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Anti-HCV, HBsAg Positive Incidences Among Patients Aged 40 Years and Over Diagnosed with B- Non-Hodgkin's Lymphoma: A Comparison with General Population of Same Age

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Objectives: There are several risk factors contribute to the development of the B-cell Non-Hodgkin's lymphoma (B-NHL) among which hepatitis B, hepatitis C virus (HBV, HCV) infection, as well as old age, are known to have a significant effect. Previous studies examining the relationship between HBV, HCV infection and B-NHL show inconsistent results in different endemic areas. **Methods:** We compared the hepatitis B surface antigen (HBsAg) and antibody against the HCV (anti-HCV) positive incidences among aged 40 years or older patients who have been newly diagnosed with B-NHL, between 2015 and 2018, to prevalence of hepatitis B and C virus infection in the general population of Mongolia in the same age by data of the general population in hepatitis screening and the results of previous studies on the Mongolian population. **Results:** A total of 187 patients, newly diagnosed with B-NHL ≥40years of age took part in our study. In case of these two groups, the prevalence of HBsAg in the B-NHL population was close to the general population while anti-HCV positive was significantly higher in the B-NHL group ($p<.00001$). **Conclusion:** Further studies are needed to clarify the reasons and contributing factors which result situations where the HBV prevalence among B-NHL patients and the general population are not significantly different.

Keywords: Hepatitis B virus, Hepatitis C virus, Non-Hodgkin's lymphoma, Prevalence

Introduction

Non-Hodgkin's lymphoma (NHL) ranked as the fifth to ninth most common cancer in most countries worldwide, with almost 510,000 new cases estimated in 2018 [1]. NHL consists of a complex group of cancers arising mainly from B lymphocytes (B cell-NHL) representing around 86% of all NHL), and occasionally from T and natural killer cells (14% in developing regions) [2].

There are several risk factors contribute to the development of the B-cell non-Hodgkin's lymphoma (B-NHL), among which viral infections such as hepatitis viruses, as well as old age, are known to have a significant effect [3,4]. Hepatitis C virus (HCV) and hepatitis B virus (HBV) have hepatotropic and lymphotropic characteristics, whereas some reports suggest that they may cause the development of malignant lymphoproliferative disorders or Lymphoma [5-7]. The exact mechanism through which HBV and HCV infection causes B-NHL remains unclear. HCV infected patients with indolent B-NHL who receive antiviral therapy can be potentially cured. Viral clearance was related to lymphoma response, a fact that highlights the probable involvement of HCV in lymphomagenesis [8]. The patients with HBV infection often develop lymphoma at more advanced clinical stages and the HBV infection status in NHL patients was significantly correlated with the patients' progression-free survival and overall survival [9,10]. Previous studies examining the relationship between HBV, HCV infection and B-NHL show inconsistent results in different endemic areas [11].

Epidemiological studies performed over the last two decades have demonstrated increasing incidences of B-NHL, throughout the world with the HBV and HCV infection rate in B-NHL patients being significantly higher than that in the general population and in patients with other diseases [5,12-15]. B-NHL can occur at any age but is most common in people aged over 40 years [4,16]. The average age of diagnosis is 60-65 years [17].

According to various prevalence studies, Mongolia is a country with a high prevalence of HBV and HCV infection [18]. Since 2016, Mongolia has been successfully implementing the "Hepatitis Prevention, Control, and Elimination Program" (HPCE Program). The HPCE Program is a comprehensive national hepatitis program that consists of three intrinsically interdependent campaigns with a specific focus on prevention, screening, and treatment. On May 5, 2017, a general population hepatitis screening was launched to identify the hepatitis infection status of every individual 15 years of age or older.

However, no studies have been conducted in Mongolia on the incidences of HBV and HCV infection among patients with B-NHL. Thus, the aim of our study was to investigate the seroprevalence of the hepatitis B surface antigen (HBsAg) and antibody against the hepatitis C virus (anti-HCV) positive incidences among aged 40 years or older patients who have newly diagnosed with B-NHL. The results were compared with those among the general population of the same age.

Materials and Methods

We performed retrospective and prospective observational study of patients newly diagnosed with B-NHL at the Center of Hematology and Bone Marrow Transplantation of the First Central Hospital of Mongolia between January 2015 and December 2018. This study was based on a review of 233 cases previously newly diagnosed with B-NHL. Inclusion criteria were as follows: (1) fulfilled histologic and immunophenotypic criteria for the diagnosis of B-NHL; (2) 40 years old and over; and (3) viral marker tests were done. One hundred ninety patients fulfilled these criteria. The clinical information from the medical history and the electronic medical record system of the First Central Hospital were acquired and collected in strict compliance with research ethics (approved by the Ethics Committee of the Ministry of Health, No.4 on June 19, 2017). Clinical information was recorded for each patient and included age, gender, date of initial diagnosis, stage of B-NHL (Ann-Arbor staging system I-IV), and HBsAg, anti-HCV markers. B-NHL had to be diagnosed by cytological examination or pathological examination according to the Revised European American lymphoma and World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues. For this study, Copenhagen Denmark protocol was used as a fundamental by adhering to the above classification and B-NHL was studied with diagnosed cases in the immunohistochemical assay laboratories using "Hans's algorithm".

Testing for HBVand HCV

The HBsAg and anti-HCV markers result of every single patient diagnosed with B-NHL were collected as indicated in the medical history and the electronic medical record system. HBsAg and anti-HCVwere tested for participants who were newly diagnosed or diagnosed and re-certified in 2017 and 2018 with the rapid diagnostic devices of CTK Biotech, San Diego, USA by following the manufacturer's instructions. Within the scope of the National Program, 5 types of HBsAg and anti-HCV markers were done for the residents of Ulaanbaatar as well as rural areas.

Clinical Staging

The clinical stage of B-NHL was determined by the Ann

Arbor staging classification. The Ann Arbor staging system is determined by clinical presentation, imaging and laboratory tests, and initial biopsy reports. The clinical stages were based on the medical history of all patients [19]. Within the scope of the HPCE Program data of the population such as: aged 40-65 years, having taken part in HBV and HCV tests in 2017, and 66 years old and over in 2018, was acquired from the Social Insurance Office. But the marker screening data of the population aged between 15 and 39 was currently inaccurate. The results of the HBsAg and the anti-HCV marker screening which was performed for 306,391 people included urban, rural, and 40 years old and over. In the present study, the incidences of HBsAg and anti-HCV positive patients 40 years old and over among the B-NHL group were compared with the screening program on the general population as well as the results of prevalence studies of HBsAg and anti-HCV among the general population aged 40 years or older.

Statistical Analysis

The patient's characteristics were analyzed using descriptive statistics and were presented as percentages and medians. The Chi-square test was used for categorical variables. The statistical analysis of the study results was performed using STATA 14 software and $p<.05$ was considered statistically significant.

Results

B-NHL Patients' Characteristics

A total of 233 Mongolian adults were newly diagnosed with B-NHL between 2015 and 2018, with 187 (81.3%) people aged 40 years or older being involved in this study. All patients were HIV-negative. Their average age was 59.95±15.6 and the gender breakdown is males 88 (47.1%) and females 99 (52.9%). B-NHL subtypes were recognized for 134 (71.7%) of them, whereas 53 (28.3%) of them had general B-NHL diagnoses. And, 12.3% of the participants were positive HBsAg and 44.9% were anti-HCV. Characteristics of B-NHL patients included in the study are presented in Table 1. B-NHL patients were divided into three sub-groups: HBsAg positive, anti-HCV positive, and without HbsAg anti-HCV positive. The sub-groups were compared by characteristics such as gender, age, and Ann-Arbor staging.

HBsAg and anti-HCV seroprevalence did not correlate with gender (p= .278) but did correlate with age and Ann-Arbor stage. The proportion of Stages III and IV patients who were alsoanti-HCV positive was significantly higher than that of Stages III and IV patients without HBsAg, anti-HCV [72.6% (61/84) vs. 56.3% (45/80); p=.028] (Table 1). Also, the proportion of anti-HCV positive patients was slightly older than the HBsAg positive patients regarding age (61.5 vs. 54.5 years, p= .035) (Table 1). Within the scope of the HPCE program, 286,898 (50.5%) of 568,320 people aged 40-65 in the Mongolian population and 19,493 (19.1%) of 102,127 people over 66 years old were involved in individual marker screening. The results of the HBsAg and the anti-HCV marker screening which was performed for 306,391 people including urban and rural and over 40 years old was used for this study and are presented in Table 2.

The first comparison was between the B-NHL group and the general population of hepatitis screening.

When we compared the two groups they were balanced for age (40–49, 50–59, 60–65, ≥66 years) (Table 2). HBsAg positive incidences were between 8.3-16.9% in the B-NHL groups and 6.1-10.05% in HPCE Program participants, meaning that there were (50-59 years old are not included) no statistically significant differences in each age group (p=.106).

However, there was a difference in the HBsAg positive incidences between the B-NHL patients and the HPCE program patient aged 50-59 years old (p=.026) (Table 2). On the other hand, the anti-HCV positive incidences were 38.7-61.3% in the B-NHL groups and 8.3-16.9% in HPCE Program participants, meaning that there are statistically significant differences (p< .00001) (Table 2). The general regularity was the same with the number of HBsAg positive cases decreasing as much as rising age in the general population and the group of B-NHL patients (10.0-6.1 vs. 12.9-8.3) and the number of anti-HCV positive cases has been increasing as much as rising in age (11.5-32.1 vs. 38.7-53.3). There was a statistical significant difference between age groups regarding the decrease in HBsAg positive cases and the increase of anti-HCV positive cases in the general population (p< .00001). But, there is no statistical difference between age groups of B-NHL groups (p=.9-.95).

The second comparison was between the results of prevalence studies on the Mongolian population and B-NHL group.

The B-NHL group was also compared with the 2 age groups of 40-49 and over 50 years as well as a similar age group study of HBsAg and anti-HCV prevalence which had been conducted

Table 1. Characteristics of B-NHL patients aged 40 years old and older (N-190*).

Characteristics, n	B-NHL patients			
	anti-HCV positive	HBsAg positive	without HBsAg and anti-HCV	Total
Age (years), mean (Std. Dev) [95% Conf. Interval]	61.5[a] (10.7) [59.1-63.8]	56.3[a] (9.5) [52.2-60.4]	59.4 (11.6) [56.8-62.1]	59.9 (10.6) [55.9-62.2]
Gender n (%)				
Male	36 (40.9)	12 (13.6)	40 (45.5)	88 (100)
Female	48 (48.5)	11 (11.1)	40 (40.4)	99 (100)
Stage (NHL) n (%)				
Ann Arbor 1-2	23 (33.8)	10 (14.7)	35 (51.5)	68 (100)
Ann Arbor 3-4	61 (51.3) [b]	13 (10.9)	45(37.5) [b]	119 (100)
Total n (%)	84 (44.9)	23 (12.3)	80 (42.8)	187 (100)

Notes: *Another 3 participants with HBsAg+ anti-HCV were not included. [a] Anti-HCV positive patients were slightly older than the HBsAg positive patients regarding age p= .035. [b] Patients with anti-HCV positive in stages 3-4 were significantly higher than patients without HBsAg and anti-HCV (p= .033).

Table 2. Comparison of HBsAg, anti-HCV positive rate among patients with B-NHL and the HPCE program participants by age groups.

Age	Total n		HbsAg positive n (%)		p-value	Anti-HCV positive n (%)		p-value
	HPCE	B-NHL	HPCE	B-NHL		HPCE	B-NHL	
40-49	119245	31	11938 (10.0)	4 (12.9)	0.592	13702 (11.5)	12 (38.7)	.00001
50-59	120712	65	10907 (9.0)	11 (16.9)	0.026	22708 (18.8)	26 (40.0)	.00001
60-65	46970	31	3348 (7.1)	3 (9.7)	0.581	12982 (27.6)	14 (45.2)	.041
≥66	19493	60	1182 (6.1)	5 (8.3)	0.462	6254 (32.1)	32 (53.3)	.0004
Total	306391	187	27375 (8.9)	23 (12.3)	0.107 [a]	55646 (18.2)	84 (44.9)	.00001 [b]

HPCE-HPCE program participants, B-NHL-B-NHL patients, [a] Between 2 groups by HBsAg-positive rate was (50-59 years old are not included) not significantly different. [b] Two groups by anti-HCV-positive rate were significantly different.

Table 3. Comparison of incidence of Anti-HCV and HBsAg positive in B-NHL patients and the general population (Dashtseren 2013) by gender.

Gender	Total n		HbsAg positive %			Anti-HCV positive %		
	B-NHL patients	General population	B-NHL patients	General population	p-value	B-NHL patients	General population	p-value
Male	88	250	13.6	8.8	0.195	40.9	14.8	.00001
Female	99	354	11.1	10.2	0.786	48.5	21.2	.00001
Total	187	604	12.3	9.6	0.288	44.9	18.5	.00001

among the general population in Mongolia by B. Dashtseren (2013) [20] (Table 3).

HBsAg positive incidences in the B-NHL group and the general population were not statistically significantly different in each age group (p=.288). Also, anti-HCV positive incidences in the B-NHL group were statistically significantly high (p<.00001). However, notable differences were observed in the anti-HCV prevalence for both male and female patients when comparing these groups by gender (p<.00001; Table 3).

Comparison of B-NHL groups and the general population groups (prevalence study of M. Takahashi's [21], B. Dashtseren's prevalence study and HPCE program) by anti-HCV and HBsAg prevalence are presented in Figure 1 and Figure 2.

The prevalence of HBsAg in the results of the general population groups was compared with each other. There was no statistical difference between them (p=.408-.843). There was no statistical difference between B-NHL patients and the general population groups regarding HBsAg positive cases

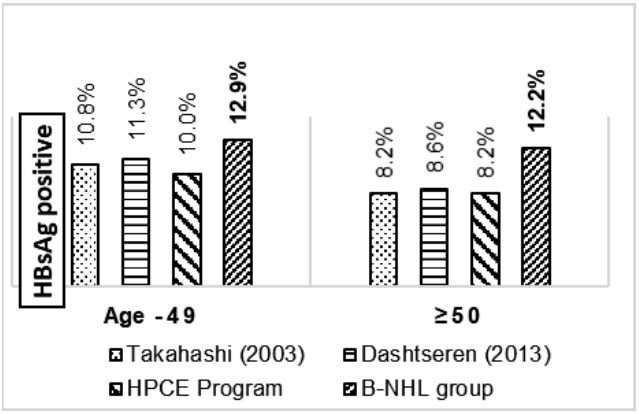

Figure 1. Comparison of B-NHL groups and the general population* by HBsAg positive prevalence was not significantly different (p=.485-.756)

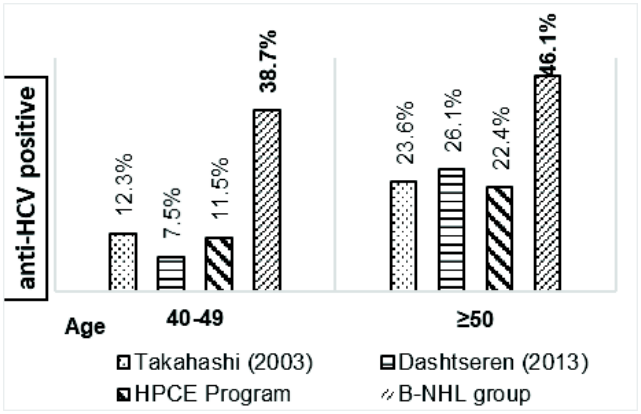

Figure 2. Comparison of B-NHL groups and the general population* by anti-HCV positive prevalence was statistically significant different (p<.00001).

Note: *General population by Takahashi, Dashtseren, and HPCE program participants was compared with each other. There was no statistical difference between them (p= .295- .993).

(p=.756) (Figure 1). Furthermore, there was no statistical difference between the prevalence of anti-HCV positive cases and the results of the general population groups (p=.295-.993). But, anti-HCV positive cases in each age group in B-NHL patients were significantly different from that among the general population groups (p<.00001) (Figure 2).

The results of these two comparisons (between the results of prevalence studies, hepatitis screening and B-NHL group) were rather identical.

Discussion

Within the factors that influence B-NHL, older ages and having hepatitis viruses are attracting more attention. The incidence of B-NHL has steadily increased in age so that about 40% of cases occur in patients over 70 years old [22, 23]. The prevalence of HBsAg and anti-HCV positive cases among B-NHL patients is significantly higher than those among the general population [5,12,13] suggesting that hepatitis virus infection might play an etiologic role in B-NHL pathogenesis [11, 24]. This study was conducted to investigate the seroprevalence of the HBsAg and anti-HCV positive incidences among newly diagnosed B-NHL patients who are 40 years old and over and compared with those among the general population of the same age. Most of the patients 187 (81.3%) who were newly diagnosed with B-NHL between 2015 and 2018 were over the age of 40. By implementing the HPCE program, Mongolia has its very first screening data of HBsAg and anti-HCV which covers the total population. For instance, 50.5% of 568,320 population [25] aged between 40 and 65 have enrolled and data of this range of age was plain. The results in which 17.21% of them were anti-HCV positive and 9.12% of them were HBsAg positive was found similar to the study of U.Enkhbayar et al. [26] with results of the national study of CLEIA method finding the prevalence of HBV (10.1%) and HCV (17%) in the 40-64 age population of Mongolia. Thus, the results of HBsAg and anti-HCV marker screening performed for 306,391 patients 40 years old and over were used in this study. Hence, we considered that comparing the prevalence of HBsAg and anti-HCV which were determined by maker screening in a population 40 years old and over with those among B-NHL patients would be more realistic. There was a statistical difference between age groups regarding the decrease of HBsAg positive cases and the increase of anti-HCV positive cases as age rose in the general population. But there was no statistically significant difference among B-NHL patients even though this general regularity was observed. It was considered that the prevalence of anti-HCV positive cases among B-NHL patients aged 40 years old and over was regular and high.

In our study, the prevalence of the HBsAg positive cases among patients with B-NHL was higher compared to that among the general population (HPCE Program participants). However, in contrast to previous findings of studies conducted in different

countries, the statistically significant difference between B-NHL positive and the general population of Mongolia is not statistically different. In contrast, positive incidences of the anti-HCV in the B-NHL group was significantly higher than that in the general population ($p<.0001$). In comparison with the results of the HBsAg and anti-HCV prevalence studies conducted by M. Takahashi (2003) [21] and B. Dashtseren (2013) [20] among the Mongolian general population, incidences of HBsAg positive cases were almost the same for age groups.

The epidemiology of hepatitis B can be described in terms of the prevalence of HBsAg in the general population, broadly classified into high (>8% HBsAg prevalence) and intermediate prevalence (2%–7%) [27]. The HBV prevalence was 11.2% among the general population of Mongolia making it a country with a high prevalence. And for their representation, research conducted in countries such as in mainland China (7.2 vs. 21.6%, $p<.001$) [10], South Korea (8.1 vs. 14 %, $p<.04$) [28], and Japan (in male 2.33 vs. 6.9 $p<.05$) suggested that the prevalence of HBV among patients with B-NHL were significantly higher than that in the general population. This situation was proven for research in low prevalence regions [14, 29, 30].

Having no significantly higher prevalence of HBsAg among the B-NHL patients compare to that among the general population may depend on several reasons. Perhaps, one of the reasons is the hepatitis D virus (HDV). Because more than 60% of the Mongolian population with HBsAg positive are co-infected with HDV [31]. Also, many in-vitro and in-vivo studies, as well as clinical observations, have indicated that the HDV is able to suppress the replication of the HBV at a certain time of point of the co-infection [32]. The age groups have high statistical significance for incidences of anti-HCV positive cases. This is consistent with the results of other studies [33, 34]. In some studies, HCV incidence is significantly higher for male patients with B-NHL than in the general population, but our study has shown that both men and women had an equally high prevalence. In addition, the number of anti-HCV positive incidences in B-NHL was significantly higher in older adults [35]. The anti-HCV positive B-NHL group had a larger proportion of late-stage lymphoma (stages III and IV) patients, indicating that the HCV infection could stimulate B-NHL progression. This finding was consistent with the results reported in the literature [36]. There is a concern that HCV is quite likely to have an effect on B-NH. HCV was highly prevalent in Mongolia during the implementation of the HPCE Program and access to HCV therapy may be beneficial for further reduction of B-NHL cases.

Limitations and Future Study

Several cases in which no information about virus markers in the clinical record of B-NHL patients was noted. In this case, we have collected data by searching from other documents related to the patients as well as by contacting the patients and their families directly. There was no information about both HBsAg and anti-HCV positive in the results of the prevalence of Takahashi's study as well as the HPCE program. Three people who were both HBsAg and anti-HCV positive were ignored and the comparison of the prevalence of HBsAg and anti-HCV was performed for patients who were either HBsAg or anti-HCV positive. Also, it will be interesting to study how HBsAg and anti-HCV co-infection affects B-NHL progress in the future.

For this study, the B-cell major category, which takes 86% of NHL applied; taking into consideration the sparse Mongolian population and short time since introduction of immunohistochemistry which started in 2013 to determine NHL subtypes. We suggest that future research needs to investigate the positive cases of HBsAg and HCV with each subtype.

Conclusion

The number of HBsAg positive incidences among B-NHL patients was comparable to that of the general population, while the number of anti-HCV positive incidences was evidently higher than the general population. Further studies are needed to clarify the reasons and contributing factors that result in situations where the HBV prevalence among B-NHL patients and the general population are not significantly different.

This research was conducted to study the prevalence of HBsAg and anti-HCV among patients newly diagnosed with B-NHL being higher than that among the general population. It has practical importance to provide physicians with information about determining serological markers of HBV (and HDV) and HCV in detail before performing anti-viral therapy with the chemotherapy if the virus infection is diagnosed.

Moreover, the prevention and treatment of HCV infection may decrease B-NHL incidence, especially in areas with a high prevalence of HCV. Also, patients with B-NHL and their physicians should be aware of the high prevalence of chronic HCV and HBV infection in Mongolia.

Conflict of Interest

The authors state no conflict of interest.

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