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ABSTRACT: **Background:** The Epstein-Barr virus (EBV) is one of the most common viruses found in humans, causing lifelong infection in up to 95% of the world population.

Objectives: To analyze the seroprevalence of EBV infection in different population groups in Croatia.

Methods: During a 2 year period (2015–2016), a total of 2022 consecutive serum samples collected from Croatian residents were tested for the presence of EBV-specific viral capsid antigen (VCA) immunoglobulin M (IgM) and IgG antibodies using an enzyme-linked immunoassay. IgM/IgG-positive samples were further tested for IgG avidity.

Results: The overall prevalence of EBV IgG antibodies was 91.4%. Females had significantly higher IgG seroprevalence than males (93.1% vs. 89.9%, $P = 0.008$). According to age, IgG seropositivity increased progressively from 59.6% in children age < 9 years to 98.3% in 30–39 year olds, and remained stable thereafter ($P < 0.001$). The IgG seroprevalence differed significantly among groups: 68.1% in children/adolescents and 95.9% in adults; multiple sclerosis (100%), hemodialysis patients (97.7%), heart transplant recipients (93.8%), hematological malignancies (91.2%), and Crohn's disease (88.5%), $P < 0.001$. IgM antibodies were detected in 9% of participants. Using IgG avidity, recent primary EBV infection was documented in 83.8% of IgM-positive subjects < 9 years old, 69.2% age 10–19, 33.3% age 20–29, and 3.6–4.2% > 40. All IgM positive participants > 40 years showed high IgG avidity. Logistic regression showed that age is associated with EBV IgG seropositivity.

Conclusions: EBV is widespread in the Croatian population. Older age appears to be the main risk factor for EBV seropositivity.

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KEY WORDS: Epstein-Barr virus (EBV) seroprevalence, Crohn's disease, multiple sclerosis, transplantation, hemodialysis

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The Epstein-Barr virus (EBV) is a double-stranded DNA γ-herpes virus. The virus is ubiquitous, causing lifelong infection with high incidence in the adult world population (up to 95%), while in children prevalence differs widely by geographic region [1-3]. EBV has the unique ability to infect, activate, and clonally expand B lymphocytes. The virus is transmitted via saliva, but it can be transmitted by blood and solid organ transplants or stem cell transplants as well [4]. Primary infection occurs mainly in early childhood or adolescence, with more than 50% seropositive children by the age of five. Following primary infection, EBV remains latent in lymphocytes and periodically can reactivate. Even though primary infection occurs within the first few years of life or in adolescence and is usually asymptomatic or manifested as infectious mononucleosis, in some cases the virus can be implicated with development of different diseases. In immunocompromised hosts, the growth-transforming properties of EBV can result in malignant diseases such as hematological (non-Hodgkin's disease, Hodgkin's disease, Burkitt's lymphoma) and gastrointestinal malignancies (gastric adenocarcinoma, nasopharyngeal carcinoma) [5]. Some studies have shown higher EBV seropositivity in patients with leukemia [6], while others found no difference in the EBV seropositivity between patients with hematological malignancies and the general population [7]. Patients with inflammatory bowel disease (IBD), including Crohn's disease, are frequently immunosuppressed and thus at risk for severe EBV infection. There are little published data on the prevalence of EBV in this population group [8]. Several observations implicate EBV in the pathogenesis of multiple sclerosis, namely universal EBV seropositivity [9]. In addition, EBV is a significant pathogen in hemodialysis patients as well as in transplant patients, who can develop post-transplant lymphoproliferative disorder (PTLD) [4,10,11].

In Croatia, there are no data on the prevalence of EBV infection. The aim of this study is to analyze the seroprevalence of EBV infection in the Croatian general adult and child popu-

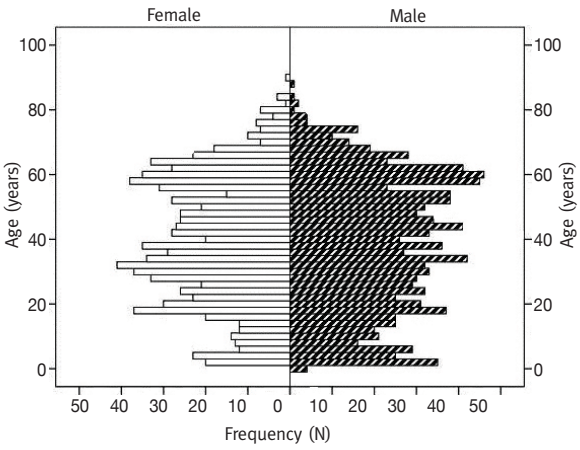
lation and in different groups of patients including patients suffering from Crohn's disease, multiple sclerosis, hematologic disorders, and hemodialysis patients. The study also analyzed EBV seroprevalence in those who underwent kidney or heart transplantation.

PATIENTS AND METHODS

During a 2 year period (2015–2016) a total of 2022 consecutive serum samples were tested for the presence of EBV viral capsid antigen (VCA) immunoglobulin M (IgM) and IgG antibodies. IgM/IgG positive samples were further tested for IgG avidity to confirm or rule out primary EBV infection. Samples were collected from patients residing in all Croatian counties who were tested at two large medical institutions (University Hospital Centre Zagreb and Croatian National Institute of Public Health). In the tested group, there were 1104 males (54.6%) and 918 females (45.4%) aged 1–84 years [Figure 1]. Patients included in the study were routinely tested for hemodialysis, hematologic check-up, preoperative check-up (cardiac and renal transplant program), elevated liver transaminases, lymphatic disorders, neurological disorders such as sclerosis multiplex, and Crohn's disease. Specific anti-EBV VCA IgM and IgG antibodies were detected using a commercial enzyme-linked fluorescent assay (ELFA; VIDAS, Bimerieux, Marcy l'Etoile, France) and enzyme-linked immunosorbent assay (ELISA; Sekisui Virotech, Rüsselsheim, Germany). Results were interpreted according to the manufacturer's recommendations: VIDAS EBV IgM ≤ 0.11 negative, 0.12–0.18 equivocal, ≥ 0.19 positive; VIDAS EBV VCA IgG ≤ 0.09 negative, 0.10–0.20 equivocal, ≥ 0.21 positive; and Virotech EBV VCA IgM and IgG < 9 VE negative, 9–11 VE equivocal, > 11 VE positive.

IgM/IgG positive samples were further tested for IgG avidity to confirm or to rule out primary EBV infection using ELISA (Euroimmun, Lübeck, Germany). The IgG avidity index (AI) was calculated and expressed as a percentage using the extinction values with and without urea treatment. The interpretation of AI results was determined as follows: AI < 40% = low avidity antibodies, indicating acute primary infection; AI 40–60% = borderline avidity, indicating recent (post-acute) infection; and AI > 60% = high avidity antibodies, indicating past EBV infection.

Figure 1. Distribution of study participants by age and gender



STATISTICAL ANALYSIS

The frequencies are shown with 95% confidence intervals (95%CI). Differences between groups were assessed using chi-square test. The strength of association between dependent and independent variables was assessed using logistic regression (crude odds ratios [OR], odds ratios adjusted for age and gender [AOR]). For statistical analysis, software package STATA/IC version 11.2 (StataCorp LP, USA) was used. The level of statistical significance was $\alpha = 0.05$.

RESULTS

Prevalence of EBV antibodies is presented in Table 1. The overall prevalence of EBV IgG antibodies was 91.4% (95%CI 90.1–92.6). Females had significantly higher IgG seroprevalence than males (93.1% vs. 89.9%, $P = 0.008$). According to age, IgG seropositivity increased progressively from 59.6% in children < 9 years of age to 98.3% in 30–39 year olds, and remained stable thereafter ($P < 0.001$). According to the population group, the prevalence was lowest in children/adolescents (68.1%) compared to 88.5%–100% in adults and other tested population groups ($P < 0.001$).

IgM antibodies were detected in 9.0% (95%CI 7.8–10.3) of participants indicating acute EBV infection. There was no significant difference in the prevalence of IgM antibodies among males and females (8.2% vs. 10.0%, $P = 0.160$). Acute infections were most commonly detected in age groups < 9 years (18.7%) and 10–19 years (22.7%). However, acute infections were reported in all age groups with prevalence of 10.6% in 20–29 year olds, 7.3% in 30–39 year olds, and 3.6–4.2% in persons > 40 years. Using IgG avidity, acute primary EBV infections (low AI) were detected in 83.8% participants in the age group < 10 years, 69.2% in the 10–19 age group, 33.3% in the 20–29 age group, and 4.0% in the 30–39 age group. All IgM positive participants older than 40 years showed high AI [Figure 2].

Results of logistic regression showed that older age was a significant risk factor for the EBV IgG seropositivity: 10–19 year age group OR = 2.556 (95%CI 1.669–3.915), 60+ year age group OR = 40.448 (95%CI 17.149-94.882) [Table 2].

DISCUSSION

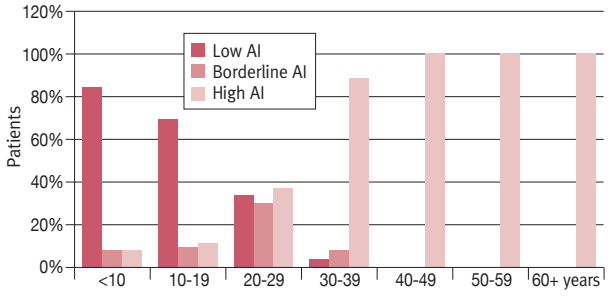
A large proportion of the adult world population is seropositive to EBV; however, in children there are significant geographic

Table 1. Prevalence of EBV antibodies according to participant characteristics

Characteristics	Tested N (%)	EBV VCA IgM N (%)	95%CI	*P*	EBV VCA IgG N (%)	95%CI	*P*
Overall	2022 (100)	182 (9.0)	7.8–10.3		1847 (91.4)	90.1–92.6	
Gender				0.160			0.008*
Male	1104 (54.6)	90 (8.2)	6.6–9.9		992 (89.9)	87.9–91.6	
Female	918 (45.4)	92 (10.0)	8.2–12.2		855 (93.1)	91.4–94.5	
Age (years)				‹ 0.001*			‹ 0.001*
‹ 9	198 (9.8)	37 (18.7)	13.5–24.8		118 (59.6)	52.4–66.5	
10–19	229 (11.3)	52 (22.7)	17.4–28.7		181 (79.0)	73.2–84.1	
20–29	283(14.0)	30 (10.6)	7.3–14.8		261 (92.2)	88.5–95.1	
30–39	343 (17.0)	25 (7.3)	4.8–10.6		337 (98.3)	96.2–99.4	
40–49	288 (14.2)	12 (4.2)	2.2–7.2		283 (98.3)	96.0–99.4	
50–59	318 (15.7)	13 (4.1)	2.2–6.9		310 (97.5)	95.1–98.9	
60+	363 (18.0)	13 (3.6)	1.9–6.0		357 (98.3)	96.4–99.4	
Population group				‹ 0.001*			
Children/adolescents	295 (14.6)	66 (22.4)	17.7–27.6		201 (68.1)	62.5–73.4	
Adult general population	1134 (56.1)	90 (7.9)	6.4–9.7		1087 (95.9)	94.5–96.9	
Hemodialysis patients	174 (8.6)	4 (2.3)	0.1–5.8		170 (97.7)	94.2–99.4	
Multiple sclerosis	37 (1.8)	2 (5.4)	0.1–18.2		37 (100)	90.5–100	
Crohn›s disease	61 (3.0)	3 (4.9)	1.0–13.7		54 (88.5)	77.8–95.3	
Heart transplant recipients	208 (10.3)	11 (5.3)	2.9–9.3		195 (93.8)	89.5–96.6	
Hematological malignancies	113 (5.6)	6 (5.3)	2.0–11.1		103 (91.2)	84.3–95.7	‹ 0.001*

EBV = Epstein-Barr virus, VCA = viral capsid antigen antibody, IgM = immunoglobulin M, IgG = immunoglobulin G, 95%CI = 95% confidence interval
*statistical significance

Figure 2. Epstein-Barr virus IgG avidity according to age



AI = avidity index

variations. In the Croatian adult general population, the overall IgG seropositivity was 95.9%, which is similar to the prevalence rate in other developed countries [1]. This study showed that 59.6% of Croatian children are infected with EBV by the age of 9 years and 79.0% by the age of 19 years. The results of the National Health and Nutrition Examination Surveys (NHANES) conducted in the United States showed similar seropositivity rates: 50% in the age group 6–8 years, 59% in the age group 12–14 years, and 89% in the age group 18–19 years [2]. Other studies showed that most of the children are infected with EBV earlier in their life. A Thai study found a seroprevalence rate of 50.4% in children younger than 2 years of age, which increased and reached 97.6% in children by the age of 12–14 years [12]. Similarly, seroprevalence was more than 50% before age 3 in Chinese children and exceeded 90% after age 8 years [13]. In addition, a high proportion of seropositive children younger than 9 years (96.3%) was reported in the Eastern Anatolian region of Turkey [14].

According to the results of our study, the EBV seroprevalence in the Croatian population tends to increase progressively with age from 59.5% in the < 9 year age group to 98.3% in 30–39 year olds, and remains stable thereafter. Similar results were found in a majority of other studies [2,3,12,13]. However, some studies showed a bimodal pattern of the increase in the EBV seropositivity. In Venezuela, the first peak occurred in children younger than 1 year, and the second one started after 16 years [15]. In Spain, peaks were observed at the age of 2–4 years and 14–18 years [1].

Our study showed that females had significantly higher IgG seroprevalence compared to males (93.1% and 89.9%, respectively), which is similar to the results of other studies [16,17]. However, in some studies there was slightly higher EBV seroprevalence in females [18] or there was no difference in EBV seropositivity between genders [3].

Many observations implicate EBV in the pathogenesis of multiple sclerosis [9]. The evidence linking EBV infection to multiple sclerosis comes from epidemiological studies showing that nearly all multiple sclerosis adult patients are seropositive for EBV. In addition, a study conducted on pediatric patients in Canada found that 86% of the children with multiple sclerosis, irrespective of geographical residence, were seropositive for remote EBV infection, compared with only 64% of matched healthy controls [14]. Moreover, a study conducted in Germany showed similar results. The children with multiple sclerosis showed a near complete seropositivity for EBV VCA (98.6%) compared to 72.1% of controls, but did not display serologic evidence for a recent EBV infection [20]. In this study, EBV seropositivity of 100% was found in the group of patients with multiple sclerosis. However, due to a small number of par-

Table 2. Univariate logistic regression for risk of EBV seropositivity

Characteristics	EBV IgM OR	95%CI OR	EBV IgM AOR*	95%CI AOR	EBV IgG OR	95%CI OR	EBV IgG AOR	95%CI AOR
Female vs. male (ref.)	1.258	0.927–1.706			1.558	1.127–2.155		
Age (years)								
‹ 9	1 (ref.)				1 (ref.)			
10–19	1.278	0.796–2.050			2.556	1.669–3.915		
20–29	0.515	0.306–0.868			8.043	4.784–13.522		
30–39	0.342	0.199–0.588			38.079	16.183–89.600		
40–49	0.189	0.095–0.373			38.372	15.160–97.127		
50–59	0.185	0.095–0.358			26.271	12.322–56.010		
60 +	0.161	0.083–0.312			40.448	17.149–94.882		
Population group								
Children/adolescents	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Adult general population	0.299	0.211–0.423	0.710	0.437–1.155	10.815	0.738–15.833	1.421	0.084–2.399
Hemodialysis patients	0.081	0.029–0.228	0.236	0.078–0.713	19.875	7.158–55.186	1.828	0.598–5.589
Multiple sclerosis	0.198	0.046–0.846	0.383	0.086–1.693	NA	NA	NA	NA
Crohn›s disease	0.179	0.054–0.591	0.356	0.104–1.211	3.607	1.581–8.228	0.743	0.300–1.843
Heart transplant recipients	0.193	0.099–0.377	0.501	0.238–1.054	7.014	3.801–12.943	1.135	0.558–2.306
Hematological malignancies	0.194	0.081–0.462	0.380	0.154–0.936	4.816	2.406–9.640	1.261	0.585–2.717

EBV = Epstein-Barr virus, VCA = viral capsid antigen antibody, IgM = immunoglobulin M, IgG = immunoglobulin G, 95%CI = 95% confidence interval, OR = odds ratio, AOR = odds ratios adjusted for age and gender

ticipants in this group, these results should be interpreted with caution.

The increase in EBV activity as a consequence of the immune suppression, steroids, and other immunosupressants may cause a high risk of lymphoma development and promote the increase of certain types of cancers, including leukemia and multiple myeloma [21]. In this study, there was no difference in the EBV seropositivity among patients with hematological malignancies and the general adult population (91.2% vs. 95.9%). An Austrian study showed similar results (89% EBV IgG seropositivity in patients with chronic lymphocytic leukemia and 94% in healthy age-matched controls) [7]. In contrast, an Iranian study showed that EBV seropositivity was significantly higher in children with acute lymphoblastic leukemia [6].

A study conducted in Canada showed a high EBV seroprevalence in patients with IBD. The prevalence of EBV in the IBD population aged 18–25 years was similar to that described in the general population (71%) and older than 25 years, seropositivity reached 100% [8]. Similarly, our results did not show higher IgG seroprevalence in this population group.

It has been documented that hemodialysis patients have impaired immune response, which predispose them to herpes virus infections, including EBV. Our study showed that EBV is highly prevalent in both hemodialysis patients (97.7%) and the adult population (95.9%). Two Iranian studies addressed the prevalence of EBV infection in hemodialysis patients. A study conducted from 2005 to 2008 showed 100% EBV seropositivity in both potential renal transplant donors and transplant recipients. A more recently published study (2011) showed a higher, but not statistically significant, difference in EBV IgG seroprevalence among pre-transplant patients and kidney donors (70% and 52%, respectively) [22,23].

Even though the role of viral infections in the pathogenesis of atherosclerosis and heart disease is still controversial in part due to the frequent inability to detect virus in atherosclerotic lesions, some clinical studies have supported the atherogenic role of viral infections. The majority of studies have indicated that viral infections can promote evolution of atherosclerosis and acute coronary events through production and release of pro-inflammatory cytokines. A study conducted in Saudi Arabia analyzed the EBV seroprevalence among patients with atherosclerotic vascular disease compared to healthy subjects. A higher percentage of patients showed EBV IgG antibodies; however, there was no significant difference between these groups [24]. In this study, heart transplant recipients showed a seroprevalence rate (93.8%) similar to the general adult population (95.9%).

In our study, the overall prevalence of IgM antibodies was 9.0%, indicating an acute EBV infection. Since IgM antibodies could be a false positive (hemodialysis patients, pregnant women), a sign of reactivation (immunocompromised patients), or a result of a polyclonal stimulation (cytomegalovirus infection, parvovirus B19), serology results should be interpreted with caution. Determination of IgG avidity in combination with classical serologic markers seems to be a reliable test for confirmation of primary EBV infection both in immunocompetent and immunocompromised patients [25]. In this study, acute primary infection detected by low AI was the most commonly documented in the age groups < 9 years and 10–19 years, while all IgM positive participants older than 40 years showed high AI indicating EBV reactivation, which is in concordance with other investigations [2,4].

CONCLUSIONS

The results of this study indicate that EBV is widespread in the Croatian population. More than half of the population (59.6%) is infected by the age of 9. Females had significantly higher IgG seroprevalence than males. Older age appeared to be the main risk factor for EBV seropositivity.

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Capsule

Body mass index, weight loss, and cause-specific mortality in rheumatoid arthritis

England and co-authors tried to examine associations of body mass index (BMI) and weight loss with cause-specific mortality in rheumatoid arthritis (RA). A cohort of U.S. veterans with RA was followed until death or through 2013. BMI was categorized as underweight, normal, overweight, and obese. Weight loss was calculated as the annualized rate of change over the preceding 13 months and the cumulative percent. Vital status and cause of death were obtained from the National Death Index. Multivariable competing-risks regression models were utilized to assess the time-varying associations of BMI and weight loss with cause-specific mortality. Among 1600 participants and 5789 patient-years of follow-up, 303 deaths occurred (95 cardiovascular, 74 cancer, and 46 respiratory). The highest weight-loss rate and weight-loss percent were associated with a higher risk of cardiovascular mortality (rate: subdistribution hazard ratio [sHR] 2.27, 95% confidence interval [95%CI] 1.61–3.19; percent: sHR 2.31, 95%CI 1.06–5.01) and cancer mortality (rate: sHR 2.36, 95%CI 1.11–5.01; percent: sHR 1.90, 95%CI 1.00–3.62]). Overweight BMI was protective of cardiovascular mortality (sHR 0.59 [95% CI 0.38–0.91]), while underweight BMI was associated with a near threefold increased risk of respiratory mortality (sHR 2.93, 95% CI 1.28–6.67). Incorporation of time-varying BMI and weight loss in the same models did not substantially alter individual associations for cardiovascular and cancer mortality, but an association between weight-loss percentage and respiratory mortality was attenuated after BMI adjustment. The authors concluded that both BMI and weight loss are predictors of cause-specific mortality in RA. Weight loss is a strong predictor of cardiovascular and cancer mortality, while underweight BMI is a stronger predictor of respiratory mortality.

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Eitan Israeli