Open Access

Original Article

Hepatitis B & C Among Patients of Non-Hodgkin's Lymphoma and its Association with Pathological Factors

Paras Memon, Ghulam Haider, Mehwish Roshan Shaikh, Bunisha, Raja Rahul, Shumaila Beg

Department of Medicine, Jinnah Postgraduate Medical Centre, Karachi Pakistan

ABSTRACT

Objective: To see the frequency of hepatitis B and C virus among patients presenting with non-Hodgkin's lymphoma and to see its association with pathological factors in Pakistani population.

Study Design: Cross sectional study.

Place and Duration of the study: Department of Medical oncology, Jinnah Postgraduate Medical Center, Karachi Pakistan, from Jan 2019 to Jan 2020.

Methodology: Total 251 patients of age more than 15 years of either gender with proven diagnosis of non-Hodgkin's Lymphoma were enrolled in the study. The sample of blood (15 ml) of each participants was taken and sent to laboratory for detection of virus. The HBsAg and HCV antibodies were detected using 3rd generation Enzyme-Linked Immunosorbent Assay (ELISA). The cut-off set for HBsAg as 2.0 and for HCV as 1.0 in the laboratory, respectively. The information regarding socio-demographics, comorbidities, risk factors and clinicopathological features were noted on pre-designed proforma.

Results: Out of 251 patients with non-Hodgkin's Lymphoma, 8.8% had hepatitis and 4% had hepatitis B No statistically significant association was found for prevalence of hepatitis B and C with respect to stage (p=0.791 and 0.299), histological type (p=0.165 and 0.398), bone marrow involvement (p=0.692 and 0.163) and site of tumor (p=0.067 and 0.116).

Conclusion: The substantial proportion of hepatitis B and C in the current study provides epidemiological evidence that such infection may play a role in NHL growth.

Keywords: Bone marrow involvement, Hepatitis B, Hepatitis C, Histological type, Non-Hodgkin's lymphoma, Pathological factors.

How to Cite This Article: *Memon P, Haider G, Shaikh MR, Bunisha, Rahul R, Beg S. Hepatitis B & C Among Patients of Non-Hodgkin's Lymphoma& Its Association with Pathological Factors. Pak Armed Forces Med J 2023; 73(Suppl-1): S97-101. DOI: https://doi.org/10.51253/pafmj.v73i1SUPPL-1.4831*

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by-nc/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

Non-Hodgkin lymphomas (NHLs) are one of the most common hematological malignancies, accounting for 3% of all malignancies worldwide.[1] In 2019, 41,090 males and 33,110 females were diagnosed with NHL in the United States, affecting children and adults respectively, while 8,460 females and 11,510 males died as a result.[2] NHL is one of the frequent cancer in Pakistan accounting for 4.4% of all malignancies.[3]

NHL incidence rates have been drastically increased all over the world over the past decades, however the NHL's etiological factors remain unknown.[4] Both genetic and environmental determinants may enhance the occurrence of NHL. The chronic antigenic stimulation because of viruses such as Epstein-Barr virus, human immunodeficiency virus, and hepatitis C virus (HCV), has a significant part to play in NHL pathogenesis.[5]

Regardless of the heterogeneous factor among NHL subtypes, in the last two decades there has been a strong link between NHL and HCV infection, indicating that around 8 percent of NHL worldwide are attributable to HCV.[6,7] Few investigations show, but not all, significant association of hepatitis B virus (HBV) infection and NHL. In addition, most of these studies have lacked information on the HbsAg and HCV antibody.[8,9]

Almost ten million people suffer from HCV in Pakistan and five million from HBV. Due to the lack of awareness, diagnostic and treatment facilities, incomplete sterilization, poorly targeted blood transfusions, unsafe injections add up to 1000 new cases every year.[10] With increasing incidence of NHL in Pakistan, there is surprisingly scarcity of data about prevalence of hepatitis B and C virus and its related risk factors. Therefore, the primary aim of current study was to assess the frequency of HBV and HCV among patients presenting with non-Hodgkin's lymphoma and secondary aim was to see its association with different pathological factors in Pakistani population.

METHODOLOGY

The cross-sectional study conducted at the department of Medical Oncology, Jinnah Postgraduate Medical Center, Karachi Pakistan, from Jan 2019 to Jan 2020. The sample size of 251 was estimated using Open

Correspondence: Dr Paras Memon, Medical Oncology, Liaqat Medical Store, VIP Road Lahori Muhalla Larkana, Pakistan

Received: 22 Jul 2020; revision received: 25 Oct 2020; accepted: 29 Oct 2020

epi online sample size calculator, by taking statistics for HBV infection as 20.5% among patients with NHL, margin of error as 5% and 95% confidence level.[11]

Inclusion Criteria: All the patients of age more than 15 years of either gender with proven diagnosis of NHL were enrolled in the study.

Exclusion Criteria: Patients with exposure of chemoradiation therapy in past, memory problems and lactating and pregnant women were excluded from the study.

The ethical approval was sought before conduct of study (ERC approval NO.F-2-81/2019-GENL/ 18991 /JPMC)and informed consent was obtained from all the eligible participants. The sample of blood (15 ml) of each participants was taken and sent to laboratory for detection of virus. The HBsAg and HCV antibodies were detected using 3rd generation Enzyme-Linked Immunosorbent Assay (ELISA). The cut-off set for HBsAg as 2.0 and for HCV as 1.0 in the laboratory, respectively. The information regarding sociodemographics, comorbidities, risk factors and clinicopathological features were noted on pre-designed proforma by researcher herself.

Data was analyzed using SPSS version 23. Binomial/categorical variables were reported as frequency and percentage. Normality of all the numeric variables was check using Shapiro-Wilks test andmedian with interquartile range were reported. Chi-square/Fisher exact test was applied to see association between HBV/HCV and different pathological features. *p*-value≤0.05 was set as statistically significant.

RESULTS

Total 251 patients were included in the study. All quantitative variables were non-normally distributed therefore median along with interquartile range were reported. The median age of the patients was reported as 50 years and median BMI as 21.3 kg/m^2. The medians of laboratory findings such as WBC, hemoglobin level, platelets, albumin, total bilirubin, ALP, uric acid, LDH and Ki67 were reported as 4675, 9.6 g/dl, 230000 counts, 2.8 g/dl, 0.3 mg/dl, 169 U/L, 4.6 mg/dl, 603.5 U/L and 75% respectively (Table-I).

Table-I: Descriptive Statistics of Study Parameters (n=251)

Study Parameters	Median	25th Percentile	75th Percentile	IQR
Age (year)	50	36	60	24
Body mass index (BMI) in kg/m^2	21.3	19.56	24.99	5.44
White blood cells (WBCs)x 10^3/µL	4675	5200	9300	4625
Hemoglobin (g/dl)	9.6	9.70	11.70	2.13
Platelet (counts)	230000	267750	397000	167000
Albumin (g/dl)	2.8	2.80	3.60	0.80
Total bilirubin (mg/dl)	0.3	0.32	0.79	0.46
Alkaline Phosphatase (ALP) (U/L)	169.0	102.00	290.25	188.25
Uric acid (mg/dl)	4.6	3.69	6.40	2.71
Lactic Acid Dehydrogenase (LDH) (U/L)	603.5	362.00	792.00	430.00
Ki67 (%)	75	50	80	30

Majority of the patients were males 152(60.6%), belonged from urban area 148(59%), had primary level education 77(30.7%), monthly income of 15,000-30,000 PKR 122(48.6%) and married 221(88%). About 86(34.3%) patients were tobacco consumers and only 6(2.4%) were alcohol consumers. About 24 patients (9.6%) had history of dental procedure, 41(16.3%) had past surgical history, 64(25.5%) had blood transfusion history, only 1 was drug user(0.4%), 94(37.5%) and 89(35.5%) patients had ear and nose piercing, only one reported about multiple sexual partners(0.4%), 43(17.1%) had history of jaundice, 126(50.2%) used to use disposal kit user for haircut/shaving and 30(12%) had endoscopy. About 44(17.5%) had diabetes mellitus, 2(0.8%) had ischemic heart disease (IHD) and 40(15.9%) had hypertension. Half of the patients had '1' ECOG status 126(50.2%) followed by '0' ECOG status 104 (41.4%). More than 65% of the patients presented with advanced stage (3-4) of tumor, 190 patients (75.7%) had nodal site involvement and only 50(19.9%) had bone marrow involvement. The most frequent histological type was diffuse large B-cell lymphoma (DLBCL) 181(72.1%) followed by follicular lymphoma 27(10.8%) (Table-II).

Out of 251 patients with NHL 22(8.8%) had HCV) (10,4%) had HBV) and only one patient was co-infected with HBV and HCV 1(0.4%).

No statistically significant association was found for prevalence of HBV and HCV with respect to stage, histological type, bone marrow involvement and site of tumor (p>0.05) (Table-III).

Table-II: Frequency Distribution of Qualitative Parameters (n=251)

Parameters	n	%	Parameters	n	%
Gender					
Male	152	60.6	**History of jaundice**		
Female	99	39.4	Yes	43	17.1
Residence			No	208	82.9
Rural	103	41	**Disposal kit user for** haircut**/shaving**		
Urban	148	59	Yes	126	50.2
Education			No	125	49.8
Illiterate	72	28.7	**Endoscopy**		
Primary	77	30.7	Yes	30	12.0
Matric	45	17.9	No	221	88.0
Intermediate	34	13.5	**Diabetes**		
Graduate	23	9.2	Yes	44	17.5
Monthly Income (PKR)			No	207	82.5
<15,000	119	47.4	**IHD**		
15,000-30,000	122	48.6	Yes	2	0.8
>30,000	10	4	No	249	99.2
Marital status			**Hypertension**		
Unmarried	30	12	Yes	40	15.9
Married	221	88	No	211	84.1
Tobacco user			**ECOG status**		
Yes	86	34.3	0	104	41.4
No	165	65.7	1	126	50.2
Alcohol consumer			2	19	7.6
Yes	6	2.4	3	2	0.8
No	245	97.6	**Stage**		
Dental procedure			1	8	3.2
Yes	24	9.6	2	73	29.1
No	227	90.4	3	107	42.6
Past surgical history			4	63	25.1
Yes	41	16.3	**Site**		
No	210	83.7	Nodal	190	75.7
History of blood transfusion			Extra nodal	61	24.3
Yes	64	25.5	**Bone marrow involvement**		
No	187	74.5	Yes	50	19.9
Drug user			No	201	80.1
Yes	1	0.4	**Histological type**		
No	250	99.6	Diffuse large B-cell lymphoma	181	72.1
Piercing ear			Follicular lymphoma	27	10.8
Yes	94	37.5	Marginal Zone Lymphoma	6	2.4
No	157	62.5	Mantle cell lymphoma	19	7.6
Piercing nose			Burkitt lymphoma	9	3.6
Yes	89	35.5	Peripheral T-Cell Lymphoma	3	1.2
No	162	64.5	Anaplastic large-cell lymphoma	3	1.2
Multiple sexual partner			NK/T-cell lymphoma	1	0.4
Yes	1	0.4	Peripheral T-cell lymphoma not otherwise specified	1	0.4
No	250	99.6	T cell histiocytic rich large B cell lymphoma	1	0.4
Acupuncture					
Yes	0	0			
No	251	100.0			

DISCUSSION

In early 1990s the NHL has been linked with HCV infection. IARC also indicated HCV as one of the cause of NHL in 2009.[12] The recent pooled-analysis also supported this finding and 1.8 times more risk of NHL among patients with HCV positive.[13] HBV or HCV are potential risk factors for hepatocellular carcinoma due to direct (e.g., interaction of HCV proteins with host

Table-III: Association of HBV and HCV with Pathological Factors (n=251)

	Hepatitis B		*p*-value	Hepatitis C		*p*-value
	Positive	Negative		Positive	Negative	
Stage						
I	0	8(100%)	0.791	1 912.5%)	7(87.5%)	0.299
II	2(2.7%)	71(97.3%)		3(4.1%9	70(95.9%)	
III	6(5.6%)	101(94.4%)		11(10.3%)	96(89.7%)	
IV	2(3.2%)	61 (96.8%)		7(11.1%)	56(88.9%)	
Bone marrow involvement						
Yes	1(2%)	49(98%)	0.692	7(14%)	43(86%)	0.163
No	9(4.5%)	192(95.5%)		15(7.5%)	186(92.5%)	
Histological type						
Diffuse large B-cell lymphoma	6(3.3%)	175(96.7%)	0.165	15(8.3%)	166(91.7%)	0.398
Follicular lymphoma	1(3.7%)	26(96.3%)		2(7.4%)	25(92.6%)	
Marginal Zone Lymphoma	1(3.7%)	5(83.3%)		0	6(100%)	
Mantle cell lymphoma	0	19(100%)		3(15.8%)	16(84.2%)	
Burkitt lymphoma	2(22.2%)	7(77.8%)		0	9(100%)	
Peripheral T-Cell Lymphoma	0	3(100%)		1(33.3%)	2(66.7%)	
Anaplastic large-cell lymphoma	0	3(100%)		1(33.3%)	2(66.7%)	
NK/T-cell lymphoma	0	1(100%)		0	1(100%)	
Peripheral T-cell lymphoma not otherwise specified	0	1(100%)		0	1(100%)	
T cell histiocytic rich large B cell lymphoma	0	1(100%)		0	1(100%)	
Site						
Nodal	5(2.6%)	184(97.4%)	0.067	20(10.6%)	169(89.4%)	0.116
Extra nodal	5(8.2%)	56(91.8%)		2(3.3%)	59(96.7%)	

proteins controlling cell proliferation, HBV DNA penetration into the host genome) and indirect (e.g., chronic inflammation, fibrosis) oncogenic impact.[14] Literature has also shown increased odds of NHL among patients with HCV or HBV infection.[15,16] However, how chronic viral infection like hepatitis may attribute to lymphomagenesis is still unclear. The capacity of HCV to multiply within lymphocytes and thus impose a direct oncogenic influence is uncertain, and an indirect impact by persistent antigenic stimulation is plausible.However, lymphoma regression in HCV-infected people after antiviral therapy clearly supports a causal association between NHL and HCV infection. While there is no similar evidence for HBV, peripheral mononuclear blood cells are known reservoir of extra-hepatic HBV.[17]

In the present study, 8.8% patients with NHL were HCV positive, 4% were HBV positive and only one patient was co-infected with HBV and HCV. In a case-control study by Taborelli *et al*. found similar results, 4% prevalence of HBV among NHL cases and prevalence of HCV RNA positive as 11.1% and only one NHL patient was co-infected by HBV and HCV.[8] A multicenter research by de Sanjose *et al*. found 3.6% of NHL cases were HCV infected.[18] In another study by Muhammad *et al*. found 2-3 folds increased of NHL development among patients with HCV and HBV positivity (p<0.05).[19] Yood *et al*. also concluded in his study that HBV positivity increases the odds of NHL by 3 times as compared to patients without HBV.[20]

In a previous study, HCV was associated with range of NHL histological subtypes (B-cells), with up to 29% prevalence of NHL patients (chronically infected). Many reports have shown a positive relationship between HCV and histological subtypes,[21] whereas no substantial correlation between Burkitt lymphoma and HCV positivity was found.[22] In another research, 65% patients with HBV positivity and NHL had B-cell type.[23] In the present research, majority of the patients had diffuse large B-cell lymphoma (DLBC) (72.1%) followed by follicular lymphoma (10.8%) and among them 6 patients were HBV positive and 15 patients were HCV positive, however no significant association was found between histological type and HCV/HBV (p>0.05). The findings of this study showed that 65% of the patients presented with advanced stage of tumor (III-IV), 75.7% had nodal site involvement and only 19.9% had bone marrow involvement. In a study Wang *et al*. observed positive HBV patients had DLBCL subtype and more advanced stage of tumor

(58%) as compared to HBV negative patients (42%) and showed statistically significant association.[24] Another frequent factor of HCV among B-NHL are involvement of extranodal and long term infection of more than 15 years.[25] In the current study, majority of patients infected with HCV had extranodal involvement whereas no difference was observed in HBV frequencies between nodal and extranodal involvement.

CONCLUSION

The substantial proportion of HBV and HCV in the current study provides epidemiological evidence that such infection may play a role in NHL growth.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

PM: & GH: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

MRS: & B: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

RR: & SB: Conception, study design, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFEERENCES

1. Singh R, Shaik S, Negi BS, Rajguru JP, Patil PB, Parihar AS, et al. Non-Hodgkin's lymphoma: A review. J. family med. prim. Care 2020; 9(4): 1834-1840. https://doi: 10.4103/jfmpc.jfmpc_1037_19.
2. ACS. Key Statistics for Non-Hodgkin Lymphoma 2019: Ame-rican Cancer Society; 2019 [cited 2020 10 Jan]. Available from: https://www.org/canlymphoma/about/key-statistics.html.
3. Idrees R, Fatima S, Abdul-Ghafar J, Raheem A, Ahmad Z. Cancer prevalence in Pakistan: meta-analysis of various published studies to determine variation in cancer figures resulting from marked population heterogeneity in different parts of the country. World J Surg Oncol 2018; 16(1): 129. https://doi: 10.1186/s12957-018-1429-z.
4. Masarone M, Persico M. Hepatitis C virus infection and non-hepatocellular malignancies in the DAA era: A systematic review and meta-analysis. Liver international official journal of the International Association for the Study of the Liver 2019; 39(7): 1292-306. https://doi: 10.1111/liv.14119. Epub 2019 May 8.
5. Marrone A, Ciotti M, Rinaldi L, Adinolfi LE, Ghany M. Hepatitis B and C virus infection and risk of haematological malignancies. J Viral Hepat 2020; 27(1): 4-12. https://doi: 10.1111/jvh.13183. Epub 2019 Aug 13.
6. Khaled H, Abu-Taleb F, Haggag R. Hepatitis C virus and non-Hodgkin's lymphomas: A minireview. J. Adv. Res 2017; 8(2): 131-7. https://doi: 10.1016/j.jare.2016.11.005.
7. Conti B, Porcu C, Viscomi C, Minutolo A, Costantini S, Corazzari M, et al. Small heterodimer partner 1 directly interacts with NS5A viral protein and has a key role in HCV related liver cell transformation. Oncotarget 2016; 7(51): 84575-84586. https://doi:list.10.18632/oncotarget.12144.
8. Taborelli M, Polesel J, Montella M, Libra M, Tedeschi R, Battiston M, et al. Hepatitis B and C viruses and risk of non-Hodgkin lymphoma: a case-control study in Italy. Infect Agent Cancer 2016; 11(1): 27. https://doi: 10.1186/s13027-016-0073-x.
9. Li M, Gan Y, Fan C, Yuan H, Zhang X. Hepatitis B virus and risk of non-Hodgkin lymphoma: An updated meta-analysis of 58 studies. J Viral Hepat 2018; 25(8): 894-903. https://doi: 10.1111/jvh.12892.
10. WHO. Hepatitis: World health organization; 2019 [cited 2020]. Available from: https://www.who.int/hepatitis/news-events/pakistan-hepatitis-elimination-plan/en/.
11. Soomro MA, Quadri HUR, Khalid SM. Frequency of hepatitis b virus (hbv) infection in patients of nonhodgkin's lymphoma (nhl) at tertiary care centers of Larkana. Medical Channel 2011; 17(3): 1-5.
12. Pozzato G, Mazzaro C, Dal Maso L, Mauro E, Zorat F, Moratelli G, et al. Hepatitis C virus and non-Hodgkin's lymphomas: Meta-analysis of epidemiology data and therapy options. World J Hepatol. 2016; 8(2): 107-116. https://doi: 10.4254/wjh.v8.i2.107.
13. Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, Skibola CF, et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. J Natl Cancer Inst Monogr 2014; 2014(48): 130-144. https://doi: 10.1093/jncimonographs/lgu013.
14. Harrod E, Moctezuma-Velazquez C, Gurakar A, Ala A, Dieterich D, Saberi B. Management of concomitant hepatocellular carcinoma and chronic hepatitis C: a review. Hepatoma Research 2019; 5(1): 28.
15. Peveling-Oberhag J, Arcaini L, Hansmann ML, Zeuzem S. Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management. J Hepatol 2013; 59(1): 169-177. https://doi: 10.1016/j.jhep.2013.03.018.
16. Kamiza AB, Su FH, Wang WC, Sung FC, Chang SN, Yeh CC. Chronic hepatitis infection is associated with extrahepatic cancer development: a nationwide population-based study in Taiwan. BMC Cancer 2016; 16(1): 861. https://doi: 10.1186/s12885-016-2918-5.
17. Vannata B, Arcaini L, Zucca E. Hepatitis C virus-associated B-cell non-Hodgkin's lymphomas: what do we know? Ther Adv Hematol 2016; 7(2): 94-107. https://doi: 10.1177/2040620715623924.
18. De Sanjose S, Benavente Y, Vajdic CM, Engels EA, Morton LM, Bracci PM, et al. Hepatitis C and non-Hodgkin lymphoma among 4784 cases and 6269 controls from the International Lymphoma Epidemiology Consortium. Clin Gastroenterol Hepatol 2008; 6(4): 451-458. https://doi: 10.1016/j.cgh.2008.02.011.
19. Muhammad SK, Shaikh BA, Gurbakhshani KM, Shah SR, Soomro MA. Association of hepetitis B & C virus infection in non Hodgkin's lymphoma: A case control study. Medical Channel 2012; 18: 31-36.
20. Ulcickas Yood M, Quesenberry CP, Jr., Guo D, Caldwell C, Wells K, Shan J, et al. Incidence of non-Hodgkin's lymphoma among individuals with chronic hepatitis B virus infection. Hepatol 2007; 46(1): 107-112. https://doi: 10.1002/hep.21642.
21. Anderson LA, Pfeiffer R, Warren JL, Landgren O, Gadalla S, Berndt SI, et al. Hematopoietic malignancies associated with viral and alcoholic hepatitis. Cancer Epidemiol Biomarkers Prev 2008; 17(11): 3069-3075. https://doi: 10.1158/1055-9965.EPI-08-0408.
22. Dal Maso L, Franceschi S. Hepatitis C virus and risk of lymphoma and other lymphoid neoplasms: a meta-analysis of epidemiologic studies. Cancer Epidemiol Biomarkers Prev 2006; 15(11): 2078-2085. https://doi: 10.1158/1055-9965.
23. Kuniyoshi M, Nakamuta M, Sakai H, Enjoji M, Kinukawa N, Kotoh K, et al. Prevalence of hepatitis B or C virus infections in patients with non-Hodgkin's lymphoma. J Gastroenterol Hepatol 2001; 16(2): 215-219. https://doi: 10.1046/j.1440-1746.2001.
24. Wang F, Xu RH, Luo HY, Zhang DS, Jiang WQ, Huang HQ, et al. Clinical and prognostic analysis of hepatitis B virus infection in diffuse large B-cell lymphoma. BMC Cancer 2008; 8 (1): 115. https://doi: 10.1186/1471-2407-8-115.
25. Tasleem S, Sood GK. Hepatitis C associated B-cell non-hodgkin lymphoma: Clinical features and the role of antiviral therapy. J. clin. transl. hepatol 2015; 3(2): 134-139. https://doi: 10.14218/JCTH.2015.00011.