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ORIGINAL ARTICLE

AN INVESTIGATION OF THE EPSTEIN-BARR VIRUS SEROLOGICAL STATUS IN THE ADULT POPULATION

ISPITIVANJE SEROLOŠKOG STATUSA NA EPŠTAJN-BAROV VIRUS U ODRASLOJ POPULACIJI

Milica Mladenović[1], Aleksandra Knežević[1,2]

[1] Univerzitet u Beogradu, Medicinski fakultet, Beograd, Srbija
[2] Univerzitet u Beogradu, Medicinski fakultet, Institut za mikrobiologiju i imunologiju, Beograd, Srbija

Correspondence: milica.cole6@gmail.com

Abstract

Introduction: Epstein-Barr virus is a ubiquitous virus from the family *Herpesviridae*, with seroprevalence > 90% of the world population. Primary infection is asymptomatic or in the form of infectious mononucleosis, depending on the age and immune status. The EBV establishes a latent infection in B-lymphocytes with occasional reactivation, and because of its oncogenic potential, there is an association with numerous malignancies. Data on the EBV seroprevalence in our population is scarce.

Aim: The study aims to investigate the EBV serological status in the adult population by detecting specific antibodies against viral antigens.

Material and methods: Serum samples of 58 individuals (age: 30.8 ± 13.7 years; gender: M = 41.4%, F = 58.6%) were tested with commercial ELISA kits (*Euroimmun*, Germany) for the presence of four antibodies against EBV (anti-VCA-IgM, anti-VCA-IgG, anti-EA-IgG, anti-EBNA-IgG). Based on recommendations from the literature, every patient was, depending on serology results, classified in an appropriate profile of EBV infection (primary, latent, or reactivation).

Results: In the 89.5% serum samples, antibodies against EBV were detected, with an increasing trend of seropositive patients with age, from 87% seropositive samples in the population 18 - 30 years, to 94.7% in the ≥ 31 age group. The profile of latent infection was detected in 81% of patients, 3.4% profile of primary infection, 3.4% profile of reactivated infection and 1.7% of indeterminate profile. There was no significant difference ($p < 0.05$) between titers of anti-VCA-IgG or anti-EBNA-IgG antibodies in different age groups, nor between genders. The significant difference was not found ($p < 0.05$) in the number of EBV seropositive samples between genders nor between age groups.

Conclusion: The study showed a high rate of latent EBV infection of 81%, which stipulates a high grade of EBV infection in the studied population. No difference in the seroprevalence among genders was found, nor among different age groups. Follow-up investigation of EBV seroprevalence in our population is needed in order to monitor the number of reactivated infections and the development of malignancies associated with EBV.

Keywords:
Epstein-Barr virus,
seroprevalence,
latency,
anti-EBV antibodies

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Sažetak

Uvod: Epštajn-Barov virus (EBV) je ubikvitarni virus iz familije *Herpesviridae*, pri čemu antitela na ovaj virus ima > 90% svetske populacije. Primarna infekcija prolazi kao asimptomatska ili u obliku infektivne mononukleoze, zavisno od uzrasta i imunološkog statusa pojedinca. Virus uspostavlja latentnu infekciju u B-limfocitima, sa povremenom reaktivacijom, a zbog svog onkogenog potencijala povezan je sa pojavom brojnih maligniteta. Podaci o EBV seroprevalenciji u populaciji zdravih odraslih osoba iz Srbije su oskudni.
Cilj: Cilj rada je ispitivanje serološkog statusa na EBV u odrasloj populaciji dokazivanjem specifičnih antitela na antigene virusa.
Materijal i metode: Uzorci seruma 58 ispitanika (starost: 30,8 ± 13,7 godina; pol: M = 41,4%, Ž = 58,6%) testirani su pomoću komercijalnih ELISA testova (*Euroimmun*, Nemačka) na prisustvo četiri antitela protiv EBV (anti-VCA-IgM, anti-VCA-IgG, anti-EA-IgG i anti-EBNA-IgG). Na osnovu preporuka iz literature, svaki ispitanik je, u zavisnosti od rezultata serološkog testa, svrstan u odgovarajući profil EBV infekcije (primarna, latentna, reaktivacija).
Rezultati: U 89,5% uzoraka seruma naših ispitanika dokazana su antitela protiv EBV sa trendom porasta procenta seropozitivnih sa godinama starosti: od 87% seropozitivnih u populaciji 18 - 30 godina do 94,7% u grupi ≥ 31 godine. Profil latentne infekcije je imalo 81% ispitanika, 3,4% ispitanika profil primarne infekcije, 3,4% profil reaktivirane infekcije, a 1,7% neodređeni profil. Nije pronađena statistički značajna razlika ($p < 0,05$) između titra anti-VCA-IgG niti anti-EBNA-IgG antitela u različitim starosnim grupama, kao ni između polova. Takođe nije pronađena značajna razlika ($p < 0,05$) ni između broja EBV seropozitivnih osoba među polovima, ni među starosnim grupama.
Zaključak: Naše istraživanje je pokazalo visoku stopu latentne EBV infekcije (81%), što ukazuje na visok stepen prokuženosti ispitivane populacije ovim virusom. Razlike u seroprevalencjii između polova, kao ni između različitih starosnih grupa nisu pronađene. Dalje istraživanje EBV seroprevalencije u našoj populaciji potrebno je zbog praćenja broja reaktiviranih infekcija, asocijacije sa razvojem malignih bolesti, kao i zbog potencijalnog razvoja i primene vakcine protiv EBV.

Ključne reči:
Epštajn-Barov virus,
seroprevalencija,
latencija,
anti-EBV antitela

Introduction

Epstein-Barr virus (EBV) belongs to the family of *Herpesviridae* and sub-family of *Gammaherpesvirinae*, known also as Human Herpes virus 4 (1, 2). It is transmitted through saliva and can infect oropharyngeal epithelial cells and local B lymphocytes. Primary infection is usually asymptomatic or in the form of mononucleosis (2, 3). Virus can also establish a latent infection in memory B cells, where the viral DNA persists in the episomal form (1). The EBV episomes can disrupt cellular gene expression and contribute to carcinogenesis, which underlies the virus's oncogenic potential (4). Malignancies associated with EBV infection primarily include hematological lymphoproliferative disorders and oropharyngeal carcinoma, among others (1).

It is an ubiquitous virus with over 90% seroprevalence in the global adult population (5,6). The period of primary infection depends on geographic region, population density, and socioeconomic status. Early-life infection, common in overcrowded and low-income regions, is usually asymptomatic. In developed countries, infection occurs mostly in adolescence or later, often presenting as infectious mononucleosis (3,6,7).

During EBV infection, an immune response is triggered against various viral antigens. Primary infection involves the production of IgM and IgG antibodies targeting the viral capsid antigen (anti-VCA) and early antigen (anti-EA) (8,9). As the infection transitions from primary to latent phase, viral gene expression changes, and antibodies against the EBV nuclear antigen (anti-EBNA) are synthesized (2). The presence or absence of IgM and/or IgG antibodies to different viral antigens indicates the patient's serological status, reflecting various stages of EBV infection (primary, latent, or reactivated). Serological diagnostics are the method of choice for assessing EBV serological status due to their simplicity, cost-effectiveness, and high sensitivity and specificity (5).

Given the limited data on EBV seroprevalence in our population, this study aims to assess the serological status of EBV in the adult population of Serbia by detecting specific antibodies to viral antigens.

Material and methods

The study included 58 participants who underwent examinations at the Faculty of Dental Medicine in Belgrade between September 2021 and June 2022. Among the participants, 34 were women (58.6%) and 24 were men (41.4%). The youngest participant was 18 years old, and the oldest was 68 (mean age 30.8 ± 13.7 years). Based on age, participants were divided into two groups: 18 – 30 years and ≥ 31 years (**Table 1**).

With consent, peripheral blood samples were taken

by venipuncture, centrifuged at 3000 rpm for 5 minutes to separate plasma, and stored at -20 °C until antibody testing. Gender and age data were obtained from patient records.

Table 1. The number of participants by age group and gender

Age group (years)	Woman	Man	The total number of participants by age group (% from total sample)
18-30	22	17	39 (67.2%)
≥ 31	12	7	19 (32.8%)

Serological methods

The EBV serological testing was performed at the Virology Laboratory of the Institute of Microbiology and Immunology, University of Belgrade. Commercial ELISA tests from *Euroimmun* (Germany) were used: Anti-VCA ELISA IgG, Anti-VCA ELISA IgM, Anti-EBNA-1 ELISA IgG, and Anti-EBV-EA-D ELISA IgG. The IgG titers were expressed in RU/mL. After constructing the calibration curve using two standards with known antibody titers (20 RU/mL and 200 RU/mL), the results were interpreted. A positive result for IgG antibodies was defined as a titer greater than 20 RU/mL. Also, IgM antibodies were determined semi quantitatively based on the serum to calibrator extinction ratio, with a ratio ≥ 1.1 considered positive.

Understanding the dynamics and combinations of different EBV antibodies' appearance allows the serological profile to accurately indicate the stage of EBV infection (8). The EBV infection status was determined according to the recommendations in **Table 2** (10).

Table 2. Interpretation of EBV infection status based on results of serological analysis

	EBV-*VCA*-IgG	EBV-*VCA*-IgM	EBV-*EA*-IgG	EBV-EBNA-IgG
No infection	-	-	-	-
Primary infection	+/-	+	+/-	-
Latent infection	+	-	-	+
Reactivation	+	-	+	+

Statistical analysis

Statistical analysis was performed using the Easy R (EZR) software. Depending on the data type, appropriate tests were applied (Fisher's test, Mann-Whitney U test). The analysis was conducted at a significance level of 0.05 ($\alpha = 0.05$), with conclusions drawn based on p-values, considering a result statistically significant if $p \leq 0.05$.

Results

The presence of at least one type of anti-EBV antibody was detected in 52/58 participants (89.5%). In the female group, 26/34 (76.4%) serum samples were seropositive, while in the male group, 21/24 (87.5%) were seropositive. No statistically significant difference ($p>0.05$) was found in the number of seropositive samples between genders.

Table 3 presents the results of individual EBV antibody analyses.

Table 3. Results of serological analyses by antibody type

	EBV-*VCA*-IgG	EBV-*VCA*-IgM	EBV-*EA*-D-IgG	EBV-EBNA-IgG
Number of positive patients/total number of patients (%)	50/58 (86.2%)	2/58 (3.4%)	2/58 (3.4%)	50/58 (86.2%)
Range of antibody concentration (RU/ml)	22 - 200	1.38 - 1.61	53.6 - 69.5	25.6 - 200
Median of antibody concentration	116.05	1.5	61.5	127

Analysis showed an increasing trend in seropositive individuals with age, from 87% (34/39 samples) in the age group 18 - 30 years, to 94.7% (18/19 samples) in the group ≥ 31 years. However, no statistical significance was found ($p > 0.05$).

Anti-VCA-IgG antibodies were found in 86.2% of participants, with a high median titer value (**Table 3**). Of the 50 positive participants for anti-VCA-IgG, 22 were men (44%) and 28 were women (56%). No significant difference in median antibody concentrations was found between genders (F = 119,2; M = 118) ($p > 0.05$). Median antibody concentrations by age group are shown in **Table 4**. No significant difference in antibody concentration or seropositivity was found across age groups ($p > 0.05$).

Table 4. Median of EBV-VCA-IgG antibody concentration

Age group (years)	Median of anti-*VCA*-IgG antibody titer (RU/ml)	% seropositive samples for anti-*VCA*-IgG
18 - 30	117.10	85%
≥ 31	113.5	89.5%

A positive result for anti-VCA-IgM antibodies was found in 2 individuals (**Table 3**), one male and one female, both belonging to the youngest age group (18 - 30 years).

Anti-EA-D-IgG antibodies were detected in two female patients (**Table 3**), aged 23 and 38, with no statistically significant difference between genders ($p > 0.05$).

Anti-EBNA-IgG antibodies were detected in 50 participants, with a high median titer value (**Table 3**), of which 21 were male (42%) and 29 female (58%). After applying the Mann-Whitney U test, no statistically significant difference in median antibody titers was found between genders (F = 121.2, M = 128.4) ($p > 0.05$). No significant difference ($p > 0.05$) was found in median antibody concentrations

across age groups, as shown in **Table 5**. Fisher's test revealed no significant difference in seropositivity percentages across age groups ($p > 0.05$).

Table 5. Median of anti-EBNA-IgG antibody concentration

Age group (years)	Median of anti-*EBNA*-IgG antibody titer (RU/ml)	% seropositive samples for anti-*EBNA*-IgG
18 - 30	123.8	82%
≥ 31	157.6	94.7%

Table 6 presents the combinations of antibodies observed in this study, the number of participants, and the stage of EBV infection indicated.

Table 6. Overall results for EBV seroprevalence in the studied population

	anti-*VCA*-IgG	anti-*VCA*-IgM	anti-*EA*-IgG	anti-EBNA-IgG	*N* - number of participants (%)	
Primary infection	+	+	-	-	1 (1.7%)	2 (3.4%)
	-	+	-	-	1 (1.7%)	
Reactivation	+	-	+	+	2 (3.4%)	
Latent infection	+	-	-	+	47 (81%)	
Indeterminate	-	-	-	+	1 (1.7%)	

The majority of participants (81%) had a profile of old/latent infection (**Table 6**). All participants with this profile were positive for two antibodies, the main markers of old infection, anti-VCA-IgG and anti-EBNA-IgG (8). The latent infection status was present in 21 men (44.7%) and 26 women (55.3%) ($p > 0.05$). The percentage of patients with latent infection increased with age, from 79.5% in the 18 - 30 years group, to 84.2% in the group ≥ 31 years. No statistically significant difference in the prevalence of latent infection across age groups was found ($p > 0.05$).

Primary infection was found in 2 patients (3.4%) with different serological results. One was positive only for anti-VCA-IgM, while the other had both IgM and IgG antibodies, with both profiles indicating primary infection (**Table 6**).

The profile of EBV reactivation was observed in 2 individuals (3.4%). Both had identical antibody test results, with positive anti-VCA-IgG, anti-EBNA-IgG, and anti-EA-IgG antibodies, which are produced against antigens from the lytic phase of the viral cycle (11).

One participant (1.7%) had an indeterminate infection profile due to the serological result showing positivity only for anti-EBNA-IgG.

Discussion

As an ubiquitous virus, EBV is capable of infecting individuals at any stage of life. Given its association with various tumors and the development of potential vaccines, understanding the serological status of the population is important (7). The detection of four antibodies against EBV antigens allows for serological determination of the infection stage (12), which was utilized in this study to identify EBV infection profiles.

A few days after EBV infection, seroconversion begins with the synthesis of anti-VCA IgM antibodies, which decrease within 2 - 6 months and rarely reappear, making them a marker of primary infection (12). Anti-VCA antibodies transition to the IgG class shortly after infection, with high titers persisting for life (7). Therefore, patients with anti-VCA IgM, with or without anti-VCA IgG, exhibit a primary EBV infection profile, observed in two participants (3.4%) in this study. The low number of primary infections aligns with the predominantly healthy population in the sample, supported by Smatti et al. (13), who found only 1.8% primary infections among 673 healthy blood donors. In contrast, Brkić et al. (8) reported anti-VCA IgM antibodies in all patients with infectious mononucleosis, which demonstrates how the choice of population (healthy vs. ill) influences the expected prevalence of these antibodies. Banko et al. (14) reported a seroprevalence of 18% for active primary EBV infection in their Serbian patient cohort - a value that, although slightly higher than the primary infection rate observed in our study, still speaks in support of a low prevalence of active primary infection in healthy individuals.

Both patients with primary infection in this study were aged between 18 and 30 years, which corresponds with the fact that most primary EBV infections and seroconversions occur in childhood and young adulthood (15).

A significant proportion of participants (86.2%) tested positive for anti-VCA-IgG. These findings align with literature reports, showing anti-VCA-IgG detection in 93% of samples in Tehran (16), 97.9% in Qatar (13), and 85% in Brazil (17).

The EBNA protein is crucial for maintaining the episome and viral latency and is not produced during the lytic phase of the viral cycle, making it a reliable marker of latent infection (3, 5, 9). A high percentage of anti-EBNA-IgG seropositive individuals was observed in study (86%), consistent with findings by Smatti et al. (13) and Lindsay et al. (9). Routine testing for IgM anti-EBNA-1 antibodies is not performed due to frequent cross-reactivity with cytomegalovirus and parvovirus B19 antigens (5).

Since the median concentration differences between genders for anti-VCA-IgG were 5.5 and for anti-EBNA-IgG 7.2, no statistically significant difference was observed for either antibody ($p > 0.05$). This aligns with literature findings, such as a study in Brazil that reported no significant gender-based differences in anti-VCA-IgG titers, reflecting the ubiquitous nature of the virus.

Due to its long persistence in serum, positive anti-VCA-IgG with a negative anti-VCA-IgM result is considered the primary marker of latent infection (5). Another key marker is anti-EBNA-IgG, which is less sensitive than anti-VCA-IgG, as studies show that 5 - 10% of infected individuals never develop detectable levels of this antibody (5). These findings suggest that the presence of anti-VCA-IgG, with or without anti-EBNA-IgG, serves as the criterion for confirming latent infection. In this study, 81% of participants met these criteria, indicating that the majority of the sampled population had previous EBV exposure, resulting in latent infection. This outcome aligns with expectations, given the ubiquitous nature of EBV (13), and is consistent with the literature, where Abrahamyan et al. (18) reported 80 - 100% of samples with latent infection in the general population.

The number of patients with latent infection increased with age, from 79.5% in the 18 - 30 age group to 84.2% in the ≥ 31 age group. A similar trend was observed in the study by German researchers, where the prevalence continued to rise even after age 50 (18).

During the lytic cycle of the virus, which occurs during primary infection and reactivation, EBV early antigens (EA) are expressed, triggering the production of anti-EA antibodies (5,8,9). A high titer of anti-EA antibodies is also found in patients with lymphoproliferative disorders (8). As anti-VCA-IgG and anti-EBNA-IgG are markers of past infection, and anti-EA-IgG indicates active viral replication, the presence of all three antibodies suggests reactivation of latent infection. This combination was observed in two female participants (3.4%). Reactivation is often triggered by biological or psychological stress or immunosuppressive therapy, implying that factors compromising the immune system likely contributed to the reactivation in these cases (19). The findings align with the literature, as Wood et al. (20) reported only 13% positive anti-EA-IgG results in healthy controls, compared to 39% in patients with systemic lupus erythematosus.

Monitoring the number of reactivated infections is crucial for early prevention and screening of EBV-associated malignancies, as well as for planning and directing healthcare resources toward these conditions.

Only one participant had an indeterminate infection profile, where only anti-EBNA-IgG antibodies were detected. This result is insufficient for definitive confirmation of latent infection (10). According to Eksi et al. (12), a possible explanation for such a finding is the loss of anti-VCA-IgG from a previous infection. For more accurate confirmation of the infection status in this individual, advanced methods such as immunoblot tests, anti-VCA-IgG avidity assay, or viral genome detection could be employed (12).

Numerous studies worldwide have demonstrated a high prevalence of EBV seropositivity (**Figure 1**). In the United Kingdom, Winter et al. (15) reported 74.6% seropositive samples among healthy adults, while Fourcade et al. (21) in France found similar rates of 82 - 88%. Comparable results were observed globally, with Balfour et al. (7) reporting 88% seropositivity and Sharifipour et al. (16) documenting 92 - 94% in Tehran. In contrast, African studies revealed significantly lower rates, such as 20% among blood donors in Ghana (22), and in Minnesota, Balfour et al. (23) reported 52 - 64% among students. Variations in seropositivity likely derive from differences in sampling populations, including age and socio-economic factors.

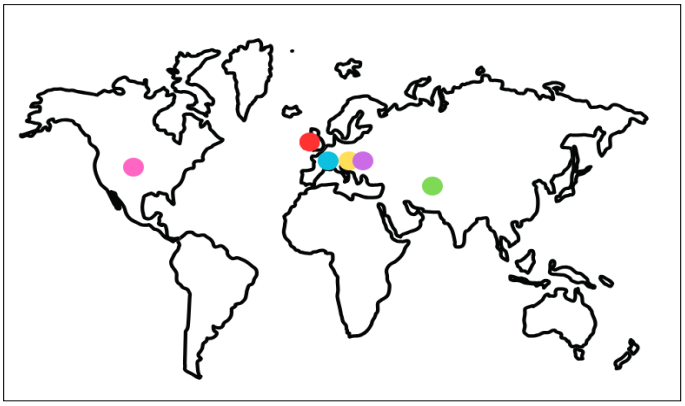

Figure 1. Overview of countries reporting high prevalence of EBV infection

Purple - Serbia, 89.5%; Yellow - Croatia, 91.4% (24); Blue - France, 82–88% (21); Pink - United States, 88% (7); Green - Iran, 92–94% (16); Red - United Kingdom, 74.6% (15). Made with canva.com

Croatian researchers, based on 2022 serum samples, showed a seropositive test in 91.4% of cases (24). Similar living conditions, cultural norms, and geographical position of the two countries explain the similar result in this study, with 89.5% seropositive individuals. In Serbia, available data on EBV seroprevalence further support our findings. Banko et al. (14) reported an 81% latent infection rate in their healthy control group (n = 99), which fully agrees with study's 81% latent infection rate and further supports the high overall infection prevalence observed in our cohort. This finding indicates high EBV exposure in the population, which is consistent with data from studies worldwide and in Europe, where seropositivity ranges from 74.6% to 94% (**Figure 1**) (7, 15, 16, 21-24).

The increase in the number of seropositive individuals from 87% (34/39 samples) by the age of 30 to 94,7% (18/19) after the age of 30 can be explained by prolonged EBV exposure. In this study, a clear rise was found in the number of seropositive individuals with age, which is consistent with the results of Smatti et al. (13), where seropositivity was 96% in the group under 30 years and 100% in individuals over 40. All the results of the study correlate with the data from the literature.

Conclusion

According to the results of this study, a high EBV infection rate of 89.5% was found in the examined population, which aligns with the ubiquitous nature of the virus. Among seropositive individuals, latent infection was the most prevalent form, accounting for 81% of cases. It was determined that seroprevalence does not differ between genders and that antibody titers are not dependent on age

or gender. Further research on EBV seroprevalence in our population is necessary to monitor the number of reactivated infections, their association with the development of malignancies, and for the potential development and application of an EBV vaccine.

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