Meta-Analysis of Risk Factors for Severe Mycoplasma pneumoniae Pneumonia in Children: Postprint

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Abstract

In recent years, the incidence of Mycoplasma pneumoniae pneumonia in children has continued to rise, with a corresponding increase in the number of severe Mycoplasma pneumoniae pneumonia cases, which has attracted widespread attention from clinicians. Understanding the risk factors associated with severe Mycoplasma pneumoniae pneumonia to assess disease severity, prevent severe cases, and reduce sequelae has been a research hotspot. Although numerous studies have investigated the risk factors for severe Mycoplasma pneumoniae pneumonia, these studies vary in time and geographical region, necessitating a systematic review and analysis for comprehensive understanding.

Objective To systematically evaluate the risk factors for severe Mycoplasma pneumoniae pneumonia.

Methods A computerized search was conducted in CNKI, Wanfang, VIP, CBM, Duxiu, Yiigle, Cochrane Library, PubMed, Embase, Web of Science, Science Direct, and BioMed Central to collect relevant studies on risk factors for severe Mycoplasma pneumoniae pneumonia in children, with the search period spanning from database inception to August 2023. After two researchers independently screened the literature, extracted data, and assessed the risk of bias in the included studies, Meta-analysis was performed using Stata 14.0 and RevMan 5.4 software.

Results A total of 22 studies, all retrospective case-control studies involving 4,531 children, were included. The Meta-analysis results showed that C-reactive protein (CRP) [OR=1.92, 95%CI (1.72-2.15), P<0.00001], erythrocyte sedimentation rate (ESR) [OR=2.61, 95%CI (2.12-3.22), P<0.00001], procalcitonin (PCT) [OR=2.60, 95%CI (1.43-4.75), P=0.002], D-dimer [OR=4.36, 95%CI

(2.93-6.50), P<0.00001], white blood cell count (WBC) [OR=1.98, 95%CI (1.66-2.36), P<0.00001], lower lobe lesions [OR=5.70, 95%CI (3.48-9.35), P<0.00001], large pulmonary consolidations [OR=6.37, 95%CI (4.09-9.92), P<0.00001], high MP antibody titer [OR=2.83, 95%CI (1.78-4.49), P<0.0001], LDH [OR=1.03, 95%CI (1.00-1.05), P=0.05], and duration of fever [OR=8.33, 95%CI (3.38-20.56), P<0.00001] were positively associated with severe Mycoplasma pneumoniae pneumonia in children.

Conclusion Elevated inflammatory markers (CRP, ESR, PCT, LDH, WBC), presence of characteristic imaging changes (large consolidations, lower lobe lesions), high MP antibody titer, elevated D-dimer, and prolonged duration of fever may be risk factors for severe Mycoplasma pneumoniae pneumonia in children. Future higher-quality studies are needed to further explore the relationship between other clinical, imaging, and laboratory findings and severe Mycoplasma pneumoniae pneumonia in children, and to establish prognostic models based on the identified risk factors.

Full Text

Introduction

Mycoplasma pneumoniae (MP) is one of the most important pathogens causing community-acquired pneumonia in children. Mycoplasma pneumoniae pneumonia (MPP) represents the most common form of atypical pneumonia in children, accounting for approximately one-third of hospitalized community-acquired pneumonia cases [**?**]. While MPP typically presents with mild clinical symptoms and responds well to macrolide antibiotics, it can progress to severe Mycoplasma pneumoniae pneumonia (SMPP), which usually occurs around one week after disease onset. SMPP is characterized by one or more of the following conditions: (1) persistent high fever (temperature $ $39°C) for 5 days or longer, or fever lasting 7 days without a downward trend in peak temperature; (2) symptoms such as wheezing, shortness of breath, dyspnea, chest pain, or hemoptysis, which may be associated with lesion severity, concurrent plastic bronchitis, asthma attacks, pleural effusion, or pulmonary embolism; (3) extrapulmonary complications that do not meet critical illness criteria; (4) oxygen saturation $ $0.93 on room air at rest; (5) imaging showing any of the following: involvement of more than two-thirds of a single lobe, uniform high-density consolidation, or high-density consolidation in two or more lobes (regardless of affected area), possibly accompanied by moderate to large pleural effusions or localized bronchiolitis manifestations. Unilateral or bilateral bronchiolitis affecting most pulmonary lobes may be present, potentially combined with bronchitis and mucus plugging leading to atelectasis; and (6) continuously worsening clinical symptoms with imaging lesion expansion exceeding 50% within 24-48 hours [**?**]. Additionally, SMPP may cause various extrapulmonary complications involving the skin, mucosa, nervous system, hematologic system, and circulatory system, potentially leading to organ damage in the liver, brain, kidneys, and car-

diovascular system. In severe cases, pulmonary structural or functional impairment such as bronchiolitis obliterans may occur, significantly impacting quality of life [**?**]. Although the pathogenesis of SMPP remains incompletely understood, investigating its risk factors to enable early identification of high-risk patients and implement appropriate therapeutic strategies is crucial for improving clinical outcomes and reducing the incidence of severe disease and sequelae.

Given the rising number of pediatric SMPP cases, its potential for multiple complications, and poor prognosis, this study employs evidence-based methodology to explore risk factors for SMPP in children, providing more scientifically robust evidence for early identification, intervention, and treatment by clinical practitioners.

1.1.1 Databases

We systematically searched the following English databases: Cochrane Library, PubMed, Embase, Web of Science, Science Direct, and BioMed Central, along with Chinese databases: China National Knowledge Infrastructure (CNKI), Wanfang Data Knowledge Service Platform, VIP Database, Chinese Biomedical Literature Database (CBMdisc), Duxiu Academic Search Database, and Yiigle Chinese Medical Journal Full-text Database. The search timeframe spanned from database inception to August 2023, targeting publicly available studies on risk factors for pediatric SMPP.

1.1.2 Search Strategy

We employed a comprehensive search strategy combining Medical Subject Headings (MeSH) terms and free-text keywords, with adjustments made according to the characteristics of each database. Additionally, we manually searched the reference lists of included studies to identify relevant literature. English search terms included: severe mycoplasma pneumoniae pneumonia, SMPP, child, children, risk factor, influencing factor, related factor, predictive factor, potential factor, risk, etc. Chinese search terms included: 儿童 (children), 小儿 (pediatric), 患儿 (pediatric patients), 重症肺炎支原体肺炎 (severe Mycoplasma pneumoniae pneumonia), 危险因素 (risk factors), 影响因素 (influencing factors), 潜在因素 (potential factors), 相关因素 (related factors), 风险因素 (risk factors), 预测因素 (predictive factors), and 风险 (risk). The PubMed search strategy is presented in Table 1 .

1.2.1 Inclusion Criteria

(1) Study design limited to case-control or cohort studies; (2) research focus on risk factors for SMPP; (3) clearly diagnosed SMPP in study subjects; (4) appropriate statistical methods employed; and (5) clearly defined outcome measures, including but not limited to calculable metrics such as odds ratios (OR).

1.2.2 Exclusion Criteria

(1) Duplicate publications; (2) reviews, animal studies, or other non-clinical research; (3) studies with incomplete data, non-extractable information, or obvious methodological/statistical errors; (4) studies where full text was unavailable; and (5) studies rated as low quality.

1.3 Literature Screening and Data Extraction

Two guideline working group members independently screened literature and extracted data, with subsequent cross-verification of results. Any discrepancies were resolved through discussion, verification, or consultation with a third researcher. The screening and extraction process involved: (1) reviewing titles and abstracts to exclude obviously irrelevant studies; (2) reading full texts of preliminarily selected studies to make final inclusion/exclusion decisions; and (3) extracting key information into Excel, including first author, publication year, study region, study period, sample size, mean age, study type, and outcome measures.

1.4 Quality Assessment

Two guideline working group members independently assessed the quality of included studies using the Newcastle-Ottawa Scale (NOS) [**?**], with cross-verification of results. Methodological quality was determined based on scores: low quality (0-3 points), moderate quality (4-6 points), and high quality (7-9 points). Disagreements between the two reviewers were resolved through consultation with a third researcher.

1.5 Statistical Methods

Statistical analysis was performed using RevMan 5.4 software. The odds ratio (OR) was selected as the primary effect measure, with corresponding 95% confidence intervals (95%CI) reported. Heterogeneity was assessed using the ^{2} test (α=0.1) combined with I^2 statistics. A fixed-effects model was employed when I^2\$ 50^{2}> 50 \$0.1. Sensitivity analyses were conducted to test result stability. Funnel plots were generated using Stata 16.0 software, with Egger's test [**?**] performed to assess publication bias. Statistical significance was defined as P<0.05.

Results

2.1 Literature Screening Process and Results

The initial search yielded 563 articles. After applying inclusion criteria, 22 studies [**?**] were ultimately included. The literature screening flowchart is presented in Figure 1 [Figure 1: see original paper].

2.2 Characteristics of Included Studies

All included studies were case-control designs published between 2011 and 2023, with a total sample of 4,531 pediatric patients (14 high-quality and 8 moderate-quality studies). Detailed characteristics of included studies are presented in Table 2 , and quality assessment results are shown in Table 3 .

2.3.1 CRP

Seventeen studies [**?**, **?**, **?**, **?**] reported associations between CRP levels and SMPP, involving 3,864 patients. Heterogeneity analysis revealed I^2=97% and P<0.00001, indicating substantial heterogeneity. A random-effects model meta-analysis showed that CRP was a significant risk factor for SMPP [OR=1.92, 95%CI (1.72-2.15), P<0.00001], as illustrated in Figure 2 [Figure 2: see original paper].

2.3.2 ESR

Fifteen studies [**?**, **?**, **?**, **?**, **?**, **?**] reported associations between ESR levels and SMPP, involving 2,810 patients. Heterogeneity analysis revealed I^2=99% and P<0.00001, indicating substantial heterogeneity. A random-effects model meta-analysis showed that ESR was a significant risk factor for SMPP [OR=2.61, 95%CI (2.12-3.22), P<0.00001], as illustrated in Figure 3 [Figure 3: see original paper].

2.3.3 PCT

Two studies [**?**, **?**] reported associations between PCT levels and SMPP, involving 216 patients. Heterogeneity analysis revealed I^2=0% and P=0.82, indicating low heterogeneity. A fixed-effects model meta-analysis showed that PCT was a significant risk factor for SMPP [OR=2.60, 95%CI (1.43-4.75), P=0.002], as illustrated in Figure 4 [Figure 4: see original paper].

2.3.4 D-dimer

Four studies [**?**, **?**, **?**] reported associations between D-dimer levels and SMPP, involving 1,265 patients. Heterogeneity analysis revealed I^2=53% and P=0.10, indicating substantial heterogeneity. A random-effects model meta-analysis showed that D-dimer was a significant risk factor for SMPP [OR=4.36, 95%CI (2.93-6.50), P<0.00001], as illustrated in Figure 5 [Figure 5: see original paper].

2.3.5 WBC

Three studies [**?**, **?**, **?**] reported associations between WBC levels and SMPP, involving 399 patients. Heterogeneity analysis revealed I^2=0% and P=0.92, indicating low heterogeneity. A fixed-effects model meta-analysis showed that WBC was a significant risk factor for SMPP [OR=1.98, 95%CI (1.66-2.36), P<0.00001], as illustrated in Figure 6 [Figure 6: see original paper].

2.3.6 Lower Lobe Lesions

Four studies [?, ?, ?, ?] reported associations between lower lobe lesions on imaging and SMPP, involving 537 patients. Heterogeneity analysis revealed I^2=80% and P=0.002, indicating substantial heterogeneity. A random-effects model meta-analysis showed that lower lobe lesions were a significant risk factor for SMPP [OR=5.70, 95%CI (3.48-9.35), P<0.00001], as illustrated in Figure 7 [Figure 7: see original paper].

2.3.7 Large Patchy Lesions

Eight studies [?, ?, ?, ?, ?] reported associations between large patchy consolidation on imaging and SMPP, involving 1,432 patients. Heterogeneity analysis revealed I^2=87% and P<0.00001, indicating substantial heterogeneity. A random-effects model meta-analysis showed that large patchy lesions were a significant risk factor for SMPP [OR=6.37, 95%CI (4.09-9.92), P<0.00001], as illustrated in Figure 8 [Figure 8: see original paper].

2.3.8 High MP Antibody Titers

Three studies [?, ?] reported associations between high MP antibody titers and SMPP, involving 835 patients. Heterogeneity analysis revealed I^2=1% and P=0.36, indicating low heterogeneity. A fixed-effects model meta-analysis showed that high MP antibody titers were a significant risk factor for SMPP [OR=2.83, 95%CI (1.78-4.49), P<0.0001], as illustrated in Figure 9 [Figure 9: see original paper].

2.3.9 LDH

Nine studies [?, ?, ?, ?, ?] reported associations between LDH levels and SMPP, involving 2,487 patients. Heterogeneity analysis revealed I^2=91% and P<0.00001, indicating substantial heterogeneity. A random-effects model meta-analysis showed that LDH was a significant risk factor for SMPP [OR=1.03, 95%CI (1.00-1.05), P=0.05], as illustrated in Figure 10 [Figure 10: see original paper].

2.3.10 Fever Duration

Six studies [?, ?, ?] reported associations between fever duration and SMPP, involving 1,458 patients. Four of these studies [?, ?, ?] with 944 patients were included in the meta-analysis. Heterogeneity analysis revealed I^2=0% and P=0.86, indicating low heterogeneity. A fixed-effects model analysis showed that fever duration was a significant risk factor for SMPP [OR=1.29, 95%CI (1.19-1.41), P<0.00001], as illustrated in Figure 11 [Figure 11: see original paper]. Additionally, two studies [?] conducted stratified analyses of fever duration in 514 pediatric patients. Heterogeneity analysis revealed I^2=0% and P=0.38, indicating low heterogeneity. A fixed-effects model analysis showed that fever

duration exceeding 5 days was a significant risk factor for SMPP [OR=8.33, 95%CI (3.38-20.56), P<0.00001], as illustrated in Figure 12 [Figure 12: see original paper].

2.4 Sensitivity Analysis

Sensitivity analyses were performed for six risk factors (CRP, ESR, D-dimer, LDH, large patchy lesions, and lower lobe lesions) using a leave-one-out approach. For D-dimer analysis, removal of the Liu Liping 2023 study [**?**] reduced the I^2 statistic from 96% to 0%, indicating this study was a major source of heterogeneity. However, because this study was of high quality without obvious bias and its removal did not affect result stability, it was retained in the analysis.

2.5 Publication Bias Assessment

Egger's test was used to assess publication bias for risk factors with $ $3 included studies. The results showed no significant publication bias for D-dimer, WBC, lower lobe lesions, high MP antibody titers, LDH, or fever duration, while significant publication bias was detected for CRP, ESR, PCT, and large patchy lesions. Detailed results are presented in Table 4 .

Discussion

Mycoplasma pneumoniae is a major pathogen causing community-acquired pneumonia in children, responsible for 20%-40% of cases during epidemics with a mortality rate of 1.38% [**?**]. Children with SMPP often have poor prognoses, potentially developing complications such as pleural effusion, bronchiectasis, and bronchiolitis obliterans, which significantly impact growth and development. Therefore, early identification and treatment of SMPP is clinically crucial, as timely intervention can prevent disease progression and improve outcomes. However, existing literature on SMPP risk factors is largely based on small-sample, single-center case-control studies with high heterogeneity and low evidence levels.

Inflammatory markers including CRP, ESR, hs-CRP, WBC, and PCT are nonspecific indicators of inflammatory response. Research indicates that SMPP is closely associated with systemic inflammatory response, and monitoring these markers can help assess MPP severity and predict SMPP development. Among these, CRP demonstrates significant predictive value [**?**]. CRP levels rise rapidly within 4-6 hours after infection, correlating with infection severity and patient prognosis, with elevated levels also associated with increased risk of pulmonary and other organ damage [**?**]. Notably, CRP expression is unaffected by gender or age [**?**]. In contrast, ESR responds more slowly, typically becoming evident 2-3 days after inflammatory onset, making it a key marker for assessing inflammation and disease activity. Although ESR levels may be influenced by age and gender, they are generally higher in SMPP patients than in non-severe cases,

likely reflecting inflammatory severity and thus serving as an indicator for MPP progression [**?**]. Studies also show that serum hs-CRP levels correlate closely with inflammatory response and MPP severity, representing an important guide for diagnosis, treatment and prognosis that could serve as a sensitive indicator for SMPP [**?**], though large-scale, multicenter studies are needed for validation.

Significant WBC elevation is associated with intense inflammatory responses, consistent with the immune-mediated injury mechanism of SMPP. When facing infection or inflammation, the immune system generates robust responses that increase WBC counts to combat threats. However, excessive or inappropriate immune responses may lead to uncontrollable disease progression and increased complication risks, promoting SMPP development. Therefore, WBC represents another SMPP risk factor. PCT, a procalcitonin precursor produced by thyroid C cells, is normally present at very low blood levels. However, during bacterial infection and inflammation, various organs including the liver, lungs, and kidneys may produce substantial PCT, leading to markedly elevated serum levels. Consequently, PCT is considered a sensitive indicator of bacterial infection, with levels rising in proportion to infection severity [**?**]. Studies demonstrate that PCT is a major potential biomarker for pneumonia risk stratification and an important predictor of severe pneumonia outcomes, providing independent prognostic information [**?**].

In summary, elevated inflammatory markers (CRP, ESR, hs-CRP, WBC, PCT) in SMPP patients may be related to immune-mediated injury mechanisms triggered by mycoplasma, intense immune responses, and potential mixed infections. Further research is needed to validate the specific diagnostic and prognostic value of these markers.

D-dimer, a specific degradation product generated when plasmin acts on fibrin, represents the smallest fibrin degradation fragment. Elevated levels indicate hypercoagulable states and excessive secondary fibrinolysis. The hypercoagulable state in MPP patients may be attributed to: (1) systemic inflammatory response syndrome induced by infection and immune injury, leading to uncontrolled release of inflammatory mediators and cytokines that damage vascular endothelium, slow microcirculatory blood flow, and activate extrinsic and intrinsic coagulation pathways; and (2) direct invasion of the organism by MP and its toxins, which activates the coagulation system, resulting in hypercoagulability while also potentially activating fibrinolytic, kinin, and complement systems, causing coagulation dysfunction [**?**]. Accumulating evidence demonstrates close associations between coagulation function and inflammatory response [**?**]. Clinical observations and chest imaging reveal that D-dimer levels in MPP patients correlate closely with disease severity, with levels exceeding 1367 ng/mL considered a high-risk factor for necrotizing pneumonia [**?**]. Therefore, significantly elevated D-dimer warrants attention for potential pulmonary necrosis risk. Low-molecular-weight heparin has long been used to treat hypercoagulable states, possessing not only anticoagulant and antithrombotic functions but also multiple biological activities and pharmacological mechanisms includ-

ing anti-inflammatory effects, antifibrotic activity, immunomodulation, and cell proliferation inhibition [?]. MP may induce production of tumor necrosis factor-α, interleukins, and other cytokines that directly cause local vascular injury and occlusion, or activate complement and D-dimer to produce systemic hypercoagulability and thrombosis [?]. Through interactions between hypercoagulability and inflammation, elevated D-dimer in MPP is associated with significantly increased incidence of pleural effusion and myocardial and hepatic injury, likely reflecting mutual enhancement of inflammatory and coagulation processes that exacerbate systemic inflammation. MPP patients with D-dimer levels exceeding 308 g/L are more prone to complications including pleural effusion, liver injury, and myocardial injury. Reports indicate that MPP patients with D-dimer levels below 0.5 mg/L have lower mortality and better prognosis [?]. Recent reports increasingly demonstrate that MPP can lead to systemic arterial and deep venous thrombosis, cerebral infarction, and even disseminated intravascular coagulation. One early study identified D-dimer as a predictor of 30-day mortality, mechanical ventilation requirement, and circulatory support need in severe pneumonia patients [?].

LDH is a glycolysis enzyme that promotes pyruvate conversion to lactate. With high sensitivity, even minor lung tissue destruction can cause serum LDH level changes [?], making it an important marker for tissue injury and disease severity [?]. In SMPP patients, mycoplasma infection-induced pulmonary hypoxia and necrosis increase cell membrane permeability, releasing LDH into the bloodstream. As demonstrated by Izumikawa et al. [?], LDH is a key early predictor of SMPP, with higher values showing better predictive performance. LDH levels also serve as an important reference for determining glucocorticoid therapy necessity [?]. Previous research reported that in MPP patients, CRP >36.0 mg/L and LDH >250 U/L should raise suspicion for severe MPP, while persistent high fever beyond 7 days, CRP >110 mg/L, LDH >478 U/L, and whole-lobe consolidation on chest CT may indicate poor response to conventional glucocorticoid therapy [?]. Furthermore, Liu et al. [?] found that LDH4 and LDH5 isoforms relative to total serum LDH are more suitable for predicting refractory Mycoplasma pneumoniae pneumonia.

MP antibody titers represent the primary diagnostic criterion for mycoplasma infection. Current understanding suggests that after MP infection, lipoproteins induce cytokine increases that trigger inflammatory responses and stimulate the immune system to produce specific antibodies [?]. Research demonstrates positive correlations between MP antibody titers and disease severity, likely related to hyperactive immune function following MP infection [?]. Increased MP antibody titers correlate with elevated SMPP risk, while immune dysfunction and production of tissue-specific autoantibodies may constitute important mechanisms for MPP deterioration [?]. Additionally, high-titer and prolonged IgM antibodies are considered risk factors for MPP sequelae. Notably, IgM positivity timing varies among individuals, so negative MP-IgM cannot completely exclude SMPP possibility [?, ?].

Imaging manifestations differ between MPP patients with varying severity levels. Chest imaging changes have predictive value for SMPP occurrence, particularly when large patchy shadows or pleural effusion appear [**?**]. Studies on lesion location indicate that lower lobe involvement is common in SMPP patients, likely associated with frequent concurrent intrapulmonary complications. Such pulmonary injury manifests not only as abnormal imaging features but also causes plasma LDH elevation [**?**, **?**].

Clinically, prolonged fever duration represents an SMPP risk factor, which may or may not be accompanied by high fever peaks. Results show that severe cases have longer fever courses than non-severe cases, typically reflecting rapid disease progression where the organism fails to clear pathogens promptly, leading to persistent inflammatory pyrogens and excessive immune responses [**?**].

Beyond the quantitatively analyzed factors, antibiotic application status, drug-resistant strain infection, and delayed macrolide use also correlate with SMPP: (1) MP lacks cell walls, making it susceptible to macrolides, quinolones, and tetracyclines. Yang et al. [**?**] treated 39 SMPP patients unresponsive to azithromycin with moxifloxacin, achieving 89.7% effectiveness. However, tetracycline and quinolone use is age-restricted, leaving limited antibiotic options for younger children and necessitating early SMPP vigilance. (2) Patients showing no improvement in fever or clinical symptoms after >72 hours of macrolide therapy have macrolide-unresponsive MPP, associated with MP carrying resistance genes. Research shows drug-resistant MP infections present with more severe clinical manifestations, large patchy shadows on chest X-ray, higher rates of extrapulmonary damage involving multiple systems, longer disease courses, prolonged macrolide use and fever duration, and greater SMPP development risk. In contrast, non-resistant MP infections show milder clinical presentations, patchy opacities on chest X-ray, milder extrapulmonary damage primarily affecting the digestive system, and shorter disease courses [**?**]. However, direct evidence technologies for diagnosing macrolide-resistant MP, such as PCR, culture, and susceptibility testing, are not universally available. Indirect evidence from macrolide application time can be used: when conventional macrolide therapy for 3-5 days fails to improve fever or imaging findings, progression to SMPP should be suspected [**?**]. (3) Timely macrolide therapy significantly reduces mortality in severe MPP patients [**?**], while delayed use represents a high-risk factor for SMPP development and even death [**?**]. Multicenter studies found early empirical macrolide use helps reduce disease duration and hospitalization time in MPP patients [**?**], and future high-quality studies could further incorporate these factors into quantitative analysis.

Furthermore, because immune function plays a crucial role in MPP pathogenesis, IgE levels are considered highly relevant to SMPP progression. Post-infection inflammatory mediator production causes immune dysfunction that accelerates disease progression [**?**]. MP surface proteins and respiratory distress syndrome toxin can elevate IgE levels, triggering allergic reactions and

airway hyperresponsiveness that reduce airway compliance [**?**]. IgE-mediated immune responses significantly impact airways and lung function, with excessive responses worsening MPP [**?**]. High IgE levels are regarded as markers of immune system dysregulation [**?**]. In MPP patients, elevated IgE correlates with tissue injury, severe systemic inflammation, prolonged fever, and more frequent intra- and extrapulmonary complications, increasing risks for SMPP and necrotizing pneumonia. Therefore, IgE may serve as a biomarker for SMPP and post-MP infection complications [**?**]. Poddiqhe et al. [**?**] found significantly elevated serum IgE levels in MP-infected patients, with even higher levels in SMPP patients with extrapulmonary manifestations. Bao et al. [**?**] confirmed that both MP load and IgE levels are elevated in SMPP patients. However, due to the lack of high-quality studies on IgE as an SMPP risk factor, quantitative analysis of this relationship requires further research.

Early and accurate SMPP identification is a critical concern for frontline pediatric practitioners managing MPP. Our findings indicate that lower lobe lesions, high MP antibody titers, large patchy consolidation, prolonged fever duration, and elevated WBC, CRP, D-dimer, LDH, ESR, and PCT are all SMPP risk factors. Additionally, unincluded but important factors such as antibiotic use status, resistant strain infection, and delayed azithromycin use represent key influences. Therefore, enhanced early identification, accurate diagnosis, and timely, targeted intervention are essential to improve vigilance against SMPP progression.

However, this study has several limitations: (1) All included studies were single-center; (2) All studies were conducted in China, potentially limiting generalizability to broader populations. Future research should focus on pediatric SMPP risk factors, particularly potentially high-value factors such as macrolide resistance, IgE, platelet count, and ferritin, though current original clinical data remain insufficient for comprehensive analysis; (3) The case-control design limits study depth and introduces unavoidable potential biases; and (4) The limited number of studies precluded detailed subgroup analyses. Future research should prioritize high-quality, multicenter, large-sample case-control and prospective studies to validate and enrich understanding of SMPP risk factors, with expert consensus methods employed to verify our findings.

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