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How does comorbid bronchiectasis affect asthmatic patients? A meta-analysis

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ABSTRACT

Objective: Asthma and bronchiectasis are known to be two distinct diseases with different etiology, pathophysiology, management, and prognosis. However, a high prevalence of bronchiectasis has been reported in patients with severe asthma. Thus, it is of great importance to identify the impact of bronchiectasis on asthmatic patients.

Data sources: Databases including PubMed, Embase, Cochrane, Web of Science were searched comprehensively to identify relevant human clinical studies published until February 2020.

Study selections: Two investigators (Gelei Lan and Guochao Shi) independently obtained the potentially eligible articles based on their titles and abstracts. When opinions differed between the investigators, discussions were made to reach an agreement. The authors of the included studies were contacted for inquiry when necessary.

Results: Six observational studies with 1004 patients were included in the meta-analysis. The mean prevalence of bronchiectasis in patients with asthma was 35.2% (ranging from 2.2% to 47%). Asthmatic patients with bronchiectasis were older, had a longer disease duration, exhibited greater severity, and showed more frequent exacerbations and hospitalization, and poorer lung function, compared with the patients without bronchiectasis.

Conclusion: Despite of the heterogeneity between included studies and detectable publication bias, this meta-analysis demonstrated the impact of comorbid bronchiectasis on asthmatic patients. Thus, coexistence of bronchiectasis should be considered a clinical phenotype of asthma, which may have associations with exacerbation and hospitalization.

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KEYWORDS

Asthma; bronchiectasis; meta-analysis

Introduction

Asthma is a heterogeneous disease characterized by recurrent episodes with three typical components: airway obstruction, airway hyperresponsiveness, and airway inflammation. Asthmatic attacks are often triggered by factors such as exercise, exposure to allergens or irritants, seasonal changes, or respiratory infections (1).

Non-cystic fibrosis bronchiectasis is characterized by irreversibly dilated bronchi and usually associated with chronic sputum production, bacterial colonization of the lower respiratory tract, inflammation, and frequent exacerbations (2). Although prevalence of bronchiectasis varies among different regions, with the development of high-resolution computed tomography (HRCT) scanning as a detection tool, bronchiectasis is increasingly recognized as an important respiratory disease in developing countries (2).

The coexistence of asthma and bronchiectasis has been observed in many patients, with a prevalence of bronchiectasis in asthmatic patients ranging from 2.2% (3) to 77% (4). However, little is known about the relationship between these two diseases. This meta-analysis, therefore, is aimed at summarizing the reports on the comorbidity of bronchiectasis and asthma and further clarifying the impact of bronchiectasis on asthmatic patients.

Methods

In this analysis, demographical and clinical characteristics, including age, gender, smoking history, disease duration, severity of asthma, exacerbation and hospitalization history, radiological characteristics, lung function, and laboratory tests, were compared between

asthmatic patients with comorbid bronchiectasis and those without.

The recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were followed for conducting and reporting of this review (5). All analyses were performed on the data extracted from previously published studies, thus ethical approval and patient consent were not required.

Search strategy: A literature search was performed to identify the clinical studies that demonstrate the impact of bronchiectasis on asthmatic patients. Databases including PubMed, Embase, Cochrane, Web of Science were searched comprehensively to identify all relevant human clinical studies published until February 2020. The search strategy used was as follows: ((bronchiectasis) AND asthma AND English [lang])

Study selections are made by two investigators (Gelei Lan and Guochao Shi), independently obtaining the potentially eligible articles based on their titles and abstracts. When opinions differed between the two investigators, discussions were made to reach an agreement. Besides, the authors of the included studies were contacted for inquiry when necessary.

Inclusion and exclusion criteria were as follows:

1. Consecutive patients aged ≥ 16 years with a diagnosis of asthma based on Global Initiative for Asthma guideline at the time of diagnosis were enrolled.
2. The diagnosis of bronchiectasis was confirmed by HRCT.
3. Patients with cystic fibrosis or traction bronchiectasis due to pulmonary fibrosis were excluded.
4. Conference abstracts, case reports, editorials, and narrative reviews were excluded in this meta-analysis.

Data extractions are made by the two investigators. They independently extracted the following data from the selected studies: the first author's name and year of publication; patients' age, gender, asthma history, symptoms, exacerbations, and hospitalizations in previous year; lung function tests; peripheral blood eosinophil level and total IgE level. The quality of included studies was evaluated according to the Agency for Healthcare Research and Quality standard (6).

Statistical analysis

The meta-analysis was conducted using the open source Review Manager (RevMan) software (Version 5.3.4, available at the website <http://ims.cochrane.org/rev-man/download>). Clinicopathological and demographic

parameters, including gender, severity of asthma, hospitalization history in the previous year, radiological characteristics, atopy, co-existence of chronic rhinosinusitis, nasal polyp, gastroesophageal reflux were assessed using the inverse variance method, and effect estimates were assessed as odds ratio (OR) (7) and 95% confidence interval (95% CI). Differences in age, smoking history, number of exacerbations in previous year, levels of total IgE and peripheral eosinophils, postbronchodilator FEV₁% predicted, and postbronchodilator ratio of FEV₁/FVC between asthmatic patients with and without comorbid bronchiectasis were estimated using the inverse variance method, and contrasts were expressed in the form of weighted mean difference (WMD) and 95% CI. For those articles without standard deviation (SD), an average SD was estimated using the methods described by Hozo et al. (8).

To test the heterogeneity of the included studies, the chi-square value was calculated for the assumption of homogeneity. The fixed-effects model was chosen when there was no heterogeneity or when the heterogeneity was negligible; while the random-effects model was chosen when there was considerable heterogeneity (defined as $I^2 \geq 75\%$, according to Cochrane Handbook) (9). Publication bias was assessed by using funnel plots.

Results

Through the database, 3505 potentially relevant articles were found. After reviewing the abstracts, 16 articles about comorbid bronchiectasis in patients with asthma were found (3,10–24). Among those, only six studies met the inclusion criteria, which included asthmatic patients with comorbid bronchiectasis ($n=385$) and asthmatic patients without comorbid bronchiectasis ($n=619$) (3,10–14). The flow diagram of the database search is represented in Figure 1.

The mean prevalence of bronchiectasis in asthmatic patients was 35.2% (range, 2.2%–47%). HRCT was used to diagnose bronchiectasis in all of the included studies. The characteristics of six studies included are summarized in Table 1. The quality evaluation of included studies is shown in Table 2.

Demographic characteristics

Asthmatic patients with comorbid bronchiectasis were older than those without bronchiectasis (WMD: 3.75 years; 95% CI: 3.13–4.36; $p < 0.00001$; Figure 2); publication bias was not detected in the funnel plot (Figure 3). Disease duration of asthmatic patients with

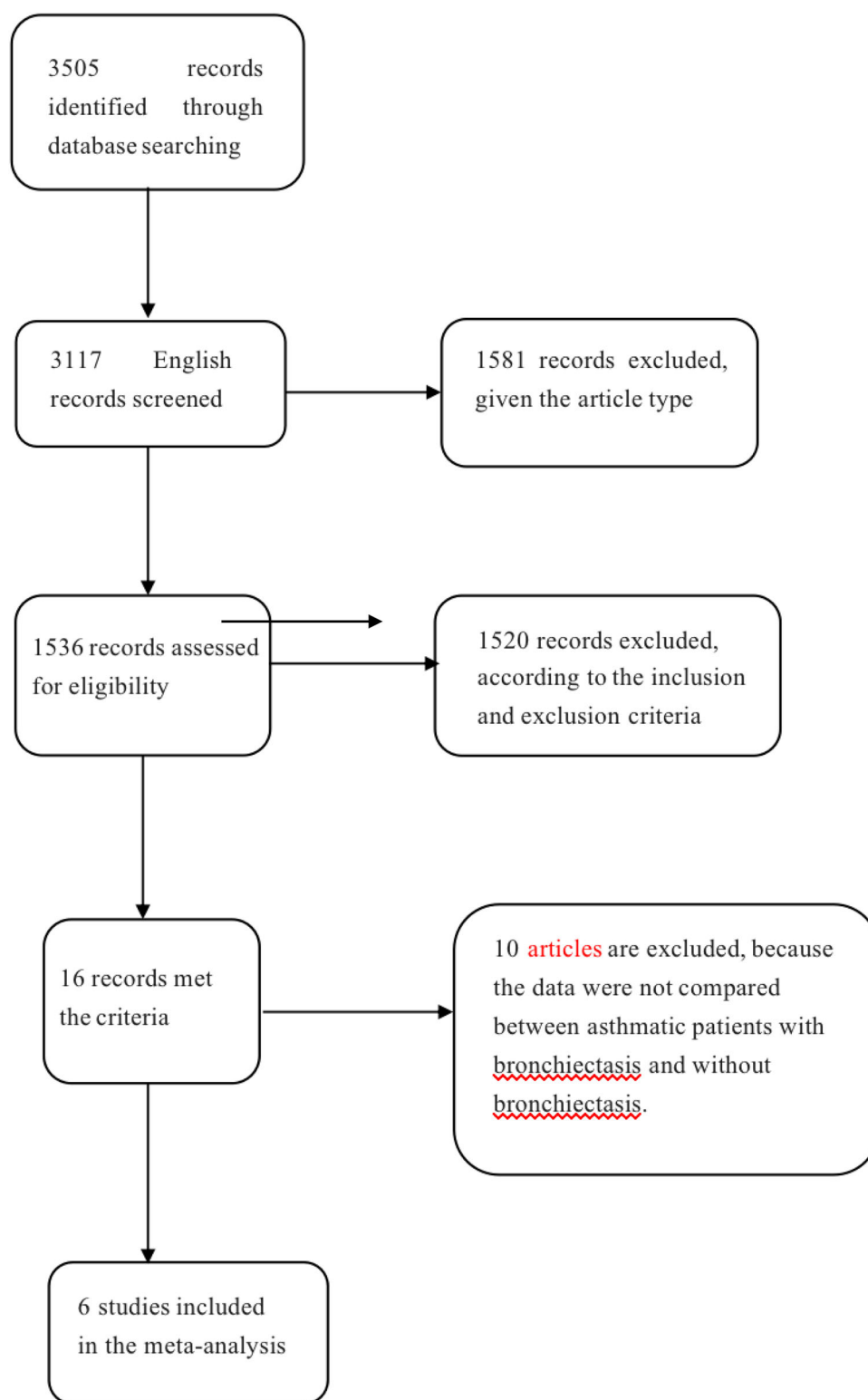


Figure 1. Flow diagram of search strategy and study selection.

bronchiectasis is longer than those without bronchiectasis (WMD: 5.89 years; 95% CI: 5.08–6.71; $p < 0.00001$; [Figure 4](#)); funnel plot did not show any publication bias ([Figure 5](#)). Whereas gender and smoking status showed no difference ([Figures 6 and 7](#)).

Clinical features

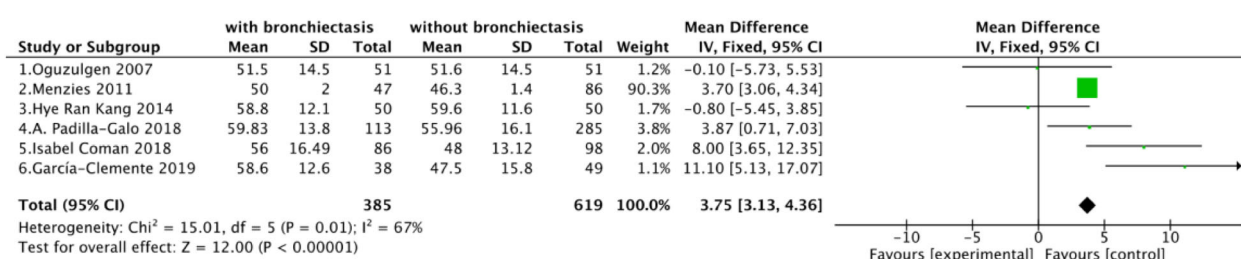
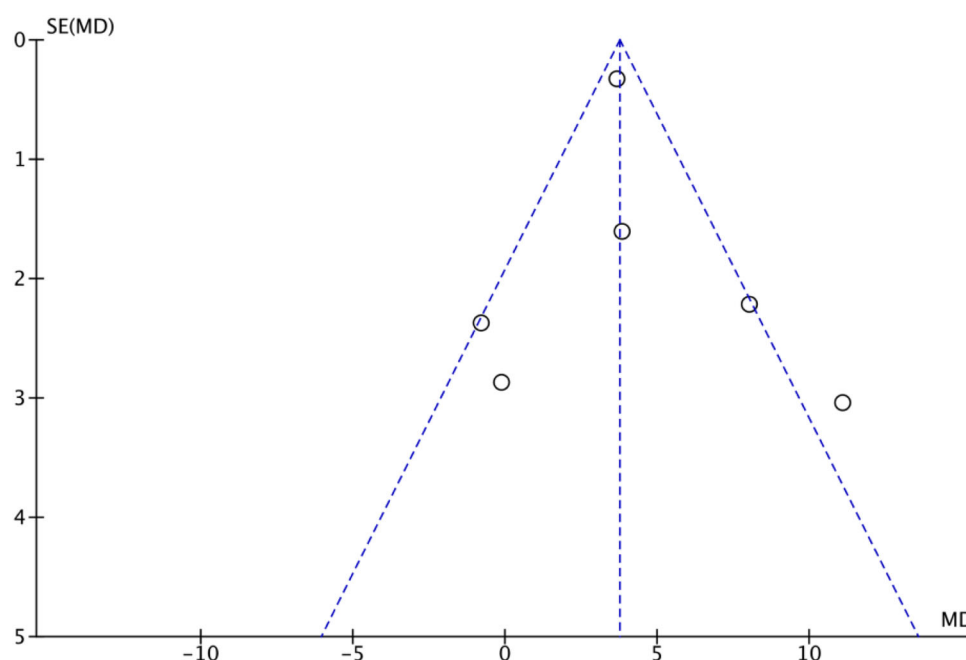
The severity of asthma was assessed according to the GINA guideline. Three of the studies mentioned the severity of asthma. Meta-analysis showed that patients with comorbid bronchiectasis were more likely to

Table 1. Characteristics of included studies.

Study number	Authors	Publication year	Time period of follow-up	Severity of asthma	Parameters under study
1	Oguzulgen et al. (11)	2007	1996–2003	Mild, moderate, severe	Age, gender, evolution of the disease, smoking status, pulmonary symptoms, atopy, history of hospitalization due to severe asthma exacerbation, presence of chronic respiratory failure, FEV ₁ % predicted, FVC%, FEV ₁ /FVC%, bronchodilator response in FEV ₁ %
2	Menzies et al. (12)	2011	Not mentioned	Severe	Age, gender, atopy, disease duration, FEV ₁ % Pre-BD, FEV ₁ /FVC% Pre-BD, FEV ₁ % Post-BD, FEV ₁ /FVC% Post-BD, ICS dose, maintenance oral steroids, findings on HRCT, bronchodilator response in FEV ₁ %, residual volume% predicted, total lung capacity% predicted, peripheral blood eosinophils and total serum IgE levels, presence of nasal polyps, Aspergillus sensitization
3	Kang et al. (3)	2014	1999–2010	Mild persistent or intermittent	Age, gender, height, weight, follow-up duration, total IgE level, atopy, smoking status, FEV ₁ % Pre-BD, FVC% Pre-BD, FEV ₁ /FVC% Pre-BD, FEV ₁ % Post-BD, FVC% Post-BD, FEV ₁ /FVC% Post-BD, change in FEV ₁ % post by bronchodilator, PC20, asthma exacerbation, steroid use, ER visit, hospitalization
4	Padilla-Galo et al. (10)	2018	Not mentioned	Moderate, severe	Age, gender, chronic expectoration, purulent sputum, dyspnea, degree of severity, evolution of asthma, exacerbations in the previous year, hospitalizations in the previous year, ED visits in the previous year, FEV ₁ % Post-BD, FVC% Post-BD, FEV ₁ /FVC% Post-BD, chronic air flow limitation, comorbidity (chronic rhinosinusitis, presence of nasal polyps, gastroesophageal reflux disease), use of antibiotics and corticoid therapy, peripheral blood eosinophils and total serum IgE levels, FeNO, Charlson index, positive sputum culture, air trapping measured by HRCT
5	Coman et al. (13)	2018	2010–2013	Severe	Age, gender, smoking status, degree of severity, treatment regimen, FEV ₁ % predicted, FEV ₁ /FVC%, atopy, presence of allergic rhinitis, chronic rhinosinusitis, atopic dermatitis, GERD, NSAIDs hypersensitivity, peripheral blood eosinophils and total serum IgE levels, eosinophil tonic protein, sensitizations, exacerbations in the previous year, hospitalizations in the previous year
6	Garcia-Clemente et al. (14)	2019	2015–2017	Severe	Age, gender, evolution of the disease, smoking status, exacerbations within the previous year, pulmonary function, treatment regimen, ICS doses, FEV ₁ % predicted, FVC%, FEV ₁ /FVC%, comorbidity (chronic rhinosinusitis, presence of nasal polyps, gastroesophageal reflux disease), atopy, hospitalizations within the previous year, cycles of antibiotic therapy in the previous year, peripheral blood eosinophils and total serum IgE levels, FeNO

Table 2. Quality evaluation of included studies.

Agency for Healthcare Research and Quality standard for cross-sectional study quality	Study number					
	1	2	3	4	5	6
Define the source of information	Yes	Yes	Yes	Yes	Yes	Yes
List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	Yes	Yes	Yes	Yes	Yes	Yes
Indicate time period used for identifying patients	Yes	No	Yes	No	Yes	Yes
Indicate whether or not subjects were consecutive if not population-based	Yes	Yes	Yes	Yes	Yes	Yes
Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	No	Yes	No	Yes	Yes	Yes
Describe any assessments undertaken for quality assurance purposes	Yes	No	Yes	No	No	No
Explain any patient exclusions from analysis	No	Yes	No	Yes	Yes	Yes
Describe how confounding was assessed and/or controlled	Yes	Unclear	Yes	Unclear	Unclear	Yes
If applicable, explain how missing data were handled in the analysis	–	–	–	–	–	–
Summarize patient response rates and completeness of data collection	Yes	Yes	Yes	Yes	Yes	Yes
Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	–	–	–	Yes	–	–

**Figure 2.** Forest plot of mean difference of age in asthmatic patients with and without bronchiectasis.**Figure 3.** Funnel plot of age in asthmatic patients with and without bronchiectasis.

present with greater severity (OR: 3.62; 95% CI: 2.40–5.49; $p < 0.00001$; **Figure 8**). And the funnel plot showed no observable publication bias (**Figure 9**).

Patients with comorbid bronchiectasis had more exacerbations (WMD: 0.71 times in the previous year; 95%

CI: 0.34–1.09; $p = 0.0002$; **Figure 10**) and greater hospitalization risk (OR: 2.28; 95% CI: 1.45–3.58; $p = 0.0004$; **Figure 12**) than those asthmatic patients without bronchiectasis. Funnel plots of these two parameters showed no observable publication bias (**Figures 11 and 13**).

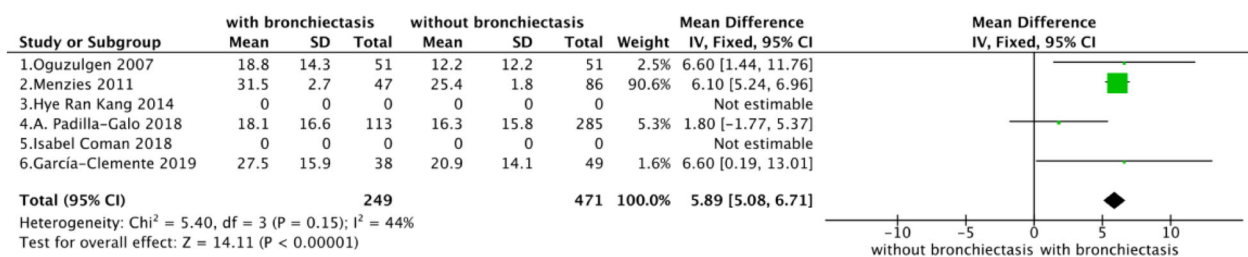


Figure 4. Forest plot of mean difference of disease duration in asthmatic patients with and without bronchiectasis.

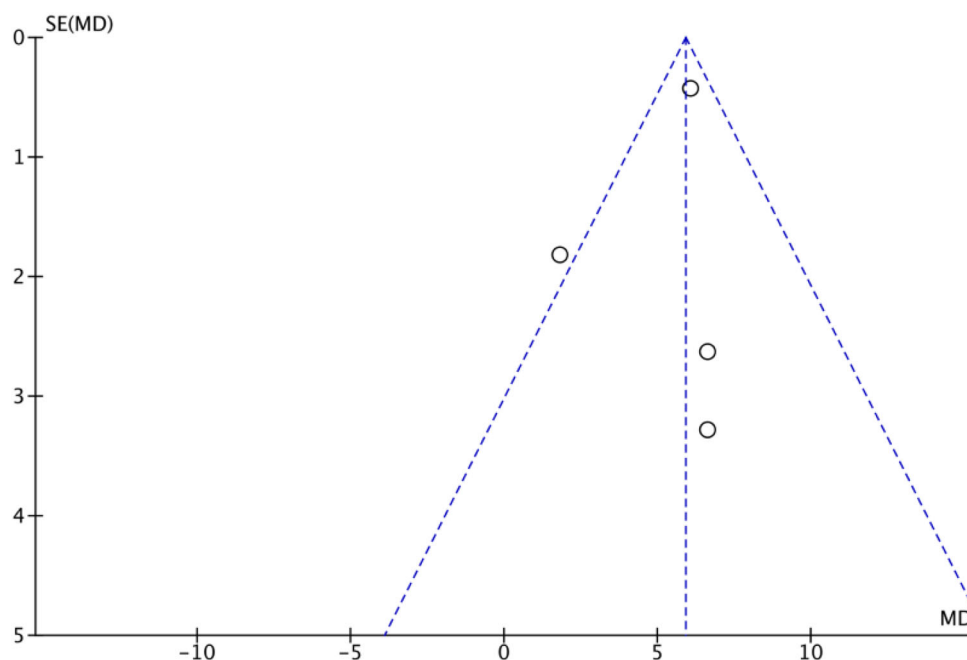


Figure 5. Funnel plot of disease duration in asthmatic patients with and without bronchiectasis.

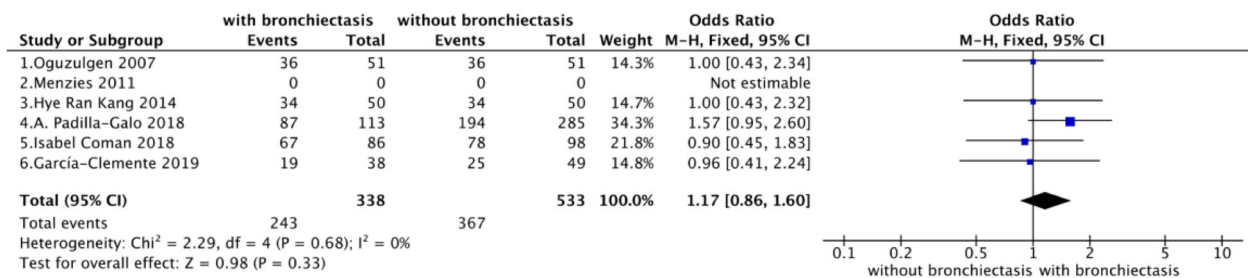


Figure 6. Forest plot of odds ratios of gender in asthmatic patients with and without bronchiectasis.

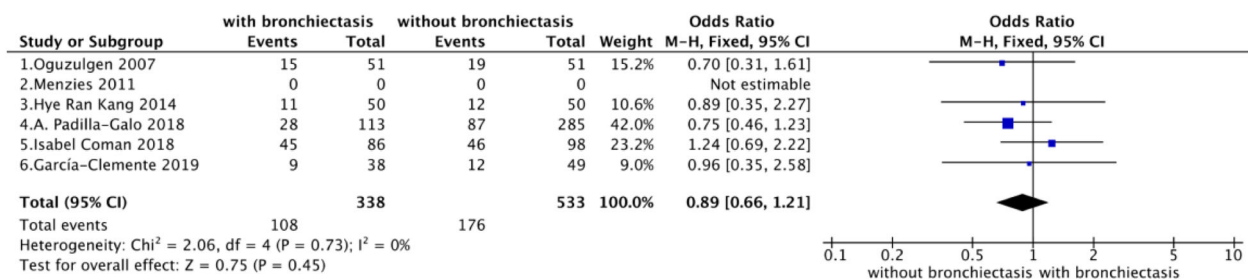


Figure 7. Forest plot of odds ratios of smoking in asthmatic patients with and without bronchiectasis.

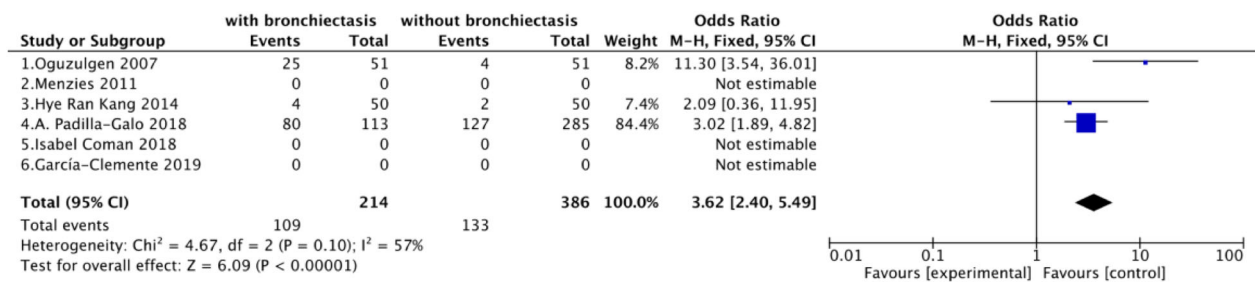


Figure 8. Forest plot of odds ratios of severity of asthma in asthmatic patients with and without bronchiectasis.

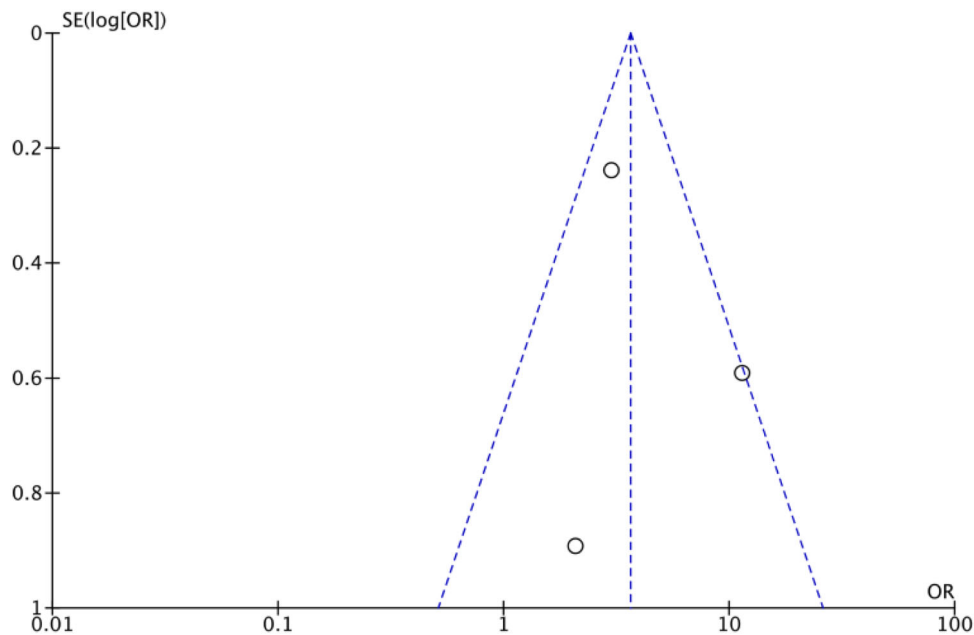


Figure 9. Funnel plot of severity of asthma in asthmatic patients with and without bronchiectasis.

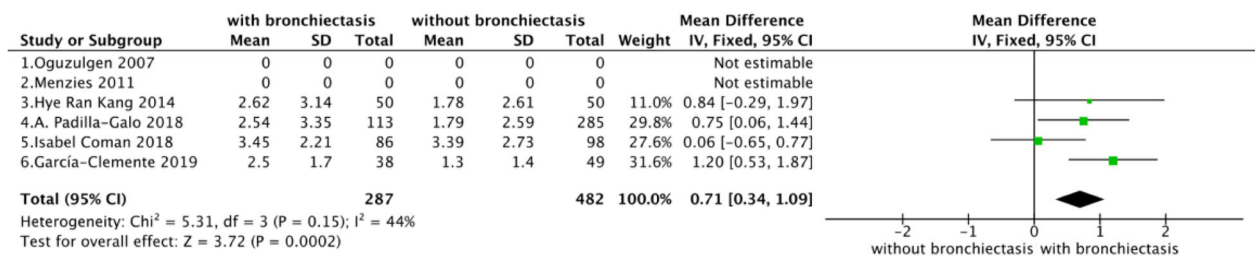


Figure 10. Forest plot of mean difference of exacerbations in asthmatic patients with and without bronchiectasis.

Radiological characteristics

Only two included articles mentioned the distribution of bronchiectasis. Oguzulgen's article reported that bronchiectasis was unilateral in 25 patients and bilateral in the remaining 26 asthmatic patients with bronchiectasis. And in the article of Padilla-Galo, 30 patients were reported to have unilateral bronchiectasis, while the other 83 patients were reported to have bilateral bronchiectasis.

Three of the included studies showed data of bronchiectasis types of these patients. In Kang's study, 30 patients presented with cylindrical bronchiectasis, 20 patients with saccular or varicose bronchiectasis, and the subtypes of bronchiectasis was not associated with disease severity. Padilla-Galo et al. showed that 105 asthmatic patients with bronchiectasis had cylindrical bronchiectasis, 8 had varicose bronchiectasis. In García-Clemente's study, 33 patients showed

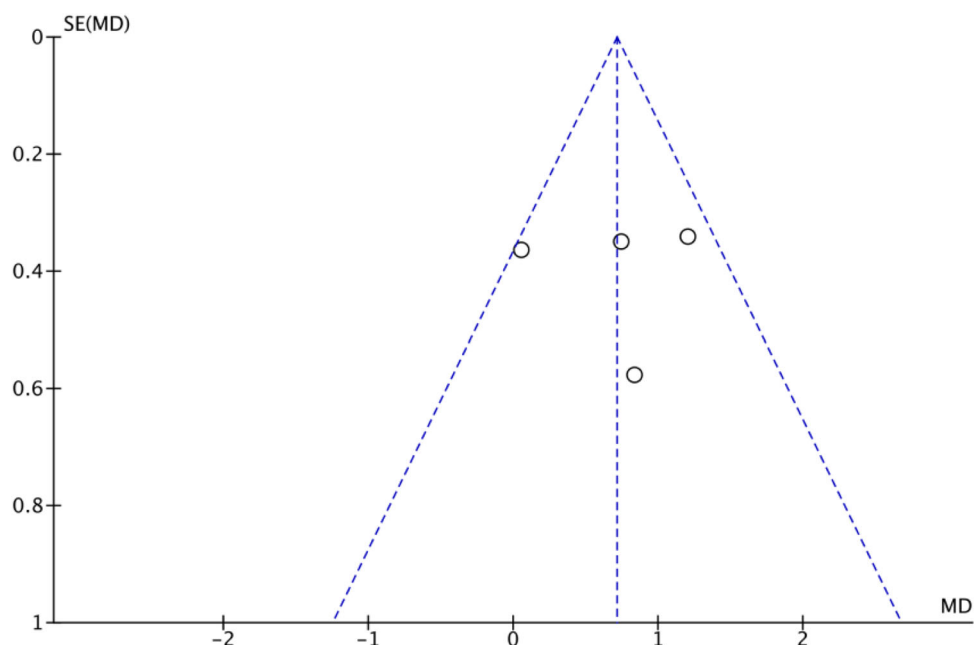


Figure 11. Funnel plot of exacerbations in asthmatic patients with and without bronchiectasis.

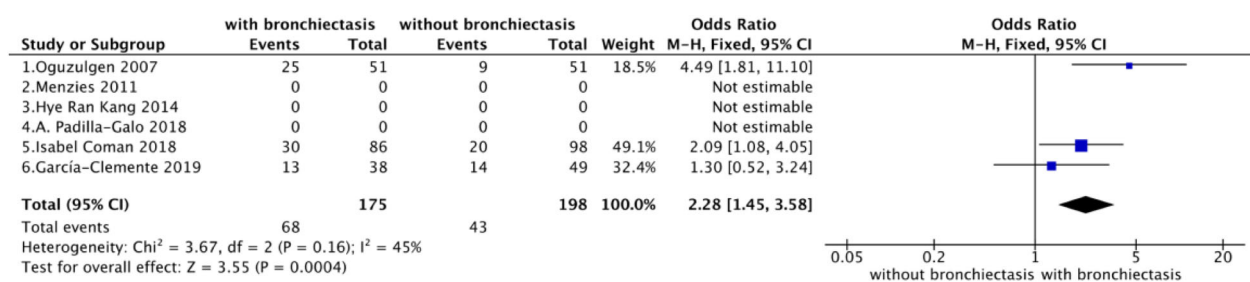


Figure 12. Forest plot of odds ratios of hospitalization risk in asthmatic patients with and without bronchiectasis.

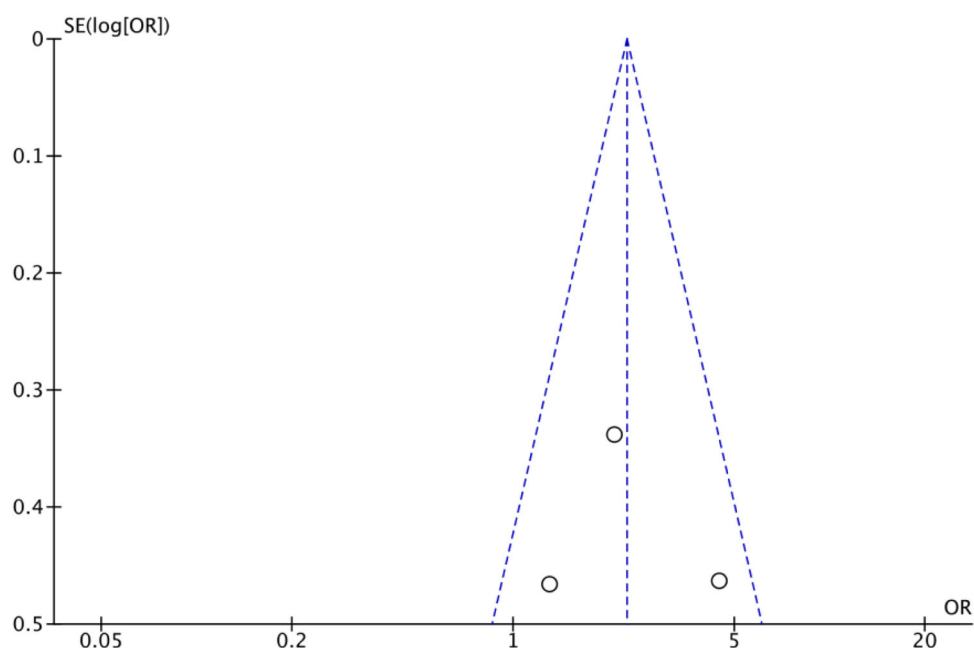


Figure 13. Funnel plot of hospitalization risk in asthmatic patients with and without bronchiectasis.

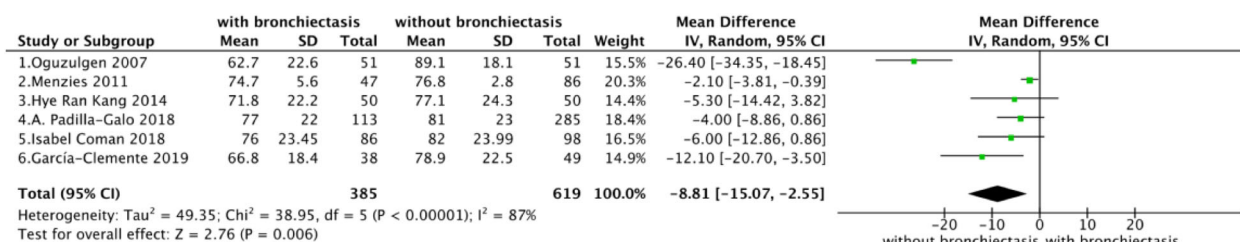


Figure 14. Forest plot of mean difference of FEV₁% predicted in asthmatic patients with and without bronchiectasis.

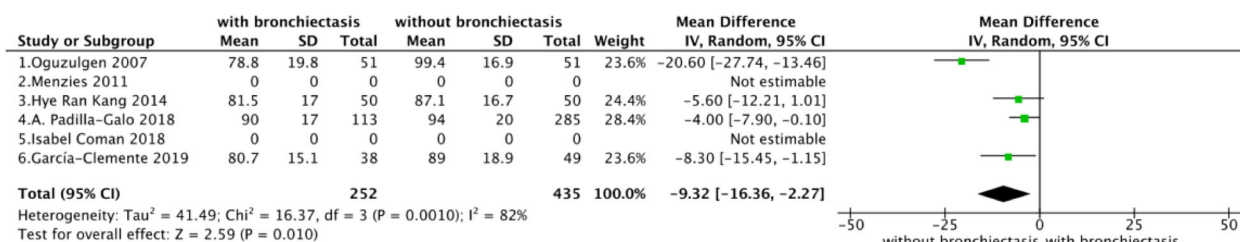


Figure 15. Forest plot of mean difference of FVC% in asthmatic patients with and without bronchiectasis.

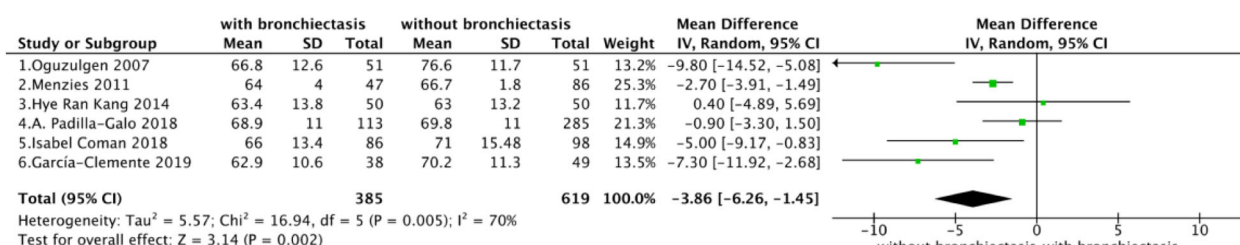


Figure 16. Forest plot of mean difference of FEV₁/FVC ratio in asthmatic patients with and without bronchiectasis.

cylindrical bronchiectasis, while 5 had varicose bronchiectasis.

Lung function

Asthmatic patients with bronchiectasis showed reduction in FEV₁% predicted (WMD: -8.81%; 95% CI: -15.06% to -2.55%; $p = 0.006$; Figure 14) and FVC% (WMD: -9.06%; 95% CI: -16.49% to -1.63%; $p = 0.02$; Figure 15). A lower FEV₁/FVC ratio (WMD: -3.86%; 95% CI: -6.26% to -1.45%; $p = 0.002$; Figure 16) was also observed in patients with asthma and bronchiectasis than those without bronchiectasis. However, funnel plots of these three parameters showed significant bias (Figures 17–19).

The heterogeneity observed in the pulmonary function tests could be explained by the fact that Oguzulgen's and Garcia-Clemente's failed to distinguish these parameters in pre- or post-bronchodilator conditions. And the I^2 could be reduced to 0 in the comparison of FEV₁% predicted and FVC%, 30% in

FEV₁/FVC ratio after excluding the studies of Oguzulgen and Garcia-Clemente.

Laboratory tests

Levels of peripheral blood eosinophils and IgE between asthmatic patients with and without comorbid bronchiectasis were analyzed (Figures 20 and 21). Considerable heterogeneities were observed. Since Menzies' study included the patients who had allergic bronchopulmonary aspergillosis, and *Aspergillus fumigatus* sensitization could elevate levels of peripheral blood eosinophilia and IgE. Heterogeneities were greatly reduced by excluding Menzies' study. We found that patients with asthma and comorbid bronchiectasis tend to have a higher level of peripheral blood eosinophils than those without bronchiectasis (WMD: 46.07 cells/ μ L; 95% CI: -1.35 to 93.50 cells/ μ L; $p = 0.06$; Figure 22). Level of IgE was higher in asthmatic patients with comorbid bronchiectasis (WMD: -88.98 IU/mL; 95% CI: -152.04 to -25.96 IU/mL;

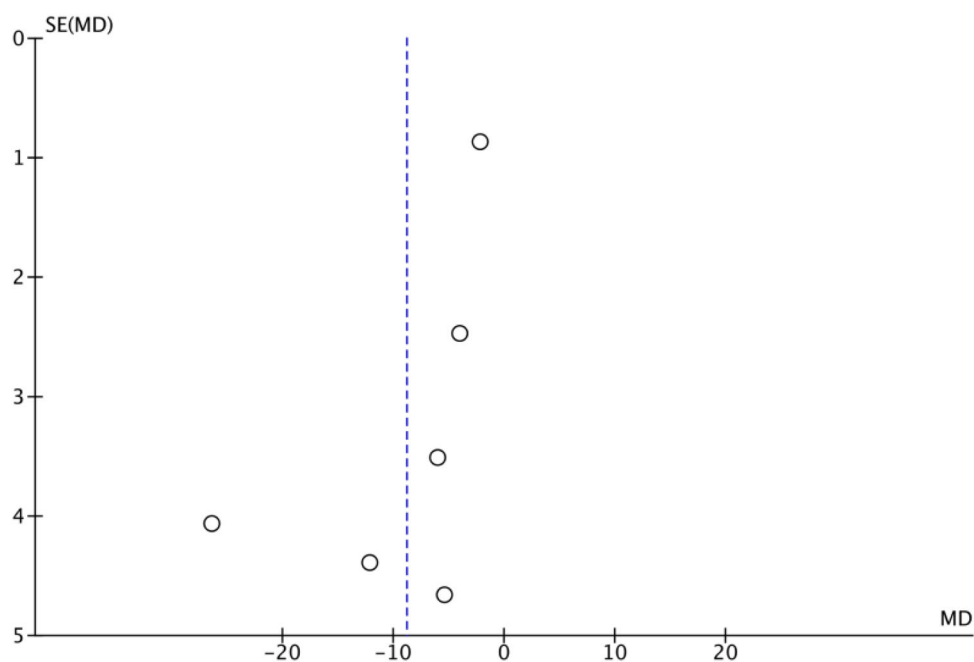


Figure 17. Funnel plot of FEV₁% predicted in asthmatic patients with and without bronchiectasis.

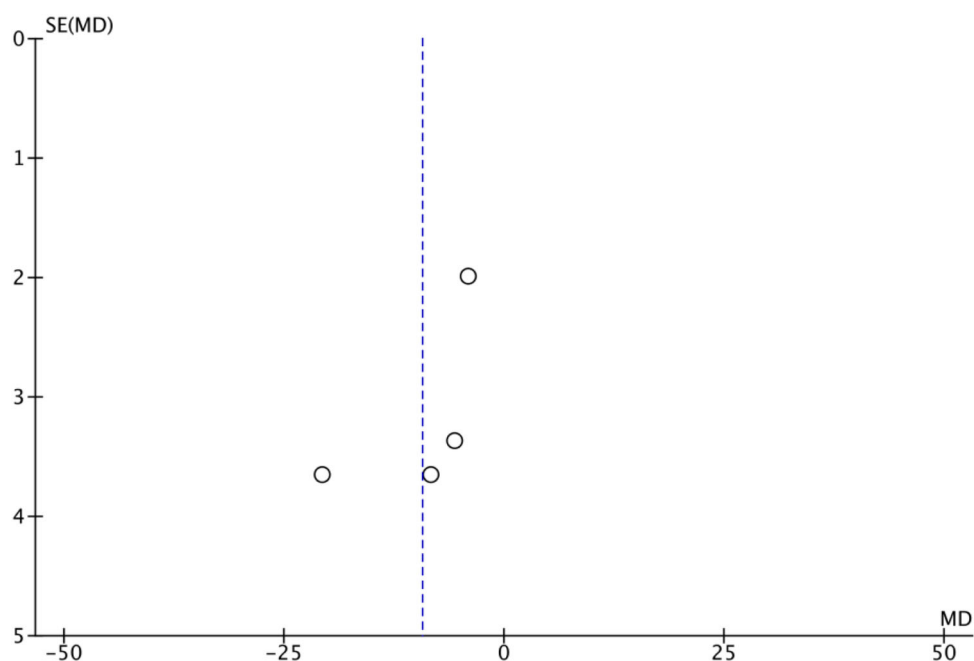


Figure 18. Funnel plot of FVC% in asthmatic patients with and without bronchiectasis.

$p = 0.006$; Figure 23). Funnel plots of these two parameters showed no publication bias (Figures 24 and 25).

Discussion

The interaction between asthma and bronchiectasis has been analyzed in various studies. The hypothesis that asthma and atopy may have a role in the pathogenesis of bronchiectasis was first postulated in 1939

(25). Since 1939 there have been many studies reporting positive relationships between bronchiectasis and bronchial hyperreactivity and/or asthma (22,26–32). In recently published studies, the detection of bronchiectasis in many asthmatic patients has led to the hypothesis that bronchial asthma might contribute to the development of bronchiectasis (10,13,33,34).

The present analysis presented that asthmatic patients with comorbid bronchiectasis were older and

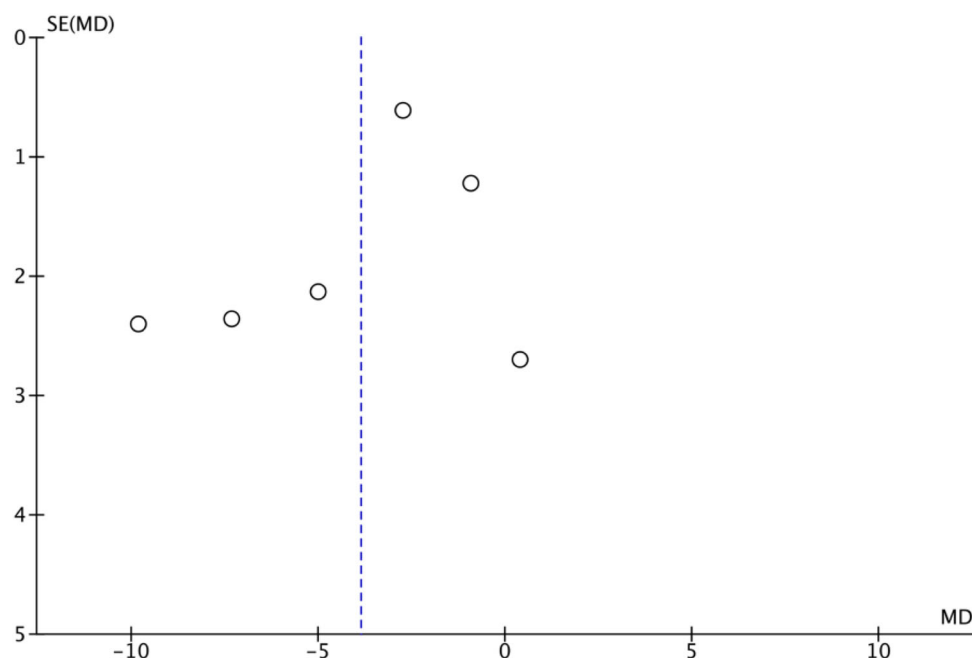


Figure 19. Funnel plot of FEV₁/FVC ratio in asthmatic patients with and without bronchiectasis.

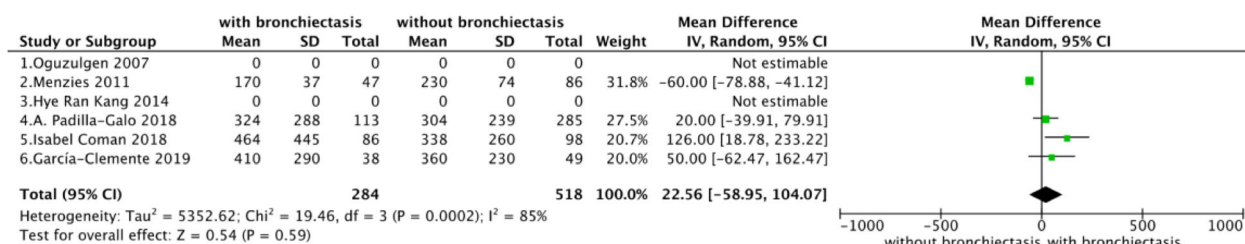


Figure 20. Forest plot of mean difference of peripheral blood eosinophil level in asthmatic patients with and without bronchiectasis (before excluding Menzies' study).

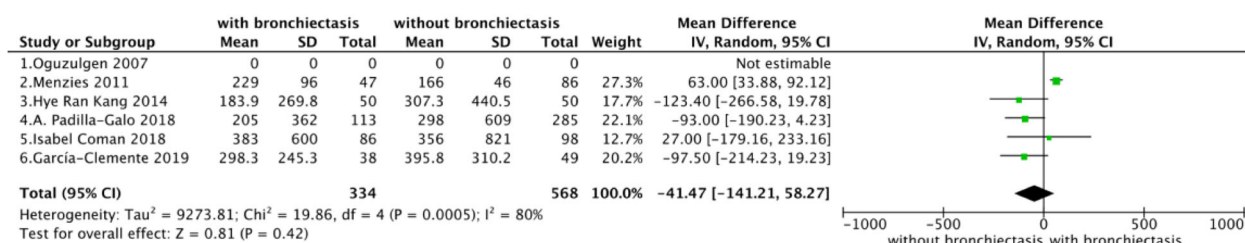


Figure 21. Forest plot of mean difference of total IgE level in asthmatic patients with and without bronchiectasis (before excluding Menzies' study).

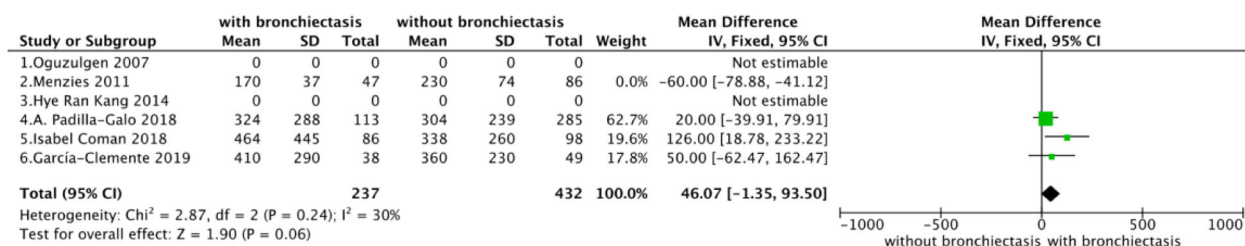


Figure 22. Forest plot of mean difference of peripheral blood eosinophil level in asthmatic patients with and without bronchiectasis (after excluding Menzies' study).

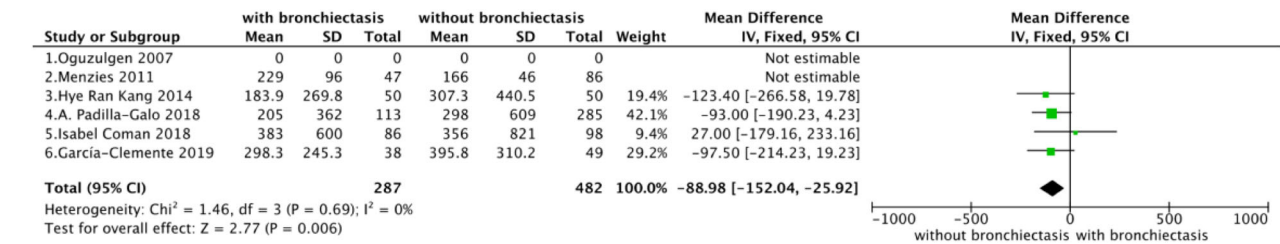


Figure 23. Forest plot of mean difference of total IgE level in asthmatic patients with and without bronchiectasis (after excluding Menzies' study).

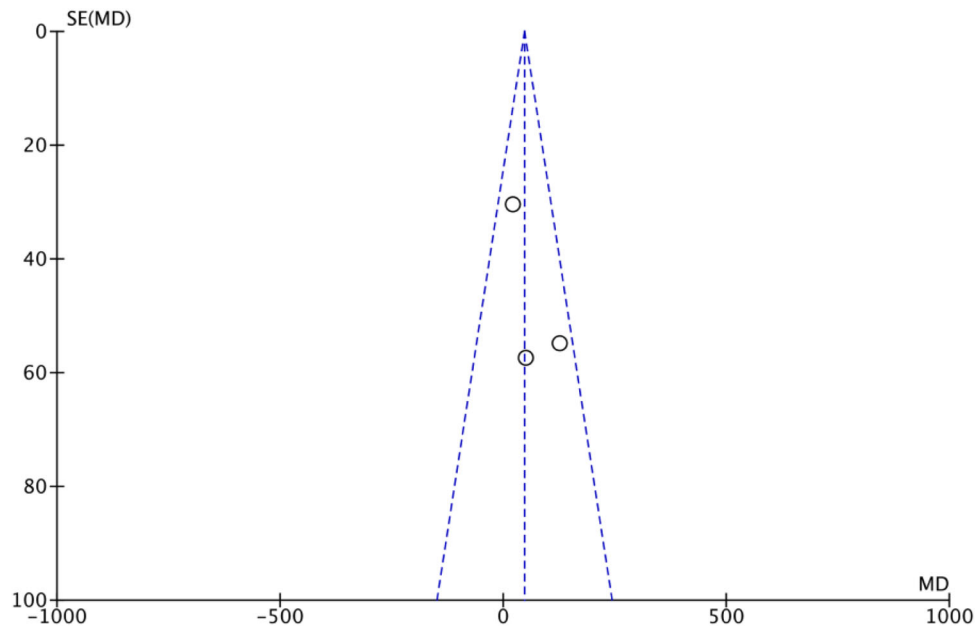


Figure 24. Funnel plot of peripheral blood eosinophil level in asthmatic patients with and without bronchiectasis (after excluding Menzies' study).

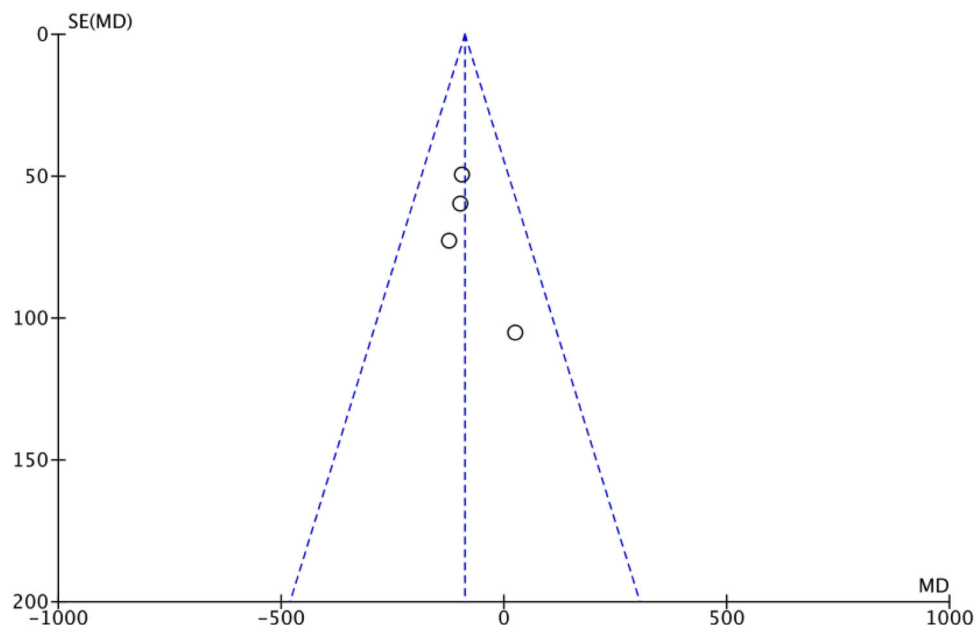


Figure 25. Funnel plot of total IgE level in asthmatic patients with and without bronchiectasis (after excluding Menzies' study).

had a longer disease duration, and showed greater severity. In patients with severe asthma, it is possible that the presence of uncontrolled bronchial inflammation leads to an increase in mucus production with subsequent formation of mucous plugs, which may induce local damage to the bronchial mucosa and could lead to structural abnormality. However, it is difficult to determine whether the severity of asthma in subjects with coexistent bronchiectasis is due to the presence of bronchiectasis, or if the presence of bronchiectasis is a manifestation of the severity of asthma itself.

In this meta-analysis, patients with asthma and comorbid bronchiectasis exhibited more frequent exacerbations and greater hospitalization risk. Persistent bacterial colonization of the airways in bronchiectasis is caused by impaired muco-ciliary transport and mucus clearance, and initiates a vicious cycle of inflammation characterized by activated neutrophils and neutrophil proteases (35). The use of inhaled antibiotics in bronchiectasis patients decreases in bacterial density, airway inflammation, and exacerbation frequency (36,37). The airway inflammation in bronchiectasis could be associated with asthma exacerbations. Nevertheless, most included studies (five studies) did not mention the microbiological characteristics of these patients, while the remaining one article only reported positive sputum culture in 22 (29.7%) asthmatic patients with bronchiectasis and 28 (21.1%) patients without bronchiectasis.

The analysis also showed poorer lung function in asthmatic patients with bronchiectasis than those without bronchiectasis. Reduction in FEV₁% predicted, FVC%, and FEV₁/FVC ratio, indicated a severe airway obstruction (38). Comorbid bronchiectasis can add to the severity of the airway obstruction in asthmatic patients.

In the present study, patients with asthma and bronchiectasis showed elevated levels of peripheral blood eosinophil and total IgE, indicating a more severe systemic eosinophilic inflammation. However, ABPA (characterized by hyper-responsiveness to aspergillus) is closely related to both bronchiectasis and asthma, and can cause elevation in eosinophil and IgE levels. Some of the included studies failed to exclude ABPA diagnosis among the enrolled patients.

The clinical significance of this analysis is that it summarized the demographic features of asthmatic patients with bronchiectasis, and concluded the impact of bronchiectasis on clinical presentation, lung function, and laboratory tests in asthmatics.

Our meta-analysis has some limitations. First, significant biases were observed for several outcomes, as

shown in funnel plots. This may have been caused by the publication bias and the small number of studies included. Second, there were detectable inter-study heterogeneities in the meta-analysis, which were difficult to avoid because the number of included studies was too small. Third, due to lack of data, analyses of parameters such as sputum characteristics, microbiological characteristics, treatment and response, blood gas analysis, and mortality were not performed.

Conclusion

Despite the limitations, this meta-analysis emphasizes the effect of bronchiectasis on asthmatic patients in several directions. Coexistence of bronchiectasis should be considered as a pathological phenotype of asthma, which may add to the asthma severity, and increase the risk of exacerbation and hospitalization.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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