# Fever in childhood Infectious Mononucleosis

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## Abstract

Fever is one of the oldest clinical indicators of disease and one of the most common reasons for medical attention worldwide especially in children. The febrile response is a significant contributor to the pathogenesis, clinical presentation and outcome of many diseases. Infectious Mononucleosis, which is the most common clinical manifestation caused by EBV infection, usually begins insidiously, with vague malaise, followed by fever, sore throat, swollen posterior cervical lymph nodes and fatigue. Of the 107 children with Infectious Mononucleosis enrolled in the study 97% had fever. Fever was the first symptom in 84% of those. 29% of children experienced high levels of fever >40**°**C. There was an association statistically significant between the duration of fever: levels of lymphocytes, levels of alanine aminotransferase, and levels of anxiety. As a conclusion it can be stated that fever is the most common symptom in children with Infectious Mononucleosis. Compared to older children, infants and young children experience higher and more prolonged fevers, more rapid temperature increases, and greater temperature fluctuations. The duration of fever in Infectious Mononucleosis is much longer than in most other viral infections of childhood. The potent innate and adaptive immune response, which occurs during primary EBV infection controls infection and is responsible for the most symptoms and signs of the disease including fever.

**Keywords:** Fever, Children, Infectious Mononucleosis, duration of fever, lymphocytes

## 1. Introduction

Fever is one of the oldest clinical indicators of disease in the mammalian host as well as one of the most common reasons for medical attention worldwide especially in children [22], [23]. The definition of fever is a regulated rise in body temperature above normal daily fluctuations occurring in conjunction with an elevated thermoregulatory set point [22], [23], [6], [35], [20]. Apart from a regulated rise in body temperature, fever is also accompanied by various sickness behavior, changes in metabolic and physiological characteristics of body systems and alterations in immune responses [23], [6]. The febrile response, therefore, remains a significant contributor to the pathogenesis, clinical presentation and outcome of many illnesses and diseases. Based on guidelines for management of febrile illnesses provided by authorities such as World Health Organization (WHO) and the Society of Critical Care Medicine and the Infectious Disease Society of America (IDSA), among others, equivalent rectal temperature of ≥38 °C (100.4 °F) or axillary temperatures of ≥ 37.5 °C (99.5 °F) are indicative of fever in both adults and children [37], [38], [26], [1], [11]. Fever is recognized an ancient adaptive compensatory defense mechanism leading to immune activation, decrease in bacterial and viral growth rate, and improve host survival in response

to invasion by foreign antigens [24]. It has been suggested that fever is necessary for evolutionary survival of species by accelerating the recovery of infected individuals with localized or mild to moderately severe systemic infections while hastening the demise of hopelessly infected individuals, who pose a threat of epidemic disease to the species [24], [8]. The raised temperature may provide protection by several mechanisms. Firstly, human infective pathogens often demonstrate optimal replication at temperatures below 37 °C; thus an elevated host temperature inhibits reproduction [21]. Secondly, increasing the temperature in vitro from 35 °C to 41.5 °C increases the antimicrobial activity of many classes of antibiotics [34]. Thirdly, a rise in temperature may also be associated with an increase in innate immunity associated with microbial destruction [28]. Interestingly, at temperatures above around 40 °C there is a further mortality increase, suggesting that at this stage the deleterious effects of hyperthermia on organ and cellular function outweigh any benefit conferred from hyperpyrexia in acute sepsis [26], [1].

## 2. Aim

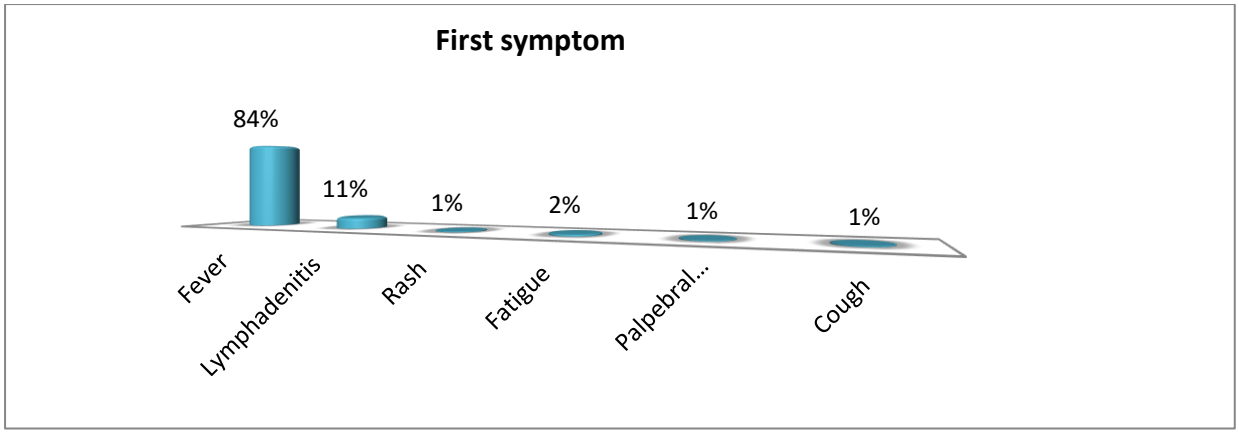
Fever is the most common symptom and the one which characterized childhood Infectious Mononucleosis. So a study was conducted to describe the characteristics of fever in children hospitalized with Infectious Mononucleosis.

## 3. Method & Material

This is a retrospective, descriptive and analytic study. In the study were enrolled 107 children aged 0-14years, diagnosed with Infectious Mononucleosis, hospitalized in Pediatric Infectious Disease Ward in the University Hospital Center of Tirana “Mother Teresa” Albania during a five-year period 2010-2014. The diagnosis was made based on detection of early immunoglobulin M antibody to EBV viral capsid antigen anti EBV VCA IgM. Information was extracted from medical records. The parameters studied were; age, symptoms and clinical signs, clinical course and outcome. Fever was divided in three groups according to its levels; < 38.5°C, 38.5°C - 40°C, > 40°C. The patients were divided in three age-groups; 0-2years, 2-6years, 6-14years. In the Hepatitis group were included all children with elevated alanine aminotransferase levels (ALT) > 45IU/L. Anxiety was identified by State Trait Anxiety of Children STAIC for self report of anxiety of the child. STAIC contains 20 situations which define how the child feels in general. The answers to this situations are built according to Likert scale which has three options: never, sometimes, often.

## 4. Results

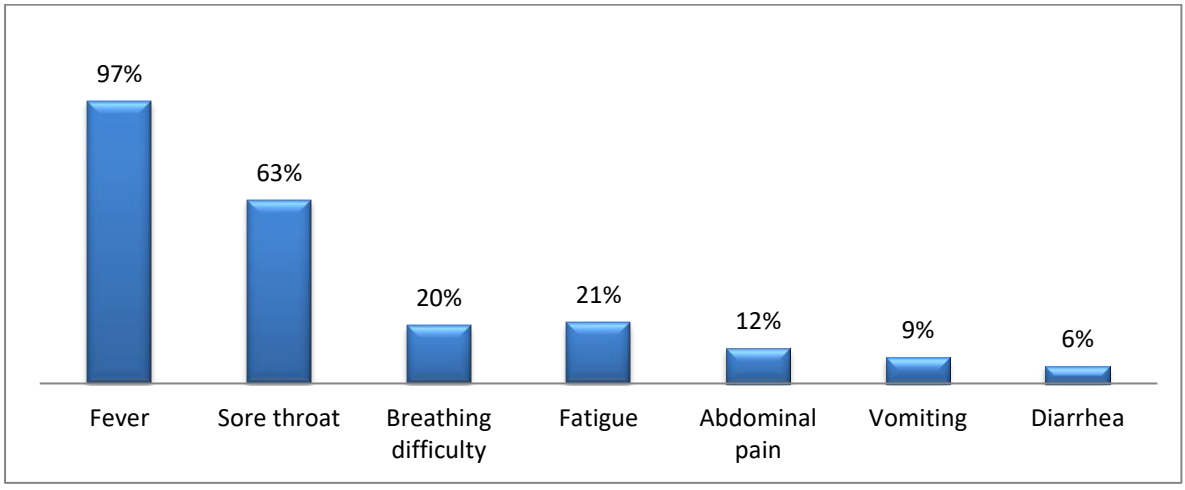
Fever was the first symptom in 84% of children followed by lymphadenitis in 11% , fatigue in 2% and rash, palpebral edema and cough in 1% of children respectively.



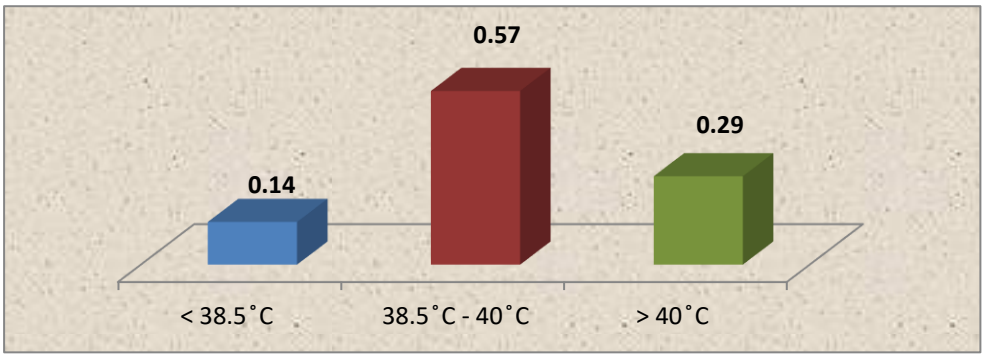

**First symptom**

| | Frequency | Percent | Valid Percent | Cumulative Percent |
|---|---|---|---|---|
| palpebral edema | 1 | ,9 | ,9 | ,9 |
| rash | 1 | ,9 | ,9 | 1,9 |
| cough | 1 | ,9 | ,9 | 2,8 |
| lymphadenitis | 12 | 11,2 | 11,2 | 14,0 |
| fatigue | 2 | 1,9 | 1,9 | 15,9 |
| fever | 90 | 84,1 | 84,1 | 100,0 |
| Total | 107 | 100,0 | 100,0 | |

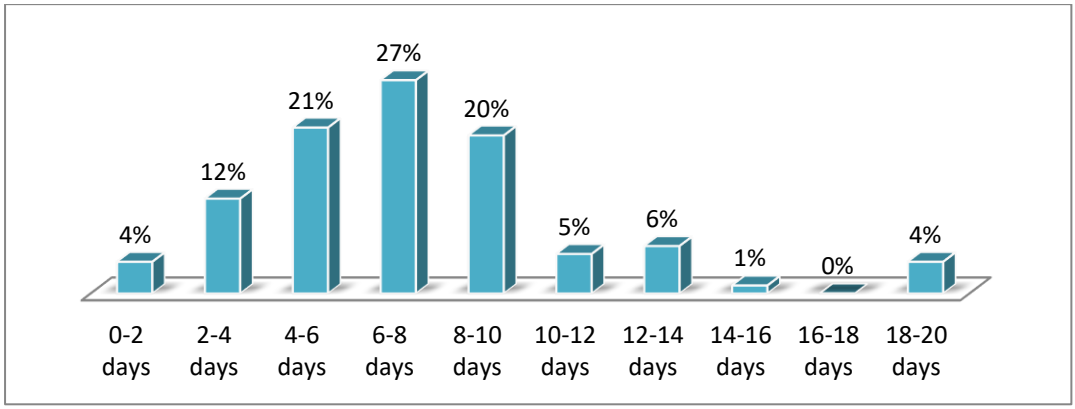
Fever was the leading symptom 97% of children had fever, 63% had sore throat, 20% had breathing difficulty, 21% had fatigue, 12% had abdominal pain, 9% vomiting and 6% diarrhea.




14% of children had fever values <38.5°C, 57% of children had fever values 38.5°C - 40°C, 29% of children had fever values >40°C.




The mean days with fever was 7.8 days ranging from 0 day to 20 days.




From the correlation analysis was detected an association between variables days with fever and levels of lymphocytes, levels of alanine aminotransferase (ALT), and levels of anxiety. The association was of small and medium magnitude, in positive direction and of statistical significance.

Pearson Correlation between the variable days with fever and the levels of lymphocytes was positive, of small magnitude, and statistically significant r=0.239 p=0.035

Pearson Correlation between the variable days with fever and the levels of alanine aminotransferase (ALT) was positive, of small magnitude, and statistically significant r=0.284 p=0.004

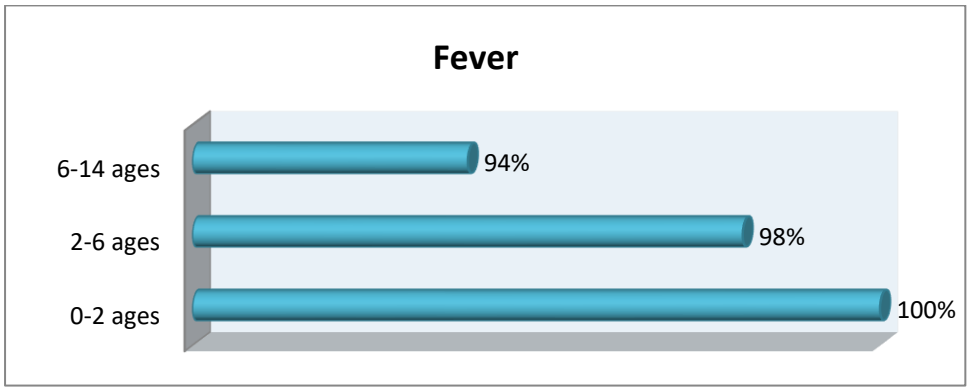
Pearson Correlation between the variable days with fever and the levels of anxiety was positive, of medium magnitude, and statistically significant r=0.420 p=0.012

| | | Lymphocytes | ALT | Anxiety |
|---|---|---|---|---|
| Days with fever | Pearson Correlation | ,239* | ,284** | ,420* |
| | Sig. (2-tailed) | .035 | .004 | .012 |
| | Sum of Squares and Cross-products | 756.385 | 14328.556 | 457.800 |
| | Covariance | 9.823 | 146.210 | 13.465 |
| | N | 78 | 99 | 35 |

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

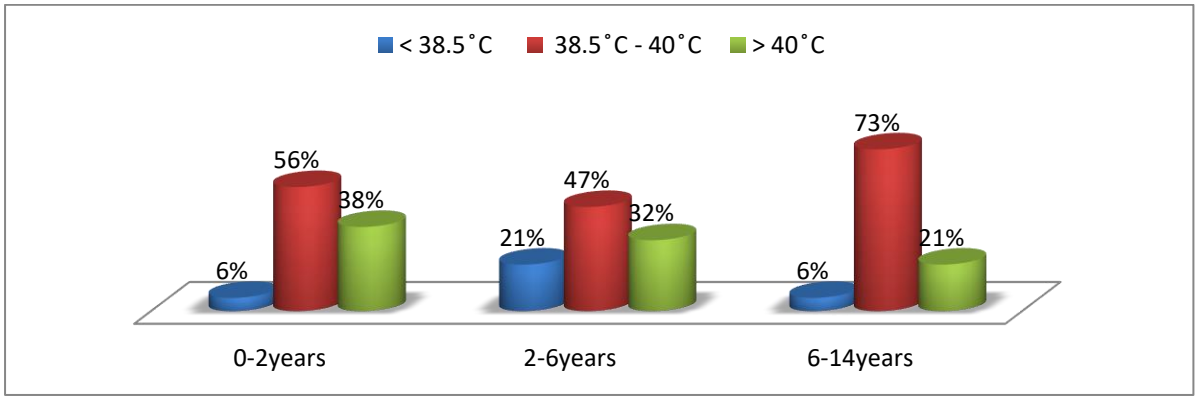
According to age-groups fever was found in 100% of children aged 0-2years, 98% of children aged 2-6years and 94% in children aged 6-14years.



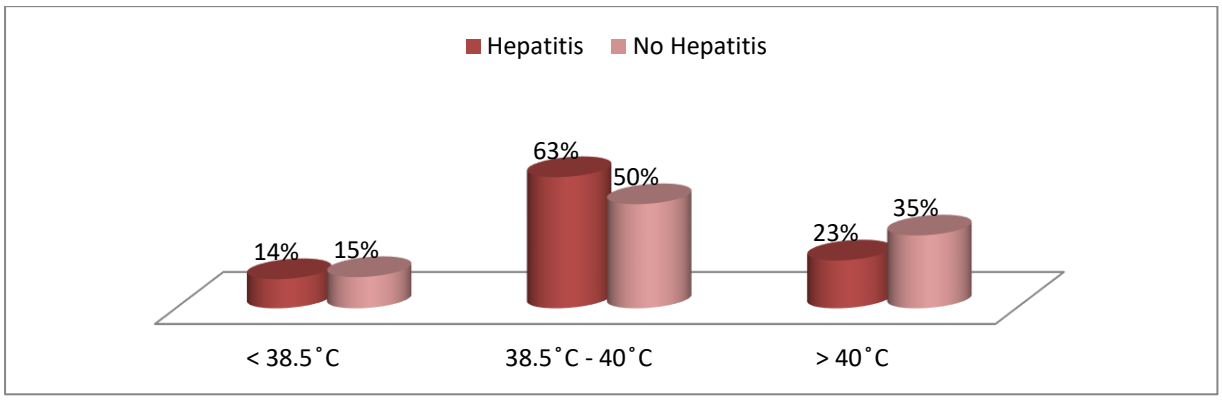

38% of children aged 0-2years had fever >40°C, 32% of children aged 2-6years had fever >40°C, and 21% of children aged 6-14years had fever >40°C.

56% of children aged 0-2years had fever 38.5°C-40°C, 47% of children aged 2-6years had fever 38.5°C-40°C, and 73% of children aged 6-14years had fever 38.5°C-40°C.

6% of children aged 0-2years had fever <38.5°C, 21% of children aged 2-6years had fever <38.5°C, and 6% of children aged 6-14years had fever <38.5°C.




59 children (53%) had EBV hepatitis (elevated levels of alanine aminotransferase).



In the Hepatitis group 14% of children had fever <38.5°C, 63% had fever 38.5°C-40°C, and 23% had fever >40°C.

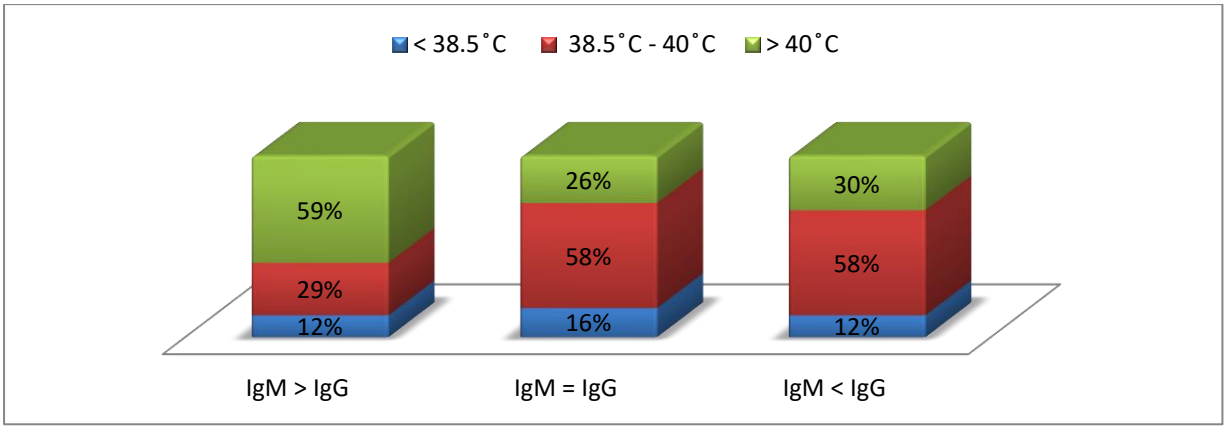
In the No Hepatitis group 15% of children had fever <38.5°C, 50% had fever 38.5°C-40°C, and 35% had fever >40°C.

The mean duration of fever in the Hepatitis group was 8.5days and the mean duration of fever in the No Hepatitis group was 7days.

Children presented in the acute phase of the disease IgM levels >IgG levels 59% had fever >40°C, 29% had fever 38.5°C-40°C, and 12% had fever <38.5°C.

Children presented in the subacute phase of the disease IgM levels = IgG levels 26% had fever >40°C, 58% had fever 38.5°C-40°C, and 16% had fever <38.5°C.

Children presented in the convalescent phase of the disease IgM levels < IgG levels 30% had fever >40°C, 58% had fever 38.5°C-40°C, and 12% had fever <38.5°C.




## 5. Discussion

Infectious Mononucleosis is the most common clinical manifestation caused by EBV infection [15]. Epstein-Barr virus (EBV) is a gamma-herpesvirus that infects a large fraction of the human population and as other herpesviruses results in lifelong infection. Initial infection occurs in the oral (tonsillar) compartment, the host cells of EBV are mainly lymphocytes and epithelial cells [18]. An important consequence of EBV infection in B cells is that they are induced to activate their growth program and trigger differentiation into memory B cells which are released into the peripheral circulation. The number of infected B cells decreases over time after the onset of symptoms of primary infection, but these cells are never eliminated entirely [13].

Young children most likely acquire primary EBV infection from close contact that involves exchange of oral secretions via shared items such as toys, bottles, and utensils. Primary infection in childhood is usually asymptomatic or produces an acute illness that is often not recognized as being due to EBV [33]. In adolescents and young adults, however, primary

EBV infection frequently presents as Infectious Mononucleosis [32]. Infectious Mononucleosis most often begins insidiously, with vague malaise, followed several days later by fever, sore throat, swollen posterior cervical lymph nodes, and fatigue. Some patients experience an abrupt influenza-like onset, with fever, chills, body aches, and sore throat [ 9], [12], [17], [25], [27], [2], [3], [4]. The median duration of Infectious Mononucleosis is 16 days, which is much longer than the duration of most acute viral illnesses, recovery is gradual, and it may take months for the patient to feel entirely well [27]. The risk of developing Infectious Mononucleosis after primary EBV infection correlates with the age of the patient [14]. Children younger than 10 years of age are usually asymptomatic or moderately ill, with a partial Infectious Mononucleosis syndrome, although classic Infectious Mononucleosis can occur in this age group [10].

A potent innate and adaptive immune response occurs during primary EBV infection which controls infection and is responsible for the most symptoms and signs of the disease. The most prominent inflammatory cytokine detected in the sera of individuals with Infectious Mononucleosis is IFN-γ. IFN-γ is produced by activated T cells and NK cells. IFN-γ is thought to be important for control of EBV infection and reactivation, based on studies of a related gamma-herpesvirus infection in mice [7], [19], [36]. However, high levels of IFN-γ likely contribute to the symptoms experienced during Infectious Mononucleosis, as this cytokine is known to cause headache, fatigue, and fever [29]. The massive lymphocytosis in the blood that characterizes Infectious Mononucleosis consists largely of CD8 T cells specific for EBV lytic antigens and is thought to be responsible for the major symptoms of Infectious Mononucleosis, as disease severity correlated more closely with lymphocytosis than with viral load in a small study [16], [31]. One of the causes that Infectious Mononucleosis syndrome during primary EBV is more common in adults than in children is proposed to be to the higher viral dose acquired through sexual activity than children do through salivary contact [5]. This higher viral dose would initiate a larger CD8 T-cell response, which would cause the symptoms of Infectious Mononucleosis through production of inflammatory cytokines. Another opinion is that preexisting immunity to other viruses which cross-reacts with EBV (called “heterologous immunity”) could provide a robust CD8 T-cell response to primary EBV and adults are likely to have broader immune experience in general [30]. Finally, it can be stated that high levels of inflammatory cytokines, produced by either innate or adaptive immune cells, are responsible for the symptoms observed during acute Infectious Mononucleosis.

So, fever was the most common symptom in children with Infectious Mononucleosis, it was found in 97% of cases. Infants experienced more fever than older children, 100% of children 0-2years had fever, 98% of children 2-6years had fever and 94% of children 6-14years had fever. Fever was the first symptom in 84% of children followed by lymphadenitis, fatigue, rash, palpebral edema, cough. 29% of children experienced high levels of fever >40°C. 38% of children 0-2years had fever >40°C compared to 32% of children 2-6years and 21% of children 6-14years. Compared to older children and adults, infants and young children experience higher and more prolonged fevers, more rapid temperature increases, and greater temperature fluctuations [11]. The mean days with fever was 7.8 days ranging from 0 day to

20 days. 4% of children had fever that lasted 20 days and their diagnosis of admission was fever of unknown origin. It is already known that EBV infection is one of the causes of fever of unknown origin. The duration of fever in infectious mononucleosis is much longer than in most other viral infections of childhood too.

There is a correlation between the duration of fever and lymphocytosis r=0.239 p=0.035 higher levels of lymphocytes are associated with longer duration of fever. Higher levels of alanine aminotransferase (ALT) are associated with longer duration of fever too r=0.284 p=0.004. The duration of fever, which is considered a sign of the disease severity, is also associated with elevated levels of anxiety in the hospitalized children with Infectious Mononucleosis r=0.420 p=0.012. Children hospitalized in the acute phase of Infectious Mononucleosis had higher levels of fever 59% of those had fever >40°C. Whereas children hospitalized in the subacute and convalescent phase of the disease had moderate levels of fever 58% of those had fever 38.5-40°C.

## 6. Conclusion

Fever is one of the oldest clinical indicators of disease and one of the most common reasons for medical attention in children. Fever is the most common symptom in children with infectious mononucleosis. Compared to older children, infants and young children experience higher and more prolonged fevers, more rapid temperature increases, and greater temperature fluctuations. The duration of fever in infectious mononucleosis is much longer than in most other viral infections of childhood. The potent innate and adaptive immune response which occurs during primary EBV infection controls infection and is responsible for the most symptoms and signs of the disease including fever.

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