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SYSTEMATIC REVIEW

Efficacy and safety of macrolides in the treatment of children with bronchiectasis: a meta-analysis

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BACKGROUND: This study summarized the available randomized controlled trials (RCTs) to assess the efficacy and safety of macrolides on pathogens, lung function, laboratory parameters, and safety in children with bronchiectasis.
METHODS: PubMed, EMBASE, and the Cochrane Library were searched for available papers published up to June 2021. The outcomes were the pathogens, adverse events (AEs), and the forced expiratory volume in one second (FEV1%) predicted.
RESULTS: Seven RCTs (633 participants) were included. The long-term use of macrolides reduced the risk of the presence of *Moraxella catarrhalis* (RR = 0.67, 95% CI: 0.30–1.50, $P = 0.001$; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.433$), but not *Haemophilus influenza* (RR = 0.19, 95% CI: 0.08–0.49, $P = 0.333$; $I^2 = 57.0\%$, $P_{heterogeneity} = 0.040$), *Streptococcus pneumonia* (RR = 0.91, 95% CI: 0.61–1.35, $P = 0.635$; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.515$), *Staphylococcus aureus* (RR = 1.01, 95% CI: 0.36–2.84, $P = 0.986$; $I^2 = 61.9\%$, $P_{heterogeneity} = 0.033$), and any pathogens present (RR = 0.61, 95% CI: 0.29–1.29, $P = 0.195$; $I^2 = 80.3\%$, $P_{heterogeneity} = 0.006$). Long-term macrolides had no effect on FEV1% predicted (WMD = 2.61, 95% CI: −1.31, 6.53, $P = 0.192$; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.896$). Long-term macrolides did not increase the risk of AEs or serious AEs.
CONCLUSION: Macrolides do not significantly reduce the risk of pathogens present (except for *Moraxella catarrhalis*) or increase FEV1% predicted among children with bronchiectasis. Moreover, macrolides were not associated with AEs. Considering the limitations of the meta-analysis, further larger-scale RCTs are needed to confirm the findings.

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IMPACT:

- Macrolides do not significantly reduce the risk of pathogens present (except for *Moraxella catarrhalis*) among children with bronchiectasis.
- Macrolides do not significantly increase FEV1% predicted among children with bronchiectasis.
- This meta-analysis reports on the efficacy and safety of macrolides in the treatment of children with bronchiectasis, providing evidence for the management of children with bronchiectasis.
- This meta-analysis does not support the use of macrolides in the management of children with bronchiectasis unless the presence of *Moraxella catarrhalis* is provenor suspected.

INTRODUCTION

Bronchiectasis is a chronic, often progressive suppurative lung disease characterized by irreversibly dilated bronchi and chronic or recurrent bronchial infection and inflammation; it may be focal, where a single lobe or segment is involved, or diffuse with the involvement of both lungs.[1–4] The exact epidemiology of bronchiectasis is unknown because many cases are misdiagnosed because of non-specific symptoms.[3] Among children, the incidence may be higher in indigenous or socioeconomically disadvantaged groups.[5] The incidence of bronchiectasis is estimated at 3.7 per 100,000 children in New Zealand[6] but 202 per 100,000 children in an indigenous population in Canada.[7] Exacerbations in children require treatments, cause parental anxiety and stress, and affect the quality of life of the whole family.[8] When severe (i.e., requiring hospital admission), the exacerbations can negatively affect lung function in adolescence and adulthood.[9,10] The complications of bronchiectasis include chronic respiratory failure, thoracic infection, cor pulmonale, hemoptysis, lung cancer, and vascular diseases.[3,11]

Macrolide antibiotics are antibacterial agents that possess anti-inflammatory and immunomodulatory properties.[12] Macrolide mechanism of action is not strictly bacteriocidal and likely includes anti-inflammatory, immunomodulatory, and mucus-decreasing effects and inhibition of bacterial quorum sensing and toxin production.[13,14] Because of these properties, a macrolide maintenance treatment might effectively prevent exacerbations inpatients with non-cystic fibrosis (CF) bronchiectasis. Indeed, macrolide antibiotics have been used to reduce the exacerbations of non-CF bronchiectasis.[13] Macrolide antibiotics reach a high plasma concentration, have a long half-life, and display a broad antimicrobial spectrum.[14] According to the guidelines, macrolides can be given to select patients with ≥3 exacerbations or ≥2

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hospitalizations within the past year, with stratification based on *Pseudomonas aeruginosa* infection.[15–17] On the other hand, the Thoracic Society of Australia and New Zealand does not support the use of long-term macrolides except in selected cases.[18]

A meta-analysis of three randomized controlled trials (RCTs) suggested that macrolides are effective in adult patients with bronchiectasis.[19] A meta-analysis of 10 trials (including three in children) reached a similar conclusion.[20] A Cochrane review that included 11 studies in adults and two studies in children supports the use of macrolides for bronchiectasis but highlights the low quality of the available evidence and the lack of data about adverse events (AEs).[21] Still, the efficacy and safety of macrolides in the treatment of children with bronchiectasis remain inconsistent. In addition, much evidence is from observational studies. Therefore, this meta-analysis aimed to summarize the available RCTs to assess the efficacy and safety of macrolides on pathogens, lung function, laboratory parameters, and safety in children with bronchiectasis.

METHODS

Literature search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline 2020.[22,23] The study was elaborated based on the PICOS principle.[24] PubMed, EMBASE, and the Cochrane Library were searched for available papers published up to June 2021 using the MeSH terms of "Bronchiectasis", "Child", "Macrolides", "Azithromycin", "Clarithromycin", "Erythromycin", "Roxithromycin", "Spiramycin", "telithromycin", "Troleandomycin", "Josamycin", and "Oleandomycin", as well as relevant keywords, followed by screening based on inclusion and exclusion criteria. The literature search process was performed independently by two investigators. This included the analysis of titles/abstracts followed by the full texts. Discrepancies were ruled by a third investigator.

Eligibility criteria

The inclusion criteria were (1) patients: children with bronchiectasis, (2) interventions: macrolides, (3) comparison: placebo or another drug, (4) study type: RCTs, and (5) outcome: compared the efficacy and safety of macrolides. The exclusion criteria were (1) conference abstract, case report, meta-analysis, review, animal study, or protocol, (2) full text not available in English, (3) full text cannot be obtained, (4) no data available, or (5) different reports for the same study (in which case only the most recent was included).

Data extraction

Data study characteristics (names of the first author, publication year, and country), characteristics of the patients (number of patients, age, and sex), treatment regimens, duration, and outcomes (pathogens, AEs, and FEV1% predicted) were extracted by two investigators using a standardized form. Discrepancies were solved by discussion until a consensus was reached.

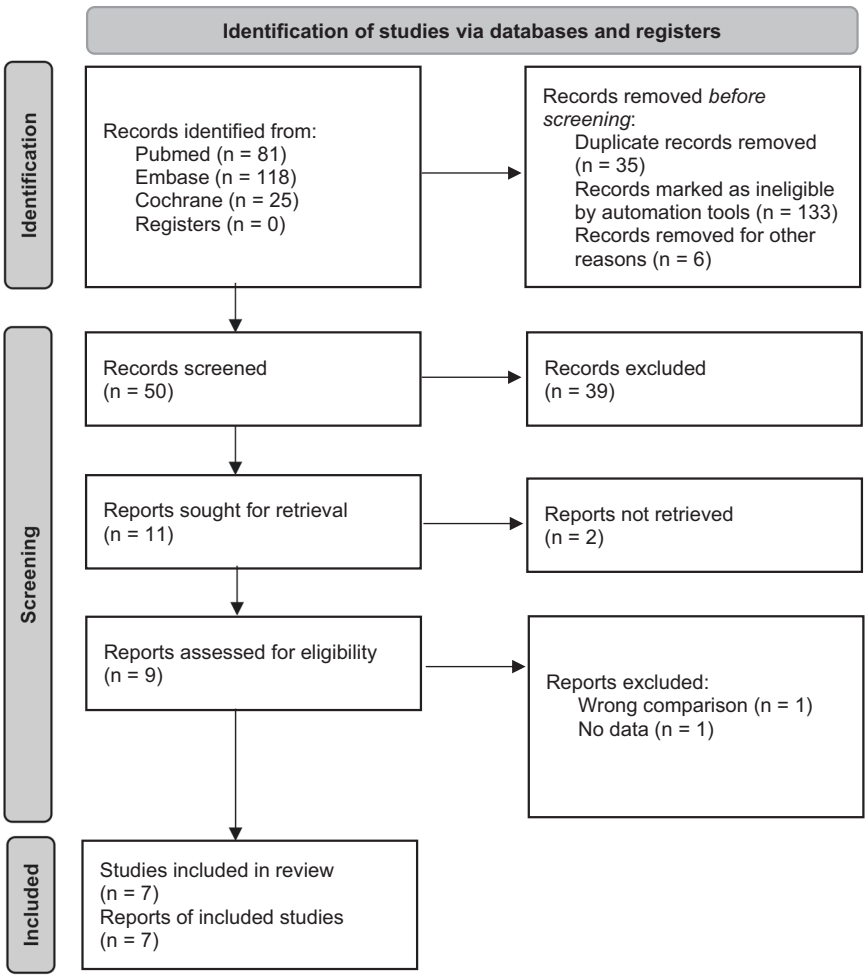

Fig. 1 Study selection process. Each rectangle represents a step in the literature screening process. The left column represents the number of papers screened at each step, and the right side states the number of documents excluded and the reasons for exclusion.

Table 1. Characteristics of the included studies.

Author, year	Location	Study design	Sample size, total (T/C) (F/M)	Age (T/C) (year, mean or median)	Diagnosis	Exacerbation history and bronchiectasis states	Macrolide dose and frequency	Comparison	Therapy duration follow-up
Goyal, 2018	Australia, New Zealand	DB-RCT	179 (82/97) (84/95)	6.4 (4.0–9.0)/ 6.8 (4.3–10.1)	Clinical features and HRCT	Stable bronchiectasis, ≥2 exacerbations in the previous 18 months	Azithromycin (5 mg/kg per day)/amoxicillin-clavulanate (22.5 mg/kg twice daily)	Placebo	3 weeks 6 months
Goyal, 2019	Australia, New Zealand	DB-RCT	197 (67/63/ 67) (93/ 104)	6.0(3.6–9.5)/ 6.0(3.7–8.6)	CT	Stable bronchiectasis, ≥2 exacerbations in the previous 18 months	Azithromycin (5 mg/kg per day (maximum 200 mg) as a once daily dose)/amoxicillin-clavulanate (45 mg/kg per day (maximum 880 mg), divided into twice daily doses)	Placebo (amoxicillin-clavulanate or azithromycin)	2 weeks 6 months
Hare, 2015	Australia, New Zealand	DB-RCT	78 (41/37) (37/41)	4.2 (1.4–8.9)/ 5.4 (1.8–9.0)	Clinical features or HRCT	Stable bronchiectasis, ≥1 exacerbation in the past year	Azithromycin (30 mg/kg, once weekly)	Placebo	24 months
Koh, 1997	Korea	DB-RCT	25 (13/12) (11/14)	10–18	Clinical features and CT	Stable bronchiectasis, increased AR	Roxithromycin 4 mg/kg twice daily	Placebo	12 weeks 12 weeks
Masekela, 2013	South Africa	DB-RCT	31 (17/14) (13/18)	6–18	HRCT	Bronchiectasis associated with HIV	Erythromycin, <15 kg 125 mg, >15 kg 250 mg per day	Placebo	52 weeks 52 weeks
Valery, 2013	Australia	DB-RCT	89 (45/44) (47/42)	1–8	HRCT	Stable bronchiectasis, ≥1 exacerbation in the past year	Azithromycin 30 mg/kg once a week	Placebo	12–24 months 12–24 months
Yalçin, 2006	Turkey	RCT	34 (17/17) (15/19)	13.1 ± 2.7/ 11.9 ± 2.9	Clinical features and HRCT	Clinically stable with no evidence of acute pulmonary exacerbation	Clarithromycin,15 mg/ kg, daily	Supportive therapies (no intervention)	3 months

AR airway responsiveness, *T/C* treat group/control group, *DB-RCT* double-blinded randomized controlled trial, *F/M* female/male, *HIV* human immunodeficiency virus, *HRCT* high-resolution CT, *LRTI* lower respiratory tract infection, *NR* not reported.

Table 2. Quality assessment of the included studies.

Study	Domain					
	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall bias
Goyal, 2018	Low	Low	Low	Low	Low	Low
Goyal, 2019	Low	Low	Low	Low	Low	Low
Hare, 2015	Low	Low	Some concerns	Low	Low	Some concerns
Koh, 1997	Low	Low	Low	Low	Low	Low
Masekela, 2013	Low	Low	Some concerns	Low	Low	Some concerns
Valery, 2013	Low	Low	Some concerns	Low	Low	Some concerns
Yalçin, 2006	Some concerns	Some concerns	Low	Low	Low	High

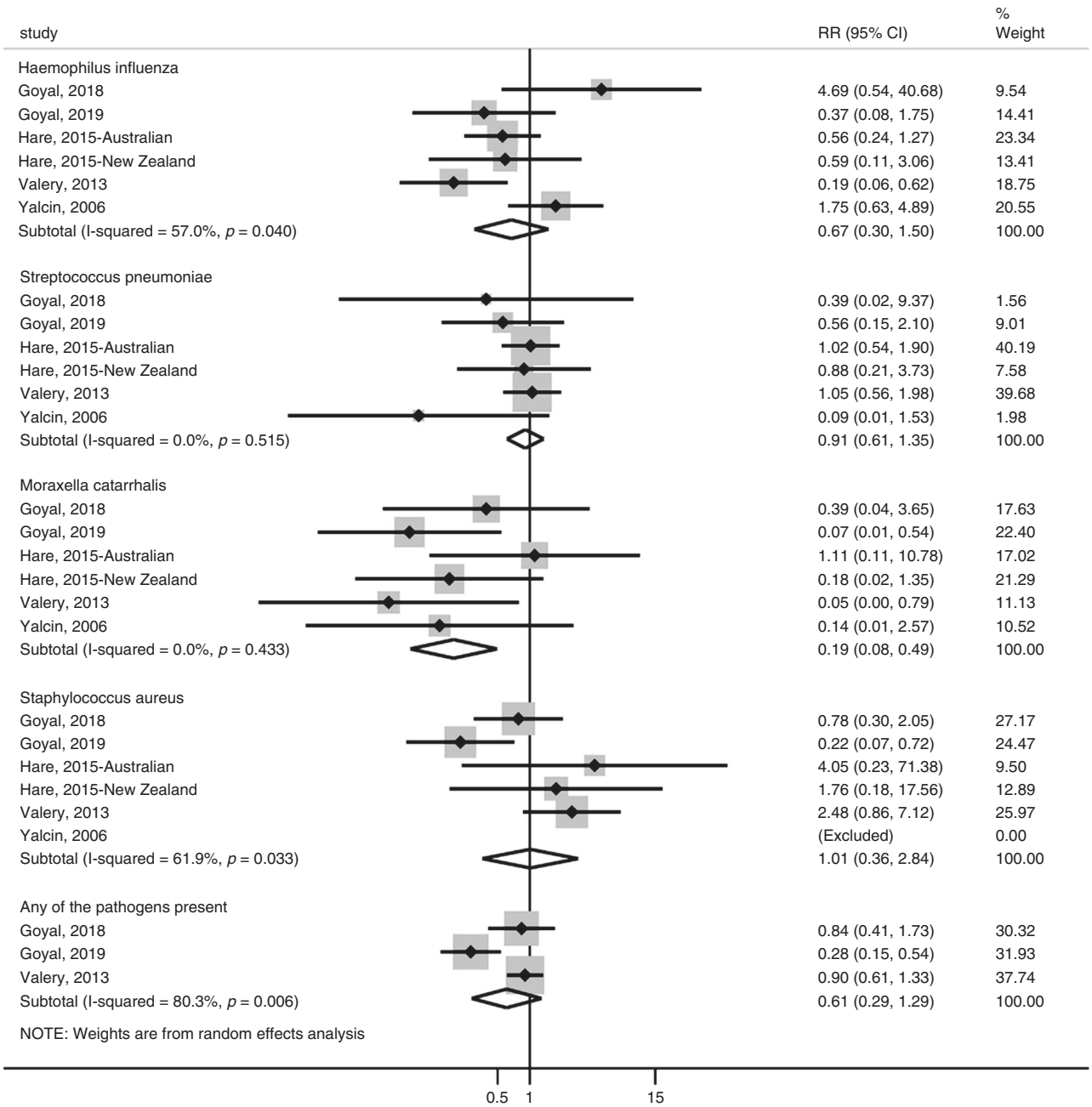

Fig. 2 Forest plot showing the effect of macrolides on pathogens. The gray box indicates the point estimate of the study results. A horizontal line represents the 95% confidence interval of the study results, and each end represents the boundary of the confidence interval. The diamond represents the point estimate and confidence interval. The larger the study, the smaller the horizontal line and the larger the gray box.

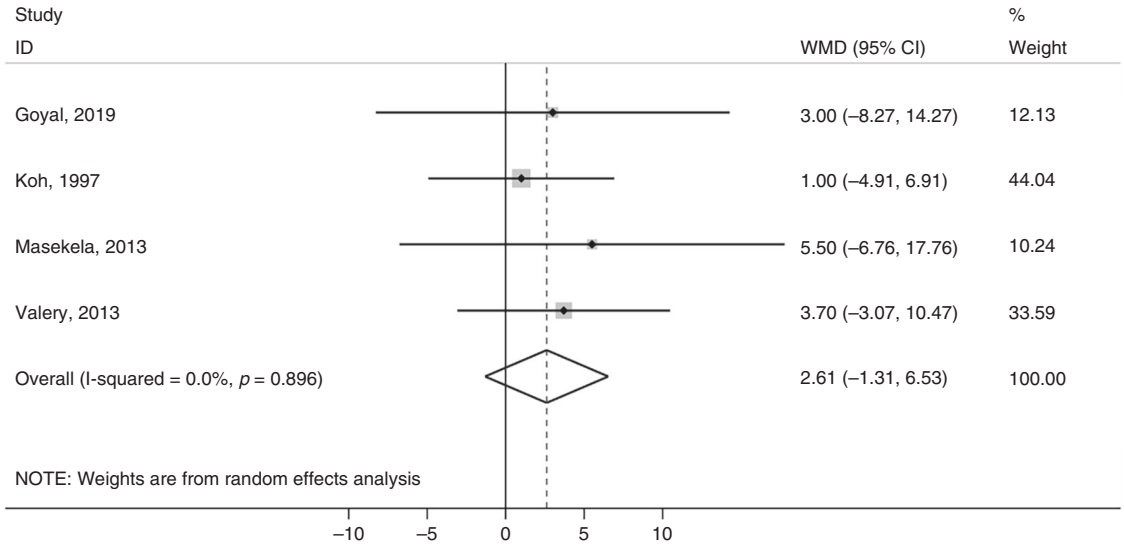

Fig. 3 Forest plot showing the effect of macrolides on FEV1% predicted. The gray box indicates the point estimate of the study results. A horizontal line represents the 95% confidence interval of the study results, and each end represents the boundary of the confidence interval. The diamond represents the point estimate and confidence interval. The larger the study, the smaller the horizontal line and the larger the gray box.

Quality assessment

The RCTs were evaluated according to the Cochrane risk bias tool (ROB2).[25]

Statistical analysis

The incidences of pathogens and AEs were treated as dichotomous variables; they were expressed as risk ratio (RR) with 95% confidence intervals (CIs) and were presented using forest plots. The mean different changes in FEV1% predicted were treated as continuous variables and were expressed as weighted mean difference (WMD) with 95% CI for each study. Cochran's Q statistic $P < 0.10$ indicated evidence of heterogeneity.[26] When significant heterogeneity ($P < 0.10$) was observed, the random-effects model was used to combine the effect sizes of the included studies; otherwise, the fixed-effects model was adopted.[27] In addition, sensitivity analyses were performed to identify the effects of individual studies on the pooled results and test the reliability of the results. Sensitivity analyses for result robustness were performed by sequentially excluding each study in turn. All analyses were performed using STATA SE 14.0 (StataCorp). $P < 0.05$ was considered statistically significant.

RESULTS

Identification of the eligible RCTs

Figure 1 presents the RCT selection process. The initial search yielded 224 records, but 174 were removed before the screening. Then, 50 records were screened, and 39 were excluded. Among the 11 reports sought for retrieval, two could not be retrieved. Then, nine reports were assessed for eligibility; one was excluded because of inadequate comparison for the present meta-analysis, and one was excluded because of the lack of usable data. Therefore, seven RCTs were included in the present meta-analysis.

Study characteristics and quality assessment

Table 1 presents the characteristics of the studies. The seven studies enrolled 633 participants. Four were from New Zealand/Australia,[28–31] one from Korea,[32] one from South Africa,[33] and one from Turkey.[34] Six were double-blind RCTs.[28–33] Three RCTs had a low risk of bias for all ROB2 items,[28,29,32] while the remaining four studies had some risk of bias for at least one item[30,31,33,34] (Table 2).

Efficacy according to the pathogens

As shown in Fig. 2, long-term macrolides reduced the risk of the sputum presence of *Moraxella catarrhalis* (RR = 0.67, 95% CI: 0.30–1.50, $P = 0.001$; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.433$), but not for *Haemophilus influenza* (RR = 0.19, 95% CI: 0.08–0.49, $P = 0.333$; $I^2 = 57.0\%$, $P_{heterogeneity} = 0.040$), *Streptococcus pneumonia* (RR = 0.91, 95% CI: 0.61–1.35, $P = 0.635$; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.515$), *Staphylococcus aureus* (RR = 1.01, 95% CI: 0.36–2.84, $P = 0.986$; $I^2 = 61.9\%$, $P_{heterogeneity} = 0.033$), and any pathogens present (RR = 0.61, 95% CI: 0.29–1.29, $P = 0.195$; $I^2 = 80.3\%$, $P_{heterogeneity} = 0.006$).

FEV1% predicted

Figure 3 shows that long-term macrolides had no effect on the FEV1% predicted (WMD = 2.61, 95% CI: −1.31, 6.53, $P = 0.192$; $I^2 = 0.0\%$, $P_{heterogeneity} = 0.896$).

AEs

Figure 4a showed that long-term macrolides were not associated with AEs (all 95% CIs include 1). The same can be seen with serious AEs (Fig. 4b).

Other outcomes

The outcomes presented by only one study and that could not be summarized are presented in Fig. 5. Long-term macrolides decreased the sputum purulence score (WMD = −0.78, 95% CI: −1.32, −0.24)[32] and increased the quality of life (WMD = 0.90, 95% CI: 0.29, 1.51).[29] Other outcomes like the sputum leukocyte score, $\Delta FEV1_{max\ \%}$, Bhalla score, exacerbations, FVC% predicted, and white blood cell count were not changed by long-term macrolides.

Sensitivity analysis

The sensitivity analysis of the effect of long-term macrolides on pathogens showed that the results were robust, and the exclusion of any study did not influence the results (Fig. 6).

DISCUSSION

The reports about the efficacy and safety of macrolides in the treatment of children with bronchiectasis remain inconsistent. This study aimed to summarize the available RCTs to assess the efficacy and safety of macrolides on pathogens, lung function, laboratory

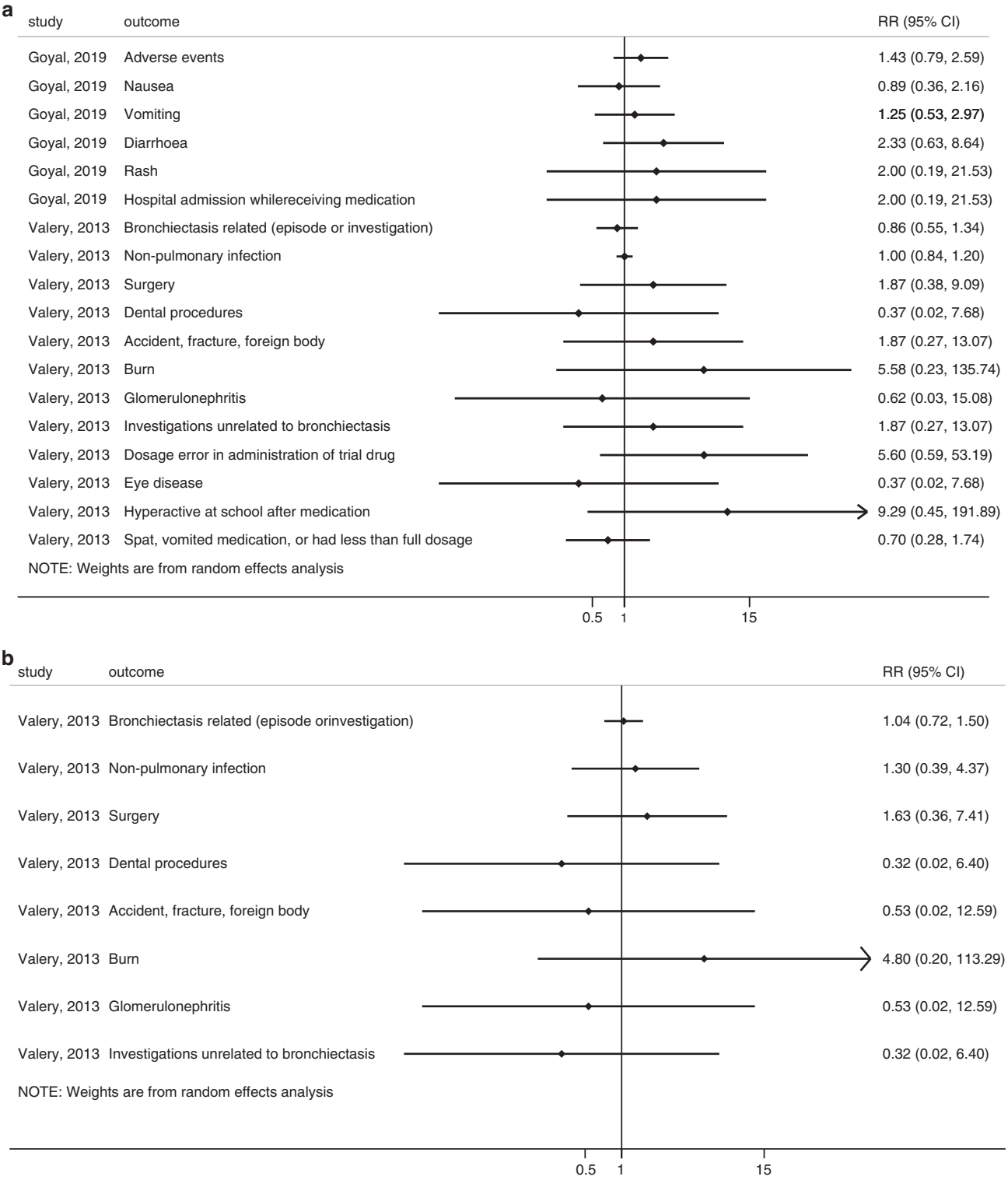

Fig. 4 Forest plot showing the outcomes of macrolides. (**a**) adverse events (**b**) serious adverse events. The black point indicates the point estimate of the study results, and the horizontal line represents the 95% confidence interval.

parameters, and safety in children with bronchiectasis. The results suggest that macrolides do not significantly reduce the risk of pathogens present in sputum (except for *Moraxella catarrhalis*) or increase the FEV1% predicted among children with bronchiectasis. Moreover, macrolides were not associated with AEs.

The available guidelines broadly recommend long-term macrolides to any patient with ≥3 exacerbations or ≥2 hospitalizations within the past year, although some guidelines make additional stratification based on the pathogens.[15–18] Still, the level of evidence in these guidelines is often moderate. Furthermore, studies

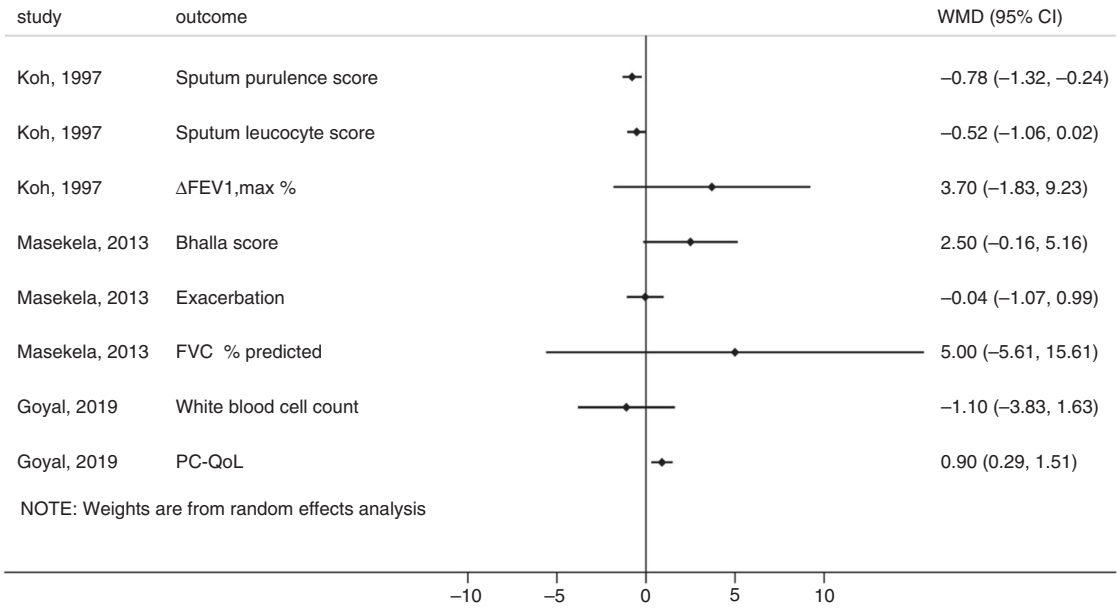

Fig. 5 Forest plot showing the other outcomes. The black point indicates the point estimate of the study results, and the horizontal line represents the 95% confidence interval.

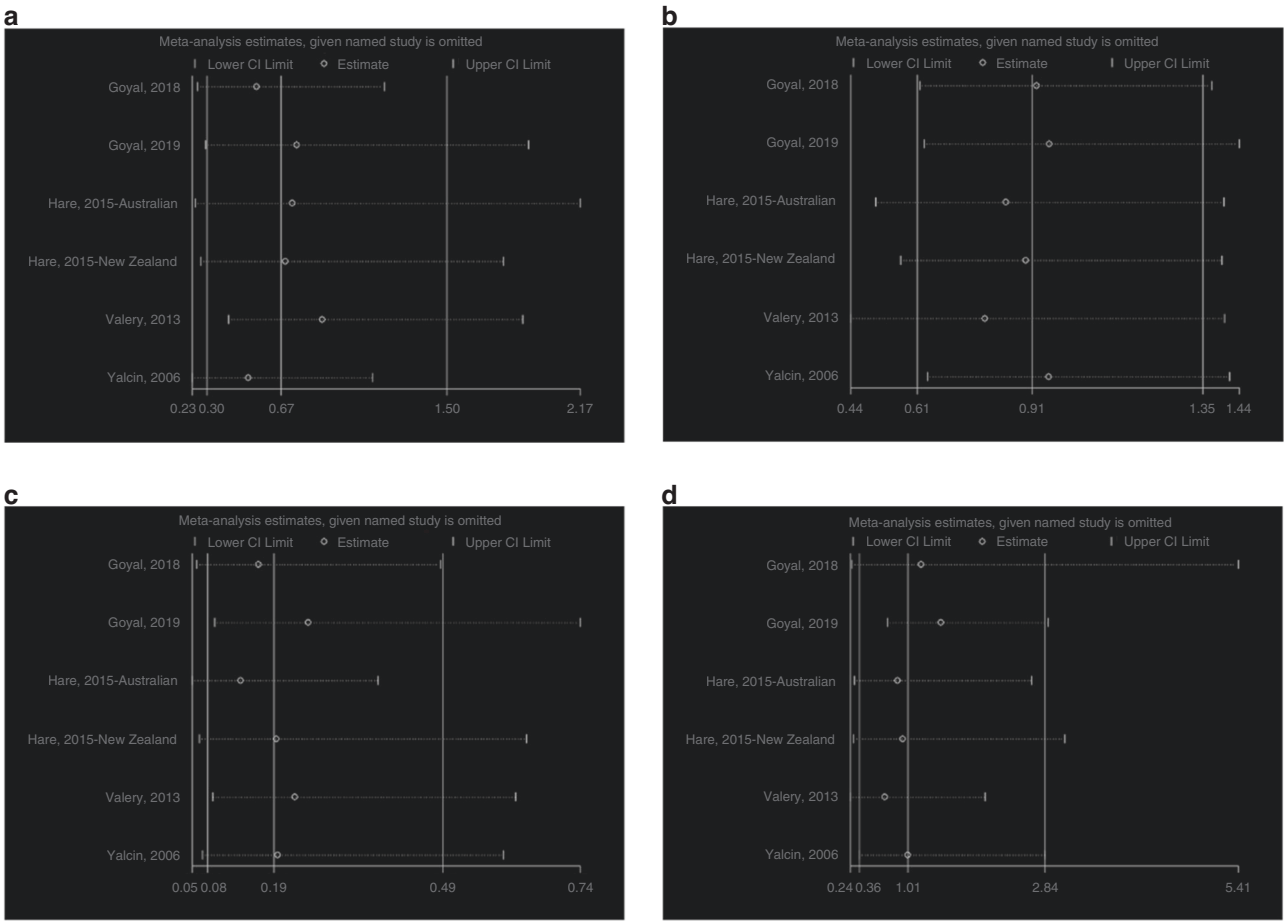

Fig. 6 Sensitivity analysis of the pathogens. a *Haemophilus influenza*. **b** *Streptococcus pneumoniae*. **c** *Moraxella catarrhalis*. **d** *Staphylococcus aureus*. The results in each row represent the overall effect estimate after excluding the studies listed on the left side of this row.

specifically on children are rare. Indeed, although previous meta-analyses suggested that macrolides are effective in patients with bronchiectasis, only five RCTs in children were identified and included.[19–21] Furthermore, a Cochrane review highlights the low quality of the available evidence and the lack of data about AEs.[21] Previous meta-analyses did not examine the pathogens. In the present meta-analysis of seven RCTs, macrolides did not significantly reduce the risk of pathogens present (except for *Moraxella catarrhalis*). Therefore, long-term macrolides could be of limited efficacy in children with bronchiectasis. Still, no study presented data about *Pseudomonas aeruginosa*, which is associated with significant morbidity and mortality in patients with lung infections due to this pathogen.[15–17] Therefore, the results of this meta-analysis must be taken with caution and highlight the lack of data about the efficacy of long-term macrolides in children with bronchiectasis.

Decreased pulmonary function in adulthood is a major concern for children with bronchiectasis and exacerbations.[3,11] The present meta-analysis observed no improvement in FEV1% predicted or FVC, but the results must be taken with caution since the pulmonary measurements in the various studies were performed during the treatment period, and no long-term data were available regarding the changes in pulmonary function from childhood to adulthood. Still, there are some reports of decreased FEV1% later in life in children who had bronchiectasis,[35,36] but additional studies will be necessary to quantify the risk and whether macrolides can slow down the process.

AEs might be a concern with the long-term use of antibiotics. Still, this study indicated no significant increase in AEs and serious AEs using long-term macrolides. Still, the examined AEs varied among the RCTs, and reporting was not uniform. Antibiotic resistance is another major public health concern with long-term antibiotics, but no data could be summarized about that. Future studies should quantify this risk, especially in the global context of the rational use of antibiotics.

Bronchiectasis significantly affects the quality of life of the patients and their families.[3] Only one of the included studies examined the quality of life and reported improvements with the long-term use of macrolides. This outcome should be included in future studies.

This meta-analysis has limitations. First, there was substantial heterogeneity among the included studies, especially in the studies reporting any pathogens present. There were important differences among the RCTs in terms of antibiotics, dosage, and comorbidities. Second, some of the included studies had a relatively small sample size, which would overestimate the treatment effect compared with larger trials. Third, the duration of follow-up varied greatly among the included studies, at 3–24 months. Fourth, the data available from the included studies did not allow analyses on some AEs, such as QT prolongation.

In conclusion, long-term macrolides do not significantly reduce the risk of pathogens present (except for *Moraxella catarrhalis*) or increase the FEV1% predicted among children with bronchiectasis. Moreover, macrolides were not associated with AEs. Considering the limitations of the meta-analysis, further larger-scale RCTs are needed to confirm the findings.

DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article.

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AUTHOR CONTRIBUTIONS

Conceptualization: G.S. Data curation: M.P., W.L. Formal analysis: M.S., B.Z. Methodology: G.S., S.Y. Writing—original draft: G.S., Y.Z. Writing—review and editing: H.Z.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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