Int J Clin Exp Med 2016;9(2):918-926
www.ijcem.com /ISSN:1940-5901/IJCEM0017699

*Original Article*

# Rituximab should be used earlier in ITP patients: a meta-analysis of randomized controlled trials

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Received October 12, 2015; Accepted January 27, 2016; Epub February 15, 2016; Published February 29, 2016

**Abstract:** To evaluate the efficacy of rituximab to treat immune thrombocytopenia, Medline (Pubmed), Embase and the Cochrane library were mainly searched to provide relevant articles. A meta-analysis of seven randomized controlled clinical trials which included 716 patients analyzed the efficacy of rituximab for treatment of immune thrombocytopenia in order to afford actual response rates. Overall response (OR) rate was achieved in 67.7% (platelets ≥$30\times10^9$/L, 95% confidence interval [CI]: 0.60-0.74) for 171 patients, 60.4% (platelets ≥$50\times10^9$/L, 95% CI: 0.45-0.73) for 188 patients, respectively; Complete response (CR) rate was 48.1% (platelets ≥$100\times10^9$/L, 95% CI: 0.37-0.59) for 251 patients, 31.8% (platelets ≥$150\times10^9$/L, 95% CI: 0.15-0.55) for 95 patients, respectively. Therefore, rituximab effectively elevated the target platelet count with excellent treatment outcomes in ITP patients.

**Keywords:** Rituximab, immune thrombocytopenia, platelet count

## Introduction

Immune thrombocytopenia (ITP) is a common autoimmune disease characterized by immune-mediated platelet destruction and insufficient platelet production, causing risk of bleeding [1-4]. Corticosteroids are the first-line treatments of ITP with response rates of 70-90% [5, 6]; however, a certain amount of ITP patients relapse during dose tapering or after corticosteroids withdrawal then require further therapy [5-9]. Additional treatments including splenectomy which is the standard second-line therapy in patients with chronic ITP are frequently required [6]. Splenectomy is an aggressive procedure associated with postoperative complications [10, 11]. Less patients are willing to undergo splenectomy because of the availability of medical alternatives [5, 12, 13]. Rituximab was a kind of monoclonal antibody that bound to the CD20 antigen present on B lymphocytes, it showed activity in miscellaneous autoimmune disorders [13-15] by decreasing circulating B cell counts with a promising response rate in up to 60% for immune thrombocytopenia in some studies [16-19]. Recently, several studies investigated low-dose RTX at a dose of 100 mg weekly for 4 weeks in ITP patients and concluded that the response rate was similar to that with standard-dose RTX (375 mg/$m^2$) [20-22].

To clarify the efficacy of rituximab in chronic ITP treatment, the first meta-analysis of randomized controlled trials (RCTs) were performed on the effect of rituximab in adult chronic ITP patients.

## Methods

### *Search strategy and data sources*

A literature search in the English language was carried out using Medline (Pubmed), Embase, Cochrane Library, Annual Meetings of the American Society of Hematology, Annual Meetings of the European Hematology Association (from inception to 2015 August 21). In addition we searched databases of ongoing and unpublished trials: http://www.controlled-trials.com, http://www.clinicaltrials.gov/ct.

The following search terms were used: (rituximab OR mabthera OR rituxan) AND (thrombo-

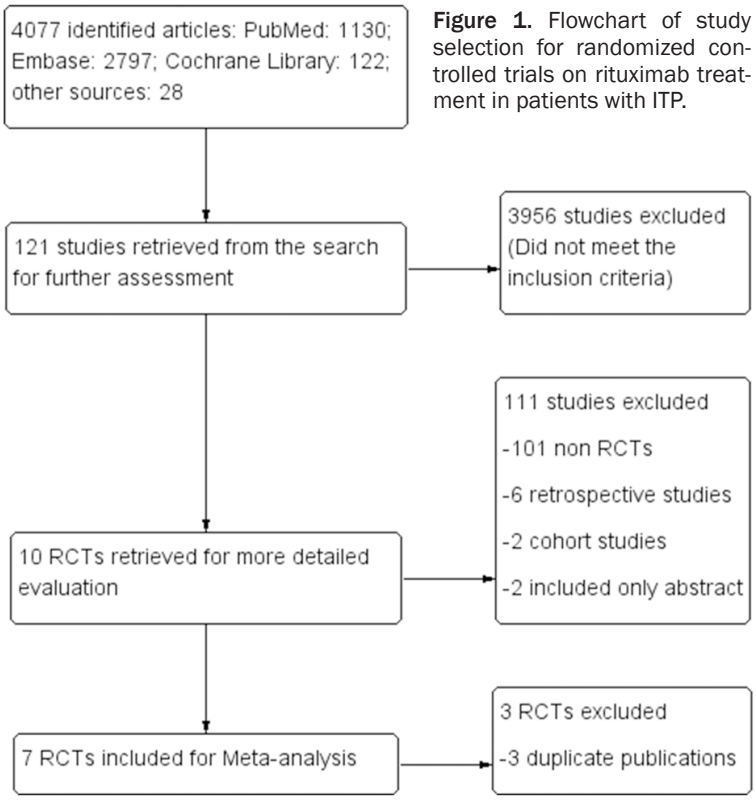


**Figure 1.** Flowchart of study selection for randomized controlled trials on rituximab treatment in patients with ITP.

cytopenia OR thrombocytopenic purpura OR ITP). In that ITP possessed various disease nomenclatures, we manually distinguished ITP from other thrombocytopenias and thrombocytopenic purpuras.

*Selection of studies*

All randomized, controlled trials comparing rituximab to placebo or other regimens in patients with ITP were collected.

Studies were included in the meta-analysis if they matched all the following criteria: (i) published in English; (ii) clinical randomized controlled trials; (iii) compared rituximab to other regimens in patients with ITP; (iv) provided OR or CR rate; (v) including at least 20 participants.

Studies were excluded if they met criteria: (i) secondary or other causes of thrombocytopenia; (ii) children <18 years old.

*Data extraction and assessment of risk of bias*

Two investigators (RF, HXZ) independently examined all references identified through our search method and supplied inclusion criteria. The discrepancies were resolved by discussion until consensus or by resorting to a specialist (CYC). The methodological quality of each included study was assessed according to the Cochrane Collaboration Reviewers' Handbook. Values of 'high', 'low', or 'unclear' were assigned to the following items: randomization, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases. Trials possessing one or more items marked with 'high' were at high risk for bias. Trials possessing all items marked with 'low' were at low risk for bias. Other trials were at unclear risk for bias (**Figures 2**, **3**) [23].

*Data synthesis and analysis*

We presented the mean OR and CR rate, together with their 95% confidence intervals (95% CI) obtained from the ITP patients treated with rituximab. The selected studies contained different controlled treatment methods, accordingly, we had no comparator arms.

The primary outcome was overall response (OR) rate and the secondary outcome was complete response (CR) rate at the end of the study period. Criterion of OR and CR differed in selected studies. Four studies recorded OR defined by platelet count $\geq 30\times10^9$/L (OR30) or $\geq 50\times10^9$/L (OR50), respectively. Six studies recorded CR defined by platelet count $\geq 100\times10^9$/L (CR100), two studies recorded OR by platelet count $\geq 150\times10^9$/L (CR150), respectively. Consequently, we reported all the OR and CR rate separately according to definitions in the analysis. In seven studies, adverse events reporting methods were various. Therefore, we abandon analyzing adverse events to appraise clinical safety of rituximab for treatment of ITP.

Here we present the mean OR and CR rate, together with their (95% confidence intervals, 95% CI) achieved for the chronic ITP patients

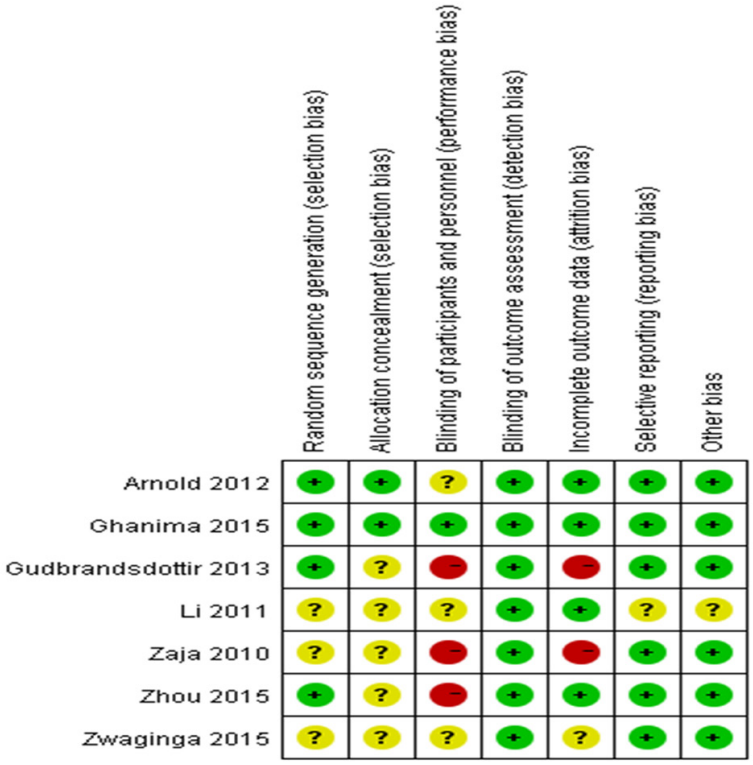


**Figure 2.** Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

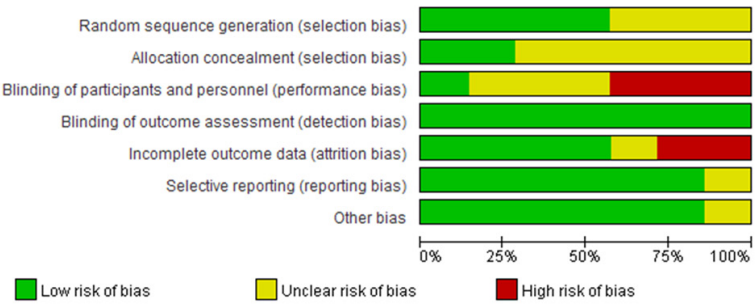


**Figure 3.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

treated with rituximab. We assessed heterogeneity using the $I^2$ statistic [24]. An $I^2$>50% and a *p* value ≤0.10 represented significant heterogeneity. Next, if possible, we conducted a subgroup meta-analysis or a sensitivity analysis explaining the source of the heterogeneity. Whether heterogeneity existed or not, we used a random effects model (Der-Simonian and Laird method) [25] conducting the meta-analysis. We assessed publication bias by constructing a funnel plot and confirmed it with Egger's test (linear regression method) [26]. Statistical analyses were accomplished with the MetaAnalyst Beta 3.13 (Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, USA). The data of evaluation for the risk of bias was acquired using the Review Manager version 5.0 (Revman; The Cochrane Collaboration, Oxford, UK).

## Results

### *Study selection and characteristics*

A total of 4077 latently relevant records were identified through electronic databases and manual seeking, as presented in **Figure 1**. After looking through the titles and abstracts, 3956 non-relevant studies were excluded. After screening full texts, 114 records were excluded because they did not meet eligibility criteria. Ultimately, seven RCTs were included in our meta-analysis [27-33]. The characteristics of the included studies are shown in **Tables 1**, **2**.

One RCT was conducted in 14 centers in Norway, Tunisia, and France [33], one in 12 centers in China [32], one in The Netherlands [31], one in 12 centers in Denmark [30], one in 7 centers in Canada [29], one in 22 centers in Italy [28], one in China [27]. The sample sizes ranged from 60 to 138 representing a total of 716 participants. OR30 and OR50 were both reported in four studies, while CR100 were reported in six studies and CR150 in two studies.

Rituximab treatments were generally applied by intravenous injection at 375 mg/m$^2$ weekly for 4 weeks in five studies. The dose was different (100 mg weekly for 4 weeks) in two studies. Two studies compared rituximab with placebo with concurrent corticosteroids only allowed.

**Table 1.** Characteristics of the 7 RCTs included in the final analysis (1)

| First author | Publication year | Study location | Study design | Sample size | |
|---|---|---|---|---|---|
| | | | | Rituximab | Control |
| Zaja | 2010 | 22 centers in Italy | RCT | 49 | 52 |
| Li | 2011 | China | RCT | 31 | 31 |
| Arnold | 2012 | 7 centers in Canada | RCT | 32 | 27 |
| Gudbrandsdottir | 2013 | 12 centers in Denmark | RCT | 62 | 71 |
| Zwaginga | 2015 | The Netherlands | RCT | 46 | 92 |
| Zhou | 2015 | 12 centers in China | RCT | 38 | 77 |
| Ghanima | 2015 | 14 centers in Norway, Tunisia, and France | RCT | 55 | 54 |

Abbreviations: RCT: randomized controlled trial.

**Table 2.** Characteristics of the 7 RCTs included in the final analysis (2)

| First author | Median age, years (range) | Females, n (%) | Rituximab dose (weekly ×4) | OR30 | OR50 | CR100 | CR150 |
|---|---|---|---|---|---|---|---|
| Zaja | 47±19* | 27 (55) | 375 mg/m$^2$ | | 31 | 26 | 21 |
| Li | 26 (18-51) | 18 (58) | 100 mg | | 25 | 21 | |
| Arnold | 40 (30-59) | 19 (57.6) | 375 mg/m$^2$ | 20 | | 17 | |
| Gudbrandsdottir | 51 (36-63) | 36 (58) | 375 mg/m$^2$ | | 36 | | |
| Zwaginga | 56 (18-77) | 27 (59) | 375 mg/m$^2$ | 29 | 19 | 19 | 10 |
| Zhou | 42.5 (12-68) | 25 (68.5) | 100 mg | 27 | | 9 | |
| Ghanima | 46 (27-61) | 40 (73) | 375 mg/m$^2$ | 40 | | 28 | |

Abbreviations: OR30, OR50: overall response rates defined as platelet count ≥30, 50×10$^9$/L, respectively; CR100, CR150: complete response defined as platelet count ≥100, 150×10$^9$/L, respectively. *; mean ± SD.

Two studies compared rituximab in combination with dexamethasone or dexamethasone alone. One study compared rituximab plus recombinant human thrombopoietin (rhTPO) with rituximab. One study evaluated three alternative dosing strategies. One study compared low-dose rituximab combined with short-term glucocorticoids with the latter.

*Primary outcome*

Four studies reported OR30 rate with the mean rate reaching 67.7% (95% CI: 0.60-0.74) for 171 patients (**Figure 4**). No heterogeneity existed after analysis ($I^2$ = 0.0%, P = 0.39). Four studies reported OR50, the mean rate was 60.4% (95% CI: 0.45-0.73) for 188 patients (**Figure 5**). Li et al.'s study may have resulted in moderate heterogeneity ($I^2$ = 42.5%, P = 0.01). The heterogeneity decreased ($I^2$ = 37.4%, P = 0.01) when we excluded this study and performed a meta-analysis of the remaining three studies.

*Secondary outcome*

Six studies reported CR100 with the mean rate 48.1% (95% CI: 0.37-0.59) for 251 patients (**Figure 6**) with mild heterogeneity ($I^2$ = 39.6%, P = 0.01). Through subgroup analysis by study design type, the heterogeneity of 375 mg/m$^2$ weekly rituximab studies was significantly reduced, which indicated that 100 mg weekly rituximab studies may introduce heterogeneity (Figure S1). By performing a subgroup analysis based on study region, we found that studies conducted in the Non-Europe area made major contributions to heterogeneity (Figure S2). One study including both Europe and Non-Europe was abnegated [33]. To evaluate the robustness of our analysis, a sensitivity analysis was conducted by excluding one study per iteration. The outcome revealed that the exclusion of any study did not change the overall result (Figure S3).

Two studies reported CR150, the mean rate was 31.8% (95% CI: 0.15-0.55) for 95 patients (**Figure 7**) with moderate heterogeneity ($I^2$ = 44.0%, P = 0.03). Rituximab combined with high dose dexamethasone for the treatment of ITP in Zaja et al.'s study may have mainly resulted in heterogeneity.

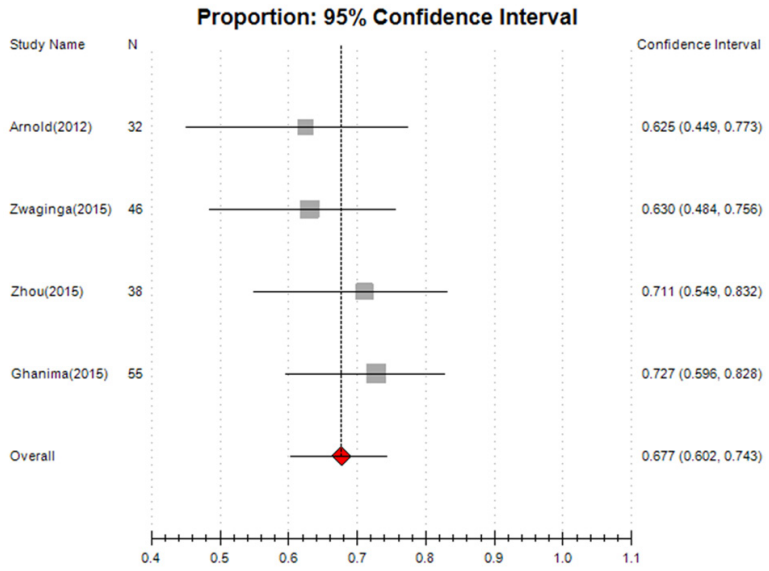


**Figure 4.** Forest plot of OR30 rate after Rituximab treatment in patients with immune thrombocytopenia.

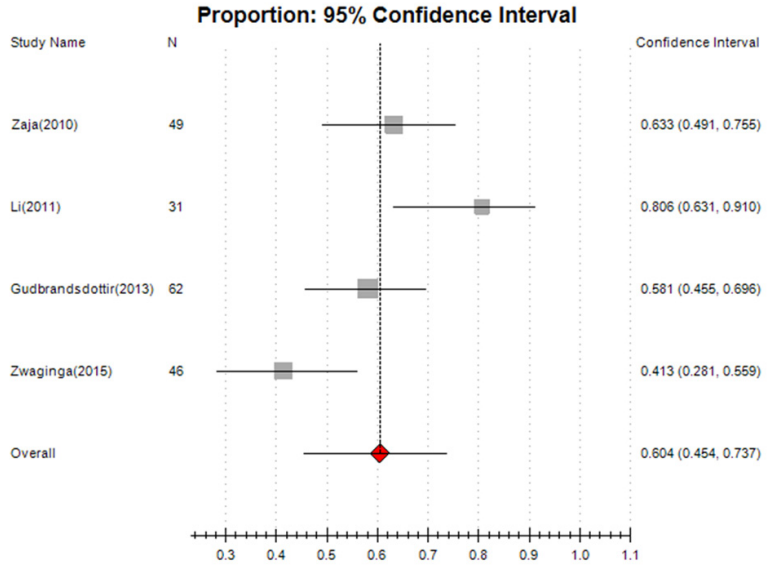


**Figure 5.** Forest plot of OR50 rate after Rituximab treatment in patients with immune thrombocytopenia.

*Risk of bias*

Random sequence generation was performed in four studies, and two studies provided adequate description. Allocation concealment was only conducted adequately in two studies. Blinding of the participants and personnel was performed only in one study, while all studies implemented reported blinding to outcome assessment. Ultimately, three studies were considered to be at high risk for bias, three studies were at unclear risk for bias and one study was at low risk for bias.

In the analysis of OR30, the funnel plot did not showed significant asymmetry and Egger linear regression test (P = 0.029, 95% CI: 0.195-1.395) indicated no obvious evidence of publication bias among the studies. In the analysis of OR50 and CR100, good symmetry in the funnel plots and Egger linear regression tests (OR50, P = 0.479, 95% CI: -1.01-1.51; CR100, P = 0.379, 95% CI: -0.552-1.16) indicated no evidence of publication bias of studies. In the analysis of CR150, an apparent asymmetry in the funnel plot suggested the presence of a potential publication bias, a language bias, inflated estimates by a flawed methodologic design in smaller studies, and/or a lack of publication of trials.

## Discussion

To the best of our knowledge, this meta-analysis was the first to calculate the response rates of rituximab for immune thrombocytopenia on randomized controlled trials. Glucocorticoids, the standard first line of treatment for ITP, enable the increasing of platelet count; nevertheless, a drop in platelet count often occurs after tapering or withdrawal. Therefore, rituximab acting as a second-line therapy is frequently required with a high response rate in ITP [34, 35].

Our meta-analysis revealed that OR30 rate was 67.7%, no heterogeneity or evidence of publication bias existed. OR50 rate was 60.4%, Li et al.'s study resulted in heterogeneity, still no evi-

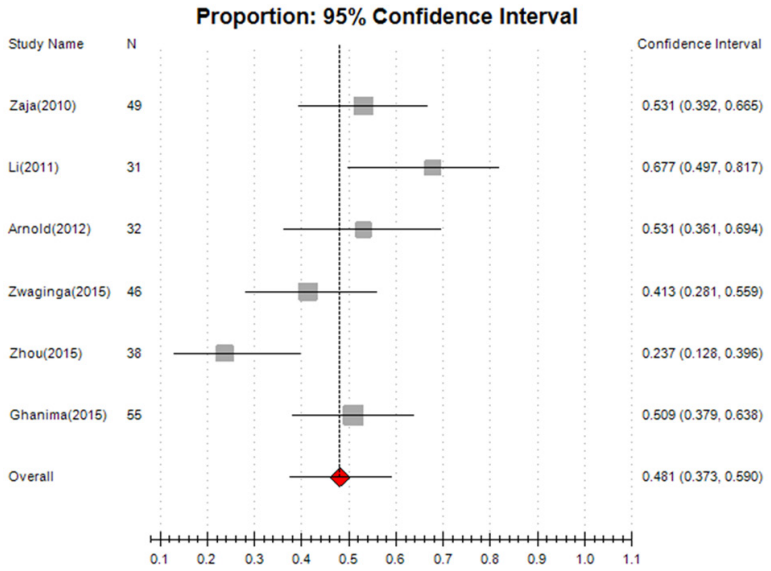


**Figure 6.** Forest plot of CR100 rate after Rituximab treatment in patients with immune thrombocytopenia.

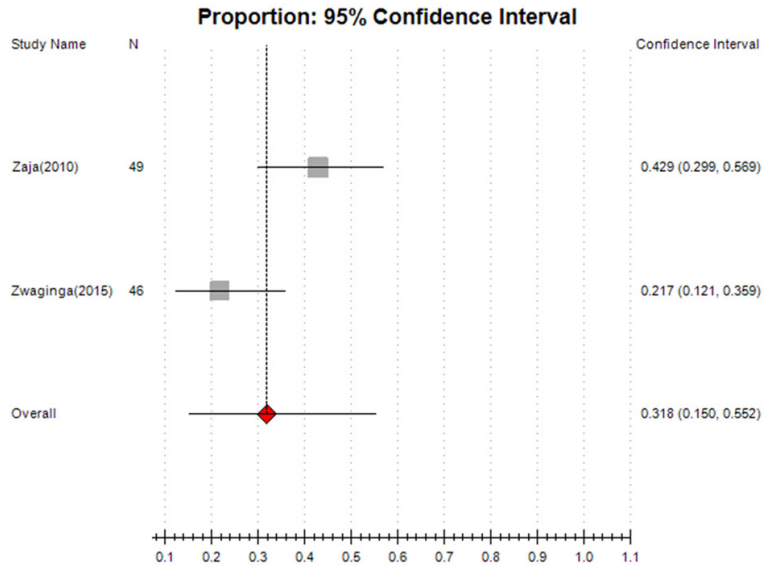


**Figure 7.** Forest plot of CR150 rate after Rituximab treatment in patients with immune thrombocytopenia.

dence of publication bias of studies was found. CR100 rate was 48.1% with mild heterogeneity, the subgroup and sensitivity analysis confirmed different dose of rituximab and different regions of studies accounted for a significant fraction of the heterogeneity for meta-analysis, no sufficient evidence of publication bias emerged. Besides, only two studies reported CR150, more comprehensive analyses are still requisite as more data are published in the aftertime. The relevant results were consistent with international consensus report on the investigation and management of primary immune thrombocytopenia stating that rituximab manifested beneficial effect for treatment of immune thrombocytopenia [5].

In addition, this meta-analysis had several limitations that should be considered. First, there were only seven RCTs being included in our meta-analysis, the number of relevant studies was still relatively small, and the sample sizes of most of the included studies were small too. Second, the methodological quality of some of the included studies was not high due to the infeasibility of utilizing a double-blind study design, which might have generated bias. Third, the degree of control for confounding variables, such as age, gender, treatment means before rituximab (splenectomized or not, for instance), and time from rituximab treatment to evaluating the response, also varied between studies, therefore, we will analyze these factors when the necessary data are available hereafter. Fourth, we were incapable of analyzing the duration of response, relapse rate or adverse events due to limitation of collected studies.

## Conclusions

In summary, rituximab yields high response rates in adults with primary immune thrombocytopenia. Thus, rituximab represents an effective treatment option and should be used in earlier in patients with ITP. However, the results of this analysis must be understood with caution due to the small number of collected studies and small sample size, mild heterogeneity

and possible risk of bias. Future adequately powered RCTs are still required.

## Acknowledgements

We acknowledge Department of Hematology, Qilu Hospital, Shandong University, Jinan, China, for providing sufficient data.

## Disclosure of conflict of interest

None.

## Authors' contributions

Conceived and designed the experiments: RF, CYC. Performed the experiments: RF, HXZ. Analyzed the data: RF, HXZ. Contributed reagents/materials/analysis tools: RF. Wrote the paper: RF, HXZ.

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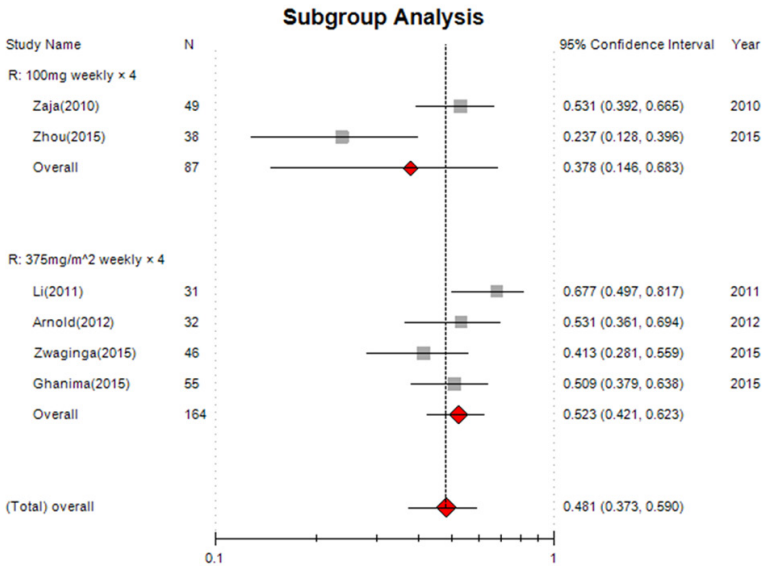


**Figure S1.** Subgroup analysis of CR100 rate after Rituximab (abbreviated to R in the figure) treatment in patients with immune thrombocytopenia.

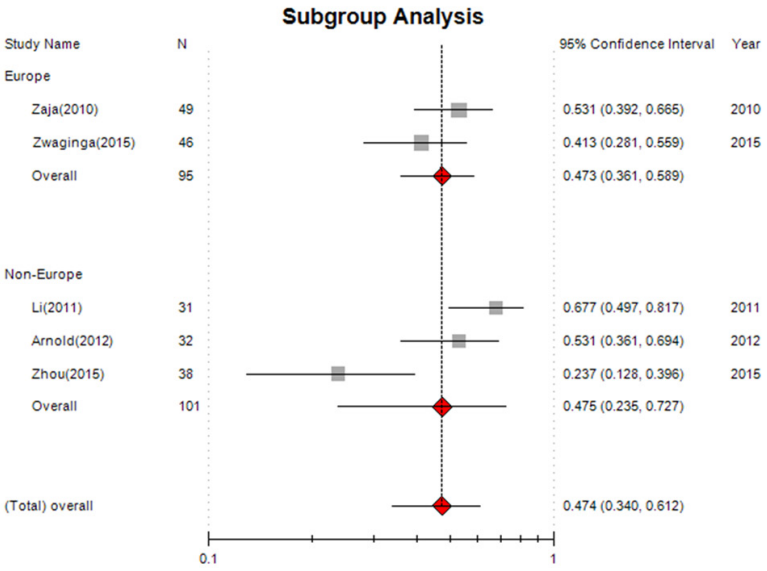


**Figure S2.** Subgroup analysis of CR100 rate after Rituximab treatment in patients with immune thrombocytopenia.

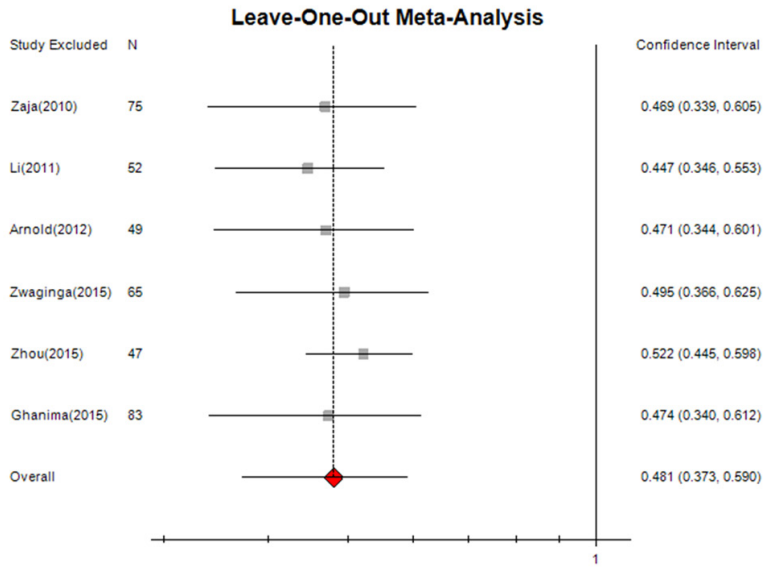


**Figure S3.** Leave-One-Out Meta-analysis of CR100 rate after Rituximab treatment in patients with immune thrombocytopenia.