Risk of Non-Hodgkin Lymphoma among Patients with Hepatitis B Virus and Hepatitis C Virus in Taiwan: A Nationwide Cohort Study

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Simple Summary: Non-Hodgkin lymphoma (NHL) is difficult to diagnose and has a high mortality rate. Large-scale database research is necessary to examine and strengthen the correlation between viral hepatitis and NHL. This retrospective cohort study analyzed differences in the risk of developing NHL for patients with hepatitis to elucidate these relationships by using nationwide data from Taiwan’s National Health Insurance Research Database. In this study, the incidence rate of NHL in patients with hepatitis B was 0.22%, and in patients with hepatitis C, the incidence rate of NHL was 0.35%. These comparisons indicate that patients with HBV or HCV have a higher incidence of NHL (OR, 2.37; 95% CI, 1.93–2.91).

Abstract: Hepatitis B virus (HBV) and hepatitis C virus (HCV) are associated with an increased risk of developing non-Hodgkin lymphoma (NHL); however, adequate data corroborating these associations are lacking. Therefore, a study based on the national database was performed to investigate the correlation between HBV and HCV with NHL in Taiwan. This research was a retrospective cohort study using a nationally representative database established by the Health and Welfare Data Science Center of the Ministry of Health and Welfare, Taiwan. The participants were patients with HBV and HCV, analyzed using the propensity score matching method. The study results indicated that the incidence rate of NHL (0.13%) was significantly higher than that in patients from the general population. After controlling related variables, the hazard ratio (HR) of the incidence of NHL in patients with hepatitis B was 2.37 (95% CI, 1.93–2.91). Furthermore, the incidence of NHL in patients with HBV was significantly higher than in patients from the general population (HR, 2.49; 95% CI, 1.94–3.19). The incidence of NHL in patients with HCV was significantly higher than in patients from the general population (HR, 2.36; 95% CI, 1.73–3.22). This study indicated that HBV and HCV significantly increase the risk of NHL.

Keywords: hepatitis B virus; hepatitis C virus; non-Hodgkin lymphoma

1. Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are key public health problems worldwide. It has been reported that HBV and HCV are relatively common in Taiwan [1,2]. Taiwan has been controlling viral hepatitis B infections through a large-scale
vaccination campaign. The anti-HBV surface antigen (HBsAg) carrier rate in children in Taipei has dropped from 11% to 0.5% between 1984 and 2014 [3]; another surveillance study indicated that the estimated age-adjusted HCV seroprevalence rate was about 3.28% in Taiwan [2].

Non-Hodgkin lymphoma (NHL) is the most common malignant lymphoid tumor, and incidence rates of NHL vary widely by world region [4]. The cause of NHL is currently unclear. Studies have indicated that the cause of NHL may be related to viral or bacterial infection or poor immune function [5,6]. Additionally, many studies have shown that chronic liver disease can also increase the risk of developing NHL [7–11]. Preventing NHL among patients with HBV and HCV requires special attention.

In southern and eastern Europe, Japan, and the southern United States, NHL and HCV have been reported to be highly correlated. In contrast, in central and northern Europe, Canada, the northern United States, and some countries in Asia, no correlation has been reported. The relatively weak odds ratios of NHL for HCV infection may explain the notable inconsistencies in the literature. The inconsistent results of these studies are likely because of differences in study design, geography, and the ethnicities of the study participants [8,12,13].

NHL is difficult to diagnose and has a high mortality rate. Large-scale database research is necessary to examine and strengthen the correlation between viral hepatitis and NHL. This retrospective cohort study analyzed differences in the risk of developing NHL for patients with HBV and HCV to elucidate these relationships by using nationwide data from Taiwan’s National Health Insurance Research Database.

2. Materials and Methods

2.1. Database

In this study, secondary data were analyzed, examining information from 2000 to 2016 obtained from the Longitudinal Health Insurance Database (LHID), which was established by Taiwan’s Ministry of Health and Welfare (MOHW). The LHID contains data on the medical records and causes of death for 2 million randomly sampled participants in Taiwan’s National Health Insurance (NHI) program. Taiwan’s NHI program has enrolled up to 99% of Taiwanese residents since 1995. Hence, the LHID represents the utilization of healthcare in Taiwan. The LHID contains anonymous data to protect the privacy of beneficiaries and is maintained by the Health and Welfare Data Science Center. Therefore, the requirement for informed consent was waived for this study, and the study protocol was approved after ethical review by the Institutional Review Board of China Medical University Hospital, Taiwan (No: CMUH107-REC2-004).

2.2. Study Participants

In this study, patients newly diagnosed as having HBV or HCV between 2002 and 2013 were selected as the research group, to ensure that each participant had undergone a follow-up period of at least 3 years [14]. Hepatitis was defined as the main diagnosis in 3 or more outpatient clinic visits within one year for HBV (International Classification of Diseases, Ninth Revision [Tenth Revision], Clinical Modification [ICD-9-CM]: 070.20–070.23, 070.30–070.33; ICD-10-CM: B16, B17.0, B18.0, B18.1, B19.1) or HCV (ICD-9-CM: 070.41, 070.44, 070.51, 070.54, 070.7, V02.62; ICD-10-CM: B17.10, B17.11, B18.2, B19.2, Z22.52) and the concurrent use of chronic hepatitis medications, including interferon and L-nucleoside agents.

We selected patients from the general population as a control group for comparison. To reduce outcome bias and avoid selection bias, we used the propensity score matching (PSM) method, which entailed patient and control matching by age and sex at a ratio of 1 (patients with chronic hepatitis) to 5 (patients from the general population) to obtain comparisons for increasing the comparability between the hepatitis cohort and the control population [15,16]. To increase the accuracy of the results, we excluded those patients who had been diagnosed with NHL before chronic hepatitis. We assigned the comparison the
same index date as the hepatitis cohort, according to a matching identification. Furthermore, patients who received NHL diagnoses before the index date were also excluded to reduce research bias.

A total of 324,942 participants were included from 2002 to 2013, of whom 54,157 were patients with HBV or HCV, and 270,785 were patients from the general population. The screening process for the selection of research participants is shown in Figure 1.

Figure 1. Screening process for the study subjects.

2.3. Study Design

The study design was a retrospective cohort study to examine the risk of NHL in patients with HBV or HCV. The date of diagnosis of chronic hepatitis was defined as the observation start date for participants in the study group, and after matching, the same date was assigned as the observation start date for corresponding members of the control group. All participants were tracked from the observation start date until death, or the participant being diagnosed with NHL, or the end date of the study. The definition of NHL in the study was based on ICD-9-CM diagnostic code 202.8 and ICD-10-CM diagnostic codes C85.8 and C85.9. The control variables in this study were the patient’s sex, age, and related
comorbid conditions. The comorbid conditions included diabetes mellitus (ICD-9-CM: 250), hypertension (ICD-9-CM: 401–405), dyslipidemia (ICD-9-CM: 272), kidney disease (ICD-9-CM: 580–588), rheumatoid arthritis (RA) (ICD-9-CM: 714), lupus erythematosus (lupus erythematosus [LSE]) (ICD-9-CM: 710), psoriasis (ICD-9-CM: 696), human immunodeficiency virus (HIV) (ICD-9-CM: 042–044), and organ transplant (NHI surgery order codes: 68035, 68037, 68047, 75020, 76020, 75418, 85213).

2.4. Statistical Analysis

All analyses in the study were performed using SAS version 9.4, and statistical significance was defined as p-values < 0.05. Descriptive statistics were used to analyze the numbers and percentages of patient characteristics (sex, age, and health status) and other variables; chi-squared analysis was performed to compare the differences in various variables. The Cox proportional hazards model was used to determine the relationship between the occurrence of NHL for patients with HBV or HCV by controlling the relevant variables.

3. Results

3.1. The Baseline Characteristic Distribution of Study Subjects after Matching

This study examined the occurrence of NHL in patients newly diagnosed with hepatitis between 2002 and 2013. After excluding patients who had previously been diagnosed with NHL, a total of 324,942 participants were included, 54,157 of whom were patients with hepatitis and 270,785 were patients from the general population. Table 1 lists the distribution of the variables of the study participants. Patients were matched by sex and age, and chi-squared tests were performed to determine any differences between the patients with hepatitis and paired patients from the general population. No statistically significant difference (p > 0.05) was observed in the matching variables, including gender and age.

| Variables          | Control Group Patients without Hepatitis | Case Group Patients with Hepatitis | Total | p-Value |
|--------------------|-----------------------------------------|-----------------------------------|-------|---------|
|                    | n (%)                                   | n (%)                             | n (%) |         |
| Total              | 270,785 100                              | 54,157 100                        | 324,942 100 | 1.000   |
| Gender 1           |                                        |                                    |       |         |
| Female             | 114,960 42.45                           | 22,992 42.45                      | 137,952 42.45 | <0.001  |
| Male               | 155,825 57.55                           | 31,165 57.55                      | 186,990 57.55 |         |
| Age (years) 1      | 48.59 ± 15.39                           | 48.78 ± 14.28                     | 48.62 ± 15.21 | <0.001  |
| 20–44              | 49,060 18.12                            | 9812 18.12                        | 58,872 18.12 |         |
| 45–54              | 94,555 34.92                            | 18,911 34.92                      | 113,466 34.92 |         |
| 55–64              | 85,985 31.75                            | 17,197 31.75                      | 103,182 31.75 |         |
| ≥65                | 41,185 15.21                            | 8237 15.21                        | 49,422 15.21 |         |
| DM 2               |                                        |                                    |       | <0.001  |
| No                 | 223,161 82.41                           | 40,342 74.49                      | 263,503 81.09 |         |
| Yes                | 47,624 17.59                            | 13,815 25.51                      | 61,439 18.91 |         |
| HTN 2              |                                        |                                    |       | <0.001  |
| No                 | 178,351 65.86                           | 32,619 60.23                      | 210,970 64.93 |         |
| Yes                | 92,434 34.14                            | 32,619 39.77                      | 113,972 35.07 |         |
| HPL 2              |                                        |                                    |       | <0.001  |
| No                 | 199,223 73.57                           | 35,406 65.38                      | 234,629 72.21 |         |
| Yes                | 71,562 26.43                            | 35,406 34.62                      | 90,313 27.79 |         |
| CKD 2              |                                        |                                    |       | <0.001  |
| No                 | 251,014 92.70                           | 47,747 88.16                      | 298,761 91.94 |         |
| Yes                | 19,771 7.30                             | 11,840 11.84                      | 31,611 8.06  |         |
| RA 2               |                                        |                                    |       | <0.001  |
| No                 | 266,645 98.47                           | 52,658 97.23                      | 319,303 98.26 |         |
| Yes                | 4140 1.53                               | 1499 2.77                        | 5639 1.74    |         |
Table 1. Cont.

| Variables                        | Control Group | Case Group | Total | p-Value |
|----------------------------------|---------------|------------|-------|---------|
|                                  | Patients without Hepatitis | Patients with Hepatitis |       |         |
|                                  | n  | %  | n  | %   | n  | %   |
| SLE 2                            |     |     |     |     |     |     |
| No                               | 265,912 | 98.20 | 52,396 | 96.75 | 318,308 | 97.96 |
| Yes                              | 4873  | 1.8  | 1761 | 3.25 | 6634  | 2.04 |
| Psoriasis                        |     |     |     |     |     |     |
| No                               | 267,992 | 98.97 | 53,389 | 98.58 | 321,381 | 98.90 |
| Yes                              | 2793  | 1.03 | 768  | 1.42 | 3561  | 1.10 |
| HIV 2                            |     |     |     |     |     |     |
| No                               | 270,562 | 99.92 | 53,774 | 99.29 | 324,336 | 99.81 |
| Yes                              | 223  | 0.08 | 383  | 0.71 | 606  | 0.19 |
| Organ transplant                 |     |     |     |     |     |     |
| No                               | 270,594 | 99.93 | 53,903 | 99.53 | 324,497 | 99.86 |
| Yes                              | 191  | 0.07 | 254  | 0.47 | 445  | 0.14 |

1 Variables for propensity score matching. 2 Abbreviations: DM, diabetes mellitus; HTN, hypertension; HPL, hyperlipidemia; CKD, chronic kidney disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus. 3 Used chi-squared test to examine the distribution of the characteristics.

3.2. The Incidence Rate of Non-Hodgkin Lymphoma

Table 2 presents the bivariate analysis for each variable and the associated occurrence of NHL. Among all patients with hepatitis, the HBV group comprised 37,656 patients (69.53%), the HCV group comprised 14,365 patients (26.52%), and 2136 patients were diagnosed as having both HBV and HCV. A total of 419 patients from this study developed NHL, and the overall incidence rate of NHL was 0.13%. The incidence rate of NHL in patients with hepatitis was 0.25%, which was significantly higher than the incidence rate of NHL in patients from the general population, which was 0.10%. For the variable “age”, older patients exhibited a higher incidence of NHL. The incidence rate of NHL in patients ≥ 65 years was 0.28%, which was significantly higher than that in patients aged 20 to 44 (0.07%) and 45 to 54 (0.07%). For patients with comorbidities, the highest incidence of NHL was 1.35%, which was for patients who had received allografts. For patients with diabetes and hypertension, the respective incidence rates of NHL were 0.17% and 0.16%; for patients with rheumatoid arthritis, the incidence rate of NHL was 0.32%; the incidence rate of NHL in patients with lupus erythematosus was 0.33%; the incidence rate of NHL in patients with psoriasis was 0.33%; and the incidence rate of NHL in patients with human immunodeficiency virus was 0.66%. All of the above differences were statistically significant (p < 0.001).

Table 2. Covariates associated with non-Hodgkin lymphoma with univariate analysis.

| Variables                        | Non-Hodgkin Lymphoma | Total | p-Value |
|----------------------------------|----------------------|-------|---------|
|                                  | No | %  | Yes | %  |       |         |
|                                  | n  | %  | n  | %   | n   | %   |
| Total                            | 324,523 | 99.87 | 419 | 0.13 | 324,942 | 100 |
| Hepatitis                        |     |     |     |     |     |     |
| No                               | 270,503 | 99.90 | 282 | 0.10 | 270,785 | 83.33 |
| Yes                              | 54,020 | 99.75 | 137 | 0.25 | 54,157 | 16.67 |
| Hepatitis types                  |     |     |     |     |     |     |
| Hepatitis B                      | 37,573 | 99.78 | 83  | 0.22 | 37,656 | 11.59 |
| Hepatitis C                      | 14,315 | 99.65 | 50  | 0.35 | 14,365 | 4.42 |
| Both                             | 2132  | 99.81 | 4   | 0.19 | 2136  | 0.66 |
### Table 2. Cont.

| Variables | Non-Hodgkin Lymphoma | Total | p-Value 2 |
|-----------|----------------------|-------|-----------|
|           | n  | %  | n  | %  | n  | %  |       |
| Gender    |    |    |    |    |    |    |       |
| Female    | 137,766 | 99.87 | 186 | 0.13 | 137,952 | 42.45 | 0.422 |
| Male      | 186,757 | 99.88 | 233 | 0.12 | 186,990 | 57.55 |       |
| Age (year) |    |    |    |    |    |    | <0.001 |
| 20–44     | 58,833 | 99.93 | 39 | 0.07 | 58,872 | 18.12 |       |
| 45–54     | 113,386 | 99.93 | 80 | 0.07 | 113,466 | 34.92 |       |
| 55–64     | 103,021 | 99.84 | 161 | 0.16 | 103,182 | 31.75 |       |
| ≥65       | 49,283 | 99.72 | 139 | 0.28 | 49,422 | 15.21 |       |
| DM 1      |    |    |    |    |    |    | 0.003  |
| No        | 263,187 | 99.88 | 316 | 0.12 | 263,503 | 81.09 |       |
| Yes       | 61,336 | 99.83 | 103 | 0.17 | 61,439 | 18.91 |       |
| HTN 1     |    |    |    |    |    |    | <0.001 |
| No        | 210,749 | 99.9  | 221 | 0.1  | 210,970 | 64.93 |       |
| Yes       | 113,774 | 99.83 | 198 | 0.17 | 113,972 | 35.07 |       |
| HPL 1     |    |    |    |    |    |    | 0.960  |
| No        | 234,326 | 99.87 | 303 | 0.13 | 234,629 | 72.21 |       |
| Yes       | 90,197 | 99.87 | 116 | 0.13 | 90,313 | 27.79 |       |
| CKD 1     |    |    |    |    |    |    | 0.193  |
| No        | 298,383 | 99.87 | 378 | 0.13 | 298,761 | 91.94 |       |
| Yes       | 26,140 | 99.84 | 41 | 0.16 | 26,181 | 8.06  |       |
| RA 1      |    |    |    |    |    |    | <0.001 |
| No        | 318,902 | 99.87 | 401 | 0.13 | 319,303 | 98.26 |       |
| Yes       | 5621 | 99.68 | 18 | 0.32 | 5639 | 1.74  |       |
| SLE 1     |    |    |    |    |    |    | <0.001 |
| No        | 317,911 | 99.88 | 397 | 0.12 | 318,308 | 97.96 |       |
| Yes       | 6612 | 99.67 | 22 | 0.33 | 6634 | 2.04  |       |
| Psoriasis |    |    |    |    |    |    | 0.110  |
| No        | 320,970 | 99.87 | 411 | 0.13 | 321,381 | 98.90 |       |
| Yes       | 3533 | 99.78 | 8 | 0.22 | 3561 | 1.10  |       |
| HIV 1     |    |    |    |    |    |    | <0.001 |
| No        | 323,921 | 99.87 | 415 | 0.13 | 324,336 | 99.81 |       |
| Yes       | 602 | 99.34 | 4 | 0.66 | 606 | 0.19  |       |
| Organ transplant |    |    |    |    |    |    | <0.001 |
| No        | 324,084 | 99.87 | 413 | 0.13 | 324,497 | 99.86 |       |
| Yes       | 439 | 98.65 | 6 | 1.35 | 445 | 0.14  |       |

1 Abbreviations: DM, diabetes mellitus; HTN, hypertension; HPL, hyperlipidemia; CKD, chronic kidney disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus. 2 Used chi-squared test to examine the characteristics distribution.

### 3.3. Risk of Non-Hodgkin Lymphoma in Hepatitis Patients

Table 3 displays the risk analysis of NHL in patients with hepatitis. After controlling other related variables, the relative risk (hazard ratio [HR]) of patients with hepatitis developing NHL was 2.37 times higher (95% CI, 1.93–2.91). The relative risk of developing NHL increased with increasing age. For example, compared with patients aged 20 to 44, the relative risk of developing NHL for patients 55 to 64 years old was 3.30 times higher (95% CI, 2.29–4.75), and the relative risk for developing NHL in patients ≥65 years old was 6.28 times higher (95% CI, 4.26–9.26). In the comorbidity analysis, patients with lupus erythematosus, human immunodeficiency virus, and organ transplant exhibited higher relative risks of developing NHL (HR, 1.82; 95% CI, 1.17–2.83; HR, 7.09; 95% CI, 2.62–19.22; HR, 6.59; 95% CI, 2.92–14.88, respectively). Patients with rheumatoid arthritis and psoriasis had a higher relative risk of developing NHL, but no statistically significant difference was observed (HR, 1.58; 95% CI, 0.97–2.57; HR, 1.43; 95% CI, 0.71–2.88); patients with
dyslipidemia and kidney disease had lower risk of developing NHL (HR, 0.69; 95% CI, 0.54–0.87; HR, 0.64; 95% CI, 0.46–0.90); patients with diabetes and hypertension also had a lower risk of developing NHL, but no statistically significant difference was observed (HR, 0.98; 95% CI, 0.77–1.26; HR, 0.94; 95% CI, 0.75–1.26). Analysis of the patients with hepatitis entailed further division of the patients into groups of those with HBV and HCV (model 2 in Table 3). After controlling other related variables, compared with general patients, the relative risk of in patients with HBV developing NHL was 2.49 times higher (95% CI, 1.94–3.19), and for patients with HCV, the relative risk was 2.36 times higher (95% CI, 1.73–3.22). For patients with HBV and HCV, a higher relative risk of NHL was observed, but this was not statistically significant (HR, 1.20; 95% CI, 0.45–3.23).

| Variables          | Model 1 |          | Model 2 |          |
|--------------------|---------|----------|---------|----------|
|                    | HR 1    | 95% CI   | p-Value | HR 1    | 95% CI   | p-Value |
| Hepatitis          |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 2.37    | 1.93–2.92| <0.001  | -       | -        |         |
| Hepatitis B        | -       | -        |         | 2.49    | 1.94–3.19| <0.001  |
| Hepatitis C        | -       | -        |         | 2.36    | 1.73–3.22| <0.001  |
| Both               | -       | 1.20     | 0.45–3.23| 0.720   |
| Gender             |         |          |         |         |          |         |
| Female (ref.)      | 1       | 0.87–1.29| 0.567   | 1       | 0.87–1.29| 0.574   |
| Male               | 1.06    | 1.06     |         | 0.98    | 0.77–1.26| 0.893   |
| Age (year)         |         |          |         |         |          |         |
| 20–44 (ref.)       | 1       | 1        |         | 1       | 1        |         |
| 45–54              | 1.29    | 0.87–1.89| 0.203   | 1.29    | 0.88–1.90| 0.194   |
| 55–64              | 3.30    | 2.29–4.75| <0.001  | 3.33    | 2.31–4.81| <0.001  |
| ≥65                | 6.28    | 4.26–9.26| <0.001  | 6.37    | 4.31–9.42| <0.001  |
| DM                 |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 0.98    | 0.77–1.26| 0.893   | 0.94    | 0.75–1.18| 0.584   |
| HLN                 |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 0.69    | 0.54–0.87| 0.002   | 0.68    | 0.54–0.86| 0.002   |
| CKD                 |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 0.64    | 0.46–0.90| 0.010   | 0.66    | 0.46–0.90| 0.011   |
| RA                  |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 1.58    | 0.97–2.57| 0.066   | 1.59    | 0.98–2.58| 0.063   |
| SLE                 |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 1.82    | 1.17–2.83| 0.008   | 1.82    | 1.17–2.83| 0.008   |
| Psoriasis           |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 1.43    | 0.71–2.88| 0.317   | 1.43    | 0.71–2.89| 0.316   |
| HIV                 |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 7.09    | 2.62–19.22| <0.001 | 7.39    | 2.72–20.10| <0.001 |
| Organ transplant    |         |          |         |         |          |         |
| No (ref.)          | 1       | 1        |         | 1       | 1        |         |
| Yes                | 6.59    | 2.92–14.88| <0.001 | 6.67    | 2.96–15.05| <0.001 |

**Table 3.** Risk of non-Hodgkin lymphoma in hepatitis patients with multivariable analysis of Cox regression analysis.

4. Discussion

In this study, the incidence rate of NHL in patients with HBV was 0.22%, and in patients with HCV, the incidence rate of NHL was 0.35%. These comparisons indicate that patients with HBV or HCV have a higher incidence of NHL (OR, 2.37; 95% CI, 1.93–2.91).
This study was a retrospective cohort follow-up study that used secondary database analysis to screen patients with HBV and HCV through disease diagnosis codes and prescribed medications, and used the PSM method to obtain a control group. In the investigation of the two hepatitis conditions and the occurrence of NHL, we determined that patients with HBV and patients with HCV both had a higher risk of developing NHL and that the higher relative risk between the groups occurred in patients with HBV.

The mechanism of HBV infection in NHL is still unclear. One hypothesis is that HBV can directly infect lymphocytes and be incorporated into the host genome, leading to the overexpression of oncogenes or downregulation of tumor suppressor genes. Additionally, viral hepatitis B replication and viral antigens may also induce the expression and release of hematopoietic tumor growth factors, leading to the proliferation of cloned lymphocytes [17]. HCV may indirectly affect B-cells and regulate oncogenic transformation through intracellular viral proteins. Such indirect effects include chronic antigen stimulation by HCV and the existence of potential antigen-selection-driven processes in the development of NHL in patients with HCV [18].

Further evidence of the indirect effect of HCV on NHL is the upregulation of the tumor necrosis factor family during chronic HCV infection [19]. The HCV genome produces structural (nucleocapsid, E1, E2) and nonstructural proteins that may result in the E2 protein of HCV causing chronic antigen-driven polyclonal B-cell proliferation [20]. Although the existence of HCV lymphocytes is disputed, CD81 on B-cells is a branded HCV internalization receptor, and the costimulatory receptor B7.2 (CD86) mediates HCV to memory B-cells [21]. HCV produces nitric oxide synthase and reactive-oxygen-induced DNA damage [22] and upregulates host B-cell receptor signaling in patients with HCV [23]. However, the underlying carcinogenic mechanisms are still unclear.

Taborelli et al. (2016) conducted a case–control study in Italy and reported that 3.7% of patients with NHL also developed HBV, which was a rate significantly higher than the 1.7% observed in the control group [24]. However, studies have produced inconsistent results, which may be due to differences in research designs, ethnicities, geography, and environments [12,13,25]. To increase the accuracy of the results in the present study, the selected participants with hepatitis had all been prescribed antiviral medications for chronic hepatitis; this confirmed the positive correlation between HBV infection and the development of NHL in the Taiwanese population.

A meta-analysis comprehensively assessed the association between HBV and NHL. The pooled estimates of 58 studies included the risk of NHL in patients with HBV, which significantly increased the overall odds ratio (sOR, 2.50; 95% CI, 2.20–2.83) regardless of study design (case–control study: sOR, 2.47; 95% CI, 2.16–2.82; cohort study: sOR, 2.64; 95% CI, 1.78–3.91) [26]. Previous studies examining the link between HBV infection and NHL have yielded conflicting results. Studies from Europe, Japan, China, and South Korea have indicated HR ranges from 1.74 to 4.87 [11,27,28]. However, other studies have found no significant association between HBV infection and NHL [13,29,30]. Studies in Taiwan have also corroborated the association between hepatitis infection and NHL [31,32]. Kleinestern et al. published a case–control study in 2016 to examine the relationship between HBV and the occurrence of NHL. The study included healthy participants as the control group and reported that the relative risk of developing NHL in patients with HBV was 2.39 times higher (95% CI, 1.13–5.06). Although patients with HBsAg antibodies were also determined to have a low relative risk of developing NHL (OR, 0.68; 95% CI, 0.51–0.92), the risk was not statistically significant for natural antibody responses (OR, 0.76; 95% CI, 0.56–1.04) [33]. This showed a link between persistent HBV infection and B-NHL. Another study reported that acquired immunity from natural infections also increases the risk of B-NHL. Therefore, regardless of whether HBsAg is cleared, the risk of B-NHL is likely to be higher in patients with hepatitis [34].

Studies and meta-analyses have identified an association between HCV infection and the development of B-NHL. The estimated risk of lymphoma development is moderate, with an average odds ratio between two and three. However, this estimate varies widely.
and depends not only on the type of histology considered, but also on the geographic locations and ethnicities of the populations included in the trials [35].

A nested large-population case–control study in Korea investigated the suspected relationship between hepatitis and NHL. The results reported that the incidence of HBV and HCV in the NHL group (3.3% and 1.3%, respectively) was higher than that in the control group (0.9% and 0.3%, respectively; \( p < 0.001 \)) [11]. In a previous study in Taiwan, chronic HCV infection was temporally associated with a twofold increase in the risk of lymphoid tumors from 2001 to 2005, especially the risk of NHL. Although 8.2% of participants received interferon-based treatment, the statistical results of the study were not significant due to the small number of participants [14].

The relative risk of developing NHL increases with increasing age. For example, compared with patients aged 20 to 44, the relative risk of developing NHL for patients aged 55 to 64 years old was 3.30 times higher (95% CI, 2.29–4.75), and the relative risk for developing NHL in patients \( \geq 65 \) years old was 6.28 times higher (95% CI, 4.26–9.26). Among older adults, a registry-based case–control study for HCV infection and the risk of cancer indicated a positive association with diffuse large B-cell lymphoma (aOR, 1.57; 95% CI, 1.34–1.84) [36]. One study reported the adjusted ORs of HBV in patients with NHL who were \(<55\) years compared with those who were \( \geq 55\) years—2.28 (\( p = 0.038\)) and 3.48 (\( p < 0.001\)), respectively—and the adjusted ORs for HCV in patients with NHL who were \(<55\) years compared with those who were \( \geq 55\) years were 2.58 (\( p = 0.114\)) and 3.24 (\( p = 0.044\)), respectively [11]. The results of the present study indicate that patients with lupus erythematosus, human immunodeficiency virus, and organ transplant were all at a higher risk of developing NHL. This confirms the correlation between immunodeficiency and NHL. The cause of NHL may be related to viral infection, bacterial infection, or weakened immune function [6]. Early research also demonstrated that several risk factors were associated with lymphoma, including immunosuppression, several autoimmune disorders (rheumatoid arthritis, celiac disease, systemic lupus erythematosus, and Sjögren’s syndrome), and certain infectious agents for NHL [37].

It has been indicated that serum HBV DNA and HCV RNA amounts reveal complex virological profiles which may be present in HBV and HCV co-infected patients [38]. In our study, patients co-infected with both HBV and HCV had a lower HR compared with HBV- and HCV-infected patients that may be due to having too few participants with NHL (n = 4). However, 95% CI is not statistically significant. The lower risk of NHL in the co-infected patients may be different depending on the geographical region and the study population. Large-scale prospective studies are warranted to assess the association between patients co-infected with both HBV and HCV and the subsequent development of NHL.

The International Agency for Research on Cancer assessed and confirmed the carcinogenicity of seven viral agents to humans, including HCV. HBV and HCV are indirect carcinogens, producing their effects through chronic inflammation [39]. A previous case–control study and meta-analysis demonstrated that chronic HBV infection was positively associated with NHL. However, acquired immunity (HBsAg−, anti-HBs+, anti-HBc+) by natural infection also increased the risk of developing B-NHL (adjusted OR, 2.25; 95% CI, 1.96–2.57) [34]. Vaccination against HBV and HCV may reduce the risk of hepatitis-related liver disease and NHL [11]. In addition, recent studies have indicated that anti-HBV and anti-HCV drugs for the treatment may contribute to the treatment of NHL [40–42].

Future experimental studies to further clarify the causal relationships between NHL and HBV and HCV infection may support the clinical necessity of such therapies. Although anti-HBV and anti-HCV agents have an impact on cancer risk, this study used HBV and HCV disease diagnostic codes in conjunction with medication usage to determine to a strict correlation between viral hepatitis medications and the risk of cancer in the participants. However, the main purpose of this study was to examine the risk of cancer in patients with HBV and HCV. Therefore, no further analysis of medications was necessary. We
recommend that future studies further analyze and study the effects of various viral hepatitis medications on NHL.

The results of this study confirmed that patients with HBV or HCV have a higher risk of developing NHL, which is consistent with the results of previous studies. Compared with related studies, the present study has several strengths. First, we used a national sampling database for analysis. The MOHW database comprises a stratified random sample of two million individuals with information on sex, age, and location. The database is nationally representative and also avoids bias in the selection of research participants. Previous investigations concerning the hepatitis virus and NHL have mostly been case-control studies. This study, however, adopted the design of a generational follow-up study, which is a comparably more rigorous design. Finally, in addition to controlling risk factors such as sex, age, and the related comorbidities of the participants, subjects who had previously been diagnosed as having NHL were excluded before study participants were selected. PSM for the study and control groups further reduced sample selectivity bias and confirmed the representativeness and reliability of the results of this study.

This study also has limitations. The study was limited to the information provided in the LHID; information regarding patient living environments, tobacco and alcohol use, dietary habits, stress levels, and family disease history, laboratory parameters (e.g., HBV DNA, HCV RNA, and genotypes), among others, is unavailable in the database but may affect NHL factors. The LHID was also missing data regarding the active chronic hepatitis, cirrhosis, and NHL histology (such as B- or T-origin, indolent or aggressive, and the World Health Organization [WHO] classification subtypes). This study reduced confounding via adjusting comorbidity disease, but clinical situations (e.g., RA, SLE, and HIV infection) could be associated with lymphoma development. Future studies are warranted to evaluate the effects of hepatitis virus infections on the occurrence of NHL, or NHL histology after excluding related autoimmune diseases. Additionally, future research should be supplemented by clinical empirical medicine and by linking other databases or questionnaires to more rigorously and thoroughly analyze correlations or causality. Hepatitis prevention and treatment is a public health issue that Taiwan has prioritized, and cancer prevention has always been a priority medical issue in Taiwan. The results of this study may provide relevant units and clinical medical personnel guidance on hepatitis prevention and treatment strategies and serve as a reference for the future development of cancer prevention and treatment strategies for patients with hepatitis.

5. Conclusions

HBV and HCV infections play a significant role in the development of NHL. In patients with HBV and patients with HCV, both receiving antiviral agents, chronic coinfection with HBV and HCV was associated with an increased risk of NHL in a Taiwanese population. In addition, the relative risk of developing NHL increases with increasing age and some comorbidities (such as HPL, CKD, SLE, HIV, and organ transplant).

Author Contributions: Conceptualization, Y.-R.L., K.-H.H. and C.-Y.L.; Formal analysis, C.-H.L. and T.-H.T.; Funding acquisition, Y.-R.L. and K.-H.H.; Investigation, K.-H.H. and C.-Y.L.; Methodology, Y.-R.L., Y.-L.C., C.-H.L. and C.-Y.L.; Validation, Y.-L.C., K.-H.H. and C.-Y.L.; Writing—original draft preparation, Y.-R.L. and Y.-L.C.; Writing—review and editing, K.-H.H. and C.-Y.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Chung Shan Medical University Hospital, Taiwan (CSH-2020-C-005), China Medical University Taiwan (CMU110-MF-113), and the Ministry of Science and Technology Taiwan (MOST 107-2410-H-039-007).

Institutional Review Board Statement: Data were obtained from the National Health Insurance Administration, Ministry of Health and Welfare Taiwan, and were provided with scrambled random identification numbers for insured patients to protect the privacy of beneficiaries. This study protocol was approved from ethical review by the Institutional Review Board of China Medical University Hospital, Taiwan (Approval date: 20 December 2019, No: CMU107-REC2-004).
Informed Consent Statement: The database was anonymous; therefore, the requirement for informed consent was waived.

Data Availability Statement: The National Health Insurance Database used to support the findings of this study was provided by the Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW) under license and so cannot be made freely available. Requests for access to these data should be made to HWDC (https://dep.mohw.gov.tw/dos/cp-5119-59201-113.html, accessed on 11 November 2021).

Acknowledgments: Our special thanks to Chung Shan Medical University, Taiwan, Chung Shan Medical University Hospital, Taiwan, China Medical University, Taiwan, and the Health Data Science Center, China Medical University Hospital, for providing administrative, technical, and funding support that has contributed to the completion of this study. This study is based, in part, on data released by the Health and Welfare Data Science Center, Ministry of Health and Welfare. The interpretation and conclusions contained herein do not represent those of the Ministry of Health and Welfare.

Conflicts of Interest: The authors declare no conflict of interest.

References
1. Chen, C.H.; Yang, P.M.; Huang, G.T.; Lee, H.S.; Sung, J.L.; Sheu, J.C. Estimation of seroprevalence of hepatitis B virus and hepatitis C virus in Taiwan from a large-scale survey of free hepatitis screening participants. J. Formos. Med. Assoc. 2007, 106, 148–155. [CrossRef]  
2. Yu, M.L.; Yeh, M.L.; Tsai, P.C.; Huang, C.I.; Huang, J.F.; Huang, C.F.; Hsieh, M.H.; Liang, P.C.; Lin, Y.H.; Hsieh, M.Y.; et al. Huge gap between clinical efficacy and community effectiveness in the treatment of chronic hepatitis C: A nationwide survey in Taiwan. Medicine 2015, 94, e690. [CrossRef] [PubMed]  
3. Liu, C.J.; Chen, P.J. Elimination of Hepatitis B in Highly Endemic Settings: Lessons Learned in Taiwan and Challenges Ahead. Viruses 2020, 12, 815. [CrossRef] [PubMed]  
4. Miranda-Filho, A.; Pineros, M.; Znaor, A.; Marcos-Gragera, R.; Steliarova-Foucher, E.; Bray, F. Global patterns and trends in the incidence of non-Hodgkin lymphoma. Cancer Causes Control 2019, 30, 489–499. [CrossRef] [PubMed]  
5. Shankland, K.R.; Armitage, J.O.; Hancock, B.W. Non-Hodgkin lymphoma. Lancet 2012, 380, 848–857. [CrossRef]  
6. Zhang, Y.; Dai, Y.; Zheng, T.; Ma, S. Risk Factors of Non-Hodgkin Lymphoma. Expert Opin. Med. Diag. 2011, 5, 539–550. [CrossRef] [PubMed]  
7. Kim, J.H.; Bang, Y.J.; Park, B.J.; Yoo, T.; Kim, C.W.; Kim, T.Y.; Heo, D.S.; Lee, H.S.; Kim, N.K. Hepatitis B virus infection and B-cell non-Hodgkin’s lymphoma in a hepatitis B endemic area: A case-control study. Jpn J. Cancer Res. 2002, 93, 471–477. [CrossRef] [PubMed]  
8. Ulcickas Yood, M.; Quesenberry, C.P., Jr., Guo, D.; Caldwell, C.; Wells, K.; Shan, J.; Sanders, L.; Skovron, M.L.; Iloeje, U.; Manos, M.M. Incidence of non-Hodgkin’s lymphoma among individuals with chronic hepatitis B virus infection. Hepatology 2007, 46, 107–112. [CrossRef]  
9. Park, S.C.; Jeong, S.H.; Kim, J.; Han, C.J.; Kim, Y.C.; Choi, K.S.; Cho, J.H.; Lee, M.; Jung, H.H.; Ki, S.S.; et al. High prevalence of hepatitis B virus infection in patients with B-cell non-Hodgkin’s lymphoma in Korea. J. Med. Virol. 2008, 80, 960–966. [CrossRef]  
10. Wang, C.; Xia, B.; Ning, Q.; Zhao, H.; Yang, H.; Zhao, Z.; Wang, X.; Wang, Y.; Yu, Y.; Zhang, Y. High prevalence of hepatitis B virus infection in patients with aggressive B cell non-Hodgkin’s lymphoma in China. Ann. Hematol. 2018, 97, 453–457. [CrossRef]  
11. Kim, M.; Lee, Y.K.; Park, B.; Oh, D.J.; Choi, H.G. Hepatitis virus B and C infections are associated with an increased risk of non-Hodgkin lymphoma: A nested case-control study using a national sample cohort. J. Med. Virol. 2020, 92, 1214–1220. [CrossRef] [PubMed]  
12. Chen, M.H.; Hsiao, L.T.; Chiou, T.J.; Liu, J.H.; Gau, J.P.; Teng, H.W.; Wang, W.S.; Chao, T.C.; Yen, C.C.; Chen, P.M. High prevalence of occult hepatitis B virus infection in patients with B cell non-Hodgkin’s lymphoma. Ann. Hematol. 2008, 87, 475–480. [CrossRef] [PubMed]  
13. Anderson, L.A.; Pfeiffer, R.; Warren, J.L.; Landgren, O.; Gadalla, S.; Berndt, S.I.; Ricker, W.; Parsons, R.; Wheeler, W.; Engels, E.A. Hematopoietic malignancies associated with viral and alcoholic hepatitis. Cancer Epidemiol. Biomark. Prev. 2008, 17, 3069–3075. [CrossRef] [PubMed]  
14. Su, T.H.; Liu, C.J.; Tseng, T.C.; Chou, S.W.; Liu, C.H.; Yang, H.C.; Wu, S.J.; Chen, P.J.; Chen, D.S.; Chen, C.L.; et al. Hepatitis C viral infection increases the risk of lymphoid-neoplasms: A population-based cohort study. Hepatology 2016, 63, 721–730. [CrossRef] [PubMed]  
15. Ury, H.K. Efficiency of case-control studies with multiple controls per case: continuous or dichotomous data. Biometrics 1975, 31, 643–649. [CrossRef] [PubMed]  
16. Austin P., C. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. Am. J. Epidemiol. 2010, 172, 1092–1097. [CrossRef]
17. Marcucci, F.; Spada, E.; Mele, A.; Caserta, C.A.; Pulsoni, A. The association of hepatitis B virus infection with B-cell non-Hodgkin lymphoma—A review. *Am. J. Blood Res.* 2012, 2, 18–28.

18. Couronne, L.; Bachy, E.; Roulland, S.; Nadel, B.; Davi, F.; Armand, M.; Canioni, D.; Michot, J.M.; Visco, C.; Arcaini, L.; et al. From hepatitis C virus infection to B-cell lymphoma. *Ann. Oncol.* 2018, 29, 92–100. [CrossRef]

19. Sene, D.; Limal, N.; Ghillani-Dalbin, P.; Saadoun, D.; Piette, J.C.; Cacoub, P. Hepatitis C virus-associated B-cell proliferation—the role of serum B lymphocyte stimulator (BlyS)/BAFF. *Rheumatology (Oxford)* 2007, 46, 65–69. [CrossRef]

20. Datta, S.; Chatterjee, S.; Policegoudra, R.S.; Gogoi, H.K.; Singh, L. Hepatitis viruses and non-Hodgkin’s lymphoma: A review. *World J. Virol.* 2012, 1, 162–173. [CrossRef]

21. Chen, C.L.; Huang, J.Y.; Tahara, S.M.; Zhou, L.; Kondo, Y.; Schechter, J.; Su, L.; Lai, M.M.; Wakita, T.; et al. Hepatitis C virus has a genetically determined lymphotropism through co-receptor B7.2. *Nat. Commun.* 2017, 8, 13882. [CrossRef]

22. Kuniyoshi, M.; Nakamura, M.; Sakai, H.; Enjoji, M.; Kinukawa, N.; Kotoh, K.; Fukutomi, M.; Yokota, M.; Nishi, H.; Iwamoto, H.; et al. Prevalence of hepatitis B or C virus infections in patients with non-Hodgkin’s lymphoma. *J. Gastroenterol. Hepatol.* 2001, 16, 215–219. [CrossRef] [PubMed]

23. Lim, S.T.; Fei, G.; Quek, R.; Lim, L.C.; Lee, L.H.; Yap, S.P.; Loong, S.; Tao, M. The relationship of hepatitis B virus infection and non-Hodgkin’s lymphoma and its outcome on clinical characteristics and prognosis. *Eur. J. Haematol.* 2007, 79, 132–137. [CrossRef] [PubMed]

24. Taborelli, M.; Polesel, J.; Montella, M.; Libera, M.; Tedeschi, R.; Battiston, M.; Spina, M.; Di Raimondo, F.; Pinto, A.; Crispo, A.; et al. Hepatitis B and C viruses and risk of non-Hodgkin lymphoma: A case-control study in Italy. *Infect. Agent. Cancer* 2016, 11, 27. [CrossRef] [PubMed]

25. Wang, F.; Xu, R.H.; Han, B.; Shi, Y.X.; Luo, H.Y.; Jiang, W.Q.; Lin, T.Y.; Huang, H.Q.; Xia, Z.J.; Guan, Z.Z. High incidence of hepatitis B virus infection in B-cell subtype non-Hodgkin lymphoma compared with other cancers. *Cancer* 2007, 109, 1360–1364. [CrossRef] [PubMed]

26. Li, M.; Gan, Y.; Fan, C.; Yuan, H.; Zhang, X.; Shen, Y.; Wang, Q.; Meng, Z.; Xu, D.; Tu, H. Hepatitis B virus and risk of non-Hodgkin lymphoma: An updated meta-analysis of 58 studies. *J. Viral Hepat.* 2018, 25, 894–903. [CrossRef]

27. Wang, Q.; De Luca, A.; Smith, C.; Zangerle, R.; Sambatakou, H.; Bonnet, F.; Smit, C.; Schommers, P.; Thornton, A.; Berenguer, J.; et al. Chronic Hepatitis B and C Virus Infection and Risk for Non-Hodgkin Lymphoma in HIV-Infected Patients: A Cohort Study. *Ann. Intern. Med.* 2017, 166, 9–17. [CrossRef]

28. Abe, S.K.; Inoue, M.; Sawada, N.; Iwasaki, M.; Shimazu, T.; Yamaji, T.; Sasazuki, S.; Tanaka, Y.; Mizokami, M.; Tsugane, S.; et al. Hepatitis B and C virus infection and risk of lymphoid malignancies: A population-based cohort study (JPHC Study). *Cancer Epidemiol.* 2015, 39, 562–566. [CrossRef]

29. Franceschi, S.; Lise, M.; Trepo, C.; Berthillon, P.; Chuang, S.C.; Nieters, A.; Travis, R.C.; Vermeulen, R.; Overvad, K.; Tjonneland, A.; et al. Infection with hepatitis B and C viruses and risk of lymphoid malignancies in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Epidemiol. Biomark.* 2011, 20, 208–214. [CrossRef]

30. Andersen, E.S.; Omland, L.H.; Jepsen, P.; Krarup, H.; Christensen, P.B.; Obel, N.; Weis, N.; Study, D.C. Risk of all-type cancer, hepatocellular carcinoma, non-Hodgkin lymphoma and pancreatic cancer in patients infected with hepatitis B virus. *J. Viral. Hepat.* 2015, 22, 828–834. [CrossRef]

31. Su, T.H.; Liu, C.J.; Tseng, T.C.; Chou, S.W.; Liu, C.H.; Yang, H.C.; Wu, S.J.; Chen, P.J.; Chen, D.S.; Chen, C.L.; et al. Chronic hepatitis B is associated with an increased risk of B-cell non-Hodgkin’s lymphoma and multiple myeloma. *Aliment. Pharmacol. Ther.* 2019, 49, 589–594. [CrossRef] [PubMed]

32. Kamiza, A.B.; Su, F.H.; Wang, W.C.; Sung, F.C.; Chang, S.N.; Yeh, C.C. Chronic hepatitis infection is associated with extrahaematological cancer development: a nationwide population-based study in Taiwan. *BMC Cancer* 2016, 16, 861. [CrossRef] [PubMed]

33. Kleinstern, G.; Seir, R.A.; Perlman, R.; Abedeen, Z.; Khatib, A.; Elyan, H.; Dann, E.J.; Edel, M.; Ellis, M.; Nagler, A.; et al. Associations between B-cell non-Hodgkin lymphoma and exposure, persistence and immune response to hepatitis B. *Haematologica* 2016, 101, e303–e305. [CrossRef] [PubMed]

34. Zhou, X.; Pan, H.; Yang, P.; Ye, P.; Cao, H.; Zhou, H. Both chronic HBV infection and naturally acquired HBV immunity confer increased risks of B-cell non-Hodgkin lymphoma. *BMC Cancer* 2019, 19, 477. [CrossRef] [PubMed]

35. Fiorino, S.; Bacchi-Reggiani, L.; de Biase, D.; Fornelli, A.; Masetti, M.; Tura, A.; Grizzi, F.; Zanello, M.; Mastrangelo, L.; Lombardi, R.; et al. Possible association between hepatitis C virus and malignancies different from hepatocellular carcinoma: a systematic review. *World J. Gastroenterol.* 2015, 21, 12896–12953. [CrossRef]

36. Mahale, P.; Torres, H.A.; Kramer, J.R.; Hwang, L.Y.; Li, R.; Brown, E.L.; Engels, E.A. Hepatitis C virus infection and the risk of cancer among elderly US adults: A registry-based case-control study. *Cancer* 2017, 123, 1202–1211. [CrossRef]

37. Morton, L.M.; Slager, S.L.; Cerhan, J.R.; Wang, S.S.; Vajdic, C.M.; Skibola, C.F.; Bracci, P.M.; de Sanjose, S.; Smedby, K.E.; Chiu, B.C.; et al. Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the InterLymph Non-Hodgkin Lymphoma Subtypes Project. *J. Natl. Cancer Inst. Monogr.* 2014, 2014, 130–144. [CrossRef]

38. Caccamo, G.; Saffioti, F.; Raimondo, G. Hepatitis B virus and hepatitis C virus dual infection. *World J. Gastroenterol.* 2014, 20, 14559–14567. [CrossRef]

39. Chen, C.J.; You, S.L.; Hsu, W.L.; Yang, H.I.; Lee, M.H.; Chen, H.C.; Chen, Y.Y.; Liu, J.; Hu, H.H.; Lin, Y.J.; et al. Epidemiology of Virus Infection and Human Cancer. *Recent Results Cancer Res.* 2021, 217, 13–45. [CrossRef]
40. Picardi, M.; Della Pepa, R.; Giordano, C.; Zacheo, I.; Pugliese, N.; Mortaruolo, C.; Trastulli, F.; Giordano, A.; Lucignano, M.; Di Perna, M.; et al. Tenofovir vs lamivudine for the prevention of hepatitis B virus reactivation in advanced-stage DLBCL. *Blood* 2019, 133, 498–501. [CrossRef]

41. Picardi, M.; Giordano, C.; Pepa, R.D.; Pugliese, N.; Leone, A.; Gentile, G.; Pane, F. Correspondence in reference to the previously published Epub manuscript: “Murt Ahmet et al. Hepatitis B reactivation in hematopoietic stem cell transplanted patients: 20 years of experience of a single center from a middle endemic country. *Ann. Hematol.* 2020, 99, 2671–2677. [CrossRef]

42. Picardi, M.; Giordano, C.; Della Pepa, R.; Pugliese, N.; Leone, A.; Delle Cave, G.; Iula, R.; Pane; Gentile, G. Hepatitis B Surface Antigen Positivity Is an Independent Unfavorable Prognostic Factor in Diffuse Large B-Cell Lymphoma in the Rituximab Era. *Oncologist* 2021, 26, e1083–e1084. [CrossRef] [PubMed]