

## Complications of Infectious Mononucleosis in Children

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### ABSTRACT

Infectious mononucleosis (IM) is detected more in preschool and infant children, with differences in clinical features. This study aimed to analyze and compare the demographic, clinical, and laboratory characteristics and complications of IM in Turkey and other nonindustrial countries.

The study was performed to retrospectively analyze the etiology of fever and lymphadenopathy in Keçiören Training and Research Hospital Pediatric Clinic between 2014 and 2018. Twenty-six patients clinically suspected of having IM and positive for Epstein-Barr virus (EBV) viral capsid antigen immunoglobulin M (IgM) antibody were included in the study.

The files of 26 (13%) patients diagnosed with IM were analyzed for EBV viral capsid antigen (VCA) IgM antibody. Twelve (46%) of the patients were male, and 14 (54%) were female; 21 (80.7%) were aged less than 3 years, and the average age was 26 months. The age of onset peaked between 0–12 months (34.6%) and 25–36 months (30.7%). Fever, lymphadenopathy, and hepatosplenomegaly were observed in all patients ( $n = 26$ ). The fever lasted for an average of 5 days. Tonsillopharyngitis (80%), skin rash (69%), conjunctivitis (65%), anemia (12%), leukocytosis (54%), and high liver function (65%) were the most common laboratory findings. The average hospital stay was 7.5 days. Patients with prolonged fever, lymphadenopathy, and hepatomegaly were more prominent, and patients with elevated liver enzymes stayed longer in the hospital.

This study showed that exposure to EBV at an early age in Turkey, like other nonindustrial countries, developed into IM; therefore, the incidence rates of hepatosplenomegaly, lymphadenopathy, and hospitalization were high. It aimed to emphasize the importance of preventing exposure at a growing age because it also led to the development of chronic diseases in advanced ages.

**Key words:** Children, early age, infectious mononucleosis, nonindustrial countries

### INTRODUCTION

Epstein-Barr virus (EBV) is a double-stranded DNA virus from the herpes virus family. It is common all over the world. Although approximately 90%–95% of adults are EBV seropositive, most infections are subclinical and silent. The infection spreads via close contact. EBV is the most common cause of infectious mononucleosis (IM). Primary IM is usually asymptomatic in children, but sometimes tonsillopharyngitis, cervical lymphadenopathy, fever, headache, nausea, vomiting, loss of appetite, and otitis media can be seen. Lymphadenopathy is symmetrical and is more common in the posterior cervical chain than in the front chain. Tonsils may be white or gray-green with

an exudate. Also, they may be necrotic, accompanied by palatal petechiae. Periorbital, palpebral edema, and maculopapular or morbilliform rashes are the skin findings that can be seen. Further, 90% of the patients have mild hepatitis and associated nausea, vomiting, and anorexia. Splenomegaly is seen in 50% of patients, but jaundice and hepatomegaly are rare (1).

Intrauterine infection is rare, as less than 5% of pregnant women are susceptible to the virus. Cases with congenital anomalies, such as biliary atresia, congenital heart disease, hypotonia, micrognathia, cataracts, and thrombocytopenia, have been reported rarely (2).

EBV infection causes many acute and chronic complications. One of the most common complications is the morbilliform rash following the administration of ampicillin and, to a lesser extent, penicillin. Hepatitis, splenic rupture, pneumonia (5%–10%), upper respiratory tract obstruction (1%–3.5%), cardiac complications (myocarditis and atherosclerosis), hematological complications (thrombocytopenia, aplastic anemia, and agranulocytosis), neurological complications (bilateral facial nerve paralysis), abducens nerve paralysis, acute encephalitis, acute cerebellitis, meningoencephalitis, transverse myelitis, myeloradiculitis, Alice in Wonderland syndrome, Guillain Barré syndrome, acute dacryocystitis, allergy, psychiatric (psychosis, depression, and anorexia), autoimmune diseases (rheumatoid arthritis, systemic erythematosus, multiple sclerosis, autoimmune thyroiditis, insulin-dependent diabetes mellitus, Sjögren's syndrome, autoimmune liver disease, systemic sclerosis, and myasthenia gravis), cancers (gastric cancers, nasopharyngeal carcinoma, Hodgkin's lymphoma, and acute conjunctival tumor), and X-linked lymphoprotein disease cholecystitis can be seen. Chronic EBV infection is an infectious disease with active viremia characterized by ongoing symptoms of a rare mononucleosis syndrome (3-8).

The most common laboratory finding for IM is lymphopenia (usually  $<4500 \mu\text{L}$ ). Lymphocytosis consisting of increased atypical lymphocytes can be detected in the peripheral smear. Most reactive lymphocytes are CD8+ cytotoxic T cells. Liver function tests may increase moderately. The heterophil antibody test is positive. Serological diagnosis in EBV infection reveals the presence of viral capsid antigen (VCA) immunoglobulin M (IgM) antibodies. It can be placed precisely in the absence of IgG EBNA antibodies. However, the presence of IgM VCA antibodies is considered to be possible IM. Antibodies to the early antigen (EA) are found at the onset of the disease. Two EA IgG subsets exist: anti-D and anti-R antibodies; their presence or absence does not exclude acute illness. EBV DNA is detected as 90% positive in blood and plasma by polymerase chain reaction (PCR) 2 weeks after the onset of the disease (9,10). Supportive care is the main treatment for IM and primary EBV disease. The disease is usually self-limited. Acetaminophen or nonsteroidal anti-inflammatory

drugs are recommended for fever, sore throat, and weakness. Adequate fluid support and rest are sufficient. Steroid therapy is recommended in the case of liver failure or respiratory distress. Although antiviral treatment is not recommended, the anecdotal use of agents such as interleukin-2, interferon-alpha, and intravenous immunoglobulins has been reported (11,12).

## MATERIAL AND METHODS

Files of 196 patients admitted to the Keçiören Training and Research Hospital Pediatric Clinic between 2014 and 2018 to investigate the etiology of fever and lymphadenopathy were retrospectively analyzed. Twenty-six cases clinically suspected of having IM and positive for EBV VCA IgM antibody were included in the study. Age, sex, physical examination findings, laboratory values, duration of fever, and hospital stay of the patients were recorded. Data were statistically analyzed done using the SPSS program 15.0.

## RESULTS

Twelve (46%) of the patients were male and 14 (54%) were female; the average age was 26 months (minimum 6 months to maximum 65 months). Twenty-one (80.7%) of the patients were aged less than 3 years and also peaked between 0–12 months (34.6%) and 25–36 months (30.7%). All patients ( $n = 26$ ) had a high fever, lymphadenopathy, and hepatosplenomegaly. The fever lasted for an average of 5.11 days. Other common physical features were tonsillopharyngitis (80%), skin rash (69%), and conjunctivitis (65%). The most common laboratory findings were as follows: anemia (42%), leukocytosis (54%), and increased liver function (65%); average hemoglobin level: 11.1 g/dL (lowest 8 g/dL to highest 13.10 g/dL); white blood cell count: mean  $12,020 \pm 5520 \text{ mmol/L}$  (lowest 3000 mmol/L to highest 21,300 mmol/L); alanine aminotransferase (ALT) level: average  $167 \pm 198 \text{ IU/L}$  (lowest 18 IU/L to highest 750 IU/L); aspartate aminotransferase (AST) level: average  $159 \pm 187 \text{ IU/L}$  (lowest 18 IU/L to highest 710 IU/L (Figure 1).

The hospitalization stay of the patients was  $7.5 \pm 1.7$  days (shortest 5 days to longest 12 days). Patients with prolonged fever, prominent lymphadenopathy and hepatomegaly, and higher levels of liver enzymes were found to stay in the hospital longer.

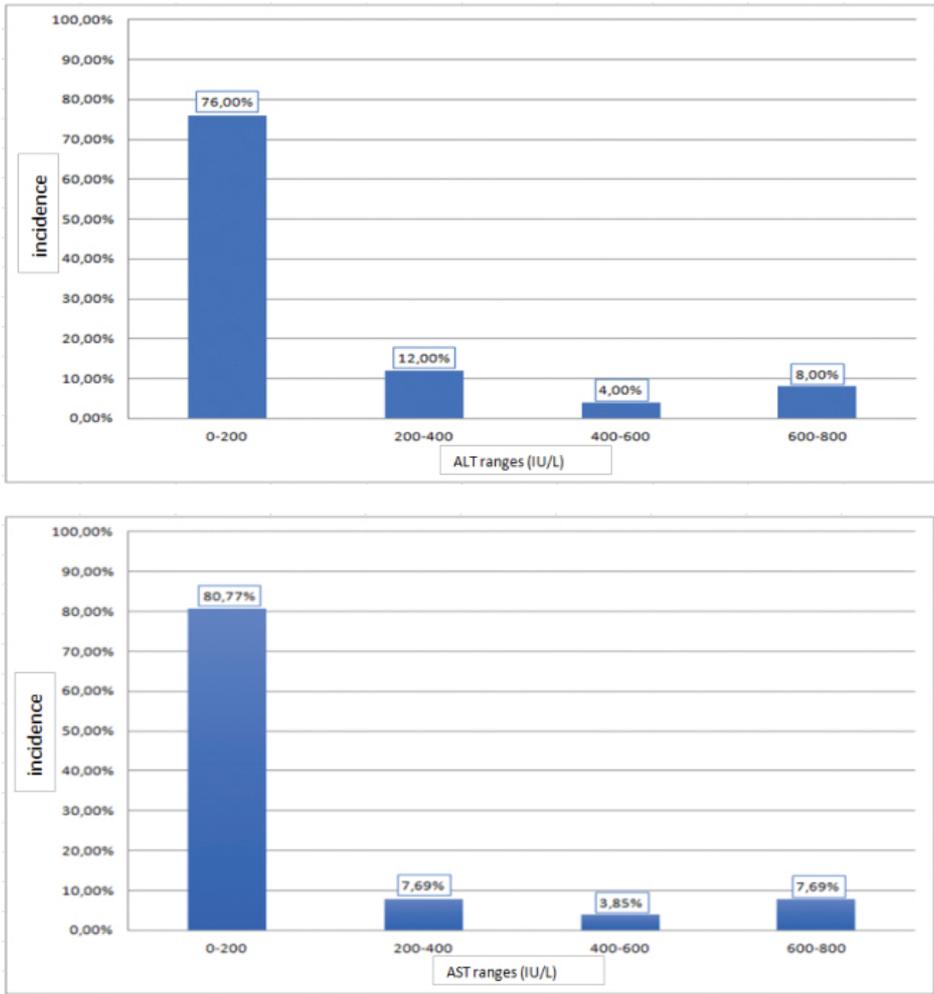


Figure 1 ALT/AST levels and incidence rates in patients.

Table 1 Clinical and laboratory characteristics of patients

|                             | N  | Minimum | Maximum | Average | St.Deviation |
|-----------------------------|----|---------|---------|---------|--------------|
| Age(month)                  | 26 | 6       | 65,00   | 25,50   | 17,96        |
| Hemoglobin (gr/dl)          | 26 | 8       | 13,10   | 11,13   | 1,58         |
| Wbc(mm3)                    | 26 | 3       | 21,30   | 12,02   | 5,43         |
| Hospitalization period(day) | 26 | 5       | 12,00   | 7,58    | 1,72         |
| Fever period(day)           | 26 | 3       | 8,00    | 5,12    | 1,31         |
| ALT(IU/L)                   | 26 | 18      | 750,00  | 167,92  | 198,56       |
| AST(IU/L)                   | 26 | 18      | 710,00  | 159,62  | 187,40       |
| N                           | 26 |         |         |         |              |

## DISCUSSION

IM is a benign lymphoproliferative disease caused by EBV. It is frequently seen in adolescents and young adults in the age range of 10–30 years. It is mild or asymptomatic in young children. However, some studies support that EM is seen in younger age groups and with different symptoms in developing countries, such as Turkey. In the study conducted by Çağlar et al, the mean age of the patients was 48 months (56.8% aged less than 5 years) (13). The average age of the patients was 69 months (51.5% aged less than 6 years; 34.8% aged less than 3 years) (14). In the study by Jiao et al. in China, 78% of the patients were aged less than 7 years (15). In the study by Gao et al. in Beijing, China, the average age was 72 months (16). Again, in China, Devkota et al. found that 74.7% of the patients were aged less than 4 years (17). In India, Balasubramanian et al. found that the average age of the patients was 22 months (18). In Mexico, Saldana et al. found that the average age was 5.2 years (19). In Korea, Son et al. showed that the average age was 6.17 years, although two peaks were detected at the age of 3 and 5 years (20). In Denmark, Topp et al. showed that the average age was 84 months (21). In the present study, similar to the aforementioned studies, the average age of patients was 26 months (80.7%, aged less than 3 years),

with two peaks between 0–12 months (34.6%) and 25–36 months (30.7%) (Figure 2).

The present study, like other studies, supported that IM was more common in infants and preschool children in developing countries, unlike industrial countries (Figure 3).

Studies explored why IM occurred at different ages in different societies. In the study by Gares et al., children with different psychosocial statuses were evaluated in terms of EBV infection at the age of 9 months and 3 years. Low social status, low maternal education level, living in a crowded home, living in social housing, humid home environment, sending to a nursery, being cold in the nursery, and living in a big city predisposed individuals to early EBV infection (22). In the study by Setoh et al. in Singapore, the seroprevalence of EBV infection in three different ethnic groups was evaluated. The seropositivity in Malaysians with the lowest socioeconomic characteristics was 81.8% at the age of less than 1 year; however, it was 64.2% and 58.4% in Chinese and Indians, respectively, similar to that in developed countries (23). In the study by Condon et al. in Minnesota, the detection of EBV seropositivity at an older age in individuals of European descent compared with other ethnicities was found to be associated with better socioeconomic

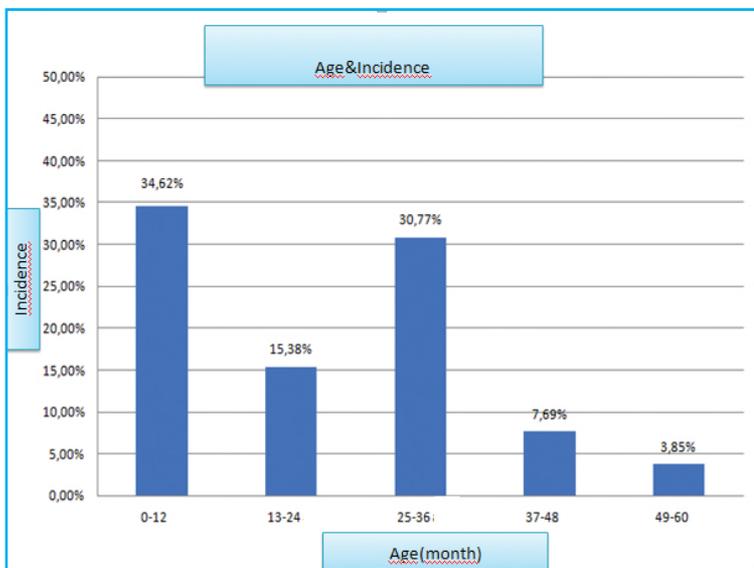


Figure 2 Age ranges of patients.

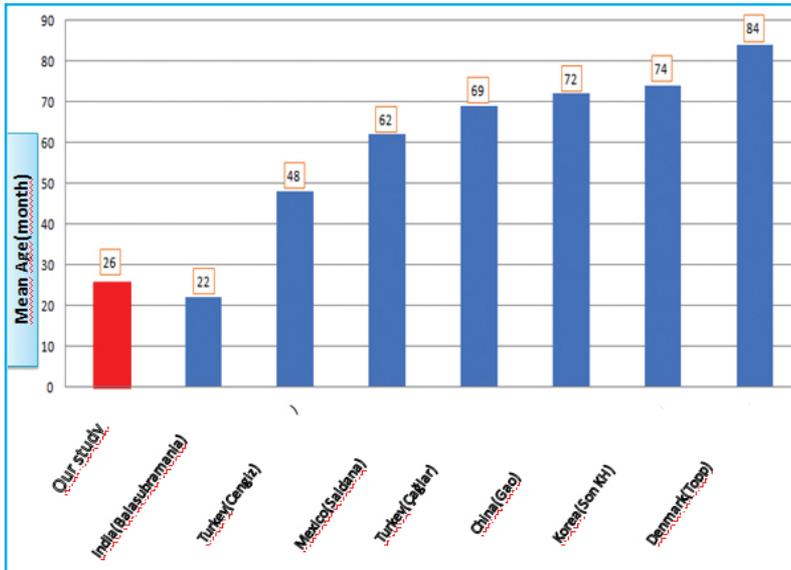


Figure 3 Average patient age in the studies reviewed.

conditions and better education level (24). HH *et al.* in Balfour examined the effect of ethnic origin and socio-economic conditions on EBV seroprevalence; the EBV seroprevalence was found to be significantly higher in individuals of African and Mexican descent in the same age group compared with those of European descent. High EBV seropositivity at an early age in individuals of African and Mexican descent was associated with low education level, poor home and living conditions, and less utilization of health services. The controversy that the tendency to develop chronic EBV infections, the development of Burkitt lymphoma, and the development of multiple sclerosis increased with EBV exposure at an early age has shown that it is important to prevent early exposure (25).

Studies performed in Turkey (13,14), China (16,17), India (18), Korea (20), and the United States demonstrated that EBV seroprevalence was higher in men than women. In Korea, the seroprevalence was found to be higher in boys before the age of 5 years, while it was more in girls after 10 years of age. In the present study, F/M was 1.17, and no significant difference was found between sexes.

Fever is the most common complaint and reason for hospitalization in IM. It can be mild or up to 39–40°C; It can last from a few days to 2 weeks. Cervi-

cal lymphadenopathy, another common symptom in EM, usually decreases significantly within 2 weeks and rarely remains palpable for months. If the shrinkage process is prolonged, it may raise concerns about cancer in families. In the study by Cengiz *et al.*, the most common reasons for admission were neck swelling (68.1%), fever (43.1%), and sore throat (25%); the most common physical examination findings were lymphadenopathy (79.5%), tonsillopharyngitis (72.7%), splenomegaly (34%), and hepatomegaly (25%) (13). In the study by Çağlar *et al.*, fever (92.4%), sore throat (43.9%), swollen neck (63.6%), rash (24.2%), respiratory distress (13.6%), nausea, vomiting (12.1%), fatigue (7.6%), abdominal pain (7.6%), and headache (3.0%) were the most common complaints; exudative membranous tonsillopharyngitis (72.7%), exudative tonsillopharyngitis (12.1%), cervical lymphadenopathy (81.8%), hepatomegaly (30.3%), and splenomegaly (42.4%) were the most common physical examination findings (14). In the study by Saldana *et al.*, lymphadenopathy (89.5%), fever (79.7%), general body pain (69.3%), pharyngitis (55.2%), hepatomegaly (47.2%), splenomegaly (36.8%), exanthema (16.5%), jaundice (9.8%), arthritis (1.84%), and conjunctivitis (0.61%) were the most common clinical findings (19). However, fever, cervical lymphadenopathy, tonsillitis, and fatigue were

the most common physical examination findings in a study by Topp et al.; splenomegaly (16.8%) and hepatomegaly (26.3%) were detected. Nonspecific symptoms such as nasal discharge and rash are more common in young children; diarrhea, vomiting, and upper respiratory tract infections were observed in those aged less than 1 year, while more typical IM symptoms were observed in older ages (21). In the study by Gao et al., fever (92.3%), tonsillopharyngitis (83.5%), cervical lymphadenopathy (95%), splenomegaly (47.4%), hepatomegaly (58.1%), maculopapular rash (14.8%), and eye edema (11.5%) were common. Tonsillopharyngitis was less common in those aged less than 1 year. While hepatomegaly, splenomegaly, and rash are observed in younger children, their incidence decreased with increasing age (16). Son et al. detected fever (90.1%), tonsillopharyngitis (46.9%), generalized lymphadenopathy (56.8%), splenomegaly (12.3%), and hepatomegaly (24.7%). No difference in terms of age was found among these findings. Headache was detected as 0% at the age of less than 5 years, 21.1% at the age of 5–9 years, and 30.8% at the age of ≥10 years (20). In the study by Balasubramanian et al., fever (100%), lymphadenopathy (84%), hepatosplenomegaly (81%), tonsillitis (45%), neck swelling (30%), upper

respiratory tract symptoms (21%), epitrochlear lymph node enlargement (20%), and vomiting and diarrhea (1%) were the most common clinical findings (18). All patients (n = 26) in the present study had a high fever, posterior cervical and submandibular lymphadenopathy, and hepatosplenomegaly. Other most common physical features were tonsillopharyngitis (80%), skin rash (69%), and conjunctivitis (65%). In the present study, similar to other studies, high fever, cervical lymphadenopathy, and tonsillopharyngitis were the most common findings. Hepatosplenomegaly, skin rash, and conjunctivitis were detected at a higher rate compared with others. In the study by Balasubramanian et al., the incidence rate of hepatosplenomegaly was as high as that in the present study. This might be due to the low average age of patients and similar socioeconomic and ethnic characteristics (Figure 4).

In the study by Cengiz et al., the leukocyte count was normal in 68.3% of the patients and high in 29.5%. The incidence rate of leukopenia, lymphocytosis, Downey cells, and thrombocytopenia was 2.2%, 44.7%, 23.6%, and 11.3%, respectively. ALT and AST elevation was present in 61.9% and 90.4% of the patients. In the study by Çağlar et al., the findings were as follows: 42.4%, lymphocytosis; 40.9%, liver enzyme

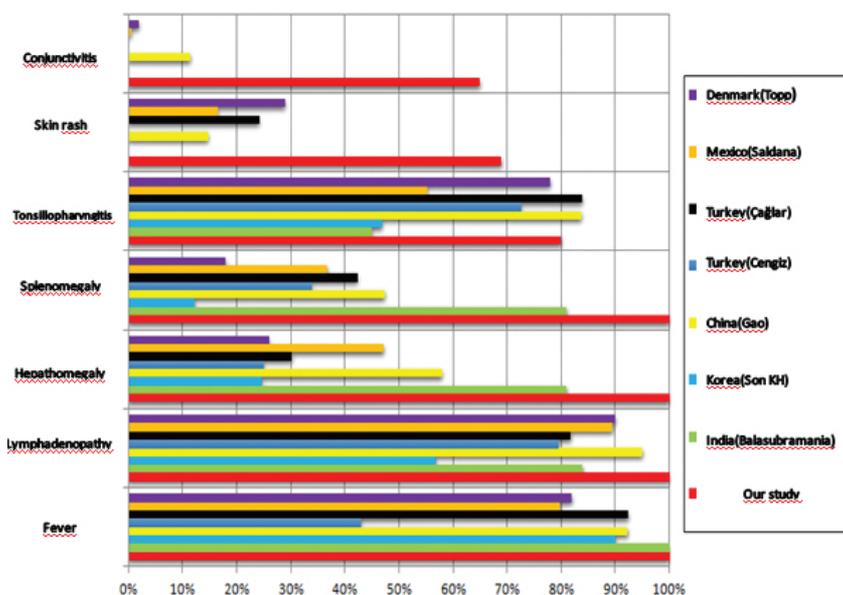


Figure 4 Most common findings from the studies reviewed.

elevation; 65.1%, leukocytosis; 57.5%, and lymphocyte/leukocyte ratio >50%; both reactive lymphocytosis and atypical lymphocytes were found in 77.2% of patients (20). In the study by Saldana et al., 41.7% of patients had lymphocytosis, 24.5% had atypical lymphocytes, and 30.9% had an increase in liver enzyme levels (19). Gao et al. found that 67.5% of patients had leukocytosis, 4.3% neutropenia, 51.9% atypical lymphocytes, 5% thrombocytopenia, and 48.6% ALT and AST elevation. While leukocytosis was higher in the infant age group, liver enzyme elevation was higher in older children (16). In a recent study by KH et al., 69.1% of patients had leukocytosis, 50% atypical lymphocytes, 9.9% mild thrombocytopenia (<150,000/ $\mu$ L), and 8.6% neutropenia; significant anemia (Hb 6.9) was found in one patient, ALT and AST elevation was detected in 26.6% of patients aged less than 5 years, 63.1% aged 5–9 years, and 76.9% aged 10 years. Leukocytosis was evident at the age of less than 5 years; as the age increased, the liver enzyme levels increased (20). In the study by Tobb et al, 75% of patients had lymphocytosis, 63% high CRP level, 50% liver enzyme elevation. Lymphocytosis and liver involvement were higher in the age range of 5–15 years compared with individuals aged less than 5 years (21). In the present

study, the most common laboratory findings were anemia (42%), leukocytosis (54%), and increased liver function (65%). In 80% of patients, ALT and AST levels were >200 IU/L. Similar to the findings of Cengiz et al., 3.8% of patients had leukopenia, and the elevation of liver enzymes was found to be higher than that in other studies. The liver enzyme levels increased with the increasing age in most of the studies. Although the age group in the present study was small, liver enzyme levels were high (Figure 5).

When acute and chronic complications developing due to EBV infection were evaluated, Cengiz *et al.* (13) found hemophagocytic syndrome in one patient; Çağlar et al. found severe upper airway obstruction in 13.6% of patients (14). Saldana et al. found that 38% and 7.3% of patients had anemia and thrombocytopenia, respectively, 6.1% hemophagocytic syndrome, 4.9% thrombotic thrombocytopenic purpura, 4.3% pneumonia, 1.8% upper airway obstruction, 1.8% hepatitis, 1.8% convulsion, 1.2% nonthrombocytopenic purpura, 0.6% myositis, and 0.6% lymphoproliferative syndrome (19). Gao *et al.* showed that 16.5% of patients had complications (14% pneumonia; 0.7% HLH) (16). Balasubramanian *et al.* also found complications (12% upper airway obstruction and 6% septic

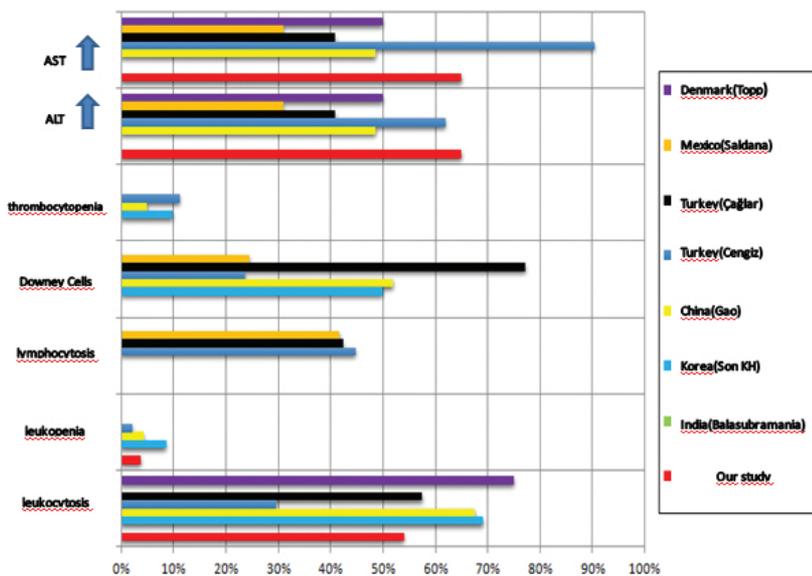


Figure 5 Most common laboratory findings in the studies reviewed.

Table 2 Summary table of the most common complications in the studies reviewed

|                        | hemophagocytic syndrome | upper airway obstruction | anemia thrombocytopenia | thrombotic thrombocytopenic purpura | pneumonia | neutrohenia | Septic shock |
|------------------------|-------------------------|--------------------------|-------------------------|-------------------------------------|-----------|-------------|--------------|
| Our study              |                         |                          | 12%                     |                                     |           | 3%          |              |
| India (Balasubramania) |                         | 12%                      |                         |                                     |           |             | 6%           |
| Korea (Son KH)         |                         |                          |                         |                                     |           |             |              |
| China (Gao)            | 1%                      | 1%                       | 5%                      |                                     | 14%       | 4,30%       |              |
| Turkey (Cengiz)        | 2,20%                   |                          |                         |                                     |           |             |              |
| Turkey (Çağlar)        |                         | 13,60%                   |                         |                                     |           |             |              |
| Mexico (Saldana)       | 6,10%                   | 1,80%                    | 7,30%                   | 4,90%                               | 4,30%     |             |              |
| Denmark (Topp)         |                         |                          | 3%                      |                                     | 1%        |             |              |

shock) in 30% of patients (18). Topp *et al.* found 28.4% with complications (pneumonia, subacute pancreatitis, anemia, and thrombotic thrombocytopenic purpura) (21). Splenic rupture was not detected in any of the studies compared. Upper airway obstruction, anemia-thrombocytopenia, pneumonia, and hemophagocytic syndrome were evaluated as common complications. In the present study, the patients had no complications other than 12% with anemia (Hb <8.9 g/dL) and 3% with neutropenia. The chronic complications

could not be evaluated due to the absence of long-term patient follow-up.

Son *et al.* found that fever lasted 7.7 days on average and longer than 10 days in 14.8% of patients; 6.8 days in those aged <5 years; 7.3 days in those aged 5–9 years, and 8.9 days in those aged ≥10 years. In other words, fever lasted longer in older children (20). Balasubramanian *et al.* found that the risk of developing complications was higher in patients with a fever lasting more than 14 days and with an EBV VCA IgM titer

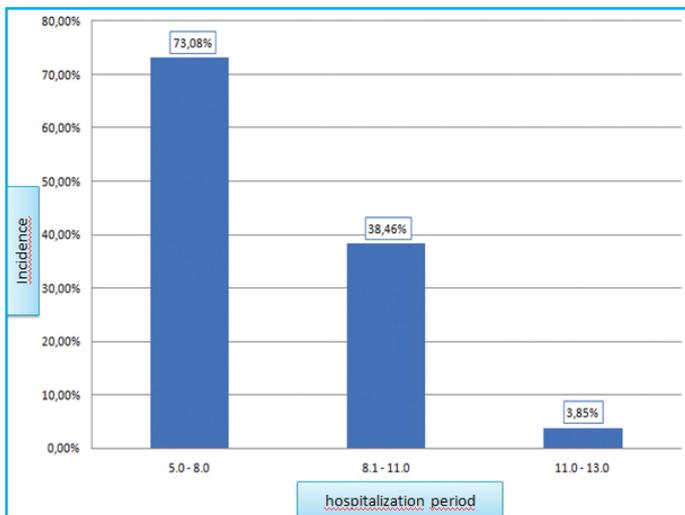


Figure 6 Hospitalization period of patients.

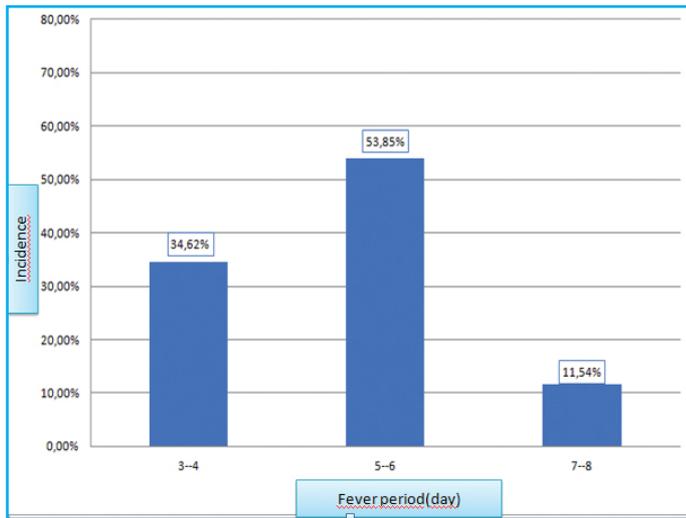


Figure 7 Duration of fever period in the present study.

>100 (18). While fever in 88% of patients lasted 3–6 days (the longest 8 days), lymphadenopathy usually resolved within 10 days (Figure 6). 73% of the patients were hospitalized for 5–8 days (Table 9). The most important factors determining the length of stay were the duration of high fever, persistence of lymphadenopathy, and higher liver function.

Hence, EBV develops at an early age in Turkey compared with developed countries. Hospital admissions with the diagnosis of IM occur in preschool and infant stages. Clinically, hepatosplenomegaly and elevated liver enzyme levels are evident. Having EBV infection at an early age lays the groundwork for chronic diseases, and, therefore, it is important to identify and prevent the causative factors.

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