Contents lists available at ScienceDirect

# Virologica Sinica

journal homepage: www.keaipublishing.com/en/journals/virologica-sinica www.virosin.org

**Research Article** 

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OBAL IMPAC

# Epidemiological characteristics and disease burden of infectious mononucleosis in hospitalized children in China: A nationwide retrospective study

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ARTICLE INFO

Keywords: Epstein-Barr virus (EBV) Infectious mononucleosis (IM) Children Epidemiological characteristics Disease burden

## ABSTRACT

Epstein-Barr virus (EBV) is very common, with the infection rate in adults over 90% worldwide. Infectious mononucleosis (IM) is caused by primary infection with EBV. Most IM patients are generally considered to have a favorable prognosis, but a few patients will also develop complications. Children with severe symptoms will require hospitalization. However, the disease burden of children hospitalized with IM in China has been rarely described. In this study, we included the Face sheets of discharge medical records from 27 member children's hospitals of Futang Research Center of Pediatric Development from Jan 1st, 2016 to Dec 31st, 2020, and medical information such as gender, age, region, time of admission, length of stay and expenditure were extracted. There were 24,120 IM cases, which accounted for 0.42% (24,120/5,693,262) of all hospitalized cases during this period. The ratio of male to female was 1.48:1. Hospitalization for IM in the 4–6 years age group was the highest among inpatients of all age groups. Case numbers increased year by year between 2016 and 2020, and the monthly hospitalization was generally high from Jul to Sep but reduced from Jan to Feb per year. Bronchitis/pneumonia and hepatic dysfunction were two common complications in hospitalized IM patients. The median length of stay was 8 days, and the median cost of hospitalization was 970.59 US dollars. This study will help understand the epidemiological characteristics and disease burden of hospitalized children with IM in China.

### 1. Introduction

Epstein-Barr virus (EBV) is a virus with envelope and double-stranded DNA. It is a human lymphotropic herpes virus, belonging to the family *Herpesviridae*, genus *Lymphocryptovirus*,  $\gamma$ -subfamily (Odumade et al., 2011). In 1968, EBV was confirmed to be associated with infectious mononucleosis (IM) (Shurin, 1979). EBV is mainly transmitted through saliva, blood transfusion, and organ transplantation (Dunmire et al., 2015, 2018; Lennon et al., 2015). After being infected with EBV, the individual becomes a lifelong carrier of this virus. The latent virus in the pharynx can be reactivated and excreted. Thus, the long-term carrier serves as an important source of infection. EBV infection is very common in the general population, with a high infection rate worldwide

(Odumade et al., 2011). Antibodies against EBV can be found in more than 90% of adults (Klutts et al., 2009). Primary EBV infection can lead to IM, as well as some serious non-neoplastic diseases that can seriously affect the health and quality of life of the children, such as chronic active EBV infection (Kimura and Cohen, 2017) and EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) (Ishii, 2016). In addition, EBV infection is also closely associated with various tumors, including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma, EBV-associated gastric carcinoma, and a variety of malignant tumors in patients with either congenital or acquired immunodeficiency (Dunmire et al., 2015).

IM is a clinical syndrome caused by primary EBV infection, which is characterized by a long incubation period of six weeks (Dunmire et al.,

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https://doi.org/10.1016/j.virs.2022.07.007

Received 15 February 2022; Accepted 7 July 2022 Available online 12 July 2022

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2018). Laboratory examination shows an increase in peripheral blood lymphocytes and atypical lymphocytes (Fernbach and Starling, 1972; Naughton et al., 2021). In children, the typical clinical manifestations of IM are the classic triad consisting of fever, pharyngitis, and lymphadenopathy, sometimes accompanied by edema of eyelids, hepatosplenomegaly, liver dysfunction (Gao et al., 2011; Hu et al., 2021). Adult IM patients may present with a sore throat, lymphadenopathy, and fatigue (Gao et al., 2011; Dunmire et al., 2015).

In developed countries, IM mainly occurs in adolescents and young adults. Primary EBV infection in children under 6 years (y) old is mostly asymptomatic or only presents non-specific manifestations such as upper respiratory symptoms. Data from a prospective study at the University of Minnesota showed that 74% of college students aged 18–22 who were experiencing EBV infection were considered IM patients (Dunmire et al., 2015). However, as a developing country, a high incidence of IM in China was found in the preschoolers, among which children aged 4–6 years reach the peak (Hu et al., 2021).

IM is a benign self-limiting disease with a favorable prognosis in most cases, while some patients may be complicated with pneumonia, encephalitis, and myocarditis, and a few may present severe complications such as HLH (Fernbach and Starling, 1972; Ishii, 2016). There are few multicenter studies on the clinical, epidemiological characteristics, and disease burden of childhood IM in China. Due to the application of the hospitals' electronic medical record management system, the medical data generated during the hospitalization of patients can be summarized into a Face sheet of discharge medical records (FSMRs) (Feng et al., 2019). Based on China's national pediatric patient medical record database, FSMRs of 5,693,262 inpatients from 27 tertiary children's hospitals from Jan 1st, 2016 to Dec 31st, 2020 were included, and we extracted relevant information for retrospective analysis. We aimed to summarize and provide relevant data on the clinical epidemiology and disease burden of IM in hospitalized children in China and provide a useful reference to clinicians.

#### 2. Materials and methods

## 2.1. Data sources

Futang Research Center of Pediatric Development (FRCPD) is the first non-profit social service organization established in China to care for children's life and health and engage in children's development research (Feng et al., 2019). The center currently consists of 47 provincial and municipal medical institutions and has established a nationwide children's health service network (Guo et al., 2021). In Dec 2015, FRCPD began to collect the data on FSMRs from its member hospitals. In 2020, FRCPD developed a system for reporting and aggregating FSMRs' data, with dedicated staff organizing and reviewing the uploaded data. It has realized data sharing among member hospitals, improved data utilization efficiency, and promoted all hospitals' common development and cooperation in FRCPD. The National Center for Children's Health (Beijing), Beijing Children's Hospital, Capital Medical University collected the data on the hospitalized children's medical records from Jan 1st, 2016, to Dec 31st, 2020, in 27 tertiary children's hospitals under the FRCPD, to form the FUTang Updating medical REcords (FUTURE) database.

## 2.2. Research design

We designed this study to collect basic medical information of children hospitalized with IM in the FUTURE database from 2016 to 2020, and we extracted information from the system based on the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) code for children hospitalized with IM diagnosis. In detail, we extracted relevant medical information such as gender, age, time of hospitalization, admission diagnosis, complications, and hospitalization expenditure for analysis. The demographic information is displayed in Table 1. Twenty-seven hospitals were divided into

#### Table 1

Demographic information of children hospitalized with IM between Jan 1st, 2016, and Dec 31st, 2020.

Categories	Hospitalization (%, n)			
No. Patients	24,120			
Gender				
Male	59.64% (14,386)			
Female	40.36% (9734)			
Age (Years, y)				
0-1 y	0.47% (114)			
1–3 у	41.75% (10,070)			
4–6 y	38.45% (9274)			
7–12 у	17.89% (4315)			
13–18 у	1.44% (347)			
Area				
Northeast China	3.45% (831)			
North China	18.23% (4397)			
Northwest China	13.91% (3354)			
Central China	17.52% (4227)			
East China	34.1% (8226)			
South China	5.32% (1284)			
Southwest China	7.47% (1801)			
Year of Hospitalization				
2016	14.65% (3534)			
2017	16.1% (3884)			
2018	19.74% (4761)			
2019	25.48% (6145)			
2020	24.03% (5796)			
Residence				
Rural	30.1% (7260)			
Urban	69.9% (16,860)			
LOS (Lenth of stay, days, median IQR)	8 (6–10)			
Expense (USD, median IQR)	970.59 (715.60–1343.29)			

seven geographic regions according to China's geographic regions, including east China, north China, central China, northwest China, southwest China, south China, and northeast China. The geographic locations of the member hospitals are shown in Table 2. Hospitalized children were divided into five groups according to age, including infant (0-1 y), toddler (1-3 y), preschooler (4-6 y), school-age children (7-12 y), adolescence (13-18 y).

### 2.3. Inclusion and exclusion criteria

This retrospective study collected basic medical information from the FUTURE database for all children hospitalized with IM based on ICD-10 codes as selection criteria. The clinical manifestations and laboratory tests of these 24,120 children met the proposed diagnostic criteria for IM (Subspecialty Group of Infectious Diseases and Children, 2016; Xie et al., 2018), and the complications were defined as reported previously (Fernbach and Starling, 1972; Jenson, 2000; Hu et al., 2021). When the aspartate aminotransferase (AST) or alanine aminotransferase (ALT) is elevated two or more times the upper limit of reference, without other causes of elevated AST or ALT, it can be diagnosed that the existence of IM is complicated by hepatic dysfunction. Data of children who had unclear gender, ethnicity, and disease burden were excluded. Patients aged >18 years who belonged to general hospitals with adult departments were excluded.

#### 2.4. Statistical analysis

The number of children hospitalized due to IM was presented in absolute percentages. Categorical variables such as gender, age, regional, year distribution, and the complication grouping were described in absolute percentages. The length of stay (LOS) and expenditure were presented in the median and interquartile range (IQR) to assess the major and discrete trends in the data. The chi-square test or Fisher exact test compared the percentages between groups for unordered categorical variables. For non–normally distributed and ordered categorical data, the nonparametric Wilcoxon test or Kruskal-Wallis test was conducted for the

#### Table 2

The geographic distribution and hose	spitalizati	on of 27	children's	hospitals in the
FUTang Updating medical REcords	(FUTURE	) databa	se.	

Region	Hospitals in FUTURE database	Cases (n)
Northeast		831
Ginna	Changchun Children's Hospital	71
	Liaoning Children's Hospital	307
	Dalian Women and Children's Medical Group	453
North China	· · · · · · · · · · · · · · · · · · ·	4397
	Beijing Children's Hospital, Capital Medical University	1054
	Children's Hospital of Hebei Province	1165
	Baoding Children's Hospital	897
	Inner Mongolia Maternity and Child Health Care Hospital	183
	Children's Hospital of Shanxi	1098
Northwest		3354
China		
	Urumqi Children's Hospital	394
	Xi'an Children's Hospital	2682
	Qinghai Province Women and Children's Hospital	10
	Gansu Provincial Maternity and Child-care Hospital	268
Central China		4227
	Henan Children's Hospital	1172
	Hunan Children's Hospital	1553
	Wuhan Children's Hospital, Tongji Medical College,	1502
	Huazhong University of Science & Technology	
East China		8226
	Children's Hospital Affiliated to Shandong University	787
	Women and Children Hospital in Liaocheng	566
	Children's Hospital of Nanjing Medical University	2432
	Children's Hospital of Soochow University	1159
	Hangzhou Children's Hospital	702
	Fuzhou Children's Hospital of Fujian Province	173
	Anhui Provincial Children's Hospital	1260
	Jiangxi Provincial Children's Hospital	1147
South China		1284
	Liuzhou Maternity and Child HealthCare Hospital	5
0 11	Shenzhen Children's Hospital	1279
Southwest		1801
China		407
	Guiyang Children's Hospital	487
	Kunming Unildren's Hospital	1314

group comparison. All statistical data were analyzed using SPSS 19.0 software (SPSS Inc., USA). *P*-value < 0.05 was considered statistically significant.

## 3. Results

## 3.1. Demographics

Based on ICD-10 disease codes, we collected information of 24,120 hospitalized children diagnosed with IM among 27 hospitals, from Jan 1st, 2016, to Dec 31st, 2020, under the FUTURE database (Table 1). From 2016 to 2020, 24,120 children were hospitalized with IM, accounting for 0.42% (24,120/5,693,262) of all hospitalized cases. Among these children, males accounted for 59.64% (14,386 cases), females accounted for 40.36% (9734 cases), and the male to female ratio was 1.48 (Table 1). The proportions of males were more than that of females in different regions, age groups, admission years, and residence (Fig. 1A-D). In all IM hospitalized cases, the children aged 1-3 years old accounted for 41.75% (10,070 cases), followed by 4-6 years old, 7-12 years old, 13-18 years old, and 0-1 year old, accounted for 38.45% (9274 cases), 17.89% (4315 cases), 1.44% (347 cases), and 0.47% (114 cases), respectively; in terms of the regional distribution, the number of hospital admissions for children in east China was the largest, accounting for 34.1% (8226 cases), then, number of admissions in north China ranked second, accounting for 18.23% (4397 cases), followed by central China, northwest China, southwest China, south China, and northeast China, with proportions of 17.52% (4227 cases), 13.91% (3354 cases), 7.47% (1801 cases), 5.32%

(1284 cases), and 3.45% (831 cases), respectively (Table 1). The number of annual hospitalizations due to IM increased year by year, among which the number of admissions in 2019 was the largest with a proportion of 25.48% (6145 cases), and that number in 2020 slightly decreased when compared with that in the previous year. Hospitalized children with IM living in urban and rural areas accounted for 69.9% (16,860 cases) and 30.1% (7260 cases), respectively. The median LOS for hospitalized IM patients was 8 d (IQR 6–10), and the median expense was 970.59 USD (IQR 715.60–1343.29) from 2016 to 2020.

## 3.2. Ratios of IM hospitalizations by region, age, year, and residence

We analyzed the ratios of IM hospitalization to total hospitalization within the corresponding groups in different regions and age groups. As shown in Fig. 2, the highest and lowest ratios of IM hospitalization were found in north China (0.53%, 4397/825,410) and south China (0.30%, 1284/421,288), respectively, and the ratios of east China (0.44%, 8226/ 1,890,164), northwest China (0.43%, 3354/772,883), southwest China (0.41%, 1801/439,962), central China (0.39%, 4227/1,095,411), and northeast China (0.33%, 831/248,144) were similar (Fig. 2A); In different age groups, the highest ratio of 0.85% (9274/1,096,791) was observed in children aged 4–6 v. followed by 1–3 v. 7–12 v. 13–18 v. 0–1 y, with 0.45% (10,070/2,239,404), 0.42% (4315/1,028,939), 0.19% (347/180,665), 0.01% (114/1,147,463), respectively (Fig. 2B). Meanwhile, we found that the ratio of hospitalizations for IM increased year by year between 2016 and 2020, from 0.35% (3534/1,017,037) in 2016 to 0.58% (5796/1,005,594) in 2020 (Fig. 2C). IM hospitalization ratios for rural and urban children were 0.37% (7260/1,978,443) and 0.45% (16,860/3,714,819), respectively (Fig. 2D).

#### 3.3. Seasonality of hospitalization with IM

Based on the data in our study, the admission time of children with IM may be seasonal to some extent (Fig. 3). The hospitalization peaked from Jul to Sep each year, gradually decreased month by month, dropped to the minimum between Dec and Feb, and gradually increased again until reaching a peak in Jul to Sep of the year (Fig. 3).

#### 3.4. Complications

Among those who were admitted to the hospital with the diagnosis of IM, 29.56% (7130/24,120) had no complications, whereas 70.44% (16,990/24,120) had (Fig. 4). We ranked the children according to the proportion of complications, enumerated the complications ranked top five, and defined the other associated complications as "Others" (mainly including neutropenia, thrombocytopenia, sepsis.) with a percentage of 28.71% (6925/24,120, Fig. 4). The largest proportion of children with bronchitis/pneumonia was found, which accounted for 21.9% (5282/ 24,120) of the total, and the second was hepatic dysfunction with 17.49% (4218/24,120). Myocardial damage, anemia, and encephalitis were miserly 1.61% (388/24,120), 0.57% (138/24,120), and 0.16% (39/24,120) of the total, respectively. Statistical analysis shows differences in the composition of complications across age groups. Bronchitis/ Pneumonia was the main complication in hospitalized IM patients aged under 6-year-old, while hepatic dysfunction was dominant in inpatients over 7-year-old (Supplementary Table S1).

#### 3.5. LOS and hospitalization expense

We conducted statistical analysis on the data of LOS and hospitalization cost of the IM children (Table 3), and found that the median LOS was 8 d (IQR 6–10) and the median hospitalization cost was 970.59 USD (IQR 715.60–1343.29). According to the classification, we found differences in LOS and costs between gender, age groups, regions, and admission years (P < 0.05). In detail, the median LOS in males was shorter than in females (Z = 3.270, P = 0.001), and the LOS in the 7–12 y



Fig. 1. Gender proportion of hospitalized children with IM in different areas (A), age groups (B), years of admission (C), and residence (D).



Fig. 2. The ratio of IM hospitalizations to total hospitalizations in different regions of China (A), age groups (B), years (C), and residence (D). Statistical analyses were performed using the chi-square test or Fisher exact test. A *P*-value < 0.05 was considered statistically significant.



Fig. 3. Monthly cases of children hospitalized for IM from Jan 1st, 2016, to Dec 31st, 2020.

was longer than that in the 4–6 y age group (Z = 3.170, P = 0.023), and the 4–6 y age group was longer than the 1–3 y (Z = 3.999, P = 0.001). LOS in children admitted to hospitals in east China was the longest. In terms of hospitalization cost, the median hospitalization expenses were 1183.91 USD (IQR 874.59–1643.43) and 1197.17 USD (IQR 880.11–1649.54) for males and females, respectively, without statistical significance (Z = 1.029, P = 0.303). The highest median expense was found in the 13–18 y age group, with discrepancies in hospitalization costs (Z = 200.487, P < 0.001). We observed that in South China, the LOS of children was the shortest (Z = 18.53, P < 0.001), and the expense was the lowest (Z = 18.53, P < 0.001). The LOS and expense in 2016 were the longest (Z = -4.28, P < 0.001) and the highest (Z = -5.664, P < 0.001).

Regarding the relationship between complications and the LOS and cost, we found that the LOS without complications was shorter, and the cost was less than that with complications (Fig. 5). The LOS of children with hepatic dysfunction and encephalitis was the longest, and the LOS and cost of children with hepatic dysfunction were higher than those of children with encephalitis (Z = 3.449, P = 0.011), while there was no statistical significance in LOS and expense among other groups (P > 0.05).

#### 3.6. Death cases

Among the 24,120 IM children included in our study, six patients died during hospitalization, accounting for 0.02% (6/24,120, Table 4). Among them, four were male, two were female, the oldest was 14 years old, and the rest were all under 6 years old; half patients were from East China, and the other half were from Northwest China. HLH occurred in four children between 2 and 6 years old.

#### 4. Discussion

IM is an acute infectious disease caused by primary EBV infection, usually is benign and self-limited. In this study, we summarized and analyzed the FSMRs information data of 24,120 hospitalized children with IM from 2016 to 2020 in China.

Our results indicate that the ratio of male to female is 1.48:1, with no preference by region, age, or year of hospitalization, which is consistent with the previous results reported in some literature. Kiran Devkota et al. reported that the male to female ratio was 1.5:1 among pediatric patients with EBV infection in Hubei, China (Devkota et al., 2018). Hu et al. analyzed the epidemiological characteristics of children hospitalized for IM in Beijing, China, and indicated that the male to female ratio was 1.6:1 (Hu et al., 2021). Keun Hyung Son et al. reported that the male-to-female ratio of hospitalized children with IM in South Korea was 1.53:1 (Son and Shin, 2011). In short, more hospitalized boys with IM were documented than girls.

In terms of the at-risk age of onset, our results showed that children hospitalized for IM were mainly 4-6 years old in China, which was similar to the data analyzed by the single-center study of hospitalized IM children (Gao et al., 2011; Hu et al., 2021). In China and other developing countries of Asia and Africa, most primary EBV infections occur in children, especially preschoolers, who make up a large portion of IM patients (Dunmire et al., 2015; Shi et al., 2022). However, in developed countries, such as Western countries, the peak age of IM is mostly in adolescence and adulthood (Dunmire et al., 2015). For instance, Dunmire et al. suggested that the seroprevalence of EBV was lower in children than in adolescents in the US (Dunmire et al., 2015, 2018). Exposure to EBV-positive saliva is considered the primary transmission route in young children, either through direct contact or food. Children in developing countries acquire EBV infection in the first few years of life, and seroconversion is usually established at 3-4 years of age, whereas infection in developed countries tends to be delayed until adolescence and beyond, which is considered a difference related to the socioeconomic status (Chabay and Preciado, 2013). In addition, based on the FUTURE database, we found that the ratio of IM hospitalization to total



Fig. 4. Distribution of complications in children hospitalized for IM (n = 24,120).

#### Table 3

Basic information on LOS and hospitalization expense by gender, age, region, and admission year.

Categories	LOS (d, Median IQR)	$\chi^2/Z$ value	<i>P</i> -value	Expense (USD, IQR)	$\chi^2/Z$ value	P-value
Gender						
Male	7 (6–10)	3.273	0.001 <sup>a</sup>	1183.91 (874.59–1643.43)	1.029	0.303
Female	8 (6–10)			1197.17 (880.11–1649.54)		
Age						
0–1 y	7 (5–10)	51.580	< 0.001 <sup>b</sup>	1237.42 (798.57–1952.22)	200.487	< 0.001 <sup>c</sup>
1–3 у	7 (6–10)			1149.25 (848.04–1574.73)		
4–6 y	8 (6–10)			1191.10 (883.47–1654.77)		
7–12 y	8 (6–10)			1264.30 (930.57–1778.34)		
13–18 у	8 (6–10)			1456.71 (1037.95-2076.81)		
Region						
Northeast China	8 (6–10)			1039.81 (823.13-1438.77)		
North China	8 (7–10)	2626.443	< 0.001 <sup>d</sup>	1613.03 (1219.62–2064.10)	3985.074	< 0.001 <sup>e</sup>
Northwest China	7 (5–8)			934.97 (688.62–1279.94)		
Central China	7 (6–9)			1042.53 (837.19–1372.43)		
East China	8 (7–10)			1320.07 (997.35-1740.05)		
South China	5 (4–6)			823.78 (661.01-1065.49)		
Southwest China	7 (7–10)			1042.15 (833.52–1349.49)		
Admission Year						
2016	8 (6–10)			991.10 (697.55–1439.38)		
2017	8 (6–10)	170.619	< 0.001 <sup>f</sup>	931.81 (686.81-1325.72)	27.518	< 0.001 <sup>g</sup>
2018	8 (6–10)			984.13 (720.45–1362.99)		
2019	7 (6–9)			964.40 (720.72–1310.93)		
2020	7 (6–9)			980.83 (731.38–1322.25)		

<sup>a</sup> Chi-squared test.

<sup>b</sup> Kruskal-Wallis test, 1–3 y vs. 4–6 y, Z = 3.999, P = 0.001; 4–6 y vs. 7–12 y, Z = 3.170, P = 0.023.

<sup>c</sup> Kruskal-Wallis test, 1–3 y vs. 4–6 y, Z = 6.141, P < 0.001; 4–6 y vs. 7–12 y, Z = 6.752, P < 0.001; 7–12 y vs. 13–18 y, Z = 4.789, P < 0.001.

<sup>d</sup> Kruskal-Wallis test, East China vs. Southwest China, Z = -6.205, P < 0.001; Southwest China vs. Central China, Z = -6.812, P < 0.001; Central China vs. Northwest China, Z = -7.600, P < 0.001; Northwest China vs. South China, Z = 18.530, P < 0.001.

<sup>e</sup> Kruskal-Wallis test, North China vs. Southwest China, Z = -6.205, P < 0.001; Northeast China vs. Central China, Z = -6.812, P < 0.001; Northwest China vs. South China, Z = 0.708, P < 0.001.

<sup>f</sup> Kruskal-Wallis test, 2016 vs. 2017, Z = -5.664, P < 0.001; 2018 vs. 2019, Z = -3.624, P < 0.001.

<sup>g</sup> Kruskal-Wallis test, 2016 vs. 2017, Z = -4.280, P < 0.001; 2018 vs. 2017, Z = 4.120, P < 0.001.

hospitalization in north China was higher than that in other regions, which has not been reported before, and the underlying reasons for the difference were unclear.

Moreover, our data showed that the hospitalization ratio for IM increased between 2016 and 2020, indicating an upward trend in the number of children with clinical symptoms requiring hospitalization after primary EBV infection in China. Although the proportion of hospitalizations due to IM to total hospitalizations had increased over the years, 5796 hospitalizations in 2020 were recorded, showing a 5.68% decrease relative to 2019. This decline may be related to prevention measures such as wearing masks and social distance to prevent the COVID-19 epidemic.

Younger children primarily infected with EBV are mostly asymptomatic, while adolescents and young adults with primary EBV infection are more likely to develop IM (Dunmire et al., 2018). Xiong et al. reported that EBV seropositivity rates dropped among young children in China (Xiong et al., 2014). Other papers described that the EBV seroprevalence of children within the same age group in different regions gradually decreased in recent years to a certain extent (Fourcade et al., 2017; Kuri et al., 2020), which suggested that the age of primary EBV infection may be increasing with an increased number of adolescent IM patients, which may be related to the year-over-year ratio of IM hospitalizations. Our previous serological study based on 733 children undergoing elective surgery found that the age of onset of primary EBV



Fig. 5. LOS and expenses of different complications. A The LOS of different complications; B The expenses of different complications.

 Table 4

 Basic sociodemographic information and disease burden of six dead children hospitalized for IM.

No.	Gender	Age (y)	Region	Admission Time (month, year)	Complication	LOS (d)	Expense (USD)
1	Male	1	East China	Aug 2016	Sepsis	7	6121.96
2	Male	2	Northwest China	May 2017	HLH	18	6505.54
3	Male	3	East China	Dec 2019	HLH	7	4407.16
4	Female	5	East China	Feb 2017	HLH	4	2520.74
5	Male	6	Northwest China	Oct 2020	HLH	6	2974.32
6	Female	14	Northwest China	Apr 2017	Leukemia	4	3036.55

infection was delayed in 2012 compared with that in the 1980s and is still further delayed as economic conditions improved (Liu et al., 2012). More urban residents than rural residents were hospitalized for IM in children, also a higher proportion of urban residents were hospitalized for IM, which may still be caused by the difference in socioeconomic status between urban and rural areas (Gao et al., 2011; Hu et al., 2021). Better medical conditions in the urban set promote more active medical visits, while reduced visit and hospitalization rates are found in rural patients.

We observed that the cases of IM admissions were higher from Jul through Sep and then decreased month by month, reaching a minimum in Feb of the following year, and then it rose again. The data for 2016–2020 were all in line with this trend. A four-year study in Israel revealed that the incidence of IM was highest in summer (Grotto et al., 2003). Moreover, another retrospective study showed that the incidence of IM in Israel peaked in the warm months (Jun–Aug) and then decreased (Levine et al., 2012). However, there have been inconsistent conclusions. A survey result published in 1972 suggested that the high-incidence month of onset of IM in Atlanta, USA was mainly in late winter and early spring (Heath et al., 1972).

Nonetheless, no seasonal pattern was also recognized in children of IM who were under 15 years old in London, UK (Newell, 1957), and another study analyzed IM cases from 1996 to 2001 and found that the temporal distribution of IM showed no obvious seasonality under the age of 15 who were hospitalized with IM (Chan et al., 2003). Due to regional and population differences, reports on the seasonal distribution of IM were inconsistent. We assume that the summer vacation in China from Jul to Sep may contribute to this annual trend, during which children spend a long time with family members. These family members are carriers who had been infected with EBV. In addition, EBV can be reactivated and secreted with saliva at varying times. Thus, children could be infected with EBV by sharing cups or utensils with family members during daily activities. However, there is no clear evidence to prove this hypothesis.

Generally, the prognosis of IM is favorable, and a few patients developed complications. Fernbach et al. pointed out that the complications of IM in children were as follows, encephalitis and neuritis, pneumonia, hepatic dysfunction, myocarditis, thrombocytopenia, and hemolytic anemia, etc. (Fernbach and Starling, 1972; Jenson, 2000). Our data showed that the majority of the hospitalized children with IM had complications, and the more common complications were bronchitis/pneumonia and hepatic dysfunction. The children with bronchitis/pneumonia were mainly in 0–1 y, 1–3 y, and 4–6 y groups, which may be caused by bacterial, viral, and mycoplasma pathogen infection (Jenson, 2000). In addition, children at 0–6 y have a high incidence of pneumonia in China (Oumei et al., 2018), thus the reason for bronchitis/pneumonia complicated with IM cannot be confirmed easily. Hepatic dysfunction is the main complication in 7–12 and 13–18 years old groups and is mostly considered to be reversible and may be only related to the severity of the condition (Fernbach and Starling, 1972; Shurin, 1979).

We analyzed the median LOS and hospitalization costs for IM patients and found that the children without complications had a shorter LOS and a lower expense than those with complications. Among children with complications, the LOS and the expense of children with hepatic dysfunction were the greatest, followed by those of encephalitis, which was consistent with common perception. Our statistics also showed that the LOS was the longest in the over 7-year-old group, and the expenses were the highest. We suppose that this phenomenon may be related to hepatic dysfunction, the most common complication in this age group. Furthermore, we found that children complicated with hepatic dysfunction had the longest LOS and the highest expenses. Additionally, in south China, the LOS was the shortest, and the expense was the lowest. Also, the LOS and the expense in 2016 were the longest and the highest. However, the reason for this finding remains unknown.

EBV-HLH is caused by EBV infection and is the most common type of virus-associated HLH during childhood. Young IM complicated with HLH is mainly associated with primary immunodeficiency, such as X-linked lymphoproliferative disease that affects males (Ishii, 2016; Chinn et al., 2018; Imashuku et al., 2021). In our study, four children died due to HLH. It is more common among Asian populations and has a poor prognosis with a fatality rate of over 50% (Qiang et al., 2012). Although the four IM children with HLH did not have primary immunodeficiency documented in the FSMRs, three of the four were male, and their mean age was 4 years, suggesting that they were likely to suffer from primary immunodeficiency. The other two dead children diagnosed with sepsis and leukemia, respectively, cannot be speculated on the relationship between death and IM.

There are some limitations to this study. 1) The FUTURE Database only contains the data generated from hospitalized children rather than outpatients. As a self-limited disease, IM is mostly treated in outpatient clinics. Thus our report only represents real data from some inpatients in China. 2) Since the FSMRs only have the basic medical information of hospitalized children, we fail to obtain more comprehensive data on clinical information and laboratory test results. 3) There was no followup to assess long-term outcomes.

## 5. Conclusions

In this study, we investigated 24,120 children cases with IM, which accounted for 0.42% (24,120/5,693,262) of all hospitalized cases from 2016 to 2020. The annual ratio of hospitalization for IM increased year by year. Hospitalizations for IM were higher among children aged 4–6 years across age groups. Most IM patients had complications, of which bronchitis/pneumonia and hepatic dysfunction were the main complications in hospitalized IM patients under 6 years and over 7 years, respectively. The median LOS of IM was about 8 d, and the hospitalization expenditure was 970.59 USD. Meanwhile, LOS and expenditure for hospitalization were closely associated with complications. These will help understand better the epidemiological feature of IM in China. The data are beneficial for developing targeted strategies related to monitoring and optimizing the allocation of medical resources.

## Data availability

The original data presented in the study are included in the article/ supplementary material, further inquiries can be directed to the corresponding authors.

## Ethics statement

The study is approved by the Ethics Committee of Beijing Children's Hospital of Capital Medical University ([2021]-E-208-R). Since this study does not involve the privacy of personal information such as names and addresses of children and only retrospectively collected indicators related to epidemiological analysis and conducted data analysis, patients' informed consent is waived. Our research data is completely anonymous and does not involve patient privacy.

#### Author contributions

Mengjia Liu: formal analysis, investigation, and writing-original draft. Xinyu Wang: data curation, methodology, writing-original draft. Linlin Zhang: data analysis and reviewing and editing. Guoshuang Feng: data curation and methodology. Yueping Zeng: data curation. Ran Wang: methodology, supervision, reviewing, and editing. Zhengde Xie: project administration, conceptualization, funding acquisition, supervision, reviewing, and editing.

## **Conflict of interest**

The authors declare that they have no conflict of interest.

## Acknowledgments

RW was supported by the National Natural Science Foundation of China (82002130); ZX was supported by the CAMS Innovation Fund for Medical Sciences (2019-I2M-5-026). We are grateful to investigators from members of the Futang Research Center of Pediatric Development (FRCPD).

# Appendix A. Supplementary data

Supplementary data to this article can be found online at https://do i.org/10.1016/j.virs.2022.07.007.

#### References

- Chabay, P.A., Preciado, M.V., 2013. EBV primary infection in childhood and its relation to B-cell lymphoma development: a mini-review from a developing region. Int. J. Cancer 133, 1286–1292.
- Chan, C.W., Chiang, A.K., Chan, K.H., Lau, A.S., 2003. Epstein-Barr virus-associated infectious mononucleosis in Chinese children. Pediatr. Infect. Dis. J. 22, 974–978.
- Chinn, I.K., Eckstein, O.S., Peckham-Gregory, E.C., Goldberg, B.R., Forbes, L.R., Nicholas, S.K., Mace, E.M., Vogel, T.P., Abhyankar, H.A., Diaz, M.I., Heslop, H.E., Krance, R.A., Martinez, C.A., Nguyen, T.C., Bashir, D.A., Goldman, J.R., Stray-Pedersen, A., Pedroza, L.A., Poli, M.C., Aldave-Becerra, J.C., McGhee, S.A., Al-Herz, W., Chamdin, A., Coban-Akdemir, Z.H., Jhangiani, S.N., Muzny, D.M., Cao, T.N., Hong, D.N., Gibbs, R.A., Lupski, J.R., Orange, J.S., McClain, K.L., Allen, C.E., 2018. Genetic and mechanistic diversity in pediatric hemophagocytic lymphohistiocytosis. Blood 132, 89–100.
- Devkota, K., He, M., Liu, M.Y., Li, Y., Zhang, Y.W., 2018. Increasing Epstein-Barr virus infection in Chinese children: a single institutional based retrospective study. F1000Res 7, 1211.
- Dunmire, S.K., Hogquist, K.A., Balfour, H.H., 2015. Infectious mononucleosis. Curr. Top. Microbiol. Immunol. 390, 211–240.
- Dunmire, S.K., Verghese, P.S., Balfour Jr., H.H., 2018. Primary Epstein-Barr virus infection. J. Clin. Virol. 102, 84–92.
- Feng, G., Zeng, Y., Tian, J., Wang, X., Tai, J., Song, F., Zhang, X., Xu, X., Chen, J., Shi, T., Ni, X., Futang Research Center of Pediatric, D., 2019. Disease spectrum analysis of hospitalized children in China: a study of 18 tertiary children's hospitals. Pediatr Investig 3, 159–164.
- Fernbach, D.J., Starling, K.A., 1972. Infectious mononucleosis. Pediatr. Clin. 19, 957–968.
  Fourcade, G., Germi, R., Guerber, F., Lupo, J., Baccard, M., Seigneurin, A., Semenova, T.,
  Morand, P., Epaulard, O., 2017. Evolution of EBV seroprevalence and primary
  infection age in a French hospital and a city laboratory network, 2000-2016. PLoS
  One 12, e0175574.
- Gao, L.W., Xie, Z.D., Liu, Y.Y., Wang, Y., Shen, K.L., 2011. Epidemiologic and clinical characteristics of infectious mononucleosis associated with Epstein-Barr virus infection in children in Beijing, China. World J Pediatr 7, 45–49.
- Grotto, I., Mimouni, D., Huerta, M., Mimouni, M., Cohen, D., Robin, G., Pitlik, S., Green, M.S., 2003. Clinical and laboratory presentation of EBV positive infectious mononucleosis in young adults. Epidemiol. Infect. 131, 683–689.
- Guo, K., Wang, X.Y., Feng, G.S., Tian, J., Zeng, Y.P., Ma, S.X., Ni, X., Futang Research Center of Pediatric, D., 2021. The epidemiology of blood transfusion in hospitalized children: a national cross-sectional study in China. Transl. Pediatr. 10, 1055–1062.
- Heath Jr., C.W., Brodsky, A.L., Potolsky, A.I., 1972. Infectious mononucleosis in a general population. Am. J. Epidemiol. 95, 46–52.
- Hu, H., Deng, H., Bi, J., Xu, Y., Li, S., Xie, Y., Sun, X., Wang, D., Li, X., Ouyang, W., Hu, B., Zhang, Y., Tang, H., Fang, C., Zhang, H., Guo, L., Wang, C., Wang, T., Yang, F., Jiang, T., Xie, Z., Liu, G., 2021. Clinical characteristics and effectiveness of antiviral agents in hospitalized children with infectious mononucleosis in China: a multicenter retrospective study. Pediatr Investig 5, 188–194.
- Imashuku, S., Morimoto, A., Ishii, E., 2021. Virus-triggered secondary hemophagocytic lymphohisticytosis. Acta Paediatr. 110, 2729–2736.
- Ishii, E., 2016. Hemophagocytic lymphohistiocytosis in children: pathogenesis and treatment. Front Pediatr 4, 47.
- Jenson, H.B., 2000. Acute complications of Epstein-Barr virus infectious mononucleosis. Curr. Opin. Pediatr. 12, 263–268.
- Kimura, H., Cohen, J.I., 2017. Chronic active epstein-barr virus disease. Front. Immunol. 8, 1867.
- Klutts, J.S., Ford, B.A., Perez, N.R., Gronowski, A.M., 2009. Evidence-based approach for interpretation of Epstein-Barr virus serological patterns. J. Clin. Microbiol. 47, 3204–3210.
- Kuri, A., Jacobs, B.M., Vickaryous, N., Pakpoor, J., Middeldorp, J., Giovannoni, G., Dobson, R., 2020. Epidemiology of Epstein-Barr virus infection and infectious mononucleosis in the United Kingdom. BMC Publ. Health 20, 912.
- Lennon, P., Crotty, M., Fenton, J.E., 2015. Infectious mononucleosis. BMJ 350, h1825.
- Levine, H., Mimouni, D., Grotto, I., Zahavi, A., Ankol, O., Huerta-Hartal, M., 2012. Secular and seasonal trends of infectious mononucleosis among young adults in Israel: 1978-2009. Eur. J. Clin. Microbiol. Infect. Dis. 31, 757–760.
- Liu, Y., Yan, J., Guan, X., Ai, J., Xie, Z., 2012. Serological epidemiology investigation of Epstein-barr virus infection based on 733 children to be operated (in Chinese). Chin. J. Evid. Based Pediatr. 7, 450–453.
- Naughton, P., Healy, M., Enright, F., Lucey, B., 2021. Infectious Mononucleosis: diagnosis and clinical interpretation. Br. J. Biomed. Sci. 78, 107–116.
- Newell, K.W., 1957. The reported incidence of glandular fever; an analysis of a report of the public health laboratory service. J. Clin. Pathol. 10, 20–22.
- Odumade, O.A., Hogquist, K.A., Balfour Jr., H.H., 2011. Progress and problems in understanding and managing primary Epstein-Barr virus infections. Clin. Microbiol. Rev. 24, 193–209.
- Oumei, H., Xuefeng, W., Jianping, L., Kunling, S., Rong, M., Zhenze, C., Li, D., Huimin, Y., Lining, W., Zhaolan, L., Xinmin, L., Hua, X., Zhiyan, J., Yanning, L., Yan, H., Baoqing, Z., Xiaochun, F., Chunhui, H., Yonghong, J., Xue, Z., Wei, W., Zi, W., 2018. Etiology of community-acquired pneumonia in 1500 hospitalized children. J. Med. Virol. 90, 421–428.
- Qiang, Q., Zhengde, X., Shuang, Y., Kunling, S., 2012. Prevalence of coinfection in children with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. J. Pediatr. Hematol. Oncol. 34, e45–48.
- Shi, T., Huang, L., Tian, J., 2022. Prevalence of Epstein-Barr Viral DNA among children at a single hospital in Suzhou, China. J. Pediatr. 98, 142–146.
- Shurin, S.B., 1979. Infectious mononucleosis. Pediatr. Clin. 26, 315-326.

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 Son, K.H., Shin, M.Y., 2011. Clinical features of Epstein-Barr virus-associated infectious mononucleosis in hospitalized Korean children. Korean J Pediatr 54, 409–413.
 Subspecialty Group of Infectious Diseases tSoP, Chinese Medical Association, Children NGoE-BVADi, 2016. Principle suggestions for diagnosis and treatment of main

- nontumorous Epstein-Barr virus-associated diseases in children (in Chinese). Chinese Journal of Pediatrics 54, 563–568.
- Xie, Z., Liu, C., Ai, J., 2018. Expert consensus on laboratory diagnosis and clinical application of Epstein-Barr virus infection (in Chinese). Chin. J. Exp. Clin. Virol. 32, 2–8.
- Xiong, G., Zhang, B., Huang, M.Y., Zhou, H., Chen, L.Z., Feng, Q.S., Luo, X., Lin, H.J., Zeng, Y.X., 2014. Epstein-Barr virus (EBV) infection in Chinese children: a retrospective study of age-specific prevalence. PLoS One 9, e99857.