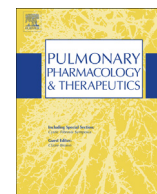




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Macrolide antibiotics for treatment of asthma in adults: A meta-analysis of 18 randomized controlled clinical studies

Xiang Tong^a, Tingting Guo^b, Sitong Liu^a, Shifeng Peng^a, Zhipeng Yan^a, Xin Yang^a, Yonggang Zhang^{c,*}, Hong Fan^{a,**}^a Department of Respiratory Medicine and Critical Care Medicine, West China School of Medicine/West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China^b The Second Affiliated Hospital of Chongqing Medical University, Chongqing 404100, China^c The Periodical Press of West China Hospital, Sichuan University, Chengdu, Sichuan 610041, China

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ABSTRACT

Mounting studies have been showed that long-term macrolides used in patients with asthma could improve the lung function and symptoms. However, a large number of studies have reported inconclusive results. The aim of this meta-analysis was to investigate the effect of macrolide antibiotics in patients with asthma. We have performed a search in PubMed, Embase, China National Knowledge Internet (CNKI), and Wanfang databases. The weighed mean difference (WMD) or standardized mean difference (SMD) was used to evaluate the pooled effect. Statistical analysis was performed by STATA 11.0 software. Totally 1306 patients were included in the meta-analysis. The overall results indicated that statistically significance of long-term macrolides therapy in patients with asthma on forced expiratory volume in 1 s (FEV1) (WMD: 0.11, $P < 0.01$), peak expiratory flow (PEF) (SMD: 0.25, $P = 0.001$), airway hyper-responsiveness (AHR) (SMD: 0.90, $P = 0.04$), forced vital capacity (FVC) (WMD: 0.18, $P = 0.05$) and FEV1/FVC (WMD: 1.93, $P < 0.001$), but no statistically significance on FEV1/predict, FVC/predict, symptom scores, quality of life scores (QOL), reliever inhaler puffs per 24 h, and cell counts in sputum and blood. The subgroup analysis indicated macrolides could increase FEV1 and PEF in Caucasian and Asian, decrease AHR in Caucasian, while cells counts of sputum improvement among Asian. Therefore, the study suggested that long-term macrolides therapy in asthma may improved the FEV1, PEF, AHR, FVC, FEV1/FVC and cells counts in sputum, but it can't improve other lung function (FEV1/predict and FVC/predict) and clinical outcomes (such as symptom, quality of life etc.).

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1. Introduction

Asthma is characterized by chronic airway inflammation and airway hyper-responsiveness (AHR), and always considered a heterogeneous disease [1]. The symptoms of asthma mainly include wheeze, chest tightness, shortness of breath, and cough with variable expiratory airflow limitation [2]. It is estimated that 1–18% of population has been influenced on the asthma in different countries [2]. In 2004, Global Initiative for Asthma (GINA) program reported that there were almost 300 million people currently having asthma in the worldwide [3]. Recent years, although lots of drugs including inhaled corticosteroids (ICS), long acting β -agonist (LABA), and theophylline could effectively managed the asthma, there is still a high morbidity and mortality of asthma [3]. It is considered that asthma accounts for about 1 per 250 deaths in the world, and there may be an additional 100 million people with asthma by 2025 [3].

Abbreviations: CNKI, China national knowledge internet; WMD, weighed mean difference; SMD, standardized mean difference; PEF, peak expiratory flow; AHR, airway hyper-responsiveness; FEV1/FVC, the ratio of forced expiratory volume in 1 s and forced vital capacity; GINA, global initiative for asthma; ICS, inhaled corticosteroids; LABA, long acting β -agonist; CAP, community acquired pneumonia; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis; SD, standard deviation; CI, confidence interval; QOL, quality of life; LTRA, leukotriene receptor antagonist.

* Corresponding author. The Periodical Press of West China Hospital, Sichuan University, Guoxuexiang 37, Chengdu, Sichuan 610041, China. Tel./fax: +86 28 85422052.

** Corresponding author. Department of Respiratory Medicine, West China Hospital of Sichuan University, Guoxuexiang 37, Chengdu, Sichuan 610041, China. Tel./fax: +86 028 85423520.

E-mail addresses: yonggang-zhang@sohu.com (Y. Zhang), fanhongfanscu@sina.cn (H. Fan).

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Macrolide antibiotics are often used as the first-line drugs in the treatment of acute respiratory tract infection, such as acute bronchitis and community acquired pneumonia (CAP) [4]. In addition to direct anti-microbial activity, increasing evidences have indicated that macrolides also have immune modulatory and anti-inflammatory effects [5,6]. In the previous studies, many patients with chronic respiratory diseases have gained benefits from long-term macrolides therapy (more than 3weeks), such as the chronic obstructive pulmonary disease (COPD) [7,8], bronchiectasis [9,10] and cystic fibrosis (CF) [11]. Furthermore, lots of studies also have focused on the efficacy of long-term macrolide used in patients with asthma in recent decades. Simpson et al. reported a reduction in wheeze and significant improvements in asthma quality of life (QOL) scores in refractory asthma patients [12]. After therapy with clarithromycin for 8 weeks, a significant reduction on AHR in patients with asthma was found by Kostadima and co-workers, however there was no significant increase on the forced expiratory volume in 1 s (FEV1) [13]. Besides, a study conducted by Cameron et al. indicated that there was no improvement in FEV1, symptoms control and peak expiratory flow (PEF) when prolonged macrolides administration in patients with asthma [14].

Since the results of previous studies are inconclusive, and a small sample sizes of each study may lack the power to provide precise conclusions, we performed a meta-analysis to investigate whether long-term macrolides used in patients with asthma can improve the asthma symptoms, quality-of-life and increased the clinical or laboratory outcomes, such as lung function, and cell counts of sputum etc. To our knowledge, this is most comprehensive meta-analysis to assess the effect of prolonged treatment with macrolide antibiotics in patients with asthma.

2. Materials and methods

2.1. Study selection

Two reviews (Xiang Tong and Tingting Guo) performed a comprehensive search about long-term macrolides used to treat asthma in PubMed, Embase, China National Knowledge Internet (CNKI), and Wanfang databases, with last updated search being conducted in May, 2014. The searching words used were as follows: 'macrolides', 'macrolide antibiotics', 'azithromycin', 'roxithromycin',

'clarithromycin', 'telithromycin', 'erythromycin' and 'asthma' or 'wheeze'. There was no language restriction. The following inclusive criteria were used: 1) the study should be designed as a randomized-controlled study; 2) the study should be to evaluated efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma; 3) the study should be provided available data for extracted or calculated the mean, standard deviation (SD), *P* value and 95% confidence interval (CI); 4) the studies should be focused on human subjects; 5) the methodology quality assessment used by Jadad score (5-points) in each study should be equal or more than two. The following exclusive items were used: 1) the study was not designed as a randomized-controlled study; 2) the participants of study included children; 3) the study is only abstracts, reviews or overlapping study; 4) the study have insufficient data for extracting or calculating the pooled results; 5) the Jadad score (5-point) was less than two.

2.2. Data extraction

According to the inclusive items, the information of studies was independently collected by two reviewers (Xiang Tong and Tingting Guo). If there is a disagreement, a third author (Sitong Liu) could assess those articles again. For each study, first author, publication year, country, ethnicity, mean age of participant, sample size of experimental and placebo group, asthma type, macrolides type, each dose and daily frequency of macrolides, duration of therapy, and end-point outcomes. These information was summarized in Tables 1 and 2.

2.3. Statistical analysis

The meta-analysis was performed by the STATA 11.0 software (STATA Corporation, Texas State, USA, <http://www.stata.com/>). Weighed mean difference (WMD) or standardized mean difference (SMD) was used to measure the efficacy of long-term macrolides therapy in patients with asthma. The SMD was performed when studies reported different scales or units of outcomes; otherwise, the WMD would be applied. Heterogeneity of the studies was assessed by the χ^2 -based *Q* statistic and *I*-squared (*I*²) test. It was considered that studies lacked the significant heterogeneity when *P* > 0.10 for the χ^2 test and *I*² < 50%, thus the WMD or SMD was

Table 1
Characteristics of included studies in the present meta-analysis.

First author	Year	Country	Ethnicity	Age	Sample size	Asthma type	Jadad score
				Experiment/placebo			
Amayasu H	2000	Japan	Asian	NA ^a	17/17	Adult	3
Black PN	2001	Muti-center ^b	Caucasian	40 ± 11.6/42 ± 11.9	105/114	Adult	4
Brusselle GG	2013	Belgium	Caucasian	53/53	53/49	Adult	5
Cameron EJ	2013	England	Caucasian	46.4 ± 8.8/42.8 ± 9.4	38/39	Adult	3
Hahn DL	2012	America	Caucasian	45.7 ± 15.5/47.1 ± 14.2	23/32	Adult	5
Hahn DL	2006	America	Caucasian	50 ± 14/45 ± 12	19/17	Adult	5
He J	2009	China	Asian	35 ± 7.3/34 ± 5.6	20/20	Adult	2
Kostadima E(BID)	2004	Greece	Caucasian	48 ± 16/41 ± 16	22/21	Adult	4
Kostadima E(TID)	2004	Greece	Caucasian	42 ± 12/41 ± 16	20/21	Adult	4
Kraft M	2002	England	Caucasian	NA	26/26	Adult	3
Shoji T	1999	Japan	Asian	NA	14/14	Adult	3
Simpson JL	2008	Australia	Caucasian	60/55	23/22	Adult	5
Sutherland E	2010	America	Caucasian	NA	41/39	Adult	4
Wang T	2014	China	Asian	28.44 ± 15.98/29.56 ± 14.21	29/29	Adult	2
Wang Y	2012	China	Asian	NA	23/22	Adult	3
Xiao KA	2013	China	Asian	34.5 ± 7.2/33.7 ± 8.3	106/104	Adult	2
Yan XQ	2008	China	Asian	38 ± 12/39 ± 12	20/20	Adult	3
Zhang LY	2013	China	Asian	NA	30/30	Adult	2

^a Not available.

^b Muti-center: Australia, New Zealand, Italy, and Argentina.

Table 2

Characteristics and outcomes of included studies in the present meta-analysis.

First author	Year	Antibiotic and dose	Duration of therapy	Outcomes
Amayasu H	2000	Clarithromycin 200 mg BID	8Wks ^a	FEV1, FVC, FVC/pre, Cell counts, Symptom
Black PN	2001	Roxithromycin 150 mg BID	6Wks	PEF
Brusselle GG	2013	Azithromycin 250 mg QD × 5D ^b + 250 mg QIW × 25Wks	26Wks	FEV1/pre, PEF, Reliever inhaler puffs/24 h, QOL scores, Symptom
Cameron EJ	2013	Azithromycin 250 mg QD	12Wks	FEV1, AHR, PEF, Reliever inhaler puffs/24 h, QOL scores, Cell counts, Symptom
Hahn DL	2012	Azithromycin 600 mg QD × 3D+600 mg QW × 11Wks	12Wks	QOL scores, Symptom
Hahn DL	2006	Azithromycin 600 mg QD × 3D+600 mg QW × 5Wks	6Wks	Reliever inhaler puffs/24 h, QOL scores, Symptom
He J	2009	Azithromycin 250 mg BIW	12Wks	FEV1, FEV1/FVC, Symptom
Kostadima E(BID)	2004	Clarithromycin 250 mg BID	8Wks	FEV1/pre, AHR, FVC/pre, FEV1/FVC
Kostadima E(TID)	2004	Clarithromycin 250 mg TID	8Wks	FEV1/pre, AHR, FVC/pre, FEV1/FVC
Kraft M	2002	Clarithromycin 500 mg BID	6Wks	FEV1
Shoji T	1999	Roxithromycin 150 mg BID	8Wks	AHR, FEV1, FVC, Cell counts, Symptom
Simpson JL	2008	Clarithromycin 500 mg BID	8Wks	FEV1/pre, QOL scores, Cell counts, Symptom
Sutherland E	2010	Clarithromycin 500 mg BID	16Wks	FEV1/pre, AHR, FEV1, PEF, Reliever inhaler puffs/24 h, QOL scores, Symptom
Wang T	2014	Azithromycin 250 mg BIW	12M ^c	FEV1, PEF
Wang Y	2012	Clarithromycin 500 mg BID	8Wks	FEV1/pre, Cell counts, Symptom
Xiao KA	2013	Roxithromycin 150 mg BID	12Wks	FEV1, FVC, PEF
Yan XQ	2008	Roxithromycin 150 mg BID	4Wks	FEV1/pre, FEV1, PEF, Cell counts, Symptom
Zhang LY	2013	Azithromycin 100 mg QD	60D	FEV1/pre

^a weeks.^b day.^c month.

estimated by fixed-effects model; if not, the random-effect model would be used. In addition, to evaluate the ethnicity-specific effects, we performed a subgroup analysis by ethnicity group. Publication bias was assessed by several methods. Visual inspection of asymmetry in Begg's funnel plot was carried out. Furthermore, Egger's liner regression test was conducted to assess the publication bias, too.

3. Results

3.1. Study characteristics

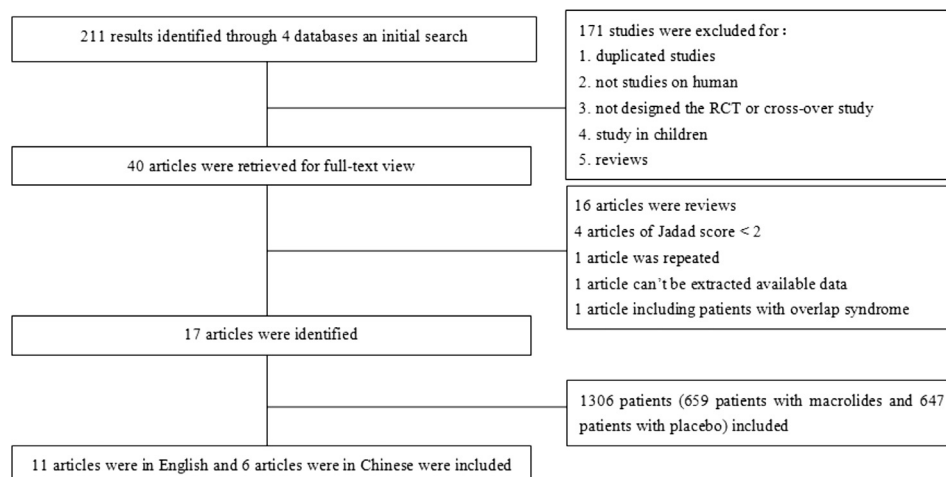
All 211 articles are meeting the search strategies after we initially searched in PubMed, Embase, CNKI, and Wanfang databases (Fig. 1). 171 articles were excluded because they are not meeting the inclusive criteria when we read the titles or abstracts. The remained 40 articles were identified for full-text view. Sixteen articles were removed since they were reviews, one of them was

excluded because it was repeated, four articles were eliminated for the Jadad score less than two, one article haven't provided sufficient data to further calculate, and one article was excluded because the patients with overlap syndrome (asthma and COPD) were included in this study. Finally, 18 studies of 17 articles [12–28] including 1306 patients (659 patients with macrolides and 647 patients with placebo) were included in the current meta-analysis. Among the 17 articles, 11 papers were in English [12–22] and 6 articles were in Chinese [23–28]. The characteristics of selected studies are summarized in Table 1.

3.2. Meta-analysis results

3.2.1. FEV1

In total, 619 participants from 9 articles were collected [14,15,18,19,21,23,25,26,28]. The χ^2 and I^2 test's results indicated it is a low heterogeneity ($I^2 = 5.6\%$, $P < 0.39$), so we used fixed-model to assess the WMD. We found the pooled effect of prolonged

**Fig. 1.** The flow diagram of included and excluded studies.

macrolide antibiotics administration in asthma on FEV1 was significant (WMD: 0.11, 95%CI: 0.06 – 0.16, $P < 0.01$) (Fig. 2). Furthermore, in the subgroup analysis by ethnicity, the results suggested statistical significance of long-term macrolides treatment in Caucasian (WMD: 0.11, 95%CI: 0.04–0.18, $P = 0.003$) and among Asian patients (WMD: 0.11, 95%CI: 0.04 – 0.18, $P = 0.002$). No publication bias was found in Begg's funnel plot or Egger's test ($P = 0.84$).

3.2.2. FEV1% predict

In this part, we collected 8 studies (435 patients) from 7 articles [12,13,17,21,24,26,27]. We performed a random-effect model to synthesize the data ($I^2 = 65.0\%$). Overall, the result indicated no significant on the FEV1% predict (FEV1% pre) in the patients with prolonged macrolides therapy (SMD: 0.27, 95%CI: –0.05 – 0.59, $P = 0.10$) (Fig. 3). Further subgroup analysis, there is also no statistical significance in Caucasian or Asian (SMD: 0.05, 95%CI: –0.17 – 0.28, $P = 0.64$; SMD: 0.73, 95%CI: –0.04 – 1.49, $P = 0.06$, respectively). No publication bias was found in Begg's funnel plot or Egger's test ($P = 0.49$).

3.2.3. PEF

All 786 cases from 7 studies were tested in our meta-analysis [14,17,21,22,25,26,28]. By total analysis, the long-term macrolide antibiotics were administrated in patients with asthma has a statistical significance when compared to control group (SMD: 0.25, 95%CI: 0.10–0.39, $P = 0.001$) (Fig. 4). We examined the pooled SMD by fixed-effect model because the test have shown no heterogeneity ($I^2 = 0\%$, $P = 0.75$). Interestingly, in subgroup analysis, there is also a significant increase on PEF after long-term macrolides therapy among Asian (SMD: 0.35, 95%CI: 0.12–0.57, $P = 0.002$) and in

Caucasian (SMD: 0.18, 95%CI: 0.00 – 0.36, $P = 0.05$). No publication bias was found in Begg's funnel plot or Egger's test ($P = 0.57$).

3.2.4. AHR

Five studies [13–15,21] of 310 participants were included to access the effect of long-term macrolides on AHR. As well known, AHR was tested by the dose (PD20) or concentration (PC20) of methacholine required to produce a 20% decrease in FEV1. The overall result indicated the prolonged macrolides administration in patients with asthma has a statistical significance on AHR (SMD: 0.90, 95%CI: 0.05–1.75, $P = 0.04$) (Fig. 5) by random model ($I^2 = 91.5\%$, $P < 0.10$). In addition, we found that macrolides have an improvement on AHR only in the Caucasian (SMD: 1.11, 95%CI: 0.08–2.14, $P = 0.03$) but not among the Asian (SMD: 0.07, 95%CI: –0.67 – 0.81, $P = 0.85$). No publication bias was found in Begg's funnel plot or Egger's test ($P = 0.11$).

3.2.5. Other lung function outcomes

In total, three articles [15,18,25] (272 patients) were reported that forced vital capacity (FVC), and other two studies¹³ (64 cases) were showed the FVC/predict (FVC/pre). After pooling the data, no statistical significance were found between the experimental group and placebo group (FVC: WMD: 0.18, 95%CI: 0.00–0.37, $P = 0.05$; FVC/pre: WMD: –2.00, 95%CI: –7.98–3.98, $P = 0.51$) (Fig. 6). In addition, we analyze the data from two articles [13,24] including three studies (93 patients) about the ratio of the FEV1 and FVC (FEV1/FVC). And we found that there is a statistical significance between the experimental group and placebo group (WMD: 1.93, 95%CI: 1.20–2.66, $P < 0.001$) (Fig. 6). The χ^2 and I^2 test suggested a low heterogeneity ($I^2 = 23.5\%$, $I^2 = 0$, $I^2 = 0$, respectively). No publication bias was found in Begg's funnel plot or Egger's test ($P = 0.58$, $P = 0.32$, $P = 0.69$, respectively).

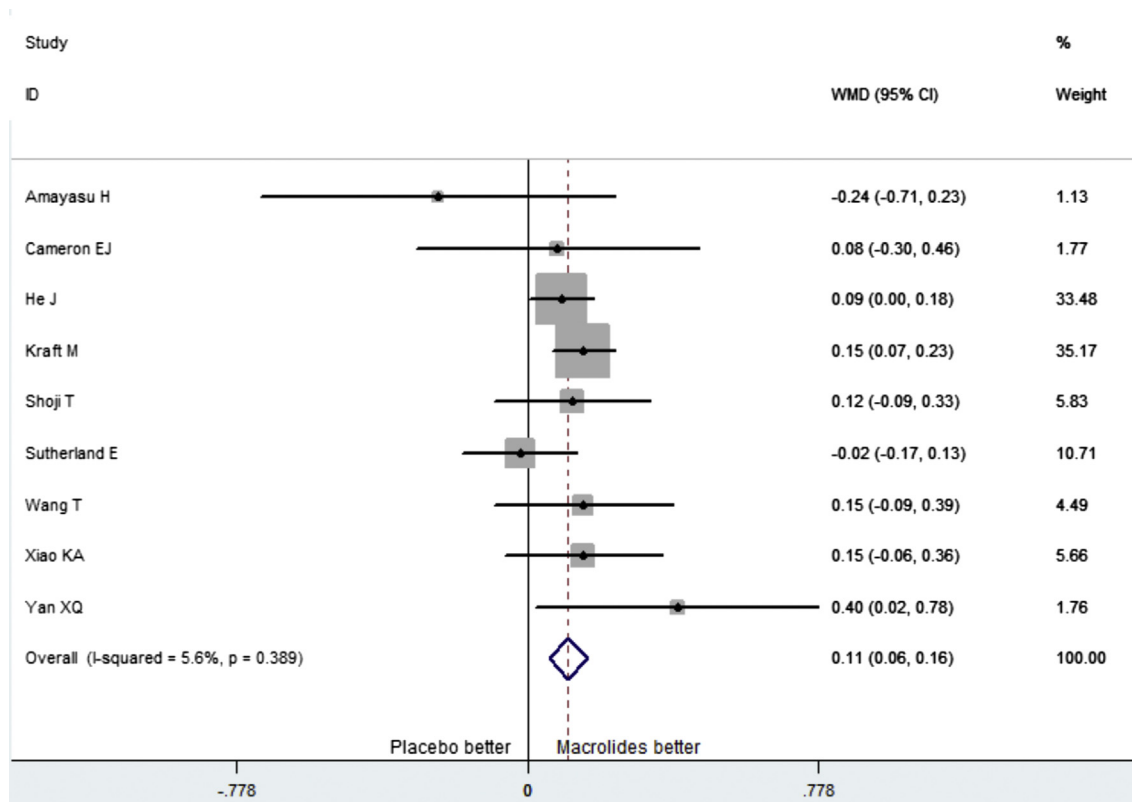


Fig. 2. Meta-analysis with a fixed-effect model for the effect of long-term macrolides administration in patients with asthma on FEV1.

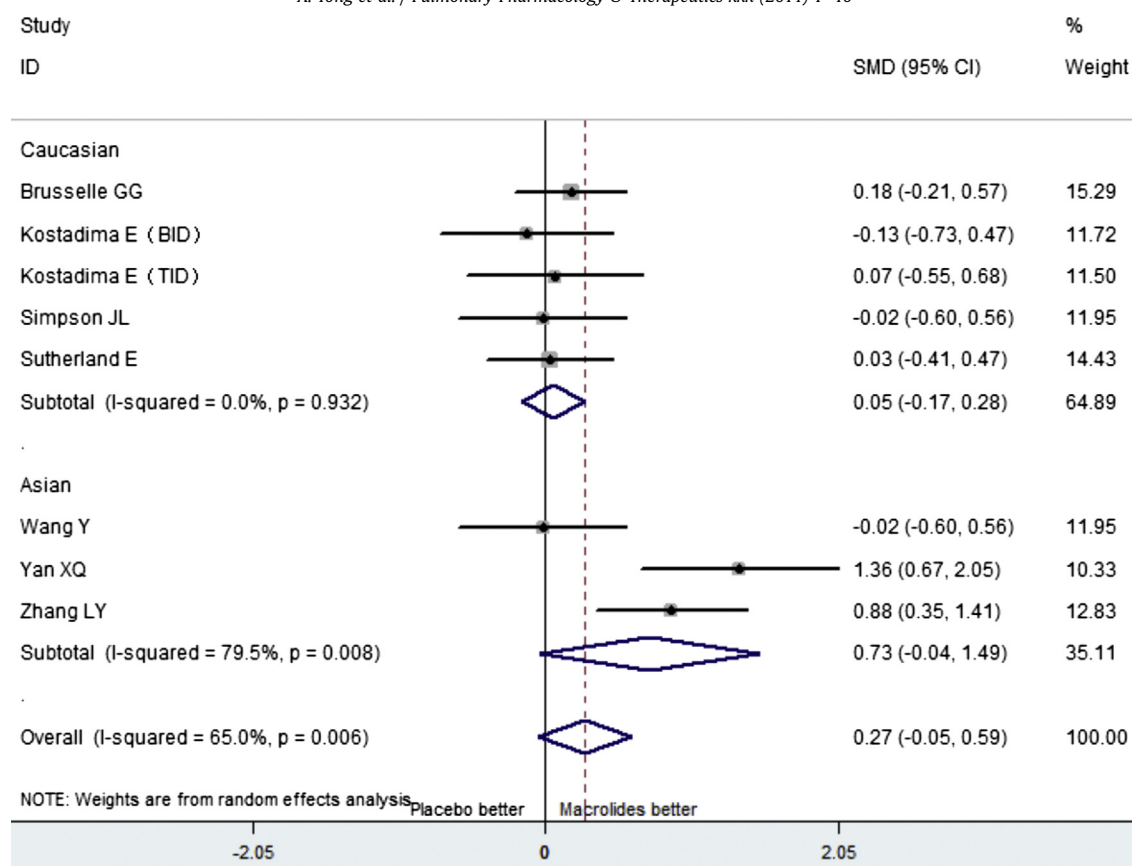


Fig. 3. Meta-analysis with a random-effect model for the effect of long-term macrolides administration in patients with asthma on FEV1/predict.

3.2.6. Asthma control and symptom scores

In totally, 582 participants from 11 articles [12,14–18,20,21,23,24,26] were investigated the effect of long-term macrolide antibiotics administration on asthma control and symptom scores. Unfortunately, we not found that the statistical significance in patients with prolonged macrolide antibiotics therapy when compared to placebo group (SMD: -0.24 , 95%CI: $-0.64 - 0.16$, $P = 0.23$) (Fig. 7) by the random model ($I^2 = 81.4\%$, $P < 0.1$). Subgroup analysis was performed after stratification of the data by ethnicity, we also not found any statistically significant among the Caucasian and Asian (SMD: -0.18 , 95%CI: $-0.41 - 0.06$, $P = 0.14$; SMD: -0.28 , 95%CI: $-1.35 - 0.79$, $P = 0.61$, respectively). There is no publication bias in Begg's or Egger's test ($P = 0.55$).

3.2.7. QOL scores and reliever inhaler puffs per 24 h

In totally, 6 studies [12,14,16,17,20,21] including 450 participants were performed on the QOL scores. The pooled result indicated no statistical significance between the experimental cohort and control cohort (SMD: 0.09 , 95%CI: $-0.11 - 0.29$, $P = 0.39$) (Fig. 8) by fixed model because it haven't heterogeneity ($I^2 = 0\%$, $P = 0.59$). In addition, there were four articles [14,17,20,21] (295 patients) reported the reliever inhaler puffs per 24 h. The overall result also suggested that there is no statistical significance between the experimental group and control group (SMD: -0.09 , 95%CI: $-0.32 - 0.14$, $P = 0.45$) (Fig. 8). We also used the fixed model to analyze the data because it just have shown a low heterogeneity ($I^2 = 32.9\%$, $P = 0.21$). No publication bias was found in Begg's or Egger's test ($P = 0.09$, $P = 0.78$, respectively).

3.2.8. Cell counts in sputum and blood

In this part, 5 articles (229 cases) [12,14,15,18,24], 1 article (34 participants) [18], 3 articles (139 patients) [14,15,18] and 3 articles (102 cases) [15,18,26] respectively reported that neutrophil cells count in sputum, neutrophil cells count in blood, eosinophil cells in sputum and eosinophil cells in blood. The overall results indicated the long-term macrolides administration in patients with asthma has no statistical significance on above four outcomes when compared to control group by the random model (SMD: -0.25 , 95%CI: $-0.62 - 0.13$, $P = 0.20$; SMD: -0.56 , 95%CI: $-1.24 - 0.13$, $P = 0.12$; SMD: -1.56 , 95%CI: $-3.47 - 0.36$, $P = 0.12$; SMD: -2.97 , 95%CI: $-6.27 - 0.32$, $P = 0.08$, respectively) (Fig. 9). However, by the subgroup analysis, there is a significant decrease in neutrophil and eosinophil cells count of sputum after long-term macrolides therapy among Asian (SMD: -0.54 , 95%CI: $-0.93 - (-0.16)$, $P = 0.006$; SMD: -2.40 , 95%CI: $-3.01 - (-1.74)$, $P < 0.001$, respectively) but not in Caucasian (SMD: -0.01 , 95%CI: $-0.34 - 0.33$, $P = 0.97$; SMD: 0.10 , 95%CI: $-0.35 - 0.54$, $P = 0.68$, respectively). No publication bias was found in Begg's or Egger's test.

4. Discussion

Macrolides whose activity is attributed to the presence of the macrocyclic lactone ring, which usually harbor 14 (such as Roxithromycin and Clarithromycin), 15 (Azithromycin) or 16 (Tylamycin etc.) members [29]. They are widely used in the treatment of infections, especially the respiratory tract infections [4,30,31]. Macrolide antibiotics act as anti-bacterial by reversibly combining with the P site on the 50S subunit of bacterial ribosomes [32]. Except for the anti-bacterial effect of macrolides, it has been known for

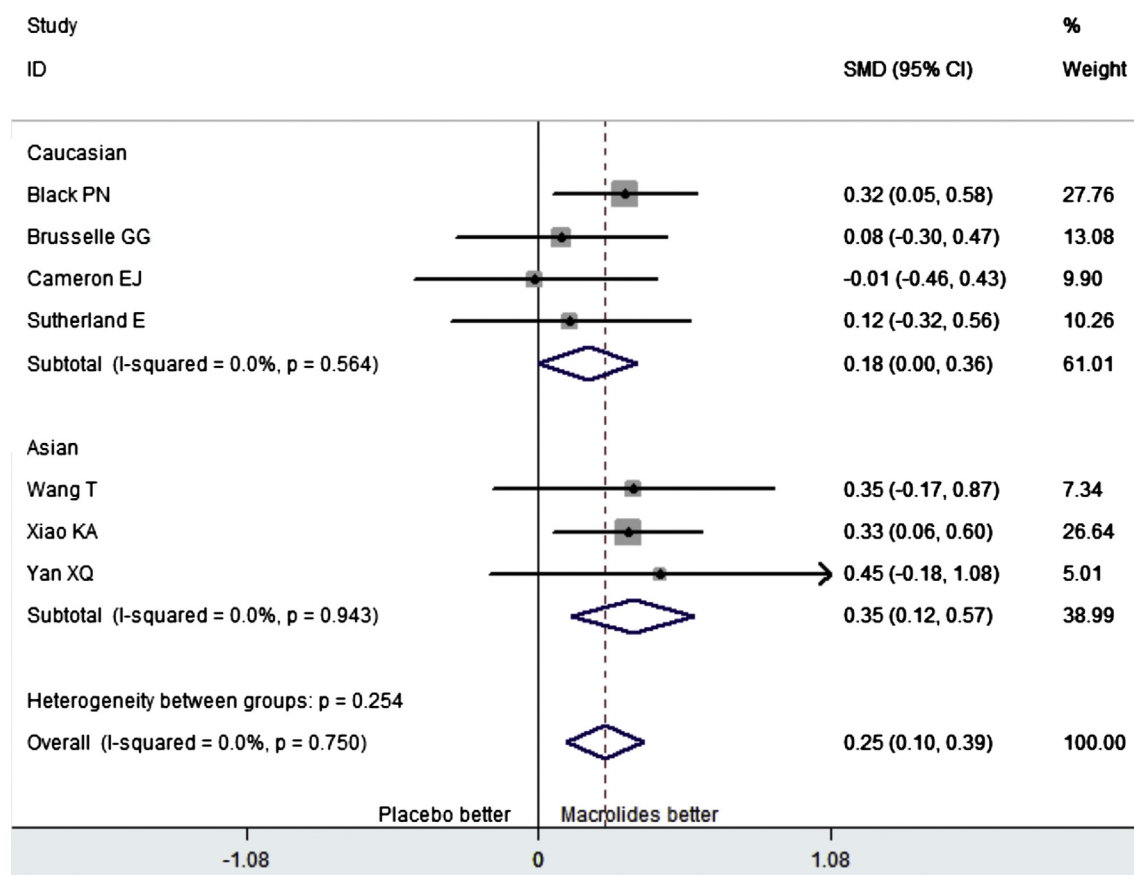


Fig. 4. Meta-analysis with a fixed-effect model for the effect of long-term macrolides administration in patients with asthma on PEF.

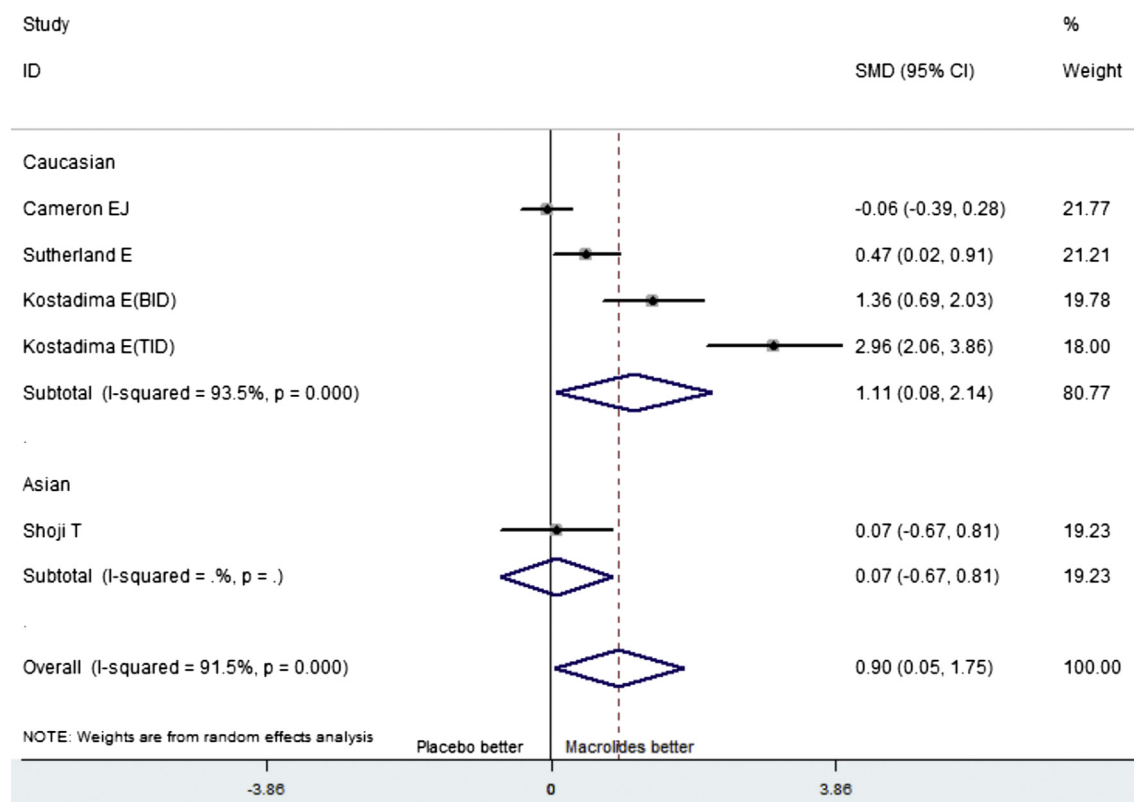


Fig. 5. Meta-analysis with a random-effect model for the effect of long-term macrolides Administration in patients with asthma on AHR.

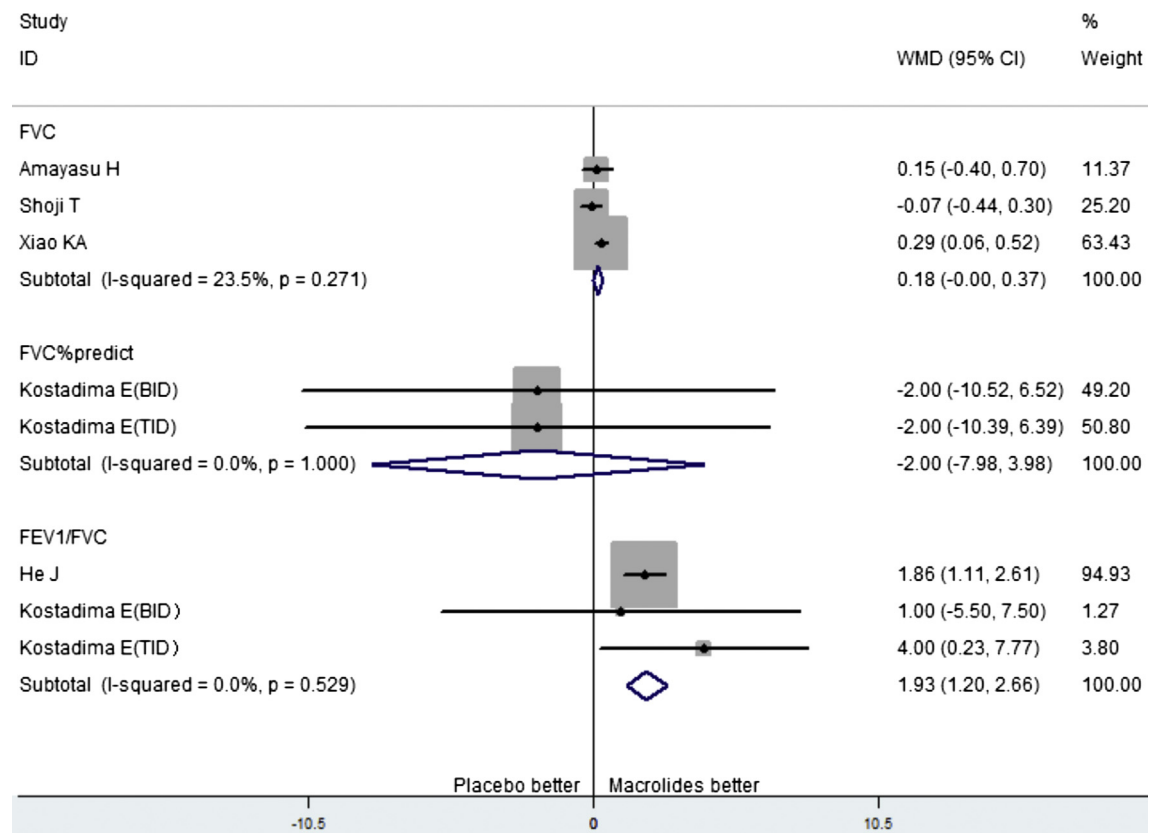


Fig. 6. Meta-analysis with a fixed-effect model for the effect of long-term macrolides administration in patients with asthma on FVC, FEV1/predict and FEV1/FVC.

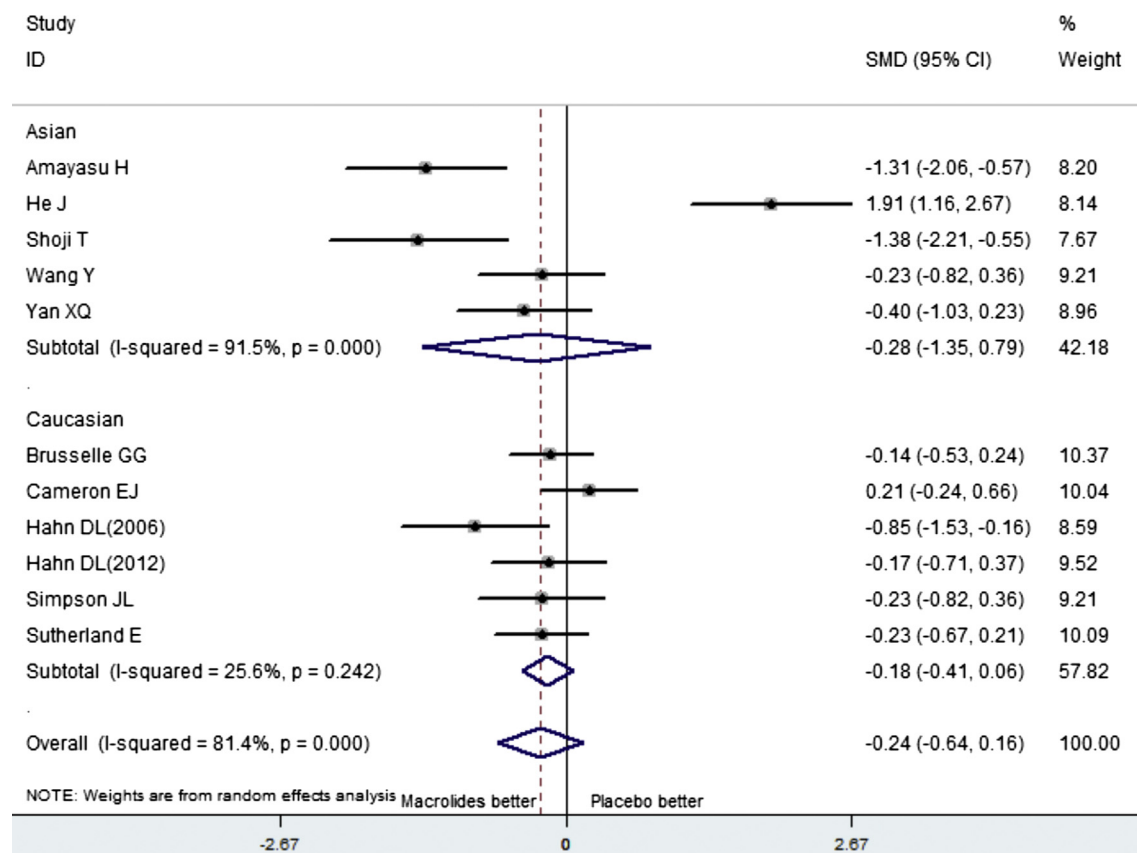


Fig. 7. Meta-analysis with a random-effect model for the effect of long-term macrolides administration in patients with asthma on symptoms.

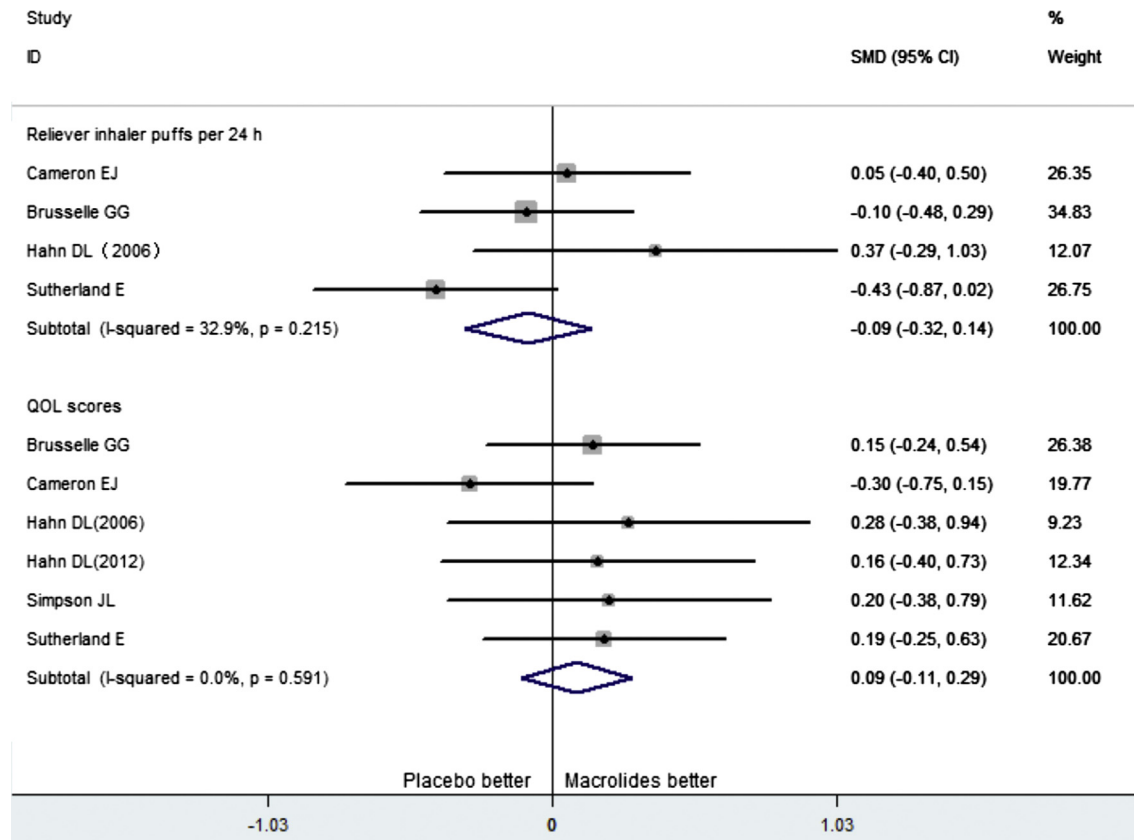


Fig. 8. Meta-analysis with a fixed-effect model for the effect of long-term macrolides administration in patients with asthma on QOL scores and reliever inhaler puffs per 24 h.

decades that the macrolides also have an effect of immune modulatory and anti-inflammatory effects [5,6,33].

Mounting clinical studies have been conducted to evaluate the immune modulatory and anti-inflammatory function of macrolides in COPD [7] and bronchiectasis [9]. In addition, many trials also pay close attention to the effect of macrolide antibiotics in asthma [12,15]. Until now, the experts still didn't well explain the causation of asthma by the current knowledge. Despite many drugs have been shown they can effectively manage and control asthma symptoms, the patients with asthma still face considerable economic cost which includes direct and indirect medical costs [34,35], morbidity and mortality [3,35].

In 2005, Richeldi et al. reported no significant difference on FEV1 in the patients with asthma for long-term macrolide administration, but there was significant difference in symptoms and inflammation cell counts in blood and sputum [36]. Unfortunately, only small number of included studies, so there is insufficient power to support or oppose the use of macrolides in asthma patients. In 2013, Reiter et al. also conducted a meta-analysis to assess the efficacy of macrolides for long-term management in patients with asthma [37]. In the study, the results indicated that prolonged macrolides used in the patients with asthma couldn't improve the FEV1, but it can improve the PEF, QOL, AHR and symptoms. Although totally 12 articles were included in Reiter's study, it not included the Chinese patients. As we known, an absolute 2% increase in the prevalence of asthma would result in an additional 20 million patients with asthma because its population and rate of economic development with associated lifestyle changes in China [3]. Furthermore, other authors reported the studies about the relationship between the long-term macrolides therapy and

asthma [14,28]. However, some articles reported the results were inconclusive. Therefore, we performed a comprehensive meta-analysis to investigate the effect of long-term macrolide antibiotics management in asthma.

In our meta-analysis, the overall results found that the long-term macrolides administration in patients with asthma can improve the FEV1, PEF, AHR, FVC and FEV1/FVC, but can't improve the FEV1/predict, FVC/predict, symptom, QOL scores, reliever inhaler puffs per 24 h, and cell counts. Interestingly, the subgroup analysis results indicated the macrolides could improve the FEV1 and PEF in Caucasian and Asian, and decrease the AHR in Caucasian. Additionally, the results also found the prolonged macrolide antibiotics administration can improve the neutrophil and eosinophil cells count of sputum among Asian, but not in Caucasian. The following reasons may explained the different results when compared with Richeldi's [36] and Reiter's [37] studies: (1) More articles which came from different countries were included in our meta-analysis, and the present results might be more closer to the real values; (2) We corrected some statistics and data errors in the Reiter's meta-analysis, so our meta-analysis pooled results may reduced bias and errors; (3) To evaluate the ethnicity-specific effects, we performed a subgroup analysis by ethnicity group. The subgroup analysis results might indicated the macrolides have different functions with different ethnicities. 4) In the present study, we investigated more clinical outcomes, such as the reliever inhaler puffs per 24 h, and cell counts in sputum and blood, and they will benefit clinical practice a lot. Since lack of sufficient data about the adverse effect and acute exacerbations in the original study, we did not carry out the meta-analysis on side effect and acute exacerbations.

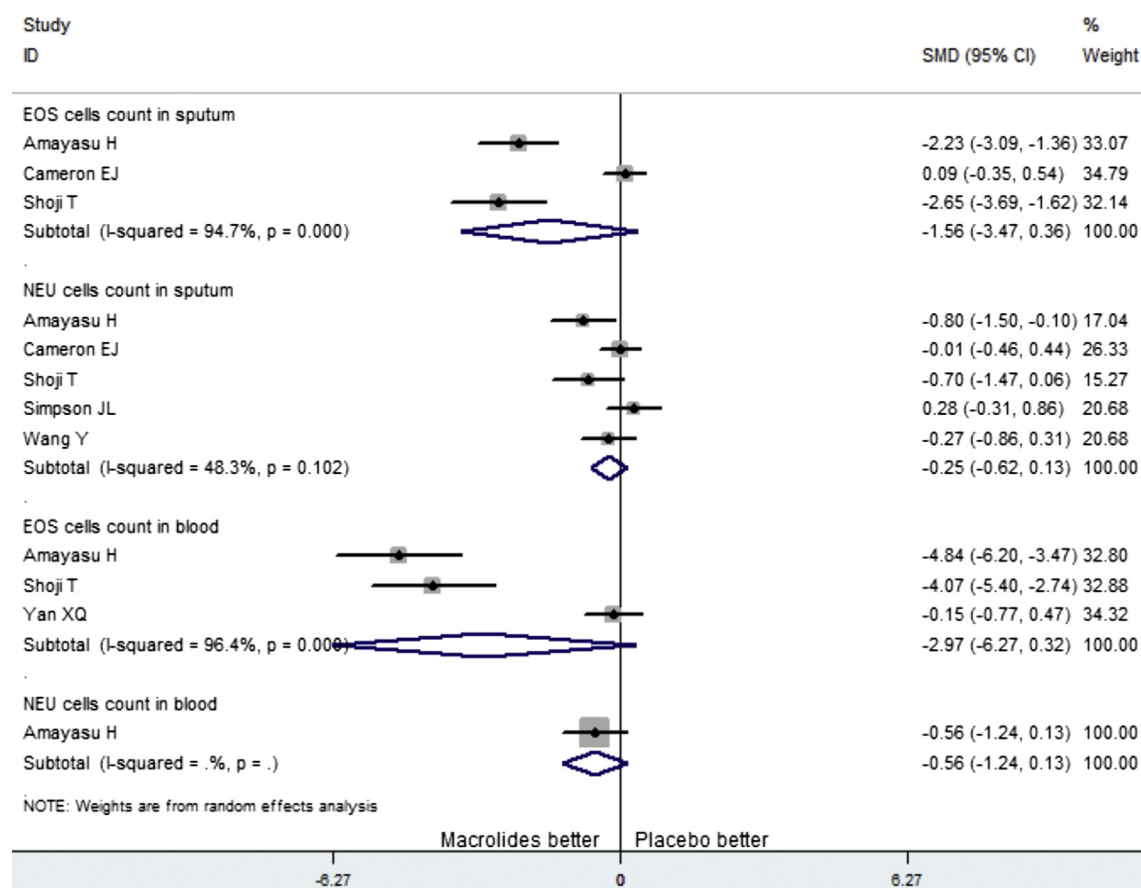


Fig. 9. Meta-analysis with a random-effect model for the effect of long-term macrolides administration in patients with asthma on inflammation cell counts in sputum and blood.

The previous studies have suggested that *Mycoplasma* or *Chlamydia pneumoniae* infection may play an important role in the pathogenesis or severity of chronic asthma [38–40]. Furthermore, a series of studies reported asthma patients with atypical organism infection can cause a decrement in pulmonary function (such as FEV1 and FVC) and an increase in AHR [41,42]. According to the previous results and binding to our meta-analysis results, despite the mechanism by which it relates to long-term macrolides administration in patients with asthma is still unclear, we could put forward some hypothesis which can explain the meta-analysis results. The atypical pathogens infection might play a critical role in the patients with asthma, so long-term macrolides administration may clear the atypical pathogens and increase the lung function (such as the FEV1, PEF, FEV1/FVC) and decrease the AHR. However, lacking the sufficient original data whether the included patients combine with atypical pathogens infection, we not investigate this association in our meta-analysis.

Moreover, the ICS, LABA, LTRA and theophylline were widely used to treat the asthma, and it is well known that these drugs can significantly increase the lung function, dilate bronchus and anti-inflammatory [2,43,44]. Interestingly, some previous studies reported the macrolides may inhibit theophylline metabolic pathways and decrease theophylline clearance [45–47]. Since there is always glucocorticoid, bronchodilator, and theophyllin combination for the treatment of included patients in original study, therefore combined with the previous studies and current pooled results, we also could put forward other hypothesis that macrolides may have a synergistic effect with these drugs or the macrolide antibiotics could inhibit these drugs metabolism, then increase the serum

concentration of these drugs, and finally improve the patient's lung function.

However, there were still several limitations of the present meta-analysis when explaining the pooled results. First, due to a lack of sufficient data for each included individuals, we failed to further perform subgroup analysis after stratification of the data by other factors such as gender, environmental exposures, and age etc., which might affect our results. Secondly, only published studies were included in a few date bases, so a publication bias may have occurred. Third, since small number of included studies about some outcomes, such as the FVC, FEV1/FVC, and cell counts in sputum and blood, so the evidence is relatively weak. Furthermore, there was moderate to high heterogeneity among studies when evaluating some lung function and clinical outcomes, for instance the AHR, symptom scores and cell counts. We think the fact that the articles were published on different date and adopted different quantitative standard may result in the high heterogeneity. Therefore in order to minimize the bias and errors, we conducted a random-effects model to account the pooled results. Despite of these limitations, we minimized the likelihood of bias through the whole process by creating a detailed protocol, by performing study identification, statistical analysis, and data selection, as well as in the control of publication bias. Anyway, the reliability of the results is guaranteed.

In conclusion, the overall results of this meta-analysis suggested long-term macrolide antibiotics administration in the patients with asthma may improve the FEV1, PEF, AHR, FVC and FEV1/FVC, but they can't improve the FEV1/predict, FVC/predict, symptom scores, QOL scores, reliever inhaler puffs per 24 h, and inflammation cell counts in sputum and blood. Interestingly, we found the macrolide

antibiotics may have different functions among different ethnicities by the sub-group analysis. Further well designed studies with larger sample size focusing on more ethnicities are in need to be conducted to confirm the results.

Author contributions

Yonggang Zhang and Hong Fan designed the study, provided resources, coordinated the study and directed its implementation. Xiang Tong and Tingting Guo searched the publications, extracted the data and wrote the manuscript. Xiang Tong, Sitong Liu, Shifeng Peng and Zhipeng Yan were responsible for data synthesis. Xin Yang wrote the introduction. All authors have read and approved the final manuscript.

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