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Original Article

Cytomegalovirus reactivation in hepatitis B and C infected population

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Abstract

Introduction: Cytomegalovirus (CMV) seroprevalence varies globally. This study aimed to detect CMV seroprevalence and reactivation among patients who had been exposed to hepatitis B virus (HBV) or hepatitis C virus (HCV).

Methodology: The study was conducted between 2017 and 2022 and included adult participants who were serologically diagnosed with hepatitis B (63 participants) or hepatitis C (69 participants), as well as 132 control respondents. CMV IgG and IgM levels were measured for all 264 respondents; CMV IgG avidity was further determined for those who tested positive for CMV IgG and IgM.

Results: The total CMV IgG seroprevalence observed in the study was 95.4%, with 98.5% in HCV-positive, 96.8% in HBV-positive, and 95.2% in control respondents; and with a slightly higher prevalence in women (97.1%) compared to men (94.9%). The overall CMV reactivation rate among anti-HCV positive respondents was 2.9%. Although no significant difference was found in the reactivation rate of CMV between anti-HCV positive and negative respondents, the reactivation rate of CMV within the subgroup of HCV RNA positive individuals was higher at 4.4%. In contrast, no CMV reactivation was observed in the respondents without detectable HCV RNA. No CMV reactivation was detected in the HBV group.

Conclusions: This study did not confirm a higher reactivation rate of CMV in HBV- or HCV-positive respondents compared to the control cases. Given the high CMV seroprevalence among adults in Bosnia and Herzegovina, future research should include CMV DNA testing for more accurate assessment.

Key words: epidemiology; CMV; HCV; HBV; reactivation.

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Introduction

Human cytomegalovirus (CMV), also known as human herpes virus 5 (HHV-5), is one of 9 herpes viruses capable of infecting humans. According to the Baltimore classification, CMV belongs to the Herpesviridae family and Betaherpesvirinae subfamily [1]. The seroprevalence of CMV infection varies worldwide depending on demographic and economic factors. A study conducted in 2019 reported that the global seroprevalence in the general population was 83% (95% CI: 78–88), seroprevalence in women of reproductive age was 86% (95% CI: 83–89), and seroprevalence in blood and organ donors was 86% (95% I: 82–89). The highest prevalence in each of the three observed groups was in the Eastern Mediterranean region of the World Health Organization (WHO) at 90% (95% CI: 85–94), and the lowest prevalence was in the European region of the WHO at 66% (95% CI: 56–74) [2]. Some previous studies also showed that CMV seroprevalence tended to be highest in South America, Africa, and Asia; and lowest in Western Europe and the United States [3].

CMV can be transmitted through saliva, sexually, transplacental, breastfeeding, blood transfusion, and solid organ and stem cell transplantation. The virus enters the cell by fusion or direct endocytosis [4]. CMV infection can occur as a primary infection or as a recurrent infection (reinfection or reactivation) [5]. CMV infection is usually asymptomatic in immunocompetent persons; but it can cause serious diseases in immunocompromised individuals such as encephalitis, pneumonitis, uveitis, hepatitis, colitis, retinitis, or graft rejection either due to primary infection or due to reactivation of the virus from the graft [6,7]. It is well known that CMV has the ability of latency with the possibility of occasional reactivation of the virus, especially in states of disordered functioning of the immune system. This primarily refers to states of a weakened immune system caused by disease or treatment, but reactivation of CMV is also known in states of prolonged immune system activation such as chronic infections or co-infection with other pathogens [8].

A study conducted in Bosnia and Herzegovina included 5222 samples tested at the University Clinical Hospital Mostar, and reported that the total

seroprevalence of CMV IgG was 81.4% (95% CI: 0.8–0.82). The prevalence was higher in women (84.9%) compared to men (77.0%), and increased with age. Thus, in children (age 1–5 years) the prevalence was 50.8%, while in people of age > 65 years it was 97.7%. Seroprevalence among cord blood samples was 92.1% [9].

Although antigens necessary for a successful vaccine against CMV are known in the literature, an effective vaccine still does not exist. Necessary efforts are ongoing to combine known antigens to create a vaccine that will provide long-term protection [1].

The aim of this research was to detect CMV IgG and IgM seroprevalence and reactivation in the general adult population and in patients that were in contact with hepatitis B virus (HBV) or hepatitis C virus (HCV) in Bosnia and Herzegovina.

Considering that CMV is also a hepatotropic virus, this research also aimed to contribute to the clarification of the connection between hepatitis B and C, and CMV.

Methodology

A case-control study was performed in the period between 2017 and 2022. The study group included persons who were referred for testing for blood-borne diseases and had tested positive for HBV and HCV markers. Every newly diagnosed case was included in the study group. The study group included 69 anti-HCV positive respondents and 63 respondents who were in contact with hepatitis B virus (anti-HBs and anti-HBc IgG + IgM positive or HBsAg positive). Each respondent in the study group was assigned a control subject who was comparable in terms of gender and age (132 control cases). The control group consisted of voluntary blood donors and people who were referred for testing for blood-borne diseases and were negative. Every new compatible case was included in the control group. The exclusion factors were acute HBV infection or other acute infection, simultaneous presence of hepatitis B and C infection markers, and chronic dialysis. Hepatitis B vaccination (positive anti-HBs) was not an exclusion factor for the anti-HCV positive subjects, nor for control cases.

A total of 264 samples were tested for the presence of CMV IgG and IgM antibodies. The IgG antibody avidity was determined for those who were both IgG and IgM positive. High avidity of IgG antibodies with the simultaneous presence of CMV IgG and IgM antibodies was considered as serologically detected reactivation.

HCV quantitative molecular testing was performed for all anti-HCV positive respondents, and genotyping was performed for HCV RNA positive respondents. HBV quantitative molecular testing was performed for those who were HBsAg positive.

The respondents were divided into 4 subgroups based on molecular testing results: anti-HCV positive with HCV RNA detected (45); anti-HCV positive, but HCV RNA not detected (24); HBsAg positive (36); and anti-HBs and anti-HBc IgG + IgM positive (27).

Serological testing was performed using the Architect system (Abbott, Abbott Park, Illinois, USA) and LIAISON® XL (DiaSorin, Saluggia, Italy); both based on chemiluminescent immunoassay technology. Molecular testing was performed using the Abbott RealTime HCV test, the Abbott RealTime HCV Genotype II test, and the Abbott RealTime HBV Assay (Abbott, Abbott Park, Illinois, USA).

All respondents signed the informed consent and filled out a self-administered questionnaire. The questionnaire focused on sociodemographic status parameters (gender, age, employment, educational level, and marital status).

Statistical analysis was performed with IBM SPSS Statistics for Windows, version 25.0 (IBM Corp, Armonk, NY, US). The Chi-square test (χ^2) and Fisher's exact test for categorical variables were used to establish the difference between HBV or HCV positive patients, and the control group based on various respondent categories. A p value of 0.05 was considered to be statistically significant.

The study was approved by the ethics committee of the Clinical Hospital Mostar (No. 1898/16) and the ethics committee of the University of Mostar, School of Medicine (No. 01-1-234/16); and was conducted in accordance with the principles of Declaration of Helsinki, 1964; as revised in 1975, 1983, 1989, 1996, and 2000.

Results

A total of 263 participants were tested for the presence of CMV IgG antibodies. Total CMV IgG seroprevalence was 95.4%. A total of 195 men were tested, of which 185 (94.9%) were CMV IgG positive; while of a total of 68 tested women, 66 (97.1%) were CMV IgG positive ($\chi^2 = 0.554$; df = 1; $p = 0.737$).

A comparison by age showed an increase in the CMV IgG seroprevalence with age, but was not confirmed as statistically significant ($\chi^2 = 2.697$; df = 2; $p = 0.260$). A total of 77 respondents in the age group ≤ 40 years were tested, of which 72 (93.5 %) were CMV IgG positive; while in the age group > 65 years, 42 were tested, of which all 42 (100%) were CMV IgG positive.

No statistically significant difference was observed

Table 1. Socio-demographic characteristics of CMV IgG positive and negative respondents.

Socio-demographic characteristics	CMV IgG negative N (%)	CMV IgG positive N (%)	Total tested CMV IgG N (%)	*p*
Gender				
Male	10 (5.1)	185 (94.9)	195 (100.0)	0.737*
Female	2 (2.9)	66 (97.1)	68 (100.0)	
Age (years)				
0–40	5 (6.5)	72 (93.5)	77 (100.0)	
41–65	7 (4.9)	137 (95.1)	144 (100.0)	0.260
> 65	0	42 (100.0)	42 (100.0)	
Employment				
Employed	10 (7.2)	129 (92.8)	139 (100.0)	
Unemployed	2 (3.4)	56 (96.6)	58 (100.0)	0.063
Retired	0	66 (100.0)	66 (100.0)	
Educational level				
Incomplete elementary school	0	8 (100.0)	8 (100.0)	
Elementary school	0	25 (100.0)	25 (100.0)	0.561
Secondary school	10 (5.6)	169 (94.4)	179 (100.0)	
High school/academy	2 (3.9)	49 (96.)	51 (100.0)	
Marital / intimate status				
Married	9 (5.3)	162 (94.7)	171 (100.0)	
Single	3 (6.0)	47 (94.0)	50 (100.0)	
Widow	0	20 (100.0)	20 (100.0)	0.656
Divorced	0	15 (100.0)	15 (100.0)	
Domestic-partnership	0	7 (100.0)	7 (100.0)	
Total	**12 (4.6)**	**251 (95.4)**	**263 (100.0)**	

*Fisher exact test; CMV: cytomegalovirus.

between CMV IgG positive and CMV IgG negative subjects in terms of any sociodemographic variable (employment, educational level, marital status) (Table 1).

A total of 264 respondents were tested for the presence of CMV IgM antibodies. Total CMV IgM seroprevalence was 1.13%. A total of 196 men were tested, of which 1 (0.05%) was CMV IgM positive; while of a total of 68 tested women, 2 (2.94%) were CMV IgM positive.

Correlations of HCV seroprevalence with CMV seroprevalence and CMV reactivation

The average age of anti-HCV positive respondents was 41.12 ± 8.464 years, where the youngest respondent was 22 years old and the oldest was 70 years old.

There were more CMV IgG positive cases among anti-HCV positive respondents. A total of 67 (98.5%), CMV IgG positive cases were identified among the anti-HCV positive respondents, compared to 64 (91.43%) CMV IgG positive among control cases; however, no statistically significant difference was observed ($\chi^2 = 3686$; df = 1; $p = 0.115$; Table 2).

Even though there were 2 (2.9%) CMV IgM positive respondents among the anti-HCV positive respondents, and there were none in the control group, no statistically significant difference was observed ($\chi^2 = 2059$; df = 1; $p = 0.244$).

Two CMV IgM positive respondents in the anti-HCV positive group (both from the subgroup with detected HCV RNA) were also CMV IgG positive. Therefore, the avidity of IgG antibodies against CMV was determined in order to assess the reactivation of the virus. In both cases, high avidity of CMV IgG antibodies was detected, which would indicate CMV reactivation.

CMV reactivation was 2.9% among the anti-HCV positive respondents, 4.4% in the group with detected HCV RNA, and 0% in the group without HCV RNA.

Correlation of HBV with CMV seroprevalence and CMV reactivation

The average age of the respondents that were in contact with HBV was 56.90 ± 15.576 years, with the youngest respondent being 19 years old and the oldest

Table 2. Correlations of HCV seroprevalence with CMV seroprevalence and CMV reactivation.

		Anti-HCV positive; N = 69	Control N = 70	*p*	HCV-RNA detected; N = 45	Control N = 45	*p*	HCV-RNA not detected; N = 24	Control N = 25	*p*
		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
CMV IgG	Positive	67 (98.5)	64 (91.4)	0.115*	43 (97.7)	43 (95.5)	1.00*	23 (97.8)	21(84.0)	0.348*
	Negative	1 (1.5)	6 (8.6)		1 (2.3)	2 (4.4)		1 (2.2)	4 (16.0)	
CMV IgM	Positive	2 (2.9)**	0	0.244*	2 (4.4)	0	0.494*	0	0	1.000*
	Negative	67 (97.1)	70 (100.0)		43 (95.4)	45 (100.0)		24 (100.0)	25 (100.0)	

* Fisher exact test; **IgG positive: IgM positive; CMV: cytomegalovirus; HCV: hepatitis C virus.

Table 3. Correlation of HBV with CMV seroprevalence.

		HBV N = 63	Control N = 62	*p*	HBsAg positive N = 36	Control N = 36	*p*	Anti-HBs, anti-HBc IgG + IgM positive N = 27	Control N = 26	*p*
		N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
CMV IgG	Positive	61 (96.8)	59 (95.2)	0.679*	36 (100.0)	35 (97.2)	1.00*	25 (92.6)	24 (92,3)	1.000*
	Negative	2 (3.2)	3 (4.8)		0	1 (2.8)		2 (7.4)	2 (7.6)	
CMV IgM	Positive	0	1 (1.6)	0.495*	0	0	1.00	0	1 (3.8) **	0.491*
	Negative	63 (100.0)	61 (98.4)		36 (100.0)	36 (100.0)		27 (100.0)	25 (96.2)	

* Fisher exact test; **IgG positive: IgM positive. HBV hepatitis B virus; CMV cytomegalovirus; anti-HBs antibody to hepatitis B surface antigen; anti-HBc antibody to hepatitis B core antigen.

91 years old.

Among the respondents who were in contact with HBV, 61 (96.8 %) were CMV IgG positive, while 59 (95.2%) were positive in the control group ($\chi^2 = 0.225$; df = 1; $p = 0.679$; Table 3).

One respondent was CMV IgM positive in the control group, while there were none in the study group. The control respondent who was CMV IgM positive was also CMV IgG positive. High avidity of CMV IgG was detected (CMV reactivation). CMV reactivation in respondents that were in contact with HBV was 0%.

Discussion

The CMV IgG seroprevalence in this study was 95.4%. It was slightly higher in women (97.1%) than in men (94.9%). An increase in seroprevalence with age was also determined. Seroprevalence was 93.5% in the age group 0–40 years, 95.1% in the age group 41–65 years, and 100% in the age group > 65 years. The youngest respondent in this study was 19 years old, which may explain the high seroprevalence. This data agrees with data from the literature that CMV is a ubiquitous virus whose prevalence increases with age and depends on the development of the country [2]. The global seroprevalence of CMV ranges from 45 to 100%. It is the highest in South America, Africa and Asia; and the lowest in developed Western European countries and the US. Globally, women have a higher seroprevalence [10].

There is limited data about the correlation of HCV and HBV with CMV infection. It is known that HCV infection leads to exhaustion of the HCV-specific cellular response, but it can disrupt the complete immune response as well. Peripheral blood dendritic cells and naïve CD4+ T lymphocytes have a reduced number and function in people with chronic HCV infection. As a result, the immune system's response to CMV infection may be impaired as well [11,12].

The CMV IgG seroprevalence among anti-HCV positive subjects in this study was 98.5%, and although it was higher compared to that in the control group which was matched by gender and age (91.4%), this difference was not statistically significant ($\chi^2 = 3686$; df = 1; $p = 0.115$). This result may be a consequence of the high prevalence of CMV in the population that is ≤ 18 years old in Herzegovina, and indicates the possibility of infection of the subjects in childhood [13].

The seroprevalence of CMV IgM among anti-HCV positive subjects was 2.9%; while in the control group matched by gender and age, but without anti-HCV, it was 0%. The difference, however, was not statistically significant ($p = 0.244$). These results did not confirm the data available in the literature regarding statistically significant higher CMV IgG and IgM seroprevalence in individuals with chronic HCV infection compared to the general population [14]. This result can be explained by the small number of subjects in the acute phase of the infection, which significantly affects the statistical analyses, and by the large percentage of individuals who had recovered from CMV infection.

HBV and CMV have the ability to persist in the host with the possibility of occasional reactivation, especially in people with weakened immunity. Therefore, it is important to understand not only co-infection of these two viruses, but also the influence of such co-infection on the host. Secondary CMV infection can lead to HBV reactivation. Previous literature has recommended protocols that specify that acute CMV coinfection should be considered in the case of any reactivation of HBV infection, with the aim of introducing therapy [15].

This research did not establish a statistically significantly higher seroprevalence of CMV IgG in individuals who were in contact with HBV (96.8 %) compared to the control group of subjects who were not in contact with HBV (95.2 %). In addition, those who recovered from HBV infection (anti-HBs + anti-HBc IgG positive) and those who were chronic carriers of HBsAg had a slightly higher CMV IgG seroprevalence (92.6% and 100.0%, respectively) compared to control group (92.3% and 97.2%, respectively). However, this difference was not statistically significant.

CMV IgM antibodies were not detected in the group of respondents that were in contact with HBV, but were detected in only one member of the control group. These data are consistent with the data of Bayram *et al.*

[16] which showed an association between human cytomegalovirus (HCMV) infection and HBV or HCV infection. CMV IgM antibodies were not detected in any respondent with hepatitis, or in any control subject in the same study. However, CMV DNA was isolated from liver biopsies in 52.3% of subjects with HBV infection, 36% of respondents with HCV, and in only 13.9% of respondents in the control group; which confirmed a statistically significant higher frequency of CMV DNA among respondents with HBV and HCV infection compared to the control group [16].

The avidity of IgG antibodies was determined for respondents who were both CMV IgG and CMV IgM positive in order to assess the risk of CMV reactivation. High avidity of IgG antibodies with the simultaneous presence of CMV IgG and IgM antibodies was considered as serologically detected reactivation. CMV reactivation among respondents with chronic HCV infection was 2/45 (4.44%), and among respondents who were chronic carriers of HBsAg was 0/36 (0%); and no statistically significant difference was noted in comparison with the control group. It is important to highlight the possible presence of CMV IgM antibodies for a longer period after acute infection, which represents one of the limitations of the study. However, it is important to note that there are studies in the literature in which CMV DNA has been demonstrated in the liver of individuals with chronic HBV and HCV infection, without serologically detected CMV IgM antibodies. Therefore, the research should definitely be extended by CMV DNA testing with the aim of contributing to the understanding of the interaction between HBV and HCV infection, and CMV [16].

Conclusions

This study did not confirm a higher rate of CMV in HBV or HCV positive respondents compared to the control cases. However, it is interesting to note that although the anti-HCV positive subjects included in this study had a lower average age than the subjects who were in contact with HBV, they still had a higher CMV IgG and IgM seroprevalence and reactivation rate.

This study has its limitations. One of the major limitations is the small number of subjects with acute CMV infection. The seroprevalence itself is a limitation since it is high in our country, and it was difficult to find a representative sample of CMV IgG negative test subjects (> 18 years), with whom the results could be compared. Future research should be directed towards testing CMV DNA from blood or tissue samples such as liver, which would provide better insights into the interaction between CMV, HBV, and HCV. Although CMV seroprevalence was higher in persons who had been in contact with HBV or HCV compared to the general population, the difference was not statistically significant. This result is explained by the high CMV seroprevalence in the general population in Herzegovina, and therefore the small number of subjects included in this study. CMV reactivation in this study was considered as the simultaneous presence of high-avidity CMV IgG antibodies and CMV IgM antibodies. However, future research should be supplemented by testing respondents and control groups for CMV DNA from blood and/or liver tissue samples.

Authors' Contributions

ITD, conceptualization, methodology, investigation, data curation, formal analysis, project administration, supervision, validation, visualization, writing—original draft, review, editing; BŠ, conceptualization, methodology, investigation, data curation, formal analysis, validation, writing—original draft, review, editing. JA, conceptualization, methodology, validation, project administration, supervision, writing—original draft, review, editing.

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Conflict of interest

No conflict of interest is declared.

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