



VIRAL HEPATITIS C – GLOBAL HEALTH PROBLEM

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ABSTRACT:

Purpose: to propose a multidisciplinary approach for early diagnosis and therapy of viral hepatitis C (VHC).

Material/Methods: A prospective cross-sectional study was conducted on epidemiological, demographic, clinical, laboratory and viral characteristics in fifty cases of VHC confirmed with positive anti-HCV (by ELISA). Thirty-eight of the cases were hospitalized in different clinics in Pleven (2017–2018). The remainders were blood-donors for the Regional Center of Transfusion Hematology – Pleven. The genotype of HCV and the viral load had been investigated by Real-Time PCR in the Laboratory of Virology at Military Medical Academy – Sofia.

Results: The most affected age groups were 30-39 years and 60-69 years (24%, respectively); males 69.81% ($p < 0.05$). Surgical interventions, blood infusions and hemodialysis (26.32%, 23.68% and 15.79%, respectively) were at the highest risk for VHC ($p > 0.05$). Thirty hospital patients were with chronic VHC (78.95%) ($p < 0.05$). Clinical symptoms suggestive of viral hepatitis were fatigue (39.47%; OR 5.25), decreased appetite (28.95%; OR 2.16), abdominal discomfort (21.05%; OR 23.33); 52.63% of patients were asymptomatic ($p < 0.0005$). Laboratory investigations revealed slightly or moderately elevated total bilirubin (mean $53.27 \pm 37.38 \mu\text{mol/L}$; 95% CI 18.48–88.06), ASAT (mean $231.36 \pm 155.82 \text{ IU/L}$; 95% CI 79.91–382.80) and ALAT (mean $294.48 \pm 196.26 \text{ IU/L}$; 95% CI 96.37–492.59) ($p > 0.05$). All isolates of HCV had been proved to be genotype 1b. The viral load was detectable in 22 samples (range 683–673,720 copies/mL).

Conclusion: VHC is mostly asymptomatic. Screening for anti-HCV in risk groups and genotyping of HCV will reduce nosocomial transmission, facilitate early therapy and prevent complications of infected individuals.

Keywords: hepatitis C, epidemiology, genotyping,

INTRODUCTION

Viral hepatitis C (VHC) is a global public health problem. 58 million people in the world have chronic hepatitis C. About 1.5 million new cases of VHC occur annually. In 2019, about 290,000 died of VHC, most often from liver cirrhosis and primary liver carcinoma (according to WHO data) [1, 2, 3].

Direct-acting antiviral (DAA) therapy with protease inhibitors is effective in up to 95% of cases, but access to early diagnosis and treatment in less developed countries is low [4]. Due to the genetic diversity of the hepatitis C virus (HCV) (8 genotypes, 84 subtypes and 21 non-permanent subtypes – quasi-types), there is still no effective vaccine against VHC [5, 6, 7].

The advantages of modern therapeutic strategies have allowed the World Health Organization (WHO) to adopt a global strategy to eliminate the disease as a public threat by 2030. Measures include: the safety of blood components and invasive medical manipulations with the aim of reducing the incidence of VHC by 80%, diagnosis of 90% of the affected population, treatment of 80% of diagnosed cases, and reducing mortality related to chronic and oncological liver damage by 65% [1, 2, 3, 4, 7].

To be in line with WHO's global strategy, we have set ourselves the **aim** of creating a reliable multidisciplinary approach for early diagnosis, epidemiological investigation and prevention of VHC.

MATERIALS AND METHODS:

A prospective cross-sectional study was conducted on epidemiological, demographic, clinical, laboratory and viral characteristics in fifty cases of VHC confirmed with positive anti-HCV (by ELISA). Thirty-eight of the cases were hospitalized in different clinics in Pleven (2017–2018); the remainders were blood-donors for the Regional Center of Transfusion Hematology – Pleven.

Methods used were: survey – interview, documentary method; clinical and laboratory methods; serological tests (anti-HAV IgM, HBs Ag, anti-HBc IgM, anti-HCV, anti-HEV IgM – by ELISA antibody tests); abdominal ul-

trasound; method of expert evaluation and method of epidemiological study. Data were entered into an electronic database (Microsoft Excel v. 2010) and analyzed using statistical software (IBM SPSS Statistics 19.0). The variables were analyzed by t-test and χ^2 test (for parametric and non-parametric distributions, respectively; $p < 0.05$ was considered as significant). The risk of the impact of factor – odds ratio (OR) was accepted at $OR > 1.0$, and the degree of risk increases with increasing OR. By modifying Pearson's correlation (ϕ -coefficient), a 5-level scale was used to assess correlation: weak correlation dependence at $\phi < 0.3$; moderate – at $0.31 < \phi < 0.5$; significant correlation dependence at $0.51 < \phi < 0.7$; high correlation dependence at $0.71 < \phi < 0.9$; extremely large correlation dependence at $\phi > 0.9$.

Molecular-genetic methods such as the determination of HCV genotype and sub-genotype and viral load had been performed in the Virology Laboratory of the Academy of Medical Sciences – Sofia. The viral load and genotyping were made using Real-time PCR. In view of the most common and prevailing genotypes and sub-genotypes in Bulgaria and Europe, as identified by Bulgarian and other researchers, we chose a kit to detect 1a, 1b, 2, 3, 4, 5a, and 6 genotypes/ sub-genotypes of HCV. The method includes the following steps: a) extracting RNA from serum; b) obtaining Copy DNA complementary to the extracted RNA through reverse transcription; c) Real-time PCR analysis using a standard protocol with fluorescent dyes HEX and FAM. Interpretation of results was

based on the fluorescent signal as relative fluorescence units (RFU). The lower limit of sensitivity of the qualitative variant test is 50 viral copies in 1 ml of blood, below which samples are accepted as negative (-) and above this limit as positive (+). Quantification (viral load in international units – IU) was only on samples with a (+) quality test. The final values of the viral load, after comparison of RFU values for the viral load with the positive standard controls, are defined in international units (IU). The final result for the viral load is presented as the number of copies of viral RNA/ml of blood after recalculation according to the formula for the kit used. The coefficient was 3.2, i.e. each IU is equal to 3.2 HCV-RNA copies.

RESULTS:

The study conducted on the incidence and registered cases of VHC in Bulgaria and the Plevan region for the period 2008-2021 found an incidence for Bulgaria ranging from 0.63 to 1.30 per 100,000 population with the highest incidence in 2009, 2012, 2013, 2014, and 2019. The incidence for the Plevan region ranged from 0.38 to 3.8 per 100,000 population with peaks in 2009, 2011, 2012, 2013, and in these years, the incidence in the Plevan region was significantly higher than that for the country ($p < 0.05$). The peak incidence of VHC in the Plevan region was in 2009 and 2013 ($p < 0.05$). The incidence trend for the country was downward, and the trend for the Plevan region was similar (Fig. 1- a, b, c).

Fig. 1a. Incidence of VHC for Bulgaria and Plevan region

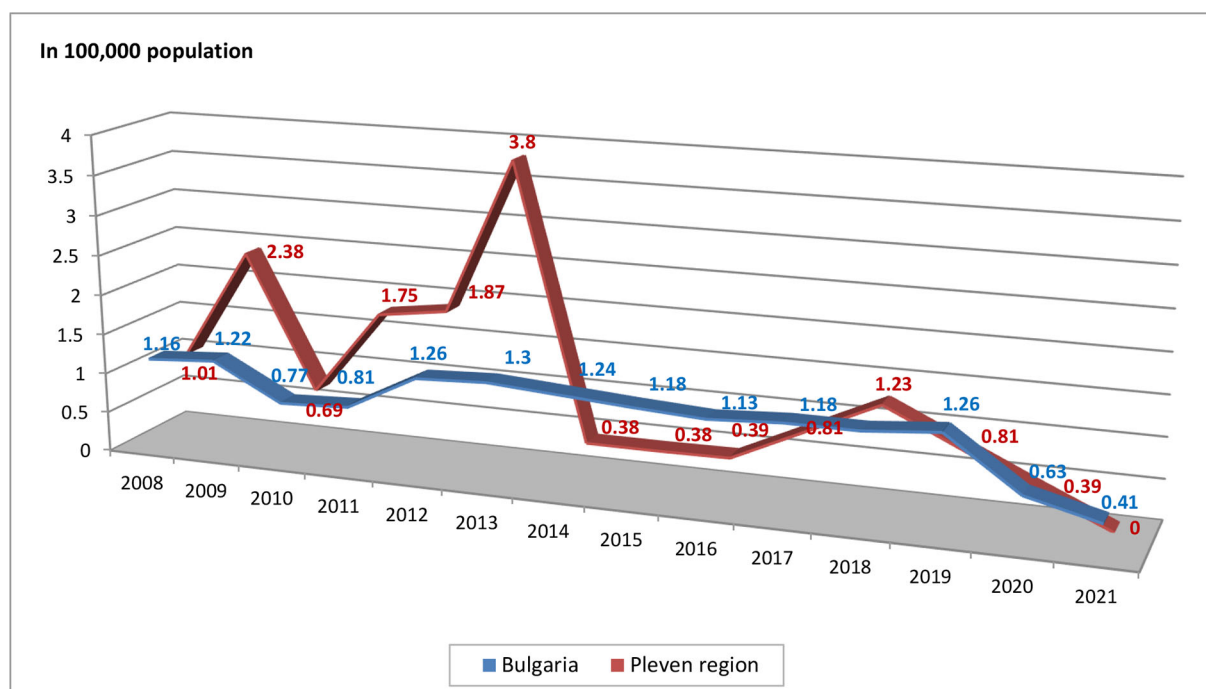


Fig. 1b. Incidence trend of VHC for Bulgaria

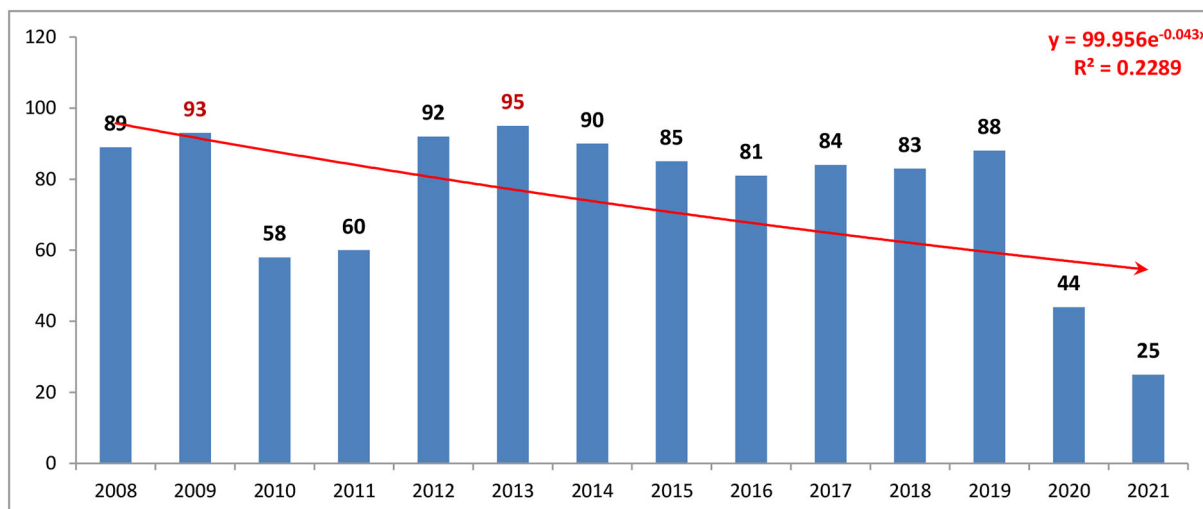


Fig. 1c. Incidence trend of VHC for the Pleven region

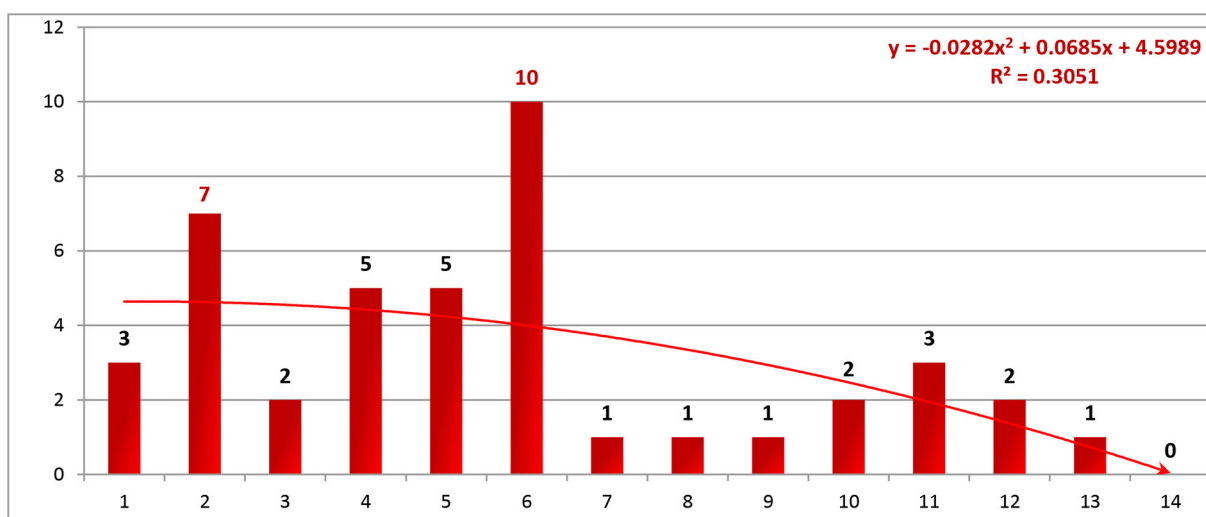
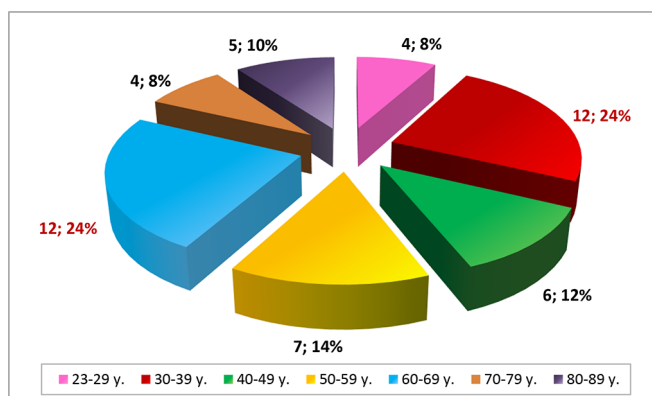


Fig. 2. Age structure of cases with VHC in the Pleven region



The distribution of 50 serologically confirmed cases of VHC showed the highest prevalence of age groups 30-39 years and 60-69 years (12/50; 24% each) ($p < 0.005$) (Fig. 2) with a significantly higher prevalence of males (35/50; 69.81%) ($p < 0.05$). It was interesting that the higher number of VHC cases in the younger age groups were males, while in females the higher number of cases were from the 70-79 age group ($p < 0.05$). The highest prevalence was the cases after operative interventions (11/50; 22%), followed by those after blood transfusion (5/50; 10%). “Body art” procedures (piercing, tattoos) (3/50; 6%), hemodialysis, intravenous drug injection and incarceration (each of them, 2/50; 4%) were less common ($p < 0.05$).

The next stage of the study focused on 38 hospital patients with a leading diagnosis of VHC or an accompanying one. The most considerable prevalence of hospital patients had been found in age 60-69 years (12/38; 31.58%) ($p < 0.05$). The main reason for admission to the hospital was any comorbidity in elderly patients. Hospitalizations of patients with HCV in clinics of gastroenterology, infec-

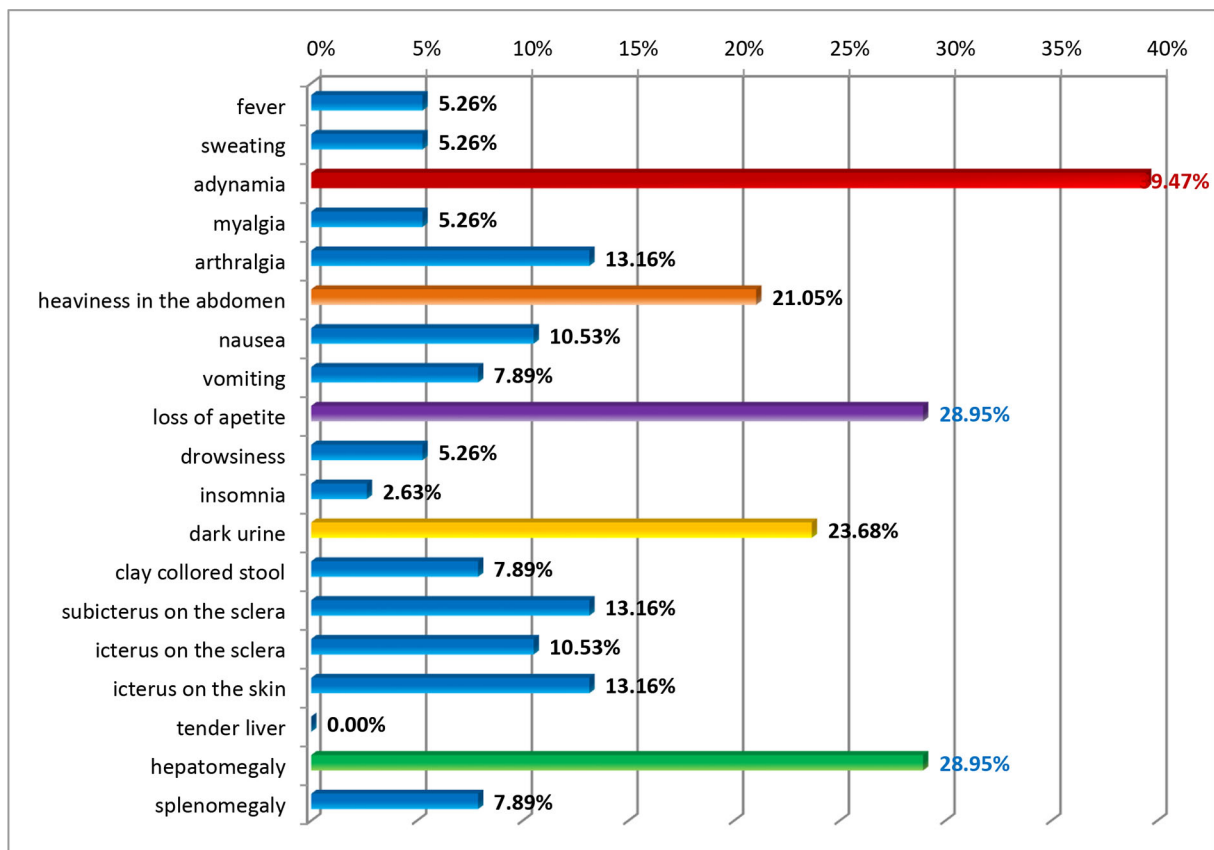
tious diseases and hematology were leading – 12 (31.58%), 9 (23.68%), and 8 patients (21.05%), respectively. Admissions of cases with chronic VHC predominated (30/38; 78.95%), mostly males (26/38; 68.42%), urban residents (25/38; 65.79%) ($p < 0.05$). Operative interventions (10/

38; 26.32%), blood transfusions (9/38; 23.68%) and invasive manipulations (3/38; 7.89%) were among the leading risk factors for possible exposure to the virus.

The clinical symptoms of the hospital patients suggesting viral hepatitis (regardless of its etiology) were as follows: fatigue (in 15/38; 39.47% of patients), decreased appetite (11/38; 28.95%), hepatomegaly (11/38; 28.95%), dark urine (9/38; 23.68%), and abdominal heaviness (8/38; 21.05%) ($p > 0.05$) (Fig. 3). Of the indicated symptoms, the heaviness in the abdomen (OR 23.33; $\phi=0.588$

– significant correlation according to the 5-point Pearson scale), fatigue (OR 5.25; $\phi = 0.311$ – moderate correlation) had a visible correlation with the severity of the course correlation scale) and reduced appetite (OR 2.16; $\phi = 0.15$ – weak correlation). Other symptoms, such as suspicion of viral hepatitis, were much less frequently reported. In the hospital patients group, twenty of them (52.63%) were asymptomatic and epidemiological history was mainly indicative of the correct diagnosis.

Fig. 3. Prevalence of the symptoms in 38 hospital patients with VHC



Laboratory investigations revealed slightly or moderately elevated total bilirubin (mean $53.27 \pm 37.38 \mu\text{mol/L}$; 95% CI 18.48 - 88.06), ASAT (mean $231.36 \pm 155.82 \text{ IU/L}$; 95% CI 79.91 - 382.80) and ALAT (mean $294.48 \pm$

196.26 IU/L ; 95% CI 96.37 - 492.59) ($p > 0.05$). The rest of the routine laboratory indicators had no specific diagnostic value for VHC (Table 1).

Table 1. Laboratory investigations of 38 hospitalized cases with VHC

	min	max	mean	sd	median	mode	95% CI
Er	2.26	6.12	4.227	0.837	4.26	4.71	3.95-4.51
Hg	46	171	124.42	25.37	125	137	115.87-132.96
MCV	66	109	87.17	7.92	87.8	88	84.5-89.84
Ht	0.25	0.52	0.38	0.07	0.38	0.38	0.35-0.4
WBC	2.7	34.5	7.35	5.16	6.3	6	5.61-9.09
Gran	13.3	85	64.88	13.69	64.95	69.8	60.14-69.63
Ly	12	82.3	27.79	12.79	28.1	15	23.35-32.22
Mo	3	29.3	7.77	4.47	6.85	5	6.22-9.32

PLT	47	434	186.63	86.42	185	89	157.11-216.15
T bil	4.8	440	53.27	37.38	12.95	NA	18.48-88.06
D bil	2.2	392	44.59	30.44	7.3	7.3	9.59-79.6
AST	7.2	2077	231.36	155.82	51	NA	79.91-382.80
ALAT	9	2757	294.48	196.26	45	20	96.37-492.59
GGT	11.8	1415	198.85	108.8	93	26	90.21-307.5
AP	35	384	125.24	85.74	100	64	94.61-155.87
LDH	233	1020	394.31	195.56	337	NA	277.15-511.46
SHE	3360	8704	6007.95	2223.39	5983.9	NA	2932-9082.9
TP	54	87.5	71.12	6.79	70.05	77	68.58-73.65
Alb	27.9	51.4	41.8	5.93	42.55	45.6	39.54-44.05
F-gen	1.47	5.76	2.89	1.02	2.86	2.3	2.51-3.27
PI	20.4	120	82.28	19.97	84.5	92	74.84-89.72
Chol	2.8	5.8	4.68	0.94	4.76	NA	3.92-5.44
3-glyc	0.98	2.61	1.56	0.55	1.58	1.7	1.11-2.02
Glucose	3.53	10.7	5.8	1.83	5.2	4.9	5.18-6.43
BUN	2.3	17.3	6.6	4.84	4.22	17.3	4.97-8.23
Creat	28	1075	138.51	197.55	74	56	71.03-206.0
Cl⁻	95	110	102.64	4.36	102	105	99.74-105.53
Na⁺	122	143	138.47	3.81	139	142	136.52-140.42
K⁺	3.6	5.9	4.65	0.61	4.6	5	4.36-4.94
UA	196	761	386.38	168.92	340	NA	285.19-487.58
CRP	0.15	37.7	11.7	12.3	9.1	NA	3.03-20.37

sd - standard deviation; CI - confidence interval; Er - erythrocytes; Hg - haemoglobin; MCV - Mean Corpuscular Volume; Ht - haematocrite; WBC - white blood cells; Gran - granulocytes; Ly - lymphocytes; Mo - monocytes; PLT - platelets; T bil - total bilirubin; D bil - direct bilirubin; AST - aspartate aminotransferase; ALT - alanine aminotransferase; GGT - gamma glutamyl transferase; AP - alkaline phosphatase; LDH - lactate dehydrogenase; SHE - serum cholinesterase; TP - total protein; Alb - albumins; F-gen - fibrinogen; PI - prothrombin index; Chol - cholesterol; 3-glyc - 3-glycerides; BUN - blood urea nitrogen; Creat - creatinine; UA - ureic acid; CRP - C-reactive protein

The duration of the disease was difficult to determine due to its detection more often in the chronic stage and predominant mild (3/38; 7.89%) to moderate (8/38; 21.05%) clinical forms determined by the clinical and laboratory profile of the hospitalized patients.

Regarding the genetic characteristics of HCV, samples from 50 individuals were examined using the Real-Time PCR method. Viral load of HCV was detectable in 22 samples (range 683 - 673,720 copies/ml). All isolates of HCV had been proved to be genotype 1b.

As a final stage of the present study, we attempted to develop criteria for a complex epidemiologic study of VHC using classical and molecular genetic methods. The criteria include individual patient information, epidemiological information regarding all possible manipulations and activities at risk for VHC, clinical and laboratory investigations to confirm the diagnosis and molecular genetic testing for genotyping and viral load determination.

Based on what has been stated so far, we consider

that it is especially important to direct attention to representatives of risk groups and to persons subject to invasive interventions. After a precise epidemiologic interview, an anti-HCV test (by ELISA) serves as a basic test. Depending on the result, PCR should be followed, if possible, to determine viral load and HCV genotype/sub-genotype. The goal is early referral for treatment and limiting the risk of nosocomial HCV infections.

DISCUSSION:

The importance of hepatitis C-related public health problems has been undiminished in recent decades. In 2016, Petruzzello A. et al. conducted a systematic study defined by the Global Burden of Diseases project (GBD), which was one of the most comprehensive effort to quantify global HCV epidemiology based on available published data between 2000 and 2015 from 138 countries, grouped in 20 geographical areas (with the exclusion of Oceania). Total global HCV prevalence was estimated at

2.5% (177.5 million HCV infected adults), ranging from 2.9% in Africa and 1.3% in the Americas, with a global viraemic rate of 67% (118.9 million HCV RNA positive cases), varying from 64.4% in Asia to 74.8% in Australasia. HCV genotype 1 is the most prevalent worldwide (49.1%), followed by genotype 3 (17.9%), 4 (16.8%) and 2 (11.0%). Genotypes 5 and 6 are responsible for the remaining <5%. While genotypes 1 and 3 are common worldwide (67.0% if considered together), the largest proportion of genotypes 4 and 5 is in lower-income countries [8]. These findings are comparable with other studies [5, 6, 9]. In our study, all isolates of HCV had been proved to be genotype 1b.

The problems of public health related to hepatitis C can be divided into two groups. In the first group are those arising from the nature of the disease (asymptomatic course in the acute stage, tendency to chronic course leading to chronic hepatitis or liver cirrhosis, the high risk of primary liver carcinoma). At the same time, the hepatitis C virus has a high mutation ability, which makes it impossible at the current time to create an effective vaccine. The second group covers problems related to negative trends in public health, influenced by social factors – an increase in the average life expectancy and the corresponding aging of the population, which leads to an increase of invasive procedures; an increase in the use of intravenous narcotic substances and performance of body “beautifying” procedures (tattoos, piercings), unprotected sex, etc. Disparities in health utilities among patients with hepatitis C also worsen the problem, as mentioned in the study of Sayed YA et al. (2023) [10].

Independent of the trends for decreasing the incidence of VHC in Bulgaria and the Pleven region, the analysis of the age structure of the cases of VHC in our study shows that the most affected ages are 30-39 years

and 60-69 years ($p < 0.005$) with a significantly higher prevalence of males (69.81%) ($p < 0.05$). The higher number of VHC cases in the younger age groups were males (with risk factors intravenous narcotic usage, “body art” procedures), while in females the higher number of cases were from the 70-79 age group (after invasive procedures because of any comorbidity) ($p < 0.05$). The symptoms reported by 38 hospital cases in our study were not strictly specific to hepatitis C. Twenty of them (52.63%) were asymptomatic, and epidemiological history was mainly indicative of the correct diagnosis.

Based on the broad distribution of hepatitis C, its prevalently asymptomatic course, and the serious sequels of the disease (chronic evolution, risk of liver cirrhosis and liver carcinoma) we are convinced that active screening for anti-HCV in risk groups and before invasive manipulation with investigation of viral load and genotyping (if it is possible) is in accordance with the strategy of WHO and will facilitate to achieve hepatitis C elimination targets to 2030 [11, 12, 13, 14].

CONCLUSIONS:

Viral hepatitis C is most often asymptomatic. Screening for anti-HCV in risk groups and HCV genotyping will improve surveillance, reduce nosocomial HCV infections, facilitate treatment, and prevent complications in those infected.

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