Duan *et al. Italian Journal of Pediatrics* (2025) 51:147
https://doi.org/10.1186/s13052-025-02012-9

Italian Journal of Pediatrics

RESEARCH Open Access

Serum cytokine levels in children with community-acquired pneumonia caused by different respiratory pathogens

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Abstract

Background Our study aims to investigate the levels of serum cytokines in children with community-acquired pneumonia (CAP) caused by different respiratory pathogens, and evaluate the predictive value of cytokines levels for severe pneumonia.

Methods A retrospective study was conducted on the clinical data of children hospitalized with CAP. According to the pathogens, patients were divided into the *M. pneumoniae* group, *Adenovirus* group, *respiratory syncytial virus* group, *H.influenzae* group, and *S.pneumoniae* group.

Results The *M. pneumoniae* group was higher than *RSV* group in the level of serum pro-inflammatory cytokines include IL-2, IL-6, IL-17 A, and IFN-γ. But *M. pneumoniae* group was higher than *Adenovirus* group only in IL-6. *M. pneumoniae* group was higher than *H. influenzae* group and *S. pneumoniae* group in IL-17 A, IFN-γ. as primary anti-inflammatory cytokine, IL-10 was lower in the *M. pneumoniae* group compared with *Adenovirus* and *RSV* groups. IL-6 was higher in *S. pneumoniae* group than *RSV* group. IFN-γ was lower in *H. influenzae* group than *Adenovirus* group and *RSV* group. IL-10 was higher in *RSV* group than *H. influenzae* group. IL-6 was higher in *Adenovirus* group than *RSV* group. In *M. pneumoniae* group and *H. influenzae* group, the levels of IL-6, IL-10, and IFN-γ were significantly higher in the severe pneumonia subgroup compared with the non-severe pneumonia subgroup ($P < 0.05$).

Conclusions Compared with other groups, *M. pneumoniae* group was higher in the level of serum proinflammatory cytokines. Additionally, the levels of IL-6, IL-10, and IFN-γ can be used as predictors of severe pneumonia caused by *M. pneumoniae* and *H. influenzae*.

Keywords Community-acquired pneumonia, Cytokines, Severe pneumonia, Respiratory pathogens

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Introduction

Community-acquired pneumonia (CAP) is a prevalent infectious disease in the pediatric population, and is the primary cause of death in children under 5 years of age [1]. *Respiratory syncytial virus, parainfluenza virus, rhinovirus, influenza virus, Mycoplasma pneumoniae, Adenovirus*, and *Streptococcus pneumoniae* are the most common pathogens that cause CAP [2]. While most CAP patients have mild symptoms and a good prognosis, some patients may develop serious complications such as pleural effusion, empyema, and lung abscess [3]. Pneumonia caused by different respiratory pathogens exhibits distinct pathophysiological mechanisms, resulting in different immune responses and clinical outcomes [4]. Cytokines, as critical mediators that regulate immune and inflammatory responses through complex networks, are soluble low-molecular-weight proteins induced by immunogens, mitogens, or other stimuli in various cells. However, excessive release of cytokines due to dysregulated inflammatory response will injure the host [5, 6]. Serum cytokines can be affected by numerous factors, especially infection in children [7, 8]. It is widely known that CAP can be caused by viruses, bacteria, and atypical pathogens. Previous study has reported that differences in serum cytokine levels between *Mycoplasma pneumoniae pneumonia(MPP)* and *non-Mycoplasma pneumoniae pneumonia(non-MPP)* [9]. However, there is a lack of clarity about the serum levels of cytokines in children with CAP caused by different respiratory pathogens. Previous studies have shown that cytokines have predictive value for severe pneumonia [10, 11], it is not konwn whether cytokines have the same predictive value for severe pneumonia caused by different pathogens. The aim of this study is to investigate the serum levels of cytokines in children with CAP caused by different respiratory pathogens, and to evaluate the predictive value of cytokine levels for severe pneumonia caused by different pathogens.

Patients and methods

The clinical data of children hospitalized with CAP at the Children's Hospital of Chongqing Medical University from February 2021 to October 2022 were retrospectively collected. Clinical information included baseline demographics and cytokine levels, as well as laboratory tests and imaging examination results. This study was approved by the Ethics Committee of Children's Hospital of Chongqing Medical University, with the approval number (521) in 2023.

Inclusion criteria:

(1) A definite diagnosis of CAP in children [12], with evidence of pneumonia on chest imaging. (2) Fever duration of ≤ 7 days upon admission and cytokine levels measured within 7 days of fever onset. (3) Age below 18 years. (4) Infection with a single respiratory tract pathogen (5) The minimum of patients are 20 cases in each pathogen group.

Exclusion criteria:

(1) Immunodeficiency; (2) Hematological malignancies; (3) Complications with other system or organ infections; (4) Rheumatic immune diseases; (5) Infection with multiple respiratory pathogens or unidentified pathogens.

Definition of community-acquired pneumonia CAP is defined as a clinical diagnosis of pneumonia caused by a community-acquired infection [12].

Detection of respiratory pathogenic microorganisms

Respiratory pathogenic microorganisms were detected using nasopharyngeal swabs or sputum secretions as specimens. Detection of Respiratory Bacteria: Bacterial cultures and real-time PCR were used to detect the nucleic acid of respiratory pathogens (*Streptococcus pneumoniae, Staphylococcus aureus, methicillin-resistant Staphylococcus, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, Haemophilus influenzae, Legionella pneumophila, Mycobacterium tuberculosis complex, Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*). PCR capillary electrophoresis was used to detect the nucleic acid of respiratory viruses (*respiratory syncytial virus, metapneumovirus, influenza A virus, parainfluenza virus, bocavirus, coronavirus, Adenovirus, rhinovirus, influenza B virus, Mycoplasma pneumoniae*, and *Chlamydia*). Detection of respiratory virus antigens: Immunofluorescence assays were conducted to detect respiratory virus antigens (*syncytial virus, Adenovirus, influenza virus*, and *parainfluenza virus*).

Definition of positive respiratory pathogen

The positive results of specimens culture or bacterial real-time PCR indicated the corresponding bacterial infection; the positive results of specimens viral antigen test or DNA PCR indicated corresponding viral infection, the positive results of *Mycoplasma pneumoniae* in specimens DNA PCR indicated *Mycoplasma pneumoniae* infection.

Definition of serum cytokine levels Venous blood samples were collected to detect Th1/Th2 cytokine levels, including IL-2, IL-4, IL-6, IL-10, IL-17 A, TNF-α, and IFN-γ, using cytometric bead assay (CBA). The normal range of these cytokines were (0 ~ 9.80),(0 ~ 3.00), (0 ~ 16.60), (0 ~ 4.90), (0 ~ 14.80), (0 ~ 5.20), and (0 ~ 17.30) pg/mL, respectively.

Grouping

(1) Patients were assigned to the *Mycoplasma pneumoniae (MP)* group, *adenovirus(Adv)* group, *respiratory syncytial virus(RSV)* group, *Haemophilus influenzae(Hin)* group, and *Streptococcus pneumoniae(SP)* group based on corresponding pathogenic infection.

(2) Patients were divided into two age subgroups refer to median age of each pathogen group.

(3) Patients were further subdivided into a severe pneumonia subgroup and a non-severe pneumonia subgroup, according to the severity evaluation of pediatric CAP in established guidelines [12]. severe pneumonia was defined as the presence of any one of the following conditions: (1) Poor general condition; (2) Disturbance of consciousness; (3) Evidence of hypoxia, such as cyanosis, tachypnea (respiratory rate in infants ≥ 70 breaths /min, and ≥ 50 breaths /min in children over 1-year-old), assisted breathing (moaning, nasal fanning, three-concave sign), intermittent breathing pauses, and oxygen saturation < 0.92; (4) Hyperpyrexia (body temperature > 41 ℃) or persistent high fever (39.1–41 ℃) for more than 5 days; (5) Refusal of water/food; (6) Chest X-ray or chest CT images displaying over 2/3 of one lung with pulmonary infiltration, multilobar pulmonary infiltration, pleural effusion, pneumothorax, atelectasis, lung necrosis, or lung abscess; (7) Extrapulmonary complications. Non-severe CAP was defined as the absence of the aforementioned manifestations of severe pneumonia.

Statistical analysis

SPSS 26 software and GraphPad 9.5 software were employed for statistical analyses. Measurement data were expressed as the median (P25,P75), whereas count data were expressed as the number of cases (percentage). Group comparisons of measurement data following a normal distribution were performed using the independent sample t-test, while measurement data with a non-normal distribution were compared in two groups using the Wilcoxon rank sum test. The receiver operating characteristic (ROC) curve was used to evaluate the predictive value of cytokines for severe pneumonia. $P < 0.05$ was considered statistically significant.

Results

According to the screening criteria, a total of 159 children with single respiratory pathogen infections were included, with a male-to-female ratio of 1.04:1. As listed in Table 1, *MP* group (54 cases), *Adv* group (20 cases), *RSV* group (34 cases), *Hin* group (31 cases), and *SP* group (20 cases) were identified. The median (P25,P75) age was 3.3 years (1.51, 6.23), but there were variations in age

Table 1 Baseline characteristics and serum cytokine levels in community-acquired pneumonia caused by different respiratory pathogens

	M. pneumoniae(54 cases)	Adenovirus(20 cases)	RSV(34 cases)	H. influenzae (31 cases)	S. pneumoniae (20 cases)
Gender male	21 (38.9%)	13 (65%)	20 (58.8%)	18 (58.1%)	9 (45%)
female	33 (61.1%)	7 (35%)	14 (41.2%)	13 (41.9%)	11 (55%)
Age (year)	6.83(4.8,8.41)	3.62(1.94,5.83)	1.6(1.03,2.66)	2.08(1.23,3.7)	3.09(1.07,3.73)
Time sequence of fever early than cough	17 (31.5%)	3 (15%)	0	5 (16.1%)	4 (20%)
Time sequence of fever late than cough	16 (29.6%)	13 (65%)	24 (70.6%)	17 (54.8%)	10 (50%)
Time sequence of fever equal to cough	21 (38.9%)	4 (20%)	10 (29.4%)	9 (29%)	6 (30%)
Wheeze at addition	5 (9.3%)	8 (40%)	24 (70.6%)	20 (64.5)	9 (45%)
Rash	5 (9.3%)	1 (5%)	1 (2.9%)	3 (9.7%)	1 (5%)
Respiratory failure	9 (16.7%)	5 (25%)	18 (52.9%)	10 (32.3%)	3 (15%)
Lung consolidation	41 (75.9%)	4 (20%)	6 (17.6%)	9 (29%)	11 (55%)
Lung atelectasis	7 (13%)	1 (5%)	2 (5.9%)	0	1 ((5%)
Pleural effusion	12 (22.2%)	2 (10%)	0	1(3.2%)	1 (5%)
Severe pneumonia	21 (38.9%)	7 (35%)	21 (61.8%)	11 (35.5%)	3 (15%)
Serum cytokines (Reference value)					
IL-2 (0 ~ 9.80)	0.42 (0,1.34)	0.005 (0, 1.18)	0 (0, 0.18)	0 (0, 1.46)	0 (0, 0.3)
IL-4 (0 ~ 3.00)	0 (0, 0.92)	0 (0, 0.33)	0 (0, 0)	0 (0, 0.61)	0 (0, 0.38)
IL-6 (0 ~ 16.60)	21.76 (12.04, 50.76)	29.08 (7.15, 48.92)	7.06 (3.57, 20.14)	12.96 (3.62, 78.56)	25.69 (5.51, 39.45)
IL-10 (0 ~ 4.90)	3.82 (2.08, 6.17)	9.82 (3.2, 18.38)	11.58 (5.05, 27.26)	4.62 (1.87, 15.57)	5.9 (1.29, 20.64)
IL-17 A (0 ~ 14.80)	0.95 (0, 4.39)	0 (0, 3.21)	0 (0, 0.09)	0 (0, 0)	0 (0, 0)
TNF-α (0 ~ 5.20)	0.45 (0, 1.81)	0.48 (0.02, 1.83)	0.24 (0, 1.76)	0.45 (0.01, 2.82)	0.22 (0, 1.19)
IFN-γ (0 ~ 17.30)	4.92 (2, 9.81)	4.93 (0.15, 21.62)	3.01 (0.8, 6.85)	0.52 (0, 2.47)	0.83 (0.3, 5.73)

distribution among the different pathogen groups, with age 6.83(4.8,8.41) years in *MP* group, age 3.62(1.94,5.83) years in *Adv* group, age 1.6(1.03,2.66) years in *RSV* group, age 2.08(1.23,3.7) years in *Hin* group, age 3.09(1.07,3.73) years in *SP* group, respectively.

There had a significant difference in clinical characteristics of CAP infected by different respiratory pathogens. Compared with other pathogen groups, patients with MP easyily occur fever before cough(31.5%), and lung consolidation(75.9%). Patients with RSV had a higher rate of wheezing at addition(70.6%), respiratory failure(52,9%), and severe pneumonia(61.8%) than other pathogen groups. Further details can be found in Table 1.

Each pathogenic infection was associated with different levels of cytokines. The level of IL-2 was significantly higher in the *MP* group [0.42 (0, 1.34)] than that of *RSV* group [0 (0, 0.18), $P<0.01$], and *SP* group [0 (0, 0.3), $P<0.01$]. However, no difference was found in the level of IL-2 between the *MP* group and the remaining groups. Similarly, the level of IL-4 was significantly higher in the *MP* group [0 (0, 0.92)] than in the *RSV* group [0 (0, 0), $P<0.01$]. However, no statistical difference was observed in the level of IL-4 between the *MP* group and the remaining groups. At the same time, the level of IL-6 was significantly higher in the *MP* group [21.76 (12.04, 50.76)] than in the *RSV* group [7.06 (3.57, 20.14), $P<0.001$]. Likewise, the level of IL-6 was significantly higher in the *Adv* group [29.08 (7.15, 48.92)] and *SP* group [25.69 (5.51, 39.45)] than in the *RSV* group [7.06 (3.57, 20.14), $P<0.05$]. On the one hand, the level of IL-10 was significantly lower in the *MP* group [3.82 (2.08, 6.17) than in the *Adv* group [9.82(3.2,18.38), $P<0.01$] and *RSV* group [11.58 (5.05, 27.26), $P<0.001$]. On the other hand, the level of IL-10 was significantly higher in the *RSV* group [11.58 (5.05, 27.26)] than in the *Hin* group [4.62 (1.87, 15.57), $P<0.05$]. However, there was no significant difference in the level of TNF-α among the different groups. Besides, the level of IL-17 A was significantly higher in the *MP* group [0.95 (0,4.39)] than in the *RSV* group [0 (0, 0.09), $P<0.01$], *Hin* group [0 (0, 0), $P<0.01$], and *SP* group [0 (0, 0), $P<0.05$]. The level of IFN-γ was significantly higher in the *MP* group [4.92 (2, 9.81)] than in the *RSV* group [3.01 (0.8, 6.85), $P<0.05$], *Hin* group [0.52 (0, 2.47), $P<0.001$], and *SP* group [0.83 (0.3, 5.73), $P<0.01$], whilst the level of IFN-γ was significantly higher in the *Adv* group [4.93 (0.15, 21.62)] and the *RSV* group [3.01 (0.8, 6.85) than in the *Hin* group [0.52 (0,2.47), $P<0.05$]. The details are illustrated in Fig. 1.

In addition, we aimed to determine whether there had statistically significant differences in cytokine levels between different age subgroups in single pathogen group. We found that the serum levels of IL-10 and TNF-α were statistically different between age subgroups in *Hin* group. However, there were no significant differences between age subgroups in other pathogen groups, listed in Table 2.

In order to further investigate the predictive value of cytokines for severe pneumonia caused by different pathogens, we compared the levels of cytokine between patients with severe pneumonia and patients

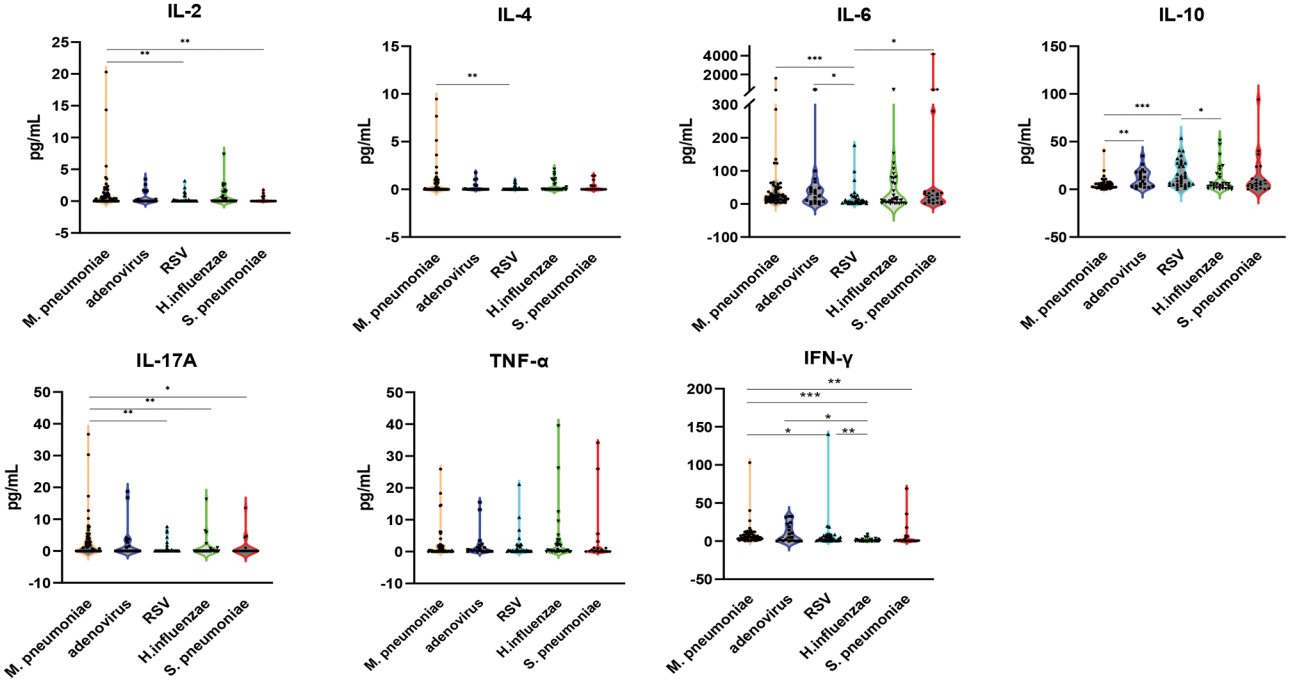

Fig. 1 comparison of serum cytokines IL-2, IL-4, IL-6, IL-10, IL-17 A, TNF-α, and IFN-γ across the five respiratory pathogen groups

Table 2 Comparison of cytokine levels between different age subgroups in same pathogen group

Pathogens	Group by age	IL-2	IL-4	IL-6	IL-10	IL-17 A	TNF-α	IFN-γ
Mycoplasma pneumoniae	<7 years(26 cases)	0.35(0,1.22)	0(0,0.76)	21.72(12.04,47.58)	2.85(1.6,5.52)	1.08(0,6)	0.46(0,1.63)	5.17(1.93,7.98)
	≥ 7 years(28 cases)	0.43(0,1.7)	0.14(0,0.94)	23.58(11.77,51.85)	4.45(2.7,7.64)	0.95(0,3.59)	0.39(0,1.9)	4.29(2.02,12)
	P	0.675	0.45	0.863	0.085	0.625	0.861	0.729
Adenovirus	<4 years(10 cases)	0.03(0,0.6)	0(0,0.56)	39.75(6.96,69.19)	6.96(2.9,19.11)	0(0,1.76)	0.12(0,2.12)	3.33(0.44,26.28)
	≥ 4 years(10 cases)	0(0,1.94)	0(0,0.13)	21.65(6.16,43.23)	12.07(3.23,18.17)	0.76(0,3.56)	0.87(0.3,1.82)	7.26(0,19.69)
	P	1.000	0.657	0.545	0.821	0.370	0.286	0.879
RSV	<2 years(19 cases)	0(0,0.17)	0(0,0)	5.92(3.63,15.24)	12.46(5.49,30.23)	0(0,0.34)	0.25(0,1.78)	1.26(0.55,4.87)
	≥ 2 years(15 cases)	0(0,0.23)	0(0,0.35)	7.16(3.39,27.14)	10.69(4.15,25.96)	0(0,0)	0.19(0.02,0.84)	5.69(0.99,8.22)
	P	0.394	0.314	0.415	0.435	0.798	0.793	0.218
Haemophilus influenzae	<2 years(14 cases)	0.22(0,1.54)	0.07(0,1.12)	46.5(4.56,96.26)	6.75(5.1,18.5)	0(0,0.47)	2.12(0.26,6.33)	1.14(0.17,2.65)
	≥ 2 years(17 cases)	0(0,1.05)	0(0,0.17)	3.41(9.14,29.77)	3.24(1.09,5.34)	0(0,0)	0.21(0,0.59)	0.24(0,1.03)
	P	0.339	0.148	0.112	**0.029***	0.588	**0.036***	0.141
Streptococcus pneumoniae	<3 years(7 cases)	0(0,0.62)	0(0,0.68)	20.59(2.93,160.3)	5.16(0.47,10.58)	0(0,2.17)	0.56(0,2.21)	1.44(0.08,6.65)
	≥ 3 years (13 cases)	0(0,0)	0(0,0.39)	31.15,12.62,37.55)	9.28(3.91,40.31)	0(0,0)	0.16(0,1.14)	0.81(0.42,1.28)
	P	0.376	0.769	0.501	0.191	0.533	0.902	0.905

Table 3 Cytokine levels in the non-severe and severe pneumonia subgroups caused by different respiratory pathogens

Different pathogen groups	IL-2	IL-4	IL-6	IL-10	IL-17 A	TNF-α	IFN-γ
Mycoplasma pneumoniae group							
Non-severe pneumonia(33 cases)	0.44 (0, 2.18)	0.11 (0, 0.93)	15.84 (8.95, 27.76)	2.74 (2.03, 5.27)	1.57 (0, 5.05)	0.32 (0, 1.83)	3.25 (1.51, 7.07)
Severe pneumonia(21 cases)	0.26 (0, 1.03)	0 (0, 0.87)	37.39 (21.18, 94.5)	5.85 (2.12, 9.01)	0 (0, 4.18)	1.1 (0, 1.85)	8.27 (4.68, 12.17)
P	0.351	0.509	**0.002***	**0.045***	0.383	0.577	**0.002***
Adenovirus group							
Non-severe pneumonia(13 cases)	0 (0, 1.55)	0 (0, 0.72)	19.5 (7.25, 44.7)	5.72 (3.05, 14.96)	0 (0, 3.55)	1.26 (0.12, 2.96)	2.05 (0.29, 11.77)
Severe pneumonia(7 cases)	0.04 (0, 0.32)	0 (0, 0)	42.83 (2.31, 76.42)	16.54 (12.71, 26.23)	0 (0, 2.74)	0.06 (0, 0.68)	18.73 (0, 31.38)
P	0.866	0.178	0.501	0.104	0.592	0.072	0.216
RSV group							
Non-severe pneumonia(13 cases)	0(0, 0.18)	0 (0, 0.31)	7.07 (2.53, 21.19)	8.68 (3.85, 24.91)	0 (0, 4.3)	0.25 (0.14, 1.59)	2.85 (0.72, 6.35)
Severe pneumonia(21 cases)	0 (0, 0.19)	0 (0, 0)	7.05 (3.51, 20.83)	14.13 (5.43, 29.22)	0 (0, 0)	0.22 (0, 1.92)	3.17 (0.64, 8.27)
P	0.700	0.219	0.845	0.280	0.067	0.668	0.901
Haemophilus influenzae group							
Non-severe pneumonia(20 cases)	0.04 (0, 1.57)	0 (0, 0.91)	6.48 (3.29, 14.28)	2.77 (0.95, 5.81)	0 (0, 0.86)	0.26 (0, 2.28)	0.23 (0, 1.4)
Severe pneumonia(11 cases)	0 (0, 0.84)	0 (0, 0.13)	78.56 (40.18, 107.23)	16.68 (6.06, 36.93)	0 (0, 0)	1.95 (0.26, 5.24)	1.03 (0.78, 2.84)
P	0.366	0.541	**0.001***	**0.000***	0.481	0.171	**0.016***

with non-severe pneumonia in single pathogen group, as detailed in Table 3.

In the *SP* group, there were only 3 cases severe pneumonia and 17 cases non-severe pneumonia, comparisons were not made due to the significant difference in sample size. In the *MP* group, the levels of IL-6, IL-10, and IFN-γ were significantly higher in the severe pneumonia subgroup than in the non-severe pneumonia subgroup ($P<0.05$). According to the ROC curve analysis, IL-6, IL-10, and IFN-γ can be used as predictors of severe *MP*-induced pneumonia, with an area under the ROC curve of 0.758 (95% CI: 0.624, 0.891, $P<0.01$; cut-off value 20.87), 0.663 (95% CI: 0.506 0.82, $P<0.05$, cut-off value 4.765), and 0.754 (95% CI: 0.625, 0.883, $P<0.01$, cut-off value 3.4), respectively. Additionally, in the *Hin* pneumonia group, the levels of IL-6, IL-10, and IFN-γ were

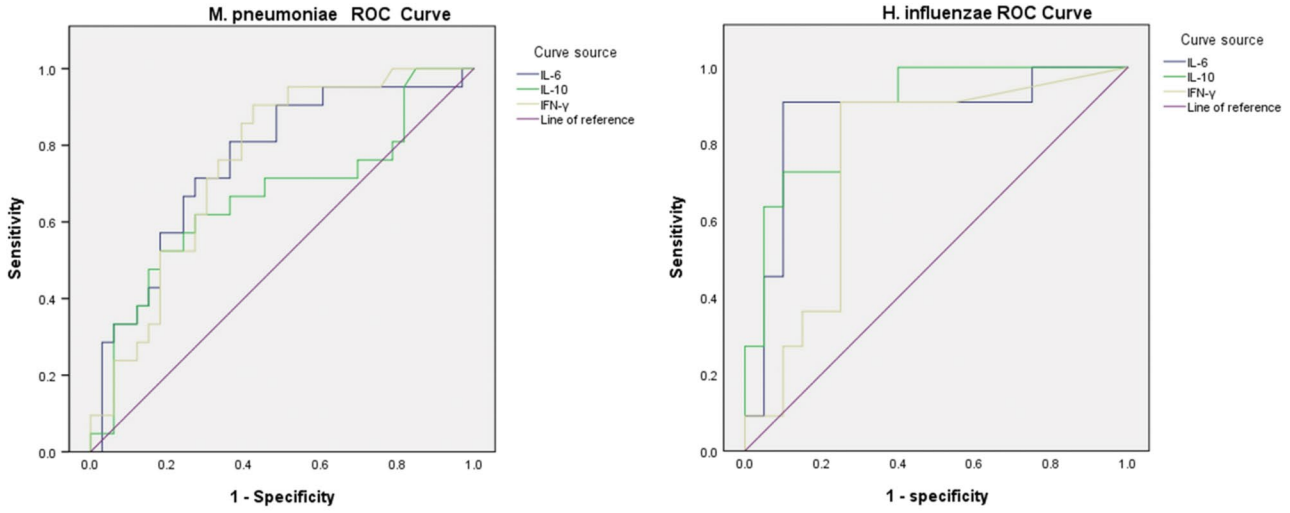

Fig. 2 ROC curves for severe *M. pneumoniae* pneumonia and severe *H. influenzae* pneumonia

significantly higher in the severe pneumonia subgroup than the non-severe pneumonia subgroup ($P<0.05$). According to the ROC curve analysis, IL-6, IL-10, and IFN-γ also can be used to predict severe *Hin* pneumonia, with the area under the ROC curve for IL-6, IL-10, and IFN-γ was 0.868 (95% CI: 0.717, 1, $P<0.01$, cut-off value 23.325), 0.891 (95% CI: 0.778, 1, $P<0.001$, cut-off value 5.175), and 0.761 (95% CI: 0.778, 1, $P<0.001$, cut-off value 5.175), respectively. as displayed in Fig. 2.

However, no statistical differences were found in the levels of cytokine between the severe and non-severe pneumonia subgroups in the *Adv* group and *RSV* group. These results indicated that IL-6, IL-10, and IFN-γ can predict the occurrence of severe pneumonia caused by *MP* and *Hin.*

Discussion

In this retrospective study, we found that the levels of cytokines were expressed differently in CAP caused by different respiratory pathogens. Specifically, we found that IL-6, IL-10, and IFN-γ can be used to predict the occurrence of severe pneumonia caused by *MP* and *Hin*. However, other cytokines such as IL-2, IL-4, IL-17 A, and TNF-α didn't have predictive value in severe pneumonia. In previous study, most of these studies have compared the levels of cytokines between the two respiratory pathogens. Xiang Wen-qing has found that patients infected with *Human metapneumovirus* had higher levels of IL-4, IFN-γ, TNF-α in comparison with patients with *Influenza virus* infection [13]. Vasconcellos ÂG conducted a study to assess the diagnostic value of cytokines in pneumococcal infection through comparing serum levels of cytokines in patients with *pneumococcal* infection and those patients with *non-pneumococcal* infection. The study found that IL-6 was an independent predictor of *pneumococcal* infection [14]. However, there are few studies to compare the levels of cytokines associated with multiple types of respiratory pathogens. Our study aimed to compare the serum levels of cytokines in children with CAP caused by different respiratory pathogens.

Cytokines are synthesized and secreted by various cells, including lymphocytes, macrophages, natural killer cells, mast cells, and stromal cells. As is well documented, cytokines participate in immune responses and play a crucial role in immune regulation [5]. Cytokines can be categorized into proinflammatory cytokines, such as IL-1, IL-6, IL-8, IL-12, TNF-α, and IFN which activate immune cells, and anti-inflammatory cytokines, such as IL-4, IL-6, IL-10, IL-11, IL-13, IL-1, and TGF-β, which suppress immune inflammation. Some cytokines, like IL-6, have both pro-inflammatory and anti-inflammatory factor [15]. The levels of cytokines in the body can be affected by pathogenic infection.

In the present study, compared with the *RSV* group, the *MP* group had significantly higher levels of IL-2, IL-6, IL-17 A, and IFN-γ. Furthermore, our results demonstrated that IL-17 A and IFN-γ levels were higher in the *MP* group than in the *SP* group and *Hin* group. A study of 33 patients with *MPP* and 38 patients with *non-MPP* found that the *MPP* group had a significantly higher levels of IL-5, IL-18, and lower level of IL-6 in comparosion with *non-MPP* group [16]. However, another study found that patients with *MPP* had significantly higher levels of IL-6 and IFN-γcompared to the *non-MPP* group [17]. This suggests that different studies may have varing results, possibly due to differences in sample size and pathogen infection. Our findings indicated that the expression of pro-inflammatory factors was higher in patients with *MP* than those with *RSV*, *SP*, and *Hin*. However, the level of the anti-inflammatory factor IL-10

in patients with *MP* was lower than that of patients with *RSV* and *Adv*, indicating *MP* was more likely to disrupt cytokine levels and induce more severe inflammatory responses compared to other pathogens. Our study also found that pulmonary complications such as lung consolidation, atelectasis, and pleural effusion were more common in *MP* group compared to other groups.

In addition, We found that the level of IL-6 was higher in patients with *SP* than in those with *RSV*. A observational study of CAP children showed that the serum IL-6 of *pneumococcal* infection with the median IL-6(pg/ml) being 31.2, was higher than other causative agents detected with the median IL-6 (pg/ml)being 9.0 [14]. This result was in accordence with our findings that the serum IL-6 of *SP* with the median being 25.69 in our study. Furethermore, our study found that the level of IL-10 was higher in patients with *RSV* compared to patients with *Hin*. Additionally, the level of IFN-γ was higher in patients with *Adv*, *RSV* compared to patients with *Hin*, indicating that viral infections may lead to higher levels of IFN-γ than bacterial infections. This is supported by previous studies in mice, which have shown that IFN-γ secreted by CD8 T cells plays a crucial role in viral clearance and can contribute to immunopathology following *RSV* infection [18, 19].

In a previous study which demonstrated that the serum level of IL-6 in patients with *Adv* infection was significantly higher than those in patients with *RSV* infection [20]. This result align with our own findings that the level of IL-6 was higher in the *Adv* group than in the *RSV* group, implying that *Adv* can induce a more robust inflammatory response compared to *RSV*.

There are scarcely any studies comparing the levels of serum cytokines in differrent bacterial pneumonias. This may be related to the fact that previous studies didn't categorize pathogens into subgroups carefully. Interestingly, our findings just fills the gap. No significant differences were noted in the levels of cytokines between the *SP* and *Hin* groups.

The balance between activation and regulation of pulmonary immunity is critical for the pathogenesis of respiratory infection [21]. Noteworthily, cytokine dysregulation, such as an inflammatory cytokine storm, can lead to organ failure and death. To further assess the influence of cytokines on disease outcomes, the predictive value of cytokines for severe pneumonia was assessed. The results of the ROC curve analysis demonstrated that IL-6, IL-10, and IFN-γ have predictive value for severe pneumonia induced by *MP* and *Hin*. Marthe S. Paats concluded that the levels of IL-6, IL-10, and IFN-γ were significantly higher in severe CAP patients than those of non-severe CAP patients [22]. Nevertheless, previous studies didn't identify the pathogens of pneumonia. It is worthwhile emphasizing that earlier studies have shown that severe cases of COVID-19 have higher levels of IL-2R, IL-6, IL-10, and TNF-α compared to moderate cases [23], and have also indicated the predictive value of IL-6 and IL-10 for severe COVID-19 [24]. Our study, along with these previous findings, has demonstrated that the levels of IL-6, IL-10, and IFN-γ have important predictive value for severe pneumonia. However, there is a lack of investigations on whether these cytokines have the same predictive value for severe pneumonia caused by differrent pathogens. Therefore, the predictive value of cytokines for severe pneumonia caused by different respiratory pathogens was analyzed in our study. Surprisingly, our results showed that the predictive value of cytokines for severe *Adv*-induced and severe *RSV*-induced pneumonia were not significant, warranting further exploration. this suggests that the predictive value of serum cytokines for severe pneumonia caused by different pathogens may vary. Taken together, this study provided a theoretical reference for future studies.

Nevertheless, our study has some limitations. This is a retrospective study, which hasn't compared with a healthy control group, there may be incomplete or inaccurate information. In addition, the sample size of each group of patients was small, due to strict control of single pathogen infection. Therefore, more prospective studies are necessary to detect the predictive value of cytokines in severe pneumonia.

Conclusion

The present study revealed that community-acquired pneumonia caused by different respiratory pathogens is associated with different expression levels of cytokines. Consequently, the predictive value of cytokines for severe pneumonia caused by different pathogens also varies. Lastly, the levels of IL-6, IL-10, and IFN-γ demonstrated predictive value for severe pneumonia caused by *Mycoplasma pneumoniae* and *Haemophilus influenzae*.

Abbreviations

CAP	Community-acquired pneumonia
MP	M. pneumoniae (Mycoplasma pneumoniae)
Adv	Adenovirus
RSV	Respiratory syncytial virus
Hin	H. influenzae (Haemophilus influenzae)
SP	S. pneumoniae (Streptococcus pneumoniae)
PCR	Polymerase chain reaction
IL-2	Interleukin-2
IL-4	Interleukin-4
IL-6	Interleukin-6
IL-10	Interleukin-10
IL-17A	Interleukin-17A
TNF-α	Tumour Necrosis Factor-alpha
IFN-γ	Interferon-gamma
ROC	Receiver operating characteristic
MPP	Mycoplasma pneumoniae pneumonia
COVID-19	Coronavirus disease 2019

Acknowledgements

the authors express their gratitude to the patients in this study.

Author contributions
YD. collected the data and wrote the article. Y.O., J.L., X.G. conducted data analysis and interpretation. J.C.Designed study. All authors have approved the final manuscript as submitted and agree to be responsible for all aspects of the work.

Funding
The study was not funded.

Data availability
Data will be made available on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Children's Hospital Affiliated with Chongqing Medical University (File No. (2023)521). Written informed consent was obtained from the parents or legal guardian upon the admission of the children to the hospital. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Received: 13 August 2024 / Accepted: 11 May 2025
Published online: 20 May 2025

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