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The Prevalence and Clinical Manifestations of Co-Infection in Pediatric Infectious Mononucleosis: A Single-Centered, Retrospective Study

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Abstract

Background: Recent studies indicate that the incidence of infectious mononucleosis (IM) has increased in China. Furthermore, it has been shown that children diagnosed with IM are prone to acquiring other pathogens. However, there is limited research on the prevalence of these co-infections in children with IM. Thus, we conducted this study to determine the prevalence of coinfections and common pathogens, as well as to compare clinical manifestations in children with and without coinfections. **Methods:** This retrospective observational study was conducted at the Department of Pediatrics Zhongnan Hospital of Wuhan University, Wuhan, China, with data from January 2018 to January 2023. Data, including demographics, symptoms, lab results, and complications, were collected from the hospital's electronic database and analyzed. The statistical analysis included descriptive statistics, independent samples t-tests and Mann-Whitney tests to compare the means of continuous variables. Statistical significance was determined by p-values less than 0.05. **Results:** The study involved 216 participants diagnosed with IM, predominantly males (61.6%) aged 0 - 4 years (50.9%). Coinfection was detected in 39.8% of children, with multiple pathogens present in 33.72% of these cases. Among coinfection cases, 40% occurred in children under 5 years old, and females made up 54.2% of these cases. Mycoplasma pneumoniae (MP) was the most prevalent pathogen, accounting for 18.1% of cases. Influenza B (IFB) and Influenza A (IFA) viruses were found in 16.7% and 13.9% of participants, respectively, indicating a notable occurrence of respiratory pathogen coinfections. Male

gender, fever, tonsillopharyngitis, lower HGB levels, higher ESR, CRP, and AST levels were correlated with coinfections. **Conclusion:** In summary, the study revealed a high prevalence of coinfections among children diagnosed with IM, particularly involving Mycoplasma pneumoniae and influenza viruses. These coinfections were notably common in children under 5 years old and were more frequent among females. Clinical manifestations such as fever and tonsillopharyngitis, along with specific laboratory findings including lower hemoglobin levels, elevated ESR, CRP and AST levels, were found to be correlated with coinfections.

Keywords

Prevalence, Mononucleosis, Coinfection, Children, Epstein-Barr Virus, Features

1. Background

Infectious mononucleosis (IM) is characterized by the clinical triad of fever, pharyngitis, and cervical lymphadenopathy, predominantly caused by the Epstein-Barr virus (EBV) and to a lesser extent by cytomegalovirus (CMV), with incidences of 7% to 16% [1]. Rare occurrences involve pathogens such as Toxoplasma gondii, viral hepatitis (A, B, C), or human herpes virus [2]. EBV, a member of the herpesvirus family, primarily replicates within B lymphocytes and can be found in epithelial cells of the pharynx and parotid ducts, predominantly affecting children and adolescents [3]. In industrialized countries, the likelihood of developing mononucleosis following EBV infection is higher during the second decade of life. Seroepidemiological studies indicate that approximately 91% of adults worldwide have been infected with EBV at some point [4], with a notable increase in seropositivity during adolescence, particularly among females [5].

A comprehensive study conducted in China from January 1st, 2016, to December 31st, 2020, recorded 24,120 cases of IM out of 5,693,262 hospitalizations, representing 0.42% of all cases during this timeframe [6]. This study also shed light on the regional distribution of cases, showing significant variations across different parts of China, and highlighted an annual increase in IM-related hospitalizations, with a notable peak in 2019. It was observed that a majority of hospitalized children with IM resided in urban areas [6]. EBV transmission primarily occurs through saliva, which has led to the disease being colloquially known as the "kissing disease", with an incubation period ranging from 4 to 8 weeks [7]. IM tends to present mildly or remain asymptomatic in young children, with fever, tonsillitis, and lymphadenopathy being the most common manifestations [8], followed by symptoms like nasal congestion and sore throat. The infection typically lasts about 16 days [4].

The diagnosis of EBV-associated IM is primarily based on clinical presentation, hematological findings, and confirmed through positive serology or the

presence of heterophile antibodies [8]. In instances where EBV is suspected but heterophile antibodies are absent, an evaluation of the EBV-specific antibody profile is advised [9]. IM due to EBV can range from mild, exhibiting symptoms akin to fatigue or allergies, to severe, leading to life-threatening complications such as splenic rupture, acute liver failure, hemophagocytic lympho-histiocytosis (HLH), and malignancy [10].

Although the literature extensively covers the epidemiology, diagnosis, clinical features, and management of IM, there is limited research concerning the prevalence of co-infections in children with IM. Therefore, we conducted this study to assess the prevalence of coinfections and common pathogens, as well as compare clinical manifestations between children with and without coinfections.

2. Methods and Materials

2.1. Study Design and Population

This was a retrospective observational study conducted at the Department of Developmental Behavioral Pediatrics of Zhongnan hospital of Wuhan university, Wuhan, China. Medical records dating medical records dating March 2021 to December 2023 for 216 children with IM were evaluated. Included children were those who admitted at the inpatient department of our hospital who were diagnosed with infectious mononucleosis. IM was diagnosed with positive EB virus DNA and EBV VCA IGM in plasma and the coinfections were diagnosed as being positive IgM positive for the pathogen on admission. The research was approved by research committee of Zhongnan hospital of Wuhan university, and Institutional consent was sought before conducting the research.

2.2. Data Collection

Data were collected from the electronic database of the hospital. The collected data comprised demographic characteristics of the children such as age and sex, clinical features, laboratory findings and complications of the children.

2.3. Data Analysis

Data analysis utilized the Statistical Package for Social Sciences (SPSS), Version 27. Continuous variables exhibiting normal distributions were represented by means along with their corresponding standard deviations (SDs). Meanwhile, categorical variables were depicted using frequencies and percentages. An independent student's t-test and a Mann-Whitney test were used to compare means of continuous variables, and a Pearson's Chi-square test was used to compare means of categorical variables. P value < 0.05 was considered statistically significant.

3. Results

3.1. Patient's Demographic Information

The present study involved 216 children diagnosed with infectious mononucle-

osis. Among the participants, the majority were males, accounting for 61.6% (33 children), while females comprised 38.4% (83 children). Regarding age distribution, 50.9% (110 children) were aged 0 - 4 years, 36.5% (79 children) were aged 5 - 8 years, and 12.5% (27 children) were aged 9 - 13 years. Comprehensive details are outlined in Table 1.

3.2. Prevalence of Coinfection

Among the 216 children studied, 86 (39.8%) had a coinfection, with 33.72% of them having more than one pathogen involved. The most common coinfecting agent was MP, affecting 39 children (18.1%). IFB 36 (16.7%), IFA 30 (13.9%), CMV 7 (3.2%), CP 6 (2.8%), ADV 4 (1.9%), LP 4 (1.9%), PIV 3 (1.4%), and RSV 1 (0.5%). Detailed information is presented Table 2.

3.3. Incidence of Coinfections

Yearly Trend: The incidence rates from 2018 to 2022 fluctuated, with the highest incidence in 2018 (9.72 per 100 cases) and the lowest in 2021 (6.48 per 100 cases). This fluctuation indicates varying rates of co-infection with infectious mononucleosis over the years.

Total Incidence over Years: The total incidence of 39.8 over the five-year period suggests that, on average, there were around 40 cases of co-infection per 100 cases of infectious mononucleosis over the studied time frame. Detailed information is in Table 3.

3.4. Seasonal Variation of Coinfecting Pathogens

The peak season for coinfections in this study is Summer, with RSV, ADV, and IFB being the leading pathogens, each showing their highest incidence during this period. Notably, Influenza B (IFB) tops the list with 12 cases, followed by Adenovirus (ADV) with 2 cases, and Respiratory Syncytial Virus (RSV) with 1 case. Autumn also shows significant activity, particularly for Influenza A (IFA) and Mycoplasma Pneumoniae (MP), with 11 and 14 cases respectively, indicating it as another critical period for respiratory coinfections. Detailed information with the frequency numbers is presented in Figure 1.

3.5. Relation between Demographics and Coinfection

In terms of age groups and coinfections, among the youngest age group (0 - 4 years), out of 110 children, 44 had a coinfection. In the middle group (5 - 8 years), there were 33 coinfections out of 79 children. The oldest group (9 - 13 years) had the fewest coinfections, with 9 out of 27 children affected. The associated P-value was calculated to be 0.740.

Regarding sex and coinfections, the proportion of coinfections in females (54.2%) was notably higher than in males (30.8%). This suggests a potential sex-related difference in the risk or detection of coinfections among children with infectious mononucleosis, with a statistically significant P-value of 0.001. Detailed information is presented Table 4.

Table 1. Demographic information of participants.

Variable	Frequency	Percentage
Age		
0 - 4 years	110	50.9
5 - 8 years	79	36.5
9 - 13 years	27	12.5
Sex		
Male	133	61.6
Female	83	38.4

Table 2. Prevalence of coinfection.

Coinfection	Frequency	Percentage
Overall	86	39.8
Single pathogen coinfection	57	66.27
Multiple pathogen coinfection	29	33.72
Mycoplasma pneumoniae	39	18.1
Influenza virus B	36	16.7
Influenza virus A	30	13.9
Cytomegalovirus	7	3.2
Chlamydia pneumoniae	6	2.8
Adenovirus	4	1.9
Legionella pneumoniae	4	1.9
Parainfluenza virus	3	1.4
Respiratory syncytial virus	1	0.5

Table 3. Incidence of coinfections.

Coinfection	2018	2019	2020	2021	2022	total
MP	10	9	5	8	7	39
IFB	7	3	7	9	10	36
IFA	6	3	6	8	7	30
CMV	1	1	1	4	0	7
CP	2	3	1	0	0	6
ADV	1	1	0	0	2	4
LP	0	2	2	0	0	4
PIV	1	0	0	1	1	3
RSV	1	0	0	0	0	1
total	21	17	16	14	18	86
incidence	9.72	7.87	7.4	6.48	8.33	39.8

Table 4. Demographics and coinfection.

	With coinfection	Without coinfection	P value
Age			
0 - 4 years	44 (51.16%)	66 (50.7%)	0.740
5 - 8 years	33 (38.37%)	46 (35.38%)	
9 - 13 years	9 (10.46%)	18 (13.84%)	
Total	86 (100)	130 (100)	
Sex			
Male	41 (47.67)	92 (70.77)	0.001*
Female	45 (52.33)	38 (29.23)	
Total	86 (100)	130 (100)	

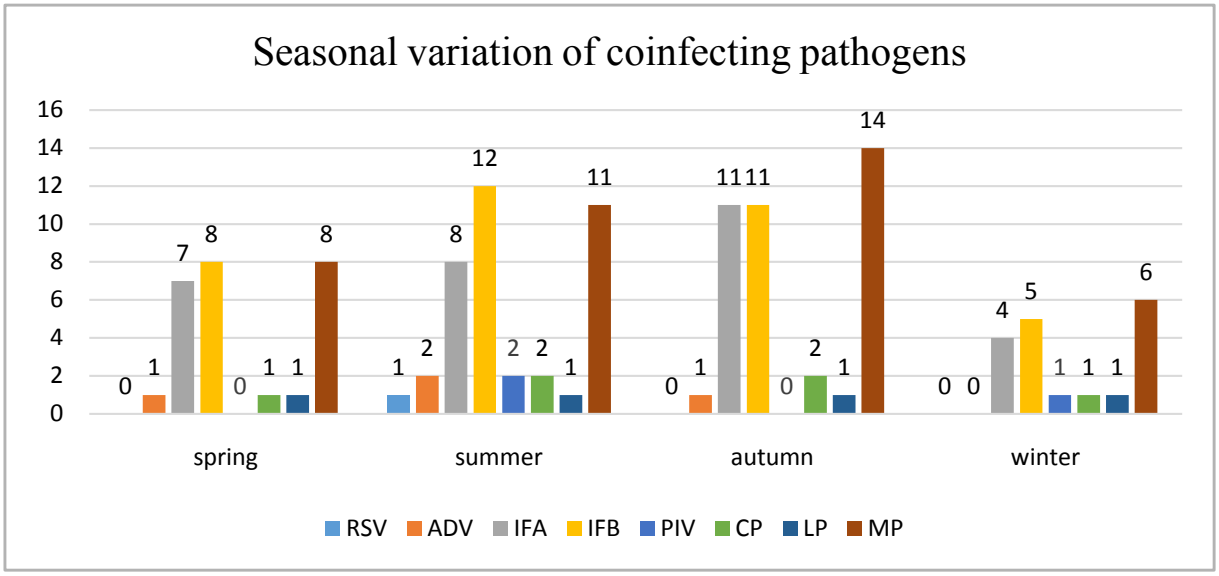

Figure 1. Frequency of coinfecting pathogens in four seasons of the year.

3.6. Clinical Features

Fever was present in 88.37 % of children with only IM and 76% in children with coinfections showing a statistically significant association between fever and coinfections P-value of 0.034, tonsillopharyngitis 65.12% in IM group and 78.46% in coinfection group with P-value of 0.030 meaning that tonsillopharyngitis were associated with IM without coinfections. Other features like lymphadenopathy 93.02%, sore throat 36.05%, runny nose 20.93%, Abdominal pain 10.47, vomiting 6.98% and splenomegaly 3.49% were more in children with coinfection than children with only EBV IM without none of them having statistically significant association with coinfection. Poor appetite 47.69%, cough 33.85%, nasal congestion 34.62%, and eyelid edema 27.69% were found to be more in children without coinfection and without a statistical significancy. Detailed information is presented (Table 5).

Table 5. Clinical manifestations.

Symptom	With coinfection (%)	Without coinfection (%)	P-value
Fever	76 (88.37)	100 (76.92)	0.034*
Lymphadenopathy	80 (93.02%)	116 (89.23)	0.347
Tonsillopharyngitis	56 (65.12)	102 (78.46)	0.030*
Poor appetite	39 (45.35%)	62 (47.69%)	0.735
Sore throat	31 (36.05)	41 (31.54)	0.491
Cough	27 (31.40)	44 (33.85)	0.707
Nasal congestion	24 (27.91)	45 (34.62)	0.301
Eyelid oedema	17 (19.77)	36 (27.69)	0.185
Runny nose	18 (20.93)	26 (20.00)	0.868
Abdominal pain	9 (10.47)	8 (6.15)	0.249
Vomiting	6 (6.98)	8 (6.15)	0.810
Splenomegaly	3 (3.49)	1 (1.54)	0.147

3.7. Laboratory Findings

For white blood cell count (WBC), the mean values were similar between the two groups, and no significant difference was found (P = 0.839). Red blood cell count (RBC) and platelet count (PLT) also showed no significant differences between the groups with P-values of 0.395 and 0.693, respectively, hemoglobin levels (HGB) displayed a statistically significant difference, with a median of 120 (range 94 - 146) in the coinfection group compared to 123 (range 72 - 144) in the group without coinfection, with a p-value of 0.009. Neutrophil counts (NEUT) and lymphocyte counts (LYMPH) were not significantly different between the groups, with P-values of 0.051 and 0.135, respectively. Monocyte counts (MONO), mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH) showed no significant differences between the two groups. Erythrocyte sedimentation rate (ESR) differed significantly, with the coinfection group having a higher median value of 18 (range 13 - 633) compared to 15 (range 0 - 69) in the group without coinfections (P = 0.019). C-reactive protein (CRPmgL) was also significantly higher in the coinfection group (P < 0.001). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was both higher in coinfection group and AST was statistically significant (P = 0.034). Detailed information is presented Table 6.

3.8. Complications and Comorbidities

Bronchopneumonia 4.6%, allergic rhinitis 3.49%, anemia 3.49%, UTI 2.33%, myocardial damage 2.33%, Acute Mesenteric Lymphadenitis 2.33%, kidney stones 1.16% and vitamin D deficiency 1.16%, were all higher in children with coinfection but none had statistically significant association with coinfection. On the other hand, conditions like acute bronchitis 11.54%, acute sinusitis 4.62%, urticaria 1.54%, and adenoid hypertrophy 1.54% were higher in children with only primary EBV IM yet none of the was associated with primary IM. Detailed information is presented Table 7.

Table 6. Laboratory findings.

Variable	Co-infection (n = 86)	Without co-infection (n = 130)	P value
WBC 10^9/L	13.0052 ± 5.42232	13.1565 ± 5.30962	0.839
RBC 10^{12}/L	4.4159 ± 0.41647	4.4661 ± 0.42708	0.395
HGB g/L	120 (94 - 146)	123 (72 - 144)	0.009*
PLT 10^9/L	233.67 ± 86.122	229.28 ± 75.533	0.693
NEUT	32.349 ± 17.0419	28.189 ± 13.9242	0.051
LYMPH	56.6936 ± 18.60659	60.3477 ± 16.80502	0.135
MONO	10.398 ± 13.6221	9.388 ± 5.5324	0.450
MCV fL	82.3162 ± 4.53549	82.1978 ± 7.14844	0.892
MCH pg	26.904 ± 1.7232	28.570 ± 8.6107	0.064
Atypical lymphocytes	21.07 ± 16.321	23.28 ± 13.555	0.294
ESR	18.71 ± 13.633	15.06 ± 9.093	0.019*
CRP mg/L	21.15 (6 - 92)	14 (2 - 87)	<0.001*
PCT ng/ml	0.79 ± 2.103	0.45 ± 0.832	0.144
ALT UL	104.674 ± 136.6342	85.796 ± 92.7459	0.228
AST UL	105.023 ± 130.0222	77.528 ± 55.4555	0.034*
TBIL micromole/L	7.1349 ± 4.05859	7.4461 ± 6.22605	0.392
DBIL	2.463 ± 1.7833	2.482 ± 1.5509	0.934
ALB g/L	39.145 ± 3.1026	38.820 ± 4.0978	0.534
Glu mmol/L	5.28990 ± 1.432141	5.56983 ± 1.266829	0.142
BUN mmolL	3.6845 ± 1.17419	3.7342 ± 1.17419	0.755
CREA micromole/L	40.7095 ± 12.49762	44.9525 ± 34.42817	0.281

(*) indicates statistically significant.

Table 7. Complications and comorbidities and coinfection.

Comorbidity/complication	With coinfection (%)	Without coinfection (%)	P-value
Acute Bronchitis	5 (5.81)	15 (11.54)	0.155
Bronchopneumonia	4 (4.65)	5 (3.85)	0.772
Acute Sinusitis	2 (2.33)	6 (4.62)	0.383
Allergic Rhinitis	3 (3.49)	2 (1.54)	0.351
Anaemia	3 (3.49)	2 (1.54)	0.351
Urticaria	1 (1.16)	2 (1.54)	0.817
Urinary Tract	2 (2.33)	1 (0.77)	0.339
Kidney Stones	1 (1.16)	1 (0.77)	0.768
Adenoid Hypertrophy	0 (0.00)	2 (1.54)	0.248
Vitamin D Deficiency	1 (1.16)	1 (0.77)	0.768
Myocardial Damage	2 (2.33)	0 (0.00)	0.081
Acute Mesenteric Lymphadenitis	2 (2.33)	0 (0.00)	0.081

4. Discussion

In our study, we observed a 39.8% coinfection rate among children with infectious mononucleosis, which is lower compared to prior findings of 61.81% [11] and other reports indicating rates of 68.9%, 81.3%, and 63.6% for EBV, CMV, or EBV/CMV infections, respectively [2]. Mycoplasma pneumoniae was the most prevalent coinfecting pathogen at 18.1%, contrasting with reports of Influenza A and B as the leading coinfections at 60% each, followed by Mycoplasma pneumoniae at 48.4% [2]. Influenza B and A viruses were also significant, with prevalences of 16.7% and 13.9%. A study identified 26% of paediatric patients with multiviral infections, with Human Rhinovirus being the most common [12]. Human Metapneumovirus was noted as the most frequent virus at 22% [12]. Analysis of 10,429 specimens showed a 27.9% coinfection rate, highlighting Mycoplasma pneumoniae, PIVs, and IFVB as key pathogens, with gender disparities in MP detection [13]. HRV/ENT emerged as the most prevalent in another cohort, with distinctions in virus prevalence between single and co-infections [14]. For bacterial co-infections, a study identified two confirmed cases out of 37 suspected, illustrating the diagnostic challenges with pathogens like Streptococcus pneumoniae [11]. The prevalence of bacterial co-infections in pneumonia-diagnosed children was notable, with Staphylococcus epidermidis, Pseudomonas aeruginosa, and Haemophilus influenzae being significant [14], underscoring the complexity in diagnosing and managing co-infections in this group.

This study's findings on the variable incidence of respiratory coinfections in children with infectious mononucleosis align with the observed impact of COVID-19 precautions on other viral diseases. The data reflect how stringent infection control measures during the pandemic led to reduced transmission of various pathogens, evidenced by the fluctuating coinfection rates from 2018 to 2022. These insights highlight the broader epidemiological effects of targeted public health interventions, underscoring the need for comprehensive strategies in disease control and prevention [15].

This study revealed that coinfections where more in summer and autumn in which IFB and MP were the leading pathogens respectively this contradicts (Çağlar İ. et al., in 2015) who claimed Many respiratory viruses show a seasonal pattern, with yearly peaks in winter and spring. However, certain viruses, like parainfluenza viruses (PIVs), are present and cause infections year-round [16].

Our study revealed a gender disparity in infectious mononucleosis (IM) prevalence, with males affected more frequently (61.6%) than females, a finding supported by Diaz *et al.* (2015) and other studies [6] [12] [14] [17] [18]. Despite males being more commonly diagnosed with IM, females showed a higher rate of coinfections (54.2% vs. 30.8%), marked by a significant P-value of 0.001, indicating potential sex-related differences in coinfection risk or detection [19]. This is in contrast to the general pathogen prevalence analysis where gender differences were not primarily focused. However, Zhong *et al.* noted a male do-

minance in viral coinfections, which diverges from our observations on Mycoplasma pneumoniae, suggesting a higher susceptibility or detection in females [13] [20]. These findings collectively suggest that biological, environmental, or behavioral factors might contribute to gender and age differences in the prevalence and risk of IM and its associated coinfections.

Age-wise, our study, along with Choo *et al*. (2022) and Çağlar *et al*. (2019), showed no significant age-related differences in coinfection prevalence, despite a notable prevalence in children under 5 years, particularly those younger than 4 years [19] [21]. This aligns with Malveste *et al*. (2023), highlighting the highest susceptibility to coinfections among the youngest children, especially with RSV and SARS-CoV-2, as well as hRV with RSV [22]. These observations suggest that various factors may influence gender and age disparities in IM prevalence and its coinfections.

Fever was a common symptom in children with IM, reported in 81.5% of cases in our study and aligning with Caglar *et al*. (2019) who found a 92.4% fever incidence in children with IM [21]. Studies from Shanghai and Mexico reported fever in 98.3% and 79.7% of pediatric cases, respectively [3] [4], with a study showing fever in all participants (n = 26) [23] and another from Beijing indicating a 75.6% prevalence of fever in EBV-IM patients [24]. Among children with coinfections, 88.37% exhibited fever, significantly associated with coinfections (P = 0.034), suggesting a stronger linkage to coinfections than to mononucleosis alone. This is consistent with Choo *et al*. (2022), who reported fever in 100% of children with coinfection [19]. The prevalence of fever varied across different infection statuses, highlighting fever as a key diagnostic indicator of IM and associated infections. Our study found no significant impact of coinfections on appetite changes in children with infectious mononucleosis (IM), with a P-value of 0.735, aligning with findings by Moreira and Pourhassan that coinfections do not significantly affect appetite [25] [26]. This suggests factors other than coinfections, possibly the immune response to Epstein-Barr virus (EBV), are more influential in appetite regulation during IM.

Lymphadenopathy was the most common symptom in our study, present in 90.7% of cases, consistent with other research but with no significant difference between children with or without coinfections (P = 0.347), highlighting its diagnostic value for IM irrespective of coinfection status [3] [4] [21] [24]. Eyelid edema's presence was not significantly influenced by coinfections (P = 0.185), similar to findings by Son and Li, indicating that coinfections may not significantly alter clinical presentations like sore throat and cough in IM [17] [27]. Our study also showed no significant association between coinfections and cough (P = 0.707), contrasting with findings by Zhong *et al*. of a higher cough incidence in children with viral coinfections [20] [28]. Tonsillopharyngitis was prevalent in 73.1% of our participantswith Smoljar *et al*. (2019), who found a universal presence of tonsillopharyngitis in children with EBV-induced IM, but interestingly, children with coinfections had a lower incidence (65.12%) compared to those without (78.46%), suggesting tonsillopharyngitis is negatively associated with

coinfections (P = 0.030) [3] [23] [29].

Sore throat and nasal congestion showed no statistically significant difference in occurrence based on coinfection status, but a notable difference in nasal congestion suggests complex interactions between EBV infections and the immune system [28] [30] [31] [32]. The study found no significant difference in the incidence of runny nose or abdominal pain between children with and without coinfections, indicating these symptoms might not be directly influenced by coinfection status [3] [33] [34] [35] [36] [37]. Vomiting incidence was similar across coinfected and non-coinfected groups, suggesting variable gastrointestinal symptom presentations in IM, aligning with literature on the systemic immune response to EBV and its effects [38] [39]. This study found marginal differences in peripheral leukocyte counts between children with coinfections (13.0052×10^9/L) and those without (13.1565×10^9/L), with no statistical significance (P = 0.839), echoing Wang *et al*. (2010) who noted lower counts in coinfected children [2]. Hemoglobin levels were slightly higher in coinfected children (123 g/L) compared to those with EBV only (120 g/L), diverging from Caglar *et al*. (2019) who reported lower levels in children with acute EBV infection without coinfections [21]. Median platelet counts were higher in our study (233.67×10^9/L) than reported by Topp *et al*. (2015), suggesting possible racial variations [8]. Lymphocyte percentages were marginally higher in children without coinfections (25.8%) than in those with (25.0%), aligning with findings from a 2022 Korean study [19]. Our study did not support Wu Y *et al*. (2020)'s findings of higher atypical lymphocyte proportions in school-aged children, showing a distribution across ages with 21% in coinfected and 23.2% in non-coinfected children [3]. Significantly higher levels of ESR and CRP were found in children with coinfections (P = 0.019 and <0.001, respectively), contrasting with Choo *et al*. (2022), who reported higher ESR in children without coinfections [19]. Procalcitonin levels were also higher in the coinfection group, differing from Choo *et al*. (2022) and Zhong P *et al*. (2019), who found similar or lower levels in coinfected patients, indicating pathogen-specific impacts on procalcitonin levels [19] [20]. Elevated liver enzymes in coinfected children, with AST showing statistical significance (P = 0.034), may reflect an intensified immune response causing hepatocyte damage. Contrarily, our findings of slightly higher albumin levels in the coinfected group suggest variability in the nutritional or inflammatory status among different studies, unlike Choo *et al*. (2022), who noted no difference between groups [19].

This study found bronchopneumonia in 4.2% of children with infectious mononucleosis (IM), a rate similar to previous studies reporting pneumonia in around 4.3% of cases [4]. Despite no significant association between coinfections and bronchopneumonia (P = 0.772), children with coinfections had a slightly higher incidence (4.65%) compared to those with only EBV (3.85%), echoing findings by Zhong *et al*. (2019) on the increased pneumonia risk in coinfected children [20]. Sun *et al*. also noted more severe disease in individuals coinfected with HBoV and RSV [40], suggesting coinfections might elevate pneumonia risk

and severity. In 216 children, acute bronchitis was identified in 5.8% with coinfections and 11.5% without, with the difference not statistically significant (P = 0.155). This reflects a higher bronchitis prevalence in children with single infections, contrasting with findings that suggest viral coinfections are more common in respiratory infections [11] [20]. This may indicate the immune response's nature to infection differs between single and co-infected patients. Allergic rhinitis occurred in 2.3% of the children, with no significant difference between coinfected children and others (P = 0.351), contrary to reports of a higher prevalence in coinfected children [19]. This suggests allergic rhinitis's association with coinfections might not be as straightforward, indicating a complex relationship between IM, coinfections, and allergic conditions.

This study observed a low incidence of acute sinusitis, with only 8 cases and no significant link to coinfections (P = 0.383), despite previous suggestions of a connection between viral and bacterial pathogens in sinusitis [40] [41]. This might highlight variability in secondary bacterial infection predisposition after a viral infection. Splenomegaly was rare and not significantly linked to coinfections, suggesting it's mainly due to the viral infection itself rather than coinfections [42] [43] [44]. Anemia was also low in prevalence with no significant association with coinfections, pointing to the complexity of factors beyond coinfections influencing anemia [45] [46]. Kidney stones and urticaria were notably infrequent, suggesting factors like lifestyle and dietary habits might be more impactful for kidney stones [47], and urticaria's occurrence in IM could be due to immunological responses not directly linked to coinfections [48]. Similarly, urinary tract infections (UTIs) showed no significant difference with coinfections, indicating UTIs' risk factors might be independent of coinfections [49]. These findings underscore the nuanced interplay between coinfections and various conditions in children with IM, highlighting the variability in clinical presentations and disease progression.

To the best of our knowledge, this is the first study to examine the prevalence coinfections in children with IM in China. While offering valuable insights into the prevalence of these co-infections, our study has several limitations to note.

Limitations

1) The research was carried out retrospectively, and as a result, it was subject to the common drawbacks associated with retrospective analyses, including recall bias and incomplete data. 2) Since the study was conducted at a single center, its results cannot be generalized to determine the prevalence of co-infections in children with IM across the country. 3) Our study did not include an examination of how seasonal changes might affect co-infection trends, which could influence both the prevalence and behavior of these infections.

5. Conclusion

In summary, this study highlights an increase in co-infections among children diagnosed with infectious mononucleosis, particularly Mycoplasma Pneumoniae

and Influenza B and A viruses, which affect approximately 49% of coinfection cases. These findings emphasize the diagnostic and treatment challenges in EBV-positive pediatric cases and underscore the need for heightened clinical and public health awareness.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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