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Systematic Review with Meta-analysis of ''Role of Rituximab in Treatment of Bullous Auto-immune Diseases''

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Keywords

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Abstract

Background: Autoimmune bullous disorders (AIBDs) are a diverse collection of uncommon illnesses, clinically defined by the presence of erosions and/or blisters. Bullous skin illnesses are classified into two types depending on whether the skin is afflicted inside the epidermis or at the epidermal-dermal junction. Rituximab (RTX) is a chimeric, humanized anti-CD20 monoclonal antibody thought to achieve its therapeutic effects in AIBD by depleting Dsg-specific IgG-positive B cells. RTX with short-term corticosteroids are safe and much more efficacious than corticosteroids alone ***Objective:*** To assess the safety and effectiveness of RTX in the treatment of AIBDs in comparison to placebo, conventional therapies, or other biologics. ***Methods:*** The PRISMA checklist directed the data reporting. We conducted a search in PubMed, Web of Science, Embase, ScienceDirect, and Scopus. ***Results:*** The literature review found 2310 publications. Following the evaluation of titles and abstracts according to the inclusion and exclusion criteria, and the assessment of full texts, 12 publications were ultimately included into the meta-analysis. ***Conclusions:*** RTX is both safe and efficacious for the managing AIBDs.

1. Introduction:

AIBDs are a heterogeneous collection of rare disorders clinically characterized by erosions and/or blisters. Since the skin is a vital organ in the protection of the body against dehydration and infections, these skin diseases may be life threatening [1].

Bullous skin illnesses are categorized into two groups depending on whether the skin is afflicted inside the epidermis or at the epidermal-dermal interface [2].

The first group is designated as pemphigus and comprises four disease types: Pemphigus vulgaris (PV), Pemphigus foliaceus (PF), Paraneoplastic pemphigus, and IgA pemphigus [2].

The second subtype entails multiple disease entities including Bullous pemphigoid (BP), Cicatricial pemphigoid, Inherited epidermolysis bullosa, Dermatitis herpetiformis, Linear Ig A disease, and Bullous systemic lupus erythematosus [3].

The management of refractory AIBDs has always been a problem.

The management of AIBDs focuses on suppressing the immunological response, namely by the elimination or neutralization of autoantibodies. Various combinations of plasmapheresis, high-dose intravenous immunoglobulins (IVIG), corticosteroids, RTX, and cyclophosphamide are used based on the disease's severity [2].

RTX is a chimeric, humanized anti-CD20 monoclonal antibody that is thought to exercise its therapeutic benefits in autoimmune blistering diseases by depleting Dsg-specific IgG-positive B cells [4, 5].

RTX with short-term corticosteroids are both safe and much more effective than corticosteroids alone [6].

The cytotoxicity of RTX is facilitated by three mechanisms: antibody-dependent cellular cytotoxicity, complement-mediated lysis, and direct interference with signaling pathways that induce apoptosis [7].

2. Materials and Methods:

We adhered to the PRISMA statement guidelines [8] in the development of this systematic review and meta-analysis, executing all procedures in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [9].

Search strategy and study selection

We conducted a search in PubMed, Scopus, Cochrane, Web of Science, Embase, and Science Direct. The search terms we utilized include: (Bullous OR BP OR Pemphigoid OR Pemphigoids OR “PV” OR “PF”) AND (Rituximab OR “CD20 Antibody, Rituximab” OR “Rituximab CD20 Antibody” OR Mabthera OR “IDEC-C2B8 Antibody” OR “IDEC C2B8 Antibody” OR “IDEC-C2B8” OR “IDEC C2B8” OR GP2013 OR Rituxan).

Eligibility criteria and study selection

We included research that met these criteria:

(1) Adult patients aged 18 and older

(2) Double and single-arm study designs

(3) Study designs included randomized controlled trials (RCTs), cohort studies, and case-control studies.

(4) English Studies

(5) Any result is permissible.

We rejected conference abstracts, unpublished data, studies not written in English, in-vitro investigations, and duplicate papers by the same author, save for those with lengthier follow-up studies. All published publications were reviewed without limits on search data. The titles and abstracts were completed in two phases, followed by full-text evaluation. The reference lists of the listed studies were carefully examined to identify any other suitable research that may have been overlooked in prior rounds.

Quality assessment

The risk of bias was assessed using the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 [10], which identified the following risks: selection bias via random sequence generation and allocation concealment, selective reporting, attrition bias, performance bias through participant and personnel blinding, and detection bias through outcome assessment blinding. Each bias domain is classified as low risk, high risk, or uncertain risk (Figure 1). Additionally, one of the studies included is a retrospective cohort, assessed using the NIH technique for quality evaluation of cohort studies, with data extraction shown in Table 1.

We acquired data from text, tables, figures (utilizing Graph Grabber version 2.0), and supplemental materials. We focused on the following result metrics: Complete remission (CR), disease flare and relapse either between RTX with other different dose or other line of treatments. We also assessed the adverse events and sever adverse events including Sepsis, Hypertension, Arthralgia, Pulmonary embolism (PE), Dyspnea, and Headache. The summary of baseline characteristics of the patients is presented in **(Table 2)**. The outcomes will be discussed in detail in the results section.

Statistical Analysis

This meta-analysis was performed using Review Manager (RevMan) (Computer software) (Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For the research results, the risk ratio (RR) with a 95% confidence interval (CI) was used for dichotomous variables, whilst the mean difference (MD) and 95% CI were reported for continuous variables. Cochrane's P values and I^2 were assessed to evaluate heterogeneity among the studies. Significant heterogeneity presumably arose from clinical and methodological variables; hence, a random effects model was used in this meta-analysis despite a minimal I2 value. The execution of funnel plots and the Egger regression test was precluded by the insufficient number of included trials. A sensitivity analysis

was conducted by successively removing trials to assess the stability of the major results.

3. Results:

1. Literature search results

The preliminary search yielded 2310 items from five databases: PubMed, Cochrane, Scopus, Web of Science (WOS), Embase, and Science Direct. We eliminated 355 items because of redundancy. In all, 1986 papers were subjected to title and abstract screening, resulting in the exclusion of 1892 articles that failed to satisfy the inclusion requirements. Ninety-four articles were subjected to comprehensive text screening. A total of twelve research were ultimately included for the comprehensive qualitative and quantitative analysis. Exclusion from the comprehensive text screening was predicated on the following justifications: Fifty-four publications did not meet eligibility requirements, twelve articles were reviewed (non-comparative research not suitable for extraction), and ten papers were case reports, two articles were single arm studies, and four papers were conference abstracts **(Figure 1).**

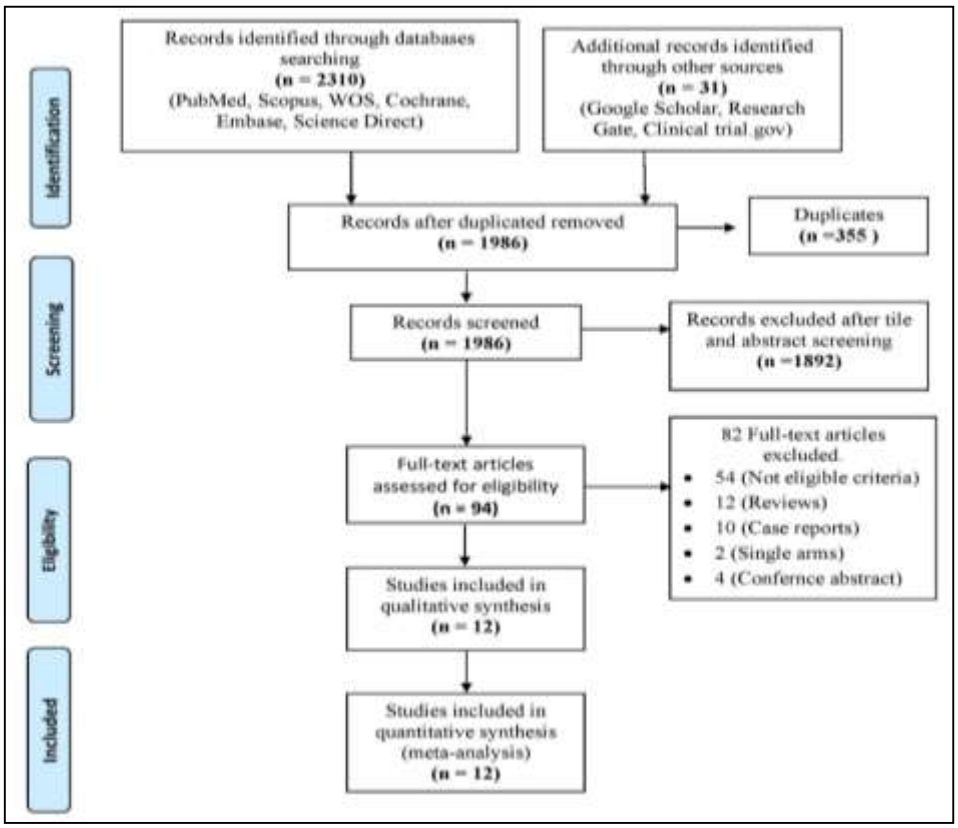

Figure (1): PRISMA flow diagram showing the literature search results.

2. Risk of bias assessment of the included studies

According to the Cochrane risk of bias tool detailed in chapter 8.5 of the Cochrane Handbook of Systematic Reviews of Interventions 5.1.0, all domains include random sequence generation, allocation concealment, selective reporting, attrition bias, performance bias via participant and personnel blinding, and detection bias through outcome assessment blinding. The five included studies indicated a low risk. The cohort study by Kim et al. [11] was rated as fair quality according to the NIH risk of bias assessment method. **Figure (2a,b).**

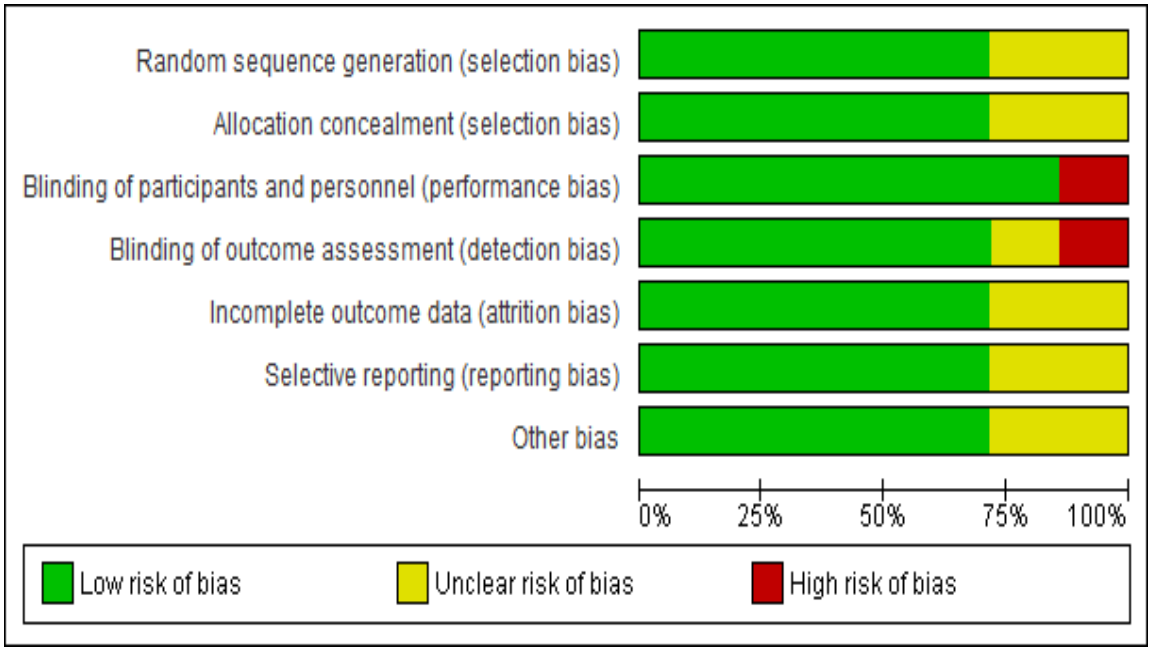

Figure (2a): risk of bias graph of the included studies.

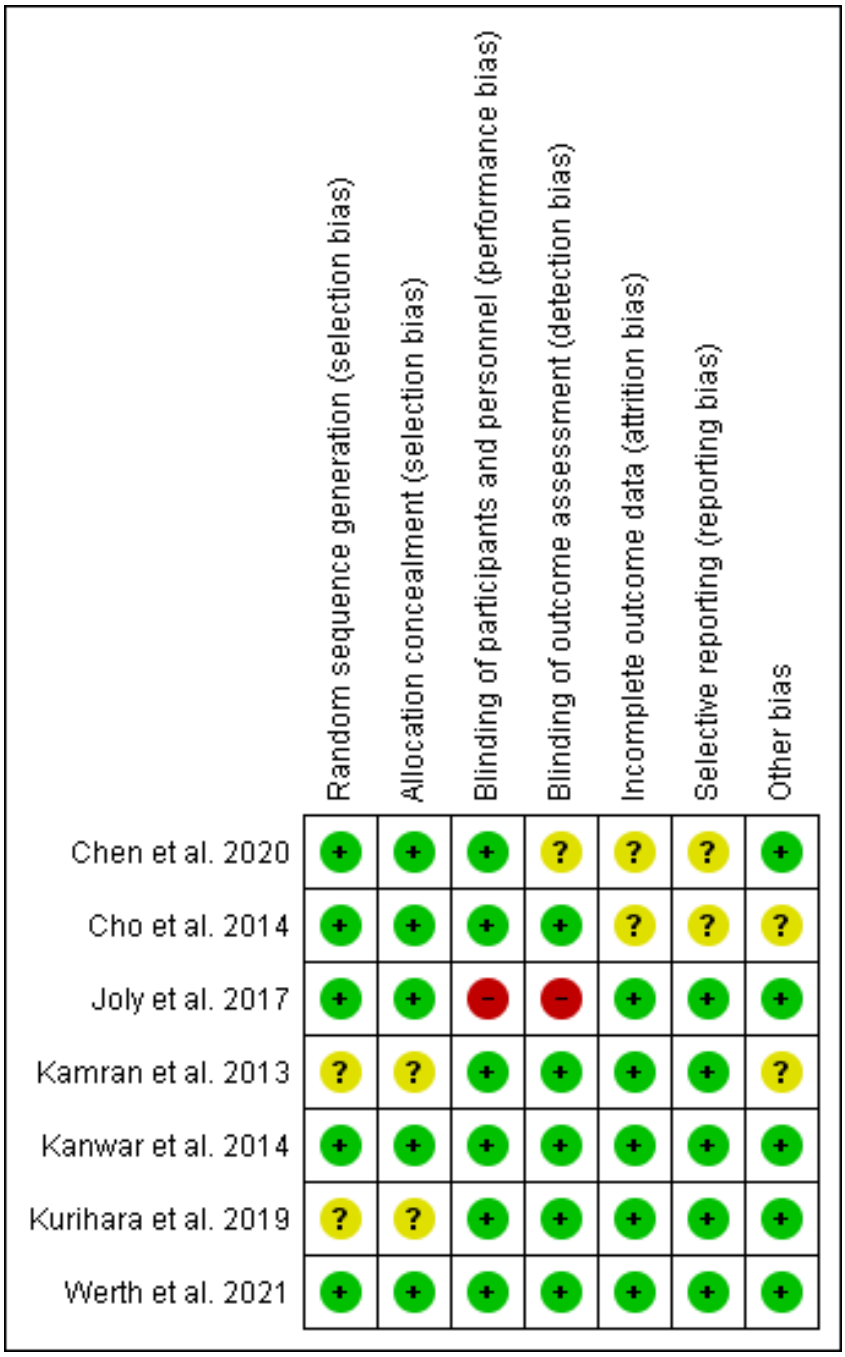

Figure (2b): Risk of bias graph of the included studies.

Table (1): Quality assessment of cohort studies by NIH tool

Domains	Kim et al. [11]	Kurihara et al. [12]	Horvath et al. [13]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	Yes	Yes	Yes
4. Were all the subjects selected or recruited from the same or similar populations? Were inclusion and exclusion criteria for being in the study pre-specified and applied uniformly to all participants?	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	NR	NR	Yes
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	NA	NA	NA
7. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	NR	Yes	NR
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	NA	Yes	NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	NR	Yes	NR
10. Was the exposure(s) assessed more than once over time?	NA	NA	NA
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	Yes	Yes	Yes
13. Was loss to follow-up after baseline 20% or less?	Yes	Yes	Yes
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) an outcome(s)?	NA	NA	NA
Total scores (Yes = 1, No = 0.5, NR & NA & CD = 0)	9	9	9
Quality rating: good (14-13 point) or fair (9-12 point) or poor (8-0 points)	Fair quality	Fair quality	Fair quality
NA: not applicable, **CD:** cannot determine, **NR:** not reported.			

3. Characteristics of the included studies

We identified six studies comparing RTX either with different dose of RTX or other line of treatment as glucocorticoid therapy. The included studies focused on the outcomes of complete or partial remission, disease flare and relapse, and some other adverse events including headache, sepsis, hypertension, PE, and arthralgia. The total number is 399 patients. Five studies had a prospective and randomized design, and one study had a retrospective cohort design Kim et al. [11].

Table (2): Study Characteristics

Study ID	Year	Study design	Sample size
Werth et al. [14]	2021	Phase 3 RCT	135
Chen et al. [15]	2014	RCT	74
Joly et al. [5]	2017	Prospective, multicenter, parallel-group, open-label randomized trial	90
Cho et al. [16]	2012	RCT	23
Kanwar et al. [17]	2014	RCT	22
Wollina et al. [18]	2008	Case series	2
Arin et al. [19]	2005	Case series	5
Kurihara et al. [12]	2019	A multicenter, open-label, single-arm, phase I, II trial	10
Kamran et al. [20]	2013	Phase II clinical trial	45
Aryanian and Posner [21]	2021	A Cohort retrospective study	999
Horvath et al. [13]	2012	Prospective cohort	15
Kim et al. [11]	2014	Retrospective cohort study	27

Table (3): Summary of the included studies

Study ID	Study Arms		Primary outcomes
Werth et al. [14]	RTX	Mycophenolate mofetil	Sustained CR at week 52
Chen et al. [15]	RTX plus prednisone	prednisone alone	Proportion of patients at month 24 who achieved CR
Joly et al. [5]	RTX combined with short-term prednisone	prednisone	Percentage of patients attaining full remission without treatment at 24 months
Cho et al. [16]	375 mg/m2 at 1-week intervals	Two infusions of RTX at the same dose	CR, recurrence, B-cell count before to and during RTX therapy
Kanwar et al. [17]	(2 x 1000 mg RTX)	(2 x 500 mg RTX)	CR, recurrence, and immunological evaluation pre- and post-RTX therapy
Wollina et al. [18]	RTX	-	Effective adjuvant administration of RTX in mucous membrane pemphigoid and PV in two individuals exhibiting the most resistant disease progression.
Arin et al. [19]	RTX	-	Disease activity score
Kurihara et al. [12]	RTX	-	Hypogammaglobulinemia, Joint infection/septic shock, Hyper gamma glutamyl transferase, Dental caries
Kamran et al. [20]	RTX	-	Nikolsky sign and re-epithelialization over the denuded surface
Aryanian and Posner [21]	RTX	-	Partial remission
Horvath et al. [13]	RTX	-	Complications of RTX
Kim et al. [11]	(375 mg m)2 per infusion weekly) Two infusion of RTX	(375 mg m)2 per infusion weekly) Three infusion of RTX	CR

Table (4): Findings of the included studies

Study ID	Conclusion
Werth et al. [14]	RTX demonstrated superiority over mycophenolate mofetil in achieving maintained full remission at 52 weeks in individuals with PV.
Chen et al. [15]	In individuals with moderate-to-severe PV and PF, the combination of RTX and short-term prednisone demonstrated superior efficacy compared to prednisone alone.
Joly et al. [5]	The first administration of RTX in conjunction with short-term prednisone in patients with moderate to severe pemphigus is more efficacious and safer than a treatment regimen consisting only of prednisone.
Cho et al. [16]	RTX is an efficacious and safe therapeutic option for both severe, recalcitrant pemphigus and mild to moderate pemphigus. A low dosage of RTX seemed enough for the treatment of mild to severe pemphigus.
Kanwar et al. [17]	Several clinical and immunological research characteristics indicate improved outcomes in individuals with high-dose (2 9 1000 mg) RTX.
Wollina et al. [18]	RTX serves as a third-line therapy for individuals with PV and mucous membrane pemphigoid.
Arin et al. [19]	This research emphasizes the enduring impact and disease management with a single administration of RTX, therefore broadening the range of therapeutic options for AIBDs..
Kurihara et al. [12]	CD19-positive B cells in the peripheral blood decreased on day 29 post-RTX therapy and persisted at reduced levels for the duration of the monitoring period (280 days). Our findings validated the effectiveness of RTX treatment for refractory AIBDs in Japan.
Kamran et al. [20]	RTX may serve as an effective adjunct to prednisolone in the treatment of PV and BP; nevertheless, its safety profile raises concerns.
Aryanian and Posner [21]	Early use of RTX benefits pemphigus patients, especially those with a mucocutaneous phenotype, pulmonary comorbidity, or history of smoking, and reduces their risk of infectious adverse events.
Horvath et al. [13]	A modest dosage of RTX is an effective and safe therapy for pemphigus. Relapses may transpire, primarily towards the conclusion of the second year. Longitudinal cost-effectiveness studies are necessary to ascertain the appropriate dose of this costly medication for pemphigus.
Kim et al. [11]	They determine that three or more infusions of RTX are superior to two infusions for the management of bullous disorders.

4. Primary and secondary outcomes

Our primary outcomes were to compare the efficacy and safety of the RTX for Bullous Auto-immune Diseases. We evaluate the efficacy of RTX regarding complete or partial remission and disease flare or relapse. We evaluated the safety of RTX regarding the evaluation of adverse events and serious adverse events including headache, arthralgia, PE, hypertension, and dyspnea.

5. Outcomes

1) Complete remission (CR):

Three investigations Werth et al. [14], Chen et al. [15], and Joly et al. [5] documented the effectiveness of RTX and other treatment modalities in achieving full remission of bullous illnesses. The pooled analysis of the included trials demonstrated a significant disparity between RTX and the comparator group, favoring RTX over the control group (RR = 2.5; 95% CI: [1.84, 3.39]; $P < 0.0001$), indicating that RTX is associated with a higher rate of full remission compared to the control group.

The pooled studies exhibited homogeneity (I2 = 26%, P = 0.26). No heterogeneity was seen in the studies examined **(Figure 3).**

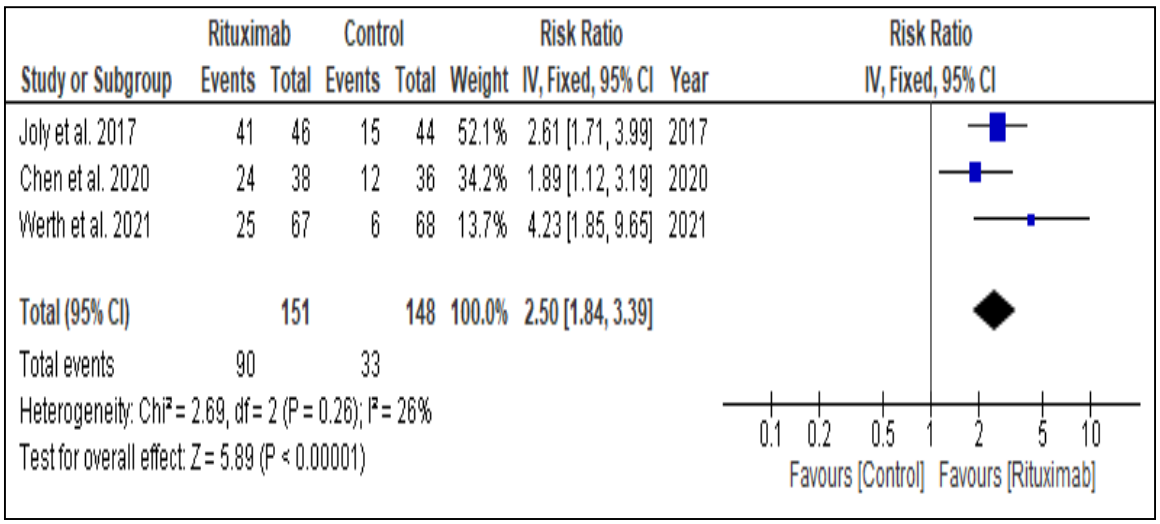

Figure (3): Forest plot showing the efficacy of the CR after RTX therapy. risk ratio (RR),confidence interval (CI).

2) Disease flare and relapse:

Three research studies Werth et al. [14], Chen et al. [15], and Joly et al. [5] documented the effectiveness of RTX and other treatment modalities for managing bullous illnesses in relation to disease exacerbation and recurrence. The pooled analysis of the trials demonstrated a substantial disparity between RTX and the comparator group, favoring RTX over the control group (RR = 0.34; 95% CI: 0.15, 0.73; P = 0.006). The pooled trials exhibited significant heterogeneity (I2 = 75%, P = 0.02), which was most effectively addressed by excluding Werth et al. [14] **(Figure 4).**

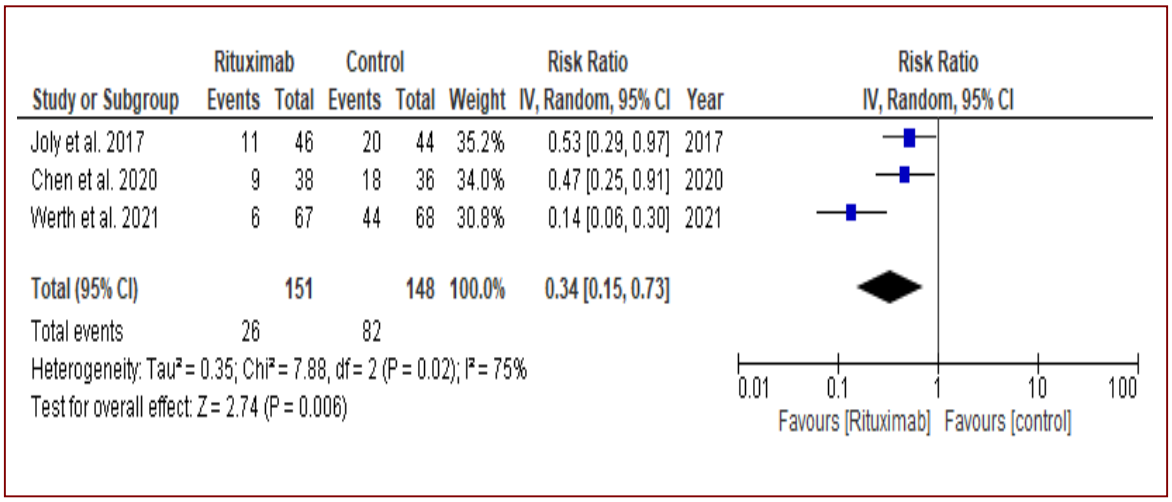

Figure (4): Forest plot showing the outcome of relapse after RTX therapy.

3) Overall adverse events:

The pooled analysis of the included trials revealed no significant difference in total adverse events between RTX and other treatment regimens. The analysis revealed no significant difference between

the intervention and control groups (RR = 1.5; 95% CI: [0.92, 1.20]; P = 0.48). The pooled studies exhibited homogeneity (I2 = 0%, P = 0.99). No heterogeneity was seen in the studies examined **(Figure 5).**

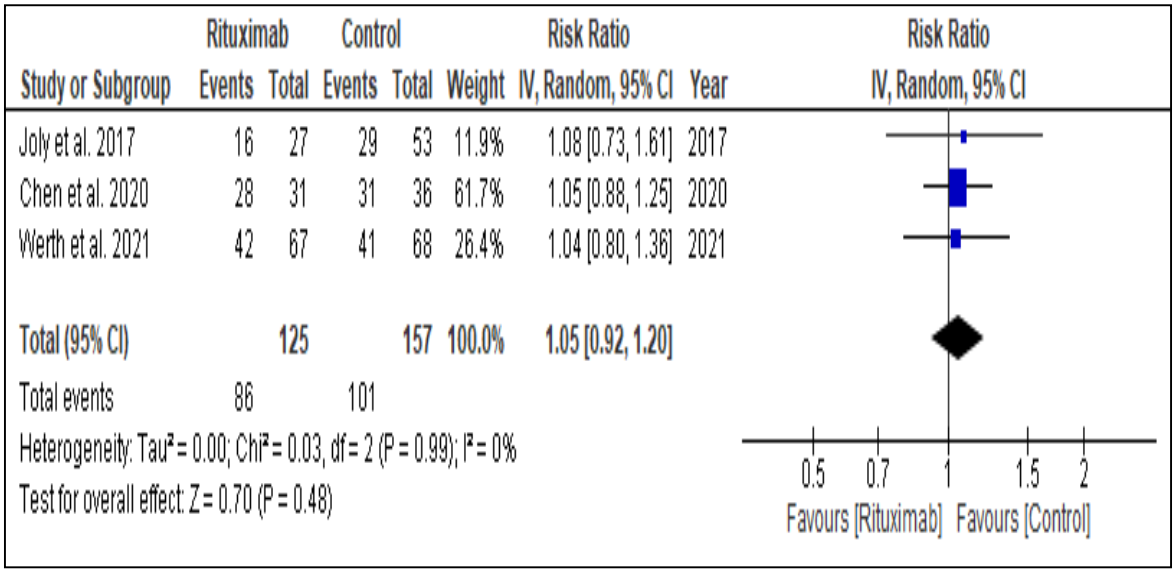

Figure (5): Forest plot of the adverse event of RTX.

4) Serious adverse events (SAE):

The pooled analysis of the included trials reveals no significant difference in total SAE between RTX and other treatment regimens. The analysis revealed no significant difference between the intervention and control groups (RR = 1.9; 95% CI: [0.82, 1.46]; P = 0.55). The pooled studies exhibited homogeneity (I2 = 0%, P = 0.33). No heterogeneity was seen in the studies examined **(Figure 6).**

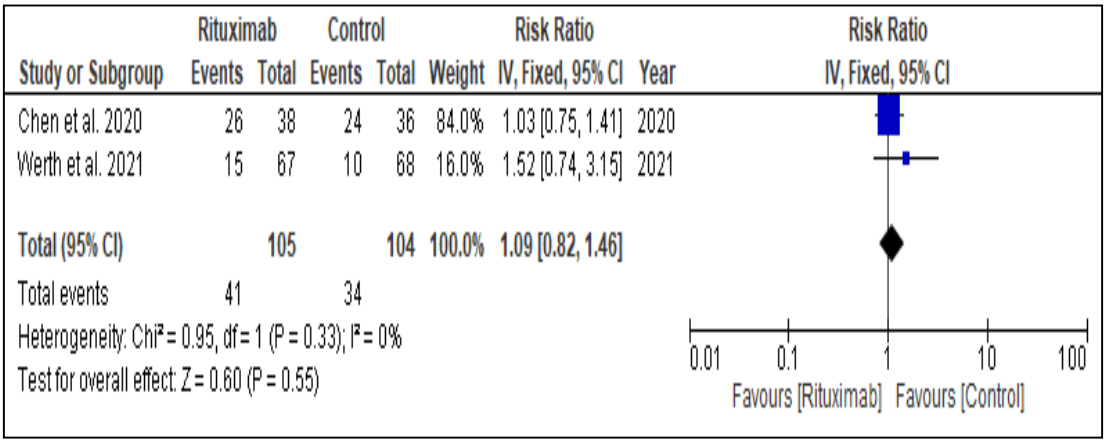

Figure (6): Forest plot of the serious adverse event (SEA) of RTX.

5) Sepsis:

Three investigations Werth et al. [14], Chen et al. [15], and Joly et al. [5] documented the incidence of sepsis as an adverse event in the RTX group compared to the control group. The

combined analysis of three trials revealed no significant difference between the RTX group and the control group (RR = 1.78; 95% CI: [0.29, 11.13]; P = 0.54). The pooled studies exhibited homogeneity (I2 = 0%, P = 0.44). No heterogeneity was seen in the studies examined **(Figure 7).**

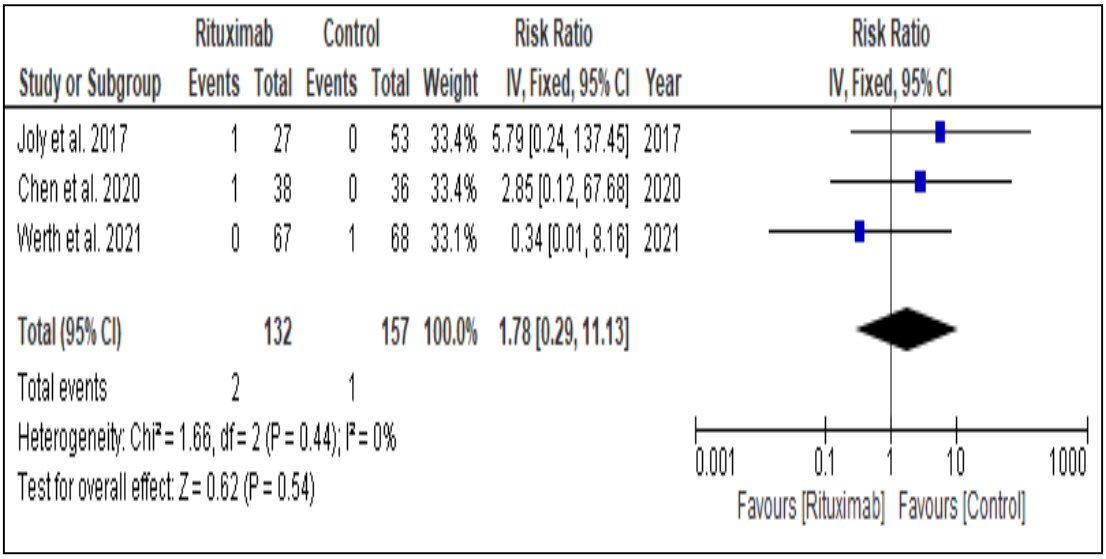

Figure (7): Forest plot of the sepsis as an adverse event of RTX.

6) Hypertension

Two research studies Werth et al. [14] and Chen et al. [15] documented the incidence of hypertension as an adverse event in the RTX group compared to the control group. The aggregated analysis of three trials revealed no significant difference between the RTX group and the control group (RR = 0.46; 95% CI: [0.11, 2.02]; P = 0.31). The pooled studies exhibited homogeneity (I2 = 0%, P = 0.82). No heterogeneity was seen in the studies examined **(Figure 8).**

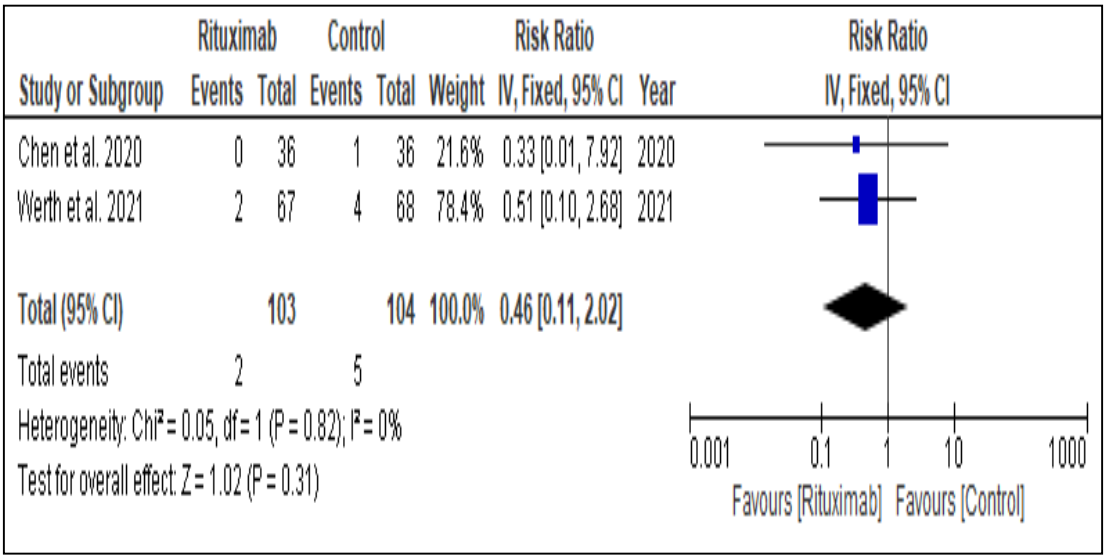

Figure (8): Forest plot of the hypertension as an adverse event of RTX.

7) Arthralgia

Two research studies Werth et al. [14] and Chen et al. [15] documented the incidence of arthralgia as an adverse event in the RTX group compared to the control group. The combined analysis of three trials revealed no significant difference between the RTX group and the control group (RR = 3.04; 95% CI: [0.75, 12.34]; P = 0.12). The pooled studies exhibited homogeneity (I2 = 0%, P = 0.99). No heterogeneity was seen in the studies examined **(Figure 9).**

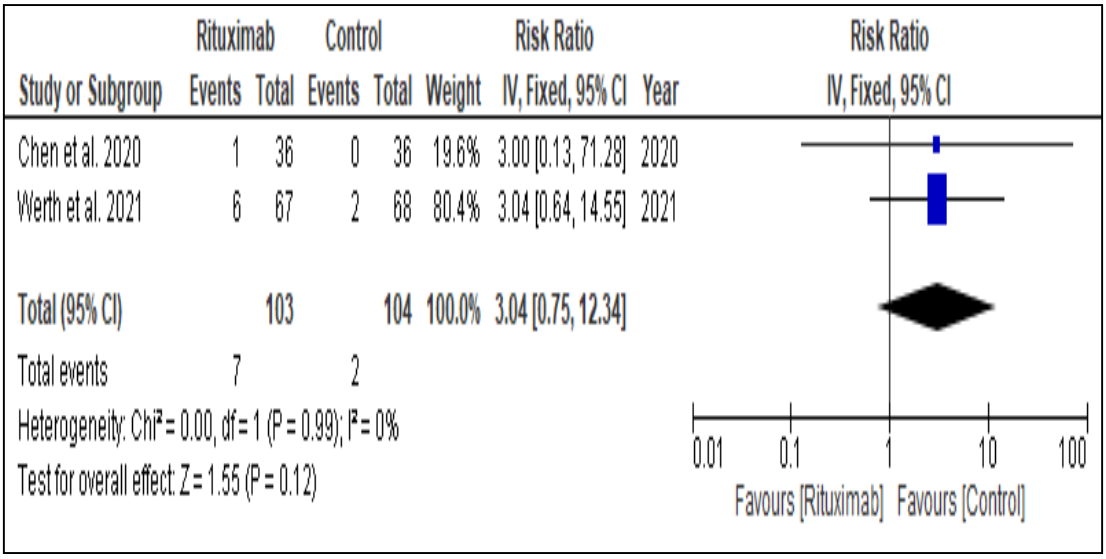

Figure (9): Forest plot of the arthralgia as an adverse event of RTX.

8) Pulmonary embolism (PE)

Three investigations Werth et al. [14], Chen et al. [15], and Joly et al. [5] documented the incidence of PE as an adverse event in both the RTX group and the control group. The combined analysis of three trials revealed no significant difference between the RTX group and the control group (RR = 0.73; 95% CI: [0.21, 2.51]; P = 0.62). The pooled studies exhibited homogeneity (I2 = 0%, P = 0.90). No heterogeneity was seen in the studies examined **(Figure 10).**

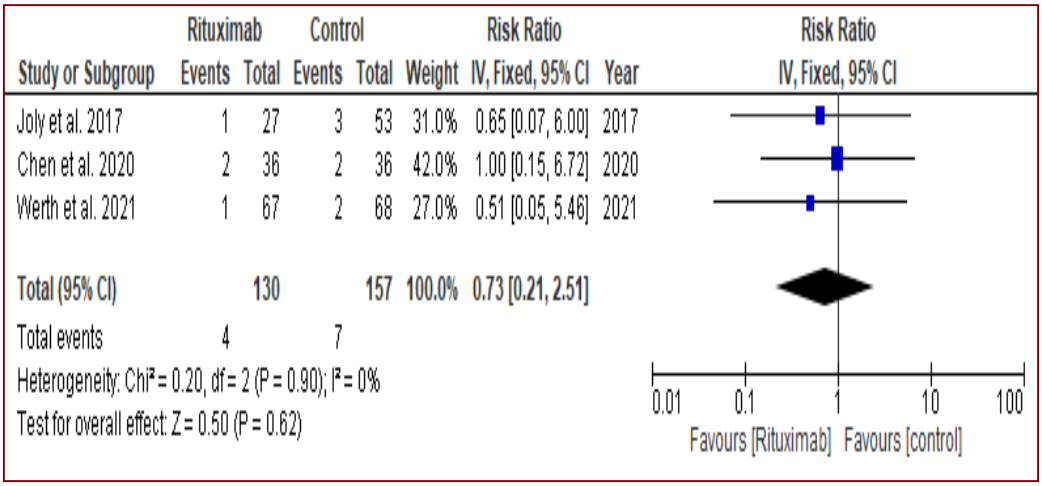

Figure (10): Forest plot of the PE as an adverse event of RTX.

9) Dyspnea

Three investigations Werth et al. [14], Chen et al. [15], and Joly et al. [5] documented the incidence of PE as an adverse event in both the RTX group and the control group. The combined analysis of three trials revealed no significant difference between the RTX group and the control group (RR = 0.73; 95% CI: [0.21, 2.51]; P = 0.62). The pooled studies exhibited homogeneity (I2 = 0%, P = 0.90). No heterogeneity was seen in the studies examined **(Figure 11).**

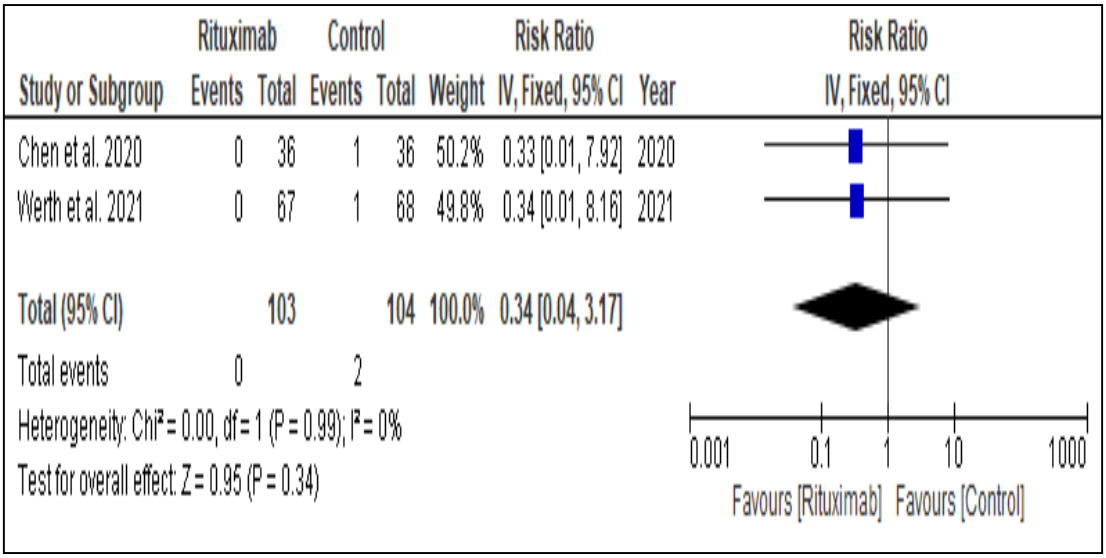

Figure (11): Forest plot of the dyspnea as an adverse event of RTX.

10) Headache

Two research investigations Werth et al. [14] and Chen et al. [15] reported the occurrence of headache as an adverse effect in the RTX group relative to the control group. The aggregate evaluation of three trials shown no statistically significant difference between the RTX group and the control group (RR = 1.77; 95% CI: [0.71, 4.42]; P = 0.22). The aggregated studies demonstrated homogeneity (I2 = 0%, P = 0.73). No heterogeneity was observed in the analyzed trials **(Figure 12).**

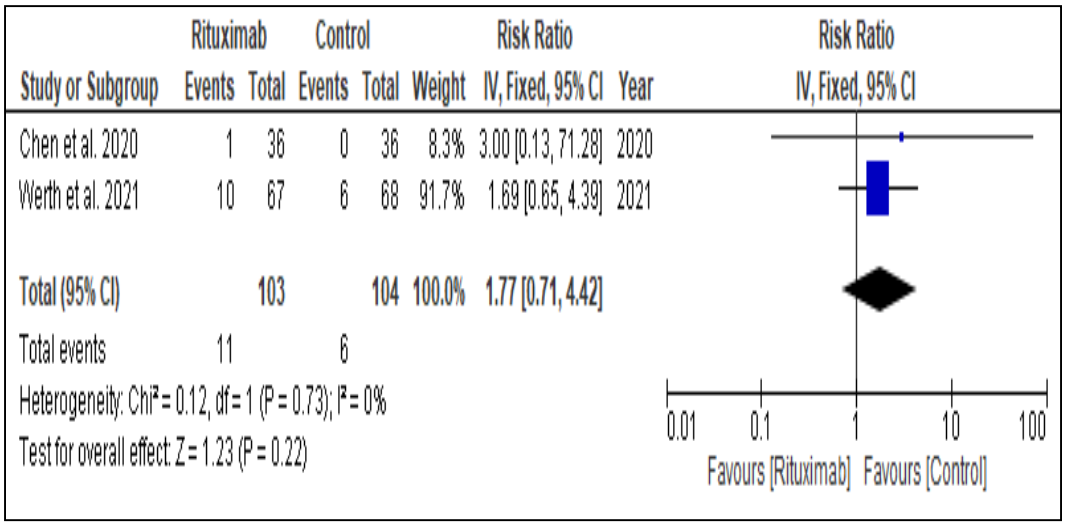

Figure (12): Forest plot of the headache as an adverse event of RTX.

11) CR (different doses of RTX)

Concerning the comparison of various dosages of RTX whether low or high; three investigations Kim et al. [11], Cho et al. [16], and Kanwar at al. [17] assessed the clinical full remission of the illness using varying doses of RTX in their respective trials. The study revealed no significant difference between the high dosage and low dose of RTX (RR = 1.01; 95% CI: [0.72, 1.40]; P = 0.97). The pooled studies exhibited homogeneity (I2 = 30%, P = 0.24). No heterogeneity was seen in the studies examined **(Figure 13).**

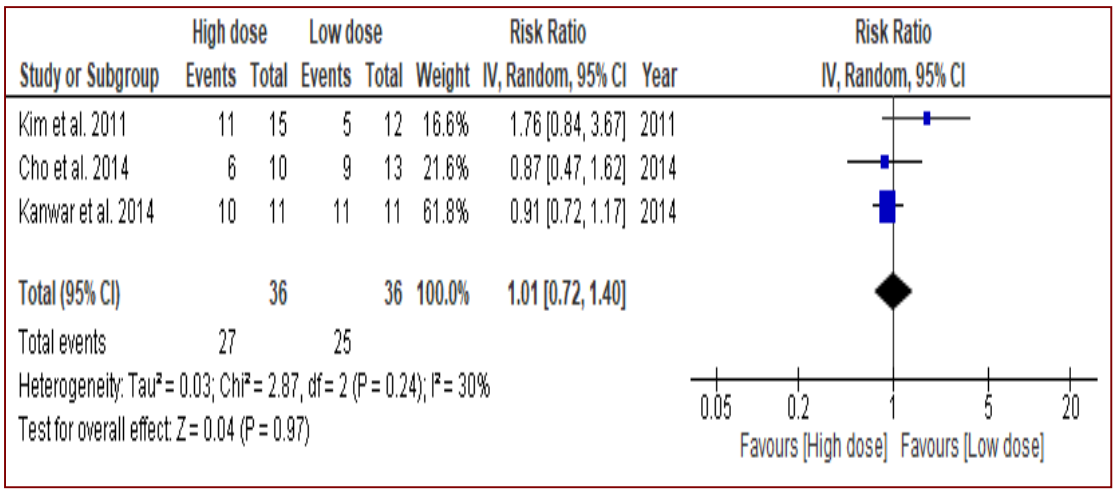

Figure (13): Forest plot showing the results of CR with different doses of RTX.

12) Relapse (different dose of RTX)

Regarding the comparison between different doses of RTX either low dose or high dose. Three studies Kim et al. [11]**, *Cho et al. [16] and Kanwar et al. [17]*** of the included studies evaluated the clinical CR of the disease with different dose of RTX. Kim et al. [11] had use 375mg/m^2 per infusion weekly two infusions of RTX as low dose.& 375mg/m^2 per infusion weekly three infusions of RTX as high dose. ***Cho et al. [16]*** had use 375mg/m^2 at one week interval as low dose.&two infusions at the same dose as high dose. ***Kanwar et al. [17]*** had use a dose of 2x 1000 mg RTX per infusion as high dose & 2x500mg RTX per the infusion as low dose. The analysis showed no significant difference between either high dose or low dose of RTX (RR = 0.59; 95% CI: [0.13, 2.78]; *P* = 0.51). Pooled studies were heterogenous (I^2 = 73%, *P* = 0.0.3). Random effect model was applied to the analysis to adjust the study weight. The heterogeneity couldn't be resolved due to the limited number of the included studies. **Figure (14)**

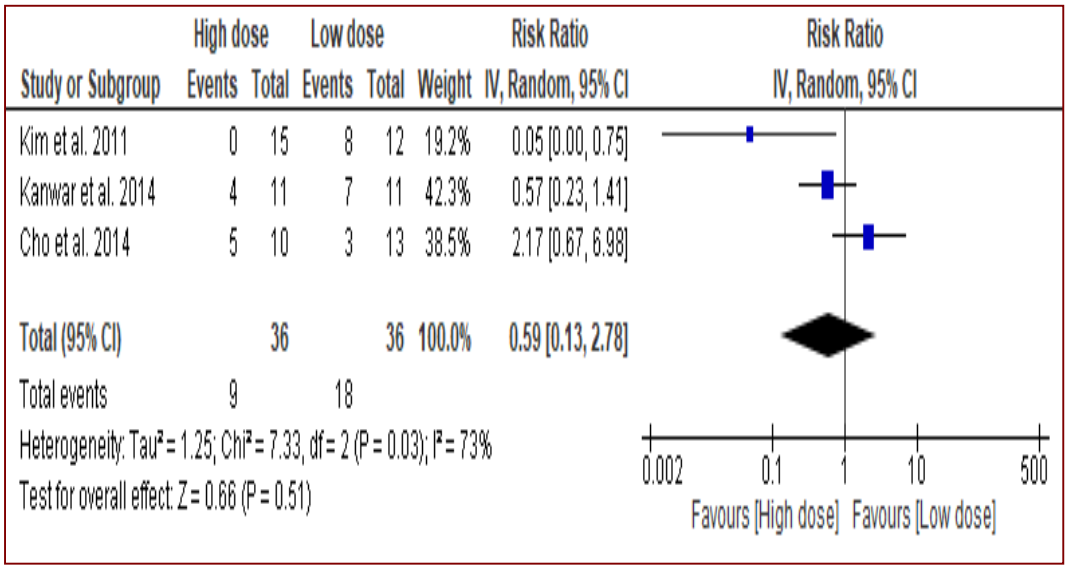

Figure (14): Forest plot showing the results of relapse with different doses of RTX.

4. Discussion:

Recent biological therapy aimed at autoreactive B cells has been used in AIBD, with favorable outcomes. Current research supports the effectiveness of RTX in treating individuals with pemphigus and other AIBD.Wang et al. [22] is one of the studies that highlighted the importance of using RTX for patients suffering from Bullous Auto-immune Diseases.

Given the often severe progression of these illnesses and the limited data on the effectiveness and safety of RTX for bullous individuals, we undertook this meta-analysis to consolidate the existing information on the use of RTX for AIBD [19].

In relation to significant aspects of bullous disorders, they were deemed deadly prior to the advent of corticosteroids [23]. The introduction of steroids reduced mortality, although morbidity persisted owing to the adverse effects of high-dose steroids. Recent pharmacological agents aimed at the molecular level reportedly exhibit reduced adverse effects and enhanced efficacy [24].

One of the recent pharmaceuticals is the anti-CD20 monoclonal antibody RTX, first sanctioned for B-cell malignancies, which is progressively used to manage other autoimmune disorders. RTX is a chimeric monoclonal antibody derived from murine and human sources, specifically targeting CD20. It functions by eliminating autoreactive B cells, with effects persisting for six to nine months [25].

The endpoint of CR was defined as total epithelialization and the absence of new or existing cutaneous and mucosal lesions [26].

In our present study, we found promising effects of RTX over the conventional therapy of corticosteroids regarding CR, we found significant positive results of RTX over the conventional therapies favoring the RTX for pemphigus patients. Our results were consistent

with the results of Chen et al. [15] reporting that RTX used with short-term prednisolone shown superior efficacy in achieving CR compared to prednisone alone. At the 24-month follow-up, a greater percentage of patients in the RTX group had CR for at least 2 months. Also, we agreed with the results of Joly et al. [5]. In their prospective randomized trial, they found after 24 months of follow-up duration, 41 of 46 patients assigned to RTX achieved CR versus 15 of 44 patients in the control group.

Regarding the disease flare and relapse, we found a significant difference favoring RTX over the control group treated by the conventional corticosteroid therapy. Similar results were obtained by Chen et al. [15], Joly et al. [5] and Wang et al. [22] reported a six-month follow-up with an overall relapse rate of 2% (n= 11/533). Our results were consistent with their results. In Joly et al. [5], at 24 months, recurrence occurred in 11 patients (24%) randomized to RTX combined with short-term prednisone. Patients who experienced recurrence required a notably extended period to achieve disease control, had a protracted consolidation phase, and had a reduced duration of remission off-treatment, while the remission group exhibited brief early endpoints and extended late endpoints [4]. Comparing full responders to incomplete responders post-RTX revealed that complete responders exhibited significant decrease of anti-Desmoglein antibodies and autoreactive B cells, with an increased presence of immature and naïve B cells, which facilitated early and prolonged remission.

We have also evaluated the high and low dosages of RTX regarding the complete response rate and recurrence. Concerning the recurrence and remission associated with varying dosages of RTX. No significant difference was seen between the groups given greater or lower dosages of RTX. Relapses often occur after RTX treatment. Wang et al. [22] documented an overall recurrence rate of 40%, indicating that an extended follow-up duration correlated with an increased relapse rate. Leshem et al. (2013) documented a 22% recurrence rate with an average follow-up of 18 months, while an 81% relapse rate was seen at a mean follow-up of 74 months [4].

Numerous patients in various trials with extended follow-up durations had multiple relapses and underwent successive cycles of RTX, with favorable results [13, 16, 20]. Certain investigations [27, 28, 29] shown a correlation between reduced illness duration and an increased rate of CR. This may substantiate the need for using RTX as a primary therapy in pemphigus, even in treatment-naïve patients. Lunardon et al. [29] proposed that administering RTX earlier in the illness progression may provide improved results. Disease severity shown only marginal relevance with CR length. This may pertain to the low sample size resulting from the restricted use of scoring instruments and the challenges in categorizing patients across various scoring systems. In Wang et al. [22], patients who had recurrence exhibited a greater mean illness

duration (21 months) compared to the remission group (6.4 months).

In many investigations [16, 30, 31], the total incidence of side events ranged from 1% to 16%. However, Wang et al. [22] showed that 35% had a substantial unfavorable impact. Approximately 20% of patients had reactivation of the herpes simplex virus; hence, prophylactic acyclovir suppression medication may be administered after RTX infusion. Prophylactic cotrimoxazole may be used for a duration of three to six months due to heightened vulnerability to bacterial infections. No life-threatening adverse reaction occurred.

Ultimately, Anandan et al. [32] found no influence of age, sex, illness extent, or Pemphigus Activity Score (PAS) on the research outcomes, nor were there any variations in these parameters between those who relapsed and those who sustained remission. This resembled the aforementioned research.

5. Conclusion:

RTX proved successful in treating AIBD, greatly surpassing standard treatments, reducing the need for supplementary steroids and other immunosuppressants, and inducing extended remission.

RTX serves as an adjuvant to corticosteroids, demonstrating considerable efficacy in reducing disease activity.

RTX had greater efficacy when administered early in the disease progression.

Both high-dose and low-dose RTX may result in CR, whereas high-dose RTX therapy might provide a prolonged period of CR. All unpleasant responses were effectively addressed.

The selection of treatment regimen is determined by illness severity, co-morbidities, and the patient's financial limitations to get optimal results. Subsequent research with bigger sample sizes and extended follow-up periods may elucidate the need for supplementary cycles of RTX to achieve persistent remission.

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