

SOCIOECONOMICS CONDITIONALITY OF SEROPREVALENCE OF HEPATITIS A IN THREE SOUTH-WEST CANTONS OF THE FEDERATION OF BOSNIA AND HERZEGOVINA

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SUMMARY

The prospective study, which was made from Jan 1st 2009. till Dec 31st 2010. in the Clinic for Infectious Diseases within Clinical Hospital Mostar has been implemented in the areas of three southwestern cantons of the Federation of Bosnia and Herzegovina.

We wanted to define the seroprevalence of the researched area using seroepidemiological testing of different groups of the population, based on the distribution by sex, age, education, residence and watersupply.

The aim of this research was to prove the hypothesis that the decrease of seroprevalency of Hepatitis A has been directly related to the improvement of socio-economic conditions of life that at the end brought the decrease of the total prevalence in patients in younger age groups.

The total of 420 examinees from the reasserted sample were analysed and they were classify into age groups. The first group was for the children up to 10 years. Then the group 11-20 follows and etc up to the last group, that complies examinees older than 60. In this way we have got seven groups of 60 examinees, from which the half of them was urban, and the other half was rural inhabitants. In every group analysed the half of examinees were females and the other half were males.

The results we acquired with this research did not show any statistically relevant differences of seroprevalence of Hepatitis A between the urban and rural areas, between the sexes, nor between the populations which used different watersupply objects.

A statistically relevant difference was found between populations of different levels of education, but the most important difference was found between seroprevalency in different age groups.

Seroprevalence in younger age groups was substantially low and increased in groups rising with age. Comparing this data to results from other similar researches from developed and undeveloped countries we concluded that the researched area, by the level of seroprevalency of Hepatitis A belongs to the category of developed countries.

Key words: hepatitis A – seroprevalency - South-west Herzegovina

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INTRODUCTION

Hepatitis A is an acute liver infection caused by the virus hepatitis A (HAV). It is epidemic, while in some regions it is present as an endemic infection.

According to the World Health Organization (WHO) assessment, about 1.5 million people worldwide are infected with HAV per year, out of which only a small number is registered. Because of bad hygienic conditions, hepatitis A occurs more often in poorer countries and according to WHO data, endemic regions of this disease are South America, Greenland, Africa, the Middle East, South Asia and the Mediterranean. (Center for Diseases control and Prevention 1995).

There is no accurate epidemiological data for Bosnia and Herzegovina (B&H), but endemic centers of hepatitis A are known to exist. These are Bosanska Krajina, especially regions around Bužim, Kladuša and Bihać.

HAV is widespread worldwide and its only reservoir is a human being. It is transmitted primarily by the fecal-oral route (food or water contaminated with feces of patients or healed virus carriers).

Hepatitis A is an illness of childhood in developing countries, associated with bad socio-economic and

hygienic conditions (Vukobrat-Bijedić 2008). In developed countries, the disease is more likely to affect adults. The prevalence in developed countries is almost as same in the city as in the countryside, because of similar hygienic conditions. Seroprevalence ceases with improvement of hygienic conditions. The general prevalence grows from the north to the south of Europe, and similar has been noticed in the United States of America (USA) (Morris 2002).

The exposure of the population to HAV in endemic regions is universal, so seroprevalence can be best estimated in children up to the age of five.

In transmission of HAV and maintaining the epidemic process the basic role has a contact and fecal-oral route of transmission, especially in overpopulated areas. The contact route of transmission is conditioned with the presence of fresh fecal contamination on finger pads. If this is the only way of transmission, epidemiological characteristics of the disease are: predominant involvement in children, seasonal dynamics, dependence of the intensity of seroprevalence on the sanitation status of the environment, hygienic habits of the population as well as the size of the groups in close contact (Vukobrat-Bijedić 2008, Lupi 2006).

The contact route of transfer is remarkably relieved in categories which don't wash hands due to: lack of water (lack of water, natural disasters, wars), impossibility of reasoning (homes for mentally retarded people) or lack of habits (people from rural or non urbanized settlements, nomads etc.). Risk groups include people who live in undeveloped countries and are subject to poor socio-economic standards and low hygienic habits (Lupi 2006, Palmović 2006).

HAV causes only an acute liver disease. It is clinically manifested from an asymptomatic infection up to a fulminant form of the disease.

The disease can be split into four stages (Vukobrat-Bijedić 2008, Lupi 2006, Palmović 2006, Beckers 2008, Vucelić & Hrستیć 2003): Incubation lasts from 10 to 50 days. The prodromal state is characterized with fatigue, general weakness, exhaustion, fever, loss of appetite, nausea and vomiting. Patients may experience epigastric pain, general algia syndrome and diarrhea. Rashes are a rare to occur. At the end of this stage the urine is of a darker color, while the stool is lighter, acholic. The icteric stage occurs one to two weeks after the start of the prodromal stage. Jaundice of the skin, mucosa and sclera appear. Clinical analysis determines abdominal ad right hypochondriac pain. The liver itself is enlarged and painful.

The most significant laboratory findings are increased values of aminotransferase, alkali phosphatase and serum bilirubin. Increased values of aminotransferase show necroinflammatory activity in the liver. Alanin aminotransferase (ALT) and aspartate aminotransferase (AST) are also increased.

Serological findings are used in diagnosing hepatitis A, i.e. the determination of antibodies by using modern, more reliable serological tests: Radioimmuno assay (RIA), ELISA (Enzyme linked immunosorbent assay), titers of specific antibodies can be determined, from which IgM fraction speaks for the fresh infection, and the IgG for the earlier infection of HAV (Abdool Karim 1993).

Treating hepatitis A is symptomatic, rest, especially in the icteric phase of the disease, hepatitis diet (food with small amounts of fat and spices and a lot of carbohydrates), while in severe clinical cases infusions of hypertonic laevulose (Vukobrat-Bijedić 2008, Lupi 2006, Palmović 2006).

Preventive measures in stopping hepatitis A are complex and imply taking hygienic-profilactic measures and measures of immunoprophylaxis. Primary directions in prevention of this disease need to be directed in leading routes of transfer, like fecal-oral infections: creating habits and a possibility of washing hands, securing enough of clean water for drinking and a hygienic disposal of waste (Beckers 2008, Vucelić 2003).

Passengers through the endemic regions need to drink only originally packed water and drinks without

ice cubes. It is also good to avoid unpeeled fruits and fresh vegetables.

The virus can survive in fresh water for 12 weeks, while it can survive for a long time in waste waters, land, sea water and other various samples of the environment which highlights the importance of fecal contamination of the environment for its transfer (Ropac 2003). Otherwise inactivity of the virus is achieved by cooking for at least 30 minutes in boiling temperature, (UV) rays, formalin solution and chlorination of water.

Immunoprophylaxis is achieved by passive and active immunization (CDC 1999, Kluge T 1969). Passive immunization implies giving a preparation of immunoglobulin, mostly of the IgG class. Vaccines represent the active part of immunization, which contains an inactive HAV antigen, which causes proliferation of specific T lymphocytes, among which are the clones with memory. Because of this the immunity after vaccination is of long lasting. Except proliferation of specific lymphocytes after vaccination, specific antibodies and productions of gama globulin are created.

Seroprevalence of hepatitis A differs in different parts of the world. In developed countries it is significantly smaller in childhood and increases with aging (Morris 2002, Ropac 2003).

In undeveloped countries we find high prevalence already with young children, which is connected to hygienic conditions in tested areas (Lupi 2006, CDC 1999).

In recent years many papers of seroprevalence have been published in certain parts of the world (Saha 2009, Sac 2009, Al-Aziz 2008, Raharimanga 2008, Samuels 2005, Yassin 2001, Antaki & Kebbewar 2000, Tanaka 2000, Abdool Karim & Coutoudis 1993, Gentile 2009, Kiyohara 2007, Antunes 2004, Junquera 2004, Denis 2003, Cunha 2001, Amin 2001, Termorshuizen 2000, Beran 1999), but we have not had available information for Bosnia and Herzegovina.

The goal of this paper was to determine seroprevalence of hepatitis A in three cantons in south west FBH, by using seroepidemiological tests, more specifically assessment of IgG antibodies on HAV.

MATERIALS AND METHODS

Examinees

The examined sample of this paper is the population of three south-western cantons of FBiH: Herzegovina-Neretva Canton (HNC), Herzeg-Bosnia Canton (HBC) and West-Herzegovina Canton (WHC), i.e. population which get their secondary and tertiary health care at University Clinical Hospital of Mostar. At the beginning of the research we had planned on taking in the examined sample, along with HBC and WHC, only the population of the western part of Mostar and the western part of HNC, as they actually medically

gravitating to Clinical Hospital Mostar(CH). During the research however we found that a large part of the population which gets their health care in the Regional Medical Centerl "Dr. Safet Mujić" Mostar (RMC Mostar), actually gets treatment in CH Mostar due to the need of a higher level of medical protection. That is why we added the people who live in the eastern part of Mostar, along with the population of the municipalities of Konjic and Jablanica to the examined sample.

The population data in the research are taken from The Register of population of RBH from 1991 and the data from statistical yearbooks of BH. The total number of residents on the researched area was 476.170 (Pilav 2000-2007, Đurđević 2000-2006, Gelo 1995). There were 420 residents analyzed in the researched area. Those were members of both genders and various age groups, categorized in seven regular age groups.

The researched sample was followed for two years starting Jan 1st, 2009. until Dec 31st, 2010. The examinees are categorized in this paper according to their gender, region and place of residency, age groups, education, water supply objects and seroprevalence on hepatitis A.

In the researched area live in total 235.134(49.4%) men and 241.043 (50.6%) women. Most of the population lives in HNC 268.928 (56.5%), while WHC had a population of only 88.992 (18.7%).

The researched sample was also divided in examinees living in an urban or rural area.

The urban area had a population of 168.835 (34.4%). The rural part of the researched was inhabited by 312.342 (65.6%) of residents. Most of the urban population came from HNC (70.1%). The same canton was inhabited by the most residents from the rural areas (49.3%).

In the researched area the largest number of residents was in the groups aged 21-30 and over 60 , each 16.1%. The least amount of residents was registered in the age group of 41-50 years (10.5%).

Out of the researched sample we analyzed 420 examinees, which we also distributed in seven groups as mentioned above. The first group was made of children up to 10 years old, then the age group of 11-20 years and so on until the last group, which includes residents older than 60. In total we also followed every age group in both urban and rural areas. That is how we compared findings from same age groups which live in different environments and under different conditions.

These were randomly picked patients which were hospitalized in the Clinic for infective diseases of CH Mostar, which didn't have a registered appearance of viral hepatitis in their medical history, nor have ever treated themselves from any liver disease. We tested 60 examinees from each age group, half of which were urban citizens, while half were rural citizens. In every analyzed group half of the examinees were women, half men.

Comparing the findings of seroprevalence in the urban and rural population and in different age groups and genders, we analyzed the dynamics of seroprevalence and calculated trends in each researched groups. That is how we were able to compare every age group with other age groups inside urban and rural populations. Based on this data we described the biggest changes of seroprevalence and linked them to existing knowledge.

Procedures

The research was done cross sectional and comparatively, based on comparing results from different age groups and subgroups. We created a questionnaire with questions for every examinee (age, sex, place of residency, vocation, earlier illness from viral hepatitis or any liver illnesses). The examinees which had any data of having hepatitis or any liver diseases in the past were not included in this research. We also examined sources of the water supply in the research area to find out what kind of water our examinees consummate.

From every patient at the Clinic for infective diseases of CH Mostar we took, with their consent, 7,5 ml of blood for serological testing. Before testing the blood we centrifuged and singled out the serum. We tested the serum for antibodies anti HAV IgG with the micro-particle-hemiluminescent technique (MEIA) on the Abbot apparatus AXYSM. The serological processing was done at the Department for transfusion of CH Mostar.

Statistics data processing

The findings of the serological processing were analyzed as absolute numbers and percentages, with which the prevalence of seropositive examinees in every age group is highlighted. Based on the prevalence, the risk factors were calculated related to seropositive examinees, using the odds ratio or relative risk. The T-test was used to analyze numeric data, while the hi square test was used for categorical data. We used the regressive coefficient and analysis of variables to analyze trends, under the hypothesis of model linearity. The CRT, classification and regression tree was used. In the last step of the analyses logistic regression was used, to determine predictors of serostatus positivity in a multivariable model. Analysis was conducted using the SPSS program version 13,0 with the level of statistic relevancy set to $P < 0.05$ (Babuš 1997, Puvačić & Puvačić 2004, Štambuk-Giljanović 1998, Anonimno 2010, Golubović 2006).

RESULTS

This research included 420 examinees in total, which were tested on anti HAV IgG. With sequences of methodological accesses, all of the examinees were split

in seven groups each with 60 examinees, 30 from rural areas and 30 from urban areas. This way a balanced sample was created which reflected a wide span of the population, based on which later analyses were conducted. The average age of the entire sample was 45.9 20.9 years, without highlighted differences in the ratio of age and sex ($t=0.73$, $P=0.464$) or their rural or urban origins ($t=0.58$, $P=0.563$). In the sample there were 210 men and 210 women which, with their place of residence were mostly from the Mostar area (43.6%), with accessible water supply (71.9%) and from the HNŽ area (67.6%).

From this table you can see that in the urban area 38.1% of the examinees were positive to HAV IgG antibodies, while in the rural area the number of positives was somewhat bigger (43.3%) and among them no major statistical change was noticed ($P=0.321$; RR 0.805; 95% CL 0.54-1.118).

In relation to the gender of the examinees, 80 (38.1%) of the tested women were positive to anti HAV IgG antibodies, while 91 (43.3%) of the male examinees

were positive. So there is no major statistical differences between the genders regarding the seroprevalence of hepatitis A ($P=0.321$; RR:1.243; 95%CL:0.841-1.835).

A large number of examinees consummated water from the waterworks (301-71.7%). Only 20 (4.8%) of examinees used well water. Between examinees who used water from different water supply objects there is no major statistical difference regarding the presence of anti HAV IgG ($P=0.119-0.963$; RR: 0.499-1.215; 95% CL 0.201-6.459).

In analyzing the examinees according to their education the total number of examinees isn't 420, but 240, because in this case we only used age groups of examinees we could determine the stage of education, age groups of 0-20 and over 60 were not taken into consideration. Results showed that prevalence of HAV IgG antibodies was higher in lower educated (79.6%), than higher educated (20.4%) examinees and a major statistical difference was recorded ($P=0.001$; RR:0.293; 95%CL 0.141-0.606).

Table 1. Distribution of examinees by serological status based on area of residence, sex, water supply and education

	Serological status of examinees (anti HAV)		P	RR	95%CI
	IgG +	IgG -			
Area			0.321	0.805	0.545-1.189
Urban	80 (38.1)	130 (61.9)			
Rural	91 (43.3)	119 (56.7)			
Sex			0.321	1.243	0.841-1.835
Men	91 (43.3)	119 (56.7)			
Women	80 (38.1)	130 (61.9)			
Sources of water supply					
Waterworks	114 (37.9)	187 (62.1)			
Cistern	41 (48.2)	44 (51.8)			
Well	11 (55.0)	9 (45.0)			
Spring water	5 (35.7)	9 (64.3)			
Waterworks/cistern			0.131	0.669	0.413-1.085
Waterworks/well			0.119	0.499	0.201-1.241
Waterworks/spring water			0.925	0.813	0.275-2.403
Cistern/well			0.925	0.813	0.275-0.403
Cistern/spring water			0.732	0.745	0.281-1.981
Well/spring water			0.963	1.215	0.411-6.459
Education			0.293	0.001	0.141-0.606
High	11 (10.4)	38 (77.6)			
Low	95 (89.6)	96 (50.3)			

Table 2. Presentation of the frequency of the positive anti HAV IgG findings by age groups, according to basic demographic indicators

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	β (P)
Sex								
Male	2 (6.67)	1 (3.33)	2 (6.67)	10 (33.33)	16 (53.55)	30 (100.00)	30 (100.00)	0.94 (0.002)
Female	0 (0)	2 (6.67)	1 (3.33)	6 (20.0)	13 (43.33)	28 (93.33)	30 (100.00)	0.93 (0.002)
Sex difference*	0.246	0.381	0.381	0.191	0.303	0.246	-	
Urbanization								
Countryside	2 (6.67)	2 (6.67)	1 (3.33)	9 (30.00)	17 (56.67)	30 (100.00)	30 (100.00)	0.93 (0.002)
City	0 (93.33)	1 (3.33)	2 (6.67)	7 (23.33)	12 (40.00)	28 (93.33)	30 (100.00)	0.94 (0.002)
Origin*	0.246	0.381	0.381	0.195	0.151	0.246	-	
Total:	2 (3.33)	3 (5.00)	3 (5.00)	16 (26.67)	29 (48.33)	58 (96.67)	60 (100.00)	0.94 (0.002)

β - standardized regressive coefficient; *using Fishers exact test

Distribution by age groups revealed an interesting pattern of an increase in positive findings in older age groups (Table 2). Analysis of the trend showed statistically significant results and a very highlighted ascending trend of frequency of positive findings of anti HAV IgG for every specific group in serial analysis.

Using classification trees pointed to a highlighted predictive value of age as a main indicator of the serostatus. When age was excluded out of the model as a predictive value, the model gave no other results, which goes in favor to the relevancy of age and the small contribution of other variables in defining the serostatus.

DISCUSSION

Results of this research showed that the total seroprevalence of hepatitis A in the researched area is 40.71% and that its different in specific age groups. Seroprevalence in the 0-10 age group was 3.3%; in the 11-20 and 21-30 years it was 5%; in the group of 31-40 it was 26.7%; in the group of 41-50 years it was 48.3%; in the group of 51-60 years it was 96.7%, while all the examinees older than 60 were positive to anti HAV IgG 100%.

In undeveloped countries, as mentioned above, seroprevalence on HAV IgG antibodies is significantly higher than those in developed countries and it is characteristic that it is already exceptionally high in children of young ages.

Unlike mentioned researches in undeveloped countries, in developed countries of the world, as in countries which tend to be among the developed, completely different results were obtained. Seroprevalence is significantly higher in older age groups.

Taking into consideration all the above, the results of this research leads us to the conclusion that our researched area by seroprevalence of hepatitis A falls under the category of developed countries. We found an exceptionally low rate of seroprevalence in younger age groups-in the first three age groups (0-30 years) the rate of seroprevalence is 3-5%, which is exceptionally low. With the aging of the population a significant increase of the rate of seroprevalence is noted, like it is noted in other researched areas in the world (20-28).

Unlike us, countries with low development, especially those from Asia, Africa and Latin America have a significantly large rate of seroprevalence in the earliest years of childhood, which tells us children meet with the hepatitis A virus very early, which is then connected to the sanitation of the environment (Saha 2009, Sac 2009, Al-Aziz & Award 2008, Raharimanga 2008, Samuels 2005, Yassin 2001, Antaki & Kebbewar 2000, Tanaka 2000, Abdool Karim & Coutsoydis 1993).

It is known that the water supply is one of the biggest problems in undeveloped countries and as the

route of transfer of hepatitis A is the fecal-oral one, it is very easy to for the virus to get into contact with the population.

The found high rate of seroprevalence in the researched area, as in other countries in the adult, especially in the third life span, in regards to younger age groups, tells us of a significant improvement and betterment of life conditions and environment sanitation in the last few decades.

Regarding living areas, we also have not found any major statistical differences ($p=0,321$), according to which we understand that the rural area, with the help of the economic and political migration of residents in areas with a high standard have gotten a satisfactory material standard and received new positive hygienic habits which they in turn used in their homeland.

Comparing seropositive findings in the higher and lower educated examinees, given results indicate higher seroprevalence in the group with lower education, in regards to the examinees with a higher education and that between these groups exists a statistically significant difference ($P=0.001$; RR 0.293; 95CL 0.41-0.606).

Considering this situation in our researched area we have reached a conclusion that the situation in the last few decades has significantly changed for the better regarding our socio-economic and sanitary situation and the increase and usage of the knowledge from the preventive medical protection (Štambuk-Giljanović 1998, Anonimno 2010, Golubović 2006).

In the rural areas sanitary facilities are not outside the homes any longer, water supply objects have been considerably improved and hygiene has been generally brought to a higher level (Štambuk-Giljanović 1998).

Likewise the quality of sanitary inspections has considerably increased which in their work use positive legal acts, which has in turn had an outcome of no large epidemics of hepatitis A and other fecal-oral infections in the last few decades (Anonimno 2010, Golubović 2006, Anonimno 2010, Anonimno 2006, Zakon o inspekcijama 2005).

In our country vaccination of hepatitis A does not come into the group of mandatory vaccination. As this study only refers to our researched area, without a broader analysis of the other parts of the country we cannot make a conclusion about a need for hepatitis A vaccination. Except researches on other parts of the country, considering the economic situation of the country, a broader research of the cost benefit of vaccination should be created. With regards to defective data and the complex economic situation in the country, for now it looks like that vaccinations are advisable, according to the recommendations of the CDC (CDC 1999), of risk groups, especially people who are traveling to countries with a high seroprevalence of hepatitis A homosexuals and intravenous addicts,

people with chronic liver diseases and the people who work in specific work places (firemen, military, police and medical personnel).

Improving measures of primary infectious disease prevention needs to be primarily insisted and constantly worked on, focusing on changing and improving hygienic habits, which would then create real assumptions for a later decrease of seroprevalence and maybe eradication of hepatitis A.

CONCLUSION

In the researched area there were no statistically major differences in the seroprevalence between genders, examinees who used different water supply objects, likewise between urban and rural population. A major statistical difference is noticed in examinees of higher and lower education. An increase of frequency in seropositive findings in older age groups has been noted and from a very low rate of seroprevalence to as high as 100% in older age groups and that the age of examinees has shown as a main predictor value in defining the serostatus. That is similar to seroprevalence in developed countries, within which was found a very low rate of seroprevalence in younger age groups. That kind of low rate tells us of hygienic habits of examinees in researched areas. For now there is no need in the researched area to include vaccination against hepatitis A in a mandatory calendar. To get a realistic picture of seroprevalence of this disease in BH, a similar research should be done in other parts of the country.

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Contribution of individual authors:

Helien Bebek-Ivanković: conception and design of the publication, literature, searches and analyses, acquisition of data, interpretation of results, writing the first draft, participate in drafting the article, execution of tables, approval of the final version, participation in statistical analysis;

Svjetlana Grgić: participation in statistical analysis, participation in revising it critically for important intellectual content, approval of the final version;

Ivo Curić: participation in revising it critically for important intellectual content, approval of the final version;

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References

1. Babić Božović I, Vraneković J. Folate and folic acid: current knowledge and gaps. *Medicina fluminensis*, 2014; 50:169-175
2. Begić D. *Psihopatologija*. Zagreb: Medicinska naklada, 2014 (str. 267-276)
3. Bilić V. *Psihološki čimbenici kod kardiovaskularnih bolesti*, *Kardio.hr*, 2010
4. Bukharaeva E, Shakirzyanova A, Khuzakhmetova V, Sidikova G, Giniatullin R. Homocysteine aggravates ROS-induced depression of transmitter release from motor nerve terminals: potential mechanism of peripheral impairment in motor neuron diseases associated with hyperhomocysteinemia. *PubMed*, 2015
5. Buljan D. *Konzultativno-suradna psihijatrija: Vodič za dijagnostiku i liječenje psihičkih smetnji u somatskoj medicini*. Jastrebarsko: Naklada Slap, 2016 (str.143-146)
6. Chan JN-M, Lee JC-D, Lee SSP, Hui KKY, Chan AHL, Fung TKH. Interaction Effect of Social Isolation and High Dose Corticosteroid on Neurogenesis and Emotional Behavior. *PubMed*, 2017
7. Chapa DW, Akintade B, Son H, Woltz P, Hunt D, Friedmann E. Pathophysiological Relationships Between Heart Failure and Depression and Anxiety. *Critical Care Nurse*, 2014; 34
8. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *PubMed*, 2017
9. Damjanov I, Jukić S, Nola M. *Patologija*. Treće izdanje. Zagreb: Medicinska naklada, 2011. (str. 297-299)
10. Dethlefsen T, Dahlke R. Bolest kao put. Kako razumijeti što nam govore simptomi bolesti. Zagreb: Nar, 2011 (str. 259-269)
11. Feng HP, Chien WC, Cheng WT, Chung CH, Cheng SM, Tzeng WC. Risk of anxiety and depressive disorders in patients with myocardial infarction: A nationwide population-based cohort study. *PubMed*, 2016
12. Filaković P. Terapija depresija kod bolesnika s komorbiditetom. *Medicus*, 2014; 13:59-67
13. Folnegović-Šmalc V, Folnegović Grošić P, Henigsberg N, Kozumplik O, Makarić G, Mimica N i sur. *Farmakoterapija depresija*. *Medicus* 2004; 13, No.1
14. Gamulin S, Marušić M, Kovač Z i sur. *Patofiziologija*. Sedmo izdanje. Zagreb: Medicinska naklada, 2011 (str. 414)
15. Geroulakos G, O'Gorman DJ, Kalodiki E, Sheridan DJ, Nicolaidis AN. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease. *PubMed*, 1994
16. Horwitz L, Krumholz H, Hunt SA, Yeon SB. Heart failure self management. *UpToDate*, 2017
17. HZJZ, Ministarstvo zdravlja Republike Hrvatske. *Kardiovaskularne bolesti u Republici Hrvatskoj*. Zagreb, 2013 dostupno na: https://hzjz.hr/wp-content/uploads/2013/11/KVBilten_2011-10-5-2013-3.pdf
18. Jakovljević M, Duplančić D. Depresija, serotonin, kardiovaskularne bolesti. U: Jakovljević M, suradnici. *Serotonin i depresija: mitovi i činjenice*. Zagreb: Pro Mente, 2013 (str.194-208)

19. Jendričko T. Razvoj psihičkih poremećaja u bolesnika s akutnim koronarnim sindromom (disertacija). Zagreb, 2012
20. Kang HJ, Stewart R, Bae KY, Kim SW, Shin IS, Kang H. Predictive value of homocysteine for depression after acute coronary syndrome. *PubMed*, 2016
21. Kim DA, McClure WG, Neighoff JB, Vaidya D, Williams MS. Platelet Response to Serotonin in Patients with Stable Coronary Heart Disease. *PubMed*, 2014
22. Lang UE, Borgwardt S. *Molecular Mechanisms of Depression: Perspectives on New Treatment Strategies*. University Hospital of Basel, Department of Psychiatry and Psychotherapy, Basel, 2013
23. Liu X, Lou X, Cheng X, Meng Y. Impact of metoprolol treatment on mental status of chronic heart failure patients with neuropsychiatric disorders. *PubMed*, 2017
24. Lopez-Vilchez I, Diaz-Ricart M, Navarro V, Torramade S, Zamorano-Leon J, Lopez-Farre A. Endothelial damage in major depression patients is modulated by SSRI treatment, as demonstrated by circulating biomarkers and an in vitro cell model. *PubMed*, 2016
25. Ma Y, Peng D, Liu C, Huang C, Luo J. Serum high concentrations of homocysteine and low levels of folic acid and vitamin B12 are significantly correlated with the categories of coronary artery disease. *PubMed*, 2017
26. Mihaljević-Peleš A. Premećaji raspoloženja. U: Begić D, Jukić V, Medved V. *Psihijatrija*. Zagreb: Medicinska naklada, 2015 (str.160-166)
27. Morscgitzky H, Sator S. Wenn die Seele durch den Körper spricht. *Psychosomatische Störungen verstehen und heilen*. Dusseldorf, 2006
28. Musliu NR, Ibishi NF, Hundozi Z. Depression and heart failure: decline in quality of life and future management considerations (Professional article). *Cardiologia Croatica* 2013; 8:83
29. Novak Sarota B, Lainscak M. *Psychocardiology in the elderly*. *Wien Klin Wochenschr* (2016) 128 [Suppl 7]:S474–S479 DOI 10.1007/s00508-016-1139-x
30. Shah SU, White A, White S, Littler WA. Heart and mind: (1) relationship between cardiovascular and psychiatric conditions (review). *BMJ Journals*, 2014; 80–950. *PubMed*
31. Smith PJ, Blumenthal JA. *Psychiatric and Behavioral Aspects of Cardiovascular Disease: Epidemiology, Mechanisms, and Treatment*. *Rev Esp Cardiol*. 2011; 64:924-33
32. Stojanović-Špehar S, Rifel J. *Depresija*. U: Katić M, Švab I. (ur). *Obiteljska medicina*. Zagreb: Alfa, 2013 (str. 140-151)
33. Stover PJ. *Physiology of Folate and Vitamin B12 in Health and Disease*. *Nutrition Reviews*, 2004; 62, No.6
34. Šagud M, Jakšić N, Vuksan-Čusa B, Lončar M, Lončar I, Mihaljević Peleš A, Miličić, Jakovljević M. Cardiovascular disease risk factors in patients with posttraumatic disorder (PTSD): a narrative review. *Psychiatria Danubina* 2017; 29: 421-430
35. Tofler GH, Silver JM, Solomon D. Psychosocial factors in acute myocardial infarction. *UpToDate* 2017
36. Topić R. Psihijatrijski aspekti kardiovaskularnih bolesti / bolesnika (pregledni rad). *Medicus* 2010; 19: 233-240
37. Trebatická J, Dukátb A, Ďuračková Z, Muchová J. Cardiovascular diseases, depression disorders and potential effects of omega-3 fatty acids. *Physiological Research* (pre-press article), 2017
38. Whooley MA. MD Veterans Affairs Medical Center and University of California, San Francisco *Ann Intern Med*. 2006;144:858-860
39. Williams J, Nieuwsma J, Elmore JG, Roy-Byrne PP, Melin JA. Screening for depression in adults. *UpToDate*
40. Williams MS. Platelets and depression in cardiovascular disease: A brief review of the current literature. *PubMed*, 2012
41. Won E, Kim Y-K. Stress, the Autonomic Nervous System, and the Immune-kynurenine Pathway in the Etiology of Depression *PubMed*, 2016
42. Young SN. Folate and depression- a neglected problem. *PubMed*, 2007
43. Žegura I. *Psihologija koronarne srčane bolesti Jastrebarsko: Naklada Slap*, 2010. (str.21-49)

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