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Role of Prior Rituximab on Outcomes of Asct in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma: A Systematic Review and Meta-Analysis

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ABSTRACT

The aim of this study was to investigate the impact of prior rituximab on the subsequent results of autologous stem cell transplantation (ASCT) for relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL). The random-effect model was used with the relative risk (RR) as the measure indicator. Patients were divided into two groups according to whether rituximab was administered (R group) or not (No-R group) prior to ASCT. The meta-analyzed RR and 95% confidence interval in the R group *versus* the No-R group were: 0.83 (0.69,0.99), 0.84 (0.72,0.98), 0.94 (0.71,1.25) for two-, three-, five-year overall survival (OS); 0.91 (0.77,1.08), 0.85 (0.69,1.06), 0.85 (0.62,1.17) for two-, three-, and five-year progress free survival (PFS); 0.46 (0.27,0.80), 0.47 (0.29,0.76), 0.74 (0.15,3.52) for two-, three-, and five-year event free survival (EFS). The results show the treatment trend of pre-treating with first-line rituximab-containing therapy for relapsed or refractory DLBCL is more favorable than with ASCT-naive.

Keywords: Autologous stem cell transplantation, Diffuse large B-cell lymphoma, Rituximab, Salvage therapy

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is a common lymphoid malignancy in adults [1-3]. It accounts for approximately 30% of new cases in non-Hodgkin lymphoma (NHL) [4]. Several factors could affect the result of treatment for DLBCL patients such as the International Prognostic Index (IPI) score and age [5-8]. Generally, patients classified as high-intermediate and high risk on the IPI scale accompanying with higher age showed a poor prognosis. The addition of rituximab to chemotherapy leads to higher response rates and improves survival for the DLBCL patients because it is effective

in removing circulating B-cells from peripheral blood. Therefore, several studies indicated the therapeutic effect of the DLBCL patients has significantly improved since the introduction of rituximab into CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisolone) [9-12]. The combination of the anti-CD20 monoclonal antibody rituximab and CHOP chemotherapy is even the standard first-line treatment for most DLBCL patients.

Sufficient evidence indicates that more than 30 percent of patients are still relapse or progress for the long term follow-up after first-line treatments [6,13-15]. Consolidation with high-dose chemotherapy supported by autologous stem cell transplant (HDC/ASCT) has gradually become the dominant salvage treatment for relapsed or primary refractory DLBCL patients, especially for the chemo-sensitive patients [16,17]. The salvage regimen has obviously improved the prognosis for the relapsed or refractory patients.

However, whether adding the rituximab to the treatment regimen before the ASCT is still a controversial problem. Recent studies indicate that prior exposure to rituximab-containing primary therapy makes it more difficult to salvage DLBCL patients who are relapsed or refractory. And not only that, there is even an inferior prognosis for DLBCL patients using the rituximab before ASCT [18,19]. Meanwhile, several studies advocate the advantage of prior exposure to the rituximab in salvage regimens [3,4].

Therefore, we conducted this systematic review and meta-analysis basing on a dual aim: to investigate the role of prior exposure to rituximab on outcomes of ASCT in patients with relapsed or refractory DLBCL; to summarize main prognostic factors.

MATERIALS AND METHODS

Literature search

We systematically searched PubMed and Web of Science (before 31 August 2016) using detailed search terms “DLBCL”, “rituximab”, “relapsed”, “refractory”, “Chemotherapy”, “ASCT”, and “Auto-SCT” for maximizing search yield (see Figure 1 for detailed search strategy). All the procedures were conducted by two reviewers (Jie Ji and Lan Lan) independently and any discrepancies were adjudicated by research team. We got the objective literature with the steps as follows. First, we combined the keywords to search the references from the two databases, and then removed the duplicated records.

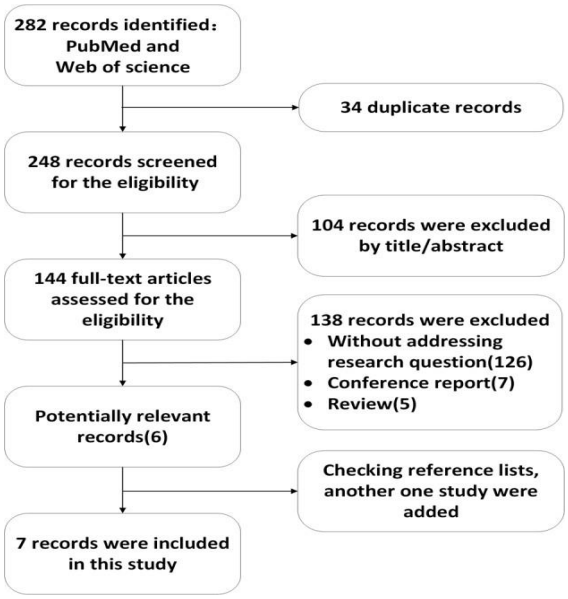


Figure 1: Literature search strategy in this work

After that, according to the title and abstract, we screened those deduplicated records. Lastly, we read the remainder full-text articles in-depth to identify the aim articles.

Inclusion and exclusion criteria

We selected studies based on the following criteria. Basically, they must investigate the influence of prior exposure to rituximab on outcomes of ASCT for patients with the DLBCL. The original studies were included if: 1) patients were diagnosed with relapsed or refractory DLBCL; 2) patients who accepted ASCT could divide into two groups: with and without prior exposure to rituximab; 3) they provided the prognostic results or the survival curves (overall survival (OS), event-free survival (EFS), and progression-free survival (PFS)). We limited the language only in English and we included only peer-reviewed original articles. The articles would be excluded when the paper is a review or conference report. Additionally, we attempt to contact the author if we cannot obtain the related information.

Extraction of data

All the related data were extracted independently by two investigators and disagreements were resolved by discussion. We extracted the following data information from the eligible papers directly: authors, the year published, the year studied, population

demographics, and the main conclusion. More importantly, we read the main survival parameters, which were calculated based on the Kaplan-Meier methodology [20,21], from the survival curves indirectly by the two investigators including OS, EFS, and PFS. The specific survival time (two-, three- and five-year) was determined depending on the survival curve. A survival parameter would be re-read if the error is more than 0.1% coming from the two investigators. Then we calculated the specific death numbers and live numbers according to participants and survival information. The specific equation is showed in Equation 1.

$$NL_{ij} = N_{ij} \times L_{ij\,and}\; ND_{ij} = N_{ij} \times (1 - LR_{ij})$$

Where NL denotes live numbers; ND denotes death numbers; LR denotes the survival rates; i denotes group, given 0 means rituximab group and 1 means non-rituximab group; j denotes different year, given j =2, 3, 5 years.

Meta-analysis

Random-effect model [22,23] was used to synthesize the influence of prior exposure to the rituximab in the salvage regimen. This model gives more weight to smaller studies and has typically wider confidence intervals because in addition to the within-study variance, they also considered potential variation between the true effects that all included studies estimate. Relative risk (RR) [24,25] and their corresponding 95% confidence intervals were used as the measure indicator. The specific equation for calculating the individual RR is shown in Equation 2. P values obtained using a two-sided test <0.05 were considered to have statistical significance. We described the between-study heterogeneity by using the i^2 metric and the between studies' variance using i^2. Forest plots were used to summarize the results of included studies [26,27]. We assessed publication bias using t° Egger's test for asymmetry. For reporting, we followed the meta-analysis of observational studies in epidemiology and the preferred reporting items for systematic review and meta-analysis guidelines. Analyses were performed using R software with "Metafor" package (v.3.22 https://cran.r-project.org/).

$$RR_j = ND_{1j} / ND_{0j}$$

Where RR denotes the relative risk.

RESULTS AND DISCUSSION

Summary of collected data

The strategies of selecting literature are shown in Figure 1. The remainders of records were 248 from the databases after the de-duplication, and all were assessed for their abstract and title. 144 studies experienced in-depth review, with seven studies fulfilling the inclusion criteria eventually.

Table 1: Contextual summary of studies included in the systematic review

Study (Refs.)	Location	Periods	Sample	Age	Status	Chemotherapy-based	Parameter
Smith et al. [3]	USA	1994-2004	257	19-72	Refractory & Relapsed	filgrastim, etoposide	PFS, OS
Kaneko et al. [28-38]	Japan	1997-2014	47	23-69	Relapsed	CHOP, MCVC	EFS, OS
Glass et al. [37]	Germany	2001-2003	93	18–60	Refractory	MegaCHOEP	EFS, OS
Redondo et al. [4]	Spain	2000-2011	375	16-69	Refractory & Relapsed	BEAM, BEAC,TBI	PFS, OS
Kewalramani et al. [36]	USA	-	183	18-72	Refractory & Relapsed	anthracycline, ICE	PFS, OS

Papajik et al. [28]	Czech	1999-2007	69	< 65	Refractory & Relapsed	BEAM	EFS, OS
Telio et al. [39]	Canada	1997-2007	111	19-67	Refractory	anthracycline	PFS, OS

CHOP: Cyclophosphamide, Adriamycin, Vincristine, and Prednisone MCVC: Ranimustine, carboplatine, VP16, and cyclophosphamide MegaCHOEP: Cyclophosphamide, adriamycin, vincristin, etoposide, prednisolone BEAM: BCNU, etoposide, cytosine arabinoside, and melphalan BEAC: Carmustin e, etoposide, cytarabine, and cyclophosphamide TBI: Total body irradiation ICE: Ifosfamide, carboplatin, and etoposide

Table 2: The main findings of these studies

Study (Refs.)	**Statistical method**	**Main findings**
Smith et al. [3]	χ^2 , Wilcoxon and *t:* Demographic characteristics; Kaplan-Meier and log-rank: Survival parameter; Cox model: Prognostic factors.	R is no less effective
Kaneko et al. [38]	Kaplan-Meier and log-rank: Survival parameter.	R may be detrimental
Glass et al. [37]	Kaplan-Meier and log-rank: Survival parameter; χ^2 : Demographic characteristics; Mann-Whitney U test: $CD34^+$ cells; Cox model: Prognostic factors.	R may be beneficial
Redondo et al. [4]	χ^2: Demographic characteristics; Logistic regression: Prognostic factors analyzed; Mann-Whitney U test: Engraftment; Kaplan-Meier and log-rank: Survival parameter. Cox model: Prognostic factors.	R is no less effective
Kewalramani et al. [36]	Fisher exact test: categorical variables; Kaplan-Meier and log-rank: Survival parameter.	It is still controversial
Papajik et al. [28]	Kaplan-Meier and log-rank: Survival parameter.	It is still controversial
Telio et al. [39]	Logistic regression: Overall response rate; Cox model: Prognostic factors; Kaplan-Meier and log-rank: Survival parameter.	R is no less effective

R: Rituximab.

Details of the studies information are presented in Table 1. All studies included examined the impact of pre-exposure to the rituximab on outcome of ASCT. Of these, about 78 percent studies published after 2010. Study sites main distributed in USA (two studies), Japan (one study), Germany (one study), Spain (one study), Czech (one study), and Canada (one study). Most DLBCL patients experienced relapse or primary refractory before ASCT for those studies. Except for being pre-treated with the rituximab, patients accepted different kinds of treatment regimens as well such as CHOP, MegaCHOEP. Additionally, the study groups were focused on the middle-aged for all the studies practically. Especially, all the studies for the survival parameters contained the OS, three studies contained the EFS, and four studies contained the PFS [28].

The statistical methodologies and major findings are summarized in Table 2. Survival analysis was performed according to the Kaplan–Meier method in the original studies, and differences in survival between the R group and No-R group were analyzed by the log-rank test [29,30]. Chi-square test, t test, and Wilcoxon statistics were used to compare demographic characteristics in the R group and the No-R group. Furthermore, the cox proportional hazard model was used in two studies to adjust the potential effects of other prognostic factors with a possible impact upon these survival outcomes.

Besides, of these studies, practically forty-three percent studies draw negative conclusion that prior exposure to rituximab may be detrimental to the outcomes of ASCT.

Main confounding factors or potential prognostic factors. A factor included one by one in the multivariate models would be considered as a confounder if its regression coefficient changes by more than 10% [31,32]. The factor relating to exposure factors, and having association with the outcomes, is also a confounder [33]. The confounder should be retained in the final model or kept balance among the study groups (Table 3).

Table 3: The main confounders or prognostic factors of these studies

Study (Refs.)	Confounders or prognostic factors	Parameter
Smith et al.[3]	previous chemotherapy, previous radiotherapy, disease stage, disease status, IPI, $CD34^+$ dose	PFS, OS
Kaneko et al. [38]	disease stage, B symptoms, extranodal lesion, GCB, LDH, IL-2R, aaIPI	EFS, OS
Glass et al. [37]	disease stage, performance status, aaIPI, B symptoms, bulky disease, extranodal disease, extranodal sites	EFS, OS
Redondo et al. [4]	B symptoms, Bulky disease, b2-microglobulin, LDH, aaIPI, status, previous treatment lines	PFS, OS
Kewalramani et al. [36]	previous chemotherapy, Karnofsky performance status, disease status, LDH, disease stage, aaIPI	PFS, OS
Papajik et al. [28]	aaIPI, IPI, bulky disease, status, b2-microglobulin, bcl-2 protein expression	EFS, OS
Telio et al. [39]	variants, LDH, disease stage, extranodal sites, performance status, aaIPI, first-line chemotherapy, status	PFS, OS

IPI: International Prognostic Index
aaIPI: Age adjusted International Prognostic Index GCB:

Germinal center B-cell

LDH: Lactic dehydrogenase IL-2R: Interleukin-2 receptor

IPI and aaIPI: IPI and age adjusted International Prognostic Index (aaIPI) are widely thought as the benchmark of DLBCL prognosis [13,34,35]. Both the IPI and aaIPI were divided into four groups: low, low intermediate, high intermediate and high [2]. Generally, the last two groups have a poor prognosis because of the high relapse rates. Benjamin supposed that the IPI or aaIPI was considered the most valuable prognostic indicator of aggressive lymphoma [36].

For the studies, the balanced line test was used to identify the distribution of the IPI or aaIPI [3,4,37,38], and three of them fulfilled a uniform distribution. Telio and Kaneko demonstrated that a high-level aaIPI was related to a bad survival [39,40]. Similarly, Yoon found DLBCL patients with an aaIPI score $\geq$ 2 showed inferior OS and PFS comparing to the aaIPI score 0 to 1. Also, Glass conducted the Cox regression model and adjusted for the factors of the aaIPI, finding that there was a statistically significant benefit for patients receiving rituximab with respect to both OS and EFS [38].

Serum LDH: Serum lactic dehydrogenase (LDH) is an important indicator of tumor activity. Evidence suggests that elevated LDH concentrations which are more than upper limit of normal were strongly associated with worse survival parameters for the DLBCL patients treated in the rituximab era [39]. Comparably, normal LDH levels were more likely to prolong survival [2].

Glass selected all patients with serum LDH concentrations above the upper normal limit to determine safety and efficacy of rituximab in combination with repetitive high-dose therapy (HDT) as primary treatment for DLBCL [38]. The balanced line test was used to assess the balance between the R group and No-R group and no significant differences were found [4, 37].

Kaneko found the LDH did not affect the EFS [39], but Telio found elevated LDH was a strong negative predictor of survival parameters (OS and PFS) [40]. Although there were inconsistent results of studies included in this work, we still cannot neglect the role of serum LDH.

Disease status: Among patients with chemosensitive disease, the disease status at transplantation appears to have a significant impact on outcome [41,42]. Comparatively, the chemosensitive DLBCL induced into CR by first-line chemotherapy inherently is more likely to be eradicated by the transplantation than into PR, which results in a better long-term PFS [43,44]. Redond and Kewalramani advocated the opinion that the high-risk DLBCL patients in CR after ASCT will get more survival benefits than in PR [4,37]. Therefore, that qualitative evidence indicated that we should select patients with CR, which is more preferable.

Disease stage: The DLBCL patients were divided into four

stages according to the Cotswold modification of Ann Arbor system [45,46]. Some studies proved that the advanced stage (III or IV) had a poor prognosis comparing with the low stage (I or II) [6,47]. However, Kaneko found no association between different stages and the survival parameters [39]. For those studies, Smith and Glass fitted a Cox regression model to adjust the effect of disease stage. Undoubtedly, the distribution of the stages should be considered among the different treatment groups (with and without the rituximab) for the DLBCL patients [37].

Meta-analysis of studies reporting

Details of the meta-analysis results are showed in Figures 2-4. Except for the five-year OS, PFS, and EFS, there was no heterogeneity for other survival parameters. The results of Egger's tests did not suggest obvious evidence of publication bias. The meta-analyzed RR and 95% confidence interval in the R group *versus* the No-R group were: 0.83 (0.69, 0.99), 0.84 (0.72, 0.98), 0.94 (0.71, 1.25) for two-, three-, five-year OS; 0.91 (0.77, 1.08), 0.85 (0.69, 1.06), 0.85 (0.62, 1.17) for two-, three-, and five-year PFS; 0.46 (0.27, 0.80), 0.47(0.29, 0.76), 0.74 (0.15, 3.52) for two-, three-, and five-year EFS.

We usually place more focus on the prognosis for the relapsed or primary refractory DLBCL [42]. Undoubtedly, the superior curative effects of the rituximab on DLBCL patients have been proved [48-51]. And the survival would prolong after ASCT for the primary refractory or relapsed DLBCL [12,52,53]. But whether prior exposure to the rituximab will consume the benefit of ASCT is highly controversial. As Martin's study, the use of highly effective rituximab containing primary therapy makes it more difficult to salvage relapsed or refractory DLBCL patients [19]. Therefore, we performed the meta-analysis of the impact of prior exposure to the rituximab on the ASCT outcomes with relapsed or refractory DLBCL.

Our results indicate that prior exposure to rituximab was associated with improved two- and three-year PFS and OS, which had reached a level of statistical significance. However, there were five survival parameters without reaching statistical significance. On the one hand, the outcomes estimating the measure indicator, especially for the PFS might be included due to the limited literature quantity. On the other hand, pre-rituximab did not improve the five-year PFS, OS, and EFS at all. Although the RR of those survival parameters between the two groups presented no statistical significance, the trend of the difference was obvious, which could hint the difference actual existed.

However, the bio-mechanism with pre-rituximab how to improve the survival of ASCT needs to be studied further. Most importantly, all efforts should be concentrated on minimizing a patient's disease burden after salvage treat such as: 1) raising the percentages of CR; 2) decreasing the concentrations of serum LDH; 3) decreasing the grades of IPI and aaIPI; 4) decreasing the grades of Ann Arbor stage.

Figure 2: Forest graphs for the parameter of two-, three- and five-year OS

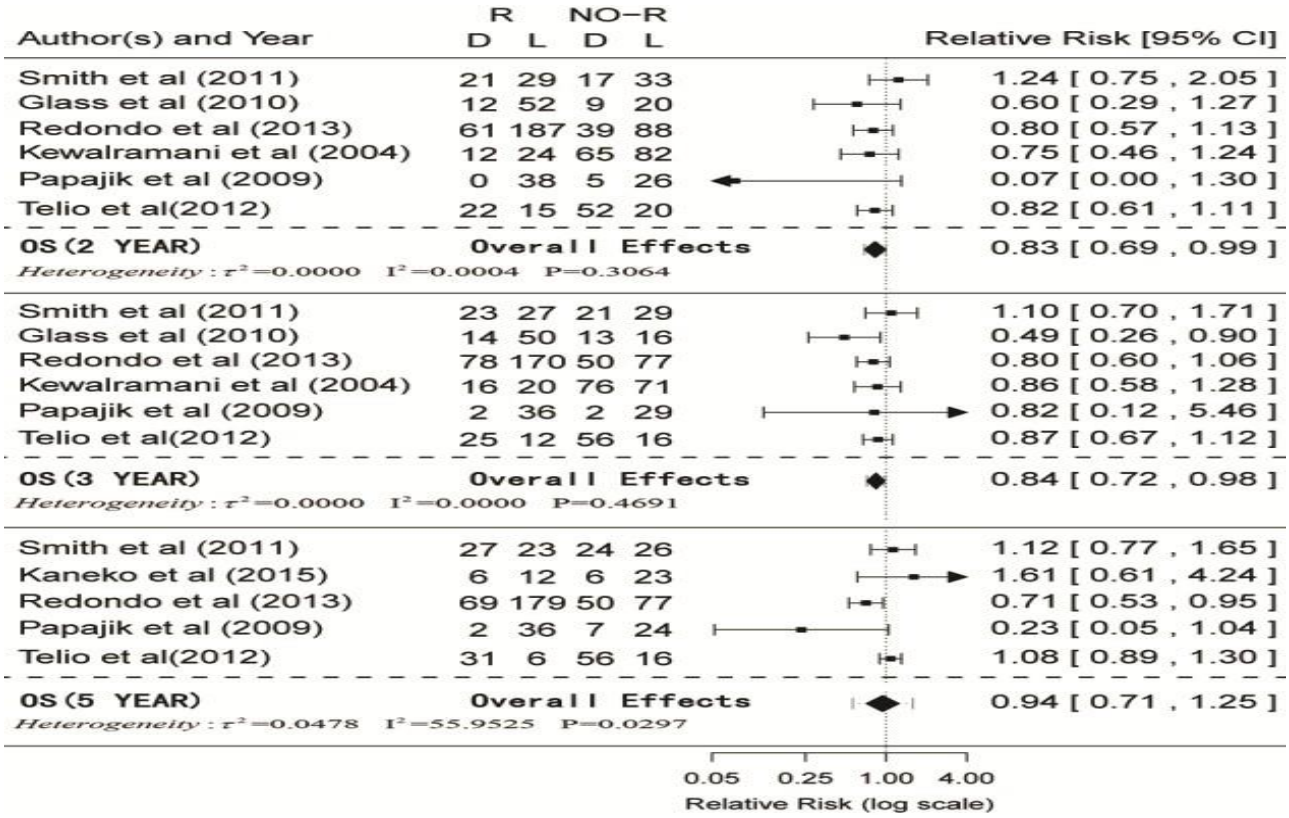


Figure 3: Forest graphs for the parameter of two-, three- and five-year PFS

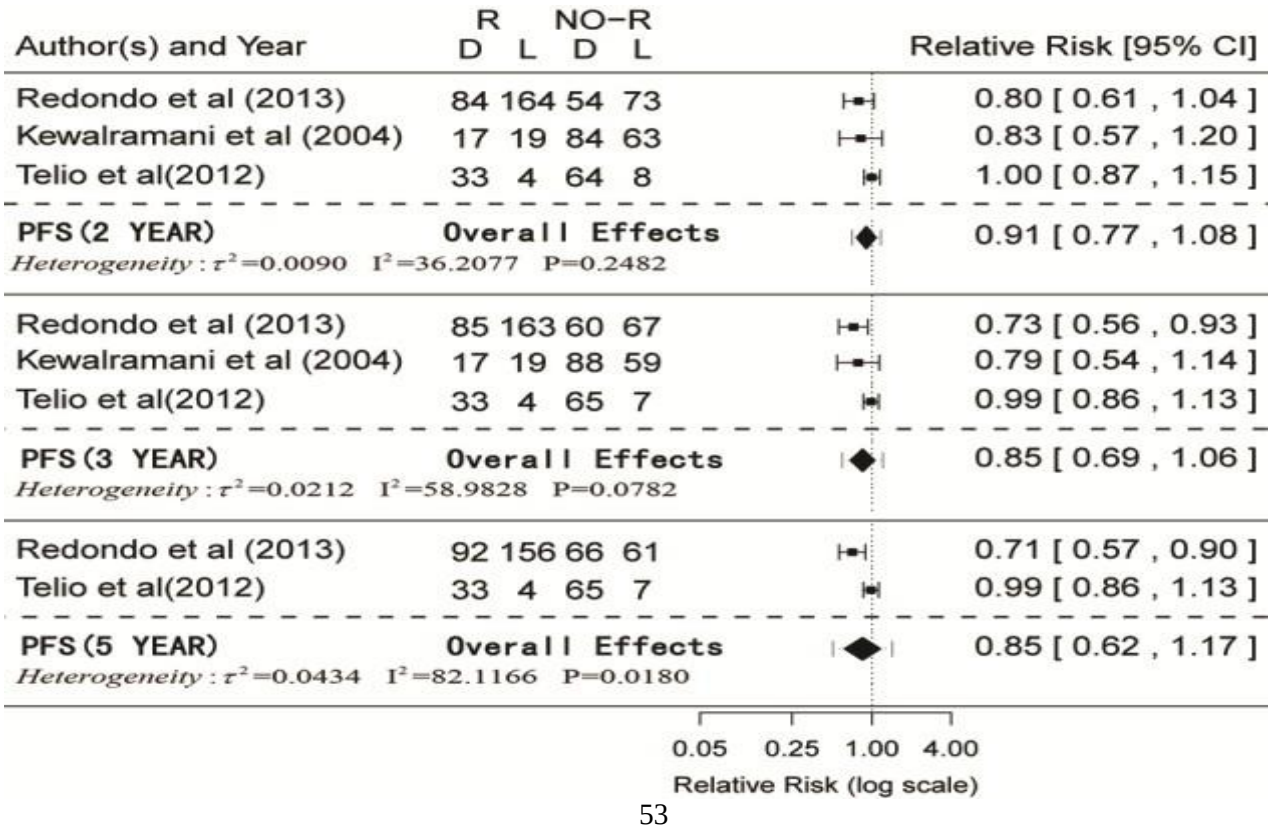
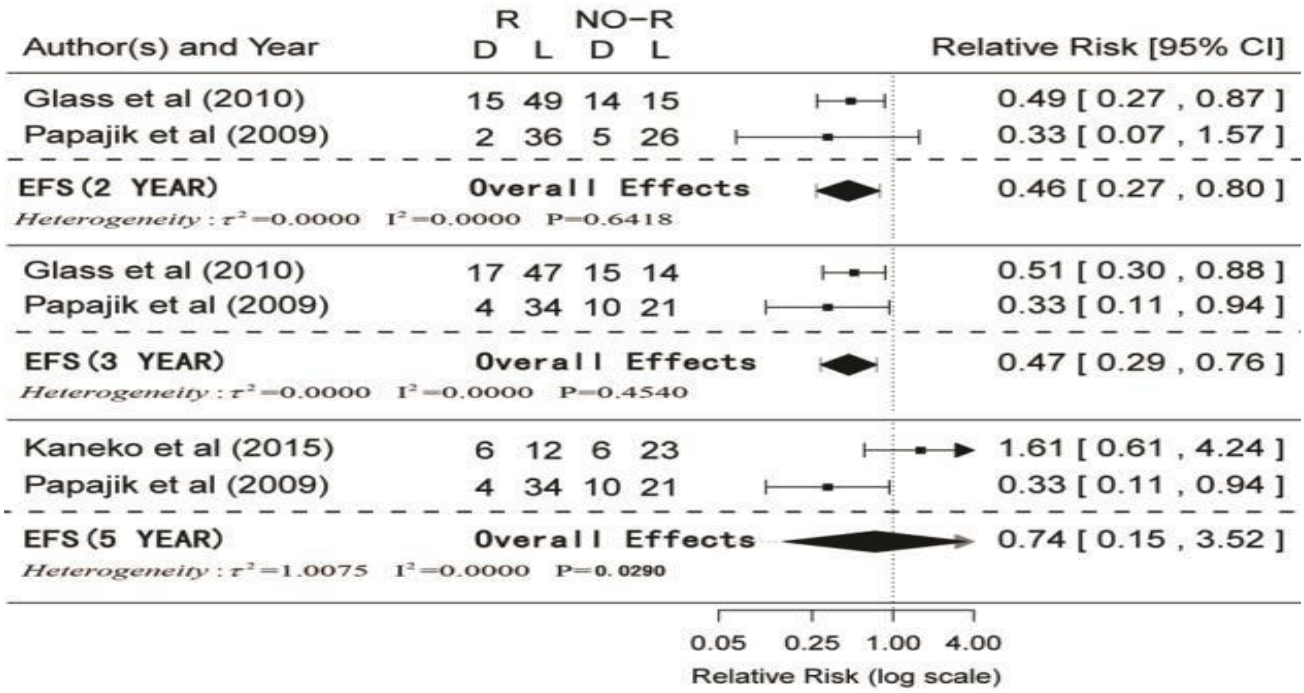


Figure 4: Forest graphs for the parameter of two-, three- and five-year EFS



CONCLUSION

These evidences indicate that prior exposure to rituximab has a positive influence on the outcome of ASCT with relapsed or primary refractory DLBCL, which prolongs survival time. However, such conclusions must be interpreted cautiously with the following two reasons. On the one hand, the studies focusing on this topic are limited so that the results of this work are not perfect. On the other hand, some data in this works were extracted from figures in original study artificially; resulting in the bias cannot be avoided after all.

CONFLICTS OF INTEREST

Conflicts of interest No conflicts of interest to declare.

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