Review Manager 5.3 and Comprehensive Meta-Analysis V2.2 to conduct the analysis.

Third, the included studies had different inclusion criteria, types of macrolides, and treatment durations. We applied subgroup and sensitivity analyses to minimize the heterogeneity. Fourth, the drug dosage, treatment regimen, and concomitant drugs (±ICS) were not considered in the statistical analyses; this may have reduced the reliability of our results. Fifth, the limited number of studies and sample size for certain subgroup analyses restricts the power of our analysis. Sixth, there were no data showing the efficacy or safety of chronic azithromycin treatment beyond 1 year except the retrospective study. Finally, the side effects of long-term macrolide therapy were varied and changed over time. We did not perform further analysis on the specific adverse events.

Conclusion

Prophylactic azithromycin or erythromycin treatment has a significant effect in reducing the frequency of AECOPD in a time-dependent manner. However, long-term macrolide treatment could increase the occurrence of adverse events and macrolide resistance. We suggest that macrolides should be carefully used as maintenance therapy in COPD patients with frequent exacerbations in the previous year despite optimal therapy. Future large-scale, well-designed RCTs with extensive follow-up would be required to confirm and update the findings of this analysis.

Acknowledgment

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Author contributions

Yanan Cui, Yan Chen, and Ping Chen conceived and designed the experiments. Yanan Cui, Lijuan Luo, and Chenbei Li were responsible for acquisition of data. Yanan Cui analyzed the data and wrote the paper. All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Study or subgroup	Macrolide treatment Events	Total	Control Events	Total	Weight (%)	OR M–H, random, 95% CI
Albert 2011	317	558	380	559	0.0	0.62 (0.49, 0.79)
Banerjee 2005	5	31	2	36	8.3	3.27 (0.59, 18.21)
Berkhof 2013	10	42	17	42	15.5	0.46 (0.18, 1.18)
Blasi 2010	4	11	10	11	0.0	0.06 (0.01, 0.63)
Brill 2015	10	25	13	24	13.3	0.56 (0.18, 1.75)
He 2010	9	18	14	18	10.3	0.29 (0.07, 1.21)
Naderi 2018	115	126	63	69	0.0	1.00 (0.35, 2.82)
Seemungal 2008	28	53	42	56	17.2	0.37 (0.17, 0.84)
Simpson 2014	4	15	9	15	9.5	0.24 (0.05, 1.13)
Suzuki 2001	6	55	30	54	14.7	0.10 (0.04, 0.27)
Uzun 2014	34	47	42	45	11.2	0.19 (0.05, 0.71)
Total (95% CI)		**286**		**290**	**100**	**0.35 (0.19, 0.63)**
Total events	106		169			

Heterogeneity: τ^2=0.39; χ^2=14.79, *df*=7 (*P*=0.04); I^2=53%
Test for overall effect: *Z*=3.44 (*P*=0.0006)

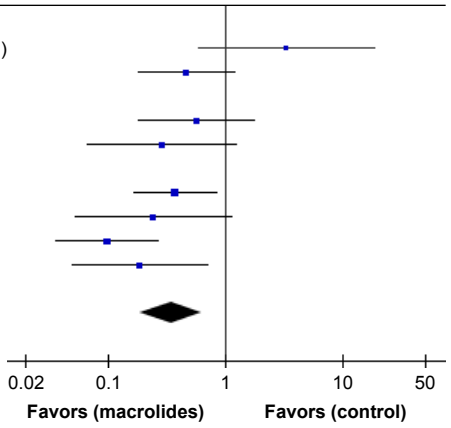

Figure S1 Sensitivity analyses of the total number of patients with one or more exacerbations treated with macrolides compared with the control.
Abbreviation: M–H, Mantel–Haenszel method.

Model	Study name	Statistics for each study: Rate ratio	Lower limit	Upper limit	*P*-value
	Banerjee 2005	3.27	0.53	20.18	0.20
	Brill 2015	0.83	0.35	1.95	0.67
	He 2010	0.55	0.31	0.98	0.04
	Seemungal 2008	0.65	0.49	0.86	0.00
	Simpson 2014	0.38	0.14	1.04	0.06
	Suzuki 2001	0.21	0.07	0.64	0.01
	Uzun 2014	0.58	0.42	0.80	0.00
Fixed		0.60	0.50	0.72	0.00

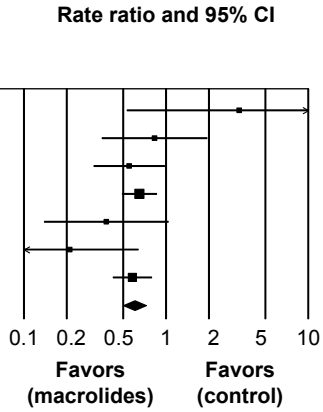

Figure S2 Sensitivity analyses of risk ratios for exacerbations per patient per year treated with macrolides compared with the control.

Study or subgroup	Macrolide treatment Events	Total	Control Events	Total	Weight (%)	OR M–H, random, 95% CI
Berkhof 2013	4	42	5	42	37.7	0.78 (0.19, 3.13)
Blasi 2010	9	11	5	11	0.0	5.40 (0.78, 37.50)
Seemungal 2008	6	53	14	56	47.3	0.38 (0.13, 1.09)
Suzuki 2001	0	55	10	54	15.0	0.04 (0.00, 0.67)
Total (95% CI)		**150**		**152**	**100**	**0.35 (0.10, 1.24)**
Total events	10		29			

Heterogeneity: τ^2=0.57; χ^2=3.84, *df*=2 (*P*=0.15); I^2=48%
Test for overall effect: *Z*=1.63 (*P*=0.10)

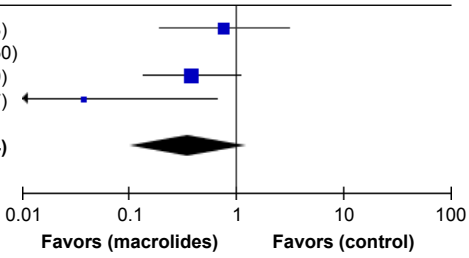

Figure S3 Sensitivity analyses of the total number of patients requiring hospitalization treated with macrolides compared with the control.
Abbreviation: M–H, Mantel–Haenszel method.

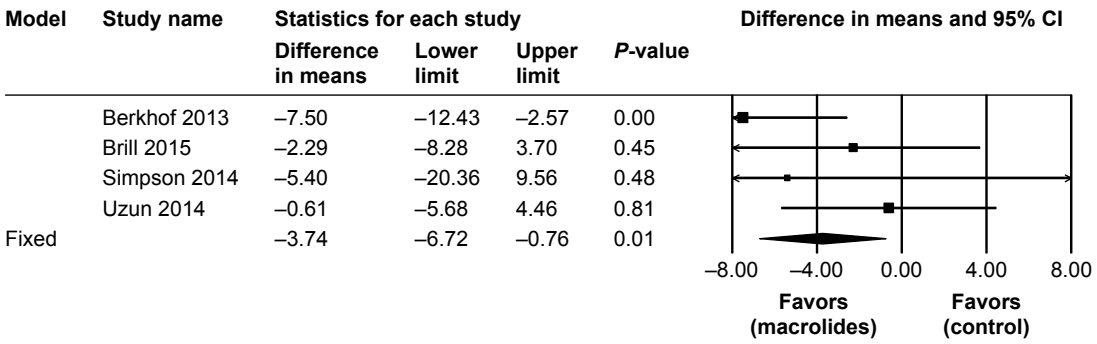

Figure S4 Sensitivity analyses of the mean differences with respect to change in total SGRQ score among patients treated with macrolides compared with the control.
Abbreviation: SGRQ, St George Respiratory Questionnaire.

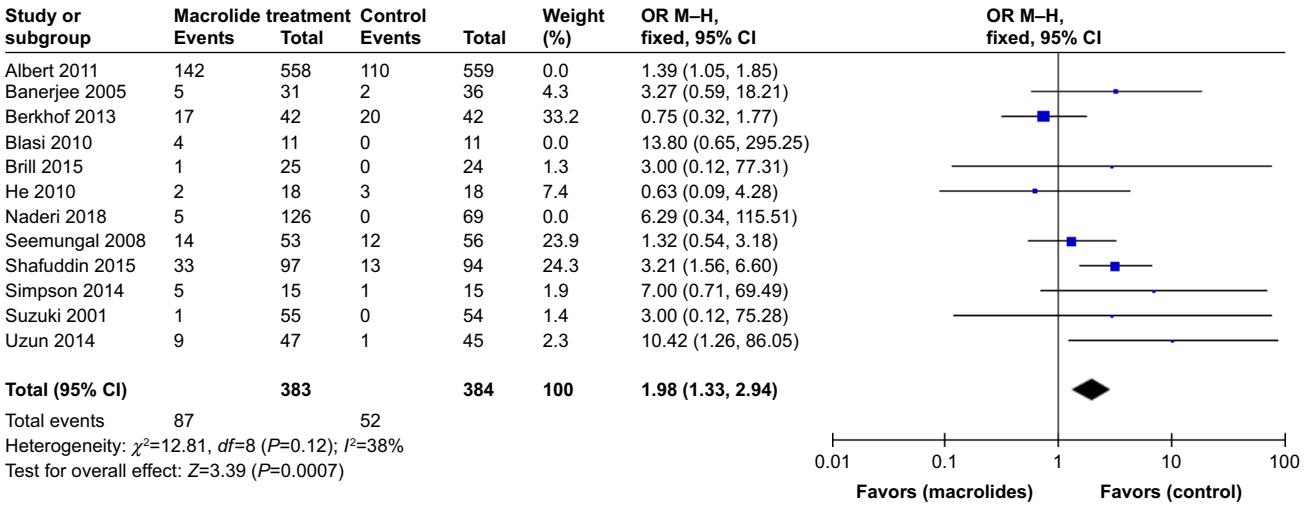

Figure S5 Sensitivity analyses of the total number of patients who experienced adverse events during follow-up after treatment with macrolides compared with the control.
Abbreviation: M–H, Mantel–Haenszel method.

Table S1 Sensitivity analyses of subgroup based on the number of patients with exacerbations and adverse effects

	Number of patients with exacerbations			Adverse effects		
	Studies (n)	OR (95% CI)	*P*-value	Studies (n)	OR (95% CI)	*P*-value
Azithromycin	4	0.37 (0.21–0.67)	0.001	4	1.38 (0.69–2.78)	0.36
Erythromycin	3	0.22 (0.09–0.53)	0.0008	3	1.23 (0.57–2.65)	0.6
Clarithromycin	1	3.27 (0.59–18.21)	0.18	1	3.27 (0.59–18.21)	0.18
Roxithromycin	0	NA	NA	1	3.21 (1.56–6.60)	0.002
Three-month treatment	4	0.60 (0.26–1.42)	0.25	5	2.06 (1.27–3.35)	0.004
Six-month treatment	2	0.17 (0.04–0.75)	0.02	2	2.01 (0.51–7.86)	0.32
Twelve-month treatment	3	0.20 (0.08–0.47)	0.0002	3	2.16 (1.03–4.53)	0.04

Abbreviation: NA, data not available.