Original Article

Association of serum interleukin-17 level and *Mycoplasma pneumoniae* pneumonia in children: a systematic review and meta-analysis

Nontaphat Leerach[1]^, Sutthirat Sitthisak[2], Thawatchai Kitti[3], Nattawat Teerawattanapong[4], Wiriya Mahikul[1], Supaporn Lamlertthon[2], Nathorn Chaiyakunapruk[5], Kannipa Tasanapak[2]^

[1]Princess Srisavangavadhana College of Medicine, Chulabhorn Royal Academy, Bangkok, Thailand; [2]Department of Microbiology and Parasitology, Faculty of Medical Science, Naresuan University, Phitsanulok, Thailand; [3]Department of Oriental Medicine, Chiang Rai College, Chiangrai, Thailand; [4]Department of Clinical Pharmacy, Faculty of Pharmacy, Mahasarakham University, Mahasarakham, Thailand; [5]Department of Pharmacotherapy, College of Pharmacy, University of Utah, Salt Lake City, UT, USA

Contributions: (I) Conception and design: N Leerach, N Chaiyakunapruk, K Tasanapak; (II) Administrative support: S Lamlertthon; (III) Provision of study materials or patients: N Leerach, S Sitthisak, T Kitti, K Tasanapak; (IV) Collection and assembly of data: N Leerach, S Sitthisak, T Kitti, K Tasanapak; (V) Data analysis and interpretation: W Mahikul, N Teerawattanapong, N Leerach; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Kannipa Tasanapak, PhD. Department of Microbiology and Parasitology, Faculty of Medical Science, Naresuan University, 99 Moo 9, Thapo Sub-district, Muang District, Phitsanulok 65000, Thailand. Email: kannipal@nu.ac.th.

Background: *Mycoplasma pneumoniae* (*M. pneumoniae*) is a common pathogen of community-acquired pneumonia. Interleukin-17 (IL-17) plays a role in host defense and contributes to disease severity in infection. This present study aims to investigate the association between *Mycoplasma pneumoniae* pneumonia (MPP) and changes of IL-17 level in the serum of pediatric patients.

Methods: The protocol has been registered in PROSPERO (CRD42023489451). A literature search was conducted in PubMed, EMBASE, Scopus, and Web of Science from inception to October 2023. A meta-analysis was performed to pool the mean difference (MD) with 95% confidence intervals (CIs) of IL-17 levels between patients and controls. Publication bias was assessed, and the risk of bias was evaluated using the Newcastle-Ottawa Scale (NOS).

Results: Out of 207 records, 10 studies were included in the review and 9 studies were included in the meta-analysis. Of these, 7 studies compared IL-17 in general MPP patients with controls, 6 studies compared severe MPP patients with mild MPP patients. Serum IL-17 levels were significantly elevated in general MPP patients compared with control (MD =33.94 pg/mL, 95% CI: 24.66, 43.22 pg/mL, P=0.01, I^2=99.07%; P=0.01). Subgroup analyses showed a difference in serum IL-17 levels treated by macrolide between patients and control (MD =83.96 pg/mL, 95% CI: 76.62, 91.29 pg/mL, P=0.01). In severe and mild MPP, the IL-17 levels were significantly increased (MD =19.08 pg/mL, 95% CI: 11.51, 26.65 pg/mL, P=0.01) and heterogeneity was appeared (I^2=99.39%; P=0.01). For the risks of bias, two studies had a "high risk" in comparability domain, and the 7 studies were classified as "low risk" and "unclear risk".

Conclusions: Our meta-analysis revealed that serum IL-17 levels are significantly elevated in pediatric with general and severe MPP. IL-17 might be a potential biomarker or therapeutic target for pneumonia caused by *M. pneumoniae*.

^ ORCID: Nontaphat Leerach, 0000-0003-1927-0855; Kannipa Tasanapak, 0009-0000-5910-3483.

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Introduction

Mycoplasma pneumoniae (*M. pneumoniae*) is fastidious, slow-growing 'atypical' bacterium that emerging as a common cause of upper respiratory tract infections and community-acquired pneumonia (CAP).

Mycoplasma pneumoniae pneumonia (MPP) has been reported to account for up to 40 percent of CAP cases, with children being the most susceptible group to *M. pneumoniae* infection (1). The clinical features of MPP include a non-productive cough, fever, chills, sore throat, headache, and hoarseness (2). In fulminant cases, which account for 0.5–2% of all MPP cases, clinical findings include respiratory failure with diffuse consolidation or an abnormal interstitial pattern on a chest radiograph (3). The pathogenesis of fulminant MPP is still unclear but may be related to a delayed hypersensitivity reaction to *M. pneumoniae* and delayed antibiotic administration, leading to disease progression (3). Diagnosis of MPP infection is typically performed using serologic methods such as enzyme immunoassays to detect immunoglobulin M (IgM), IgG, and IgA antibodies to *M. pneumoniae*, as well as agglutination and immunofluorescence assays (4). Additionally, polymerase chain reaction (PCR) and real-time PCR have demonstrated fast, sensitive, and specific results for amplifying *M. pneumoniae* nucleic acid (4).

The immune response plays a crucial role in the pathogenesis of MPP, with various cytokines implicated in the inflammatory process. Serum cytokine profiling reveals that the immune response patterns of general MPP (GMPP) and severe MPP (SMPP) differ during the acute phase (5). Interleukin-17 (IL-17), a pro-inflammatory cytokine primarily produced by T helper 17 (Th17) cells, plays a critical role in host defense against extracellular bacterial infections, as demonstrated in mice (6,7). It plays a key role in recruiting neutrophils, activating T cells, and stimulating macrophages and epithelial cells. Ultimately, IL-17 contributes to the production of a range of pro-inflammatory cytokines, leading to inflammatory reactions within the body. Some studies have reported elevated serum IL-17 levels in children with MPP compared to healthy controls (8-14). IL-17 is strongly associated with the severity of MPP, making it a valuable biomarker for distinguishing between mild and severe cases of the disease. Consequently, IL-17 could play a critical role in identifying and differentiating the underlying causes of pneumonia, guiding the selection of appropriate therapies or initial treatments. Selecting the correct treatment, such as the first-line use of macrolide antibiotics, could also help prevent the progression from mild to severe disease, particularly in pediatric patients (8-10). The increase in IL-17 suggests a potential role for this cytokine in host defense against *M. pneumoniae* and in the inflammatory response within the lungs. Furthermore, elevated IL-17 levels have been associated with disease severity and clinical outcomes, indicating a possible prognostic value for IL-17 measurement in pediatric MPP. Similar to other biomarkers like IL-6 and C-reactive protein (CRP), circulating IL-17 in plasma can be easily detected using immunoassays such

Highlight box

Key findings

- Association between *Mycoplasma pneumoniae* (*M. pneumoniae*) pneumonia (MPP) and the level of interleukin-17 (IL-17) in plasma of child patients.

What is known and what is new?

- The rise in IL-17 points to a possible function for this cytokine in both the inflammatory response in the lungs and the host defense against *M. pneumoniae*. Additionally, there may be a predictive utility to measuring IL-17 in child MPP since increased levels have been linked to clinical outcomes and illness severity.
- The elevated IL-17 levels in MPP pediatric cases, implying a potential prognostic importance of assessing IL-17 levels in of *M. pneumoniae* infection.

What is the implication, and what should change now?

- In order to improve the efficacy of *M. pneumoniae* infection diagnosis and treatment, we proposed that future research look at the sensitivity and specificity of elevated IL-17 levels in order to assess the usefulness of measuring IL-17 levels for detecting *M. pneumoniae* infection and tracking pneumonia severity.

as Enzyme-Linked Immunosorbent Assay, which is the standard method for detection. In healthy individuals and patients without infection or underlying autoimmune diseases, IL-17 levels are generally low compared to MPP (9-14). Thus, in this systematic review and meta-analysis, we aimed to summarize the association of IL-17 levels in children with MPP to elucidate the mechanisms underlying IL-17-mediated immune responses in *M. pneumoniae* infection and to clarify its clinical significance as a biomarker or therapeutic target. We present this systematic review and meta-analysis in accordance with the PRISMA reporting checklist (15) (available at https://tp.amegroups.com/article/view/10.21037/tp-24-218/rc).

Methods

Registration

The protocol of this systematic review was registered with PROSPERO (CRD42023489451).

Data sources and search strategy

A systematic search on the electronic online database included PubMed, EMBASE, Scopus, and Web of Science was performed from inception to October 2023 to retrieve studies reporting the serum level IL-17 in MPP. The search strategy combined key words with Boolean operators (AND, OR) as follows: ("Mycoplasma" AND "Pneumonia" OR "respiratory tract infectious disorder" OR "respiratory system disease" OR "Bacterial pneumonia" OR "lobar-pneumonia" OR "bronchopneumonia" OR "interstitial plasma cell pneumonia" OR "respiratory illness" OR "respiratory disorder" OR "lobar pneumonia" OR "bronchial pneumonia" OR "pleuropneumonia") AND ("children" OR "pediatric") AND ("Interleukin-17 levels" OR "IL-17 levels" OR "IL17" OR "Interleukin-17"). There was no limitation regarding language or region of study in this literature search.

Study selection

The inclusion criteria of study were: (I) patients with MPP; (II) conducting in children; (III) measured IL-17 in plasma or serum; (IV) availability of full text; (V) age of healthy control group matched with subjects. The exclusion criteria were: (I) pneumonia patients with other bacterial or viral infection; (II) pneumonia in immunocompromised patients; (III) IL-17 was not measured; (IV) case report or systematic review and meta-analysis; (V) results about patients were ineligible; (VI) reports were not in English. Two reviewers selected the identified articles by screening title and abstract independently. Then the full text of the studies that potentially met the criteria was obtained. The disagreements between two reviewers were resolved by consultation with a third investigator if necessary.

Data extraction and quality assessment

Data extraction was performed manually by N.L., S.S., K.T. and T.K. After accessing and reading the full text of the articles, the first author's name, publication year, country, sample size, the confirmation of *M. pneumoniae* infection, antibiotics treatment, the matched healthy controls, age, method which used to detect cytokine, specimen, mean and the standard deviation of IL-17 levels which reported in pg/mL, pg/L or ng/mL unit were extracted or checked by two authors. The units were converted into pg/mL before pooling in meta-analysis. Disagreements between individual judgements were resolved by third reviewer and discussion. The risk of bias table of the included studies was assessed according to the Newcastle-Ottawa Scale (NOS). Articles with scores of 6 or above were regarded as high-quality articles (16). Risk-of-bias VISualization (robvis) software was used to outline the risk of bias appraisal (17).

Statistical analysis

The meta-analyses were conducted with the STATA 16 software package (Stata Corporation, College Station, TX, USA) to evaluate the association between serum/plasma IL-17 and MPP in child patients. Level of IL-17 in MPP pediatric patients and healthy controls were calculated mean difference (MD) with 95% confidence interval (CI). The random-effects model in the meta-analysis was applied when the heterogeneity I^2 statistic was >25% and P value <0.1 using Cochran's *Q* test. In addition, the publication bias was assessed by means of Begg's funnel plots and Egger's statistical test. The subgroup analysis between antibiotic-treated and non-treatment was performed across studies to further investigate the study heterogeneity. In addition, the patients with mild and severe MPP were sub-group analyzed in order to sought out the source of heterogeneity. Statistical analysis will be performed using STATA 16 software package (Stata Corporation). A P value <0.05 was considered to be statistically significant.

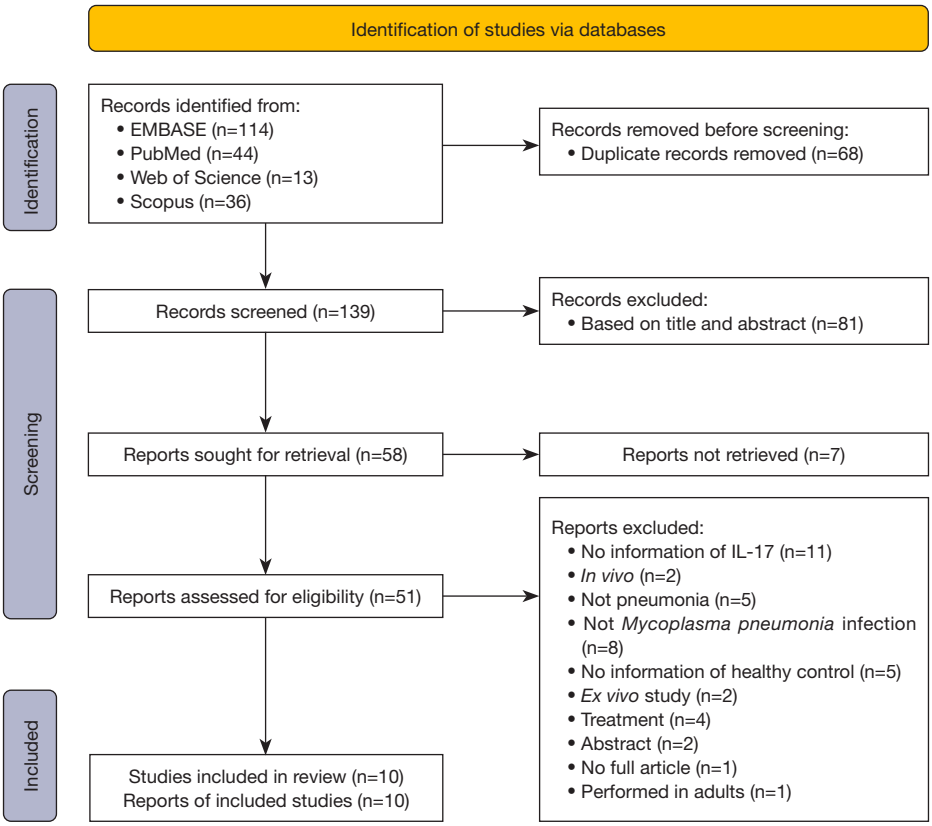

Figure 1 Study flow diagram. The flowchart demonstrates the selection of potentially relevant studies.

Results

Search results

The steps of screening of the study were shown in the PRISMA diagram (*Figure 1*), The studies were searched from PubMed, EMBASE, Scopus, and Web of Science. Total 207 relevant studies were initially identified, and 68 articles were excluded due to duplication. One hundred and thirty-nine articles were screened based on title and abstract, 51 publications met the study inclusion criteria. After reading the full text, 10 studies were included in systematic review. The findings were described in *Table 1* which revealed the tendency increasing of IL-17 in pneumonia patients.

Characteristics of included studies

In nine out of the 10 studies, the focus was on comparing IL-17 levels between pediatric patients and a control group of children (8-14,18,19). The remaining study compared IL-17 levels between children and adults (20). Therefore, data from 9 studies which conducted in children met the eligibility criteria and were able to pool in the meta-analysis. Among these 9 articles, 7 articles compared IL-17 in general MPP with those of healthy control (8-14), 6 articles compared IL-17 in refractory (severe) MPP with non-refractory (mild) MPP (10,11,13,14,18,19). The detailed characteristics of the included studies was shown in *Table 1*, the confirmation methods across studies were relied on clinical symptoms, IgG or IgM antibody titer, radiological findings, as well as PCR to detect *M. pneumonia* from specimens. All these studies were published in the period from 2016 to 2023. Among 9 studies, 7 articles compared IL-17 in general MPP with those of healthy control (8-14), and 6 articles compared IL-17 in refractory (severe) MPP with non-refractory (mild) MPP (10,11,13,14,18,19).

Quality assessment

Table 1 exhibits characteristics and shows quality scores for the studies. Eight studies were of excellent quality, and two was fair quality due to there were no explanation of

Table 1 Comparison of IL-17 levels in patients with MPP

No.	Authors	Study location	Age range (years)		MPP confirmation	Antibiotics treatment	Clinical symptoms of pneumonia	Sampling time	IL-17 level in pneumonia patients	NOS
			MPP	Control						
1	Chen *et al.* 2022 (8)	China	3.32–9.88	3.48–9.82	Clinical features of mycoplasma pneumonia ELISA test for IgM antibodies PCR to detect mycoplasma DNA from sputum	Not applicable	Fever, dry or productive cough, dyspnea, abnormal breath sounds	Not applicable	There was no differential serum expression of cytokines IL-17A in control and pneumonia	8
2	Choi *et al.* 2019 (18)	Korea	5.0–7.0	NA	Clinical features of mycoplasma pneumonia Radiological findings Serological tests such as agglutination test and ELISA to identify MP	Macrolide	Fever (>38.5 ℃), paroxysmal dry hacking cough with dyspnea, and crackles. Radiological findings of pneumonia	On admission day	The IL-17 was increased in pneumonia patients compared to control, but data was not significant	8
3	Fan *et al.* 2019 (9)	China	1.0–10.4	1.25–9.33	Clinical features of mycoplasma pneumonia Positive for *M. pneumoniae*-specific IgM and/or detection of mycoplasma DNA in throat swabs by PCR at the time of admission	Not applicable	Fever, acute respiratory symptoms (cough, tachypnoea, and difficult breathing), or both, along with the presence of new infiltrate detected by chest radiography and/or consolidation	Within 48 hours after admission	The cytokines in the plasma from the MPP patients indicated that the level of IL-17 was increased significantly compared to the healthy children	8
4	Guo *et al.* 2016 (10)	China	4.20–9.41	4.57–9.63	MPP was diagnosed on the basis of radiologic findings and confirmed by serologic testing The level of IgM MP was increased	Macrolide and a broad-spectrum antibiotic (amoxicillin/clavulanate or cefuroxime)	Macrolide responsive MP patients showed the bronchopneumonia. Refractory MPP patients showed the segmental/lobar pneumonia	In the morning after admission day	IL-17 was significantly increased compared with controls. IL-17 was found to be dramatically elevated in the patients with refractory MPP than macrolide responsive MPP patients	8
5	Li *et al.* 2019 (11)	China	3.66–9.16	Matched	Detection of *M. pneumoniae* DNA in nasopharyngeal aspirates by real-time PCR Elevated of specific IgM and IgG antibodies against *M. pneumoniae* in paired sera by ELISA	Not applicable	Fever, chest radiography, chest CT, and thoracic ultrasound	Within 24 hours after admission	Children with MPP had significantly higher level of IL-17 compared to controls	8
6	Zhao *et al.* 2020 (19)	China	6.0–12.0	NA	Clinical features of mycoplasma pneumonia Detection of anti-MP IgM antibody PCR to detect mycoplasma DNA	Not applicable	Symptoms of respiratory tract infection and a chest radiograph showing manifestations of pneumonia, with or without pleural effusion, tachypnea, cyanosis, hypoxia, segmental or lobar pneumonia	On admission day	IL-17 was significantly increased and used to predict refractory MPP	6
7	Wang *et al.* 2023 (20)	China	4.87–10.70	21.78–35.40	Positive for serum *M. pneumoniae* IgM antibody with the titers ≥1:80 Positive for serum *M. pneumoniae* by agglutination test	Not applicable	Not reported	Within 24 hours after admission	The levels of IL-17 in children with MPP were significantly higher than those in the adult control group	8
8	Wang *et al.* 2020 (12)	China	3.90–10.10	4.50–10.90	Clinical features of mycoplasma pneumonia Positive for anti-mycoplasma IgM antibody (titers were ≥1) Four-fold increase of anti-*M. pneumoniae* IgG	Not applicable	Fever, cough, dyspnea, and crackles, and radiological findings	On admission day	The IL-17 level was significantly increased in patients with MPP compared with healthy control group	9
9	Xu *et al.* 2019 (13)	China	3.77–4.87	4.34	Clinical features of mycoplasma pneumonia Serological tests PCR tests to detect mycoplasma DNA from nasopharyngeal secretions	Macrolide (azithromycin)	Mild MPP was defined as: respiratory rate <70 breaths/min at age <3 years old or respiratory rate <50 breaths/min at age ≥3 years old, normal food-intake, no dehydration Severe MPP was defined as: respiratory rate ≥70 breaths/min at age <3 years old or respiratory rate >50 breaths/min at age ≥3 years old, cyanosis, flaring of the nares, marked retractions, anorexia, dehydration, pleural effusion, lung necrosis/lung abscess and other complications in lung	Within 24 hours after admission	Compared with the control subjects, in both mild and severe MPP patients exhibited the significantly higher level of IL-17 in plasma	8
10	Zhang *et al.* 2023 (14)	China	1.70–7.40	NA	Clinical features of mycoplasma pneumonia Detection of serum MP-IgM Detection of nasopharyngeal aspirate MP-deoxyribonucleic acid >1.0×10^5 copies/L	Not applicable	Fever, cough, dyspnea, and abnormal lung auscultation, and the laboratory findings included new infiltrates on chest radiography	Within 24 hours after admission	IL-17 in the RMPP group were significantly higher than those in the normal control and GMPP groups	6

IL, interleukin; MPP, Mycoplasma pneumoniae pneumonia; NOS, Newcastle-Ottawa Scale; ELISA, Enzyme-Linked Immunosorbent Assay; IgM, immunoglobulin M; PCR, polymerase chain reaction; NA, not applicable; MP, *Mycoplasma pneumoniae*; IgG, immunoglobulin G; CT, computed tomography; RMPP, refractory MPP; GMPP, general MPP.

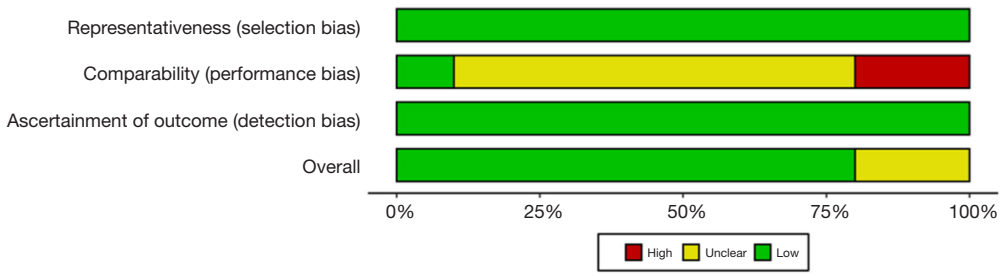

Figure 2 Risk of bias graph.

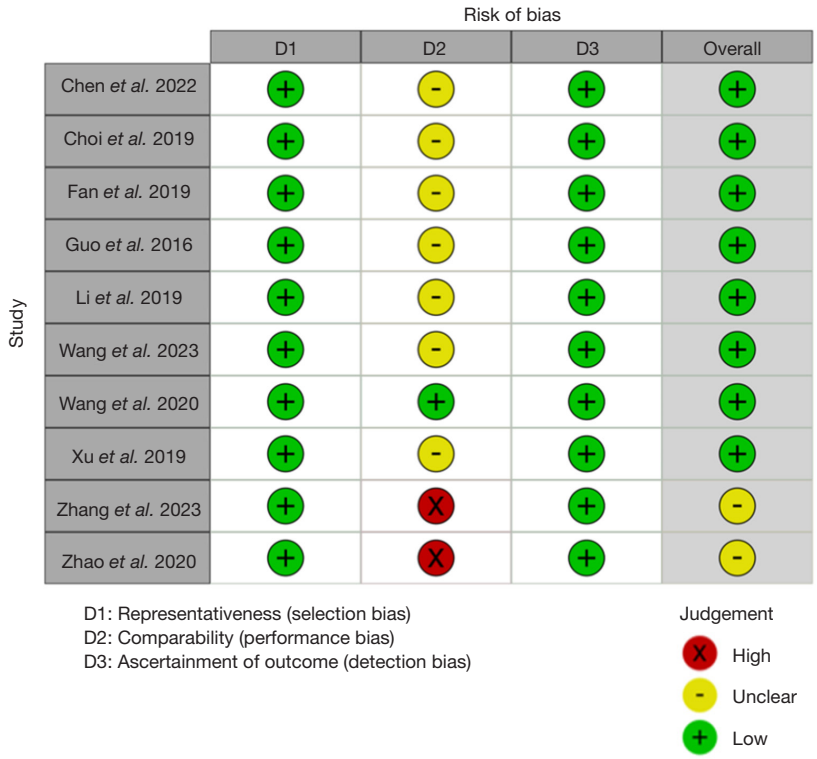

Figure 3 Risk of bias summary.

inclusion criteria of healthy individual for control group. The risk of bias for included studies in meta-analysis are showed in *Figures 2,3*.

Results of meta-analysis

Meta-analysis of serum IL-17 level in general MPP patients and healthy control

Seven studies compared serum IL-17 level in general MPP with healthy control (8-14). The forest plot for serum IL-17 level in different groups is shown in *Figure 4*. Total IL-17 was detected by magnetic-beads assay (8,9), and ELISA (10-14). The overall results reported that serum IL-17 levels were statistically significantly increased in general MPP compared to healthy control. The overall result is shown in *Figure 4* (MD =33.94 pg/mL, 95% CI: 24.66, 43.22 pg/mL, P=0.01, P for heterogeneity was 0.01, I^2=99.07%). In order to sought out the source of heterogeneity, the sub-group analysis of antibiotic-treated and non-treatment was performed.

Although the above result revealed that serum IL-17 levels significantly differed between children with MPP and healthy

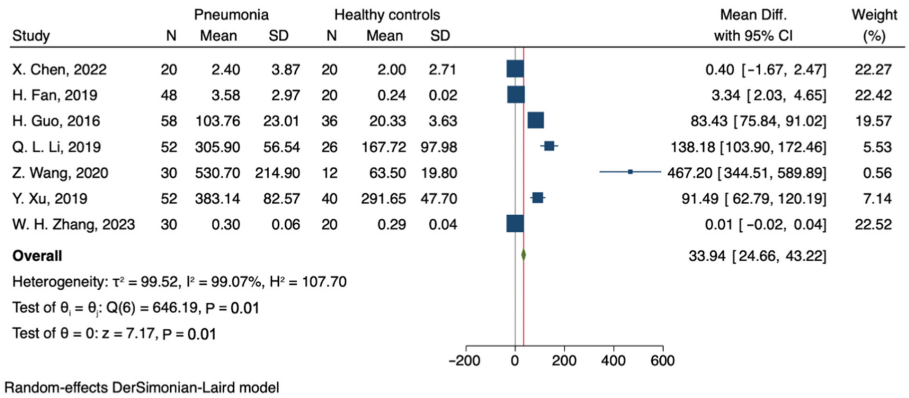

Figure 4 The forest plot showing the difference in the IL-17 levels between pneumonia patients and healthy controls, included antibiotic treatment and non-treatment. The measurement method used to detect IL-17 were magnetic-beads assay and ELISA. N, number of participants; SD, standard deviation; Mean diff., mean difference; CI, confidence interval; IL-17, interleukin-17; ELISA, Enzyme-Linked Immunosorbent Assay.

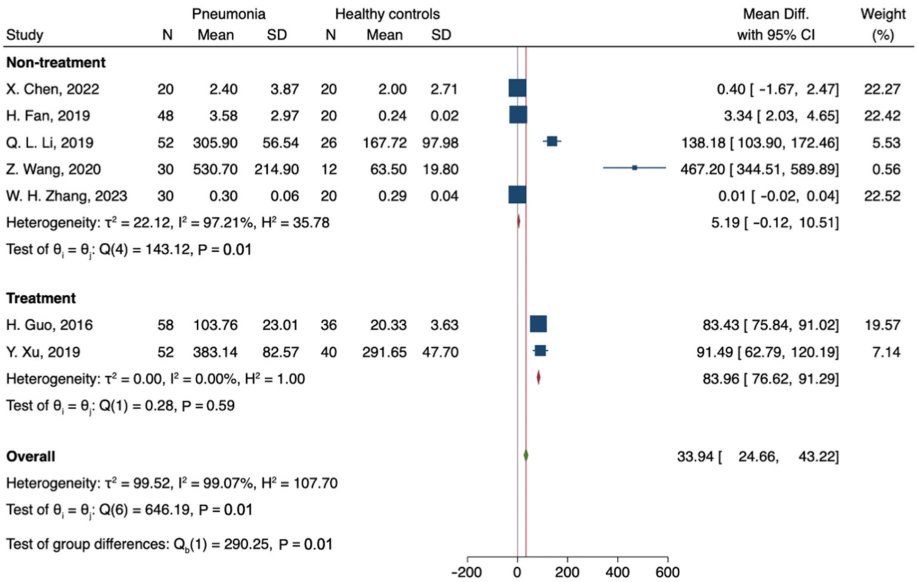

Figure 5 Forest plot showing the difference in the IL-17 levels between pneumonia patients and healthy controls. The sub-group analysis between antibiotic treatment and non-treatment. The methods were magnetic beads and ELISA. N, number of participants; SD, standard deviation; Mean diff., mean difference; CI, confidence interval; IL-17, interleukin-17; ELISA, Enzyme-Linked Immunosorbent Assay.

children, levels in pediatric MPP with and without macrolide treatment were remained elusive. Here, we found that IL-17 levels were significantly different in MPP children with antibiotic-treatment (MD =83.96 pg/mL, 95% CI: 76.62, 91.29 pg/mL) as shown in *Figure 5* while IL-17 levels were not significantly different in MPP children with non-treatment (MD =5.19 pg/mL, 95% CI: −0.12, 10.51 pg/mL). The P value of group difference between antibiotic-treatment and non-treatment was 0.01. In the subgroup analysis, significant heterogeneity was observed for non-treatment (I^2=97.21%; P=0.01) while treatment was not (I^2=0.00%; P=0.59) (*Figure 5*).

Meta-analysis of serum IL-17 level in refractory (severe) MPP and non-refractory (mild) MPP

Six studies compared serum IL-17 level in refractory (severe)

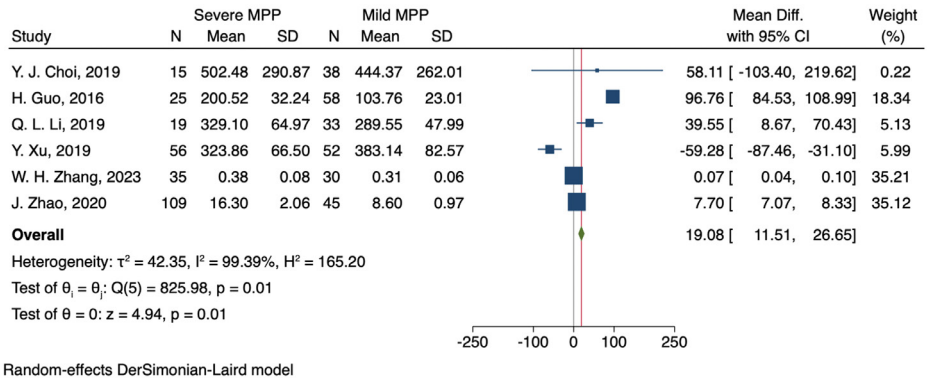

Figure 6 Forest plot showing the difference in the IL-17 levels between severe pneumonia and mild pneumonia patients. MPP, *Mycoplasma pneumoniae* pneumonia; N, number of participants; SD, standard deviation; Mean diff., mean difference; CI, confidence interval; IL-17, interleukin-17.

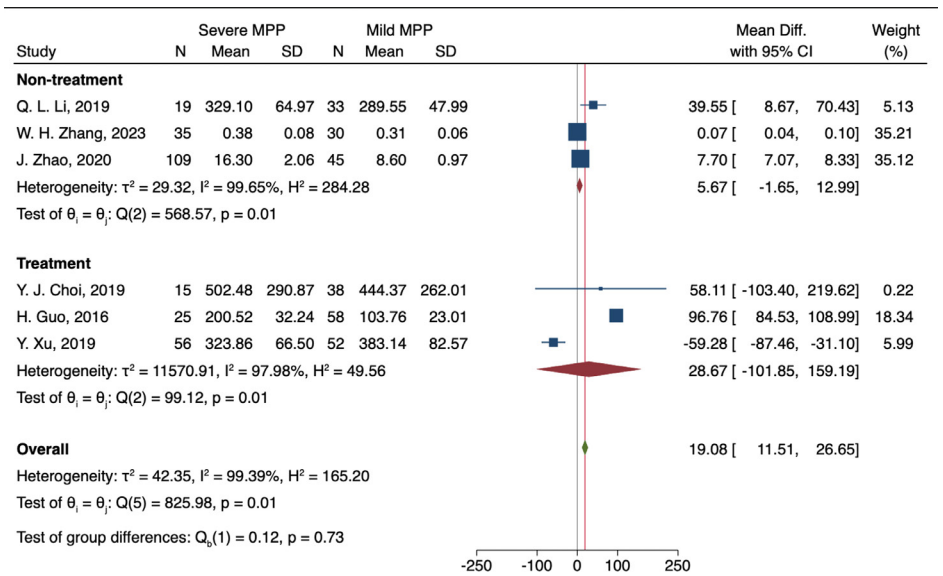

Figure 7 Forest plot showing the difference in the IL-17 levels between severe pneumonia and mild pneumonia patients. The sub-group analysis between antibiotic treatment and non-treatment. MPP, *Mycoplasma pneumoniae* pneumonia; N, number of participants; SD, standard deviation; Mean diff., mean difference; CI, confidence interval; IL-17, interleukin-17.

MPP and non-refractory (mild) MPP (10,11,13,14,18,19). The forest plot for serum IL-17 levels in severe and mild MPP was shown in *Figure 6*. Total IL-17 was detected by ELISA. According to meta-analysis, IL-17 levels were significantly increased in severe pneumonia (MD =19.08 pg/mL, 95% CI: 11.51, 26.65 pg/mL, P=0.01; P for heterogeneity =0.01, I^2=99.39%). Although a high degree of heterogeneity of the outcome presented, the meta-analysis results implied that IL-17 is associated with MPP severity.

The levels of IL-17 were not significant different in severe MPP and mild MPP with antibiotic-treatment and non-treatment. The results showed in *Figure 7* (non-treatment: MD =5.67 pg/mL, 95% CI: –1.64, 12.99 pg/mL; treatment: MD =28.67 pg/mL, 95% CI: –101.85, 159.19 pg/mL, respectively). The P value of group difference in severe MPP and mild MPP with antibiotic-treatment and non-treatment was 0.73. In the subgroup analysis, significant heterogeneity was observed both for non-treatment

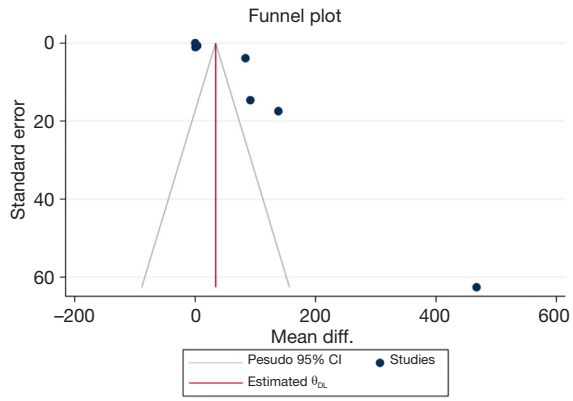

Figure 8 Funnel plot of effect sizes included in the meta-analyses for IL-17 levels between pneumonia patients and healthy controls in children, included antibiotic treatment and non-treatment. Mean diff., mean difference; CI, confidence interval; IL-17, interleukin-17.

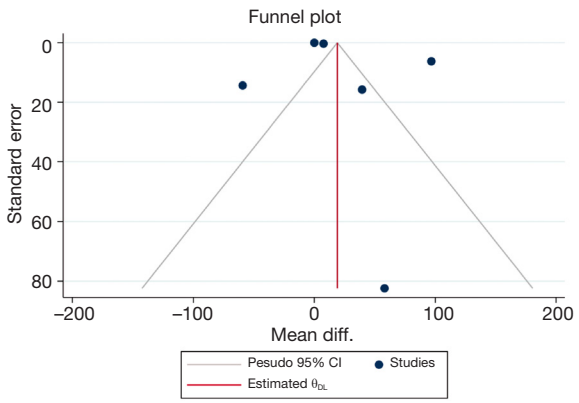

Figure 9 Funnel plot of effect sizes included in the meta-analyses for IL-17 levels between severe pneumonia and mild pneumonia patients. Mean diff., mean difference; CI, confidence interval; IL-17, interleukin-17.

(I^2=99.65%; P=0.01) and treatment (I^2=97.98%; P=0.01).

Assessment of publication bias

A funnel plot for serum IL-17 level in general MPP and healthy control (*Figure 8*), and mild MPP and severe MPP (*Figure 9*) were performed. Funnel plot showing an asymmetrical distribution of the effect estimates between the middle line of the plot. The results exhibited some publication bias since the graph show the asymmetrical characteristic of the funnel plot. Publication bias underwent visual assessment using funnel plots and statistical evaluation through Egger's test with P value was 0.01. The analysis of publication bias depicted in this figure visually demonstrates the skewness of the observed effect sizes, as depicted in *Figures 6*,7. Asymmetry of the funnel plot was suspected, and this asymmetry might by due to the presented of heterogeneity of data showing that publication bias was discovered.

Discussion

M. pneumoniae is one of the most common causes of CAP in children. Community-acquired *M. pneumoniae* epidemics typically present in school-aged children and young adults (21,22). *M. pneumoniae* infection in young children has been receiving more attention and the high prevalence of *M. pneumoniae* infection in children can be attributed to several factors such as close contact in group settings, immature immune systems, lack of pre-existing immunity (1). Given the high prevalence influenced by these factors, our study was focused on IL-17 levels in pediatric populations. Ten studies were included in the systematic review and nine studies were from China. We observed that the prevalence rate of MPP in China is the highest compared to other countries (23). In addition, according to a study on global research trends in MPP, China ranked first in terms of the number of publications (24). Several factors may contribute to the higher prevalence of *M. pneumoniae* infections in China, including population density, climate variations, and the presence of antibiotic-resistant strains (23).

Our results revealed that all seven studies reported a statistically significant increase in serum IL-17 levels in pediatric patients with MPP compared to healthy controls. This consistency across multiple studies strengthens the reliability of the findings and suggests a robust association between MPP and elevated IL-17 levels. Recent progress shows importance of IL-17 in both innate and acquired immunity against infections, it is considered as an important inflammatory mediator that is critical in the protection from pneumococcal colonization in airways (11,25). These evidence supports the potential utility of IL-17 in clinical practice as a biomarker for *M. pneumoniae* infection.

Macrolides are the first-line treatments for *M. pneumoniae* infections in children for its low minimum inhibitory concentrations (MICs) and toxicity (26). The results indicate that there is a significant increase in

IL-17 levels in children with MPP who were treated and non-treated with antibiotics compared to those with healthy control. Increase IL-17 may be involved in the macrolide resistance of *M. pneumoniae*. Many publications have reported, macrolide resistance has been rapidly rising worldwide. In addition, effecting of antimicrobial treatment for *M. pneumoniae* has been found to be related to immune reaction (27). Macrolide-resistant MPP (MRMP) first developed in Asia, where MRMP rates have increased to 90–100% in China (28).

The pathogenesis of *M. pneumoniae* infections results from the immunological response following infection generates inflammatory reactions that may cause pneumonia (29). IL-17 is primarily produced by Th17 cells and plays a pivotal role in recruiting neutrophils and enhancing antimicrobial activity in the lungs. During mycoplasma infection, IL-17 may contribute to the pathogenesis of MPP by promoting inflammation and tissue damage (30). Animal study has demonstrated that IL-17 mediates lung injury by promoting neutrophil accumulation led to pleuropneumonia (31). Thus, we performed meta-analysis of serum IL-17 level in refractory (severe) MPP and non-refractory (mild) MPP. The result showed significantly increased IL-17 levels in severe pneumonia cases. Therefore, IL-17 is associated with the severity outcome of MPP. Given that treatment and management strategies vary depending on the infectious agent, it is essential to accurately identify the cause of pneumonia. In cases of *M. pneumoniae* with viral co-infection, patients typically receive macrolide antibiotics. Since IL-17 levels are not elevated in viral pneumonia cases, this cytokine could serve as a potential biomarker for distinguishing between pneumonia caused by *M. pneumoniae* and that caused by viruses (18). Additionally, IL-17 is significantly correlated with the severity of MPP, providing a means to differentiate between mild and severe pneumonia, whereas other biomarkers such as CRP and interferon-γ inducible protein 10 (IP-10) do not demonstrate the same correlation. Moreover, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a recently identified biomarker, has been found to significantly increase in cases of pneumonia positive for *M. pneumoniae* (32). Therefore, IL-17 could play a crucial role in identifying and differentiating the causes of pneumonia, guiding the selection of appropriate therapies or initial treatments, such as steroids and antibiotics, and improving risk stratification. IL-17 also has predictive value for disease severity, and regular monitoring of IL-17 levels during treatment could provide valuable insights into the effectiveness of therapeutic interventions, allowing for adjustments based on the patient's inflammatory status. Consequently, combining IL-17 detection with TRAIL could enhance the diagnosis of MPP, facilitating the differentiation between healthy individuals and those with severe or non-severe MPP.

The current study has some limitations, as the data included in this analysis exhibited significant heterogeneity. The presence of heterogeneity in the results could be linked to differences in study designs, methodologies, and sampling time. According to methodologies, some studies utilized magnetic beads-based assay while other studies used ELISA for IL-17 measurement. Additionally, different ELISA manufacturers provided different lower detection limits, which could also contribute to the heterogeneity observed. Blood samples from patients were collected either on the day of admission or within 24 hours, which is considered the optimal timing for sample collection in clinical practice. However, one study reported blood collection within 48 hours after admission, and another did not specify the timing. Additionally, each study confirmed MPP in patients using standardized methods before performing IL-17 detection. These methods included ELISA IgM titers, PCR, and clinical features of MPP, ensuring a consistent approach across the studies. However, the findings should be interpreted with caution, taking into account the potential variability across different study settings. Finally, there were a limited set of studies included in the meta-analysis which investigated the differences in IL-17 levels among severe and non-severe MPP cases, as well as between individuals with pneumonia and those without the conditions. Thus, more evidence with larger sample sizes, is needed to investigate the association of IL-17 levels with MPP in further studies.

Conclusions

In conclusion, this systematic review and meta-analysis revealed the elevated IL-17 levels in MPP pediatric cases, implying a potential prognostic importance of assessing IL-17 levels in of *M. pneumoniae* infection. We suggested that forthcoming research should examine the sensitivity and specificity of elevated IL-17 levels to evaluate the efficacy of measuring IL-17 levels for detecting *M. pneumoniae* infection and monitoring pneumonia severity, aiming to enhance the effectiveness of *M. pneumoniae* infection

diagnosis and management.

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Footnote

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