Therapy with of RCHOP-14 Versus RCHOP-21 for People With Aggressive or Advanced Stage Indolent B-Cell Non-Hodgkins Lymphoma: A Systematic Review and Meta-Analysis

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Research

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Abstract

Background: With the advent of rituximab, RCHOP is considered the appropriate chemotherapy for aggressive or advanced stage indolent B-cell Non-Hodgkins Lymphoma(NHL). RCHOP-14 seems to achieve better outcomes than RCHOP -21 in aggressive or advanced stage indolent B-cell NHL patients in recent years.

Methods: To verify the befitting chemotherapy regimens for B-cell NHL patients, we searched the electronic databases for relevant English-language literature published through 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 clinical randomized controlled trials (RCTs) and two high-quality observational comparative studies (OCSs)were extracted, and 5565 B-cell NHL patients involved in evaluable.

Results: The analysis demonstrated no significant difference for CR rate (OR= 0.98,95%CI 0.77-1.24，P=0.85)between RCHOP-14 and RCHOP-21. Compared with RCHOP-21, the merged hazard ratio (HR) for PFS and OS was, respectively, 0.94 (95% CI: 0.84-1.06, P=0.32) and 0.91(95% CI: 0.83-1.01, P= 0.08) after treatment with RCHOP-14.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 prognosis. The frequency of toxic side-effects was similar between schemes.

Conclusions: Therefore, the data presented suggest that the efficacy and safety of both regimens are comparable and that R-CHOP14 remains a viable plan in B-cell NHL patients who prefer a shorter therapy course.

Background

Aggressive and indolent lymphomas are two subtypes of B-cell-derived NHL, and they have different chemotherapy regimens depending on the prognosis. Aggressive NHL is a highly aggressive malignancy with a poor outcome,which is a greatly chemo-sensitive tumor and is highly curable(1). Advanced stage indolent NHL is often incurable and can easily be converted to aggressive lymphoma, but 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)is the most common subtype of aggressive lymphoma, which is a disease of biologically, histopathologically, and clinically heterogeneous entity(4). The median survival of NHL patients without prompt treatment was less than one year, on account of its aggressive nature(5, 6). For a long time, the first-line chemotherapy treatment for DLBCL is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), which is more reasonable to choose CHOP-21 that is every 3 weeks in combination. Some RCTs were enquired about the survival analysis of dose-intensified regimens, and then showing that the two-week cycle of chemotherapy (CHOP-14) is superordinate than the CHOP-21(7, 8).

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

We implement trails from RCTs and OCSs to estimate the efficacy and toxicity of a chemotherapy regimen as RCHOP-14 compared to RCHOP-21 for patients with B-cell NHL, the results as an on CR, PFS, OS and toxic.

Methods

Search strategy

Firstly, we search to conduct a systematic and comprehensive search from original to January 2020 throughout databases, including PubMed, Web of Science, Embase, Cochrane Library, ClinicalTrials.gov.The predefined keywords with Boolean operators were used 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 certain a full-scale investigation.

Selection criteria

We enrolled trials must meeting the below inclusion criteria: (1) studies based on RCTs and high-quality OCSs;(2) participants were newly diagnosed aggressive lymphoma at clinical stage I to IV or untreated advanced-stage indolent B-cell NHL;(3) comparative analysis of RCHOP-14 and RCHOP-21 for treating B-cell NHL; (4) follow-up duration longer than 36 months (5) CR□PFS or OS was existence outcome in the articles. The containing of duplicated data that might lead to an overestimation of intervention effects was cautious. Review articles, conference abstracts, nonhuman studies, case reports, abstracts, and unpublished data were excluded from consideration. Moreover, studies had no extractable data that were also excluded. A senior referee was consulted if divergence regarding which studies to include.

Data extraction and quality assessment

Relevant Data were extracted from included articles by two authors independently. The following data were extracted: the first author, published year, location, disease, stage, median age, median follow-up, number of patients with 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 Man5.3. The quality of selected studies will be 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 3 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 bias of OCSs.

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, and heterogeneity will be considered substantive if $I^2 > 50\%$(13). The fixed-effect model and the random-effects model were utilized for consistent and heterogeneous studies, respectively, 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 to weigh the size of the individual effect.CR rate was calculated by odds ratio (OR) with the random-effects model (M-H methods), and adverse events to analyze using the Risk Ratio(RR) were calculated either the same model. Then, the forest map for meta-analysis was drawn. If possible, sensibility analysis is conducted to investigate the origins of heterogeneity. Funnel plots were performed to confirm attest to 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 from PubMed, 59 from Embase, 173 from Web of Science, 134 from Cochrane Library and 6 from clinicaltrials.gov. Then, 181 papers not relevant articles and 142 duplicated articles were expurgated by carefully reviewing the titles and abstracts. 66 pieces of literature were deleted by reason that these trials were conference reports, non-original data or data scarcity, review or meta-analysis, not RCHOP-14 VS RCHOP-21 and relative results. Finally, 6 RCTs (Cunningham et al., 2013, Delarue et al.,2013, Payandeh et al.,2016, Watanabe et al.,2018, Li et al.,2019, Gleeson et al.2016)and 2 OCSs (Wästerlid et al.,2017, Knauf et al.,2019) met all inclusion criteria entered in this meta-analysis(14-21).

Type of patients

In total, five studies included 5565 patients with B-cell NHL, whom 2892 underwent RCHOP-14, and 2673 underwent RCHOP-21 only. The experimental characteristics of each RCT are summarized in Table 1. Most of the enrolled trials in different countries, four of which are included in Europe, four trails accounting for studies were in Asian. We collected patients with clinical stage I -IV aggressive lymphoma and untreated III-IVV stage indolent B-cell NHL, who were older than 18 years. G-CSF(Granulocyte ColonyFactor) was applied to both the RCHOP-14 group and the RCHOP-21 group to shorten CHOP. -Stimulating Moreover, the sample sizes for individual studies varied widely from 50 to 2106 despite were multi-center clinical trials.

Qualityassessment

Six RCTs were assessed as low risk in the light of a suitable option (Figure 2A and 2B). However, four of RCTs have 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 and 2D). 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

Complete response rate data were available from 8 studies(14-21)，incorporating 2657 patients from the RCHOP-14 therapeutic regimen and 2415 patients from the RCHOP-21 regimen. As shown in Figure 3, we find that significant heterogeneity within these two regimes (χ^2=17.69, P=0.007, I^2=66 %)，then the random-effects model was used.CR rate not meliorated 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 versus RCHOP-21 as the main long-term clinical outcome evaluation with B-cell lymphoma. Figure 4 and 5 suggest that no significant between-trial heterogeneity was observed between PFS and OS, then, we choose 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 IPI.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，, in other words, the two regimens of chemotherapy are equivalent for patients with aggressive or indolent lymphoma. As shown in Figure 5, regarding OS, there was a tendency that RCHOP-14 was superior to RCHOP-21 (HR=0.91, 95% CI 0.83–1.01, P= 0.08). However, there was still no statistical difference among the trials. After stratification according to the IPI score, the OS of patients with different prognosis was in agreement with the outcome indicators of all patients.

Treatment-related toxicity

AEs with both RCHOP-14 and RCHOP-21 treatment protocol were reviewed in all RCTs, including both hematological and non-hematological toxicities. Table 3 summarizes the grade ≥ 3 adverse events.we have used RR(Risk Ratio) values to compare the adverse events of the five studies in the supplementary picture, the toxicity of RCHOP-14 regimen and RCHOP-21 regimen has no significant 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 that the incidences of thrombocytopenia(RR= 0.87, 95% CI 0.60–1.25, P= 0.44) were higher in the RCHOP-14 arm[9, 10, 12-14], although there is no statistical significance. One of subgroup analysis were observed with patients who received RCHOP-21, which has a higher trend to have Anemia when removing to Watanabe et.al. (RR= 1.15, 95% CI 0.88–1.50, P= 0.29) (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 were not statistically significant(RR= 1.41, 95% CI 0.85–2.33, P= 0.18).

Discussion

In clinical, RCHOP-14 and RCHOP-21 are the two different international standards, respectively, which were used for the treatment of B-cell lymphoma. This manuscript implies that the CR rate, PFS, and OS were higher in patients who assigned to RCHOP-14 therapy, but its outcomes did not differ significantly. This indicates that the CR rate, PFS, and OS in these patients may be unable to be improved through the way RCHOP-14. Whether the addition of radiotherapy can change this outcome requires more RCTs to confirm. The previous meta-analysis has shown that the treatment options of RCHOP were manifested to prolong OS when given every 14 days instead of 21 days as in case rituximab is omitted(22). In our analysis, it showed that RCHOP-14 and RCHOP-21 have no statistically significant difference in FPS and OS, which is inconsistent with previous findings. Nevertheless, many researchers do not embrace that R-CHOP-14 is the first-line treatment of DLBCL until bringing a randomized study with a control arm of R-CHOP-21 into force, also, the fear that it is too toxic of RCHOP-14 regimen is another reason.

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). But our study shows that the toxic of R-CHOP-14 regimen is the same as the RCHOP-21 regimen in B-cell patients, rather than exceed. One reason for the RCHOP-14 regimen has the same safety maybe that prophylactic recombinant human granulocyte colony-stimulating factor(G-CSF). G-CSF has often been used to potentiate the antibody-dependent cell-mediated cytotoxicity of rituximab(26, 27), then can be shortened CHOP intervals(7, 8, 28, 29).In spite of prophylactic recombinant human G-CSF, patients were given every 14 days developed more grade 3 to 4 neutropenia than reported previously(14). One of toxic is thrombocytopenia, which more obviously in the RCHOP-14 regimen, and thus may increase the chance of intravenous platelet. Meanwhile, RCHOP-21 is more likely to occur anemia events, which lead to the frequency of transfusion. Another obvious reason is that there is greater heterogeneity between subgroups and the results may be unreliable.

As far as we can see, it is the first meta-analysis to assess the efficacy and toxicity based on rituximab with the CHOP regimen in patients with aggressive or advanced stage indolent B-cell NHL, and it is the first to analyze survival outcomes for patients with different prognostic outcomes based on IPI scores. The data suggested that we would face type 2 errors in the RCTs, the main argument for including OCSs is

trying to avoid making this mistake. But the meta-analysis is still some limitations. Firstly, two studies maybe cause performance and detection biases because of they were open-label trails. In the second place, the low number of included studies made it difficult to probe in-depth with in detail and to interpret potential underlying heterogeneity. When we ascertaining heterogeneity among individual studies for toxic, which is still significantly high after removing the relevant study. The reason for the high heterogeneity may be the different prognosis of B-cell NHL and the inconsistent chemotherapy cycle. Therefore, we need more RCT to explore the potential causes of heterogeneity. In the end, other covariates, such as supportive therapy, preventive measures of toxicity, and the proficiency of the doctor, could not be balanced in the study.

Conclusions

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

Abbreviations

RCHOP: rituximab combined with cyclophosphamide, doxorubicin, vincristine, and prednisolone

NHL:Non-Hodgkins Lymphoma

CR: complete response

PFS:progression-free survival

OS:overall survival

AEs:Adverse events

RCTs:randomized controlled trials

OCSs: observational comparative studies

HR:hazard ratio

IPI: international prognostic index

DLBCL:Diffuse large B-cell lymphoma

CHOP:cyclophosphamide, doxorubicin, vincristine, and prednisone

RT:radiotherapy

FL:follicular lymphoma

ML:mantle cell lymphoma

NOS:Newcastle-Ottawa-Scale

HRs: hazard ratios

OR: odds ratio

RR:Risk Ratio

NOS:The Newcastle-Ottawa-Scale

G-CSF(Granulocyte ColonyFactor

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

No potential conflicts of interest were disclosed.

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Authors' contributions

Conception and design of the research: YH. Acquisition of data: WqT.Analysis and interpretation of the data: DxJ. Statistical analysis :WL . Obtaining financing : None. Writing of the manuscript : YX. Critical revision of the manuscript for intellectual content : GaC.

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Tables

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	RCHOP-14/RCHOP-21	RCHOP-14	RCHOP-21
Cunningham2013[14]	UK	DLBCL	I -IV	46	540/540	6 plus 2 R/8	Given to all patients	54% of patients
Delarue2013 [15]	France Belgium Switzerl Portugal	DLBCL	□ - □	56	304/298	8/8	90% of patients,decision of the treating physician	74% of patients, decision of the treating physician
Gleeson2016[21]	UK	DLBCL	I-II	86.4	22/28	6 plus 2 R/8	Given to all patients	54% of patients
Payandeh2016[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
Watanabe2018[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

Note:*:observational comparative studies;R:rituximab;G-CSF:Granulocyte Colony-Stimulating Factor;DLBCL:Diffuse large B-cell lymphoma;PMBL:Primary mediastinal B-cell lymphoma.

Table 2
Quality assessment of observational comparative studies by NOS scale.

Study		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	*	*

Table 3
.Incidence and relative risk of specific severe adverse events (SAEs) in included trials

		RCHOP-14	RCHOP-21			Heterogeneity	
Specific adverse events	Number of studies	Pts with SAE/total Pts	Pts with SAE/total Pts	Relative risk (95% CI)	P value	P value	I^2 (%)
Neutropenia	5	722/1340	896/1408	0.93(0.64–1.36)	0.71	<0.00001	98
Thrombocytopenia	5	102/1340	132/1408	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	209/1238	225/1331	1.18(0.72–1.91)	0.51	0.0003	84
Gastrointestinal toxicity	4	70/1238	74/1331	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

Figures

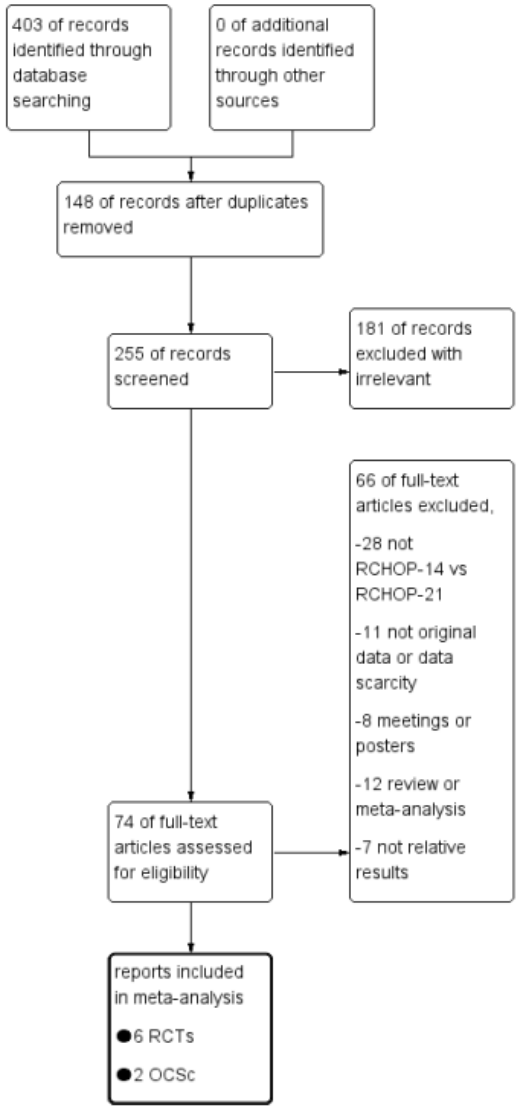

Figure 1

Flow diagram of the study selection process.

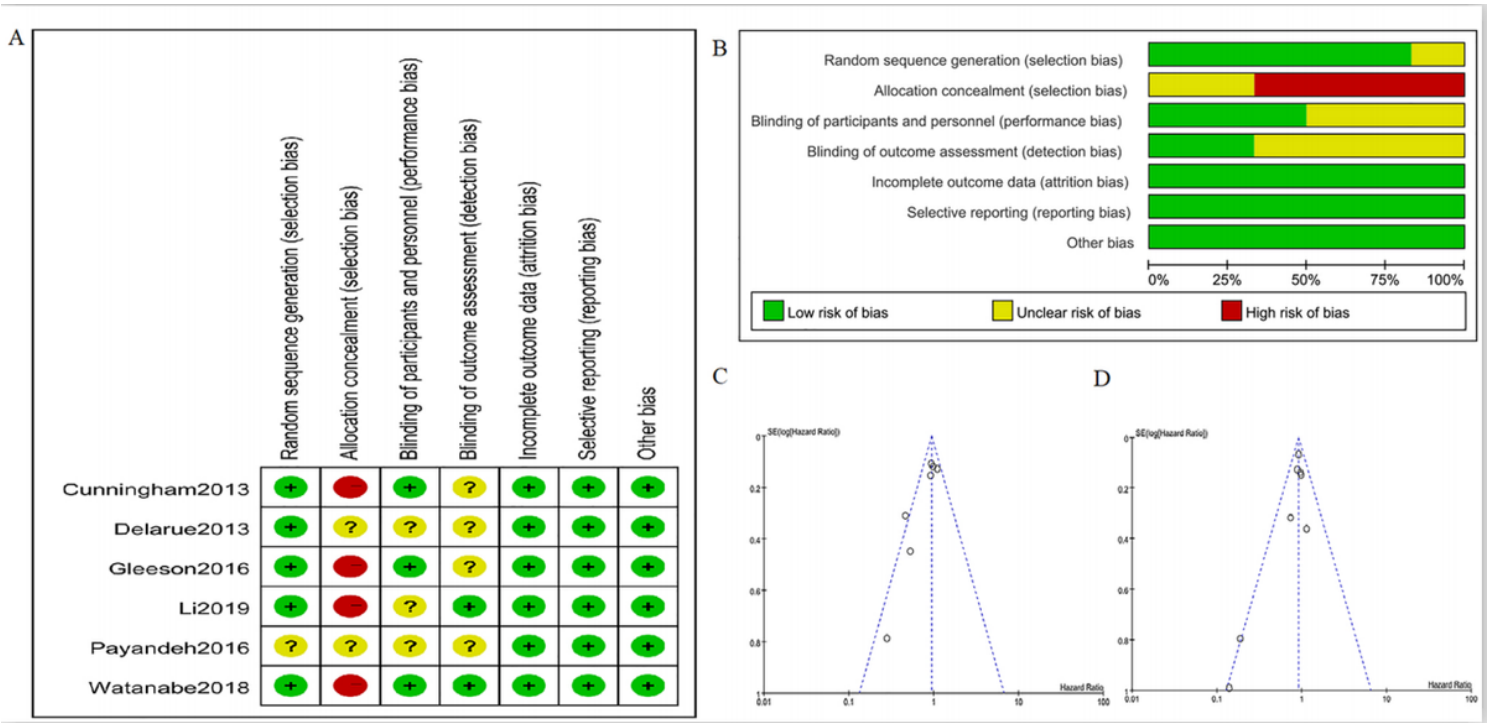

Figure 2

A: Risk of bias summary, B: risk of bias graph, C: PFS Funnel plot, D:OS Funnel plot.

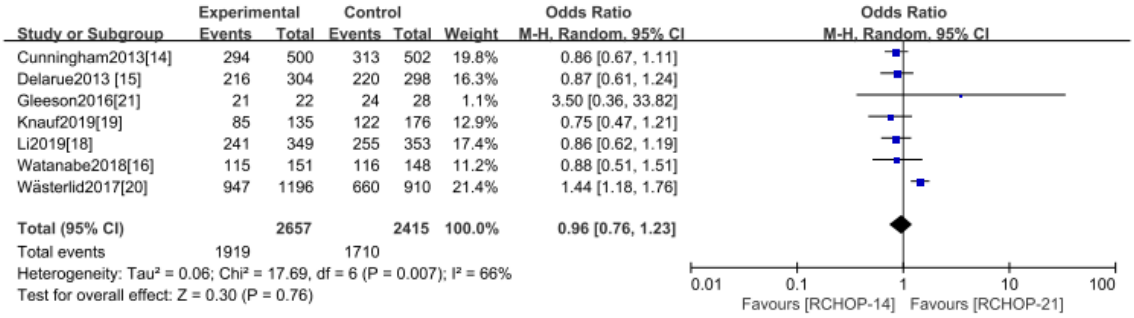

Figure 3

CR rate for RCHOP-14 VS RCHOP-21.

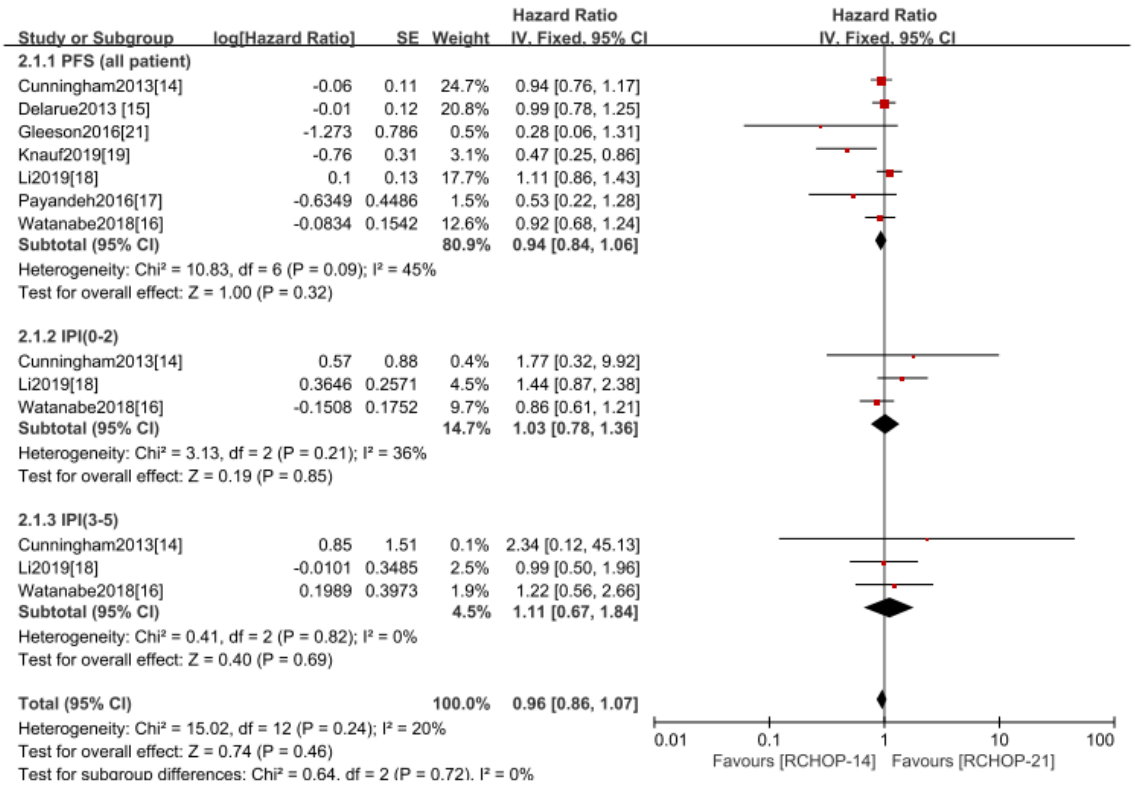

Figure 4

PFS for RCHOP-14 VS RCHOP-21 of all patients and different IPI scores patient.

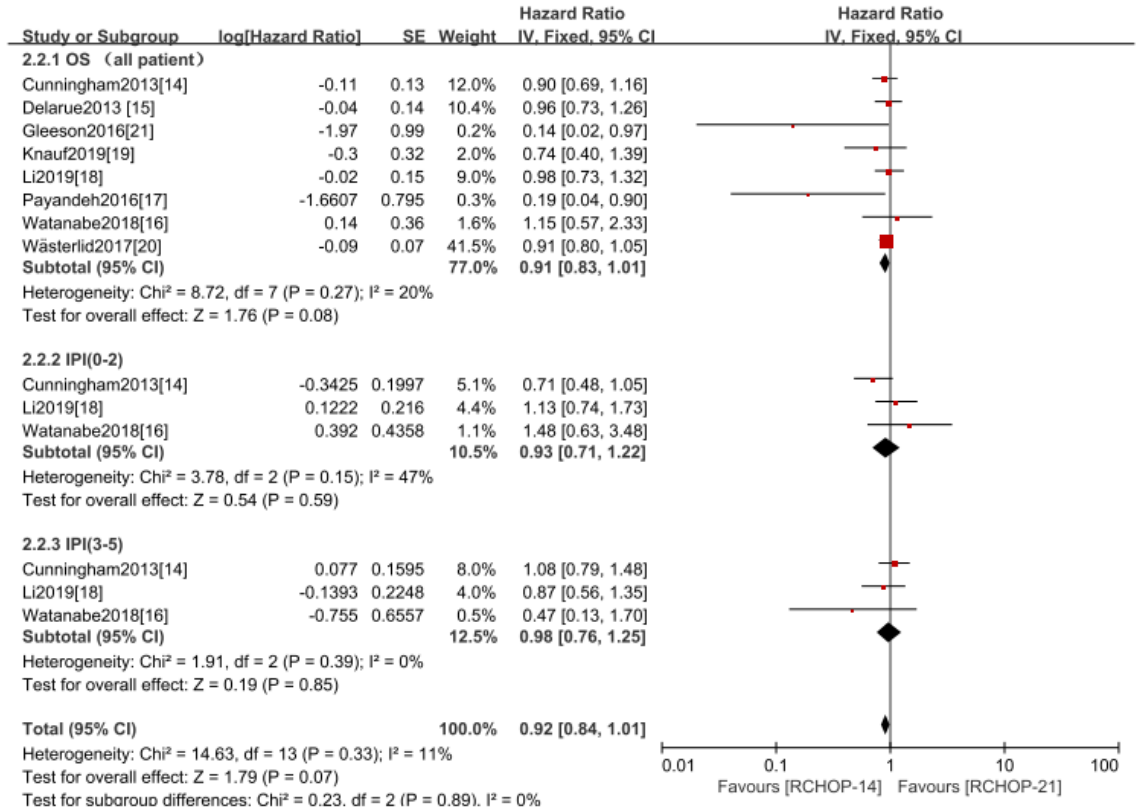

Figure 5

OS for RCHOP-14 VS RCHOP-21 of all patients and different IPI scores patient.