Original Investigation / *Özgün Araştırma*

**DOI:** 10.5578/ced.20239903 • *J Pediatr Inf 2023;17(1):e14-e19*

# Change of Laboratory Findings of Acute Epstein-Barr Virus Infection According to Age Groups

## Akut Epstein-Barr Enfeksiyonunun Yaş Gruplarına Göre Laboratuvar Bulgularının Değişimi

Kamile Arıkan[1](İD), Eda Karadağ-Öncel[2](İD), Ateş Kara[3](İD), Ali Bülent Cengiz[3](İD), Mehmet Ceyhan[3](İD)

[1] *Clinic of Pediatric Infectious Diseases, Buca Training and Research Hospital, İzmir Demokrasi University, İzmir, Türkiye*
[2] *Clinic of Pediatric Infectious Diseases, İzmir Tepecik Training and Research Hospital, İzmir, Türkiye*
[3] *Department of Pediatric Infectious Diseases, Hacettepe University Faculty of Medicine, Ankara, Türkiye*

**Cite this article as:** Arıkan K, Karadağ-Öncel E, Kara A, Cengiz AB, Ceyhan M. Change of laboratory findings of acute Epstein-Barr virus infection according to age groups. J Pediatr Inf 2023;17(1):e14-e19.

**Abstract**

**Objective:** The aim of this study was to investigate the clinical and laboratory findings of patients diagnosed with acute Epstein-Barr virus (EBV) infection according to age groups.

**Material and Methods:** Patients diagnosed with acute EBV infection were enrolled in this cross-sectional study.

**Results:** Totally, 894 patients diagnosed as acute EBV infection were included in the study. Of them, 540 (60.5%) patients were males (male/female=1.52). Median age of the patients was four years (57 days-18 years). Seropositivity rate increased statistically as age increased (47.9%, 73.8% and 87.2%, respectively). Seventy patients were admitted with clinical presentation of IM with a median age of seven years (3 years-18 years). Serum median hemoglobin, leukocyte, thrombocyte, mean platelet values were statistically signficifantly different according to age groups (for all p< 0.001). Leukocytosis was more commonly encountered in EBV infected children <6 years old of age compared to 6-15 years old age and >15 years old of age (29.3%, 17.1% and 7.7%, respectively, p< 0.001). Neutropenia was present in 157 (17.6%) patients. Mean platelet volume (MPV) increased statistically significantly as age increased (p< 0.001). MPV/platelet ratio increased significantly as age increased (p< 0.001). MPV/platelet ratio was higher in IM cases. High serum CRP was more common in <6 years old of age compared to 6-15 years old age and >15 years old of age [304 (49.4%), 204 (33.2%), 107 (17.4%), respectively, p= 0.04].

**Conclusion:** EBV infection causes different laboratory findings and clinical presentations according to age groups.

**Keywords:** Epstein-Barr virus infection, age groups, infectious mononecleosis, hematological findings, mean platelet volume, MPV/platelet ratio

**Öz**

**Giriş:** Bu çalışmada akut Epstein-Barr virüs (EBV) ile enfekte hastalarda yaş gruplarına göre klinik ve laboratuvar bulgularının araştırılması amaçlanmıştır.

**Gereç ve Yöntemler:** Bu kesitsel çalışmaya akut EBV enfeksiyonu tanısı konan hastalar dahil edilmiştir.

**Bulgular:** Çalışmaya akut EBV enfeksiyonu tanısı konan, ortanca yaşı dört (57 gün-18 yıl) olan 540 (%60.5)'ı erkek (erkek/kadın= 1.52) toplam 894 hasta dahil edilmiştir. Seropozitiflik oranı, yaş artıkça istatistiksel anlamlı olarak artmıştır (%47.9; %73.8 ve %87.2). Ortanca yaşı yedi (3-18 yaş) olan toplam 70 hasta enfeksiyöz mononükleoz kliniği ile başvurmuştur. Yaş gruplarına göre serum ortanca hemaoglobin, lökosit, trombosit, ortalama platelet hacmi değerleri anlamlı şekilde farklı bulunmuştur (p< 0.001). Lökositoz <6 yaş olan hastalarda, 6-15 yaş arası olanlara ve >15 yaş olanlara göre anlamlı şekilde daha sık saptanmıştır (%29.3 versus %17.1 ve %7.7 p< 0.001). Nötropeni 157 (%17.6) hastada saptanmıştır. Yaşla beraber ortalama platelet hacmi anlamlı olarak artmıştır (p< 0.001). MPV/platelet oranı yaş artıkça anlamlı olarak artmıştır (p< 0.001). MPV/platelet oranı enfeksiyöz mononükleoz kliniği olan hastalarda daha yüksek bulunmuştur. Serum C-reaktif protein yüksekliği <6 yaş hastalarda, 6-15 yaş arası hastalarda ve >15 yaş hastalarda daha sık saptanmıştır [304 (%49.4); 204 (%33.2); 107 (%17.4) p= 0.04].

**Sonuç:** EBV enfeksiyonu yaş gruplarına göre farklı klinik tablolara ve laboratuvar bulgularına neden olmaktadır.

**Anahtar Kelimeler:** Epstein-Barr virüs enfeksiyonu, enfeksiyöz mononükleosis, hematolojik bulgular, ortalama platelet hacmi, MPV/platelet oranı

**Correspondence Address/Yazışma Adresi**

**Kamile Arıkan**

İzmir Demokrasi Üniversitesi,
Buca Eğitim ve Araştırma Hastanesi,
Çocuk Enfeksiyon Hastalıkları Kliniği,
İzmir, Türkiye

**E-mail:** kamilearikan15@gmail.com

**Received:** 07.12.2021 **Accepted:** 25.06.2022 **Available Online Date:** 31.03.2023

## Introduction

Epstein-Barr virus (EBV) is an extremely common herpesvirus that is the etiologic agent of classic infectious mononucleosis (IM). In developing countries, EBV infection generally occurs at an early age; 80 to 100 percent of children become infected by the time they reach three to six years of age. In these settings, most children with primary EBV infection have clinically silent or mild disease. In privileged communities and in industrialized countries, primary infection with EBV commonly occurs later in life. In these settings and for reasons that are unclear, primary infection in older age groups, for example, in individuals between 10 and 30 years of age, is more likely to induce clinical symptoms, most often a mononucleosis syndrome (1,2).

Young adults who undergo primary infection are more likely to present with classic findings of IM. Most patients with IM have leukocytosis with an absolute increase in the number of peripheral mononuclear cells, heterophile antibodies, elevated serum aminotransferase levels, atypical lymphocytes and drug reactions. Mild thrombocytopenia occurs in 25% to 50% of patients and is rarely associated with symptoms. Severe thrombocytopenia rarely occurs. Mild elevation of hepatic transaminases is seen in approximately 50% of uncomplicated cases, but liver involvement is usually asymptomatic without jaundice (3-6).

Viral-specific diagnosis of EBV-associated primary infections as IM in immunocompetent individuals (and commonly in immunocompromised patients) usually requires three types of antibody analysis on acute serum: IgG to EB anti-viral capsid antigen (VCA IgG), IgM to EB VCA (VCA IgM), and IgG to anti-EBV nuclear antigen (EBNA IgG). Anti-VCA IgM antibody, however, quickly disappears, and false-positive IgM reactions occur due to cross-reactivity with other recent infections. Anti-early antigen (anti-EA) IgG was detected in only 60% of infants with anti-VCA-IgG seroconversion, and 12% of infants were found to have anti-EA-IgG delayed by four months. This variability of serologic findings complicates the diagnosis of IM, especially in children (8).

C-reactive protein (CRP) is an acute inflammatory protein that increases up to 1.000-fold at sites of infection or inflammation. CRP is synthesized primarily in liver hepatocytes but also by smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes. C-reactive protein is a marker for inflammation, and its levels increase during bacterial infection (10) However, the change in CRP level in viral infections is obscure (11,12).

The aim of the present study was to describe the clinical features and laboratory findings as well as CRP levels of children with acute EBV infection diagnosis in a pediatric infectious disease ward during an eight-year period.

## Materials and Methods

Patients diagnosed with acute EBV infection upon analysis of serum EBV antibodies between January 2010 and February 2017 at the infectious diseases department of a tertiary referral hospital were enrolled in this cross-sectional study.

### Enrollment Criteria

Among the patients aged 0-17 years with suspected acute EBV infection based on their symptoms and clinical findings, patients with anti VCA IgM ± EA positive and anti-EBNA IgG negative with ELISA-test (quantitative microplate ELISA Euroimmun®) were enrolled in the study. Patients were considered to have acute/primary EBV infection in the presence of EBV viral capsid antigen (VCA) IgM positivity while EBV nuclear antigen (EBNA) IgG was negative. Individuals with missing medical records or positive EBNA IgG result were not included in the study. The diagnosis of IM was based on clinical and serological findings. The presence of splenomegaly, posterior cervical adenopathy, axillary adenopathy, and inguinal adenopathy and positive serological test results were used to support the diagnosis of IM (13).

### Parameters Reviewed for Patients

The information obtained from the files of patients and other hospital records were entered into a standard data form and were encoded and transferred to a computerized setting. Laboratory tests of the patients were reviewed and recorded, including their hemoglobin values, leukocyte and thrombocyte counts, peripheral blood smear findings, presence of Downey cells, mean platelet volume (MPV), acute phase reactants [erythrocyte sedimentation rate (ESR), CRP levels], liver function test results [serum alanine aminotransferase (ALT)], aspartate aminotransferase (AST), total bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH)], VCA IgM, VCA IgG, EA and EBNA IgG tests, any antibody positivity or negativity against cytomegalovirus (CMV), rubella and other viruses, throat culture results. In EBV infected children diagnosed with the support of clinical and laboratory findings, false positivity of concomitantly sent other viral serological results were recorded.

### Statistical Analysis

Statistical analysis was performed using SPSS version 15.0 (IBM SPSS, Chicago, Illinois). Quantitative data were shown as mean ± standard deviation (SD) or median with interquartile ranges (Q1-Q3). Qualitative variables were expressed as absolute and relative frequencies. Chi-square, with Fisher's exact correction where required for discrete variables, and Student's t-test for parametric and Wilcoxon rank sum test for non-parametric continuous variables were used. Significance was set at $p< 0.05$.

## Results

Totally, 6538 EBV serological and/or microbiological test results were analyzed. Between January 2010 and February 2017, 894 patients were diagnosed as acute EBV infection and included into the study (Figure 1).

Of them, 541 (60.5%) patients were males (male/female= 1.52). Median age of the patients was four years (57 days-18 years). Majority of EBV infected children were under six years old of age (n= 518, 57.9%), followed by 228 (25.5%) children between 6-15 years old of age and 148 (16.6%) children above 15 years old of age. Most of the EBV infected cases were in winter and early spring months (Figure 2). The most common symptom of the patients on admission was fever (n= 222, 24.8%). Other frequent symptoms were as follows: sore throat (n= 194, 21.7%), neck swelling (n= 68, 7.6%), rash (n= 54, 6%), respiratory symptoms (n= 23, 2.6%), abdominal pain (n= 17, 1.9%) and diarrhea (n= 5, 0.6%) (Table 1). History of fever for longer than five days was present in 118 (13.2%) patients. Prolonged fever was statistically more common in children

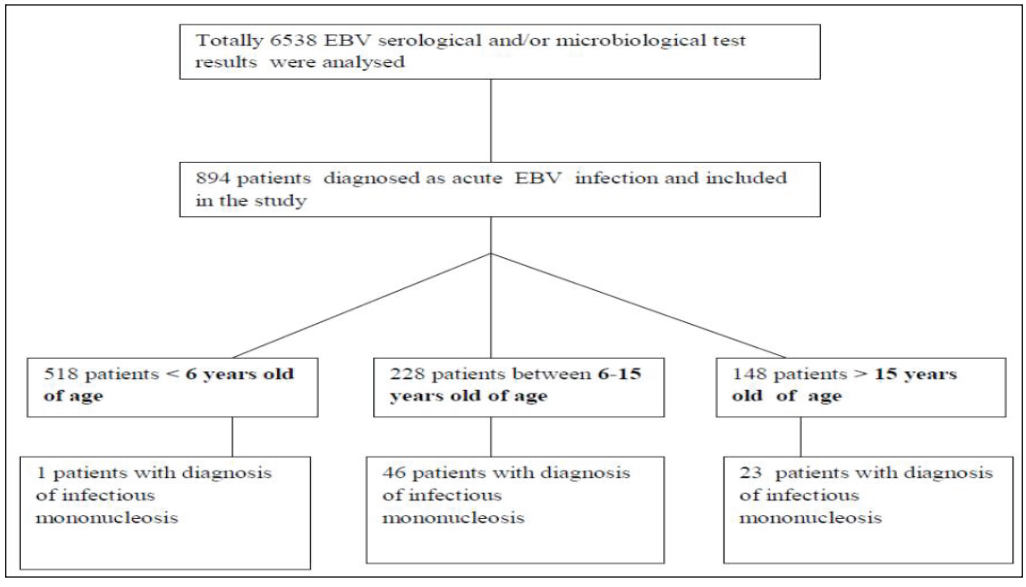


**Figure 1.** Flow chart of the cases according to age groups.

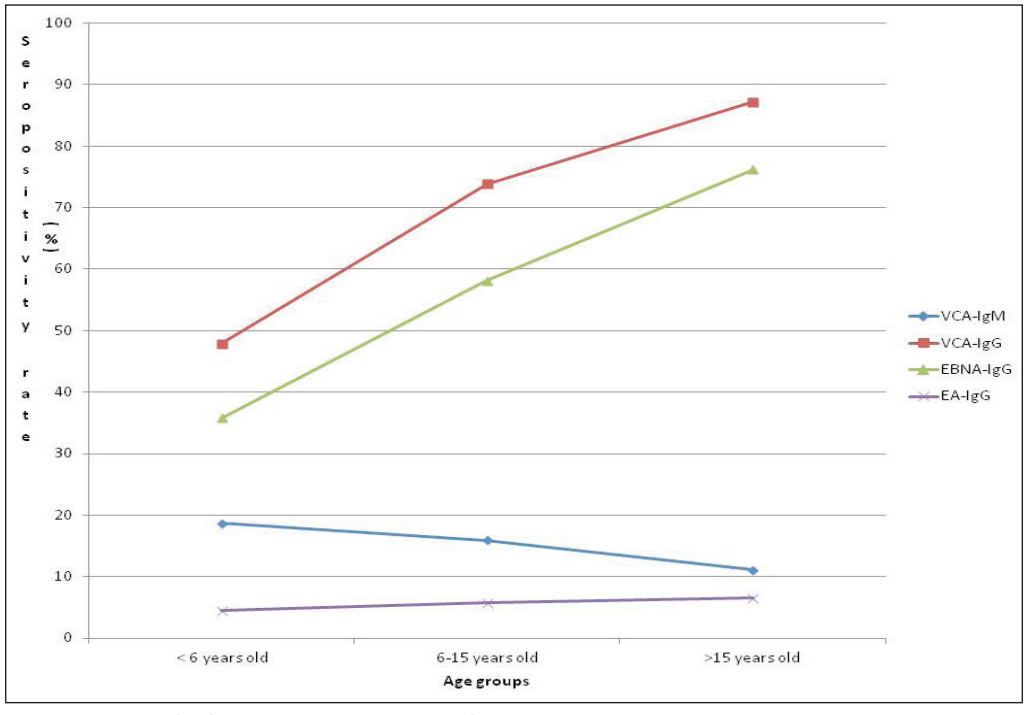


**Figure 2.** EBV antibody seropositivity rates according to age groups.

**Table 1.** Sociodemographic variables and clinical presentations of EBV infected children

| Variable | n= 894 |
|---|---|
| **Age*** | Four years (57 days-17 years) |
| **Sex**** | |
| **Female** | 75 (39.5) |
| **Male** | 541 (60.5) |
| **Clinical symptoms**** | |
| **Fever** | 222 (24.8) |
| **Sore throat** | 194 (21.7) |
| **Neck swelling** | 68 (7.6) |
| **Rash** | 54 (6) |
| **Respiratory symptoms** | 23 (2.6) |
| **Abdominal pain** | 17 (1.9) |
| **Diarrhea** | 5 (0.6) |

*: median (minimum-maximum).
**: n (%).

<6 years old of age (n= 78, %66.1, p= 0.045). Seropositivity rate increased statistically as age increased (47.9%, 73.8% and 87.2%, respectively). Seventy patients were admitted with clinical presentation of IM with a median age of seven years (3 years-18 years). Majority of the children with IM clinical presentation was above six years old of age (98.6%). Rash was more commonly seen as a presenting sign under six years old of age (90.6%).

Serum median hemoglobin, leukocyte, thrombocyte, mean platelet values were statistically significantly different according to age groups (for all p< 0.001, Table 2). Leukocytosis was more commonly encountered in EBV infected children <6 years old of age, compared to 6-15 years old age and >15 years old of age (29.3% versus 17.1% and 7.7% respectively, p< 0.001). Neutropenia was present in 157 (17.6%) patients. Majority of the children with EBV related neutropenia was under six years old of age (58.7%). Thrombocytopenia was encountered in 96 (10.7 %) patients. Serum CRP was high in 295 (33.1%) patients. High serum CRP was more commonly encountered in EBV infected children <6 years old of age, compared to 6-15 years old age and >15 years old of age [155 (52.5%), 95 (32.2%), 45(15.3%), respectively, p= 0.04].

Sedimentation rate was high in 17.9% of the patients. High sedimentation rate was more commonly encountered in EBV infected children between 6-15 years old age, compared to <6 years old of age and >15 years old of age (41.4%, 39.8%, 36.4%, respectively, p= 0.8). Serum ALT and AST were high in 170 (19%) and 162 (18.1%) patients, respectively. Serum lactate dehydrogenase level (LDH) was statistically higher in children under six years old of age, compared to 6-15 years old age and >15 years old of age [431 IU/L (28-2450), 414 IU/L (44-5297), IU/L 321 (51-1820), respectively, p= 0.002].

Laboratory findings of EBV infected children according to age groups are depicted in Table 2 and Figure 2.

Under the study conditions, no co-infections were observed.

Mean platelet volume (MPV) increased statistically significantly as age increased (p< 0.001). MPV/platelet ratio increased significantly as age increased (p< 0.001). MPV/platelet ratio was higher in IM cases, but it was not statistically significant. In patients with IM clinical presentation, serum ALT was statistically significantly higher when compared to patients without IM clinical presentation (p= 0.017).

False positivity of serological tests was encountered in 73 (8.2%) EBV infected cases, mostly with cytomegalovirus serological tests.

**Table 2.** Laboratory findings of children with acute Epstein-Barr Virus (EBV) infection according to age groups

| | Age groups | | | |
|---|---|---|---|---|
| | <6 years | 6-15 years | >15 years | p |
| **Hemoglobin (gr/dL)*** | 11.6 (6.8-14.6) | 12.5 (8.5-16.7) | 12.4 (9.8-15.5) | **<0.001** |
| **Leucocyte (x10$^3$/µL)*** | 12.1 (1.4-34.5) | 10.9 (1.3-41.5) | 8.8 (3.4-17.1) | **<0.001** |
| **Trombocyte (x10$^3$/µL)*** | 270 (14-596) | 247 (83-1.800) | 216 (112-322) | **<0.001** |
| **Mean platelet volume (fL)*** | 7.5 (5.6-14) | 7.7 (5.5-10.6) | 8.1 (6.4-12.1) | **<0.001** |
| **Serum AST (IU/L)*** | 38 (1-671) | 52 (1-365) | 60 (2-237) | 0.49 |
| **Serum ALT** | 33 (6-910) | 43 (8-792) | 58 (7-358) | 0.12 |
| **Serum LDH (IU/L)*** | 431 (28-2450) | 414 (44-5297) | 321 (51-1820) | **0.002** |
| **C-reactive protein (gr/dL)*** | 1.21 (0-30) | 1 (0.1-38) | 0.65 (0.12-9.1) | 0.95 |
| **Sedimentation (mm/hour)*** | 17 (2-86) | 15 (2-86) | 13 (2-55) | 0.45 |

*:median (minimum-maximum)
AST: Aspartate aminotransferase, ALT:Alanine aminotransferase, LDH: Lactate dehydrogenase.

## Discussion

Herein, we analyzed laboratory parameters and clinical presentations of EBV infected patients according to age groups. Majority of acute EBV infected children were under six years old of age. In a study conducted in primary EBV infected 103 children, with a median age of seven years (3-12.5 years), authors have concluded that primary infection by EBV mainly occurs in younger children, with a predominance of oligosymptomatic presentations, similar to our findings (12).

EBV seropositivity rate was 87.9% after 15 years old age. From two recent studies of EBV seroprevalence in children and teenagers in the U.S. ranging from 6 to 19 years old conducted by the National Health and Nutrition Examination Surveys (NHANES), authors have concluded that the seroprevalence of six to eight-year-olds during 2009-2010 was 50% and 54.1%, and in 18 and 19-year olds, the seroprevalence was 82.9 and 89%, respectively, similar to our results (14,15)

Prolonged fever and rash were more commonly seen as presenting signs under six years old of age in our study population. In a study from Spain, the most common symptoms have been reported as fever, lymphadenopathy and exudative tonsillitis. In that study, almost two-thirds of the patients presented with typical clinical signs of mononucleosis syndrome (12). Our results showed that only 7.8% of the patients were diagnosed as IM. This low rate may be attributable to the retrospective nature of the study in which we focused on laboratory results. Majority of the children with IM clinical presentation was above six years old of age. In industrialized countries, EBV-associated IM is considered to occur most often in adolescents and young adults while younger children are often described with a mild subclinical primary EBV infection. In a study conducted in 95 children divided into three age groups (0-4 years, 5-10 years and 11-15 years), similar to our study, authors have concluded that the oldest age groups significantly more frequently suffered from headache, tonsillitis, sore throat, abdominal pain and nausea. Young children were typically found to present with a runny nose, fever, fatigue and cervical adenitis (16).

Laboratory findings can be encountered in a wide variety. Leukocytosis and lymphocytosis are the most frequent EBV associated laboratory findings, and these findings can change according to age groups (16). In our results, serum median hemoglobin, leukocyte, thrombocyte, mean platelet values were statistically significantly different between the age groups. Leukocytosis was more commonly encountered in EBV infected children <6 years old of age, compared to 6-15 years old age and >15 years old of age. In a study conducted in 89 EBV infected children, it has been concluded that 32 patients (36.0%) showed high peripheral blood leukocytes, and the highest incidence was seen in the age group of 0-4 years, similar to our findings (17).

In our results, MPV increased as age increased. MPV mainly reflects proliferation, metabolism and platelet production of megakaryocytes in the bone marrow. In addition, it reflects the survival time of platelets in the circulation. When the function of myeloproliferation is normal, the decrease in the number of platelets stimulates the production of large-volume platelets by megakaryocytes, resulting in an increase in MPV. In our results, mean platelet volume and MPV/platelet ratio increased significantly as age increased ($p< 0.001$). MPV/platelet ratio was higher in IM cases but not statistically significant. In a study conducted in 141 children with EBV related IM clinical presentation, authors have concluded that MPV/PLT ratio may be a novel diagnostic indicator for pediatric IM (18).

Serum LDH was statistically higher in children under six years old of age compared to 6-15 years old age and >15 years old of age. In patients with IM, serum ALT was statistically significantly higher. In a study conducted in 110 acutely EBV infected children, serum LDH was elevated in children between 5-15 years old of age (16).

Interesting finding of our study concluded that serum CRP was high in one third of the patients. There are limited number of studies regarding CRP level and acute EBV infection. In a study conducted in 200 adolescents, CRP has been found to correlate to chronic fatigue syndrome after EBV infection (19). CRP is mainly synthesized by the liver and is regulated by pro-inflammatory cytokines, primarily tumor necrosis factor alpha, and interleukin. In healthy individuals, CRP is found in trace amounts with a median plasma concentration of 0.8 mg/L, while CRP values rise sharply up to 1.000-fold after an inflammatory stimulus. CRP remains stable over prolonged time periods and has a half-life of 19-20 hours (20). Although CRP was thought as a marker of bacterial infection, CRP has been found to be a predictor of respiratory failure in COVID-19 patients in some studies (21). In other studies, increased levels of CRP have been found in patients infected with the most virulent types of influenza A virus. Thus, human influenza disease outcome has been associated with enhanced production of CRP, with the highest CRP levels correlating with the more severe symptoms and even mortality (22). In another study, higher values of CRP were found in exanthematic virus infection compared to respiratory virus infection (11).

Our study had some limitations due to its retrospective design. The data of the study was obtained from files and computer records of our hospital, and therefore some of the data may not be available. In addition, we had no data available for longer follow-up to have an opinion about the long term complications of EBV.

The present study demonstrates that acute EBV infection results in different clinical presentations and different laboratory findings in different age groups and can cause IM clinical presentation even in the preschool period. Serum CRP may be high in children mostly under six years old. This study shows that CRP values do not discriminate every viral and bacterial infections. More studies are needed to explain pathogenesis of serum CRP values in EBV infected children.

**Ethics Committe Approval:** This study was approved by Hacettepe University Non-Invasive Clinical Research Ethics Committee (Decision no: GO 16/747-12, Date: 20.12.2016).

**Informed Consent:** Patient consent was obtained.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept- KA, EKÖ; Design- KA; Supervision- All of authors; Resource- KA; Data Collection and/or Processing- KA; Analysis and/or Interpretation- KA, EKÖ; Literature Search - All of authors; Writing- KA; Critical Review- All of authors.

**Conflict of Interest:** All authors declare that they have no conflicts of interest or funding to disclose.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

1. *Sitki-Green DL, Edwards RH, Covington MM, Raab-Traub N. Biology of Epstein-Barr virus during infectious mononucleosis. J Infect Dis 2004;189:483-92. https://doi.org/10.1086/380800*
2. *Kimura H, Hoshino Y, Kanegane H, Tsuge I, Okamura T, Kawa K, et al. Clinical and virologic characteristics of chronic active Epstein-Barr virus infection. Blood 2001;98:280-6. https://doi.org/10.1182/blood.V98.2.280*
3. *Koutras A. Epstein-Barr virus infection with pancreatitis, hepatitis and proctitis. Pediatr Infect Dis 1983;2:312-13. https://doi.org/10.1097/00006454-198307000-00014*
4. *Nowalk A, Green M. Epstein-Barr virus. Microbiol Spectr 2016;4(3):10. https://doi.org/10.1128/microbiolspec.DMIH2-0011-2015*
5. *Cohen JI. Epstein-Barr virus infection. N Engl J Med 2000;343(7):481-92. https://doi.org/10.1056/NEJM200008173430707*
6. *Dunmire SK, Verghese PS, Balfour HH Jr. Primary Epstein-Barr virus infection. J Clin Virol 2018;102:84-92. https://doi.org/10.1016/j.jcv.2018.03.001*
7. *Kawa K. Epstein-Barr virus-associated diseases in humans. Int J Hematol 2000;71(2):108-17.*
8. *Niller HH, Bauer G. Epstein-Barr virus: Clinical diagnostics. Methods Mol Biol 2017;1532:33-55. https://doi.org/10.1007/978-1-4939-6655-4_2*
9. *Chen HS, Ho MC, Hu RH, Wu JF, Chen HL, Ni YH, et al. Roles of Epstein-Barr virus viral load monitoring in the prediction of posttransplant lymphoproliferative disorder in pediatric liver transplantation. J Formos Med Assoc 2019;118(9):1362-8. https://doi.org/10.1016/j.jfma.2018.12.007*
10. *Black S, Kushner I, Samols D. C-reactive protein. J Biol Chem 2004;279(47):48487-90. https://doi.org/10.1074/jbc.R400025200*
11. *Durán A, González A, Delgado L, Mosquera J, Valero N. Serum level of C-reactive protein is not a parameter to determine the difference between viral and atypical bacterial infections. J Med Virol 2016;88(2):351-5. https://doi.org/10.1002/jmv.24341*
12. *García-Peris M, Jiménez Candel MI, Mañes Jiménez Y, Pariente Martí M, González Granda D, Calvo Rigual F. Primoinfección por el virus de Epstein-Barr en niños sanos [Epstein-Barr virus primary infection in healthy children]. An Pediatr (Barc) 2019;90(6):376-85. https://doi.org/10.1016/j.anpedi.2018.09.003*
13. *American Academy of Pediatrics. [Epstein-Barr Virus Infections (Infectious Mononucleosis).] In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2015 Report of the Committee on Infectious Diseases. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015:336-40.*
14. *Dowd JB, Palermo T, Brite J, McDade TW, Aiello A. Seroprevalence of Epstein-Barr virus infection in U.S. children ages 6-19, 2003-2010. PLoS One 2013;8(5):e64921. https://doi.org/10.1371/journal.pone.0064921*
15. *Balfour HH Jr, Sifakis F, Sliman JA, Knight JA, Schmeling DO, Thomas W. Age-specific prevalence of Epstein-Barr virus (EBV) infection among children in the United States and factors affecting its acquisition. J Infect Dis 2013;208(08):1286-93. https://doi.org/10.1093/infdis/jit321*
16. *Topp SK, Rosenfeldt V, Vestergaard H, Christiansen CB, Von Linstow ML. Clinical characteristics and laboratory findings in Danish children hospitalized with primary Epstein-Barr virus infection. Infect Dis (Lond) 2015;47(12):908-14. https://doi.org/10.3109/23744235.2015.1082036*
17. *Cheng H, Chen D, Peng X, Wu P, Jiang L, Hu Y. Clinical characteristics of Epstein-Barr virus infection in the pediatric nervous system. BMC Infect Dis 2020;20(1):886. https://doi.org/10.1186/s12879-020-05623-1*
18. *Han X, Xu P, Duan X, Liu Y, Zhang J, Xu H. High mean platelet volume-to-platelet count ratio as a diagnostic maker for increased risk of liver function damage in pediatric patients with infectious mononucleosis in China. Exp Ther Med 2019;18(6):4523-7. https://doi.org/10.3892/etm.2019.8104*
19. *Pedersen M, Asprusten TT, Godang K, Leegaard TM, Osnes LT, Skovlund E, et al. Predictors of chronic fatigue in adolescents six months after acute Epstein-Barr virus infection: A prospective cohort study. Brain Behav Immun 2019;75:94-100. https://doi.org/10.1016/j.bbi.2018.09.023*
20. *Slaats J, Ten Oever J, van de Veerdonk FL, Netea MG. IL-1β/IL-6/CRP and IL-18/ferritin: Distinct inflammatory programs in infections. PLoS Pathog 2016;12(12):e1005973. https://doi.org/10.1371/journal.ppat.1005973*
21. *Poggiali E, Zaino D, Immovilli P, Rovero L, Losi G, Dacrema A, et al. Lactate dehydrogenase and C-reactive protein as predictors of respiratory failure in COVID-19 patients. Clin Chim Acta 2020;509:135-8. https://doi.org/10.1016/j.cca.2020.06.012*
22. *Perez L. Acute phase protein response to viral infection and vaccination. Arch Biochem Biophys 2019;671:196-202. https://doi.org/10.1016/j.abb.2019.07.013*