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ORIGINAL ARTICLE

Diagnostic Value of Serum ELISA of *Mycoplasma Pneumoniae* IgM and IgG and Passive Particle Agglutination for *Mycoplasma Pneumoniae* Pneumonia in Children

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SUMMARY

Background: **The study was aimed to compare ELISA results of *Mycoplasma pneumoniae* IgG (MP-IgG) and *Mycoplasma pneumoniae* IgM (MP-IgM) with the passive particle agglutination (PA) test, as well as to evaluate their application value in the diagnosis of *Mycoplasma pneumoniae* pneumonia (MPP) in children.**
Methods: **Serum MP antibodies were detected by ELISA for MP-IgM, MP-IgG, and PA for 292 patients in the MPP group and 89 patients in NMP group. The PA results were used as reference standards. These patients were treated in the respiratory department of Children's Hospital Capital Institute of Pediatrics, China, from July to December, 2019.**
Results: **In the MPP group, the positive rate for MP-IgM was 75% higher than that of the PA titer (73.97%), Pearson's coefficient was 0.711, and the Kappa coefficient was 0.662, $p < 0.01$, suggesting that both the correlation and the consistency of the two methods were high. In the PA-negative group (< 1:160), 22.38% of patients were MP-IgM positive, indicating that the sensitivity to MP-IgM was higher compared to PA, when the disease duration was less than 7 days. The diagnostic value for MP-IgG was lower than that for MP-IgM, and the high positive rate of MP-IgG (48.31%) in the NMP group suggested a high background value of MP-IgG in children. Testing of paired serum obtained a more accurate diagnosis. At admission, 47.57% of patients with paired serum who were negative for MP-IgM, converted to a net positive after 4 – 6 days, except for one patient. In the paired serum, 57.8% of patients had a 4-fold increase of MP-IgG.**
Conclusions: **MP-IgM was a sensitive indicator of MP infection in children with a high consistency and correlation with the reference positive standard of PA titer ≥ 1:160. For a more accurate diagnosis, testing of paired serum is still necessary, and a 4-fold increase in MP-IgG could be the supplementary diagnosis method.**
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KEY WORDS

Mycoplasma pneumoniae IgM, *Mycoplasma pneumoniae* IgG, passive agglutination, children, *Mycoplasma pneumoniae* infection

INTRODUCTION

Mycoplasma pneumoniae (MP) is one of the most important pathogens in community-acquired pneumonia (CAP) in children, accounting for around 10% - 40% of the pediatric CAP cases [1,2]. Approximately 18% of MP-infected children in China require hospitalization

[3,4]. Therefore, it is essential to select the optimal laboratory tests, establish certain diagnostic criteria for obtaining a definitive diagnosis, and initiating timely and effective treatment [5].

Currently, diagnosis of MP infection relies on serologic tests, culture, and molecular detection by polymerase chain reaction (PCR). The culture test is an important standard for the detection of MP infection, but it is rarely used as diagnostic tool because of the requirement for special culture media. It is difficult to culture and has a very low growth rate; thus, culture-based approaches are usually not helpful clinically. PCR is rapid and effective in the detection of MP, but the procedure cannot distinguish MP carriers from MP infected patients, because MP is present in 0.1% - 13.5% of healthy individuals [6,7]. A rapid and reliable serologic test for MP antibodies was the important laboratory testing method. The passive particle agglutination (PA) test is conventionally used to detect MP-specific antibodies in the serum, and its diagnostic value for MP infection has been demonstrated in clinical settings, but it is largely limited by its inability to discriminate between IgG and IgM because of nonspecific reactions [8]. The enzyme-linked immunosorbent assay (ELISA) is the most common diagnostic method for MP detection because of the low cost and relatively high sensitivity and specificity. Compared with the PA, the ELISA can be used to detect *Mycoplasma pneumoniae* IgM (MP-IgM) and *Mycoplasma pneumoniae* IgG (MP-IgG) antibodies. In addition, the use of an automated enzyme immunoassay analyzer enables easy MP-IgM and MP-IgG detection and the objective interpretation of results. These two detection methods are widely used in the diagnosis and treatment of *Mycoplasma pneumoniae* infection in children, but few studies have evaluated the correlation between the two methods and their application value in the diagnosis and treatment process.

The purpose of this study is to evaluate the correlation between ELISA for IgG and IgM and PA and their application value in the diagnosis of *Mycoplasma pneumoniae* pneumonia (MPP) in children.

MATERIALS AND METHODS

Patients

The study enrolled a total of 381 patients who were treated in the respiratory department of Affiliated Children's Hospital of Capital Institute of Pediatrics, China, from July to December, 2019. All patients had respiratory symptoms, including acute bronchitis, bronchial asthma, upper respiratory tract infection, and acute tonsillitis, and thus MP infection was suspected. The patients were eventually divided into the Mycoplasma pneumoniae pneumonia (MPP) group and the community-acquired pneumonia (CAP) group with non-*Mycoplasma pneumoniae* (NMP). In addition to the above clinical symptoms, patients in the MPP group should show one of the conditions: (1) MP PA titers < 1:160 at admission and increased at least 4-fold within seven days; (2) MP PA titers ≥ 1:640 at admission; (3) MP PA titers ≥ 1:160 at admission and RNA positive for MP from a pharyngeal swab or alveolar lavage fluid. Patients with CAP who did not meet these criteria and are diagnosed with a different bacterial pathogen were assigned to the CAP with NMP group.

There were 292 patients in the MPP group, including 147 males (50.3%) and 145 females (49.7%) with a mean age of 5.7 years (range: 6 months to 16 years). There were 89 patients in the CAP with NMP group (NMP), including 51 males (57.3%) and 48 females (42.7%) with a mean age of 4.6 years (range: 2 months to 14 years). At admission, the resident doctors recorded the patient's current symptoms in detail, and course day calculation would start from the occurrence of fever symptoms. The average disease duration was 8.59 ± 3.73 days, and 34.9% (102/292) of patients were within one week. This study was conducted with the approval of the Institution Human Ethics Committee of the Affiliated Children's Hospital of Capital Institute of Pediatrics.

Methods

The PA test was used to detect MP antibody titer. Regents for PA (Serodia-MYCO II) were purchased from FUJIREBIO Co., Ltd., (Tokyo, Japan), according to the manufacturer's instructions. ELISA was used to detect MP-IgM and MP-IgG antibodies. Reagents were purchased from EUROIMMUN Medical Laboratory Diagnostics (Lubeck, Germany).

PA was used to detect MP antibody titer, and the results were expressed as follows: negative (titer: < 1:40) and positive (titers: 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280, 1:2,560, 1:5,120, 1:10,280, and 01:10,280).

ELISA was used to detect MP-IgM and MP-IgG antibodies. The results of ELISA MP-IgM based on S/CO value were interpreted as follows: negative if < 0.8, equivocal if 0.8 - 1.1, and positive if ≥ 1.1. The results of ELISA MP-IgG were interpreted as follows: negative if < 16 RU/mL, equivocal if 16 - 22 RU/mL, and positive if ≥ 22 RU/mL. For both ELISA MP-IgM and MP-IgG, samples with results within the equivocal range were tested again. If the mean is still in the equivocal range or positive, the result is counted as positive; otherwise, it is counted as negative.

Statistical analysis

Qualitative data were expressed as percentage and were analyzed using the χ^2 test. Quantitative data that followed a normal distribution were expressed as mean ± standard deviation ($\overline{x} \pm S$) and were analyzed using the *t*-test. Quantitative data that did not follow a normal distribution were expressed as median (interquartile range) and were analyzed using the Kruskal-Wallis H test and Wilcoxon test. The Kappa coefficient was calculated to evaluate consistency. Correlation analyses were conducted using linear regression and Pearson's coefficient. All statistical analyses were performed using SPSS

20.0. Differences with $p < 0.05$ were considered statistically significant.

RESULTS

Comparison of PA and ELISA (MP-IgM and MP-IgG) methods to detect MP antibodies in the MPP and NMP groups at admission

For PA, based on the qualitative analysis using titer 1:160 as the cutoff value for MP infection, the positive rate in the MPP group, 73.97% (216/292), was significantly higher than that in the NMP group 15.73% (14/89) (Table 1). For MP-IgM and MP-IgG, the positive rates in MPP group (75.0% and 61.3%, respectively) were both higher than in the NMP group (15.73% and 48.31%, respectively). In the MPP group, the positive rate for MP-IgM was higher than for MP-IgG, but the opposite was true in the NMP group. The consistency check for MP-IgM and MP-IgG with PA titer was investigated in the two groups. In the MPP group, compared with PA (titer = 1:160), the Kappa coefficient for MP-IgM was higher (0.662, $p < 0.01$) and for M-IgG it was 0.391, $p < 0.01$. In the NMP group, the consistency is poor, for MP-IgG, the Kappa value was 0.287, $p < 0.01$.

Consistency and correlation analysis of MP-IgM and MP-IgG with PA in the two groups

Because the diagnostic value of PA for MP infection has been demonstrated in clinical settings, it was used as reference method (titer ≥ 1:160 is positive) [9-11]. In the MPP group, the positive rates of MP-IgM and MP-IgG were significantly increased as the titer of PA increased. With the PA titer = 1:160, the positive rate of MP-IgM was 65.90%; with the PA titer ≥ 1:640, it was 100%. The positive rate of MP-IgG was lower than that of MP-IgM with the same titer, as with the PA titer = 1:640, the positive rate was only 62.90%. In the PA-negative group (titer < 1:160), the positive rates of MP-IgM and MP-IgG were 22.38% (15/67) and 23.88% (16/67), respectively. In the PA-positive group (titer ≥ 1:160), the positive rates of MP-IgM and MP-IgG were 90.67% (204/225) and 72.44% (163/225), respectively. In the NMP group, the positive rate of MP-IgM was lower than that in the MPP group with the same titer, but for MP-IgG the rate was on the opposite. The average course days corresponding to the titer were shown, for PA titer = 1:160, the average course days were 7.23 days (Table 2).

We analyzed the correlation between the concentrations of MP-IgM, MP-IgG and the PA, in the two groups (Figure 1). In the MPP group, the concentrations of MP-IgM ($Y = 0.436X - 0.578$, $F = 296.97$, $p < 0.01$) and MP-IgG ($Y = 8.624X - 5.516$, $F = 121.78$, $p < 0.01$) were both significantly positively correlated with the PA titer, and Pearson's coefficients were 0.711 and 0.544, respectively ($p < 0.01$). In the NMP group, the results showed that MP-IgG ($Y = 14.600X - 6.419$, $F = 19.05$, $p < 0.01$) and MP-IgM ($Y = 0.054X + 0.497$, $F = 4.674$, $p = 0.033$) were also positively correlated with the PA titer, but Pearson's coefficient (MP-IgG = 0.424, MP-IgM 0.226) was lower than in the MPP group.

Disease duration is the most important factor affecting detection rate

In order to compare the positive rates of MP-IgM, MP-IgG, and PA in different stages of the disease duration, 394 serum results (paired serum was obtained from a total of 292 patients in the MPP group and 102 patients in the NMP group) in the MPP group were analyzed and divided into 6 groups according to the duration of disease (0 - 3, 4 - 6, 7 - 9, 10 - 12, 13 - 15, and > 15 days). Prolonged disease duration coincided with a significant increase in the positive rates of MP-IgM, MP-IgG, and PA titer (Figure 2). The positive rate of MP-IgM was higher than that of MP-IgG in all groups. Using titer = 1:160 as the positive criteria, the positive rate of PA (0 - 3 days = 18.18%, 4 - 6 days = 45.45%) was lower than that of MP-IgM (0 - 3 days = 36.36%, 4 - 6 days = 55.14%) when the disease duration was < 7 days. Then, we analyzed the correlation between the concentrations of MP-IgM and MP-IgG and the disease duration, and the results showed that both MP-IgM ($Y = 0.143X + 0.815$, $F = 62.428$, $p < 0.01$) and MP-IgG ($Y = 0.327X - 0.735$, $F = 101.119$, $p < 0.01$) were significantly positively correlated with the disease duration. Pearson's coefficient was 0.371 and 0.467, respectively ($p < 0.01$).

The concentration change trend and combination form of MP-IgG and MP-IgM in the paired serum were different in the MPP and NMP groups

Paired sera were obtained from 102 patients in the MPP group and 19 patients in the NMP group. The paired sera were obtained at admission and before discharge (4 - 6 days after admission). The results were divided into the following four subgroups: MP-IgM+/IgG+, MP-IgM+/IgG-, MP-IgM-/IgG+, and MP-IgM-/IgG-. In the MPP group, the seroconversion in paired sera of MP-IgM was very obvious. At admission, 37.86% (38/102) of patients were in the MP-IgM-/IgG- subgroup, and 9.71% (10/102) of patients were in the MP-IgM-/IgG+ subgroup. Most of the patients converted to MP-IgM+/IgG- or MP-IgM+/IgG+ subgroups, only one (0.98%) patient was MP-IgG single positive in the paired sera. In order to analyze the concentration distribution of MP-IgM and MP-IgG for the paired sera in the MPP and NMP groups, we expressed the concentration distribution as the median (interquartile range) (Figure 3). In the MPP group, the concentrations of MP-IgM [2.06 (1.35 - 3.648)] and MP-IgG [59.135 (36.55 - 101.4)] before discharge were significantly higher than at admission [0.89 (0.5 - 1.655)], [11.87 (4.91 - 40.57)], $p < 0.01$, and the average increase multiple was 2.31 and 4.98, respectively. Between admission and before discharge 57.8% (59/102) patients had a ≥ 4-fold change in

Table 1. The positive rate for MP-IgM, MP-IgG and the PA titer at admission.

Group	Titer ≥ 1:160	MP-IgM	MP-IgG	p-value
MPP group	73.97	75.00	61.30	< 0.01
	(216/292)	(219/292)	(179/292)	
NMP group	15.73	15.73	48.31	< 0.01
	(14/89)	(14/89)	(43/89)	
p-value	< 0.01	< 0.01	0.02	

MP-IgM - *Mycoplasma pneumoniae*-IgM, MP-IgG - *Mycoplasma pneumoniae*-IgG, MPP group - Mycoplasma pneumoniae pneumonia group, NMP group - community-acquired pneumonia with non-Mycoplasma pneumoniae group, PA - passive particle agglutination. Data are shown as percentages and analyzed using the χ^2 test.

Table 2. The consistency of MP-IgM and MP-IgG with the PA titer.

	MPP group				NMP groups		
PA	N	duration	MP-IgM	MP-IgG	N	MP-IgM	MP-IgG
			Positive% (n/N)	Positive% (n/N)		Positive% (n/N)	Positive% (n/N)
< 1:40	15	5.13 ± 1.92	13.33 (2/15)	13.33 (2/15)	17	0.00 (0/17)	11.8 (2/17)
1:40	24	5.83 ± 1.63	16.67 (4/24)	12.50 (3/24)	28	14.28 (4/28)	46.42 (13/28)
1:80	28	6.15 ± 2.63	32.14 (9/28)	39.28 (11/28)	30	23.00 (7/30)	50.00 (14/30)
1:160	44	7.23 ± 2.44	65.90 (29/44)	43.18 (19/44)	13	23.07 (3/13)	100.0 (13/13)
1:320	40	7.98 ± 2.35	85.00 (34/40)	70.00 (28/40)	1	0.00 (0/1)	100.0 (1/1)
1:640	35	8.93 ± 1.95	100.00 (35/35)	62.90 (22/35)			
1:1,280	23	8.95 ± 1.46	100.00 (23/23)	78.20 (18/23)			
1:2,560	22	10.73 ± 3.38	100.00 (22/22)	90.90 (20/22)			
1:5,120	15	12.53 ± 3.83	100.00 (15/15)	93.33 (14/15)			
1:10,240	21	11.95 ± 2.85	100.00 (21/21)	90.47 (19/21)			
1:20,480	13	14.09 ± 3.98	100.00 (13/13)	84.62 (11/13)			
> 1:20,480	12	14.18 ± 4.36	100.00 (12/12)	100.00 (12/12)			
Total	292	8.59 ± 3.73	75.68 (219/292)	61.30 (179/292)	89	15.73 (14/89)	48.31 (43/89)

MP-IgM - *Mycoplasma pneumoniae*-IgM, MP-IgG - *Mycoplasma pneumoniae*-IgG, MPP group - Mycoplasma pneumoniae pneumonia group, NMP group - community-acquired pneumonia with non-Mycoplasma pneumoniae group, PA - passive particle agglutination. In the brackets, "n" represents the number of samples meeting the requirements and "N" represents the total number of samples in each group.

MP-IgG. But in the NMP group, both for MP-IgM and MP-IgG, there was no significant change at the two time points (p = 0.569, p = 0.331). At admission, for MP-IgM, the median of the MPP group (0.89) was higher than of the NMP group (0.68), and for MP-IgG, it was the opposite (MPP group 11.87, NMP group 28.42), but both of the differences were not statistically significant.

DISCUSSION

In this study, PA was used as the reference standard to investigate the diagnostic value of ELISA MP-IgM and MP-IgG in children. There was a consensus in available literature that a single serum MP antibody titer of ≥ 1:160 detected by PA should be used as a reference for the diagnosis of recent MP infection [12]. In the MPP group, the positive rate of MP-IgM was 75% higher than that of PA titer (73.97%), and both correlation and consistency of the two methods were high in children.

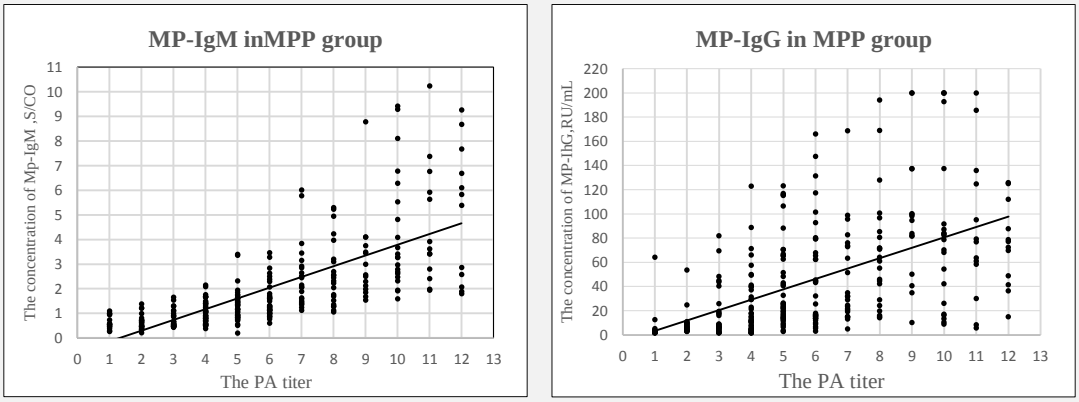

Figure 1. The correlation between the concentrations of MP-IgM and MP-IgG and the PA titer were shown, where Y and X represent the concentrations and PA titer, respectively, and the titers obtained by the PA (from < 1:40 to > 1:20,480) were replaced with a value of 0 to 12.

The equation of regression of MP-IgM in the MPP group was Y = 0.436X-0.578, F = 296.79, R^2 = 0.504, p < 0.01. The equation of regression of MP-IgG in the MPP group was Y = 8.624X - 5.516, F = 121.73, R^2 = 0.293, p < 0.01.

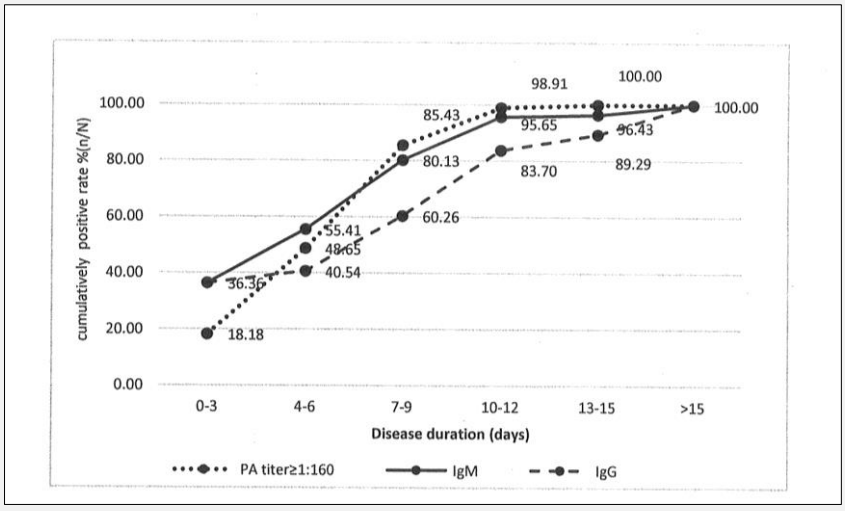

Figure 2. Positivity rates for MP-IgM, MP-IgG, and PA titer = 1:160 with different durations of the disease.

The patients were divided into 6 groups based on the duration of disease (0 - 3, 4 - 6, 7 - 9, 10 - 12, 13 - 15, > 15 days).

Thus, the diagnostic value of IgM positive alone is high and can be used as a diagnostic reference of MP infection in children [13], compared with the PA titer ≥ 1:160. The positive rate of the two methods were higher, which was associated with the time of onset. The average disease duration was 8.59 ± 3.73 days in the study, and most of them were severe cases and had a long period. In the PA-negative group (< 1:160), 22.38% patients were MP-IgM positive, which indicated that the sensitivity of MP-IgM was higher than of

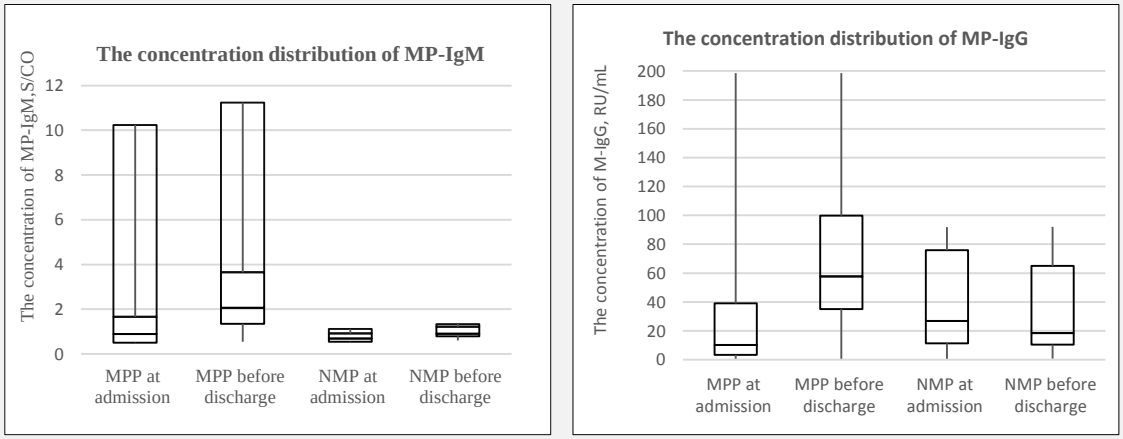

Figure 3. For the patients with paired serum in MPP and NMP groups, the concentration distributions of MP-IgM(S/CO) and MP-IgG were shown.

Data was expressed as median (interquartile range) and analyzed using the Mann-Whitney U and Wilcoxon Test, $p < 0.05$ was considered statistically significant.
For MP-IgM, in the MPP group: at admission [0.89 (0.5 - 1.655)] vs. before discharge [2.06 (1.35 - 3.648)], $p < 0.01$; in the NMP group: at admission [0.68 (0.54 - 0.915)] vs. before discharge [0.69 (0.58 - 1.00)], $p = 0.569$. For MP-IgM, at admission: MPP group vs. NMP group $p = 0.165$, before discharge: MPP group vs. NMP group, $p < 0.01$.
For MP-IgG, in the MPP group: at admission [11.87 (4.91 - 40.57)] vs. before discharge [59.135 (36.55 - 101.4)], $p < 0.01$; in the NMP group: at admission [28.42 (12.77 - 77.34)] vs. before discharge [19.74 (11.88 - 66.34)], $p = 0.331$. For MP-IgG, at admission: MPP group vs. NMP group $p = 0.124$, before discharge: MPP group vs. NMP group, $p = 0.012$.

PA. If the patients with low PA titer could be tested for MP-IgM, the misdiagnosis rate could be dramatically decreased, and the diagnosis and treatment efficiency can be improved.

MP-IgM was regarded as an indicator of infection for MP because it appeared during the first week of illness and reached peak titers during the second or third week. However, a recent study reported that MP-IgM might not be elevated in adults with poor antigenic response after repeated exposure [14]. The positive detection rate is related to age for patients under 20 years of age and is approximately 78%, whereas for adult patients it is only 34% [12]. The possible reasons were that initial infection can lead to the production of memory B cells and T cells, which could be rapidly activated upon reinfection. So MP-IgM rose and achieved a peak after 2 - 3 days of infection and then showed an immediate rise in IgG level. For adults, coughing is the main symptom, and the visit time is more than 1 week, so it was easy to miss the short period of IgM rise. However, fever symptoms appeared early in children, therefore, they would be brought to the hospital sooner, and in our study 34.9% children with MP infection were admitted to hospital within the first week. Thus, due to strong MP-IgM production ability and the early detection time, MP-IgM is a better indicator for children in the acute stage of MP infection.

In the study, the concentration of MP-IgM was positively correlated with the disease duration. The timing of blood sampling was the important influencing factor for the positive rate of serology, so negative serology could not exclude the possibility of MP infection. In recent studies, the MP-IgM positive rate in children was 62.2% in the first week, and it could reach 70.9% to 81.8% in the second week of the illness [15-17]. In our study, paired serum was obtained from 102 patients in the MPP group, and the seroconversion of MP-IgM was very high, 47.57% patients with negative MP-IgM at admission converted to positive, except for one patient with single MP-IgG positive in the paired serum. Therefore, repeat serological testing may be considered in patients with a high clinical suspicion of MP infection but an initially negative MP-IgM.

The positive rate of MP-IgG was always lower than MP-IgM, only when the disease duration was ≥ 7 days did it increase significantly, and at 13-15 days, the positive rate was 89.29%. All these suggested that MP-IgG antibodies are produced later, in the second week of the illness, and their sensitivity to diagnosis in the acute phase was lower than that of MP-IgM. In the NMP group, the positive rate of MP-IgG (48.31%) was high at admission, and with the increase in PA titer, the positive rate of MP-IgG increased significantly, while the positive rate of MP-IgM still remained at a low level.

The 14 patients with PA ≥ 1:160 in the NMP group were all MP-IgG-positive. These suggested that the proportion of children with previous MP infection was high, and the high background value of MP-IgG is the main cause of high PA titer in non-MP patients. Therefore, the patients may be misdiagnosed by PA results only, especially when the PA titer is low. In the study, with PA titer ≥ 1:160 as the diagnostic criteria, the false-positivity rate was 5.86% (14/239) (Table 2); therefore, this criterion was only a reference standard for acute infection. PA titer included MP-IgM and MP-IgG antibodies. For the patients with acute infection, IgM is the main form; for non-MP patients, IgG is the main form. Though the background value of IgM existed but was far lower than IgG (Table 2), the false-positivity rate of IgM was 6.00% (14/233). For the patients in the NMP group, the background values of MP-IgG and MP-IgM are constant in the two paired sera, while for the patients in the MPP group, the concentrations increased significantly in the second serum (Figure 3). A 4-fold increase in MP-IgG concentration in acute- and convalescent-phase sera is considered to be the gold standard for the diagnosis of acute MP infection [18]. While the rate of 4-fold increase of MP-IgG was different in studies. It ranged from 2.4% to 90%, with positive throat swabs tested via PCR [19,20]. In the study, for the paired sera in the MPP group, 57.8% of patients had a 4-fold increase. The average increase multiple was 4.98. Lina Wu et al. reported that the proportion of single positive IgG patients in acute and recovery period is high, so the MP-IgG had high diagnostic value for adults, owing to the potential lack of an IgM response in adults re-infected with MP [19]. But in the study, only one patient was MP-IgG single positive and exhibited a 4-fold increase in the paired serum. As MP-IgG with 4-fold increase cannot provide an instant diagnosis and obtaining second blood samples from children can be difficult in the convalescence phase, it does not seem to be an optimal tool for the early diagnosis of MP infection. However, for MP-IgM-negative or low PA titer children at admission, MP-IgG with a 4-fold increase could be used as an important method of supplementary diagnosis [21] and could effectively exclude uninfected patients with high IgG background values.

In conclusion, MP-IgM was highly consistent and correlative with the reference positive standard of PA titer ≥ 1:160. The sensitivity was even better than the PA method in the early stage of duration, though these methods still exhibit some false positive results. For a more accurate diagnosis of MP infection in children, testing of paired serum is still necessary. A 4-fold increase in MP-IgG could be the supplementary diagnosis method.

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Declaration of Interest:

The authors stated that there are no conflicts of interest regarding the publication of this article.

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