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Laboratory abnormalities in children with refractory mycoplasma pneumoniae pneumonia: a systematic review and meta-analysis

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Abstract

Objective: To evaluate the discriminative ability of laboratory abnormalities between general *mycoplasma pneumoniae* pneumonia (GMPP) and refractory MPP (RMPP) in children.

Methods: An electronic search in PubMed, Web of Science, Embase, and Cochrane Library was performed to identify studies reporting on laboratory abnormalities in children with GMPP and RMPP. Data were independently extracted by two reviewers. Meta-analyses within the random-effects model were used to synthesize data. Effect sizes were calculated as standardized mean differences (SMD) or weighted mean difference (WMD). The Newcastle-Ottawa Scale (NOS) was used to assess the methodologic quality of included studies.

Results: Twenty-one articles (3,877 patients) comparing laboratory findings between patients with GMPP and RMPP were eligible for this meta-analysis. Patients with RMPP had significantly increased neutrophils, $CD8^+$ lymphocytes, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), D-dimer, total IgA, total IgM, as well as decreased lymphocytes, hemoglobin, and albumin. Multiple inflammatory biomarkers (C-reactive protein [CRP], procalcitonin [PCT], erythrocyte sedimentation rate [ESR], ferritin, interleukin [IL]-6, IL-10, IL-17, IL-18, interferon-γ [IFN-γ], and tumor necrosis factor-α [TNF-α]) were also markedly elevated in RMPP patients.

Conclusions: Elevated levels of $CD8^+$ lymphocytes, LDH, AST, D-dimer, total IgA, total IgM, inflammatory biomarkers (CRP, PCT, ESR, ferritin, IL-6, IL-10, IL-17, IL-18, IFN-γ, and TNF-α), and lower lymphocytes, hemoglobin, and albumin are associated with RMPP and thus may be used as early identification or even prediction of RMPP in children.

Keywords: Child; Refractory Mycoplasma pneumoniae pneumonia; clinical chemistry; meta-analysis.

Introduction

Mycoplasma pneumoniae pneumonia (MPP) is a common aetiology of pediatric community-acquired pneumonia, accounting for 10-30% of cases [1]. Epidemics occur every 3-7 years and are usually 1-2 years in duration [2]. Generally, macrolides are used as first−line antibiotics for the treatment of MPP [3]. Although MPP in children is typically a mild and self-limiting disease, sometimes it may progress to life-threatening refractory *Mycoplasma pneumoniae* pneumonia (RMPP), characterized by prolonged fever, deterioration of imaging and clinical findings, respiratory distress syndrome, and even necrotizing pneumonia despite macrolide therapy [4-6].

It has been reported that excessive immune response may play an important role in the development of RMPP [7, 8]. However, the pathophysiologic mechanisms underlying RMPP are incompletely understood. Moreover, there are no specific biomarkers to provide early diagnosis and prognosis prediction of RMPP. Therefore, it is critical to identify clinical and laboratory predictors for the progression of refractory forms in order to improve the prognosis of RMPP patients. In earlier reports, lactate dehydrogenase (LDH) has been identified as an important predictor of refractory cases [5, 9, 10]. Recently, increasing reports of RMPP have been published, enabling a more comprehensive analysis of laboratory data on RMPP.

The aim of this systematic review and meta-analysis was to analyze laboratory abnormalities in children with general *mycoplasma pneumoniae* pneumonia (GMPP) and RMPP, in order to define which parameters can discriminate between those who are at higher risk of developing RMPP.

Methods

In conducting this systematic review we followed PRISMA [11] (Preferred Reporting Items for

Systematic reviews and Meta-analyses) and MOOSE [12] (Meta-analysis of Observational Studies) guidelines. This systematic review was registered on PROSPERO with registration number: CRD42020215983.

Search strategy and eligibility criteria

Pubmed, Web of science, Embase, and Cochrane Library were searched by one reviewer (ZL Wang) from inception to Oct 26, 2020 using a combination of Medical Subject Headings (MeSH) and text words (see **Additional file 1**). We did not restrict our search by language or year of publication. We also reviewed the reference lists of included studies for relevant studies that may have been missed in the initial electronic search.

Studies were included if they met the following criteria: (1) case-control studies or cohort studies reported extractable data on laboratory abnormalities in both GMPP and RMPP children aged < 18 years; (2) MPP was diagnosed with serology or polymerase chain reaction, and refractories were defined clinically; (3) published in English.

Editorials, reviews, comments, letters, conference abstracts, case reports and case series were excluded.

Outcomes

Outcomes for this meta-analysis were as follows: (1) haematological parameters (white blood count, neutrophils, platelets, hemoglobin (Hb), lymphocytes and subsets (CD3+, CD4+, CD8+, CD19+, CD56+); (2)blood biochemical parameters (LDH, alanine aminotransferase, aspartate aminotransferase [AST], pre-albumin, albumin (ALB), MB isoenzyme of creatine kinase; (3) coagulation tests (fibrinogen, D-dimer); (4) immunological tests (total IgA, IgM, IgG, and IgE); (5) plasma inflammatory biomarkers (C-reactive protein [CRP], procalcitonin [PCT], erythrocyte sedimentation rate [ESR], ferritin, interleukin [IL]-2, IL-4, IL-6, IL-10, IL-17, IL-18, interferon-γ

[IFN-γ], and tumor necrosis factor-α [TNF-α]).

Data extraction and quality assessment

Two investigators (ZL Wang and Y He) independently extracted the following data from the included studies: study name, research publication date, study design, authors, sample size, country of study, sex and age of participants, laboratory tests performed with their corresponding values, and relevant elements of bias risk assessment. When unavailable, we extrapolated the mean and standard deviations (SDs) of laboratory values from median, sample size, and interquartile range (IQR), according to Hozo et al [13]. Additional data were sought from original study authors when appropriate.

The quality of included studies was independently evaluated by the two reviewers based on the Newcastle-Ottawa Scale (NOS) guidelines [14]. Any disagreement was resolved by another reviewer. Studies were rated as high quality if they had a total score of 7-9, moderate quality with a score of 4-6, and poor quality with a score of 3 or lower.

Statistical analysis

Results were merged across studies with STATA version 15.1 and meta-analysis forest plots were constructed for each parameters using R (version 4.0.2) package ‘forestplot’. We used a random-effects meta-analysis model due to the high likelihood of between-study variance from different study designs, populations, and effect sizes. Weighted mean difference (WMD) or standardized mean difference (SMD) were calculated with the corresponding 95%CI between groups for continuous variables. Heterogeneity was assessed using the P value of the Cochran’s Q statistic and the I^2 statistic [15]. Significant heterogeneity among studies was indicated by a Cochran’s Q P value of < 0.10. As for the I^2 statistic, heterogeneity was classified as results were interpreted as 25%, 50% and 75%, representing low, moderate, and high heterogeneity, respectively [15]. To

investigate potential sources of heterogeneity, we carried out sensitivity analyses to evaluate the effects of excluding studies that had different diagnostic criteria for RMPP from others or studies with a sample size of fewer than 50. We also planed to perform subgroup analysis and meta-regression for each outcome based on different age groups. However, we could not conduct these analyses because we failed to contact the authors to obtain the original data of some included studies. Funnel plot (when meta-analysis includes 10 or more studies) and Egger's test use were used to assessed publication bias [16].

Results

Literature search, study characteristics and quality assessment

A flow chart of studies through the analysis is presented in **Fig. 1**. Initially, 345 articles were identified were identified through database probing. After deleting duplicate records, a total of 184 records were retained. Then, 105 articles were excluded by the titles and abstracts, and 58 of the remaining 79 articles were deleted for various reasons (**Fig. 1**). Finally, 21 studies [4, 5, 7, 9, 10, 17-32] involving 3,877 patients were included in the meta-analysis.

The characteristics of the included studies are shown in **Table 1**. All studies were from China, except for two: one from Korea [21] and the other from Japan [5]. Among these studies, 20 were case-control studies [4, 5, 7, 9, 10, 17-19, 21-32], and one was cohort study [20]. All of the selected studies were published from 2014 to 2020 with different sample sizes ranged from 10 to 653 patients. The median ages ranged from 4 to 9.3 years old in the RMPP group and from 3 to 8.8 years old in the GMPP group across the enrolled studies. The diagnostic criteria for RMPP were based on poor response to macrolide or antibiotic treatment in most studies, while the definitions were poor response to corticosteroids (or combined with macrolide) in the other four

studies [20, 23, 28, 29].

We analyzed 34 factors in the meta-analyses (**Table 2**). The NOS for observational case-control and cohort studies assessment were showed in **Additional file 2**. The 21 included studies scored between 5 and 6. None of the studies were considered to be poor quality.

Meta-analysis of laboratory abnormalities

Full results are shown in **Table 2** and forest plots in **Fig. 2.** In terms of hematologic parameters, we detected that RMPP cases had higher neutrophils (WMD=1.321, 95% CI, 0.784, 1.858, I^2=95.90%), and $CD8^+$ lymphocytes (WMD=1.124, 95% CI, 0.057, 2.191, I^2=0.00%), with lower levels of lymphocytes (WMD= -0.559, 95% CI, -0.891, -0.226, I^2=49.50%), and Hb (WMD= -3.578, 95% CI, -5.945, -1.211, I^2=84.90%). Concerning the biochemical indicators, significantly elevated LDH (WMD= 122.638, 95% CI, 97.668, 147.609, I^2=77.40%) and AST (WMD= 10.983, 95% CI, 0.470, 21.496, I^2=84.90%) were correlated with RMPP cases. Patients in RMPP group also displayed lower ALB (WMD= -5.7, 95% CI, -7.165, -4.235). With respect to coagulation functions, the D-dimer in RMPP group was higher than that in GMPP patients. RMPP group also showed elevating total IgA (WMD= 0.303, 95% CI, 0.026, 0.581, I^2=89.60%) and total IgM (WMD= 0.28, 95% CI, 0.142, 0.4184, I^2=40.00%) than those in the GMPP group. Regarding inflammatory biomarkers, RMPP cases showed markedly increased CRP, PCT, ESR, ferritin, IL-6, IL-10, IL-17, IL-18, IFN-γ, and TNF-α compared to GMPP cases (**Table 2** and **Fig. 2**).

Sensitivity analysis and publication bias

To clarify the sources of heterogeneity, we conducted sensitivity analyses by excluding studies that had different definitions for RMPP or with a sample size of fewer than 50. However, between−study heterogeneity remained substantial after excluding studies with potential sources of bias (see **Additional file 3 & 4**). $CD8^+$ cell proportions became not statistically significant after

excluding studies with different definitions of RMPP, while IL-17 and TNF-α became not significant after the exclusion of studies with a small sample size. No significant changes were noted in any other sensitivity analyses (see **Additional file 3 & 4**). The *P* values derived using the Egger's test for all outcomes (see **Additional file 5**) showed potential publication bias of CRP (*P*=0.04). Funnel plots based on the outcomes of WBC, CRP, and LDH were roughly symmetrical, indicating that publication bias was negligible (**Fig. 3**).

Discussion

This first meta-analysis systematically summarized the laboratory characteristics of GMPP and RMPP patients, a clear pattern of inflammatory, hematologic, biochemical, immune, and coagulation biomarker abnormalities could be found between GMPP and RMPP cases. Based on the analysis of available studies, laboratory predictors for progressing to RMPP from MPP include higher levels of neutrophils, $CD8^+$ cell, LDH, AST, D-dimer, total IgA, total IgM, multiple inflammatory biomarkers (CRP, PCT, ESR, ferritin, IL-6, IL-10, IL-17, IL-18, IFN-γ, and TNF-α), as well as lower lymphocytes, Hb, and ALB.

Several hematologic differences were observed between the refractory and general cohorts. Mild elevation of neutrophils accompanied by decreased lymphocytes were correlated with refractory disease. We found that IL-17 from the children with RMPP was significantly higher than children with GMPP. IL-17 is important for the prevention of microbial invasion and plays an essential role in the recruitment of neutrophils [33, 34]. Thus, elevated IL-17 may lead to an increase in neutrophil numbers in RMPP patients. It is believed that excessive immune response is involved in the pathogenesis of RMPP. Imbalanced immune response in RMPP cases, accompanied by

lymphocyte necrosis and apoptosis, may result in lymphopenia. Interestingly, $CD8^+$ lymphocyte proportions increased in RMPP patients. However, relative proportions could not represent the absolute count of CD8, further studies are needed to clarify the role of $CD8^+$ lymphocytes in the pathogenesis of RMPP.

We also found that elevated LDH, AST and decreased ALB in the RMPP group, which suggested that the cardiac, liver and other important organ functions might be more severely damaged in RMPP cases. LDH is known to catalyze the oxidative conversion of the substrate pyruvate to lactate, and is released from cells after cell damage and can be used to monitor cell and tissue damage [35]. Several studies have shown that LDH is closely associated with the severity of lung injury or refractory illness in MPP patients [9, 10, 36]. *Mycoplasma pneumoniae* infection can also cause extrapulmonary manifestations on account of excessive immune responses [37]. Combined with abnormalities in AST and ALB, suggesting potential liver injury from progression in patients who develop the refractory form of the disease. Besides, elevated D-dimer was noted in children with RMPP, indicating potential hypercoagulability in RMPP patients. Nevertheless, the number of studies considering impairments of extra-pulmonary organ was small, which encourages more research on the extra-pulmonary abnormalities such as hepatic, renal and coagulation dysfunctions.

With respect to immunologic biomarkers, higher levels of total IgG and IgA were found in RMPP cases. RMPP seemed to occur in older children in several studies [4, 9, 20, 29-31], children older than 5 years have a relatively more mature immune function than younger children, so it is possible that elevated levels of antibody may be related to advancing age [29]. However, we were unable to perform subgroup analysis by different age groups due to insufficient data, additional

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194 research is needed to explore potentially various antibody levels at different ages in RMPP
195 patients.

196 Elevation of various inflammatory biomarkers in MPP patients might have contributed to severe
197 disease and lung injury [20, 38]. We noted that multiple inflammatory factors (ESR, CRP, PCT,
198 ferritin, IL-6, IL-17, IL-18, IFN-γ, and TNF-α) considerably increased in RMPP patients than
199 GMPP patients. This phenomenon illustrates that refractory cases may have more severe systemic
200 inflammatory response. What's more, it has been reported that immunosuppressants could inhibit
201 lung injury and infammatory infiltration after mycoplasma pneumoniae infection [8].Thus,
202 attention should be paid to appropriate anti-inflammatory treatment towards RMPP patients.
203 Additionally, elevated IL-10 was observed in RMPP patients, which may be related to
204 compensatory anti-inflammatory response [39].

205 This systematic review and meta-analysis has several limitations. First, although our meta-analysis
206 rigorously analyzed data from a large sample of MPP patients, our results are limited by the
207 heterogeneity across studies. We performed sensitivity analyses to detect the potential source of
208 heterogeneity, but heterogeneity still exists. Second, given that most of the included studies were
209 single-center, retrospective studies, it was difficult to control confounding factors, such as the
210 participants' inclusion criteria, various age groups, and the study design. We intended to conduct
211 subgroup analyses to investigate different age effects on different laboratory parameters, however,
212 we were unable to perform these analyses owing to limited data. Additionally, the majority of the
213 studies included in our meta-analysis were from China, whether these results are consistent with
214 data from other countries needs to be further investigated.

215 In conclusion, current evidence showed that, elevated neutrophils, $CD8^+$ lymphocytes, LDH, AST,

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216 D-dimer, total IgA, total IgM, inflammatory biomarkers (CRP, PCT, ESR, ferritin, IL-6, IL-10, IL-
217 17, IL-18, IFN-γ, and TNF-α), as well as lower lymphocytes, Hb, and ALB are associated with
218 RMPP. Therefore, these laboratory parameters could be used as early identification or even
219 prediction of refractory illness. Due to the limited quality of the included studies, high quality
220 prospective studies are required to verify the above conclusions.

221

222 **Abbreviations**

223 ALB: Albumin; AST: aspartate aminotransferase; CRP: C-reactive protein; CKMB: MB
224 isoenzyme of creatine kinase; ESR: erythrocyte sedimentation rate; Fib: fibrinogen; GMPP:
225 general Mycoplasma pneumoniae pneumonia; Hb: hemoglobin; IL: interleukin; IFN-γ: interferon-
226 γ; LDH: lactate dehydrogenase; Lym: lymphocytes; MPP: Mycoplasma pneumoniae pneumonia;
227 Neu: neutrophils; NOS: Newcastle-Ottawa Scale; PLT: platelets; PCT: procalcitonin; RMPP:
228 refractory Mycoplasma pneumoniae pneumonia; SMD: standardized mean difference; TNF-α:
229 tumor necrosis factor-α; WBC: white blood count; WMD: Weighted mean difference.
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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflict of interest.

Funding

Not applicable.

Authors' contributions

ZL Wang had the idea for and designed the study, searched the literature, collected, analyzed, and interpreted data, and wrote the manuscript. Y He collected, analyzed, and interpreted data, and revised the manuscript. ZX Luo had the idea for and designed the study, supervised the study, and gave administrative and technical support. All authors read and approved the final manuscript.

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Figure legends

Fig.1: Study selection flowchart.

Fig.2: Meta-analysis for laboratory abnormalities between GMPP and RMPP patients.

Fig.3: Funnel plots of (a) White blood count, (b) Lactate dehydrogenase, (c) C-reactive protein.

Table 1. Characteristics of the included studies.

Study	Year	Research type	Country	Number of patients, n		Age, mean, y		Diagnostic criteria of Refractory MP pneumonia
				Refractory	Genaral	Refractory	Genaral	
Inamura [5]	2014	Case control	Japan	5	15	6.2	8.0	Prolonged fever and deterioration of clinical and radiological findings after appropriate antibiotics ≥ 7 d.
Wang [29]	2014	Case control	China	76	26	5.6	4.0	Prolonged fever (>38.5 °C) and radiological deterioration after therapy of macrolide combined with oral prednisolone ≥ 7 d.
Shin [21]	2014	Case control	Korea	26	177	4.7	5.6	Persistent fever **>** 38.3 °C and a progressive pulmonary consolidation or pleural effusion despite macrolide therapy ≥ 5 d.
Lu [9]	2015	Case control	China	300	353	5.6	4.3	Prolonged fever accompanied by deterioration of radiological findings despite macrolide treatment for ≥ 7 d.
Guo [20]	2016	Prospective cohort	China	25	58	7.1	6.1	Persistent fever for **>** 5 d after the use of the corticosteroids.
Yu [31]	2016	Case control	China	5	5	7.1	6.1	Prolonged fever ≥ 7 d and increasing cough and infiltrates in chest radiograph despite appropriate antibiotics therepy.
Zhang [4]	2016	Case control	China	145	489	5.9	3.9	Persistent fever and clinical as well as radiological deterioration after azithromycin treatment ≥ 7 d.
Zhang [22]	2016	Case control	China	65	115	8.2	8.0	Persistent fever and clinical as well as radiological deterioration after azithromycin treatment ≥ 7 d.
Liu [10]	2017	Case control	China	16	54	5.8	7.2	Persistent fever and/or deterioration of radiological findings for ≥ 7 despite management with azithromycin.
Wang [28]	2017	Case control	China	101	62	6.1	5.7	Persistent fever and radiological deterioration after therapy of macrolide combined with oral prednisolone for ≥ 7 d.
Wang [30]	2017	Case control	China	49	185	7.0	5.2	Clinical and radiographic progression despite appropriate macrolide antibiotic treatment for ≥ 7 d.

Ding [18]	2018	Case control	China	108	344	5.2	3.0	Clinical and radiological deterioration despite macrolide antibiotic therapy for ≥ 7 d.
Fan [19]	2019	Case control	China	30	18	5.0	7.4	Prolonged fever for ≥ 7 d or increasing cough and infiltrates by chest radiography despite appropriate antibiotics therapy.
Li [23]	2019	Case control	China	21	50	5.4	5.4	Prolonged fever (>38.5°C), radiological deterioration after macrolide combined oral prednisolone therapy for ≥ 7 d.
Cheng [17]	2020	Case control	China	73	146	6.5	6.4	Persistent fever and/or deterioration of radiological findings for ≥ 7 d despite appropriate management with macrolides.
Lee [7]	2020	Case control	China	9	33	5.8	7.2	Prolonged fever and deterioration of clinical and radiological findings, regardless of appropriate antibiotic therapy.
Zhao [25]	2020	Case control	China	45	109	9.3	8.8	Prolonged fever and aggravation of radiological manifestations despite appropriate antibiotic treatment for ≥ 7 d.
Li [26]	2020	Case control	China	30	45	7.2	7.5	Prolonged fever for ≥ 7 d or increasing cough and infiltrates by chest radiography despite the therapy of appropriate antibiotics
Zhou [32]	2020	Case control	China	56	51	4.8	3.7	Sustained fever ≥ 7 d and increasing cough and infiltrates on chest radiographs despite therapy of macrolide antibiotics.
Li [24]	2020	Case control	China	29	152	4.0	4.9	Persistent fever and clinical manifestations as well as radiological deterioration after macrolides treatment for ≥ 7 d.
Ling [27]	2020	Case control	China	86	190	6.0	5.6	Persistent fever and exacerbations of clinical symptoms, signs, and radiological findings after treatment of macrolide for ≥ 7 d.

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360 **Table 2.** Meta analyses of different laboratory parameters for RMPP compared with GMPP.

Laboratory parameters	No. studies	No. patients	Heterogeneity		Model	Meta analysis	
			Q	I^2		WMD/SMD (95%CI)	*P*
Hematologic							
WBC (×10^9)	20	3796	64.26	70.40%	Random	0.147 (-0.314, 0.607)	0.532
Neu (×10^9)	9	2833	193.95	95.90%	Random	1.321 (0.784, 1.858)	0.000
Lym (×10^9)	5	1099	7.92	49.50%	Random	-0.559 (-0.891, -0.226)	0.001
PLT (×10^12)	8	1325	41.38	83.10%	Random	-11.952 (-31.154, 7.249)	0.222
Hb (g/L)	6	771	33.08	84.90%	Random	-3.578 (-5.945, -1.211)	0.003
CD3 (%)	4	987	2.15	0.00%	Random	1.324 (-0.279, 2.928)	0.105
CD4 (%)	4	987	1.10	0.00%	Random	-0.127 (-1.417, 1.163)	0.847
CD8 (%)	4	987	1.91	0.00%	Random	1.124 (0.057, 2.191)	0.039
CD19 (%)	2	173	0.15	0.00%	Random	-0.307 (-3.332, 2.718)	0.842
CD56 (%)	2	173	0.77	0.00%	Random	-0.213 (-2.342, 1.916)	0.844
Biochemical							
LDH (IU/L)	18	3343	75.07	77.40%	Random	122.638 (97.668, 147.609)	0.000
ALT (IU/L)	6	1433	25.77	80.60%	Random	5.475 (-1.659, 12.610)	0.133
AST (IU/L)	4	1168	22.26	86.50%	Random	10.983 (0.470, 21.496)	0.041
Pre-ALB (g/L)	2	815	44.37	97.70%	Random	-18.548 (-55.631, 18.534)	0.327
ALB (g/L)	1	239	NA	NA	Random	-5.700 (-7.165, -4.235)	0.000
CKMB (IU/L)	3	974	6.01	66.70%	Random	0.893 (-2.134, 3.921)	0.563
Coagulation							
Fib (g/L)	2	439	3.47	71.20%	Random	0.143 (-0.774, 1.060)	0.760
D-dimer (mg/L)	1	276	NA	NA	Random	1.370 (0.424, 2.316)	0.005
Immunology							
IgG (g/L)	4	1368	35.37	91.50%	Random	0.597 (-0.703, 1.897)	0.368
IgA (g/L)	4	1368	28.78	89.60%	Random	0.303 (0.026, 0.581)	0.032
IgM (g/L)	4	1368	5	40.00%	Random	0.280 (0.142, 0.418)	0.000
IgE (g/L)	2	437	17.93	94.40%	Random	0.806 (-0.329,1.941)	0.164
Inflammatory biomarkers							
CRP (g/L)	21	3513	152.56	90.20%	Random	17.590 (11.438, 23.742)	0.000
PCT (SMD)	5	1064	61.40	93.50%	Random	0.610 (0.047, 1.173)	0.034
ESR (mm/h)	6	1434	27.39	81.70%	Random	6.733 (2.210, 11.256)	0.004
Ferritin (SMD)	3	611	10.01	80.00%	Random	0.698 (0.261, 1.134)	0.002
IL-2 (pg/ml)	3	834	0.56	0.0%	Random	-0.085 (-0.307, 0.137)	0.454
IL-4 (pg/ml)	3	834	0.37	0.0%	Random	0.069 (-0.082, 0.220)	0.369
IL-6 (pg/ml)	7	1685	47.02	87.2%	Random	10.764 (5.937 ,15.590)	0.000
IL-10 (pg/ml)	3	834	2.78	28.0%	Random	2.776 (1.932, 3.620)	0.000
IL-17 (pg/ml)	3	285	185.25	98.9%	Random	31.588 (4.988, 58.188)	0.020
IL-18 (pg/ml)	2	174	0.58	0.0%	Random	220.749 (126.371, 315.128)	0.000
IFN-γ (pg/ml)	4	867	249.27	98.8%	Random	86.489 (29.648, 143.330)	0.003
TNF-α (pg/ml)	7	1442	1483.55	99.7%	Random	16.145 (10.802, 21.488)	0.000

361 ALB: Albumin; AST: aspartate aminotransferase; CRP: C-reactive protein; CKMB: MB isoenzyme of creatine

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kinase; ESR: erythrocyte sedimentation rate; Fib: fibrinogen; GMPP: general Mycoplasma pneumoniae pneumonia; Hb: hemoglobin; IL: interleukin; IFN-γ: interferon-γ; Lym: lymphocytes; LDH: lactate dehydrogenase; Neu: neutrophils; PCT: procalcitonin; PLT: platelets; RMPP: refractory Mycoplasma pneumoniae pneumonia; SMD: standardized mean difference; TNF-α: tumor necrosis factor-α; WBC: white blood count,WMD: Weighted mean difference.