



RCHOP-14 therapy versus RCHOP-21 therapy for people with aggressive or advanced-stage indolent B-cell non-Hodgkins lymphoma: a systematic review and meta-analysis

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Background: With the advent of rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (RCHOP) treatment has become considered the appropriate chemotherapy treatment for aggressive or advanced-stage indolent B-cell non-Hodgkins lymphoma (NHL). In recent years, RCHOP-14 seems to have achieved better outcomes in patients with aggressive or advanced-stage indolent B-cell NHL than RCHOP-21.

Methods: To verify the befitting chemotherapy regimens for patients with B-cell NHL, we searched the electronic databases for relevant English-language literature published in January 2020. The primary outcomes were complete response (CR), progression-free survival (PFS), overall survival (OS), and adverse events (AEs). Six eligible Phase II and III randomized controlled clinical trials (RCTs) and two high-quality observational comparative studies (OCSs) were extracted, with 5,565 patients with B-cell NHL involved in the evaluation.

Results: The analysis demonstrated no significant difference in RCHOP-14 and RCHOP-21 CR rates [odds ratio (OR) =0.98, 95% CI: 0.77–1.24, P=0.85]. Compared with RCHOP-21, the merged hazard ratio (HR) after treatment with RCHOP-14 for PFS and OS was 0.94 (95% CI: 0.84–1.06, P=0.32) and 0.91 (95% CI: 0.83–1.01, P=0.08), respectively. A subgroup analysis based on the international prognostic index (IPI) score showed that both chemotherapy regimens were applicable in B-cell NHL patients with different prognoses. The frequency of toxic side-effects was similar between schemes.

Conclusions: The data presented suggest that the efficacy and safety of both regimens are comparable and that RCHOP-14 remains a viable plan in patients with B-cell NHL who prefer a shorter therapy course.

Keywords: Aggressive; indolent; B-cell lymphoma; rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (RCHOP); a systematic review

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Introduction

Aggressive and indolent lymphomas are two subtypes of B-cell-derived non-Hodgkins lymphoma (NHL) and are treated with different chemotherapy regimens depending

on the prognosis. Aggressive NHL is a highly aggressive malignancy with a poor outcome. It is a greatly chemosensitive tumor and is highly curable (1). An advanced-stage indolent NHL is often incurable and can easily

transform into an aggressive lymphoma. However, it can be alleviated with a regimen of rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone (RCHOP) (2,3). Diffuse large B-cell lymphoma (DLBCL), a disease of biologically, histopathologically, and clinically heterogeneous entities (4), is the most common subtype of aggressive lymphoma. The median survival time of patients with DLBCL who did not undergo prompt treatment is less than 1 year on account of the DLBCL's aggressive nature (5,6). For a long time, the first-line chemotherapy treatment for DLBCL was cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) treatment. It is more reasonable to choose to combine this treatment with CHOP-21 every 3 weeks. Several randomized controlled clinical trials (RCTs) regarding the survival analysis of dose-intensified regimens were conducted, which showed that the CHOP-14 2-week cycle of chemotherapy is superior to the CHOP-21 treatment (7,8).

The human/murine chimeric anti-CD20 monoclonal antibody called rituximab has a credible efficacy. It is well-defined and adequately safe for patients with various CD20-expressing lymphoid malignancies, such as aggressive and indolent forms of B-cell NHL (9). Follicular lymphoma (FL) is a neoplasm comprising germinal center B cells and is a subgroup of indolent lymphomas. The standard option for patients with advanced-stage FL is rituximab-CHOP (10). NHL (PMBL) is a unique subtype of DLBCL originating from thymic B-cells in the mediastinum. The RCHOP regimen, with or without consolidative radiotherapy, is first-line PMBL management (11). It can be observed in all of these diseases, which include DLBL, FL, mantle cell lymphoma, and chronic lymphocytic leukemia, that rituximab-based treatment not only extends the time of the patient's progression-free survival (PFS) but also prolongs his/her overall survival (OS) time (12). Therefore, it is meaningful to discuss the choice between rituximab-based RCHOP-14 and 21 chemotherapy regimens for aggressive or advanced-stage indolent B-cell NHL.

We implement trails from RCTs and observational comparative studies (OCSs) to estimate the efficacy and toxicity of a chemotherapy regimen, comparing RCHOP-14 to RCHOP-21 in patients with B-cell NHL. The results include complete response (CR), PFS, OS, and toxicity levels. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-3123>).

Methods

Search strategy

First, we conducted a systematic and comprehensive search from original to January 2020 throughout databases, including PubMed, Web of Science, Embase, Cochrane Library, and ClinicalTrials.gov. The predefined keywords were used with Boolean operators for the search: "RCHOP-14 AND RCHOP-21" OR "dose-dense" AND "lymphoma". The electronic search was complemented by a manual search for additional articles in reference lists and previous reviews, rendering a full-scale investigation.

Selection criteria

We enrolled trials meeting the below inclusion criteria: (I) high-quality OCS and studies based on RCTs; (II) participants newly diagnosed with aggressive lymphoma at clinical stages I–IV or untreated advanced-stage indolent B-cell NHL; (III) comparative analysis of RCHOP-14 and RCHOP-21 for treating B-cell NHL; (IV) follow-up duration longer than 36 months (V) an existence outcome of CR, PFS or OS in the articles. Duplicated data that might lead to an overestimation of intervention effects was contained cautiously. Review articles, conference abstracts, nonhuman studies, case reports, abstracts, and unpublished data were excluded from consideration. Moreover, studies that did not exclude data were not included. If there were differences regarding which studies should be included, experts decided whether to include them or not.

Data extraction and quality assessment

Relevant Data were independently extracted from included articles by two authors. The following data were extracted: the first author, published year, location, disease, stage, median age, median follow-up, number of patients with international prognostic index (IPI) at different levels, sample size, number of cycles, and clinical outcomes (including CR, PFS, OS and toxicity). We assessed the quality of RCTs using the Cochrane Collaboration's risk of bias tool, Rev Man 5.3. The quality of selected studies was appraised with methodological domains as follows: risks of selection, performance, detection, attrition, and reporting biases. For the included study, types of bias are divided into three levels: low, unclear, high. The Newcastle-Ottawa scale (NOS) uses three categories, the selection of study groups,

comparability, and outcome assessment, respectively, to evaluate the risk of OCS biases.

Statistical analysis

A meta-analysis of variables with three or more studies was performed when the outcome was reported. Statistical heterogeneity among individual studies was calculated by the P and I^2 test, where heterogeneity will be considered substantive if $I^2 > 50\%$ (13). The fixed-effect model and the random-effects models were utilized for both consistent and heterogeneous studies in accordance with the previously published guidelines for statistical reporting and a systematic review manual on Cochrane interventions. PFS and OS, as the dichotomous data, were reported with hazard ratios (HRs) and 95% CIs. HR is calculated by the inverse of variance. It is used to weigh the size of the individual effect. The CR rate was calculated through the odds ratio (OR) with the random-effects model (M-H methods) and adverse events (AEs), used to analyze the risk ratio (RR), were calculated with the same model. Next, the forest map for meta-analysis was drawn. When possible, sensibility analysis was conducted to investigate the origins of heterogeneity. Funnel plots were performed to attest the presence of publication bias. All statistical analyses were conducted in Review Manager 5.3.

Results

Description of studies

A total of 403 potentially relevant studies were ascertained after the initial search (Figure 1). Of these, 31 articles were from PubMed, 59 from Embase, 173 from Web of Science, 134 from Cochrane Library and 6 from clinicaltrials.gov. One hundred eighty-one irrelevant articles and 142 duplicated articles were expurgated by carefully reviewing the titles and abstracts. Sixty-six pieces of literature were deleted for the reason that these trials were conference reports, non-original or scarce data, review or meta-analysis, or weren't RCHOP-14 vs. RCHOP-21 and related results. Finally, six RCTs—Cunningham *et al.* (2013), Delarue *et al.* (2013), Payandeh *et al.* (2016), Watanabe *et al.* (2018), Li *et al.*, (2019), and Gleeson *et al.* (2016)—and two OCSs—Wästerlid *et al.* (2017) and Knauf *et al.* (2019)—met all inclusion criteria entered in this meta-analysis (14-21).

Patients types

In total, the five studies included 5,565 patients with B-cell NHL, of whom 2,892 underwent RCHOP-14 and 2,673 only underwent RCHOP-21. The experimental characteristics of each RCT are summarized in Table 1. Most of the enrolled trials were from different countries, four of which are in Europe. Four trails accounting for studies were from Asia. We collected patients above the age of 18 with clinical stage I–IV aggressive lymphoma and untreated stage III–IVV indolent B-cell NHL. The granulocyte colony-stimulating factor (G-CSF) was applied to both the RCHOP-14 group and the RCHOP-21 group to shorten the CHOP treatment. Stimulating Moreover, the sample sizes for individual studies varied widely from 50 to 2,106 despite being multi-center clinical trials.

Quality assessment

Six RCTs were assessed as low risk in the light of a suitable option (Figure 2A,B). However, four RCTs had a high risk of selection bias as allocation concealment (14,16,18,21). All funnel plots of PFS and OS were symmetrical, indicating no publication bias (Figure 2C,D). The selection of high-quality OCSs was based on a validated tool. Two OCSs were evaluated by NOS (Table 2), and the results suggested that both of them were high-quality literature.

Efficacy

CR rate data were available from eight studies (14-21), incorporating 2,657 patients from the RCHOP-14 therapeutic regimen and 2,415 patients from the RCHOP-21 regimen. A significant heterogeneity was found within these two regimes ($\chi^2=17.69$, $P=0.007$, $I^2=66\%$) (Figure 3). The random-effects model was subsequently used. The CR rate did not meliorate with RCHOP-14 regimens in patients (OR =0.96, 95% CI: 0.76–1.23, $P=0.76$). The results of the RCTs and OCSs were consistent, so we calculated the data together and displayed it on a graph.

Survival

The PFS and OS of RCHOP-14 vs. RCHOP-21 was the main long-term clinical outcome evaluation with B-cell

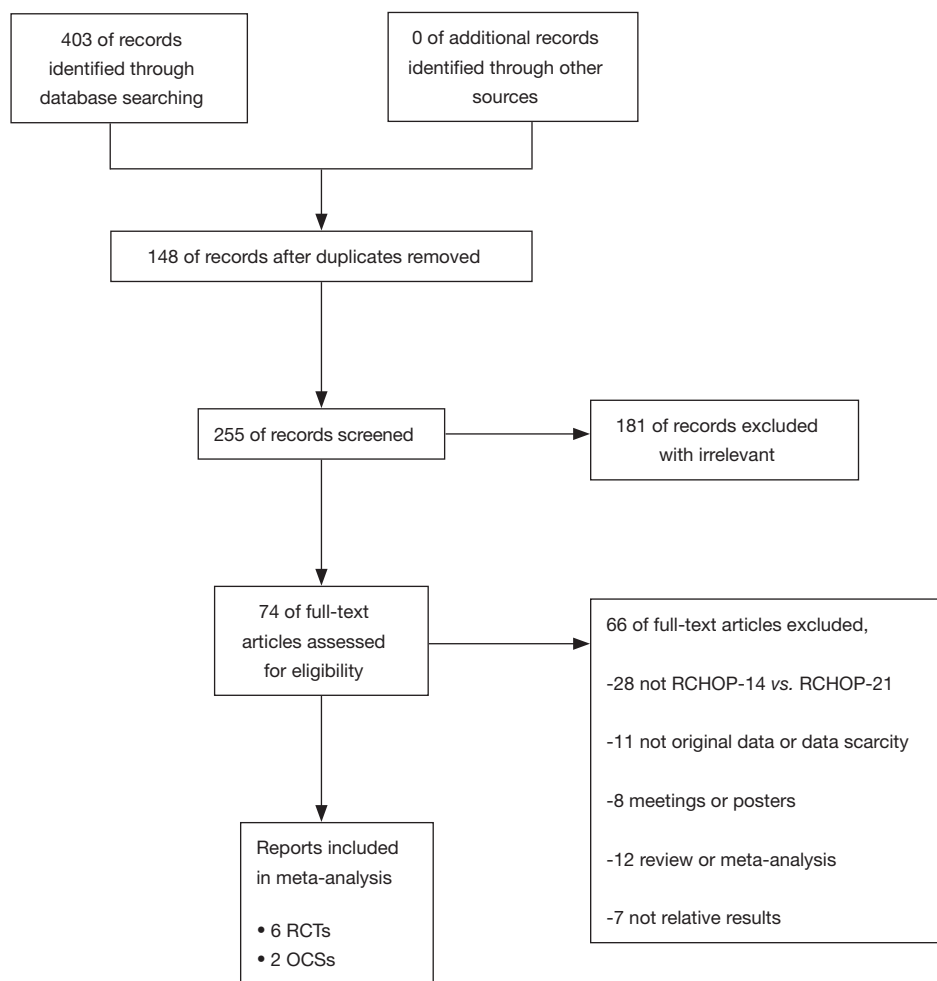


Figure 1 Flow diagram of the study selection process. RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone; RCTs, randomized controlled clinical trials; OCSs, observational comparative studies.

lymphoma. *Figures 4,5* suggest that no significant between-trial heterogeneity was observed between PFS and OS. Hence, we chose the fixed-effect model. The results of the OCSs were consistent with the RCTs, so we presented these data in a single graph and stratified the clinical outcomes of patients with different prognoses based on the IPI scores. For the comparison, PFS was curtailed in RCHOP-14, but it showed no significant difference (HR =0.94, 95% CI: 0.84–1.06, P=0.32). Results were not altered after differentiating patients with different IPI scores (*Figure 4*). Regarding OS, RCHOP-14 was superior to RCHOP-21 (HR =0.91, 95% CI: 0.83–1.01, P=0.08) (*Figure 5*). However, there was still no statistical difference among the trials. After stratification according to the IPI score, the OS of patients with different prognoses was in agreement with

the outcome indicators of all patients.

Treatment-related toxicity

AEs, including both hematological and non-hematological toxicities, with both RCHOP-14 and RCHOP-21 treatment protocols were reviewed in all RCTs. *Table 3* summarizes the grade ≥ 3 AEs. We have used RR values to compare the AEs of the five studies in the supplementary picture, and the toxicity of the RCHOP-14 regimen and RCHOP-21 regimen does not have a significantly high risk (RR =0.98, 95% CI: 0.83–1.15, P=0.73). $I^2=85\%$ suggested greater heterogeneity among the trials, which was statistically significant. The subgroup analysis results on hematological AEs show that the incidences of thrombocytopenia (RR

Table 1 Description of include studies

Study	Location	Disease	Stage	Median follow-up (months)	Sample size		Number of cycles		Use of G-CSF	
					RCHOP-14/ RCHOP-21	540/540	RCHOP-14/ RCHOP-21	RCHOP-14/ RCHOP-21	RCHOP-14	RCHOP-21
Cunningham 2013 (14)	UK	DLBCL	I-IV	46		540/540	6 plus 2 R/8	Given to all patients		54% of patients
Delarue 2013 (15)	France, Belgium, Switzerland, Portugal	DLBCL	I-IV	56		304/298	8/8	90% of patients, decision of the treating physician		74% of patients, decision of the treating physician
Gleeson 2016 (21)	UK	DLBCL	I-II	86.4		22/28	6 plus 2 R/8	Given to all patients		54% of patients
Payandeh 2016 (17)	Iran	B-cell NHL	III-IV	45		66/77	6-8/6-8	Given to all patients		At the desertion of the treating physician
Watanabe 2018 (16)	Japan	Untreated advanced-stage FL	III-IV	134.4		151/149	6/6	Given to all patients		At the desertion of the treating physician
Li 2019 (18)	China	DLBCL	I-IV	45.6		349/353	6-8/6-8	Given to all patients		The investigator's discretion
Wästerlid 2017 (20)*	Swedish	PMBL	I-IV	47.4		1196/910	6/6	Not report		Not report
Knauf 2019 (19)*	German	DLBCL	I-IV	60		264/318	6/6	73% of patients use it at least once		48.7% of patients use it at least once

* , OCSS. G-CSF, granulocyte colony-stimulating factor; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone; DLBCL, diffuse large B-cell lymphoma; PMBL, primary mediastinal B-cell lymphoma; FL, follicular lymphoma; R, rituximab; OCSS, observational comparative studies.

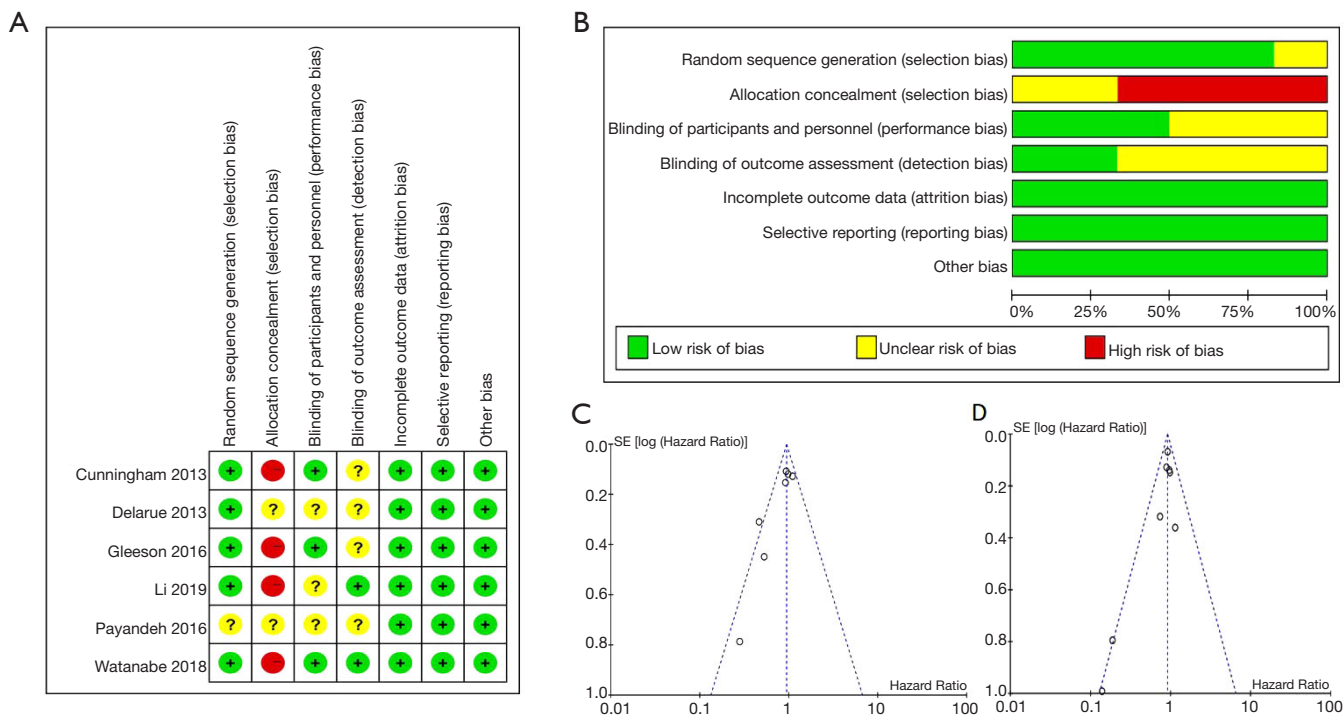


Figure 2 The risk of bias. (A) Risk of bias summary; (B) risk of bias graph; (C) PFS funnel plot; (D) OS funnel plot. PFS, progression-free survival; OS, overall survival.

Table 2 Quality assessment of OCSs by NOS scale

Study	Items	Wästerlid 2017 (20)	Knauf 2019 (19)
Selection	Representativeness of the exposed cohort	*	*
	Selection of the non-exposed cohort	*	*
	Ascertainment of exposure	*	*
	Demonstration that outcome of interest was not present at start of study	*	*
Comparability	Comparability of cohorts on the basis of the design or analysis	**	**
Outcome	Assessment of outcome	*	*
	Was follow-up long enough for outcomes to occur	*	*
	Adequacy of follow up of cohorts	*	*

*, star-rating in NOS, each study can have a maximum of one star per entry in “Selection”, “Outcome” and a maximum of two stars per entry in “Comparability”. OCSs, observational comparative studies; NOS, Newcastle-Ottawa scale.

=0.87, 95% CI: 0.60–1.25, P=0.44) were higher in the RCHOP-14 arm (9,10,12–14), although this has no statistical significance. One of the subgroup analyses with patients who received RCHOP-21, who have a higher trend of anemia when ceasing treatment Watanabe *et al.* (RR

=1.15, 95% CI: 0.88–1.50, P=0.29), was observed (14,17,18). The subgroup analysis on non-hematological AEs indicates that patients treated with RCHOP-21 had a higher risk of neurological-related, which was not statistically significant (RR =1.41, 95% CI: 0.85–2.33, P=0.18).

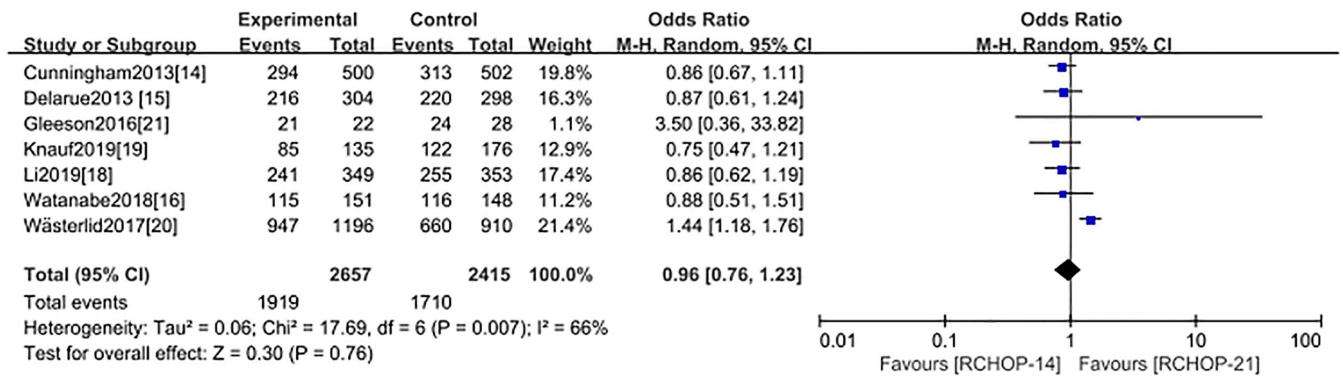


Figure 3 CR rate for RCHOP-14 vs. RCHOP-21. CR, complete response; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone.

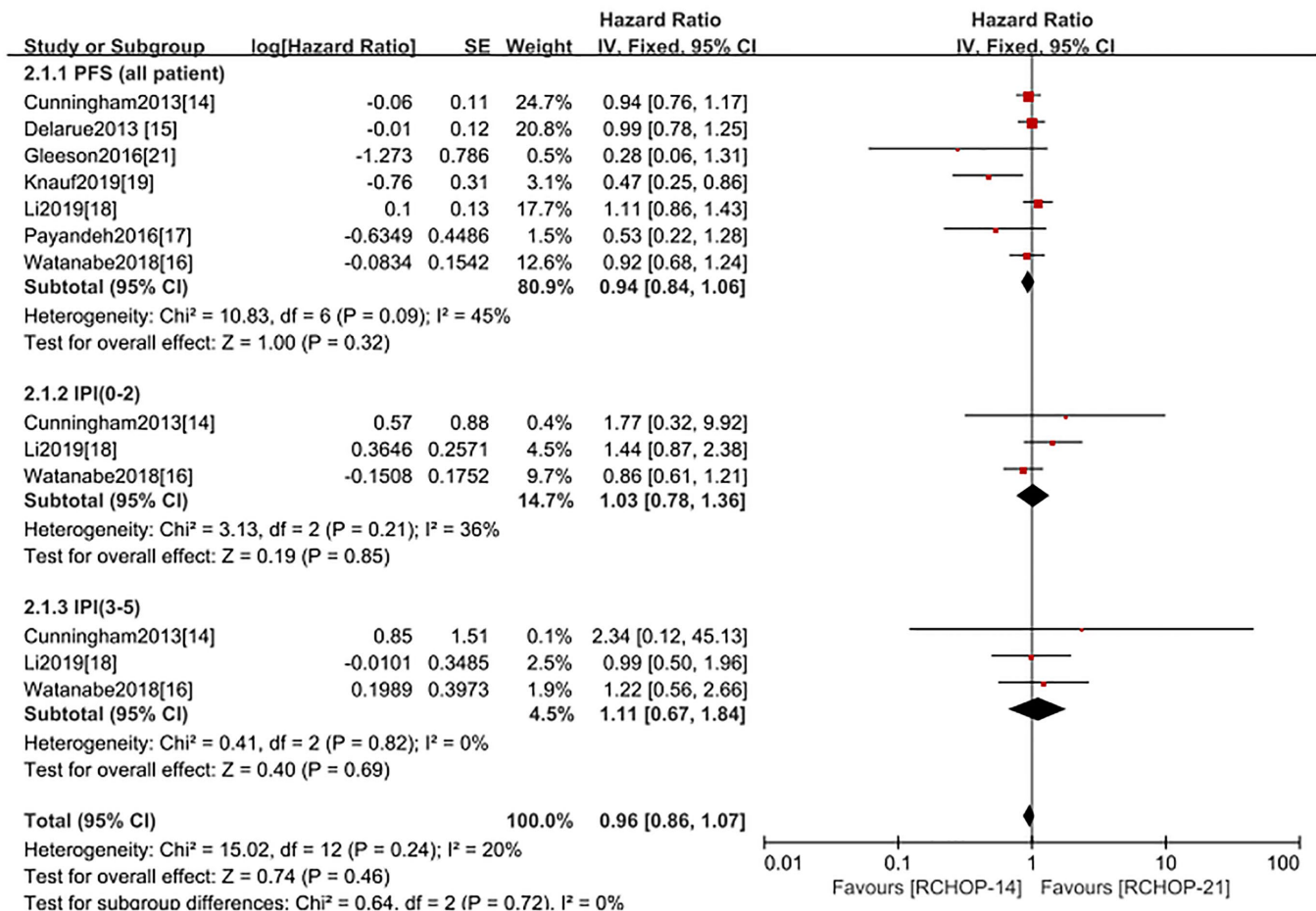


Figure 4 PFS for RCHOP-14 vs. RCHOP-21 of all patients and different IPI scores patient. PFS, progression-free survival; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone; IPI, international prognostic index.

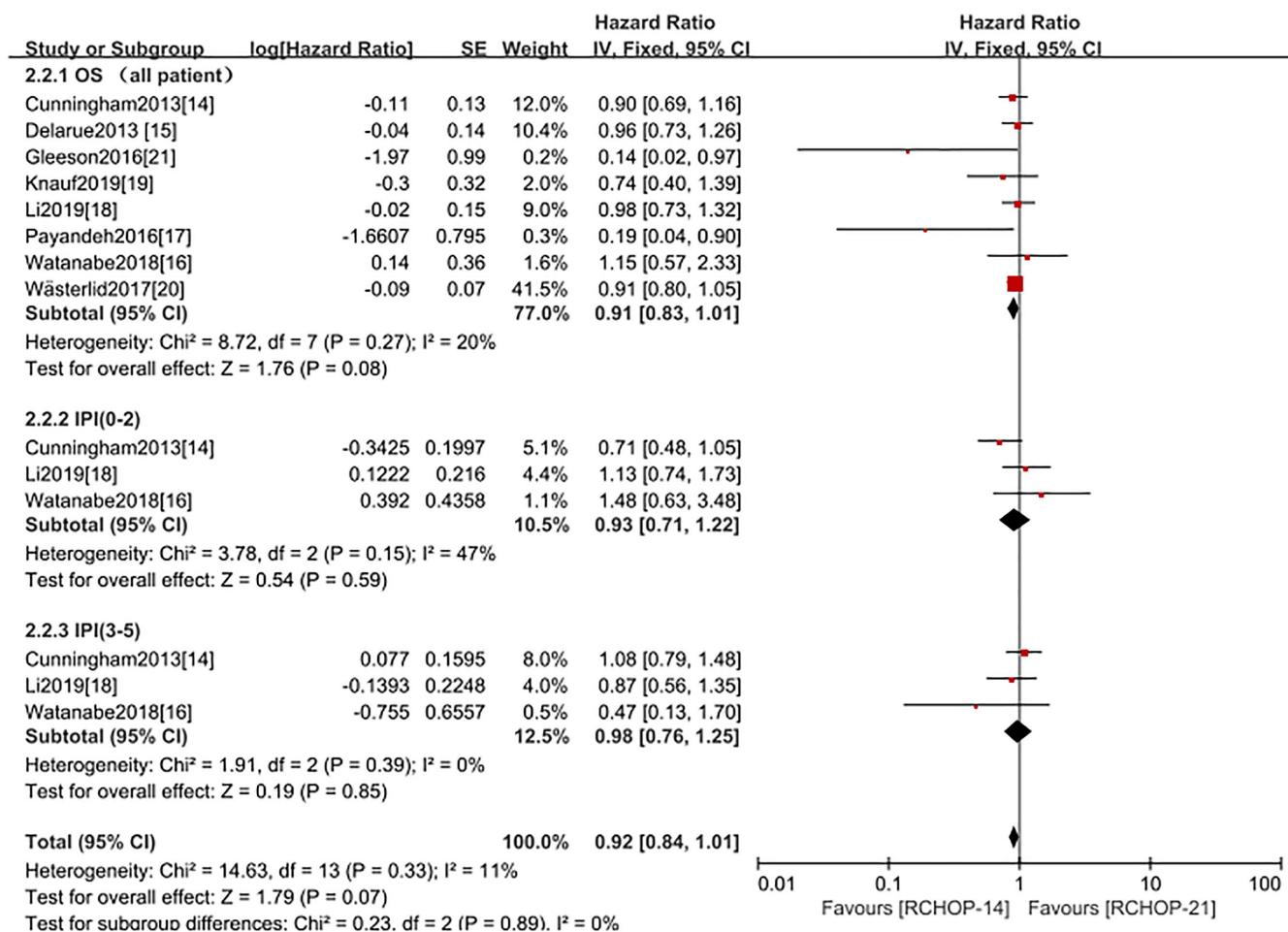


Figure 5 OS for RCHOP-14 vs. RCHOP-21 of all patients and different IPI scores patient. OS, overall survival; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone; IPI, international prognostic index.

Discussion

At a clinical level, RCHOP-14 and RCHOP-21 are the two different international standards used for the treatment of B-cell lymphoma. This manuscript implies that the CR rate, PFS, and OS were higher in patients who were assigned RCHOP-14 therapy. However, its outcomes did not differ significantly. This indicates that improvement of the CR rate, PFS, and OS in these patients may not be possible through RCHOP-14. More RCTs are required in order to confirm whether the addition of radiotherapy can change this outcome or not. The previous meta-analysis shows that the treatment options of RCHOP were manifested to prolong OS when given every 14 days instead of 21 days in case rituximab was omitted (22). Our analysis showed

that RCHOP-14 and RCHOP-21 have no statistically significant difference in PFS and OS.

Toxicity was an important endpoint of our study. There is a higher risk of infectious complications associated with RCHOP14, particularly febrile neutropenia, due to infections caused by opportunistic pathogens (23-25). However, our study shows that the toxicity of RCHOP-14 regimen is the same as the toxicity of the RCHOP-21 regimen in B-cell patients, rather than higher. One reason why the RCHOP-14 regimen has the same safety-rate as the prophylactic recombinant human G-CSF. G-CSF has often been used to potentiate the antibody-dependent cell-mediated cytotoxicity of rituximab (26,27), after which CHOP intervals can be shortened (7,8,28,29). More patients who were given the prophylactic recombinant

Table 3 Incidence and relative risk of specific SAEs in included trials

Specific AEs	Number of studies	RCHOP-14		RCHOP-21		Heterogeneity	
		Pts with SAE/total pts	Pts with SAE/total pts	Relative risk (95% CI)	P value	P value	I ² (%)
Neutropenia	5	722/1,340	896/1,408	0.93 (0.64–1.36)	0.71	<0.00001	98
Thrombocytopenia	5	102/1,340	132/1,408	0.87 (0.60–1.25)	0.44	0.15	41
Anemia	4	121/770	97/874	1.15 (0.88–1.50)	0.29	0.48	0
Febrile neutropenia	3	103/989	134/978	0.66 (0.33–1.30)	0.23	0.001	85
Infection	4	209/1,238	225/1,331	1.18 (0.72–1.91)	0.51	0.0003	84
Gastrointestinal toxicity	4	70/1,238	74/1,331	1.00 (0.73–1.38)	0.98	0.52	0
Increase in amount of liver enzymes	3	21/521	21/521	1.04 (0.58–1.86)	0.9	0.99	0
Cardiac-related	3	15/521	14/521	1.04 (0.15–7.34)	0.97	0.02	74
Neurological-related	3	80/989	57/978	1.41 (0.85–2.33)	0.18	0.19	40

SAE, severe adverse event; AE, adverse event; RCHOP, rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone.

human G-CSF every 14 days developed grade 3–4 neutropenia than reported previously (14). One type of toxicity is thrombocytopenia, especially in the RCHOP-14 regimen. It may increase the chance of intravenous platelet. Meanwhile, anemia is more likely to occur for RCHOP-21, which leads frequent transfusions. Another apparent reason is that there is greater heterogeneity between subgroups and the results may be unreliable.

As far as we can see, this study is the first meta-analysis to assess the efficacy and toxicity of the CHOP regimen in patients with aggressive or advanced-stage indolent B-cell NHL based on rituximab. It is also the first to analyze survival outcomes for patients with different prognostic outcomes based on IPI scores. The data suggests that we could face type 2 errors in the RCTs. The main argument for including OCSs is trying to avoid making this mistake. However, the meta-analysis still has some limitations. Firstly, it is possible that two studies caused performance and detection biases because of they were open-label trails. In the second place, the low number of included studies made it difficult for a detailed, in-depth probe and an interpretation of a potential underlying heterogeneity. When ascertaining heterogeneity among individual studies for toxicity, which is still significantly high after removing the relevant study. The reason for the high heterogeneity may be the different B-cell NHL prognoses and the inconsistent chemotherapy cycle. Therefore, we need more RCTs to explore the potential causes of heterogeneity.

In the end, other covariates, such as supportive therapy, preventive measures of toxicity, and the proficiency of a doctor, could not be balanced in the study.

Conclusions

To sum up the study, an analysis of data from clinical trials of RCHOP-14 treatment showed that the therapies are safe and effective compared with the RCHOP-21 treatment. However, there was no significant difference in PFS and OS, and that it produces clinical responses similar to those in CR rate. Additional considerations in regard to choosing the treatment strategy and balancing treatment-related toxicity may help us to decide whether to treat with RCHOP-14 or RCHOP-21.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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