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The risk factors of children acquiring refractory mycoplasma pneumoniae pneumonia

A meta-analysis

Hui Gong, MM[a], Baijun Sun, MD[b], Ye Chen, MM[b], Huijie Chen, MPH[b,*]

Abstract

Objectives: Refractory mycoplasma pneumoniae pneumonia (RMPP) in children has been increasing worldwide. In this study, we conducted a meta-analysis to generate large-scale evidence on the risk factors of RMPP to provide suggestions on prevention and controlling for children.

Methods: Web of Science, PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, and Wanfang (Chinese) were searched to identify relevant articles. All analyses were performed using Stata 14.0.

Results: We conducted a meta-analysis of 15 separate studies. Fever for more than 10 days (odds ratio [OR] 3.965, 95% confidence interval [CI] 2.109–7.456), pleural effusion (OR 6.922, 95% CI 2.058–23.282), extra-pulmonary complications (OR 17.762, 95% CI 11.146–28.305), pulmonary X-ray consolidation ≥2/3 (OR 8.245, 95% CI 1.990–34.153), CRP >40 mg/L (OR 4.975, 95% CI 2.116–11.697) were significantly related to the risk of RMPP. We did not find an association between male sex (OR 0.808, 95% CI 0.548–1.189), LDH >410IU/L (OR 1.033, 95% CI 0.979–1.091) and the risk of RMPP.

Conclusions: Fever for more than 10 days, pleural effusion, extra-pulmonary complications, pulmonary X-ray consolidation≥ 2/3 and CRP >40 mg/L are risk factors for early evaluation of RMPP.

Abbreviations: CI = confidence intervals, GMPP = general mycoplasma pneumoniae pneumonia, MPP = mycoplasma pneumoniae pneumonia, OR = odds ratio, RMPP = refractory mycoplasma pneumoniae pneumonia.

Keywords: children, meta-analysis, refractory mycoplasma pneumoniae pneumonia, risk factor

1. Introduction

Mycoplasma pneumoniae pneumonia (MPP) mainly caused by mycoplasma pneumoniae is a common disease of respiratory system in children and accounts for about 10% to 40% of community-acquired pneumonia cases in children.[1–3] Although mycoplasma pneumonia due to mycoplasma pneumoniae is usually a benign and self-limited disease, some cases become refractory or severe and life-threatening,[4–6] which were defined as refractory mycoplasma pneumoniae pneumonia (RMPP) characterized by long course of disease, poor curative effect and many complications, even endangering the lives of children.[7] In recent years, with the increase of drug-resistant mycoplasma pneumoniae strains, the incidence of RMPP in children's community-acquired pneumonia is on the rise.[8–10] Previous studies have shown that the rapidity of response to treatment of RMPP with systemic corticosteroid was satisfying, and it significantly improved the clinical symptoms and outcomes.[4,11]

Therefore, it is extremely necessary to identify the risk factors which predict the occurrence of RMPP.[12] Meta-analysis is a means of increasing the effective sample size under investigation through pooling of data from individual association studies, thus enhancing the statistical power.[13] In order to identify risk factors of children acquiring RMPP, prevent the progress of the disease and reduce complications, we conducted this meta-analysis to determine the risk factors for RMPP.

2. Materials and methods

A systematic review was conducted using the Preferred Reporting Items for a Systematic Review and Meta-analysis statement as guideline.[14]

2.1. Study selection

A systematic search of the literature from the following electronic databases: Web of Science, PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure, and Wanfang (Chinese). The following keywords were used: RMPP, risk factors and case control study.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

[a] Department of Pediatrics, Shenyang Fifth People's Hospital, [b] Department of Infectious Disease, Shenyang Center for Disease Control and Prevention.

[*] Correspondence: Huijie Chen, Department of Infectious Disease, Shenyang Center for Disease Control and Prevention, NO.37 Qishan Middle Road, Shenyang, China (e-mail: chj1317@126.com).

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The quality of the included studies was assessed using the Newcastle-Ottawa Scale, and studies achieving 6 or more points were considered to be of high quality.[15,16]

2.2. Inclusion and exclusion criteria

Two investigators searched the electronic databases independently according to the following criteria for inclusion:

1. case–control study including RMPP and general mycoplasma pneumoniae pneumonia (GMPP) patient groups;
2. published up to December 2019;
3. diagnosis of RMPP and GMPP consistent with the criteria defined by us.

Abstracts, reviews, case reports, noncomparative studies and low-quality studies were excluded. In cases of disagreement, a third investigator acted as an arbitrator and the disagreements were resolved with the research team by discussion.

2.3. Data extraction and quality assessment

The following items were extracted from the included studies: the first author name, the year of publication, source of publication, type of study, risk factors, total sample size, the number of RMPP and GMPP cases, odds ratio (OR) and 95% confidence intervals (CI).

The publication bias was evaluated using the Egger test.[17] If $P > .05$ the publication bias exist otherwise the publication bias does not exist.

2.4. Definitions

MPP cases were divided into refractory mycoplasma pneumoniae pneumonia(RMPP) and general mycoplasma pneumoniae pneumonia (GMPP) according to MPP diagnostic criteria of Applied Pediatrics[18] and Management Guidelines of Community-Acquired Pneumonia in children (revised in 2013).[7] GMPP was defined as Clinical manifestations of cough, fever, pulmonary X-ray suggests different levels of inflammatory change, etiology detecting serum specificity MP-IgM antibody positive.[7,18,19] RMPP was defined as meeting the diagnosis of MPP with persistent fever and aggravation of clinical symptoms and pulmonary imaging manifestations after a week or more of regular treatment with macrolide antibiotics.[7,18,19] The duration of fever was defined as body temperature$\geqslant$37.5°C.

2.5. Ethical review

The data of this meta-analysis are based on previously published literature, ethical approval is not necessary.

2.6. Meta-analysis methods

Stata 14.0 was used for the statistical analysis. The OR and 95% CI were calculated using fixed effect model or random effect model and the choice for statistical model was determined by their heterogeneity which were assessed by the X^2 and I^2 statistics.[20,21] $I^2 > 50\%$ and X^2-statistic ($P < .05$) was considered to show significant heterogeneity and the random effect model was adopted, otherwise, the fixed effect model was used. The OR and 95% CI were used as summary statistics for the comparison of the following risk factors: male, fever for more than 10 days, pleural effusion, extra-pulmonary complications, pulmonary X-ray consolidation$\geq$2/3, LDH (lactate dehydrogenase) >410IU/L, CRP (C reactive protein) >40 mg/L.

The pooled estimate of risk was obtained by Mantel–Haenszel method in the fixed effect model and by M-H heterogeneity method in the random effect model. All P values were 2-sided. A P value less than .05 was considered to be statistically significant.

3. Results

3.1. Characteristics of include studies

The first search strategy generated 141 studies. Only 15 articles[22–36] met the inclusion criteria. The selection process is shown in Figure 1. All the studies were of high quality according to the Newcastle-Ottawa Scale. The sample sizes of the included studies ranged from 45 to 653 and amounted to 3912 subjects in total. There were 1189 patients in the RMPP group and 2723 patients in the GMPP group. The study characteristics and patient characteristics are summarized in Table 1. The 2 groups were similar with regard to age and gender.

3.2. Risk factors of severe HFMD

In 8 studies, fever for more than 10 days was related to the risk of RMPP (OR 3.965, 95% CI 2.109–7.456). In 4 studies, pleural effusion was significantly associated with RMPP (OR 6.922, 95% CI 2.058–23.282). In 3 studies, extra-pulmonary complications was significantly associated with RMPP (OR 17.762, 95% CI 11.146–28.305). In 4 studies, pulmonary X-ray consolidation $\geq$2/3 was significantly associated with RMPP (OR 8.245, 95% CI 1.990–34.153). In 10 studies, CRP >40 mg/L was significantly associated with RMPP (OR 4.975, 95% CI 2.116–11.697). However, we found no significant association between male sex, LDH >410IU/L and RMPP. Table 2, Figures 2–8.

3.3. Evaluation of publication bias

The Egger test analysis of total complications was performed. The results are shown in Table 3. Six compared factors had no publication bias and one risk factor did (X-ray consolidation $\geq$2/3).

4. Discussion

MPP can occur throughout the year, often from late autumn to early winter and it has been observed that epidemic of MPP infection occurs every 3 to 7 years.[37–40] At present, a large number of literatures had reported the risk factors of RMPP in children, but most of them have problems such as small observation sample and inconsistent experimental results.[12] Therefore, this study adopted the method of meta-analysis to summarize and analyze relevant literatures, thus increasing the reliability of the study by expanding the sample size.

A recent meta-analysis involving 23 separate studies[12] found that fever for more than 10 days and CRP >40 mg/L were significantly related to the risk of RMPP which is consistent with our findings. Other than these risk factors, we also found pleural effusion, extra-pulmonary complications, X-ray consolidation $\geq$2/3 significantly increased the risk of RMPP. The meta-analysis[12] found that there was no significant association

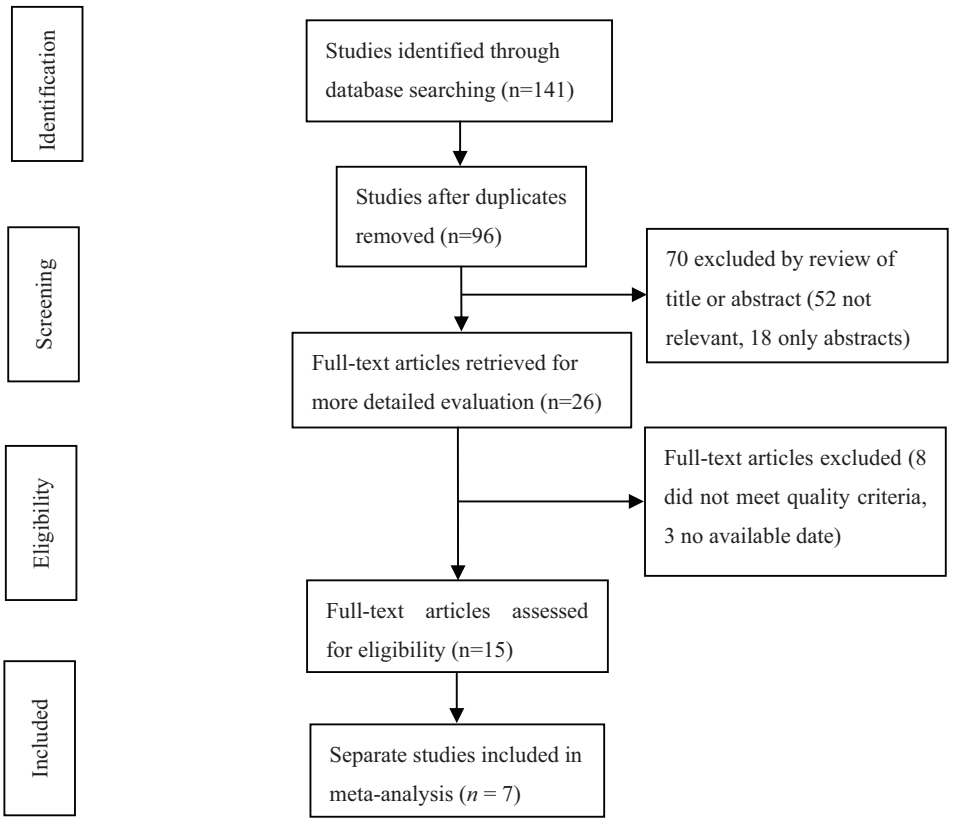

Figure 1. Flow chart showing the selection process for the meta-analysis.

between male and RMPP which is consistent with our finding. However, the meta-analysis[12] found that LDH >410IU/L was significantly related to the risk of RMPP which is not consistent with our finding, our finding found that there was no significant association between LDH >410IU/L and RMPP.

Previous studies[12,22,23,33] on gender found that there was no significant association between gender and RMPP and this study also found there was no significant association between male and RMPP which further confirmed that the occurrence of RMPP has nothing to do with gender.

Although the underlying mechanisms of RMPP are still uncertain, the macrolide-resistant MP infection and excessive immunological inflammation are most commonly proposed.[41–44] Persistent fever is one of the important clinical manifestations of RMPP, and it is generally believed that persistent fever is related to the excessive inflammatory response caused by MP

Table 1

Characteristics of the included studies and patients into meta-analysis.

Author	Year	Country	RMPP	GMPP	Study quality(score)	Age(years) RMPP VS GMPP	Male (%) RMPP VS GMPP
Ying Zhu[22]	2018	China	49	60	******	6.8/6.9 $P=.722$	51.0/55.0 $P=.679$
Xinfeng Liu[23]	2017	China	96	247	******	NR	59.4/66.4 $P=.223$
Yuxia Mei[24]	2014	China	30	112	******	6.0/5.0 $P=.007$	60.0/54.5 $P=.589$
Ting Wang[25]	2016	China	97	97	*******	6.7/4.1 $P<.01$	58.8/54.6 $P=.66$
Jiayu Zhai[26]	2017	China	142	486	******	4.6/6.8 $P=.015$	58.0/49.3 $P=.065$
Yong Yang[27]	2010	China	21	127	*******	NR	57.1/46.5 $P=.365$
Yan Zhang[28]	2015	China	47	60	******	NR	NR
Baina Qu[29]	2016	China	70	133	******	7.0/5.8 $P=.005$	48.6/45.1 $P>.05$
Mei Lu[30]	2018	China	17	159	******	2.8/4.5 $P<.05$	52.9/56.6 $P=.772$
Xiaomei Liu[31]	2019	China	32	153	******	6.8/5.8 $P=.079$	56.3/48.4 $P=.417$
Xianmei Gong[32]	2019	China	81	81	******	7.1/4.3 $P<.001$	53.1/55.6 $P=.752$
Seo Yeol Choi[33]	2018	Korea	26	19	******	6.5/6.8 $P=.139$	NR
Yongdong Yan[34]	2016	China	36	147	******	6.6/6.1 $P=.65$	47.2/53.1 $P=.53$
Yuanyuan Zhang[35]	2016	China	145	489	******	5.9/3.4 $P<.001$	48.3/57.3 $P=.058$
Aizhen Lu MD PhD[36]	2015	China	300	353	******	5.6/4.3 $P<.001$	57.0/62.6 $P=.15$

NR = not reported, NS = not significant.

Table 2

Meta-analysis of risk factors for RMPP in 7 separate studies.

Risk factors	No. of studies	OR (95% CI)	Model*	Test of heterogeneity		
				Chi-Squared	*P* Value	I^2%
Male	3	0.808 (0.548,1.189)	F	0.54	.764	0.0
Fever for more than 10 days	7	3.965 (2.109,7.456)	R	52.04	.000	88.5
Pleural effusion	4	6.922 (2.058,23.282)	R	14.22	.003	78.9
Extra-pulmonary complications	3	17.762 (11.146,28.305)	F	3.70	.157	46.0
Pulmonary X-ray consolidation ≥2/3	4	8.245 (1.990,34.153)	R	22.74	.000	86.8
LDH >410IU/L	6	1.033 (0.979,1.091)	R	53.43	.000	90.6
CRP >40 mg/L	10	4.975 (2.116,11.697)	R	197.45	.000	95.4

* R, random effect model; F, fixed effect model.

CI = confidence interval, CRP = C reactive protein, LDH = lactate dehydrogenase, OR = odds ratio.

infection.[41] Currently, most studies[22,23,27–31,34] compared the duration of fever in children with RMPP and children with GMPP and found that fever for more than 10 days was a risk factor for RMPP.[22,23,27–31,34] This study once again confirmed that fever for more than 10 days was a risk factor for RMPP. Strong immune response is usually manifested by large dense lung consolidation, combined with a large amount of pleural effusion,[45] etc. In this study, it was found that the incidence of pulmonary X-ray consolidation ≥2/3 and pleural effusion in the RMPP group were significantly higher than that in the GMPP group which were consistent with previous studies[23–25,28,31–33] suggesting that adequate attention should be paid to the patients with pulmonary X-ray consolidation and pleural effusion.[25]

Previous study found that the incidence of extra-pulmonary damage during MP infection could reach 25% to 50%, but the pathogenesis of extra-pulmonary complications is not clear.[46] Generally, the stronger the immune response is, the more serious the organ damage is and the host's response largely determines the occurrence and prognosis of RMPP.[47] This study found that extra-pulmonary complications were risk factors of RMPP, which was consistent with previous studies.[23,24,28]

CRP reflected the acute severe systemic inflammatory reactions to MP infection and was suggestive of a well-developed immune system.[35] CRP is a kind of specific inflammatory markers and

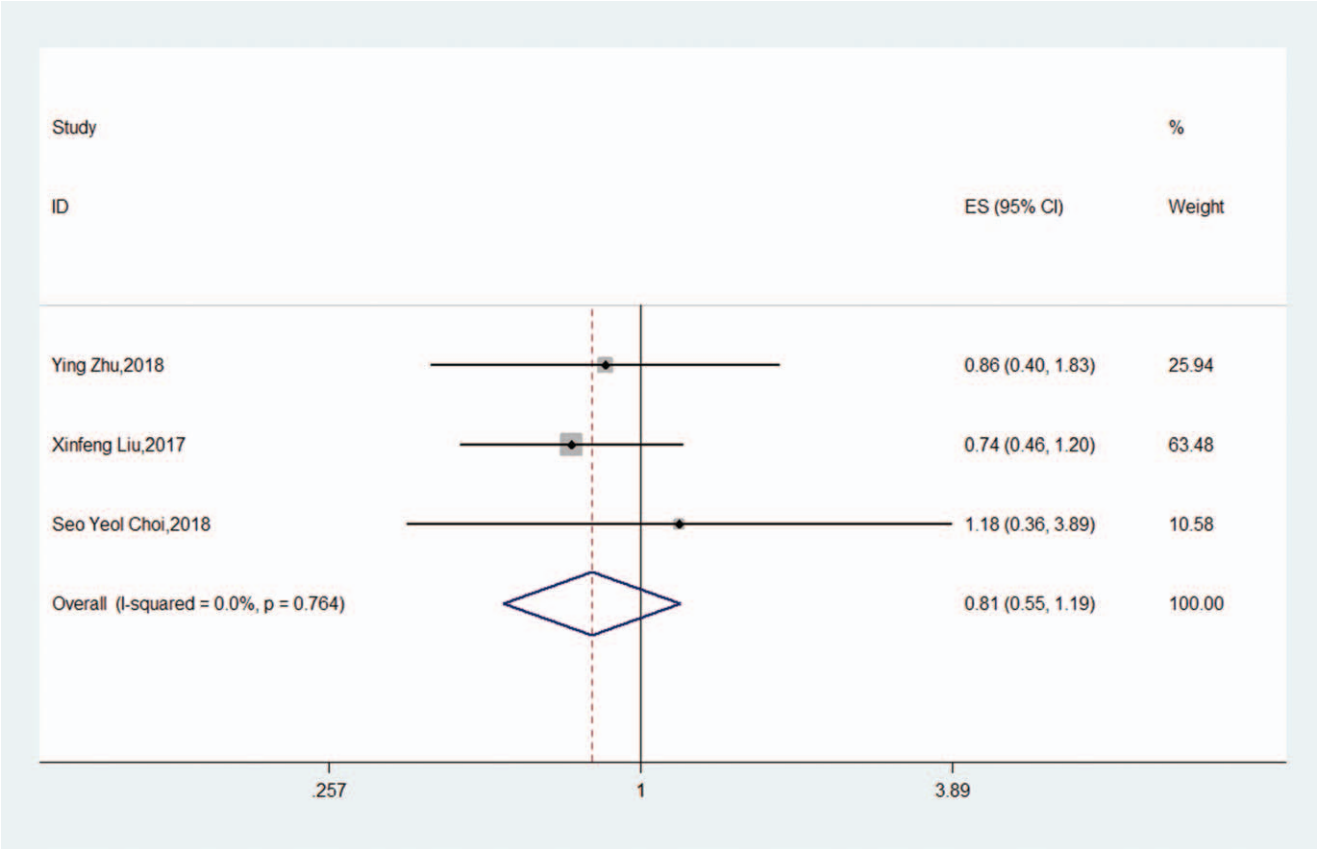

Figure 2. Forest plots showing the results of the meta-analysis regarding male. Fixed effect model was used. The pooled OR was 0.81 (95% CI: 0.55–1.19). It indicates that there was no significant association between male sex and RMPP. RMPP = refractory mycoplasma pneumoniae pneumonia.

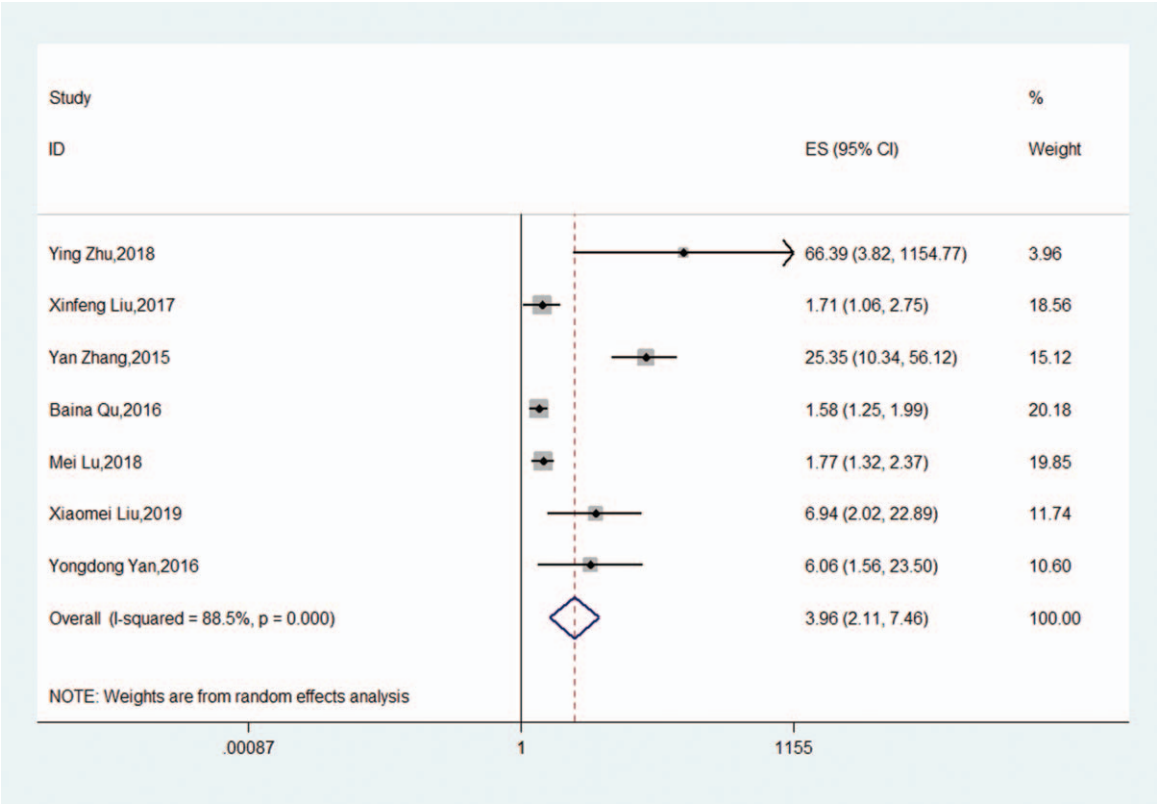

Figure 3. Forest plots showing the results of the meta-analysis regarding fever for more than 10 days. Random effect model was used. The pooled OR was 3.96 (95% CI: 2.11–7.46). It indicates that fever for more than 10 days was related to the risk of RMPP. RMPP = refractory mycoplasma pneumoniae pneumonia.

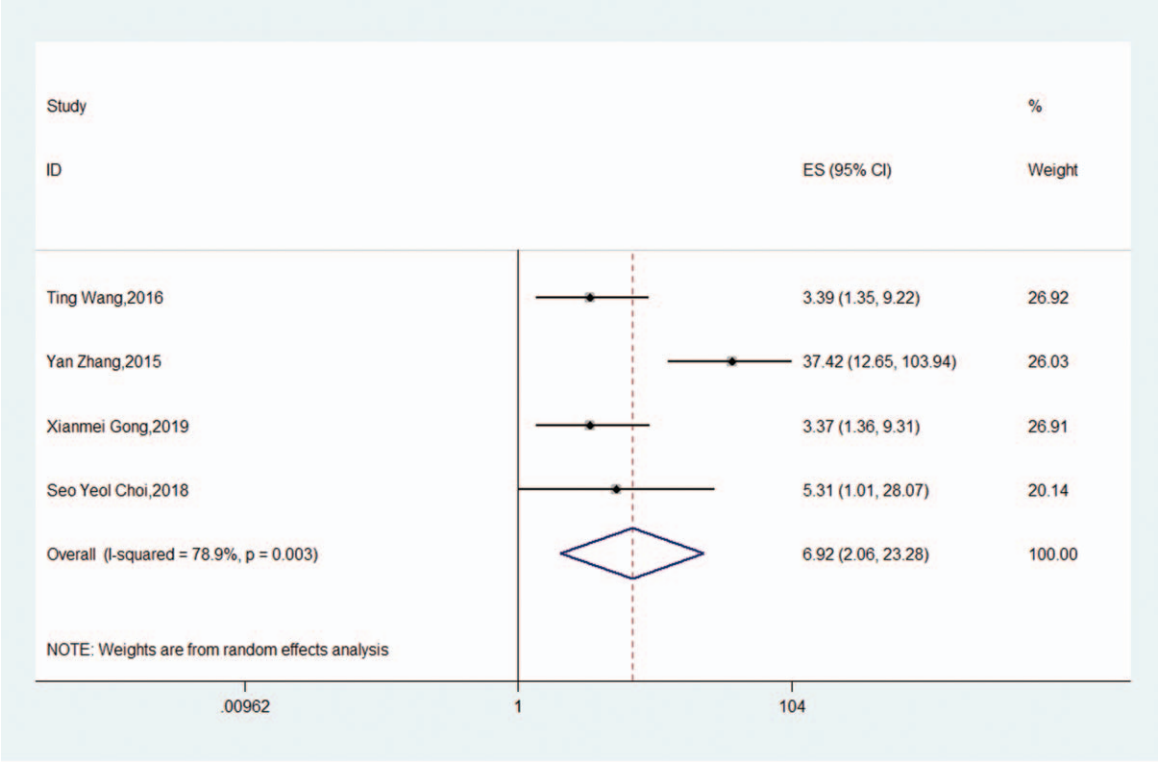

Figure 4. Forest plots showing the results of the meta-analysis regarding pleural effusion. Random effect model was used. The pooled OR was 6.92 (95% CI: 2.06–23.28). It indicates that pleural effusion was significantly associated with RMPP. RMPP = refractory mycoplasma pneumoniae pneumonia.

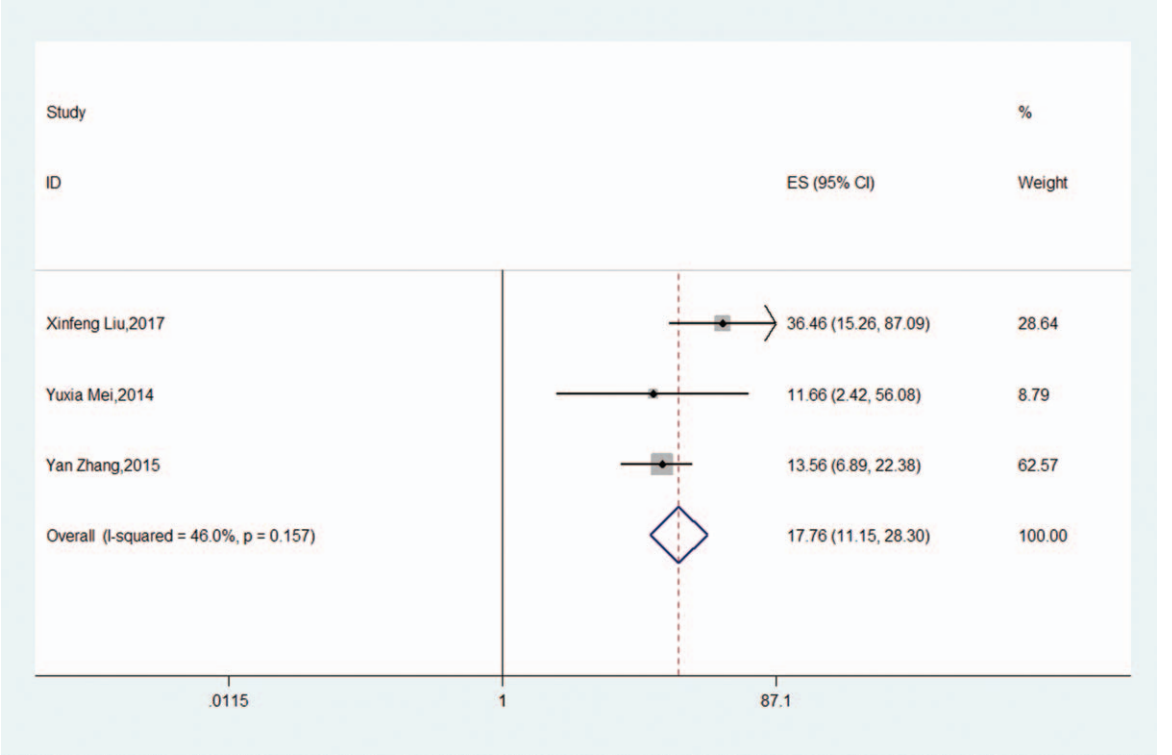

Figure 5. Forest plots showing the results of the meta-analysis regarding extra-pulmonary complications. Fixed effect model was used. The pooled OR was 17.76 (95% CI: 11.15–28.30). It indicates that extra-pulmonary complications was significantly associated with RMPP. RMPP = refractory mycoplasma pneumoniae pneumonia.

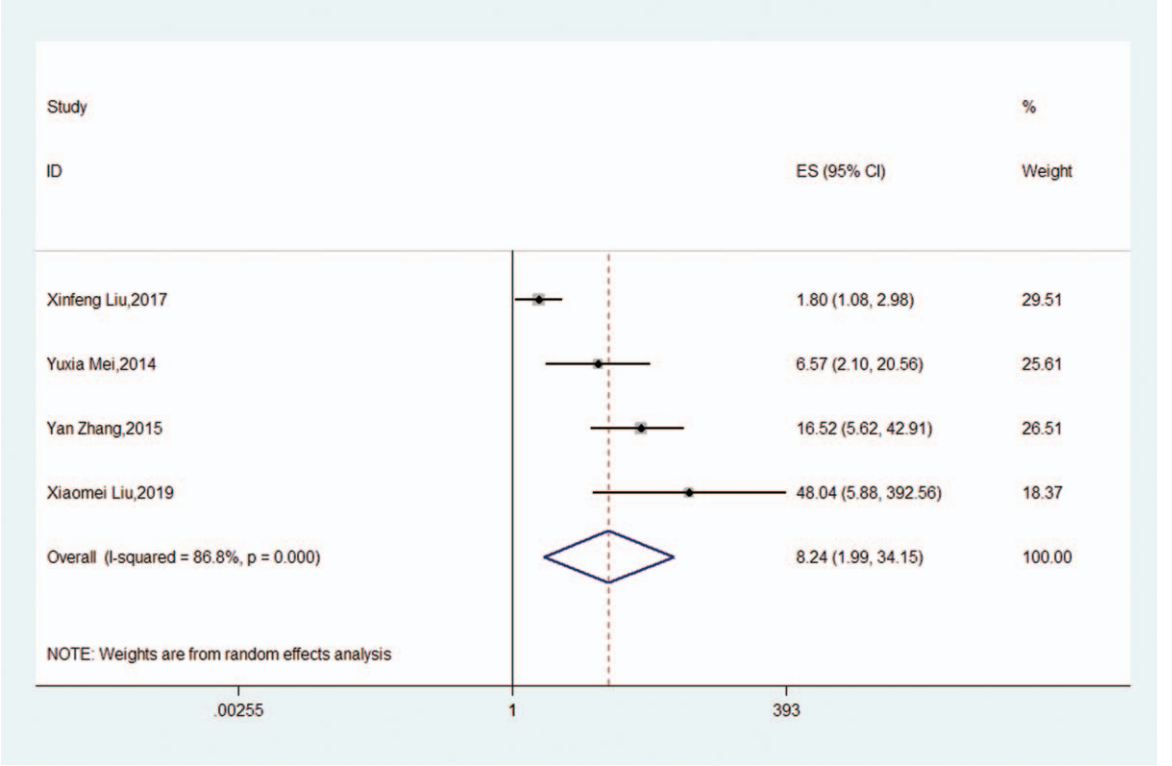

Figure 6. Forest plots showing the results of the meta-analysis regarding pulmonary X-ray consolidation ≥2/3. Random effect model was used. The pooled OR was 8.24 (95% CI: 1.99–34.15). It indicates that pulmonary X-ray consolidation ≥2/3 was significantly associated with RMPP. RMPP = refractory mycoplasma pneumoniae pneumonia.

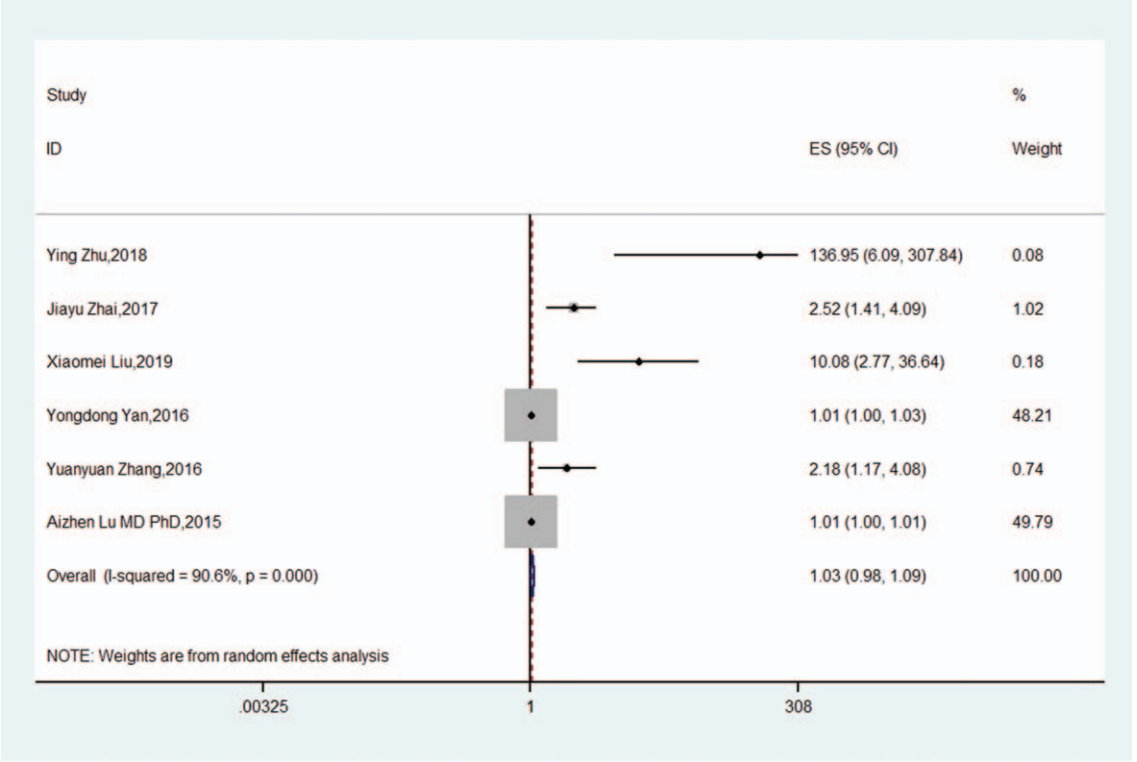

Figure 7. Forest plots showing the results of the meta-analysis regarding LDH >410IU/L. Random effect model was used. The pooled OR was 1.03 (95% CI: 0.98–1.09). It indicates that there was no significant association between LDH >410IU/L and RMPP. RMPP = refractory mycoplasma pneumoniae pneumonia.

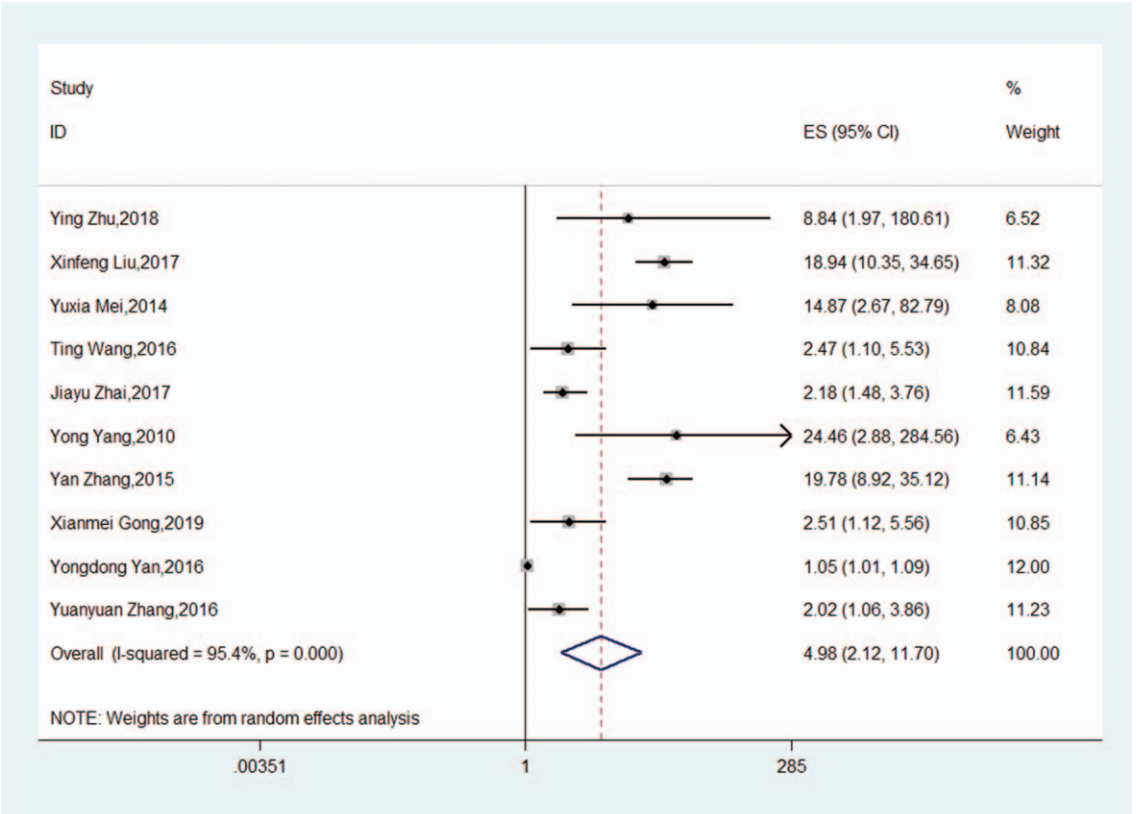

Figure 8. Forest plots showing the results of the meta-analysis regarding CRP >40 mg/L. Random effect model was used. The pooled OR was 4.98 (95%CI: 2.12–11.70). It indicates that CRP >40 mg/L was significantly associated with RMPP. RMPP = refractory mycoplasma pneumoniae pneumonia.

Table 3

Egger test of all risk factors.

Risk factors	No. of studies	Egger test		Publication bias Yes or NO	Model*
		t value	*P* value		
Male	3	10.02	.063	NO	F
Fever for more than 10 days	7	2.46	.058	NO	R
Pleural effusion	4	0.26	.817	NO	R
Extra-pulmonary complications	3	0.64	.636	NO	F
Pulmonary X-ray consolidation ≥ 2/3	4	5.15	.036	YES	R
LDH >410IU/L	6	1.49	.209	NO	R
CRP >40 mg/L	10	1.86	.100	NO	R

* R, random effect model; F, fixed effect model.

rises when there is a strong immune response which played a prompt action for judgment of the degree of the disease.[48] This study found that CRP >40 mg/L was a risk factor of RMPP, which was consistent with previous studies.[22–28,32,34,35]

It has been reported that serum LDH is a reliable indicator to predict refractory mycoplasma pneumoniae pneumonia and medication can be adjusted by testing this indicator.[49] LDH was associated with many pulmonary diseases, such as obstructive diseases, microbial pulmonary diseases, and interstitial lung diseases.[50] Several studies[51,52] also found that serum LDH was elevated in RMPP. Previous studies on LDH have different conclusions, some studies[12,22,26,31,35] thought that LDH >410IU/L was a risk factor of attacking RMPP, however, some studies[34,36] did not think there is a connection and our analysis found that there's no association between LDH >410IU/L and RMPP.

This study has several limitations. Firstly, all the included studies found that fever for more than 10 days, pleural effusion, extra-pulmonary complications, pulmonary X-ray consolidation ≥2/3, CRP >40 mg/L were risk factors of RMPP and our study just confirmed that they were risk factors again. Secondly, almost all of the included studies came from china and probably could not be representative of the entire population. So, more studies on risk factors of RMPP in children will be carried out in the future.

5. Conclusions

In conclusion, we found that 5 factors are associated with RMPP in children. Fever for more than 10 days, pleural effusion, extra-pulmonary complications, pulmonary X-ray consolidation ≥2/3 and CRP >40 mg/L are risk factors for early evaluation of RMPP in children which generating evidence for rapidly response to systemic treatment of RMPP.

Author contributions

Data curation: Hui Gong.
Formal analysis: Hui Gong
Investigation: Baijun Sun.
Methodology: Ye Chen, Baijun Sun.
Project administration: Huijie Chen.
Resources: Ye Chen.
Supervision: Huijie Chen.
Validation: Huijie Chen.
Writing – original draft: Hui Gong.
Writing – review & editing: Huijie Chen.
Optional Supplementary Materials,http://links.lww.com/MD/F775

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