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Original Article

Rituximab therapy and increased risk of side effects in patients with relapsed lymphomas: a meta-analysis

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Abstract: Follicular lymphomas (FLs) and diffuse large B-cell lymphomas (DLBCLs) are two frequent types of lymphomas. Controversial results exist about whether rituximab (R) induction therapy or R maintenance therapy is associated with increased risk of side effects. Literature retrieval was performed in three databases up to July, 2015 by two independent investigators basing on predefined strategies. Quality of the included studies was evaluated by the Cochrane bias risk assessment tool. Risk ratio (RR) with corresponding 95% confidence interval (CI) was used as the effect size to evaluate the side effects in a fixed- or randomized- effects model. Teneligible studies were included in this meta-analysis, and majority of them are high-qualified. As a result, the combination of R with other drugs obviously increased the risk of any grade ≥ 3 adverse event (AE) (R vs. R + drug: RR = 0.52; 95% CI: 0.38, 0.70; $P < 0.01$) and any serious AE (R vs. R + drug: RR = 0.65; 95% CI: 0.48, 0.90; $P = 0.009$), while the maintenance therapy with R attained a significantly higher risk of Grade III/IV side effects (RR = 1.69; 95% CI: 1.25, 2.30; $P < 0.01$) and infections of grade 3/4 (RR = 2.66; 95% CI: 1.20, 5.93; $P = 0.02$) than the observation group. R therapy could highly increase the risk of several side effects for the management of relapsed FLs and DLBCLs. It should be cautious when administrate this regimen for the relapsed patients.

Keywords: Follicular lymphomas, diffuse large B-cell lymphomas, relapse, rituximab, infections, meta-analysis

Introduction

Follicular lymphomas (FLs) is one of the most common types of non-Hodgkin lymphomas (NHLs) in adults, characterized by a response to initial treatment, and then relapses [1]. Diffuse large B-cell lymphomas (DLBCLs) is another frequent type of NHL that belongs to the aggressive lymphomas [2]. Reportedly, the 3-year survival rate of DLBCL is about 60% [3]. Additionally, only less than 50% DLBCL patients could be cured by anthracycline-based chemotherapy [4]. The high recurrent rate [5, 6] might be the causative factor.

The application of rituximab (R) into the management of lymphomas of the B-cell lineage has a profound influence on the treatment of these diseases. Combination of R with other chemotherapy is reported to achieve an improved outcome for the treatments of the two most common types of lymphoma, FL and DLBCL [7]. Currently, typical treatment for FL is the chemotherapy combined with the anti-CD20 monoclonal antibody rituximab (RTX) [8]; while the standard treatment for DLBCL is the R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone), which contributes much to the improvement of survival rate [9]. Although these combination therapies have achieved several encouraging results, the beneficial value of adding R is not clearly defined in patients with relapsed diseases [10]. Moreover, several side effects after adding R or the maintenance R therapy have been reported [11, 12]. For instance, patients with lymphomas who are treated with R could achieve an increased incidence of infections [13]. However, there is not a consistent conclusion about whether combination therapies of R with other chemotherapy or the maintenance R therapy would increase the risk of hematologic side effects such as hematologic toxicity (Anemia, Neutropenia, and Thrombocytopenia, non-hematologic side effects such as non-hematologic toxicity (infection and pneumonia) and any grade ≥ 3 adverse event (AE) [12, 14].

Therefore, we retrieved the databases basing on predefined searching strategies and conducted this study using meta-analysis, which is statistically powerful for the evaluation of the indictors based on small samples [15], to comprehensively ascertain the adverse effects of adding R therapy on the treatment of relapsed lymphomas such as FLs and DLBCLs.

Materials and methods

Literature retrieval

Literature retrieval was performed in the databases including PubMed, Embase and Cochrane library to search the relevant randomized controlled trials (RCTs), with the key searching terms of "rituximab" AND "lymphoma" AND "relapse" AND "randomized controlled trail". The searching date was set as before July, 2015.

Study selection

Two investigators independently retrieved the databases basing on the predefined criteria. A discussion with a third investigator was required when disagreements appeared.

The inclusions were: (1) the study was a RCT treating with R in patients with relapsed lymphoma; (2) the induction therapy or the maintenance therapy was concerned in the study; (3) the side effects on the patient after R treatment was considered as the outcomes in the study; (4) for the duplicate publications basing on one data set, we only included the one with the most complete information and high quality; (5) the study should be an English publication.

The exclusion criteria were: (1) the study was a letter, conference abstract or reviewer; (2) the study was with low-quality that did not elaborate the surgical procedure.

Quality assessment and data extraction

The quality assessment and the data extraction were also conducted by two independent investigators. Likewise, the disagreement was resolved through discussion. The required information was abstracted, including the authors' information, publication time, country, the case inclusion time, follow-up time, lymphoma types, drug administration, case number, mean age of all the cases and the side effects with the treatment. The Cochrane bias risk assessment tool was used to evaluate the qualities of the included studies [16].

Statistical analysis

As the side effects were all dichotomous variables, risk ratio (RR) with the corresponding 95% confidence interval (CI) was used as the effect size to evaluate the side effects. Cochran-based Q statistical and I^2 test were applied to determine the heterogeneity across studies by Stata 12.0 (STATA, College Station, TX, USA). Significant heterogeneity was indicated when $P < 0.05$ or $I^2 > 50\%$ [17], and arandomized-effects model was selected to calculate the pooled results; while, a fixed-effects model was used if there lacked significant heterogeneity ($P > 0.05$ or $I^2 < 50\%$). RevMan 5.3 (Cochrane Collaboration, http://ims.cochrane.org/revman) was utilized to calculate the pooled results. Publication bias was evaluated by Egger's test, and a $P < 0.05$ indicates significant publication bias [18].

Sensitive analysis

To investigate whether the combined result would be affected by a specific study, we conducted the sensitive analysis by comparing the pooled results before and after removing a single study at one time using Stata 12.0 (STATA, College Station, TX, USA). A reverse result indicated an instable result of the meta-analysis.

Results

Eligible studies in the meta-analysis

As a result, a set of 729 studies (165 in PubMed; 429 in Embase and 135 in Cochrane library) were selected with the preliminary retrieval. Then after abstract reading, 37 studies were remained and subjected to the full text reading, by which a total of 27 studies were excluded (18 were non-relapsed lymphoma, 5 were irrelevant with R, 2 were duplicate publications, 1 did not contain the side effects of the outcomes and 1 was non-RCT). Finally, 10 [7, 12, 14, 19-25] eligible studies were included in our meta-analysis. The detailed selection procedures are shown in **Figure 1**.

Characteristics of the included studies

As presented in **Table 1**, all the 10 studies in the meta-analysis were RCTs, and 7 [12, 14, 19, 22-25] of them reported the side effects of

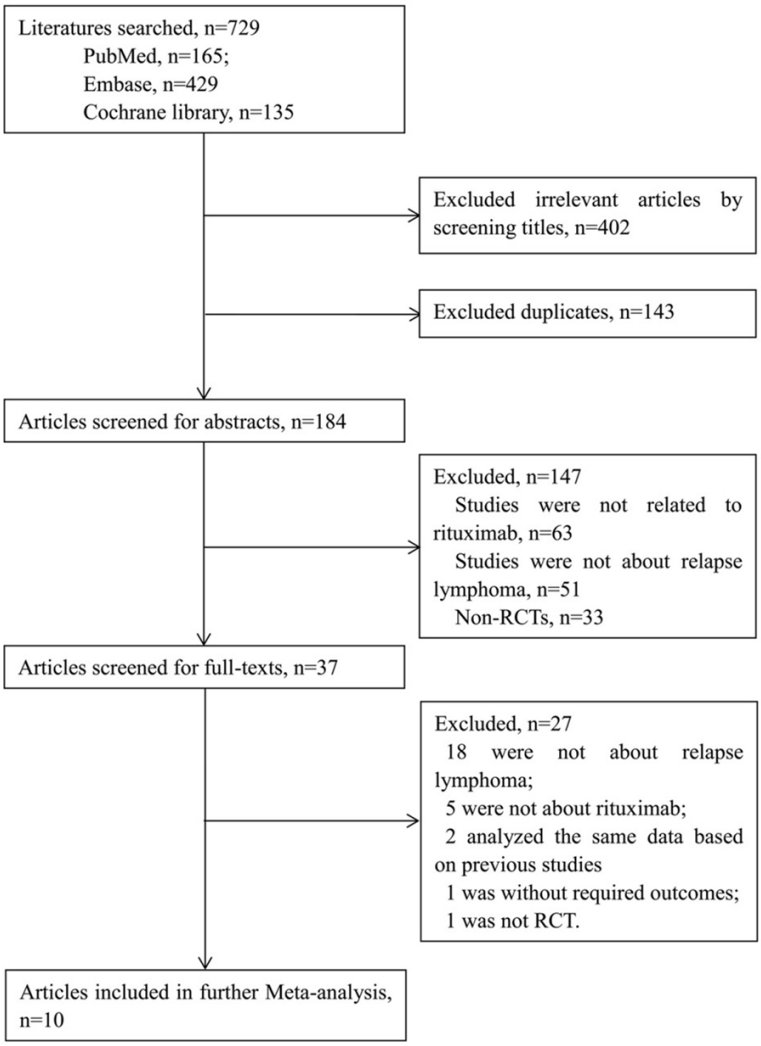


Figure 1. Diagram illustration of the study selection.

induction therapy, consisting of 2128 cases (R group: 1058, R + drug group: 1070); while 4 studies [7, 20, 21, 23] examined the side effects of the maintenance therapy involving 889 cases (R group: 442, observation group: 447). Lymphoma type in three studies [19, 21, 23] was DLBCL, while in the remaining ones was FL. Based on the Cochrane evaluation system, all the indicators presented a low bias risk, except "blinding of participants and personnel", which showed a relative higher bias risk, (**Figure 2**), and the result suggested a relatively high quality of the included studies.

Outcomes

Comparison of side effects of the induction therapy in R and R + drug groups: For the induction therapy, side effect indicators included the hematologic side effects (hematologic toxicity: anemia, neutropenia and thrombocytopenia); the non-hematologic side effects (non-hematologic toxicity: infection and pneumonia); the overall side effects indexes (any grade ≥ 3 AE, any serious AE and any AE leading to treatment withdrawal) and the deaths within 30 days of last dose of the prescribed drug.

Significant heterogeneity was observed for the evaluation of three indicators (any AE leading to treatment withdrawal, neutropenia and infection) ($P < 0.05$ or $I^2 > 50\%$, **Figure 3A**) and consequently a randomized-effects model was used, whereas all the remaining indicators applied the fixed-effects model due to the lack of obvious heterogeneity. The pooled results indicated that the combination of R with other drugs obviously increased the risk of any grade ≥ 3 AE (R vs. R + drug: RR = 0.52; 95% CI: 0.38, 0.70; $P < 0.01$) and any serious AE (R vs. R + drug: RR = 0.65; 95% CI: 0.48, 0.90; $P = 0.009$), compared with the R treatment (**Figure 3B**). There were no pronounced differences between R and the combination therapy in other indicators ($P > 0.05$, **Figure 3C-I**).

No obvious publication bias was detected across studies that evaluated outcomes such as anemia (P = 0.604), neutropenia (P = 0.186), thrombocytopenia (P = 0.221), infection (P = 0.638), pneumonia (P = 0.520) and any AE leading to treatment withdrawal (P = 0.861).

Comparison of side effects of the maintenance therapy in R and observation groups: For the maintenance therapy, the outcomes were Grade III/IV side effects, neutropenia, infections of grade 3/4 and non-hematologic toxicity of all types.

Due to the absence of significant heterogeneity ($P > 0.05$ and $I^2 < 50\%$, **Figure 4**), the fixed-

Table 1. Characteristics of the included studies

Author, year	Study period	Country	Follow-up	Disease	Study period	Group	Dosing strategy	No. (M/F)	Age, year
Aviles, 2010	NA	Mexico	64.5 months	Relapsed or refractory DLBCL	Induction	R-ESHAP	375 mg/m^2 day 1 I.V. every cycle	47 (20/17)	48.3 (48-61)
						ESHAP	6 cycles of reinduction chemotherapy ESHAP at conventional doses.	53 (28/25)	51.8 (32-63)
Coiffier, 2011	2006.04-2008.08	29 countries	33.9 months	Relapsed grade 1 or 2 FL	Induction	R	5 cycles (35-day/cycle): R-375 mg/m^2 on days 1, 8, 15, and 22 of cycle 1, and on day 1 of cycles 2-5, I.V.	340 (137/203)	57 (21-84)
						R-B	B: 1.6 mg/m^2, on days 1, 8, 15, and 22 of all cycles; I.V.	336 (172/164)	57 (24-83)
Forstpointner, 2006	1998.11-2005.04	Germany	NA	Recurring or refractory FL	Maintenance	R	2 courses of R to be given 3 and 9 months	52 (22/30)	59 (41-78)
						O	No further treatment	53 (27/26)	61 (35-80)
				Recurring or refractory MCL	Maintenance	R	2 courses of R to be given 3 and 9 months	28 (18/10)	63 (49-74)
						O	No further treatment	29 (23/6)	63 (39-78)
Ghielmini, 2004	1998.01-2001.02	Switzerland	35 months	Refractory/relapsed FL	Maintenance	R	375 mg/m^2 every 2 months for 4 times	73 (33/40)	56 (31-79)
						O	No further treatment	78 (29/49)	57 (28-81)
Gisselbrecht, 2012	NA	USA	44 months	Relapsed CD20+ DLBCL	Maintenance	R	375 mg m^2/8 weeks/12 months	122 (76/46)	54 (19-65)
						O	No further treatment	120 (83/37)	54 (19-65)
Glass, 2014	2004.06-2009.03	Germany	4.5 years	Aggressive B-cell or T-cell lymphoma	Induction	R	375 mg/m^2 on days 21, 28, 35, 42, 175, 182, 189, and 196	42 (33/9)	47 (38-54)
			3.9 years			R-drug	fludarabine (125 mg/m^2), busulfan (12 mg/kg oral or 9.6 mg/kg I.V.), and cyclophosphamide (120 mg/kg)	42 (25/17)	49.5 (43-57)
Habermann, 2006	1998.02-2001.07	USA	3.5 years	Relapsed DLBCL	Induction	R-CHOP	375 mg/m^2 7 and 3 days before cycle 1 and 2 days before cycles 3, 5	267 (52/215)	69 (60-92)
						CHOP	Administered in the standard dosage	279 (48/231)	70 (60-90)
					Maintenance	R	Four courses at 6-month intervals, with each course consisting of 375 mg/m^2 weekly times four.	174	NA
						O	No further treatment	178	NA
Hainsworth, 2014	2005.08-2012.03	USA	34 months	Relapsed FL	Induction	R	375 mg/m^2 I.V. weekly for 4 weeks	31 (18/13)	65 (47-80)
						R-B	10 mg/kg I.V. on days 3 and 15	29 (13/16)	68 (45-91)
van Oers MH, 2006	1998.11-2004.04	Canada, Australia/ New Zealand, Europe, and South Africa	7 years	Relapsed/resistant FL (CD20+ grade 1 to 3)	Induction	R-CHOP	375 mg/m^2 I.V., day 1	234 (108/126)	54 (26-80)
						CHOP	6 cycles of standard CHOP	231 (118/113)	55 (27-78)
Zinzani, 2012	2006.04-2008.08	29 countries	35.2 months	High-risk, relapsed, rituximab-naïve or rituximab-sensitive FL	Induction	R	R: 375 mg/m^2, days 1, 8, 15, and 22, cycle 1, and day 1, cycles 2-5	98 (42/56)	60 (21-84)
						R-B	B: 1.6 mg/m^2, days 1, 8, 15, and 22, all cycles	103 (53/50)	61 (38-83)

Abbreviations: R: rituximab; ESHAP: etoposide, methylprednisolone, cytosine arabinoside, and platinum; B: bortezomib; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisone; DHAP: cisplatincytarabine-dexamethasone; O: observation; FL: follicular lymphoma; DLBCL: diffuse large B-cell lymphoma; I.V. intravenous; NA: not available.

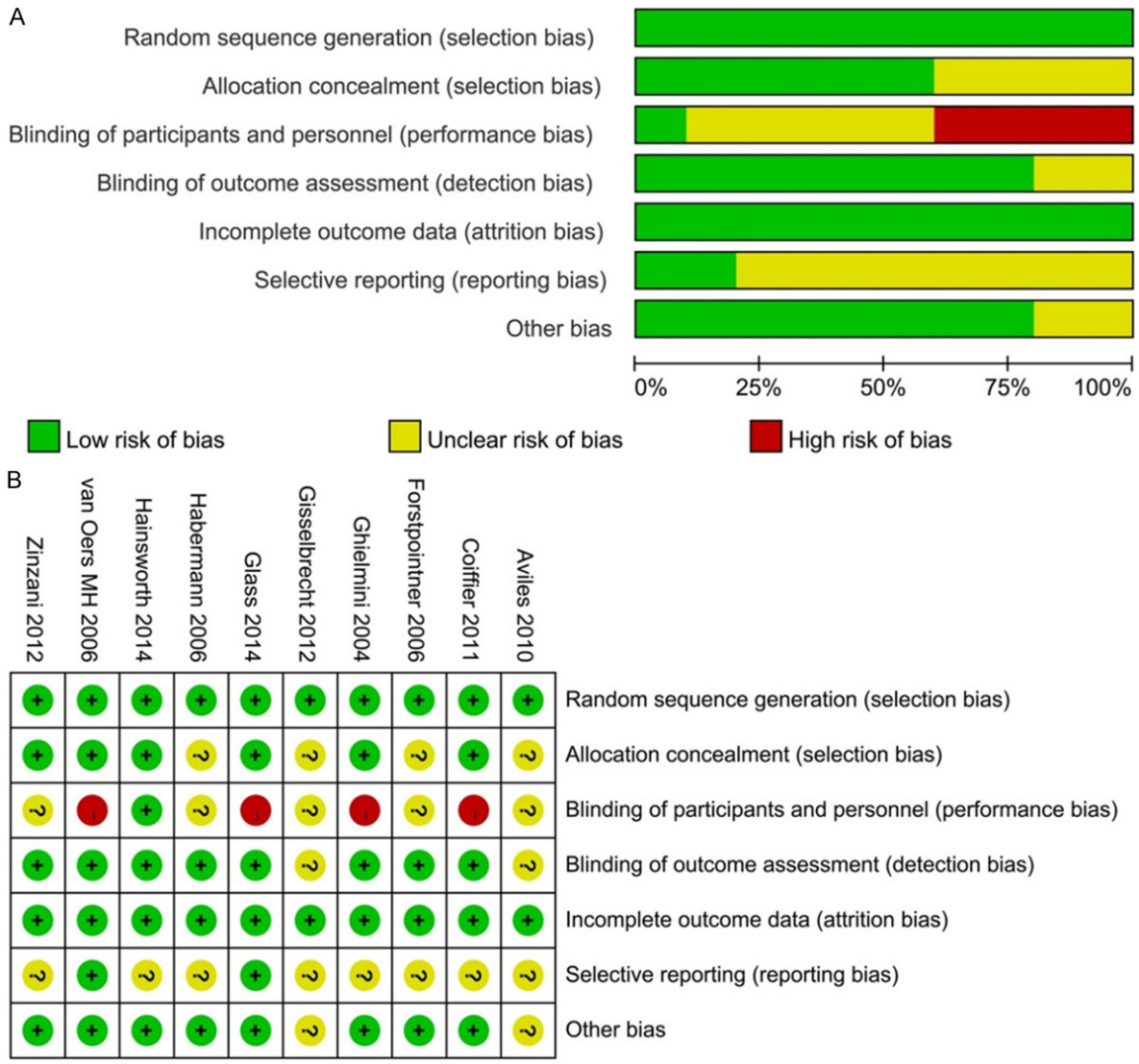


Figure 2. Quality assessments of the included studies. A: Bias risk of the identified studies; B: Sensitivity and specificity of the 10 studies, where "+" denotes Low risk of bias; "?" represents unclear risk of bias; and "-" denotes high risk of bias.

effect model was selected for the four indicators. As a result, the maintenance therapy with R attained a significantly higher risk of Grade III/IV side effects (RR = 1.69; 95% CI: 1.25, 2.30; $P < 0.01$, **Figure 4A**) and infections of grade 3/4 (RR = 2.66; 95% CI: 1.20, 5.93; $P = 0.02$), than the observation group (**Figure 4C**).

Likewise, there did not observe significant publication bias across studies regarding to outcomes such as Grade III/IV side effects (P = 0.250) and non-hematologic toxicity of all types (P = 0.634).

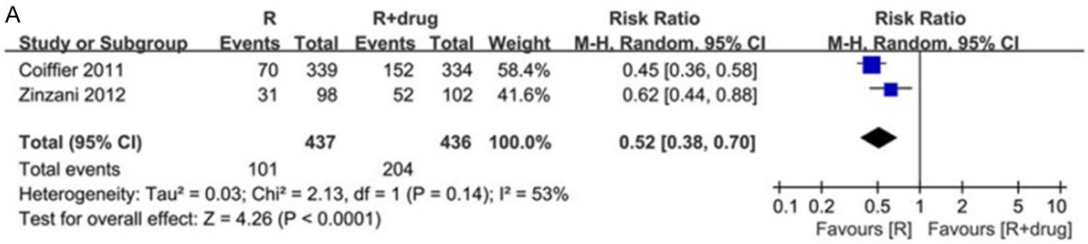
Sensitive analysis

The results suggested that for the induction therapy, after eliminating the study of Habermann et al. [23] or van Oers et al. [25], a reverse result was discovered for the indicator of neutropenia (data not shown). The same result was detected for the indicator thrombocytopenia after eliminating the study of Habermann et al. [23] (data not shown). These all suggested instable results on the two indicators; hence more RCTs with large scaled samples are needed to provide a more exact evaluation on the indicator of neutropenia and thrombocytopenia. Nevertheless, in other indicators, any reverse result was not observed.

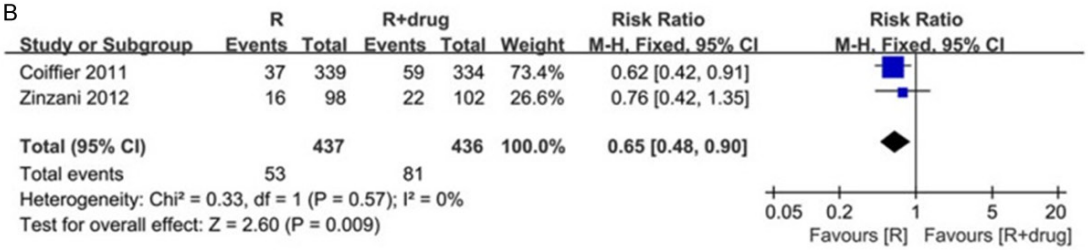
Discussion

Relapsed lymphoma is the major cause for poor survival rate after chemotherapy treat-

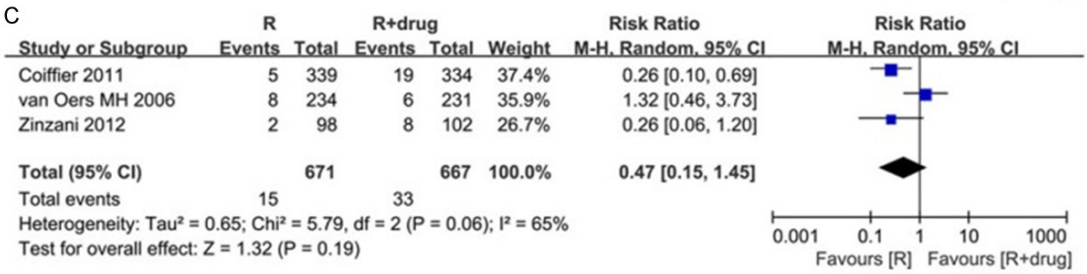
A


R
R+drug
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Coiffier 2011 70 339 152 334 58.4% 0.45 [0.36, 0.58]
Zinzani 2012 31 98 52 102 41.6% 0.62 [0.44, 0.88]
Total (95% CI) 437 436 100.0% 0.52 [0.38, 0.70]
Total events 101 204
Heterogeneity: Tau² = 0.03; Chi² = 2.13, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 4.26 (P < 0.0001)
0.1 0.2 0.5 1 2 5 10
Favours [R] Favours [R+drug]

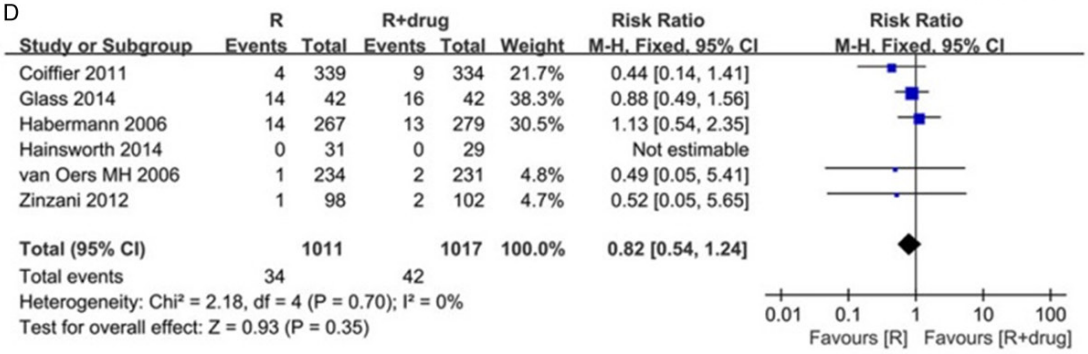
B


R
R+drug
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Coiffier 2011 37 339 59 334 73.4% 0.62 [0.42, 0.91]
Zinzani 2012 16 98 22 102 26.6% 0.76 [0.42, 1.35]
Total (95% CI) 437 436 100.0% 0.65 [0.48, 0.90]
Total events 53 81
Heterogeneity: Chi² = 0.33, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)
0.05 0.2 1 5 20
Favours [R] Favours [R+drug]

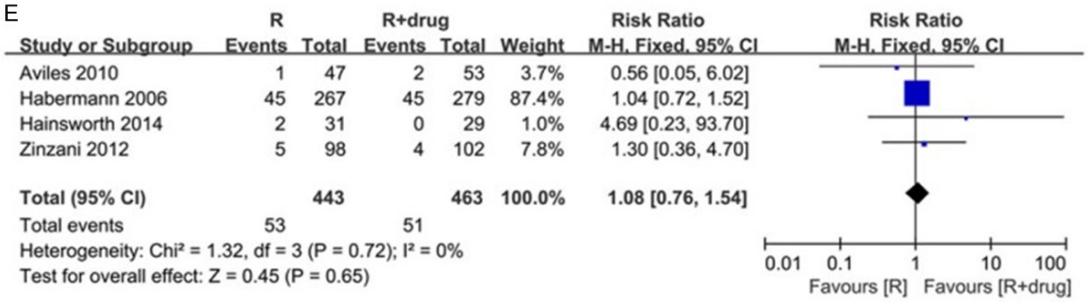
C


R
R+drug
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Coiffier 2011 5 339 19 334 37.4% 0.26 [0.10, 0.69]
van Oers MH 2006 8 234 6 231 35.9% 1.32 [0.46, 3.73]
Zinzani 2012 2 98 8 102 26.7% 0.26 [0.06, 1.20]
Total (95% CI) 671 667 100.0% 0.47 [0.15, 1.45]
Total events 15 33
Heterogeneity: Tau² = 0.65; Chi² = 5.79, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 1.32 (P = 0.19)
0.001 0.1 1 10 1000
Favours [R] Favours [R+drug]

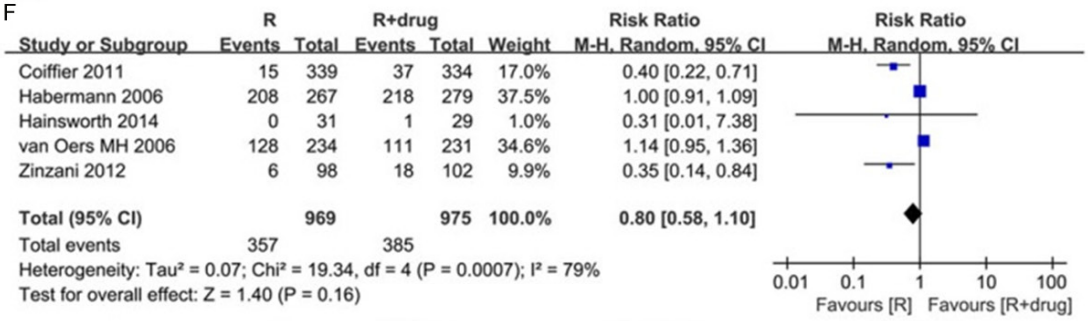
D


R
R+drug
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Coiffier 2011 4 339 9 334 21.7% 0.44 [0.14, 1.41]
Glass 2014 14 42 16 42 38.3% 0.88 [0.49, 1.56]
Habermann 2006 14 267 13 279 30.5% 1.13 [0.54, 2.35]
Hainsworth 2014 0 31 0 29 Not estimable
van Oers MH 2006 1 234 2 231 4.8% 0.49 [0.05, 5.41]
Zinzani 2012 1 98 2 102 4.7% 0.52 [0.05, 5.65]
Total (95% CI) 1011 1017 100.0% 0.82 [0.54, 1.24]
Total events 34 42
Heterogeneity: Chi² = 2.18, df = 4 (P = 0.70); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
0.01 0.1 1 10 100
Favours [R] Favours [R+drug]

E


R
R+drug
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI
M-H, Fixed, 95% CI
Aviles 2010 1 47 2 53 3.7% 0.56 [0.05, 6.02]
Habermann 2006 45 267 45 279 87.4% 1.04 [0.72, 1.52]
Hainsworth 2014 2 31 0 29 1.0% 4.69 [0.23, 93.70]
Zinzani 2012 5 98 4 102 7.8% 1.30 [0.36, 4.70]
Total (95% CI) 443 463 100.0% 1.08 [0.76, 1.54]
Total events 53 51
Heterogeneity: Chi² = 1.32, df = 3 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
0.01 0.1 1 10 100
Favours [R] Favours [R+drug]

F


R
R+drug
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Coiffier 2011 15 339 37 334 17.0% 0.40 [0.22, 0.71]
Habermann 2006 208 267 218 279 37.5% 1.00 [0.91, 1.09]
Hainsworth 2014 0 31 1 29 1.0% 0.31 [0.01, 7.38]
van Oers MH 2006 128 234 111 231 34.6% 1.14 [0.95, 1.36]
Zinzani 2012 6 98 18 102 9.9% 0.35 [0.14, 0.84]
Total (95% CI) 969 975 100.0% 0.80 [0.58, 1.10]
Total events 357 385
Heterogeneity: Tau² = 0.07; Chi² = 19.34, df = 4 (P = 0.0007); I² = 79%
Test for overall effect: Z = 1.40 (P = 0.16)
0.01 0.1 1 10 100
Favours [R] Favours [R+drug]

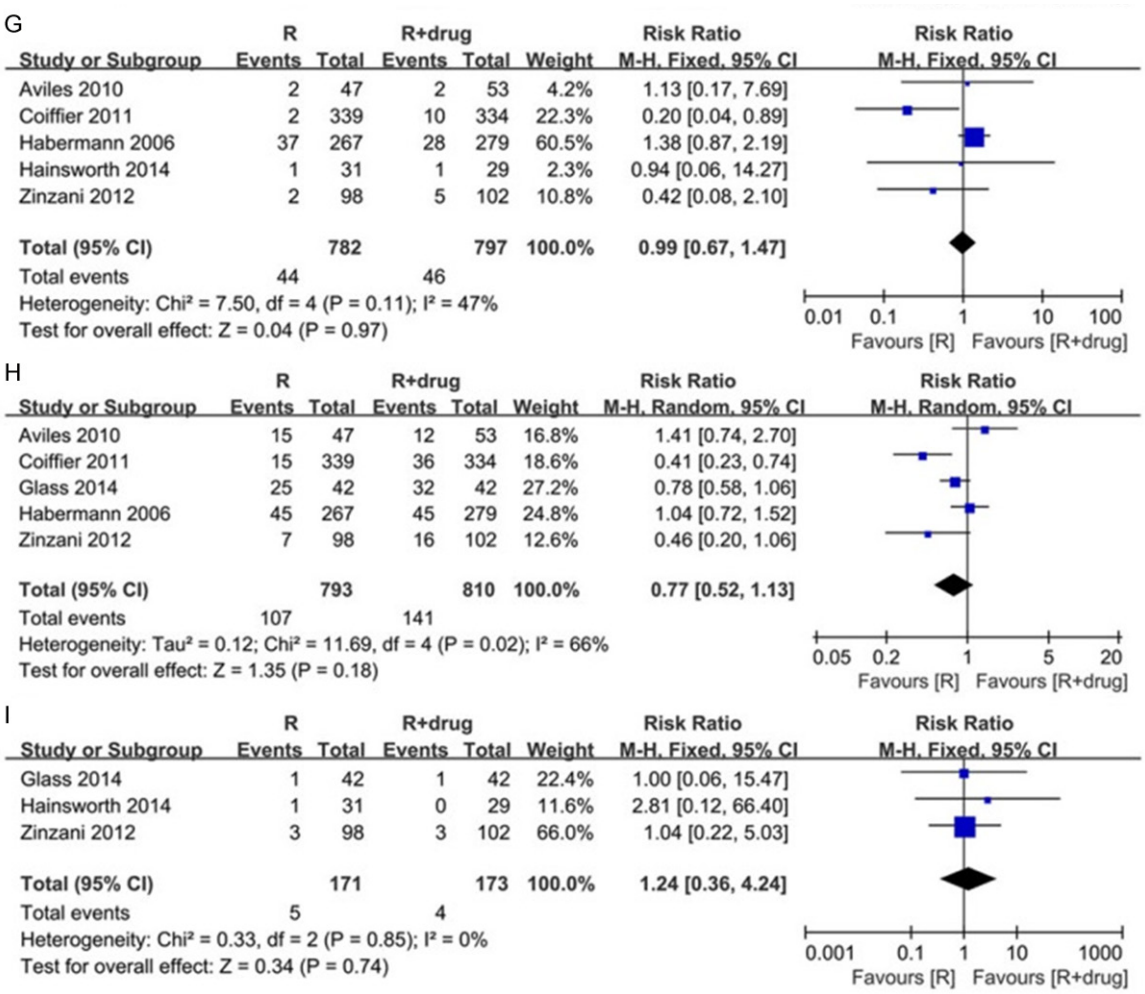


Figure 3. Association of induction therapy rituximab (R) and the risk of side effects in patients with relapsed lymphomas. A: Comparison of any grade 3 adverse event (AE) between R plus drugs and R groups; B: Comparison of any serious AE between two groups; C: Comparison of any AE leading to treatment withdrawal between two groups; D: Comparison of deaths within 30 days of last dose of study drug between two groups; E: Comparison of anemia between two groups; F: Comparison of neutropenia between two groups; G: Comparison of thrombocytopenia between two groups; H: Comparison of infection between two groups; I: Comparison of pneumonia between two groups. Squares represent the study-specific outcome estimates, and the size of the square represents the study-specific weight. Horizontal lines and figures in parentheses denote the 95% confidential interval (CI). Diamonds represent the overall outcomes with the corresponding 95% CI.

ment. Reportedly, adding R to the chemotherapies such as CHOP improves the outcome; however, also causes several side effects [13, 26]. In our present study, we included ten eligible studies to perform a meta-analysis, and found that adding R to other chemotherapies was tightly associated with the increased risk of any grade ≥ 3 AE and any serious AE for the induction therapy of relapsed FL and DLBCL. Meanwhile, for the maintenance therapy, R treatment also increased the risk of Grade III/IV side effects and the infections of grade 3/4.

Rituximab is considered as an active monotherapy in relapsed DLBCL patients [27]. A number of studies have confirmed the beneficial effect of adding R to the chemotherapy (such as R-CHOP) for elder patients with DLBCL, with a tolerable toxicity [28, 29]. However, controversial results are exhibited for the treatment of relapsed DLBCL. A phase 2 trial finds that only one patient (the total sample size is 23) exhibits mild reaction with the combination of R and lenalidomide [30]. Additionally, no pronounced differences are detected between the R + group (R-ESHAP [rituximab plus etoposide, cytarabine, cisplatinum and methylprednisolone], patient: 94) and the R-group (without R patient: 69) with regard to the hematological or infectious toxicity [31]. By contrast, serious AEs such

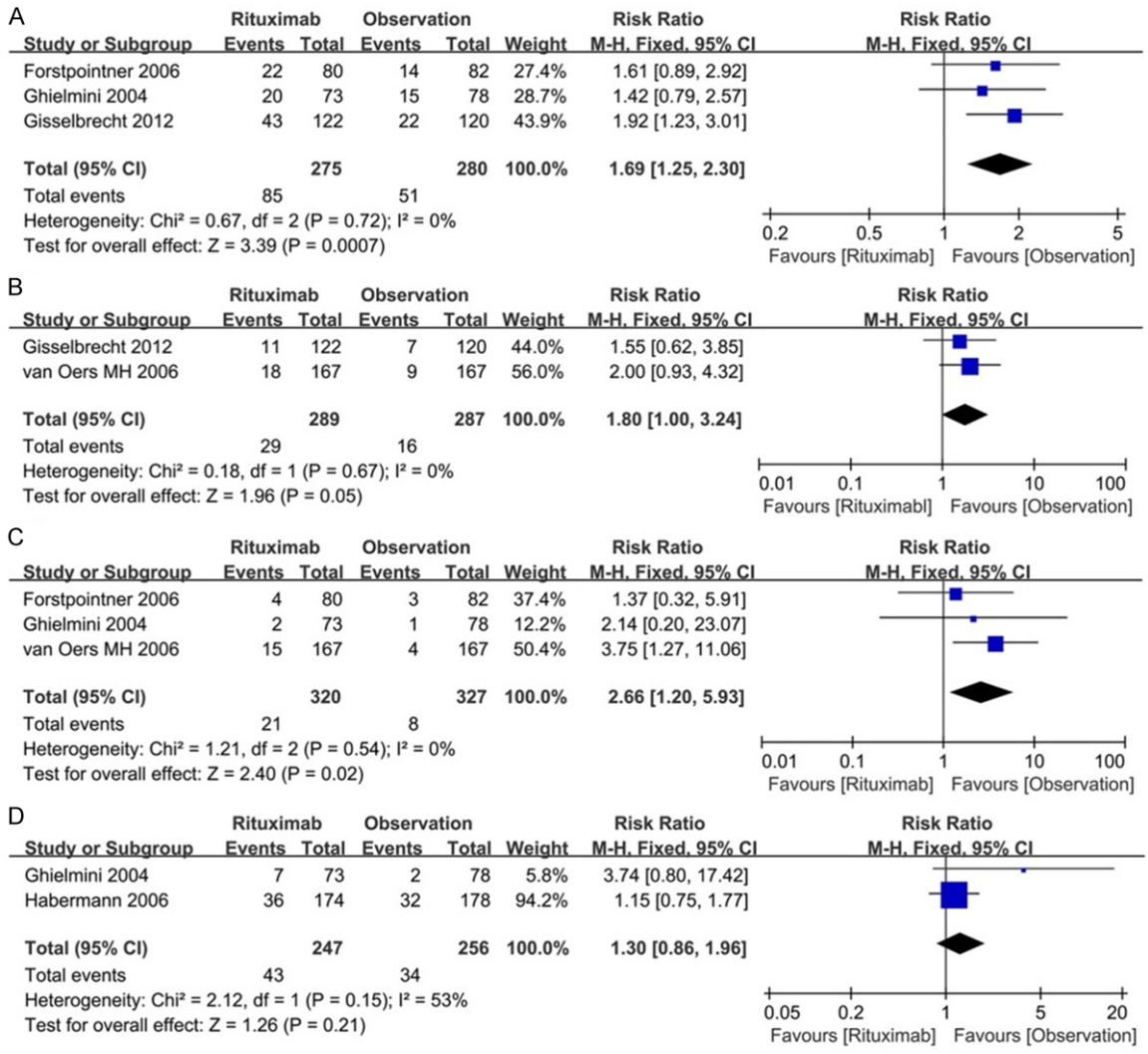


Figure 4. Association of maintenance rituximab (R) and the risk of side effects in patients with relapsed lymphomas. A: Comparison of Grade III IV side effects between R plus drugs and R groups; B: Comparison of neutropenia between two groups; C: Comparison of infections of grade 3-4 between two groups; D: Comparison of non-hematologic toxicity between two groups. Squares represent the study-specific outcome estimates, and the size of the square represents the study-specific weight. Horizontal lines and figures in parentheses denote the 95% confidential interval (CI). Diamonds represent the overall outcomes with the corresponding 95% CI.

as infection, neutropenia and grade 3-4 non-hematologic toxicities are reported in another study with large sample size (396 patients) in the combination of R with other agents, such as R-ICE (rituximab, ifosfamide, etoposide, and carboplatin) and R-DHAP (rituximab, dexamethasone, high-dose cytarabine, and cisplatin) [32]. For the treatment of FL, most studies also confirm that addition of R in chemotherapies such as cyclophosphamide, CVP (vincristine and prednisone) could not induce any excessive hematological toxicity [33]. However, Coiffier et al. find a higher rate of serious AEs in the combination group (R plus bortezomib) than in R group (18% vs. 11%) for the treatment of FL, with a large sample size of 339 patients [12]. In accordance with this finding, a randomized phase 3 LYM3001 trial involving 201 patients also discovers that R plus bortezomib achieves an increased occurrence of grade ≥ 3 AEs (51% vs. 32%) and serious AEs (22% vs. 16%), compared with the monotherapy of R [14]. These instances collectively suggest that the sample size might be the major factor leading to the inconsistent results.

Maintenance therapy for FLs and DLBCLs are also widely applied. For the management of

DLBCL, the R maintenance therapy after autologous stem-cell transplantation (ASCT) shows a slightly higher AE rate than the observation only after ASCT (47% vs. 42%) [21]. Another phase 3 intergroup study indicates a pronounced increasing grade 3-4 infection rate in the maintenance therapy with R for the relapsed FL, compared with the observation group (9% vs. 2.4%) [25]. The common concept is that R maintenance therapy will not increase the risk for infections [34]. However, several studies point out although no accumulated toxicities are detected in patients receiving R maintenance therapy, compared with observation regimen for low-grade lymphomas, B-cells are depleted during the maintenance period and prone to increase the patients' risk for infections [35]. A meta-analysis incorporating 5 RCTs concludes that R maintenance therapy is tightly associated with the increased risk of infection and neutropenia in patients with lymphoma [35]. Interestingly, our study also suggested that R maintenance therapy could remarkably increase the risk of side effects such as infections of grade 3/4.

Despite the obvious advantages of this meta-analysis, such as the high quality of majority of the included studies, we should note that there are several limitations. First, as indicated in the sensitive analysis, two indicators attained reverse results after eliminating a certain study, suggesting the instability of several combined results; second, substantial heterogeneity were exhibited among several studies, which might derive from different therapies before the application of R, different degree of the disease severity and different nursing care due to diverse living standard; and this consequently might distort the final determination; third, we did not conduct the subgroup analysis or the meta-regression analysis due to a small bunch of available studies. These collectively suggested that more RCTs with large samples are warranted to support our findings.

In conclusion, adding R to other chemotherapies or the maintenance R therapy could highly increase the risk of several side effects for the management of relapsed FLs and DLBCLs. Therefore it should be cautious when administrate this regimen for patients with relapsed DLBCL or FL.

Disclosure of conflict of interest

None.

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