Clinical and epidemiological characteristics of children with community-acquired mycoplasma pneumonia in Nanjing

Changdi Xu
Children's Hospital of Nanjing Medical University
Xiao Ma
Children's Hospital of Nanjing Medical University https://orcid.org/0000-0002-6409-4347
Fengxia Zhang
Children's Hospital of Nanjing Medical University
Ying Bi
Children's Hospital of Nanjing Medical University
Qiangquan Rong
Gaochun People's Hospital
Yao Quan
Gaochun People's Hospital
Yifan Zhu (846206101@qq.com)
Deyu Zhao
Children's hospital of Nanjing Medical University

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Abstract

Background Mycoplasma pneumoniae is a ubiquitous pathogen, causing various manifestations of community-acquired pneumonia (CAP). This study aimed to update the epidemiology and clinical manifestations of community-acquired mycoplasma pneumonia (CAMP) in hospitalized children in Nanjing and to investigate the association of age, sex, and season of onset with the prognosis of CAMP. Methods The clinical data of children <18 years old, hospitalized for CAP in 2016, were collected and reviewed. Blood and nasopharyngeal aspirates were obtained for pathogen detection, including cultivation, immunofluorescence, and polymerase chain reaction and acid tests. Demographic, clinical, radiographic, and laboratory data were analyzed using SPSS version 21.0 software. Results Of 3377 eligible children with radiographic confirmation of pneumonia, 1249 (36.99%) had M. pneumoniae infection. Although most children (614, 49.16%) with M. pneumoniae infection were ≤3 years old, CAMP occurred mostly in those aged 5-10 years (70.23%). The peak incidence was recorded between July and September (49.05%). Children aged 5-10 years had significantly longer hospitalization and more frequent atelectasis. No significant difference in CAMP was found between the sexes. Conclusions M. pneumoniae remains one of the leading pathogens in pediatric CAP .Particular care is necessary for children older than 5 years and during the peak periods of disease.

Background

Community-acquired pneumonia (CAP) remains the most common acute infectious cause of childhood disease worldwide. It is the leading cause of death in children under 5 years old in the developing world and the most common cause of hospitalization for children in industrialized countries [1]. Numerous agents can lead to CAP, including bacteria, viruses, and atypical pathogens.

Mycoplasma pneumoniae is one of the most common atypical pathogens and is able to infect both the upper and lower respiratory tracts. School-aged children and adolescents are most affected by *M. pneumoniae*, with manifestations ranging from mild upper respiratory symptoms to pneumonia and other extrapulmonary presentations, including dermatologic, cardiovascular, and central nervous system findings [2]. Reports show that children younger than 3 years tend to develop upper airway infection, while children older than 5 years tend to develop acute bronchitis and pneumonia [3-5].

The increasing incidence of pneumonia caused by *M. pneumoniae* has been reported worldwide. The Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) study reported that *M. pneumoniae* was the most commonly detected bacterial pathogen among enrolled children (<18 years old) in America [6]. As described in other studies, *M. pneumoniae* is responsible for 10 to 40% of all cases of pediatric CAP [4, 7].

Drug resistance, changes in demography like urban-rural migration, immigration changes, etc have changed the epidemiology and clinical manifestations of community-acquired mycoplasma pneumonia (CAMP) in hospitalized children in Nanjing nowadays. To better understand it, we collected and analyzed

data on children hospitalized for CAP in 2016. We further compared the data by groups to investigate whether age, sex, or season of onset was associated with the prognosis of CAMP in order to supplement the knowledge from previously published studies.

Methods

Study Population and Enrollment criteria

The population studied in this retrospective study consisted of children <18 years old, hospitalized at Children's Hospital of Nanjing Medical University, and treated for CAP with radiographic evidence in 2016.

The criteria for inclusion in the study were as follows: 1) evidence of an acute infection, defined as reported fever or chills, documented fever or hypothermia, leukocytosis, or leukopenia; 2) symptoms of new cough or sputum production, dyspnea, tachypnea, or chest pain; abnormal lung examination; or respiratory failure consistent with an acute onset of respiratory disease; and 3) chest radiographic findings compatible with pneumonia within ≤72 hours of admission [8]. The included children met all these three criteria. Children frequently hospitalized because of severe immunodeficiency were excluded from the study.

The study protocol was approved by the institutional ethical review board and written informed consent was obtained from the children's parents. The enrolled children were further divided into four groups by age: ≤3 years, 3-5 years, 5-10 years, and >10 years. Moreover, they were divided based on the month they were hospitalized into four groups: January-March, April-June, July-September, and October-December. The demographic data, clinical features, laboratory findings, and radiographic evidence obtained from the Haitai electronic medical record system were analyzed.

Radiological Definitions and Confirmation

Radiographic pneumonia was defined as the presence of consolidation, other infiltrate, or pleural effusion [9]. Inclusion in the study required independent confirmation of diagnosis on chest radiographs (obtained within 72 hours of admission) by at least two pediatric radiologists from the Children's Hospital of Nanjing Medical University.

Blood and Nasopharyngeal Aspirates Collection and Laboratory Testing

Blood and respiratory specimens were obtained for pathogen testing. Briefly, one to three milliliters of venous blood were drawn under aseptic conditions from each child. Nasopharyngeal aspirates were collected with a fine catheter from the nasopharynx by applying negative pressure.

Polymerase chain reaction (PCR) and nucleic acid tests were performed on nasopharyngeal aspirates. Serum samples were tested for the presence of antibodies to *M. pneumoniae*. Cultures were performed both on nasopharyngeal aspirates and venous blood.

Case Definitions

The criteria for the definition of *M. pneumoniae* infection were as follows: 1) positivity for mycoplasma IgM in the acute stage, 2) detection of *M. pneumoniae* in nasopharyngeal aspirates by PCR, 3) a four-fold or greater increase in the mycoplasma IgG titer in the acute and convalescent stages. The defined *M. pneumoniae* infection met one of these three criteria.

Statistical Analysis

Clinical characteristics were analyzed and compared by age, sex, and seasonal distribution. All data were analyzed using SPSS version 21.0 software (IBM, Armonk, NY). Quantitative data results are expressed as mean±standard deviation. Pairwise comparisons were performed using the t-test. Enumeration data were analyzed using the chi-square test. $P<0.05$ was considered statistically significant.

Results

Study Population and Clinical Findings

Among the 3377 eligible children with radiographic confirmation of pneumonia, 1249 (36.99%) were diagnosed with *M. pneumoniae* infection, with a male-to-female ratio of 1.23:1 and a mean age of 3.11±2.80 years. Of these 1249 cases, the incidence of *M. pneumoniae* infection was highest in the age group ≤3 years (49%), followed by the 5-10 years age group (25%). All the children presented with cough and 78% presented with fever. Twenty-eight percent of the children had an underlying condition, such as asthma/reactive airway disease, chromosomal disorders including Down syndrome, chronic liver disease, chronic kidney disease, congenital diseases, diabetes mellitus, mild immunosuppression, neurological disorders, preterm birth, and splenectomy. Radiography showed atelectasis and pleural effusion in 8.0% and 9.8% of patients, respectively. The median length of hospital stay was 8.6 days (interquartile range [IQR] 7-10). (Table 1)

We analyzed the data of the 1249 children and found that most children (614, 49.16%) with *M. pneumoniae* infection were ≤3 years old. However, CAMP was most frequent in children aged 5-10 years old (70.23%), with the >10 years age group following (55.07%) (Figure 1). In the group of children aged ≤3 years old, only 26.75% had CAMP. Analysis of the distribution of mycoplasma pneumonia based on seasonality showed that the number of cases increased from July to September. Regarding the ratio of

CAMP to CAP, the peak incidence was also between July and September (49.05%). The lowest incidence was between January and March (29.18%, Figure 2).

Comparison of Clinical Characteristics between the ≤3 Years, 3-5 Years, 5-10 Years, and >10 Years Age Groups

Of the 1249 children, a total of 957 (28.34%) were infected with *M. pneumoniae* alone. We analyzed and compared the clinical data of these 957 cases by age group and the results are shown in Table 2 & 3. The length of stay for the ≤3 years, 3-5 years, 5-10 years, and >10 years age groups was 8.32±2.549, 8.40±2.863, 9.20±3.672, and 8.76±2.994 days, respectively; the chi-square test showed a significant difference between the lengths of stay of the age groups. There was a significant difference in both the percentage of peripheral blood neutrophils and the levels of C-reactive protein based on the age distribution (P<0.05). There was no significant difference in peripheral blood leukocyte count between the four groups. The incidences of fever and atelectasis were significantly lower in the ≤3 years age group (70.71% and 4.05%, respectively) than in the 3-5 years (84.30% and 8.52%, respectively) and 5-10 years (87.00% and 15.52%, respectively) age groups (P<0.05). The incidence of atelectasis (15.52% vs 8.52%) was significantly higher in the 5-10 years age group than in the 3-5 years age group (P=0.02).

Comparison of Clinical Data Based on the Month Distribution

The comparison of the clinical data of 957 patients hospitalized during different months is reported in Table 4 & 5. There were significant differences in the duration of hospitalization, peripheral blood neutrophil percentage, and ratio of patients presenting with fever between the four groups (P<0.05). The length of stay from April-June (7.98±2.498 days) was significantly less than that for January-March (8.56±3.164 days), July-September (9.00±2.940 days), and October-December (8.75±3.430 days). The incidence of fever was significantly lower during April-June (73.16%) than during both January-March (82.99%) and October-December (82.93%) (P<0.05). In comparison, there was no significant difference in the incidence of atelectasis between the groups. There were also significant differences in aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatine kinase (CK) levels between the four groups (P<0.05).

Comparison of Clinical Characteristics Based on Sex

A comparison of clinical characteristics based on sex is outlined in Table 6. The duration of hospitalization was 8.65±3.078 and 8.56±2.957 days for the male and female patients, respectively. Fever was noted in 76.7% and 82.0% of male and female patients, respectively, with a significant difference between the groups (P=0.043). Overall, 83 children had atelectasis, comprising 43 boys and 40 girls. There was no significant difference in the rate of atelectasis between the boys and girls (8.2% vs 9.2%). ALT (22.47±19.53 vs 19.38±16.32 U/L, P<0.05) and CK (106.67±131.70 vs. 90.75±63.98 U/L, P<0.05) levels were significantly higher in the male patients. The female patients had a significantly higher percentage of neutrophils (54.80±17.69 vs. 51.91±18.15, P<0.05).

Discussion

In this retrospective study, we analyzed data from children aged 0-17 years hospitalized at Children's Hospital of Nanjing Medical University for CAP in 2016, to clarify the epidemiology and clinical characteristics of CAMP in this population. Overall, we found that the prevalence of *M. pneumoniae* infection was 36.99%, in line with previous reports that demonstrated that *M. pneumoniae* was responsible for 10 to 40% of all cases of pediatric CAP [4, 7].

A review of the literature showed that cough was a finding in *M. pneumoniae* infection in Turkish and Brazilian studies [10, 11]. Moreover, some clinical features such as headache and wheezing found to be more common in mycoplasma pneumonia in a previous study, may aid in differentiating CAMP from CAP caused by other pathogens [12].

We found that although most children with only *M. pneumoniae* infection were ≤3 years old, children over 5 years old had the greatest prevalence of CAMP, and the following reasons may explain this finding. First, children ≤3 years old have a relatively weaker immune function and are more likely to be attacked by pathogen-related pneumonia. Second, as reported in a study of childhood pneumonia etiology initiated in both hospital and primary healthcare settings, younger ill children were more likely to be sent to hospital for diagnosis and treatment because of uncertainties about management [13]. These two factors may lead to a greater tendency for younger children with CAP to be hospitalized, compared to school-aged children, as seen in the higher proportion of ≤3-year-old children in all CAMP cases. However, the immune system of children gradually improves with age, protecting older children from most typical pathogens. As a result, few of the ill children over 5 years required hospitalization for treatment. Furthermore, the higher rate of school attendance in those older than 5 years may contribute to a higher carriage rate of *M. pneumoniae*, leading to a higher risk of *M. pneumoniae* infection in this age group. Thus, both the smaller risk of hospitalization-necessary pneumonia and higher risk of infection by *M. pneumoniae* contribute to the higher ratio of CAMP/CAP in this age group. Consistent with our findings, former reports on the review and recent advances of CAP also demonstrated that mycoplasma pneumonia tended to be more prevalent in older children and adolescents [14].

By comparison, the duration of hospitalization was significantly longer and the incidence of atelectasis was significantly higher in children aged 5-10 years than in those aged ≤3 years and 3-5 years.

Accordingly, it may be concluded that CAMP among 5-10 years aged children was more severe, while CAMP in younger children tended to be less severe, similar to previous clinical reviews which describe the clinical course and outcome of children over 5 years as being associated with more complications [4, 15-16].

Regarding seasonal frequency, both the largest number of cases and peak incidence were seen from July to September. A previous review demonstrated identical findings where mycoplasma pneumonia tended to occur in the late summer and early fall [12]. An epidemiological study of mycoplasma pneumonia in Korea also found that cases increased from early summer, peaked in September or October, and then slowly faded after several months [17]. The reason for this could be attributed to the fact that the climate in the region during this period is conducive to the growth and spread of *M. pneumoniae*.

It is noteworthy that there is still no gold standard for the diagnosis of mycoplasma pneumonia. Regarding widely available and convenient diagnostic techniques, the diagnostic yield of serologic testing kits such as enzyme immunoassay and indirect immunofluorescence was reported to be 10-30% in patients with pneumonia, varying widely with differences in the epidemiology of pathogens and study population [18], while PCR could improve the yield by 8-15% when combined with these methods [19]. The combination of serologic detection in acute-phase serum and PCR as a valid diagnostic approach is possibly the recommended way to diagnose *M. pneumoniae* infection.

There are some limitations to our study. First, the representativeness of the results might be limited because children in this study were treated in a tertiary hospital with relatively more severe infections. Second, the inclusion criteria and the definition of *M. pneumoniae* infection adopted here are not well-acknowledged as there is still no gold standard for the diagnosis of mycoplasma pneumonia. Third, definitions of codetection, coinfection, or contamination of coexisting pathogens were unclear. Moreover, the lack of extensive microbiological testing and the shortage of pathogen-detection technology may have biased the detection rate of some pathogens.

Conclusion

M. pneumoniae remains one of the leading pathogens in pediatric CAP. CAMP requiring hospitalization was highest among children above 5 years old who had a more complicated clinical course and worse outcome. The hospitalization rate was also high in preschool children suggesting that age might aid in the diagnosis of the pathogen but cannot serve as a standard diagnostic indicator. Moreover, the peak incidence of mycoplasma pneumonia was from July to September. Thus, parents should be advised regarding the prevention of *M. pneumonia* infection and physicians should consider the possibility of *M. pneumonia* infection and perform routine screening for this pathogen in pediatric patients with infections especially during the peak months.

Abbreviations

ALT alanine aminotransferase

AST aspartate aminotransferase

CAMP community-acquired mycoplasma pneumonia

CAP community-acquired pneumonia

CDC Centers for Disease Control and Prevention

CK creatine kinase

IQR interquartile range

PCR polymerase chain reaction

Declarations

Authors' Contributions

Changdi XU and Xiao Ma analyzed the data and drafted the manuscript. Fengxia Zhang, Ying Bi, and Yao Quan collected the data. Qiangquan Rong conceived of the study and participated in its design. Yifan Zhu helped in statistical analysis. Deyu Zhao designed the study. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The report was approved by IEC of Nanjing Children's Hospital Affiliated to Nanjing Medical University.

Consent to publish

Not applicable.

Availability of data and materials

The dataset used in the study is available from the corresponding author.

Competing Interests

The authors declare that they have no conflict of interest.

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Contributor Information

Changdi Xu, Email: xcd_118@163.com

Xiao Ma, Email: 386496215@qq.com

Fengxia Zhang, Email: zfxelena@163.com

Ying Bi, Email: 1278025361@qq.com

Qiangquan Rong, Email: ydrqq@sina.com

Yao Quan, Email:936306268@qq.com

Yifan Zhu, Email: 846206101@qq.com

Deyu Zhao, Email: Zhaodeyu98@126.com

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Tables

Table 1. Characteristics of children with M. pneumoniae infection requiring hospitalization

Characteristic	Children with M. pneumoniae infection (n=1249)
Age groups – no. (%)	
≤3 years	614 (49)
3-5 years	288 (23)
5-10 years	309 (25)
10 years	38 (3)
Symptoms – no. (%)	
Cough	1245 (100)
Fever	970 (78)
Any underlying condition* – no. (%)	350 (28)
Radiographic findings† – no. (%)	
Atelectasis	100 (8.0)
Pleural effusion	122 (9.8)
Hospitalization characteristics	
Length of stay – median days, IQR	8.6 (7-10)

*

Underlying conditions included asthma/reactive airway disease, chromosomal disorders including Down syndrome, chronic liver disease, chronic kidney disease, congenital diseases, diabetes mellitus, immunosuppression, neurological disorders, pre-term birth, and splenectomy.

†

Findings are not mutually exclusive and therefore do not add to 100%.

IQR: Interquartile range

Table 2 & 3 . Comparison of clinical characteristics based on the age distribution

Age(yrs)	≤3(n=420)	3-5(n=223)	5-10(n=277)	10(n=37)	F / χ^2	P
Length of stay	8.32±2.55	8.40±2.86	9.20±3.67	8.76±2.99	32.952	0.000
WBC	10.61±4.74	18.80±132.	62 8.64±3.58	9.19±4.91	0.089	0.766
N%	44.04±17.92	57.62±14.39	62.28±14.24	64.37±11.92	81.831	0.000
CRP	25.23±23.78	27.97±26.61	29.37±26.43	40.64±39.26	10.331	0.002
Fever/n(%)	297/70.71	188/84.30	241/87.00	32/86.49	33.325	0.000
Atelectasis/n(%)	17/4.05	19/8.52	43/15.52	4/10.81	28.130	0.000
AST	39.61±18.87	30.94±15.85	31.84±26.06	29.52±18.28	0.047	0.828
ALT	22.77±15.44	18.58±14.15	20.49±23.90	21.66±18.72	0.015	0.903
LDH	405.37±249.47	361.22±155.41	359.40±166.87	359.00±271.92	2.536	0.112
CK	99.24±68.82	89.18±52.64	107.79±170.34	102.26±73.27	0.641	0.423
CK-MB	35.94±29.25	30.22±24.22	25.42±18.35	27.81±59.87	0.889	0.346

Age(yrs)		P		
		Length of stay	Fever/n□□□	Atelectasis/n□□□
≤3	3-5	0.717	0.000	0.029
	5-10	0.001	0.000	0.000
	□10	0.324	0.054	0.080
3-5	5-10	0.006	0.440	0.020
	□10	0.485	1.000	0.753
5-10	□10	0.484	1.000	0.624

Table 3 & 4. Comparison of Clinical Data Based on the Month Distribution

Month	1-3(n=194)	4-6(n=231)	7-9(n=327)	10-12(n=205)	F / χ^2	P
Length of stay	8.56±3.16	7.98±2.50	9.00±2.940	8.75±3.430	5.394	0.001
WBC	20.00±142.17	10.44±5.58	9.53±3.77	9.64±4.53	1.302	0.272
N%	51.52±19.43	53.84±19.34	51.84±16.54	56.47±16.75	3.561	0.014
CRP	31.08±25.20	28.38±27.48	23.97±21.75	31.59±31.88	1.644	0.179
Fever/n(%)	161/82.99	169/73.16	258/78.90	170/82.93	8.555	0.036
Atelectasis/n(%)	15/7.73	27/11.69	28/8.56	13/6.34	4.280	0.233
AST	39.38±17.88	35.25±16.61	36.36±19.26	28.65±28.11	9.318	0.000
ALT	19.91±14.51	19.37±17.49	18.51±14.46	28.10±24.60	13.206	0.000
LDH	368.40±177.66	386.79±291.99	392.71±183.57	364.11±162.63	0.990	0.397
CK	105.80±108.26	115.79±169.77	95.43±68.43	82.56±47.12	3.703	0.011
CK-MB	30.30±23.30	31.59±32.77	32.61±28.66	29.61±21.84	0.569	0.635

Month		P		
		Length of stay	Fever/n□□□	Atelectasis/n□□□
1-3	4-6	0.048	0.019	0.223
	7-9	0.106	0.304	0.409
	10-12	0.518	1.000	0.862
4-6	7-9	0.000	0.128	0.250
	10-12	0.007	0.016	0.091
7-9	10-12	0.358	0.264	0.295

Table 5. Data analysis on the clinical characteristics between the boys and the girls

Sex	boys□n=523□	girls□n=434□	t □χ2	P
Length of stay	8.65±3.078	8.56±2.957	0.493	0.622
WBC	10.06±4.70	14.11±95.23	-0.969	0.333
N%	51.91±18.15	54.80±17.69	0.391	0.014
CRP	28.32±26.49	28.51±27.04	0.766	0.946
Fever/n(%)	401/76.7	356/82.0	4.114	0.043
Atelectasis/n(%)	43/8.2	40/9.2	1.515	0.469
AST	35.31±20.47	34.61±21.68	0.722	0.618
ALT	22.47±19.53	19.38±16.32	0.002	0.010
LDH	376.97±181.04	383.07±241.04	0.182	0.667
CK	106.67±131.70	90.75±63.98	0.066	0.027
CK-MB	31.07±26.98	31.42±27.87	0.280	0.849

Figures

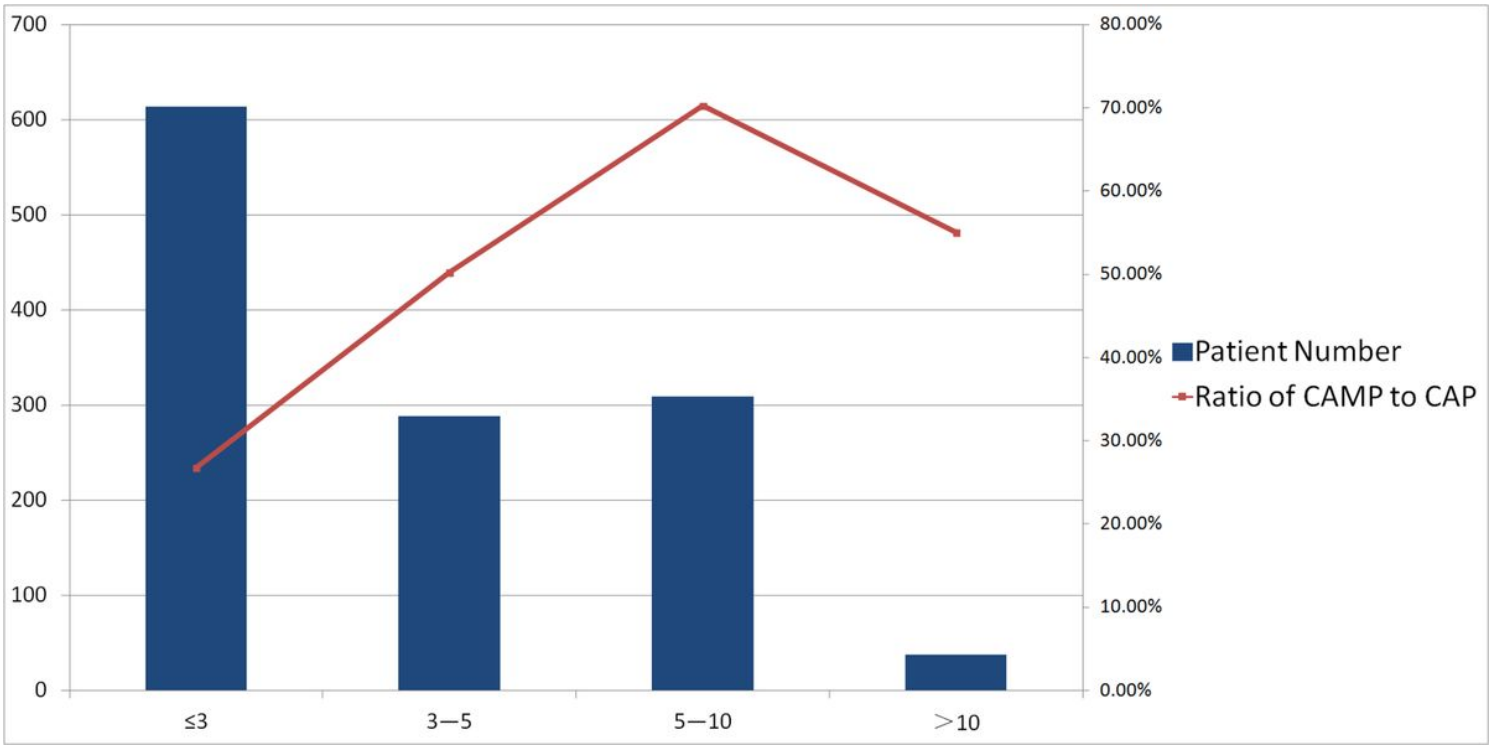

Figure 1

Age distribution of children with CAMP and the ratio of CAMP to CAP in 2016 in Children's Hospital of Nanjing Medical University. The bar chart shows the number of children with CAMP. The line chart shows the ratio of CAMP to CAP.

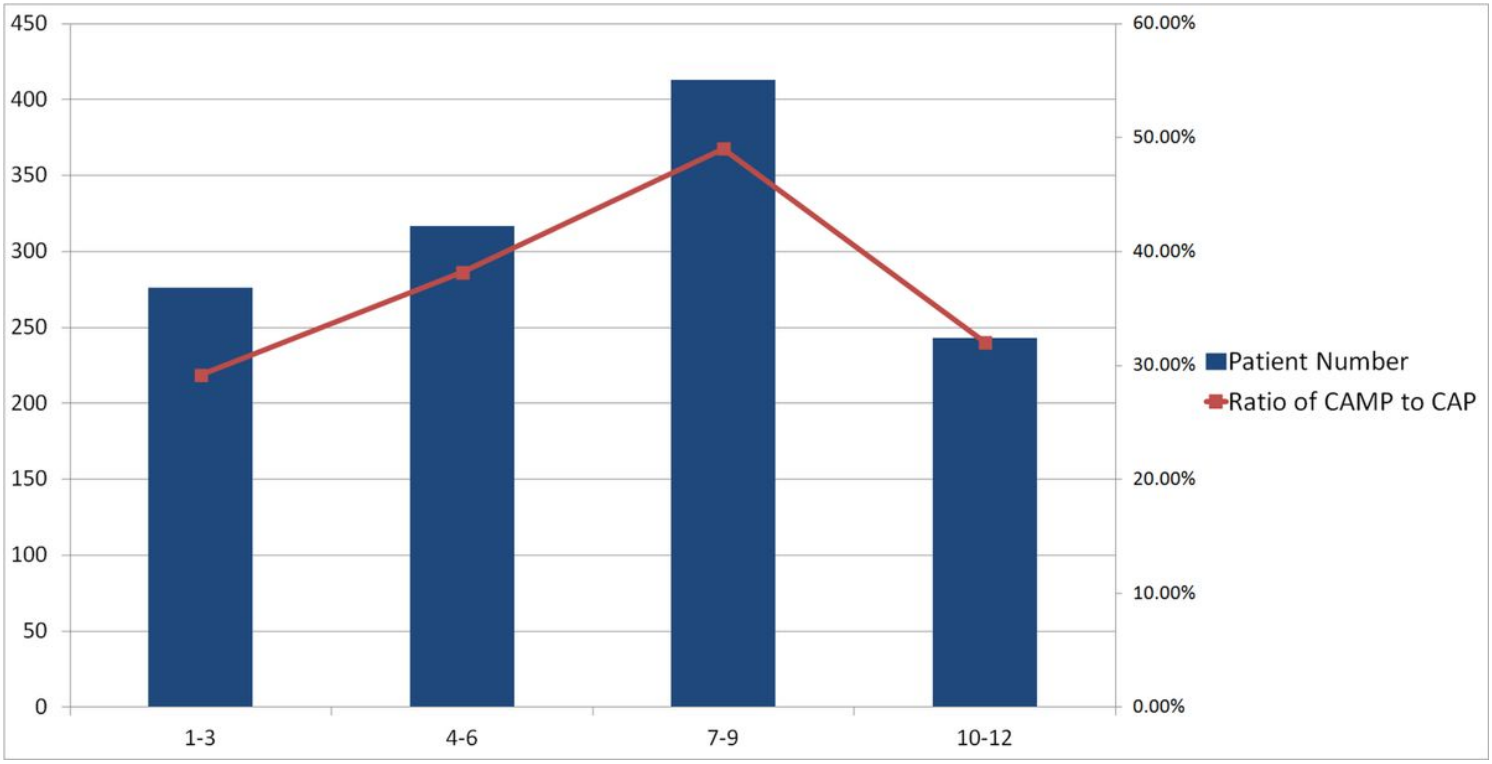

Figure 2

Month distribution of children with CAMP and the ratio of CAMP to CAP during 2016 in Children's Hospital of Nanjing Medical University. The bar chart shows the number of children with CAMP. The line chart shows the ratio of CAMP to CAP.