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Original Article

Hepatitis B and C infections among lymphoma patients: a national study in the Republic of Moldova

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Abstract

Introduction: Hepatitis B virus (HBV) and hepatitis C virus (HCV) represent common infections that are presumably associated with various types of lymphoma and specific clinical features. However, conclusive data are lacking and results from different regional studies are conflicting. Hence, a national study was performed in order to investigate potential associations between hepatitis infections and lymphoma in the Republic of Moldova.

Methodology: Data were collected from newly diagnosed adult lymphoma patients from January 2020 to January 2022. Patients who were not tested for HBsAg and anti-HCV and those with an undetermined lymphoma subtype diagnosis were excluded from the study. Subjects with and without viral hepatitis were then evaluated on the basis of clinical and pathological characteristics.

Results: One hundred and twenty-nine lymphoma patients were included in the study; 15 (11.6%) patients were diagnosed with hepatitis B, 21 (16.3%) patients with hepatitis C, and 1 (0.78%) patient was positive for both. The majority of hepatitis patients were over 60 years old (62.2%), presented with stage III or IV (81%), had normal lactate dehydrogenase (58.3%) and 0 or 1 extranodal sites (78.4%). The most common lymphoma subtypes were diffuse large B-cell lymphoma (64.9%) and marginal zone lymphoma (8.1%). We did not find any statistically significant differences between infected and uninfected lymphoma patients in regards to clinical features, specific lymphoma subtypes, and presence and location of extranodal involvement.

Conclusions: Presence of hepatitis B or C virus infections is not associated with specific clinical and pathological features in Moldovan lymphoma patients.

Key words: hepatitis C virus; hepatitis B virus; lymphoma.

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Introduction

The hepatitis B virus (HBV) and the hepatitis C virus (HCV) are important global public health issues. According to the World Health Organization (WHO) data, around 3.5% of the world population is affected by HBV and around 1% is affected by HCV [1]. The geographical distribution is uneven, with most HBV infections affecting the African and Western Pacific regions, while HCV mostly affects the European and Eastern Mediterranean regions. In Europe, HBV and HCV prevalence is estimated at around 0.9% and 1.1%, respectively, but varies significantly from country to country [2]. The Republic of Moldova is a developing country and is commonly considered to be an endemic region for chronic HCV and HBV infections; however, an annual decline in disease rates was observed. The overall prevalence has been approximated in recent years to be around 1-5% for HCV and 1-2% for HBV [3-7].

Lymphoma represents a diverse group of malignant lymphoid tumors. Most frequent subtypes include diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) [8]. The role of various infectious agents is well established in cancer development, and lymphoma is not an exception. It is well known that viruses and bacteria, like the Epstein-Barr virus (EBV), Human Immunodeficiency virus (HIV), Human Herpesvirus – 8 (HHV-8), *Helicobacter pylori* and others can serve as a cause or a risk factor for the development of lymphoma, either through direct involvement of lymphocytes, or indirectly, through immune stimulation and eventual transformation [9-11]. Hepatitis infections have been a source of controversy in regards to their role in lymphomagenesis. Some studies, such as the ones realized in South Korea, Japan, Italy, and China have shown a significant association between HBV or HCV infections and lymphoma [10,12-15]. At the same time,

others, such as those performed in Canada and northern USA, failed to find evidence for the role of viral hepatitis in lymphoma [15,16]. Thus, there is heterogeneity in the extent of association across studies that have found a positive association. This could be indicative of either regional and demographic differences or differences in study design, as most data indicating a positive association were established in regions of higher prevalence of hepatitis infections. Potential mechanisms of lymphomagenesis are also unclear. Viral replication, continuous viral antigen production and binding to B-cell receptors could stimulate tumoral growth factors and lead to proliferation of clonal lymphocytes [17]. Additionally, HCV is able to directly infect lymphocytes, causing accumulation of reactive oxygen species and nitric oxide in HCV-infected cells and DNA damage and mutations of various oncogenes, such as TP53, CTNNB1, BCL 6 [18]. Nevertheless, evidence of somatic hypermutation and intraclonal diversity was found in cases of HCV-associated lymphomas, which is consistent with a process driven by chronic antigen stimulation [19]. HBV is also able to reproduce in lymphatic tissue, i.e., bone marrow and lymph nodes, and viral particles have been detected in lymphoma tissue, but chronic antigen stimulation of B-cells is more likely to be responsible for clonal transformation [12-14,17].

Whether viral hepatitis infections are associated with all lymphoma subtypes or only specific subtypes is a key issue. Subgroup assessments with respect to lymphoma subtypes are required, but were not always performed in earlier epidemiologic studies, in part due to the small number of HCV- and HBV-infected subjects among included lymphoma patients [9,12-17]. Chronic hepatitis infections were previously associated with both indolent and aggressive lymphomas, but the results are inconclusive. Several earlier studies have shown an association of both HCV and HBV infections with most major indolent and aggressive lymphomas, while others did not find any significant difference among various subtypes; however, different classifications were used, and lymphoma subtypes were reported inconsistently [12-17]. Nevertheless, a more recent meta-analysis study evaluating patients with HBV and lymphoma has shown that patients with HBV infections often presented with B-cell lymphomas, and a significant association was observed with DLBCL and follicular lymphoma [15]. HCV infection is also reportedly more prevalent in specific subtypes of indolent lymphomas, namely marginal zone and follicular lymphomas, but an association with DLBCL has also been shown [20]. Other clinical characteristics have also been studied. For instance, the risk of non-Hodgkin lymphoma in HBV-infected individuals was highest in the younger age groups, and the median age was significantly lower among HBsAg-positive patients [17].

In summary, there is inconsistent data provided by previous epidemiological research and regional variance, and local studies need to be conducted in order to explore the associations between viral hepatitis infections and lymphoma, especially in endemic HBV and HCV countries such as the Republic of Moldova. The aim of the present study was to establish the prevalence of hepatitis infections among patients with lymphoma and to determine potential associations between the presence of hepatitis infections and various clinical and pathological features in lymphoma patients.

Methodology

Ethics statement

This study was approved by the ethics committee of the State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, Republic of Moldova, January 28th, 2020, session nr. 32. Informed consent was obtained from all participants included in the study.

Data collection and patient selection

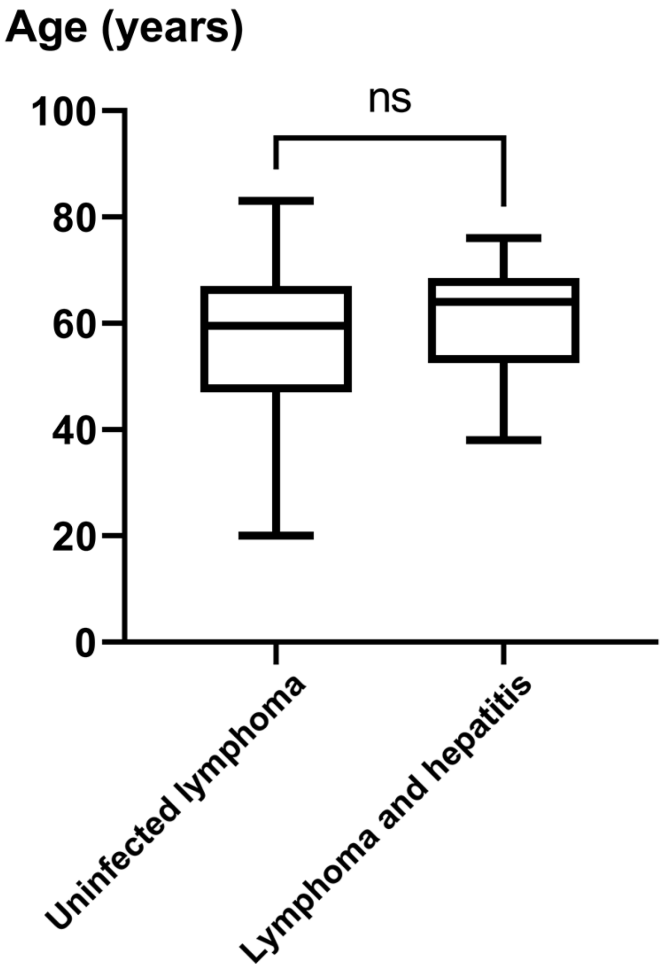
This study was performed in the Oncologic Institute, Chisinau, Republic of Moldova. Adult patients (aged over 18 years old) diagnosed with lymphoma between January 2020 and January 2022 were included in the present study. Patients with lymphoma were selected in accordance with the International Classification of Diseases, version 10 (ICD-10) codes (C81, Hodgkin lymphoma; C82, follicular lymphoma; C83, non-follicular lymphoma; C84, Mature T/NK-cell lymphomas; C85, other specified and unspecified types of non-Hodgkin lymphoma, C86, other specified types of T/NK-cell lymphoma). Presence or absence of hepatitis B or C infection was based on the results of relevant screening tests: patients were considered hepatitis B or C infected if a positive HBsAg or Anti-HCV assay was available, respectively. Patients with an unspecified lymphoma subtype and patients untested for the presence of hepatitis infections were excluded from the study.

Variables

Age, gender, lactate dehydrogenase (LDH) level, lymphoma stage and subtypes, presence of B symptoms, presence and location of extranodal

involvement were used as criteria for patient characteristics and group comparison. The age groups were stratified into 6 intervals, as follows: 18-30, 31-40, 41-50, 51-60, 61-70 and 71+ years old. Lymphoma stages (I, II, III, IV) were based on the Lugano modification of the Ann-Arbor staging system [21]. Presence of B symptoms (subgroups A and B) was determined as one of: fevers greater than 38.3°C, weight loss of more than 10% of body mass over 6 months, and drenching night sweats [22]. Abnormal LDH was defined as above the laboratory normal range values (207-414 U/L). Presence of extranodal involvement was determined based on imaging data (ultrasonography, magnetic resonance imaging, computed tomography or positron emission tomography–computed tomography, when available). Spleen, tonsils and the Waldeyer's ring were considered nodal tissue. Subjects with both primary and secondary extranodal involvement were included. Non-Hodgkin lymphoma subtypes were stratified into indolent and aggressive types [23,24].

Figure 1. A box and whisker plot for age of lymphoma patients with and without hepatitis infection.



Difference was not statistically significant (p = 0.2).

Statistical analyses

Mann-Whitney test was used to compare age medians, Fisher's exact test and logistic regression were used for group comparison utilizing the GraphPad Prism ver. 9.3.0 software. Two-tailed analyses were used, and *p* values less than 0.05 were considered significant.

Results

Two hundred and twenty-three patients were diagnosed with lymphoma in the Oncologic Institute in the time period between Jan 2020 and Jan 2022. Patients that were not tested for the presence of hepatitis infection (n = 71) and patients with an unspecified lymphoma subtype diagnosis (n = 23) were excluded. In total, 129 patients were included in the study. Considering that lymphoma patients with HBV and HCV were reported to have similar clinical and pathological features, for comparative analysis subjects were additionally divided into 2 main subgroups: uninfected lymphoma patients (negative for hepatitis B and C markers) and lymphoma patients infected with hepatitis B and/or C virus.

Out of 129 included patients, 92 (71.3%) patients were uninfected, 15 (11.6%) patients were diagnosed with hepatitis B, 21 (16.3%) patients were diagnosed with hepatitis C and only 1 subject had both hepatis B and C. In total, 37 (28.7%) were diagnosed with hepatitis B, C, or both. Patients in all groups were mostly older adults, with the majority being 61-70 years old (45%). Uninfected lymphoma patients were marginally younger (mean 56.4 years, 95% CI 53.5 – 59.3, median 59.5 years) than patients with lymphoma and hepatitis (mean 59.8 years, 95% CI 56 – 63.7, median 64 years), and the minimal age in the hepatitis group was higher (38-76 years, interquartile range [IQR] 52.5, 68.5) when compared to uninfected patients (20-83 years, IQR 47, 67; Figure 1); however, the difference in age was not statistically significant (p = 0.2). Mean patient age in the HBV group was 59.6 years (95% CI 52.9-66.3), median: 64 years (38 to 74 years, IQR 53, 69), mean age in the HCV group was 60.8 years (95% CI 55.7-65.9), median: 64 years (40 to 76 years, IQR 53.5, 68.5). No significant age difference was determined between HBV and HCV patients (odds ratio [OR] - 1.01, 95% CI 0.95-1.07, p = 0.8), HBV and uninfected patients (OR - 1.01, 95% CI 0.98-1.07, p = 0.4), HCV and uninfected patients (OR - 1.02, 95% CI 0.99-1.07, p = 0.2). Distribution between genders was

approximately even. The majority of patients in all groups were characterized by advanced stages (III-IV), normal LDH and minimal extranodal involvement (0 or 1). More hepatitis patients had no B symptoms (n = 20, 54.1%) while the majority of uninfected patients manifested B symptoms (n = 53, 57.6%). General patient characteristics can be seen in Table 1.

For additional comparisons between lymphoma patients with and without hepatitis infections, subjects were further subdivided into larger subgroups, as follows: age ≤ 60 and > 60 years old, male and female, stage I-II (localized) and III-IV (advanced), presence and absence of B symptoms (A or B), extranodal involvement (0-1 and ≥ 2 involved organs), and LDH (normal and abnormal). The overall median of age (60 years) was chosen as the cut-off value for age grouping.

The results of group comparison are presented in Table 2. Overall, no statistically significant difference was observed between the two patient groups for age (OR - 0.51, 95% CI 0.24-1.1; $p = 0.1$), gender (OR - 1.1, 95% CI 0.51-2.4; $p = 0.8$), stage (OR - 0.9, 95% CI 0.35-2.39; $p > 0.99$), presence or absence of B symptoms (OR – 1.6, 95% CI 0.74-3.54; $p = 0.2$), extranodal involvement (OR - 1.02, 95% CI 0.4-2.5; $p > 0.99$) and LDH level (OR - 0.96, 95% CI 0.44-2.03; $p > 0.99$).

Similarly, no statistically significant difference was observed between HBV and HCV patients in regards to gender (OR – 0.5, 95% CI 0.12-1.89; $p = 0.3$), stage (OR – 4.3, 95% CI 0.6-89.2; $p = 0.2$), presence of B symptoms (OR – 1.7, 95% CI 0.44-6.6; $p = 0.5$), extranodal involvement (OR – 2.6, 95% CI 0.5-19.9; $p = 0.3$) and LDH (OR – 0.62, 95% CI 0.15-2.4; $p = 0.5$).

Based on the histological diagnoses, the most frequently observed lymphoma subtypes in uninfected patients were diffuse large B-cell lymphoma (n = 46, 50%), mantle cell lymphoma (n = 10, 10.9%) and marginal zone lymphoma (n = 8, 8.7%). In patients with hepatitis, DLBCL (n = 24, 64.9%) was also the most common subtype, followed by marginal zone lymphoma (n = 3, 8.1%), with fewer cases of other subtypes. Additionally, no classical Hodgkin lymphoma cases were observed in hepatitis subjects. Overall, no statistically significant association was observed between specific subtypes of lymphoma and presence of an HBV or HCV infection. The distribution of subtypes are presented in Table 3.

Table 1. General patient characteristics.

Criteria	Total (%) n = 129	Uninfected lymphoma (%) n = 92 (71.3%)	Lymphoma and hepatitis (%) n = 37 (28.7%)	Hepatitis B (%) n = 15 (11.6%)	Hepatitis C (%) n = 21 (16.3%)
Age					
18-30	4 (3.1)	4 (4.3)	0 (0)	0 (0)	0 (0)
31-40	16 (12.4)	10 (10.9)	3 (8.1)	2 (13.3)	1 (4.8)
41-50	24 (18.6)	15 (16.3)	5 (13.5)	1 (6.7)	3 (14.3)
51-60	33 (25.6)	21 (22.8)	6 (16.2)	2 (13.3)	4 (19)
61-70	58 (45)	26 (28.3)	16 (43.2)	6 (40)	10 (47.6)
71+	30 (23.3)	16 (17.4)	7 (18.9)	4 (26.7)	3 (14.3)
Gender					
M	64 (49.6)	45 (48.9)	19 (51.4)	6 (40)	12 (57.1)
F	65 (50.4)	47 (51.1)	18 (48.6)	9 (60)	9 (42.9)
Stage					
I	7 (5.4)	5 (5.4)	2 (5.4)	0 (0)	1 (4.8)
II	19 (14.7)	14 (15.2)	5 (13.5)	1 (6.7)	4 (19)
III	25 (19.4)	19 (20.7)	6 (16.2)	5 (33.3)	1 (4.8)
IV	78 (60.5)	54 (58.7)	24 (64.9)	9 (60)	15 (71.4)
B symptoms					
A	59 (45.7)	39 (42.4)	20 (54.1)	9 (60)	10 (47.6)
B	70 (54.3)	53 (57.6)	17 (45.9)	6 (40)	11 (52.4)
Extranodal sites					
0	45 (34.9)	35 (38)	10 (27.)	6 (40)	4 (19)
1	55 (42.6)	36 (39.1)	19 (51.4)	7 (46.7)	11 (52.4)
2	22 (17.1)	16 (17.4)	6 (16.2)	2 (13.3)	4 (19)
≥ 3	6 (4.7)	4 (4.3)	2 (5.4)	0 (0)	2 (9.5)
LDH					
Normal	75 (58.1)	54 (58.7)	21 (56.8)	7 (46.7)	13 (61.9)
Abnormal	52 (40.3)	37 (40.2)	15 (40.5)	7 (46.7)	8 (38.1)
Unknown	2 (1.6)	1 (1.1)	1 (2.7)	1 (6.7)	0 (0)

LDH: lactate dehydrogenase.

Table 2. Group comparison of lymphoma patients with and without hepatitis B or C infections.

Criteria	Uninfected lymphoma (%)	Lymphoma and hepatitis (%)	OR (95% CI)	*p* value
Age				
≤ 60	50 (54.3)	14 (37.8)	0.51 (0.24 to 1.1)	0.1
> 60	42 (45.7)	23 (62.2)		
Gender				
F	47 (48.9)	18 (51.3)	1.1 (0.51 to 2.4)	0.8
M	45 (51.1)	19 (48.7)		
Stage				
I-II	19 (20.6)	7 (19)	0.9 (0.35 to 2.9)	> 0.99
III-IV	73 (79.4)	30 (81)		
B symptoms				
A	39 (42.4)	20 (54)	1.6 (0.74 to 3.54)	0.2
B	53 (57.6)	17 (46)		
Extranodal sites				
0-1	71 (78)	29 (78.4)	1.02 (0.4 to 2.5)	> 0.99
≥ 2	20 (22)	8 (21.6)		
LDH				
Normal	54 (59.3)	21 (58.3)	0.96 (0.44 to 2.03)	> 0.99
Abnormal	37 (40.7)	15 (41.7)		

LDH: lactate dehydrogenase.

Table 3. Prevalence of specific lymphoma types in patients with and without hepatitis B or C infections.

Type of lymphoma	Total (%)	Uninfected lymphoma (%)	Lymphoma and hepatitis (%)	Hepatitis B (%)	Hepatitis C (%)	*p* value †
Diffuse large B-cell lymphoma	70 (54.2)	46 (50)	24 (64.9)	7 (46.7)	16 (76.2)	0.2
Mantle cell lymphoma	12 (9.3)	10 (10.9)	2 (5.4)	1 (6.7)	1 (4.8)	0.5
Marginal zone lymphoma	11 (8.5)	8 (8.7)	3 (8.1)	2 (13.3)	1 (4.8)	> 0.99
Small lymphocytic lymphoma	8 (6.2)	7 (7.6)	1 (2.7)	1 (6.7)	0 (0)	0.4
Classical Hodgkin lymphoma	7 (5.4)	7 (7.6)	0 (0)	0 (0)	0 (0)	0.2
T-cell lymphoma	7 (5.4)	5 (5.4)	2 (5.4)	1 (6.7)	1 (4.8)	> 0.99
Follicular lymphoma	6 (4.7)	4 (4.3)	2 (5.4)	1 (6.7)	1 (4.8)	> 0.99
Lymphoblastic lymphoma	5 (3.9)	4 (4.3)	1 (2.7)	1 (6.7)	0 (0)	> 0.99
Composite lymphoma ‡	1 (0.8)	0 (0)	1 (2.7)	0 (0)	1 (4.8)	0.3
Lymphoplasmacytic lymphoma	1 (0.8)	0 (0)	1 (2.7)	1 (6.7)	0 (0)	0.3
Plasmablastic lymphoma	1 (0.8)	1 (1.1)	0 (0)	0 (0)	0 (0)	> 0.99

† *p*-value for ORs (not shown) comparing patients with uninfected lymphoma and lymphoma associated with viral hepatitis. ‡ Specifically, B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma.

Table 4. Distribution of aggressive and indolent lymphoma subtypes in patients with and without hepatitis B or C infections.

Type	Lymphoma and hepatitis (%)	Uninfected lymphoma (%)	OR (95% CI)	*p* value
Aggressive	30 (81)	65 (76.5)		
Indolent	7 (19)	20 (23.5)	1.3 (0.5 to 3.3)	0.6
Total	37	85		

Table 5. Distribution of extranodal disease sites.

Criteria	Overall (%) n = 83 (64.3%)	Uninfected lymphoma (%) n = 56 (60.9%)	Lymphoma and hepatitis (%) n = 27 (73%)	Hepatitis B (%) n = 9 (60%)	Hepatitis C (%) n = 17 (81%)	*p* value †
Liver	29 (34.9)	19 (33.9)	10 (37)	3 (33.3)	7 (41.2)	0.8
Bone marrow	20 (24.1)	13 (23.2)	7 (25.9)	4 (44.4)	3 (17.6)	0.8
Stomach	13 (15.7)	9 (16.1)	4 (14.8)	0 (0)	3 (17.6)	> 0.99
Bones	11 (13.3)	6 (10.7)	5 (18.5)	3 (33.3)	2 (11.8)	0.5
Lung	11 (13.3)	11 (19.6)	0 (0)	0 (0)	0 (0)	0.01
Skin	7 (8.4)	4 (7.1)	3 (11.1)	0 (0)	3 (17.6)	0.7
Pleura	5 (6)	4 (7.1)	1 (3.7)	0 (0)	1 (5.9)	> 0.99
Small and Large intestine	5 (6)	4 (7.1)	1 (3.7)	1 (11.1)	0 (0)	> 0.99
Breast	3 (3.6)	3 (5.4)	0 (0)	0 (0)	0 (0)	0.5
Pancreas	3 (3.6)	2 (3.6)	1 (3.7)	0 (0)	1 (5.9)	> 0.99
Uterus	2 (2.4)	2 (3.6)	0 (0)	0 (0)	0 (0)	> 0.99
Ureters	2 (2.4)	2 (3.6)	0 (0)	0 (0)	0 (0)	> 0.99
Thyroid	2 (2.4)	1 (1.8)	1 (3.7)	0 (0)	1 (5.9)	0.5
Parotid gland	1 (1.2)	0 (0)	1 (3.7)	0 (0)	1 (5.9)	0.3
Testis	1 (1.2)	0 (0)	1 (3.7)	0 (0)	1 (5.9)	0.3
Heart	1 (1.2)	1 (1.8)	0 (0)	0 (0)	0 (0)	> 0.99
Other ‡	4 (4.8)	2 (3.6)	2 (7.4)	0 (0)	2 (11.8)	0.6

† *p* value for ORs (not shown) comparing patients with uninfected lymphoma and lymphoma associated with viral hepatitis. ‡ Muscle tissue, blood vessels.

For further analysis, subjects with non-Hodgkin lymphoma were additionally grouped as aggressive and indolent cases. The majority of lymphomas in both patient groups were classified as aggressive (n = 30, 81% in cases with viral hepatitis and n = 65, 76.5% in uninfected patients). Once again, no statistically significant difference was observed between infected and uninfected patients (OR 1.3, 95% CI 0.5-3.3; p = 0.6). The results are presented in Table 4.

Lastly, patients with and without viral hepatitis infections were evaluated based on the presence and location of extranodal disease. In total, 83 (64.3%) patients had at least 1 site of extranodal involvement: 27 (73%) patients with viral hepatitis and 56 (60.9%) in the uninfected group. Liver, bone marrow, stomach and bones were the most frequently affected regions in both patient groups; however, there were 11 cases of lung involvement in uninfected patients and no cases in patients with viral hepatitis (p = 0.01). No statistically significant difference was determined for other regions of extranodal disease. The results are presented in Table 5.

Discussion

We have performed a national study in order investigate the relationship between HCV/HBV infections and different types of lymphoma. As mentioned earlier, previous studies investigating the association between hepatitis infections and lymphomas have yielded contradictory results. Some studies performed in Europe and America have shown no association between HCV, HBV and lymphoma [16,25-27]. However, other studies (mostly in Asia and countries with high incidence of chronic viral hepatitis infections) reported both HBV and HCV to be associated with an increased risk of lymphoma, particularly B-cell non-Hodgkin lymphoma [12-15, 28-32]. Two meta-analysis studies have shown ORs of 2.5 (95% CI 2.20-2.83) and 2.24 (95% CI 1.80-2.78) for risk of developing non-Hodgkin lymphoma in subjects with an HBV infection while three other meta-analyses have shown an OR of 5.7 (95% CI 4.09-7.96) and pooled risk ratios (RR) of 2.5 (95% CI 2.1-3.0) and 2.4 (95% CI 2.0-3.0) for non-Hodgkin lymphoma among HCV-positive individuals [15,33-36].

Despite significant progress in the identification and treatment, hepatitis B and C, infections remain a public health issue in the Republic of Moldova. Currently, there are approximately 80,000-90,000 registered cases of chronic hepatitis, the majority being of viral etiology; however, the burden of viral hepatitis has been reportedly declining in recent years and estimated at around 1-5% for HCV and 1-2% for HBV [2-7]. In the present study, the prevalence of both infections was higher among patients with lymphoma when compared to the reported prevalence in the general population in the Republic of Moldova. While age could be an important confounder, we did not observe a statistically significant age difference between lymphoma patients with and without viral hepatitis. Furthermore, the reported prevalence of both hepatitis B and C in European countries and in the Republic of Moldova is highest among young adults and not in patients aged 60 and more [37-39].

Although inconsistent, the overall association of HCV and HBV infections with lymphoma appears to be more established than with specific lymphoma subtypes. As mentioned previously, analyses of specific lymphoma subtypes have shown controversial results, and some degree of evidence was reported for most major subtypes [12-17,20]. However, a strong association was previously shown between DLBCL, follicular lymphoma and HBV, with several meta-analyses reporting ORs of 1.84 (95% CI 1.13–3.01), 2.06 (95% CI 1.48-2.88) for DLBCL and 1.66 (95% CI 1.02–2.70), 1.54 (95% CI 1.11- 2.12) for follicular lymphoma [15,35]. An association between HBV and marginal zone lymphoma has also been reported, with an estimated 3-fold risk compared to the general population [40]. Similarly, HCV is also commonly associated with DLBCL, follicular lymphoma and marginal zone lymphoma, in addition to lymphoplasmacytic lymphoma [14,20,40-42]. Additionally, no association of HBV and HCV with Hodgkin lymphoma has been reported previously [43]. Accordingly, in the present study no cases of Hodgkin lymphoma were found among patients with viral hepatitis. This finding might also be age related (as patients with Hodgkin lymphoma were mostly young adults while patients with hepatitis were mostly aged 60 and older) or related to other risk factors like the Epstein-Barr virus, which is not routinely investigated at our institution. Most of the hepatitis cases in our study were diagnosed with DLBCL, followed by marginal zone lymphoma with only a few cases of other lymphoma subtypes. A similar pattern was observed for uninfected patients, and our study did not find any significant relationship between the presence of hepatitis and any specific histological subtypes.

Finally, patients with HBV and HCV were previously shown to manifest lymphoma at a younger age; the more advanced stages (stage III-IV), had abnormal LDH and responded poorly to initial treatment when compared to uninfected subjects

[17,44-46]. However, the present study did not find any significant association between hepatitis infections and age, gender, stage, LDH, and extranodal disease. Incidentally, we have found 11 cases of lung involvement by lymphoma among uninfected individuals and none among patients with viral hepatitis. This finding could be related to an unidentified risk factor.

There were several limitations in this study. Firstly, a number of potential subjects were excluded from the study either because they weren't tested for anti-HCV and HBsAg or because they did not have conclusive data for a specific lymphoma subtype diagnosis. Overall, only around 200 adult and pediatric patients were diagnosed with lymphoma in the Republic of Moldova during the study period. This has resulted in a relatively small sample size. Although the majority of adult lymphoma patients were included, basing the study on a larger sample size could have generated more accurate results. Secondly, some degree of selection bias needs to be considered. Close, over time monitoring of HCV- and HBV-infected individuals by infectious disease specialists could have led to selective identification of affected individuals and referral to a hematology specialist. Regardless, most patients in the present study were first identified as HBV- or HCV-positive at the time of lymphoma diagnosis, and did not receive any prior treatment. Thirdly, while the high prevalence of HBV and HCV infections in our patient group could serve as potential epidemiologic evidence for the involvement of HCV and HBV in lymphomagenesis, additional local epidemiologic studies involving a control group are needed in order to confirm the relevance of this finding.

Conclusion

To our knowledge, this is the first study evaluating patients with viral hepatitis and lymphoma in the Republic of Moldova. We did not observe any significant differences between infected and uninfected lymphoma patients in regards to distinct clinical characteristics and the presence of viral hepatitis C or B infection was not associated with any specific lymphoma subtypes. A high prevalence of hepatitis B and C viruses in lymphoma patients when compared to the reported prevalence in the general population of Moldova indicates the need for further epidemiological or experimental studies involving a larger number of patients and a control group in order to confirm the possible role of hepatitis infections in lymphomagenesis. As previous studies have shown significant regional differences, this is especially important for countries with higher prevalence of viral hepatitis infections, such as the Republic of Moldova.

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