Distinct Clinical Features and Prognostic Factors in Hepatitis C Virus-Associated Non-Hodgkin’s Lymphoma: A Systematic Review and Meta-Analysis

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Primary research

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Abstract

Background: Increasing evidence suggested that hepatitis C virus (HCV) infection was associated with non-Hodgkin's lymphoma (NHL). However, no clear consensus has been reached about the clinical features and the effective treatment in HCV-associated NHL patients. We therefore performed a systematic review and meta-analysis to explore the clinical characteristics and effect of antiviral treatment or rituximab administration in NHL patients with HCV infection.

Methods: PubMed, Embase, Web of Science, and OVID database were searched for eligible studies up to Feb 28, 2021. Hazard ratio (HR) or odds ratio (OR) corresponding to 95% confidence interval (CI) were calculated to estimate outcomes. Publication biases were assessed by Egger’s test and Begg’s test. Statistical analysis was performed by software RevMan 5.4 and Stata version 15.

Results: There were 27 shortlisted articles out of a total of 13368 NHL patients included in the current meta-analysis. Our results demonstrated that NHL patients with HCV infection showed significantly shorter overall survival (OS: HR 1.89; 95% CI 1.42-2.51, P<0.0001) and progress-free survival (PFS: HR 1.58; 95% CI 1.26-1.98, P<0.0001), lower overall response rate (ORR: OR 0.58, 95% CI 0.46-0.73, P<0.0001) and higher incidence of hepatic dysfunction during chemotherapy (OR 5.96; 95% CI 2.61-13.62, P<0.0001) compared with NHL patients without HCV infection. HCV-positive NHL patients exhibited advanced disease stage, elevated level of LDH, high-intermediate and high IPI/FLIPI risk as well as higher incidence of spleen and liver involvement. Moreover, antiviral treatment could prolong survivals (OS: HR 0.38; 95% CI 0.24-0.60, P<0.0001), reduce disease progression [PFS/DFS (disease-free survival): HR 0.63; 95% CI 0.46-0.86, P<0.003] and reinforce treatment response (OR: OR 2.62; 95% CI 1.34-5.11, P<0.005) in HCV-infected NHL patients. Finally, rituximab administration was associated with a favorable OS while liver cirrhosis and low levels of albumin were inferior prognostic factors of OS for HCV-positive NHL patients.

Conclusions: The current study provided the compelling evidence about an inferior prognosis and distinct clinical characteristics in HCV-associated NHL patients. Antiviral treatment and rituximab-containing regimes were shown to be efficacious to improve clinical outcomes of NHL patients with HCV infection.

Background

Non-Hodgkin's lymphoma (NHL) is a group of lymphoid malignancies with high heterogeneity. It can be classified into B-cell, T-cell, and natural killer (NK)-cell lymphoma. Increasing evidence has implicated that pathogen infection contributed to the pathogenesis of different subtypes of lymphoma, such as Epstein-Barr virus (EBV) in Hodgkin disease or Burkitt's lymphoma, human T-cell leukemia virus type 1 in adult T cell leukemia and lymphoma, and Helicobacter pylori in gastric mucosa-associated lymphoid tissue [1–3]. According to the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms, two subtypes of NHL associated with specific viral infection, EBV-positive diffuse large B-cell lymphoma (DLBCL) and human herpesvirus type-8 (HHV-8)-positive DLBCL, have been classified as separated subtypes of DLBCL [4]. These new categories strongly suggested that NHL patients with specific infection displayed distinct clinical manifestations and prognosis.

Recently, hepatitis C virus (HCV) was found in peripheral blood mononuclear cells and lymph nodes [5, 6] and hepatitis C NS3 protein could be detected in tumor cells from patients with HCV-associated B cell-lymphoma [7], hence suggesting that HCV is also lymphotropic. On the other hand, meta-analysis provided quantitative evidence that HCV infection could lead to a 2.5-fold increased risk of developing NHL [8]. Nevertheless, the clinical characteristics and prognosis of HCV-associated lymphoma is still undefined.

Arising clinical attention to the association of HCV infection and clinical outcomes of NHL patients has been paid. However, the results were still inconsistent based on existing retrospective studies with small sample sizes [9–18]. Hosry J et al [17] found that HCV-associated DLBCL had unique clinical features and poor outcomes. However, other studies [14, 18] had shown that HCV infection was not associated with NHL patients’ survivals. In addition, increasing studies have explored the survival benefit of antiviral treatment or rituximab-containing chemotherapy in NHL patients with HCV infection yet results were also controversial [15, 19–22]. In view of the limitations of previous studies, we hereby performed a systematic review and meta-analysis aiming to evaluate the clinical features and prognostic factors in HCV-associated NHL patients. Moreover, the effect of antiviral treatment and rituximab administration on NHL patients with HCV infection was also investigated in the current study.

Methods

Identification of relevant studies

To identify all studies that explored the impact of HCV infection on the clinical outcomes of NHL patients or the effect of antiviral treatment and rituximab administration on NHL patients with HCV infection, a literature search of four electronic databases, including PubMed, OVID, Web of Science, and Embase, up to Feb 28, 2021, was conducted. The search strategy was based on combinations of the following keywords and search terms without language limitation: (“lymphoma” [MeSH] or “Lymphoma, Non-Hodgkin” [MeSH] or “Non-Hodgkin lymphoma” or “NHL”) AND (“hepatitis C” [MeSH] or “hepatitis C virus” or “HCV” or “Hep C virus” or “Hep C”). References of the retrieved studies, meeting abstracts, relevant meta-analyses and systematic reviews were also screened. Case reports, editorials and review articles were excluded. When a publication overlapped with other publication of the same trial, only the article with more details or the most recent article was retained.

Selection criteria
The studies included in the meta-analysis should satisfy all the following criteria: (1) the study population was NHL patients; (2) the study consisted of two groups: NHL patients with and without HCV infection, or HCV infected NHL patients receiving and not receiving antiviral/rituximab treatment; (3) clinical features and survivals between two groups of patients were compared. Exclusion criteria were: (1) patients co-infected with human immunodeficiency virus (HIV); (2) patient with post-transplant lymphoproliferative disorder; (3) patient number less than or equal to ten in any study groups. When the relevant data was not reported in paper, we contacted the author to get the relevant information by e-mail or telephone.

The primary outcomes assessed the impact of HCV infection on NHL patients' prognoses, including overall survival (OS) and disease progression [progress-free survival (PFS) / disease-free survival (DFS)]. The other outcomes measured treatment response [overall response rate (ORR)] and clinical characteristics of NHL patients with HCV infection, including age of disease onset (< 60 years old), presence of B symptoms, advanced disease stage (Ann Arbor staging III/IV), involvement of spleen, liver and bone marrow, elevated LDH level, high-intermediate and high IPI/FLIPI risk and incidence of hepatic dysfunction during chemotherapy. Furthermore, the effect of antiviral therapy or rituximab administration as well as liver-related prognostic factors for HCV-positive NHL patients was also investigated. Since PFS and DFS were similar outcomes of disease progression, we pooled PFS and DFS as the same outcome indicators to analyze in the current study.

Data extraction and study quality

Two reviewers (Gao F and Peng L) independently extracted data and outcomes using an electronic standard form. The following information from each study was summarized: (1) first author, (2) year of publication, (3) country, (4) subtypes of NHL, (5) number of patients with and without HCV infection, (6) number of HCV positive NHL patients receiving and not receiving antiviral/rituximab treatment, (7) anti-lymphoma therapeutic regimens, (8) antiviral treatment regimens, (9) patient's characteristics. Any discrepancies amongst the two reviewers were resolved by an additional investigator, Zhang M.

Quality assessment

Newcastle-Ottawa Quality Assessment Scale (NOS) was adopted to assess the methodological quality of the included studies [23]. The following three items were evaluated including: (1) patient selection, (2) comparability of interventions and observations group, and (3) assessment of outcome.

Statistical analysis

Hazard ratio (HR) corresponding to 95% confidence interval (CI) were used to assess OS and PFS/DFS. If both univariate and multivariate analyses results were reported in the included study, the latter will be used in the meta-analysis. If HRs and 95% CIs were not available from the original article, Kaplan–Meier curves of the included studies were read and re-analyzed by software Engauge digitizer. HRs and 95% CIs were indirectly calculated from Kaplan–Meier curve using Tiemey's methods [24]. Odds ratio (OR) corresponding to 95% CI were calculated to estimate other outcomes. Publication biases were assessed by Egger's test and Begg's test. When the outcome with less than five included studies, publication biases was not performed. The methods of meta-analysis and publication biases tests were detailed in our previous publications [25–28]. Statistical analysis was performed by software ReviewManager 5.4 (The Cochrane Collaboration, Oxford, UK) and Stata version 15 (Stata Corp, College Station, Texas, USA). All P-values were both-sided and P-value of < 0.05 was considered significance.

Results

Characteristics of studies

After the comprehensive literature search based on the criteria above, 2599 articles were identified as potentially relevant publications. Upon further evaluation of the full-text, 17 articles were excluded from the calculations of this systematic review. Thus, 27 articles (29 studies) [9–22, 29–41] with a total of 13368 NHL patients, including 3063 patients with HCV infection and 10305 patients without HCV infection, fulfilled the inclusion criteria and were included in current meta-analysis (Figure.1). The characteristics of the included articles were summarized in Table 1. The articles were published between 1997 and 2020 with sample size ranging from 58 to 5586. Majority of studies were conducted in Italy (n = 11), Japan (n = 4), Egypt (n = 3), China (n = 2), French (n = 2) and the United States (n = 2). The other articles consisted of single study conducted in Russia, Korea, and Spain. Among the included articles, 14 articles focused on DLBCL, two articles on follicular lymphoma and two articles on marginal zone lymphoma. In addition to the aforementioned lymphoma subtypes, the patients in 9 articles consisted of more than two subtypes of NHL. With regards to the methodological quality, most of included articles had reliable quality as indicated by NOS scores ≥ 6 points except for 2 articles [30, 38] with NOS scores 5 points (Table S1).
## Table 1
Baseline characteristics of included studies

| Author          | Year | Country | Diagnosis | Regimes of anti-lymphoma treatment | Regimes of AT treatment | Follow-up (m) | HCV infection | R use in HCV+ patients | AT in HCV+ patients | Hazard ratio |
|-----------------|------|---------|-----------|-------------------------------------|--------------------------|---------------|---------------|------------------------|----------------------|--------------|
| Besson C        | 2006 | France  | DLBCL     | -                                   | -                        | 47 (0-112)    | 26            | -                      | -                    | extrapolated |
| Chen TT         | 2015 | China   | DLBCL     | I-CHT                               | -                        | 36 (0.84-96.24) | 29            | 29                     | 0                    | extrapolated |
| Chen YY         | 2015 | China   | DLBCL     | I-CHT                               | -                        | 22            | 102           | 15                     | 7                    | reported     |
| Dlouhy I        | 2017 | Spain   | DLBCL     | I-CHT                               | -                        | 48 (1.2-146.4) | 31            | 290                    | 31                   | extrapolated |
| Elbedewy TA     | 2020 | Egypt   | DLBCL     | I-CHT                               | -                        | 76            | 277           | 33                     | 43                   | reported     |
| Ennishi D       | 2010 | Japan   | DLBCL     | I-CHT                               | DAA                      | HCV+31 (4-42) | 131           | 422                    | 131                  | reported     |
| Hosry J         | 2016 | USA     | DLBCL     | I-CHT                               | IFN, Rib, DAA            | >6            | 76            | 228                    | 76                   | extrapolated |
| Nishikawa H     | 2012 | Japan   | DLBCL     | I-CHT                               | -                        | HCV+40.8 (3.6-92.4), HCV-31.2 (2.4-94.8) | 28            | 220                    | 28                   | 0            | 0                      | 28           | extrapolated |
| Park BB         | 2008 | Korea   | DLBCL     | I-CHT                               | -                        | 37.8          | 32            | 371                    | -                    | extrapolated |
| Shimono J       | 2019 | Japan   | ps-DLBCL  | I-CHT                               | -                        | HCV+46.9 (4.0-94.3), HCV-36.8 (0.8-133.5) | 12            | 46                     | 10                    | 2            | -                      | -            | extrapolated |
| Ordinary DLBCL  |      |         |           | I-CHT                               | -                        | HCV+27.8 (1.9-122.1), HCV-35.9 (0.1-90.1) | 25            | 120                    | -                     | -            | -                      | -            | extrapolated |
| Arcaini L       | 2007 | Italy   | Non-gastric MALToma | CHT, RT, surgery | -                        | 60            | 112           | -                      | -                    | extrapolated |
| Arcaini L       | 2006 | Italy   | SMZL      | Splenectomy, IFN                     | -                        | 37.2          | 49            | 206                    | -                    | -            | -                      | -            | -            |
| Hosry J         | 2020 | USA     | FL        | I-CHT, RT                            | IFN, Rib, DAA            | -             | 19            | 57                     | -                    | 13           | 6                      | -            | -            |
| Nesterova E     | 2020 | Russia  | FL        | I-CHT                               | DAA                      | -             | 11            | 105                    | 11                   | 0            | 0                      | -            | -            |
| De Vita S       | 1997 | Italy   | B-NHL     | -                                    | -                        | 35            | 122           | -                      | -                    | -            | -                      | -            | -            |

**Abbreviation**
- AT: antiviral treatment
- CHT: chemotherapy
- DAA: direct-acting antiviral
- DLBCL: diffuse large B-cell lymphoma
- FL: follicular lymphoma
- I-CHT: immunochemotherapy
- IFN: interferon
- MALToma: mucosa-associated lymphoid tissue lymphoma
- NHL: non-Hodgkin's lymphoma
- OA: ocular adnexal
- ps-DLBCL: primary splenic diffuse large B-cell lymphoma
- SMZL: splenic marginal zone lymphoma
- R: rituximab
- RT: radiotherapy
- Rib: Ribavirin
**The impact of HCV infection on NHL patients’ prognosis**

Among all 27 studies, 15 studies were available for analyses of OS. Due to obvious heterogeneity among these studies ($I^2 = 47\%$, $P_{\text{heterogeneity}} = 0.02$), a random-effects model was employed to pool all of HRs and their 95% CIs. Meta-analysis revealed that HCV positive patients had significantly worse OS than HCV negative patients (HR 1.89; 95% CI 1.42–2.51, $P < 0.0001$; Figure. 2a).

A total of 8 studies were eligible for the assessment of PFS. The fixed-effects model was used to calculate the result as there was no heterogeneity among the included studies ($I^2 = 0\%$, $P_{\text{heterogeneity}} = 0.59$). Similarly, the result demonstrated that patients with HCV infection showed significantly shortened PFS compared with the patients without HCV infection (HR 1.58; 95% CI 1.26–1.98, $P < 0.00001$; Figure. 2b).

**HCV infection and treatment response**

Eleven studies were identified to assess ORR between NHL patients with and without HCV infection. The OR and 95% CI of ORR was pooled by using fixed-effects model as the heterogeneity tests suggested no significant heterogeneity ($I^2 = 28\%$, $P_{\text{heterogeneity}} = 0.18$). The combined results showed that ORR of HCV-positive NHL patients was significantly lower than that of HCV-negative NHL patients (OR 0.58, 95% CI 0.46–0.73, $P < 0.00001$, Figure. 3).

**HCV infection and hepatic dysfunction during chemotherapy**

Totally, 7 studies including 2095 participants (DLBCL patients) were eligible to analyze this outcome by the random-effects mode ($I^2 = 78\%$, $P_{\text{heterogeneity}} = 0.0001$). As shown in Figure. 4, higher incidence of hepatic dysfunction during chemotherapy was observed in HCV infected patients in comparison to HCV non-infected patients (OR 5.96; 95% CI 2.61–13.62, $P < 0.0001$).

**HCV infection and clinical characteristics**
Clinical features of NHL patients were also comprehensively compared between HCV positive and negative NHL patients. The results indicated that HCV infection was associated with advanced disease stage (OR 1.42, 95% CI 1.14–1.76, P = 0.001, Figure. S1), elevated level of LDH (OR 1.44; 95% CI 1.17–1.79, P = 0.0008, Figure. S2), high-intermediate and high IPI/FLIPI risk (OR 1.29; 95% CI 1.07–1.56, P = 0.008, Figure. S3), as well as higher incidence of spleen involvement (OR 2.95; 95% CI 2.17–4.02, P < 0.00001, Figure. S4) and liver involvement (OR 2.01; 95% CI 1.46–2.78, P < 0.0001, Figure. S5). However, there was no significant difference in age of disease onset (Figure. S6), presence of B symptoms (Figure. S7) and incidence of involvement of bone marrow (Figure. S8) between two groups of patients.

Effect of antiviral treatment and rituximab administration on HCV-associated NHL patients

Since NHL patients with HCV infection were found to have disadvantages of survivals and treatment response, whether antiviral treatment may improve clinical outcomes of HCV-associated NHL patients was also investigated. Of all the studies reviewed, 9 studies including 1838 HCV infected NHL patients were included to evaluate the impact of antiviral treatment on OS, PFS/DFS and ORR. As shown in Fig. 5, antiviral treatment was associated with improved OS (HR 0.38; 95% CI 0.24–0.60, P < 0.0001; Figure. 5a) and PFS/DFS (HR 0.63; 95% CI 0.46–0.86, P = 0.003; Figure. 5b), as well as higher ORR (OR 2.62; 95% CI 1.34–5.11, P = 0.005, Figure. 5c) in comparison with patients without antiviral treatment.

In addition, we also explored whether rituximab-containing regimes could improve the clinical prognosis of HCV positive NHL patients. Four studies comprising of 688 participants (DLBCL patients) were evaluated. The results demonstrated that patients treated with rituximab-containing chemotherapy exhibited favorable OS compared with those receiving rituximab-free chemotherapy (HR 0.68; 95% CI 0.54–0.86, P = 0.001; Figure. 6a). However, no difference in PFS was observed between these two groups of patients (HR 0.97; 95% CI 0.70–1.36, P = 0.88; Figure. 6b).

Liver-related survival factors in HCV-associated NHL patients

We subsequently evaluated liver-related survival factors in HCV-associated NHL patients, including liver cirrhosis, liver involvement, low level of albumin (< 3.5 g/dl) and elevated alanine transaminase (ALT). As shown in Figure. 7a-d, low level of albumin (HR 2.61; 95% CI 1.71–3.97, P < 0.00001; Figure. 7a) and liver cirrhosis (HR 2.91; 95% CI 1.44–5.88, P = 0.003; Figure. 7b) were significantly associated with inferior OS. There was a trend for an association between liver involvement and short OS (HR 1.27; 95% CI 0.96–1.67, P = 0.09; Figure. 7c). However, no association was found between elevated ALT and OS (HR 1.09; 95% CI 0.86–1.37, P = 0.50; Figure. 7d).

Subgroup analysis

Firstly, subgroup analysis was conducted based on prevalence of HCV infection. According to the report of prevalence of HCV infection form global hepatitis report 2017 from WHO [42], the countries of included studies were divided into high prevalence of HCV infection, including Italy, Spain, France, Russia and Egypt, and low prevalence of HCV infection, including United States, Japan, Korea, and China (cut-off value of HCV infection prevalence as 1.5%). The results of subgroup analysis were shown in Table 2 (high prevalence) and Table 3 (low prevalence). Compared with the results from overall population, similar results could be observed from subgroup analysis. NHL patients with HCV infection had inferior prognosis, lower treatment response and high incidence of hepatic dysfunction in both sub-populations. With regards to clinical features, HCV infection had no effect on the IPI/FLIPI risk in neither of subgroups of patients, which was inconsistent with this outcome in overall population. In addition, HCV-associated NHL patient had an early age of disease onset among the countries with lower prevalence of HCV infection. For the outcomes of the effect of antiviral and rituximab treatment as well as survival factors in HCV-positive NHL patients, all the included studies were performed in the countries with high prevalence of HCV infection except one study [17]. Therefore, subgroup analysis was not performed.
Table 2
Subgroup analysis in countries with high prevalence of HCV infection

| Outcome                      | Studies | HR/OR (95%CI)       | P value | Heterogeneity |
|------------------------------|---------|---------------------|---------|---------------|
|                              |         |                     |         | I² | P value |
| Impact of HCV infection      |         |                     |         |    |         |
| Overall survival             | 7       | 2.07 (1.37–3.14)    | 0.0006  | 61 | 0.02   |
| Progress-free survival       | 2       | 1.89 (1.27–2.82)    | 0.002   | 0  | 0.66   |
| Overall response rate        | 6       | 0.51 (0.38–0.68)    | <0.00001| 46 | 0.10   |
| Hepatic dysfunction          | 2       | 30.13 (1.75–517.77) | 0.02    | 84 | 0.01   |
| Age of onset                 | 5       | 1.04 (0.50–2.16)    | 0.92    | 79 | 0.0009 |
| Advanced disease stage       | 11      | 1.53 (1.22–1.91)    | 0.0002  | 44 | 0.06   |
| Presence of B symptom       | 6       | 0.99 (0.53–1.84)    | 0.97    | 63 | 0.02   |
| Elevated LDH level           | 5       | 1.33 (0.96–1.84)    | 0.09    | 49 | 0.10   |
| H-I/H risk                   | 6       | 1.53 (0.96–2.44)    | 0.07    | 60 | 0.03   |
| Spleen involvement           | 4       | 3.74 (2.32–6.02)    | <0.00001| 0  | 0.52   |
| Liver involvement            | 5       | 1.98 (1.23–3.20)    | 0.005   | 41 | 0.15   |
| Bone marrow involvement      | 6       | 1.39 (0.97–2.00)    | 0.07    | 46 | 0.10   |

Abbreviation: H-I/H high-intermediate and high

Table 3
Subgroup analysis in countries with low prevalence of HCV infection

| Outcome                      | Studies | HR/OR (95%CI)       | P value | Heterogeneity |
|------------------------------|---------|---------------------|---------|---------------|
|                              |         |                     |         | I² | P value |
| Impact of HCV infection      |         |                     |         |    |         |
| Overall survival             | 8       | 1.59 (1.16–2.17)    | 0.004   | 16 | 0.31   |
| Progress-free survival       | 6       | 1.45 (1.10–1.90)    | 0.008   | 0  | 0.52   |
| Overall response rate        | 5       | 0.70 (0.49–1.00)    | 0.05    | 0  | 0.59   |
| Hepatic dysfunction          | 5       | 3.87 (1.60–9.36)    | 0.003   | 76 | 0.002  |
| Age of onset                 | 4       | 1.97 (1.18–3.28)    | 0.01    | 4  | 0.37   |
| Advanced disease stage       | 10      | 1.22 (0.98–1.52)    | 0.07    | 28 | 0.18   |
| Presence of B symptom       | 4       | 0.80 (0.53–1.21)    | 0.30    | 47 | 0.13   |
| Elevated LDH level           | 6       | 1.54 (1.16–2.04)    | 0.003   | 26 | 0.24   |
| H-I/H risk                   | 8       | 1.16 (0.89–1.51)    | 0.26    | 0  | 0.52   |
| Spleen involvement           | 5       | 2.48 (1.65–3.74)    | <0.00001| 0  | 0.63   |
| Liver involvement            | 7       | 2.04 (1.32–3.15)    | 0.001   | 17 | 0.30   |
| Bone marrow involvement      | 8       | 0.98 (0.72–1.34)    | 0.90    | 0  | 0.46   |

Abbreviation: H-I/H high-intermediate and high

Since NHL is a group of heterogeneous diseases, we performed subgroup analysis based on pathological types of NHL. In the current study, majority of the included studies focused on DLBCL hence subgroup analysis was conducted in DLBCL patients. Similar to overall patients, DLBCL patients with HCV infection had shorter OS and PFS, lower ORR and distinct clinical features in comparison to DLBCL patients without HCV infection. Moreover, HCV-associated DLBCL patients receiving antiviral treatment shared a better OS and PFS/DFS than patients without antiviral treatment. Due to small sample size, subgroup analysis was not performed in terms of the outcomes of liver-related survival factors. The results of subgroup analysis in DLBCL patients were summarized in Table 4.
Table 4
Subgroup analysis in DLBCL patients

| Outcome                        | Studies | HR/OR (95%CI)       | P value | Heterogeneity |
|--------------------------------|---------|---------------------|---------|--------------|
|                                |         |                     |         | p² %          | P value      |
| Impact of HCV infection        |         |                     |         |               |             |
| Overall survival               | 11      | 2.29 (1.85–2.84)    | <0.00001| 46            | 0.05         |
| Progress-free survival         | 7       | 1.55 (1.23–1.95)    | 0.0002  | 0             | 0.54         |
| Overall response rate          | 8       | 0.55 (0.42–0.72)    | <0.00001| 23            | 0.24         |
| Hepatic dysfunction            | 6       | 5.89 (2.31–15.01)   | 0.0002  | 82            | <0.0001      |
| Age of onset                   | 7       | 1.31 (0.67–2.57)    | 0.43    | 70            | 0.003        |
| Advanced disease stage         | 11      | 1.20 (0.98–1.48)    | 0.08    | 14            | 0.31         |
| Presence of B symptom          | 6       | 1.16 (0.70–1.94)    | 0.56    | 59            | 0.03         |
| Elevated LDH level             | 9       | 1.47 (1.17–1.85)    | 0.0009  | 46            | 0.06         |
| HH/H risk                      | 10      | 1.34 (1.07–1.67)    | 0.01    | 0             | 0.48         |
| Spleen involvement             | 5       | 2.75 (1.92–3.95)    | <0.00001| 0             | 0.55         |
| Liver involvement              | 7       | 1.87 (1.22–2.85)    | 0.004   | 0             | 0.60         |
| Bone marrow involvement        | 6       | 1.03 (0.71–1.50)    | 0.86    | 17            | 0.31         |
| Impact of anti-viral treatment |         |                     |         |               |             |
| Overall survival               | 5       | 0.40 (0.24–0.66)    | 0.0003  | 37            | 0.18         |
| Progress-free survival         | 4       | 0.60 (0.39–0.92)    | 0.02    | 41            | 0.17         |

In terms of antiviral treatment, subgroup analysis was performed based on the regimes of antiviral treatment. Among the 9 included studies, patients in most studies (n = 6) received interferon (IFN) +/- ribavirin as antiviral treatment. Only two study [13, 40] focused on new direct-acting antiviral (DAA) treatments of HCV and another study [17] consisted of different types of antiviral treatment. Therefore, subgroup analysis was conducted in patients receiving IFN +/- ribavirin. The results suggested that patients receiving IFN +/- ribavirin had obvious improved OS (HR 0.25; 95% CI 0.12–0.52, P = 0.0002, figure not shown) and PFS (HR 0.63; 95% CI 0.44–0.90, P = 0.01, figure not shown) in comparison with patients without antiviral treatment.

Sensitivity analysis

Sensitivity analysis was performed by a sequential exclusion of individual studies to find the origin of the heterogeneity and verify the sensitivity of results. The origin of the heterogeneity and overall effect after removal of origin of the heterogeneity for each outcome were summarized in Table 5. The results showed that removal of the origin of the heterogeneity did not affect the effect size for each outcome, suggesting the stability of the result of meta-analysis. However, for the outcomes of age of disease onset, hepatic dysfunction during chemotherapy and liver cirrhosis, the heterogeneity still existed even though studies were excluded one by one.

Table 5
Results of sensitivity analysis

| Outcome                  | Origin of heterogeneity | Overall effect | P value |
|--------------------------|-------------------------|----------------|---------|
| Overall survival         | Dlouhy I 2017 [12]      | 1.78 (1.45–2.18) | <0.00001|
| Advanced disease stage   | Vallisa D 1999 [39]     | 1.28 (1.09–1.51) | 0.003   |
| Presence of B symptoms   | Arcaini L 2006 [31]     | 1.09 (0.84–1.41) | 0.51    |
| Liver cirrhosis          | Hosry J 2016 [17]       | 1.84 (1.26–2.69) | 0.002   |

Publication bias

Begg’s test and Egger’s test were performed to assess the publication bias. As was shown in Table 6, no significant publication bias was observed for all the outcomes.
Table 6
Results of Begg's test and Egger's test

| Outcome                        | P_Begg's test | P_Egger's test |
|--------------------------------|---------------|----------------|
| Impact of HCV infection        |               |                |
| Overall survival               | 1.000         | 0.619          |
| Progress-free survival         | 0.386         | 0.871          |
| Overall response rate          | 0.276         | 0.373          |
| Hepatic dysfunction            | 0.452         | 0.236          |
| Age of onset                   | 1.000         | 0.499          |
| Advanced disease stage         | 0.162         | 0.468          |
| Presence of B symptom          | 0.074         | 0.065          |
| Elevated LDH level             | 0.533         | 0.639          |
| HI/H risk                      | 0.125         | 0.379          |
| Spleen involvement             | 0.386         | 0.878          |
| Liver involvement              | 1.000         | 0.895          |
| Bone marrow involvement        | 0.100         | 0.167          |
| Impact of antiviral treatment  |               |                |
| Overall survival               | 0.917         | 0.407          |
| Progress-free survival         | 0.260         | 0.070          |
| Liver-related survival factors |               |                |
| Liver cirrhosis                | 0.707         | 0.262          |

Abbreviation: H-I/H high-intermediate and high

Discussion

Over the past two decades, considerable studies have been investigated the contribution of HCV infection to lymphomagenesis. However, the mechanisms of HCV-associated lymphoma remained elusive. Experimental data implicated that HCV-induced lymphoma development may act through multistep processes, resulting from a variety of oncogenic mechanisms, such as HCV-induced chronic B-cell immune-stimulation, genetic damages, dysregulation of signaling pathways (NF-kB, JNK, ERK and NOTCH signaling pathways), etc. [43–48]. A prognostic evaluation of clinical outcomes and therapeutic responses in HCV-associated lymphoma is essential to antitumor treatment. Herein, we performed a systematic review and meta-analysis to assess the impact of HCV infection on NHL patients. Furthermore, subgroup analysis was also performed based on the prevalence of HCV infection and pathological types of lymphoma. The results of current study collectively indicated that HCV-positive NHL patients had significantly inferior survival, earlier disease progression, poorer treatment response and distinct clinical characters. In addition to recognized survival factors of NHL, our study also demonstrated that liver cirrhosis and low level of albumin were inferior prognostic factors of OS for HCV-associated NHL patients.

Furthermore, this study implicated the anti-lymphoma efficacy of antiviral treatment, especially IFN+-/- ribavirin regimes, in HCV-associated NHL patients, which was similar to the recent meta-analysis conducted by Peveling-Oberhag, et al [49]. The authors found the good overall lymphoma response rate through the application of antiviral treatment in HCV-infected NHL patients. However, their meta-analysis was based on small studies, mostly case reports or small cohorts with less than 20 cases. Nevertheless, DAA treatments are radically changing the landscape of anti-HCV therapy. In the current study, whether HCV-associated NHL patients can benefit from DAA treatment couldn't be expounded due to small patient sample size. In the era of DAA, future studies should illuminate the anti-lymphoma activity of DAA treatment in NHL patients with HCV infection. On the other hand, rituximab-containing regimes have been proven to be associated with better treatment response and clinical prognosis in DLBCL over the past two decades. In the current study, we also found that rituximab administration could improve OS in DLBCL patients with HCV infection. However, the association between PFS and rituximab administration couldn't be observed in this specific subtype of DLBCL patients, which might be due to small samples size. Whether rituximab-containing regimes can improve treatment response and PFS warrants further study with large cohorts.

To the best of our knowledge, this is the first meta-analysis that systematically assessed the clinical outcomes and treatment of HCV-associated NHL patients. We are confident that our results were reliable, which was supported by large sample size, moderate to high methodological quality of included studies, low heterogeneity, and no publication bias. However, there were several limitations in this study. Firstly, when evaluating OS or PFS/DFS, HR and 95% CI in some of individual studies were not available from the original articles, hence they were indirectly calculated from Kaplan-Meier curve. Secondly, our study implicated that higher incidence of hepatic dysfunction was observed in HCV infected NHL patients, probably leading to delay or
termination of chemotherapy or even death. However, the direct cause-and-effect relationship between hepatic dysfunction and inferior prognosis remained unknown. On the other hand, it was still unclear whether survival benefit of antiviral treatment attributed to restoring hepatic dysfunction and reducing chance of termination or delay of chemotherapy caused by HCV-induced hepatotoxicity so far. Third, our study indicated that HCV infection was associated with poor survivals in NHL patients. Despite we attempted to further perform prognostic evaluation of HCV viral loading (HCV-RNA) in HCV infected NHL patients. However, only two articles investigated prognostic value of HCV-RNA and the results were contradictory. Fourthly, it should be noted that when analyzing some outcomes, such as prognostic factors and effect of rituximab administration in HCV-associated NHL patients, only a few studies with small sample size could be included. Therefore, the results of these outcomes need to be interpreted with caution. Lastly, patients in most of included studies were DLBCL. There were only a few studies focusing on indolent lymphoma, such as follicular lymphoma and marginal zone lymphoma hence subgroup analysis could not be carried out in indolent lymphoma patients. In view of the limitations of the current study, well-designed perspective studies with large cohorts should be performed in different subtypes of NHL, especially indolent lymphoma, to address the issues mentioned above in the future.

Conclusions

This meta-analysis confirmed the inferior prognosis and distinct clinical characteristics in HCV-associated NHL patients, especially in DLBCL. Patients with HCV infection were prone to undergoing hepatic dysfunction during the chemotherapy. Moreover, our data provided the compelling evidence that antiviral treatment combined with immunochemotherapy may represent an effective approach for HCV-positive NHL patients.

Abbreviations

ALT alanine transaminase
CI confidence interval
DAA direct-acting antiviral
DFS disease-free survival
DLBCL diffuse large B-cell lymphoma
HCV hepatitis C virus
HR hazard ratio
IFN interferon
NHL non-Hodgkin's lymphoma
NOS Newcastle-Ottawa Quality Assessment Scale
PFS progress-free survival
OR Odds ratio
ORR overall response rate
OS overall survival
WHO World Health Organization

Declarations

Availability of data and materials

The datasets used in this study are available from the corresponding author upon reasonable request.

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Authors' contributions
Ni B and Zhao P performed literature research. Zhang M, Gao F and Peng L extracted and analyzed the data. Zhang M, Gao F and Shen L wrote the manuscript; Huang H and Hou J conceived and designed this study. All authors reviewed and approved the final manuscript.

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Ethics declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

References
1. de The G. Viruses and human cancers: challenges for preventive strategies. Environmental health perspectives. 1995; 103 Suppl 8:269 – 73.
2. Parsonnet J, Isaacman PG. Bacterial infection and MALT lymphoma. N Engl J Med. 2004;350(3):213–5.
3. Raderer M, Kiesewetter B, Ferreri AJ. Clinicopathologic characteristics and treatment of marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). CA Cancer J Clin. 2016;66(2):153–71.
4. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90.
5. Pal S, Sullivan DG, Kim S, Lai KK, Kae J, Cotler SJ, et al. Productive replication of hepatitis C virus in perihepatic lymph nodes in vivo: implications of HCV lymphotropism. Gastroenterology. 2006;130(4):1107–16.
6. Pham TN, King D, Macparland SA, McGrath JS, Reddy SB, Bursey FR, et al. Hepatitis C virus replicates in the same immune cell subsets in chronic hepatitis C and occult infection. Gastroenterology. 2008;134(3):812–22.
7. Canioni D, Michot JM, Rabiega P, Molina TJ, Charlotte F, Lazure T, et al. In Situ Hepatitis C NS3 Protein Detection Is Associated with High Grade Features in Hepatitis C-Associated B-Cell Non-Hodgkin Lymphomas. PLoS One. 2016;11(6):e0156384.
8. 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):2078–85.
9. Besson C, Canioni D, Lepage E, Pol S, Morel P, Lederlin P, et al. Characteristics and outcome of diffuse large B-cell lymphoma in hepatitis C virus-positive patients in LNH 93 and LNH 98 Groupe d’Etude des Lymphomes de l’Adulte programs. J Clin Oncol. 2006;24(6):953–60.
10. Chen TT, Chiu CF, Yang TY, Lin CC, Sargeant AM, Yeh SP, et al. Hepatitis C infection is associated with hepatic toxicity but does not compromise the survival of patients with diffuse large B cell lymphoma treated with rituximab-based chemotherapy. Leuk Res. 2015;39(2):151–6.
11. Chen YY, Huang CE, Liang FW, Lu CH, Chen PT, Lee KD, et al. Prognostic impact of hepatitis C virus infection in patients with diffuse large B-cell lymphoma treated with immunochemo therapy in the context of a novel prognostic index. Cancer Epidemiol. 2015;39(3):382–7.
12. Dlouhy I, Torrente MA, Lens S, Rovira J, Magnano L, Gine E, et al. Clinico-biological characteristics and outcome of hepatitis C virus-positive patients with B-cell diffuse large lymphoma treated with immunochemo therapy. Ann Hematol. 2017;96(3):405–10.
13. Elbedewy TA, Elashtokhy HEA, Abd-ElSalam S, Suliman MA. Hepatitis C Virus Infection and Treatment as Independent Prognostic Factors in Diffuse Large B-Cell Lymphoma Egyptian Patients. Curr Cancer Drug Targets. 2020;20(8):638–45.
14. Ennishi D, Maeda Y, Niitsu N, Kojima M, Izutsu K, Takizawa J, et al. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood. 2010;116(24):5119–25.
15. Merli M, Visco C, Spina M, Luminari S, Ferretti VV, Gotti M, et al. Outcome prediction of diffuse large B-cell lymphomas associated with hepatitis C virus infection: a study on behalf of the Fondazione Italiana Linfomi. Haematologica. 2014;99(3):489–96.
16. Park BB, Kim JS, Lee YY, Kang HJ, Ryoo BY, Kang JH, et al. Clinical characteristics and outcome for hepatitis C virus-positive diffuse large B-cell lymphoma. Leuk Lymphoma. 2008;49(1):88–94.
17. Hosry J, Mahale P, Turturro F, Miranda RN, Economides MP, Granwehr BP, et al. Antiviral therapy improves overall survival in hepatitis C virus-infected patients who develop diffuse large B-cell lymphoma. Int J Cancer. 2016;139(11):2519–28.
18. Shimono J, Miyoshi H, Arakawa F, Yamada K, Sugio T, Miyawaki K, et al. Clinicopathological features of HCV-positive splenic diffuse large B cell lymphoma. Ann Hematol. 2019;98(5):1197–207.
19. Arcaini L, Vallisa D, Rattotti S, Ferretti VV, Ferreri AJM, Bemuzzi P, et al. Antiviral treatment in patients with indolent B-cell lymphomas associated with HCV infection: a study of the Fondazione Italiana Linfomi. Ann Oncol. 2014;25(7):1404–10.
20. Michot JM, Canioni D, Driss H, Alric L, Cacoub P, Suarez F, et al. Antiviral therapy is associated with a better survival in patients with hepatitis C virus and B-cell non-Hodgkin lymphomas, ANRS HC-13 lympho-C study. Am J Hematol. 2015;90(3):149–96.
21. Rattotti S, Ferretti VV, Rusconi C, Rossi A, Fogazzi S, Baldini L, et al. Lymphomas associated with chronic hepatitis C virus infection: A prospective multicenter cohort study from the Rete Ematologica Lombarda (REL) clinical network. Hematol Oncol. 2019;37(2):160–7.
22. Ennishi D, Maeda Y, Niitsu N, Kojima M, Izutsu K, Takizawa J, et al. Hepatic toxicity and prognosis in hepatitis C virus-infected patients with diffuse large B-cell lymphoma treated with rituximab-containing chemotherapy regimens: a Japanese multicenter analysis. Blood. 2010;116(24):5119–25.
23. Zaky AH, Bakry R, El-sayed MI, Elwanis MA, Nabih O. Impact of treatment-related toxicity on outcome of HCV-positive diffuse large B-cell lymphoma treated with immunochemotherapy. Am J Hematol. 2008;8:16.
24. Tierney JF, Stewart LA, Gherdi S, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
25. Zhang MY, Chen FY, Zhong H. Meta-analysis of human leukocyte antigen genetic polymorphisms and susceptibility to chronic myelogenous leukemia in Chinese population. Leukemia research. 2011;35(12):1564–70.
26. Zhang MY, Miao L, Li YS, Hu GY. Meta-analysis of the methylenetetrahydrofolate reductase C677T polymorphism and susceptibility to Alzheimer’s disease. Neuroscience research. 2010;68(2):142–50.
27. Zhang MY, Zhu GQ, Shi KQ, Zheng JN, Cheng Z, Zou ZL, et al. Systematic review with network meta-analysis: Comparative efficacy of oral nucleos(t)ide analogues for the prevention of chemotherapy-induced hepatitis B virus reactivation. Oncotarget. 2016;7(21):30642–58.
28. Zhang MY, Zhu GQ, Zheng JN, Cheng Z, Van Poucke S, Shi KQ, et al. Nucleos(t)ide analogues for preventing HBV reactivation in immunosuppressed patients with hematological malignancies: a network meta-analysis. Expert review of anti-infective therapy. 2017;15(5):503–13.

29. Nishikawa H, Tsudo M, Osaki Y. Clinical outcome in diffuse large B-cell lymphoma with hepatitis C virus infection in the rituximab era: a single center experience. Oncol Rep. 2012;28(3):835–40.

30. Arcaini L, Burcheri S, Rossi A, Paulli M, Bruno R, Passamonti F, et al. Prevalence of HCV infection in nongastric marginal zone B-cell lymphoma of MALT. Ann Oncol. 2007;18(2):346–50.

31. Arcaini L, Lazzarino M, Colombo N, Burcheri S, Boveri E, Paulli M, et al. Splenic marginal zone lymphoma: a prognostic model for clinical use. Blood. 2006;107(12):4643–9.

32. Hosy J, Miranda RN, Samaniego F, Angelidakis G, Torres HA. Clinicopathologic characteristics of follicular lymphoma in hepatitis C virus-infected patients. Hematol Oncol. 2020;38(3):301–8.

33. Nesterova E, Tanaschuk E, Abdurakhmanov D, Gemdzhian E, Kravchenko S, Mangasarova Y, et al. Safe and effective treatment of follicular lymphoma in patients with HCV infection. Hematol Oncol. 2020;38(4):604–6.

34. De Vita S, Sacco C, Sansonno D, Gloghini A, Dammacco F, Crovatto M, et al. Characterization of overt B-cell lymphomas in patients with hepatitis C virus infection. Blood. 1997;90(2):776–82.

35. Luppi M, Longo G, Ferrari MG, Barozzi P, Marasca R, Morselli M, et al. Clinico-pathological characterization of hepatitis C virus-related B-cell non-Hodgkin's lymphomas without symptomatic cryoglobulinemia. Ann Oncol. 1998;9(5):495–8.

36. La Mura V, De Renzo A, Perna F, D'Agostino D, Masarone M, Romano M, et al. Antiviral therapy after complete response to chemotherapy could be efficacious in HCV-positive non-Hodgkin's lymphoma. J Hepatol. 2008;49(4):557–63.

37. Strianese D, Tranfa F, Finelli M, De Renzo A, Staibano S, Schiemer R, et al. Hepatitis C virus infection in ocular adnexal lymphomas. Arch Ophthalmol. 2010;128(10):1295–9.

38. Tajima K, Takahashi N, Ishizawa K, Murai K, Akagi T, Noji H, et al. Clinicopathological characteristics of malignant lymphoma in patients with hepatitis C virus infection in the Tohoku district in Eastern Japan. Leuk Lymphoma. 2017;58(6):1509–11.

39. Vallisa D, Bertè R, Rocca A, Civardi G, Giangregorio F, Ferrari B, et al. Association between hepatitis C virus and non-Hodgkin's lymphoma, and effects of viral infection on histologic subtype and clinical course. Am J Med. 1999;106(5):556–60.

40. Persico M, Aglitti A, Caruso R, De Renzo A, Selleri C, Califano C, et al. Efficacy and safety of new direct antiviral agents in hepatitis C virus-infected patients with diffuse large B-cell non-Hodgkin's lymphoma. Hepatology. 2018;67(1):48–55.

41. Salah-Eldin MA, Ebrahim MA, El-Sadda W. Clinical outcome of HCV-positive patients with diffuse large B-cell lymphoma treated with rituximab-based chemotherapy. Ann Hematol. 2014;93(11):1903–11.

42. Global Hepatitis Report. 2017. In. Geneva: World Health Organization; 2017.

43. Marcucci F, Mele A. Hepatitis viruses and non-Hodgkin lymphoma: epidemiology, mechanisms of tumorigenesis, and therapeutic opportunities. Blood. 2011;117(6):1792–8.

44. Weng WK, Levy S. Hepatitis C virus (HCV) and lymphomagenesis. Leuk Lymphoma. 2003;44(7):1113–20.

45. Küppers R, Dalla-Favera R. Mechanisms of chromosomal translocations in B cell lymphomas. Oncogene. 2001;20(40):5580–94.

46. Ferri C, Sebastiani M, Giuglioli D, Colaci M, Fallahi P, Piluso A, et al. Hepatitis C virus syndrome: A constellation of organ- and non-organ specific autoimmune disorders, B-cell non-Hodgkin's lymphoma, and cancer. World J Hepatol. 2015;7(3):327–43.

47. Forghieri F, Luppi M, Barozzi P, Maffei R, Potenza L, Nami F, et al. Pathogenetic mechanisms of hepatitis C virus-induced B-cell lymphomagenesis. Clin Dev Immunol. 2012;2012:807351.

48. 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):169–77.

49. Peveling-Oberhag J, Arcaini L, Bankov K, Zeuzem S, Herrmann E. The anti-lymphoma activity of antiviral therapy in HCV-associated B-cell non-Hodgkin lymphomas: a meta-analysis. J Viral Hepat. 2016;23(7):536–44.

**Figures**
Figure 1

Literature search and selection.
Figure 2

(a) Meta-analysis of the association between status of HCV and prognosis of NHL patients. (a) overall survival (OS); (b) progress-free survival (PFS).

Meta-analysis of the association between status of HCV and prognosis of NHL patients. (a) overall survival (OS); (b) progress-free survival (PFS).
### Figure 3

Meta-analysis of the association between status of HCV and overall response rate (ORR) of NHL patients.

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total | Weight | Odds Ratio M–H, Fixed, 95% CI | Odds Ratio M–H, Fixed, 95% CI |
|-------------------|---------------------|----------------|--------------|-------|--------|-------------------------------|-------------------------------|
| Arcaini L 2006    | 22                  | 49             | 128          | 206   | 14.3%  | 0.50 [0.26, 0.93]              |                               |
| Arcaini L 2007    | 56                  | 60             | 98           | 112   | 2.4%   | 2.00 [0.63, 6.37]              |                               |
| Besson C 2006     | 17                  | 24             | 58           | 72    | 4.5%   | 0.59 [0.20, 1.69]              |                               |
| Chen TT 2015      | 20                  | 29             | 107          | 139   | 6.1%   | 0.66 [0.28, 1.60]              |                               |
| D'lovery I 2017   | 18                  | 31             | 205          | 290   | 8.8%   | 0.57 [0.27, 1.22]              |                               |
| Elbedawy TA 2020  | 41                  | 76             | 220          | 277   | 23.0%  | 0.30 [0.18, 0.52]              |                               |
| Ennishi D 2010    | 106                 | 131            | 350          | 422   | 16.7%  | 0.87 [0.53, 1.44]              |                               |
| Hosy J 2016       | 24                  | 36             | 165          | 198   | 8.9%   | 0.40 [0.18, 0.88]              |                               |
| Nikishinova H 2012| 26                  | 28             | 211          | 220   | 1.8%   | 0.55 [0.11, 2.71]              |                               |
| Park B 2008       | 26                  | 29             | 289          | 316   | 2.7%   | 0.81 [0.23, 2.85]              |                               |
| Vallisa 1999      | 40                  | 61             | 81           | 105   | 10.8%  | 0.56 [0.28, 1.13]              |                               |

**Total (95% CI):** 554 / 2357 (100.0%) 0.58 [0.46, 0.73]

Heterogeneity: $\chi^2 = 13.95, df = 10 (P = 0.18); I^2 = 28$

Test for overall effect: $Z = 4.77 (P < 0.00001)$

### Figure 4

Meta-analysis of the association between status of HCV and hepatic dysfunction in NHL patients during chemotherapy.

| Study or Subgroup | Experimental Events | Control Events | Total Events | Total | Weight | Odds Ratio M–H, Random, 95% CI | Odds Ratio M–H, Random, 95% CI |
|-------------------|---------------------|----------------|--------------|-------|--------|-------------------------------|-------------------------------|
| Besson C 2006     | 16                  | 24             | 1            | 72    | 8.4%   | 1.42 [0.57, 3.52]              |                               |
| Chen TT 2015      | 16                  | 29             | 32           | 139   | 16.4%  | 2.22 [1.79, 2.77]              |                               |
| Chen YY 2015      | 5                   | 12             | 21           | 55    | 13.4%  | 1.19 [0.61, 2.31]              |                               |
| D'lovery I 2017   | 12                  | 28             | 22           | 282   | 16.1%  | 2.51 [2.04, 3.08]              |                               |
| Ennishi D 2010    | 36                  | 131            | 33           | 422   | 17.4%  | 11.09 [6.09, 23.35]            |                               |
| Nikishinova H 2012| 7                   | 28             | 35           | 220   | 15.7%  | 1.76 [0.70, 4.46]              |                               |
| Tajima K 2017     | 3                   | 40             | 7            | 613   | 12.6%  | 7.10 [1.74, 28.26]             |                               |

**Total (95% CI):** 292 / 1803 (100.0%) 5.96 [2.61, 13.62]

Heterogeneity: $\tau^2 = 0.91; \chi^2 = 27.11, df = 6 (P = 0.0001); I^2 = 78$

Test for overall effect: $Z = 4.24 (P < 0.0001)$
Figure 5

Meta-analysis of clinical outcomes between HCV-associated NHL patients receiving antiviral treatment and not receiving antiviral treatment. (a) overall survival (OS); (b) progress-free survival (PFS); (c) overall response rate (ORR).
Figure 6

Meta-analysis of clinical outcomes between HCV-associated NHL patients receiving rituximab-containing chemotherapy and rituximab-free chemotherapy. (a) overall survival (OS); (b) progress-free survival (PFS).
**Figure 7**

Meta-analysis of prognostic factors in HCV-associated NHL patients. (a) liver cirrhosis; (b) low level of albumin; (c) liver involvement; (d) elevated alanine transaminase (ALT)

**Supplementary Files**

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