



Hepatitis C Virus Infection in Non-Hodgkin's Lymphoma: A Case-Control Study

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ABSTRACT

Background: Hepatitis C virus (HCV) is the most common cause of chronic liver disease in Pakistan (1). Globally, an estimated 170 million people are infected with HCV, with approximately 3–4 million new cases each year (2, 3). Currently, the prevalence of HCV in Pakistan is 4–7% (4–6). HCV is a hepatotropic virus that causes chronic hepatitis in at least 80% of infected individuals. If untreated, 20–30% of the cases will eventually develop cirrhosis, with average latency of 15–25 years, and hepatocellular carcinoma, at the rate of 1–5% per year and average latency of 20–30 years (3, 7).

Objectives: We examined the association between HCV infection and non-Hodgkin's lymphoma (NHL).

Patients and Methods: This 2-year case control study was conducted From January 1, 2009 to December 31, 2010. A total of 292 NHL patients underwent staging, according to the Ann Arbor staging criteria, and were graded, according to the Working Formulation Classification. Anti-HCV antibodies (Abs) were used in an enzyme-linked immunosorbent assay (ELISA) to detect HCV in blood samples from the 292 NHL patients and 1168 age- and sex-matched control patients (2 groups) who met our selection criteria. The chi-square test was applied to compare anti-HCV Ab seropositivity in the cases and controls, and odds ratio values were computed. The NHL patients were divided into anti-HCV Ab seronegative and seropositive groups to compare the effect of anti-HCV Ab seropositivity on NHL stages and grades. A *P* value of 0.05 was considered statistically significant.

Results: A total of 52 (17.8%) cases, including 45 (7.7%) controls in group 1 (1st degree relatives) and 50 (8.6%) controls in group 2 (non-hematological malignancy), showed positive results for anti-HCV Abs and had a odds ratio value of 2.59 (95% CI: 1.69–3.97) for group 1 and 2.31 (95% CI: 1.52–3.50) for group 2 (*P* value of 0.000 for both groups). NHL patients who showed positive results for anti-HCV Abs were likely to be middle-aged patients (40–60 years; odds ratio, 3.68; 95%CI: 2.07–6.50). Anti-HCV Ab seropositivity did not significantly affect the grades and stages of NHL.

Conclusions: NHL is strongly associated with anti-HCV Ab seropositivity (odds risk, 2–2.5), and seropositive cases were generally middle-aged and younger patients.

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► Implication for health policy/practice/research/medical education:

The association of HCV in development of NHL is well established, but no data is available from Pakistan. This study will bring light to this issue. The observations are eye opener for policy makers to pursue this issue in our society.

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1. Background

Hepatitis C virus (HCV) is the most common cause of chronic liver disease in Pakistan (1). Globally, an estimated 170 million people are infected with HCV, with approximately 3–4 million new cases each year (2, 3). Currently, the prevalence of HCV in Pakistan is 4–7% (4–6). HCV is a hepatotropic virus that causes chronic hepatitis in at least 80% of the infected individuals. If left untreated, 20–30% of the cases will eventually develop cirrhosis, with an average latency of 15–25 years, and hepatocellular carcinoma, at the rate of 1–5% per year and average latency of 20–30 years (3, 7). In addition to chronic viral hepatitis, HCV is associated with extrahepatic manifestations such as mixed essential cryoglobulinemia, porphyria cutanea tarda, type 2 diabetes mellitus, lichen planus, thyroid disorders, and peripheral neuropathy (8–10). Recent reports have documented that HCV is also lymphotropic; by infecting peripheral mononuclear cells, HCV can predispose patients to lymph proliferative disorders such as non-Hodgkin's lymphoma (NHL) (11, 12). NHL is a lymph proliferative disorder with an annual incidence of 12 new cases/100,000 persons worldwide; this rate has increased steadily over the past several decades, with an annual increase in incidence of 1–4% (13, 14). Recently, HCV has been associated with the development of NHL (15–17). Persistence of chronic HCV in lymphocytes along with the involvement of genetic and environmental factors have been hypothesized (18). Increased frequency of B-cell clonality, t (14: 18) bcl-2 and bcl-6 gene translocation, STAT3 activation, and upregulation of ERK and p38 MAPK signaling pathways is observed in NHL patients infected with HCV and HBV. Possible mechanisms for malignant transformation include clonal proliferation of B cells, inhibition of apoptotic cell death, or both (19–24). The 5-year survival rate of NHL patients who undergo the current standard therapy is 64.5%, depending on stage, grade, histological diagnosis, and age. NHL associated with HCV shows excellent response to interferon- alpha 2, and 75–100% of the patients become disease-free after the treatment. Thus, with early detection and treatment of HCV infection, subsequent development of NHL can be prevented and the survival rate can be improved (25–29). The number of studies conducted to examine these issues has been limited. A large number of international studies have documented a very high prevalence of HCV infection in NHL patients, but few of these studies have analyzed the impact of HCV seropositivity on NHL stages and grades (30–37). Given the documented association between non-Hodgkin's lymphoma and HCV infection, we conducted this case-control study to determine the current frequency of HCV infection in NHL patients and compared this frequency with that in patients with other non-hematological malignancies and in the disease-free relatives of NHL patients. This study not only revealed the number of NHL patients with HCV but also provided useful information regarding the association of HCV infection and NHL. We also determined the impact of HCV infection on the stages and grades of NHL.

2. Objectives

We examined the association between HCV infection and NHL.

3. Patients and Methods

3.1. Design

This was a hospital-based, matched case-control study.

3.2. Duration

The study took place over 2 years, from January 2009 to December 2010.

3.3. Setting

We enrolled patients from the Chandka Medical College (CMC) of Larkana and Larkana Institute of Nuclear Medicine And Radiotherapy (LINAR). CMC Larkana is the only tertiary care hospital in rural Sindh, and it is equipped with modern facilities and provides health care services to the Sindh and Balochistan provinces. LINAR was formed and is administered by the Atomic Energy Commission of Pakistan and is affiliated with CMC Larkana. LINAR is a highly equipped and modernized institute that provides chemotherapy and radiotherapy services to patients.

3.4. Sampling Technique

A purposive sampling technique was employed using the specific criteria discussed below.

3.5. Inclusion Criteria

Cases: All consecutive, male or female NHL patients of any age who had their diagnosis confirmed by biopsy, were newly diagnosed, or had not received treatment were enrolled in the study.

Control group 1: This group included 2 age- (± 5 years) and gender-matched first-degree relatives for each case.

Control group 2: This group included 2 age- (± 5 years) and gender-matched patients with non-hematological malignancies for each case.

3.6. Exclusion Criteria

Cases were excluded for the following reasons:

- Previously diagnosed with HCV
- Exposure to radiations or had undergone chemotherapy
- Had received palliative treatment for NHL
- Had received or was undergoing blood transfusion or had undergone a major surgical procedure in the past 6 months
- Previously diagnosed with a medical disorder, for example, hemophilia and thalassemias, that required parenteral medications
- Co-infection with human immunodeficiency virus (HIV) or HBV with hepatitis delta virus (HDV)
- Suffering from an immunodeficiency or autoimmune

immune disorders

Relatives were excluded from control group 1 for the following reasons:

- Previously diagnosed with HCV
- Had received or were undergoing blood transfusion or had undergone any major surgical procedure in the last 6 months
- Diagnosed with a medical disorder, for example, hemophilia, thalassemias, that required parenteral medications
- Co-infection with HIV or HBV with HDV
- Suffering from immunodeficiency or autoimmune disorders

Patients were excluded from the control group 2 on the basis of the following reasons:

- Previously diagnosed with HCV
- Had received or were undergoing blood transfusion or had undergone any major surgical procedure in

the last 6 months

- Diagnosed with a medical disorder, for example, hemophilia, thalassemias, that required parenteral medications
- Co-infection with HIV or HBV with HDV
- Suffering from immunodeficiency or autoimmune disorders
- Suffering from hepatocellular carcinoma

3.7. Selection of Cases and Controls

A total of 378 consecutive newly diagnosed NHL patients were enrolled during the study period. A detailed history was acquired for all the patients; five patients were excluded because they had received blood transfusion, received parenteral symptomatic medications, or had undergone surgical intervention in the past 6 months. One patient had a history of irradiation exposure and was also excluded. Four HIV-infected, 74 HBV-infected, and 2

Table 1. Demographic Profile of the Case and Control Patients

	Case (n = 292)	Control 1 ^a (n = 584)	Control 2 ^b (n = 584)	P value ^c
Age, y				0.000
Mean ± SD	44.23 ± 20.23	45.11 ± 19.50	46.83 ± 19.12	
Range	70 (4-74)	66 (8-74)	64 (9-73)	
Age category, y, No. (%)				0.243
< 20	34 (11.6)	83 (14.2)	82 (14.0)	
20-39	82 (28.1)	136 (23.3)	137 (23.5)	
40-59	71 (24.3)	161 (27.6)	161 (27.6)	
> 60	105 (36.0)	204 (34.9)	204 (34.9)	
Gender, No. (%)				1.000
Male	171 (58.6)	342 (58.6)	342 (58.6)	
Female	121 (41.4)	242 (41.4)	242 (41.4)	
HCV seropositivity, No. (%)				0.000
Positive	52 (17.8)	45 (7.7)	50 (8.6)	
Negative	240 (82.8)	539 (92.3)	534 (91.4)	

^a Control group 1 = age- and sex-matched 1st degree relatives

^b Control group 2 = age- and sex-matched patients with non-hematological malignancies

^c Pearson chi-square test; 2-sided significance

Table 2. Odds Risk and P values for the Association of HCV and NHL in the Case and Control Patients

	Anti-HCV Ab Positive	P value ^d
Control 1		< 0.000
OR ^a	2.59	
95% CI	(1.69-3.97)	
Control 2		< 0.000
OR ^b	2.31	
95% CI	(1.52-3.50)	
Total		< 0.000
OR ^c	2.44	
95% CI	(1.69-3.52)	

^a Risk of NHL by using control group 1 as the reference

^b Risk of NHL by using control group 2 as the reference

^c Risk of NHL by using control groups 1 and 2 as references

^d Pearson chi-square test; 2-sided significance

HDV-infected patients were also excluded from the study. The remaining 292 NHL cases were selected and labeled as the case group.

Patients were placed into 2 gender- and age-matched (\pm 5 years) control groups. For each case, two controls were selected from each control group.

Control group 1 (n = 584) consisted of two first-degree relatives for each case; cases were also matched by their district of origin (native place of residence).

Control group 2 (n = 584) consisted of two age- and sex-matched patients with non-hematological malignancies who were admitted in different wards of the CMC Hospital of Larkana and LINAR. The controls in group 2 were also matched by the date of admission (\leq 7 days).

3.8. Data Collection

A total of 292 NHL patients underwent detailed clinical and radiological staging and a review of their history

Table 3. Anti-HCV Ab-Positive Rates According to Age Groups in Case and Control Patients

	< 20, y	20–40, y	40–60, y	> 60, y
Cases				
Anti-HCV Ab-Positive, No.	9	6	27	10
NHL, No.	34	82	71	105
Percent	26.47	7.31	38.03	9.52
Control 1				
Anti-HCV Ab-Positive, No.	7	8	22	8
NHL, No.	83	136	161	204
Percent	8.43	5.88	13.66	3.92
OR ^a (95% CI)	3.909 (1.31–11.58)	1.263 (0.42–3.77)	3.877 (2.01–7.48)	2.579 (0.98–6.74)
P value ^b	< 0.010 ^c	< 0.676	< 0.000 ^c	< 0.046 ^c
Control 2				
Anti-HCV Ab-Positive, No.	9	8	24	9
NHL, No.	82	137	161	204
Percent	10.97	5.84	14.91	4.41
OR ^d (95% CI)	2.92 (1.04–8.175)	1.273 (0.42–3.80)	3.50 (1.83–6.68)	2.28 (0.89–5.88)
P value ^b	< 0.036 ^c	< 0.665	< 0.000 ^c	< 0.076
Controls 1 & 2				
Anti-HCV Ab-Positive, No.	16	16	46	17
NHL, No.	165	273	322	408
Percent	9.69	5.86	14.28	4.16
OR ^e (95% CI)	3.35 (1.33–8.40)	1.26 (0.47–3.35)	3.68 (2.07–6.50)	2.42 (1.07–5.45)
P value ^b	< 0.007 ^c	< 0.631	< 0.000 ^c	< 0.028 ^c

^a Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups by using control group 1 as the reference group^b Pearson chi-square test; 2-sided significance^c Statistically significant ($P < 0.05$)^d Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups by using control group 2 as the reference group^e Risks of non-Hodgkin's lymphoma among HBsAg-positive patients within specified age groups by using both control groups 1 and 2 as the reference groups**Table 4.** Comparison of Age Categories, Stage and Grade in Anti-HCV Ab Seropositive ($n = 52$), and Seronegative ($n = 240$) NHL Cases with Odd Ratios, Confidence Intervals, and P value

	Seropositive, No. (%) ($n = 52$)	Seronegative, No. (%) ($n = 240$)	OR (95% CI)	P value ^a
Stage				
Stage I	6 (11.5)	14 (5.8)	2.10 (0.76–5.70)	< 0.140
Stage II	21 (40.4)	111 (46.3)	0.78 (0.42–1.44)	< 0.441
Stage III	13 (25.0)	68 (28.3)	0.84 (0.42–1.67)	< 0.626
Stage IV	12 (23.1)	47 (19.6)	1.23 (0.60–2.53)	< 0.569
B Symptoms	28 (53.8)	127 (52.9)	1.03 (0.56–1.89)	< 0.903
Grades				
Low-grade	23 (44.2)	77 (32.1)	1.67 (0.91–3.09)	< 0.094
Intermediate-grade	11 (21.2)	56 (23.3)	0.88 (0.42–1.82)	< 0.735
High-grade	18 (34.6)	107 (44.6)	0.65 (0.35–1.23)	< 0.188

^a Pearson chi-square test; 2-sided significance

for the presence of B symptoms. Staging was done according to Ann Arbor Staging criteria, and grading was performed according to the Working Formulation Classification criteria. An enzyme-linked immunosorbent assay (ELISA) of blood samples from the case and control groups was performed in the Pathology Department of the CMC Hospital, Larkana, to detect the anti-HCV anti-

body (Ab) in the 3rd generation. The results were collected by the principal researchers.

3.9. Data Analysis

The data obtained from a total of 292 NHL patients and 584 controls in each control group were analyzed using

SPSS version 10 (SPSS, Inc., Cary, NC, USA). The chi-square test was applied to determine whether there was a significant association between HCV seropositivity and NHL cases. Anti-HCV Ab seropositivity rates were compared in both case and control groups to observe the impact of seropositivity in different age categories. To observe the impact of HCV seropositivity on NHL stages and grades, the NHL patients were divided into 2 groups on the basis of HCV seropositivity. Staging, grading, and presence or absence of B symptoms were compared in both the anti-HCV Ab positive and negative groups. Chi-square test was applied to detect statistical significance and odds ratio values, and 95% CI was computed for stages, presence of B symptoms, and grades of NHL in anti-HCV Ab seropositive and seronegative cases. A *P*-value of less than 0.05 was considered statistically significant.

4. Results

A total of 292 cases and 1168 controls were enrolled in the study. The case group comprised 171 men (58.6%) and 121 women (41.4%). The demographic characteristics of the patients are summarized in Table 1. The case and control groups were similar with respect to sex and age. Fifty-two of 292 NHL patients (17.8%), 45 of 584 relatives (7.7%) in control group 1, and 50 of 584 subjects (8.6%) in control group 2 showed positive results for anti-HCV Abs. A higher risk of NHL was observed in anti-HCV Ab-positive rather than anti-HCV Ab-negative subjects. The odds ratio value for case group versus control group 1 was 2.59 (1.69–3.97) and that of case group versus control group 2 was 2.31 (1.52–3.50) (*P* = 0.000 for both groups). The association between HCV infection and NHL remained significant, with a mean odds risk value of 2.44 (1.69–3.52) (Table 2). The anti-HCV Ab-positive rate was consistently higher in NHL patients in every age group. Risk of NHL was most evident in the anti-HCV Ab-positive patients who were 40–60 years and < 20 years of age. The odds ratio values were 3.35, 1.26, 3.68, and 2.42 in NHL patients who were < 20 years, 20–40 years, 40–60 years, and > 60 years of age, respectively (Table 3). There was no statistically significant difference in stages, B symptoms, and grades between HCV seropositive and seronegative NHL patients (Table 4).

5. Discussion

This was first study conducted in Pakistan to observe the association between HCV and NHL and to observe the impact of anti-HCV Ab seropositivity on the stages and grades of NHL. In our study, we excluded NHL patients who had experienced exposure to any known risk factor for lymphoma development such as irradiation exposure, HIV infection, HBV infection, exposure to cytotoxic or immunosuppressive drugs, autoimmune disorders, and connective tissue disorders. We also excluded patients with a history of transfusion or parenteral medication or surgical procedures in the last 6 months as well as known patients with hemophilia or thalassemias since

these disorders may falsely elevate the number of patients in the anti-HCV Ab-positive group. After exclusion, a total of 292 patients were enrolled in our study. For the cases, we used age- and sex-matched controls. Advantages in selecting 1st degree relatives as control group 1 were that the relative belonged to the same locality of origin, experienced the same environmental factors, and had a genetic makeup similar to that of the patient. Control group 2 consisted of patients with non-hematological malignancy and was used to compute the odds of NHL in HCV, as compared to other non-hematological malignancies.

In our study, we identified statistically significant (*P* < 0.000) odds ratio values for HCV in NHL patients. The HCV-infected NHL patients were younger (*P* < 0.000) than the non-infected individuals, but the risk was higher in young (< 20 years) and middle-aged (40–60 years) patients. There was no significant impact of HCV seropositivity on the stages and grades of NHL. Similar results were reported by researchers in Egypt and Saudi Arabia. In Egypt, Cowgill *et al.* (30) observed a significant association between NHL and HCV, but they did not evaluate the impact of HCV infection on the stages and grades of NHL. HCV infection in NHL patients is reportedly independent of age. Polymerase chain reaction, which was used in a previous study, was better than ELISA for the detection of HCV infection. In Saudi Arabia, Harakati *et al.* (31) reported that HCV-infected NHL patients were more likely to have intermediate-grade NHL than non-infected patients. Researchers in Europe also documented a similar association between NHL and HCV infection, but few studies have been conducted to evaluate the impact of the stages and grades of NHL in detail. Mele *et al.* (32) documented a strong association and concluded that in Italy, 1 of 20 instances of B-NHL may be attributable to HCV infection, and thus, the patients may benefit from antiviral treatment. In Turkey, Isikdogan *et al.* (33) observed that HCV-seropositive NHL patients were more likely to have intermediate-grade NHL. In France, Seve *et al.* (34) documented a positive but non-significant trend towards an association between NHL and HCV infection (odds ratio, 1.31; 95% CI, 0.51–3.36). In Spain, De Sanjose *et al.* (35) found no significant difference in HCV seropositivity between nodal and extranodal NHL cases. Similar to our study, all these studies reported a positive association between NHL and HCV. A Spanish study reported results similar to those of our study regarding the impact on the grades of NHL, but a Turkish study reported contradictory results. Studies performed in other countries have also reported a strong association between HCV and NHL. Spinelli *et al.* (36) in Canada, Takeshita *et al.* (37) in Japan, Masami *et al.* (38) and Nieters *et al.* (39) in a European multicenter case-control study (EPILYMPH), and El-Sayed *et al.* (40) in Egypt also reported similar results. Most of these studies did not examine the impact of HCV seropositivity on the stages, grades, and B symptoms of NHL. Our study not only studied the association between NHL and HCV but also examined its impact on the stages

and grades of NHL. In addition, this was the first study performed in Pakistan on this issue. The literature supports the concept that hepatitis C and NHL are associated. However, limited studies have been conducted in Pakistan to explore this issue. The incidences of these disorders are currently increasing. The primary reasons for increase in HCV infections in developing countries such as Pakistan include poverty, lack of public awareness, non-availability of vaccines, and lack of health care facilities. Furthermore, the incidence of NHL is also increasing at a rate of 1-4% per year. This association of HCV with NHL may put the public at risk of an NHL epidemic, particularly in developing countries such as Pakistan. This may ultimately result in decreased life expectancy and loss of young people in developing nations.

In conclusion, HCV infection is strongly associated with NHL. HCV was 2-3 times more prevalent in NHL patients than in the controls. HCV infection in NHL patients was more frequently observed in young and middle-aged subjects. No statistically significant impact was observed regarding anti-HCV Ab seropositivity on the stages and grades of NHL. On the basis of our results, larger epidemiological studies can be conducted. Our study results also provide information for health policy and decision makers that can be used to control a combined epidemic.

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Authors' Contribution

All the authors contributed to all parts of research, contribution is based on approximate time contributed by all.

Shaikh Khalid Muhammad (50%); Mujahid Ali Chandio (20%); Muhammad Aslam Soomro (15%); Bashir Ahmed Shaikh (15%)

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