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Original article

METABOLIC AND CARDIOVASCULAR COMORBIDITIES IN BULGARIAN PATIENTS WITH CHRONIC VIRAL B AND C HEPATITIS

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SUMMARY:

Recent epidemiologic data on chronic viral B and C hepatitis in Bulgaria are limited. The evolution of these infections depends on liver complications and the presence of nonliver comorbidities. The aim of the study was to assess the frequencies of arterial hypertension, ischemic heart disease, myocardial infarction, chronic heart failure, type 2 diabetes mellitus and metabolic syndrome in patients with chronic viral B and C hepatitis, associated liver cirrhosis and to compare with those of uninfected controls.

Material/Methods: We conducted a retrospective cross-sectional study in the period 2003-2023. We included 1803 patients, 474 with chronic hepatitis B, 482 with chronic hepatitis C and 847 uninfected controls. The patient's medical records were analyzed for the presence of arterial hypertension, ischemic heart disease, myocardial infarction, chronic heart failure, type 2 diabetes mellitus and metabolic syndrome.

Results: The most common comorbidity in the three groups was arterial hypertension, followed by type 2 diabetes mellitus. The frequency increased in chronically infected patients with liver cirrhosis. We observed a higher prevalence of myocardial infarctions in the patients with chronic hepatitis C (p=0.045) and of metabolic syndrome in the hepatitis B group (p=0.028). A higher prevalence of ischemic heart disease was observed in the group with chronic hepatitis B and liver cirrhosis (p=0.01).

Conclusions: Chronic hepatitis B and C in our groups were associated with significant morbidity, particularly with arterial hypertension and type 2 diabetes mellitus. The finding was more pronounced in patients with already developed liver cirrhosis.

Keywords: chronic hepatitis B, chronic hepatitis C, comorbidities,

INTRODUCTION:

According to the World Health Organization, 254 million people live with chronic hepatitis B (CHB) and around 50 million with chronic hepatitis C (CHC) globally. There were 2.2 million new viral hepatitis infections in 2022, 1.2 million new hepatitis B virus (HBV) infections and nearly 1.0 million new hepatitis C virus (HCV) infections [1].

The patients with chronic viral hepatitis represent an aging population [2, 3]. This is the result of early childhood hepatitis B vaccination, advances in treatment options and improved outcomes for those affected. The introduction of direct-acting antiviral medications for the treatment of CHC has dramatically changed the management of the disease, resulting in a high level of sustained virologic response. The development of complications and the life expectancy of these patients are highly dependent on the presence of liver cirrhosis, hepatocellular carcinoma and nonliver comorbidities.

The prevalence of CHB in Bulgaria is about 2.6% [4]. The overall prevalence of hepatitis C antibodies in the country is 1.08% [5]. Active CHC infection was reported as 0.9% in a single wide Bulgarian region [6]. There is a gap in the epidemiological data on the prevalence of concomitant diseases among patients with chronic viral hepatitis in the country. We focused on the study of cardiovascular and metabolic disorders in these patients because of the previous data on their high frequency in our population. The age-standardized prevalence rate of cardiovascular diseases (CVD) in Bulgaria was 7,102.1 per 100,000 in 2021 [7]. Prognosis and associated mortality in patients with advanced CVD are strongly associated with the presence of comorbidities such as arterial hypertension (AH), valvular diseases, myocardial infarctions (MI), and anemia [8]. Metabolic syndrome (MS) is a combination of dysregulation of glucose homeostasis, arterial hypertension, central obesity with insulin resistance, and dyslipidemia. It is a significant risk factor for the development of CVD and type 2 diabetes mellitus (DM2).

The International Diabetes Federation reports a diabetes prevalence of 9,9% for the Bulgarian population in

2023 [9]. According to the Eurostat public database, Bulgaria has the highest overall mortality in Europe for 2022, with CVD as the most important contributing factors [10]. However, a local study of the comorbidity of the most common CV and metabolic diseases with target groups, for example, liver disease, has not, to our knowledge, been published in recent years. We aimed to assess the frequencies of AH, ischemic heart disease (IHD), MI, chronic heart failure (CHF), DM2 and MS in patients with CHB and CHC and associated liver cirrhosis and compare them with those of uninfected controls.

MATERIALS AND METHODS:

The cross-sectional study included 1803 patients, 474 with CHB, 482 with CHC, and 847 uninfected controls. Patients were retrospectively selected from the database of the Clinic of Propedeutics of Internal Medicine, Medical University - Sofia, for the period 2000-2020. The control group consisted of randomly selected individuals seen as outpatients at the clinic who were tested for serum markers of viral hepatitis B and C and were negative. All participants were over 18 years of age and signed written consent.

The diagnosis of CHB was accepted when HBsAg was positive in serum for at least 6 months.

The diagnosis of CHC was confirmed by the presence of serum antibodies - anti HCV and viral load by polymerase chain reaction 6 months after the first positive result.

Medical files and records were reviewed, and the following cardiovascular and metabolic diseases were recorded: AH, IHD, MI, CHF, DM2 and MS. AH was accepted if the diagnosis was previously established with the corresponding International Classification of Diseases (ICD) code and the presence of antihypertensive medications. IHD was diagnosed on the basis of coronary angiography or other non-invasive testing, such as contrast-enhanced computer tomography, with sclerotic coronary artery stenoses or previous myocardial infarction diagnosed and recorded in the medical file with the corresponding ICD code.

CHF was accepted with objective data from echocardiography and a specialist †s conclusion with a corresponding ICD code. DM2 and MS were diagnosed by an endocrinologist and assigned the correct ICD codes. All patients with DM2 were on appropriate anti-diabetic treatment.

The patient's blood analysis was performed to diagnose liver disease and included platelets, transaminase level - aspartate transaminase (AST), alanine transaminase (ALT), serum alkaline phosphatase (AF), gamma-glutamyl transferase (GGT), bilirubin, protein, albumin, creatinine, cholesterol and triglycerides. All patients with viral hepatitis underwent liver biopsy to evaluate fibrosis, except those with decompensated liver disease.

Statistical methods:

Descriptive statistics was used to present the main characteristics of the patients- age, sex, body mass index (BMI), laboratory results. All continuous variables were tested for normal distribution with the Kolmogorov-Smirnov test and reported as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were recorded as number or percentage. A t-test was used to compare customarily distributed numerical variables of independent samples. In the case of non-normal distribution, the Mann-Whitney test was applied. The Kruskal-Wallis test was used to compare the continuous variables of three independent samples. Categorical variables were compared using the chi–square (x^2) test. Null hypotheses were rejected at $p \leq 0.05$.

RESULTS:

The main demographic and anthropometric characteristics of controls, CHB, CHC patients are presented in Table 1.

Table 1. Basic demographic and anthropometric data of controls and patients with CHB and CHC

	Controls	CHB	CHC	p
Total	847	474	482	
Age	51 (±14.827)	46 (±14.471)	50 (36-62)	
Males	391 (46.2%)	286 (60.3%)	203 (42.1%)	
Females	456 (53.8%)	187 (39.5%)	279 (57.9%)	
BMI	26.18 (±4.864)	26,58 (±5.768)	25.81 (±5.230)	0.574

Most of the participants collected with CHB were men- 60.5%. Their mean age was 45.62 years (SD ±14.230), and for the women: 46.93 (SD ±14.837), (p=0.350). 96 or 20.3% of the patients with CHB had liver cirrhosis.

Women in the CHC group slightly outnumbered men: 57.9%. The age range for the whole group spanned the interval from 20 to 83 years. The median age for men was 41 years (IQR 34-56), and for women, the mean age was calculated to be 52 years (SD ±15.080) (p<0.0001). 81 patients, or 16.8%, had liver cirrhosis. We found no significant difference in the prevalence of liver cirrhosis between the two types of viral hepatitis (p=0.170).

The control group included 847 individuals with a mean age of 51.34 years (SD ±14.855). There were 391 males with a median age of 55.00 years (IQR 35-67) and 456 females with a mean age of 49.74 years (SD ±13.243) (p=0.001).

Table 2 presents the results of the laboratory tests of the infected persons at the first admission to the hospital. We observed no significant differences between hepatitis C and B patients except for GGT levels - significantly higher in patients affected by CHC (p=0.0001) and creatinine with a higher mean rank in the CBH group (p=0.001).

Table 2. Comparison of laboratory blood parameters of patients with hepatitis B and C

Median (IQR)	CHB	CHC	p
ASAT U/l	39.50 (23-70.25)	40 (25-74)	0.384
ALAT U/l	46 (24-93.25)	50.50 (27-90.25)	0.984
GGT U/l	34.50 (20-69)	45 (24-92)	0.0001
AP U/l	86.50 (67.75-116)	83 (63-109)	0.06
Platelets 10^9/L	206 (141.75- 249)	204 (141-254)	0.898
Albumin g/l	41 (37-45)	42 (38-45)	0.097
Protein g/l	74 (68-77)	74 (69-78)	0.141
Bilirubin μmol/l	11 (8-15)	11 (8-15)	0.91
Creatinine μmol/l	77 (66-89)	73 (62-84)	0.001
Glucose mmol/l	5 (5-5)	5 (4-5)	0.353
Cholesterol	4.44 (±1.21)	4.58 (±1.09)	0.842
Triglycerides	1.04 (0.72-1.89)	0.91 (0.80-1.12)	0.819

The prevalence results of CV and metabolic diseases in the three study groups are presented in Table 3. AH was the most frequently recorded diagnosis among participants in all groups and affected more than one-third of infected patients and controls. We found no statistically significant difference in its prevalence in all three studied groups. We were unable to detect an association of AH with CHB or CHC. The mean age of hypertensive patients with CHB was 55.45 (SD± 11.134), and for normotensive subjects, the median was 40 (IQR 30-51) years, p=0.0001. Patients with CHC and hypertension were significantly older than those without, with a mean age of 60.65 (SD± 11.188) versus 43.37 (SD± 13.596) years, p=0.0001.

Table 3. Presence of AH, DM2, MS, IHD, MI in patients with B and C hepatitis and uninfected controls

	Controls	CHB	CHC	p
AH	333 (39.3%)	162 (34.2%)	163 (33.8%)	0.066
DM2	121 (14.3%)	63 (13.3%)	65 (13.5%)	0.861
MS	39 (4.6%)	38 (8.0%)	24 (5.0%)	0.028
IHD	58 (6.8%)	35 (7.4%)	37 (7.7%)	0.842
MI	10 (1.2%)	6 (1.3%)	14 (2.9%)	0.045
HF	20 (2.4%)	5 (1.1%)	9 (1.9%)	0.246

The second common comorbidity was DM2. It was observed in 14.3% of controls, 13.3% of CBH, and 13.5% of the CHC patients, slightly more frequently than reported for the general population, but with no significant difference between groups. As expected, DM2 patients were older. In the CHB group, the mean age of diabetics was 55.70 (SD±10,706) and for non-diabetics - 45 (IQR 33-55.25) (p=0.0001). For hepatitis C, the mean age of patients with DM2 was 61.09 (SD± 10.386), and for those without - median 46 (IQR 35-58) years, (p=0.0001).

Regarding CHF and IHD, we could find no association with any type of viral hepatitis. Cases of MI were more common in patients with CHC - 2.9%. In the CBH group, they were registered in 1.3% and in the controls in 1.2%. The difference was statistically significant (p=0.045). People with CHC and MI were 28.6% male and 71.4% female (p= 0,298). All affected individuals were significantly older, with a mean age of 64.07 (SD±14.621), compared to unaffected subjects who had a median age of 49 (IQR 36-61) years (p=0.001). Their BMI was higher at 30.83 (SD± 2.927) compared to the unaffected 25. 62 (SD ±5.208), (p=0.016).

MS was more prevalent in the CHB group than in the CHC and the control group. It was found in 4.9% of controls, 5.1% of CHC patients and 8.0% in the CHB group (p=0.028). Patients with CHB and MS were 52.6% men and 47.4% women (p=0.298). They were older, with a mean age of 52.58 (SD± 11.152) compared to those without MS: 46 (IQR 33-56) years. They had a higher BMI of 30.60 (SD ±7.015) than the unaffected subgroup with a mean BMI of 26.08 (SD± 5.415) (pÂ0.0001).

In chronically infected persons with liver cirrhosis, AH was diagnosed in 49% of patients with CHB and 43.8% of those with CHC (p=0.490). DM2 was found in 24% of the cases with hepatitis B- associated cirrhosis and

in 18.8% of those with HCV infection and cirrhosis (p= 0.403). We found no significant difference in the prevalence of MS, which was present in 8.3% of CHB and 4% of patients with CHC cirrhosis, respectively (p=0.211). IHD was recorded in 15 subjects with HBV-related cirrhosis (15.6%) and in only 3 (3.8%) with hepatitis C cirrhosis (p=0.01). Single cases of MI were observed in both chronic infection and cirrhosis groups.

DISCUSSION:

Patients with viral hepatitis B and C have a high prevalence of comorbidity and multimorbidity [11]. Diseases such as AH, obesity, dyslipidemia, DM2 in CHB patients are associated with a higher risk of liver-related events, especially in patients with multiple comorbidities [12]. We found a high prevalence of AH and DM2 in the studied groups, but viral hepatitis itself was not associated with their higher frequency compared to controls. Comorbid patients were older, which explains the concentration of pathological conditions and with a higher BMI – a confirmed risk factor for the development of CVD, MS and DM2. A similar high frequency of AH in patients with CHC was also found in samples from other populations, up to 39%, and in patients with C hepatitis related cirrhosis, up to 47.6%. So, it was suggested that CHC is a non-classical risk factor for cardiovascular morbidity and AH [13]. According to studies by other researchers, patients with arterial hypertension and CHC have high necroinflammatory activity. This may partly explain the high prevalence of AH in cirrhotic patients [14]. Moreover, treatment of hepatitis C with antiviral agents may lead to better BP control in patients with compensated liver disease [15].

The association of CHB and CHC with CVD, DM2 and MS is controversial. Abnormalities of glucose metabolism are common in patients with chronic hepatitis and liver cirrhosis because of the significant contribution of the liver to glucose metabolism. More than 90% of patients with hepatitis have insulin resistance, and about 30% develop diabetes [16]. Our results are similar to those of a previous study of a Bulgarian population sample, which showed a relatively high frequency of DM2 in patients with CHB (20%) and CHC (30%) after an oral glucose tolerance test [17]. Recently published studies have shown the aging of CHB patients as well as similar to our results showing a higher incidence of MS and other metabolic disorders in CHB. [18]. Unlike CHC, liver steatosis is not typical of CHB. In their combination, lower levels of HBV DNA were observed [19]. Steatosis increases the chance of HBV surface antigen clearance [20]. However, the combination of CHB with MS leads to increased necro-inflammatory fibrotic activity as well as increased liver-related events and mortality [21]. Long-term follow-up is needed to clarify the conflicting association of CHB with nonalcoholic liver disease, and MS. CHC is associated with insulin resistance, DM2, MS and hepatic steatosis. A population-based cohort study clearly demonstrated the association of CHC with MS [22]. We were not able to observe such a finding in our study group.

Chronic viral hepatitis has been postulated to be a proatherogenic condition. A meta-analysis of observational studies showed that HCV infected patients had an increased risk of CVD related mortality, carotid plaque development and cerebrovascular events. The risk of cerebrovascular disease was higher in populations with a higher prevalence of DM2 or AH [23]. Patients with CHC and hepatocellular carcinoma have been found to have an increased risk of developing IHD [24]. The study sample had a significant association between MI incidence and CHC, but the finding was weak due to the small group.

In both groups with chronic hepatitis, there was an increase in the percentage of patients with AH and DM2 in liver cirrhosis. IHD was registered significantly more often in patients with CHB and cirrhosis. The possible relationship needs to be tested in a larger group of patients followed for a long time. It is possible that the result is due to confounding dietary and behavioral factors, dysregulation of lipid metabolism, genetic predisposition and familial burden.

CONCLUSIONS:

The obtained results provide a basis for frequent and thorough monitoring of multimorbid patients with chronic viral B and C hepatitis. The local economic burden associated with effective therapy and follow-up is expected to increase. Overall, monitoring by a team of specialists is crucial for better management and control of chronic viral hepatitis in Bulgaria.

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